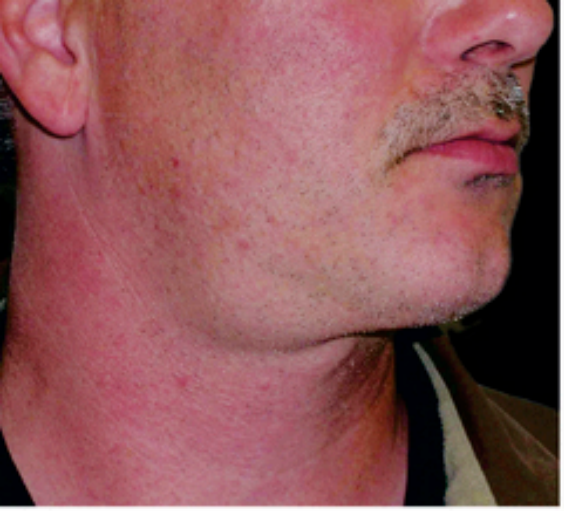

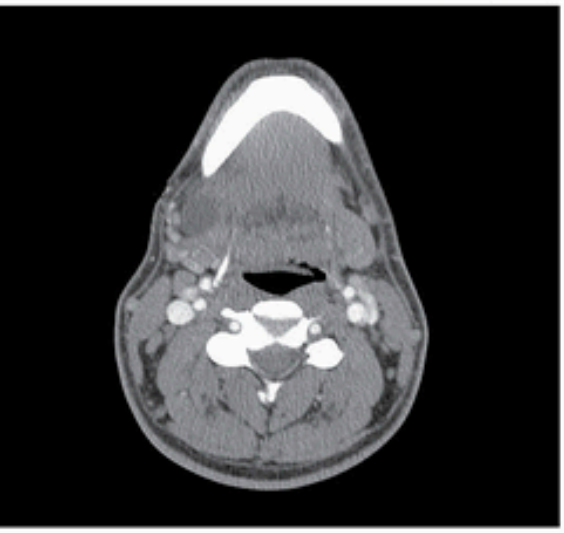

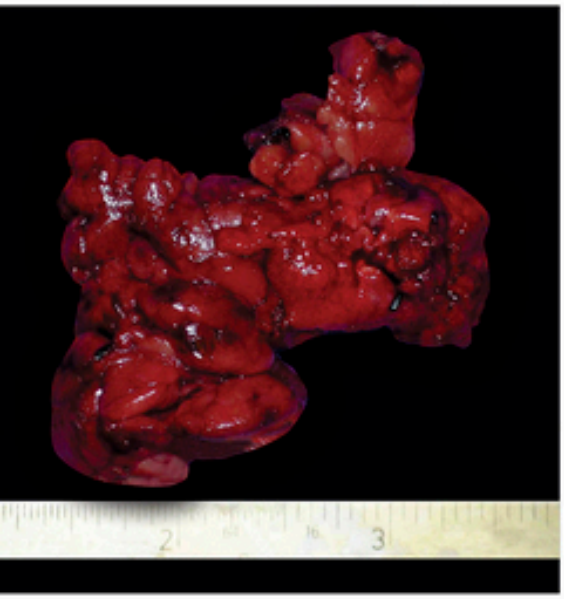

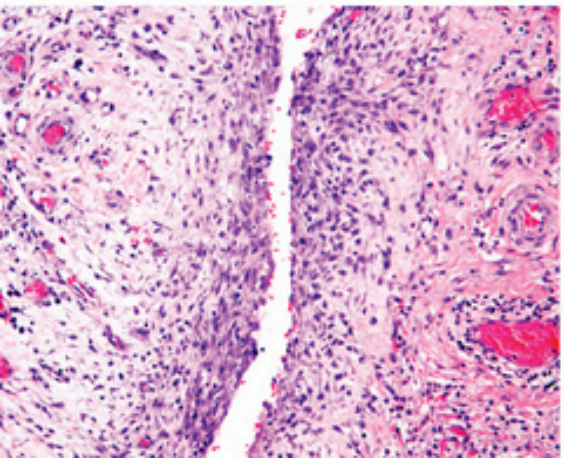

SALIVARY GLAND PATHOLOGY

DIAGNOSIS AND MANAGEMENT

SECOND EDITION

EDITED BY
ERIC R. CARLSON
ROBERT A. ORD

WILEY Blackwell

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Foreword First Edition

The mention of "head and neck cancer" immediately connotes the sobering realities and potentials of oral squamous cell carcinoma. Left to secondary recollection and awareness is the significance of salivary gland malignancy. The same can be said for the general perception of benign salivary neoplasia. In this brilliant new textbook, authors Carlson and Ord correct these notions, focusing proper emphasis on the group of diseases that, in their malignant form, represent some 3% of all North American head and neck tumors, affecting a minimum of 2500 victims per year.

One marvels at the dedication, energies, and resources – to say nothing of the expertise – mustered to produce a volume of this depth and expanse. While almost 40% of the effort is directed toward the vitally significant elements of classification, diagnosis, and clinical care of neoplasia, there is more – much more – here, for both the training and practicing readerships. The whole array of salivary gland dysfunctions is marvelously displayed in meaningful clinical color, in easily grasped sketches and graphs, and in well-chosen descriptive imaging. From the mandatory fundaments for such an undertaking – John Langdon's discourse on macro- and microanatomy, Pradeep Jacob's presentation on imaging diagnostics (45 pages!), John Sauk's explanations of current classification and staging of tumors – to the surgical demonstrations of pathology, anatomy, and technique, the visual material is extraordinary.

What are the vagaries in defining the SMAS layer? Can cell type be distinguished on the basis of imaging alone? What influence do genomics and biomarkers have in clinical classification? Does contemporary understanding explain the etiology of mucous escape phenomena? Up-to-date propositions on such topics occupy these chapters. Clinical challenges, traditional and new, for example, transection of ducts and nerves, intraductal micromanipulations, salivary diagnostics – they're all here, presented in clear, expansive, prose (28 pages of information on sialolithiasis alone!). The detriments of age and metabolic disorder on gland function, the genesis of non-salivary tumors inside the glands, and the lodging of metastatic disease within their confines receive emphasis in these pages. So do the presence of aberrant glands and the esoteric transplantation of salivary tissue in the management of xerophthalmia.

The *Textbook and Color Atlas of Salivary Gland Pathology* is authoritative. Its authors do not write anecdotally, but from the combined experience of decades, which has elevated them both to international recognition in the field of head and neck neoplasia. Their clinical material here presented represents volumes in the operating room, and the comprehensive bibliographies in each of the text's chapters testify to the authors' awareness of their topic and their world-views. Eric Carlson displays the fruits of his earlier endeavors in Pittsburgh, Detroit, and Miami, and speaks now from his position as Professor and Chairman in the Department of Oral and Maxillofacial Surgery at the University of Tennessee Graduate School of Medicine in Knoxville. Robert Ord established his worthy reputation in Britain before resettling himself in Baltimore on the western shores of the Atlantic some 20 years ago, where he now serves as Professor and Chairman of the Department of Oral and Maxillofacial Surgery at the University of Maryland. Theirs is the first tome in this domain engineered authoritatively by oral and maxillofacial surgeons, and does honor to their colleagues and forebears in the specialty who have toiled in the vineyards of salivary gland pathology. Neither in design nor execution, however, is their marvelous achievement directed to a parochial audience. Rather, surgeons or clinicians of whatever ilk will offer the authors a nod of appreciation in benefitting from this text.

Probably, one day, an expansion of this work will be written; and, undoubtedly, Carlson and Ord will write it.

R. Bruce MacIntosh, DDS
Detroit
June, 2008

Foreword Second Edition

Casual students of surgery or pathology might be inclined to ask what can possibly have transpired over the past seven years to warrant a new edition of a text concerning salivary gland dysfunction only first published in 2008. The prevalence of salivary gland neoplasia in comparison to other oral tumors is very small, and to whole body cancer even smaller; significant trauma to the glands ranks low in incidence compared to the rest of maxillofacial injuries; no one dies from inflammatory or immune disease of the glands; don't these facts mitigate against the need for a new textbook on the salivary glands every few years?

Quite the contrary! Because the 2008 Carlson-Ord volume was one of the very few works – and certainly the most comprehensive – dedicated solely to their topic, it is almost mandatory that it be reviewed and up-dated on a regular basis to provide clinicians and educators an authoritative repository of new information in this specialized field of interest.

And, indeed, there is new information! The complexity, variety, and heterogeneity in the origins of salivary gland tumors (as discussed in the new Chapter 8) makes these lesions an ideal study group for the development of all malignant neoplasia; they give credence to the notion that all disease, particularly malignant, is ultimately individualized and not to be boxed into currently recognized classifications. Senior readers will well remember the teaching axiom that salivary gland malignancies are impervious to radiation therapy; this new edition's Chapter 12 effectively disassembles that contention. Concurrently with the burgeoning understanding of cellular pathology at the subcellular and molecular levels, the concept of systemic chemotherapy, even targeted therapy, for salivary gland cancers has demanded re-evaluation over the past decade; this is illuminated in the new Chapter 13. Further, the authors have combined their first-hand knowledge with a compilation of all pertinent literature to offer a unique assembly of pediatric salivary gland pathology in Chapter 15, another addition.

While new knowledge – most excitingly provided in Chapters 8, 12 and 13 – and up-dated bibliographies, sketches, highlighted algorithms, and investigational studies are features of the new text, the focus of these elements and the overall emphasis of the work remains the surgical treatment of patients. Illustrative surgeries from the first edition have been retained, and new cases added to demonstrate principles and additional techniques. Management of the more common salivary tumors, injuries, and infections is well exhibited, but room is provided for illustration of rarer entities (Primary desmoid melanoma of the parotid?! Central (osseous) mucoepidermoid carcinoma of the mandibular ramus?!). Mundane or rare, the range of these maladies, plus the scope and depth of their demonstrated knowledge, attest to the broad experiences of Carlson and Ord in the field of salivary gland abnormality, and deservedly position them in the upper echelons of American salivary gland surgeons.

One could anticipate in 2008 that Carlson-Ord would recognize the abiding need for pertinence and currency in their text; indeed they have, and have delivered again.

Robert Bruce MacIntosh, D.D.S.
Formerly Section Chief, Division of Oral and Maxillofacial Surgery in the Department of Oral and Maxillofacial Surgery/Hospital Dentistry, Sinai Hospital, and Program Director, Oral and Maxillofacial Surgery, Henry Ford Hospital, Detroit

Preface First Edition

The concept of this book devoted to the diagnosis and management of salivary gland pathology arose from our longstanding friendship and professional relationship where we first collaborated in the early 1990s. This led to a trip to India with the Health Volunteers Overseas in 1996, where we operated numerous complex cancer cases, including many salivary gland malignancies. Dr. Carlson's interest in benign and malignant tumor surgery was fostered by the expert surgical tutelage of Dr. Robert E. Marx at the University of Miami Miller School of Medicine/Jackson Memorial Hospital in Miami, Florida. It was the training by Professor John Langdon that nurtured Dr. Ord's love of the parotidectomy. Over the years, following the publication of several papers and book chapters devoted to salivary gland surgery, we realized that a textbook and atlas related to this discipline should be produced. It was believed that a work written by two surgeons who shared similar surgical philosophies would be a unique addition to the current literature. This has been a project that we have approached with energy and enthusiasm which hopefully is evident to the reader.

The diagnosis and management of salivary gland pathology is an exciting and thought provoking discipline in medicine, dentistry and surgery. It is incumbent on the clinician examining a patient with a suspected developmental, neoplastic or non-neoplastic lesion of the major or minor salivary glands to obtain a comprehensive history and physical examination, after which time a differential diagnosis is established. A definitive diagnosis is provided with either an excisional or incisional biopsy depending on the gland involved and the differential diagnosis established pre-operatively. A complete understanding of the anatomic barriers surrounding a salivary gland lesion is paramount when performing surgery for a salivary gland neoplasm.

It is the purpose of this *Textbook and Color Atlas of Salivary Gland Pathology* to provide both text and clinical images, thereby making this a singular work. The reader interested in the science and evidence based medicine associated with the management of salivary gland pathology will be attracted to our text. The reader interested in how to perform salivary gland surgery as a function of diagnosis and anatomic site will find the real-time images useful. To that end, artist sketches are limited in this book. Where appropriate, algorithms have been included as a guide for diagnosis and management. It is our hope that this text and atlas will find a home on the bookshelves of those surgeons who share our fascination with the diagnosis and management of salivary gland disease.

Eric R. Carlson, DMD, MD, FACS
Robert A. Ord, DDS, MD, FRCS, FACS, MS

Preface Second Edition

In 2008 we published our first work entitled *Textbook and Color Atlas of Salivary Gland Pathology – Diagnosis and Management*. In preparation for the development and publication of the second edition of this book, several issues became apparent that resulted in changes and additions to our first edition. The first change is the title. We selected *Salivary Gland Pathology – Diagnosis and Management*, due to the inherent and obvious textbook nature of this work. In addition, our readership is aware that our teaching mission involves the use of high quality color images to illustrate the cases included in each chapter and to guide the reader through the workup and execution of the medical and surgical management of salivary gland pathology. The title was shortened accordingly. All chapters have been updated in terms of references and the addition of new cases to illustrate important points within each chapter. This includes Chapter 7, "Classification, Grading, and Staging of Salivary Gland Tumors," where histomicrographs of most of the benign and malignant salivary gland neoplasms are now illustrated in the chapter. In keeping with our expanding knowledge base of the diagnosis and management of salivary gland pathology, we have included four new chapters in this second edition, including those devoted to the molecular biology of benign and malignant salivary gland tumors, radiation therapy for salivary gland tumors, systemic therapy for salivary gland cancer, and pediatric salivary gland pathology. Four new authors have been added including Drs. Joseph Kelley, J. Michael McCoy, Janakiraman Subramanian, and Randy Todd. Where appropriate, algorithms have been included in the chapters to assist in decision making processes associated with the management of salivary gland pathology.

As with the first edition of this textbook, it is our expressed purpose to make this second edition a singular work with extensive text and clinical images. It is our hope that this textbook will provide a useful update to our colleagues who benefited from the first edition.

Eric R. Carlson, DMD, MD, FACS
Robert A. Ord, DDS, MD, FRCS, FACS, MS, MBA

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I would like to thank my mentors, Drs. Guy Catone, Robert Marx, and John Bell for teaching me; my patients for trusting me; my father, Reinhold Carlson, for encouraging me; my residents and fellows for challenging me; and most of all, my family, Susan, Katie, and Kristen for supporting me. I am grateful to all of you.

Eric R. Carlson

To my wife, Sue, my inspiration as always.

Robert A. Ord

Chapter 1

Surgical Anatomy, Embryology, and Physiology of the Salivary Glands

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King's College, London, UK

Outline

Introduction

There are three pairs of major salivary glands consisting of the parotid, submandibular, and sublingual glands. In addition, there are numerous minor glands distributed throughout the oral cavity within the mucosa and submucosa.

On average, about 0.5 liters of saliva are produced each day but the rate varies throughout the day. At rest, about 0.3 ml/min are produced but this rises to 2.0 ml/min with stimulation. The contribution from each gland also varies. At rest, the parotid produces 20%, the submandibular gland 65%, and the sublingual and minor glands 15%. On stimulation, the parotid secretion rises to 50%. The nature of the secretion also varies from gland to gland. Parotid secretions are almost exclusively serous, the submandibular secretions are mixed and the sublingual and minor gland secretions are predominantly mucinous.

Saliva is essential for mucosal lubrication, speech, and swallowing. It also performs an essential buffering role that influences demineralization of teeth as part of the carious process. When there is a marked deficiency in saliva production, xerostomia, rampant caries, and destructive periodontal disease ensues. Various digestive enzymes – salivary amylase – and antimicrobial

Salivary Gland Pathology: Diagnosis and Management, Second Edition. Edited by Eric R. Carlson and Robert A. Ord.

agents – IgA, lysozyme, and lactoferrin – are also secreted with the saliva.

The Parotid Gland

EMBRYOLOGY

The parotid gland develops as a thickening of the epithelium in the cheek of the oral cavity in the 15 mm Crown Rump length embryo. This thickening extends backwards towards the ear in a plane superficial to the developing facial nerve. The deep aspect of the developing parotid gland produces bud like projections between the branches of the facial nerve in the third month of intra-uterine life. These projections then merge to form the deep lobe of the parotid gland. By the sixth month of intra-uterine life the gland is completely canalized. Although not embryologically a bilobed structure, the parotid comes to form a larger (80%) superficial lobe and a smaller (20%) deep lobe joined by an isthmus between the two major divisions of the facial nerve. The branches of the nerve lie between these lobes invested in loose connective tissue. This observation is vital in the understanding of the anatomy of the facial nerve and surgery in this region (Berkovitz, et al. 2003).

ANATOMY

The parotid is the largest of the major salivary glands. It is a compound, tubuloacinar, merocrine, exocrine gland. In the adult, the gland is composed entirely of serous acini.

The gland is situated in the space between the posterior border of the mandibular ramus and the mastoid process of the temporal bone. The external acoustic meatus and the glenoid fossa lie above together with the zygomatic process of the temporal bone (Figure 1.1). On its deep (medial) aspect lies the styloid process of the temporal bone. Inferiorly, the parotid frequently overlaps the angle of the mandible and its deep surface overlies the transverse process of the atlas vertebra.

The shape of the parotid gland is variable. Often it is triangular with the apex directed inferiorly. However, on occasion it is more or less of even width and occasionally it is triangular with the apex superiorly. On average, the gland is 6 cm in length with a maximum of 3.3 cm in width. In 20% of subjects a smaller accessory lobe arises from the upper border of the parotid duct approximately 6 mm in front of the main gland. This accessory lobe overlies the zygomatic arch.

The gland is surrounded by a fibrous capsule previously thought to be formed from the investing layer of deep cervical fascia. This fascia passes up from the neck and was thought to split to enclose the gland. The deep layer is attached to the mandible and the temporal bone at the tympanic plate and styloid and mastoid processes (McMinn, et al. 1984; Berkovitz and Moxham 1988; Williams 1995; Ellis 1997). Recent investigations suggest that the superficial layer of the parotid capsule is not formed in this way, but is part of the superficial musculo-aponeurotic system (SMAS) (Mitz and

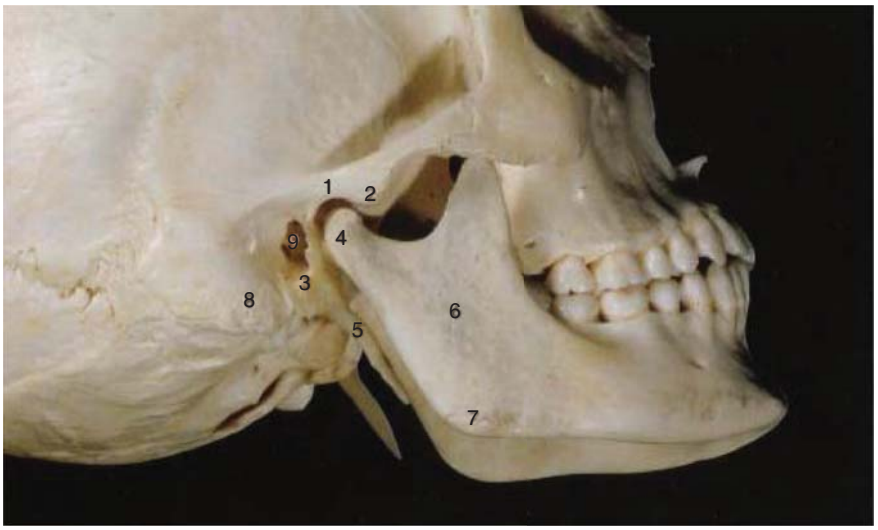

Figure 1.1. A lateral view of the skull showing some of the bony features related to the bed of the parotid gland. 1: Mandibular fossa; 2: Articular eminence; 3: Tympanic plate; 4: Mandibular condyle; 5: Styloid process; 6: Ramus of mandible; 7: Angle of mandible; 8: Mastoid process; 9: External acoustic meatus. Source: *Surgical Management of the Infratemporal Fossa*. (J. Langdon, B. Berkovitz & B. Moxham). ISBN 9781899066797. Reproduced with permission of Taylor & Francis Books UK.

Peyronie 1976; Jost and Levet 1983; Wassef 1987; Thaller, et al. 1989; Zigiotti, et al. 1991; Gosain, et al. 1993; Flatau and Mills 1995). Anteriorly, the superficial layer of the parotid capsule is thick and fibrous but more posteriorly, it becomes a thin translucent membrane. Within this fascia are scant muscle fibers running parallel with those of the platysma. This superficial layer of the parotid capsule appears to be continuous with the fascia overlying the platysma muscle. Anteriorly, it forms a separate layer overlying the masseteric fascia, which is itself an extension of the deep cervical fascia. The peripheral branches of the facial nerve and the parotid duct lie within a loose cellular layer between these two sheets of fascia. This observation is important in parotid surgery. When operating on the parotid gland, the skin flap can either be raised in the subcutaneous fat layer or deep to the SMAS layer. The SMAS layer itself can be mobilized as a separate flap and can be used to mask the cosmetic defect following parotidectomy by reattaching it firmly to the anterior border of the sternocleidomastoid muscle as an advancement flap (Meningaud, et al. 2006).

The superior border of the parotid gland (usually the base of the triangle) is closely molded

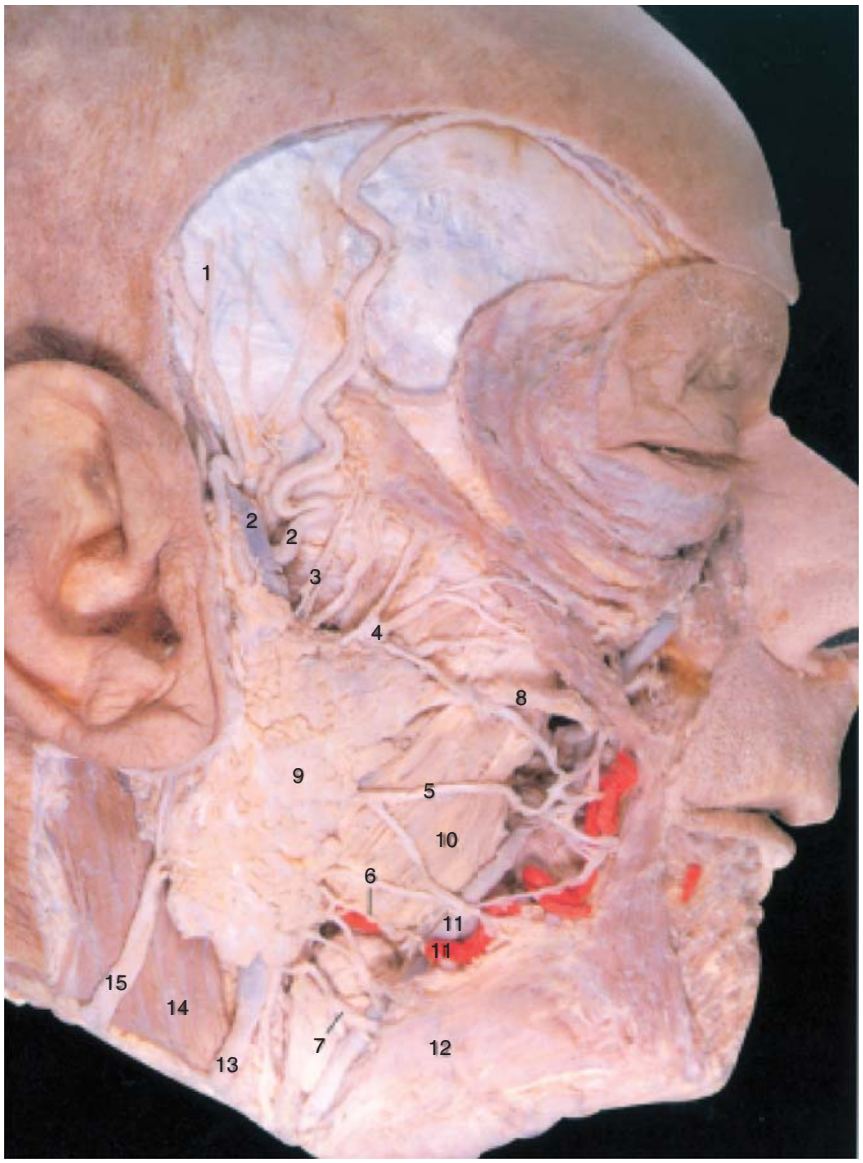

Figure 1.2. The parotid gland and associated structures. 1: Auriculotemporal nerve; 2: Superficial temporal vessels; 3: Temporal branch of facial nerve; 4: Zygomatic branch of facial nerve; 5: Buccal branch of facial nerve; 6: Mandibular branch of facial nerve; 7: Cervical branch of facial nerve; 8: Parotid duct; 9: Parotid gland; 10: Masseter muscle; 11: Facial vessels; 12: Platysma muscle; 13: External jugular vein; 14: Sternocleidomastoid muscle; 15: Great auricular nerve. Source: *Surgical Management of the Infratemporal Fossa*. (J. Langdon, B. Berkovitz & B. Moxham). ISBN 9781899066797. Reproduced with permission of Taylor & Francis Books UK.

around the external acoustic meatus and the temporomandibular joint. An avascular plane exists between the gland capsule and the cartilaginous and bony acoustic meatus (Figure 1.2). The inferior border (usually the apex) is at the angle of the mandible and often extends beyond this to overlap the digastric triangle where it may lie very close to the posterior pole of the submandibular salivary gland. The anterior border just overlaps the posterior border of the masseter muscle and the posterior border overlaps the anterior border of the sternocleidomastoid muscle.

The superficial surface of the gland is covered by skin and platysma muscle. Some terminal branches of the great auricular nerve also lie superficial to the gland. At the superior border of the parotid lie the superficial temporal vessels with the artery in front of the vein. The auriculotemporal branch of the mandibular nerve runs at a deeper level just behind the superficial temporal vessels.

The branches of the facial nerve emerge from the anterior border of the gland. The parotid duct also emerges to run horizontally across the masseter muscle before piercing the buccinator muscle anteriorly to end at the parotid papilla. The transverse facial artery (a branch of the superficial temporal artery) runs across the area parallel to and approximately 1 cm above the parotid duct. The anterior and posterior branches of the facial vein emerge from the inferior border.

The deep (medial) surface of the parotid gland lies on those structures forming the parotid bed. Anteriorly, the gland lies over the masseter muscle and the posterior border of the mandibular ramus from the angle up to the condyle. As the gland wraps itself around the ramus it is related to the medial pterygoid muscle at its insertion on to the deep aspect of the angle. More posteriorly, the parotid is molded around the styloid process and the styloglossus, stylohyoid, and stylopharyngeus muscles from below upwards. Behind this, the parotid lies on the posterior belly of the digastric muscle and the sternocleidomastoid muscle. The digastric and the styloid muscles separate the gland from the underlying internal jugular vein, the external and internal carotid arteries and the glossopharyngeal, vagus, accessory, and hypoglossal nerves, and the sympathetic trunk.

The fascia that covers the muscles in the parotid bed thickens to form two named ligaments (Figure 1.3). The stylomandibular ligament passes from the styloid process to the angle of the mandible. The mandibulostylohyoid ligament (the angular tract) passes between the angle of the mandible and the stylohyoid ligament. Inferiorly, it usually extends down to the hyoid bone. These ligaments are all that separates the parotid gland anteriorly from the posterior pole of the superficial lobe of the submandibular gland.

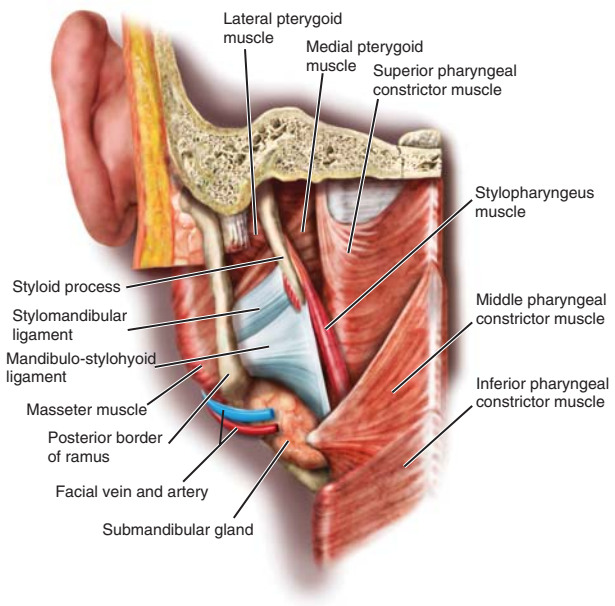

Figure 1.3. The mandibulostylohyoid ligament and surrounding anatomy.

CONTENTS OF THE PAROTID GLAND

The Facial Nerve

From superficial to deep, the facial nerve, the auriculotemporal nerve, the retromandibular vein, and the external carotid artery pass through the substance of the parotid gland.

The facial nerve exits the skull base at the stylomastoid foramen. The surgical landmarks are important (Figure 1.4). To expose the trunk of the facial nerve at the stylomastoid foramen the dissection passes down the avascular plane between the parotid gland and the external acoustic canal until the junction of the cartilaginous and bony canals can be palpated. A small triangular extension of the cartilage points towards the facial nerve as it exits the foramen (Langdon 1998b). The nerve lies about

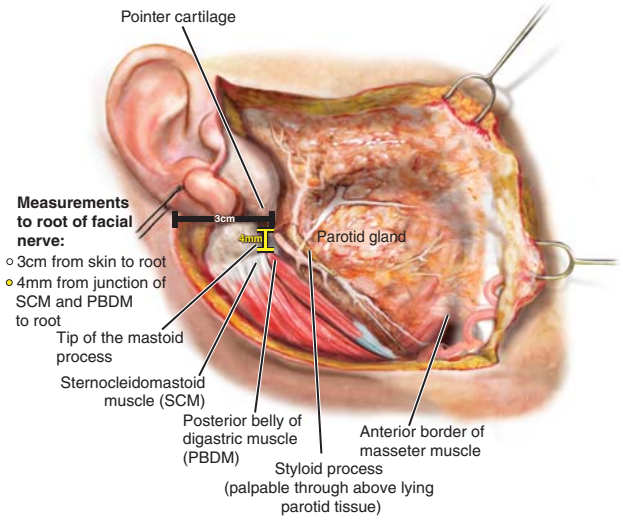

Figure 1.4. Anatomical landmarks of the extratemporal facial nerve.

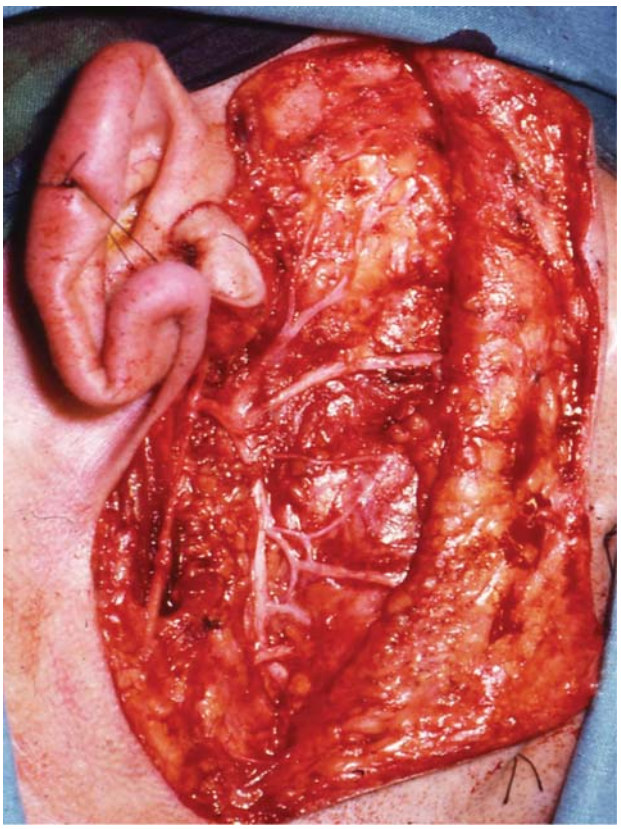

Figure 1.5. Clinical photograph of dissected facial nerve following superficial parotidectomy.

9 mm from the posterior belly of the digastric muscle and 11 mm from the bony external meatus (Holt 1996). The facial nerve then passes downwards and forwards over the styloid process and associated muscles for about 1.3 cm before entering the substance of the parotid gland (Hawthorn and Flatau 1990). The first part of the facial nerve gives off the posterior auricular nerve supplying the auricular muscles and also branches to the posterior belly of the digastric and stylohyoid muscles.

On entering the parotid gland the facial nerve divides into two divisions, temporofacial and cervicofacial, the former being the larger. The division of the facial nerve is sometimes called the pes anserinus due to its resemblance to the foot of a goose. From the temporofacial and cervicofacial divisions, the facial nerve gives rise to five named branches – temporal, zygomatic, buccal, mandibular, and cervical (Figure 1.5). The peripheral branches of the facial nerve form anastomotic arcades between adjacent branches to form the parotid plexus. These anastomoses are important during facial nerve dissection as accidental damage to a small branch often fails to result in any facial weakness due to dual innervation from adjacent branches. Davis et al. (1956) studied these patterns following the dissection of 350 facial nerves in cadavers. The anastomotic relationships between adjacent branches fell into six patterns (Figure 1.6). They showed that in only 6% of cases (type VI) is there any anastomosis between the mandibular branch and adjacent branches. This explains why, when transient facial weakness follows facial nerve dissection, it is usually the mandibular branch that is affected.

Auriculotemporal Nerve

The auriculotemporal nerve arises from the posterior division of the mandibular division of the trigeminal nerve in the infratemporal fossa. It runs backwards beneath the lateral pterygoid muscle between the medial aspect of the condylar neck and the sphenomandibular ligament. It enters the anteromedial surface of the parotid gland passing upwards and outwards to emerge at the superior border of the gland between the temporomandibular joint and the external acoustic meatus. This nerve communicates widely with the temporofacial division of the facial nerve and limits the mobility of the facial nerve during surgery (Flatau and Mills 1995). Further communications with the temporal and zygomatic branches loop around the

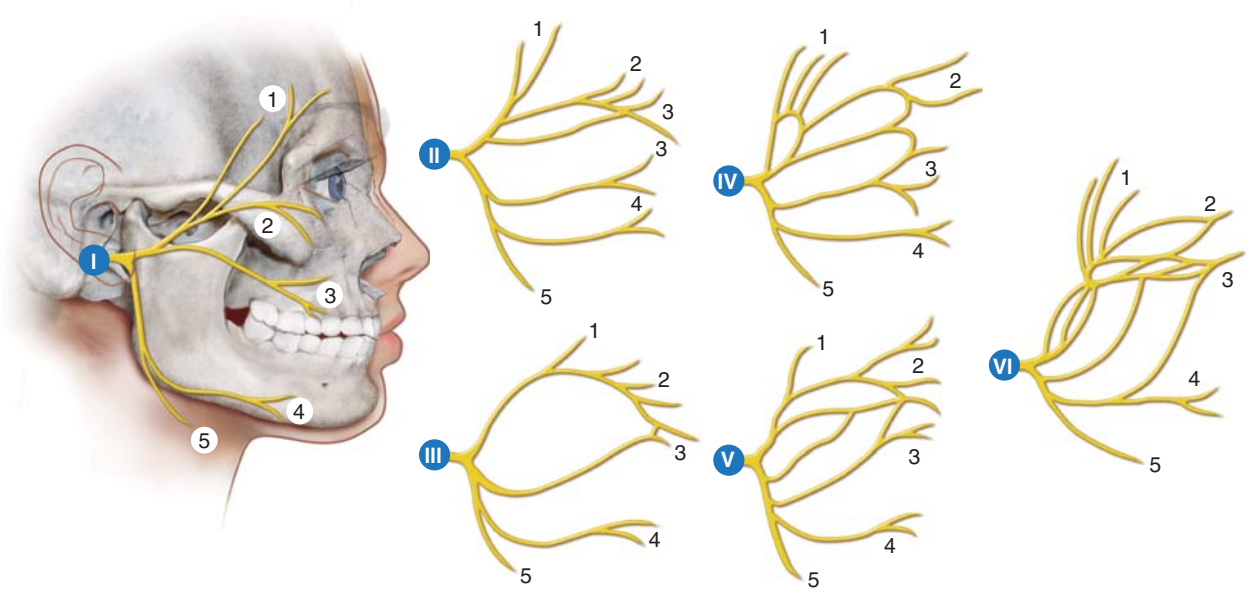

Figure 1.6. The branching patterns of the facial nerve.

transverse facial and superficial temporal vessels (Bernstein and Nelson 1984).

Retromandibular Vein

The vein is formed within the parotid gland by the union of the superficial temporal vein and the maxillary vein. The retromandibular vein passes downwards and close to the lower pole of the parotid where it often divides into two branches passing out of the gland. The posterior branch passes backwards to unite with the posterior auricular vein on the surface of the sternocleidomastoid muscle to form the external jugular vein. The anterior branch passes forward to join the facial vein.

The retromandibular vein is an important landmark during parotid gland surgery. The division of the facial nerve into its temporofacial and cervicofacial divisions occurs just behind the retromandibular vein (Figure 1.7). The two divisions lie just superficial to the vein in contact with it. It is all too easy to tear the vein whilst exposing the division of the facial nerve!

External Carotid Artery

The external carotid artery runs deeply within the parotid gland. It appears from behind the posterior belly of the digastric muscle and grooves the parotid before entering it. It gives off the posterior auricular artery before ascending and dividing into its terminal branches, the superficial temporal and maxillary arteries at the level of the condyle. The superficial temporal artery continues vertically to emerge at the superior border of the gland and crosses the zygomatic arch. Within the substance of the parotid it gives off the transverse facial artery, which emerges at the anterior border of the gland to run across the face above the parotid duct. The maxillary artery emerges from the deep aspect of the gland anteriorly to enter the infratemporal fossa. The maxillary artery gives off the deep auricular artery and the anterior tympanic artery within the substance of the parotid. All these branches from the external carotid also give off numerous small branches within the parotid to supply the gland itself.

Parotid Lymph Nodes

Lymph nodes are found within the subcutaneous tissues overlying the parotid to form the preauricular nodes and also within the substance of the gland. There are typically 10 nodes within the substance of the gland, the majority being within the superficial lobe and therefore superficial to the plane of the facial nerve. Only one or two nodes lie within the deep lobe (Marks 1984; McKean, et al. 1985; Garatea-Crelgo, et al. 1993). All the parotid nodes drain into the upper deep cervical chain.

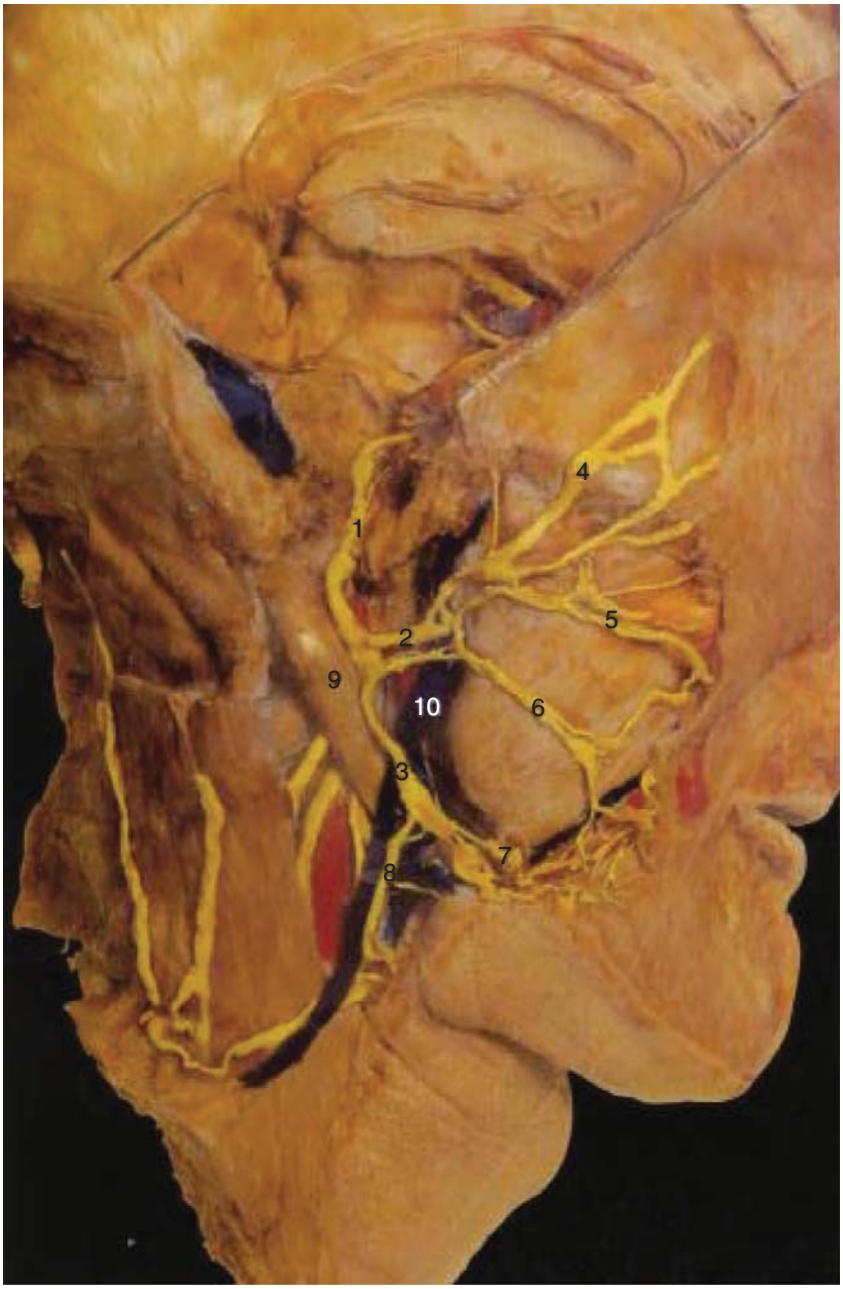

Figure 1.7. The facial nerve and its relationship to the retromandibular vein within the parotid gland. Source: *Surgical Management of the Infratemporal Fossa*. (J. Langdon, B. Berkovitz & B. Moxham). ISBN 9781899066797. Reproduced with permission of Taylor & Francis Books UK.

Parotid Duct

The parotid duct emerges from the anterior border of the parotid gland and passes horizontally across the masseter muscle. The surface markings of the duct are obtained by drawing a line from the lowest point of the alar cartilage to the angle of the mouth (Figure 1.8). This line is bisected and its midpoint is joined with a straight line to the most anterior point of the tragus. This line is divided into three equal parts and the middle section corresponds to the position of the parotid duct. The duct lies approximately 1 cm below the transverse facial vessels. The accessory lobe of the parotid gland, when present, drains into its upper border via one or two tributaries. Anastomosing branches between the buccal and zygomatic branches of the facial nerve cross the duct. At the anterior border of the masseter, the duct bends sharply to perforate the buccal pad of fat

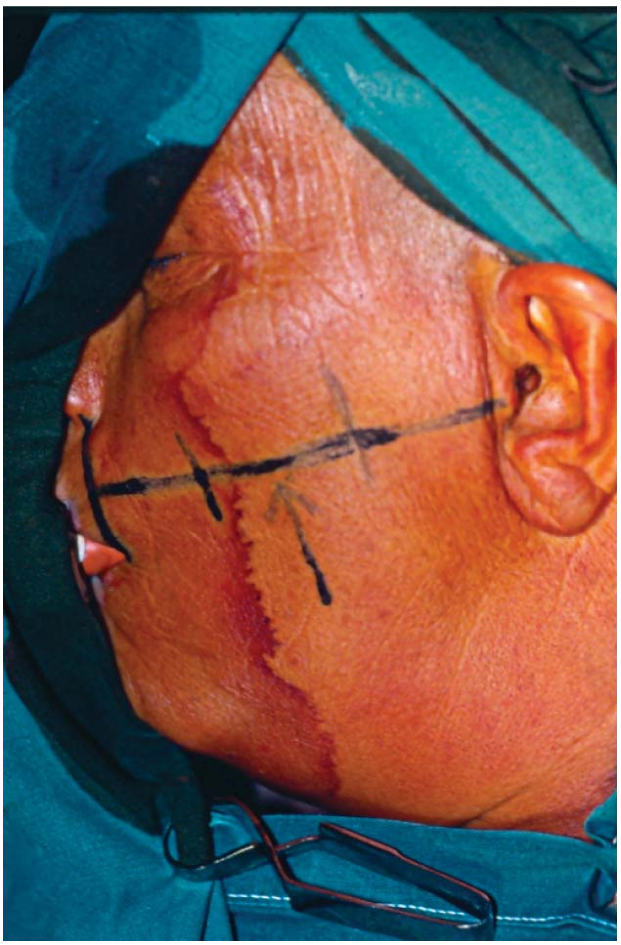

Figure 1.8. The surface markings for the parotid duct.

and the buccinator muscle at the level of the upper molar teeth. The duct then bends again to pass forward for a short distance before entering the oral cavity at the parotid papilla.

Nerve Supply to the Parotid

The parasympathetic secretomotor nerve supply comes from the inferior salivatory nucleus in the brain stem (Figure 1.9). From there, the fibers run in the tympanic branch of the glossopharyngeal nerve contributing to the tympanic plexus in the middle ear. The lesser petrosal nerve arises from the tympanic plexus leaving the middle ear and running in a groove on the petrous temporal bone in the middle cranial fossa. From here it exits through the foramen ovale to the otic ganglion, which lies on the medial aspect of the mandibular branch of the trigeminal nerve. Postsynaptic postganglionic fibers leave the ganglion to join the auriculotemporal nerve, which distributes the parasympathetic secretomotor fibers throughout the parotid gland. Some authorities suggest that there are also some parasympathetic innervations to the parotid from the chorda tympani branch of the facial nerve.

The sympathetic nerve supply to the parotid arises from the superior cervical sympathetic ganglion. The sympathetic fibers reach the gland via the plexus around the middle meningeal artery. They then pass through the otic ganglion without synapsing and innervate the gland through the auriculotemporal nerve. There is also sympathetic innervation to the gland arising from the plexuses that accompany the blood vessels supplying the gland.

Sensory fibers arising from the connective tissue within the parotid gland merge into the auriculotemporal nerve and pass proximally through the otic ganglion without synapsing. From there the fibers join the mandibular division of the trigeminal nerve. The sensory innervation of the parotid capsule is via the great auricular nerve.

The Submandibular Gland

EMBRYOLOGY

The submandibular gland begins to form at the 13 mm stage as an epithelial outgrowth into the mesenchyme forming the floor of the mouth in the linguogingival groove. This proliferates rapidly giving off numerous branching processes, which eventually develop lumina. Initially the developing gland opens into the floor of the mouth posteriorly, lateral to the tongue. The walls of the groove into which it drains come together to form the submandibular duct. This process commences posteriorly and moves forwards so that ultimately the orifice of the duct comes to lie anteriorly below the tip of the tongue close to the midline.

ANATOMY

The submandibular gland consists of a larger superficial lobe lying within the digastric triangle in the neck and a smaller deep lobe lying within the floor of the mouth posteriorly (Figure 1.10). The two lobes are continuous with each other around the posterior border of the mylohyoid muscle. As in the parotid gland, the two “lobes” are

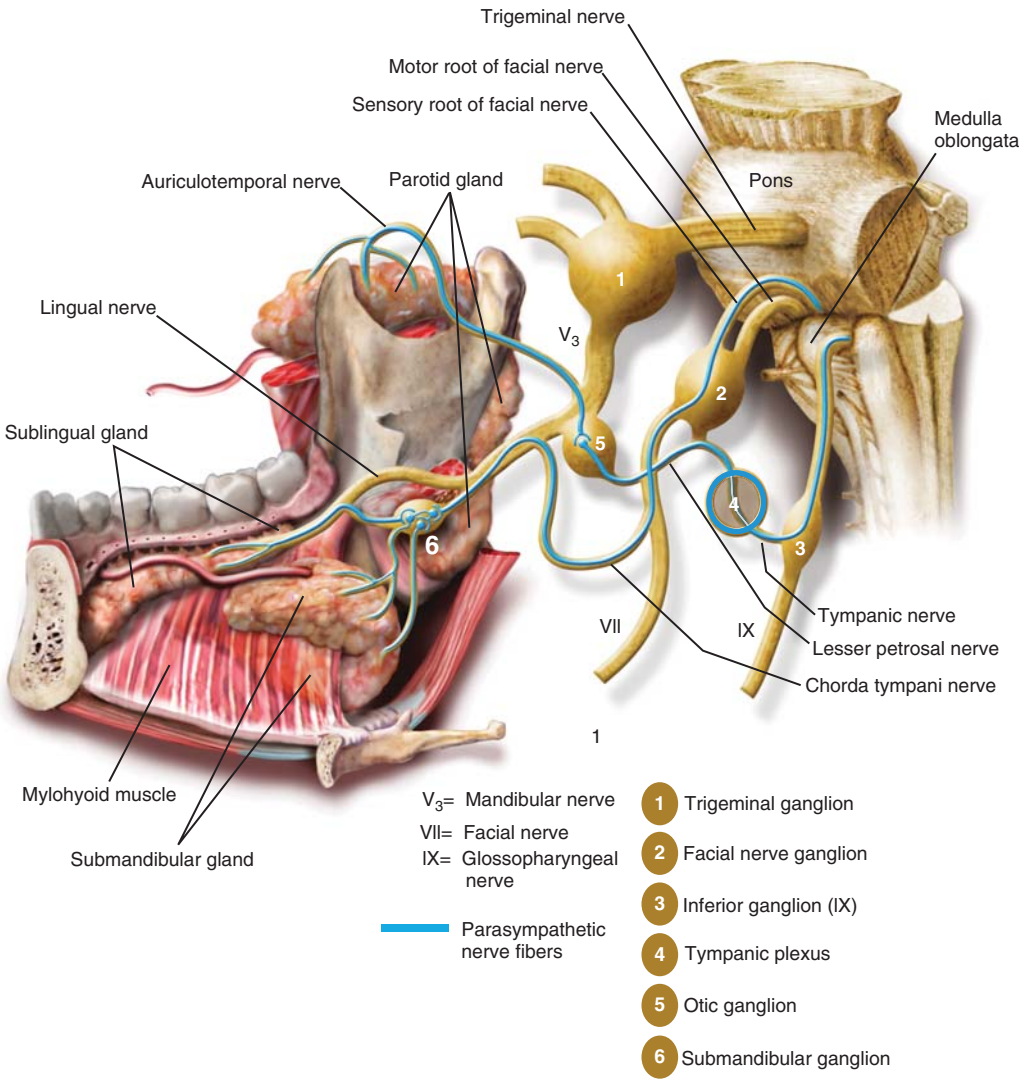

Figure 1.9. The parasympathetic innervations of the salivary glands. The parasympathetic fibers are shown as blue lines.

not true lobes embryologically, as the gland arises as a single epithelial outgrowth (Langdon 1998a). However, surgically it consists of the two lobes as described previously. It is a mixed seromucinous gland.

The Superficial Lobe

The superficial lobe lies within the digastric triangle. Its anterior pole reaches the anterior belly of the digastric muscle and the posterior pole reaches the stylomandibular ligament. This structure is all that separates the superficial lobe of the submandibular gland from the parotid gland. It is important to realize just how close the lower pole of the parotid is to the posterior pole of the submandibular gland as confusion can arise if a mass in the region is incorrectly ascribed to the wrong anatomical structure (Figure 1.2). Superiorly, the superficial lobe lies medial to the body of the mandible. Inferiorly, it often overlaps the intermediate tendon of the digastric muscles and the insertion of the stylohyoid muscle. The lobe is partially enclosed between the two layers of the deep cervical fascia that arise from the greater cornu of the hyoid bone and is in intimate proximity of the facial vein and artery (Figure 1.11). The superficial layer of the fascia is attached to

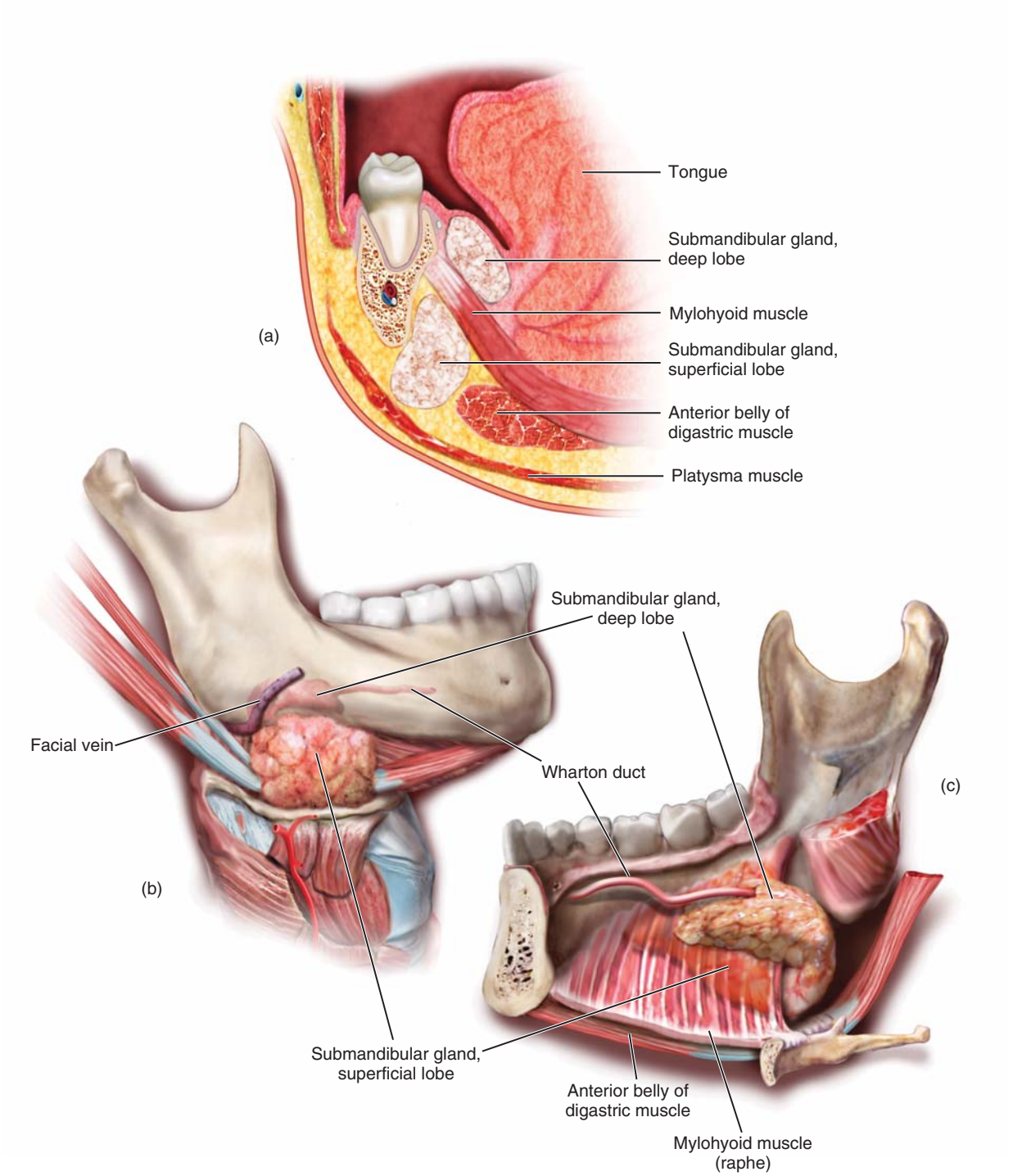

Figure 1.10. The relationship of the superficial and deep lobes of the submandibular gland. (a) cross-sectional anatomy. (b) The superficial lobe from outside. (c) The relationship of the deep and superficial lobes to the mylohyoid muscle.

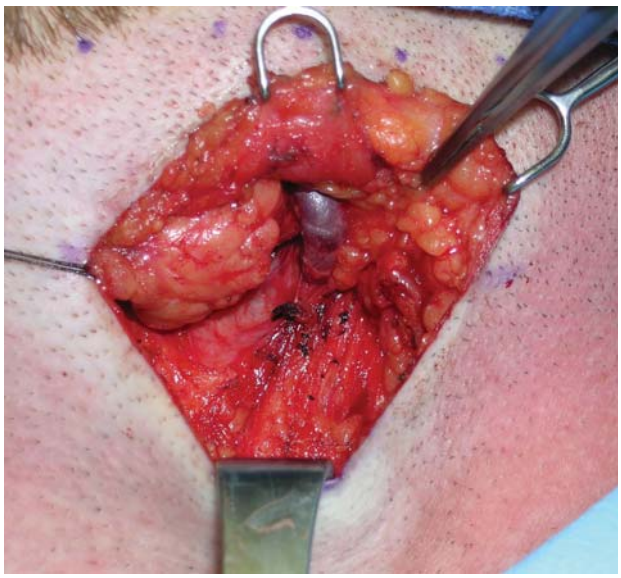

Figure 1.11. Superficial dissection of the left submandibular gland. The investing layer of the deep cervical fascia is elevated off of the submandibular gland and the facial vein is identified.

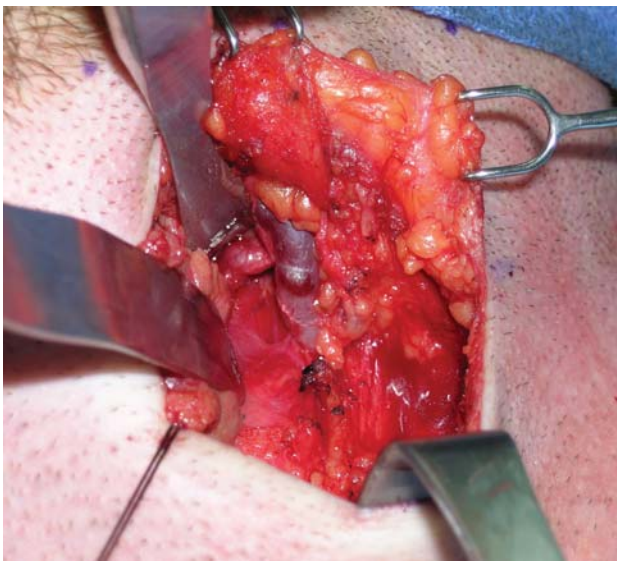

Figure 1.12. Deep dissection of the left submandibular gland. With the submandibular gland retracted, the facial artery is identified in proximity to the facial vein.

the lower border of the mandible and covers the inferior surface of the superficial lobe. The deep layer of fascia is attached to the mylohyoid line on the inner aspect of the mandible and therefore covers the medial surface of the lobe.

The inferior surface, which is covered by skin, subcutaneous fat, platysma, and the deep fascia, is crossed by the facial vein and the cervical branch of the facial nerve, which loops down from the angle of the mandible and subsequently innervates the lower lip. The submandibular lymph nodes lie between the salivary gland and the mandible. Sometimes one or more lymph nodes may be embedded within the salivary gland.

The lateral surface of the superficial lobe is related to the submandibular fossa, a concavity on the medial surface of the mandible, and the attachment of the medial pterygoid muscle. The facial artery grooves its posterior part lying at first deep to the lobe and then emerging between its lateral surface and the mandibular attachment of the medial pterygoid muscle from which it reaches the lower border of the mandible.

The medial surface is related anteriorly to the mylohyoid from which it is separated by the mylohyoid nerve and submental vessels. Posteriorly, it is related to styloglossus muscle, the stylohyoid ligament, and the glossopharyngeal nerve separating it from the pharynx. Between these, the medial aspect of the lobe is related to hyoglossus muscle from which it is separated by styloglossus muscle, the lingual nerve, submandibular ganglion, hypoglossal nerve, and deep lingual vein. More inferiorly, the medial surface is related to the stylohyoid muscle and the posterior belly of digastric.

The Deep Lobe

The deep lobe of the gland arises from the superficial lobe at the posterior free edge of the mylohyoid muscle and extends forward to the back of the sublingual gland (Figure 1.12). It lies between mylohyoid inferolaterally, hyoglossus, and styloglossus muscles medially, the lingual nerve superiorly, and the hypoglossal nerve and deep lingual vein inferiorly.

The Submandibular Duct

The submandibular duct is about 5 cm long in the adult. The wall of the submandibular duct is thinner than that of the parotid duct. It arises from numerous tributaries in the superficial lobe and emerges from the medial surface of this lobe just behind the posterior border of the mylohyoid. It crosses the deep lobe, passing upwards and slightly backwards for 5 mm before running forwards between the mylohyoid and hyoglossus

muscles. As it passes forward, it runs between the sublingual gland and genioglossus to open into the floor of the mouth on the summit of the sublingual papilla at the side of the lingual frenum just below the tip of the tongue. It lies between the lingual and hypoglossal nerves on the hyoglossus. At the anterior border of hyoglossus muscle it is crossed by the lingual nerve. As the duct traverses the deep lobe of the gland it receives tributaries draining that lobe.

Blood Supply and Lymphatic Drainage

The arterial blood supply arises from multiple branches of the facial and lingual arteries. Venous blood drains predominantly into the deep lingual vein. The lymphatics drain into the deep cervical group of nodes, mostly into the jugulo-omohyoid node, via the submandibular nodes.

Nerve Supply to the Submandibular Gland

Parasympathetic Innervation

The secretomotor supply to the submandibular gland arises from the submandibular (sublingual) ganglion. This is a small ganglion lying on the upper part of the hyoglossus muscle. There are additional ganglion cells at the hilum of the gland. The submandibular ganglion is suspended from the lingual nerve by anterior and posterior filaments (Figure 1.13).

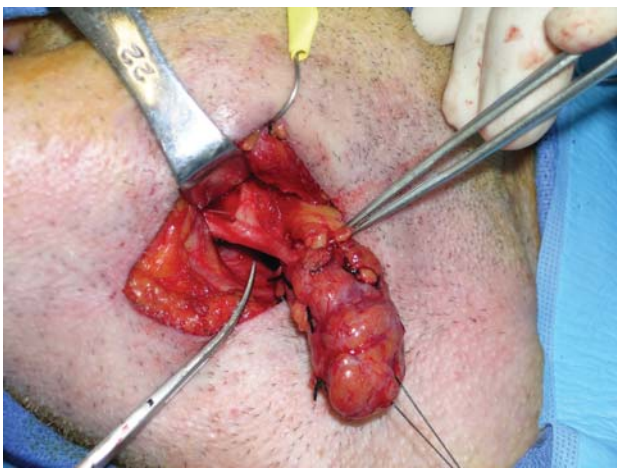

Figure 1.13. Clinical photograph showing the relationship of the lingual nerve to the submandibular gland.

The parasympathetic secretomotor fibers originate in the superior salivatory nucleus and the preganglionic fibers then travel via the facial nerve, chorda tympani, and lingual nerve to the ganglion via the posterior filaments connecting the ganglion to the lingual nerve. They synapse within the ganglion and the postganglionic fibers innervate the submandibular and sublingual glands (Figure 1.9). Some fibers are thought to reach the lower pole of the parotid gland.

Sympathetic Innervation

The sympathetic root is derived from the plexus on the facial artery. The postganglionic fibers arise from the superior cervical ganglion and pass through the submandibular ganglion without synapsing. They are vasomotor to the vessels supplying the submandibular and sublingual glands. Five or six branches from the ganglion supply the submandibular gland and its duct. Others pass back into the lingual nerve via the anterior filament to innervate the sublingual and other minor salivary glands in the region.

Sensory Innervation

Sensory fibers arising from the submandibular and sublingual glands pass through the ganglion without synapsing and join the lingual nerve, itself a branch of the trigeminal nerve.

The Sublingual Gland

EMBRYOLOGY

The sublingual gland arises in 20 mm embryos as a number of small epithelial thickenings in the linguogingival groove and on the outer side of the groove. Each thickening forms its own canal and so many of the sublingual ducts open directly onto the summit of the sublingual fold. Those that arise within the linguogingival grove end up draining into the submandibular duct.

ANATOMY

The sublingual gland is the smallest of the major salivary glands. It is almond shaped and weighs approximately 4 g. It is predominantly a mucous gland. The gland lies on the mylohyoid and is

covered by the mucosa of the floor of the mouth, which is raised as it overlies the gland to form the sublingual fold. Posteriorly, the sublingual gland is in contact with the deep lobe of the submandibular gland. The sublingual fossa of the mandible is located laterally and the genioglossus muscle is located medially. The lingual nerve and the submandibular duct lie medial to the sublingual gland between it and the genioglossus.

Sublingual Ducts

The gland has a variable number of excretory ducts ranging from 8 to 20. The majority drain into the floor of the mouth at the crest of the sublingual fold. A few drain into the submandibular duct. Sometimes, a collection of draining ducts coalesce anteriorly to form a major duct (Bartholin's duct) which opens with the orifice of the submandibular duct at the sublingual papilla.

Blood Supply, Innervation, and Lymphatic Drainage

The arterial supply is from the sublingual branch of the lingual artery and also the submental branch of the facial artery. Innervation is via the sublingual ganglion as described above. The lymphatics drain to the submental nodes.

Minor Salivary Glands

Minor salivary glands are distributed widely in the oral cavity and oropharynx. They are grouped as labial, buccal, palatoglossal, palatal, and lingual glands. The labial and buccal glands contain both mucous and serous acini, whereas the palatoglossal glands are mucous secreting. The palatal glands that are also mucous secreting occur in both the hard and soft palates. The anterior and posterior lingual glands are mainly mucous. The anterior glands are embedded within the muscle ventrally and they drain via four or five ducts near the lingual frenum. The posterior lingual glands are located at the root of the tongue. The deep posterior lingual glands are predominantly serous. Additional serous glands (of von Ebner) occur around the circumvallate papillae on the dorsum of the tongue. Their watery secretion is thought to be important in spreading taste stimuli over the taste buds.

Histology of the Salivary Glands

The salivary glands are composed of large numbers of secretory acini, which may be tubular or globular in shape. Each acinus drains into a duct. These microscopic ducts coalesce to form lobular ducts. Each lobule has its own duct and these then merge to form the main ducts. The individual lobes and lobules are separated by dense connective tissue which is continuous with the gland capsule. The ducts, blood vessels, lymphatics, and nerves run through and are supported by this connective tissue.

The acini are the primary secretory organs but the saliva is modified as it passes through the intercalated, striated, and excretory ducts before being discharged into the mouth and oropharynx (Figure 1.14). The lobules also contain significant amounts of adipose tissue particularly in the parotid gland. The proportion of adipose tissue relative to excretory acinar cells increases with age.

In the human parotid, the excretory acini are almost entirely serous. In the submandibular gland, again, the secretory units are mostly serous but there are additional mucous tubules and acini. In some areas the mucinous acini have crescentic "caps" of serous cells called serous demilunes. In the sublingual gland the acini are almost entirely mucinous, although there are occasional serous acini or demilunes.

The serous cells contain numerous proteinaceous secretory (zymogen) granules. These granules contain high levels of amylase. In addition, the secretory cells produce kallikrein, lactoferrin, and lysozyme. In mucous cells, the cytoplasm is packed with large pale secretory droplets.

Initially the secretory acini drain into intercalated ducts. These function mainly to conduct the saliva but they may also modify the electrolyte content and secrete immunoglobulin A. The intercalated ducts drain into striated ducts, which coalesce into intralobular and extralobular collecting ducts. The intercalated duct cells are very active metabolically and they transport potassium and bicarbonate into saliva. They reabsorb sodium and chloride ions so that the resulting saliva is hypotonic. They also secrete immunoglobulin A, lysozyme, and kallikrein. The immunoglobulin is produced by plasma cells adjacent to the striated duct cells and it is then transported through the epithelial lining into the saliva. The main collecting

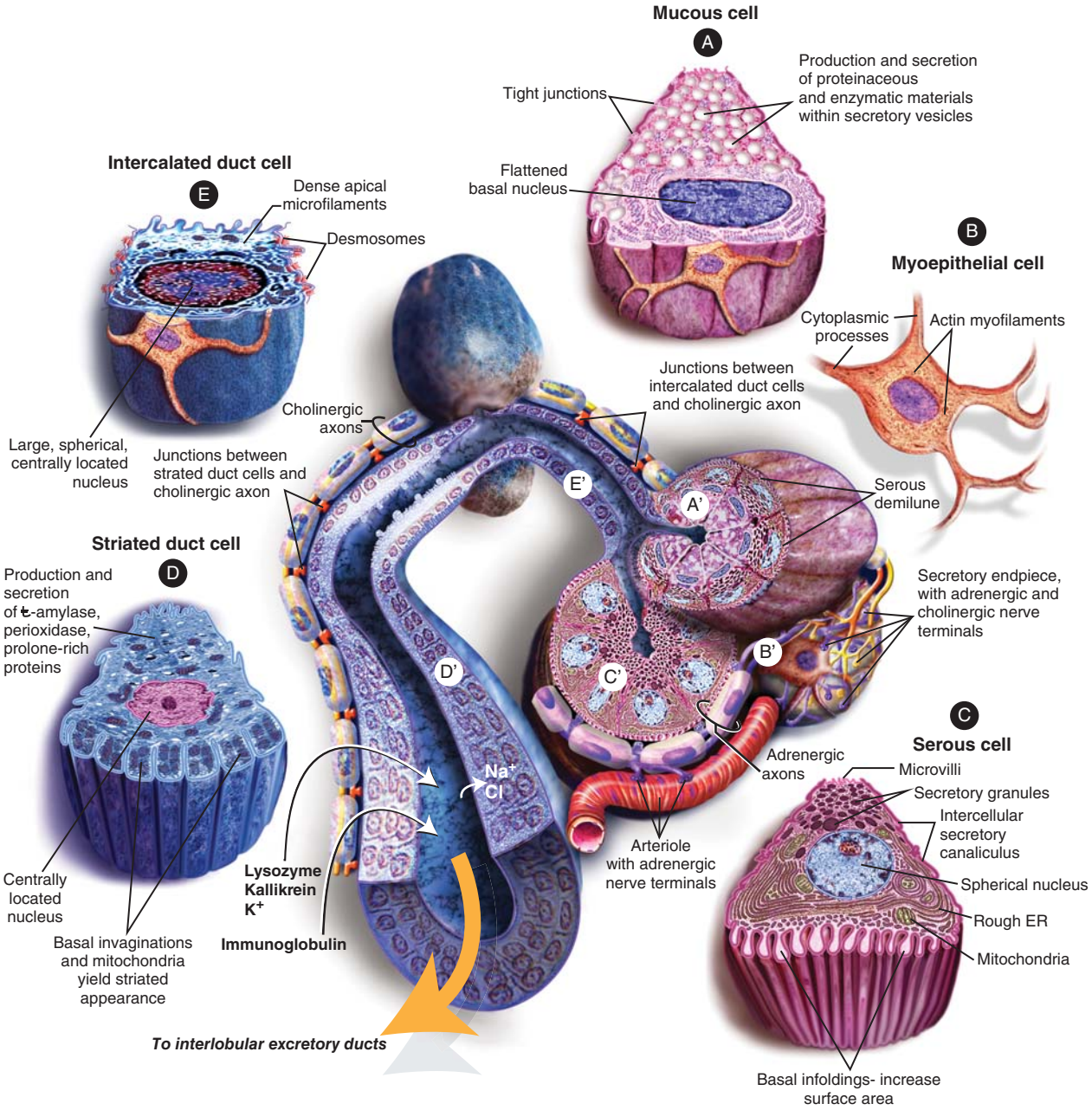

Figure 1.14. Diagram showing the histology of the major components of the salivary glands.

ducts are simple conduits for saliva and do not modify the composition of the saliva.

Myoepithelial cells are contractile cells closely related to the secretory acini and also much of the duct system. The myoepithelial cells lie between the basal lamina and the epithelial cells. Numerous cytoplasmic processes arise from them and surround the serous acini as basket cells. Those associated with the duct cells are more fusiform and are aligned along the length of the ducts. The cytoplasm of the myoepithelial cells contains actin myofilaments which contract as a result of both parasympathetic and sympathetic activity. Thus, the myoepithelial cells "squeeze" the saliva out

of the secretory acini and ducts and add to the salivary secretory pressure.

Control of Salivation

There is a continuous low background saliva production, which is stimulated by drying of the oral and pharyngeal mucosa. A rapid increase in the resting levels occurs as a reflex in response to masticatory stimuli including the mechanoreceptors and taste fibers. Other sensory modalities such as smell are also involved. The afferent input is via the salivatory centers, which are themselves influenced by the higher centers. The higher centers may be facilitory or inhibitory, depending on the circumstances. The efferent secretory drive to the salivary glands passes via the parasympathetic and sympathetic pathways. There are no peripheral inhibitory mechanisms.

Cholinergic nerves (parasympathetic) often accompany ducts and branch freely around the secretory endpieces (acini). Adrenergic nerves (sympathetic) usually enter the glands along the arteries and arterioles and ramify with them. Within the glands, the nerve fibers intermingle such that cholinergic and adrenergic axons frequently lie in adjacent invaginations of a single Schwann cell. Secretion and vasoconstriction are mediated by separate sympathetic axons whereas a single parasympathetic axon may, through serial terminals, result in vasodilatation, secretion, and constriction of myoepithelial cells.

Secretory endpieces are the most densely innervated structures in the salivary glands. Individual acinar cells may have both cholinergic and adrenergic nerve endings. The secretion of water and electrolytes, which accounts for the volume of saliva produced, results from a complex set of stimuli which are largely parasympathetic. The active secretion of proteins into the saliva depends upon the relative levels of both sympathetic and parasympathetic stimulation.

Although the ducts are less densely innervated than secretory acini, they do influence the composition of the saliva. Adrenal aldosterone promotes resorption of sodium and secretion of potassium into the saliva by striated ductal cells. Myoepithelial cell contraction is stimulated predominantly by adrenergic fibers, although there may be an additional role for cholinergic axons.

Summary

- Although embryologically the parotid consists of a single lobe, anatomically the facial nerve lies in a distinct plane between the anatomical superficial and deep lobes.
- There are fixed anatomical landmarks indicating the origin of the extracranial facial nerve as it leaves the stylomastoid foramen.
- The lower pole of the parotid gland is separated from the posterior pole of the submandibular gland by only thin fascia. This can lead to diagnostic confusion in determining the origin of a swelling in this area.
- The relationship of the submandibular salivary duct to the lingual nerve is critical to the safe removal of stones within the duct
- Great care must be taken to identify the lingual nerve when excising the submandibular gland. The lingual nerve is attached to the gland by the parasympathetic fibers synapsing in the submandibular (sublingual) ganglion.
- The sublingual gland may drain into the submandibular duct or it may drain directly into the floor of the mouth via multiple secretory ducts.

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Chapter 2

Diagnostic Imaging of Salivary Gland Pathology

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Outline

Salivary Gland Pathology: Diagnosis and Management, Second Edition. Edited by Eric R. Carlson and Robert A. Ord.

Introduction

Anatomic and functional diagnostic imaging plays a central role in modern medicine. Virtually all specialties of medicine to varying degrees depend on diagnostic imaging for diagnosis, therapy, and follow-up of treatment. Because of the complexity of the anatomy, treatment of diseases of the head and neck, including those of the salivary glands, are particularly dependent on quality medical imaging and interpretation. Medical diagnostic imaging is divided primarily into two major categories, anatomic and functional. The *anatomic* imaging modalities include computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography (US). Although occasionally obtained, plain film radiography for the head and neck, including salivary gland disease, is mostly of historical interest. In a similar manner, the use of sialography has been significantly reduced, although both plain films and sialography are of some use in imaging sialoliths. *Functional* diagnostic imaging techniques include planar scintigraphy, single photon emission computed tomography (SPECT), positron emission tomography (PET), and magnetic resonance spectroscopy (MRS), all of which are promising technologies. Recently, the use of a combined anatomic and functional modality in the form of PET/CT has proved invaluable in head and neck imaging. Previously widely employed procedures including gallium radionuclide imaging are less important today than in the past.

Imaging Modalities

COMPUTED TOMOGRAPHY (CT)

CT has become indispensable in the diagnosis, treatment and follow-up of diseases of the head and neck. The latest generation of multiple-row detector CT (MDCT) provides excellent soft-tissue and osseous delineation. The rapid speed with which images can be obtained along with the high spatial resolution and tissue contrast makes CT the imaging modality of choice in head and neck imaging. True volumetric data sets obtained from multidetector row scanners allow for excellent coronal, sagittal or oblique reformation of images as well as a variety of 3-D renderings. This allows the radiologist and surgeon to characterize a lesion, assess involvement of adjacent structures or local spread from the orthogonal projections or 3-D rendering. The ability to manipulate images is critical when assessing pathology in complex anatomy, such as evaluation of parotid gland masses to determine deep lobe involvement, facial nerve involvement, or extension into the skull base. Images in the coronal plane are important in evaluating the submandibular gland in relation to the floor of mouth. Lymphadenopathy and its relationship to the carotid sheath and its contents and other structures are also well delineated. CT is also superior to MRI in demonstrating bone detail and calcifications. CT is also the fastest method of imaging head and neck anatomy. Other advantages include widespread availability of scanners, high resolution images, and speed of image acquisition also reduces motion artifacts. Exposure to ionizing radiation and the administration of IV contrast are the only significant disadvantages to CT scanning.

CT Technique

The CT scanner contains a gantry, which holds an X-ray tube and a set of detectors. The X-ray tube is positioned opposite the detectors and is physically coupled. A "fan beam" of X-rays is produced and passes through the patient to the detectors as the tube and detector rotate around the patient. In newer generation of scanners, the multiple rows of detectors are fixed around the gantry and only the tube rotates. A table carries the patient through the gantry. The detectors send signals, dependent on the degree of X-ray attenuation, to a computer that uses this data to construct an image using complex algorithms.

For most CT studies (especially in the head and neck) intravenous contrast is administered. IV contrast is a solution consisting of organic compounds bonded with Iodine molecules. Iodine is a dense atom with an atomic weight of 127, which is good at absorbing X-rays and is biocompatible. IV contrast readily attenuates the X-ray beam at concentrations optimal for vascular and soft tissue "enhancement," but short of causing attenuation related artifacts. Streak artifacts, however, can occur if the concentration is too high, as seen occasionally at the thoracic inlet and supraclavicular region from dense opacification of the subclavian vein during rapid bolus injection of IV contrast.

CT of the neck should be performed with intravenous contrast whenever possible to optimize delineation of masses, inflammatory or

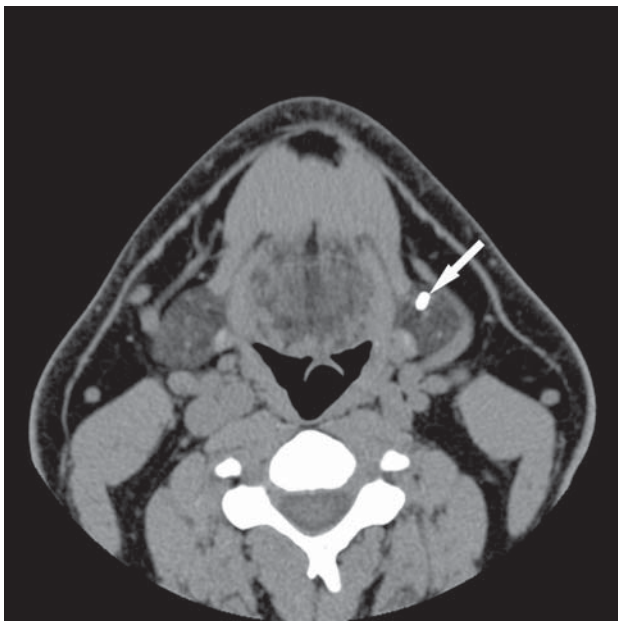


Figure 2.1. Axial CT of the neck in soft tissue window without contrast demonstrating poor definition between soft tissue structures. The blood vessels are unopacified and cannot be easily distinguished from lymph nodes. Note the sialolith (arrow) in the hilum of the left submandibular gland.

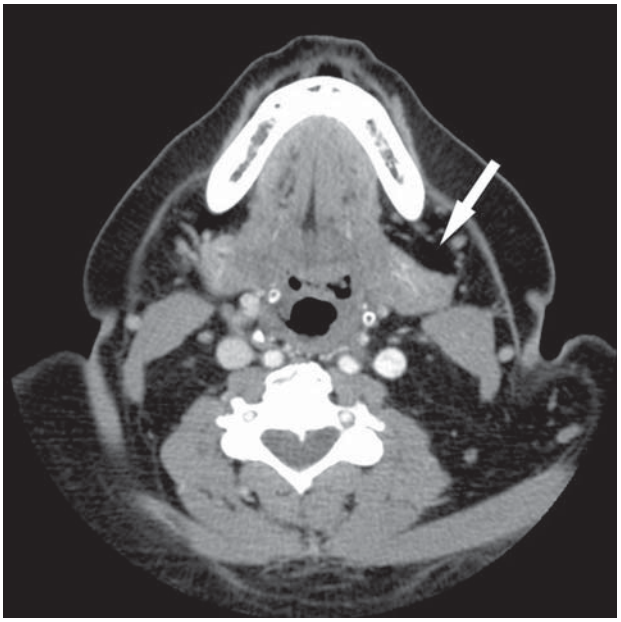


Figure 2.2. Axial CT of the neck in soft tissue window with IV contrast demonstrates improved visualization of structures with enhancement of tissues and vasculature. Note the small lipoma (arrow) anterior to the left submandibular gland, which distorts the anterior aspect of the gland with slight posterior displacement.

infectious changes in the tissues, and enhance vascular structures. Imaging is obtained from the level of the orbits through the aortic arch in the axial plane with breath hold. The images are reconstructed using a computer algorithm to optimize soft tissue delineation, and displayed in soft tissue window and level settings (Figures 2.1 and 2.2). In a similar manner images are reconstructed using a computer algorithm to optimize bone details as more sharp and defined (Figure 2.3). The lung apex is often imaged in a complete neck evaluation and displayed using lung window settings (Figure 2.4a). Dedicated CT scans of the chest are beneficial in the postoperative evaluation of patients with salivary gland malignancies as lung nodules can be observed, possibly indicative of metastatic disease (Figure 2.4b). Multiplanar reformatted images of the neck are obtained typically in the coronal and sagittal planes, (Figures 2.5 and 2.6), although they may be obtained in virtually any plane desired or in a 3-D rendering.

The Hounsfield unit (H) (named after Godfrey Hounsfield, inventor of the CT scanner) is the unit of density measurement for CT. These units are assigned based on the degree of attenuation of

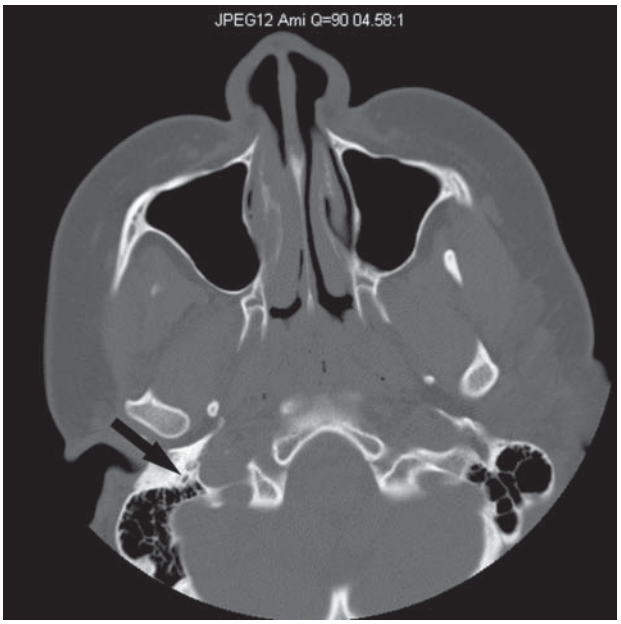
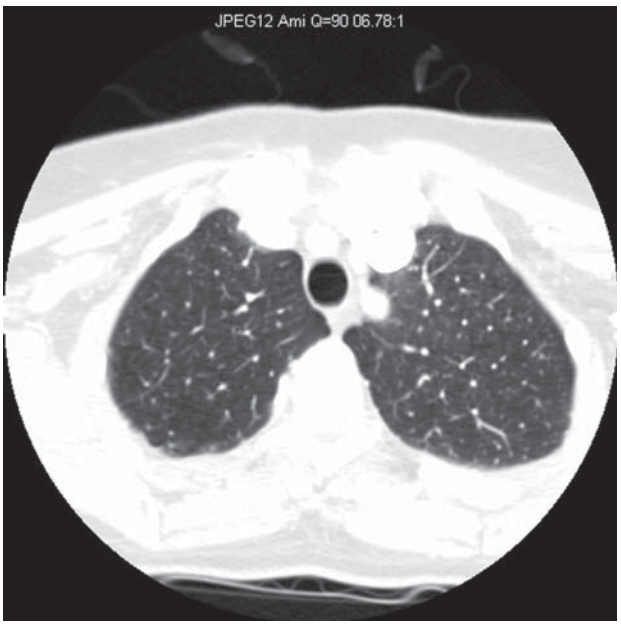
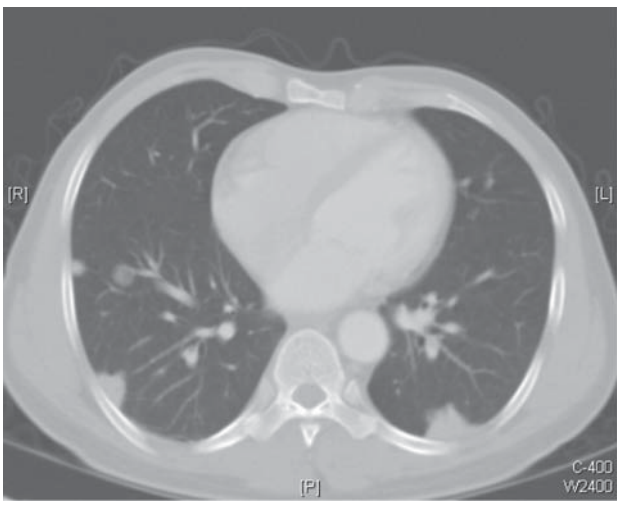


Figure 2.3. Axial CT of the skull base reconstructed in a sharp algorithm and in bone window and level display demonstrating sharp bone detail. Note the sharply defined normal right stylomastoid foramen (arrow).



(a)



(b)

Figure 2.4. Axial CT of the neck at the thoracic inlet in lung windows demonstrating lung parenchyma (a). Axial image of dedicated CT of chest demonstrating cannon ball lesions in a patient previously treated for adenoid cystic carcinoma of the palate (b). These lesions are representative of diffuse metastatic disease of the lungs, but not pathognomonic of adenoid cystic carcinoma.

the X-ray beam by tissue in a given voxel (volume element) and are assigned relative to water (0 H) (Table 2.1). The scale ranges from −1024 H for air, to +4000 H for very dense bone. The images are created based on a grayscale from black (−1024 H) to white (+4000 H) and shades of gray. Despite

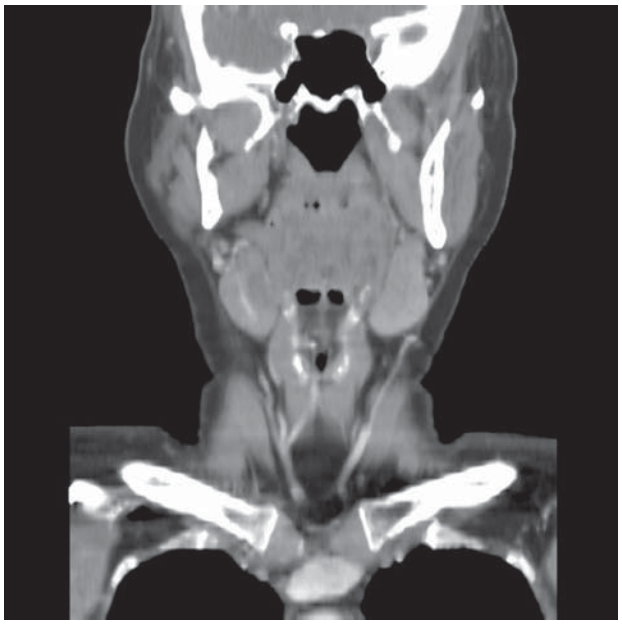


Figure 2.5. Coronal CT reformation of the neck in soft tissue window at the level of the submandibular glands. Orthogonal images with MDCT offer very good soft tissue detail in virtually any plane of interest in order to assess anatomic and pathologic relationships.

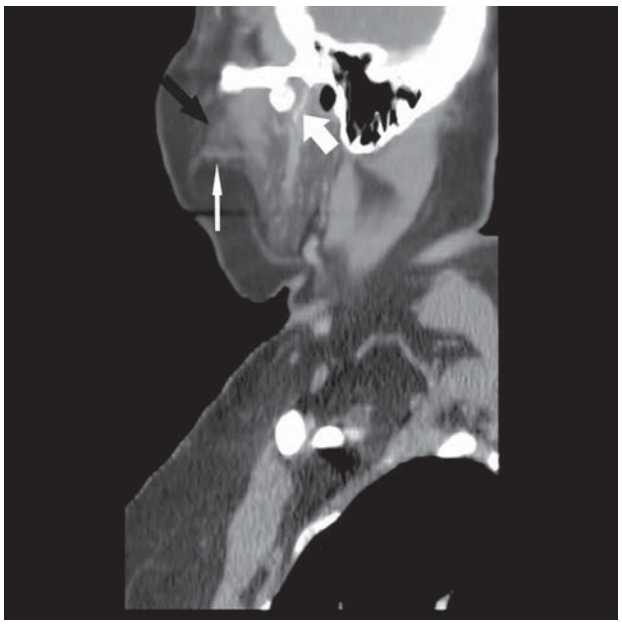


Figure 2.6. Sagittal CT reformation of the neck in soft tissue window at the level of the parotid gland. Note the accessory parotid gland (black arrow) sitting atop the parotid (Stensen) duct (thin white arrow). Also note the retromandibular vein (large white arrow) and external auditory canal.

Table 2.1. CT density in Hounsfield Units (H).

Tissue or Structure	Hounsfield Unit (H)
Water or CSF	0
Fat	–30––100
Soft tissue, muscle[a]	50–60
Unclotted blood[b]	35–50
Clotted blood[b]	50–75
Parotid gland[c]	–10–+30
Submandibular gland[c]	30–60
Sublingual gland[d]	60–90
Bone	1000
Lung	–850
Air	–1000
Calcification	150–200
Grey matter	35–40
White matter	25–35

Notes: Depends on degree of fat deposition.
[a]Depends on the hemoglobin concentration and hematocrit.
[b]Depends on age and fat deposition.
[c]Very limited evaluation secondary to partial volume effect.
[d]CSF = cerebrospinal fluid.

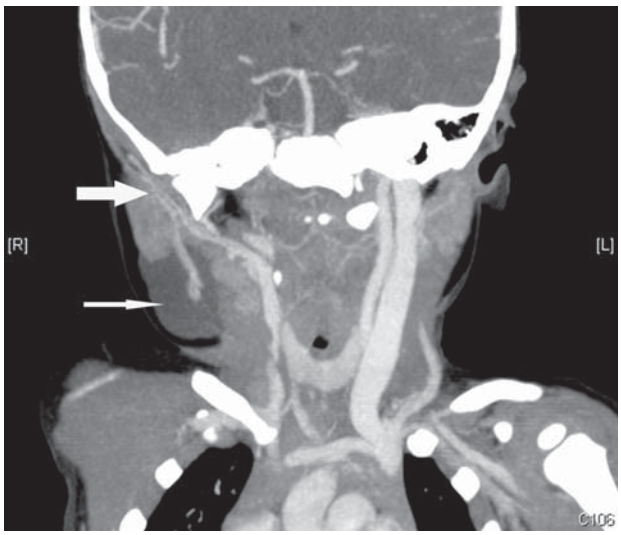


Figure 2.7. CT angiogram (CTA) of the neck at the level of the parotid gland demonstrating the retromandibular vein and adjacent external carotid artery (large white arrow). Note the right cervical lymphangioma (thin white arrow) associated with the tail of the right parotid gland.

the wide range of units, majority of tissues in the human body are between −100 and +100 H. Soft tissues and parenchymal organs are in a range between 20–80 H, whereas fat is approximately −100 H. Simple fluid is 0 H, but proteinaceous fluid can be upward of 25 H. Unclotted and clotted blood varies depending on the hemoglobin concentration and hematocrit but average measurements are 50 and 80 H, respectively. CT images are displayed using a combination of "window widths" (WW, range of CT numbers from black to white), and "window levels" (WL, position of the window on the scale), which are based on the attenuation characteristics of tissues. Typically, head and neck images are interpreted using "soft-tissue windows" (WW 500H, WL 30H), "bone windows" (WW 2000, WL 500), or "lung windows" (WW 1500, WL-500). "soft-tissue windows" demonstrate the slight density differences of soft tissues, whereas "bone windows" demonstrated cortical and medullary features of bones with sharp detail. "Lung windows" demonstrate the sharp interface of air and the fine soft tissue components of lung parenchyma.

Although the density of the salivary glands is variable, the parotid glands tend to be slightly lower in density relative to muscle, secondary to a higher fat content and become progressively more fat replaced over time. The CT density of parotid glands varies from −10 to +30 Hounsfield units (H). The submandibular glands are denser than parotid glands and are equivalent in density to muscle. The submandibular glands vary in density from +30 to +60 H.

CT angiography (CTA) is a powerful method which allows visualization of arterial vasculature, demonstrating the vascular anatomy of arteries and veins. CTA can be critical in preoperative evaluation to determine the degree of vascularity of lesions and plan an appropriate surgical approach to minimize blood loss or perform preoperative embolization. CTA is obtained with fast image acquisition over a defined region of interest while administering a rapid IV contrast bolus timed to arrive in the region of interest during image acquisition. CTA images may be rendered in 3-D data sets and rotated in any plane (Figure 2.7). CTA is not only useful for preoperative planning, but it can also be quite useful in diagnosis of salivary gland vascular pathology, such as aneurysms or arteriovenous fistulas (AVFs) (Wong 2004).

CT scanning, as with all imaging modalities, is prone to artifacts. Artifacts can be caused by motion, very dense or metallic implants (dental amalgam), and volume averaging. The motion

artifact is common and may result from breathing, swallowing, coughing, or sneezing during the image acquisition or from an unaware or uncooperative patient. Metallic implants cause complete attenuation of X-rays in the beam and result in focal loss of data and bright and dark steaks in the image. Because the image is created from a three-dimensional section of tissue averaged to form a two-dimensional image, the partial volume or volume averaging artifact results from partial inclusion of structures in adjacent images. Finally, the beam hardening artifact is produced by attenuation of low energy X-rays, by dense objects, from the energy spectrum of the X-ray beam, resulting in a residual average high energy beam (or hard X-rays), which results in loss of data and dark lines on the image. This phenomenon is often seen in the posterior fossa of head CT scans caused by the very dense petrous bones. A multidetector row CT scanner can help reduce metallic artifacts using advanced algorithms, and reduce motion artifacts secondary to faster scanning speeds.

Advanced Computed Tomography

Newer CT techniques including CT perfusion, and dynamic contrast enhanced multi-slice CT have been studied. Dynamic multi-slice contrast enhanced CT is obtained while scanning over a region of interest and simultaneously administering IV contrast. The characteristics of tissues can then be studied as the contrast bolus arrives at the lesion and "washes in" to the tumor, reaches a peak presence within the mass, and then decreases over time, that is, "washes out." This technique has demonstrated differences in various histologic types of tumors, for example, with early enhancement in the Warthin tumor with a time to peak at 30 seconds and subsequent fast washout. The malignant tumors show a time to peak at 90 seconds. The pleomorphic adenomas demonstrate a continued rise in enhancement in all four phases (Yerli 2007).

CT perfusion attempts to study physiologic parameters of blood volume, blood flow, mean transit time, and capillary permeability surface product. Statistically significant differences between malignant and benign tumors have been demonstrated with the mean transit time measurement. A rapid mean transit time of less than 3.5 seconds is seen with most malignant tumors, but with benign tumors or normal tissue the mean transit time is significantly longer (Rumboldt 2005).

MAGNETIC RESONANCE IMAGING (MRI)

Magnetic resonance imaging represents imaging technology with great promise in characterizing salivary gland pathology. The higher tissue contrast of MRI, when compared to CT, enables subtle differences in soft tissues to be demonstrated. Gadolinium contrast-enhanced MRI further accentuates the soft tissue contrast. Subtle pathologic states such as perineural spread of disease are better delineated when compared with CT. This, along with excellent resolution and exquisite details, makes MRI a very powerful technique in head and neck imaging, particularly at the skull base. However, its susceptibility to motion artifacts and long imaging time as well as contraindication due to claustrophobia, pacemakers, aneurysm clips, deep brain, and vagal nerve stimulators, limit its usefulness in the general population as a *routine* initial diagnostic and follow-up imaging modality. Many of the safety considerations are well defined and detailed on the popular web site, www.mrisafety.com.

MRI Technique

Although the physics and instrumentation of MRI are beyond the scope of this text, a fundamental understanding of the variety of different imaging sequences and techniques should be understood by clinicians in order to facilitate reciprocal communication of the clinical problem, and understanding of imaging reports.

In contrast to CT, which is based on the use of ionizing radiation, MRI utilizes a high magnetic field and pulsed radiofrequency waves in order to create an image or obtain spectroscopic data. MRI is based on the proton (hydrogen ion) distribution throughout the body. The basic concept is that protons are normally oriented in a random state. However, once placed in the imaging magnet, a high magnetic field, a large proportion of protons align with the magnetic field. The protons remain aligned and precess (spin) in the magnetic field until an external force acts upon them and forces them out of alignment. This force is an applied radiofrequency pulse, applied for a specified time and specified frequency by an antenna called a

transmit coil. As the protons return to the aligned state, they give off energy in the form of their own radiofrequency pulse, determined by their local chemical state and tissue structure. The radiofrequency pulse given off is captured by an antenna, called a receive coil. The energy of the pulse and location is recorded and the process repeated multiple times and averaged, as the signal is weak. The recorded signal is used to form the image. Several different types of applied pulse sequences of radio waves result in different types of images.

The impact of MRI is in the soft tissue contrast that can be obtained, non-invasively. The relaxation times of tissues can be manipulated to bring out soft tissue detail. The routine sequences used in clinical scanning are spin-echo (SE), gradient echo (GRE), and echo-planar (EPI). Typical pulse sequences for head and neck and brain imaging include spin-echo T1, spin-echo T2, proton density (PD), FLAIR, dwi, post-contrast T1, and STIR. A variant of the spin-echo, the fast spin-echo sequence (FSE) allows for a more rapid acquisition of spin-echo images. Any one of these can be obtained in the three standard orientations of axial, coronal, and sagittal planes. Oblique planes may be obtained in special circumstances.

Spin Echo T1

On T1 weighted images a short repetition time (tr) and short echo time (te) are applied resulting in an image commonly used for anatomic depiction. Water signal is very low and is displayed as dark gray to black pixels on the gray scale. Fat is very bright, allowing tissue planes to be delineated. Fast flowing blood is devoid of signal and is therefore very black. Muscle tissue is an intermediate gray. Bone which has few free protons is also largely devoid of signal. Bone marrow, however, will vary depending on the relative percentage of red versus yellow marrow. Red marrow will have a signal similar to but slightly lower than muscle, whereas yellow marrow (fat replaced) will be bright. In the brain, CSF is dark and flowing blood is black. Grey matter is dark relative to white matter (contains fatty myelin) but both are higher than cerebrospinal fluid (CSF) but less than fat. Cysts (simple) are dark in signal unless they are complicated by hemorrhage or infection or have elevated protein concentration, which results in an increased signal and slightly brighter display (Figure 2.8, Table 2.2).

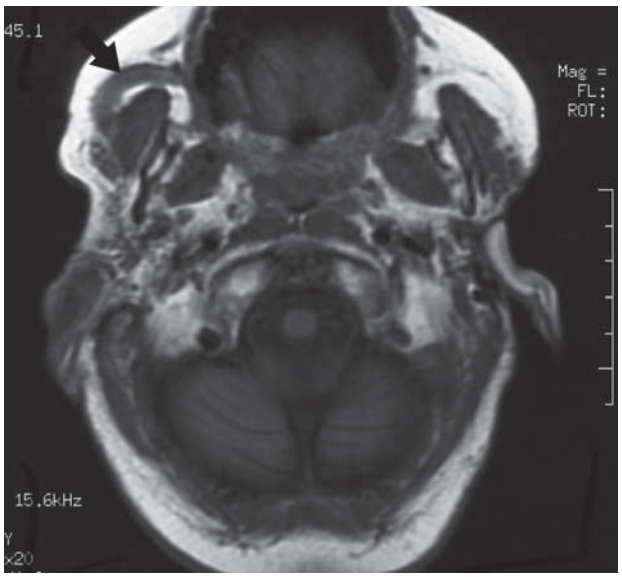


Figure 2.8. Axial MRI T1 weighted image at level of the skull base and brainstem without contrast demonstrating high signal in the subcutaneous fat, intermediate signal of the brain and low signal of the CSF and mucosa. Note dilated right parotid duct (arrow).

Spin Echo T2

The T2 images are obtained with a long tr and te. The T2 image is sensitive to the presence of water in tissues and depicts edema as a very bright signal. Therefore, CSF or fluid containing structures such as cysts are very bright. Complicated cysts can vary in T2 images. If hemorrhagic, they can have heterogenous or even uniformly dark signal caused by a susceptibility artifact. These artifacts can be caused by metals, melanin, forms of calcium, and the iron in hemoglobin. Increased tissue water from edema stands out as bright relative to the isointense soft tissue. The fast spin-echo T2 is a common sequence, which is many times faster than the conventional spin-echo T2 but does alter the image. Fat stays brighter on the fast spin echo (fse) sequence relative to the conventional (Figure 2.9, Table 2.2).

Proton Density Images (PD)

Proton density images are obtained with a long tr but short te, resulting in an image with less tissue contrast but high signal to noise ratio. These are uncommonly used in the head and neck.

Table 2.2. Tissue characteristics on T1 and T2 MRI ∗.

	T1	T2
Increased signal	– Calcium[a] – Proteinaceous fluid (high)[b] – Slow flowing blood – Melanin – Hyperacute hemorrhage (#) (oxyhemoglobin) – Subacute hemorrhage (intracellular and extracellular methemoglobin) – Gadolinium contrast – Manganese – Cholesterol	– Water (CSF) or edema – Proteinaceous fluid – Hyperacute hemorrhage (oxyhemoglobin – Subacute hemorrhage (extracellular methemoglobin) – Slow flowing blood – Fat (FSE T2 scans)
Intermediate signal	– Hyperacute hemorrhage (oxyhemoglobin) – Acute hemorrhage (deoxyhemoglobin) – Calcium[a] – Grey matter – White matter (brighter than grey matter) – Soft tissue (muscle) – Proteinaceous fluid[b]	– Grey matter (brighter than white matter) – White matter – Proteinaceous fluid[b] – Calcium[a]
Decreased signal	– Water (CSF) or edema – Fast flowing blood – Calcium[a] – Soft tissue – Acute hemorrhage (deoxyhemoglobin) – Chronic hemorrhage (hemosiderin) – Calcification – Air – Simple cyst (low protein)	– Calcium[a] – Melanin – Hemosiderin – Flowing blood – Hemorrhagic cyst – Iron deposition – Acute hemorrhage (deoxyhemoglobin) – Early subacute hemorrhage (intracellular methemoglobin) – Chronic hemorrhage (hemosiderin) – Air – Fast flow – Fat (conventional or non-FSE T2 scan)

∗MRI signal on T1 and T2 predominantly from intracranial exam at 1.5T (Tesla).
[#]MRI signal of intracranial hemorrhage is quite complex and dependent on multiple factors with degrees of variability.
[a]Signal from calcium deposition is complex. Calcium concentration of under 30% by weight have a high T1 signal and intermediate T2 signal, but over 40% have a decreasing signal on T1 and T2. The surface area of the calcium particle also has an effect, with a large surface area resulting in increased T1 signal (Henkelman 1991).
[b]Depends on the protein concentration (complex cysts, abscess).
CSF = cerebrospinal fluid.

Gradient Recalled Echo Imaging (GRE)

Gradient recalled echo imaging is the second most common type of imaging sequence after the spin echo. This sequence is very susceptible (more than spin echo T2) to magnetic field inhomogeneity and is commonly used in the brain to identify blood products, metal deposition such as iron, manganese, and non-metals such as calcium.

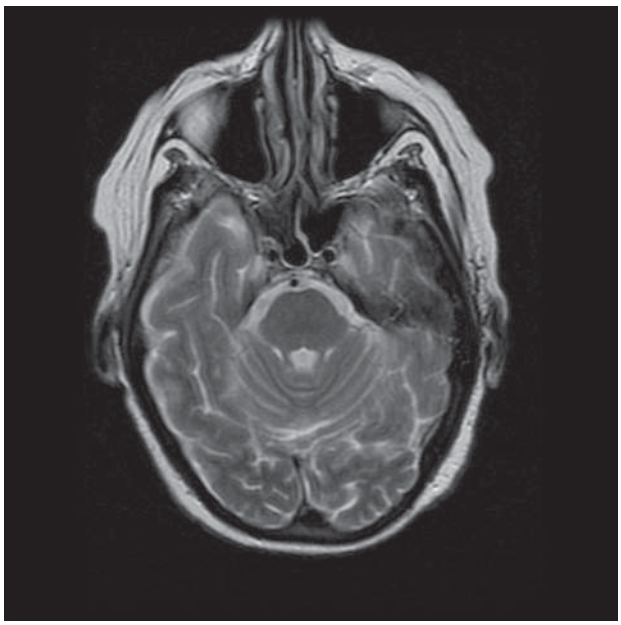


Figure 2.9. Axial MRI FSE T2 weighted image demonstrating the high signal of CSF and subcutaneous fat, intermediate signal of the brain and mucosa, and the low signal in the arteries.

This sequence is very sensitive but not specific. The "flip angle" used in obtaining GRE can be altered resulting in either T1 weighted (long flip angle) or T2 weighted (short flip angle) images (Figure 2.10).

Short Tau Inversion Recovery (STIR)

Short tau inversion recovery (STIR) is commonly acquired because of its very high sensitivity to fluid and readily detects subtle edema in tissues. When acquired in the conventional method, STIR also results in nulling the fat signal, thereby further increasing the signal of tissue fluid relative to background. This is the best sequence for edema, particularly when trying to determine bone invasion by tumors. It can also be useful in assessing skull base foramina (Figures 2.11 and 2.12).

Gadolinium (Gd) Contrast

Intravenous contrast with gadolinium, a paramagnetic element, alters (shortens) T1 and T2 relaxation times, which results in a brighter signal. Its effect is greater on T1 than on T2 weighted images. Areas of tissue that accumulate Gd will have a higher or brighter signal and "enhance."

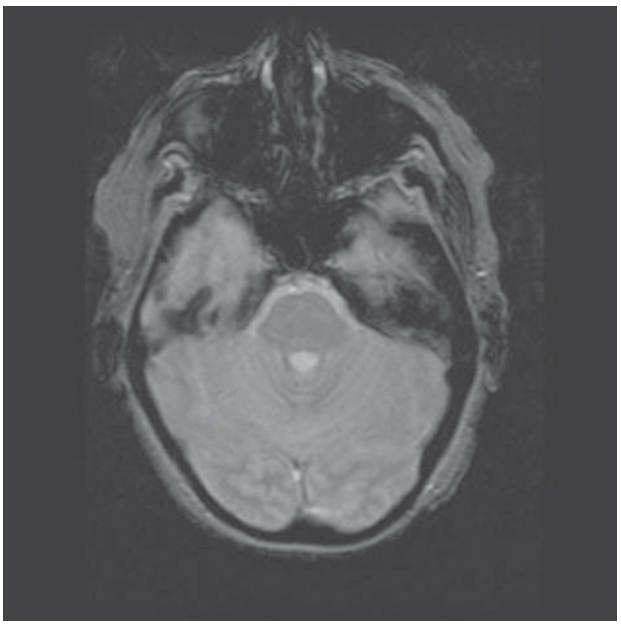


Figure 2.10. Axial MRI GRE image.

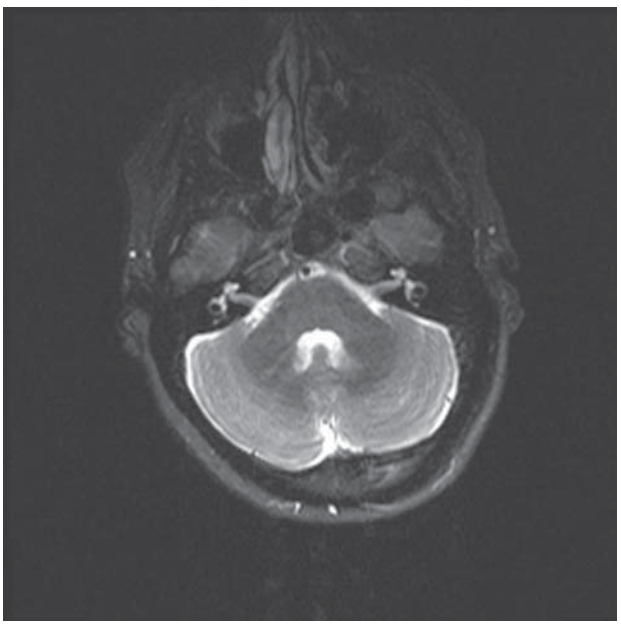


Figure 2.11. Axial MRI STIR image at the skull base demonstrating the high signal of CSF but suppression of subcutaneous fat signal.

In the head and neck, post-contrast T1 images should be performed with fat saturation to null the fat signal and therefore increase the signal of Gd accumulation (Figure 2.13).

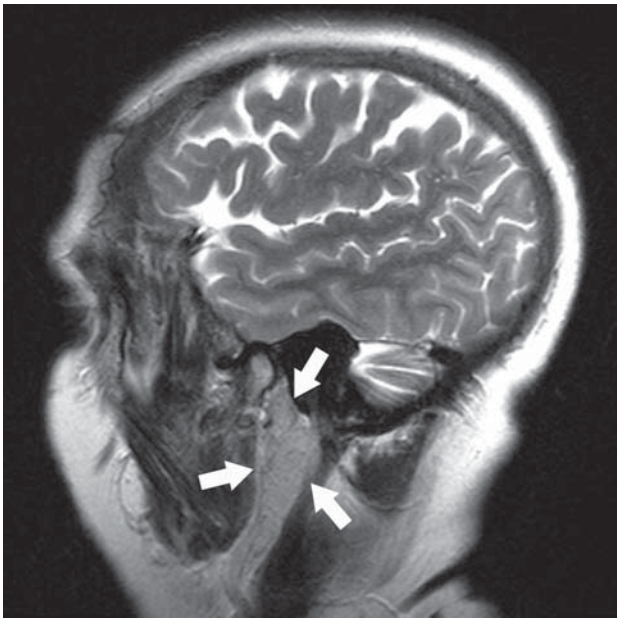


Figure 2.12. Sagittal MRI STIR image at the level of the parotid gland demonstrating the deep lobe seen through the stylomandibular tunnel (arrows). Note the parotid gland extending superiorly to the skull base.

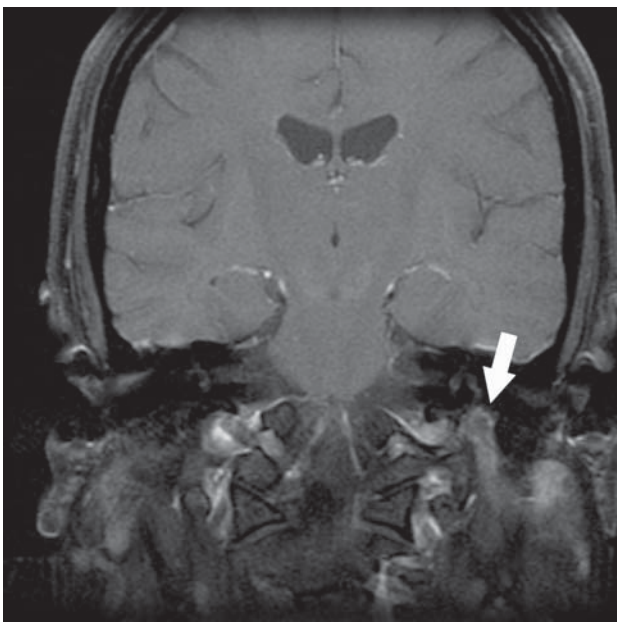


Figure 2.13. Coronal MRI T1 post-contrast fat saturated image of the skull base demonstrating a mass in the left parotid gland extending to the stylomastoid foramen (arrow). Note the mild vascular enhancement and suppression of fat high signal on T1 weighted image.

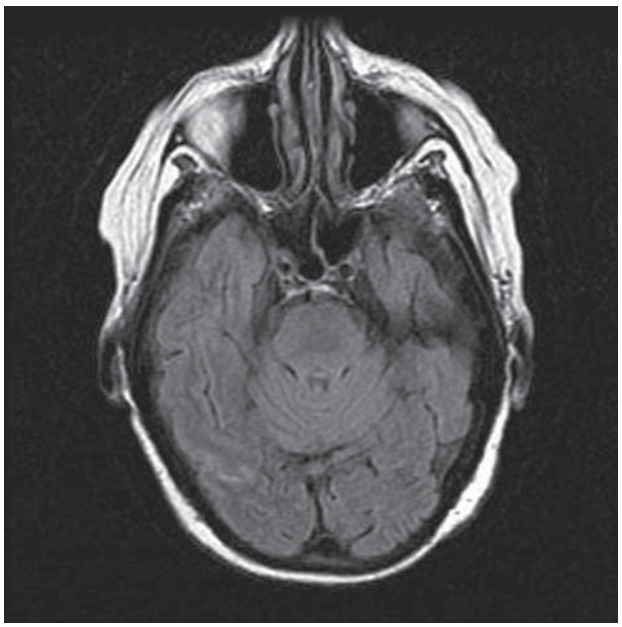


Figure 2.14. Axial MRI FLAIR image at the skull base demonstrating CSF flow related artifactual increased signal in the right prepontine cistern.

Fluid Attenuation Inversion Recovery (FLAIR)

Fluid attenuation inversion recovery (FLAIR) is not as commonly used in the neck but is a necessity in brain imaging. By nulling the CSF signal, brain tissue edema from a variety of causes stands out and easily identified. It is, however, not specific. FLAIR can be useful for assessing skull base or foraminal invasion by tumors. However, artifacts can result from CSF pulsation or high FiO_2 administration and can mimic pathologic processes such as subarachnoid hemorrhage or meningitis (bacterial, carcinomatous, viral, or aseptic) (Figure 2.14).

Diffusion Weighted Images (DWI)

DWIs are not routinely clinically used in the neck or head but are indispensable in the brain. Typical intracranial application is for assessing acute stroke, but can be applied for the assessment of active multiple sclerosis (MS) plaques and abscesses (Figure 2.15). The concept of DWI is based on the molecular motion of water and the sensitivity of certain MRI sequences to detect the diffusion or movement of water in tissues at the cellular level.

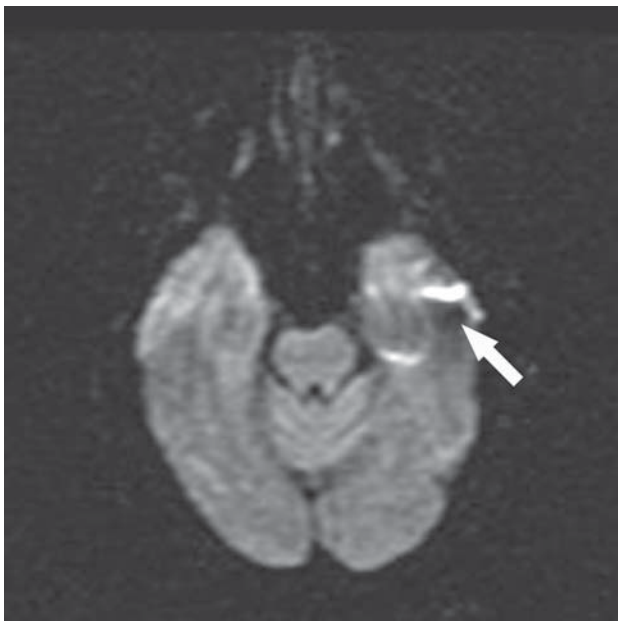


Figure 2.15. Axial MRI DWI image at the skull base demonstrating susceptibility artifact adjacent to the left temporal bone (arrow).

The use of DWI and specifically apparent diffusion coefficient (ADC) values and maps for salivary gland imaging are under investigation and show promise in differentiating benign from malignant tissues (Shah, et al. 2003; Abdel-Razek, et al. 2007; Eida, et al. 2007; Haberman, et al. 2007). The ADC values are affected by technical factors (b-value setting, image resolution, choice of region-of-interest, susceptibility artifacts, and adequate shimming) as well as physiologic factors (biochemical composition of tumors, hemorrhage, perfusion, and salivary flow) (Eida, et al. 2007). The ADC values of salivary glands change with gustatory stimulation. Although there are mixed results reported, there is generally and increase in the ADC value from pre-stimulation to post-stimulation measurements (Haberman, et al. 2007). The normal parotid, submandibular, and sublingual glands have measured ADC values of $0.63 +/- 0.11 \times 10^{-3}$ mm^2/s, $0.97 +/- 0.09 \times 10^{-3}$ mm^2/s, and $0.87 +/- 0.05 \times 10^{-3}$ mm^2/s (Eida, et al. 2007). In pleomorphic adenomas the ADC maps demonstrate areas of cellular proliferation to have intermediate ADC levels and areas of myxomatous changes to have high ADC values (Eida, et al. 2007). The Warthin tumor showed lymphoid tissue to have a very low ADC, necrosis with intermediate ADC, and low ADC in cysts among the lymphoid tissue (Eida, et al. 2007). Among the malignant lesions, mucoepidermoid carcinoma shows low ADC in a more homogenous pattern, whereas the adenoid cystic carcinomas demonstrated a more speckled pattern with areas of low and high ADC likely from multiple areas of cystic or necrotic change (Eida, et al. 2007). Lymphoma in salivary glands has been demonstrated to have a diffuse extremely low ADC likely from the diffuse uniform cellularity of lymphoma (Eida, et al. 2007). In general cystic, necrotic, or myxomatous changes tend to have higher ADC and regions of cellularity, low ADC. Malignant tumors tend to show very low to intermediate ADC whereas benign lesion have higher ADC, but with a heterogenous pattern. Overlaps do occur, for example, with the Warthin tumor demonstrating very low ADC regions and adenoid cystic carcinoma with areas of high ADC (Eida, et al. 2007).

Evaluating postoperative changes for residual or recurrent tumors is also an area where DWI and ADC may have a significant impact. In general (with overlap of data) residual or recurrent lesions have been shown to have ADC values lower then post-treatment changes (Abdel Razek, et al. 2007). The lower ADC may be a result of smaller diffusion spaces for water in intracellular and extracellular tissues in hypercellular tumors. The benign post-treatment tissue with edema and inflammatory changes has fewer barriers to diffusion and increased extracellular space resulting in a higher ADC (Abdel Razek, et al. 2007).

Evaluation of connective tissue disorders with DWI has demonstrated early changes with increase in ADC prior to changes on other MRI sequences. This may be a result of early edema and or early lymphocellular infiltration (Patel, et al. 2004). Therefore, DWI and ADC may play an important role in early assessment of connective tissue disorders, preoperative evaluation of salivary tumors, as well as surveillance for recurrent disease.

MR Spectroscopy (MRS)

MRS falls under the category of functional MRI (fMRI) which contains a variety of different exams created to elucidate physiologic functions of the body. DWI, spectroscopy, perfusion weighted imaging (PWI), and activation studies are examples of fMRI. Of these, MRS of brain lesions is the most commonly performed functional study in clinical

imaging. Spectroscopy is, after all the basis for MRI. MRS attempts to elicit the chemical processes in tissues. Although a variety of nuclei may be interrogated, protons, demonstrating the highest concentration in tissues, are the most practical to evaluate. The majority of MRS studies are performed for the brain, but several recent studies have evaluated head and neck tumors. The need for a very homogenous magnetic field and patient cooperation (prevention of motion) are the keys to successful MRS. Susceptibility artifact and vascular pulsation artifact add to the challenge of MRS. With higher field strength magnets, MRS shows promise in determining the biochemical nature of tissues (King, et al. 2005).

As in brain tumors, the most reliable markers for tumors are choline and creatine. Choline is considered to be an important constituent of cell membranes. Increased levels of choline are thought to be related to increased biosynthesis of cell membranes which is seen in tumors, particularly those demonstrating rapid proliferation. The choline signal is comprised of signals from choline, phosphocholine, phosphatidylcholine, and glycerophosphocholine. Elevation of the choline peak in the MR spectra is associated with tumors relative to normal tissue. This unfortunately can be seen in malignant lesions, inflammatory processes, and hypercellular benign lesions (King, et al. 2005). Another important constituent is creatine, a marker for energy metabolism. Its peak is comprised of creatine and phosphocreatine. The reduction of the creatine peak in neoplasms may represent the higher energy demands of neoplasms. The elevation of choline, and more importantly the elevation of the ratio of choline to creatine, has been associated with neoplasms relative to normal tissue. The elevation of choline is not tumor specific and may be seen with squamous cell carcinomas as well as a variety of salivary gland tumors, including benign tumors. It has been described in the Warthin tumor, pleomorphic adenomas, glomus tumors, schwannomas, inflammatory polyps, and inverting papillomas (Shah, et al. 2003). In fact, Warthin tumor and pleomorphic adenoma demonstrate higher choline to creatine ratios than other tumors (King, et al. 2005). King, et al. also evaluated choline to water ratios and suggest that this may be an alternative method (King, et al. 2005). Although the role of MRS in distinguishing between benign and malignant tumors may be limited, it nevertheless remains an important biomarker for neoplasms and plays a complimentary role to other functional parameters and imaging characteristics (Shah, et al. 2003). An area where MRS may play a more significant role is in a tumors response to therapy and assessment of recurrence. Elevation of the choline to creatine ratio is seen in recurrent tumors whereas the ratio remains low in post-treatment changes. Progressive reduction of choline is seen with a positive response to therapy and persistent elevation is seen in failure of therapy (Shah, et al. 2003). Use of artificial intelligence and neural network analysis of MR spectroscopy has demonstrated improved diagnostic accuracy of MRS using neural network analysis over linear discriminate analysis (Gerstle, et al. 2000). Currently, MRS of salivary gland tumors is under study and not employed clinically.

Dynamic Contrast Enhanced Magnetic Resonance Imaging

Dynamic contrast enhanced MRI has demonstrated improved diagnostic capability of tumor masses in the salivary glands and elsewhere in the body. Distinct enhancement curves can be generated based on the time points of acquisition resulting in improved differentiation of tumors (Yabuuchi, et al. 2002; Shah, et al. 2003; Alibek, et al. 2007). However, data demonstrates similar characteristics in Warthin tumor and malignant tumors, with a rapid increase in the signal intensity post-contrast. Pleomorphic adenoma demonstrates a more gradual increase in intensity (Yabuuchi, et al. 2002; Alibek, et al. 2007). Primary salivary duct carcinomas have also demonstrated the rapid enhancement as well as low ADC values, as are seen with the more common primary malignancies of the salivary glands (Motoori, et al. 2005).

Other Magnetic Resonance Imaging Techniques

In order to replace the invasive technique of digital subtraction sialography, attempts have been made to develop MR sialography. The techniques are based on acquiring heavily T2 weighted images in order to depict the ducts and branches. The lower spatial resolution and other technical factors have not allowed MR sialography to become a standard of care. This may change with newer single shot MR sequences and higher field strength magnets (Kalinowski, et al. 2002; Shah, et al. 2003; Takagi, et al. 2005b). Dynamic MR sialography has also

been used to assess function of parotid and submandibular glands at rest and under stimulation (Tanaka, et al. 2007).

An extension of this concept is MR virtual endoscopy. MR virtual endoscopy can provide high resolution images of the lumen of salivary ducts comparable to sialoendoscopy (Su, et al. 2006). Although this initial experience was a pre-operative assessment of the technology, it appears to be a promising method of non-invasive assessment of the ducts. In a similar manner, MR microscopy is a high-resolution, imaging technique employing tiny coils enabling highly detailed images of the glands (Takagi et al. 2005a). This technique was used to demonstrate morphologic changes in Sjogren syndrome.

Use of supraparamagnetic iron oxide particle MR contrast agents has been under investigation for several years. The particles used for evaluation of lymph nodes are 20 nm or less. These are intravenously injected and are taken up by the cells in the reticuloendothelial system (RES). Since normal lymph nodes have a RES that is intact they readily take up the iron oxide agents. MR imaging using T2 and T2* weighted images demonstrate susceptibility to the iron oxide and result in signal loss at sites of iron accumulation. Therefore, normal lymph nodes lose signal whereas metastatic lymph nodes whose RES has been replaced by metastases, do not take up the particles and do not lose signal (Shah, et al. 2003). Although not a direct imaging technique for the salivary glands, it may prove to be useful in the evaluation of nodal metastases.

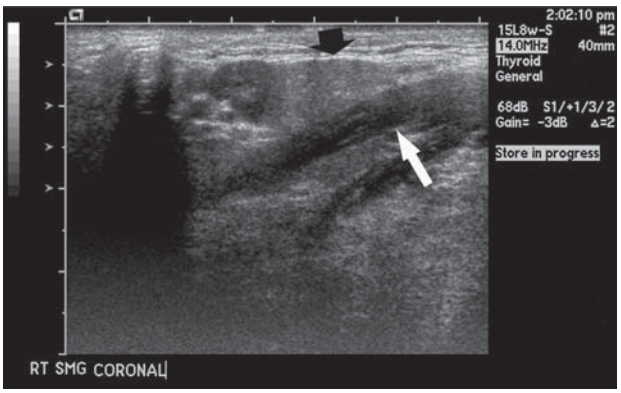


Figure 2.16. Ultrasound of the submandibular gland (black arrow) adjacent to the mylohyoid muscle (white arrow).

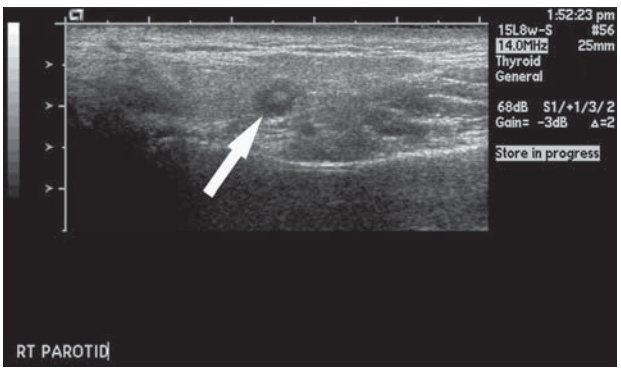


Figure 2.17. Ultrasound of the parotid gland demonstrating a normal intraparotid lymph node on a hyperechoic background. The lymph node is round and has a hypoechoic rim but demonstrates a fatty hyperechoic hilum (arrow).

ULTRASONOGRAPHY (US)

US is performed infrequently for head and neck imaging relative to CT and MRI. Although US is able to depict normal anatomy and pathology in the major salivary glands, it is limited in evaluation of the deep lobe of the parotid and submandibular gland (Figures 2.16 and 2.17). US is operator dependent and takes significantly longer to perform on bilateral individual salivary glands when compared to contrast enhanced CT of the entire neck. US is quite effective at delineating cystic from solid masses, and determining degree of vascularity. US can be used to image calculi and observe the resulting ductal dilatation. Normal lymph nodes and lymphadenopathy can also be reliably distinguished. US can be used to initially stage disease. It is not, however, optimal for post-therapy followup, be it radiation or surgery. When compared with CT or MRI, US significantly lacks in soft tissue resolution and contrast. Because of its real-time imaging capability and ease of hand held imaging, US is quite good at image guided fine needle aspiration and biopsy. The application of color Doppler or power Doppler US can distinguish arteries from veins which are critical for image guided biopsy (Figures 2.18 and 2.19). Eighteen gauge core biopsies of the parotid may be safely performed under US guidance (Wan, et al. 2004).

Ultrasound Technique

High-frequency transducers such as 5, 7.5, or 10 MHz are typically applied to image superficial small

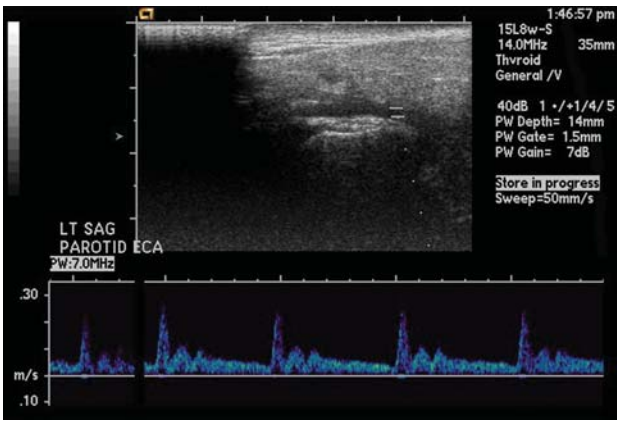


Figure 2.18. Ultrasound of the parotid gland in longitudinal orientation demonstrating the Doppler signal of the external carotid artery.

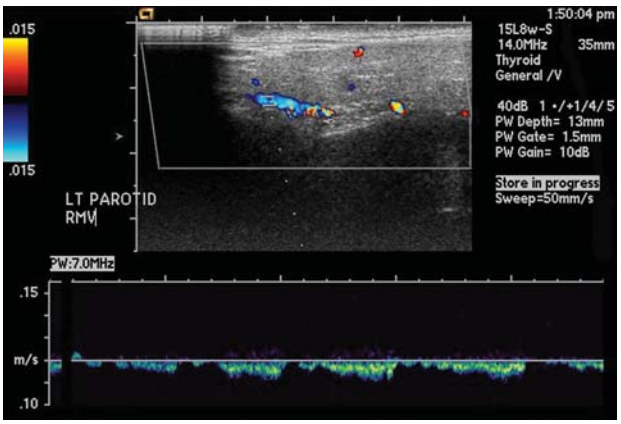


Figure 2.19. Ultrasound of the parotid gland in longitudinal orientation demonstrating the Doppler signal of the retromandibular vein.

parts. Real-time imaging and image acquisition is performed by a technologist or physician. Doppler US may be applied to observe the vascularity of the glands (increased in inflammatory conditions) or tumors within the glands. Doppler US can easily determine arterial from venous channels.

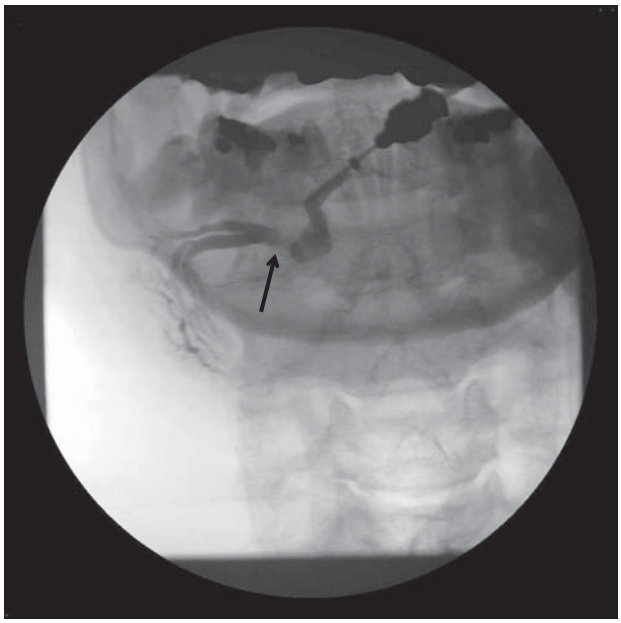
SIALOGRAPHY

Invasive salivary gland imaging was first introduced in 1904 when mercury was injected into surgical pathology and autopsy specimens, which were then visualized by X-rays. Development continued and in 1925 potassium iodide solution was injected into a human parotid gland thus initiating the radiographic technique of sialography. Many modifications of sialography have been introduced since that time. These progressive changes brought sialography into the realm of practical salivary gland imaging. Since the advent of CT and MRI, sialography has to some extent been replaced as a diagnostic tool in salivary gland imaging. Only within the last few years has there be resurgence in its use, particularly in the diagnosis and treatment of obstructive and metabolic salivary gland disease (Mosier 2009). The specific choice of imaging depends predominately on the patient's clinical presentation as well as the patient's specific needs (Burke 2011).

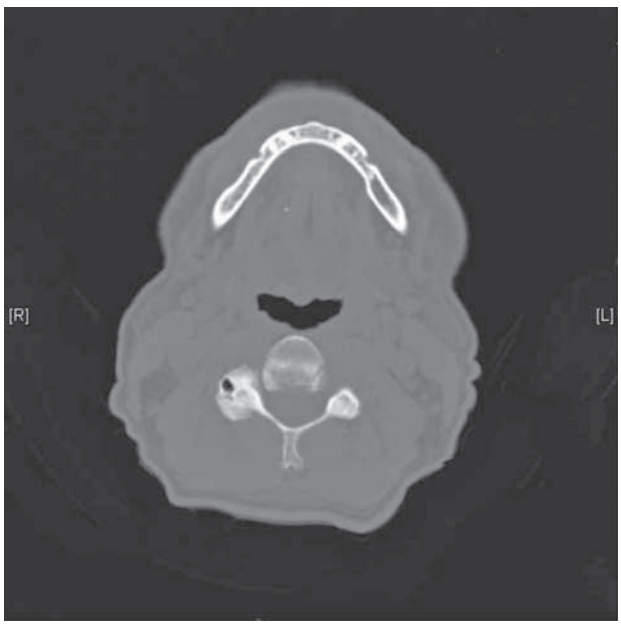
Most authorities believe the principal value of sialography is in the diagnosis of obstructive salivary gland disease. While a large number of sialoliths are calcified and thus opaque when visualized with X-ray, 20% of submandibular and 40% of parotid stones are either non-calcified or only partially calcified and consequently are non-opaque when examined by way of plain X-ray and occasionally CT imaging (Sobrino-Guijarro, et al. 2013) (Figure 2.20). Initially, sialographic imaging was essential in the delineation of benign and malignant masses, but imaging of such lesions has now been replaced by the more modern techniques of CT and MRI. The major present day indications of sialography are: (1) ductal anomalies such as sialoceles or salivary fistulas, (2) obstructive and restrictive disease (Figure 2.21) including stones (Figure 2.22), mucous plugs and intraductal neoplastic or inflammatory lesions, and (3) chronic systemic parenchymal diseases of salivary gland such as those seen with Sjogren syndrome or sarcoidosis (Hasson 2010).

The only two (paired) salivary glands for which conventional sialography is suitable are the parotid and the submandibular glands. Even though the anatomy of every individual gland varies with the patient being studied, each separate gland has a single primary duct that excretes saliva. It is through this solitary duct that contrast can be introduced and the various anatomic and pathologic variances be imaged.

Conventional sialography is a painless and minimally invasive technique, which is generally quite successful. The mechanics of sialography, for the most part, are relatively simple. Initially the patient is questioned regarding contrast allergies. In addition, it should be noted that the patient



(a)



(b)

Figure 2.20. Submandibular sialogram (a). Note the continuity defect that represents a sialolith (arrow). The corresponding submandibular CT (b) demonstrates a partially calcified stone that is less impressive compared to the sialogram.

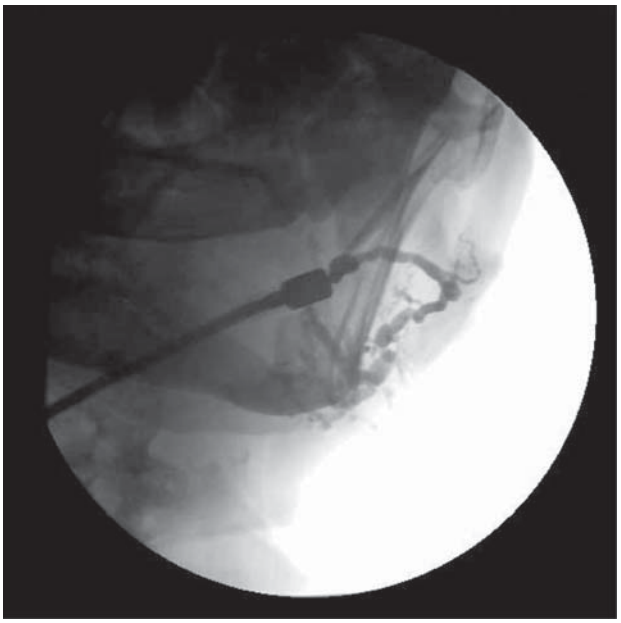


Figure 2.21. Parotid sialogram. Note the numerous areas of duct dilatation and stenosis. These features are diagnostic of obstructive disease.

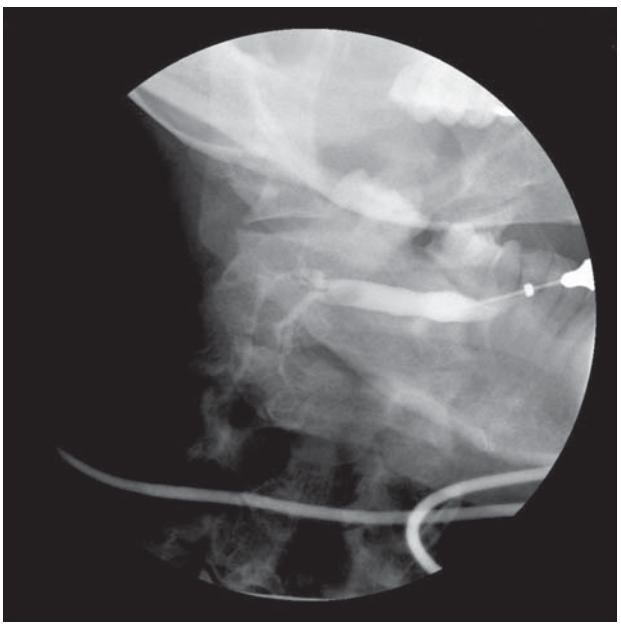


Figure 2.22. Submandibular sialogram: Note the "soft" non-calcified stone filling the duct.

cannot be imaged if there is evidence of an ongoing salivary gland infection. Once the patient is placed supine on the examination table, they are given lemon juice to stimulate salivation. Using various sized lacrimal probes, the duct orifice is dilated for a length of 1–3 cm. Following dilation, a 23–25 gauge catheter is placed into the main duct and 1–3 cc of contrast is infused into the gland taking great care not to damage the duct. Even though non-water soluble contrast usually delineates ductal walls more distinctly, water-soluble contrast leaves no residual opacity to contend with at a later time. Following contrast administration, images are acquired in various views (frontal, lateral, etc.). The patient is then once again given lemon juice allowing the contrast to be expelled. If the patient experiences pain during the procedure, a local anesthetic such as lidocaine can be infused into the ductal system in the same manner as the contrast agent.

During sialography there are two major phases of contrast filling: ductal and acinar. The initial or ductal phase will demonstrate the major or primary duct as well as the smaller secondary and tertiary ducts. The acinar phase is seen as the contrast "blush" and demonstrates the parenchymal portion of the gland. A sialographic finding in obstructive disease will demonstrate the anatomy of both the main and the secondary ducts. Visualized will be strictures, obstructions, accessory glands, and sialoliths. The observed obstructions include calcified and non-calcified sialoliths, mucous plugs, fibrin or other soft tissue plugs, intraductal tumors, duct stenosis and strictures, and various anatomical kinking of the ducts.

The major parenchymal disorder of salivary gland which can be identified by sialography is the glandular change seen in Sjogren syndrome (Figure 2.23). This systemic autoimmune condition affects the majority of human exocrine glands but much more so the major and minor salivary glands (Golder and Stiller 2014). During the early phase of this syndrome, when imaged these glands appear unremarkable, but as Sjogren syndrome progresses the salivary glands diffusely enlarge mimicking chronic sialadenitis. Imaging of the salivary glands during this later time period will demonstrate discrete tiny collections of contrast within the parenchyma of the salivary gland without interconnecting ducts. Advanced imaging techniques such as ultrasound, MRI, and CT have attempted to demonstrate these findings, but ultimately conventional sialography has proven to be the technique of choice for definitive imaging of patients afflicted with Sjogren syndrome.

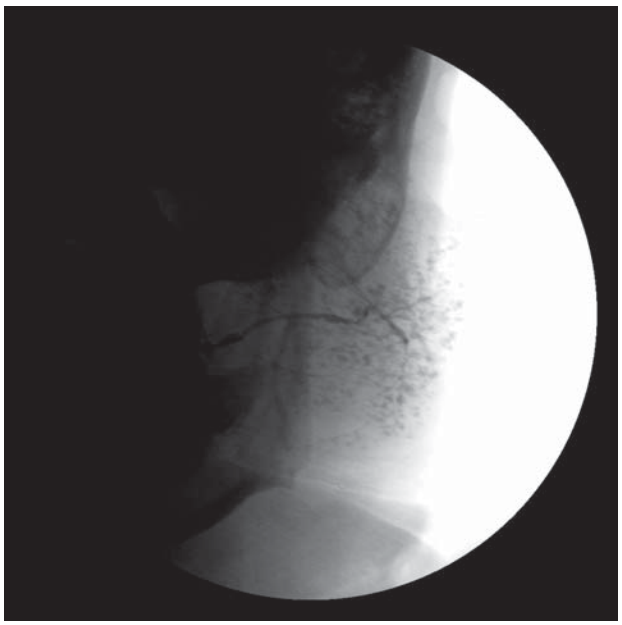


Figure 2.23. Parotid sialogram. Note the punctate filling areas without ductal involvement. These findings are seen predominately in Sjogren syndrome patients.

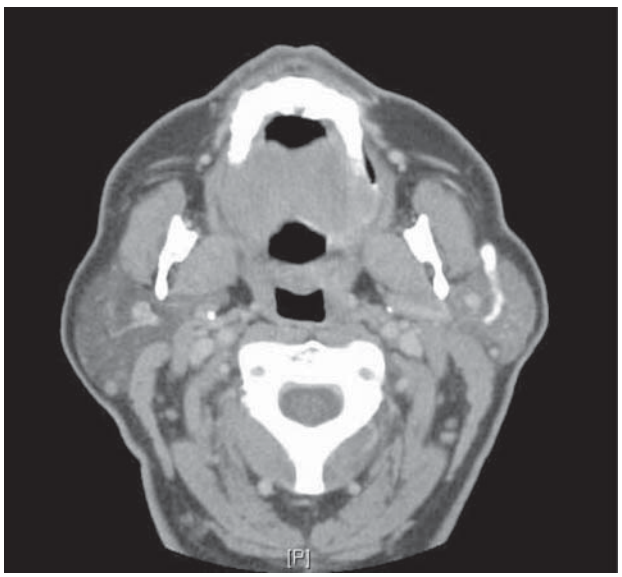


Figure 2.24. Parotid sialo-CT. Although the main duct is opacified, it is impossible to determine areas of stenosis and/or dilatation.

In addition to conventional sialography, MR sialography, CT sialography (Figure 2.24), and digital subtraction sialography are also available.

Each of these methods attempts to better identify the primary and secondary ductal systems and thus better define the exact nature of the clinical salivary malady.

Digital subtraction sialography utilizes the images obtained from conventional sialography and masks out the underlying osseous structures by means of computer revision to better visualize the duct system. This type of examination is more time consuming and can be quite difficult to interpret except by very experienced radiographers. In addition this technique is considerably more expensive than conventional sialography without significant clinical benefit.

CT sialography allows better visualization of gland parenchyma and is widely available in most medical centers today. In this method, contrast media is injected into the primary duct and the CT is then completed. Today's multi-detector computed tomography will allow reconstruction or reformatting of the original axial CT image into images representing many orthogonal planes. The major disadvantage of this method is one cannot visualize the dynamic duct filling and thus inadvertent overpressure may cause duct damage or rupture. In addition, it is very difficult to distinguish duct stenosis from anatomic variances of the normal duct system.

MR sialography appears to delineate the salivary ductal system as well as conventional sialography without the need of duct catheterization and subsequent contrast administration. Fluid sensitive MR sequences now obviate this clinical need. MR can detect obstructions, stenosis, and strictures of the primary, secondary, and often tertiary ducts as well as conventional sialography. In addition, advances in 3-D MRI will allow the production of virtual endoscopic views from available MR data. Even with all these advantages, MR sialography has little clinical use secondary to its cost, time expenditure, and the specific software needed to produce such images.

RADIONUCLIDE IMAGING (RNI)

Radionuclide imaging (RNI) has, throughout its history, been a functional imaging modality without the quality of anatomic depiction when compared with CT, MRI, or even US. The majority of radionuclide imaging has been performed with planar imaging systems which produce single view images of functional processes. All RNI exams employ a radioactive tracer either bound to a ligand (radiopharmaceutical) or injected directly (radionuclide). As the radionuclide undergoes radioactive decay it emits either a gamma ray (photon), and/or a particle such as an alpha particle (Helium nucleus), beta particle (electron), or a positron (a positively charged electron). Gamma rays differ from X-rays in that gamma rays (for medical imaging) are an inherent nuclear event and are emitted from the nucleus of an unstable atom in order to achieve stability. X-rays (in the conventional sense) are produced in the electron cloud surrounding the nucleus. In medical imaging, X-rays are artificially or intentionally produced on demand, whereas gamma rays (and other particles) are part of an on-going nuclear decay enabling unstable radioactive atoms to reach a stable state. The length of time it takes for one half of the unstable atoms to reach there stable state is called their half-life. Radionuclide imaging involves the emission of a photon, which is imaged using a crystal or solid state detector. The detector may be static and produces images of the event in a single plane or the detector may be rotated about the patient in order to gather three-dimensional data and reconstruct a tomographic image in the same manner as a CT scanner. This is the basis for single photon emission computed tomography (SPECT). Examples of planar images used in salivary gland diseases include Gallium (^{67}Ga) for evaluation of inflammation, infection, and neoplasms (lymphoma). SPECT, which produces tomographic cross sectional images, is less commonly used in oncologic imaging, although novel radionuclides and ligands are under investigation. The recent introduction of SPECT/CT, a combined functional and anatomic imaging machine may breathe new life into SPECT imaging.

POSITRON EMISSION TOMOGRAPHY (PET)

Positron emission tomography (PET) is a unique imaging modality that records a series of radioactive decay events. Positron emission is a form of radioactive decay in which a positron (positively charged electron) is emitted from the unstable atom in order to achieve a more stable state. The positron almost immediately collides with an electron (negatively charged) and undergoes an annihilation event in which both particles are

destroyed and converted into pure energy. The annihilation event produces two gamma rays, each with 511 keV (kilo electron volt) of energy and traveling in 180-degree opposition. By using sophisticated solid state detectors and coincidence circuitry, the PET system is able to record the source of the event, thereby localizing the event in three-dimensional space. Using a complex algorithm similar to SPECT and CT, a three-dimensional block of data is produced and can be "sliced" in any plane, but most commonly in axial, coronal, and sagittal planes, as well as a maximum intensity projection (MIP) rendering.

PET radionuclides are produced in a cyclotron and are relatively short lived. Typical radionuclides include ^{18}F, ^{11}C, ^{15}O, ^{82}Rb, and ^{13}N. A variety of ligands have been labeled and studied for the evaluation of perfusion, metabolism, and cell surface receptors. The most commonly available is ^{18}F-deoxyglucose (FDG), which is used to study glucose metabolism of cells. Most common uses of FDG include oncology, cardiac viability, and brain metabolism. PET has a higher spatial resolution than SPECT. Both systems are prone to multiple artifacts, especially motion. Acquisition times for both are quite long, limiting the exam to patients who can lie still for prolonged periods of time. Both systems, PET in particular, are very costly to install and maintain. Radiopharmaceuticals are now widely available to most institutions through a network of nuclear pharmacies.

The oncologic principle behind FDG PET is that neoplastic tissues can have a much higher metabolism than normal tissues and utilize glucose at a higher rate (Warburg 1925). Glucose metabolism in the brain was extensively studied using autoradiography by Sokoloff and colleagues at The National Institutes of Health (NIH) (Sokoloff 1961). The deoxyglucose metabolism is unique in that it mimics glucose and is taken up by cells using the same transporter proteins. Both glucose and deoxyglucose undergo phosphorylation by hexokinase to form glucose-6-phosphate. This is where the similarities end. Glucose-6-phosphate continues to be metabolized, eventually to form CO_2 and H_2O. Deoxyglucose-6-phosphate cannot be further metabolized and becomes trapped in the cell as it cannot diffuse out through the cell membrane. Therefore, the accumulation of FDG reflects the relative metabolism of tissues (Sokoloff 1986). The characteristic increased rate of glucose metabolism by malignant tumors was initially described by Warburg and is the basis of FDG PET imaging of neoplasms (Warburg 1925).

FDG PET takes advantage of the higher utilization of glucose by neoplastic tissues to produce a map of glucose metabolism. Although the FDG PET system is sensitive, it is not specific. Several processes can elevate glucose metabolism, including neoplastic tissue, inflammatory or infected tissue, and normal tissue in a high metabolic state. An example of the latter includes uptake of FDG in skeletal muscle that was actively contracting during the uptake phase of the study (Figure 2.25 a–d). Another peculiar hypermetabolic phenomenon is brown adipose tissue (BAT) FDG uptake (Figure 2.26 a–d). BAT is distributed in multiple sites in the body including interscapular, paravertebral, around large blood vessels, deep cervical, axillary, mediastinal, and intercostal fat, but is concentrated in the supraclavicular regions (Cohade, et al. 2003; Tatsumi, et al. 2004). BAT functions as a thermogenic organ producing heat in mammals and most commonly demonstrates uptake in the winter (Tatsumi, et al. 2004). BAT is innervated by the sympathetic nervous system, has a higher concentration of mitochondria, and is stimulated by cold temperatures (Cohade, et al. 2003; Tatsumi, et al. 2004). Administration of Ketamine anesthesia in rats markedly increased FDG uptake, presumably from sympathetic stimulation (Tatsumi, et al. 2004). Although typically described on FDG PET/CT exams, it can be demonstrated with ^{18}F-Fluorodopamine PET/CT, ^{99}mTc-Tetrofosmin, and ^{123}I-MIBG SPECT as well as ^{201}TlCl, and ^{3}H-l-methionine (Baba, et al. 2007; Hadi, et al. 2007). Propranalol and Reserpine administration appears to decrease the degree of FDG uptake whereas diazepam does not appear to have as significant an effect (Tatsumi, et al. 2004). Exposure to nicotine and ephedrine also resulted in increased BAT uptake, therefore, avoiding these substances prior to PET scanning can prevent or reduce BAT uptake (Baba, et al. 2007). Preventing BAT uptake of FDG can be accomplished by having the patient stay in a warm ambient temperature for 48 hours before the study and by keeping the patient warm during the uptake phase of FDG PET (Delbeke, et al. 2006; Cohade, et al. 2003). Although somewhat controversial, diazepam or lorazepam and propranalol can reduce BAT uptake by blocking sympathetic activity, as well as reducing skeletal muscle uptake from reduced anxiety and improved relaxation (Delbeke, et al. 2006).

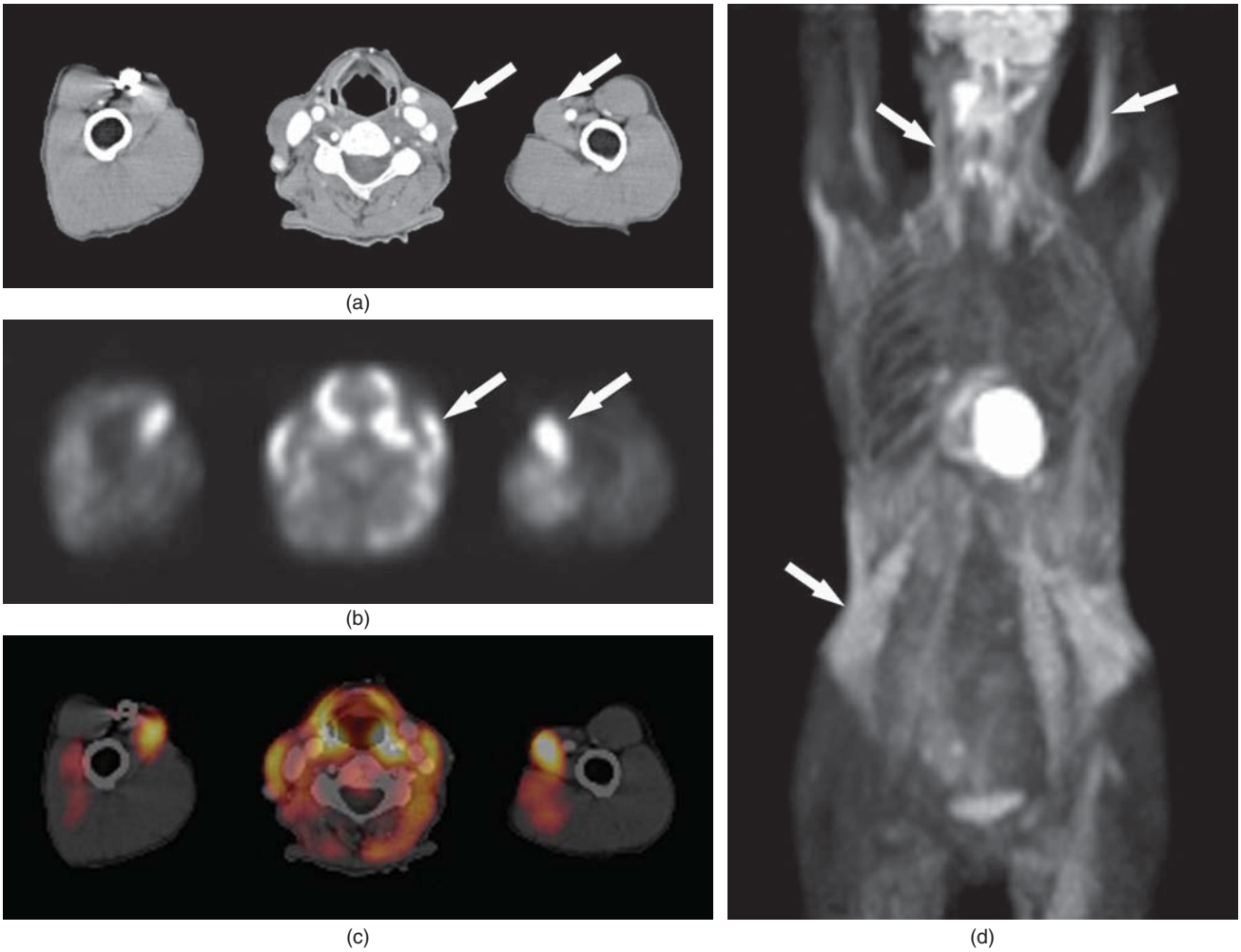


Figure 2.25. CT (a), PET (b), and fused PET/CT (c) images in axial plane, and an anterior maximum intensity projection (MIP) image (d) demonstrating skeletal muscle uptake in the sternocleidomastoid muscle and biceps muscle (arrows). Also note the intense uptake in the abdominal, psoas, and intercostal muscles on the MIP image. The very high focal uptake in the middle of the image is myocardial activity.

Understanding the distribution of BAT and the physiology that activates BAT, as well as recognizing the uptake of FDG in BAT in clinical studies is critical in preventing false positive diagnosis of supraclavicular, paravertebral, and cervical masses or lymphadenopathy.

FDG uptake in all salivary glands in the normal state is usually mild and homogenous (Burrell, et al. 2005; Wang, et al. 2007) (Figures 2.27 a and b and 2.28 a and b). After therapy, radiation or chemotherapy, the uptake can be very high (Burrell, et al. 2005). Standardized uptake values (SUV), a semi-quantitative measurement of the degree of uptake of a radiotracer (FDG), may be calculated on PET scans. There are many factors that impact the measurement of SUVs, including the method of attenuation correction and reconstruction, size of lesion, size of region of interest, motion of lesion, recovery coefficient, plasma glucose concentration, body habitus, and time from injection to imaging (Beaulieu, et al. 2003; Schoder, et al. 2003; Wang, et al. 2007).

A range of SUVs can be calculated in normal volunteers for each salivary gland. Wang, et al. measured SUVs in normal tissues to determine the maximum SUV and mean SUV as well as assignment of an uptake grade ranging from none (mean SUV less than aortic blood pool), mild (mean SUV

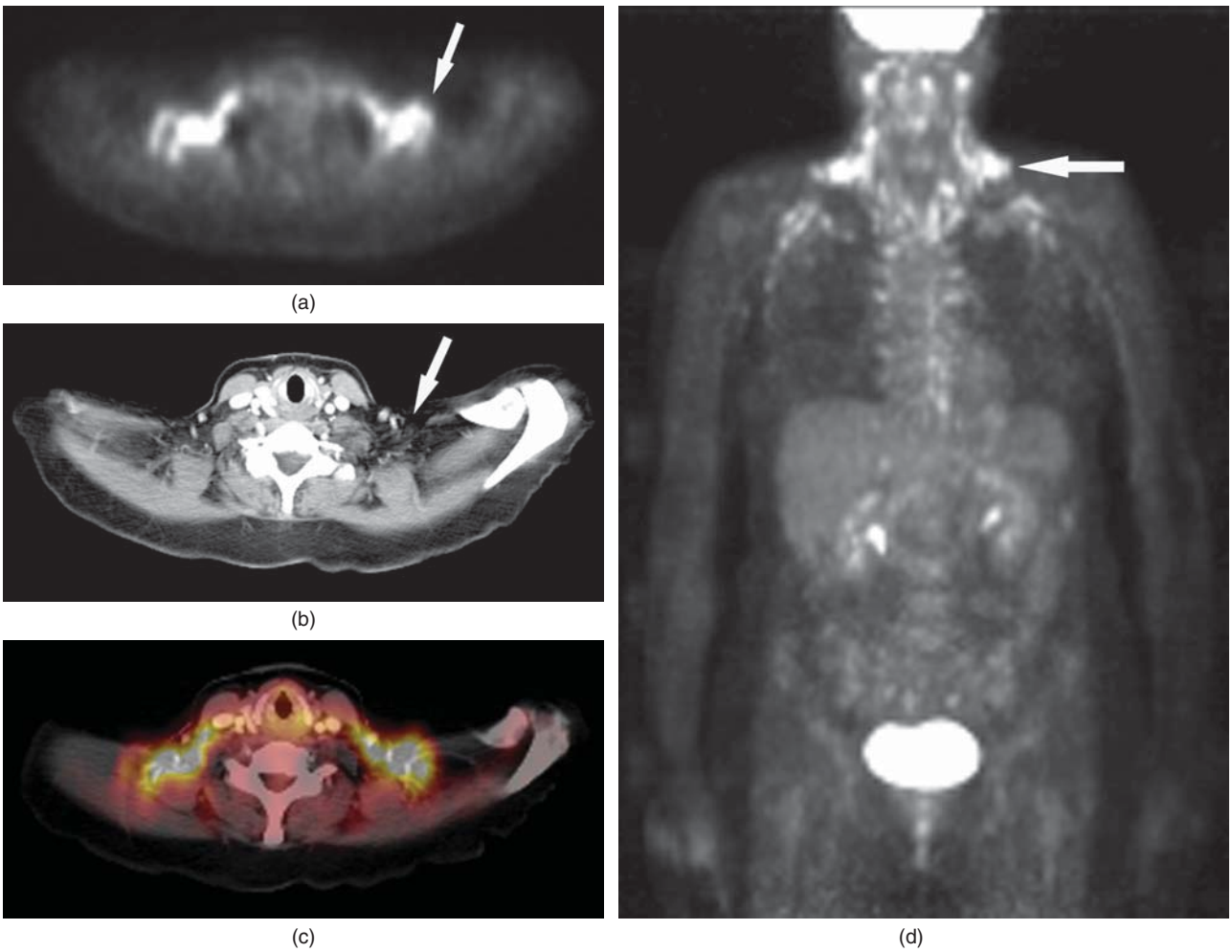
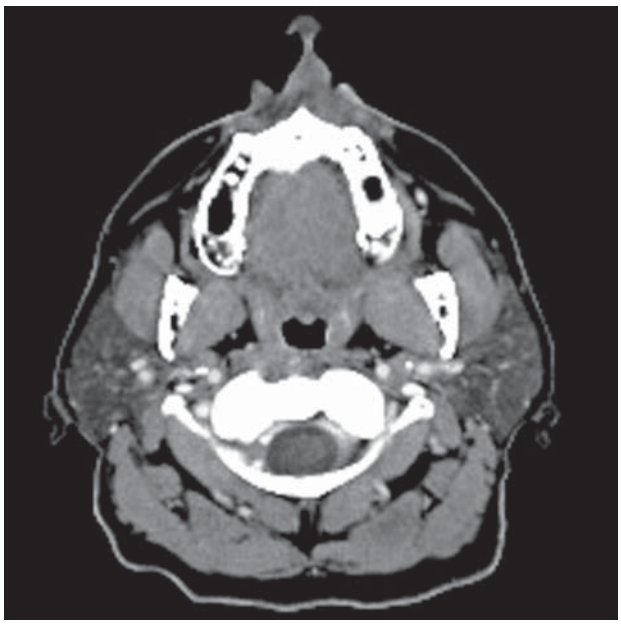


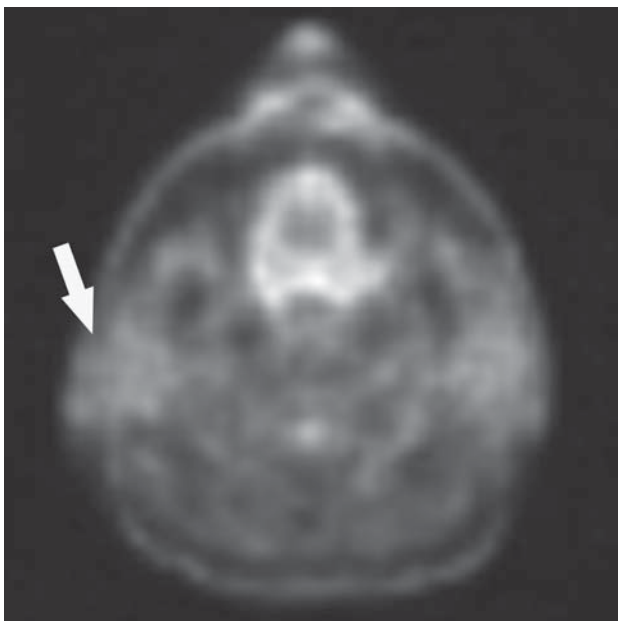
Figure 2.26. PET image (a), corresponding CT image (b), and a fused PET/CT image (c) in the axial plane demonstrating Brown adipose tissue (BAT) uptake in the supraclavicular regions bilaterally which could mimic lymphadenopathy (see arrows on a and b). Direct correlation enabled by the PET/CT prevents a false positive finding. Note the similar uptake on the MIP image (arrow) (d) including paraspinal BAT uptake.

greater than mean SUV of aortic blood pool but less than 2.5), moderate (mean SUV between 2.5 and 5.0), and intense (mean SUV greater than 5.0). SUV greater than 2.5 was considered significant (Wang, et al. 2007). Parotid glands (n = 97) had a range of SUVmax of 0.78–20.45 and a SUVmean range of 1.75 +/− 0.79. Fifty-three percent of the SUV measurements fell into the "none" category, 33% into the "mild" category, and 14% into the "moderate" category. No SUV measurement fell into the "intense" category. Submandibular glands (n = 99) had a SUVmax range of 0.56–5.14 and a SUVmean of 2.22 +/− 0.77. The uptake grades consisted of the following, 25% were in the "none" category, 44% in the "mild", and 31% were "moderate." The sublingual gland (n = 102) had a SUVmax range of 0.93–5.91 and a SUVmean of 4.06 +/− 1.76. Four percent of these fell into the "none" category, 19% in the "mild", 54% in the "moderate," and 23% in the "intense" group (Wang, et al. 2007). Similar work by Nakamoto, et al. demonstrated a SUVmean of 1.9 +/− 0.68 for the parotid gland, 2.11 +/− 0.57 for the submandibular gland and 2.93 +/− 1.39 for the sublingual gland (Nakamoto, et al. 2005). This demonstrates the wide range of normal uptake values (Table 2.3).

Although FDG does accumulate in the saliva, the concentration varies from 0.2–0.4 SUV but

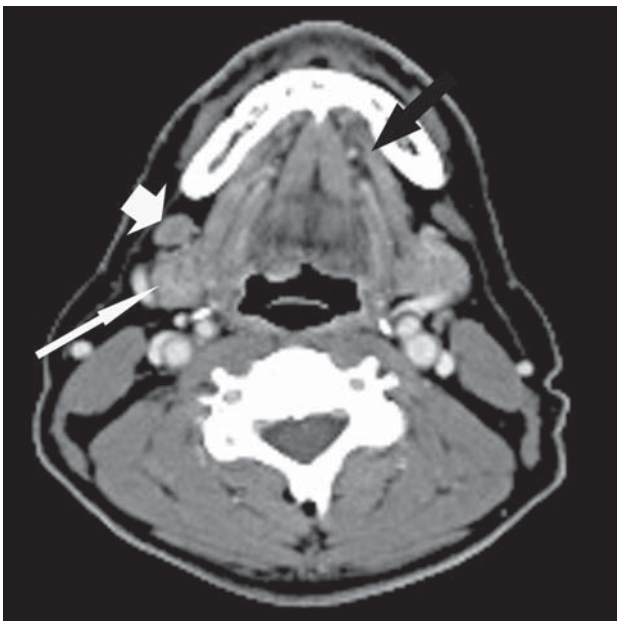


(a)

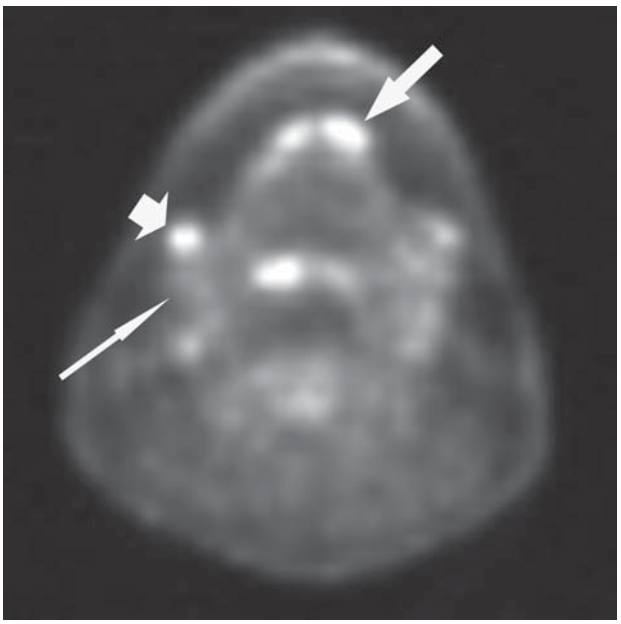


(b)

Figure 2.27. CT (a) and PET (b) images in axial plane demonstrating normal parotid gland activity (arrow).



(a)



(b)

Figure 2.28. CT (a) and PET (b) images in axial plane demonstrating normal submandibular (long, thin arrow) and sublingual gland (medium arrow) activity. Note the abnormal uptake higher than and anterior to the submandibular glands (short, fat arrow). Metastatic lymphadenopathy was diagnosed at the time of surgery.

Table 2.3. SUV of salivary glands.

Gland	SUVmax (range)[a]	SUVmean +/– SD[a]	SUVmean +/– SD[b]
Parotid gland	0.78–20.45	1.75 +/– 0.79	1.90 +/– 0.68
Submandibular gland	0.56–5.14	2.22 +/– 0.77	2.11 +/– 0.57
Sublingual gland	0.93–5.91	4.06 +/– 1.76	2.93 +/– 1.39

SD = standard deviation.
[a](Wang 2007).
[b](Nakamoto 2005).

does not influence FDG imaging (Stahl et al. 2002). An SUV greater than 2.5 has become a threshold for abnormal or neoplastic uptake (originally described by Patz, et al. 2003) (Wang, et al. 2007). However, careful analysis must be undertaken when evaluating lesions based on SUVs as there is a significant overlap of SUVs for malignant and benign tumors and inflammatory conditions. One cannot depend on SUV measurements alone, and must take into consideration clinical data as well as radiologic imaging findings.

POSITRON EMISSION TOMOGRAPHY/ COMPUTED TOMOGRAPHY (PET/CT)

Head and neck imaging has greatly benefited from the use FDG PET imaging for the staging, restaging, and follow-up of neoplasms. The recent introduction of PET/CT has dramatically changed the imaging of diseases of the head and neck by directly combining anatomic and functional imaging.

The evaluation of the head and neck with FDG PET/CT has been significantly and positively affected with detection and demonstration of the extent of primary disease, lymphadenopathy, and scar versus recurrent or residual disease, pre-surgical staging, pre-radiosurgery planning, and follow-up post-therapy.

The role of FDG PET or PET/CT and that of conventional CT and MRI on the diagnosis, staging, restaging, and followup post-therapy of salivary gland tumors have been studied (Keyes, et al. 1994; Bui, et al. 2003; Otsuka, et al. 2005; De Ru, et al. 2007; Roh, et al. 2007). Although both CT and MRI are relatively equal in anatomic localization of disease and the effect of the tumors on local invasion and cervical nodal metastases, FDG PET/CT significantly improved sensitivity and specificity for salivary malignancies including nodal metastases (Otsuka, et al. 2005; Uchida, et al. 2005; De Ru, et al. 2007; Jeong, et al. 2007; Roh, et al. 2007).

Early studies have demonstrated FDG PETs relative inability to distinguish benign from malignant salivary neoplasms (Keyes, et al. 1994). The variable uptake of FDG by pleomorphic adenomas and the increased uptake and SUVs by the Warthin tumor result in significant false positives (Jeong, et al. 2007; Roh, et al. 2007). In a similar manner, adenoid cystic carcinomas, which are relatively slower growing, may not accumulate significant concentrations of FDG and demonstrate low SUVs and therefore contribute to the false negatives (Keyes, et al. 1994; Jeong, et al. 2007). False negatives may also be caused by the relatively lower mean SUV of salivary tumors (SUV 3.8 +/– 2.1) relative to squamous cell carcinoma (SUV 7.5 +/– 3.4) (Roh, et al. 2007). The low SUV of salivary neoplasms may also be obscured by the normal uptake of FDG by salivary glands (Roh, et al. 2007). In general, FDG PET has demonstrated that lower grade malignancies tend to have lower SUV and vice versa for higher grade malignancies (Jeong, et al. 2007; Roh, et al. 2007). FDG PET has been shown to be more sensitive and specific compared to conventional CT or MRI (Otsuka, et al. 2005; Cermik, et al. 2007; Roh, et al. 2007). Small tumor size can contribute to false negative results and inflammatory changes contribute to false positive results (Roh, et al. 2007). The use of concurrent salivary scintigraphy with ^{99}mTc-pertechnetate imaging can improve the false positive rate by identifying Warthin tumors and oncocytomas, which tend to accumulate pertechnetate (and retain it after induced salivary gland washout) and have increased uptake of FDG (Uchida, et al. 2005).

Diagnostic Imaging Anatomy

PAROTID GLANDS

The average adult parotid gland measures 3.4 cm in AP, 3.7 cm in LR, and 5.8 cm in SI dimensions and is the largest salivary gland. The parotid gland is positioned high in the suprahyoid neck directly inferior to the external auditory canal (EAC) and wedged between the posterior border of the mandible and anterior border of the styloid process, sternocleidomastoid muscle, and posterior belly of the digastric muscle (Figures 2.29–2.35; also see Figures 2.17–2.19). This position, as well as the seventh cranial nerve which traverses the gland, divides the gland functionally (not anatomically) into superficial and deep "lobes." Its inferior extent is to the level of the angle of the mandible where its "tail" is interposed between the platysma superficially and the sternocleidomastoid muscle (SCM) deep to the tail of the parotid. The parotid gland is surrounded by the superficial layer of the deep cervical fascia. The parotid space is bordered medially by the parapharyngeal space (PPS), the carotid space (CS), and the posterior belly of the digastric muscle. The anterior border is made up of the angle and ramus of the mandible along with the masticator space (MS). The posterior border is made up of the styloid and mastoid processes and the SCM. The gland traverses the stylomandibular tunnel which is formed by the posterior border of the mandibular ramus, the anterior border of the sternocleidomastoid muscle, the anterior border of the stylomandibular ligament, and the anterior border of the posterior belly of the digastric muscle and the skull base on its superior aspect (Som, et al. 1996; Beale and Madani 2006). The external carotid artery (ECA) and retromandibular vein (RMV) traverse the gland in a craniocaudal direction, posterior to the posterior border of the mandibular ramus. The seventh cranial nerve (CN VII) traverses the gland in the slightly oblique antero-posterior direction from the stylomastoid foramen to the anterior border of the gland passing just lateral to the RMV. The seventh cranial nerve

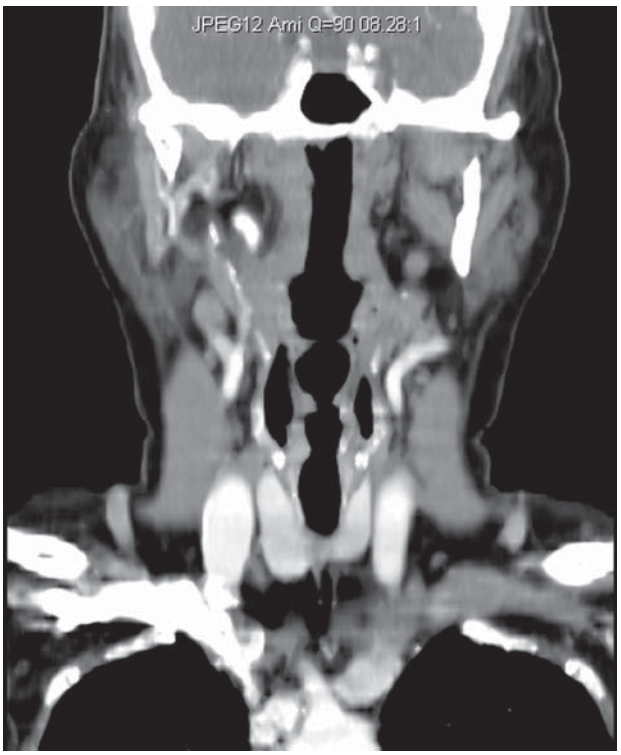


Figure 2.30. Reformatted coronal CT of the neck at the level of the parotid gland demonstrating its relationship to adjacent structures. Note the distinct soft tissue anatomy below the skull base.

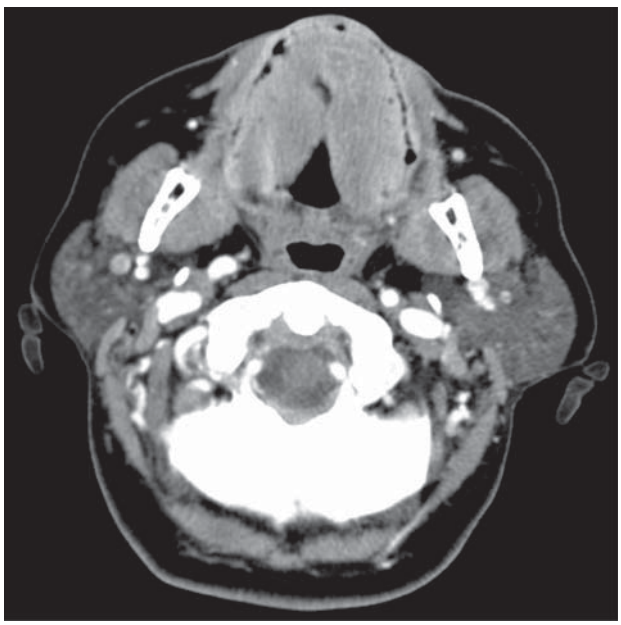


Figure 2.29. Axial CT of the neck demonstrates the intermediate to low density of the parotid gland.

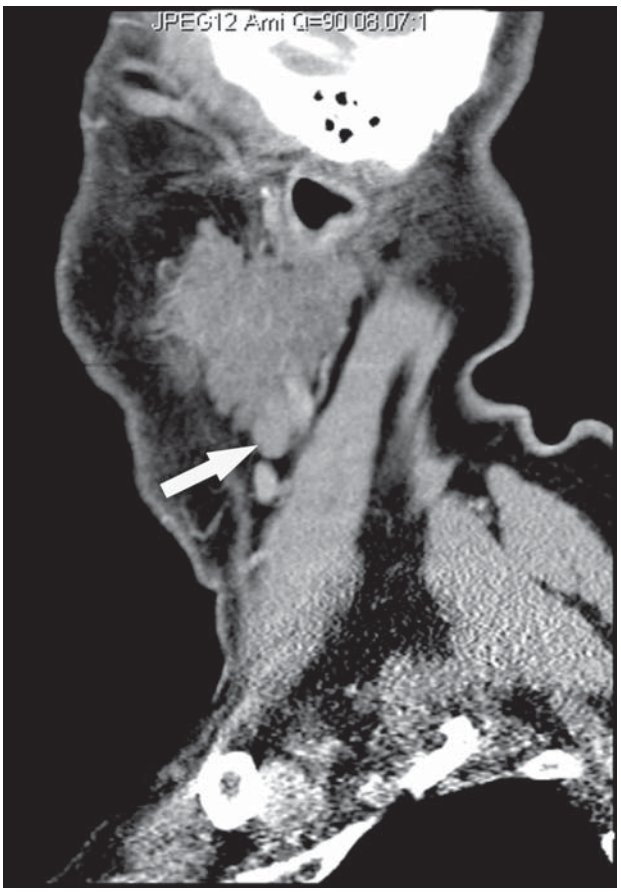


Figure 2.31. Reformatted sagittal CT of the neck at the level of the parotid gland demonstrating its relationship to adjacent structures including the external auditory canal. Note the slightly denser soft tissue density in the parotid tail, the so-called "earring lesion" of the parotid gland. Cervical lymphadenopathy (arrow) was diagnosed at surgery.

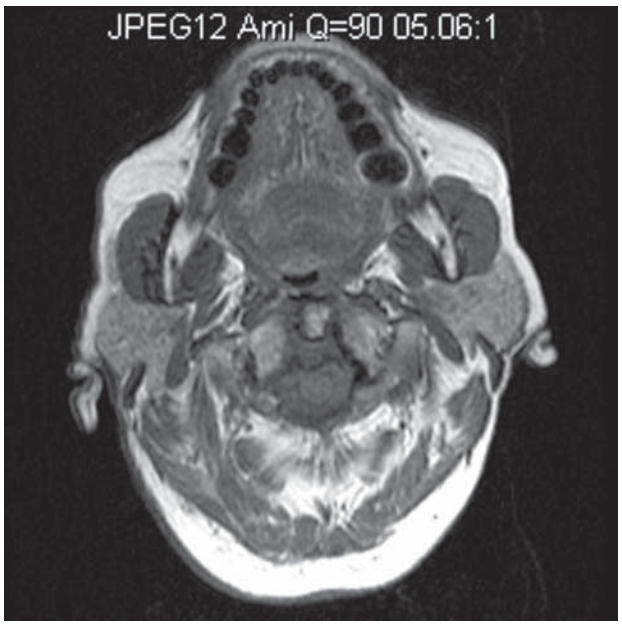


Figure 2.32. Axial T1 MRI image at the level of the parotid gland demonstrating the slightly higher signal as compared to skeletal muscle but less than subcutaneous fat.

divides into five branches (temporal, zygomatic, buccal, mandibular, and cervical) within the substance of the gland. Prior to entering the substance of the parotid gland, the facial nerve gives off small branches, the posterior auricular, posterior digastric, and the stylohyoid nerves. The intraparotid facial nerve and duct can be demonstrated by MRI using surface coils and high resolution acquisition (Takahashi, et al. 2005). Because the parotid gland encapsulates later in development than other salivary gland, lymph nodes become incorporated into the substance of the gland. The parotid duct emanates from the superficial anterior part of the gland and is positioned along the superficial surface of the masseter muscle. Along the anterior aspect of the masseter muscle the duct turns medially, posterior to the zygomaticus major and minor muscle to penetrate the buccinator muscle and terminates in the oral mucosa lateral to the maxillary second molar. Fifteen to 20% of the general population also has an accessory parotid gland that lies along the surface of the masseter muscle in the path of the parotid duct.

In the pediatric population, the parotid gland is isodense to skeletal muscle by CT and becomes progressively but variably fatty replaced with aging. Therefore, the CT density will progressively decrease over time (Drummond 1995). By MRI the parotid gland is isointense to skeletal muscle on T1 and T2 weighted images, but with progressive fatty replacement demonstrates progressive increase in signal (brighter) similar to but remaining less than subcutaneous fat. Administration of iodinated contrast for CT results in slight enhancement (increase in density and therefore brightness). Administration of intravenous gadolinium (Gd) contrast results in an increase in signal (T1 shortening) and therefore brighter on MRI scans. By US the acoustic signature is isoechoic to muscle, but with fatty replacement becomes hyperechoic (more heterogenous gray). Therefore, masses tend to stand out as less echogenic foci. Normal uptake

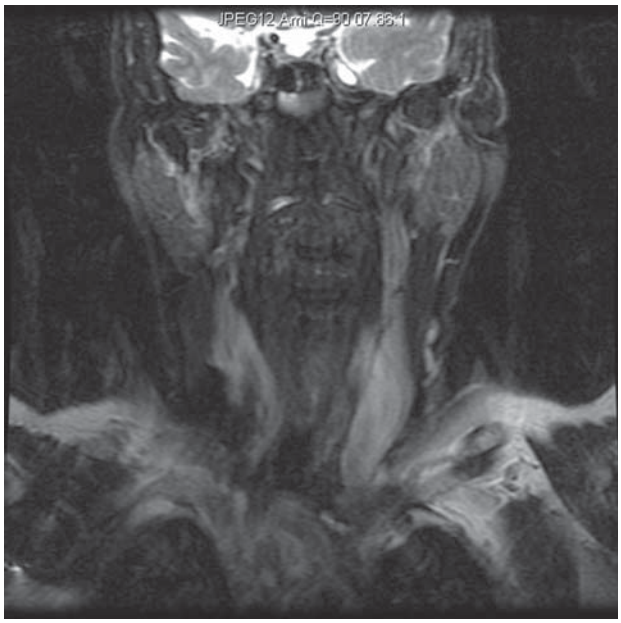


Figure 2.33. Coronal STIR MRI image at the level of the parotid gland demonstrating the nulling of the subcutaneous fat signal on STIR images and low signal from the partially fatty parotid gland.

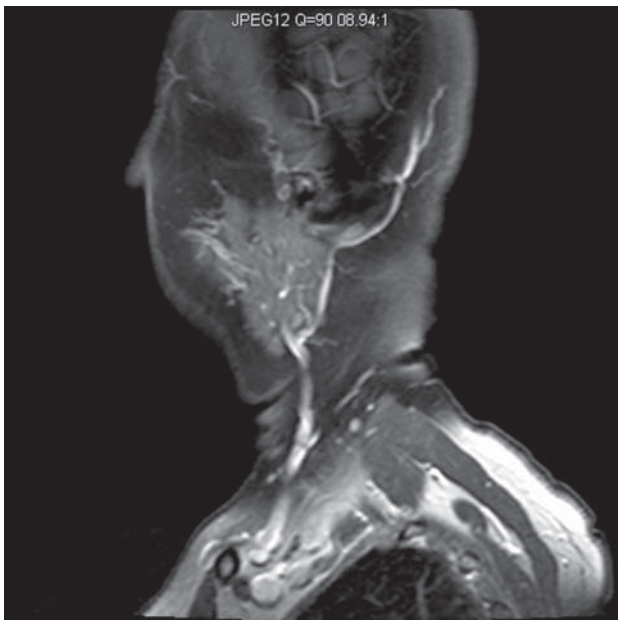
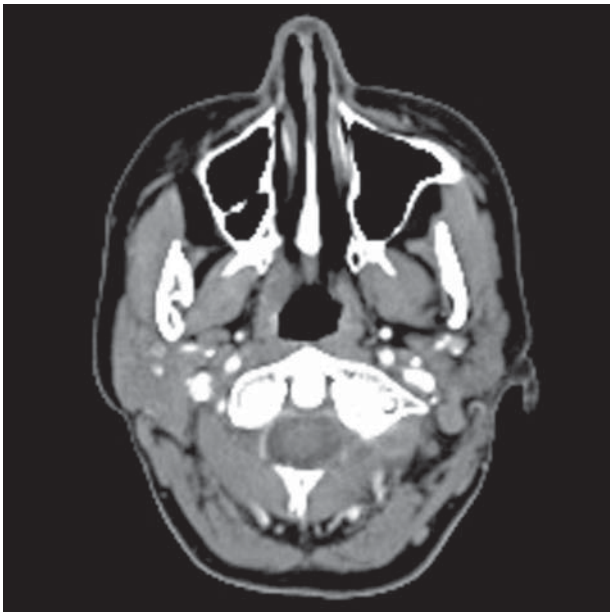
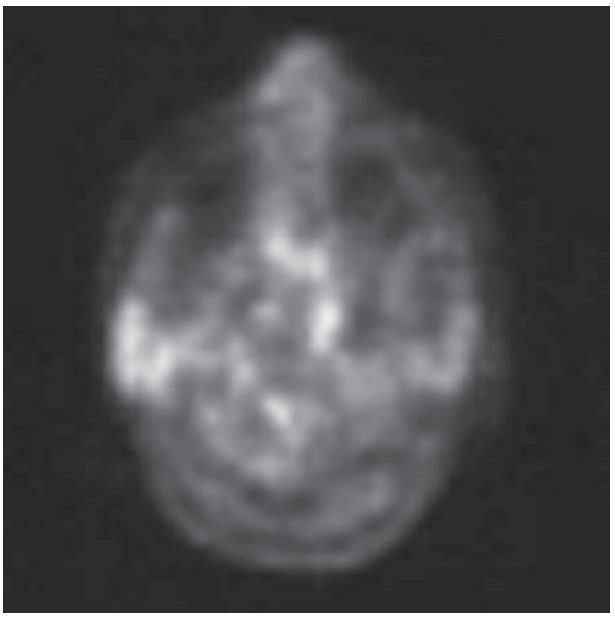


Figure 2.34. Sagittal fat suppressed T1 MRI image of the parotid gland demonstrating mild enhancement and lack of subcutaneous fat signal in the upper neck but incomplete fat suppression at the base of the neck.



(a)



(b)

Figure 2.35. Axial CT scan (a) and corresponding PET scan (b) at the level of the parotid gland. Note the asymmetric slightly higher uptake on the right corresponding to partially resected parotid gland on the left, confirmed by CT.

on FDG PET varies but is mild to moderate relative to muscle and decreases over age.

SUBMANDIBULAR GLANDS

The submandibular gland (SMG) is located in the upper neck in the submandibular space (SMS) and the posterior oral cavity in the sublingual space (SLS). The SMG is more difficult to measure but the average adult superficial submandibular gland measures 3.5 cm in oblique AP, 1.4 cm in oblique LR, and 3.3 cm in SI dimensions. The gland "wraps" around the posterior border of the mylohyoid muscle and traverses the two spaces. The superficial portion is in the SMS adjacent to level one lymph nodes (level 1b). The deep portion of the submandibular gland is located in the SLS. The SMS is bordered inferiorly by the hyoid bone and platysma and superiorly by the mylohyoid muscle. It is bordered laterally by the mandible and it is surrounded by the superficial layer of deep cervical fascia. Its medial border is a combination of the mylohyoid sling and anterior belly of the digastric muscle (Beale and Madani 2006) (Figures 2.36 through 2.42).

The submandibular duct emanates from the anterior-superior aspect of the gland and turns anteriorly and lies along the superior surface of the mylohyoid muscle between the genioglossus muscle medially and the sublingual gland laterally. The ducts open into the anterior medial (paramidline) floor of mouth at the sublingual papillae.

On CT scans the submandibular gland has a density that is isodense to slightly hyperdense relative to skeletal muscle. The gland does not become as fatty replaced as the parotid gland. The SMG demonstrates a signal characteristic similar to that of skeletal muscle on T1 and T2 weighted images and is less intense when compared to the parotid gland secondary to less fatty replacement. The FDG uptake is moderate but higher than that of the parotid gland. The SMG undergoes contrast enhancement by CT and MRI (Kaneda 1996).

SUBLINGUAL GLANDS

The sublingual gland (SLG) is the smallest of the major salivary glands and is the least likely to be involved with pathology. The SLG measures an approximately 3.5 cm in oblique AP, 1.0 cm in

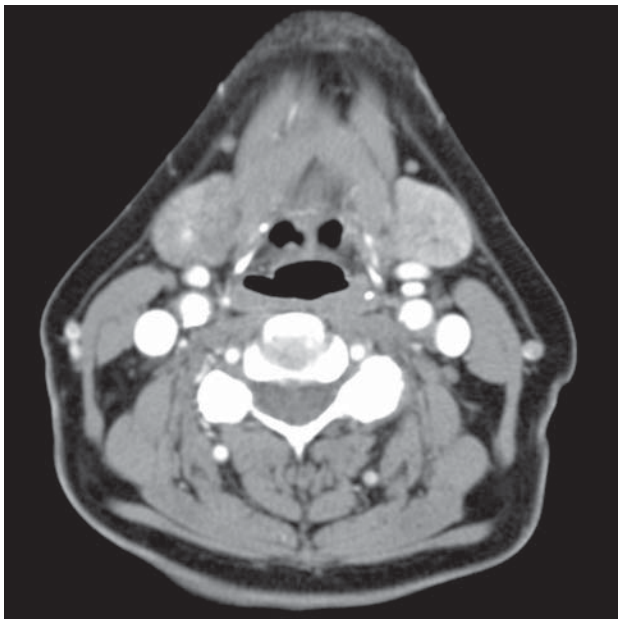


Figure 2.36. Axial CT at the level of the submandibular gland demonstrating density higher than skeletal muscle.

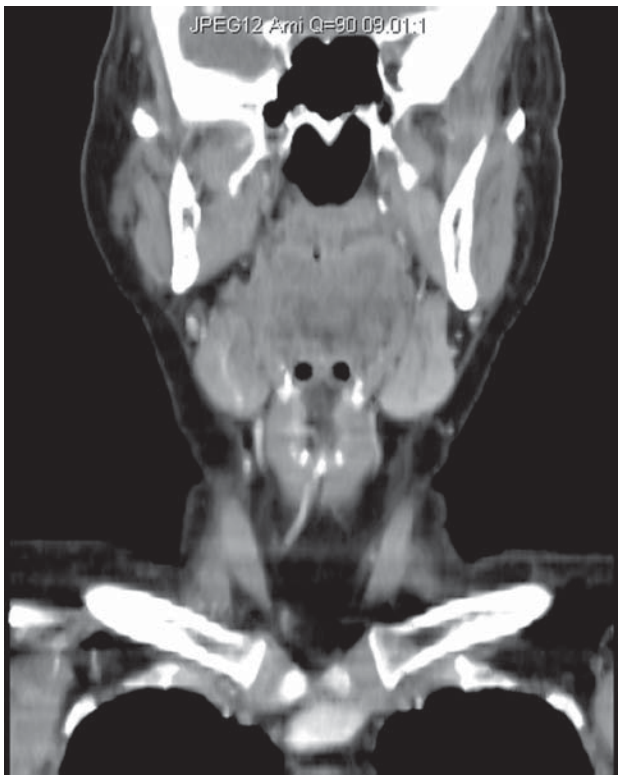


Figure 2.37. Reformatted coronal CT at the level of the submandibular gland demonstrating its relationship to the mylohyoid muscle and floor of mouth.

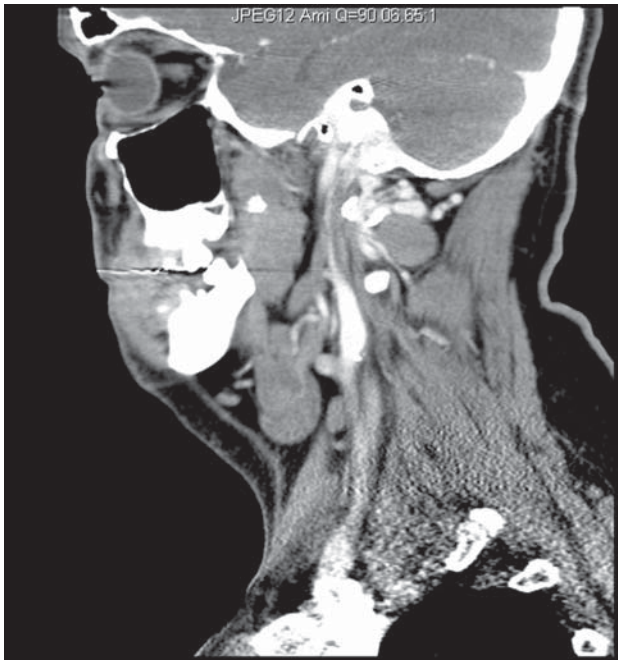


Figure 2.38. Reformatted sagittal CT at the level of the submandibular gland demonstrating its relationship to the floor of mouth. Note the slight notch at the hilum of the gland. Majority of the gland "hangs" below the mylohyoid muscle.

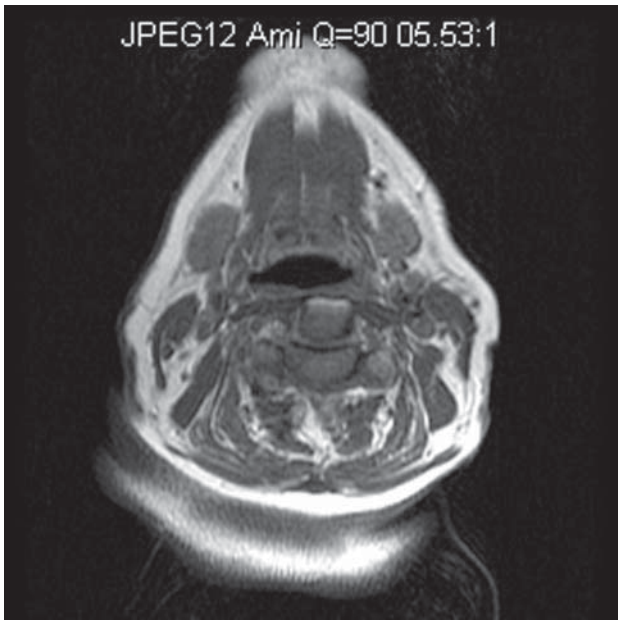


Figure 2.39. Axial T1 MRI of the submandibular gland demonstrating slight hyperintensity to muscle. Note the bright subcutaneous fat.

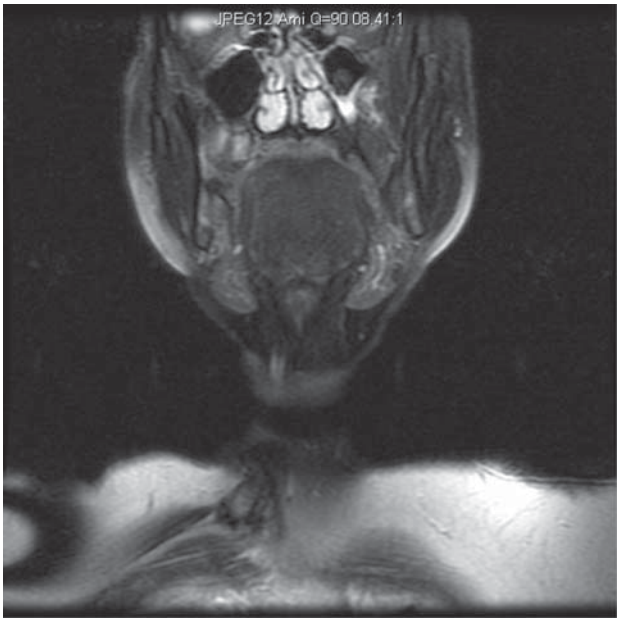


Figure 2.40. Coronal fat saturated T2 MRI of the submandibular gland. Note the slightly incomplete fat suppression and the engorged and edematous mucosa of the nasal cavity and turbinates.

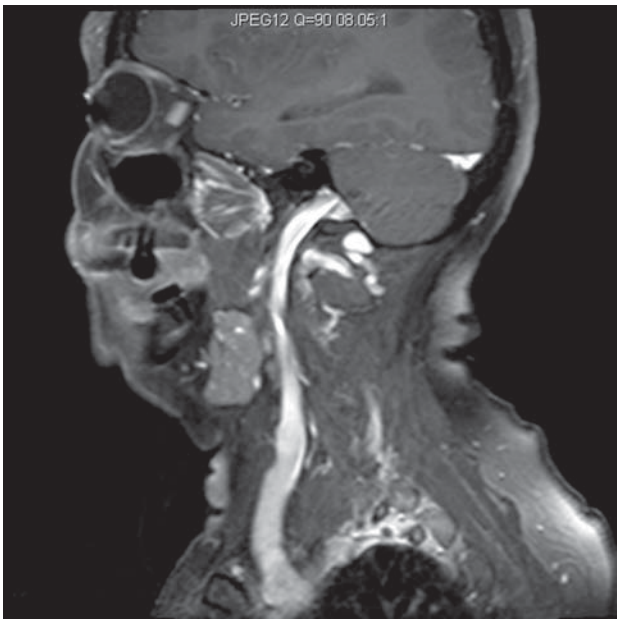
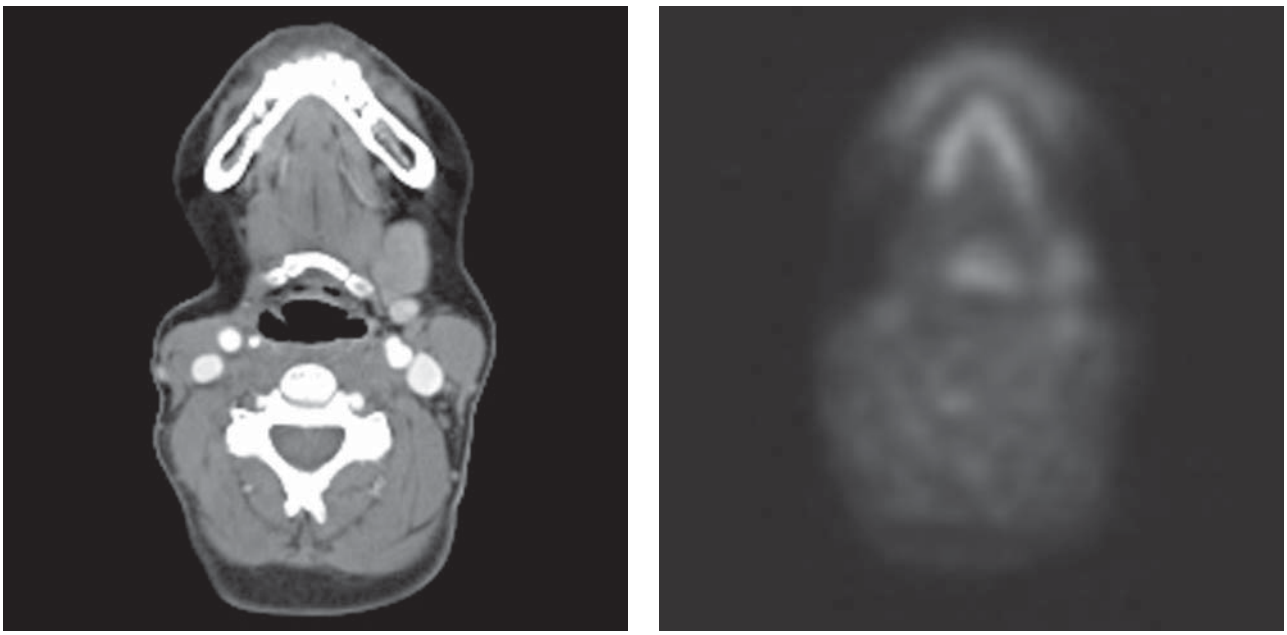


Figure 2.41. Sagittal T1 fat saturated MRI of the submandibular gland demonstrating the well-defined appearance on a fat suppressed background. Note the slight notch at the hilum. Also note the entire internal jugular vein is visualized.



(a) (b)

Figure 2.42. Axial CT (a) and corresponding PET (b) of the submandibular gland demonstrating slight normal uptake. Note the strong asymmetry of uptake on the PET corresponds to the absent submandibular gland on the right confirmed by the CT.

oblique LR, and 1.5 cm in SI dimensions. Anatomically, the SLGs are located in the floor of mouth and lie on the superior surface of the mylohyoid muscle, bordered anteriorly and laterally by the mandible, and medially by the submandibular duct, genioglossus muscle, and geniohyoid muscle. The submandibular gland serves as its posterior border (Figures 2.43–2.45). The sublingual gland communicates with the oral cavity via multiple small ducts (ducts of Rivinus) which open into the floor of mouth adjacent to the sublingual papilla. These small ducts may be fused and form a larger single duct (duct of Bartholin) and empty into the submandibular duct (Beale and Madani 2006).

The SLG can be seen by CT and MRI and is similar in appearance to the SMG, although smaller. (Sumi 1999a) FDG uptake is less well defined since it is small and closely approximated to adjacent skeletal muscle, but the uptake is moderate.

Occasionally accessory salivary tissue is found in the SMS along the anterior aspect (anterior to the normal submandibular gland). This is caused by herniation of sublingual gland through defects in the mylohyoid muscle, called a mylohyoid boutonniere, which typically occurs between the anterior and posterior parts of the mylohyoid muscle. The accessory gland may be accompanied by sublingual branches of the facial artery and vein. Although the accessory tissue may mimic a tumor, this should be readily identified as normal since the accessory tissue has the same characteristics on CT and MRI as normal sublingual or submandibular gland (White, et al. 2001; Hopp, et al. 2004).

MINOR SALIVARY GLANDS

The minor salivary glands are unevenly distributed throughout the upper aerodigestive tract and are submucosal in location. They are more concentrated in the oral mucosa where they inhabit the mucosa of the hard and soft palate, buccal mucosa, floor of mouth, as well as the mucosa of the lips, gingiva, and tongue. They are also found in the pharynx (nasal and oral), sinonasal spaces, larynx, trachea, and bronchi. Functionally, they are either mucinous (predominantly in the palatal mucosa) or mixed seromucinous glands. The serous minor salivary glands are found only on the tongue at the circumvallate papilla. The minor salivary glands do

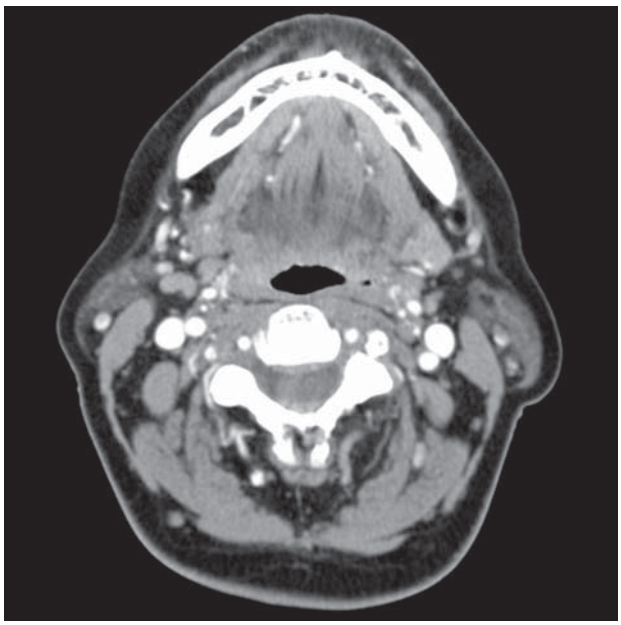
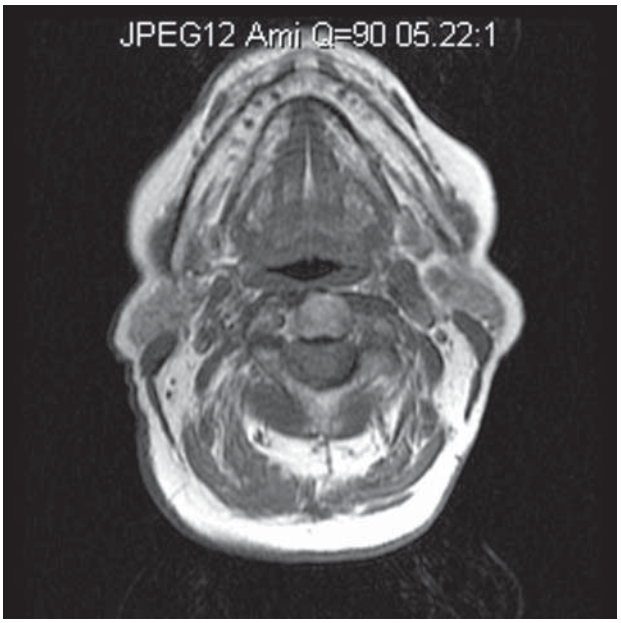


Figure 2.43. Axial CT of the neck at the level of the sublingual gland demonstrating mild normal enhancement along the lateral floor of mouth.

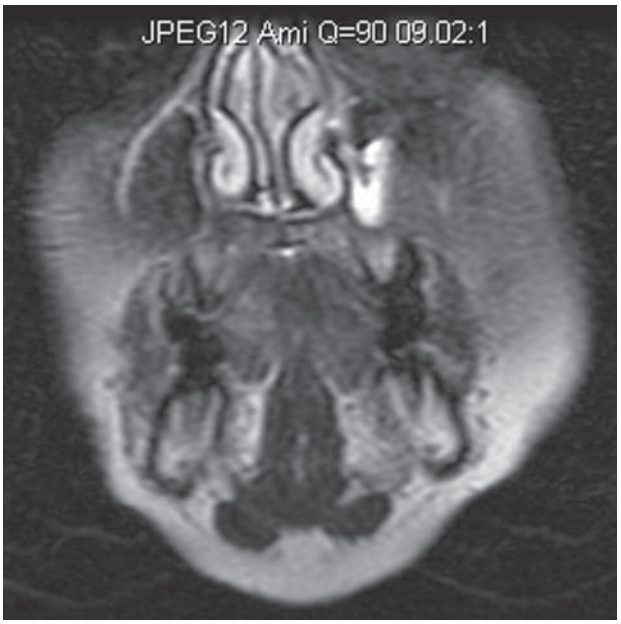
not have large defined ducts but do contain multiple small excretory ducts. MRI of minor salivary glands has been achieved with high-resolution surface coils of the upper and lower lips. Patients with Sjogren disease had smaller gland area relative to normal, best demonstrated in the upper lip (Sumi, et al. 2007).

Pathology of the Salivary Glands

Pathologic states of the salivary glands include tumors (epithelial and non-epithelial), infections and inflammation, autoimmune diseases, vascular lesion, and non-salivary tumors. Of all salivary gland tumors, the vast majority (80%) are found in the parotid gland. The submandubular gland contains approximately 10% with the remainder in the sublingual and minor salivary glands. Of all parotid gland tumors, 80% are benign and 20% malignant. About 50% of submandibular gland tumors are benign and the vast majority of sublingual gland tumors are malignant. About 50% of minor salivary gland tumors are benign. The smaller the gland, the more likely that a mass within it is malignant. The pleomorphic adenoma and papillary cystadenoma



(a)



(b)

Figure 2.44. Axial contrast enhanced T1 MRI of the sublingual gland demonstrating enhancement (a). Note the deep lobe of the submandibular glands seen at the posterior margin of the sublingual glands. Coronal T2 weighted image demonstrating the sublingual gland "cradled" between the mandible laterally, the genioglossus muscle medially, the geniohyoid muscle inferomedially, and the combined mylohyoid and digastric muscles inferiorly (b).

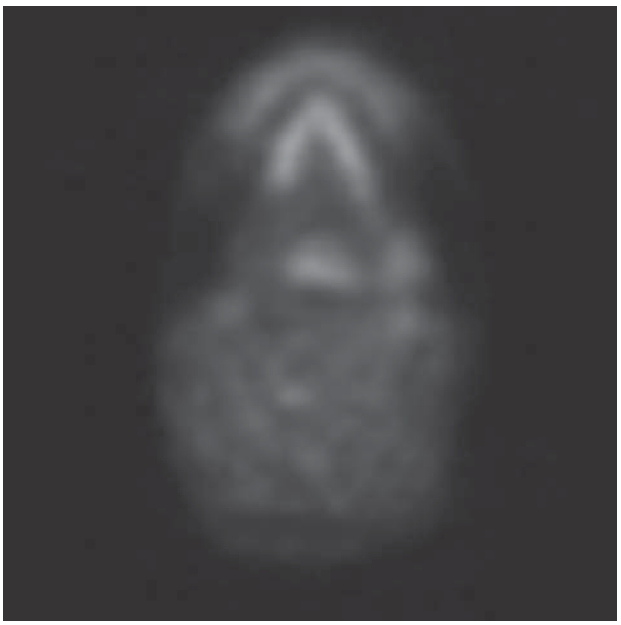


Figure 2.45. Axial PET of the sublingual gland demonstrating the intense uptake seen in the sublingual glands bilaterally medial to the mandible (photopenic linear regions).

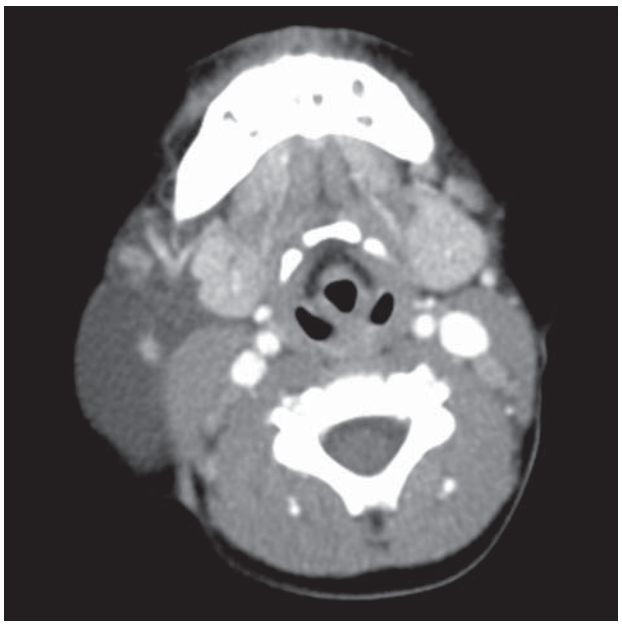


Figure 2.46. Axial contrast enhanced CT of the neck at the level of the submandibular glands demonstrating a low density structure on the right of approximately fluid density (compare to the CSF in the spinal canal), which is intermediate in density relative to the muscles and subcutaneous fat. A large lymphangioma associated with the right submandibular gland was diagnosed.

lymphomatosum (Warthin) account for the vast majority of benign salivary tumors, with the former being the more common at about 80% of benign and latter less common at about 15% of benign masses. Most of the malignant salivary gland tumors are represented by mucoepidermoid and adenoid cystic carcinomas.

Malignancies of the parotid gland may result in metastatic involvement of intraparotid and adjacent level II and III jugular chain lymph nodes. The SMG drains primarily into adjacent level Ib lymph nodes and then into the jugular chain and deep cervical nodes. The SLG drains into both level IA and IB nodes and then subsequently into the jugular chain and deep cervical nodes.

VASCULAR LESIONS

Lymphangioma (Cystic Hygroma)

The cystic hygroma is included in this discussion because of its transpatial location and may mimic other cystic masses. It is typically multilocular and has an epicenter in the posterior triangle, but may be found in the submandibular space and less commonly in the sublingual space. The imaging characteristics are those of cysts and follow fluid density on CT and signal intensity on MRI, although do typically demonstrate internal architecture from septation with varying thickness. CT typically demonstrates isodensity to simple fluid or slight hyperdensity if infected or contains products of hemorrhage (Koeller, et al. 1999; Makariou, et al. 2003) (Figure 2.46). US demonstrates anechoic spaces consistent with simple fluid with septa of variable thickness. Like cystic (and few solid lesions) lesions there is increased through transmission. Infection and hemorrhage cause variable degrees of echogenicity and thicker septations (Koeller, et al. 1999; Makariou, et al. 2003). MRI, however, can be variable on both T1 and T2 sequences based on the fluid characteristics. With simple fluid, T1 and T2 are isointense to simple fluid (CSF) but with infection, or hemorrhage products the increased protein concentration as well as cellular debris and iron from hemoglobin can result in varying degrees of T1 hyperintensity and variable hypo- or hyperintensity on T2 (Figure 2.47). Any of these modalities may demonstrate fluid-fluid or fluid-debris layers. Both CT

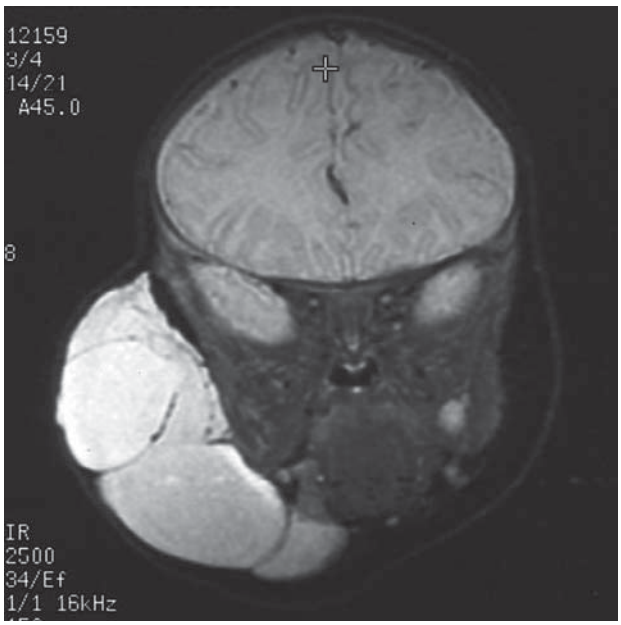


Figure 2.47. Coronal STIR MRI of the face of a different patient with a very large lymphangioma with large septations. Note the lymphangioma fluid is brighter than the CSF and there is fat suppression of the subcutaneous fat.

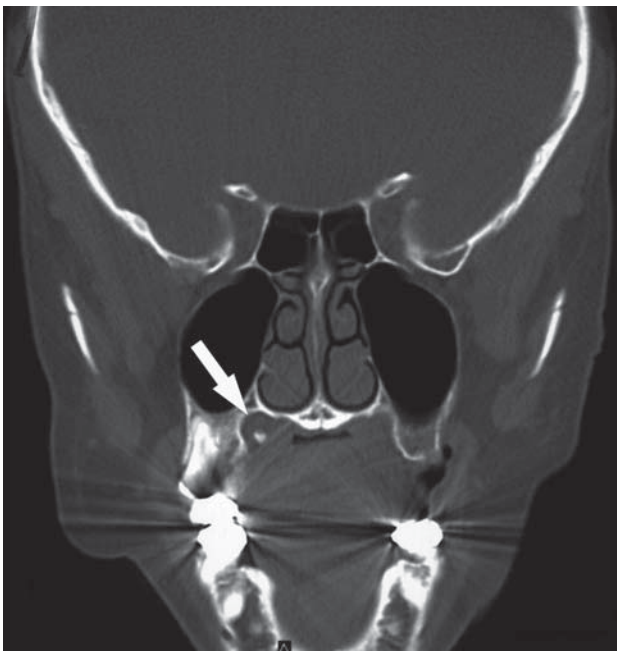


Figure 2.48. Direct coronal CT displayed in bone window demonstrating smooth erosion of the hard palate on the right lateral aspect, along with a dense calcification consistent with a phlebolith (arrow). A hemangioma is presumed based on this CT scan.

and MRI will demonstrate enhancement in the setting of infection (MacDonald, et al. 2003). These lesions are more common in the pediatric age group, although small lesions may persist into adulthood. When found in the submandibular or sublingual space, they may be mistaken for a ranula (especially giant or plunging ranulae) and less likely hemangioma or thyroglossal duct cyst if midline (MacDonald, et al. 2003; Kurabayashi, et al. 2000). Although dermoids are in the differential diagnosis, they are usually identified by their imaging characteristics secondary to their contents of fat and dermal elements. Epidermoid cysts may be more difficult to differentiate from cystic hygromas and ranulae because of similar imaging characteristics (Koeller, et al. 1999). Because the lymphangiomas have a vasculolymphatic origin, they may be associated with venous anomalies and rarely saccular venous aneurysms (Makariou, et al. 2003). Vascular flow signals may be seen with Doppler US. The venous anomalies or aneurysms may be difficult to differentiate from other vascular malformations however their association with typical findings of lymphangiomas may assist in diagnosis.

Hemangioma

Hemangiomas are typically found in the pediatric age group. The majority are of the cavernous type and less likely the capillary type. They are best demonstrated by MRI and show marked enhancement. They are also very bright on T2 MRI. Foci of signal void may be vascular channels or phleboliths (Figures 2.48, 2.49 and 2.50). They are typically slow flow lesions and may not be angiographically evident. US can vary from hypoechoic to heterogenous (Wong 2004).

Other rare vascular lesions within salivary glands, most commonly the parotid gland, include aneurysms, pseudoaneurysms, and arteriovenous fistulae (AVFs). The aneurysms or pseudoaneurysms are most commonly associated with trauma or infection (mycotic). MRI in high flow lesions demonstrates "flow voids" or an absence of signal but slow flow lesions or turbulent flow can demonstrate heterogenous signal mimicking a mass. Contrast enhancement and MRA can help delineate vascular lesions from masses. CT without contrast, however, demonstrates a mass or masses isodense to skeletal muscle or normal

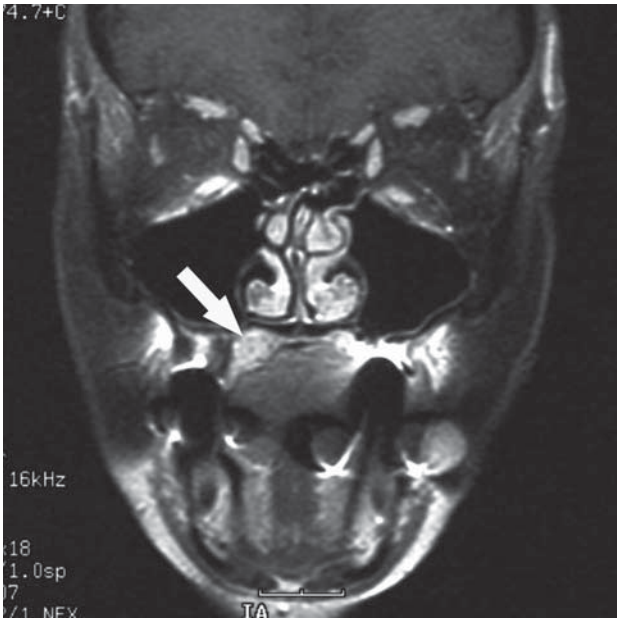


Figure 2.49. Coronal fat suppressed contrast enhanced T1 MRI image corresponding to the same level as Figure 2.48, demonstrating a sharply marginated homogenously enhancing mass (arrow).

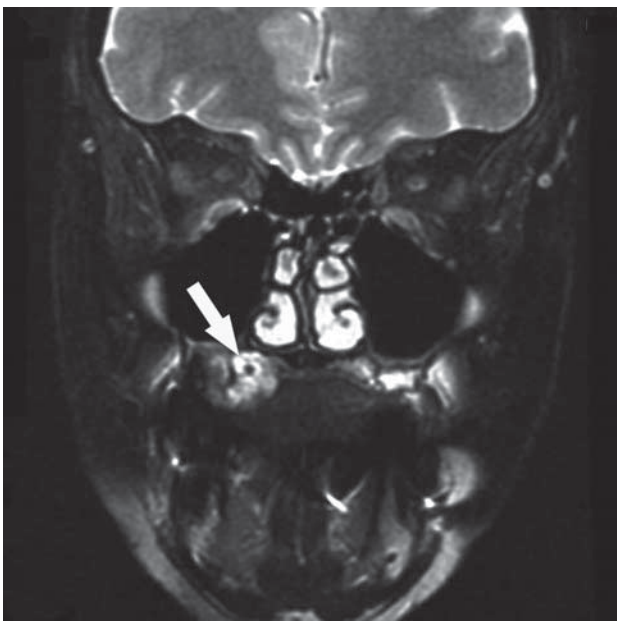


Figure 2.50. Coronal fat saturated T2 MRI image demonstrating a well demarcated hyperintense mass with a focal signal void centrally. A hemangioma containing a phlebolith (arrow) was presumed based on this MRI.

blood vessels. With contrast the often large vascular channels become more obvious, although smaller lesions may still mimic a mass. US (especially Doppler US) can reveal characteristic flow patterns of arterial waveforms in the venous channels for AVFs. US can also delineate aneurysms with their turbulent flow patterns. Angiography is typically reserved for endovascular treatment. CTA or MRA is useful for non-invasive assessment of arterial feeders and venous anatomy in AVFs and in defining aneurysms (Wong 2004).

ACUTE SIALADENITIS

Acute sialadenitis may be bacterial or viral in nature and may be a result of obstruction from a calculus, stricture or mass (see Chapters 3 and 5). Viral parotitis or mumps may be caused by a variety of viruses but most commonly the paromyxovirus is the culprit. The patient presents with an enlarged, tender, and painful gland. Acute suppurative parotitis (sialadenitis) presents in a similar manner as viral parotitis with the additional sign of purulent exudate. Oral bacterial pathogens are the causative agents, with staphylococcal and streptococcal species being the most common. CT scan demonstrates an enlarged gland with ill-defined margins and infiltration of the surrounding fat by edema fluid. The gland, especially the parotid, is increased in density because of the edema fluid, which is of higher density than fat. CT contrast demonstrates heterogenous enhancement and may show an abscess. On a T1 MRI scan the overall gland signal may be decreased slightly from the edema but does enhance heterogeneously with contrast. A T2 MRI scan shows increased signal secondary to edema. Both CT and MRI may demonstrate enhancement and enlargement of the parotid (or sublingual) duct. US shows a slight decrease in echogenicity relative to normal. These patterns are not unique to bacterial or viral infection or inflammation and may be seen with autoimmune diseases such as Sjogren syndrome or a diffusely infiltrating mass. The surrounding subcutaneous fat also demonstrates heterogenous increased density from edema resulting in a "dirty fat" appearance. There is also thickening of fascia and the platysma muscle (Shah 2002; Bialek, et al. 2006; Madani and Beale 2006a).

With acute submandibular sialadenitis the gland becomes enlarged and may be associated

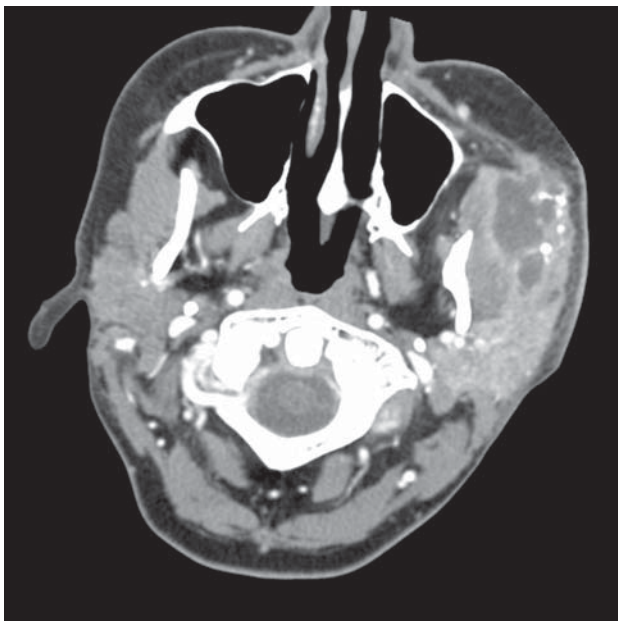


Figure 2.51. Axial CT with contrast at the level of the masseter muscles demonstrating a left accessory parotid gland abscess.

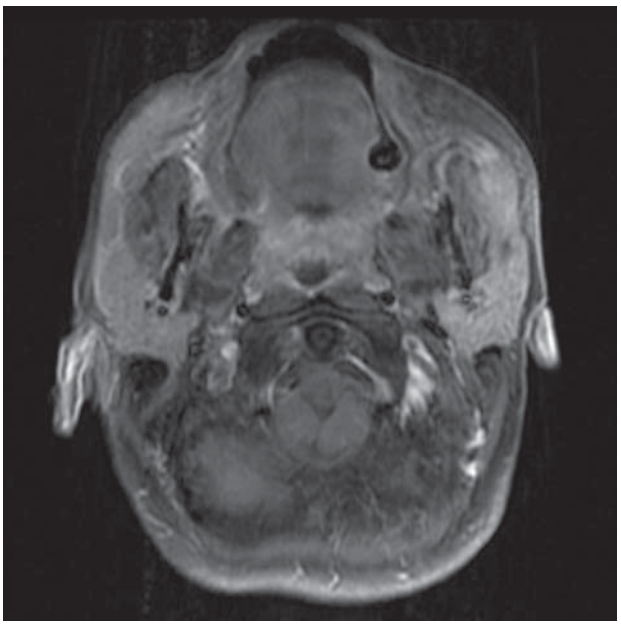


Figure 2.52. Axial contrast enhanced fat saturated T1 MRI demonstrating heterogenous enhancement consistent with abscess of the left accessory parotid gland.

with a dilated duct if a sialolith is present. By CT the calculus may be readily identified but not as easily seen by MRI. There may be varying degrees of cellulitis or frank abscess formation. The inflamed gland undergoes greater contrast enhancement. MRI demonstrates an enlarged heterogenous gland with dilated fluid filled duct and gland, which on T2 images is of a high signal. On ultrasound the acutely inflamed gland demonstrates enlargement with focal hypoechoic foci (Shah, 2002; Bialek, et al. 2006; Madani and Beale 2006a), (Figures 2.51–2.53).

CHRONIC SIALADENITIS

The etiology of chronic inflammatory states of the salivary glands varies by the particular gland in question. Chronic inflammatory changes in the parotid gland tend to be related to autoimmune disease (Sjogren syndrome), recurrent suppurative parotitis or radiation injury. Other etiologies include granulomatous infections such as tuberculosis or sarcoidosis. Chronic inflammation of the submandibular gland, and to a lesser degree the sublingual gland, is more commonly due to obstructive disease, particularly sialolithiasis. In the chronically inflamed state the glands are

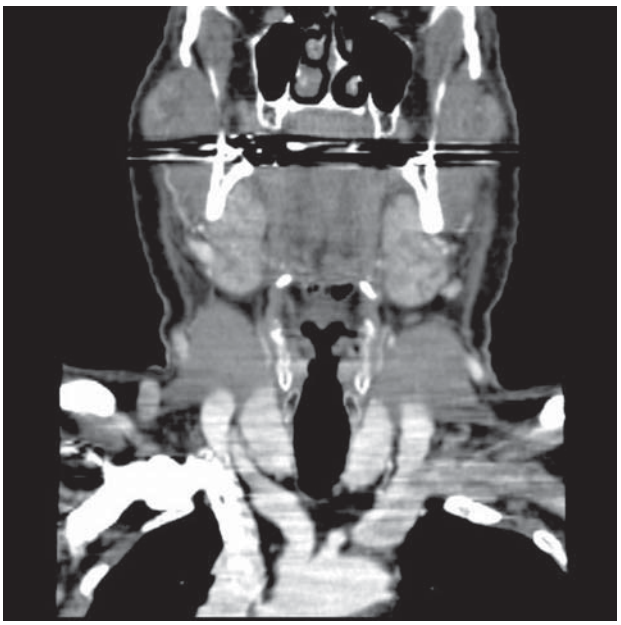


Figure 2.53. Reformatted coronal CT demonstrating enlargement and enhancement of the submandibular glands consistent with viral sialadenitis.

enlarged but over longer periods of time progressively reduced in size, and heterogenous density may be seen on CT with extensive fibrosis and small focal (punctate) calcification. The density on

CT is often increased due to cellular infiltration and edema during acute phases of exacerbation. The surrounding subcutaneous fat may not show signs of edema as is seen with acute sialadenitis. MRI demonstrates similar changes with heterogenous signal on both T1 and T2. The duct or ducts may be dilated, strictured, or both. Both may be visible by contrast CT and MRI (Sumi 1999b; Shah 2002; Bialek, et al. 2006; Madani and Beale 2006a). Chronic sclerosing sialadenitis (aka the Küttner tumor) can mimic a mass of the salivary (most commonly submandibular) glands (Huang, et al. 2002). It presents with a firm, enlarged gland mimicking a tumor. The most common etiology is sialolithiasis (50–83%) but other etiologies include chronic inflammation from autoimmune disease (Sjogren syndrome), congenital ductal dilatation and stasis, and disorders of secretion (Huang, et al. 2002). It is best diagnosed by gland removal and pathologic examination as fine needle aspiration biopsy may be misleading (Huang, et al. 2002). Chronic sialadenitis can also be caused by chronic radiation injury. US studies have demonstrated a difference in imaging characteristics between submandibular sialadenitis caused by acalculus versus calculus disease. The acalculus sialadenitis submandibular gland US demonstrates multiple hypoechoic lesions, mimicking cysts, with diffuse distribution throughout a heterogenous hypoechoic gland. They did not, however, demonstrate increased through transmission, which is typically seen with cysts and some soft tissue tumors. Sialadenitis caused by calculus disease demonstrates hyperechoic glands relative to the adjacent digastric muscle, but some are iso- or hypoechoic relative to the contralateral gland (Ching, et al. 2000).

HIV–LYMPHOEPITHELIAL LESIONS

These lesions are comprised of mixed cystic and solid masses within the parotid (much less in the SMG and SLG). CT shows multiple cystic and solid masses with associated parotid enlargement. IV contrast shows mild peripheral enhancement in the cysts and more heterogenous enhancement in the solid lesions (Figure 2.54). MRI images of the cysts are typical with a low signal on T1 and high on T2. The more solid lesions are of heterogenous soft tissue signal on T1 and increase on T2. Contrast MRI images follow the same pattern as CT

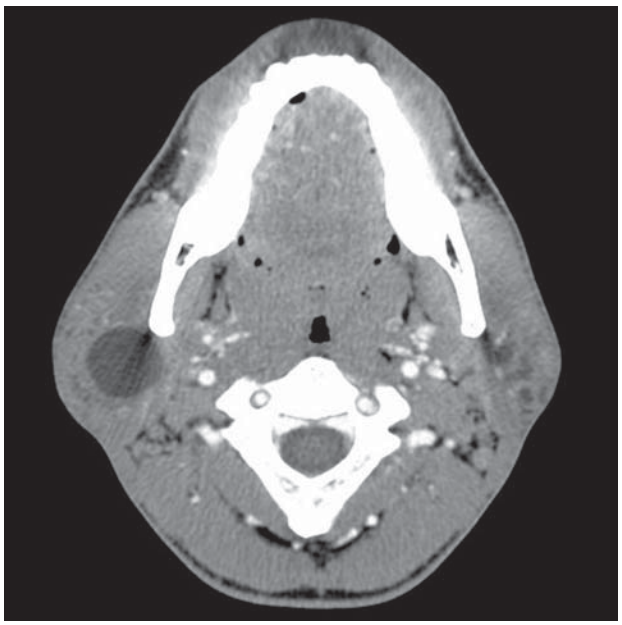


Figure 2.54. Axial CT demonstrating a large cystic lesion in the right parotid gland and multiple small lesions in the left parotid diagnosed as lymphoepithelial cysts.

(Holliday 1998). The US images show heterogenous cystic lesions with internal architecture of septation and vascularity and slightly hypoechoic signal of the solid masses. Mural nodules may be seen in predominantly cystic lesion. Associated cervical lymphadenopathy is commonly seen as well as hypertrophy of tonsillar tissues. Differential diagnosis of these findings includes Sjogren syndrome, lymphoma, sarcoidosis, other granulomatous diseases, metastases, and Warthin tumor (Kirshenbaum and Nadimpalli 1991; Martinoli, et al. 1995; Som, et al. 1995; Shah 2002; Madani and Beale 2006a).

MUCOUS ESCAPE PHENOMENA

The mucous escape phenomenon most commonly results from obstruction in the sublingual gland resulting in a back-up of salivary secretions (see Chapter 4). Ductal obstruction may be caused by calculi, stricture from prior infection or trauma. The chronic dilatation of the duct and accumulation of fluid produces a cystic mass by CT, MRI, and US. The simple ranula remains in the sublingual space and typically presents with a unilocular, well demarcated, and homogenous structure unless complicated by hemorrhage or infection. The

walls may enhance slightly if a ranula remains contained above the mylohyoid muscle. However, it may rupture into the surrounding tissues and extravasate along a path of least resistance and extend inferiorly into the submandibular space or posteriorly into the parapharyngeal space, under which circumstances it is termed a plunging ranula (see Chapter 4). The non-plunging ranula has a dilated ovoid configuration on axial images, but when it herniates into the submandibular space the dilated space shrinks into a tail-like configuration in the sublingual space. The tail sign is pathognomonic for ranulae and may be seen in both simple and plunging types. The ranula can usually be differentiated from a hemangioma and lymphangioma by its lack of internal architecture (unless complicated). The ranulae are typically homogenous internally with well-defined margins, unless infected or hemorrhagic, follow fluid density on CT (isodense to simple fluid) and intensity on MRI (low on T1 and high on T2. Both simple and plunging ranulae have these characteristics. The plunging component may be in the parapharyngeal space if the lesion plunges posterior to the mylohyoid muscle or in the anterior submandibular space if it plunges through the anterior and posterior portions of the mylohyoid muscle or through a defect in the muscle. Involvement of the parapharyngeal space and the submandibular space results in a large cystic mass termed "giant ranula" and may mimic a cystic hygroma (Kurabayashi, et al. 2000; MacDonald, et al. 2003; Makariou, et al. 2003; Cholankeril and Scioscia 1993).

SIALADENOSIS (SIALOSIS)

Sialadenosis, also known as sialosis, is a painless bilateral enlargement of the parotid glands and less commonly the submandibular and sublingual glands (see Chapter 6). It is typically bilateral and without inflammatory changes. No underlying mass is present. It has been associated with malnutrition, alcoholism, medications, and a variety of endocrine abnormalities, the most common of which is diabetes mellitus. In the early stages there is gland enlargement but may progress to fatty replacement and reduction in size by late stages. By CT there is slight increase in density of the entire gland in the early setting but the density decreases in the late stage when the gland is predominantly fatty. On T1 weighted MRI images in the early stage, the gland demonstrates a slight decrease in signal corresponding to the lower fat content and increased cellular component. T2 images show a slight increase in signal (Som, et al. 1996; Bialek, et al. 2006; Madani and Beale 2006a).

SIALOLITHIASIS

Approximately 80–90% of salivary calculi form in the submandibular gland due to the chemistry of the secretions as well as the orientation and size of the duct in the floor of mouth. Eighty percent of submandibular calculi are radio-opaque while approximately 40% of parotid sialoliths are radio-opaque (see Chapter 5). CT without contrast is the imaging modality of choice as it easily depicts the dense calculi (Figures 2.55–2.57). MRI is less sensitive and may miss calculi. Vascular flow voids can be false positives on MRI. MR sialography, as previously discussed, may become more important in the assessment of calculi not readily visible by CT or for evaluation of strictures and is more important as part of therapeutic maneuvers. US can demonstrate stones over two millimeters with distal shadowing (Shah 2002; Bialek, et al. 2006; Madani and Beale 2006a).

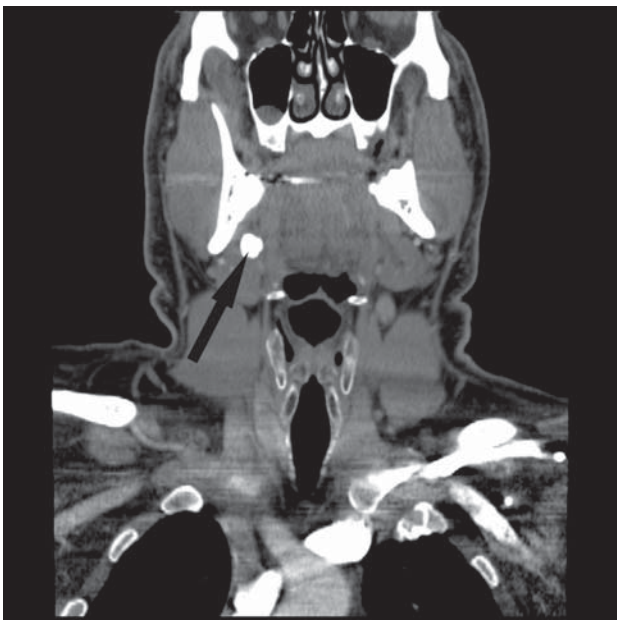


Figure 2.55. Reformatted coronal contrast enhanced CT of the submandibular gland demonstrating a sialolith in the hilum of the right submandibular gland.

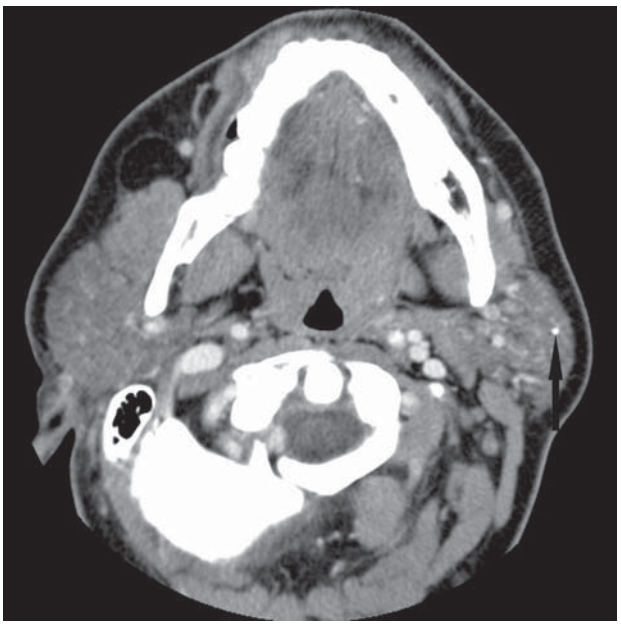


Figure 2.56. Axial contrast enhanced CT of the parotid gland demonstrating a small left parotid sialolith (black arrow).

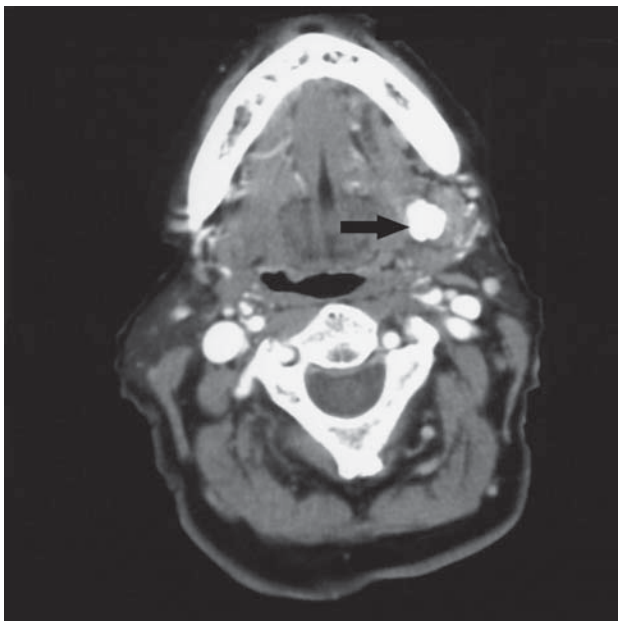


Figure 2.57. Axial contrast enhanced CT at the level of the submandibular glands with a very large left hilum sialolith (black arrow).

SJOGREN SYNDROME

This autoimmune disease affects the salivary glands and lacrimal glands and is called primary Sjogren if no systemic connective tissue disease is present but considered secondary Sjogren if the salivary disease is associated with systemic connective tissue disease (Madani and Beale 2006a). The presentations vary radiographically according to stage. Typically, early in the disease the gland may appear normal on CT and MRI. Early in the course of disease there may be premature fat deposition, which may be demonstrated radiographically and may be correlated with abnormal salivary flow (Izumi 1997). Also, in the early course of disease tiny cysts may form consistent with dilated acinar ducts and either enlarge or coalesce as the disease progresses. These can give a mixed density appearance of the gland with focal areas of increased and decreased density by CT and areas of increased and decreased signal on T1 and T2 MRI giving a "salt and pepper" appearance (Takashima, et al. 1991, 1992). There may be either diffuse glandular swelling from the inflammatory reaction or this may present as a focal area of swelling. The diffuse swelling may mimic viral or bacterial sialadenitis. The focal swelling may mimic a tumor, benign or malignant, including lymphoma. Pseudotumors may be cystic lesions from coalescence or formation of cysts or dilatation of ducts, or they may be solid from lymphocytic infiltrates (Takashima, et al. 1991, 1992). As glandular enlargement and cellular infiltration replaces the fatty elements, the gland appears denser on CT and lower in signal on T1 and T2 MRI. But when chronic inflammatory changes have progressed, tiny or course calcifications may develop. The cysts are variable in size, and the larger cysts may represent confluent small cysts or abscesses. The CT and MRI appearance can be similar to that of lymphoepitheial lesions seen with HIV but does include calcifications. Typically, there is no diffuse cervical lymphadenopathy. The development of cervical adenopathy may indicate development of lymphoma (Takashima, et al. 1992). Solid nodules or masses can also represent underlying lymphoma (non-Hodgkin type) to which these patients are prone (Sugai 2002). The latter stages of the disease produce a smaller and more fibrotic gland (Shah 2002; Bialek, et al. 2006; Madani 2006a).

SARCOIDOSIS

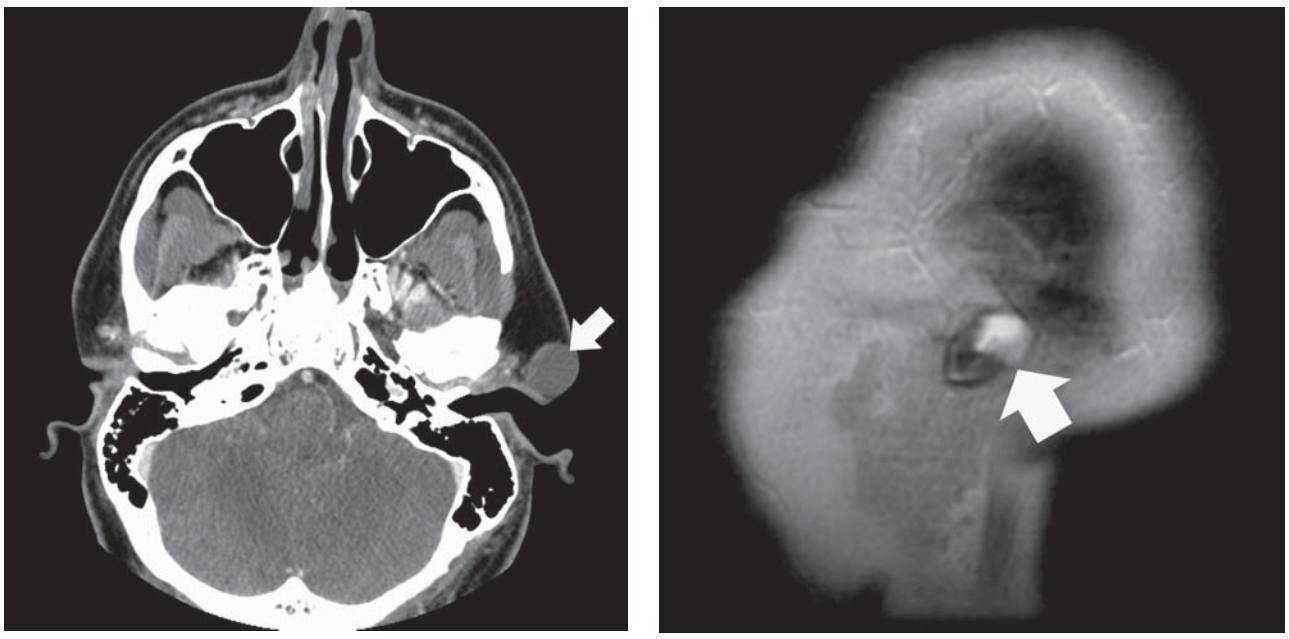
Sarcoidosis is a granulomatous disease of unknown etiology (see Chapter 6). It typically presents with

bilateral parotid enlargement. It may be an asymptomatic enlargement or may mimic a neoplasm with facial nerve palsy. The parotid gland usually demonstrates multiple masses bilaterally, which is a nonspecific finding and can also be seen with lymphoma, tuberculosis (TB), or other granulomatous infections, including cat-scratch disease. There is usually associated cervical lymphadenopathy. The CT characteristics of the masses are slightly hypodense to muscle but hyperdense to the more fatty parotid gland. MRI also demonstrates nonspecific findings. Doppler US demonstrates hypervascularity, which may be seen with any inflammatory process. The classically described "panda sign" seen with uptake of ^{67}Ga-citrate in sarcoidosis is also not pathognomonic for this disease and may be seen with Sjogren syndrome, mycobacterial diseases, and lymphoma.

CONGENITAL ANOMALIES OF THE SALIVARY GLANDS

First Branchial Cleft Cyst

This congenital lesion is in the differential diagnosis of cystic masses in and around the parotid gland along with lymphoepithelial lesions, abscesses, infected or necrotic lymph nodes, cystic hygromas, and Sjogren syndrome. Pathologically, the first branchial cleft cyst is a remnant of the first branchial apparatus. Radiographically, it has typical characteristics of a benign cyst if uncomplicated by infection or hemorrhage, with water density by CT and signal intensity by MRI. It may demonstrate slightly increased signal on T1 and T2 images if the protein concentration is elevated and may be heterogenous if infected or hemorrhagic. Contrast enhancement by either modality is seen if infection is present. Ultrasound demonstrates hypoechoic or anechoic signal if uncomplicated and hyperechoic if infected or hemorrhagic. There is no increase in FDG uptake unless complicated. Anatomically it may be intimately associated with the facial nerve or branches. They are classified as type I (Figure 2.58) if found in the external auditory canal (less common of the two types) and type II if found in the parotid gland or adjacent to the angle of the mandible (Figure 2.59) and may extend into the parapharyngeal space. It may have a fistulous connection to the external auditory canal or the skin surface. Infected or previously infected cysts may mimic a malignant tumor. Although not typically associated with either the parotid or submandibular glands, the second branchial cleft cyst, which



(a) (b)

Figure 2.58. Axial contrast enhanced CT (a) of the head with a cystic mass at the level of the left external auditory canal and sagittal T2 MRI of a different patient (b) consistent with a type 1 branchial cleft cyst.

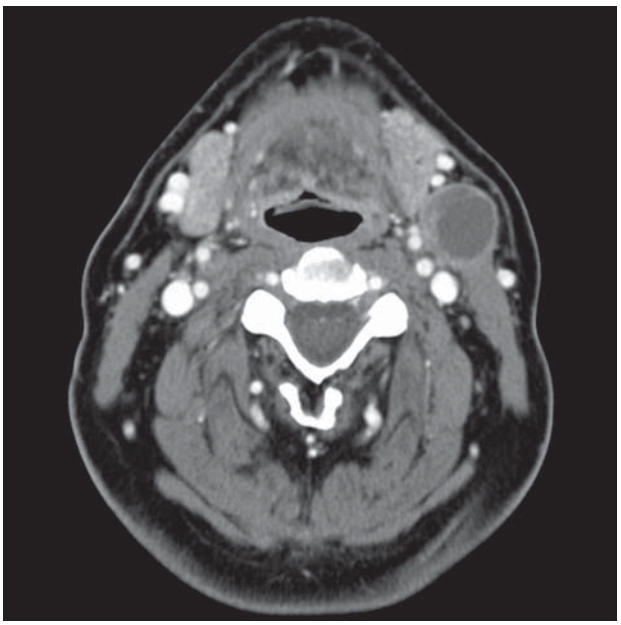


Figure 2.59. Axial contrast enhanced CT of the maxillofacial soft tissues with a cystic mass interposed between the left submandibular gland and sternocleidomastoid muscle, consistent with a type 2 branchial cleft cyst.

is found associated with the sternocleidomastoid muscle and carotid sheath, may extend superiorly to the tail of the parotid or antero-inferiorly to the posterior border of the submandibular gland. It has imaging characteristics similar to the first branchial cleft cyst. Therefore, this must be differentiated from cervical chain lymphadenopathy or exophytic salivary masses. The third and fourth branchial cleft cysts are rare and are not associated with the salivary glands and are found in the posterior triangle and adjacent to the thyroid gland, respectively (Koeller, et al. 1999).

NEOPLASMS – SALIVARY, EPITHELIAL

Benign

Pleomorphic Adenoma

Pleomorphic adenoma (PA) is the most common tumor of the salivary glands and is comprised of epithelial, myoepithelial, and stromal components. It is also the most common benign tumor of the minor salivary glands (Jansisyanont, et al. 2002). Typically, unilateral, lobulated and most commonly sharply marginated, the PA can vary in size and be up to 8 cm in long dimension and involve superficial and deep parotid lobes. The lobulated regions are sometimes referred to as a "cluster of grapes." (Shah 2002) The majority (80%) are located in the superficial lobe of the parotid gland. Small lesions are better circumscribed, have homogenous enhancement, and are of uniform soft tissue density (skeletal muscle). There can be mild to moderate enhancement and is the lesion is relatively homogenous. The larger lesions have heterogenous density, enhancement pattern and low attenuation foci from necrosis and cyst formation as well as calcification. The T1 signal can be as variable as the density on CT but tend to follow muscle or soft tissue signal against a background of fat of the normal parotid gland (Figure 2.60). The masses may be hypointense when small, then become heterogenous with the cystic and calcific changes, and can be hyperintense secondary to areas of hemorrhage and calcifications. The T2 imaging characteristic is that

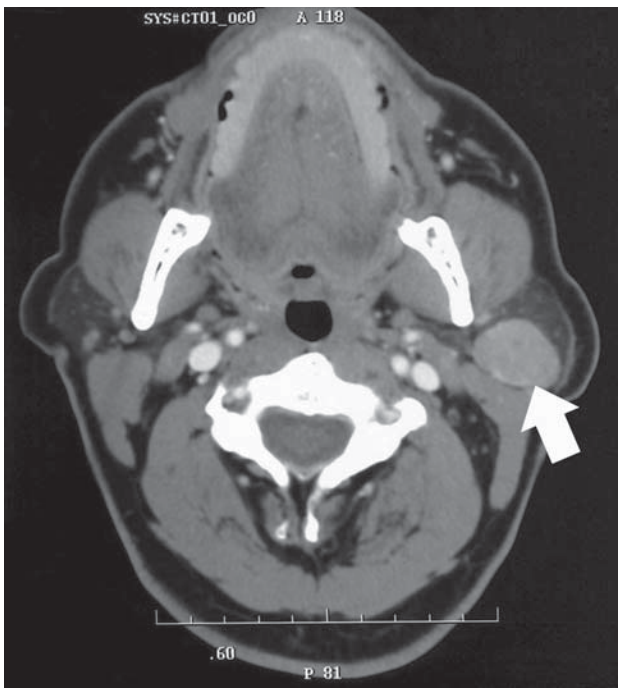


Figure 2.60. Axial contrast enhanced CT of the parotid gland with a heterogenous mass with cystic changes. A pleomorphic adenoma (arrow) was diagnosed at surgery.

of high signal intensity with a thin low signal rim, except when hemorrhage may cause the signal to be heterogenous. The cystic or necrotic regions will tend to be low to intermediate signal on T1 and high on T2. There is mild homogenous enhancement when small and heterogenous when large. US usually demonstrates a homogenous hypoechoic mass but may also have heterogenous hypoechoic features with slight increase in through transmission (Madani and Beale 2006b). These features may be shared with other benign and malignant lesions but only tumors that have both lobulation of the contour and a well-defined pseudocapsule are benign (Ikeda, et al. 1996). The tumors components, cellular or myxoid, determine the MRI signal. The hypercellular regions have lower signal on T2 and STIR sequences as well as reduced ADC values on DWI and earlier TIC (time versus signal intensity curves) peak on dynamic MRI (Motoori, et al. 2004). The high cellular components may be seen with other tumor types including malignant types. The myxoid components, which are more diagnostic of PAs result in high T2 and STIR signal, high ADC values on DWI and progressive enhancement on dynamic MRI (Motoori, et al. 2004). In fact, of the three types of PAs, myxoid, cellular, and classic, the myxoid is the most common and the most common to recur (Moonis, et al. 2007). MRI with T2 and STIR sequences has been shown to be quite sensitive in detecting recurrent PA of the myxoid type by demonstrating the focal, diffuse or multifocal high signal of the myxoid material (Kinoshita and Okitsu 2004; Moonis, et al. 2007). While most PAs demonstrate the benign and non-aggressive features of smooth margins and homogenous enhancement, the more aggressive and invasive features may be seen with carcinoma-ex pleomorphic adenoma, which is seen in areas of previously or concurrently benign PAs. Carcinoma-ex pleomorphic adenomas can result in distance metastatic foci, including the brain (Sheedy, et al. 2006). Heterogenous signal within PAs can indicate a concurrent high grade malignancy, which can be low on T1 and T2 (Kinoshita and Okitsu 2004). FDG PET can be variable but tends to have increased uptake (Figure 2.61). Benignancy cannot be determined by imaging and therefore the differential includes primary parotid malignancy, metastases, and lymphoma, as well as benign Warthin tumors (Shah 2002; Madani and Beale 2006b; Thoeny 2007).

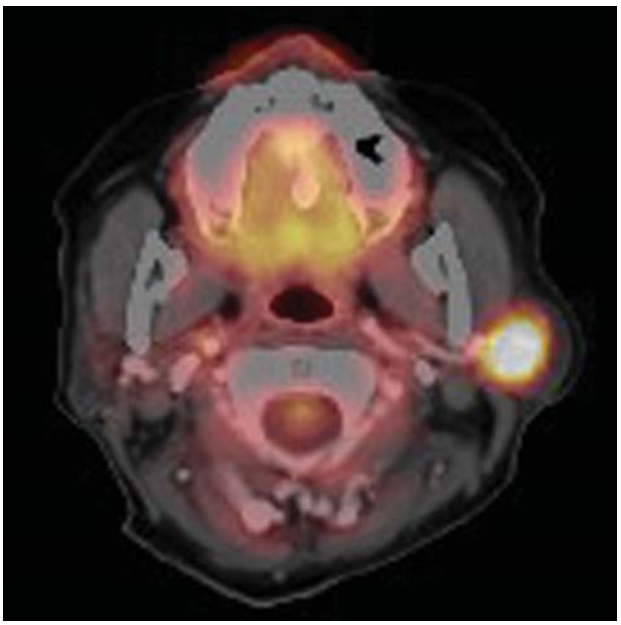


Figure 2.61. Axial PET/CT fused image demonstrating intense FDG uptake in a parotid mass. Pleomorphic adenoma was diagnosed at surgery.

Warthin Tumor

Papillary cystadenoma lymphomatosum, or the Warthin tumor, is the second most common benign lesion of the salivary glands. These tumors are typically well marginated but inhomogenous and found in the parotid tail of the superficial lobe. 15% present as bilateral or multicentric disease (Madani and Beale 2006b). There is by CT a heterogenous density and very mild enhancement (Figure 2.62). They typically have small cysts but do not demonstrate calcifications. Therefore, the differential diagnosis includes lymphoepithelial cysts, primary neoplasms, metastatic disease, and lymphoma. The MRI signal on T1 is generally low but may be heterogenous and T2 is either high signal based on its more cystic features or heterogenous. If the tumor is primarily solid, the imaging characteristics may mimic a PA with relatively homogenous hypoechoic architecture. Contrast with Gd follows CT characteristics. FDG

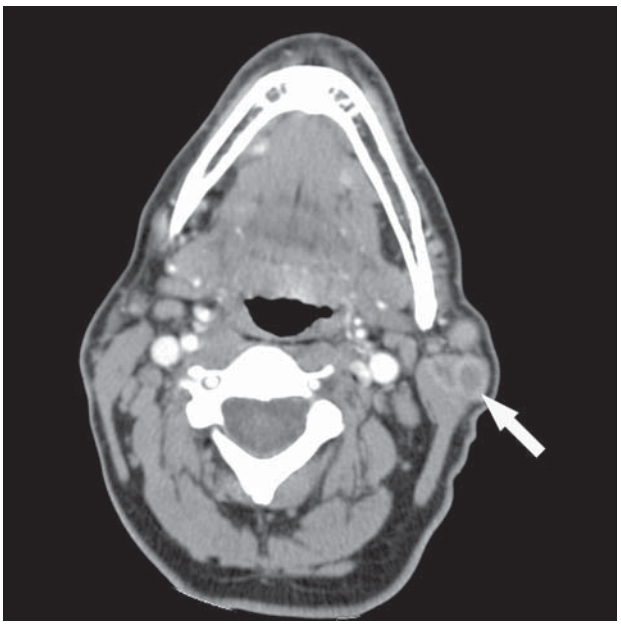


Figure 2.62. Axial contrast enhanced CT of a heterogenous parotid mass at the tail of the gland, with multiplicity and cystic or necrotic changes, diagnosed as a Warthin tumor (arrow).

uptake can be high on PET imaging. Warthin tumors contain oncocytes and are thought to be the mechanism by which they tend to accumulate ^{99}mTc-pertechnetate. The ^{99}mTc-pertechnetate uptake and retention after lemon juice stimulated washout by the normal tissue is a good indicator of the diagnosis of Warthin tumor (Miyake, et al. 2001). This pattern is much less commonly seen by other lesions such as lymphoepithelial cysts, PAs, and oncocytomas. This technique allows visualization of Warthin tumors as small as 9 mm (Miyake, et al. 2001). By its peripheral location and cystic components, it can be mistaken for a necrotic lymph node or second branchial cleft cyst (Ikeda, et al. 2004). The tail of the parotid region can be difficult to differentiate from adjacent cervical lymphadenopathy. However, coronal images can aid in determining the site of origin. If the lesion is medial to the parotid tail it is more likely cervical jugular chain lymphadenopathy and if it is more laterally located, it is more likely an exophytic tumor from the parotid gland (Hamilton, et al. 2003).

Oncocytoma

These relatively rare tumors exist primarily in the parotid gland. Their imaging characteristics are that of PAs, except that they do accumulate ^{99}mTc-pertechnetate. They are also reported to have high 18F-FDG uptake. They are considered benign but may have some invasive features.

Malignant

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma is the most common malignant lesion of the salivary glands. They are also the most common salivary malignancy in the pediatric population. One half occur in the parotid gland and the other half in minor salivary glands (Jansisyanont, et al. 2002; Shah 2002). The imaging characteristics of mucoepidermoid carcinoma are based on histologic grade. The low-grade lesions are sharply marginated and inhomogenous, mimicking PA and Warthin tumor. These well-differentiated lesions can have increased signal on T2 weighted sequences. The low-grade lesions are more commonly cystic (Madani and Beale 2006b). The high-grade, invasive lesions mimic adenoid cystic carcinoma and lymphoma or large heterogenous PAs or carcinoma ex. pleomorphic adenoma. They tend to have a lower signal of T2. Contrast enhanced studies demonstrate enhancement in the more solid components (Sigal 1992; Lowe 2001; Bialek, et al. 2006; Madani and Beale 2006b) (Figures 2.63–2.65). Therefore, standard imaging cannot exclude a malignant neoplasm. Defining the tumor's extent is critical. Contrast MRI, especially in the coronal or sagittal plane, is essential to identify perineural invasion into the skull base.

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma has similar characteristics as mucoepidermoid carcinoma in that their imaging findings are based on histologic grade. Adenoid cystic carcinoma is the most common malignant neoplasm of the submandibular and sublingual glands as well as the minor salivary glands in the palate. These tumors have a high rate of local recurrence, higher rate of distance metastases as opposed to nodal disease, and may recur after a long latency period (Madani and Beale 2006b). MRI is the imaging method of choice demonstrating high signal due to increased water content. Contrast enhanced fat saturated images are critical to evaluate for perineural spread which

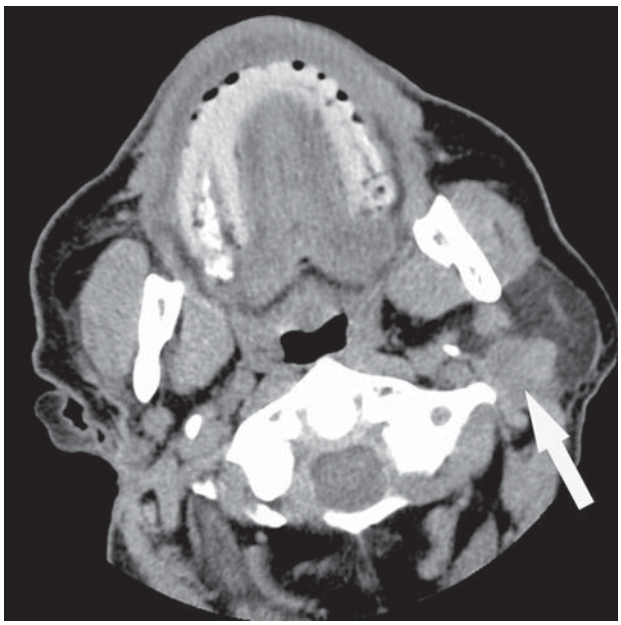


Figure 2.63. Axial contrast enhanced CT demonstrating an ill-defined mass diagnosed as a mucoepidermoid carcinoma (arrow).

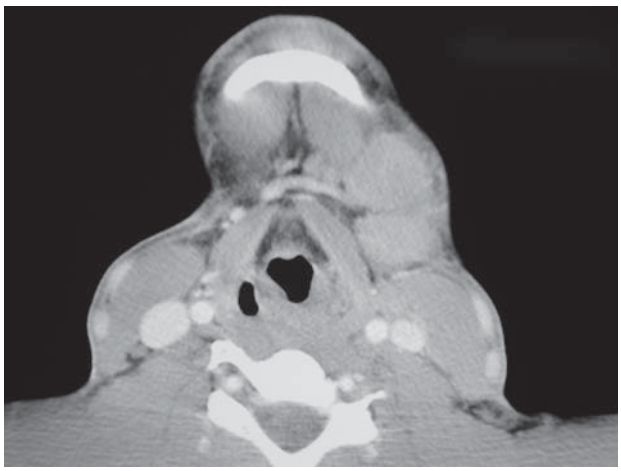


Figure 2.64. Axial contrast enhanced CT demonstrating large bulky cervical lymphadenopathy with ill-defined borders, diagnosed as a mucoepidermoid carcinoma.

is demonstrated by nerve thickening and enhancement (Shah 2002; Madani and Beale 2006b). CT can be helpful to evaluate bone destruction or foraminal widening. It is important to define the tumor's extent and identify perineural invasion into the skull base (Figures 2.66–2.70).

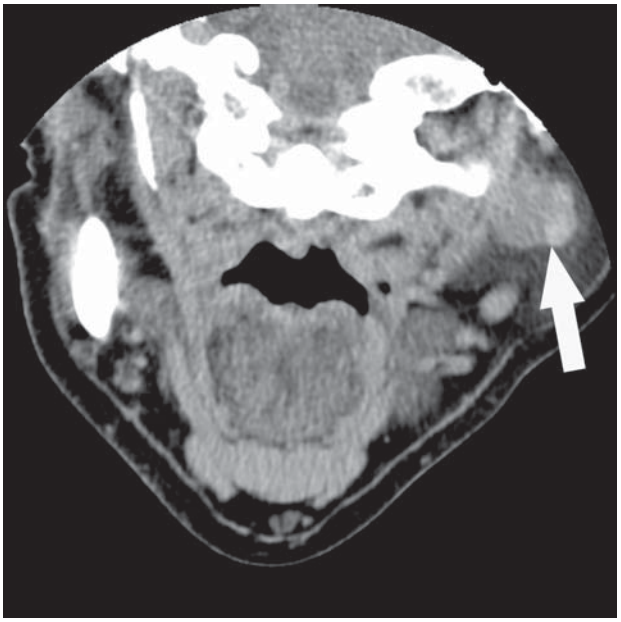


Figure 2.65. Reformatted coronal contrast enhanced CT demonstrating an ill-defined heterogenous density mass diagnosed as a mucoepidermoid carcinoma (arrow).

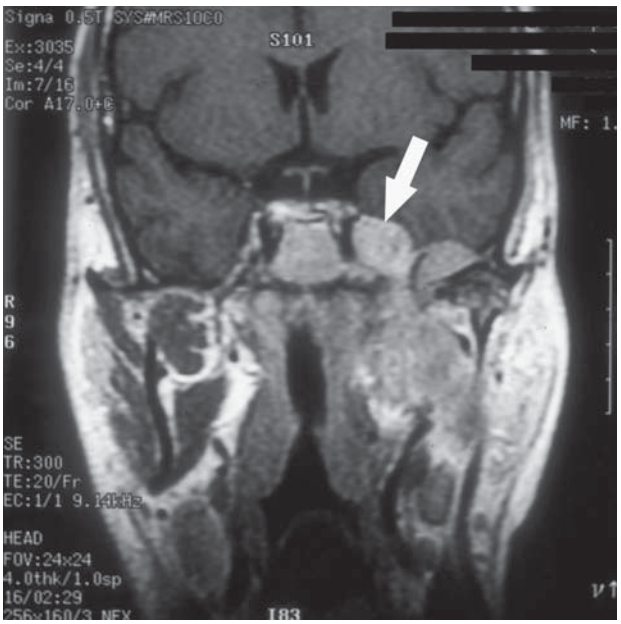


Figure 2.66. Coronal contrast enhanced MRI of the skull base demonstrating a mass extending through the skull base via the left foramen ovale (arrow), diagnosed as an adenoid cystic carcinoma originating from a minor salivary gland of the pharyngeal mucosa.

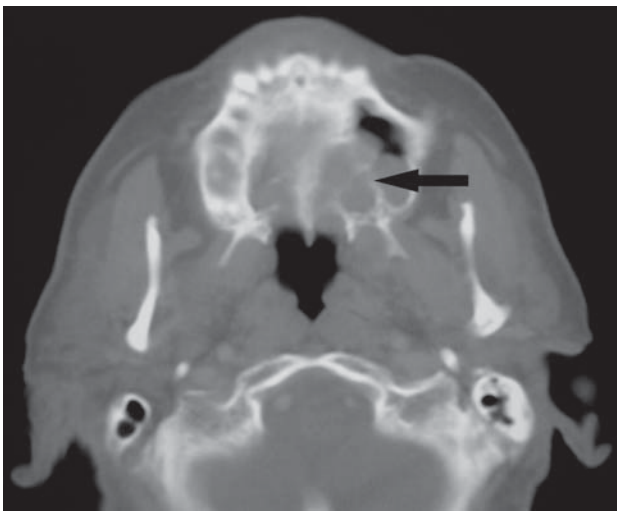


Figure 2.67. Axial CT in bone window demonstrating a mass eroding through the left side of the hard palate and extending into the maxillary sinus (arrow) diagnosed as adenoid cystic carcinoma.

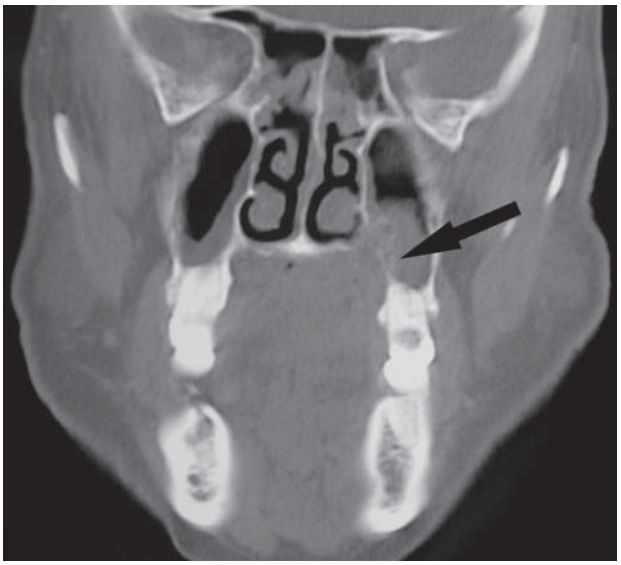


Figure 2.68. Coronal CT corresponding to the case illustrated in Figure 2.67 with a mass eroding the hard palate and extending into the left maxillary sinus (arrow).

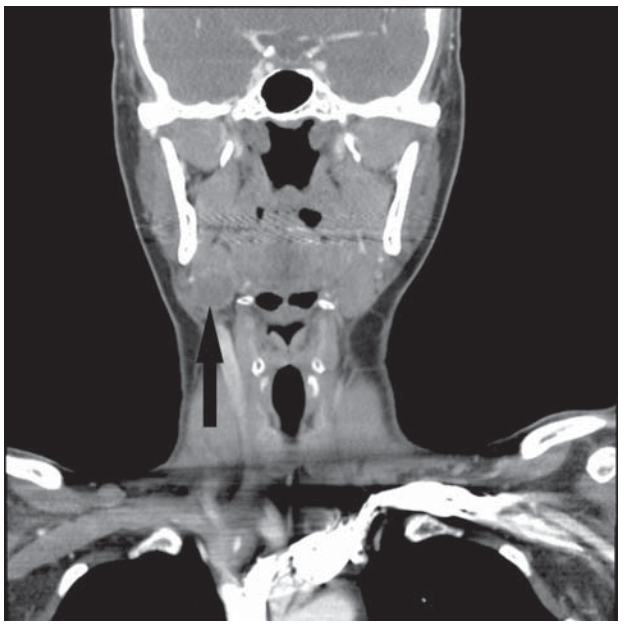


Figure 2.69. Reformatted contrast enhanced coronal CT with a mass in the right submandibular gland (arrow) diagnosed as an adenoid cystic carcinoma.

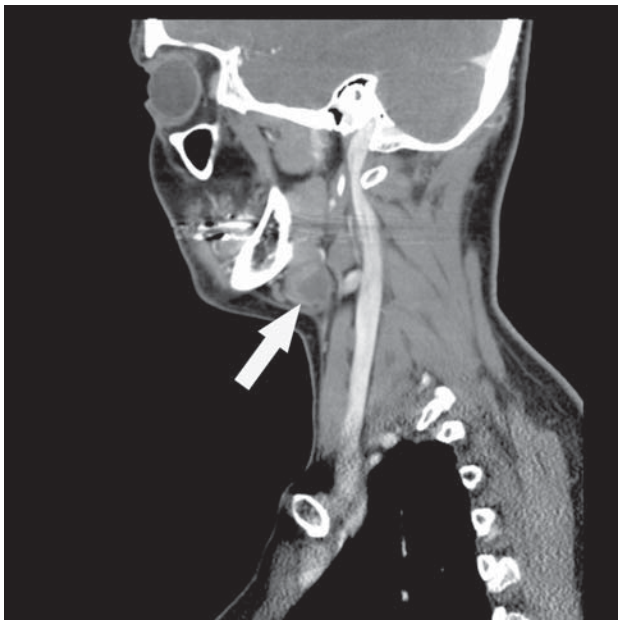


Figure 2.70. Reformatted sagittal contrast enhanced CT corresponding to the case illustrated in Figure 2.64.

NEOPLASMS – NON-SALIVARY

Benign

Lipoma

In the cervical soft tissues, lipomas are slightly more commonly seen within the parotid gland rather than peri-parotid. Lipomas of the salivary glands are uncommon (Shah 2002). The CT and MRI characteristics are those of subcutaneous fat with CT density very low (−100 H) and hyperintense on both T1 and T2. Lipomas tend to be

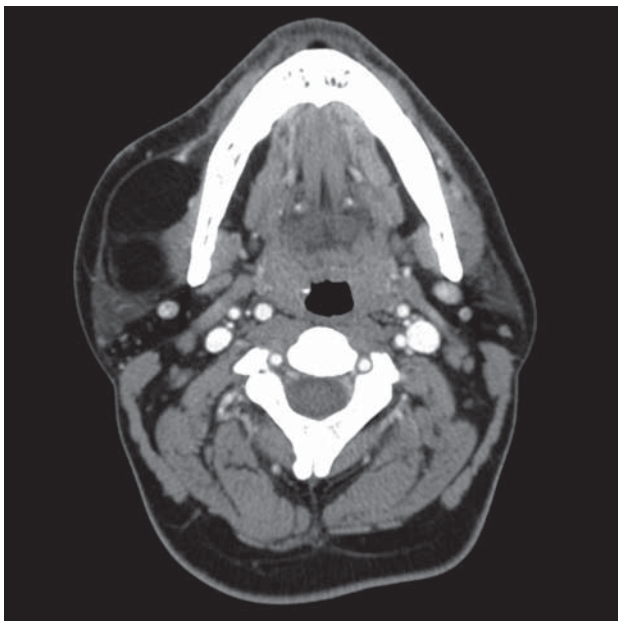


Figure 2.71. Axial contrasted enhanced CT of the head with a fat density mass at the level of the parotid gland and extending to the submandibular gland, diagnosed as a lipoma.

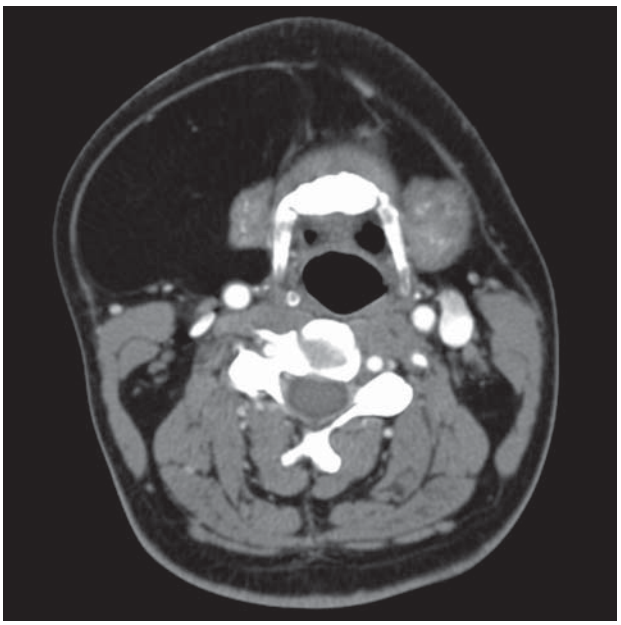


Figure 2.72. Axial contrast enhanced CT through the submandibular gland with fat density mass partially surrounding the gland. A lipoma was diagnosed.

echogenic on US. They may be uniform on imaging but may have areas of fibrosis. The heterogenous density from fibrosis, or hemorrhage, carries the additional differential diagnosis of liposarcoma or other neoplasms (Som, et al. 1995) (Figures 2.71 and 2.72).

Neurogenic Tumors

Neurogenic tumors are uncommon in the salivary glands but when encountered are most commonly found in the parotid gland. The majority of the facial nerve schwannomas are on the intratemporal facial nerve with only 9% extra-temporal and in the parotid gland (Shimizu, et al. 2005) (Figures 2.73–2.75). These are difficult to preoperatively diagnose as they do not typically present with facial nerve dysfunction. As seen in other parts of the body they tend to be sharply marginated and have an ovoid shape along the axis of the involved nerve, such as the facial nerve. The CT density is that of soft tissue but post-contrast both enhance (schwannoma slightly greater than neurofibroma). Both are seen as low signal on T1 and high on T2. The MRI enhancement pattern follows that of CT. They may demonstrate a target sign appearance with peripheral hyperintensity relative to a central hypointensity (Martin, et al. 1992; Suh, et al. 1992; Shimizu, et al. 2005). However, this sign is not pathognomonic and may be seen in schwannomas or neurofibromas. Increased uptake is seen on FDG PET in both diseases. The neurofibroma may be associated with Von Recklinghausen disease. Although, the vast majority of schwannomas and neurofibromas are benign, they are reported as demonstrating increased uptake (hypermetabolism of glucose) of ^{18}F-FDG on PET imaging (Hsu, et al. 2003). Although the calculated standard uptake value (SUV) can be helpful in differentiating benign from malignant lesions, there is a significant overlap (Ioannidis and Lau 2002). There is difficulty in separating low grade malignant lesions from benign lesions (Ioannidis and Lau 2002) (Figures 2.76 and 2.77). Plexiform neurofibromas are also slow-growing and rare. They present with multiple cord-like masses and are also far more common in the parotid gland relative to other salivary glands. By CT and MRI they are sometimes described as a "branching" pattern or "bag of worms" secondary to the multiple lesions growing along nerve branches. They have CT and MRI signal characteristics similar to the neurofibromas and schwannomas including the "target sign" (Lin and Martel 2001; Aribandi et al. 2006). The target sign may also be seen by US as a hypoechoic

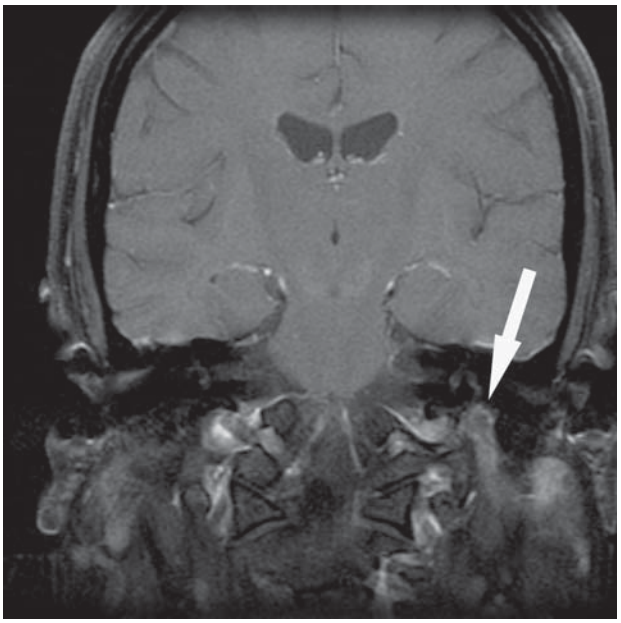


Figure 2.73. Coronal T1 contrast enhanced MRI demonstrating a mass in the left parotid gland with smooth margins. The mass extends superiorly into the skull base at the stylomastoid foramen (arrow). A benign schwannoma was diagnosed.

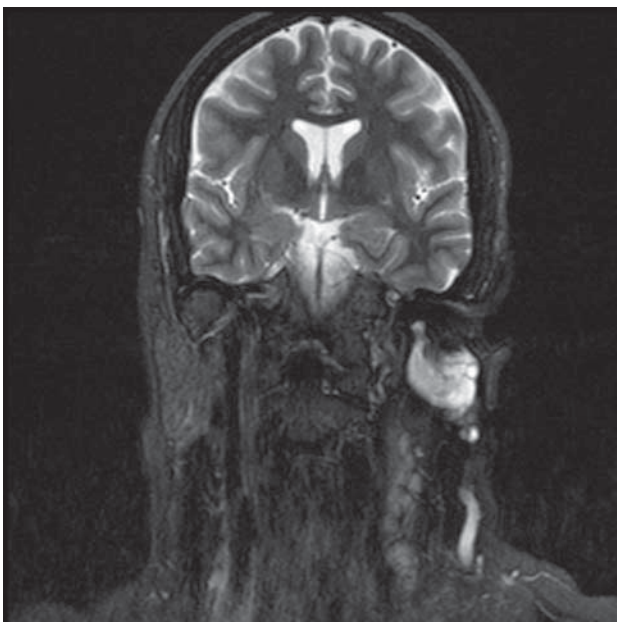


Figure 2.74. Coronal T2 MRI corresponding to the case illustrated in Figure 2.73.

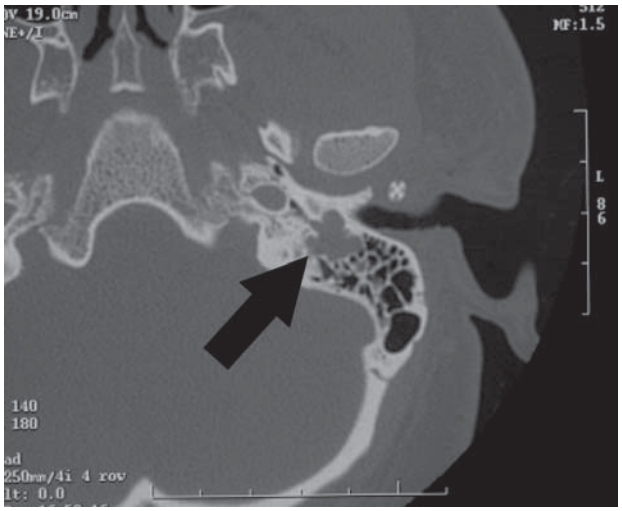


Figure 2.75. Axial CT at the skull base displayed in bone window showing dilatation of the stylomastoid foramen with soft tissue mass (arrow). A benign schwannoma was diagnosed.

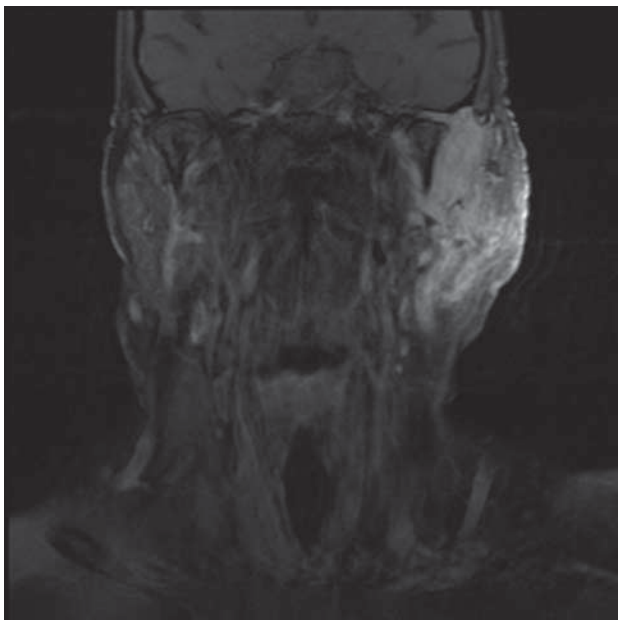


Figure 2.76. Coronal T1 contrast image showing a very ill defined mass with heterogenous enhancement in the parotid gland with skull base extension via the stylomastoid foramen. A malignant schwannoma was diagnosed.

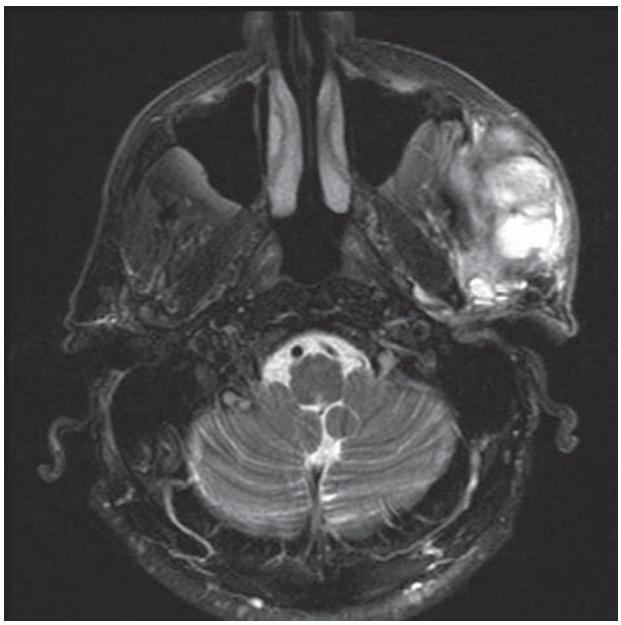


Figure 2.77. Axial T2 MRI image corresponding to the case illustrated in Figure 2.76.

periphery surrounding a subtle slightly hyperechoic center. There may also be slight increased through-transmission (Lin and Martel 2001).

Malignant

Lymphoma

Both primary and secondary lymphomas of the salivary glands are rare. Primary lymphoma of the salivary glands is the mucosa associated lymphoid tissue subtype (MALT). MALT lymphomas constitute about 5% of non-Hodgkin lymphomas (Jhanvar and Straus 2006). These lymphomas are seen in the gastrointestinal tract and are associated with chronic inflammatory or autoimmune diseases. The salivary glands do not typically contain MALT but may in the setting of chronic inflammation (Ando, et al. 2005). The MALT lymphomas found in the gastrointestinal tract are not typically associated with Sjogren syndrome. The MALT lymphoma, a low-grade B-cell type, tends to be a slow growing neoplasm. Metastases tend to be to other mucosal sites, a demonstration of tissue tropism. The MALT lymphomas are amenable to radiotherapy but can relapse in the contralateral gland, demonstrating tropism for the glandular tissue (MacManus, et al. 2007). In Sjogren syndrome, there is an approximately 40-fold increased incidence of developing lymphoma compared to age controlled populations. Of the various subtypes of lymphoma that are seen associated with Sjogren syndrome, (follicular, diffuse large B-cell, large cell, and immunoblastic), the MALT subtype is the most common at around 50% (Tonami, et al. 2002, 2005). The parotid gland is the most commonly affected (80%). Less commonly the submandibular, and rarely, the sublingual gland may be involved. Clinically, it may present with a focal mass or diffuse unilateral or bilateral glandular swelling.

^{67}Ga-citrate scintigraphy had been the standard imaging modality used to assess staging and post-therapy follow-up for lymphomas (Hodgkin and non-Hodgkin) for many decades. PET/CT with FDG is quickly becoming the standard for staging and follow-up for many lymphoma subtypes (Jhanvar and Straus 2006).

The imaging findings in salivary lymphomas, however, are not specific. CT may demonstrate focal or diffuse low to intermediate density mass with cystic areas and calcifications. MRI shows the soft tissue areas to be isointense to skeletal muscle on T1 images and hypointense relative to fat on T2 images along with diffuse enhancement post-contrast (Tonami, et al. 2002). Although, there may be cystic changes demonstrated by CT, MRI, or US, they are thought to be dilated ducts as a result of compression of terminal ducts (Ando, et al. 2005). The US characteristics of MALT lymphoma may demonstrate multifocal hypoechoic intraparotid nodules and cysts (which may be dilated ducts) and calcification as well. Large B-cell intraparotid lymphoma has been described as a hypoechoic, homogenous, well-marginated mass exhibiting increased through-transmission (a characteristic of cysts) and hypervascularity (Eichhorn, et al. 2002). Although there are reports of hypermetabolism in MALT lymphomas, PET imaging findings are also not conclusive (MacManus, et al. 2007). Uptake in the tumor, and a background of chronic inflammatory changes of chronic sialadenitis, may result in variably elevated uptake of FDG.

Secondary lymphomas (Hodgkin and non-Hodgkin) are also quite rare, with the histology most commonly encountered being of the large cell type. There is typically extra-glandular lymphadenopathy associated. The imaging features are also non-specific, although there is usually no associated chronic sialadenitis (Figures 2.78–2.80).

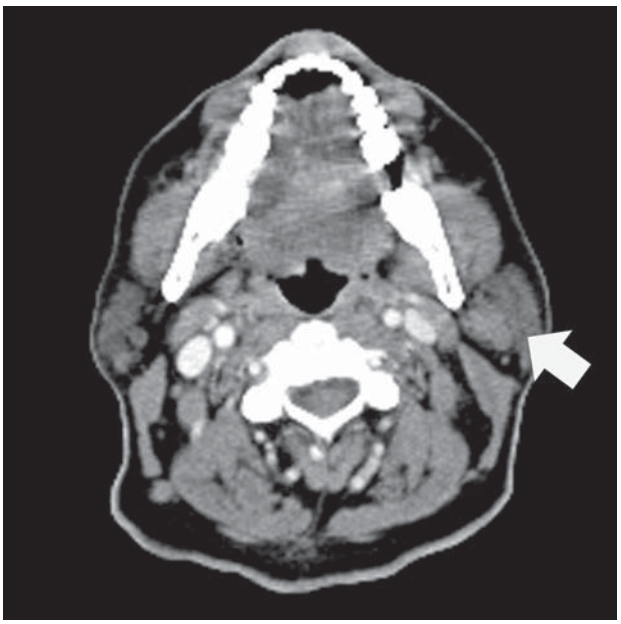


Figure 2.78. Axial CT scan with contrast at the level of the parotid tail demonstrating an ill-defined heterogeneously enhancing mass adjacent to or exophytic from the parotid tail medially (arrow). Lymphoma in cervical lymphadenopathy was diagnosed at surgery.

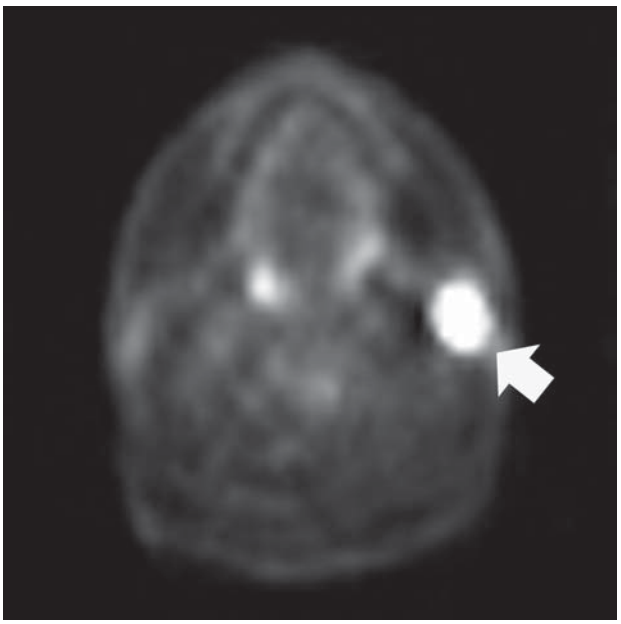


Figure 2.79. Axial PET scan image corresponding to the case in Figure 2.78. A large mass of the left parotid gland (arrow) is noted.

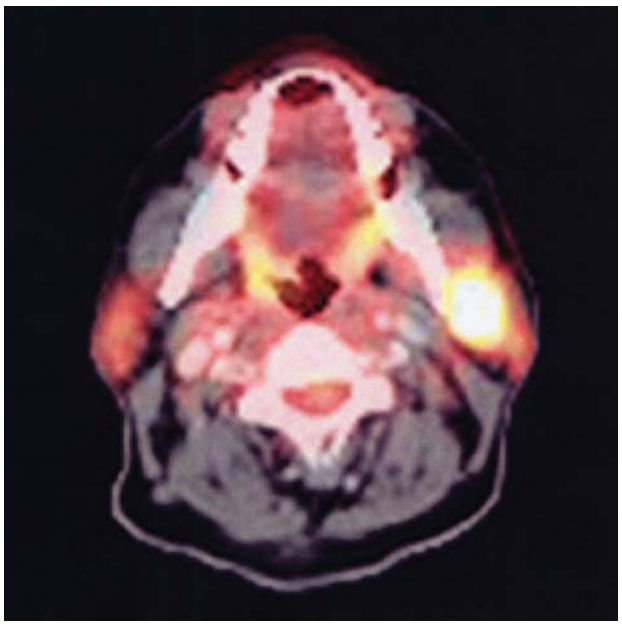


Figure 2.80. Fused axial PET/CT image corresponding to the case illustrated in Figure 2.78.

Metastases

Intraglandular lymph nodes are found in the parotid gland due to its early encapsulation during development. The sublingual gland and submandibular gland do not contain lymph nodes. The parotid and periparotid lymph nodes are the first order nodal site for lesions that affect the scalp, skin of the upper face, and external ear (Ollila, et al. 1999). The most common malignancy to metastasize to the parotid nodes is squamous cell carcinoma followed by melanoma and less commonly Merkel cell carcinoma (Bron, et al. 2003) (Figures 2.81–2.83).

The imaging findings are not specific. CT in early stages demonstrates the nodes to have sharp margins, round or ovoid architecture, but without a fatty hilum. Late in the disease, the mass can mimic infected or inflammatory nodes with heterogenous borders, enhancement, and necrosis. Late in the disease with extranodal spread, the margins blur and are ill defined. Contrast enhancement is heterogenous. Similar findings are seen on MRI with T1 showing low to intermediate signal pre-contrast and homogenous to heterogenous signal post-contrast depending on intranodal versus extranodal disease. PET with FDG is abnormal in

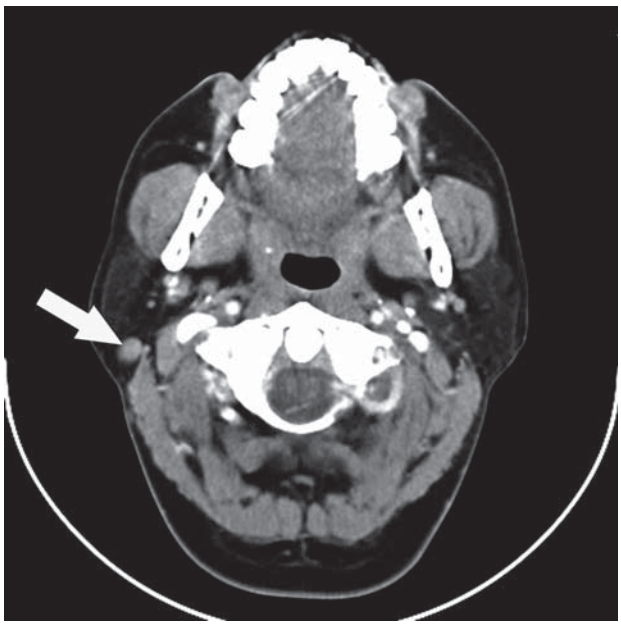


Figure 2.81. Axial CT of a mass (arrow) in the right parotid gland with homogenous enhancement. The patient had a history of right facial melanoma. Metastatic melanoma was diagnosed at surgery.

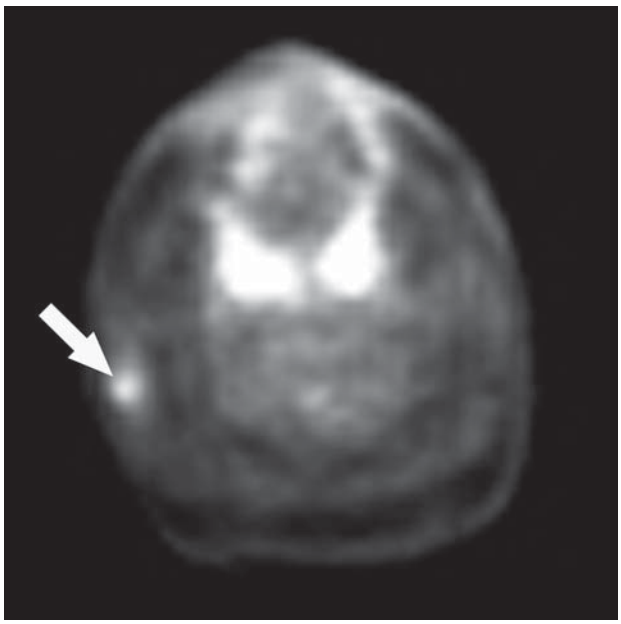


Figure 2.82. Axial PET scan corresponding to the case illustrated in Figure 2.81. The mass in the right parotid gland (arrow) is hypermetabolic. Also note two foci of intense uptake corresponding to inflammatory changes in the tonsils.

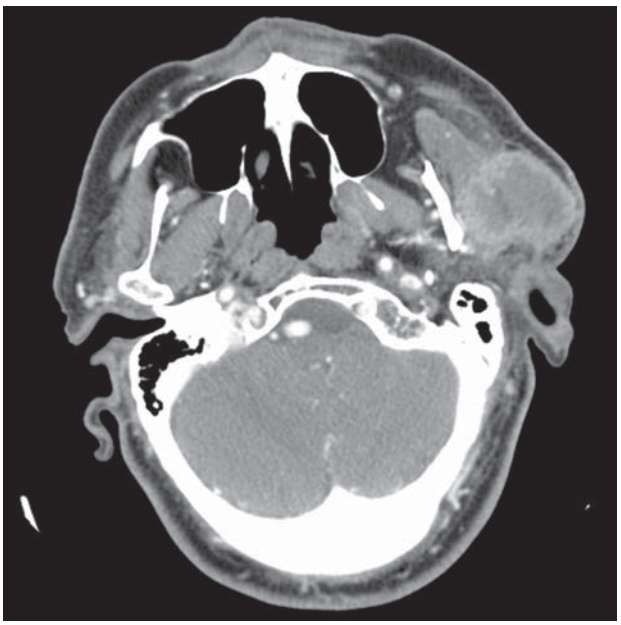


Figure 2.83. Axial contrast enhanced CT scan through the parotid glands demonstrating a large mass of heterogenous density and enhancement partially exophytic from the gland. Metastatic squamous cell carcinoma from the scalp was diagnosed.

infectious, inflammatory, and neoplastic etiology and is not typically helpful within the parotid, but can aid in localizing the site of the primary lesion as well as other sites of metastases. This can be significant since the incidence of clinically occult neck disease is high in skin cancer metastatic to the parotid gland (Bron, et al. 2003). Local failure was highest with metastatic squamous cell carcinoma and distant metastases were higher in melanoma (Bron, et al. 2003).

With either squamous cell carcinoma or melanoma there is also a concern for perineural invasion and spread. Tumors commonly known to have perineural spread in addition to the previously mentioned include adenoid cystic carcinoma, lymphoma, and schwannoma. The desmoplastic subtype of melanoma has a predilection for neurotropism (Chang, et al. 2004). The perineural spread along the facial nerve in the parotid gland and into the skull base at the stylomastoid foramen must be carefully assessed. MRI with contrast is the best means of evaluating the skull base foramina for perineural invasion. Gadolinium enhanced T1

MRI in the coronal plane provides optimal view of the skull base (Chang, et al. 2004). There may also be symptomatic facial nerve involvement with lymphadenopathy from severe infectious adenopathy, or inflammatory diseases such as sarcoidosis.

Summary

- Among the choices for imaging of the salivary glands, CT with IV contrast is the most commonly performed procedure. Coronal and sagittal reformatted images provide excellent evaluation soft tissues in orthogonal planes. The latest generation MDCT scanners provide rapid image acquisition reducing motion artifact and produce exquisite multiplanar reformatted images.
- US has the inherent limitation of being operator dependent, poor at assessing deep lobe of the parotid gland and surveying the neck for lymphadenopathy, as well as time consuming relative to the latest generation MDCT scanners.
- MRI should not be used as a primary imaging modality but reserved for special situations, such as assessment of the skull base for perineural spread of tumors. Although MRI provides similar information to CT, it is more susceptible to motion and has longer image acquisition time but has better soft tissue delineation.
- PET/CT can also be utilized for initial diagnosis and staging but excels in localizing recurrent disease in post-surgical or radiation fields. Its limitations are specificity, as inflammatory diseases and some benign lesions can mimic malignant neoplasms, and malignant lesions such as adenoid cystic carcinoma may not demonstrate significantly increased uptake of FDG. A major benefit is its ability to perform combined anatomic and functional evaluation of the head and neck as well as upper and lower torso in the same setting. The serial acquisitions are fused in order to provide a direct anatomic correlate to a focus of radiotracer uptake.
- Newer MRI techniques such as dynamic contrast enhancement, MR sialography, diffusion weighted imaging, MR spectroscopy, and MR microscopy are challenging PET/CT in functional evaluation of salivary gland disease and delineation of benign versus malignant tumors. However, PET/CT with novel tracers may repel this challenge.
- Conventional radionuclide scintigraphic imaging has largely been displaced. However, Conventional scintigraphy with ^{99}mTc-pertechnetate can be useful for the evaluation of masses suspected to be a Warthin tumor or oncocytoma, which accumulate the tracer and retain it after washout of the normal gland with acid stimulants. The advent of SPECT/CT in a similar manner to PET/CT may breathe new life into older scintigraphic exams.
- Radiology continues to provide a very significant contribution to clinicians and surgeons in the diagnosis, staging, and post-therapy follow-up of disease. Because of the complex anatomy of the head and neck, imaging is even more important in evaluation of diseases affecting this region. The anatomic and functional imaging, as well as the direct fusion of data from these methods, has had a beneficial effect on disease treatment and outcome. A close working relationship is important between radiologists and clinicians and surgeons in order to achieve these goals.

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Chapter 3

Infections of the Salivary Glands

Outline

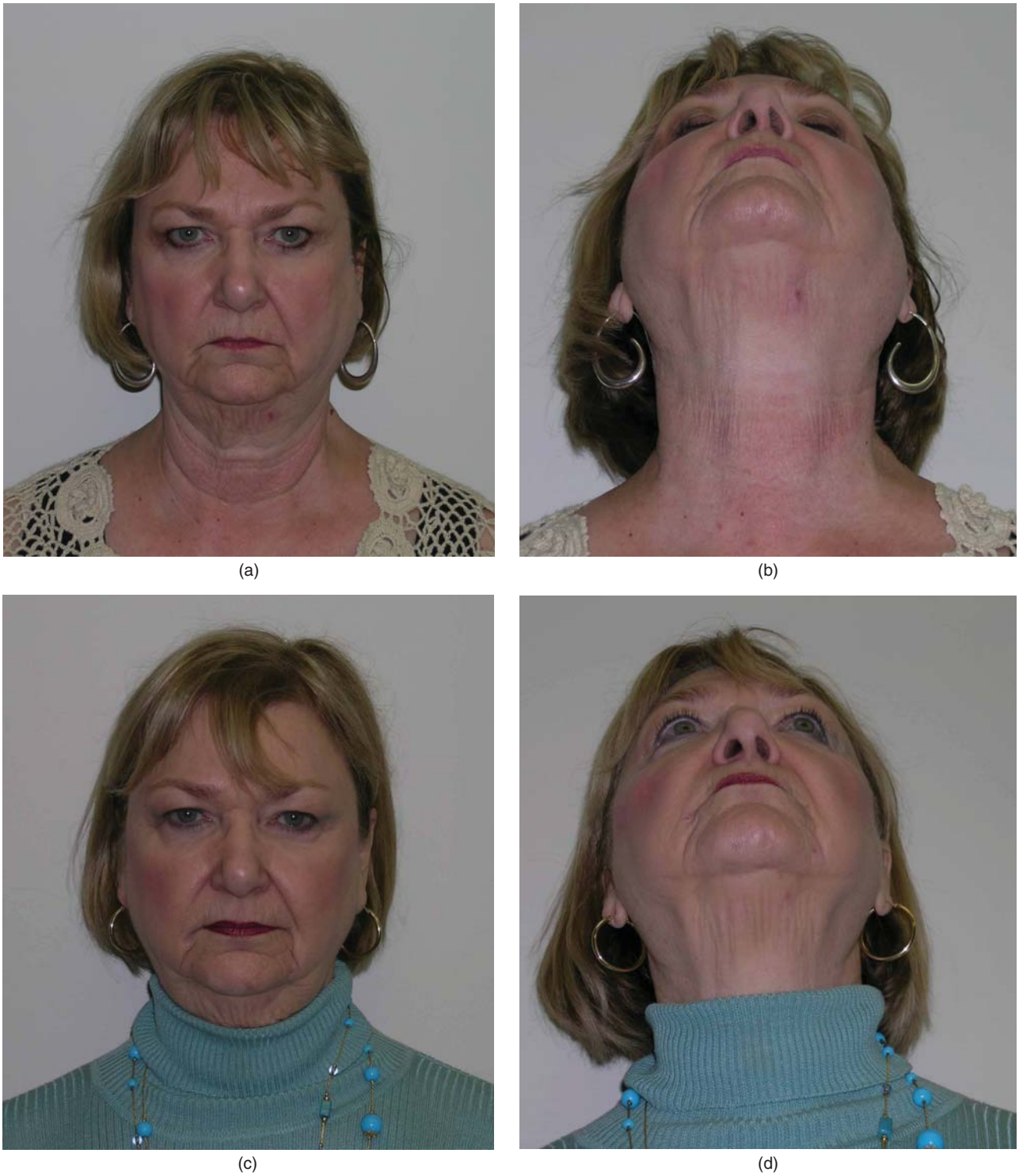
Introduction

Most non-neoplastic swellings of the major salivary glands represent acute or chronic infections of these glands. Sialadenitis, a generic term to describe infection of the salivary glands, has a diverse range of signs and symptoms and predisposing factors. Although any of the major and minor salivary glands can become infected, these conditions most commonly occur in the parotid (Figure 3.1) and submandibular glands (Figure 3.2), with minor salivary gland and sublingual gland infections being very rare. From an etiologic standpoint, these infections may be related to underlying bacterial, viral, fungal, mycobacterial, parasitic, or immunologically mediated infections (Miloro and Goldberg 2002). The most common of these diagnoses include acute bacterial parotitis and acute submandibular sialadenitis (see Table 3.1). A number of risk factors may predispose patients to sialadenitis. The classic risk factor is the hospitalized patient who recently underwent surgery with general anesthesia. Dehydration may exacerbate this condition. In general terms, stasis and decreased salivary flow predispose patients to sialadenitis, although medications and comorbid diagnoses may also contribute to this problem (see Table 3.2).

General Considerations

Evaluation and treatment of the patient with sialadenitis begins with a thorough history and physical examination. The setting in which the evaluation occurs, for example a hospital ward versus an office, may provide information as to the underlying cause of the infection. Many cases of acute bacterial parotitis (ABP) occur in elderly debilitated patients, some of whom are admitted to the hospital, who demonstrate inadequate fluid intake with resultant dehydration. This notwithstanding, many cases of acute bacterial parotitis and submandibular sialadenitis are evaluated initially in an outpatient setting. The formal history taking begins by obtaining the chief complaint. Sialadenitis commonly begins as swelling of the salivary gland with pain due to stretching of that gland's innervated capsule. Patients may or may not describe the perception of pus associated with

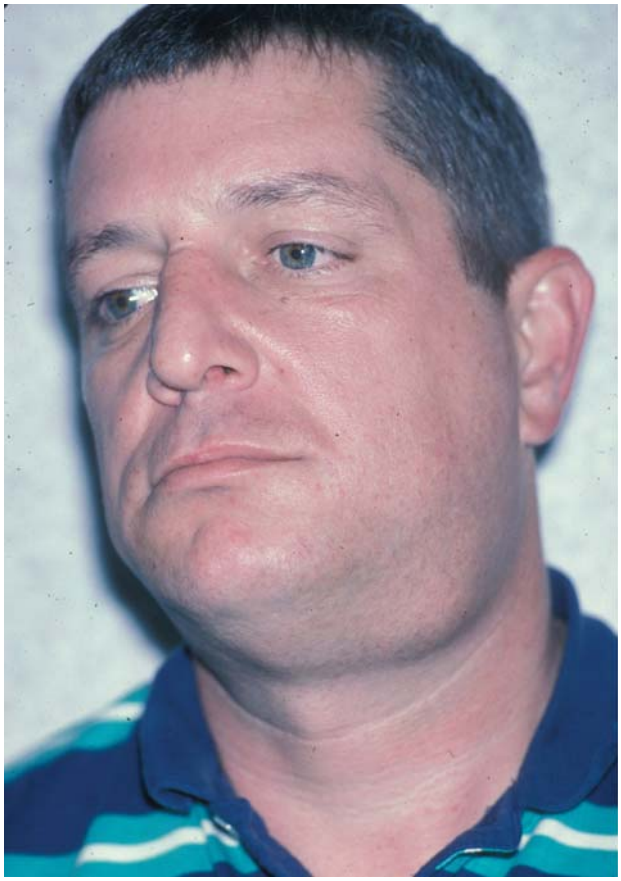
Salivary Gland Pathology: Diagnosis and Management, Second Edition. Edited by Eric R. Carlson and Robert A. Ord.



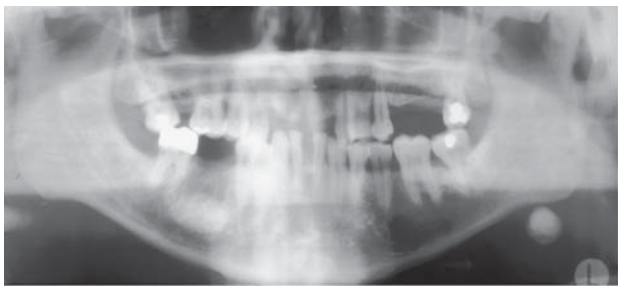
(a) (b)

(c) (d)

Figure 3.1. A 55-year-old woman (a and b) with a one week history of pain and swelling in the left parotid gland. No pus was present at the Stensen duct. The diagnosis was community acquired acute bacterial parotitis (APB). Conservative measures were instituted including the use of oral antibiotics, warm compresses to the left face, sialogogues, and digital massage. Two weeks later, she was asymptomatic, and physical examination revealed resolution of her swelling (c and d).



(a)



(b)

Figure 3.2. A 45-year-old man (a) with a 6-month history of left submandibular pain and swelling. A clinical diagnosis of chronic submandibular sialadenitis was made. A screening panoramic radiograph is obtained in a similar patient that revealed the presence of a large sialolith in the gland (b). As such, the obstruction of salivary outflow by the sialolith was responsible for the chronic sialadenitis. This case underscores the importance of obtaining a screening panoramic radiograph in a patient with a clinical diagnosis of sialadenitis, as it permitted expedient diagnosis of sialolithiasis.

Table 3.1. Classification of salivary gland infections.

Bacterial infections
Acute bacterial parotitis
Chronic bacterial parotitis
Chronic recurrent juvenile parotitis
Acute suppurative submandibular sialadenitis
Chronic recurrent submandibular sialadenitis
Acute allergic sialadenitis
Viral infections
Mumps
HIV/AIDS
Cytomegalovirus
Fungal infections
Mycobacterial infections
Tuberculosis
Atypical mycobacteria
Parasitic infections
Autoimmune related infections
Systenmic lupus erythematosus
Sarcoidosis
Sjogren syndrome

salivary secretions, and the absence of pus may be confirmed on physical examination.

History taking is important so as to disclose the acute or chronic nature of the problem that will significantly impact on how the sialadenitis is ultimately managed. For the purpose of prognosis and the anticipation as to the possible need for future surgical intervention, an acute sialadenitis is somewhat arbitrarily classified as one where symptoms are less than one month in duration, while a chronic sialadenitis is defined as having been present for longer than one month. In addition, the history will permit the clinician to assess the risk factors associated with the condition. In so doing, the realization of modifiable versus relatively non-modifiable versus non-modifiable risk factors can be determined. For example, dehydration, recent surgery, oral infection, and some medications represent modifiable risk factors predisposing patients to sialadenitis. On the other hand, advanced age is a non-modifiable risk factor, and chronic medical illnesses and radiation therapy constitute relatively non-modifiable risk factors associated with these infections. The distinction between modifiable and relatively non-modifiable risk factors is not intuitive. For example, dehydration is obviously modifiable. The sialadenitis

Table 3.2. Risk factors associated with salivary gland infections.

Modifiable risk factors
Dehydration
Recent surgery and anesthesia
Malnutrition
Medications
Antihistamines
Diuretics
Tricyclic antidepressants
Phenothiazines
Antihypertensives
Barbiturates
Antisialogogues
Anticholinergics
Chemotherapeutic agents
Sialolithiasis
Oral infection
Non-modifiable risk factors
Advanced age
Relatively non-modifiable risk factors
Radiation therapy where cytoprotective agents were not administered
Renal failure
Hepatic failure
Congestive heart failure
HIV/AIDS
Diabetes mellitus
Anorexia nervosa/bulimia
Cystic fibrosis
Cushing disease

associated with diabetes mellitus may abate clinically as evidenced by decreased swelling and pain, however, the underlying medical condition is not reversible. The same is true for HIV/AIDS. While much medical comorbidity can be controlled and palliated, these conditions often are not curable such that patients may be fraught with recurrent sialadenitis at unpredictable time frames following the initial event. As such, these and many other risk factors are considered relatively non-modifiable.

Other features of the history, such as the presence or absence of prandial pain may direct the physical and radiographic examinations to the existence of an obstructive phenomenon. The presence of medical conditions and the use of medications to manage these conditions are very important elements of the history taking of a patient with a chief complaint suggestive of sialadenitis. They may be determined to be of etiologic significance when the physical examination confirms the diagnosis of sialadenitis. Musicians playing wind instruments who present for evaluation of bilateral parotid swelling and pain after a concert may have acute air insufflation of the parotid glands as part of the "trumpet blower's syndrome" (Miloro and Goldberg 2002). Recent dental work, specifically the application of orthodontic brackets, may result in traumatic introduction of bacteria into the ductal system with resultant retrograde sialadenitis. Deep facial lacerations proximal to an imaginary line connecting the lateral canthus of the eye to the oral commissure, and along an imaginary line connecting the tragus to the mid-philtrum of the lip may violate the integrity of the Stensen duct. While a thorough exploration of these wounds with cannulation and repair of the Stensen duct is meticulously performed, it is possible for foreign bodies to result in obstruction of salivary flow with resultant parotid swelling. A number of autoimmune diseases with immune complex formation can also be responsible for sialadenitis and confirmation of their diagnosis should be sought during the history and physical examination.

After the history has been completed, the physical examination should be performed. In the patient with suspected sialadenitis, the examination is focused on the head and neck and begins with the extraoral examination followed by the intraoral examination. In particular, the salivary glands should be assessed in a bimanual fashion for asymmetries, erythema, tenderness to palpation, swellings, and warmth. In so doing, one of the most important aspects of this examination is to rule out the presence of a tumor. A neoplastic process of the parotid gland presents as a *discrete* mass within the gland, with or without symptoms of pain. An infectious process presents as a *diffuse* enlargement of the parotid gland that is commonly symptomatic. It is possible for an indurated inflammatory lymph node within the parotid gland to simulate neoplastic disease. The distinction in the character of the parotid gland is important so as to not waste time treating a patient for an infectious process when they have a tumor in the parotid gland, particularly in the event of a malignancy. Evidence of facial trauma, including healing facial lacerations or ecchymoses, should be ascertained. The intraoral examination focuses on the observation of the quality and quantity of

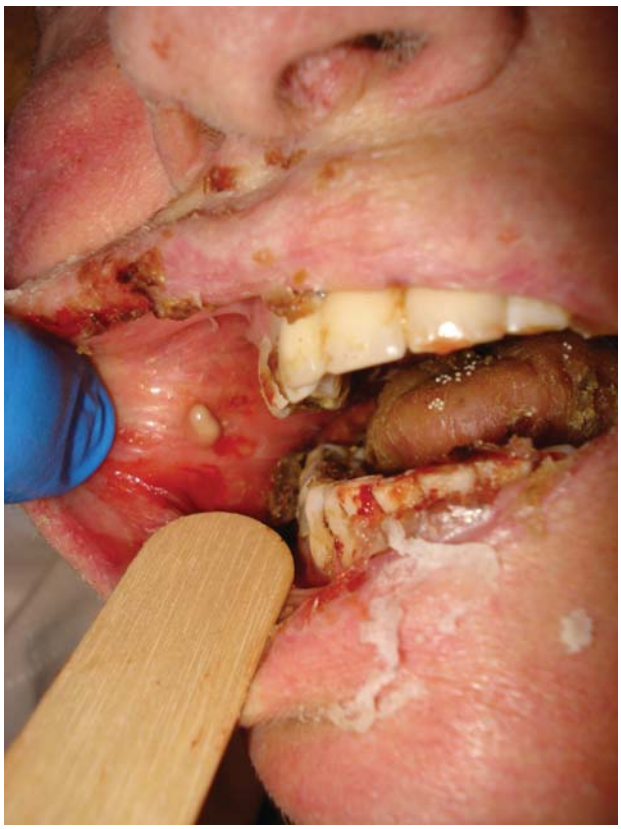


Figure 3.3. A severe case of hospital acquired parotitis related to insufficient rehydration of this patient.

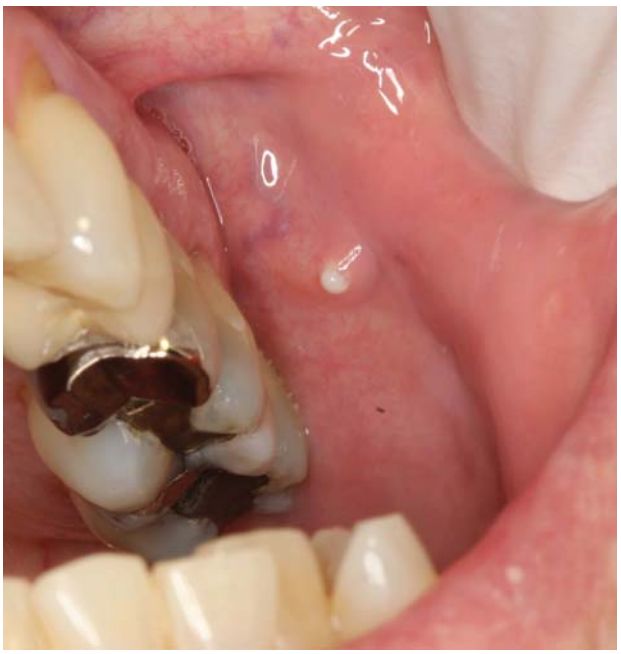


Figure 3.4. A mild case of community acquired parotitis is noted by the expression of pus at the left Stensen duct.

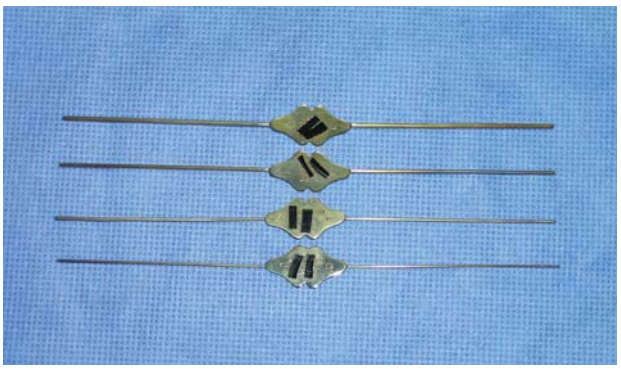


Figure 3.5. Lacrimal probes are utilized to probe the salivary ducts. The four shown in this figure incrementally increase in size. Cannulation of salivary ducts begins with the smallest probe and proceeds sequentially to the largest so as to properly dilate the duct. It is recommended that patients initiate a course of antibiotics prior to probing salivary ducts so as to not exacerbate the sialadenitis by introducing oral bacteria into the gland.

spontaneous and stimulated salivary flow. It is important to understand, however, that the anxiety and sympathomimetic response associated with the examination is likely to decrease salivary flow. Nonetheless, an advanced case of sialadenitis will often allow the clinician to appreciate the flow of pus from the salivary ducts (Figures 3.3 and 3.4). If pus is not observed, mucous plugs, small stones or "salivary sludge" may be noted. As part of the examination, it may be appropriate to perform cannulation of the salivary duct with a series of lacrimal probes (Figure 3.5). This maneuver may dislodge obstructive material or diagnose an obstruction. The decision to perform this instrumentation, however, must not be made indiscriminately. This procedure may introduce bacteria into the salivary duct that normally colonize around the ductal orifice thereby permitting retrograde contamination of the gland. This procedure is probably contraindicated in acute bacterial parotitis. The head and neck examination concludes by palpating the regional lymph nodes, including those in the preauricular and cervical regions.

Radiographs of the salivary glands may be obtained after performing the history and physical examination. Since radiographic analysis of the salivary glands is the subject of Chapter 2, they

will not be discussed in detail in this chapter. Nonetheless, plain films and specialized imaging studies may be of value in evaluating patients with a clinical diagnosis of sialadenitis. Obtaining screening plain radiographs such as a panoramic radiograph and/or an occlusal radiograph is important data to obtain when a history exists that suggests an obstructive phenomenon. The presence of a sialolith on plain films, for example, represents very important information with which to direct therapy. It permits the clinician to identify the etiology of the sialadenitis and to remove the stone at an early time frame. Such expedience may permit the avoidance of chronicity such that gland function can be maintained.

Bacterial Salivary Gland Infections

ACUTE BACTERIAL PAROTITIS

World history indicates that acute bacterial parotitis (ABP) played a significant role in its chronicles, particularly in the United States. We are told that the first case of APB occurred in Paris in 1829 in a 71-year-old man where the parotitis progressed to gangrene (McQuone 1999; Miloro and Goldberg 2002). As mumps plays a role in the differential diagnosis of infectious parotitis, Brodie's distinction between APB and viral mumps in 1834 represents a major inroad into the understanding of this pathologic process (Brodie 1834; Goldberg and Bevilacqua 1995). Prior to the modern surgical era, ABP was not uncommonly observed, and indeed represented a dreaded complication of major surgery, with a mortality rate as high as 50% (Goldberg and Bevilacqua 1995). Ineffective postoperative intravascular volume repletion with resultant diminished salivary flow and dry mouth were the norm rather than the exception. President Garfield sustained a gunshot wound to the abdomen in July 1881 and developed chronic peritonitis and ultimately died several weeks later. The terminal event was described as suppurative parotitis that led to sepsis (Goldberg and Bevilacqua 1995). It has been pointed out that upper and lower aerodigestive tract surgeries require patients to be without oral nutritional intake or with limited oral intake postoperatively (McQuone 1999). The reduction of salivary stimulation predisposes these patients to APB, with an estimated incidence of 1 in 1000 postoperative patients (Andrews, et al. 1989). Other figures showed 3.68 cases per 10,000 operations in the preantibiotic era compared with 0.173 in 10,000 operations in the antibiotic era (Robinson 1955). The prophylactic use of antibiotics has probably contributed to the reduction of cases of APB. In addition, intraoperative and postoperative intravenous hydration became well accepted in the 1930s, particularly during World War II, therefore also contributing to the reduction in the incidence of ABP. In 1958, Petersdorf reported seven cases of staphylococcal parotitis and the 1960s ushered in several reports of ABP as a disease making a comeback (Petersdorf 1958; Goldberg and Bevilacqua 1995). Of Petersdorf's seven cases, five of the patients had undergone surgery and two of the patients died in the hospital. Oral and maxillofacial surgeons began to report cases of ABP in the literature in the 1960s (Goldberg and Harrigan 1965; Guralnick, et al. 1968).

The parotid gland's relative propensity for infection results from physiologic and anatomic factors. Parotid saliva differs from that of the submandibular and sublingual glands. Parotid saliva is predominantly serous compared to the mucinous saliva from the submandibular and sublingual glands. Mucoid saliva contains lysosomes and IgA antibodies which protect against bacterial infection. Mucins also contain sialic acid, which agglutinates bacteria, thereby preventing its adherence to host tissues. Glycoproteins found in mucins bind epithelial cells, thereby inhibiting bacterial attachment to the epithelial cells of the salivary duct.

Variants of ABP and Their Etiology

Over the past several decades changes have occurred in the bacterial flora of the oral cavity that directly reflect the identification of organisms in ABP. In part, this change is evident due to the increased incidence of nosocomial and opportunistic infections in patients who are immunocompromised as well as those critically ill patients in hospital intensive care units whose mouths became colonized with micro-organisms that were previously only rarely found in the oral cavity (Figure 3.3). Moreover, improved culturing techniques have permitted the identification of anaerobes that were previously difficult to recover in the microbiology laboratory. Finally, the occasionally indiscriminate use of antibiotics has allowed for the occupation of other organisms in the oral cavity

such as gram negative enteric organisms. Bacterial Darwinism has also occurred such that iatrogenically and genetically altered staphylococcal organisms have developed penicillin resistance.

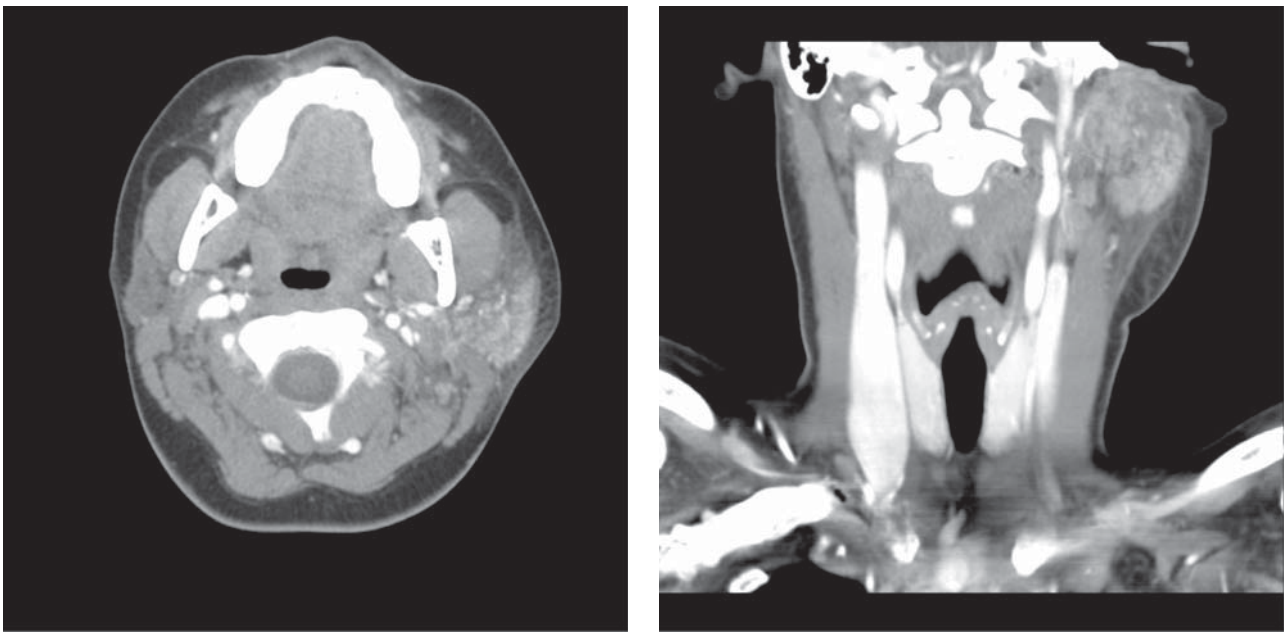
APB has two well defined presentations, *hospital acquired* (Figure 3.3) and *community acquired* (Figure 3.4) variants. Numerous factors predispose the parotid gland to sialadenitis. Retrograde infection is recognized as the major cause of ABP. As a result of acute illness, sepsis, trauma or surgery, depleted intravascular volume may result in diminished salivary flow that in turn diminishes the normal flushing action of saliva as it passes through the Stensen duct. Patients with salivary secretions of modest flow rates show bacteria at the duct papillae and in cannulated ducts, while patients with salivary secretions of high rates show bacteria at the duct papillae but not within the duct (Katz, et al. 1990). In a healthy state, fibronectin exists in high concentrations within parotid saliva which promotes the adherence of *Streptococcus* species and *S. aureus* around the ductal orifice of the Stensen duct (Katz, et al. 1990). Low levels of fibronectin as occur in the unhealthy host are known to promote the adherence of *pseudomonas* and *E. coli*. This observation explains the clinical situation whereby colonization as a result of dehydration leads to a gram positive sialadenitis in ABP compared to the development of gram negative sialadenitis of the parotid gland in immunocompromised patients (Miloro and Goldberg 2002). Depending on the health of the host, therefore, specific colonized bacteria are able to infect the parotid gland in a retrograde fashion. Hospital acquired ABP still shows cultures of *Staphylococcus aureus* in over 50% of cases (Goldberg and Bevilacqua 1995). Methicillin resistant *Staphylococcus aureus* should be ruled out in this population of in-patients. Critically ill and immunocompromised in-patients may also show *Pseudomonas*, *Klebsiella*, *Escherichia coli*, *Proteus*, *Eikenella corrodens*, *Haemophilus influenzae*, *Prevotella* and *Fusobacterium* species. Postoperative parotitis has been reported from 1 to 15 weeks following surgery, but most commonly occurs within 2 weeks after surgery (McQuone 1999). The peak incidence of this disease seems to be between postoperative days 5 and 7.

Community acquired ABP is diagnosed five times more commonly than hospital acquired ABP and is diagnosed in emergency departments, offices and outpatient clinics. This variant of ABP is most commonly associated with staphylococcal and streptococcal species. As community acquired methicillin resistant staphylococcus aureus becomes more common in society, this organism will become more prevalent in community acquired ABP. Etiologic factors in community acquired ABP include medications that decrease salivary flow, trauma to the Stensen duct, cheek biting, toothbrush trauma, trumpet blower's syndrome, and medical conditions such as diabetes, malnutrition, and dehydration from acute or chronic gastrointestinal disorders with loss of intravascular volume. Sialoliths present in the Stensen duct with retrograde infection are less common than in the Wharton duct, but this possibility should also be considered in the patient with community acquired ABP.

Diagnosis of ABP

Diagnosis of ABP requires a thorough history and physical examination followed by laboratory and radiographic corroboration of the clinical diagnosis. Whether occurring in out-patient or in-patient arenas, a history of use of antisialogogue medications, dehydration, malnutrition, diabetes mellitus, immunosuppression, surgery, or systemic disease supports this diagnosis. A predilection for males exists for ABP, and the average age at presentation is 60 years (Miloro and Goldberg 2002). A systemic disorder will result in both glands being affected, but when one gland is affected, the right gland seems to be involved more commonly than the left gland (Miloro and Goldberg 2002). The declaration of acute requires that the parotitis has been present for one month or shorter.

The classic symptoms include an abrupt history of painful swelling of the parotid region, typically when eating. The physical findings are commonly dramatic, with parotid enlargement, often displacing the ear lobe, and tenderness to palpation. If the Stensen duct is patent, milking the gland may produce pus (Figures 3.3 and Figure 3.4). A comparison of salivary flow should be performed by also examining the contralateral parotid gland as well as the bilateral submandibular glands. The identification of pus should alert the clinician to the need to obtain a sterile culture and sensitivity. Constitutional symptoms may be present, including fever and chills, and temperature elevation may exist as long as the gland is infected. If glandular obstruction is present without infection, temperature elevation may not



(a) (b)

Figure 3.6. Axial (a) and coronal (b) CT scans of a patient with a hospital acquired parotitis. The degree of swelling led to the acquisition of these scans so as to rule out intra-parotid abscess.

be present. Laboratory values will show a leukocytosis with a bandemia in the presence of true bacterial infection, with elevated hematocrit, blood urea nitrogen and urine specific gravity if the patient is dehydrated. Electrolyte determinations should be performed in this patient population, particularly in in-patients and out-patients who are malnourished. Probing of the Stensen duct is considered contraindicated in ABP. The concern is for pushing purulent material proximally in the gland, although an argument exists that probing may relieve duct strictures and mucous plugging.

The radiographic assessment of ABP is discussed in detail in Chapter 2. Briefly, plain films are of importance so as to rule out sialoliths, and special imaging studies may be indicated to further image the parotid gland depending on the magnitude of the swelling and the patient's signs and symptoms (Figure 3.6). The presence of an intra-parotid abscess on special imaging studies, for example, may direct the clinician to the need for expedient incision and drainage.

Treatment of ABP

The treatment of ABP is a function of the setting in which ABP is diagnosed, as well as the severity of the disease within the parotid gland and the presence of medical comorbidities (Figure 3.7). In the outpatient setting, the presence or absence of pus will assist in directing specific therapy. The presence of pus should result in culture and sensitivity. Early species-specific antibiotic therapy is the sine qua non of treatment of ABP. Empiric antibiotic therapy should be based on a Gram stain of ductal exudates. In general terms, an anti-staphylococcal penicillin or a first-generation cephalosporin is a proper choice. Antibiotics should be changed if cultures and sensitivities show methicillin resistant staphylococcal species, in which case clindamycin is indicated in community acquired ABP. In the absence of pus, empiric antibiotic therapy should be instituted as described previously. Antibiotic compliance is often difficult for patients such that once- or twice-daily antibiotics are always preferable. In all patients with community acquired ABP, other general measures should be followed including the stimulation of salivary flow with digital massage, the use of dry heat, and the use of sour ball candies. Sugarless sour ball candies should be recommended for diabetics or those with impaired glucose tolerance. Some elderly and debilitated out-patients may require admission to the hospital in which case intravenous antibiotic therapy will be instituted and incision and drainage may be required. Alteration of anti-sialogogue medications

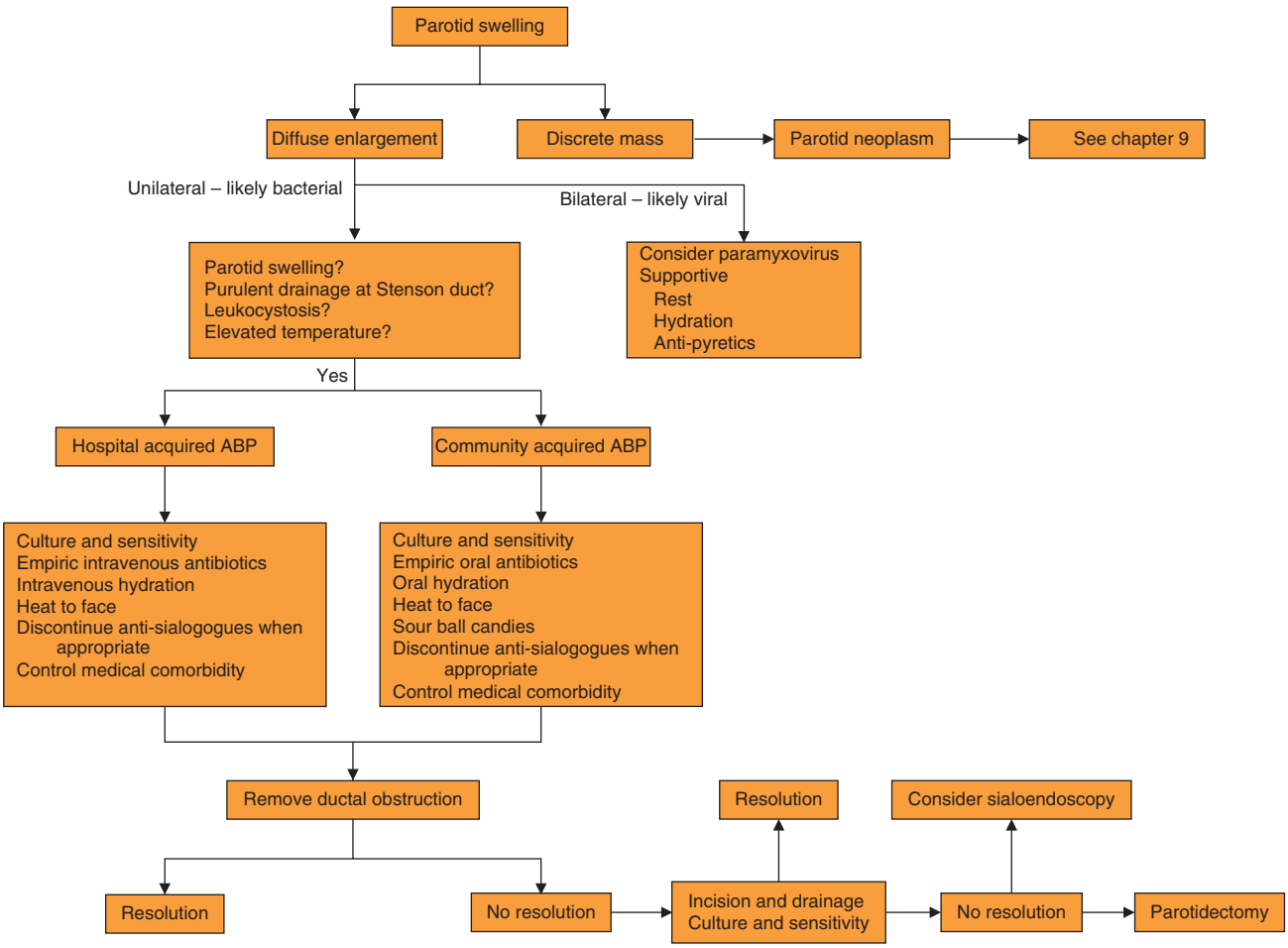


Figure 3.7. The algorithm for diagnosis and treatment of a unilateral or bilateral parotid swelling.

should be accomplished as soon as possible. In the out-patient setting, these commonly include urinary incontinence medications, loop diuretics, beta blockers, and antihistamines. Glycemic control in diabetics is beneficial in the control of ABP. Finally, effective control of viral load in HIV infected patients is of utmost importance.

Imaging of outpatients with community acquired ABP is based on the severity of the clinical disease, its chronicity and the clinician's suspicion for intra-parotid abscess. Obtaining routine plain films, such as a panoramic radiograph is certainly indicated so as to investigate for the presence of a sialolith. It may be acceptable, however, to defer special imaging studies in these patients until refractory infection develops. Patients with severe symptoms, fever, and concern for abscess formation within the parotid gland should be imaged with CT scans in an expedient fashion (Figure 3.6). Except in the presence of severe immunosuppression or other medical co-morbidity, refractory infections are uncommonly seen in ABP.

The general principles of the management of hospital acquired ABP are identical to those of the community acquired ABP. As previously described, however, the risk factors differ. In these in-patients, rehydration should be performed with caution to avoid cardiac overload. Empiric intravenous antibiotics should be instituted in these patients, and confirmed as to their efficacy with culture and sensitivity of purulent parotid exudates whenever possible. The use of heat to the affected gland is appropriate in this setting, as well. The in-patient should be monitored closely for clinical improvement. Despite the institution of conservative measures, if the patient's course deteriorates within 48–72 hours as evident by increased swelling and pain, or an increase in white blood cell count, an incision and drainage procedure is indicated (Figure 3.8). Such a procedure must be

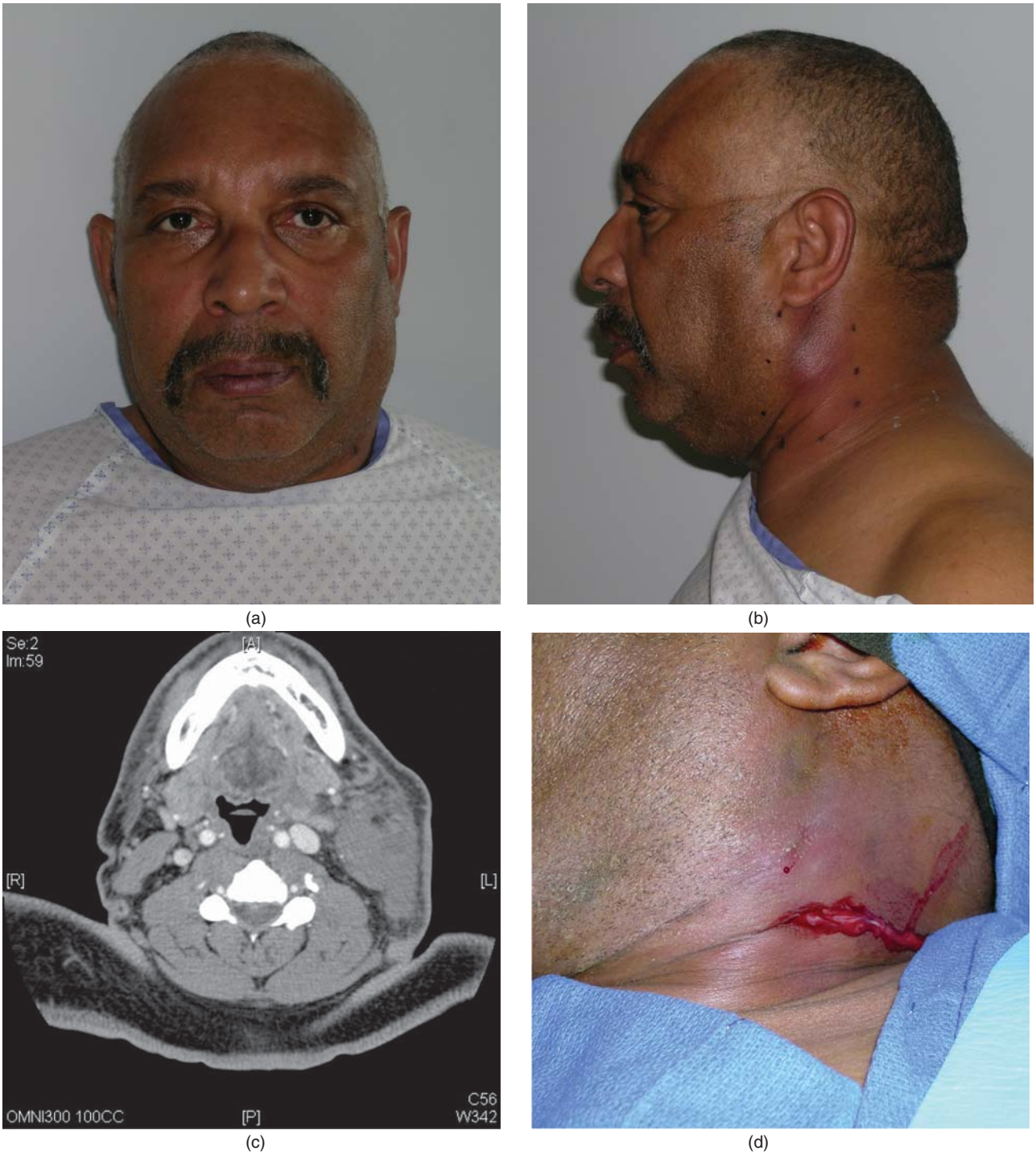
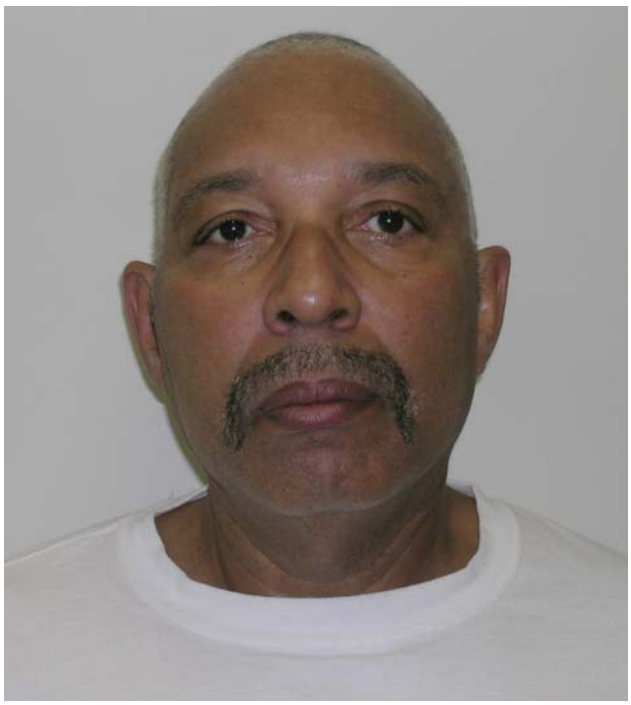


Figure 3.8. A 65-year-old man with a two week history of left parotid/neck swelling and pain (a and b). Computerized tomograms (c) revealed an abscess within the tail of the left parotid gland. The patient underwent incision and drainage in the operating room for a diagnosis of community acquired APB with abscess formation (d). Methicillin resistant staph aureus species were cultured. At two months postoperatively (e and f) he showed resolution of his disease.



(e)

(f)

Figure 3.8. (*Continued*).

guided by CT scans so as to explore all loculations of pus. A needle aspiration of a parotid abscess is unlikely to represent a definitive drainage procedure, although it will permit the procurement of a sample of pus prior to instituting antibiotic therapy in preparation for incision and drainage.

CHRONIC (RECURRENT OR REFRACTORY) BACTERIAL PAROTITIS

Chronic bacterial parotitis occurs in at least three clinical settings. The first is in which the patient defers evaluation such that the condition has persisted for at least one month. The second includes the setting in which APB was managed conservatively, but without resolution (refractory sialadenitis). Finally, it is possible for a successfully treated parotitis to become recurrent such that periods of remission separate recurrent episodes of ABP. The parotid gland may demonstrate evidence of latent infection despite clinical resolution of the disease. The result is scarring in the gland such that function is impaired. Histology will show dilation of glandular ducts, abscess formation, and atrophy (Patey 1965). Pus is rarely observed in chronic bacterial parotitis (Baurmash 2004). Rather, there is a marked reduction of salivary glow, and the parotid secretions are viscous and milky in appearance. The microbiologic etiology of chronic bacterial parotitis is most commonly *streptococci* and *staphylococci*, but other organisms may be found as a function of the patient's immune status, the setting in which the parotitis originally occurred and medical comorbidity. It has been suggested that the accumulation of a semisolid material that obstructs the parotid duct is the culprit in chronic bacterial parotitis (Baurmash 2004). The clinical course of the disease shows pain and swelling waxing and waning. As with APB, a screening panoramic radiograph or CT scans should be obtained to rule out the presence of a sialolith (Carlson 2009).

Treatment of Chronic Bacterial Parotitis

Treatment of chronic bacterial parotitis centers on palliative therapy with parotidectomy reserved as

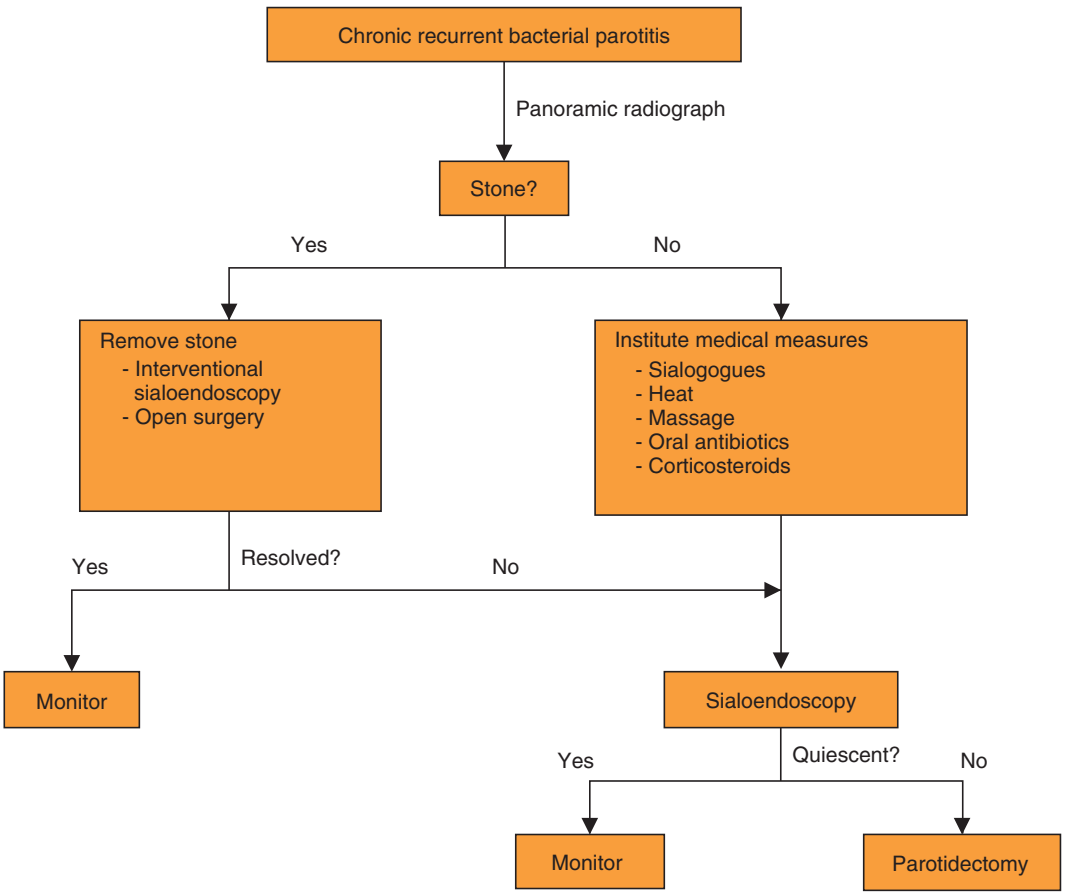
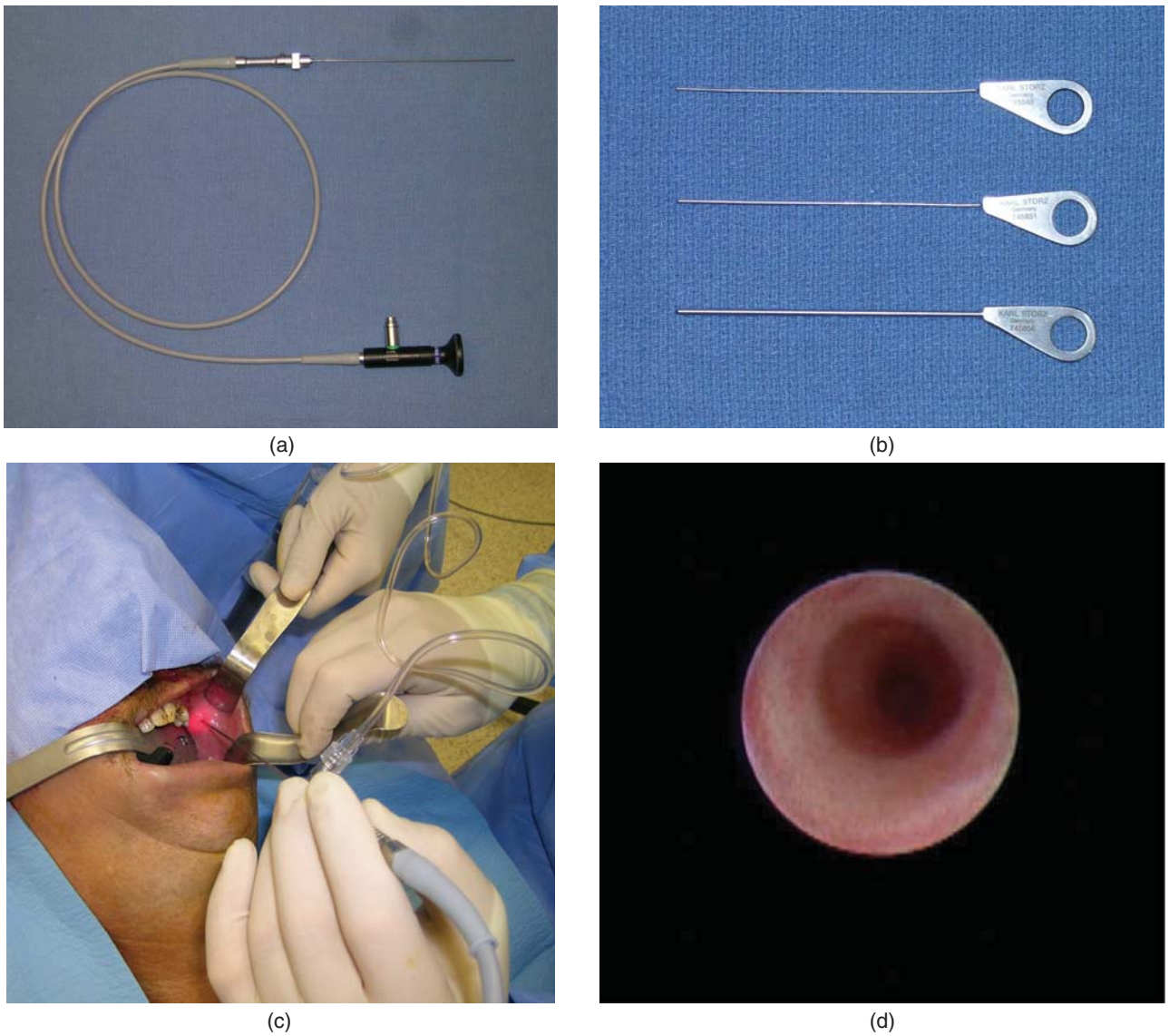


Figure 3.9. Algorithm for the management of chronic recurrent bacterial parotitis.

a last resort (Figure 3.9). Effective treatment is centered on the gland inflammation as well as the precipitated intraductal material. Patients should be treated with culture specific systemic antibiotics, ductal antibiotic irrigations during periods of remission, analgesics, and avoidance of dehydration and antisialogogue medications (Goldberg and Bevilacqua 1995). The identification of a sialolith should result in expedient removal. Sialoendoscopy represents a technique that may obviate the need for aggressive surgical intervention (Nahlieli, et al. 2006; Hasson 2007). Sialoendoscopic findings of patients with chronic obstructive parotitis include ductal stricture, mucous plugs, and desquamative epithelial cells and inflammatory cells (Qi, et al. 2005). A sialoendoscopic procedure may address any or all of these problems, thereby sparing the gland (Figure 3.10). If pain and swelling become intolerable for the patient, or if special imaging studies reveal abscess formation in the parotid gland, then nerve sparing parotidectomy is the treatment of choice (Figure 3.11).

CHRONIC RECURRENT JUVENILE PAROTITIS

Recurrent juvenile parotitis is commonly noted prior to puberty and is manifested by numerous episodes of painful enlargements of the parotid gland. Chronic recurrent parotitis in children is 10 times more common than chronic recurrent parotitis in adults (Baurmash 2004). Several etiologies have been offered including congenital abnormalities or strictures of the Stensen duct, trauma, foreign bodies with the duct, or a history of viral mumps. Many cases will resolve prior to the onset of puberty such that conservative measures are recommended. These include long term antibiotics and analgesia. Spontaneous regeneration of salivary function has been reported (Galili and Marmary 1985).

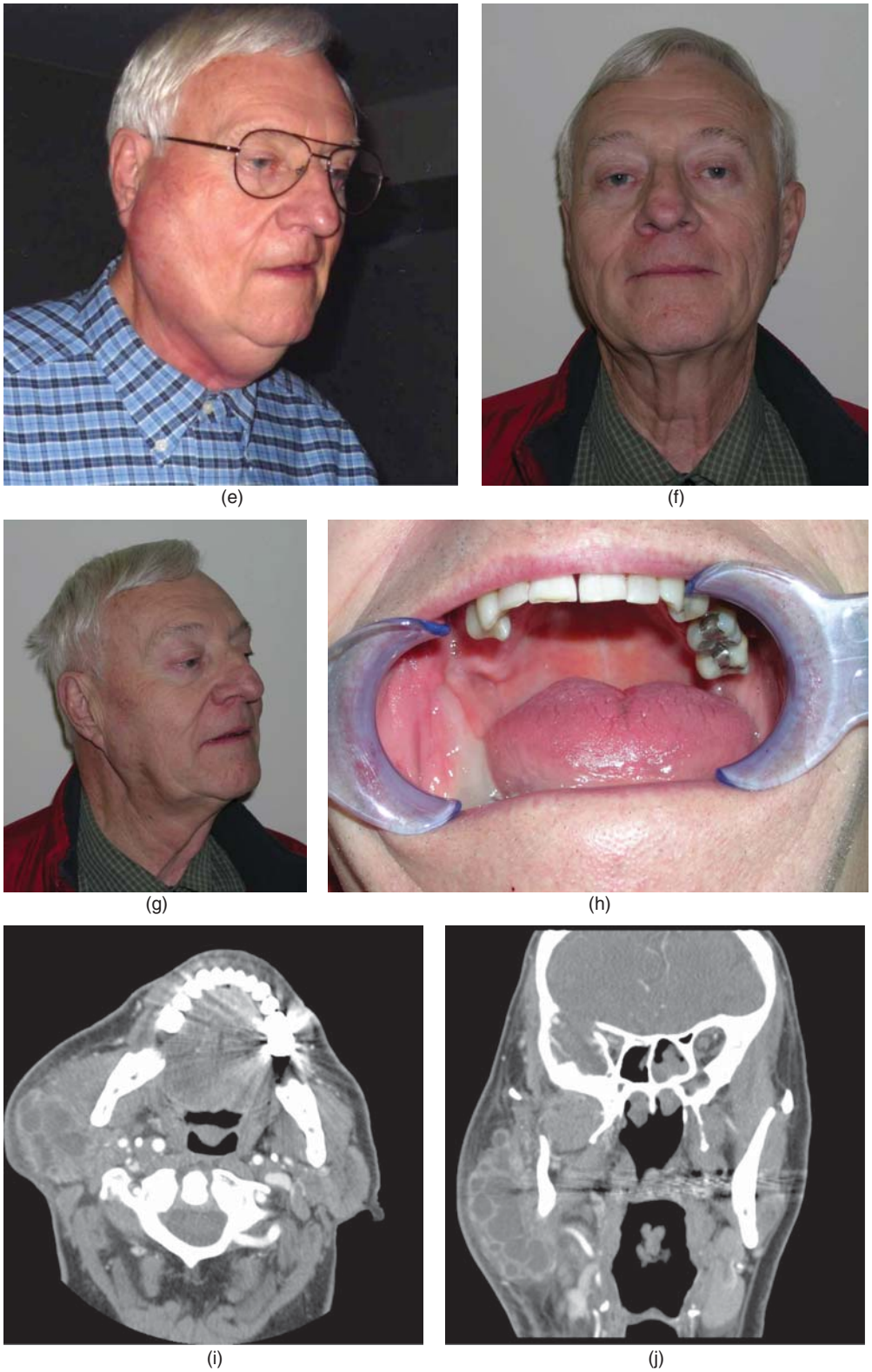


(a) (b) (c) (d)

Figure 3.10. The miniature endoscope for diagnostic and interventional sialoendoscopic procedures (a – Karl Storz Endoscopy, Germany). The instrumentation seen here is utilized for diagnostic procedures only. The endoscope may be connected to an operating sheath for interventional procedures (see Chapter 5). A series of duct dilators (b) are inserted in the Stensen duct prior to placing the sialoendoscope (c). A representative image is noted in (d) that demonstrates normal findings in a patient with chronic parotid pain. The sialoendoscopy procedure, including dilatation and irrigation of the duct, resulted in resolution of symptoms. A 76-year-old-man (e) with a chronic history of right parotid swelling. His symptom of right facial swelling waxed and waned (f and g) and he was noted to have the forced expression of pus from the right Stensen duct (h). He underwent imaging studies (i and j) due to the chronicity of his diagnosis of chronic parotitis. A sialoendoscopy was performed (k) that identified thick mucus in his main Stensen duct (l) and strictures in his distal ductwork within the gland (m).

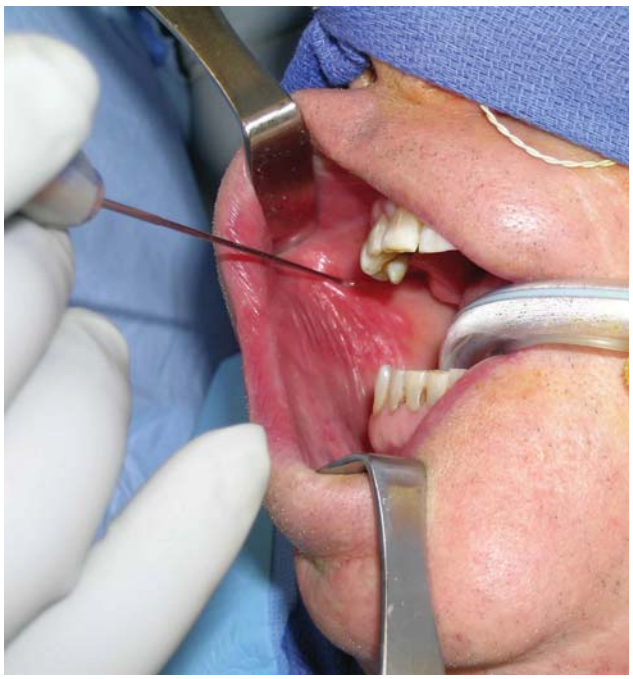
ACUTE BACTERIAL SUBMANDIBULAR SIALADENITIS

Acute bacterial submandibular sialadenitis (ABSS) is usually associated with physical obstruction of Wharton duct and therefore presents as swelling associated with the submandibular gland. That said, physical examination of the patient with submandibular swelling may not immediately disclose whether the swelling is related to sialadenitis

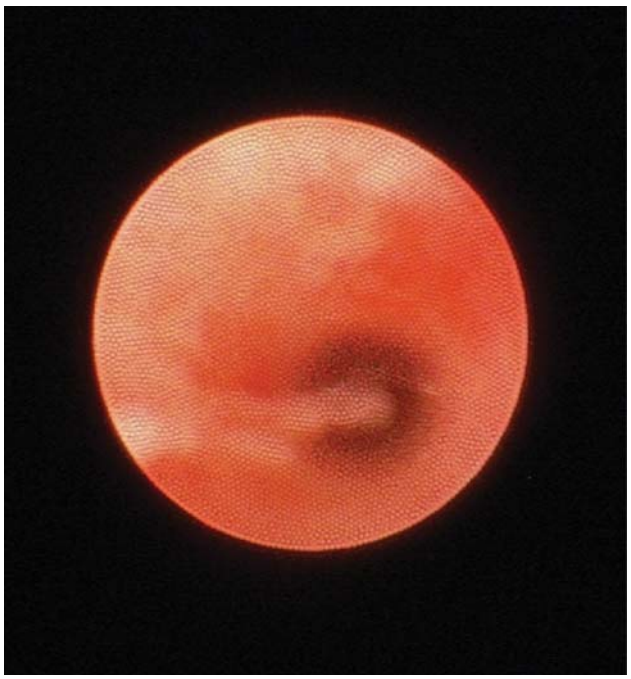


(e) (f) (g) (h) (i) (j)

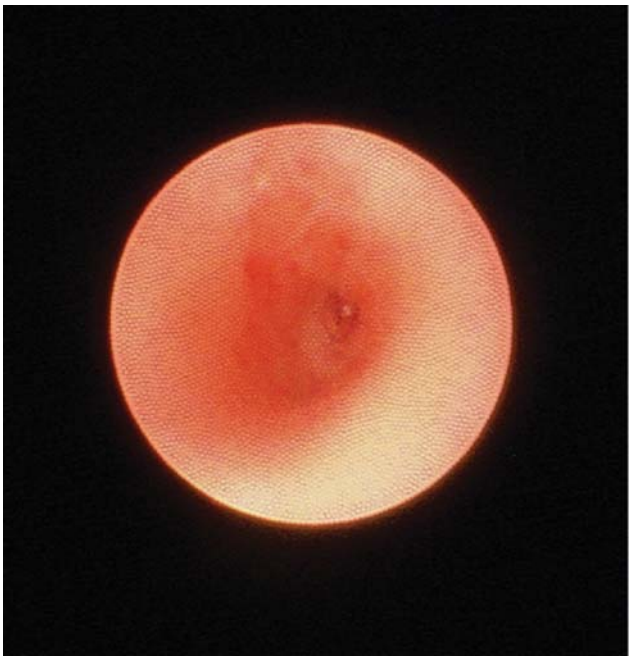
Figure 3.10. (*Continued*).



(k)



(l)



(m)

Figure 3.10. (*Continued*).

of the submandibular gland, to neoplastic disease of the submandibular gland, or due to a process extrinsic to the submandibular gland. As such, CT scans become required when the distinction cannot be made entirely on physical findings alone (Figure 3.12a). This notwithstanding, sialolithiasis, the likely cause of obstruction of the duct with resultant submandibular gland swelling, is discussed in Chapter 5 so it is only briefly mentioned here. Suffice it to say that the

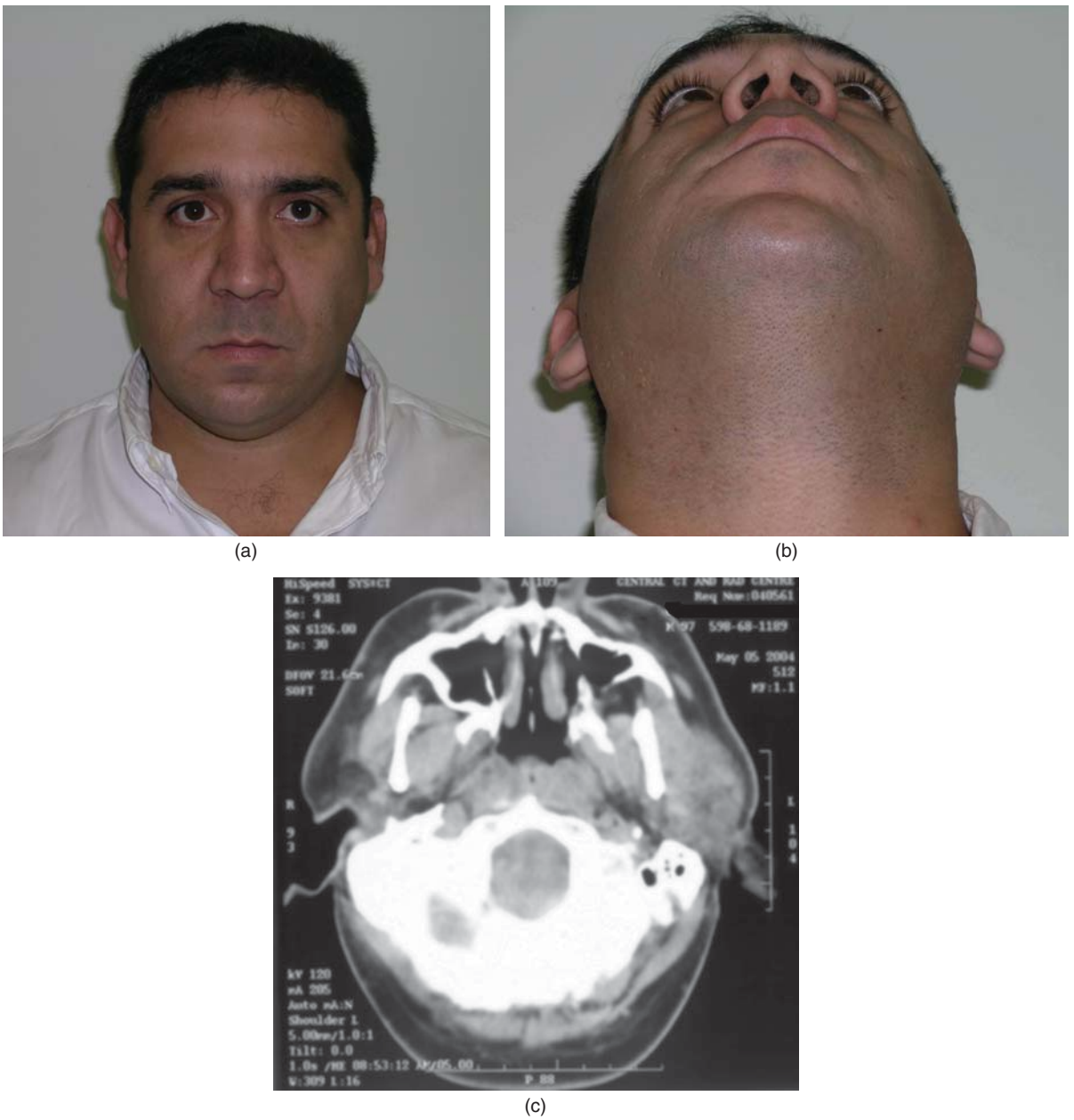
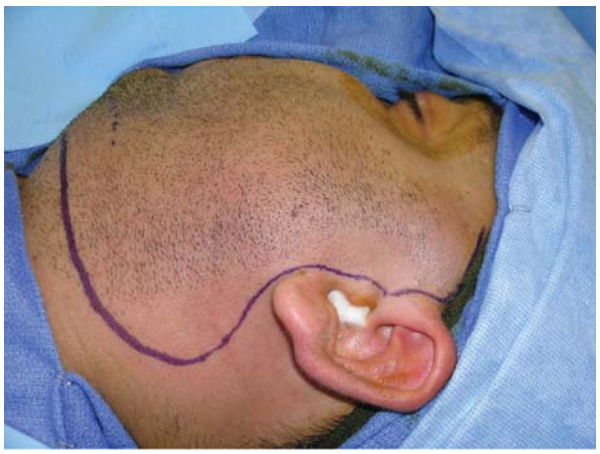


Figure 3.11. A 35-year-old man with a 2-year history of left parotid pain and swelling (a and b). Computerized tomograms (c) showed sclerosis of the parotid parenchyma as well as a suspected abscess. The patient underwent left superficial parotidectomy with a clinical and radiographic diagnosis of chronic bacterial parotitis with abscess formation. The superficial parotidectomy was accessed with a standard incision (d). A nerve sparing approach was followed (e) that allowed for delivery of the specimen (f). Histopathology showed chronic sialadenitis with abscess formation (g). At 3 years postoperatively (h and i) he displays resolution of his disease.

submandibular ductal system is prone to stone formation. The common features of ABSS are swelling in the submandibular region associated with prandial pain. ABSS is a community acquired disease that less frequently is associated with dehydration and hospitalization as compared to ABP. Purulence may be expressed from the opening of the Wharton duct, but in many cases complete obstruction to pus and saliva occurs. As in the case of APB, imaging studies are also obtained in



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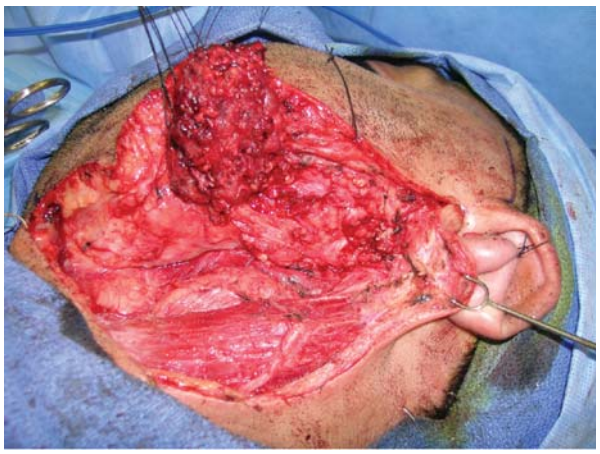

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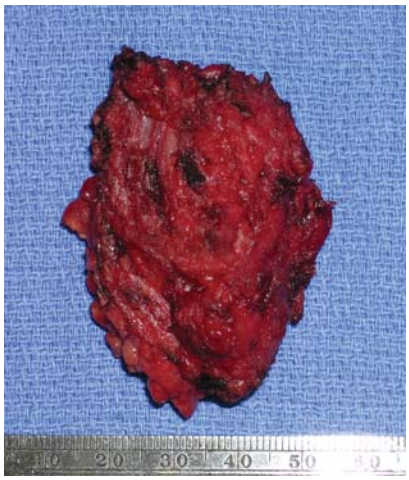

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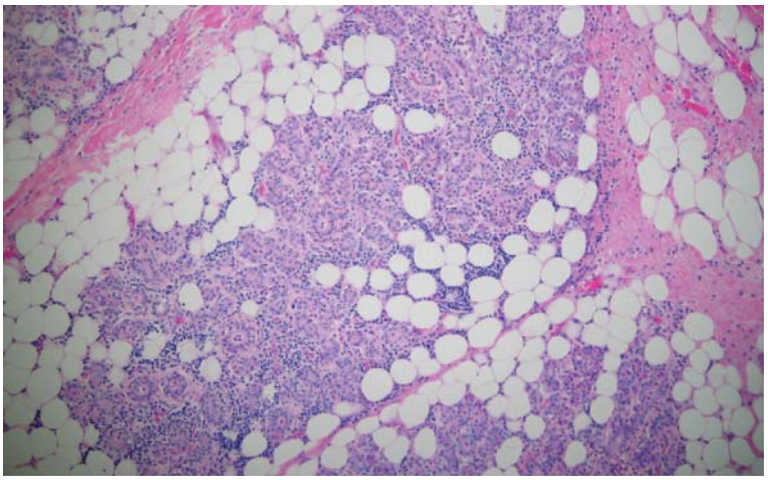

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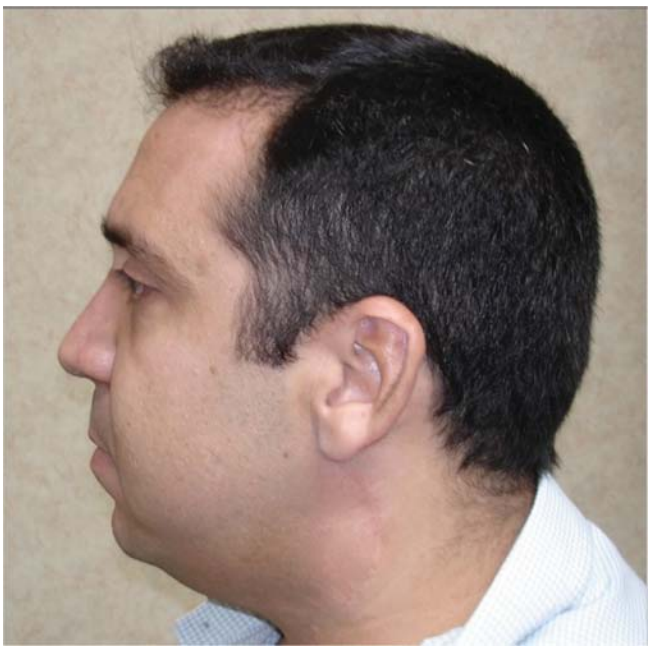

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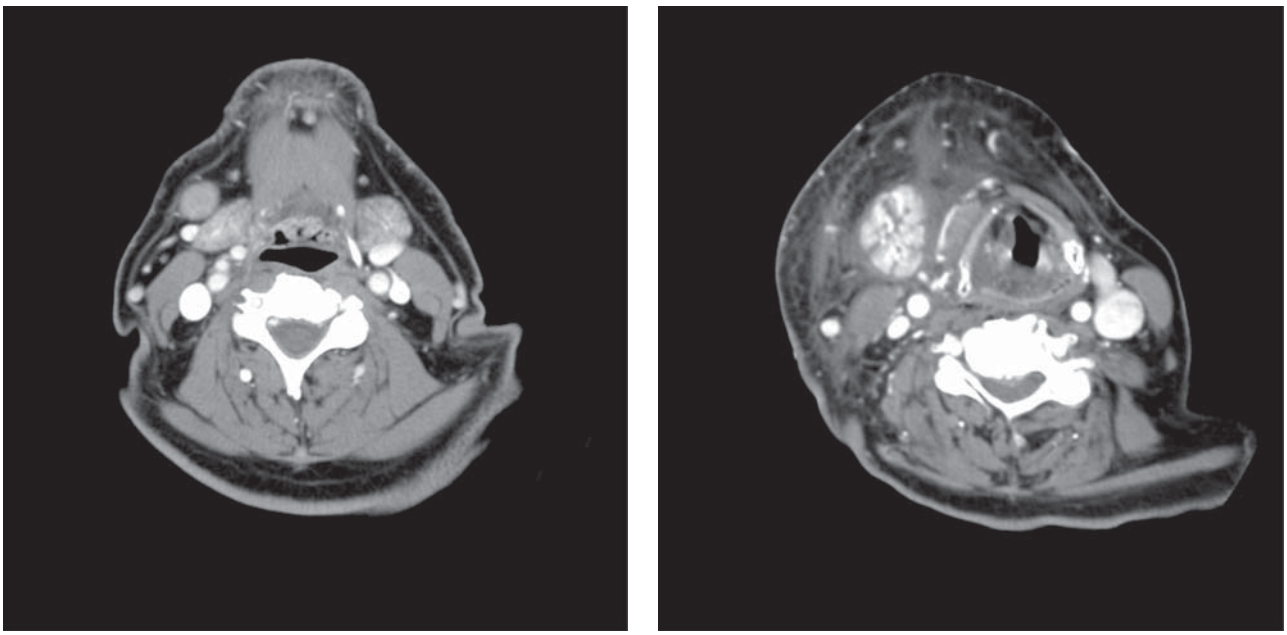


(a) (b)

Figure 3.12. The CT scan (a) of a 73-year-old man with a one year history of right submandibular swelling. Physical examination of the neck identified a mass with a differential diagnosis of submandibular gland mass versus enlarged lymph node in the submandibular region. This CT scan was obtained due to the equivocal nature of the finding on physical examination. Fine needle aspiration biopsy of this mass led to a diagnosis of low-grade lymphoma. By distinction, a 24-year-old woman with right submandibular swelling and pain who underwent a CT scan that identified intense uptake of intravenous contrast of the right submandibular gland indicative of acute bacterial submandibular sialadenitis (b). Fat stranding in the left neck indicative of inflammation is also noted.

patients with clinically unequivocal acute bacterial submandibular sialadenitis when signs and symptoms are of a magnitude to justify acquiring CT scans (Figure 3.12b).

Treatment of Acute Bacterial Submandibular Sialadenitis

Treatment of ABSS consists of antibiotic therapy, hydration, avoidance of antisialogogues, and removal of a sialolith, if one is identified (Figure 3.13). Empiric antibiotics used to treat ABSS are similar to ABP, including an extended spectrum penicillin, a first generation cephalosporin, clindamycin, or a macrolide. Patients are also encouraged to use sialogogues, such as sour ball candies.

CHRONIC RECURRENT SUBMANDIBULAR SIALADENITIS

Chronic recurrent submandibular sialadenitis usually follows ABSS and is associated with untreated sialolithiasis. Chronic recurrent submandibular sialadenitis occurs more commonly than chronic recurrent bacterial parotitis. Initial treatment for chronic recurrent submandibular sialadenitis begins with antibiotic therapy, sialogogues, and hydration. Sialolithotomy is required if diagnosed. Sialoendoscopic intervention may also be of benefit in the treatment of chronic recurrent submandibular sialadenitis prior to subjecting the patient to submandibular gland removal. Ultimately, removal of the submandibular gland is often necessary (Figure 3.14).

BARTONELLA HENSELAE (CAT SCRATCH DISEASE)

Cat scratch disease (CSD) is a granulomatous lymphadenitis that most commonly results from cutaneous inoculation caused by a scratch from a domestic cat. The causative microorganism is *Bartonella henselae*, a gram negative bacillus. Approximately 90% of patients who have cat

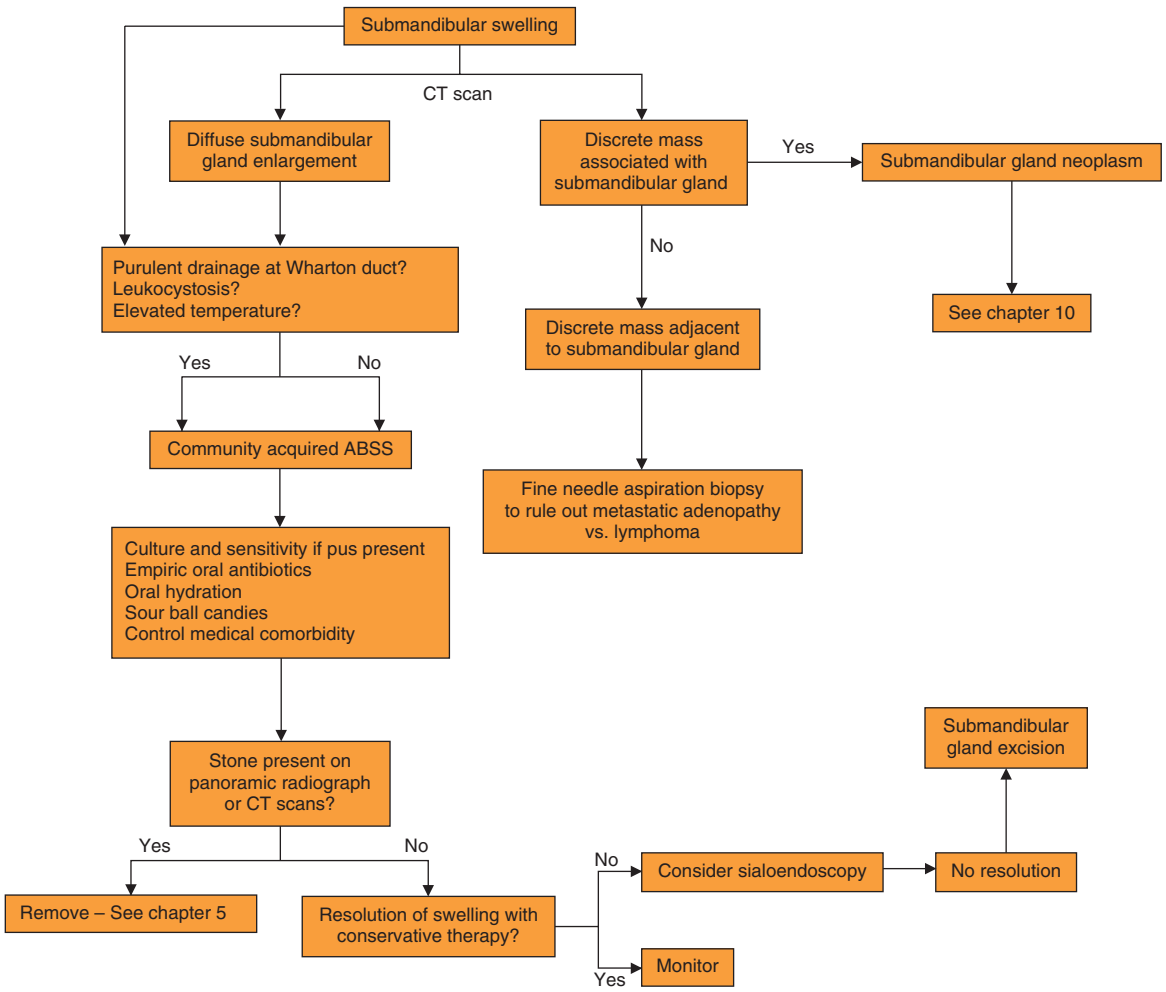


Figure 3.13. Algorithm for diagnosis and management of acute bacterial submandibular sialadenitis (ABSS).

scratch disease have a history of exposure to cats and 75% of these patients report a cat scratch or bite (Arrieta and McCaffrey 2005). Dogs have been implicated in 5% in these cases. This disease process begins in the preauricular and cervical lymph nodes as a chronic lymphadenitis and may ultimately involve the salivary glands, most commonly the parotid gland by contiguous spread (English, et al. 1988).

The diagnosis of CSD has changed with advances in serologic and molecular biologic techniques. These methods have replaced the need for the Rose Hanger skin test previously used. Testing for the presence of antibodies to *B. henselae* is now the most commonly used test to confirm the diagnosis. The two methods used for antibody detection are the indirect fluorescent antibody (IFA) and the enzyme immunoassay (EIA). When tissue is removed for diagnosis, histologic examination might demonstrate bacilli with the use of Warthin–Starry staining or a Steiner stain. Lymph node involvement shows reticular cell hyperplasia, granuloma formation and occasionally a stellate abscess.

In most cases, no active therapy is required. The patient should be reassured that the lymphadenopathy is self-limited and will spontaneously resolve in 2–4 months. Antibiotic therapy is indicated when patients are symptomatic. Antibiotics reported to be most effective include rifampin, erythromycin, gentamycin, azithromycin, and ciprofloxacin. Surgery becomes necessary when the diagnosis is equivocal, or when incision and drainage is indicated (Figure 3.15).

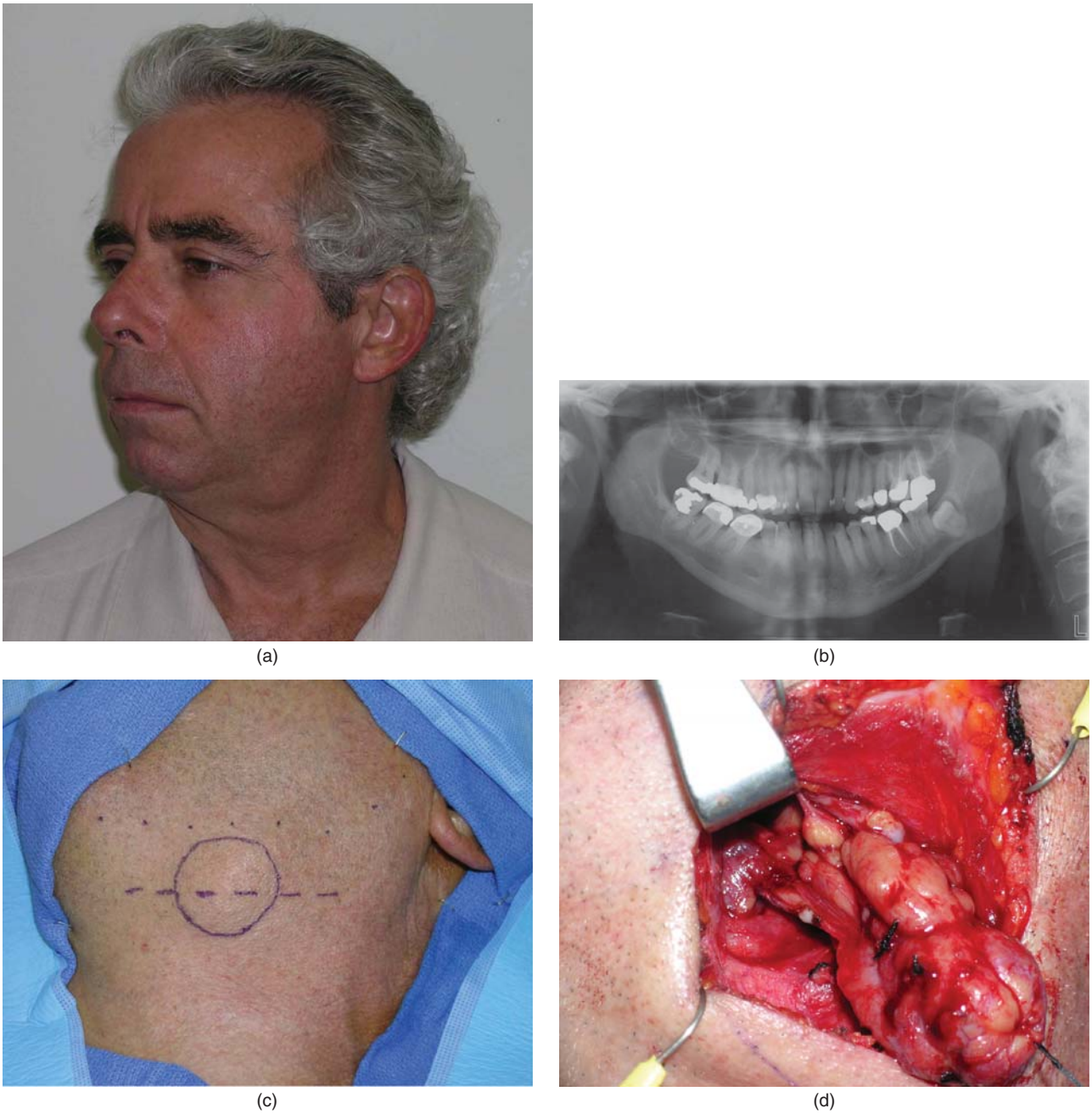
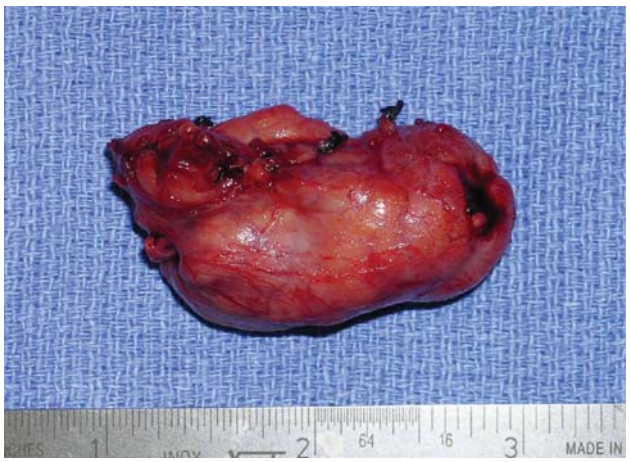


Figure 3.14. A 52-year-old man (a) with a 1-year history of vague discomfort in the left upper neck. Screening panoramic radiograph (b) showed no evidence of a sialolith. His diagnosis was chronic submandibular sialadenitis and he was prepared for left submandibular gland excision (c). The surgery was carried through anatomic planes, including the investing layer of the deep cervical fascia (d). The dissection is carried deep to this layer since a cancer surgery is not being performed that would require a dissection superficial to the investing fascia. Exposure of the gland demonstrates a small submandibular gland due to scar contracture (e). Inferior retraction of the gland allows for identification and preservation of the lingual nerve (f). The specimen (g) is bivalved (h) which allows for the appreciation of scar within the gland. The resultant tissue bed (i) shows the hypoglossal nerve which is routinely preserved in excision of the submandibular gland. Histopathology shows a sclerosing sialadenitis (j). The patient's symptoms were eliminated postoperatively, and he healed uneventfully, as noted at 1 year following the surgery (k).



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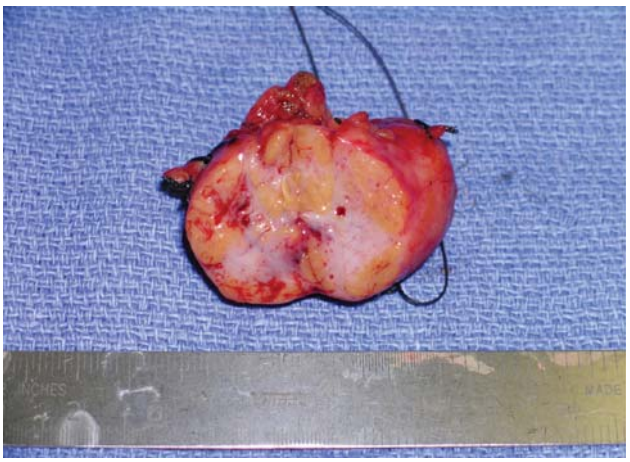

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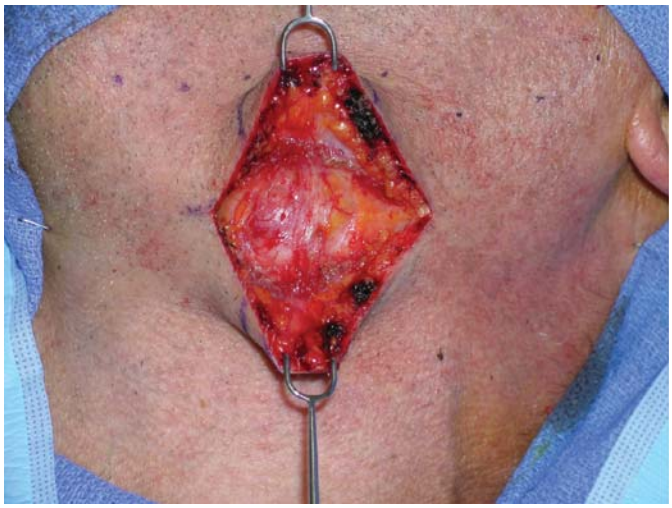

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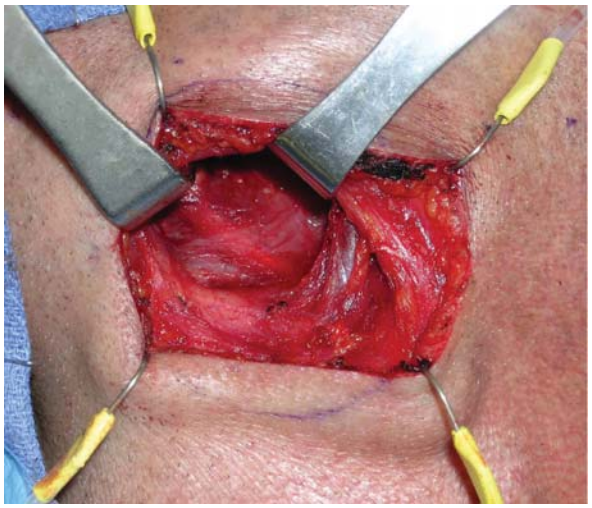

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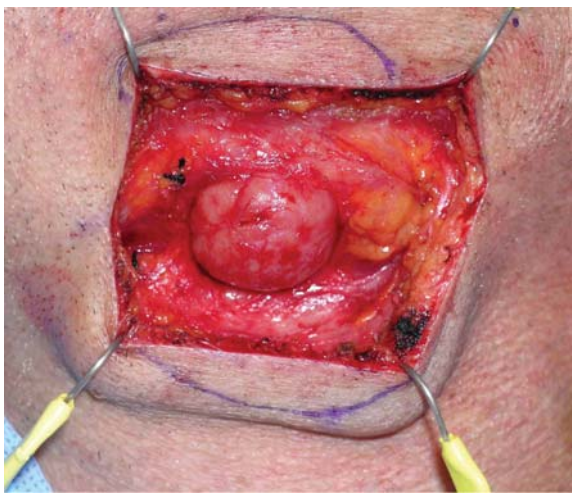

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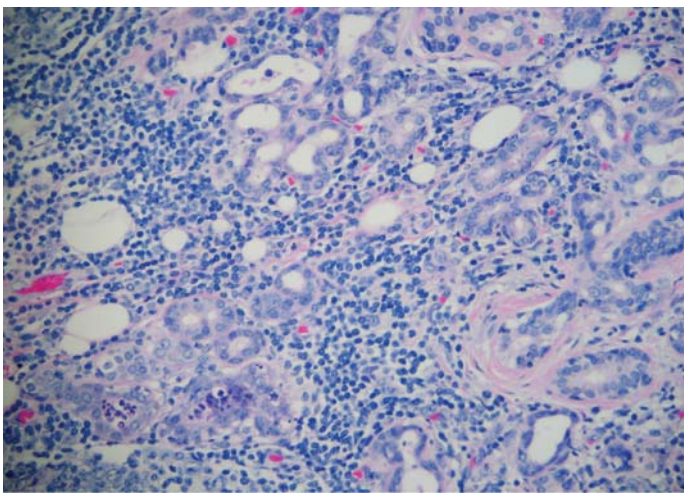

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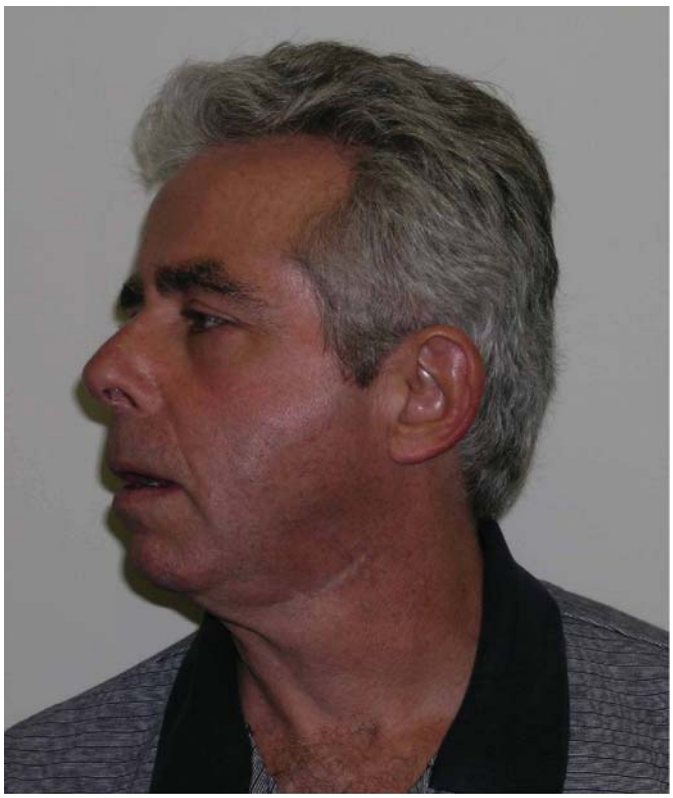

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Figure 3.14. (*Continued*).

TUBERCULOUS MYCOBACTERIAL DISEASE

The most common head and neck manifestation of mycobacterium tuberculosis is infection of the cervical lymph nodes. Tuberculous infection of the salivary glands is generally seen in older children and adults. The infection is believed to originate in the tonsils or gingiva and most commonly ascends to the parotid gland via its duct (Arrieta and McCaffrey 2005). Secondary infection of the salivary glands occurs by way of the lymphatic or hematogenous spread from the lungs. Clinically, tuberculous salivary gland infection presents in two different forms. The first is an acute inflammatory lesion with diffuse glandular edema that may be confused with an acute sialadenitis or abscess. The chronic lesion occurs as a slow growing mass that mimics a tumor.

NONTUBERCULOUS MYCOBACTERIAL DISEASE

Nontuberculous mycobacterial disease has become an important entity in the pediatric population. It has been estimated that greater than 92% of mycobacterial cervicofacial infections in children are a result of nontuberculous mycobacteria (Arrieta and McCaffrey 2005). The disease primarily affects children younger than 5 years of age. The specific organisms are *M. Kansasii*, *M. avium-intracellulare*, and *M. scrofulaceum*. The typical clinical presentation is that of a rapidly enlarging and persistent parotid and/or neck mass that has failed to resolve with antibiotic therapy (Figure 3.16). A characteristic violaceous discoloration to the skin develops. The treatment of choice is surgical removal of the involved salivary gland and associated lymph nodes.

Viral Salivary Gland Infections

MUMPS

Viral mumps is an acute, nonsuppurative communicable disease that often occurs in epidemics during the spring and winter months. The term mumps is derived from the Danish "mompen" which refers to mumbling, thereby describing the

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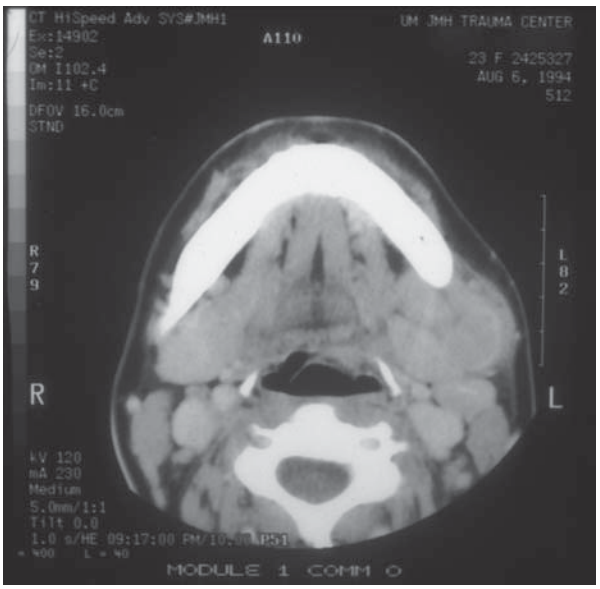

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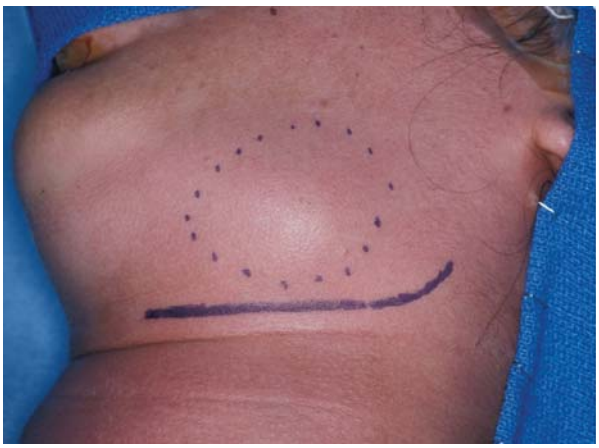

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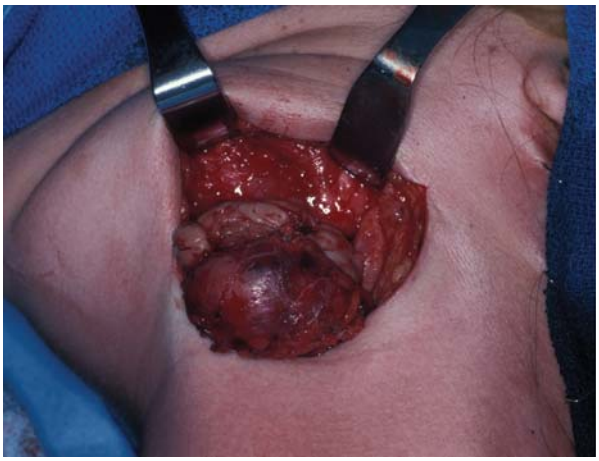

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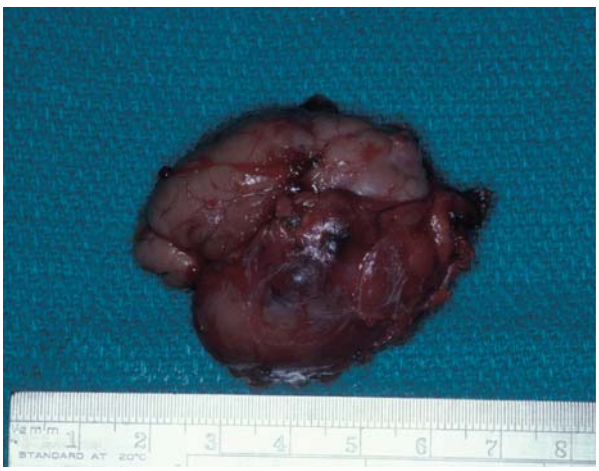
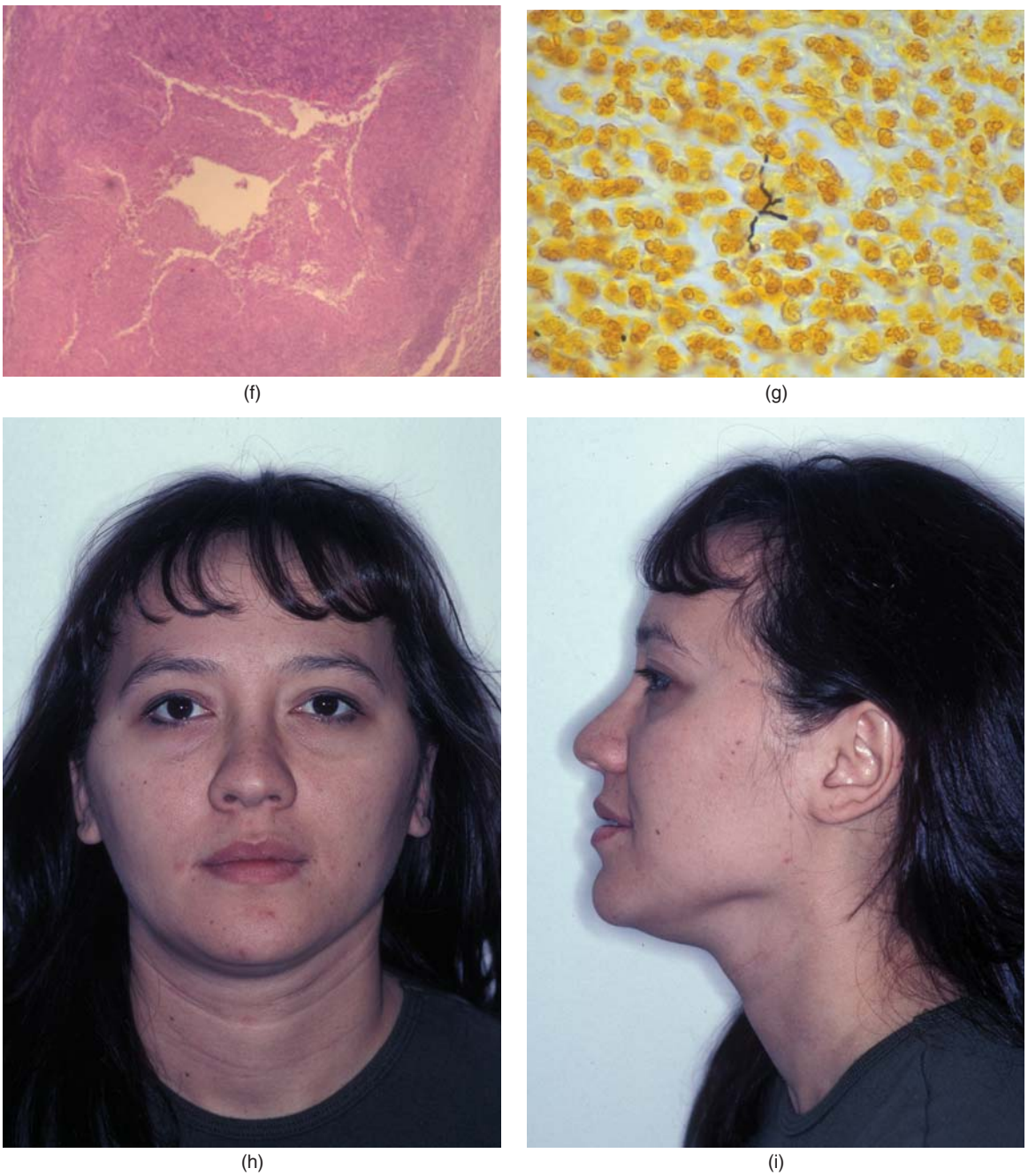


(e)

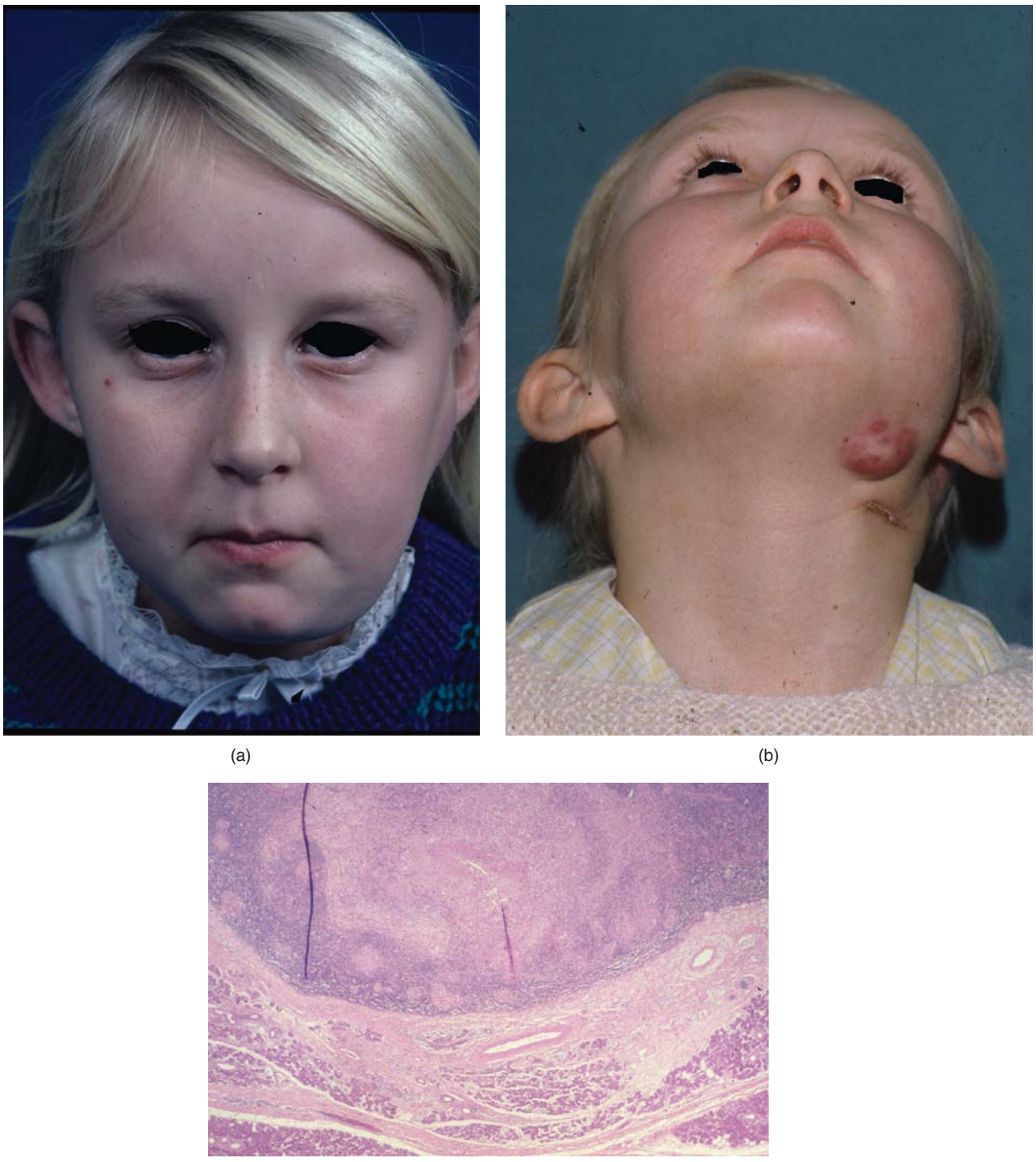
Figure 3.15. A 23-year-old woman (a) with a 2-week history of left submandibular pain and swelling. A history of animal scratch was provided. Computerized tomograms (b) revealed a mass of the left submandibular gland. The patient was taken to the operating room where excision of the submandibular gland and mass was performed. Wide access was afforded (c) and the mass was exposed (d). The specimen is noted in (e). Histopathology showed a stellate abscess (f). A Steiner stain (g) showed *Bartonella* (gram negative bacillus). Her disease resolved without long term antibiotics as seen in five year postoperative images (h and i).



(f) (g) (h) (i)

Figure 3.15. (*Continued*).

difficulty with speech because of inflammation and trismus (McQuone 1999; Arrieta and McCaffrey 2005). The nearly routine administration of the measles-mumps-rubella (MMR) vaccination has decreased the incidence of mumps in industrialized nations. Since the introduction of the live attenuated vaccine in the United States in 1967 and its administration as part of the MMR vaccine, the yearly incidence of mumps cases has declined from 76 to 2 cases per 100,000 (Murray, et al. 1994). Mumps characteristically occurs in the parotid glands. Although the disease is typically seen in children between 6 and 8 years of age, it may occur in adults who have avoided childhood infection, as well, and displays an equal sex predilection. The disease is caused most



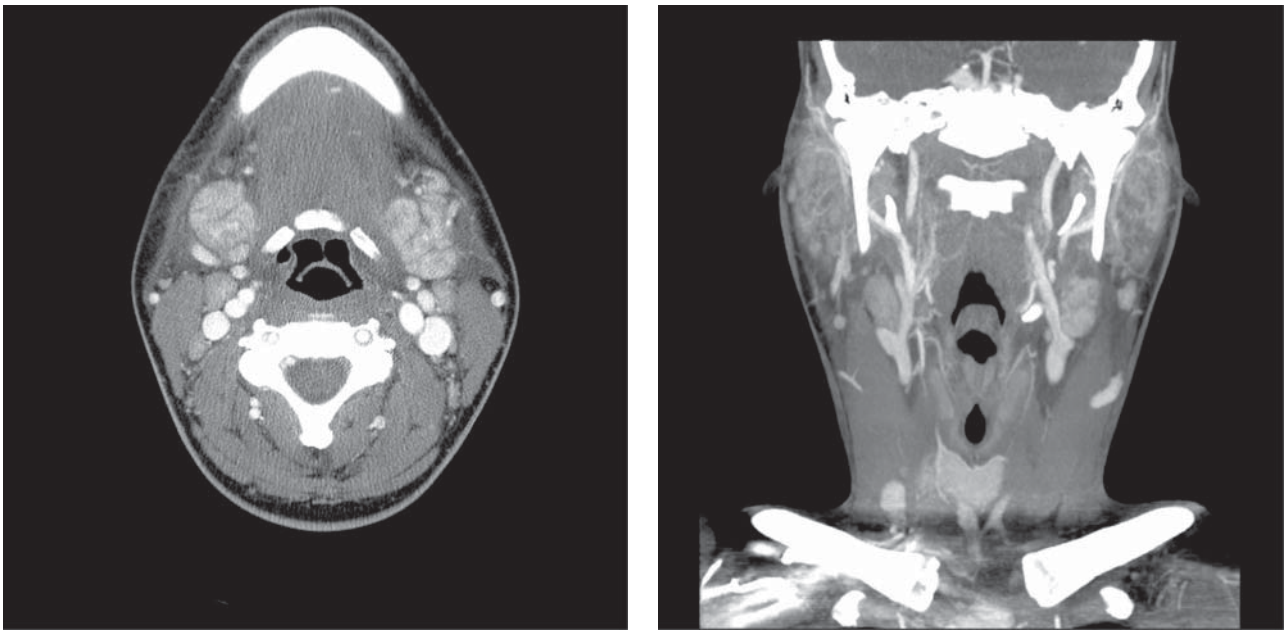
(a) (b)

(c)

Figure 3.16. A 9-year-old girl with a left parotid swelling with overlying erythema of skin but no signs of acute infection (a). The patient underwent left superficial parotidectomy and excision of a submandibular lymph node. Histopathology showed non-caseating granulomas (b), and cultures showed mycobacterium avium intracellulare. Two months following the parotidectomy, a left submandibular lymph node became enlarged (c) and was treated with medical therapy. Source: Mitchell DA, Ord RA. 1988. Atypical mycobacterial infection presenting as a parotid mass in a child. *J. Cranio Max. Fac. Surg*. 16:221–223. Reproduced with permission of Elsevier.

commonly by a paramyxovirus, a ribonucleic acid virus related to the influenza and parainfluenza virus groups. Several other nonparamyxoviruses may cause mumps, including coxsackie A and B viruses, Epstein–Barr virus, influenza and parainfluenza viruses, enteric cytopathic human orphan (ECHO) virus, and human immunodeficiency virus (HIV). Mumps is transmitted by infected saliva and urine. The incubation period between exposure and the development of signs and symptoms is 15–18 days. A prodromal period occurs that lasts 24–48 hours and involves fever, chills, headache, and preauricular tenderness. Following the prodromal period, rapid and painful unilateral or bilateral swelling of the parotid glands occurs. Features that distinguish sialadenitis due to mumps versus bacteria include a lack of purulent discharge, positive serum titers for mumps, and a relative lymphocytosis in mumps. In addition, the clinical presentation of mumps is mild; not infrequently patients may be asymptomatic (Schreiber and Hershman 2009). The diagnosis is made by demonstrating complement-fixing soluble (S) antibodies to the nucleoprotein core of the virus, which are the earliest antibodies to appear. These antibodies peak at 10 days to 2 weeks and disappear within 8–9 months. The S antibodies are therefore associated with active infection. The complement-fixing viral (V) antibodies are against outer surface hemagglutinin and appear later than S antibodies but persist at low levels for years. The diagnosis may also be made by isolating the virus from urine, which is possible up to 6 days prior and 13 days after the salivary gland symptoms occur (Rice 1998). Serum amylase levels may be elevated regardless of an associated pancreatitis. Abdominal pain is often indicative of mumps pancreatitis. Mumps orchitis occurs in 20% of adult males who have mumps parotitis (Goldberg and Bevilacqua 1995). Approximately half of these males will experience secondary testicular atrophy that may result in sterility if the testicular atrophy occurs bilaterally. Other rare complications of mumps include mumps hepatitis, mumps myocarditis, and mumps thyroiditis.

Treatment of mumps is supportive as spontaneous resolution of the disease occurs within 5–10 days. Such supportive care includes bedrest, proper hydration, and dietary modifications to minimize glandular activity. Persistent or recurrent parotid swelling may indicate the presence of sialadenitis. In the presence of such symptoms, a CT scan may be ordered that will frequently identify generalized sialadenitis to all salivary glands (Figure 3.17).



(a) (b)

Figure 3.17. Axial (a) and coronal (b) CT images demonstrating contrast enhancement of bilateral submandibular and parotid glands in a patient with a clinical viral prodrome.

HUMAN IMMUNODEFICIENCY VIRUS

HIV infection is associated with numerous pathologic processes involving the salivary glands, with the parotid gland being the most common. Parotid gland enlargement is estimated to occur in 1–10% of HIV-infected patients (Shanti and Aziz 2009). HIV-associated salivary gland disease (HIV-SGD) is a term used to describe the diffuse enlargement of the salivary glands. HIV-SGD may affect patients throughout all stages of the infection, and may be the initial manifestation of HIV infection (Schiodt, et al. 1992).

Patients with HIV-SGD present with a history of nontender swelling of one or more of the salivary glands (Figure 3.18). These swellings may fluctuate, but are generally persistent. Imaging studies are generally beneficial so as to diagnose lymphoepithelial cysts in this patient population that may clinically resemble the nontender swellings of the parotid glands in this patient population. Decreased salivary gland function results in xerostomia and sicca symptoms. This sicca symptom complex mimics Sjogren syndrome and has resulted in the classification of another HIV-related salivary gland process known as the diffuse infiltrative lymphocytosis syndrome (DILS). This pathologic process is characterized by the presence of persistent circulating CD8 lymphocytes and infiltration of organs by CD8 lymphocytes that occur predominantly in the salivary glands and lungs. While DILS appears similar to Sjogren syndrome, it can be differentiated by the presence of extraglandular involvement of the lungs, kidneys, and gastrointestinal tract. In addition, Sjogren autoantibodies will be absent in patients with DILS.

Medical management of HIV-SGD involves the use of antiretrovirals, observing meticulous oral hygiene, and the use of sialogogues. Corticosteroids may also be of use.

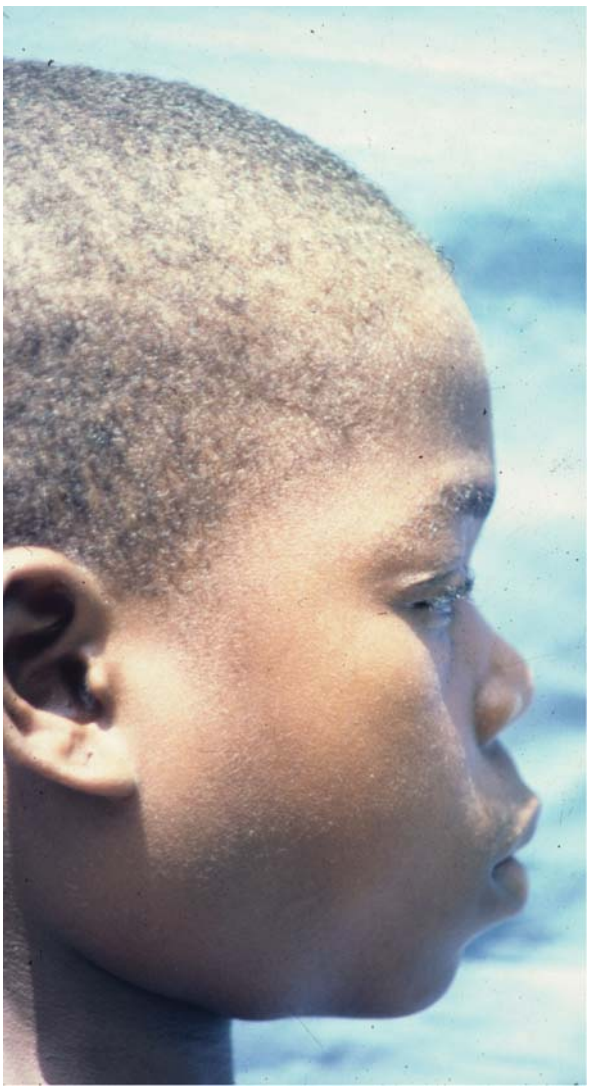


Figure 3.18. A 6-year-old African female with AIDS showing involvement of the right parotid gland by diffuse infiltrative lymphocytosis syndrome (DILS).

Collagen Sialadenitis

All of the collagen vascular diseases may affect the salivary glands, including polymyositis, dermatomyositis, and scleroderma, however, systemic lupus erythematosus is most commonly responsible. This disease is most frequently seen in fourth and fifth decade women. Any of the salivary glands may become involved, and a slowly enlarging gland is the presentation. The diagnosis is made by identification of the underlying systemic disorder, and salivary chemistry levels will reveal sodium and chloride ion levels that are elevated two to three times normal levels (Miloro and Goldberg 2002). The treatment of collagen sialadenitis involves treatment of the responsible systemic disease.

Summary

- Sialadenitis is an infection of salivary glands that has numerous etiologies including micro-organisms, and autoimmune diseases.

- Staphylococcal and streptococcal species are involved in community acquired acute bacterial parotitis (APB), and *Pseudomonas*, *Klebsiella*, *Prevotella*, *Fusobacterium*, *Hemophilus*, and *Proteus* species are cultured from hospital acquired cases of APB. Methicillin resistant staphylococcal aureus may be cultured from cases of community acquired and hospital acquired APB.
- The clinician must rule out a neoplastic process in a prompt fashion during the course of treating the sialadenitis.
- The presence of a sialolith must be considered in the initial workup of patients with a clinical diagnosis of sialadenitis. A screening panoramic radiograph or occlusal radiograph should be obtained. If identified, the expedient removal of a sialolith may permit functional recovery of the salivary gland.
- The parotid and submandibular glands are the most commonly affected salivary glands by sialadenitis.
- The purpose of initial treatment for sialadenitis is to provide medical therapy for the disorder, with surgical therapy being introduced if the disorder becomes refractory to medical treatment.
- Minimally invasive strategies have a role to play in the surgical treatment of sialadenitis, as well as surgical removal of the salivary gland.

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Chapter 4

Cysts and Cyst-like Lesions of the Salivary Glands

Outline

Introduction

Cysts of the salivary glands may originate as benign non-neoplastic entities, or in association with benign and malignant tumors of the salivary glands. Cystic development as part of specific neoplasms of the salivary glands is well recognized, including those that occur in the pleomorphic adenoma, Warthin tumor, mucoepidermoid carcinoma, acinic cell carcinoma, and the adenoid cystic carcinoma. The histologic features of these neoplasms are sufficiently distinctive; however, non-neoplastic salivary gland cysts do require differentiation from cystadenoma, mucoepidermoid carcinoma, and acinic carcinoma (Dardick 1996). Many cysts of the salivary glands may be generically attributed to an obstructive process. They can occur as a result of traumatic severance of salivary gland ducts, partial or complete blockage of the excretory ducts, or stasis of salivary flow in ducts. For the purpose of this chapter, salivary cysts are categorized in many ways, including those that originate directly from the salivary gland and those entities that are associated with the salivary glands. In addition, there are those salivary cysts that exhibit a true cystic epithelium and those that are lined with a non-epithelial lining, that is, pseudocysts. Finally, it is possible to categorize these lesions as acquired (obstructive due to stricture, neoplasms, sialoliths, or trauma) and developmental (dermoid, branchial cleft, branchial pouch, and ductal). It is the purpose of this chapter to discuss those salivary gland cysts and cyst-like lesions that are developmental and acquired in a non-neoplastic nature (see Table 4.1).

Mucous Escape Reaction

The mucous escape reaction can be defined as a pooling of salivary mucus within a connective tissue lining. This concept is defined by a number of names including mucocele, ranula, mucous retention phenomenon, and mucus retention cyst. Of these, mucocele and ranula are the two best known entities to clinicians diagnosing and managing pathology in the head and neck region. It was once believed that the lesion developed as a result of obstruction of a salivary gland's excretory duct with the subsequent formation of an epithelially lined cyst (Thoma, 1950). Early studies investigated the result of ligation of the excretory ducts of the submandibular and sublingual glands (Bhaskar, et al. 1956a,b). A mucous escape reaction did not result, thereby leading to further investigation.

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Table 4.1. Cysts and cyst-like lesions of the salivary glands – Nomenclature and Classification

Nomenclature
- Mucous escape reaction
  - Mucocele
  - Ranula
- Mucous retention cysts
- Lymphoepithelial cysts
  - HIV-associated lymphoepithelial cysts
- Developmental cysts
  - Branchial cleft cysts
  - Dermoid cysts
  - Polycystic (dysgenetic) disease

Classification
- I. Etiology
  - a. *Origination from* salivary gland tissue
    - i. Mucous escape reaction
    - ii. Mucous retention cyst
  - b. *Association with* salivary gland tissue
- II. Lining
  - a. True cystic lining
    - i. Mucous retention cyst
  - b. Non-epithelial lining (pseudocyst)
    - i. Mucous escape reaction
      1. Mucocele
      2. Ranula
- III. Occurrence
  - a. Acquired
    - i. Mucous escape reaction
    - ii. Mucous retention cyst
  - b. Developmental

The complete obstruction of a salivary duct by the presence of a sialolith without the development of a mucous escape reaction substantiates the lack of a cause and effect relationship. Subsequent studies determined that severance of the excretory duct was required to produce extravasation of salivary mucin into the surrounding tissues with the development of a lesion histologically identical to the mucus escape reaction observed in humans (Bhaskar, et al. 1956a,b). It is now accepted that severance of a salivary duct with resultant pooling of mucus into surrounding tissues is the pathophysiology of the mucus escape reaction. The fibrous connective tissue encasing the pooled saliva is presumably due to the foreign body nature of the saliva. The occasional report of an epithelial-like lining can be explained as a misinterpretation of compressed macrophages resembling a layer of cuboidal-shaped cells (van den Akker, et al. 1978). When these lesions occur in the floor of the mouth, a designation of ranula is given, while a similar lesion in the lower lip carries a designation of mucocele.

CLINICAL FEATURES AND TREATMENT OF THE MUCUS ESCAPE REACTION

The mucus escape reaction may develop from a major or minor salivary gland, but seems to be more commonly observed in the minor glands. Armed Forces Institute of Pathology data of 2339 cases indicates that the minor glands are the site of predilection of this lesion, with 2273 (97.2%) of the 2339 lesions occurring in these glands. The lip accounted for 1502 of these lesions (64.2%) with the lower lip being the most common site (98.8% when the site was specified). This figure is consistent with other series that indicate a predilection of lower lip lesions (Cataldo and Mosadomi 1970). The major glands showed a nearly equal distribution of occurrence in the parotid, submandibular and sublingual glands, and collectively accounted for only 2.9% of the 2339 cases.

Most investigators consider these lesions to be most common in children and young adults, with a mean age of 25 years. No significant sex predilection has been offered. The clinical appearance of these lesions differs depending on their depth within surrounding soft tissues. Superficial lesions present as blue, raised soft tissue swellings with a fluctuant character on palpation (Figure 4.1). The blue hue is generally reflective of the color of pooled saliva at the mucosal surface. Lesions that are located more deeply in the soft tissues take on the color of the surrounding soft tissues; however, they may retain their fluctuant character. The most common clinical course of mucous escape reactions is that of a painless mucosal swelling that develops during a period of between a few days to 1 week and ruptures with apparent resolution with subsequent recurrence occurring within 1 month. Mild symptoms of pain may accompany mucus escape reactions if secondary trauma or inflammation occurs. Pain may also occur in the rare event that the mucus escape reaction impedes the flow of saliva due to obstruction (Figure 4.2).

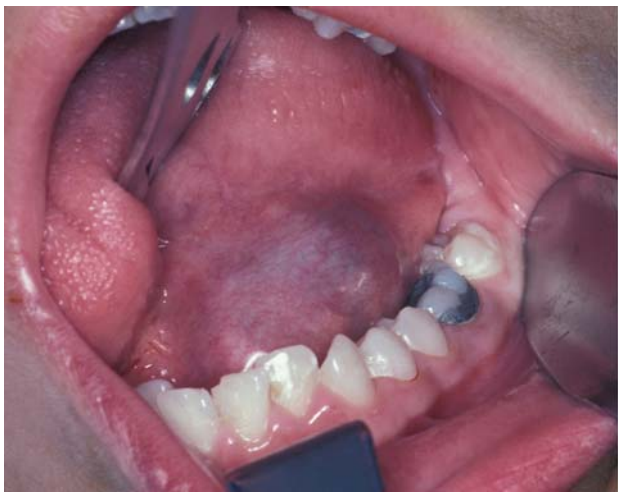


Figure 4.1. The typical appearance of a ranula of the floor of mouth. The characteristically raised nature of the lesion, as well as its blue hue, is appreciated.

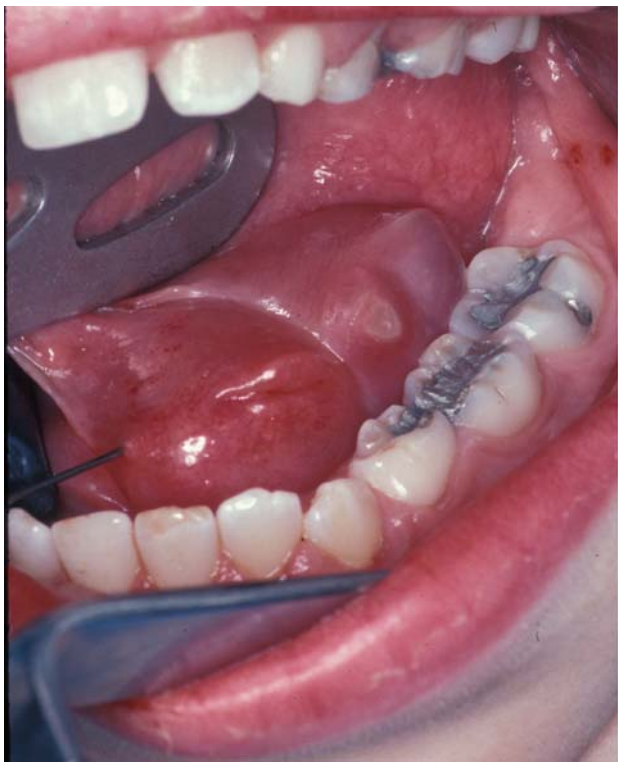


Figure 4.2. This ranula has resulted in significant pain experienced by the patient. The size of the ranula has resulted in obstruction of the sublingual gland.

Mucocele

Mucoceles are common lesions of the oral mucosa, and perhaps the most common benign salivary gland lesion in the oral cavity. The incidence of mucoceles is understandable due to the prevalence of minor salivary gland tissue in the oral cavity and the frequent occurrence of trauma to these tissues, which results in their formation. These lesions are painless, freely movable, smooth, and fluctuant. Their appearance is so characteristic that the clinical diagnosis is most frequently confirmed by subsequent histopathologic diagnosis following removal (Figure 4.3). As such, an incisional biopsy is not required for proper surgical treatment of the mucocele. Clearly, the most common location for these lesions is the lip, and specifically the lower lip. This notwithstanding, mucoceles occur on the buccal mucosa, tongue, and palate. Patients often give a history of the lesions spontaneously bursting with predictable recurrence. Mucoceles occur most commonly in children and young adults, probably due to the relatively high incidence of oral trauma in younger patients. Treatment with surgical excision of the mucocele and its associated minor salivary gland tissue is highly curable.

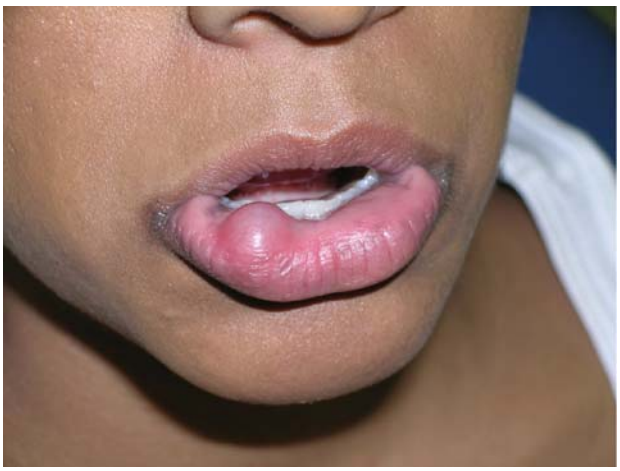


Figure 4.3. The classic appearance of a mucocele of the lower lip. Similar to a ranula of the floor of mouth, it shows an elevated blue lesion.

Ranula and Plunging Ranula

The ranula represents the prototypical mucus escape reaction occurring in the floor of mouth. Its nomenclature stems from its derivation from the Latin diminutive “rana,” or frog that refers to its resemblance to the belly of a frog (Figure 4.4). The lesion has a characteristic appearance and history, commonly exhibiting a blue color and displaying periods of bursting of the lesion with liberation of saliva, only to relapse some time thereafter

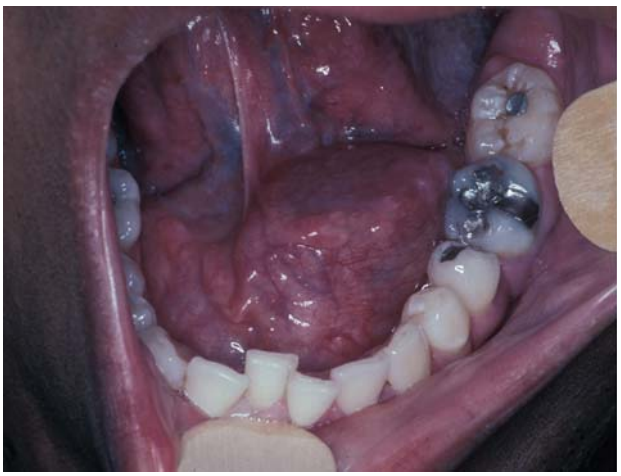


Figure 4.4. A ranula of the left floor of mouth. While the lesion is clearly elevated, only subtle signs exist of its blue color.

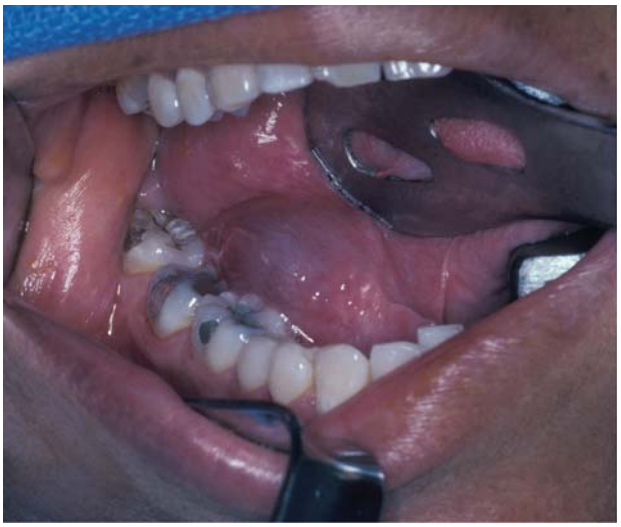


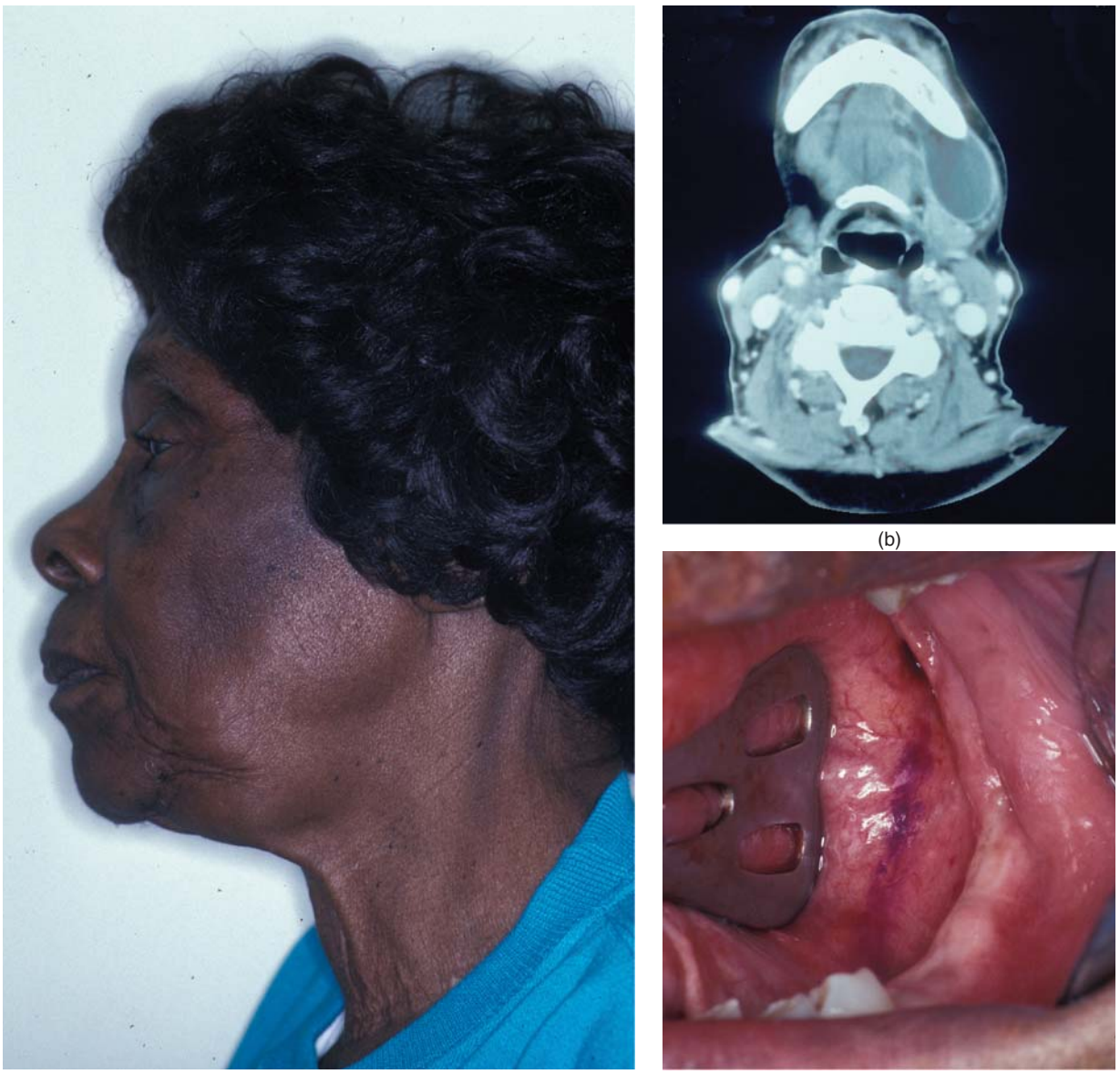
Figure 4.5. A ranula of the right floor of mouth. Classic signs of elevation and the blue discoloration are present.

(Figure 4.5). The development of a cervical component of the ranula has been a subject of fascination for centuries (Catone 1995). The oral and cervical mucus escape reactions may exist simultaneously (Figure 4.6), or they may occur independently of one another. As such, it was once considered possible that they had different etiologies, with the oral lesion being derived from the sublingual gland and the cervical lesion being derived from the submandibular gland. Some observed that the neck mass was often preceded by repeated spontaneous evacuations or surgical drainages of the oral

(a)

(b)

Figure 4.6. An 8-year-old girl with obvious right submandibular swelling (a) as well as simultaneous clinical evidence of a ranula in the right floor of mouth (b).



(a) (b) (c)

Figure 4.7. This elderly woman shows left submandibular swelling (a). Her history includes numerous aspirations of fluid within a ranula of the left floor of mouth. Computerized tomograms of the neck show a fluid filled lesion of the submandibular region (b). A diagnosis of plunging ranula was made and the patient underwent left sublingual gland excision (c). Examination of the left floor of mouth did not show signs of ranula in this region. Scar tissue formation from her previous aspirations resulted in the development of a plunging ranula.

lesion. This was perhaps the first explanation that scar tissue formation in the mucosa of the floor of mouth was responsible for the development of the cervical mass as it descended through the cleft of the posterior extent of the mylohyoid muscle as a path of least resistance (Figure 4.7) (Braun and Sotereanos 1982). The anatomy of the mylohyoid muscle and its hiatus or cleft, and herniations within the mylohyoid muscle, has been studied to explain the development of a plunging ranula. In their study of 23 adult cadavers, Harrison, et al. identified a bilateral mylohyoid hiatus to exist in ten of their 23 specimens (43%), with the hiatus being unilateral in six (26%) and bilateral in four

(17%) cadavers (Harrison et al. 2013). The median anteroposterior dimension of the hiatus was 7 mm with a range of 2–11 mm, and the median mediolateral dimension was 14 mm with a range of 7–20 mm. The authors identified sublingual gland tissue in nine hernias and fat in six hernias. Other authors have demonstrated that approximately one third of the population has discontinuities of the mylohyoid muscle such that direct invasion of the pseudocyst through these defects of the muscle permits extension into the neck (McClatchey, et al. 1984). While the pathophysiology of the plunging ranula is now well understood from an anatomic perspective, the literature continues to identify controversy with regard to the most appropriate means to treat the ranula and plunging ranula (Patel, et al. 2009; Harrison 2010; Lesperance, et al. 2013; Sigismund, et al. 2013).

If anything has been learned by reading the scientific literature on the topic of cyst-like lesions of the salivary glands, it is the common pathogenesis of three clinical entities: the mucocele, the oral ranula, and the plunging ranula. Specifically, it is their lack of an epithelial lining, and their association with a salivary gland, whether major or minor, that these entities share in common. If the offending sublingual salivary gland is not removed, the lesion has a statistical likelihood of recurrence (Catone, et al. 1969; Suresh, et al. 2012). This notwithstanding, while the diagnosis of the conventional, non-plunging ranula remains straightforward, its management has historically been variable and controversial, ranging from incision and marsupialization to sublingual gland excision. Interestingly, most mucoceles are located in the lower lip and are treated with an excision of the mucocele and associated etiologic minor salivary gland tissue of the lower lip. Ironically, although the ranula of the floor of mouth is the second most common type of mucocele, removal of the ranula and the associated salivary gland, in this case the sublingual gland, has not been uniformly accepted as standard treatment of the ranula as it is for the lower lip mucocele. To this end, there are several published papers adamantly recommending that more conservative procedures be performed as first line therapy (Baurmash 1992, 2007). One such procedure is marsupialization with packing (Baurmash 1992). The author contends that routine sublingual removal is inappropriate therapy for several reasons. The first is that the term "ranula" is loosely applied to any cyst-like structure of the floor of mouth. He believes that some of these lesions are unrelated to the sublingual gland, such that its removal is not indicated. Specifically, he cites the existence of mucoceles arising from the mucus-secreting incisal gland in the anterior floor of mouth, single or multiple retention cysts involving the openings of the ducts of Rivinus, and retention cysts at the Wharton duct orifice that can resemble the sublingual gland associated ranula, but that would possibly not be cured with sublingual gland removal. Moreover, the author states that sublingual gland excision is potentially associated with significant morbidity such as injury to the Wharton duct with resultant salivary obstruction or salivary leakage, and lingual nerve injury (Baurmash 1992). Zhao and his group presented an objective assessment of complications associated with surgical management of ranulas treated with a variety of procedures (Zhao, et al. 2005). These included 9 marsupializations, 28 excisions of the ranula only, 356 sublingual gland excisions, and 213 excisions of both the sublingual gland and ranula. A total of 569 sublingual gland excisions were performed in 571 patients undergoing 606 operations. Injury to the Wharton duct occurred in 11 of 569 patients who underwent excision of the sublingual gland with or without excision of the ranula compared to 0 of 37 patients who did not undergo sublingual gland excision. Injury to the lingual nerve occurred in 21 of patients who underwent sublingual gland excision compared to 0 patients who did not undergo sublingual gland excision. Of particular note is that recurrence of the ranula occurred in 1.2% of patients who underwent excision of their sublingual glands compared to 60% of patients who underwent marsupialization or excision of the ranula only. Baurmash laments that simple marsupialization has fallen into disfavor because of the excessive number of failures associated with this procedure (Baurmash 1992). The recurrence patterns have been confirmed by other authors, as well (Yoshimura, et al. 1995). As such, he recommends packing the cystic cavity with gauze for 7–10 days. In so doing, he reports that the recurrence rate is reduced to 10–12% (Baurmash 2007). McGurk points out that the disadvantage of this procedure is that the results are unpredictable and that the packing is uncomfortable for the patient (McGurk 2007). He concludes by stating that reliable eradication of the ranula comes from removal of the sublingual gland. Further work

by this author has led to a recommendation for conservative treatment of the oral ranula by partial excision of the sublingual gland (McGurk et al. 2008). It is true that the sublingual gland excision requires an anatomically precise approach such that some surgeons may wish to defer the sublingual gland excision for recurrences. Unfortunately, the development of scar tissue in the floor of mouth is such that the anatomy may be more obscured related to a recurrence after a marsupialization and packing procedure. With this issue in mind, a sublingual gland excision should probably be performed from the outset (Figure 4.8). While the anatomy of the floor of mouth might

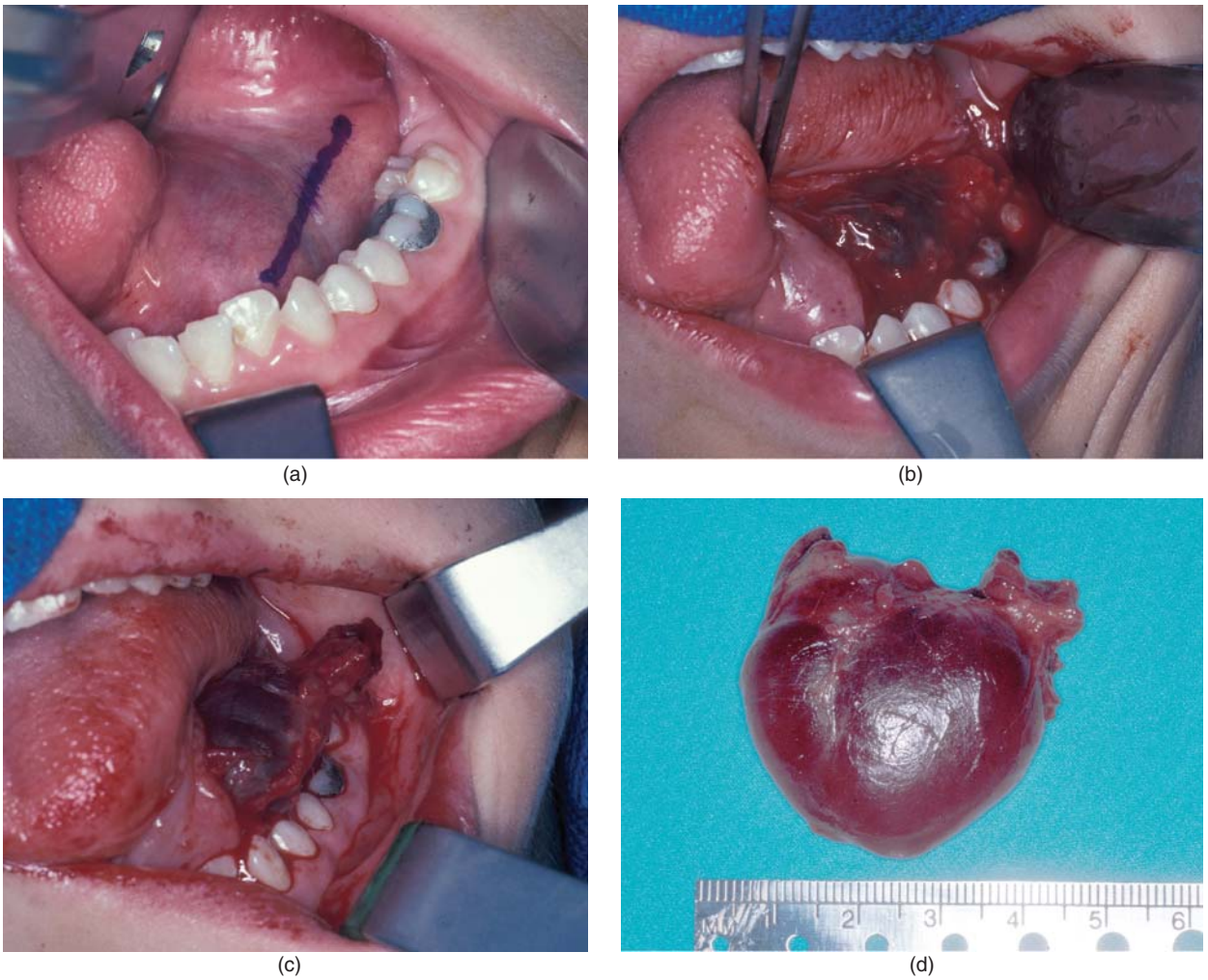
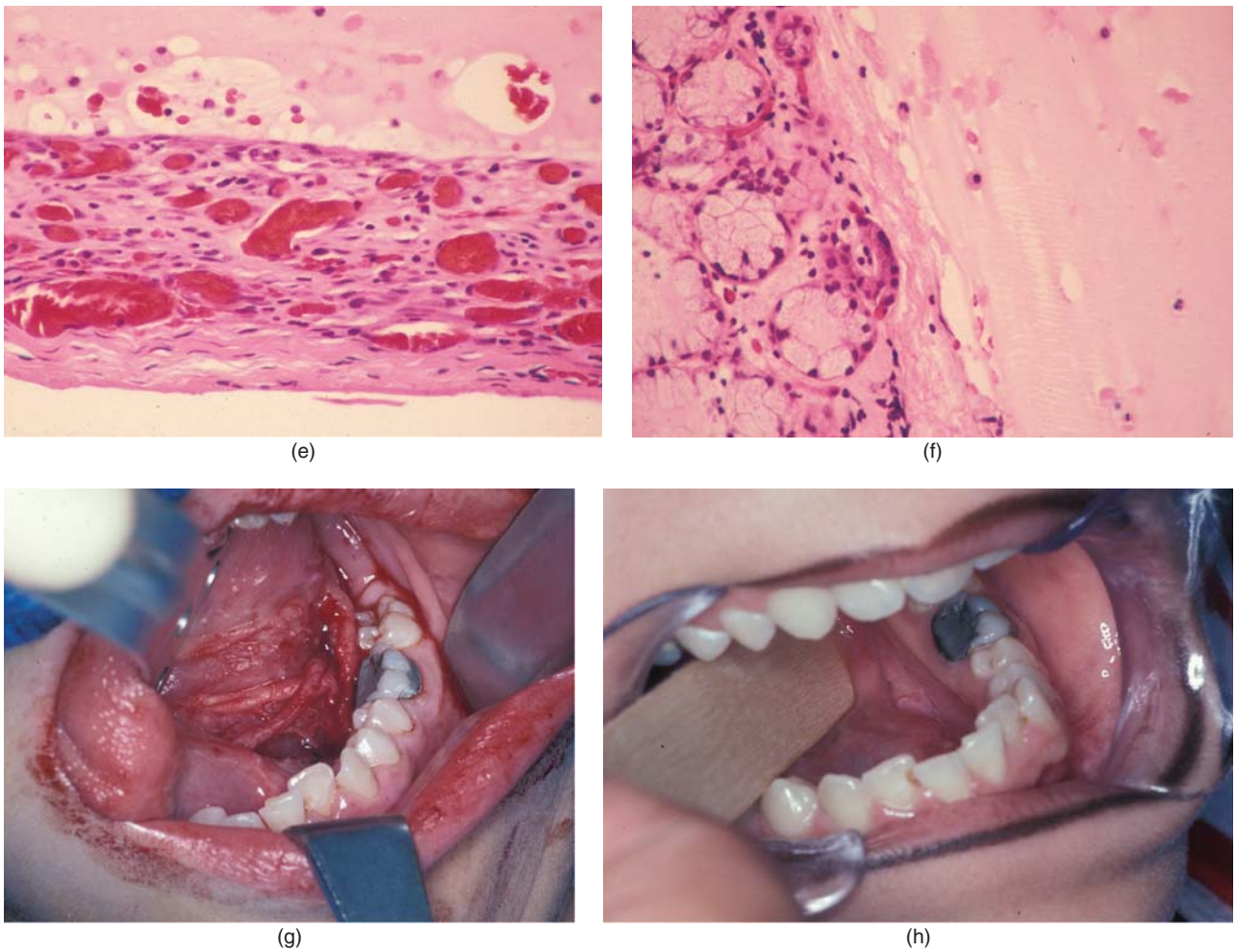


Figure 4.8. The excision of the sublingual gland and associated ranula from Figure 4.1. An incision is designed over the prominence of the sublingual gland and ranula, and lateral to the Wharton duct (a). Careful dissection allows for separation of the mucosa from the underlying pseudocystic membrane (b). The dissection continues to separate the sublingual gland from surrounding tissues, including the underlying Wharton duct and the lingual nerve beneath the Wharton duct (c). The specimen and ranula are able to be delivered en bloc (d). If the pseudocyst bursts intraoperatively, no compromise in cure exists as long as the sublingual gland is completely excised. The histopathology shows the non-epithelial lining (e) and the intimate association of the sublingual gland and mucus escape reaction (f). The remaining tissue bed shows the anatomic relationship of the preserved superficial Wharton duct and underlying lingual nerve (g). Wharton duct originates posteriorly in a medial position to the lingual nerve and terminates in a position lateral to the nerve. The sublingual vein can be visualized in the tissue bed lateral to the anterior aspect of Wharton duct (g). Healing is uneventful as noted in the one month postoperative image (h).



(e) (f) (g) (h)

Figure 4.8. (*Continued*)

be considered foreign and intimidating to some surgeons, preservation of the lingual nerve and Wharton duct is not a difficult task, and treatment of this pathologic process with sublingual excision should be a curative procedure. One pathologic and clinical similarity of the ranula and mucocele is their derivation from salivary gland tissue. As stated previously, there does not seem to be a dispute amongst clinicians as to the best surgical therapy for the mucocele, with complete surgical excision of the etiologic minor salivary tissue along with the mucus escape reaction being highly accepted (Figure 4.9). As such, it is advisable to apply the same approach to the ranula that only differs from the mucocele in the anatomic region in which it occurs. With regard to the ranula and plunging ranula, even the most extensive lesions are predictably treated for cure with excision of the offending sublingual gland. While it is not essential to remove the non-epithelial lined pseudocyst with the sublingual gland, it is common for the tightly adherent pseudocyst to be delivered with the sublingual gland specimen (Figure 4.10). As such, documentation of a plunging component to the ranula serves a matter of medical completeness rather than representing an implication for surgical treatment.

Submandibular Gland Mucocele

Clinical experience demonstrates that patients occasionally present with a neck examination consistent with a diagnosis of plunging ranula, yet without signs of ranula on oral examination.

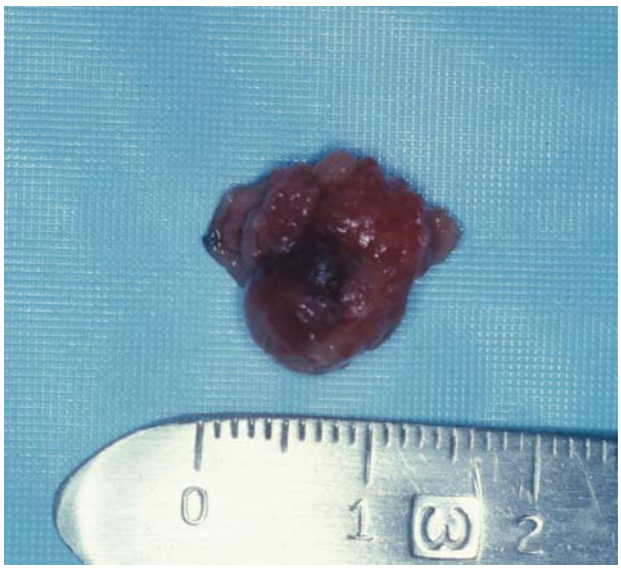


Figure 4.9. The specimen from the excision of the mucocele seen in Figure 4.3. The minor salivary gland tissue remains attached to the mucus escape reaction.

Moreover, many of these patients will demonstrate CT evidence of a fluid filled lesion originating from the submandibular gland rather than from the sublingual gland. These rare cases are typically diagnosed as submandibular gland mucoceles (Ozturk, et al. 2005; Hze-Khoong, et al. 2012) on clinical grounds and should be treated with excision of the offending submandibular gland and associated mucocele (Figure 4.11). A thorough analysis of the CT scans is thought to be able to distinguish the sublingual gland ranula from the submandibular mucocele by identifying the tail-like extension of the ranula to the sublingual gland that is absent in the submandibular gland mucocele (Anastassov, et al. 2000). This notwithstanding, the management of the submandibular gland mucocele requires removal of the submandibular gland and its associated mucocele. Excision of the sublingual gland en bloc with the submandibular gland and mucocele may be performed when the mucocele appears to be intimately associated the sublingual gland (Ozturk, et al. 2005). The surgeon's intraoperative discretion dictates whether the sublingual gland is indicated for removal when providing surgical treatment for the submandibular gland mucocele. As with the mucocele and the ranula, appropriate surgical management of the submandibular mucocele represents a curative procedure for this diagnosis.

Cyst of Blandin and Nuhn Glands

On rare occasions, the mucosa of the ventral surface of the tongue may become a source for the development of a mucous escape reaction. This process is referred to as a cyst of Blandin and Nuhn gland (Figure 4.12). This designation is a misnomer, as this process represents a mucous escape reaction, rather than a true cyst. In this sense, then, it represents a ranula of the tongue. Simple excision of the "cyst" and the associated gland of Blandin and Nuhn is the treatment of choice with recurrence being uncommon.

Mucous Retention Cysts

The mucus retention cyst is less common than the mucus escape reaction. This entity is a true cyst that is lined by epithelium. The exact classification of this lesion seems to be in question. Some prefer to simply include it with the more common mucus escape reaction, whereas others describe it as a separate entity (Koudelka 1991). The pathogenesis seems to be related to partial obstruction of a duct, as opposed to complete severance of the salivary duct that is seen in the mucus escape reaction. The increased pressure in the salivary duct causes dilatation without rupture such that proliferation of the ductal epithelium occurs. The Armed Forces Institute of Pathology reviewed 178 cases of mucus retention cysts, accounting for 0.9% of all salivary gland pathology cases in their files (Koudelka 1991). One hundred and seventy-one cases (96%) occurred in the major salivary glands with 156 (87.6%) occurring in the parotid gland (Figure 4.13), 14 cases (7.8%) occurring in the submandibular gland, and only 1 case occurring in the sublingual gland. Only one case was specifically documented as occurring in the minor salivary glands. The mean age of patients is late 40s, with a nearly equal gender predilection. The clinical presentation of the mucus retention cyst is that of a slowly enlarging, painless, fluctuant soft tissue swelling that may persist from months to years. These cysts vary in their size, and the color of the overlying tissues depends on their depth within the soft tissue. Superficial lesions are blue in color, whereas deep lesions take on the same color of the overlying tissue. Some pathologists have split the mucus retention cysts into separate categories. Eversole has categorized these lesions as mucus retention cysts, reactive oncocytoid cysts,

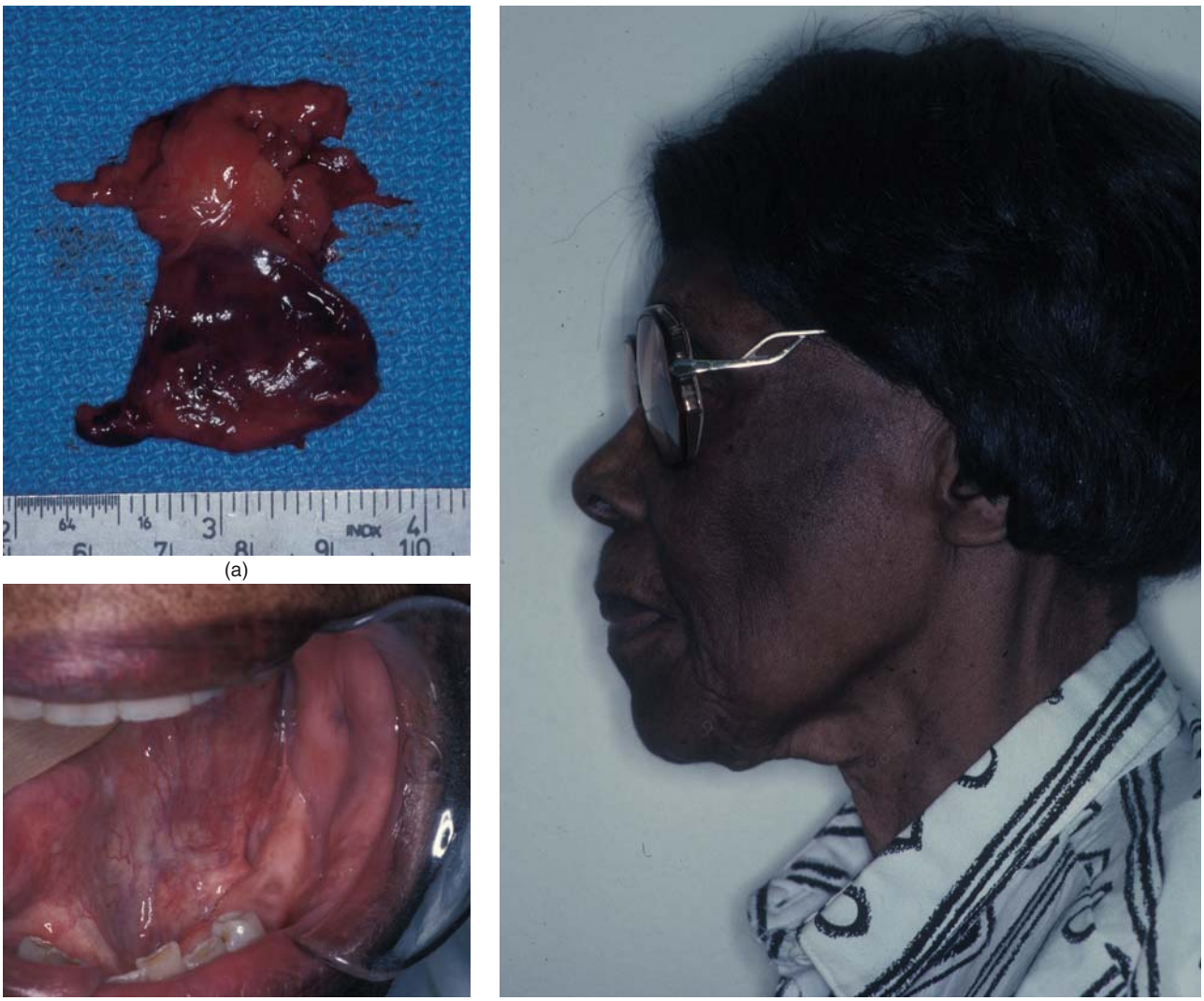


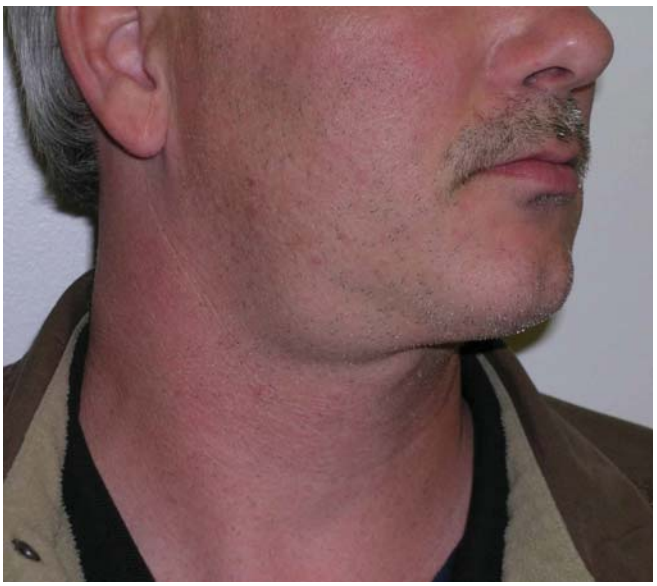
Figure 4.10. The patient seen in Figure 4.7 underwent excision of her left sublingual gland for her plunging ranula. The specimen (a) includes the sublingual gland and associated mucus escape reaction. Her 2-year postoperative examination shows no mass in the submandibular region (b) and a normal oral examination without recurrence of the ranula (c).

and mucopapillary cysts (Eversole 1987). In his series of 121 mucus retention cysts, he found 70 mucus retention cysts, 41 reactive oncocytoid cysts, and 10 mucopapillary cysts. From a pathologic and surgical standpoint, perhaps the most striking piece of information in this report was the need to distinguish the mucopapillary cyst from the low-grade mucoepidermoid carcinoma.

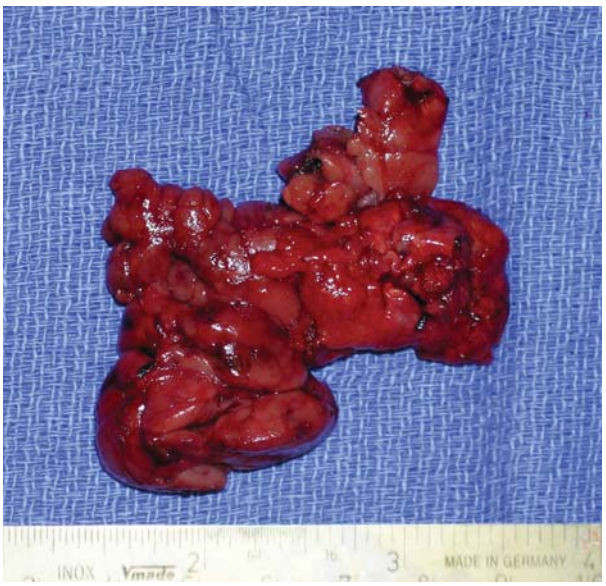
Treatment of mucus retention cysts is most commonly conservative surgical excision (Figure 4.13). Cysts within or closely associated with a salivary gland should include that salivary gland with the excision. Some mucus retention cysts, however, may be removed without the inclusion of the salivary gland, a distinct departure from the recommendations associated with mucus escape reactions.

Parotid Cysts Associated with Human Immunodeficiency Virus Infection

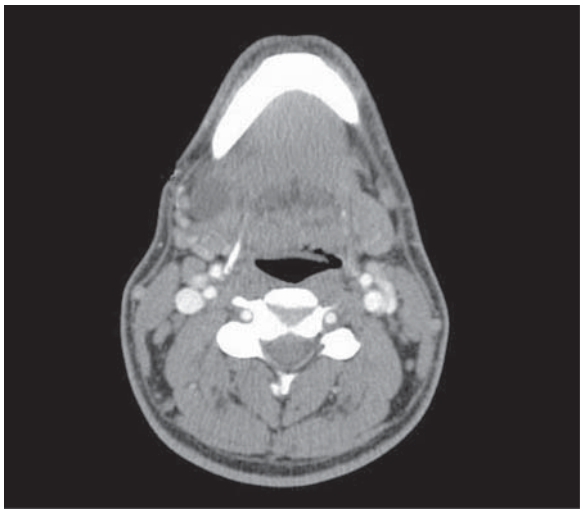
Infection with the human immunodeficiency virus has been shown to manifest in variety of ways.



(a)



(c)



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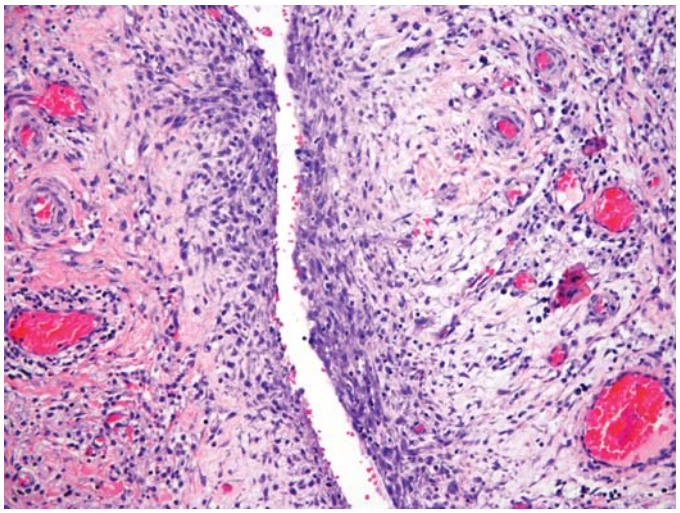


(d)

Figure 4.11. A 48-year-old man with a swelling of the right submandibular region (a). Palpation of this swelling revealed a ballotable mass. A CT scan revealed a fluid filled lesion intimately associated with the right submandibular gland (b). A clinical diagnosis of submandibular gland mucocele was made and the patient underwent excision of his right sublingual gland and submandibular gland/mucocele (c). The presence of a submandibular gland mucocele was confirmed by histopathology (d). Hematoxylin and eosin, original magnification ×100.

Symptoms related to the head and neck have historically been encountered in this disease. It has been reported that 41% of patients with acquired immunodeficiency syndrome (AIDS) initially presented with signs or symptoms of head and neck disease (Marcussen and Sooy 1985). Salivary gland diseases include the enlargement of major salivary glands with or without hypofunction and xerostomia (Owotade et al. 2005). In early lesions the submandibular and sublingual glands are often initially affected and enlarged. As the disease progresses, however, parotid gland swelling is more commonly noted. As many as 5–10% of patients with HIV-1 infection have been reported to have

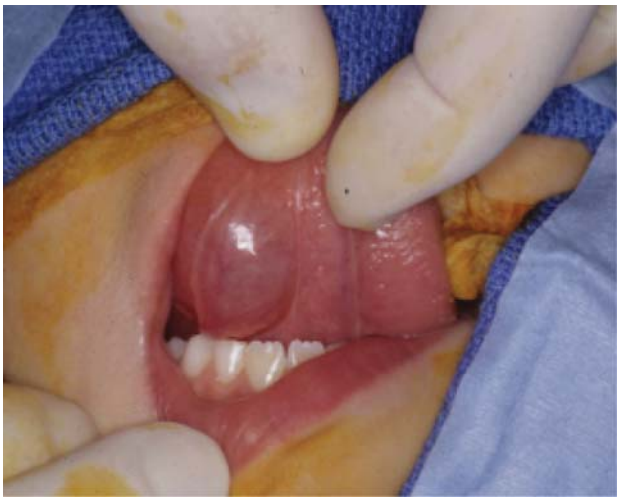
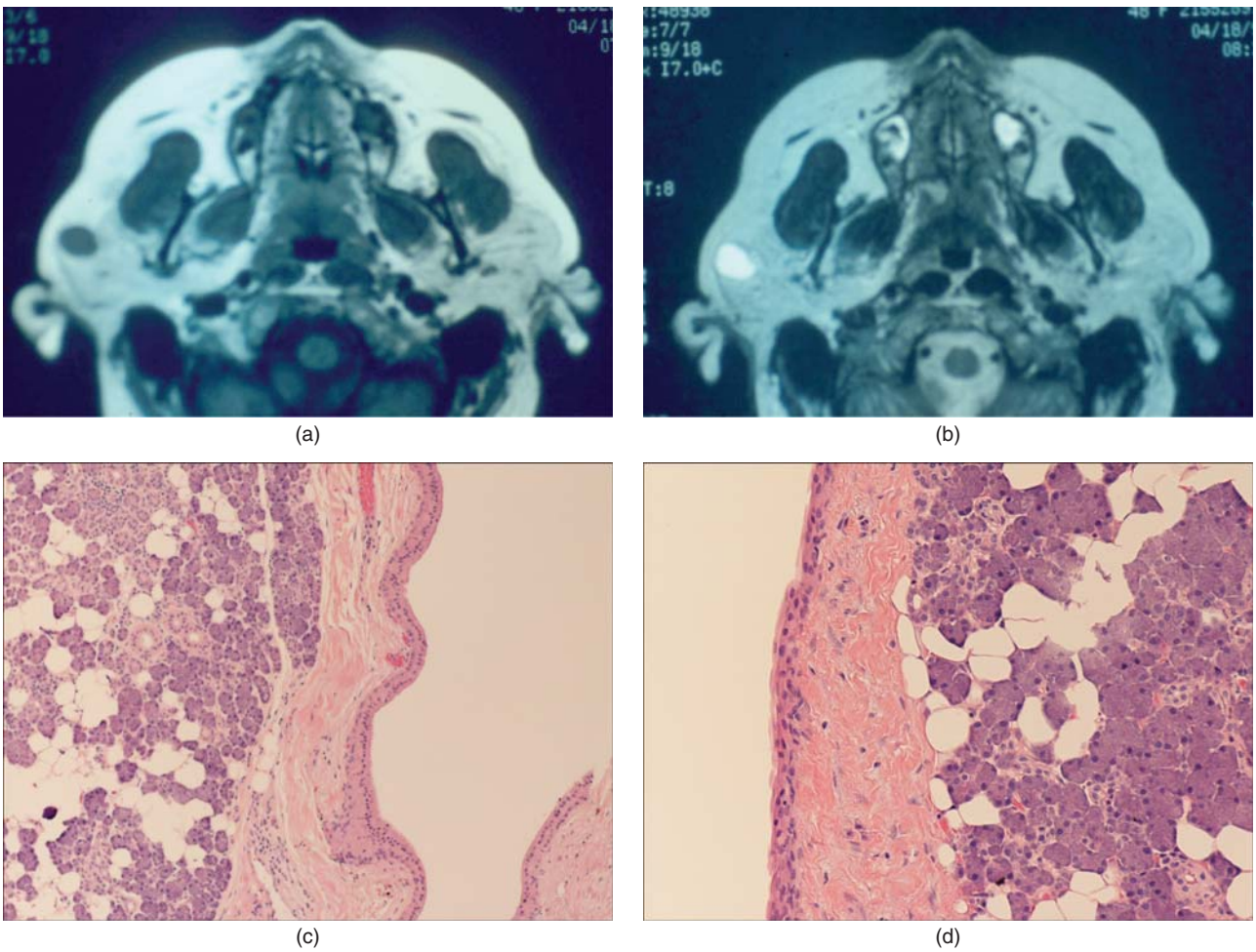


Figure 4.12. A cyst of Blandin and Nuhn of the ventral surface of the tongue. Simple excision of the cyst and associated minor salivary gland tissue is curative for this mucus escape phenomenon.

parotid swelling with the incidence increasing to approximately 20% in AIDS patients (Owotade, et al. 2005). Ryan and his group were the first to describe salivary gland involvement in HIV disease as intrasalivary gland lymphadenopathy (Ryan, et al. 1985). Shortly thereafter, parotid gland cysts were reported, and were noted to resemble the benign lymphoepithelial lesion (BLL) histologically (Colebunders, et al. 1988). The BLL is a benign sialadenopathy associated with Sjogren syndrome with pathognomonic epimyoepithelial islands. It is felt to represent an autoimmune reaction in Sjogren syndrome, but the BLL is felt to be of unknown pathogenesis in HIV (Sperling, et al. 1990). It remains unclear whether lymphoepithelial cysts within parotid glands in HIV/AIDS patients develop from pre-existing salivary gland inclusions in intra-parotid lymph nodes or from a lymphoepithelial lesion of the parenchyma of the salivary gland.



(a) (b) (c) (d)

Figure 4.13. A mucous retention cyst of the parotid gland as noted on MRI (T1 images – a; T2 images – b). The patient underwent a superficial parotidectomy due to the concern for a cystic neoplasm. Histopathology showed a parotid cyst lined by columnar epithelium in one section of the cyst (c) and squamoid epithelium in another section (d).

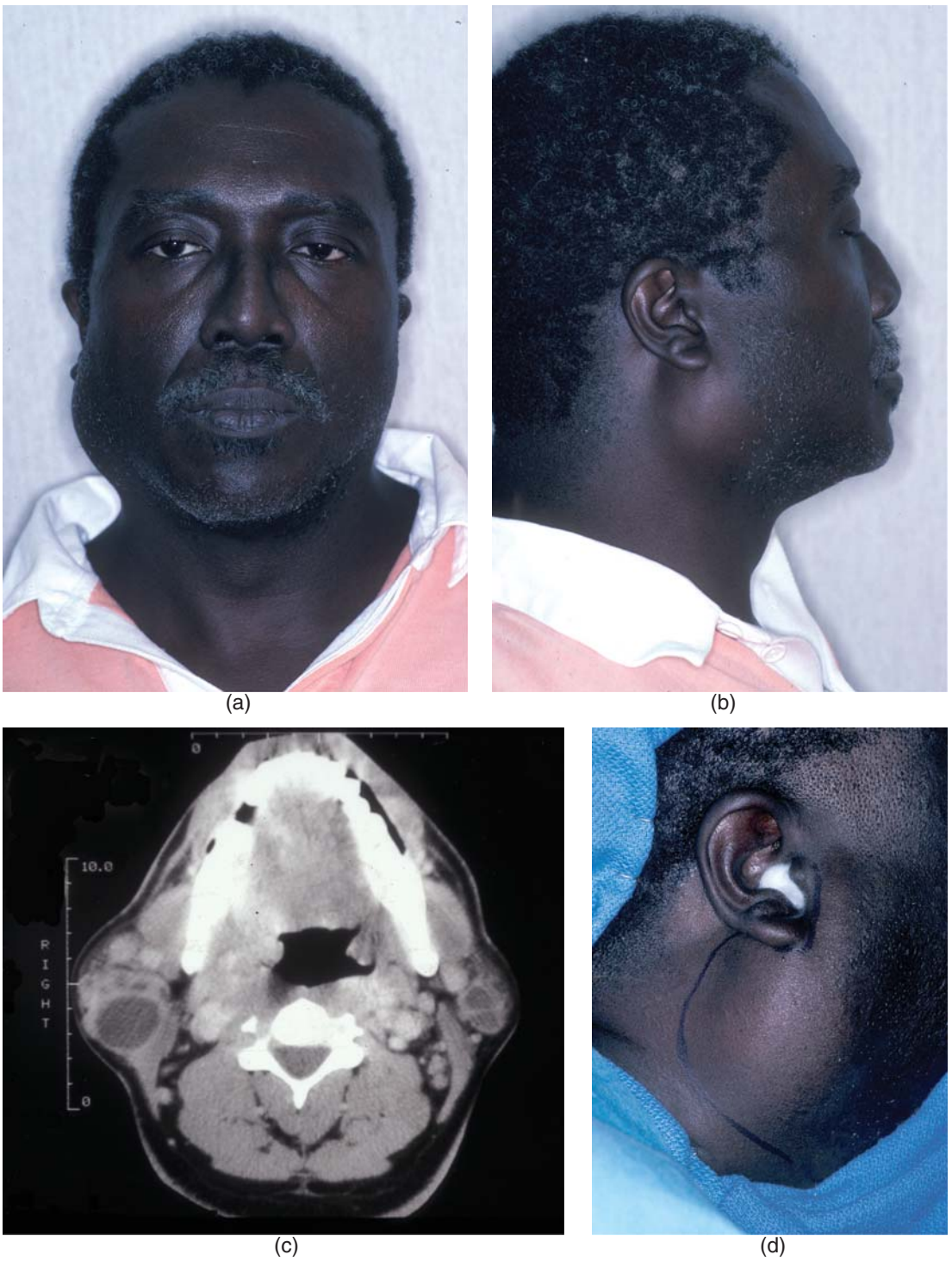


Figure 4.14. A 50-year-old HIV positive male presented in 1994 with obvious right parotid swelling (a,b). This time period pre-dated the development of HAART. Examination of the bilateral parotid gland regions revealed a large mass of the right parotid gland, and a smaller mass of the left parotid gland. Computerized tomograms (c) confirmed the findings of the physical examination. A clinical diagnosis of bilateral lymphoepithelial cysts was made. The patient requested removal of these cysts. A standard incision was made (d). This permitted unroofing of the large cyst in the right parotid gland (e) and the smaller cysts in the left parotid gland (f). The specimen from the right parotid gland (g) and the left parotid gland (h) showed typical gross signs of lymphoepithelial cysts. The resultant right parotid tissue bed is noted (i). Six months postoperatively, the patient showed well healed surgical sites without signs of recurrent lymphoepithelial cysts (figures j, k, l, and m).

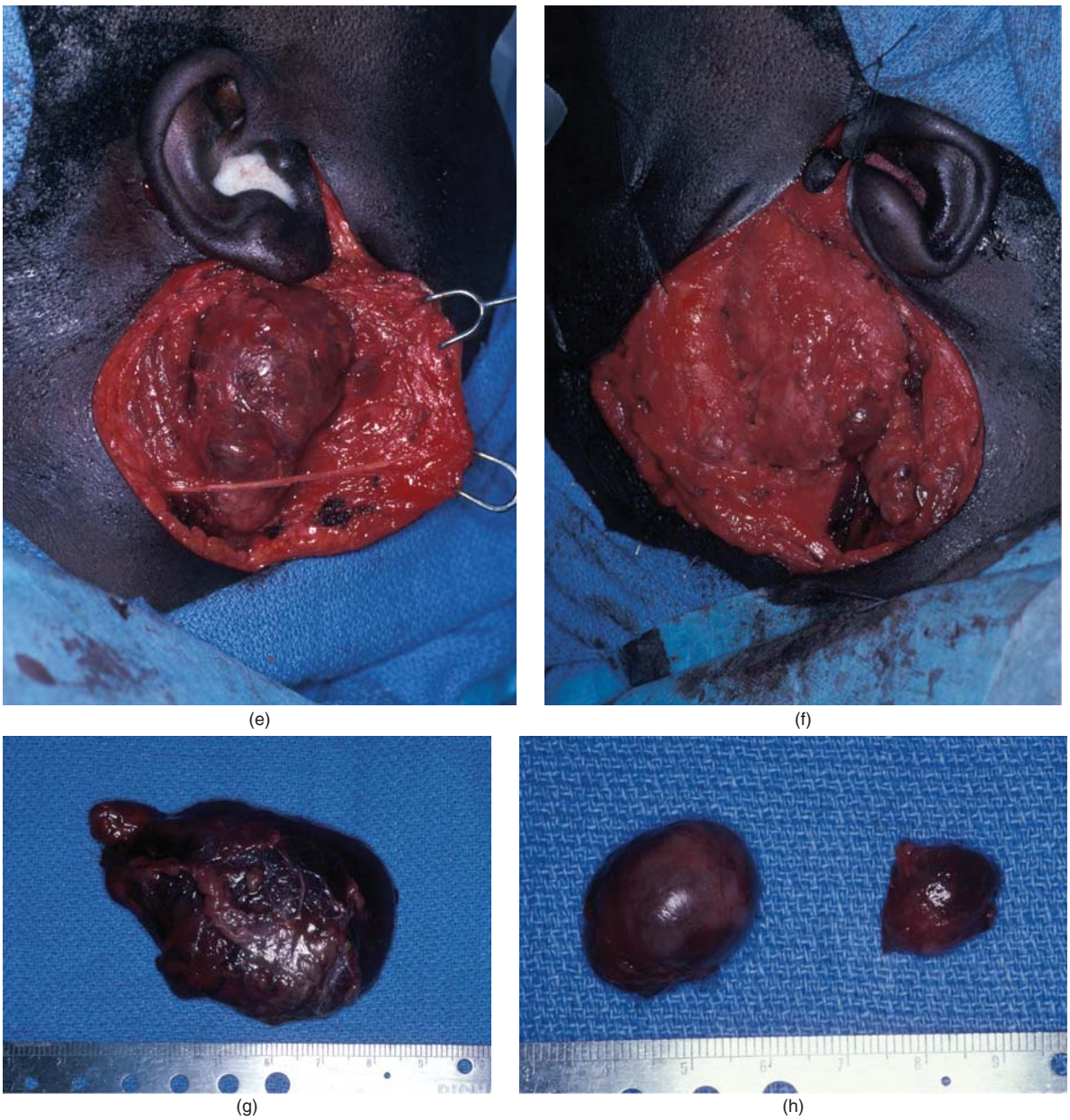
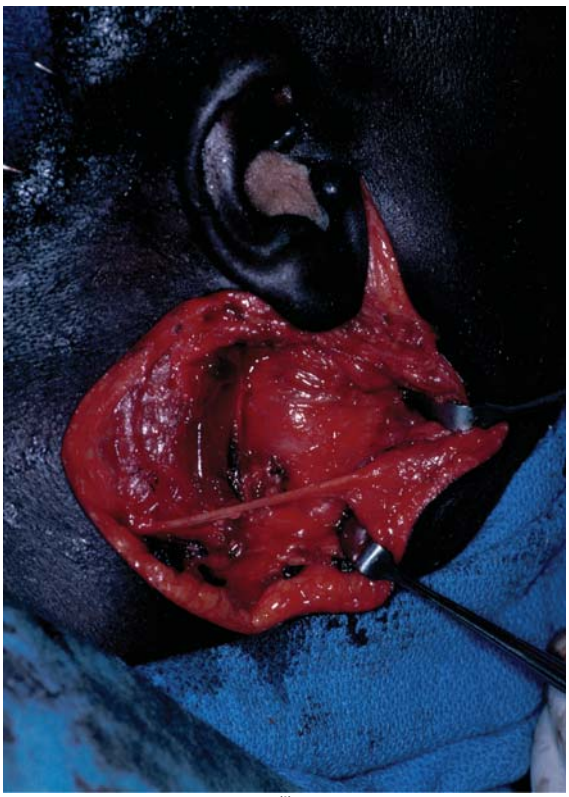


Figure 4.14. (*Continued*)

Treatment of lymphoepithelial cysts of the parotid gland in HIV/AIDS patients is a function of the size of the cysts, the patient's concern for cosmetics, and compliance with medical therapy. Following their original description, these cysts were managed in a variety of ways including periodic aspirations, simple excision of the cysts, and nerve sparing superficial parotidectomy (Figure 4.14). Shaha and his group reported an early experience with 50 patients with lymphoepithelial cysts of the bilateral parotid glands (Shaha, et al. 1993). Their initial approach involved superficial parotidectomy with identification and preservation of the facial nerve. They subsequently performed excision of the cyst only. Ferraro and his group recommended against superficial parotidectomy due to possible recurrence in the deep lobe at a later date (Ferraro, et al. 1993). They



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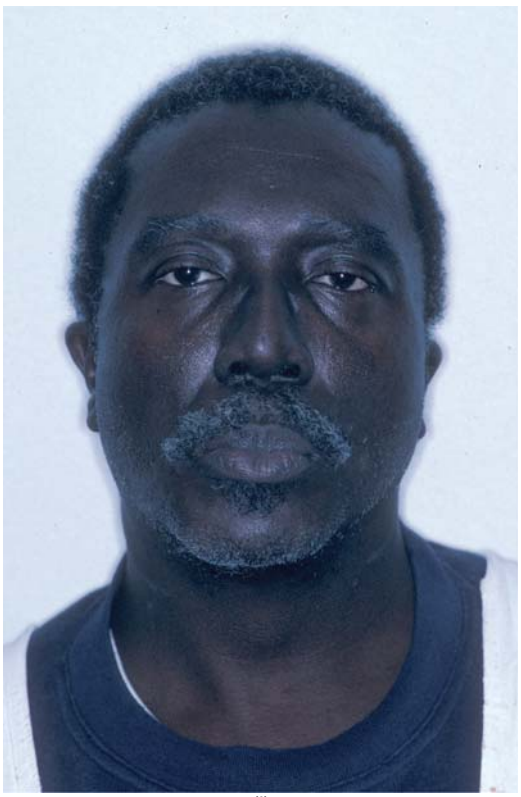

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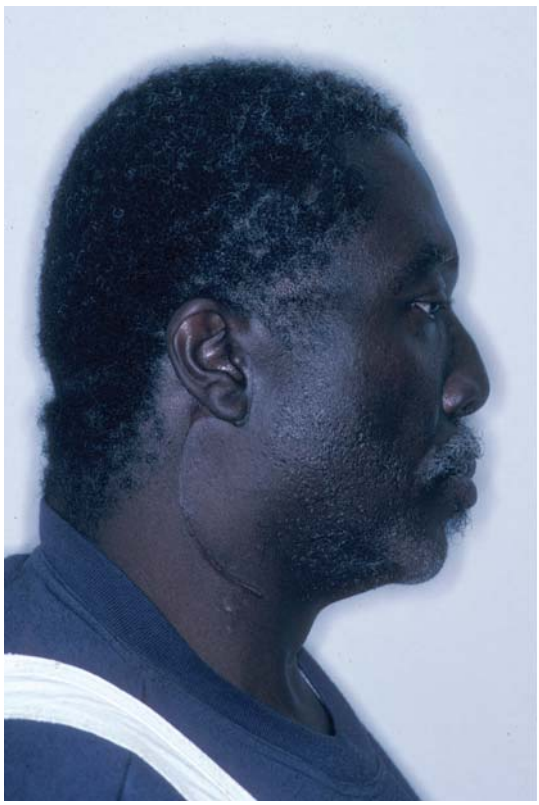

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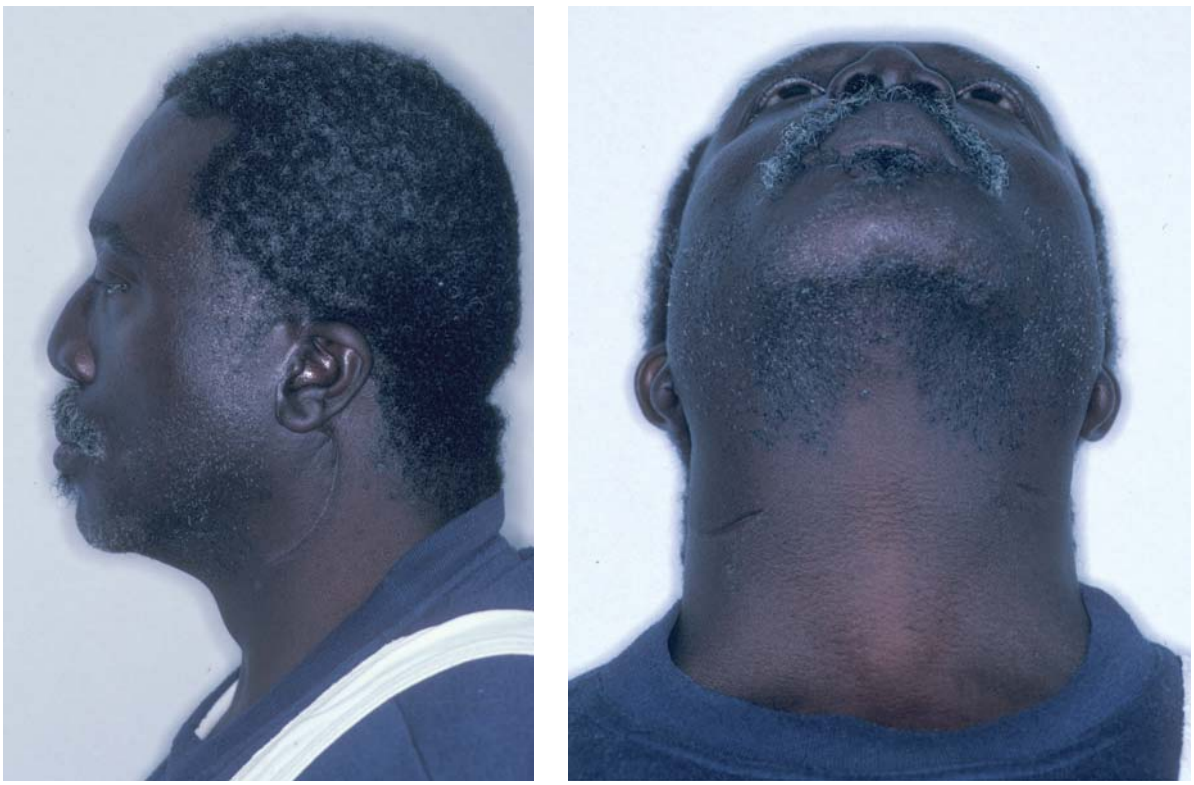


(l) (m)

Figure 4.14. (*Continued*)

indicated that aspiration is usually ineffective as a long term solution because of the high rates of recurrence, in addition to the inability to obtain a tissue diagnosis of the cyst wall. Their solution to recurrence of the cyst was a second enucleation procedure.

Improved and evolving pharmacologic therapy of HIV/AIDS has changed the management of these cysts. Highly active antiretroviral therapy (HAART) uses combinations of drugs to maximize viral suppression and minimize selection of drug-resistant strains. Most commonly, HAART consists of a backbone of 2-nucleoside analogue reverse transcriptase inhibitors in combination with either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. Gland enlargement has been shown to be significantly and positively associated with viral load in a linear fashion (Mulligan, et al. 2000). Compliance with HAART, therefore, has led to the observation that this therapy will result in these cysts subsiding without the need for surgery (Figure 4.15).

Branchial Cleft Cysts

Patients with first branchial anomalies usually present with a unilateral painless swelling of the parotid gland. Bilateral swelling is rare. Work has classified these cysts as types I and II (Work 1977). Type I branchial defects are duplication anomalies of the membranous external auditory canal. These defects are composed of ectoderm only. They are located within the preauricular soft tissues and parotid gland and present as sinus tracts or areas of localized swelling near the anterior tragus. Complete surgical removal is curative. Type II branchial anomalies are less common than type I anomalies. This defect is a duplication anomaly consisting of an anomalous membranous and cartilaginous

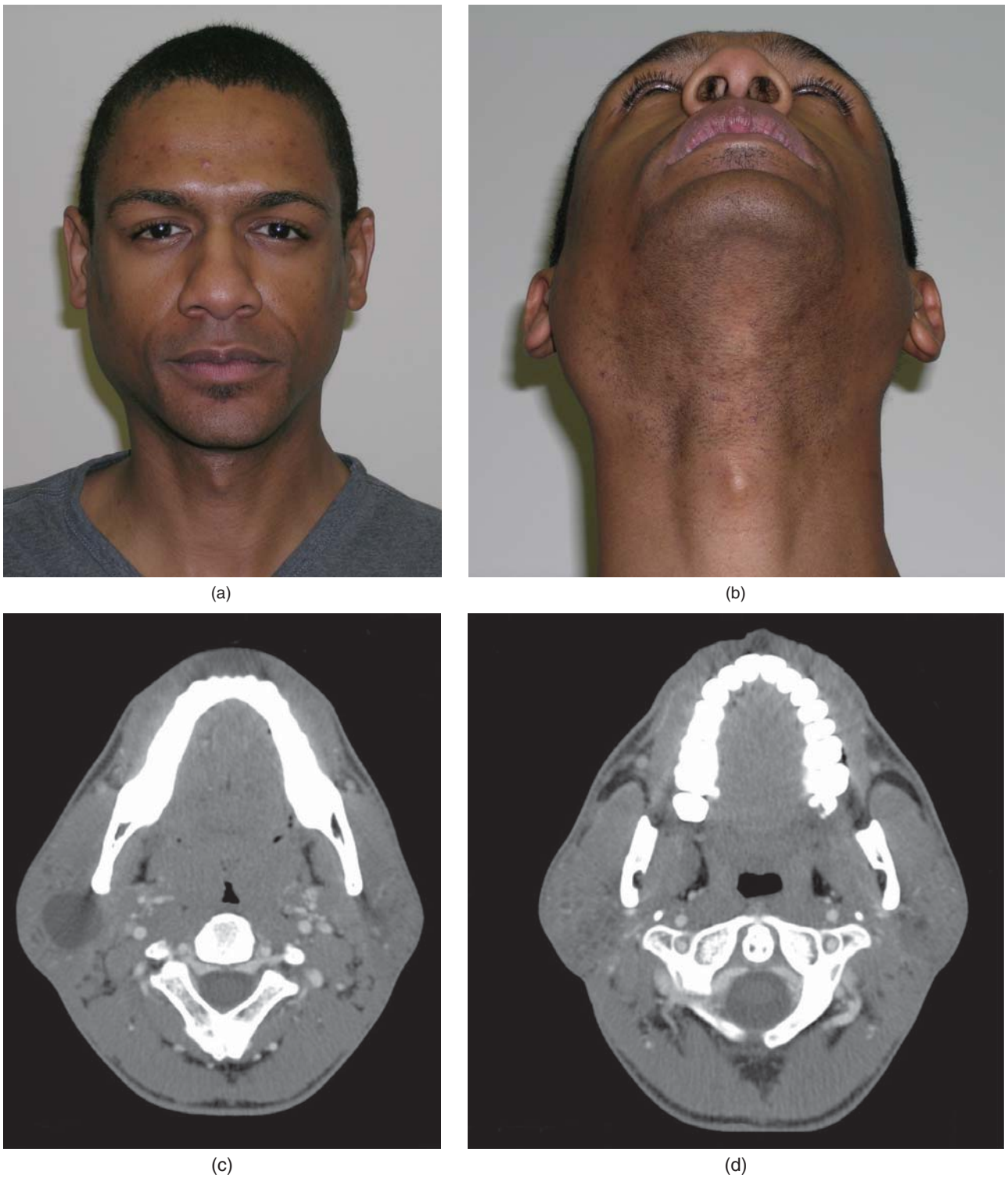
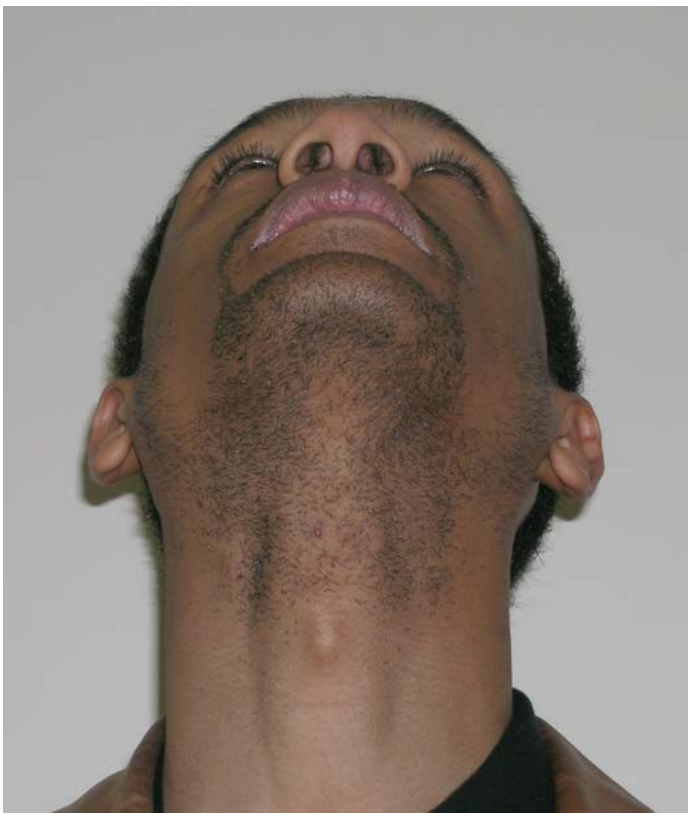


Figure 4.15. A 35-year-old HIV positive man presented in 2005 with a complaint of bilateral parotid swellings. He admitted to non-compliance with his HAART. His CD4/CD8 was 0.69 at the time of initial consultation. Physical examination revealed an obvious right parotid swelling and a subtle mass of the left parotid gland (a and b). Computerized tomograms (c and d) confirmed these findings. A fine needle aspiration biopsy was performed that yielded thick white fluid. A diagnosis of lymphoepithelial cysts was made. The patient resumed his HAART and was the cysts regressed as noted on an examination 4 months later (e and f). His CD4/CD8 was 1.12 at this time.

(e)



(f)

Figure 4.15. (*Continued*)

external auditory canal. Unlike type I cysts, type II cysts are composed of ectoderm and mesoderm. They commonly present in the upper neck and are located posterior or inferior to the angle of the mandible and can extend into the external auditory canal or middle ear cavity. Sinus tracts are common and abscess formation may also occur. Complete surgical excision during an asymptomatic period is the treatment of choice. The reader is directed to Chapter 17 for a more detailed discussion and illustration of these pathologic processes.

Summary

- Cysts of the salivary glands may be associated with neoplasms or they may occur independently.
- While these lesions are collectively referred to as cysts, many are not actually lined by epithelium and therefore are more accurately referred to as cyst-like lesions owing to fluid filled soft tissue lining.
- The ranula and mucocele are examples of mucous escape reactions that are not lined by epithelium.
- Severance of a salivary duct due to trauma with resultant pooling of mucous into surrounding tissues is the pathophysiology of the mucous escape reaction.
- Excision of the salivary gland with or without the associated mucous escape reaction represents curative therapy for this process.
- The mucous escape reaction is most commonly seen in the minor salivary glands.
- Mucous retention cysts are lined by epithelium, but are very rare.
- When mucous retention cysts do occur, they seem to be most common in the major salivary

glands, particularly the parotid gland. Simple excision is the treatment of choice.

- As many as 5–10% of patients with HIV-1 infection have been reported to have parotid swelling with the incidence increasing to approximately 20% in AIDS patients. Lymphoepithelial cysts account for the majority of these swellings.

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Chapter 5

Sialolithiasis

Outline

Introduction

Sialolithiasis is a relatively common disorder of the salivary glands characterized by the development of calculi. Sialolithiasis is thought to affect approximately 1% of the population based on autopsy studies (Williams 1999). It has been estimated to represent more than 50% of major salivary gland disease and is the most common cause of acute and chronic salivary gland infections (Escudier 1998). Sialadenitis (see Chapter 3) and sialolithiasis are disorders of the salivary glands that go hand in hand. Some consider sialolithiasis to be both a consequence and cause of sialadenitis (Berry 1995). For example, in some cases, the presence of a sialolith may cause obstruction such that the salivary gland is predisposed to retrograde infection. In other cases, the presence of sialadenitis may result in a change in the characteristics of the saliva thereby favoring the deposition of calcium and subsequent formation of a sialolith. In addition, the development of edema within a salivary duct can exacerbate existing obstruction when a small sialolith is present. As such, sialadenitis and sialolithiasis should be considered together. Which of these pathologic processes is the instigating causative factor, however, is unknown (Williams 1999). This chapter will therefore discuss sialolithiasis and review some important concepts of sialadenitis previously discussed in Chapter 3.

Pathophysiology of Sialolithiasis

Sialolithiasis results from the deposition of calcium salts within the ductal system of salivary glands. The salivary stones are comprised primarily of calcium phosphate with traces of magnesium and ammonia with an organic matrix consisting of carbohydrates and amino acids. Historically, it has been taught that salivary stones develop around a central nidus of any number of elements, including desquamated epithelial cells, foreign bodies, microorganisms, and mucous plugs (Bodner 1993). Progression occurs once the nidus becomes lodged within the salivary ductal system. Stagnation of saliva enhances the development of the sialolith and occurs secondary to either the nidus itself, or due to the tortuosity of the ductal system. The nidus subsequently becomes bathed in a solution supersaturated with respect to calcium and phosphate and slowly calcifies. This pathophysiologic mechanism has been empirically accepted for decades, while a paucity of evidence exists on the specific cause of sialolith formation. Kasaboglu, et al. (2004) analyzed the chemical composition and micromorphology of sialoliths

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using X-ray diffraction analysis (EDX) and scanning electron microscopy (SEM) (Kasaboglu, et al. 2004). In their reported six cases, X-ray diffraction analysis determined that the sialoliths were comprised completely of multiple and polymorphous hydroxyapatite crystals. In their SEM evaluation, no foreign body or organic material, and no signs of microorganism-dependent core formation was detected.

There are several reasons for sialolithiasis being observed most commonly in the submandibular system. First, the submandibular gland lies inferior to the Wharton duct such that the flow of saliva must travel against the forces of gravity. The physical characteristics of the Wharton duct, specifically its length and two acute bends, also theoretically predispose the ductal system to the development of sialolithiasis. The relatively long duct increases the transit time of saliva in the ductal system. The first bend occurs as the gland courses posterior to the mylohyoid muscle, and the second occurs just proximal to the exit of the duct superiorly into the anterior floor of mouth. While the anatomic nature of the Wharton duct has been considered to be etiologic in the genesis of sialoliths in this system, the angle of the genu of the duct has been investigated as to whether it represents a significant contributory factor (Drage, et al. 2002). Specifically, these researchers retrospectively studied this issue using sialograms in 23 patients with sialadenitis, 61 patients with sialolithiasis, and a control group of 18 patients. There were no statistical differences in the angle of the genu in three groups suggesting that the difference in the angle of the genu of the submandibular duct in the sagittal plane is not of etiologic significance in the formation of sialoliths. The authors indicated that the *length* of the duct might be of significance in the formation of stones; however, that parameter was not investigated in their study. One final issue related to submandibular sialolithiasis is the alkaline nature of the saliva, its viscosity, and relatively high content of calcium salts, specifically phosphates, carbonates, and oxalates that make the submandibular saliva more prone to sialolithiasis than the other major glands (see Table 5.1). All of these features contribute to salivary stasis, crystallization of precipitated calcium salts with calculus formation, obstruction to salivary flow, and infection. Interestingly, *partial* obstruction appears to be of great importance in the development of sialoliths. A completely obstructed gland, although possessing salivary stagnation, does not result in an increase in stone formation (Williams 1999). In completely obstructed glands, the calcium secretory granules in the acini become depleted and the saliva is less likely to produce stones. Baurmash has stated that salivary stasis and salivary viscosity, rather than the calcium content of the salivary secretion determine the development of sialoliths (Baurmash 2004).

Table 5.1. Composition of normal adult saliva

	Submandibular Gland	Parotid Gland
Calcium	3.6 mEq/L	2.0 mEq/L
Phosphate	4.5 mEq/L	6.0 mEq/L
Bicarbonate	18 mEq/L	20 mEq/L
Sodium	21 mEq/L	23 mEq/L
Potassium	17 mEq/L	20 mEq/L
Chloride	20 mEq/L	23 mEq/L
Magnesium	0.3 mEq/L	0.2 mEq/L
Urea	7.0 mEq/L	15 mEq/L
Proteins	150 mg/dL	250 mg/dL
Amino acids	<1 mg/dL	1.5 mg/dL
Fatty acids	<1 mg/dL	1 mg/dL
Glucose	<1 mg/dL	<1 mg/dL

Clinical Features of Sialolithiasis

Approximately 85% of sialoliths occur in the submandibular gland, 10% in the parotid gland, 5% in the sublingual gland, and the incidence of this pathology is extremely rare in the minor salivary glands (Miloro 1998). When involved, minor salivary gland sialoliths occur in the buccal mucosa or upper lip, forming an indurated nodule that may mimic a neoplastic process. Sialolithiasis occurs more often in males, with a peak age of occurrence between 20 and 50 years of age (Lustmann, et al. 1990). Sialolithiasis in children comprises only 3% of cases (Liu and Rawal 2013) with the youngest documented age being 2 years of age (Kim, et al. 2013).

The left submandibular gland is more often affected than the right gland, and bilateral involvement in the absence of another systemic disorder is rare. In fact, stone formation is not highly associated with systemic abnormalities of calcium metabolism (King, et al. 1990). Gout is the only

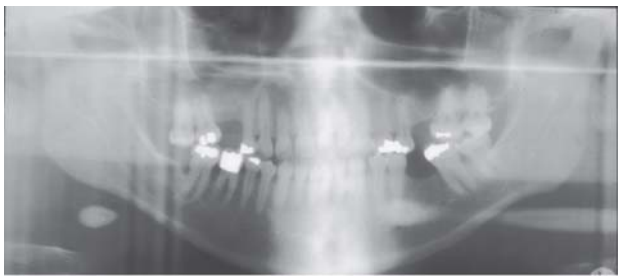


Figure 5.1. A single sialolith noted within the right submandibular gland. Isolated stones are most common in the submandibular system.

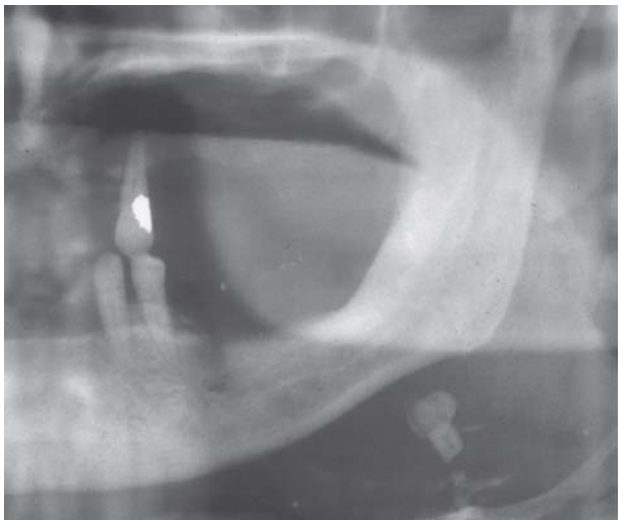


Figure 5.2. This panoramic radiograph close-up shows two sialoliths within the left submandibular gland.

systemic disease known to predispose to salivary stone formation. These stones are primarily made up of uric acid. Multiple occurrences of sialolith formation independent of systemic illness in the same gland, however, are common. While salivary stones are single in 70–80% of cases (Figure 5.1), two calculi occur in 20% of cases, and more than two calculi occur in 5% of cases (Williams 1999; Miloro and Goldberg 2002) (Figure 5.2). Sialolithiasis of the parotid gland is rare. When stones occur in the parotid gland, they are smaller than submandibular gland stones, and more often multiple (Figure 5.3). With regard to location, submandibular stones are located in the duct 75–85% of the time, while parotid stones are located in the hilum or gland parenchyma in at least half of cases (Williams 1999). Submandibular stones located within the gland are oval in shape (Figure 5.4) and elongated in shape when they occur in the

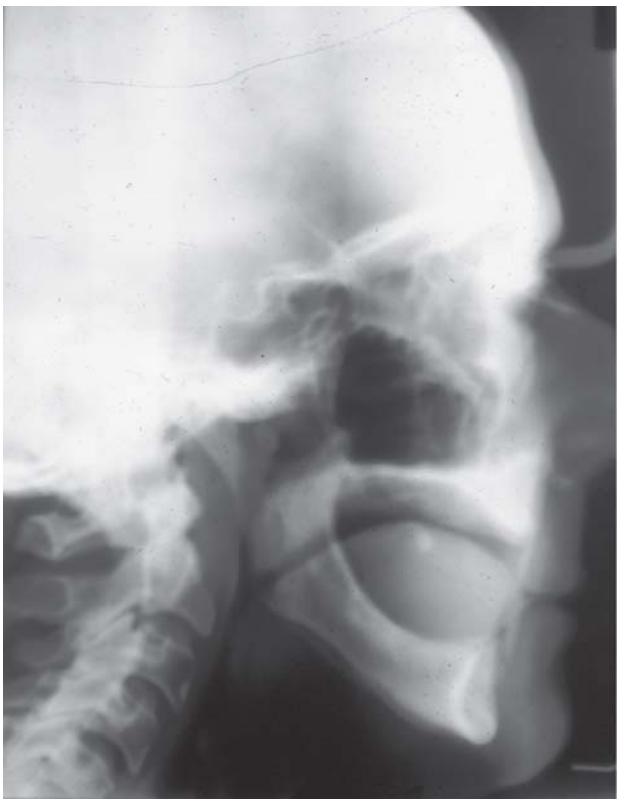


Figure 5.3. This lateral cephalometric radiograph shows a single stone located within the Stensen duct.

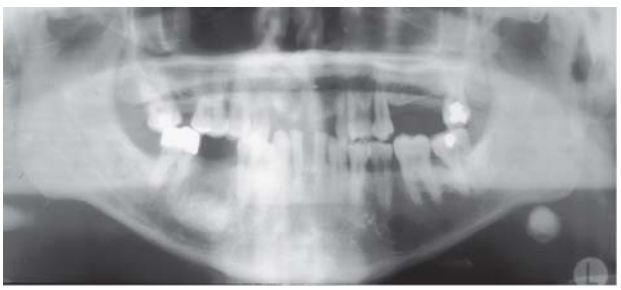
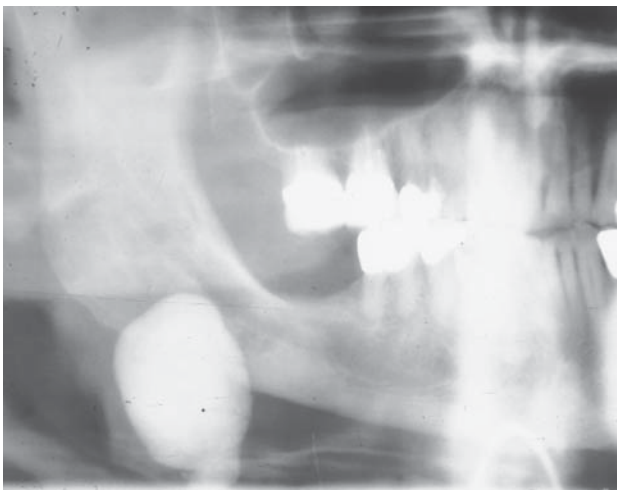


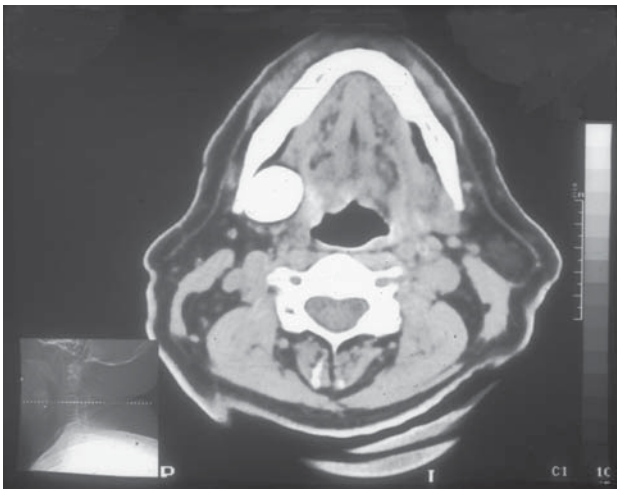
Figure 5.4. This panoramic radiograph shows an oval sialolith of the left submandibular gland.

duct. When present for long periods of time, these stones may become quite large (Figure 5.5). Bilateral salivary stones are quite rare; however, they have been observed (Lutcavage and Schaberg 1991) (Figure 5.6).

Sialolithiasis most commonly presents with painful swelling, although painless swelling or pain only are occasionally reported as symptoms. Lustmann's study showed swelling to be present in 94% of their 245 cases of sialolithiasis, while pain occurred in 65.2%, pus secretion in 15.5%, and



(a)



(b)

Figure 5.5. This very large sialolith is associated with the right submandibular gland as seen on panoramic radiograph (a). Due to its size, it might be confused with an osteoma of the mandible such that computerized tomograms help to identify its presence within the submandibular gland (b).

an absence of symptoms in 2.4% of their patients (Lustmann, et al. 1990). When symptoms do occur, their magnitude seems to vary according to the gland involved and the location and size of the sialolith. A small sialolith may be asymptomatic and serendipitously discovered during routine dental radiographic examination. Once the stone increases in size, salivary flow will be impaired, and spasmodic pain occurs during eating. Purulent infection may accompany sialolithiasis.

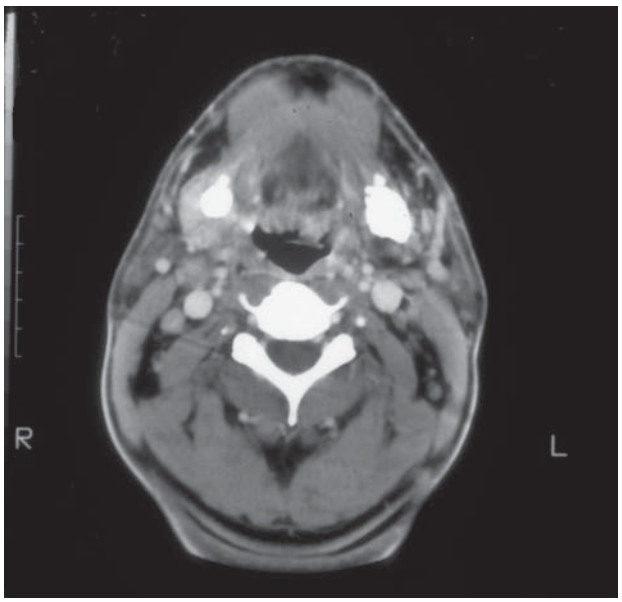


Figure 5.6. This axial section of computerized tomograms show the presence of bilateral sialoliths of the submandibular glands.

MULTIPLE SIALOLITHS

It has long been believed that multiple stones of the salivary glands represent an uncommon occurrence. With the increasing sophistication and resolution of imaging studies and the increasing use of sialoendoscopy; however, it has become apparent that multiple sialoliths are uncommon but not rare as once believed (Ardekian, et al. 2014). In their study of 530 consecutive cases of sialolithiasis, Ardekian, et al. (2014) identified multiple calculi in 37 of 530 (7%) of these cases. The mean number of sialoliths per patient was 3.4 with 16 sialoliths being the largest number present in one patient in this series. The submandibular gland was affected in 33 cases (90%), and the parotid gland was affected in the remaining 4 cases (10%). Preoperative imaging identified a solitary sialolith in 3 of the 37 cases (8%) of multiple sialoliths where additional sialoliths were discovered by sialoendoscopy. In other words, 92% of the cases of multiple sialoliths were correctly identified by preoperative imaging. Of the multiple submandibular sialoliths, 40% were located in the proximal aspect of the duct and 60% were located distally. The multiple parotid sialoliths were located in the duct and were typically smaller than those located in the submandibular system.

BILATERAL SIALOLITHS

Simultaneous sialolithiasis of more than one salivary gland is less common than multiple sialoliths and is estimated to occur in fewer than 3% of cases of sialolithiasis (Sunder, et al. 2014). This notwithstanding, surgeons must be vigilant in terms of investigating for the possibility of multiple gland involvement when preparing a patient for surgery related to a diagnosis of sialolithiasis. A review of the literature indicates that when multiple sialoliths occur, they occur in a bilateral same gland fashion rather than involving two different salivary glands.

Differential Diagnosis and Diagnosis of Sialolithiasis

Patients with sialolithiasis most commonly present with clinical and historical evidence of salivary calculi. A history of submandibular swelling, prandial pain, and bouts of sialadenitis are highly suggestive of a diagnosis of sialolithiasis. This notwithstanding, many patients are asymptomatic such that only a panoramic radiograph may allow for the diagnosis of submandibular sialolithiasis as it may reveal calcifications within the submandibular triangle. It has been observed that submandibular stones located anteriorly are more often symptomatic than those lodged in the intraglandular portion of the duct (Karas 1998). While such calcifications may lead to a diagnosis of submandibular sialolithiasis, it is important for the clinician to consider other diagnoses that present with submandibular calcifications, particularly when pain is absent. Amongst these are calcified lymph nodes associated with mycobacterial adenitis (scrofula) (Figure 5.7), phleboliths associated with oral/facial hemangiomas (Figure 5.8), and a mandibular osteoma as might occur in Gardner syndrome (Figure 5.9). All of these calcifications may, at first glance, appear similar to submandibular sialolithiasis. Close examination of panoramic radiographs may, however, allow for the clinician to establish a radiographic diagnosis other than submandibular sialolithiasis (Mandel 2006). Most submandibular calculi contain smooth borders when they exist within the gland. Calcified lymph nodes generally show irregular borders, and osteomas of the mandible are larger than most salivary gland stones, and are intimately associated with the mandible. Phleboliths are commonly multiple in number and also exist within the neck outside of the submandibular triangle. They are scattered and have a classic lamellated appearance with a lucent core. Finally, phleboliths are smaller than sialoliths and demonstrate an oval shape, compared to the sialolith whose elliptical shape has been created by a salivary duct (Mandel and Surattanont 2004). One further entity worthy of mention is calcified atheromas of the carotid artery which is sufficiently distant from the submandibular triangle so as to not be confused with a submandibular sialolith. These are most commonly located inferior and posterior to the mandibular angle adjacent to the intervertebral space between cervical vertebrae 3 and 4 (Friedlander and Freymiller 2003).

While the diagnosis of sialolithiasis is frequently confirmed radiographically, it is important for the clinician to not obtain radiographs prior to performing a physical examination. Bimanual palpation of the floor of mouth may reveal evidence of a stone in a large number of patients. Similar palpation of the gland may also permit detection of a stone as well as the degree of fibrosis present within the gland. Examining the opening of the Wharton duct for the flow of saliva or pus is an important aspect of the evaluation. It has been estimated that approximately one quarter of symptomatic submandibular glands that harbor stones are non-functional or hypofunctional. Radiographs should be obtained, and may reveal the presence of a stone. It has been reported that 80% of submandibular stones are radio-opaque, 40% of parotid stones are radio-opaque, and 20% of sublingual gland stones are radio-opaque (Miloro 1998).

Treatment of Sialolithiasis

General principles of management of patients with sialolithiasis include conservative measures such as effective hydration, the use of heat, gland massage, and sialogogues that might result in flushing a small stone out of the duct. A course of oral antibiotics may also be beneficial. These measures may be particularly appropriate since some patients may carry a clinical diagnosis of sialadenitis in case of a radiolucent sialolith. As such, the treatment is the same in the initial management of both diagnoses.

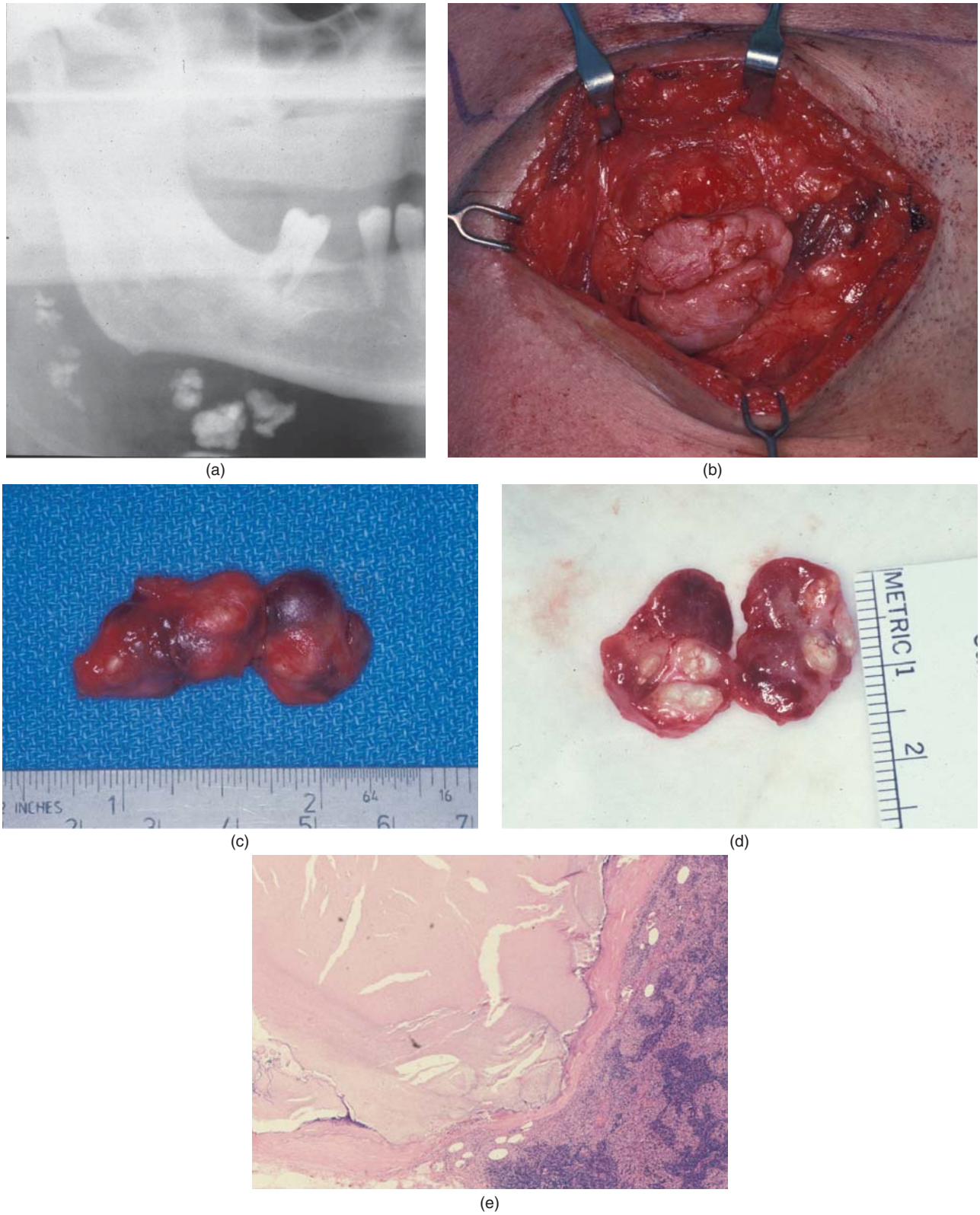
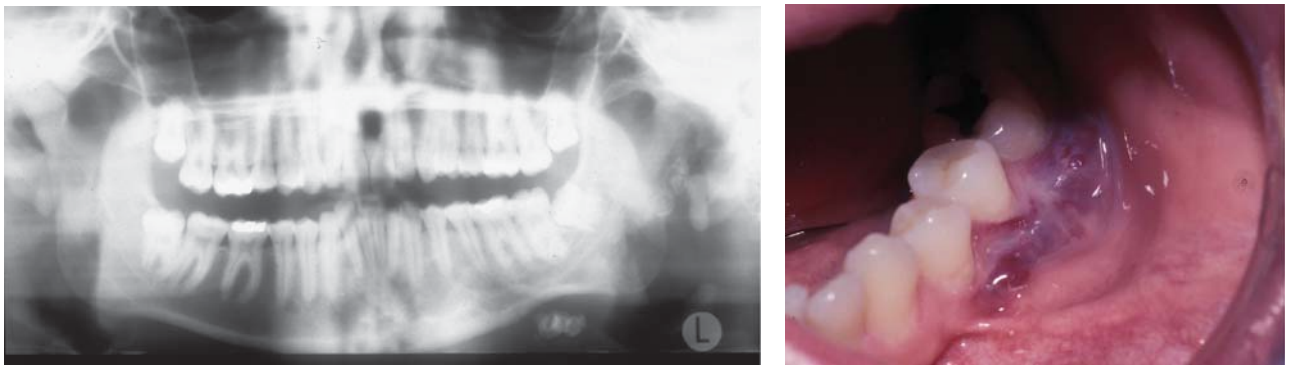


Figure 5.7. A close-up of a panoramic radiograph obtained in a patient with a chief complaint of right submandibular pain (a). The calcifications noted on this radiograph are located in the retromandibular region as well as the submandibular gland area. Exploration of the neck showed indurated lymph nodes present in association with the right submandibular gland, but clearly not sialoliths (b). The lymph nodes were removed (c) and bisected, showing macroscopic (d) and microscopic evidence of caseous necrosis (e). A diagnosis of tuberculous adenitis was therefore established. The patient was subjected to a purified protein derivative (PPD) skin test that was positive.



(a) (b)

Figure 5.8. A panoramic radiograph demonstrating calcifications within the left submandibular region (a). At first glance of the radiograph, submandibular sialolithiasis is a reasonable consideration. Close examination of the radiograph reveals multicentric lamellated calcifications in the submandibular and preauricular regions, as well as a calcification superimposed on the left mandibular second molar roots. A complete physical examination revealed signs consistent with a hemangioma associated with the left mandibular gingiva (b). As such, the calcifications are presumed to represent phleboliths, and are not removed. It is important, therefore, to diagnose sialolithiasis based on a review of a radiograph as well as a physical examination.

SUBMANDIBULAR SIALOLITHIASIS

The treatment of salivary calculi of the submandibular gland is a function of the location and size of the sialolith (Figure 5.10). For example, sialoliths present within the duct may often be retrieved with a transoral sialolithotomy procedure and sialodochoplasty. In general terms, if the stone can be palpated transorally, it can probably be removed transorally. A review of 172 patients who underwent intraoral sialolithotomy of a submandibular stone assessed results as to complete removal, partial removal, and failure (Park, et al. 2006). The effect of location, size, presence of infection, and palpability of the calculi on the results was assessed. Univariate analysis showed that palpability and the presence of infection were statistically significant factors affecting transoral sialolithotomy. Palpability was the only significant factor after multivariate analysis. This study provides scientific evidence supporting intraoral removal of extraglandular submandibular gland stones regardless of location, size, presence of infection, or recurrence of calculi as long as the calculi are palpable. This procedure involves excising the Wharton duct overlying the stone thereby permitting its retrieval (Figure 5.11). Reconstruction of the duct in the form of a sialodochoplasty permits shortening of the duct and enlargement of salivary outflow thereby preventing recurrence and allowing for healing of the gland (Rontal and Rontal 1987). A properly performed sialodochoplasty ensures effective flow of saliva from the gland in hopes of maintaining the health of the salivary gland. This procedure involves suturing the edges of the duct's mucosa to the surrounding oral mucosa (Figure 5.11). The number of sutures placed is arbitrary; however, a sufficient number of sutures is required so as to stabilize the reconstructed duct to the floor of mouth. Proper postoperative hydration of the patient with free flowing saliva maintains patency of the sialodochoplasty, thereby enhancing the potential for reversal or stabilization of the underlying sialadenitis. Chronic submandibular obstructive sialolithiasis clearly leads to chronic sialadenitis with presumed parenchymal destruction. After removal of the sialolith, however, the apparent resiliency of the submandibular gland usually results in no adverse symptoms (Baurmash 2004). As such, the ability to effectively retrieve a sialolith usually refutes the need to also remove the affected salivary gland. Sialoliths located within the submandibular gland or its hilum are most commonly managed with submandibular gland excision (Figure 5.12). This controversial statement is made based on the relative difficulty to retrieve stones from this anatomic region of the gland, rather than based on the assumption that proximal stones cause permanent structural damage

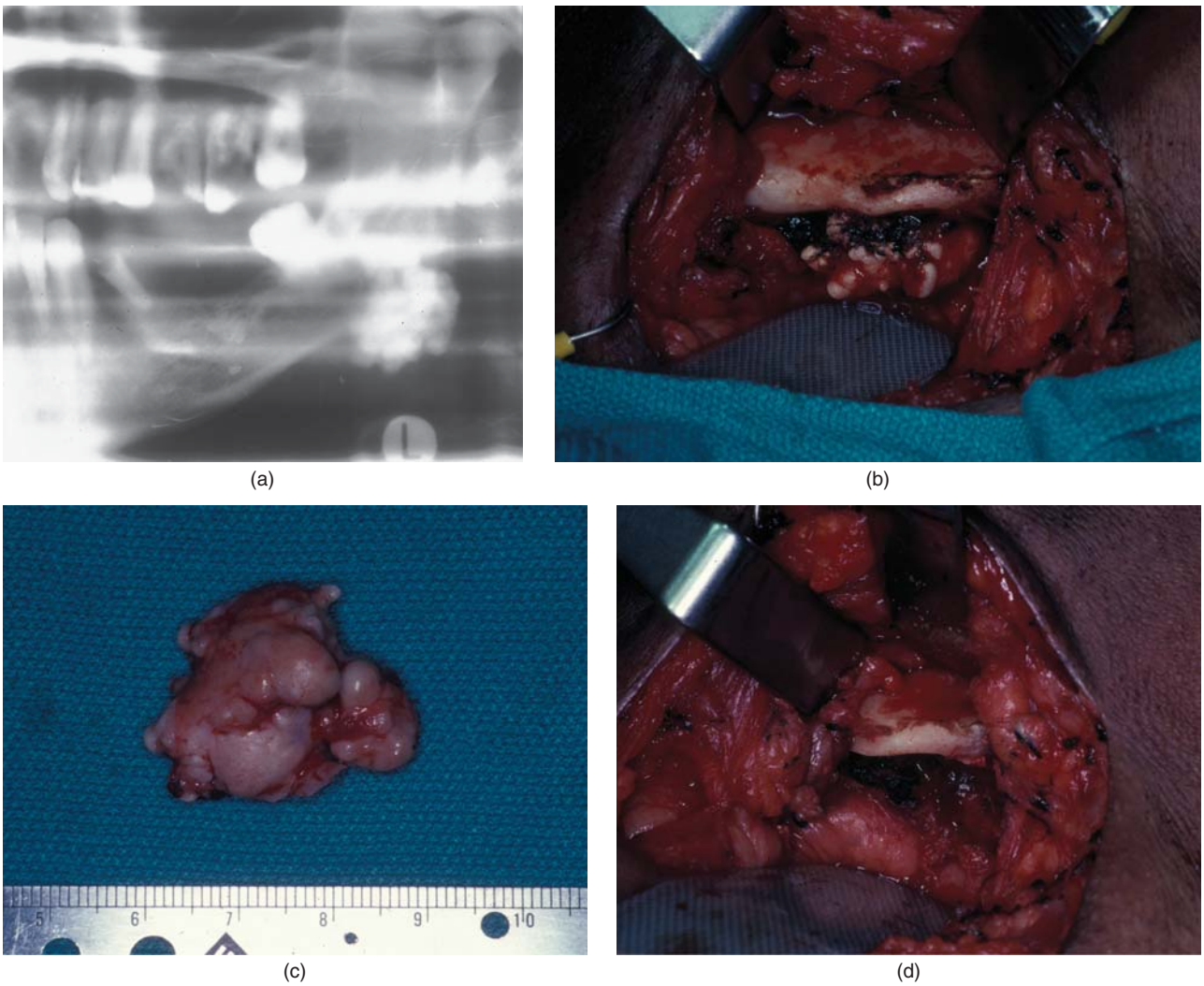


Figure 5.9. This panoramic radiographic close-up shows an irregular mass associated with the left submandibular region (a). Computerized tomograms were not obtained preoperatively, and a differential diagnosis of submandibular sialolithiasis was established. The calcification, however, does not show typical radiographic signs of a sialolith, including its irregular borders. The patient underwent exploration of the left submandibular region, whereupon the calcified mass was identified as a distinct entity from the left submandibular gland (b). The mass was removed (c) and the left submandibular gland remained in the tissue bed (d). A histopathologic diagnosis of osteoma was made. A subsequent diagnosis of Gardner syndrome was made, and the patient underwent colectomy when a diagnosis of adenocarcinoma of the colon was established.

to the gland that results in the need for removal of the gland. To this end, a study examined a series of 55 consecutive patients who underwent transoral removal of stones from the hilum of the submandibular gland (McGurk, et al. 2004b). Stones were able to be retrieved in 54 patients (98%), but four glands (8%) required subsequent removal due to recurrent obstruction. The authors emphasized that it was necessary for the stone to be palpable and no limitation of oral opening should exist in order for patients to undergo their technique. They reported an acceptable incidence of complications associated with their technique, although they lamented that it remained to be seen if the asymptomatic nature of their patients would be maintained over time.

Shock wave lithotripsy has been reported as a primary form of treatment for submandibular salivary gland stones. Salivary stone lithotripsy requires a gland to be functional by virtue of

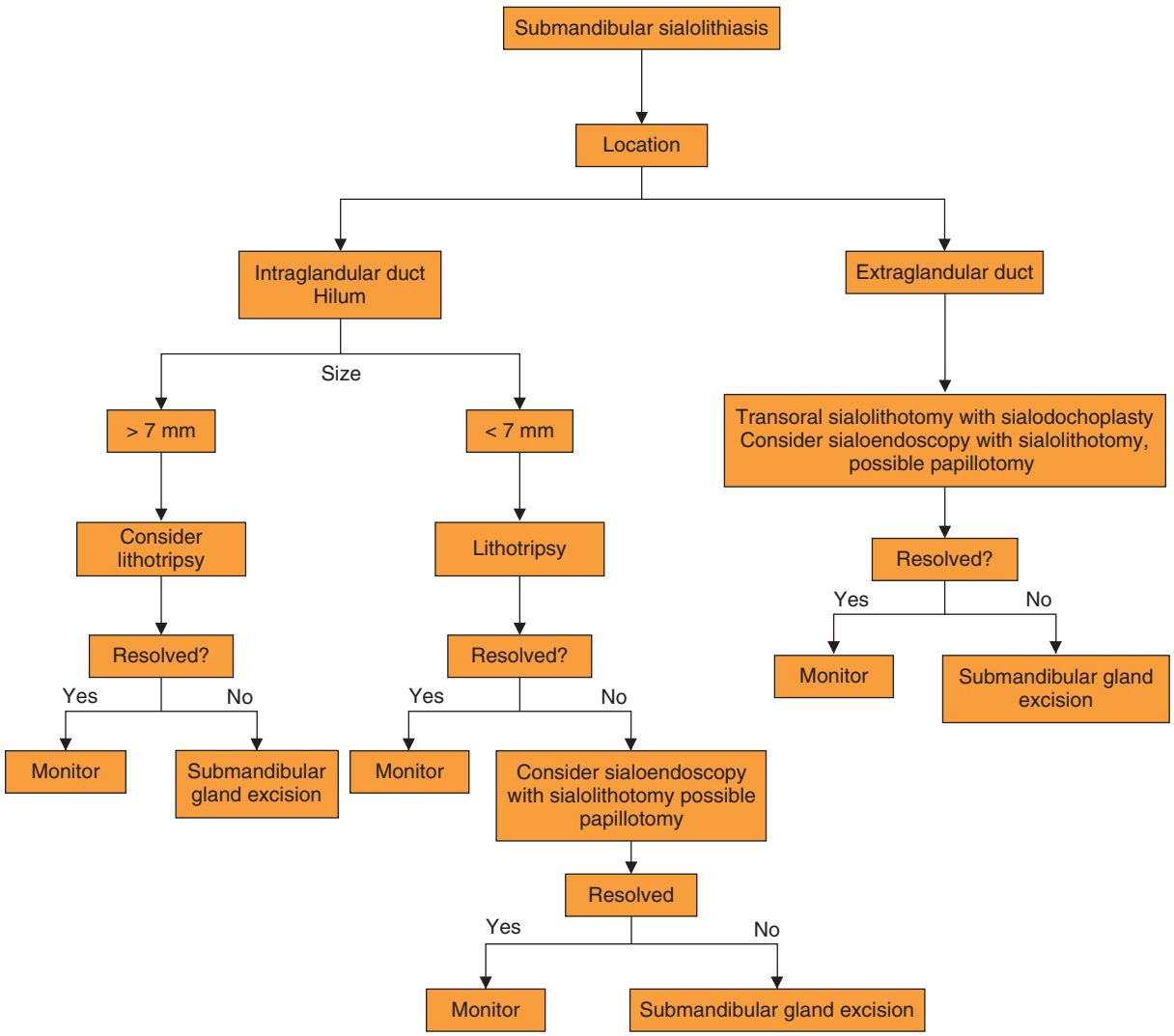


Figure 5.10. Algorithm for submandibular sialolithiasis.

production of saliva in order for the stone fragments to be eliminated from the duct. Some authors have implemented a sour gum test prior to performing extracorporeal lithotripsy (Williams 1999). This test involves the patient chewing sour gum whereby the clinician looks for swelling of the gland. The development of swelling indicates that the gland is functional such that extracorporeal lithotripsy may be attempted. In the absence of swelling, extracorporeal lithotripsy is contraindicated, and the gland is planned for removal. Two techniques of salivary lithotripsy have been developed, including extracorporeal, sonographically controlled lithotripsy, and intracorporeal endoscopically guided lithotripsy (Escudier 1998). Extracorporeal shockwave lithotripsy was first used to treat renal stones in the early 1980s. The shockwaves can be generated by electromagnetic, piezoelectric, and electrohydraulic mechanisms and the resultant waves are brought to a focus through acoustic lenses. They then pass through a water-filled cushion to the stone where stress and cavitation act to fracture the stone. At the sialolith-water interface a compressive wave is propagated through the stone thereby subjecting it to stress. Cavitation occurs when reflected energy at the sialolith-water interface results in a rebounding tensile or expansion wave which induces bubbles. When these bubbles collapse a jet of water is projected through the bubble onto

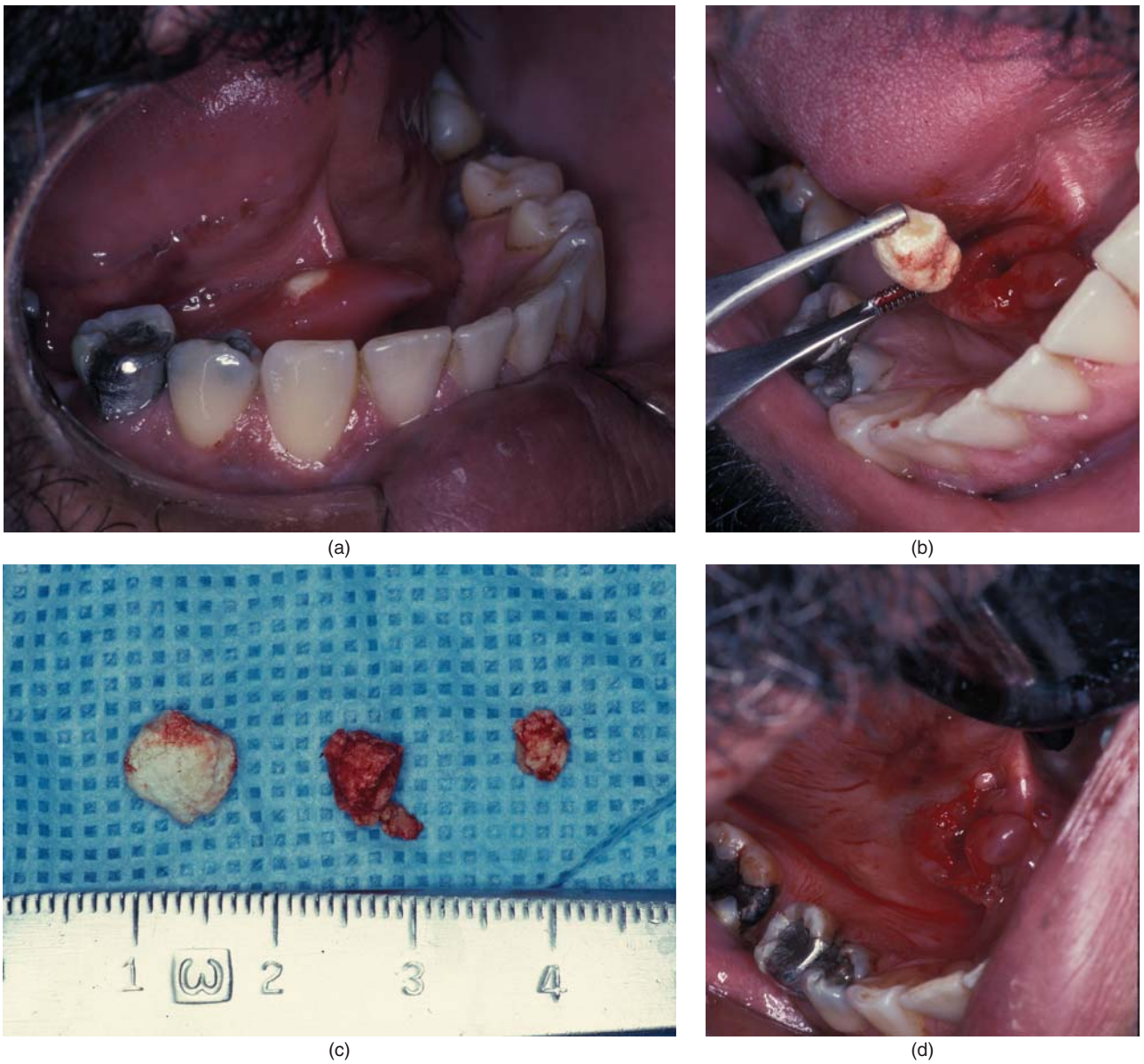


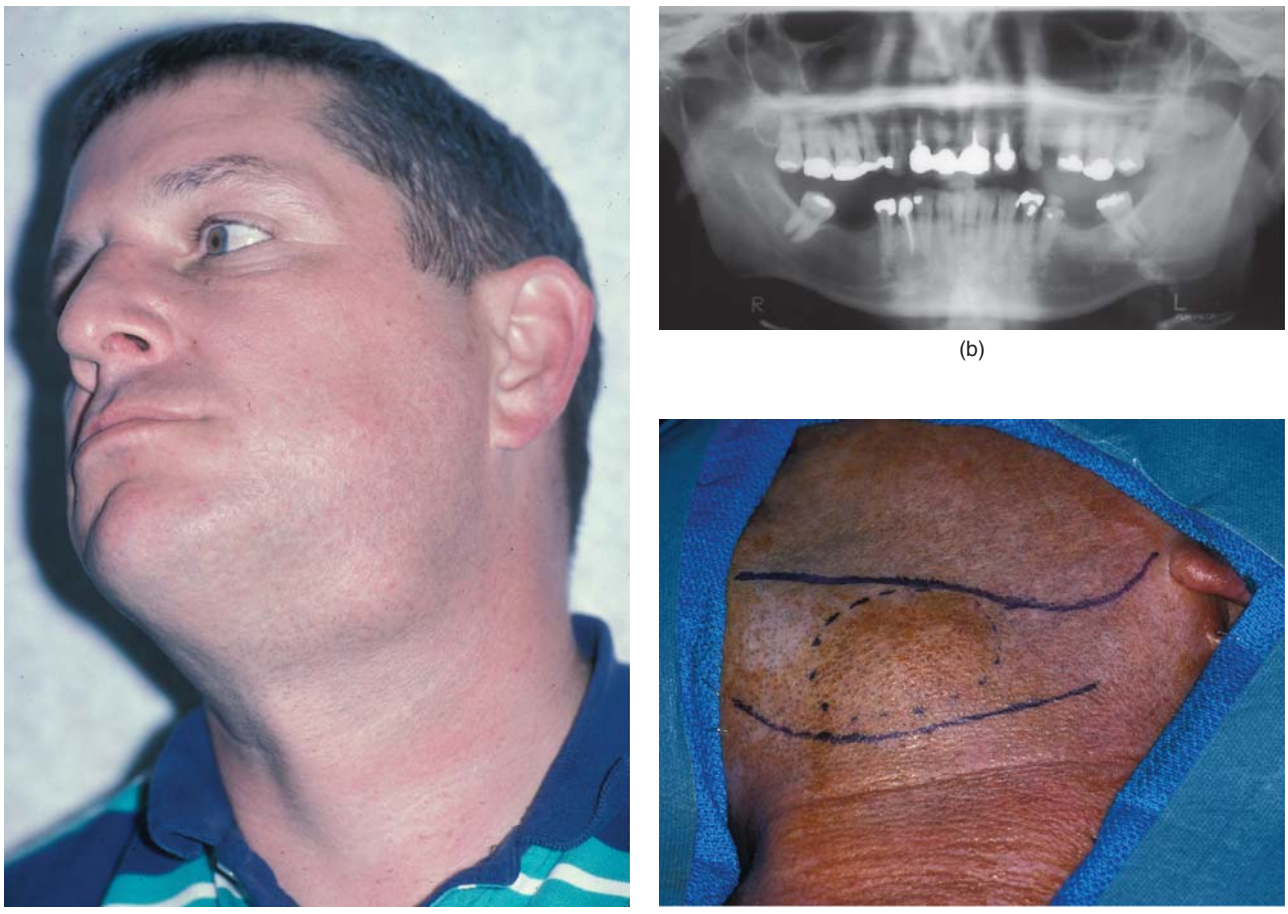
Figure 5.11. A sialolith is noted at the opening of the right Wharton duct (a). Since this stone was able to be palpated on oral examination, it was removed transorally without necessitating the removal of the right submandibular gland. The main stone was removed (b), after which time exploration of the proximal duct revealed two additional stones that were also removed (c). A sialodochoplasty was performed to widen and shorten the right Wharton duct (d). A sialodochoplasty performed near the papilla of the Wharton duct is termed a papillotomy.

the stone's surface. This force is sufficient to pit the stone and break it. Extracorporeal lithotripsy for submandibular gland stones is somewhat less successful than that of parotid stones (Williams 1999). Ottaviani and his group evaluated the results of 52 patients treated with electromagnetic extracorporeal lithotripsy for calculi of the submandibular gland (n = 36 patients) and parotid gland (n = 16 patients) (Ottaviani, et al. 1996). Complete disintegration was achieved in 46.1% of patients, including 15 with submandibular sialolithiasis and 9 with parotid sialolithiasis. Elimination of the stones was confirmed by sonogram. Residual concrements were detected by

ultrasound in 30.8% of patients, including 9 with submandibular stones, and 7 with parotid stones. Four patients with residual submandibular stones required surgical retrieval. The authors concluded by indicating that if hilar and intraglandular duct stones are smaller than 7 mm in size, they may be successfully treated with lithotripsy (Williams 1999). The surgeon should proceed with submandibular gland excision if this trial of lithotripsy is not successful, or if stones larger than 7 mm are identified.

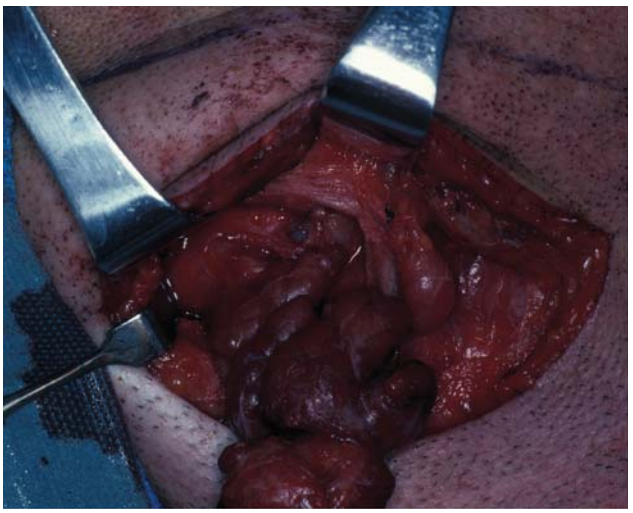
Intracorporeal lithotripsy techniques are now used in which a miniature endoscope is utilized to manipulate the stone under direct vision. In this technique, shockwaves are applied directly to the surface of the stone under endoscopic guidance. The shockwave may be derived from an electrohydraulic source, a pneumoballistic source, or from a laser. Pneumoballistic energy has been shown to produce calculus fragmentation with greater efficiency than lasertripsy (Arzoz, et al. 1996). The disadvantage of these techniques is that the size of the endoscope and probe requires that the duct be incised so as to facilitate entry.

Finally, interventional sialoendoscopy has been developed that may permit the use of a fine sialoendoscope to retrieve salivary stones (Nakayama, et al. 2003), (Figure 5.13). The size of some sialoliths, however, is such that an incision

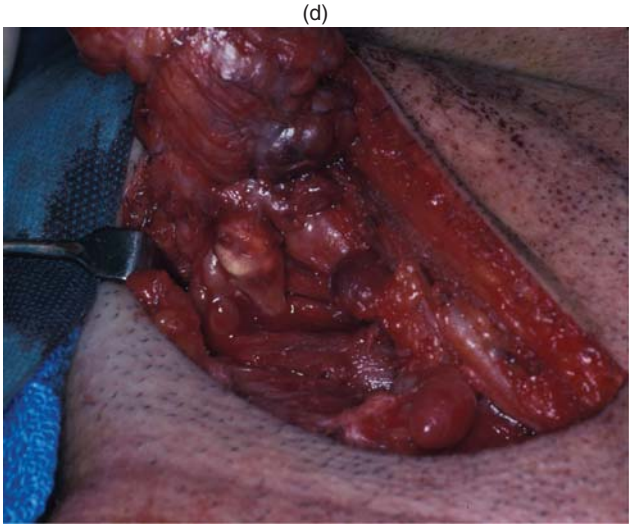


(a) (b) (c)

Figure 5.12. The clinical appearance of a man with pain and left submandibular swelling (a). His panoramic radiographic (b) shows a sialolith in the left submandibular gland. A standard transcutaneous approach was followed to submandibular gland excision (c). A subfascial dissection of the gland was performed. Inferior retraction on the gland allowed for preservation of the marginal mandibular branch of the facial nerve (d). Superior and anterior retraction of the gland allowed for identification of the sialolith that was located at the hilum of the gland (e). The excised gland (f) was bisected (g) and demonstrated significant scar tissue formation.



(d)



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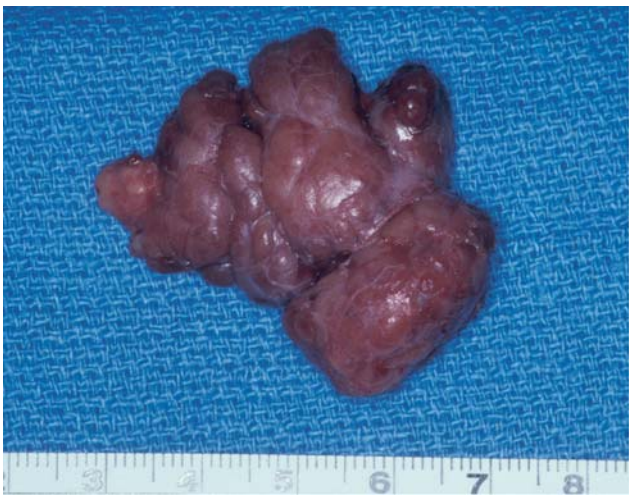

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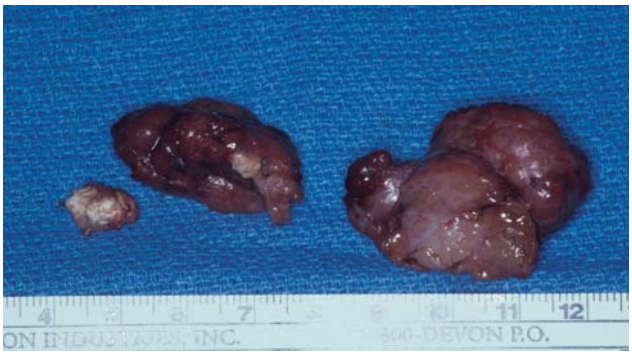


(g)

Figure 5.12. (*Continued*).

of the papilla may be necessary for their delivery. Interventional sialoendoscopy may be used with lithotripsy to fragment large stones so as to achieve a completely noninvasive therapeutic sialoendoscopy.

McGurk, et al. (2004a) assessed the efficacy of extracorporeal shock wave lithotripsy, basket retrieval as part of interventional sialoendoscopy, and intraoral surgical removal of salivary calculi. Three hundred and twenty-three patients with submandibular calculi were managed. Extracorporeal shock wave lithotripsy was successful in 43 of 131 (32.8%) patients, basket retrieval was successful in 80 of 109 (73.4%) patients and surgical removal was successful in 137 of 143 (95.8%) patients with submandibular stones.

PAROTID SIALOLITHIASIS

Sialoliths of the parotid gland are divided anatomically into those that are located within the intraglandular duct and the extraglandular duct (Figure 5.14). Extraglandular duct sialoliths may be removed surgically through and intraoral approach (Figure 5.15). In this procedure, a C-shaped incision is made anterior to the Stensen papilla. Dissection is performed deep (lateral) to the duct such that it is included in the mucosal flap such that the duct is separated from the more lateral soft

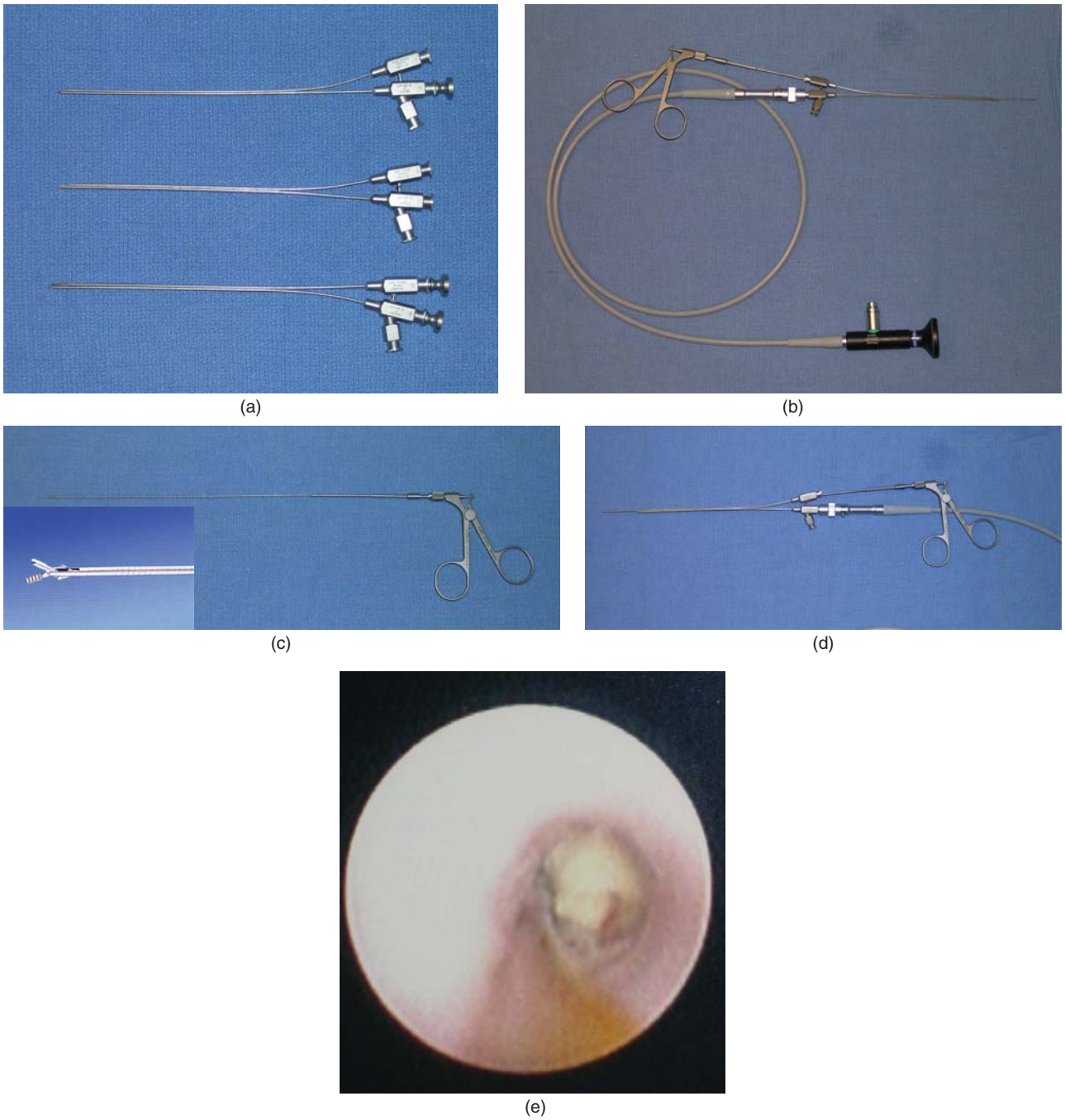


Figure 5.13. Interventional sialoendoscopic instrumentation for retrieval of salivary calculus, including the operating sheaths (a) that accept the miniature endoscope in the *telescope* channel (b). The grasping forceps (c), are placed within the *working* channel of the operating sheaths (d), and are able to retrieve stones that may be identified on diagnostic sialoendoscopy (e). Figure 5.13(e) Source: Maria Troulis, Boston, Massachusetts.

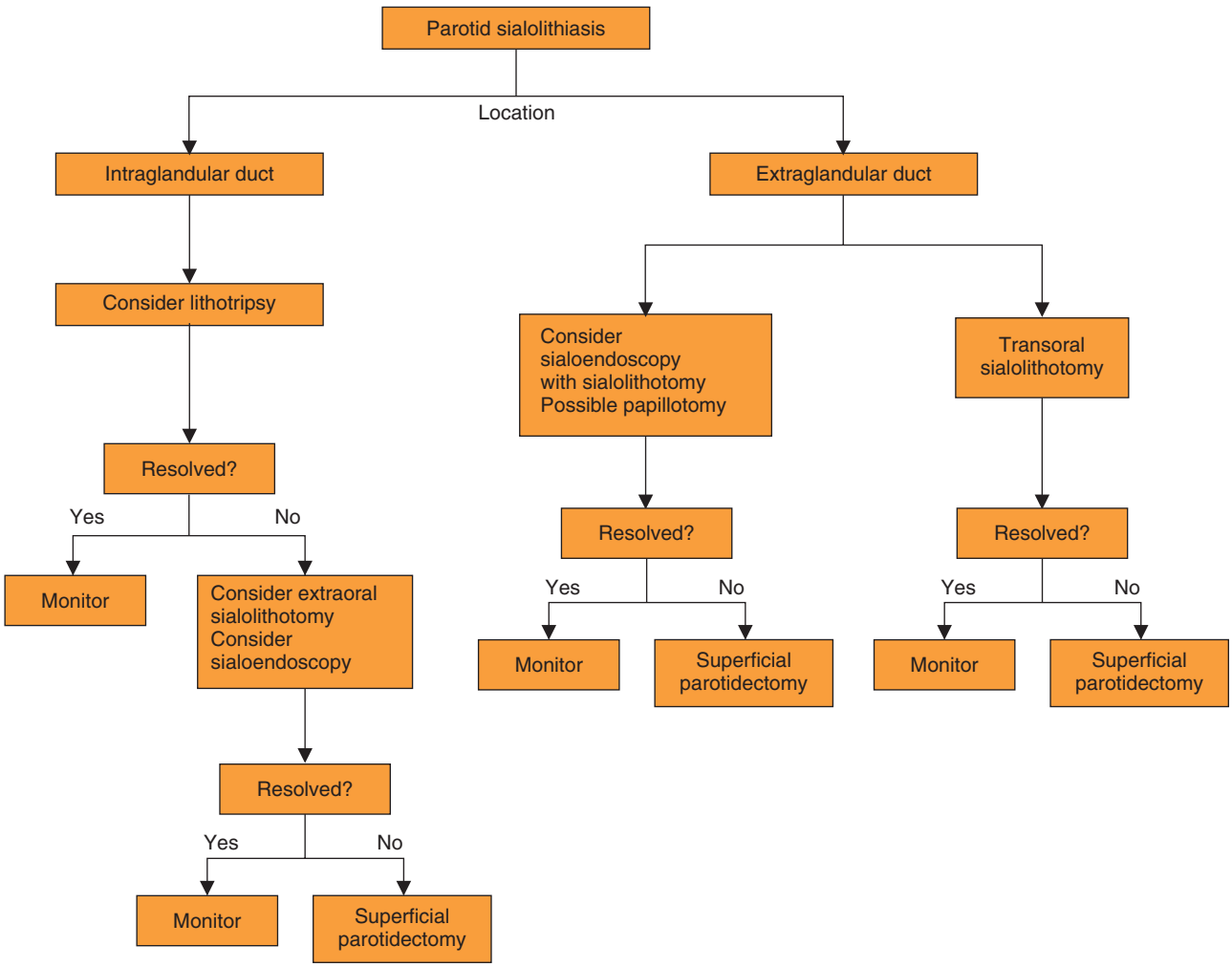


Figure 5.14. Algorithm for parotid sialolithiasis.

tissues. A retraction suture may be placed at the anterior aspect of the mucosal aspect of the flap. The duct is dissected from anterior to posterior so as to identify the stone within the duct. Once the stone is located, the duct is incised longitudinally thereby allowing for retrieval of the sialolith. The mucosal flap is reapproximated; however, the incision in the duct is not sutured. These longitudinal incisions placed in the duct do not appear to result in the formation of strictures, although transverse incisions in the duct may result in stricture formation (Seward 1968; Berry 1995). Strictures in the parotid duct will respond favorable to intermittent dilation; however, submandibular duct strictures usually require surgical intervention.

Parotid sialoliths located within the intraglandular portion of the ductal system may be addressed through an extraoral approach. Two options exist, one involving a traditional parotidectomy approach (without performing a parotidectomy) with a curvilinear skin incision in the preauricular and upper neck regions (Berry 1995), and the other involving a horizontal incision over the duct in the cheek region (Baurmash and Dechiara 1991). In the former approach, the skin flap is elevated superficial to the parotid fascia, and the duct is identified at the point where it exits the anterior border of the gland. The placement of a lacrimal probe within the Stenson duct may permit accurate identification of the duct. Once the duct is located, it is dissected posteriorly into the gland and the stone is identified. A longitudinal incision is made over the duct and the stone is retrieved (Figure 5.16). As in the

case of a transoral sialolithotomy, the incision in the Stenson duct is not closed at the conclusion of the surgery. Sialolithotomy performed with a transcutaneous approach in the cheek may also be accomplished for a diagnosis of parotid sialolithiasis (Figure 5.17).

Extracorporeal lithotripsy seems to be quite effective for the treatment of intraparotid stones. With three outpatient treatments, 50% of patients have been reported to be rendered free of calculus (Williams 1999). Half of the remaining patients may be rendered free of symptoms, but

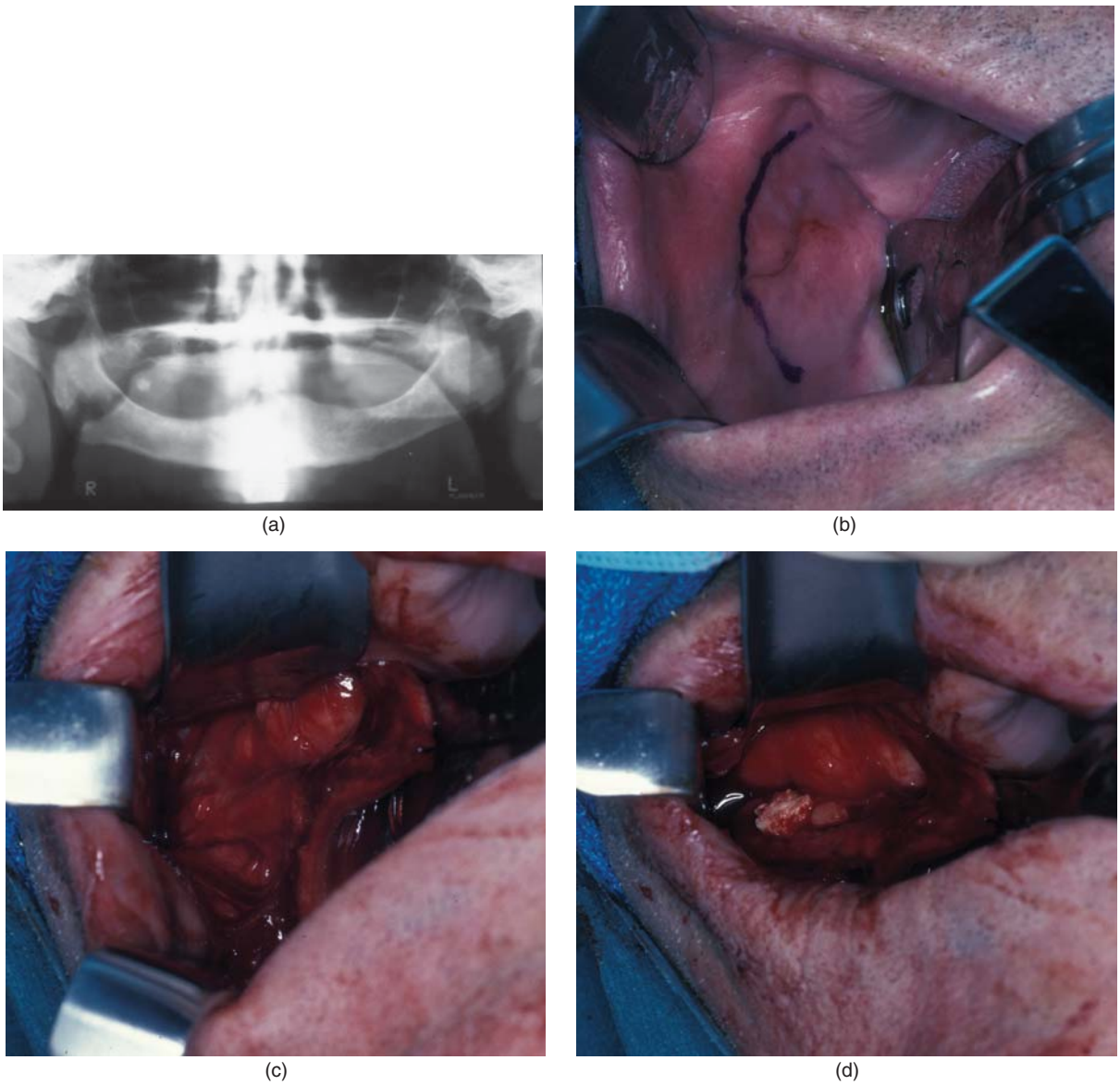


Figure 5.15. Management of an extraglandular parotid duct sialolith. The panoramic radiograph demonstrates a small sialolith in the right Stensen duct (a). The approach for this transoral sialolithotomy involved a mucosal incision anterior to the Stensen papilla (b). A mucosal flap was developed that included the Stensen duct such that the dissection occurred lateral to the duct (c). Continued dissection allowed for palpation of the sialolith within the duct. The duct was longitudinally incised over the sialolith (d), such that the stone was able to be removed (e). The mucosal flap was sutured without reapproximating the incision in the Stensen duct (f). Patent salivary flow was re-established as noted two months postoperatively (g). No further treatment of the gland was required.

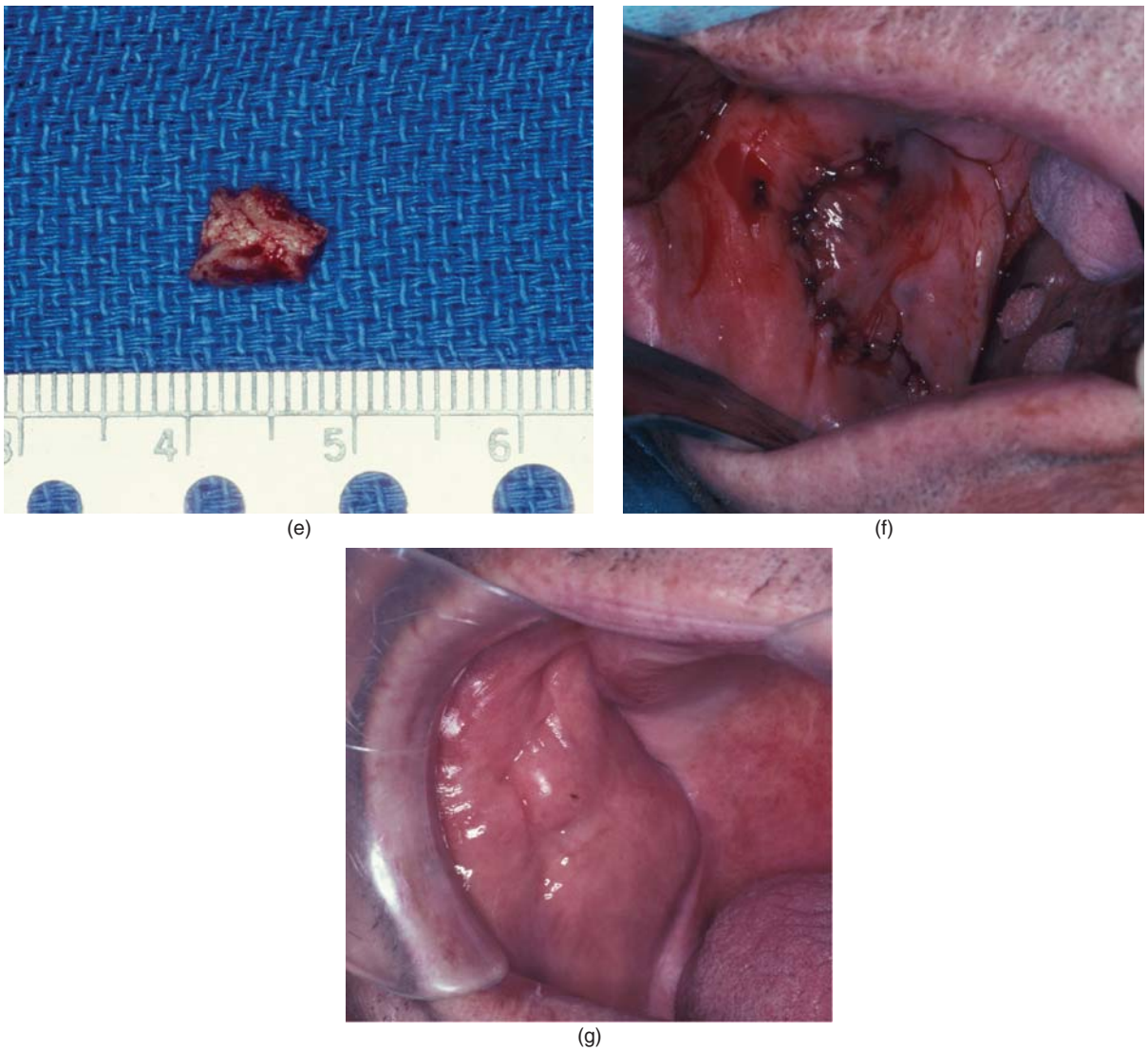


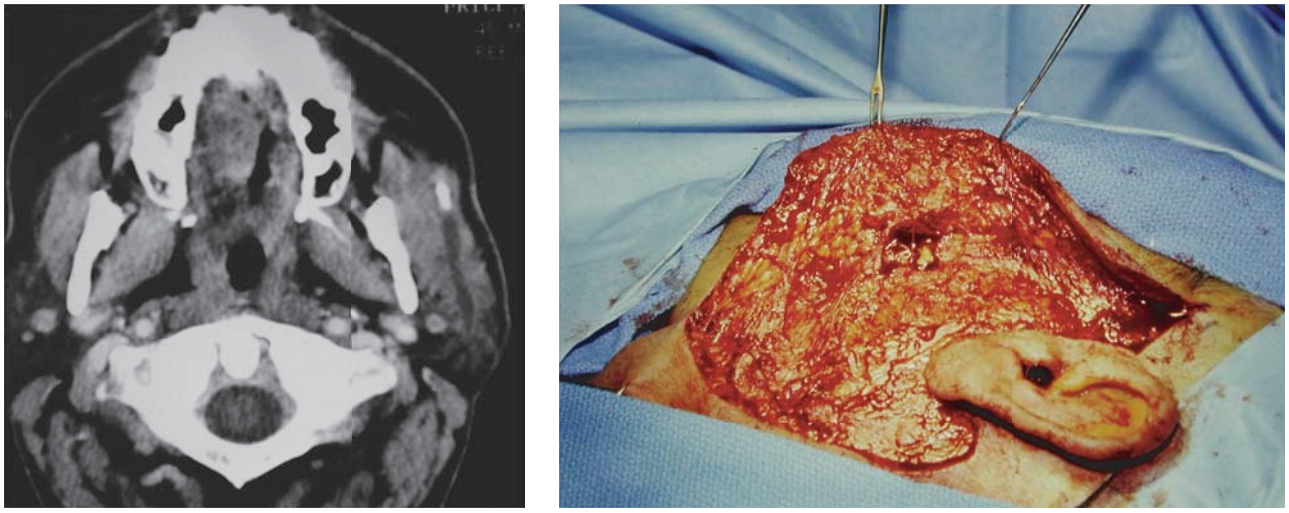
Figure 5.15. (*Continued*).

having small fragments left in the ductal system. In Ottaviani's cohort of 16 patients with parotid stones, all were relieved of their symptoms with extracorporeal lithotripsy (Ottaviani, et al. 1996). Nine of their 16 patients experienced complete disintegration and elimination of stones and 7 patients showed residual stone fragments that were able to be flushed out spontaneously or with salivation induced by citric acid (Ottaviani, et al. 1996).

McGurk, et al. (2004a) found extracorporeal shock wave lithotripsy to be successful in 44 of 90 (48.9%) patients with parotid sialoliths, and basket retrieval was successful in 44 of 57 (77.2%) of patients with parotid sialoliths. Interestingly, no patients with parotid stones underwent transoral surgical removal.

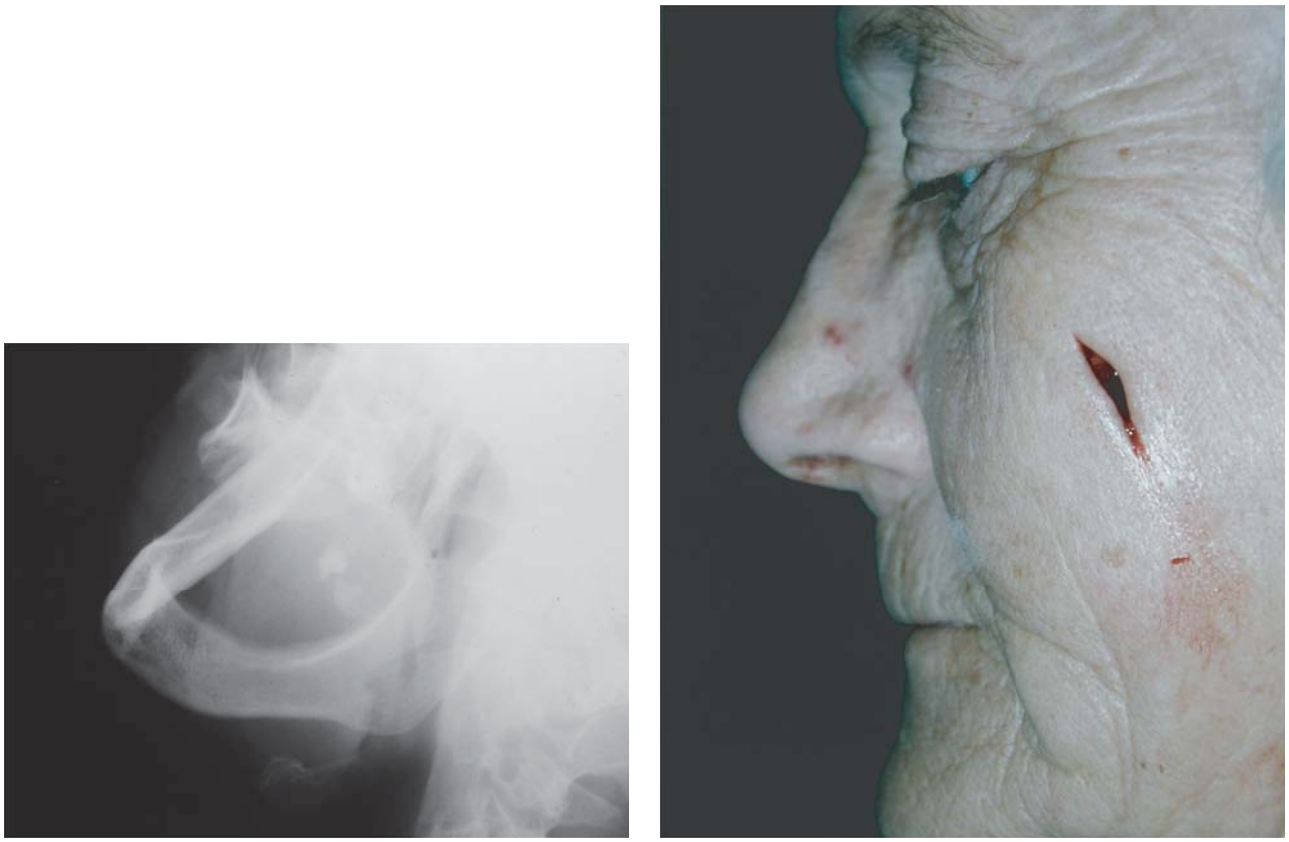
TREATMENT OF MULTIPLE SIALOLITHS AND BILATERAL (MULTIPLE GLAND) SIALOLITHS

While rare, the incidence of multiple sialoliths within one salivary gland and synchronous multiple gland sialoliths requires that all patients



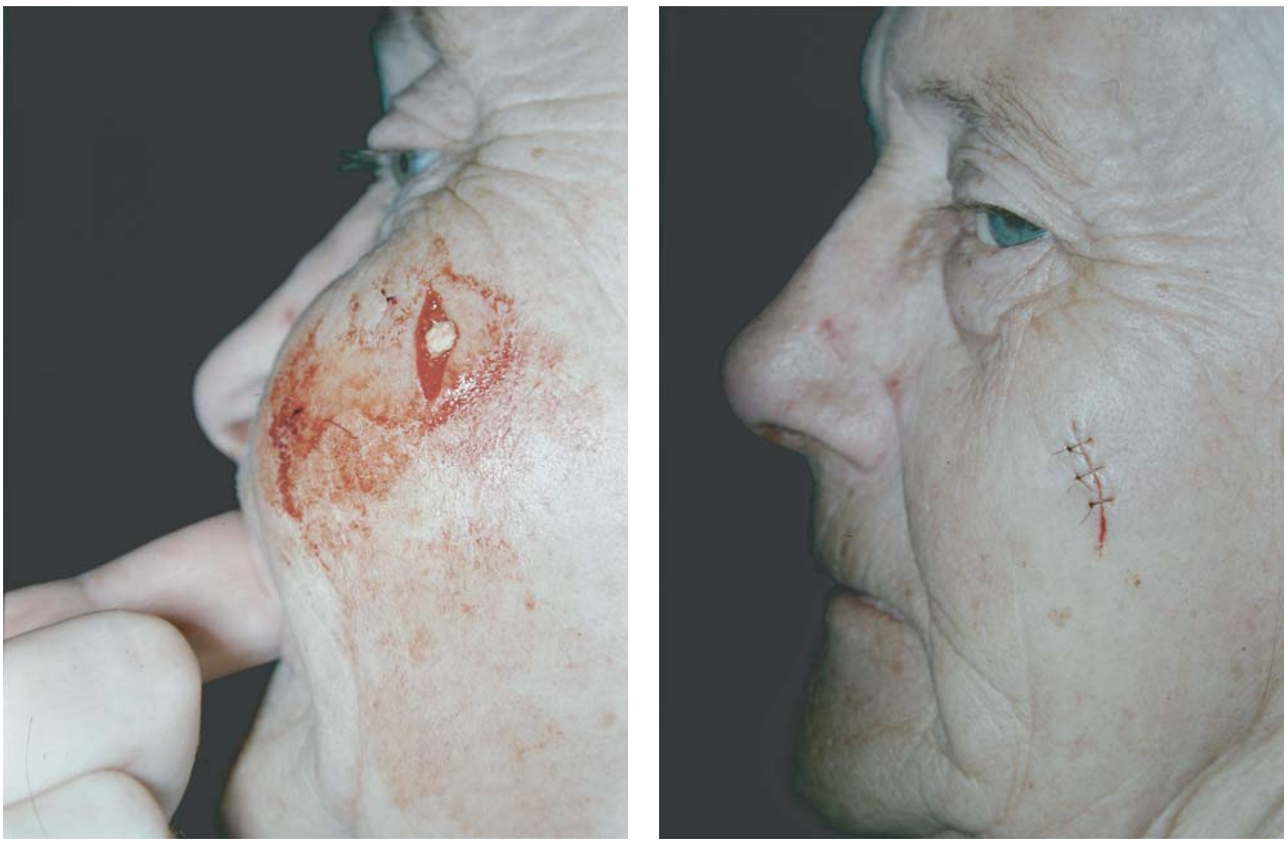
(a) (b)

Figure 5.16. Axial CT scan demonstrating a parotid sialolith at the hilum with proximal dilatation of the duct due to obstruction of salivary flow (a). A parotidectomy approach to stone retrieval was performed without parotidectomy (b).



(a) (b)

Figure 5.17. A lateral oblique plain film demonstrating two sialoliths of the Stenson duct (a). An incision through skin was placed in a resting tension line of the cheek (b). A finger was inserted in the oral cavity to created better access to the duct, thereby permitting stone retrieval (c). A primary closure was obtained (d). Source: Ord RA: Salivary gland disease. In: Fonseca R (ed.), *Oral and Maxillofacial Surgery, Volume 5, Surgical Pathology*. Philadelphia, W.B. Saunders Co., pp. 273–293. Reproduced with permission of Elsevier.



(c) (d)

Figure 5.17. (*Continued*).

undergo CT imaging when a diagnosis of sialolithiasis has been made (Figure 5.18). In so doing, a review of these CT scans should rule out multiple gland involvement and the presence of multiple sialoliths. When the review of the CT scan reveals multiple sialoliths in a single gland system, the count must be verified at the time of surgery. When multiple salivary glands are involved with the sialolithiasis, the surgeon should treat each gland according to standard, single gland protocols discussed in this chapter.

Miscellaneous Sialolithiasis

The incidence of sialolithiasis of the sublingual gland and the minor salivary glands is very rare. In McGurk, et al.'s (2004a) study of 455 cases of salivary calculi, no cases were present in the sublingual gland or minor salivary glands. As such, swellings of these glands are most likely to engender a clinical diagnosis of neoplastic disease, with the diagnosis of sialolithiasis made only after final histopathologic analysis of the gland occurs (Figure 5.19). One report examining sialolithiasis of the minor salivary glands found that only 20% of cases were correctly clinically diagnosed as sialolithiasis (Anneroth and Hansen 1983). The paucity of accurate diagnosis may also stem from the frequent spontaneous resolution of the problem due to ejection of the calculus (Lagha, et al, 2005). Two stages of minor salivary gland sialolithiasis have been described including an acute stage characterized by inflamed overlying soft tissue whereby the most common clinical diagnosis is cellulitis of the soft tissue. The chronic stage follows and calls to mind a differential diagnosis of neoplasm, irritation fibroma, or foreign body. An anatomic distribution of 126 cases of sialolithiasis of the minor salivary glands identified a significant majority occurring in either the upper

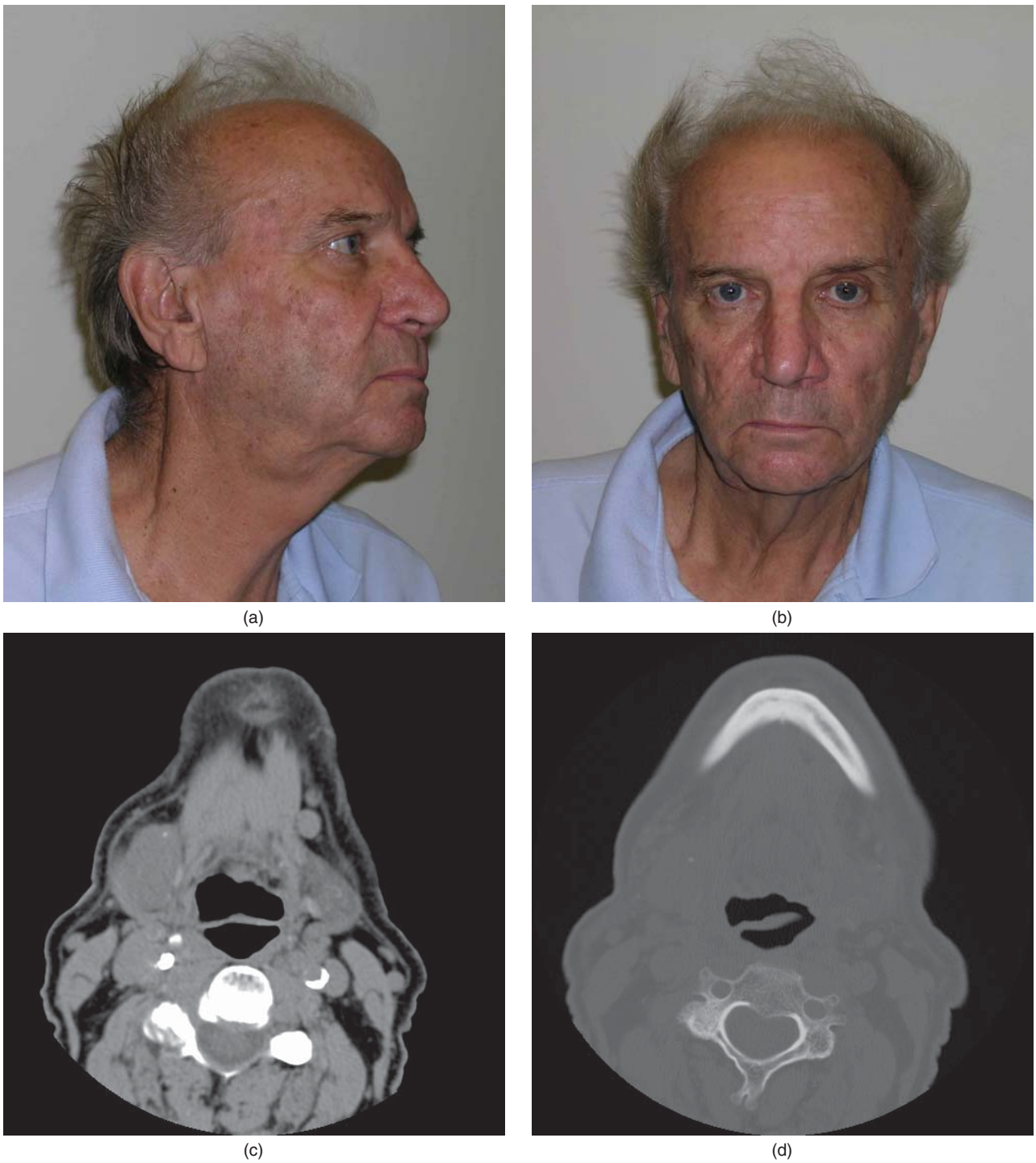
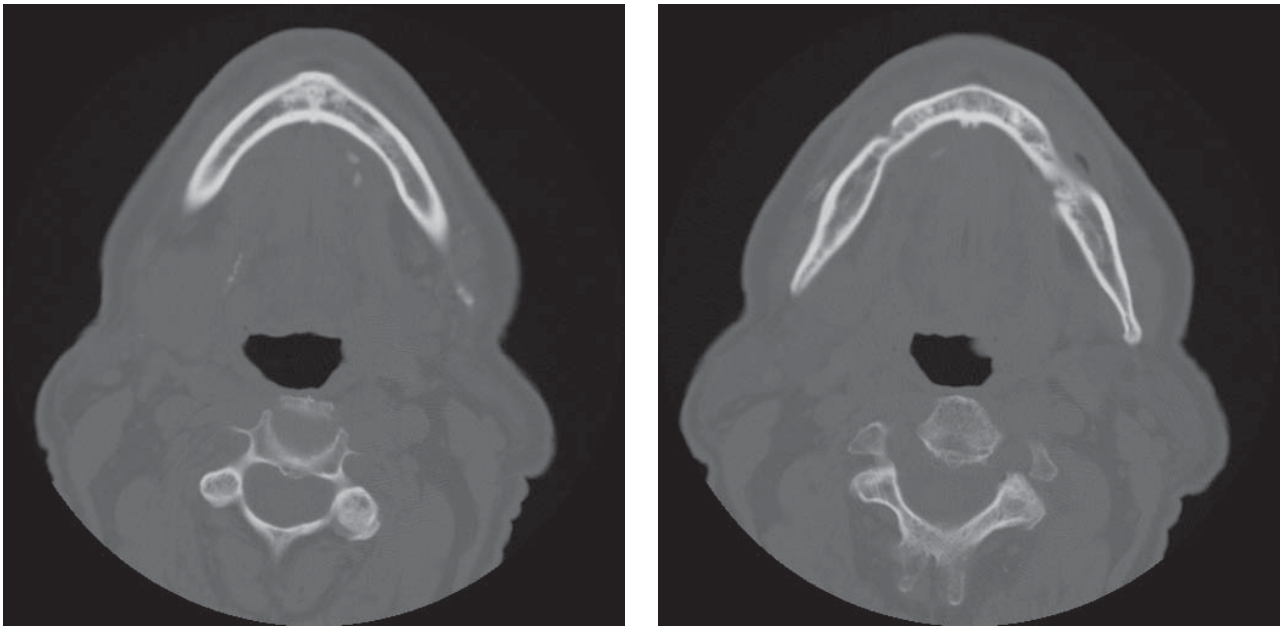
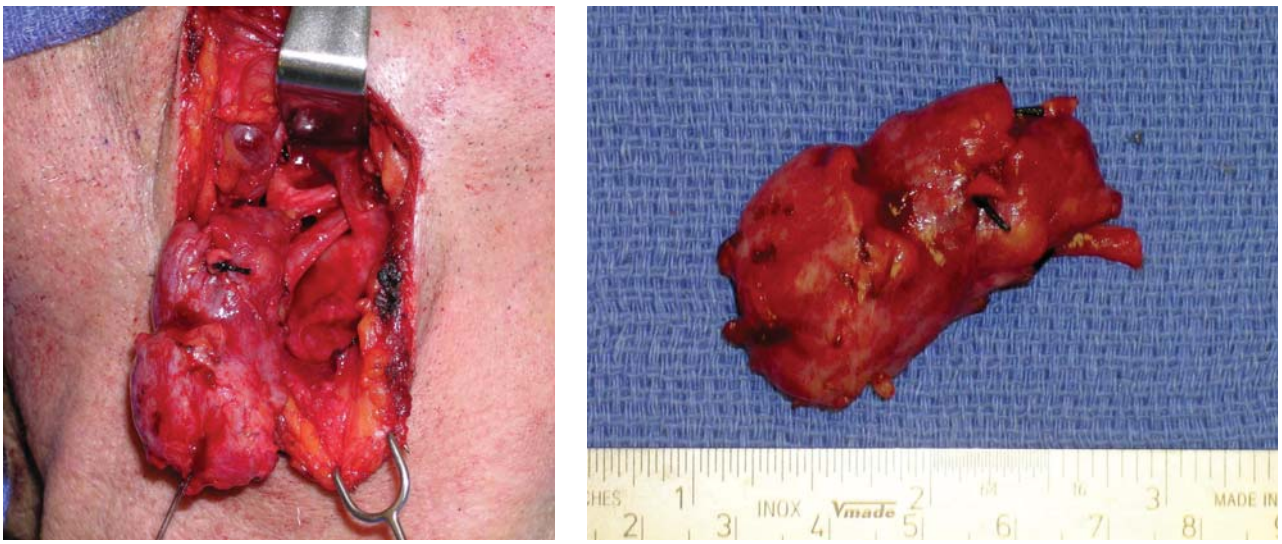


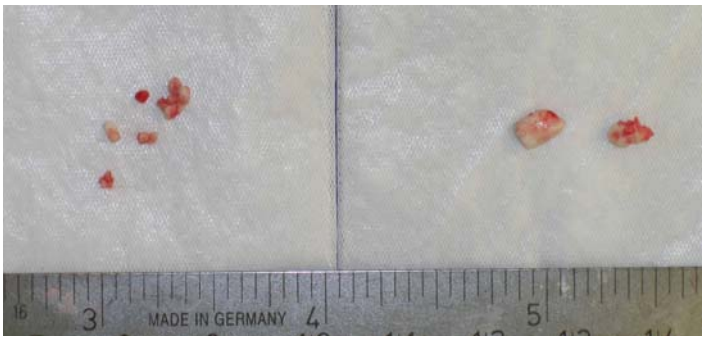
Figure 5.18. A 72-year-old man with pain and swelling of one month's duration in the right submandibular gland (a). Physical examination was significant for a tender right submandibular gland but no symptoms associated with the left submandibular gland (b). The patient underwent CT scanning that demonstrated an enlarged right submandibular gland with the presence of a single intraglandular sialolith (c and d). Thorough evaluation of the CT scans also identified five extraglandular right submandibular stones and two extraglandular left submandibular stones (e, and f). The patient underwent right submandibular gland excision in a standard fashion (g and h) with exploration of bilateral Wharton ducts so as to remove five right extraglandular stones and two left extraglandular stones (i). A left Wharton sialodochoplasty was performed.



(e) (f)



(g) (h)



(i)

Figure 5.18. (*Continued*).

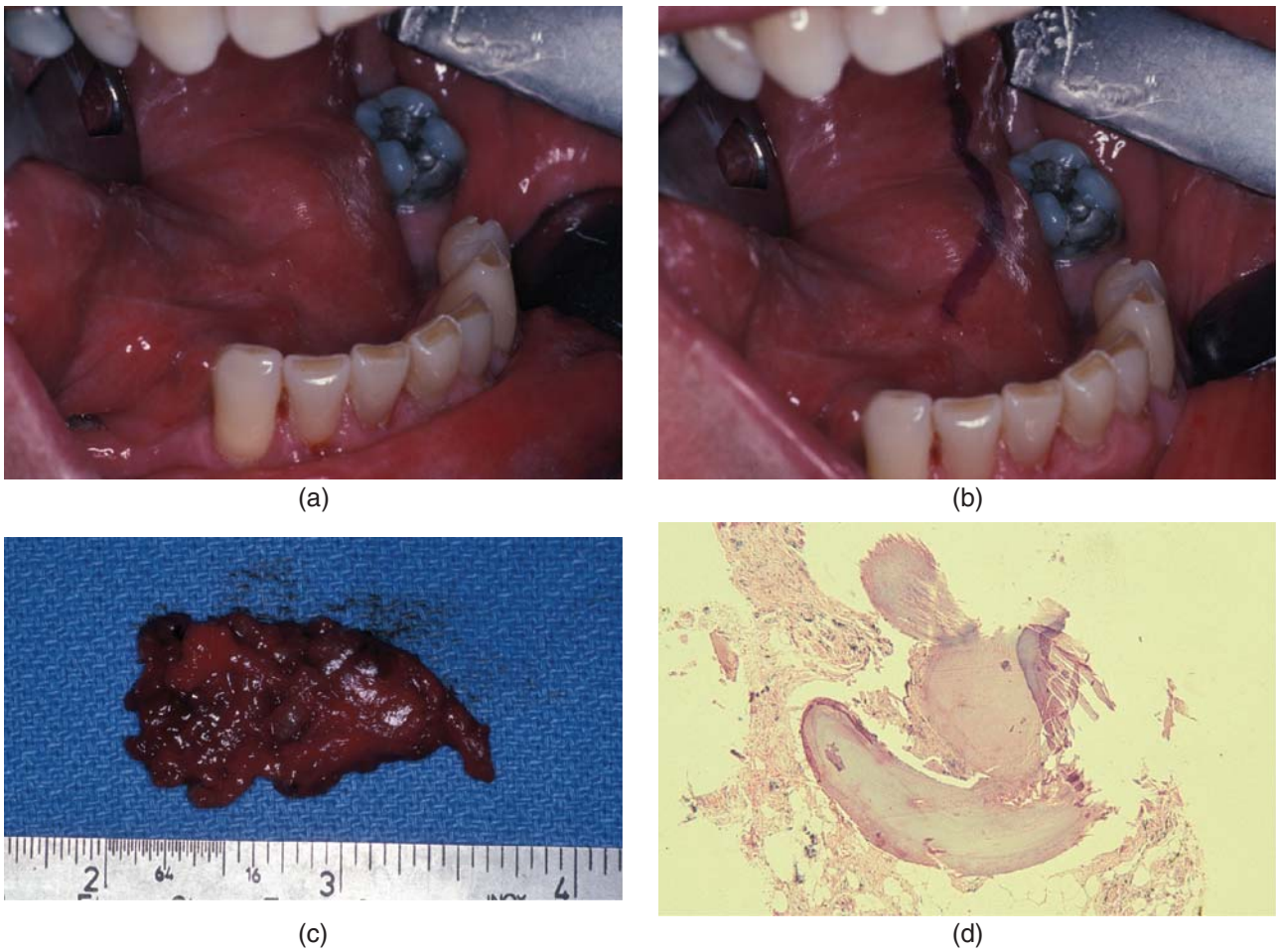
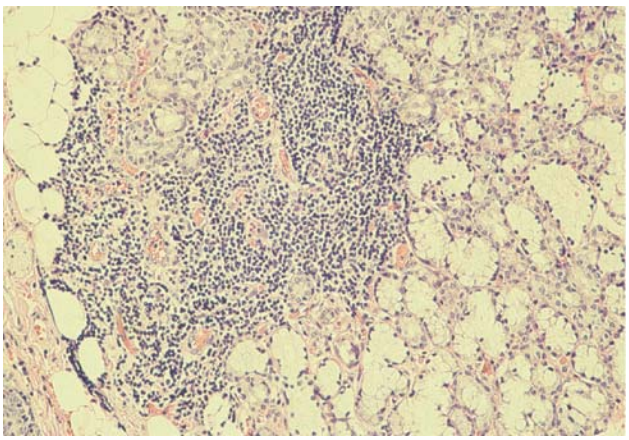


Figure 5.19. Floor of mouth swelling present in a 55-year-old woman (a). A diffuse mass is noted beneath the surface mucosa that is smooth and of normal color. A presumptive diagnosis of ranula versus neoplasm was established. A left sublingual gland excision was performed in the standard fashion (b). The specimen (c) exhibited mild induration without signs of ranula, such that a neoplastic process was favored while the possibility of a mucous escape reaction was discarded. Final histopathology showed a sialolith (d) in the background of sialadenitis (e). The tissue bed is noted (f), particularly the lingual nerve (retracted with the vessel loop) and the Wharton duct. A 6-month postoperative evaluation showed acceptable healing (g).

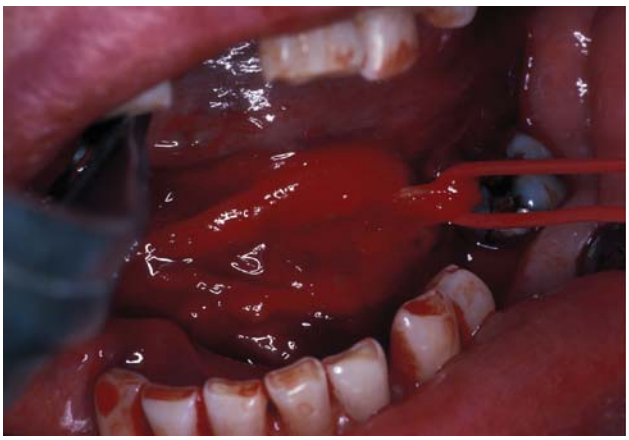
lip or the buccal mucosa. As such, sialolithiasis should be included on the differential diagnosis of an indurated submucosal nodule of the upper lip or buccal mucosa, and surgical excision should be performed.

Summary

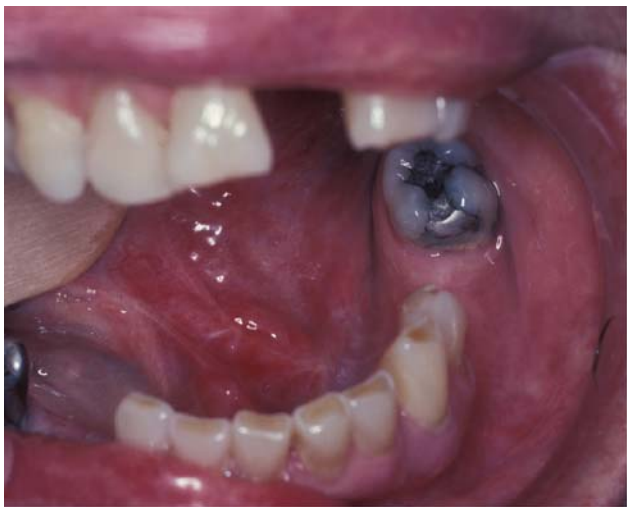
- Sialoliths are calcium phosphate stones that develop within the ductal system of salivary glands.
- Sialolithiasis is thought to affect approximately 1% of the population based on autopsy studies.
- Sialolithiasis has been estimated to represent more than 50% of major salivary gland disease and is the most common cause of acute and chronic salivary gland infections.
- Approximately 85% of sialolithiasis occurs in the submandibular gland, 10% in the parotid gland, 5% in the sublingual gland, and the incidence of this pathology is rare in the sublingual gland and minor salivary glands.



(e)



(f)



(g)

Figure 5.19. (*Continued*).

- 80% of submandibular sialoliths are radio-opaque, while 40% of sialoliths of the parotid gland are radio-opaque.
- Approximately 7% of sialoliths are bilateral.
- Approximately 3% of cases of sialolithiasis occur simultaneously in multiple glands.
- Systemic disorders of calcium metabolism do not seem to represent predisposing factors to sialolithiasis. The one exception to this rule is gout where a higher incidence of uric acid stones has been observed.
- 75–85% of submandibular stones are located in the duct, while parotid stones are located in the hilum or gland parenchyma in at least half of cases.
- Several "great imitators" of submandibular sialolithiasis exist, including scrofula, phleboliths, osteomas, and occasionally, carotid plaques.
- Numerous techniques are available to treat sialolithiasis including surgical sialolithotomy with or without sialodochoplasty, sialoendoscopy with sialolithotomy, intracorporeal or extracorporeal lithotripsy, or gland removal.

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Chapter 6

Systemic Diseases Affecting the Salivary Glands

Outline

Introduction

A number of systemic autoimmune diseases result in infiltration of the salivary glands. It is estimated that approximately 5–8% of the general population is affected by any of the 80 known autoimmune diseases (Jonsson and Olofsson 2011). Among those infiltrating the salivary glands include immune-modulated or idiopathic diseases such as sarcoidosis, Sjogren disease, sialosis, and lymphoepithelial lesions. Each of these processes involves multiple physiologic systems and may be diagnosed based on clinical signs and symptoms, many of which are very common yet may be easily overlooked and considered as non-specific. In addition, these diseases may be diagnosed at an early stage with salivary gland biopsy. It is the purpose of this chapter to describe the clinical features of salivary gland involvement of autoimmune systemic diseases.

Sjogren Syndrome

Sjogren syndrome is an inflammatory autoimmune disease that manifests as a chronic, slowly progressive disease characterized by keratoconjunctivitis sicca and xerostomia. The disease was originally named for Henrik Sjogren, a Swedish ophthalmologist whose doctoral dissertation in 1933 reported the specific clinical and microscopic findings in 19 women with xerostomia and keratoconjunctivitis sicca, 13 of whom also had arthritis (Jonsson and Olofsson 2011). Since 1965, Sjogren syndrome has been defined as a triad of dry eyes, dry mouth, and rheumatoid arthritis or other connective tissue diseases (Daniels 1991). This process may evolve from an exocrine organ specific disorder to an extraglandular multisystem disease affecting the lungs, kidneys, blood vessels, and muscles (Table 6.1). Sjogren syndrome is believed to affect 0.2–3.0% of the population with approximately one million people diagnosed in the United States (Reksten and Jonsson 2014; Turner 2014). It predominantly occurs in women between 40 and 60 years of age with a 9:1 female:male ratio (Reksten and Jonsson 2014). Because of the insidious onset of symptoms, an average time of 10 years occurs between the development of first symptoms and

Salivary Gland Pathology: Diagnosis and Management, Second Edition. Edited by Eric R. Carlson and Robert A. Ord.

Table 6.1. Frequency of extraglandular findings in primary Sjogren syndrome

Clinical Involvement	Percent
Arthritis	60
Kidney	9
Liver	6
Lung	14
Lymphadenopathy	14
Lymphoma	6
Myositis	1
Peripheral neuropathy	5
Raynaud phenomenon	35
Splenomegaly	3

the diagnosis of the disease (Turner 2014). One confounder in the recognition of Sjogren syndrome is that symptoms do not typically occur concurrently such that individual symptoms might be treated independently by individual doctors, thereby delaying the diagnosis of the disease.

PATHOPHYSIOLOGY OF SJOGREN SYNDROME

The pathophysiology of Sjogren syndrome is believed to be the result of activation of both the cellular and humoral immune systems with resultant inflammation and cellular infiltration of the salivary and lacrimal glands and other affected organs. While the inciting event in the development of Sjogren syndrome is still unknown, a popular hypothesis is that a viral infection initiates the cascade of autoimmunity (Turner 2014). The autoantibodies in Sjogren syndrome include those produced to the ribonucleoprotein particles SS-A/Ro and SS-B/La, and these are thought to interfere with muscarinic receptors (Garcia-Carrasco, et al. 2006). One study identified IgG from patients with primary Sjogren syndrome containing autoantibodies capable of damaging saliva production and contributing to xerostomia (Dawson, et al. 2006). Other mechanisms of glandular dysfunction include destruction of glandular elements by cell-mediated mechanisms; secretion of cytokines that activate pathways bearing the signature of type 1 and 2 interferons (IFN); and secretion of metalloproteinases (MMP) that interfere with the interaction of the glandular cell with its extracellular matrix (Garcia-Carrasco, et al. 2006). The presence of IFN induces the expression of B-cell activating factor (BAFF) that causes a migration and infiltration of T- and B-lymphocytes into the salivary gland cells. In addition, increased MMP-3 and MMP-9 expression has been found to be responsible for acinar destruction in Sjogren syndrome (Perez, et al. 2005). These substantial increases in MMP expression in diseased labial salivary glands may be potentiated by moderate decreases in tissue inhibitors of matrix metalloproteinases (TIMP).

CLINICAL MANIFESTATIONS OF SJOGREN SYNDROME

Primary Sjogren syndrome is designated when it is not associated with other connective tissue diseases. This notwithstanding, evidence exists that shows genetic aggregation of autoimmune diseases in families of patients with primary Sjogren syndrome (Anaya et al. 2006). The suggestion is that autoimmune diseases in general may aggregate as a trait favoring a common immunogenetic origin for diverse autoimmune phenotypes, such that a risk factor exists for the development of primary Sjogren syndrome and other autoimmune diseases. Secondary Sjogren syndrome is defined when the disease is associated with other clinically expressed autoimmune processes, specifically, rheumatoid arthritis, systemic lupus erythematosus, myositis, biliary cirrhosis, systemic sclerosis, chronic hepatitis, cryoglobulinemia, thyroiditis, and vasculitis. Following rheumatoid arthritis, Sjogren syndrome is the second most common autoimmune rheumatic disorder (Moutsopoulos 1993). Eight to ten years are generally required for the disorder to progress from initial symptoms to the development of the syndrome. Although typically seen in middle aged women, Sjogren syndrome can occur in all ages and in males. It has been estimated that 80–90% of patients are women, and that the mean age at diagnosis is 50 years (Daniels 1991).

Most patients with Sjogren syndrome develop symptoms related to decreased salivary gland and lacrimal gland function. Primary Sjogren syndrome patients generally complain of dry eyes, often described as a sandy or gritty feeling under the eyelids. Other symptoms such as itching of the eyes, eye fatigue, and increased sensitivity to light

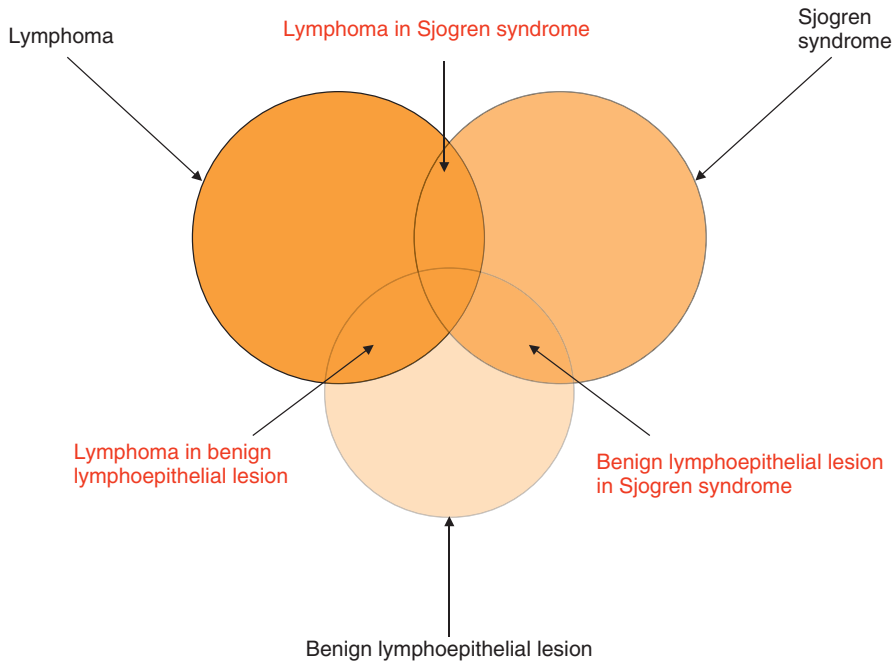


Figure 6.1. The association between the lymphoepithelial lesion, Sjogren syndrome, and lymphoma.

can accompany the primary symptoms. Many of these symptoms are due to the destruction of corneal and bulbar conjunctival epithelium and come under the diagnosis of keratoconjunctivitis sicca. This disorder is assessed by tear flow and composition. Tear flow is measured using the Schirmer test, while tear composition can be determined by tear break-up time or tear lysozyme content. The Schirmer test is considered positive when filter paper wetting of less than 5 mm occurs in 5 minutes, and suggests clinically significant keratoconjunctivitis sicca (Moutsopoulos 1993). There are, nonetheless, numerous false positive and negative results, such that the predictive value is limited. The integrity of the corneal and bulbar conjunctiva may be assessed using the Rose Bengal staining procedure and slit lamp examination. Punctate corneal ulcerations and attached filaments of corneal epithelium indicative of corneal and bulbar conjunctival epithelial destruction are noted on slip lamp examination in Sjogren patients.

Xerostomia is the second principal symptom of Sjogren syndrome. Xerostomia can be documented by salivary glow measurements, parotid sialography, and salivary scintigraphy. Salivary flow measurements must be adjusted for age, time of day, gender, and concomitant medications. Patients with dry mouths complain of a burning oral discomfort and difficulty in chewing and swallowing dry foods. Xerostomia is commonly associated with changes in taste and the inability to speak continuously for longer than several minutes.

Salivary gland enlargement occurs in as many as 30% of patients with Sjogren syndrome during the course of their illness, with the parotid gland being most often enlarged (Figure 6.1) (Kulkarni 2005). It is estimated that bilateral parotid gland enlargement is found in 25–60% of patients with Sjogren syndrome (Turner 2014). Bilateral painful submandibular glands have been described as a presenting symptom of this syndrome (Kulkarni 2005). While the parotid glands are most commonly enlarged, they may be the last glands to be affected in patients with Sjogren syndrome from the standpoint of decreased saliva production (Pijpe, et al. 2007). The parotid glands have a longer-lasting secretory capacity in patients with Sjogren syndrome and therefore are the last glands to manifest hyposalivation during the disease. In the more advanced stages of the disease, both unstimulated and stimulated submandibular, sublingual, and parotid functions fall to a low level. The accelerated development of dental caries is also noted. Enlargement of the lacrimal glands is uncommon. Even when the salivary glands are not enlarged, they always exhibit lymphohistiocyte-mediated acinar destruction (Marx 1995). When enlarged, however,

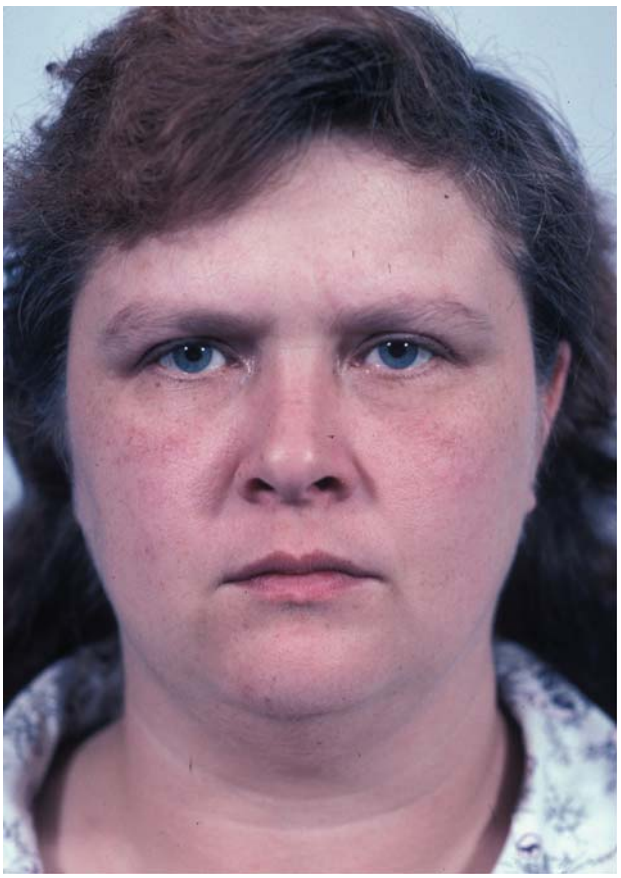


Figure 6.2. A 36-year-old woman with a known history of Sjogren syndrome associated with rheumatoid arthritis. She described a recent history of painful swelling of the right parotid gland such that an incisional parotid biopsy was recommended.

they show features of the benign lymphoepithelial lesion (BLL) in almost all cases. These lesions may occur in patients who do not have Sjogren syndrome. Furthermore, they may undergo malignant transformation to lymphomas in patients with or without Sjogren syndrome (Figure 6.2).

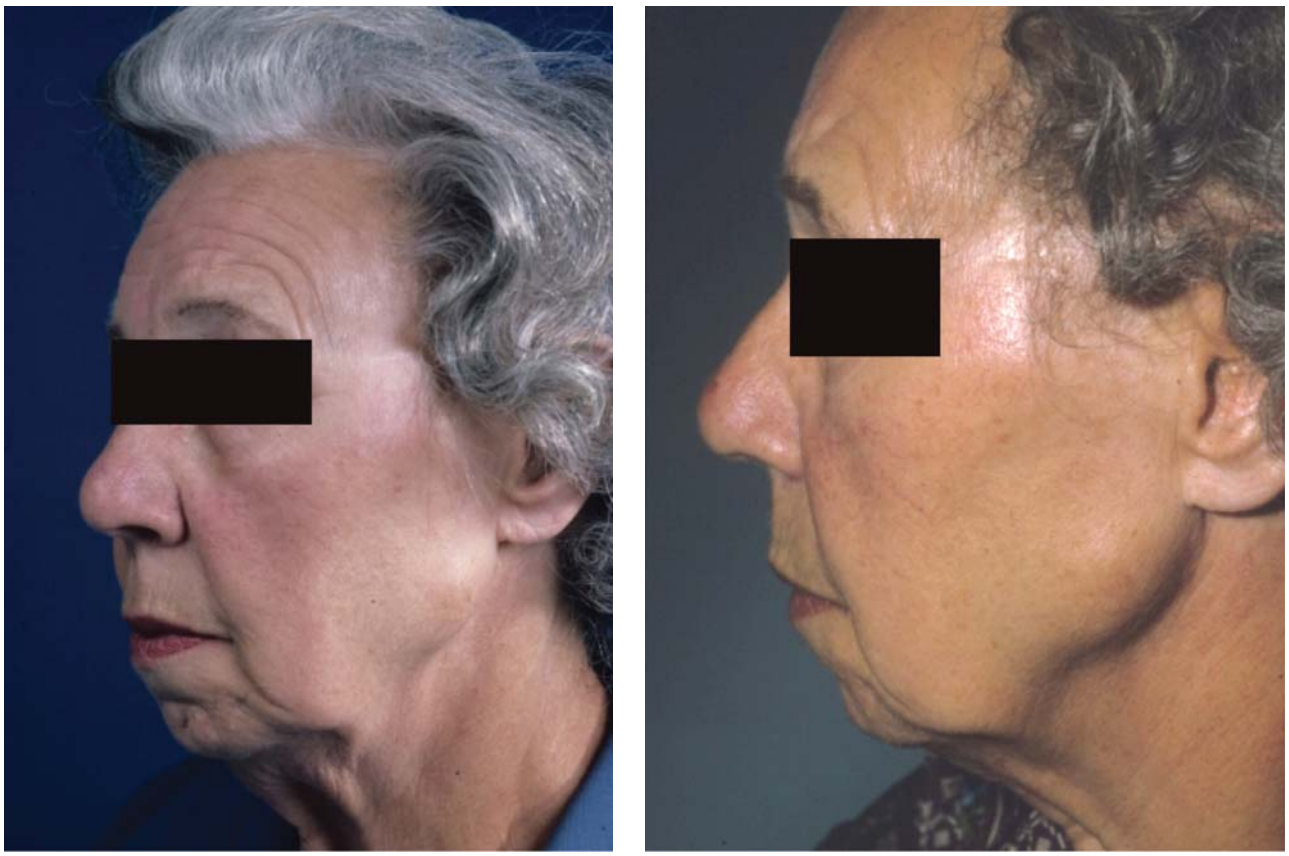
LYMPHOMA AND SJOGREN SYNDROME

One of the most concerning features of Sjogren syndrome is the possible development of non-Hodgkin lymphomas (NHL). It has been estimated that 4% of patients with Sjogren syndrome will develop lymphomas by 7.5 years following their initial diagnosis, with the most common type of NHL being the mucosa-associated lymphoid tissue lymphoma (MALT), a B-cell lymphoma. The risk of lymphoma formation seems to be directly related to prolonged B-cell survival and excessive B-cell activity most likely resulting from an increased production of BAFF. These B-cells have also been noted to produce rheumatoid factor (RF). The more aggressive diffuse large B-cell lymphoma (DLBCL) is also seen in Sjogren syndrome patients, and it has been estimated that 10% of MALT lymphomas will transform into DLBCL. Clinical suspicion of NHL in patients with Sjogren syndrome should occur in symptomatic unilateral or bilateral parotid enlargement, palpable purpura, splenomegaly, and lymphadenopathy (Figure 6.2).

Patients with diagnosed MALT lymphoma of the salivary glands who have isolated, asymptomatic disease without bone marrow involvement may be managed by observation. Patients with advanced stage MALT lymphomas of the salivary glands may be managed with rituximab alone or in combination with other chemotherapeutic agents. Rituximab is a monoclonal antibody that targets the CD20 protein found on B-cells thereby resulting in their destruction. The presence of DLBCL of the salivary glands will result in treatment with rituximab and CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone).

MIKULICZ DISEASE AND THE BENIGN LYMPHOEPITHELIAL LESION

The pathologic entity known as the benign lymphoepithelial lesion was once referred to as Mikulicz disease. The German surgeon, Johann Mikulicz first described the benign lymphoepithelial lesion in 1888 in a report of a single case of lacrimal gland involvement (Daniels 1991). The lacrimal gland enlargement was followed by enlargement of the submandibular and parotid glands, as well as minor salivary gland tissue. The term Mikulicz disease was subsequently applied to a variety of cases of bilateral salivary or lacrimal gland enlargement, including those caused by sarcoidosis, lymphoma, tuberculosis, or syphilis. The term *lymphoepithelial lesion* was proposed by Godwin in 1952 to describe parotid gland lesions previously called Mikulicz disease, adenolymphoma, chronic inflammation, lymphoepithelioma, or lymphocytic tumor (Godwin 1952). One year later in 1953, Morgan and Castleman observed



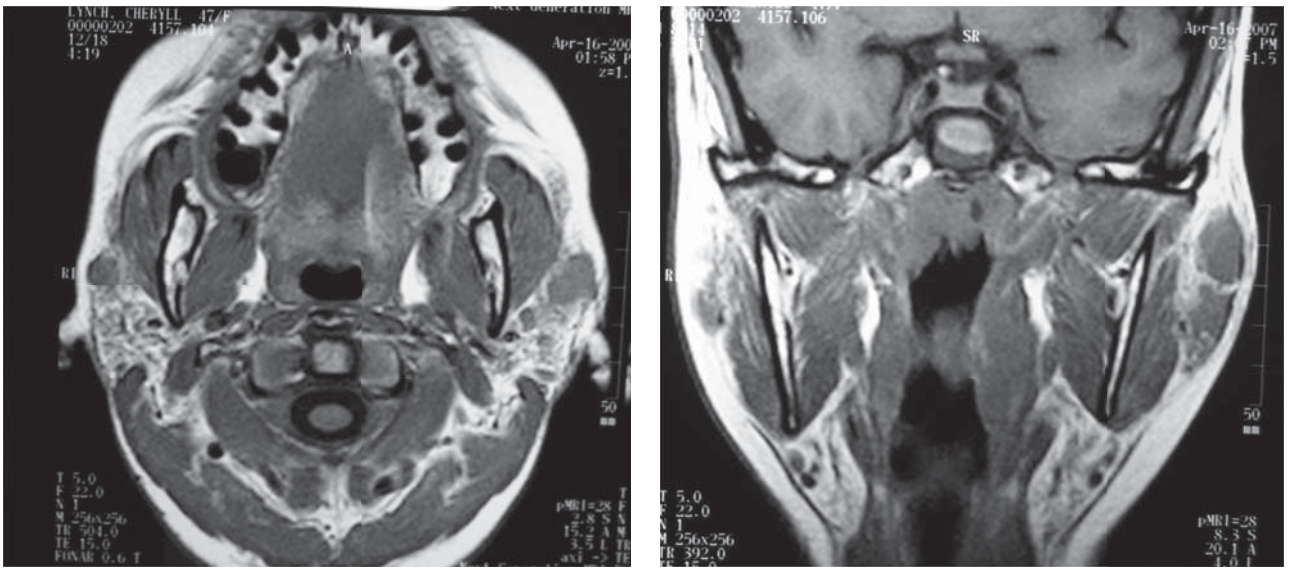
(a) (b)

Figure 6.3. A 75-year-old woman (a, b) with a left parotid mass. Fine needle aspiration biopsy suggested lymphoma, leading to superficial parotidectomy. Histopathology identified benign lymphoepithelial lesion.

numerous similarities of the benign lymphoepithelial lesion to the histopathology of Sjogren syndrome, and proposed that Mikulicz disease is not a distinct clinical and pathologic entity but rather one manifestation of the symptom complex of the syndrome (Morgan and Castleman 1953). They are, in essence, the same pathologic process (Jonsson and Olofsson 2011). The benign lymphoepithelial lesion may become large enough to present as a mass resembling a parotid tumor (Figure 6.3).

Acinar degeneration and hyperplasia and metaplasia of the ducts led to the formation of the pathognomonic epimyoepithelial islands, which define the condition. Whether myoepithelial cells or ductal basal cells are responsible for these islands has been questioned. An immunohistochemical investigation has shown that myoepithelial cells do not play a role in the formation of these islands and they should be designated lymphoepithelial metaplasia (Ihrler, et al. 1999). The condition is often a manifestation of Sjogren syndrome or other immunological abnormality but may occur outside the Sjogren disease process. Usually the lesion starts unilaterally but becomes bilateral in the parotids (Figure 6.4). It is less common in the submandibular and minor salivary glands (Figure 6.5).

The lesion may reach a large size although it is usually asymptomatic. It may be diagnosed by fine needle aspiration if the etiology is uncertain and may require removal by parotidectomy for esthetic reasons. Sudden growth or pain may be an ominous feature as benign lymphoepithelial lesion can undergo malignant change and is perhaps not as benign as its name suggests. The lymphocytic component can undergo change to MALT lymphoma (see Chapter 11) particularly in Sjogren syndrome (Abbondanzo 2001) but also in HIV infections (Del Bono, et al. 2000). Recurrent benign lymphoepithelial lesion may also undergo



(a) (b)

Figure 6.4. A 45-year-old woman diagnosed with Sjogren syndrome with bilateral parotid lesions shown on axial (a) and coronal images (b).

malignant change of its epithelial component to become an undifferentiated carcinoma with lymphoid stroma (see Chapter 8) (Cai, et al. 2002).

DIAGNOSIS OF SJOGREN SYNDROME WITH SALIVARY GLAND BIOPSY

Incisional biopsy of minor salivary glands was introduced as a clinical diagnostic procedure for Sjogren syndrome in 1966. Many studies since that time have examined the value of this biopsy procedure (Marx, et al. 1988). One study graded inflammation in labial salivary gland biopsy specimens from patients with various rheumatologic diseases and in postmortem specimens (Chisolm and Mason 1968). A grading scheme of lymphocytes and plasma cells per 4 mm^2 was established and has been described by numerous authors since its original description (Greenspan, et al. 1974). Grade 0 referred to the absence of these cells, grade 1 showed a slight infiltrate, grade 2 showed a moderate infiltrate or less than one focus per 4 mm^2, grade 3 showed one focus per 4 mm^2, and grade 4 showed more than one focus per 4 mm^2. It has been noted that grade 4 (more than one focus of 50 or more lymphocytes per 4 mm^2 area of gland) is seen only in patients with Sjogren syndrome and was not seen in postmortem specimens. Due to the strong association with the presence of Sjogren syndrome, focal sialadenitis in a labial minor salivary gland incisional biopsy specimen with a focus score of more than 1 focus/4 mm^2 has been proposed as the diagnostic criterion for the salivary component of this disease (Daniels, et al. 1975). It has been pointed out that the focus score cannot separate early from late disease as chronicity of symptoms and focus score did not show a relationship (Greenspan, et al. 1974). The highest focus score, however, was seen in patients with the sicca components of Sjogren syndrome without associated connective tissue disease. Finally, since variation of disease apparently exists from minor salivary gland lobe to lobe, at least 4–7 lobes of minor salivary gland tissue should be removed and examined microscopically (Greenspan, et al. 1974).

Incisional biopsy of the parotid gland has at least theoretical benefit and justification in the diagnosis of Sjogren syndrome. Previous recommendations for major salivary gland biopsy reported potential complications of facial nerve damage, cutaneous fistula, and scarring of the facial skin when utilizing a parotid biopsy to establish or confirm a diagnosis of Sjogren syndrome. Incisional parotid biopsy may be performed without assuming any of these complications, except in very rare circumstances (Marx, et al. 1988). Recent studies, in fact, point to a higher yield of

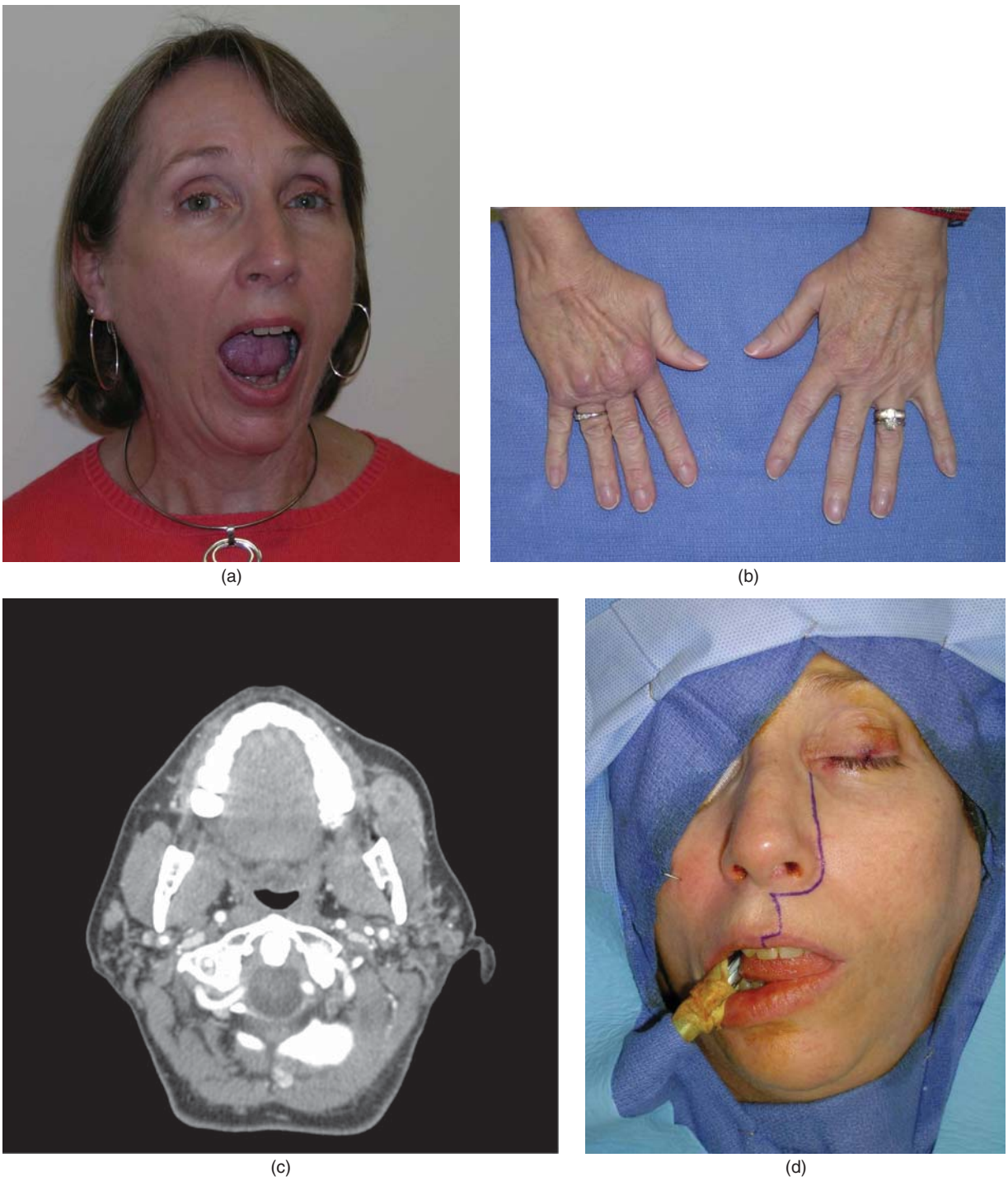
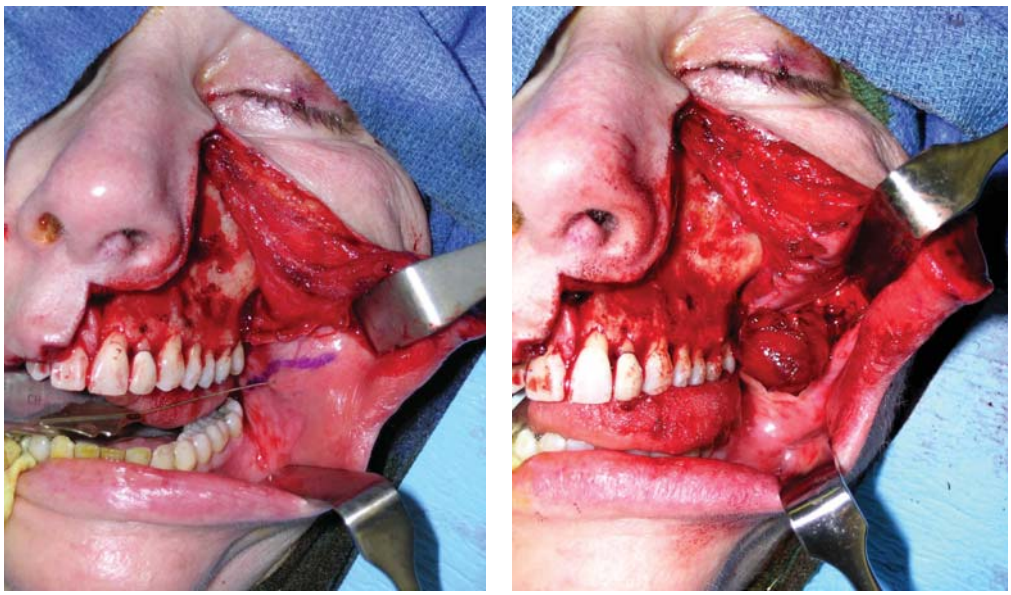
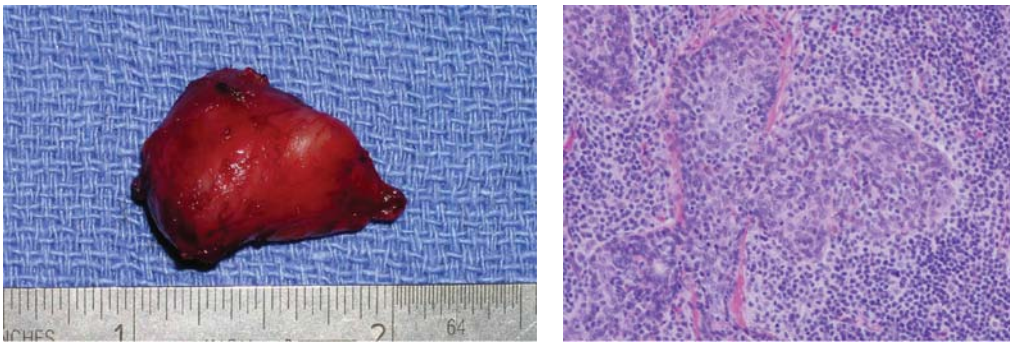


Figure 6.5. A 55-year-old woman (a) with a 10-year history of a progressively enlarging mass of the left cheek that is able to be visualized inferior to her left zygomatic buttress when she opens her mouth. She reported a history of Sjogren syndrome and rheumatoid arthritis of the hands (b). Computerized tomograms (c) identified a heterogenous mass of the left buccal region, associated with minor salivary gland tissue versus an accessory parotid gland. A salivary gland neoplasm was favored based on clinical and radiographic information. Excision was accomplished with a Weber–Ferguson incision (d) so as to provide access and minimize trauma to the Stenson duct and the buccal branch of the facial nerve. An incision in the buccal mucosa (e) was also utilized, which permitted effective dissection of the tissue bed (f). The specimen was able to be removed without difficulty (g) and was diagnosed as a lymphoepithelial lesion (h, Hematoxylin and eosin, original magnification ×200). She healed well and without recurrence of her lymphoepithelial lesion as noted at 5 years postoperatively (i).



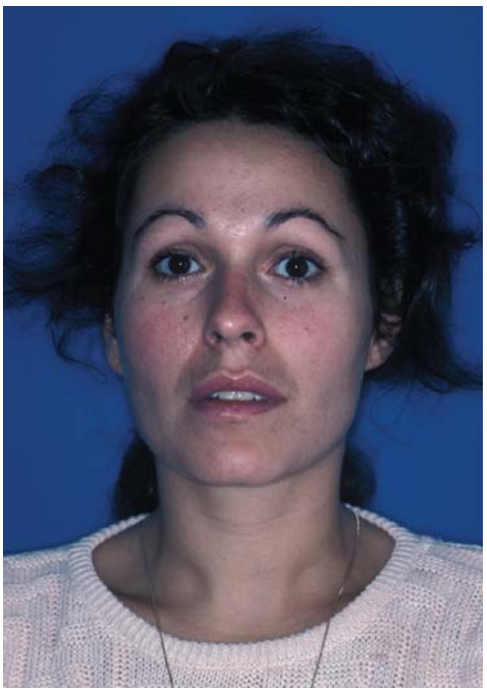
(e) (f)



(g) (h)

(i)

Figure 6.5. (*Continued*)



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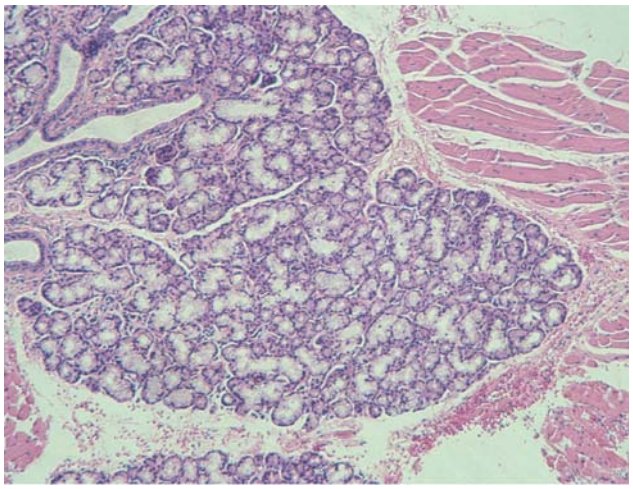

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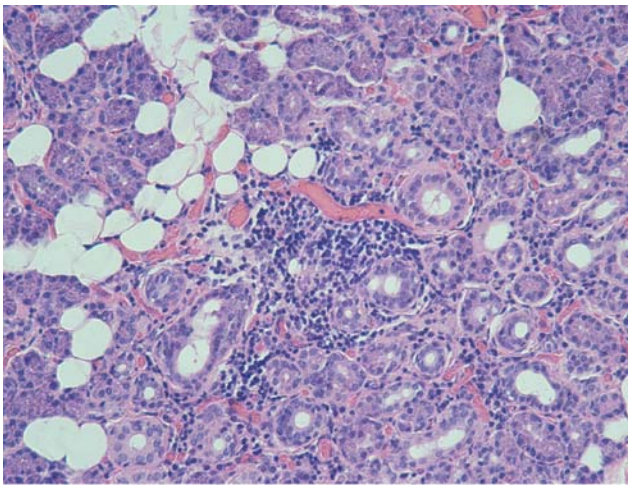
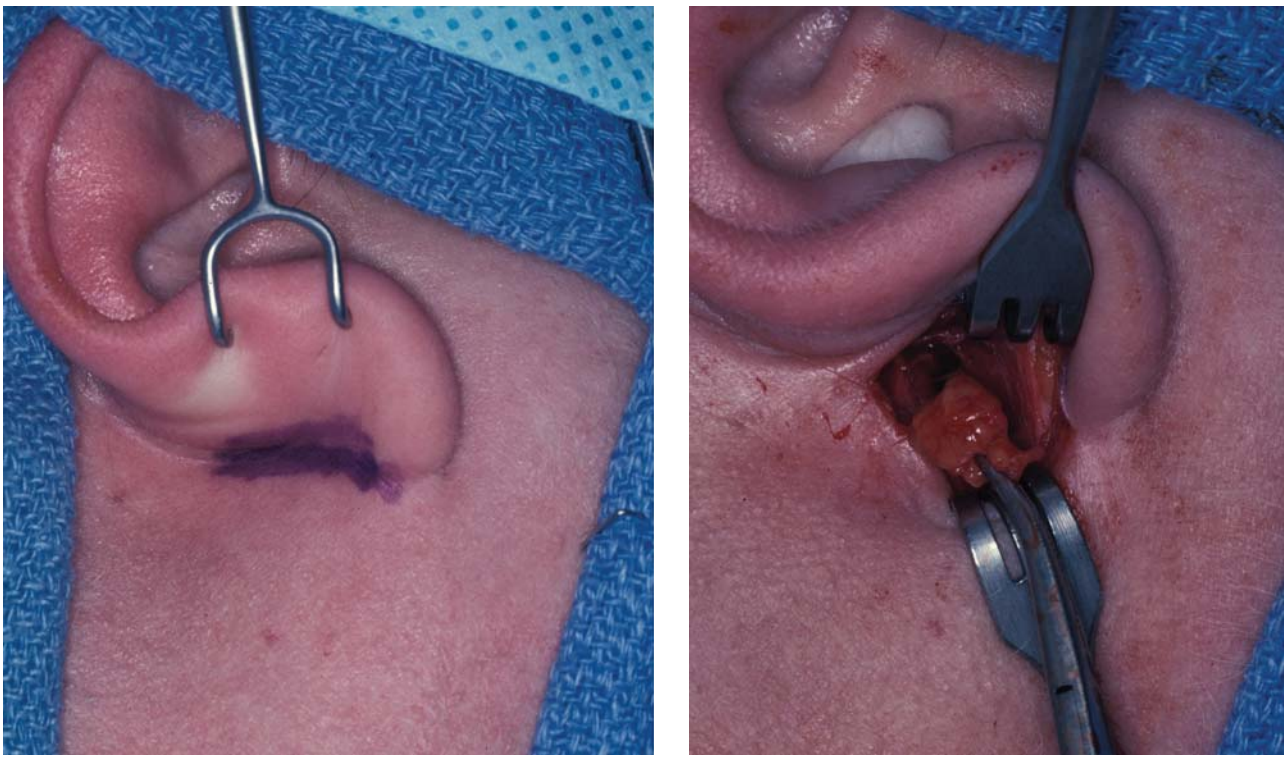


(c)

Figure 6.6. A 32-year-old woman with the recent development of dry eyes and mouth, possibly suggestive of Sjogren syndrome (a). No swelling of the parotid glands was appreciated on physical examination. An incisional biopsy of the lower lip and right parotid gland were performed. The histopathology showed a normal lower lip biopsy (b – hematoxylin and eosin, original magnification ×100) and signs consistent with Sjogren syndrome on parotid biopsy (c – hematoxylin and eosin, original magnification ×200).

diagnosis when using the parotid biopsy (Marx 1995) (Figure 6.6). In his series of 54 patients with Sjogren syndrome, 31 (58%) had a positive labial biopsy, while 54 (100%) had a positive parotid biopsy (Marx 1995). He concluded his study by stating that incisional parotid biopsy will confirm and definitively document the diagnosis of Sjogren syndrome (Figure 6.7). The incisional parotid



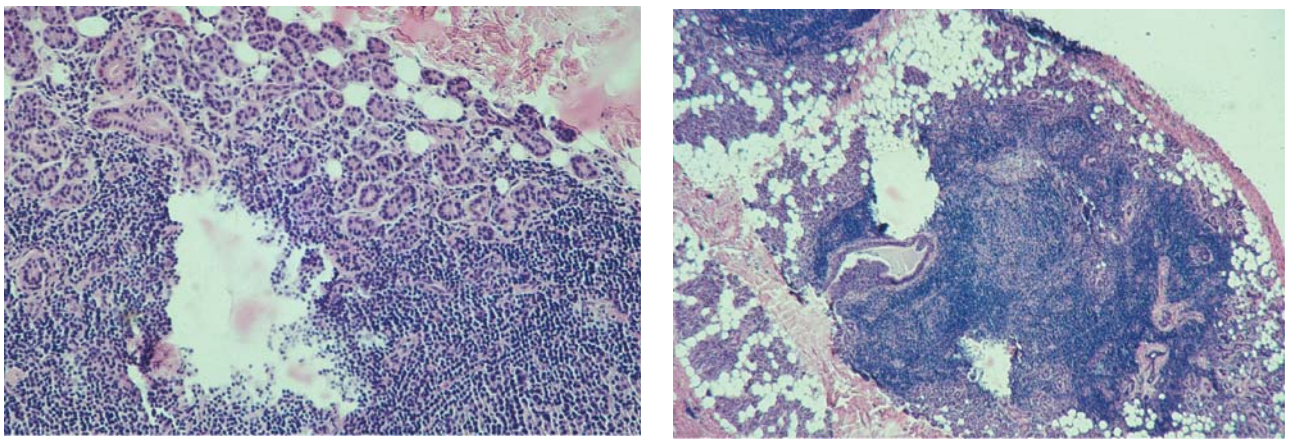
(a) (b)

Figure 6.7. An incisional parotid biopsy was performed on the patient seen in Figure 6.1. The incision is placed behind the right ear, which enables the surgeon to procure sufficient parotid tissue to establish a diagnosis, while also providing a cosmetic scar (a). The dissection proceeds through skin and subcutaneous tissue after which time the parotid capsule is noted. This is incised and a 1 cm^2 specimen of parotid gland is removed (b). The closure requires a reapproximation of the parotid capsule so as to avoid a salivary fistula postoperatively.

biopsy will also serve to rule out the presence of lymphoma, which is observed to develop in approximately 5–10% of patients with Sjogren syndrome (Talal and Bunim 1964; Daniels 1991). Patients with Sjogren syndrome are felt to have 47 times greater incidence of lymphoma than that of an age controlled population (Marx, et al. 1988). Ten such lymphomas were reported in Marx's study. They developed 4–12 years after the diagnosis of Sjogren syndrome was made, with a mean of 7.2 years. In 8 of the 10 cases, a rapid change in the size of the parotid enlargement was noted, and all of the patients exhibited a darkening of the skin overlying the enlarged parotid gland. These changes dictated biopsy of the parotid gland in the background of the systemic disease, with the knowledge that lymphoma does not develop in the lower lip in patients with Sjogren syndrome.

Histopathology of Sjogren Syndrome

Abnormal salivary gland function is associated with well-defined histologic alterations including clustering of lymphocytic infiltrates as a common feature of all salivary glands and other organs affected by Sjogren syndrome (Figure 6.8). Histologic evaluation of enlarged parotid or submandibular glands usually reveals the benign lymphoepithelial lesion, with a lymphocytic infiltrate and epimyoepithelial islands. These features are not invariably noted in the major salivary glands, however (Daniels 1991). The characteristic microscopic feature of Sjogren syndrome in the minor glands is a focal lymphocytic infiltrate, and includes focal aggregates of 50 or more lymphocytes, defined as a focus, that are adjacent to normal appearing acini and the consistent presence of these foci in all or most of the glands in the specimen (Daniels 1991). Epimyoepithelial islands



(a) (b)

Figure 6.8. The histopathology of the incisional parotid biopsy of the patient in Figure 6.1 (a, b). Signs consistent with Sjogren syndrome were noted including an intense lymphocytic infiltrate and destruction of acinar tissue. (a = hematoxylin and eosin, original magnification ×200. b = hematoxylin and eosin, original magnification ×40).

occur uncommonly in minor glands of patients affected by Sjogren syndrome.

Sarcoidosis

Sarcoidosis is a chronic systemic disease characterized by the production of non-caseating granulomas whose etiology is unknown. It can affect any organ system, thereby mimicking rheumatic diseases causing fever, arthritis, uveitis, myositis, and rash (Table 6.2). The peripheral blood shows a dichotomy of depressed cellular immunity and enhanced humoral immunity. Depressed cellular immunity is manifested by lymphopenia and cutaneous anergy. The enhanced humoral immunity is noted by polyclonal gammopathy and autoantibody production.

Table 6.2. Clinical involvement by sarcoidosis

Clinical Finding	Frequency in Sarcoidosis (%)	Differential Diagnosis
Arthritis	15	Rheumatoid arthritis
Parotid gland enlargement	5	Sjogren syndrome
Upper airway disease	3	Wegener granulomatosis
Uveitis	18	Spondyloarthropathies
Facial nerve palsy	2	Lyme disease
Keratoconjunctivitis	5	Sjogren syndrome

PATHOPHYSIOLOGY OF SARCOIDOSIS

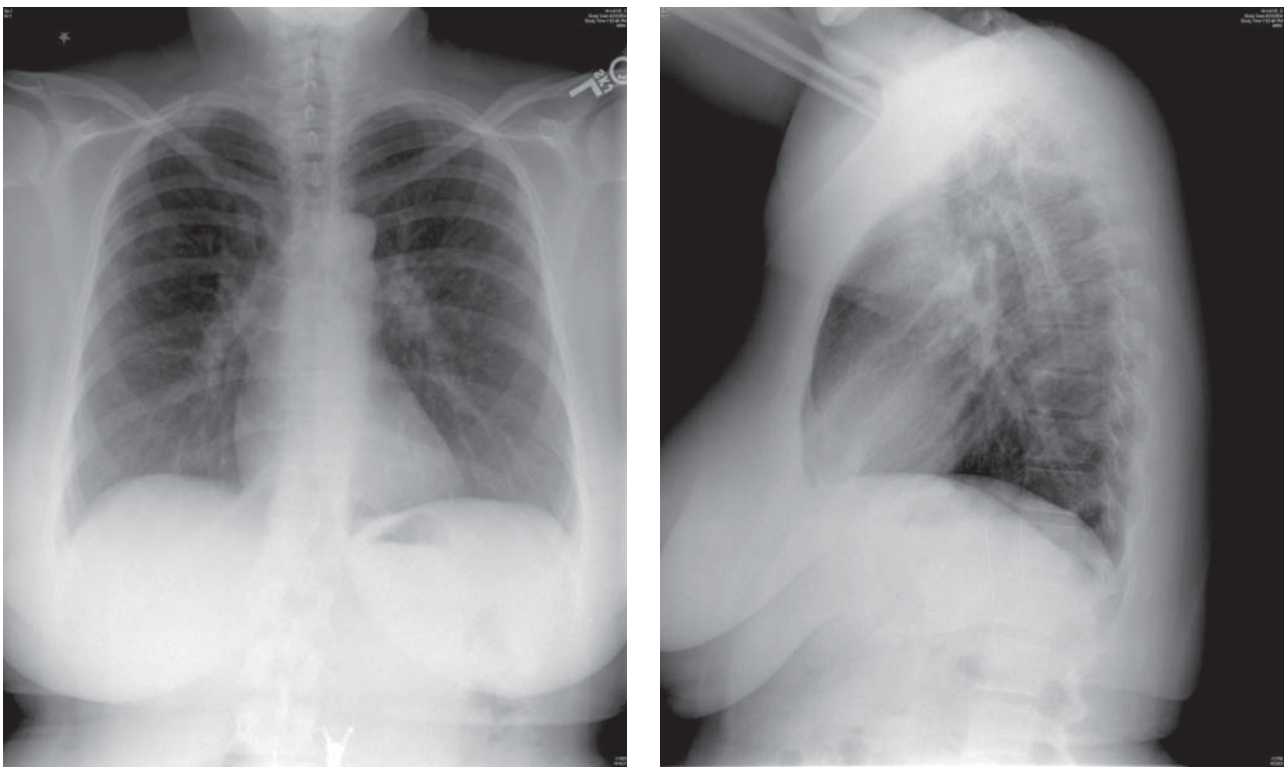
The exact cause of sarcoidosis is unknown. The current hypothesis is that an alteration in the immune response occurs in genetically susceptible patients exposed to an environmental, occupation, or infectious agent. Sarcoidosis has been associated with heavy metal exposures such as beryllium and its salts, although the American Thoracic Society criteria lists berylliosis as a separate entity (Heinle and Chang 2014). Firefighters who responded to the collapse of the World Trade Center have a higher incidence of sarcoid-like pulmonary disease and this may be a result of exposure to an unidentified substance (Izbicki, et al. 2007). Sarcoidosis has also been linked to infectious agents such as *propionibacterium* and *mycobacterium*. Finally, there is a well-accepted genetic component to the pathophysiology of sarcoidosis, since certain HLA alleles appear to confer susceptibility to sarcoidosis such as HLA DR 11, 12, 14, 15, and 17, while others result in a protective effect, including HLA DR1, and DR4.

CLINICAL MANIFESTATIONS OF SARCOIDOSIS

Sarcoidosis occurs most commonly in American blacks and northern European Caucasians. It is eight times more common in American blacks than American Caucasians (Hellmann 1993). Women are affected slightly more frequently than men. An average incidence of 16.5 cases per 100,000 men and 19 cases per 1,000,000 women has been reported (Jonsson and Olofsson 2011). Onset is usually between and ages of 20 and 40, yet a second peak of disease incidence occurs in women older than 50 years (Jonsson and Olofsson 2011). Patients with sarcoidosis generally present with one of the following four problems: respiratory symptoms such as dry cough, shortness of breath, and chest pain (40–50%), constitutional symptoms such as fever, weight loss, and malaise (25%), extrathoracic inflammation such as peripheral lymphadenopathy (25%), and rheumatic symptoms such as arthritis (5–10%) (Hellmann 1993).

Respiratory symptoms are the most common presenting chief complaints including those previously mentioned. Regardless of symptoms, greater than 90% of patients with sarcoidosis have an abnormal chest radiograph. Four types of radiographic appearance have been described: type 0 is normal; type I shows enlargement of hilar, mediastinal, and occasionally paratracheal lymph nodes; type II shows the adenopathy seen in type I as well as pulmonary infiltrates (Figure 6.9). Type III demonstrates the infiltrates without the adenopathy. Type II involvement is the most common amongst patients with sarcoidosis who have respiratory distress.

Two patterns of arthritis are observed in sarcoidosis and are classified as to whether the arthritis occurs within the first 6 months after the onset of the disease, or late in the course of the disease. The early form of arthritis often begins in the ankles and may spread to involve the knees and other joints. The axial skeleton is typically spared. Monarthritis in the early phase is unusual. *Erythema nodosum*, a syndrome of



(a) (b)

Figure 6.9. Posterior-anterior (a) and lateral (b) chest radiographs of a patient with type II sarcoidosis. This patient presented with severe shortness of breath.

inflammatory cutaneous nodules frequently found on the extensor surfaces of the lower extremities, occurs in about two-thirds of patients and is strikingly associated with early arthritis. *Lofgren syndrome* involves a triad of hilar lymphadenopathy, erythema nodosum, and arthritis. The late form of arthritis occurs at least 6 months after the onset of sarcoidosis, and is generally less dramatic than the early form. The knees are the most common joints to be involved, followed by the ankles. Monarthritis can occur in the late form of arthritis and erythema nodosum is not commonly noted.

Other rheumatic manifestations associated with sarcoidosis include involvement of the larynx, nasal turbinates, and nasal cartilage, thereby resembling the clinical presentation of Wegener granulomatosis (Figure 6.10) (Fatahzadeh and Rinaggio, 2006). Eye involvement occurs in 22% of patients, with uveitis being most common (Hellmann 1993). The triad of anterior uveitis in conjunction with parotitis and facial nerve palsy has been referred to as *Heerfordt syndrome,* also known as uveoparotid fever.

While salivary gland involvement seems to primarily involve the parotid gland (Figure 6.11), the submandibular gland can also be involved (Werning 1991; Vairaktaris, et al. 2005). The Armed Forces Institute of Pathology registry identified 85 cases of sarcoidosis. In the 77 cases in which a gland was specified, parotid involvement occurred in 65% of the cases, while the submandibular gland accounted for 13% of cases (Werning 1991). Submandibular gland enlargement may occur in the absence of parotid swelling, with or without clinical evidence of minor salivary gland involvement (Figure 6.12). Minor salivary gland involvement is occasionally noted histologically in the presence of clinically apparent major salivary gland swelling (Mandel and Kaynar 1994). In fact, enlargement of the major salivary glands may be the first identifiable sign of sarcoidosis (Fatahzadeh and Rinaggio 2006). When this occurs, therefore, it is important to differentiate the parotid swelling associated with sarcoidosis from that of Sjogren syndrome (Folwaczny, et al. 2002). Salivary gland biopsy with histopathologic examination is one means to make this distinction.

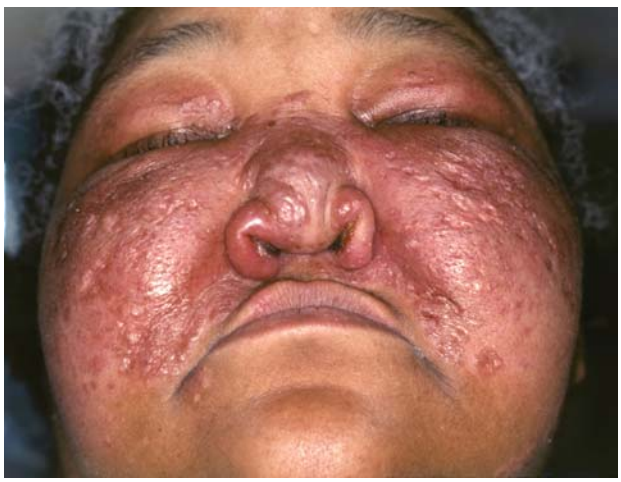


Figure 6.10. Severe nasal cartilage involvement by sarcoidosis in this elderly woman. Source: Image courtesy of Dr. James Sciubba.

DIAGNOSIS OF SARCOIDOSIS WITH SALIVARY GLAND BIOPSY

As with Sjogren syndrome diagnoses with salivary gland biopsies, early stage disease is perhaps more readily diagnosed with a parotid biopsy rather than a minor salivary gland biopsy. It has been pointed out that cases of sarcoidosis that do not clinically produce parotid enlargement nonetheless show involvement at the microscopic level (Marx 1995). In this review, the labial biopsy was positive in 38% of cases while 88% of parotid biopsies were positive for sarcoidosis. The lesions of sarcoidosis in labial salivary gland biopsies tend to be sparse such that multiple labial glands require excision for microscopic analysis. Another report investigated the yield of minor salivary gland biopsy in the diagnosis of sarcoidosis (Nessan and Jacoway 1979). In this study of 75 patients, non-caseating granulomas were present in minor salivary gland biopsies in 44 patients (58%). There was no correlation with minor salivary gland biopsy yield and stage of the disease. The highest yield for diagnosis of sarcoidosis was found in transbronchial lung biopsies (93%). Nonetheless, the diagnosis of sarcoidosis is one of exclusion, owing to an absence of a diagnostic gold standard. As such, a compatible clinical picture is established based on the patient's symptoms, physical, and radiographic findings. The biopsy of salivary gland tissue or other tissue identifies the presence of non-caseating granulomas such that a provisional diagnosis of sarcoidosis is made. It then becomes necessary to exclude other sources of granulomatous inflammation, such as Crohn's disease, deep fungal

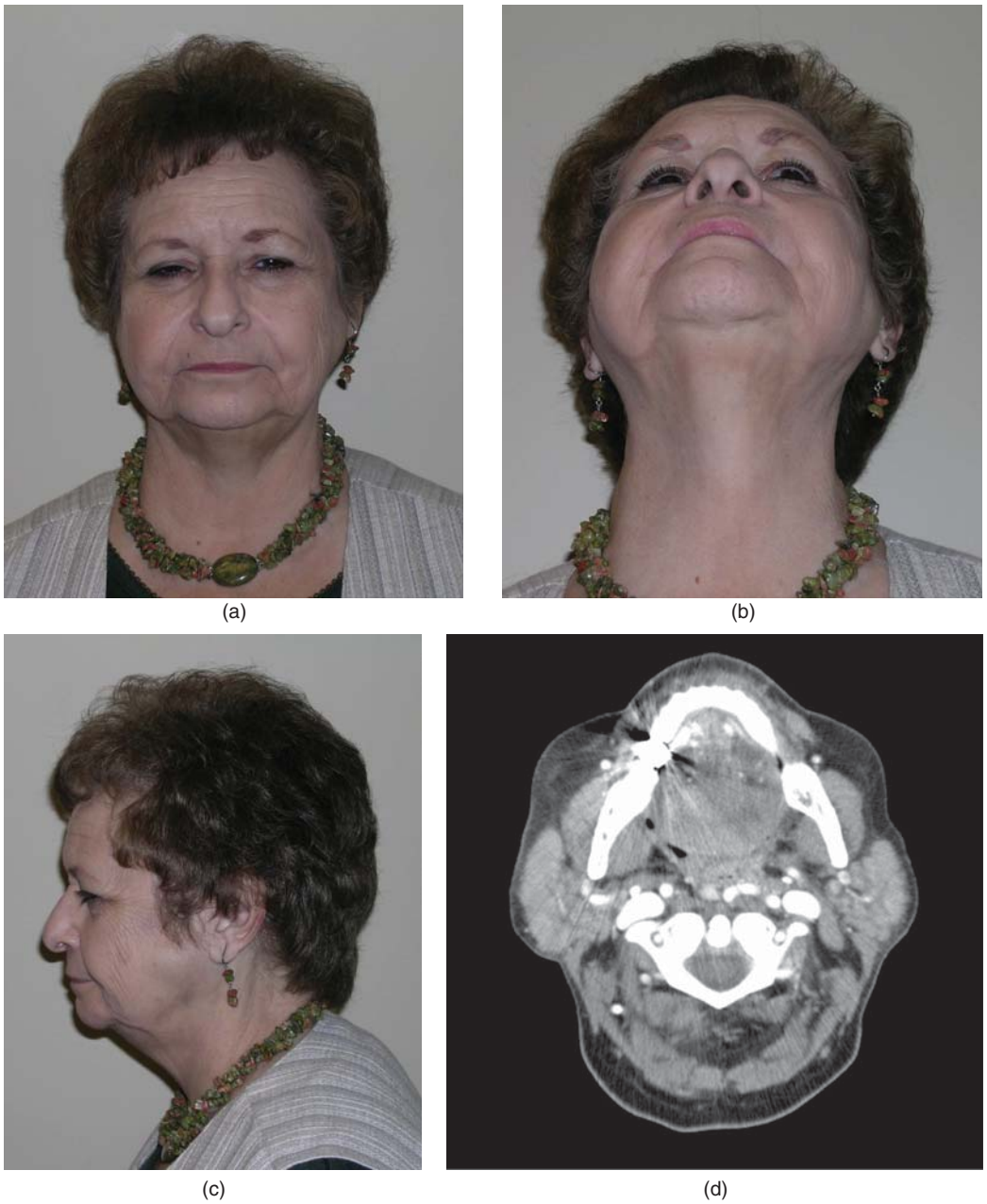
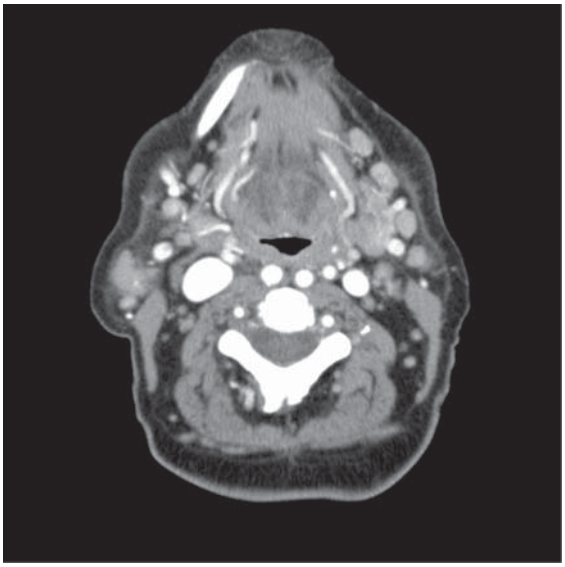


Figure 6.11. A 64-year-old woman with parotid swelling of 2 months' duration. The patient had been clinically diagnosed with Sjogren syndrome yet serology was negative. A fine needle aspiration biopsy of the left parotid gland swelling had been performed that suggested a Warthin tumor. Physical examination identified tender swellings of the bilateral parotid glands, with the left being larger than the right (a, b, c). CT examination identified diffuse enlargement of the parotid glands (d) and multiple enlarged lymph nodes in the left submandibular region (e). Her chest radiograph identified bilateral interstitial prominence (f). With an equivocal diagnosis of her left parotid swelling, the patient underwent left superficial parotidectomy and removal of left submandibular lymph nodes in a standard fashion (g, h, i). Final histopathology (j – hematoxylin and eosin, original magnification ×100) demonstrated non-caseating granulomas consistent with a diagnosis of sarcoidosis. The excised submandibular lymph nodes showed identical histopathology. The patient was treated with a 54-week course of prednisone and methotrexate for her diagnosis of pulmonary and extrapulmonary sarcoidosis, and showed a favorable response. She was doing well at her 5-year postoperative evaluation (k, l).



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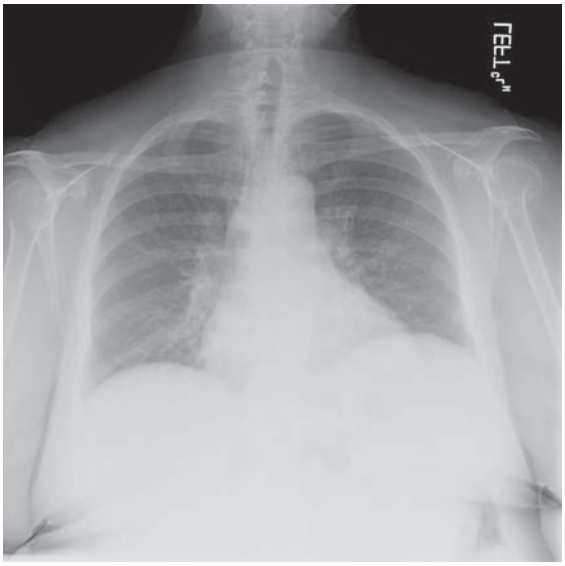

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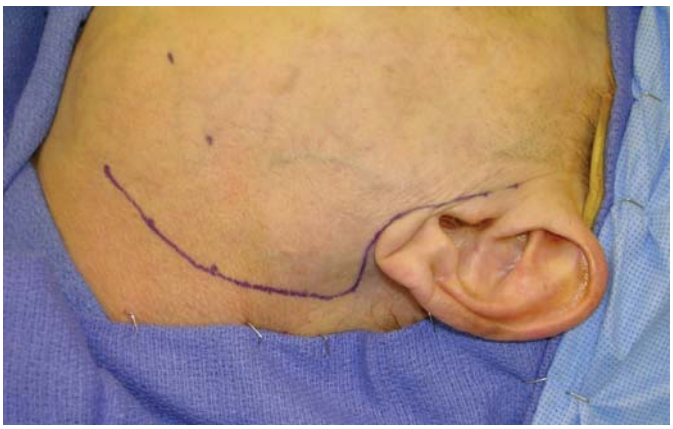

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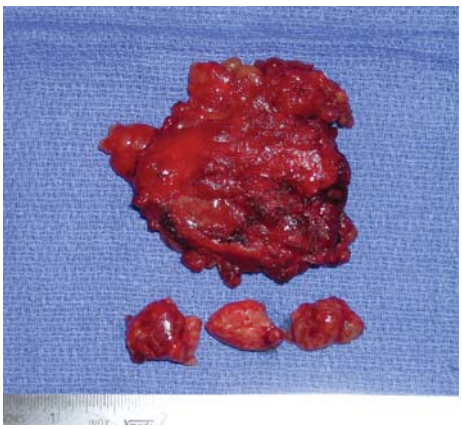

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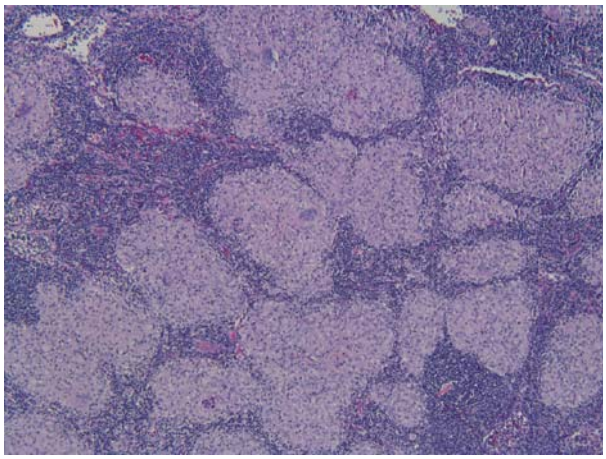

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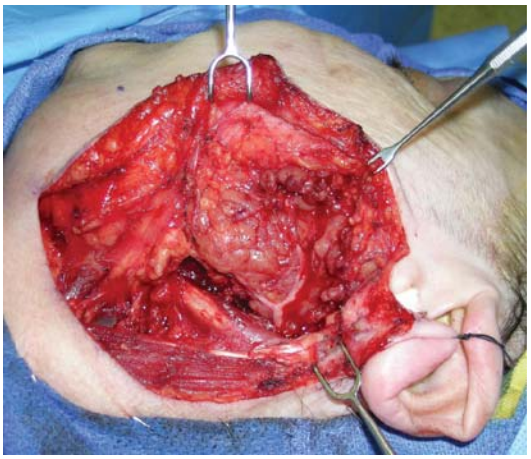


(j)

Figure 6.11. (*Continued*)


(k)


(l)

Figure 6.11. (*Continued*)

infections, and others. It is important to point out that there are no pathognomonic diagnostic tests for sarcoidosis. Rather, the salivary biopsy must be considered with an elevated angiotensin converting enzyme (ACE) and lysozyme result, and an altered ratio of CD4/CD8 cells, among others so as to offer a diagnosis of sarcoidosis (Kasamatsu, et al. 2007).

Histopathology of Sarcoidosis

Numerous granulomas may be seen in the salivary gland biopsy. The typical sarcoid granuloma is non-caseating and consists of a tightly packed central focus of histiocytes that is surrounded by lymphocytes and fibroblasts at its periphery (Figure 6.13). The histiocytes may be epithelioid and may join to form multinucleated giant cells, frequently of the Langhans type.

Sialosis

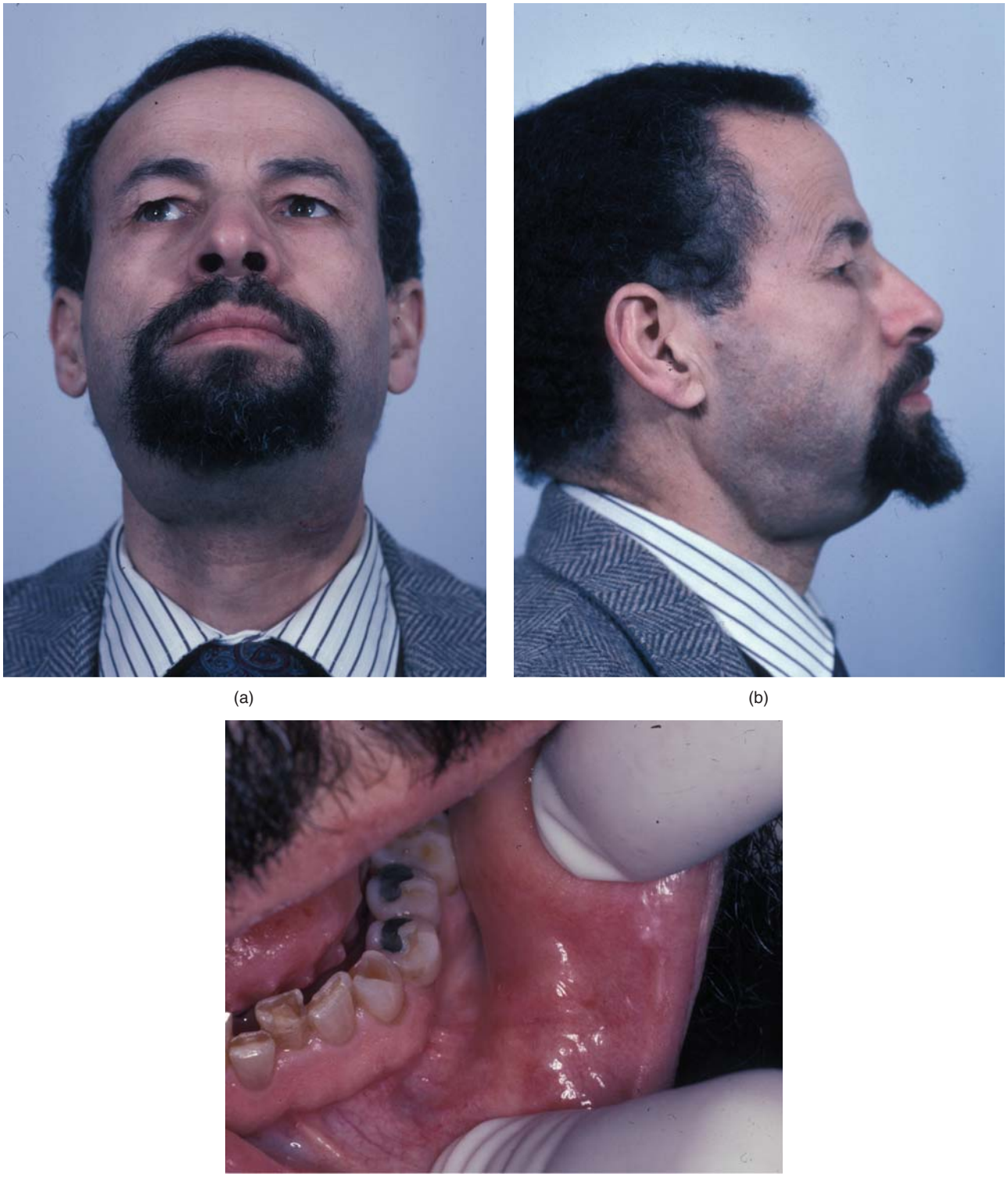
Sialosis, also known as sialadenosis represents a bilateral enlargement of the parotid gland that is multifactorial in its etiology (Table 6.3). It is not commonly associated with an autoimmune phenomenon as is the case for Sjogren syndrome and sarcoidosis, although it can easily be confused with these two pathologic processes due to its clinical presentation (Figure 6.14). Quite commonly, sialosis is caused by nutritional disturbances such as alcoholism, bulimia, or in the rare case of achalasia (Figure 6.15). Chronic alcoholism, with or without cirrhosis, results in asymptomatic enlargement of the parotid glands in 30–80% of these patients (Regezi, et al. 2003). In such cases, parotid enlargement has been attributed to protein deficiency. In diabetes mellitus, the mechanism of acinar hypertrophy associated with this condition is unknown. Due to the numerous causes of sialosis, as well as a large number of diagnoses that can clinically resemble sialosis, the patient's history is paramount in such cases so as to properly initiate the diagnostic process. In addition, the treatment for these disorders differs significantly.

CLINICAL MANIFESTATIONS OF SIALOSIS

Sialosis is characterized by chronic, afebrile salivary enlargement. The enlargement is described by patients as slowly evolving and recurrent. A thorough history will most frequently divulge symptoms associated with comorbid disease such as diabetes mellitus, achalasia, alcoholism, or others.

DIAGNOSIS OF SIALOSIS WITH SALIVARY GLAND BIOPSY

The role of salivary gland biopsy in a patient suspected as having sialosis is to rule out Sjogren syndrome, sarcoidosis and lymphoma. Sialosis is a disease limited to the major salivary glands such that



(a) (b)

(c)

Figure 6.12. A 55-year-old man with bilateral submandibular gland swellings (a, b), as well as lower lip lesions (c). Excision of the left submandibular gland and biopsy of the lower lip swelling identified non-caseating granulomas. Additional workup identified signs consistent with sarcoidosis.

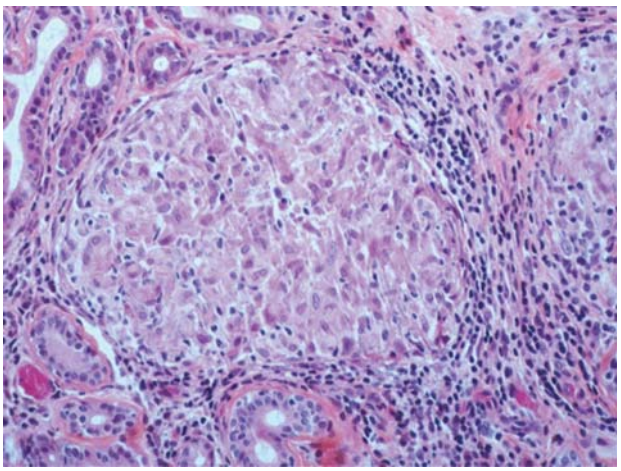


Figure 6.13. Histopathology of sarcoidosis (hematoxylin and eosin, original magnification ×200). Source: Image courtesy of Dr. Joseph A. Regezi.

Table 6.3. Classification of sialosis

Malnutritional sialosis
Achalasia
Bulemia
Alcoholism
Hormonal sialosis
Sex hormonal sialosis
Diabetic sialosis
Thyroid sialosis
Pituitary and adrenocortical disorders
Neurohumoral sialosis
Peripheral neurohumoral sialosis
Central neurogenous sialosis
Dysenzymatic sialosis
Hepatogenic sialosis
Pancreatogenic (exocrine) sialosis
Nephrogenic sialosis
Dysproteinemic sialosis
Mucoviscidosis
Drug-induced sialosis

Source: Werning 1991. Reproduced with permission of Elsevier.

an incisional biopsy of parotid enlargement is indicated, rather than an incisional biopsy of the lip as might be considered in Sjogren syndrome or sarcoidosis. As such, a minor salivary gland biopsy is of no value in making a diagnosis of sialosis. While

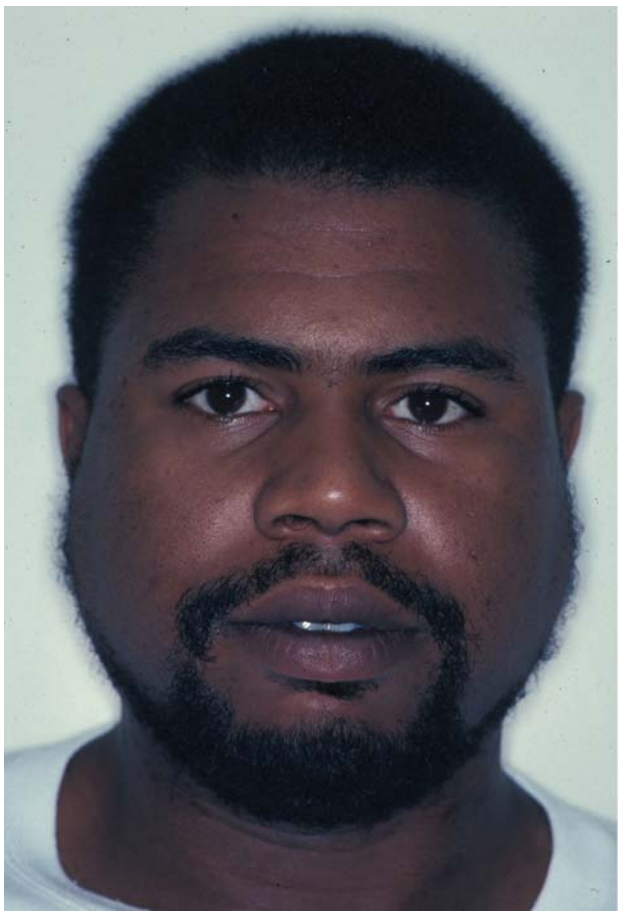


Figure 6.14. A 32-year-old man with a chronic history of bilateral parotid swellings. He gave a history of achalasia. The history suggested that the parotid swellings were consistent with a diagnosis of sialosis. There were no physical or historical findings suggestive of another diagnosis.

histopathologic confirmation of this process is valuable, it is certainly possible to make a clinical diagnosis of sialosis based on historical findings (Mandel, et al. 2005). In addition, once a histopathologic diagnosis of sialosis has been established, the underlying cause of this disorder must be ascertained, if not already known preoperatively. Prompt treatment of the underlying disease process must then occur.

Histopathology of Sialosis

The parotid swelling of sialosis is due to acinar enlargement (Figure 6.16). The diameter of the acinar cell tends to increase by two to three times that of normal. The nuclei tend to be basally situated, and the cytoplasm tends to the packed

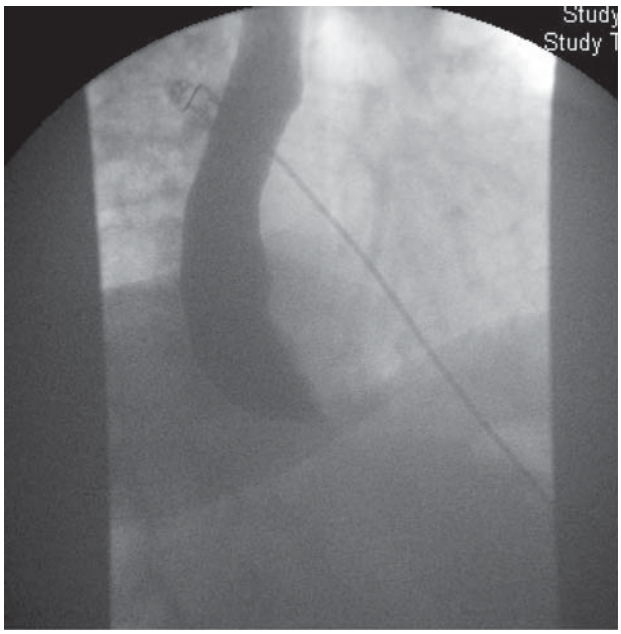


Figure 6.15. The fluoroscopic images of the barium swallow performed in the patient in Figure 6.14. The characteristic "bird's beak" deformity is noted, reflective of failure of the lower esophageal sphincter to relax. This is diagnostic of achalasia.

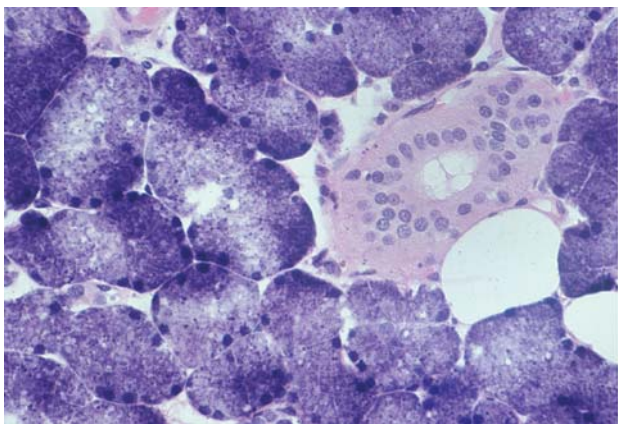


Figure 6.16. The histopathology of the incisional parotid biopsy performed on the patient in Figure 6.14 (hematoxylin and eosin, original magnification ×200). Acinar hypertrophy is noted. The physical, radiographic, and histologic information confirms a diagnosis of achalasia. He was treated with surgical myotomy of the lower esophageal sphincter.

with granules. There is no correlation between the specific clinical type of sialosis and the histologic appearance. Inflammatory cells tend to be absent. The long-standing nature of the underlying disease may ultimately lead to acinar atrophy and replacement with fat (Werning 1991).

Summary

- A number of systemic diseases may infiltrate salivary gland tissue, including Sjogren syndrome, sarcoidosis, and sialosis.
- Sjogren syndrome and sarcoidosis are autoimmune disorders while sialosis is not.
- Sjogren syndrome is characterized by keratoconjunctivitis sicca and xerostomia, with or without association with another connective tissue disease.
- Approximately 30% of patients with Sjogren syndrome will develop salivary gland enlargement, most commonly the parotid gland.
- A salivary gland biopsy may confirm the patient's diagnosis of Sjogren syndrome. Either a labial biopsy or parotid gland biopsy may be performed. Disease may be identified more often in a parotid biopsy, even when the patient does not demonstrate parotid swelling.
- Another benefit of parotid biopsy is the identification of lymphoma that is known to develop in 5–10% of patients with Sjogren syndrome.
- Specific histologic criteria have been established for the diagnosis of Sjogren syndrome in salivary gland biopsies, specifically referred to as a focus.
- Sarcoidosis is a multi-system disease, with particular proclivity for lung involvement.
- Erythema nodosum represents cutaneous nodules most commonly involving the extensor surfaces of the lower extremities, and occurs in about two-thirds of patients with sarcoidosis.
- Lofgren syndrome involves a triad of hilar lymphadenopathy, erythema nodosum, and arthritis.
- Approximately 5% of patients with sarcoidosis have parotid gland enlargement.
- The triad of anterior uveitis in conjunction with parotitis and facial nerve palsy has been referred to as Heerfordt syndrome.
- As with Sjogren syndrome, there is a higher yield of positive findings to make a diagnosis of sarcoidosis based on parotid biopsy compared to lip biopsy.
- Sialosis is a non-inflammatory, non-neoplastic, non-autoimmune disorder with enlargement of

the salivary glands, most notably the parotid gland.

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Chapter 7

Classification, Grading, and Staging of Salivary Gland Tumors

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Outline

Salivary Gland Pathology: Diagnosis and Management, Second Edition. Edited by Eric R. Carlson and Robert A. Ord.

Introduction

Scientific classification is a method by which researchers and clinicians categorize species of organisms. Modern classification has its roots in the work of Carolus Linnaeus, also known as Carl von Linné, the Father of Taxonomy, who grouped species according to shared physical characteristics. Accordingly, scientific classification belongs to the science of taxonomy or biological systematics. Molecular systematics, which uses genomic and proteomic expression data, has driven many recent revisions in these systems. In a like manner, surgeons, pathologists, and oncologists have endeavored to systematically categorize tumors on the basis of designated characteristics so as to predict probable biological behavior. This in turn would help dictate appropriate therapeutic modalities to be employed and help forecast a credible prognosis. As such, the "designated characteristics" upon which tumors have been classified may be in more contemporary terms considered as "biomarkers". In a like fashion, genomic and proteomic expression profiles of tumors have thrust pathology and oncology into molecular systematics to develop classifications.

The role of molecular profiling or systematics for clinical decision making and taxonomy has been recently considered and the classification of tissue or other specimens for diagnostic, prognostic, and predictive purposes based on multiple gene expression and proteomics has been noted to hold major promise for optimizing the management of patients with cancer (Ioannidis 2007). However, assay development and data analysis have been principally investigative, and there exists a lofty potential for the introduction of bias. Most troubling is that standardization of profiles has been the exception. Moreover, classifier performance is typically over-interpreted by conveying the results as p-values or multiplicative effects, whereas the absolute sensitivity and specificity of classification are modest, particularly when tested in large validation samples (Ioannidis 2007). Furthermore, validation has frequently been made with less than favorable consideration for methodology and safeguarding for bias. Most disconcerting is that the postulated classifier performance can be inflated compared to what these profiles can accomplish.

Whether traditional morphological designated characteristics or molecular systematics are employed, the aim of any classification is to demonstrate diagnostic, prognostic, and predictive performance. This can generally be accomplished for any data set by training. However, it is well known that unless training is unsupervised (no knowledge of the correct class is involved), the performance of the system being tested on the training dataset is totally uninformative about its true operation (Ioannidis 2007). Cross-validation and independent validation are two methods to determine whether the proposed scheme is an accurate classifier (Allison, et al. 2006). Despite the method employed, different metrics can be used to describe the classifier performance. These may include statistical testing measures, multiplicative effect measures such as likelihood ratios or hazard ratios, or absolute effect measures. Although all information has some value, absolute effect measures (sensitivity and specificity) are the most meaningful from a clinical perspective (Buyse, et al. 2006).

Classification Systems for Salivary Gland Neoplasms

The classification system for salivary gland neoplasms has evolved with the accumulation of clinical experience and our understanding of the basis of neoplasia. Although a variety of classifications have been advocated, there has been some geographic variation in terminology and classification between European and American authors. Historically, the first most notable classification was that put forth by Foote and Frazell (1954). Later systems reflect the recognition and description of previously unrecognized entities or the deletion of some terms that were misnomers or were considered meaningless. The succeeding classifications include those by: Thackray and Lucas (1974); Evans and Cruickshank (1970); the World Health Organization (WHO; Thackray and Sobin 1972); Batsakis (1979); Seifert, et al. (1986b); and Auclair and Ellis (1991). The most recent AFIP fascicle on the subject provides a stepwise evolution of these taxonomies (Ellis and Auclair 2008).

THE CELLULAR CLASSIFICATION OF SALIVARY GLAND NEOPLASMS

Salivary gland neoplasms are noted for their histological variability. Reflecting the anatomy of these glands, benign and malignant salivary

gland neoplasms may arise either from epithelial, mesenchymal, or lymphoid origins. The complexity of the classification and the rarity of some of these tumors, some of which display a wide spectrum of morphological patterns within the same tumor when added to the existence of hybrid lesions, challenge the surgical pathologist with a difficult task in differentiating benign from malignant tumors (Seifert and Donath 1996; Speight and Barrett 2002). At the present time, the surgical pathologists often must use every available tool in order to properly diagnose and classify tumors arising from the major and minor salivary glands. No longer can histology alone be used for such determinations. The pathologist at the moment uses not only routine light microscopy but also immunohistochemistry, specialized imaging, and clinical characteristics of each tumor in order to establish the exact diagnosis. Time after time, immunohistochemistry has proved to be an excellent diagnostic adjunct to routine light microscopy.

Immunohistochemistry (IHC) is the method by which one can detect antigens in tumor cells by way of antigen/antibody testing. This method is widely used today to define the distinction between benign and malignant cells as well as the determination of exact tumor cell types (Nagao, et al. 2012).

The use of IHC has become an excellent and effective manner to determine the exact cellular proteins involved with specific cell types. While still evolving, the technique of immunostaining is widely used by most if not all surgical pathology laboratories for immunophenotyping tumors. At the present time, most diagnostic labs have 150–200 commercially prepared immuno markers available with many more being developed yearly. Some of the more common available markers or stains used in salivary gland pathology include: (1) various *cytokeratins (CK)* for determining epithelial cell origin, (2) *CD20* for the determination of B-cell lymphomas, (3) *CD3* for the identification of T-cell lymphomas, (4) *Smooth Muscle Actin (SMA)* and *Muscle Specific Actin (MSA)* for the identification of myoepithelial cells, (5) *Ki67 Index* to help distinguish malignant from benign lesions, (6) *CD117* to distinguish basal cell adenomas from pleomorphic adenomas, (7) *HMB45* to identify melanin producing cells, (8) *Chromogranin* to distinguish and identify neuroendocrine cells, and (9) *S-100* to distinguish various neural tissues. Many more additional immunostains are now available to aid in the determination and correct identification of salivary gland lesions.

The following cellular classification system reiterates that advocated by the National Cancer Institute of the USPHS (National Cancer Institute, www.cancer.gov), which is derived heavily from that published by the Armed Forces Institute of Pathology (AFIP) (Ellis and Auclair 2008) (Table 7.1). Similar to the NCI scheme we also include malignant non-epithelial neoplasms since these lesions embrace a sizable proportion of salivary gland neoplasms. Though less common, the inclusion of malignant secondary tumors is presented to be inclusive.

As noted in the introduction, statistics regarding the incidence, frequency, and prognosis have varied depending on the study. Moreover, a cursory review of the literature generally reveals that power analyses are rarely performed to access the necessary sample size for many of these studies and most rudimentary statistical measures are employed to arrive at conclusions. In large part, these deficiencies have stemmed from the general rare incidence of many salivary gland neoplasms. Although the AFIP statistics have been criticized to be biased because of the methods of case accrual as a reference service, these data are probably the most reliable especially for rare and unusual lesions.

Benign Salivary Gland Neoplasms

Pleomorphic Adenoma (Benign Mixed Tumor)

The pleomorphic adenoma (Figure 7.1a) or benign mixed tumor is the most common salivary gland neoplasm representing 35% of all salivary gland tumors. Clinically the tumors are smooth, multilobular, and appear encapsulated. However, microscopically, tumor cells may be seen extending beyond the apparent capsule. The tumor is cytologically varied depending on the cellularity and the mesenchymal-appearing content. The presence of both epithelial and mesenchymal-like elements resulting from epithelial cells and myoepithelial cells produces significant diversity in the appearance of these tumors. Most notable is that the stromal component may encompass myxoid, fibroid, chondroid, and even osteoid features providing the mixed appearance of these lesions (Ellis and Auclair 2008). Even with this varied histology, the pleomorphic adenoma is

Table 7.1. Cellular classification of salivary gland tumors.

- Epithelial neoplasms
  - Benign epithelial neoplasms
    - Pleomorphic adenoma or mixed tumor
    - Papillary cystadenoma lymphomatosum or Warthin tumor
    - Monomorphic adenomas
      - Basal cell adenoma
      - Canalicular adenoma
      - Oncocytoma
      - Sebaceous adenoma
      - Sebaceous lymphadenoma
    - Myoepithelioma
    - Cystadenoma
    - Ductal papillomas
    - Sialoblastoma
  - Malignant epithelial neoplasms
    - Mucoepidermoid carcinoma
    - Adenoid cystic carcinoma
    - Adenocarcinomas
      - Acinic cell carcinoma
      - Polymorphous low-grade adenocarcinoma
      - Adenocarcinoma, NOS
      - Rare adenocarcinomas
        - Basal cell adenocarcinoma
        - Clear cell carcinoma
        - Cystadenocarcinoma
        - Sebaceous adenocarcinoma
        - Sebaceous lymphadenocarcinoma
        - Oncocytic carcinoma
        - Salivary duct carcinoma
        - Mucinous adenocarcinoma
        - Malignant mixed tumors
          - Carcinoma ex pleomorphic adenoma
          - Carcinosarcoma
          - Metastasizing mixed tumor
    - Rare carcinomas
      - Primary squamous cell carcinoma
      - Epithelial-myoepithelial carcinoma
      - Anaplastic small cell carcinoma
      - Undifferentiated carcinomas
        - Small cell undifferentiated carcinoma
        - Large cell undifferentiated carcinoma
        - Lymphoepithelial carcinoma
        - Myoepithelial carcinoma
        - Adenosquamous carcinoma
- Non-epithelial neoplasms
  - Lymphomas and benign lymphoepithelial lesion
  - Mesenchymal neoplasms
  - Malignant mesenchymal neoplasms

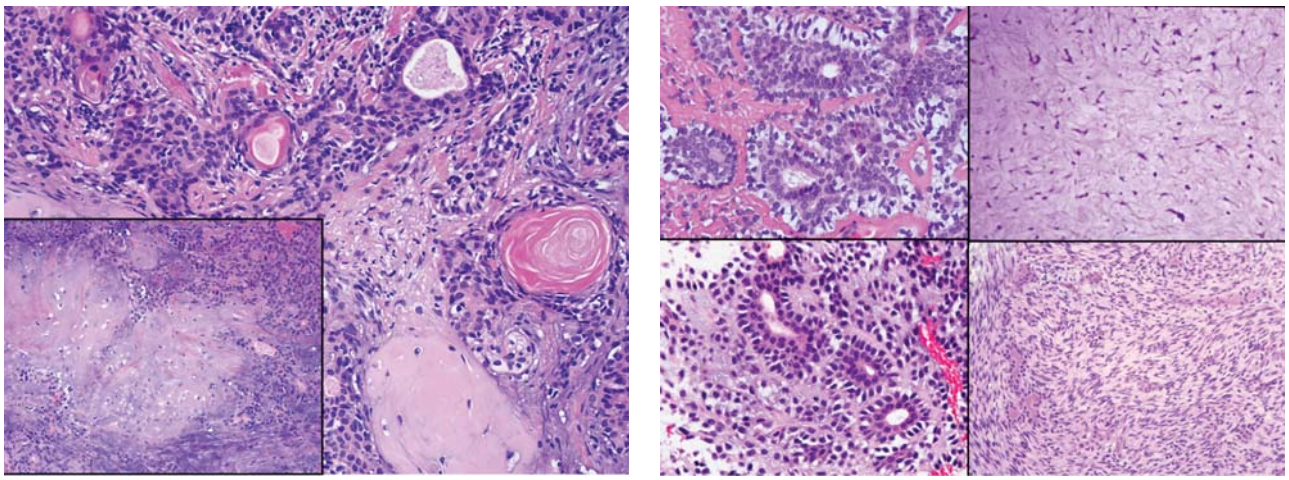
completely epithelial in origin with no true mesenchymal element involved. For this reason, the mesenchymal-appearing cells arising from myoepithelial cells will be immunoreactive with antibodies to smooth muscle specific proteins such as MSA and SMA (Figure 7.1b).

Over-expression of the proto-oncogene pleomorphic adenoma gene 1 (*PLAG1*) plays a crucial role in development of pleomorphic adenomas. *PLAG1* over-expression is usually caused by chromosomal aberrations resulting in fusion genes with promoter swapping, including *CTNNB1-PLAG1*, *CHCHD7-PLAG1*, *LIFR-PLAG*, *and TCEA-PLAG1* (Matsuyama, et al. 2012). Recent evidence indicates that the target genes of *PLAG1* include: Bax, Fas, p53, p21, p16, Cyclin D1, EGFR, Trail-R/DR5, c-Fos, c-myc, and Igf2. *PLAG1* not only activates genes that promote cell proliferation and tumor formation but also genes that inhibit these cellular processes (Wang, et al. 2013b). Although human papilloma virus (HPV) 16 and 18 have been demonstrated among some pleomorphic adenomas with p16 expression, it appears that pleomorphic adenoma of salivary glands represents a category of tumors in which the p16 positive staining is not biologically relevant to the oncogenic role of HPV infection (Hafed, et al. 2012; Tarakji, et al. 2013; Skalova, et al. 2013a).

Papillary Cystadenoma Lymphomatosum (Warthin Tumor)

The papillary cystadenoma lymphomatosum or Warthin tumor has been regarded as the second-most common benign salivary gland neoplasm and comprises 6–10% of all parotid tumors. These tumors seldom arise in the submandibular or minor salivary glands but are occasionally seen there. Men are more commonly affected than women, with a gender ratio of 5:1. Interestingly, the prevalence increases in smokers and bilateral distribution has been noted in ~12% of cases (Ellis and Auclair 2008).

The Warthin tumor is characterized by oncocytic epithelium arranged in a papillary configuration while being accompanied by diffuse aggregates of lymphocytes (Figure 7.2). Quite often follicular centers are seen within the lymphocytes aggregates. These microscopic characteristics are unique within the groupings of benign salivary gland tumors and are unlike those of any other primary salivary neoplasm. Immunostaining has



(a) (b)

Figure 7.1. (a) Pleomorphic adenoma containing tubular and solid structures composed of round to basaloid cells. Foci of squamous, myxoid, and chondroid metaplasia are seen as well. (Lower left panel.) H&E staining, 200×. (b) Composite figure of a pleomorphic adenoma demonstrating myxoid components (upper right), spindle-cell components (lower right), clear ductal cells surrounded by hyaline stroma (upper left), and tubular elements surrounded by a loose basophilic stroma (lower left). H&E staining, 400×.

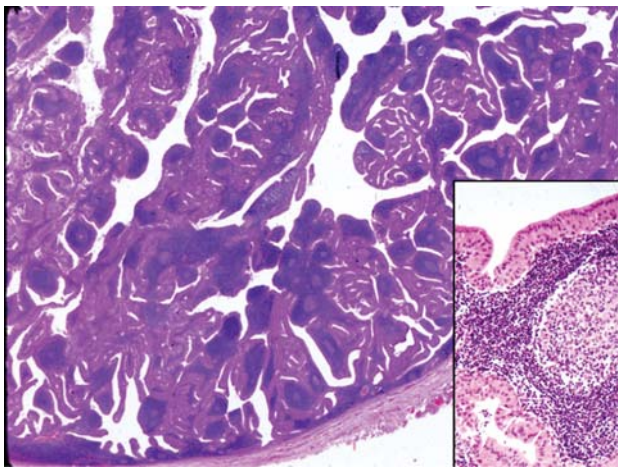


Figure 7.2. Warthin tumor with well- developed fibrous capsule delineating the lesion from normal parotid gland. The tumor is characterized by bilayered oncocytic epithelium lining cystic spaces closely associated with lymphoid tissue. Lower right panel depicting the oncocytic epithelium in close proximity to a lymphoid aggregate. H&E staining, 200×/400×. Source: Courtesy of Dr. Mark Bernstein.

been of little help in determining the exact origin of Warthin tumor.

Early studies have indicated that the *CRTC1-MAML2* fusion was not exclusive to mucoepidermoid carcinoma and could be found in Warthin tumor. More recent studies have indicated that neither *CRTC1-MAML2* nor *CRTC3-MAML2* fusions could be detected in metaplastic Warthin tumor or metaplastic pleomorphic adenoma (Skalova, et al. 2013a).

Monomorphic Adenomas

Basal Cell Adenoma

Once termed a form of monomorphic adenoma, the basal cell adenoma is a lesion characterized by a monotonous uniform basaloid pattern lacking any myxochondroid features typical of mixed tumors (Figure 7.3). The basal cell adenoma comprises between 5 and 10% of all benign salivary gland tumors with the majority of cases arising within the parotid gland. A simultaneous occurrence of the basal cell adenoma and the eccrine cylindroma had been identified. Both ductal cells and myoepithelial cells can be identified by IHC means.

Canalicular Adenoma

Once described as a form of monomorphic adenoma, the canalicular adenoma (Figure 7.4) is a benign salivary gland tumor composed of interconnecting and branching cords of columnar epithelium manifesting as single or double rows of cells. These tumors are usually small with

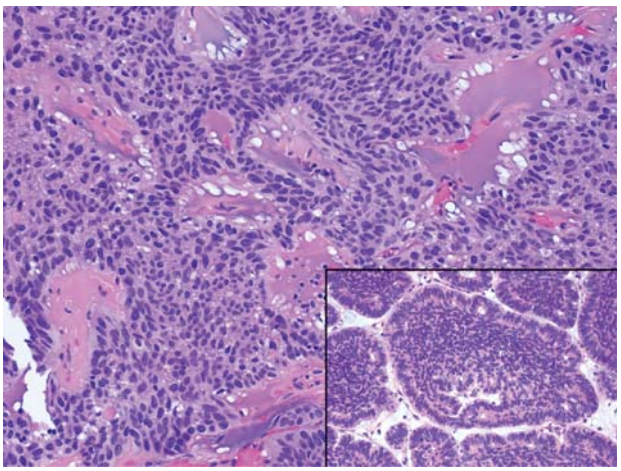


Figure 7.3. Basal cell adenoma consisting of monotonous sheets of basaloid cells lacking any myxochondroid tissues, spindled or plasmacytoid cells observed in pleomorphic adenomas. Lower right panel depicting palisaded basaloid cells surrounding a tumor cell nest. H&E staining, 200×. Source: Courtesy of Dr. Mark Bernstein.

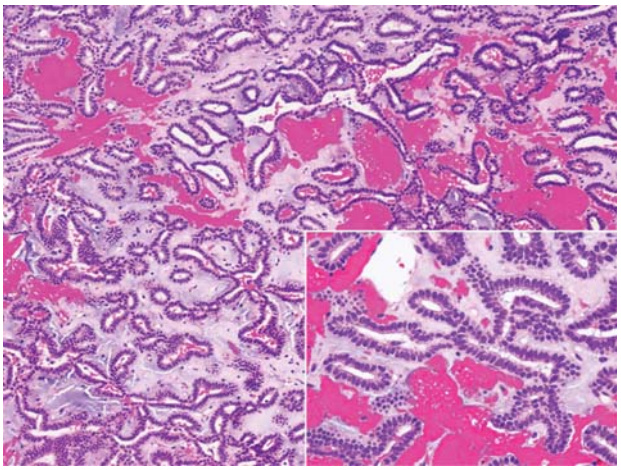


Figure 7.4. Canalicular adenoma demonstrating columns of columnar cells lining canaliculi forming interconnecting tubules and microcysts. Lower right panel higher magnification detail. H&E staining, 100×/200×. Source: Courtesy of Dr. Mark Bernstein.

a well-defined capsule. A unique feature of the canalicular adenoma is that it quite often is multifocal with tumor nodules seen throughout the surrounding salivary tissue. Unlike any other salivary gland tumors, the canalicular adenoma has a significant predilection to occur in the upper lip. This tumor makes up less than 5% of all benign salivary tumors, although it makes up at least 10%

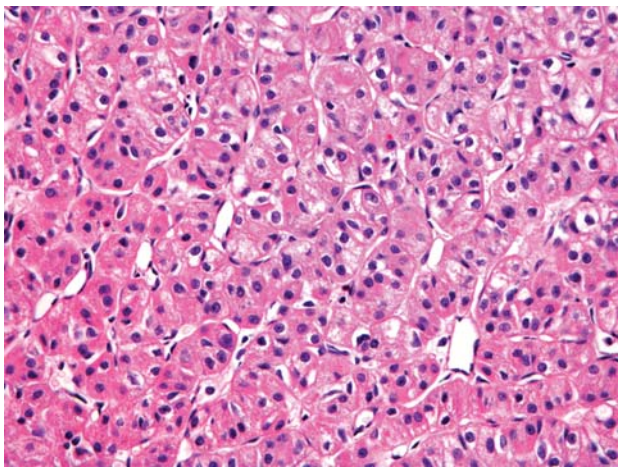


Figure 7.5. Oncocytoma characterized by eosinophilic, granular cytoplasm, with stippled nuclei. H&E staining, 400×.

of all such lesions arising within minor glands. As the canalicular adenoma is comprised only of ductal cells without a myoepithelial component, only the IHC stains for ductal cells (CD117, CK7, CK8) are positive, while the common myoepithelial immunostains (SMA, MSA) are negative.

Oncocytoma

The oncocytoma is a rare benign salivary gland neoplasm composed of large, polyhedral, eosinophilic granular cells (oncocytes) containing numerous atypical mitochondria (Figure 7.5). Such cells are found not only in salivary tissue but also in thyroid, breast, and kidney. Although most oncocytomas are solid, a few demonstrate a papillary appearance. The vast majority of oncocytomas arise in the parotid gland though a few have been described in minor glands. In addition, the majority of these lesions occur in older individuals with the peak incidence in the seventh and eighth decades of life. No myoepithelial component is identified by means of IHC staining. Recognition is unremarkable although there is a clear-cell variant that must be distinguished from mucoepidermoid carcinoma and other clear-cell malignancies.

Sebaceous Adenoma

The sebaceous adenoma is a rare benign salivary gland neoplasm that demonstrates sebaceous differentiation (Figure 7.6). This lesion has been identified in both the major and minor salivary glands

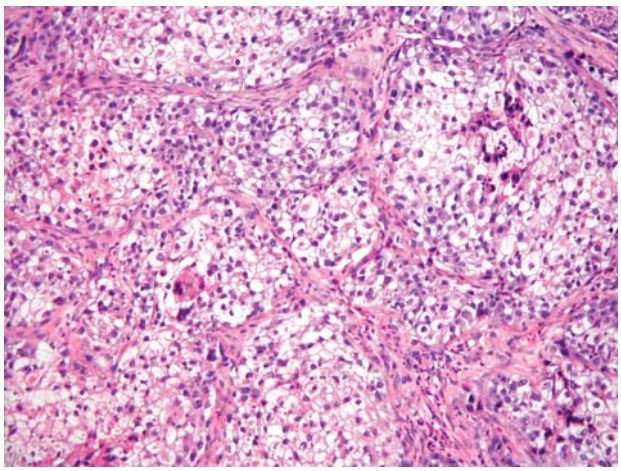


Figure 7.6. Sebaceous adenoma demonstrating numerous islands of tumor cells exhibiting both squamous and sebaceous differentiation. H&E staining, 200×.

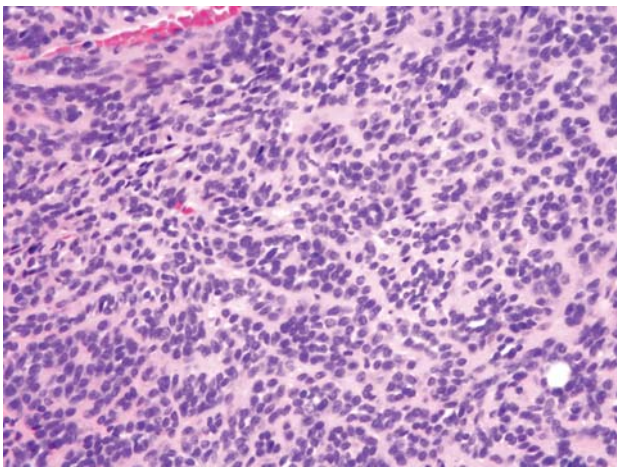


Figure 7.7. One morphologic pattern of myoepithelioma demonstrating a monotonous population of myoepithelial cells with uniform nuclei. H&E staining, 200×.

with the buccal mucosa being the most common area of minor gland occurrence. These tumors are usually encapsulated and are comprised of nests of squamous cells demonstrating well-defined sebaceous metaplasia.

Sebaceous Lymphadenoma

The sebaceous lymphadenoma is believed by some to be a variant of the sebaceous adenoma, but which contain sebaceous glands that are surrounded by lymphoid elements. The lymphoid makeup of this tumor is histologically quite similar to that of the Warthin tumor. As with the sebaceous adenoma, the neoplastic part of this lesion is comprised of squamous cells that undergo sebaceous metaplasia though these neoplastic islands of the latter are usually much smaller than in the former tumor.

Myoepithelioma

Myoepitheliomas are tumors that demonstrate pure myoepithelial differentiation and are believed to represent a spectrum of mixed tumors but which lack epithelial features. Histologically, the myoepithelioma demonstrates only myoepithelial elements with no evidence of ductal or glandular formation identified (Figure 7.7). Various cell types are seen within the myoepithelioma including plasmacytoid, epithelioid, and spindle cells. The myoepithelioma makes up between 1 and 2% of all benign salivary gland tumors and usually involve either the parotid gland or the palate. Although there is significant variability, the myoepithelial cells are immunoreactive with MSA, SMA, and CK5/6 as are most myoepithelial cells. In addition, IHC is extremely helpful in distinguishing the myoepithelioma from true mesenchymal tumors such as the leiomyosarcoma, synovial sarcoma, and solitary fibrous tumor which may occur in the same anatomical area.

Cystadenoma

The cystadenoma is a rare benign tumor that is characterized by unicystic or polycystic growths that contain regions of overgrowth that may at times be papillary in character. These benign lesions occur in both the major and the minor salivary glands with the minor gland variety more common and usually presenting much smaller in size. The cystadenoma occurs in all age groups although quite rare in children. The epithelial lining of these lesions range from cuboidal to columnar with occasional oncocytic and mucous cell types identified (Figure 7.8). The cystadenoma is often confused microscopically with a low-grade mucoepidermoid carcinoma with invasion of the surrounding soft tissue often being the only significant microscopic difference between the two.

Ductal Papilloma

Ductal papillomas have been categorized by the WHO into three morphological types. These

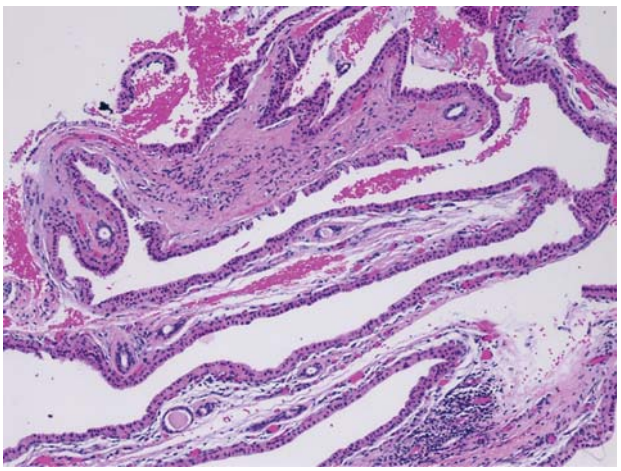


Figure 7.8. Cystadenoma characterized by tortuous cystic spaces cystic spaces lined by cuboidal epithelium. H&E staining, 100×.

include: (1) Intraductal papillomas, which are luminal papillary lesions that result in cystic dilatation of a duct; (2) Inverted duct papillomas, a papillary proliferation that occurs at the junction of salivary duct and mucosal surface; and (3) sialadenoma papilliferum, an exophytic growth involving the mucosal surface and salivary ductal structures (Figure 7.9).

Collectively, these tumors arise in the sixth to eighth decades of life with a slight male predominance. Evidence suggests that inverted ductal papillomas arise from superficial excretory ducts, while intraductal papillomas evolve from deeper excretory ducts. Sialadenoma papilleferum appears to have a biphasic growth pattern suggesting origins from the exophytic and endophytic elements. Currently, there is strong support to regard these three entities as distinct based on clinical and histological parameters (Brannon, et al. 2001).

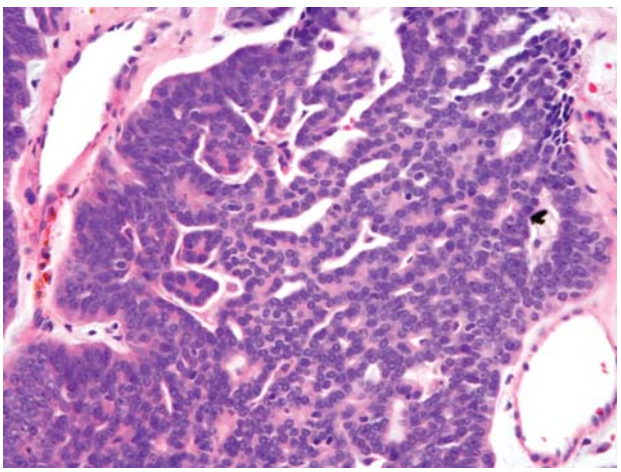


Figure 7.9. Sialadenoma papilliferum demonstrating papillary stalks composed of uniform cuboidal epithelium. H&E staining, 200×.

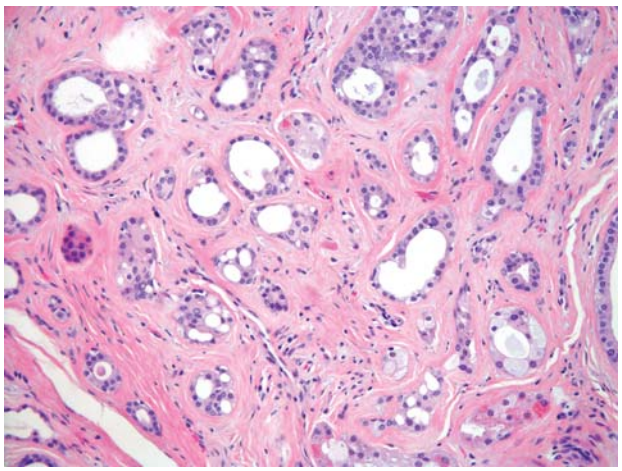


Figure 7.10. Polycystic sclerosing adenosis composed of numerous tubuloacinar structures within a dense sclerotic stroma. H&E staining, 200×.

Sclerosing Polycystic Adenosis

Sclerosing polycystic adenosis is a rare, benign and in all probability an inflammatory lesion of salivary gland that, more often than not, is confused both histologically and clinically with salivary gland neoplasia. Most cases have been described within the major glands, particularly the parotid, but are also seen in the minor glands. Clinically the lesions are firm and often nodular. Microscopically, these lesions are always well-circumscribed but not encapsulated. There is cystic dilation of the ducts with prominent fibrosis within each lobule (Figure 7.10). Tubuloacinar hyperplasia in a nodular pattern is a distinctive pattern. All of these features are quite similar to fibrocystic disease of the breast, although the two entities do not appear to be related.

Malignant Epithelial Neoplasms

Mucoepidermoid Carcinoma

There still exists some conjecture whether mucoepidermoid carcinoma (MEC) exists as only low-grade and high-grade neoplasms rather than

the three categories that are classically discussed (Spiro, et al. 1978). The presence of mucoepidermoid carcinoma in the parotid gland is usually asymptomatic and generally presents as a solitary, painless mass. If present within the parotid gland, symptoms encompass pain, drainage from the ipsilateral ear, dysphagia, trismus, and often facial paralysis (Ellis and Auclair 2008). On rare occasion, mucoepidermoid carcinoma may occur within the bony mandible or maxilla (3:1) (Brookstone and Huvos 1992). These tumors are referred to as central mucoepidermoid carcinomas and make up less than 4% of all mucoepidermoid carcinomas (Ellis and Auclair 2008).

Mucoepidermoid carcinomas (Figure 7.11) may consist of diverse proportions of mucous, epidermoid, intermediate, columnar, and clear cells, and are often cystic in pattern. These tumors constitute 29–34% and thus the majority of malignant neoplasms found in both major and minor salivary glands (Spiro, et al. 1978; Spitz and Batsakis 1984; Eveson and Cawson 1985; Speight and Barrett 2002; Ellis and Auclair 2008). The best evidence to date indicates that 45% of these neoplasms initiate within the parotid glands (Goode, et al. 1998; Guzzo, et al. 2002). Among the minor salivary glands, mucoepidermoid carcinoma has an affinity for the buccal mucosa and the palate (Ellis and Auclair 2008). Unlike other salivary gland tumors, the MEC occur more often in the lower lip than in the upper. Generally, the mean age for these carcinomas is 47 years, however, there exists a broad age range of 8–92 years, and is one of the few salivary gland malignancies occurring in childhood (Ellis and Auclair 2008). As with the majority of other salivary gland tumors, the MEC is more common in the female population. Notably, previous exposure to ionizing radiation has been suggested to significantly increase the risk of mucoepidermoid carcinomas of the major salivary glands (Guzzo, et al. 2002; Ellis and Auclair 2008).

The level of microscopic grading of mucoepidermoid carcinoma is of paramount importance in establishing the prognosis (Auclair, et al. 1992; Goode, et al. 1998; Speight and Barrett 2002). These tumors are graded as low grade, intermediate grade, or high grade, depending upon their cellular differentiation. The grade of a lesion is ascertained as a sum of five microscopic parameters. Sums that are 0–4 are regarded as low grade, those that are 5–6 are considered intermediate grade, and sums 7–14 are regarded as high-grade cancers. The five microscopic parameters considered are (Figures 7.12 and 7.13):

1 Decreased intracystic component (+2).
2 Neural invasion present (+2).
3 Necrosis present (+3).
4 Mitosis (≥4 per 10 high-power field (+3).
5 Anaplasia present (+4).

Important is the fact that retrospective reviews of mucoepidermoid carcinoma of the major salivary glands have revealed a statistical correlation between this point-based grading system and

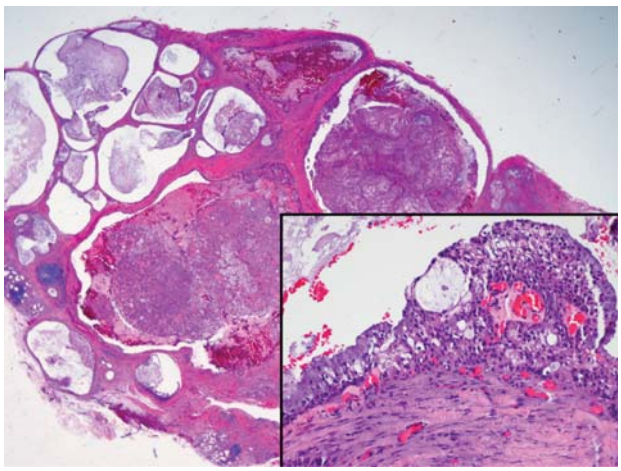


Figure 7.11. Mucoepidermoid carcinoma exhibiting large cystic spaces containing mucin and solid tumor elements. Lower right panel depicting epidermoid, intermediate and mucous cells. H&E staining, 100×/200×. Source: Courtesy of Dr. Mark Bernstein.

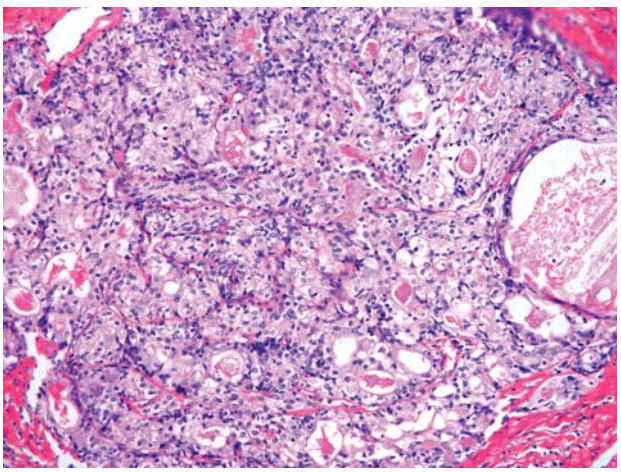


Figure 7.12. Intermediate grade mucoepidermoid carcinoma with mostly solid features and few mucous cells. H&E staining, 200×.

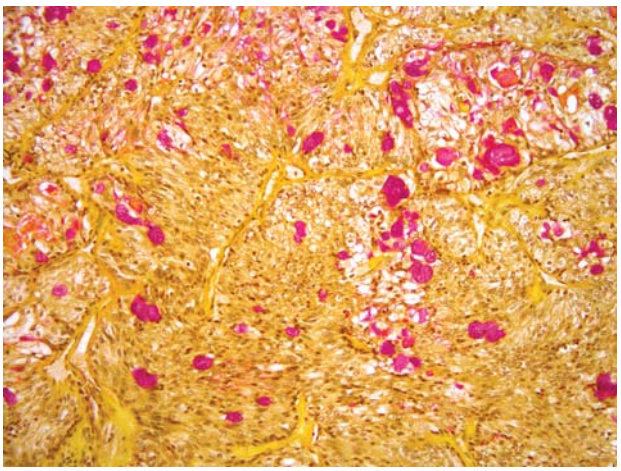


Figure 7.13. Intermediate grade mucoepidermoid carcinoma from Figure 7.12 demonstrating numerous areas of mucin production/deposition. Mucicarmine stain, 200×.

outcome for parotid tumors; however, similar rigor was not deemed useful for tumors of the submandibular glands (Goode, et al. 1998) or minor salivary glands (Guzzo, et al. 2002). However, when more emphasis on features of tumor invasion was employed better correlations were obtained, indicating that tumor staging may be a better indicator of prognosis (Ellis and Auclair 2008). These results reinforce the need for analyses that encompass clinical tumor presentation as well as histopathology (Brandwein et al. 2001).

Cytokeratin immunostains usually react with the intermediate and large cells of the MEC as does EMA. The smaller cells and the pure mucous cells do not demonstrate the same staining qualities. As one would expect, none of the MEC cell types react with myoepithelial immunostains. There appears to be no correlation between immunostaining and tumor grade.

A chromosomal translocation *t*(11;19) generates a fusion oncogene, which consists of the mucoepidermoid carcinoma translocated gene (*Mect)*-1 (or *Crtc1*,or *Torc1)* fused to the mastermind-like gene family (*Maml*)-2 is present in 38–81% of mucoepidermoid carcinomas (Warner, et al. 2013). The resulting fusion protein has been generally associated with low/intermediate grade mucoepidermoid carcinomas and correlated with clinical outcomes. The tumorigenetic effect of the *Crtc1-Maml2* fusion involves activation of the Notch and/or cAMP-responsive element binding protein (CREB) signaling pathways (Kaye 2006). Recently, there has been speculation that MECT1-*MAML2* fusion protein may promote sustained E6/E7 over-expression in the increased numbers of HR-HPV subjects manifesting mucoepidermoid after 2001 (Isayeva, et al. 2013).

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma (ACC) is a slow-growing nevertheless aggressive neoplasm with a notable capacity for recurrence (Brookstone and Huvos 1992). In earlier times, the ACC was known as the cylindroma or adenocystic carcinoma. To avoid confusion with similar eccrine tumors, these other designations are no longer in use. These malignant salivary tumors apparently arise from both myoepithelial and ductal cells. Three growth patterns have been acknowledged; cribriform, tubular, and a solid (basaloid) pattern (Figure 7.14). The tumors are classified according to the predominant pattern (Batsakis, et al. 1990; Brookstone and Huvos 1992; Ellis and Auclair 2008). The cribriform pattern is the most common, while the solid pattern is the least (Perzin, et al. 1978). Solid adenoid cystic carcinoma is a high-grade lesion with reported recurrence rates of as much as 100% compared with 50–80% for the tubular and cribriform variants (Ellis and Auclair 2008).

Reports from the AFIP indicate that adenoid cystic carcinoma is the fifth most common malignant epithelial tumor of the minor salivary

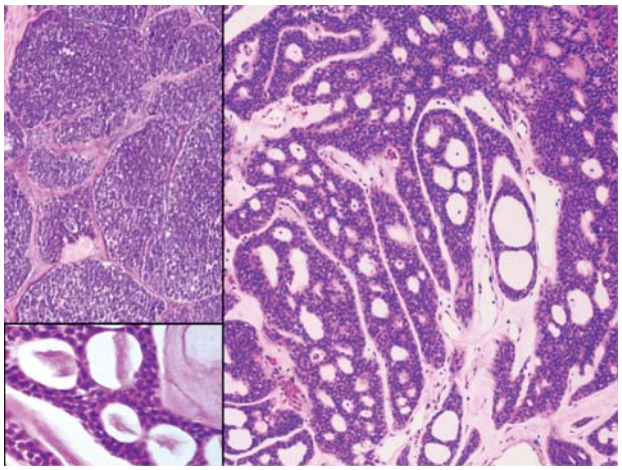


Figure 7.14. Adenoid cystic carcinoma manifesting cribriform and tubular patterns, right panel and lower left panel. Solid pattern of growth shown in upper left panel. H&E staining, 200×/400×. Source: Courtesy of Dr. Mark Bernstein.

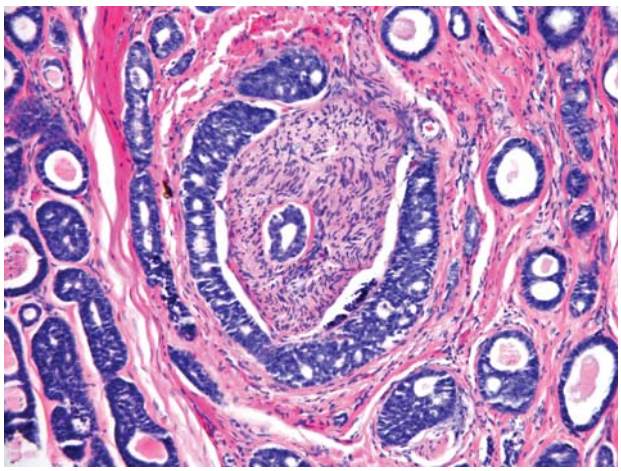


Figure 7.15. Adenoid cystic carcinoma demonstrating classic nerve invasion pattern. H&E staining, 400×.

glands after mucoepidermoid carcinomas, adenocarcinomas, NOS, acinic cell carcinomas, and polymorphous low-grade adenocarcinomas (PLGA) (Ellis and Auclair 2008). It ranks fourth occurring in the major glands as the polymorphous low-grade adenocarcinoma is rare in the major glands. The peak incidence for this tumor is stated to be in the fourth through sixth decades of life (Ellis and Auclair 2008).

These neoplasms characteristically progress as slow growing lesions in the preauricular, submandibular, and other related regions. Not infrequently, pain and facial paralysis are noted with progressive growth of the tumors, which may be attributed to their propensity to invade nerves (Figure 7.15) (Chen, et al. 2007; Ellis and Auclair 2008). Adenoid cystic carcinomas have a tendency to have an extended course resulting in a poor clinical result. The 10-year survival for these tumors (stages I-IV) is considered to be less than 50% (Speight and Barrett 2002). In that these carcinomas characteristically recur repeatedly and spur late distant metastases, clinical staging of these lesions appears to be a superior prognostic indicator than histologic grade (Hamper, et al. 1990; Speight and Barrett 2002; Friedrich and Bleckmann 2003). Thus, as one would expect, larger tumors with local/regional metastases demonstrate the worst prognostic pattern.

Microscopically, the ACC is histomorphologically diverse with the three major morphologic patterns quite often all being present within a single tumor. The most common cribriform pattern demonstrates a "swiss-cheese" appearance with numerous cyst-like structures of varying size being characteristic. Both duct and myoepithelial cells comprise this pattern. As the histologic pattern becomes more solid, the ductal cells decrease while the myoepithelial cells then predominate. Immunologically, the expression of cytokeratins, SMA, MSA, and vimentin by the tumor cells substantiates the primase of a dual-cell population.

Adenoid cystic carcinomas characteristically possess a recurrent *t*(6;9)(q2–23;p23–24) translocation that results in a novel fusion of the *MYB* proto-oncogene with the transcription factor gene *NFIB. MYB* is a hallmark of adenoid cystic carcinomas and is observed in adenoid cystic carcinomas from a variety of sites including; salivary gland, sinonasal cavity, tracheobronchial tree, larynx, breast, and vulva (Brill, et al. 2011). Moreover, copy number alterations have included losses involving 12q, 6q, 9p,11q, 14q, 1p, and 5q and gains involving 1q, 9p, and 22q. Losses of 1p, 6q, and 15q have been associated with high-grade tumors, whereas, losses of 14q have been observed in Grade I tumors (Kasamatsu, et al. 2005). The *t*(6;9) rearrangements have been associated with a complex pattern of break-points, deletions, insertions, inversions, and, for 9p, gains (Persson, et al. 2012a).

Adenocarcinomas

Acinic Cell Carcinoma

The acinic cell carcinoma, once described as an acinic cell tumor, has also been referred to as an acinic cell adenocarcinoma. It is a malignant epithelial neoplasm in which the tumor cells convey serous or serous-like acinar differentiation as opposed to mucous acinar cells (Ellis and Auclair 2008). AFIP data has indicated that acinic cell carcinoma is the third most common malignant epithelial salivary gland neoplasm after mucoepidermoid carcinoma and adenocarcinoma, NOS. Moreover, acinic cell carcinoma comprised 17% of primary malignant salivary gland tumors with more than 80% occurring in the parotid gland. When arising in minor glands, the acinic cell carcinoma is most commonly seen in the upper lip or buccal mucosa. The acinic cell carcinoma is the most common malignant salivary gland tumor that occurs bilaterally. Women are generally more affected more than males; with a mean age of 44 years. However, others have reported a 0–19% frequency of acinic cell carcinoma amongst malignant salivary gland neoplasms (Ellis and Auclair 2008).

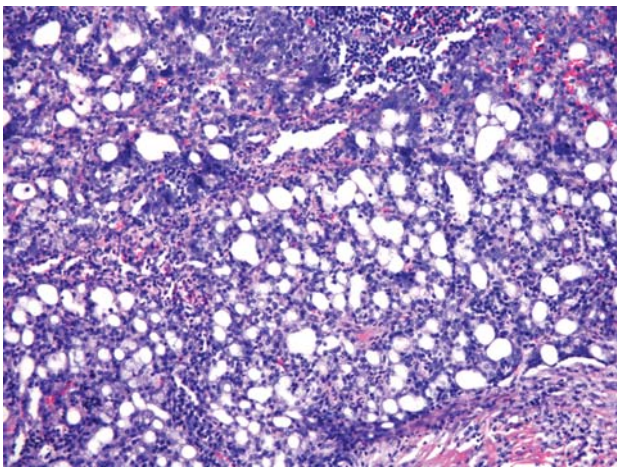


Figure 7.16. Acinic cell carcinoma of the microcystic pattern type. H&E staining, 200×.

Patients usually present with a slowly increasing mass in the parotid. Pain is a symptom in approximately 33% of patients. Again, staging appears to be a better prognostic predictor than histologic grading (Ellis and Auclair 2008).

Acinic cell carcinomas demonstrate various histological patterns (Figure 7.16). The present architectural classification characterizes them as solid, microcystic, papillary-cystic, and follicular (Figure 7.17). Most large tumors present as a spectrum of these features. The majority of acinic cell carcinomas are reactive with cytokeratin and other immunostains for epithelial cells while they are rarely reactive with immunostains for myoepithelial cells.

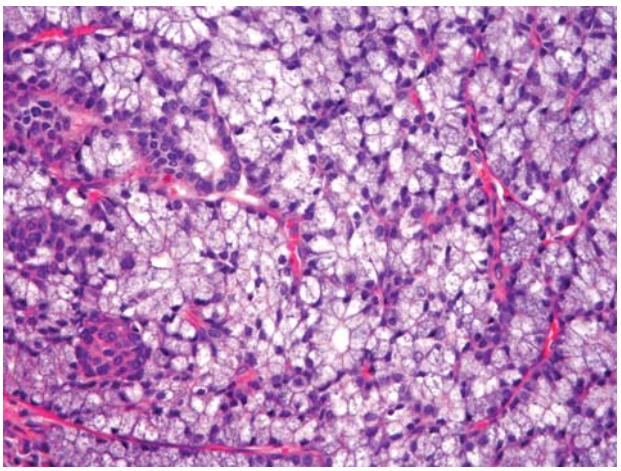


Figure 7.17. Acinic cell carcinoma composed predominately of acinar cells. H&E staining, 200×.

Polymorphous Low-Grade Adenocarcinoma

Polymorphous low-grade adenocarcinoma (PLGA) is a malignant tumor that is predominately restricted to minor salivary glands. The tumors are distinguished by bland, uniform nuclear features, varied but distinctive architecture, invasive growth, and perineural infiltration (Ellis and Auclair 2008). PLGAs have been reported to represent ~11% of all tumors of salivary glands and ~26% of malignant neoplasms. These malignant tumors characteristically emerge as solid, non-tender swellings of the mucosa of the hard and soft palates, buccal mucosa, or upper lip with the palate being the most common site. Soreness, hemorrhage, telangiectasia, or ulceration has been associated with these lesions (Ellis and Auclair 2008). The PLGA is a slowly progressive salivary gland neoplasms with an apparent survival approaching 80% at 25 years (Evans and Luna 2000). Noteworthy, is that since some of these tumors may behave capriciously that the qualifying term, low grade, may be deceptive and that the term, polymorphous adenocarcinoma is preferable (Speight and Barrett 2002).

The average age of patients has been 59 years, with the vast majority of cases occurring between the ages of 50 and 79 years. The gender predisposition is in favor of females in a ratio of ~2:1. Among minor gland tumors, PLGA is twice as frequent as adenoid cystic carcinoma (Ellis and Auclair 2008). The AFIP series indicates that >60% of PLGA occur in the mucosa of either the soft or hard palates. The next most frequent sites being buccal mucosa (16%) and the upper lip (12%). The copy number alterations in polymorphous low-grade carcinomas is low indicating that these tumors are genetically stable and supports the notion that PLGA is a slow-growing, low-grade carcinoma with low metastatic potential (Persson, et al. 2012b).

This salivary gland malignancy demonstrates a quite variable microscopic pattern as the name implies. This tumor is almost always well-circumscribed but never encapsulated. The central portion of the PLGA is usual solid and lobulated but the periphery often demonstrates single columns or rows of tumor cells extending into the surrounding connective tissue (Figure 7.18). Many times, the cells of the PLGA are arranged in concentric circles much like paper targets (Figure 7.19). The PLGA demonstrates perineural invasion more commonly than any other salivary

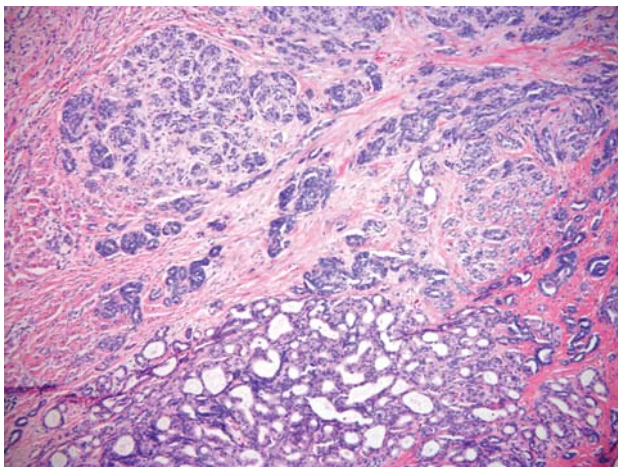


Figure 7.18. Polymorphous low grade adenocarcinoma comprised of both small and intermediate size tumor cells. H&E staining, 100×.

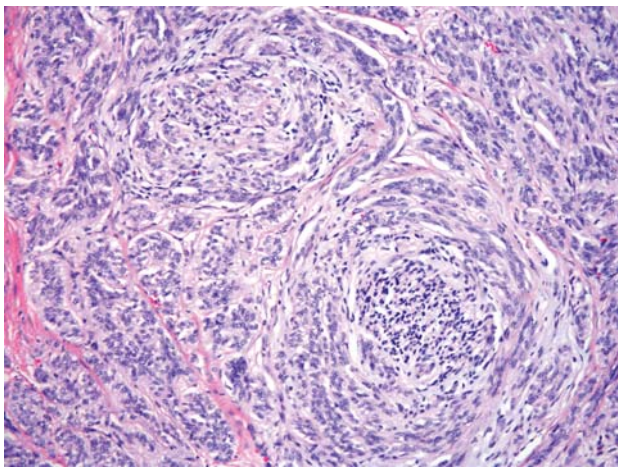


Figure 7.19. Polymorphous low grade adenocarcinoma arranged in a concentric pattern. Near the center is peripheral nerve infiltration. H&E staining, 200×.

gland tumor including the adenoid cystic carcinoma. The PLGA cells for the most part react with both antibodies to epithelial cells and myoepithelial cells. Oftentimes, immunostaining is utilized to distinguish PLGA from pleomorphic adenoma as well as from the cells of the adenoid cystic carcinoma.

Adenocarcinoma not Otherwise Specified (NOS)

Adenocarcinoma, NOS demonstrates glandular or ductal differentiation but does not have any of the distinct morphologic features that typify the other, more explicit carcinoma types. The diagnosis of adenocarcinoma, NOS, is fundamentally one of elimination. Adenocarcinoma, NOS has been suggested to be only second to mucoepidermoid carcinoma in frequency among malignant salivary gland neoplasms (Ellis and Auclair 2008). However, reports have shown a varied incidence from 4 to 10% (Speight and Barrett 2002). The AFIP reports a the mean patient age of 58 years with roughly 40 and 60% of tumors occurring in the major and minor salivary glands, correspondingly, with 90% of tumors occurring in the parotid gland (Ellis and Auclair 2008). Adenocarcinoma, NOS is graded according to the degree of differentiation as low-grade, intermediate-grade, and high-grade tumors (Speight and Barrett 2002; Ellis and Auclair 2008). Some reports have indicated that survival is superior for patients with tumors of the oral cavity than for those with tumors of the major glands (Matsuba, et al. 1988; Ellis and Auclair 2008).

Adenocarcinoma, NOS demonstrates an extensive range of histologic features, many of which occur within the same tumor. Formed can be cords, sheets, rows, and islands of tumor cells but in every tumor either ducts or glands will be evident (Figure 7.20). Oftentimes, a small aggregate of a specific type of salivary gland malignancy, such as acinic cell carcinoma, will be identified within the larger tumor mass.

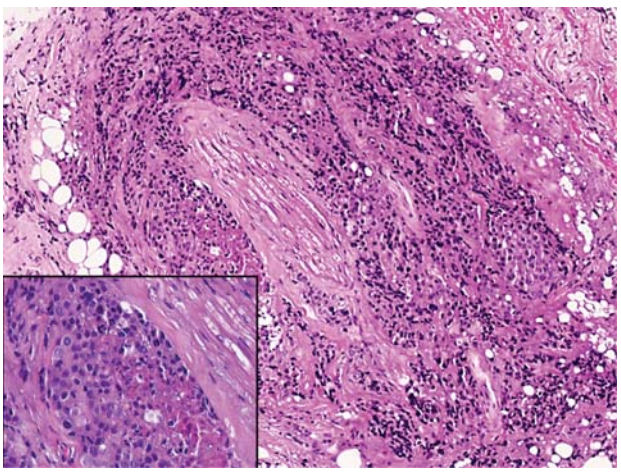


Figure 7.20. Adenocarcinoma, NOS: Infiltrative growth of neoplastic epithelium forming islands, cords and dense cell sheets invading a peripheral nerve. H&E staining, 200×/400×.

Rare Adenocarcinomas

Basal Cell Adenocarcinoma

Basal cell adenocarcinoma, also known as basaloid salivary carcinoma, carcinoma ex. monomorphic adenoma, malignant basal cell adenoma, malignant basal cell tumor, and basal cell carcinoma, is a low-grade malignant epithelial neoplasm that is cytologically similar to the basal cell adenoma, but is infiltrative and has a small potential for metastasis (Ellis and Auclair 2008). In AFIP case files spanning almost 11 years, basal cell adenocarcinoma comprised 1.6% of all salivary gland neoplasms and 2.9% of salivary gland malignancies (Ellis and Auclair 2008). Nearly 90% of tumors occurred in the parotid gland (Muller and Barnes 1996). The average age of patients is reported to be 60 years (Ellis and Auclair 2008).

Similar to most salivary gland neoplasms, swelling is typically the only sign or symptom experienced (Muller and Barnes 1996). A sudden increase in size may occur in a few patients (Ellis and Auclair 2008). Basal cell carcinomas are low-grade carcinomas that are infiltrative, locally destructive, and tend to recur, but only occasionally metastasize. In a retrospective series of 29 cases, there were recurrences in 7 and metastases in 3 (Muller and Barnes 1996). In another retrospective review of 72 cases, 37% involved local recurrences (Ellis and Auclair 2008). The overall prognosis for patients with this tumor is good (Muller and Barnes 1996; Ellis and Auclair 2008; Ward, et al. 2009; Jung, et al. 2013).

The histologic features of the basal cell carcinoma are quite similar to its benign counterpart, the basal cell adenoma (Figure 7.21). Cytologic atypia, such as the finding of atypical mitotic figures, is helpful if available. Other times, this atypia is almost nonexistent. Infiltrative growth through the capsule if present or extensions into periglandular fat or muscle are very helpful findings in this type of carcinoma. Immunohistochemistry is variable from tumor to tumor but the majority of tumors will show at least partial staining for myoepithelial cells.

Clear Cell Carcinoma

Clear cell carcinoma, also known as clear cell adenocarcinoma, is a very rare malignant epithelial neoplasm composed of a monomorphous population of cells that have optically clear cytoplasm with standard hematoxylin and eosin stains and lack features of other specific neoplasms (Figure 7.22). Because of inconsistencies in the methods of reporting salivary gland neoplasms, meaningful incidence rates for this tumor are difficult to derive from the literature (Ellis and Auclair 2008). Most cases involve the minor salivary glands. In the AFIP case files, the mean age of patients is approximately 58 years (Ellis and Auclair 2008).

Several other types of both primary and secondary salivary gland malignancies can also demonstrate the formation of clear cells. These include the mucoepidermoid carcinoma (Figure 7.23), the acinic cell carcinoma, the oncocytoma, the epithelial-myoepithelial carcinoma,

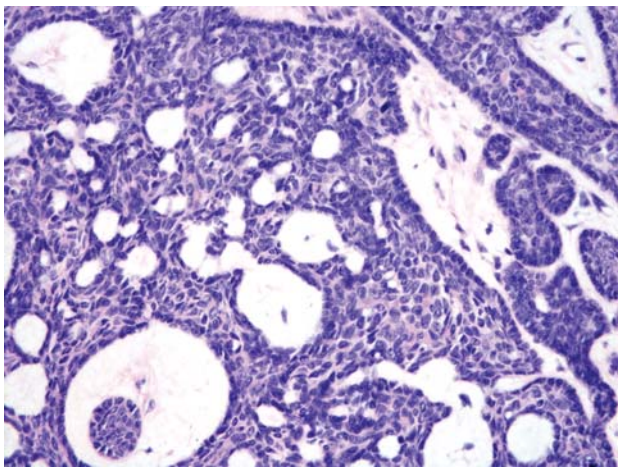


Figure 7.21. Basal cell adenocarcinoma arranged much like a basal cell adenoma but with atypical cellular features. H&E staining, 200×.

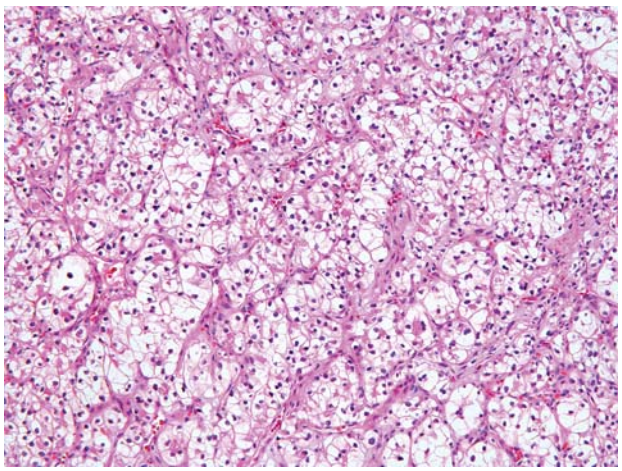


Figure 7.22. Primary clear cell carcinoma arising within the parotid gland. H&E staining, 100×.

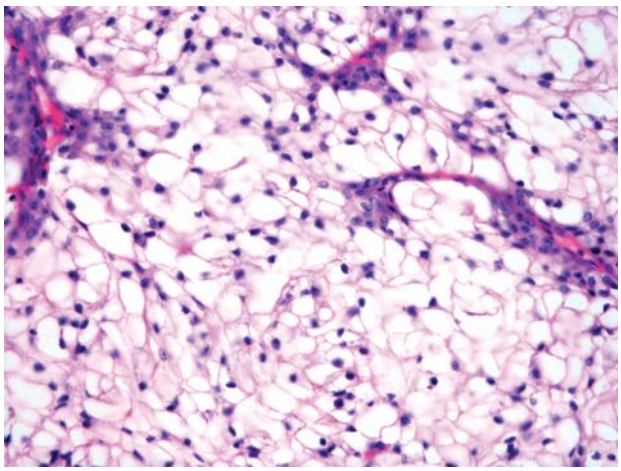


Figure 7.23. A clear cell variant of a mucoepidermoid carcinoma. H&E staining, 200×.

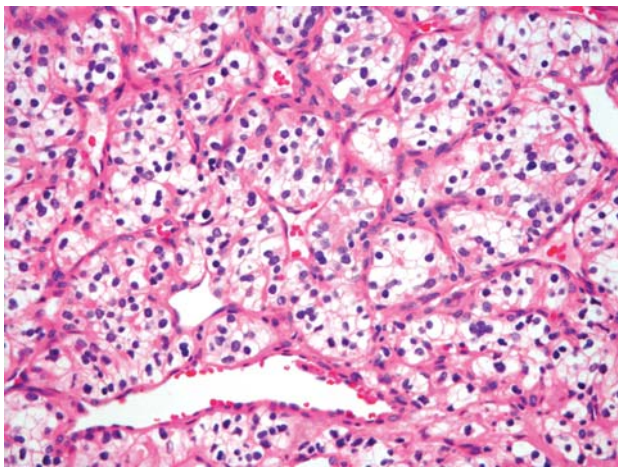


Figure 7.24. The classic clear cell variant of a renal cell carcinoma metastatic to the parotid gland. H&E staining, 200×.

the sebaceous carcinoma, and others. Metastasis from a malignancy is often indistinguishable from a primary clear cell salivary gland carcinoma. The most commonly encountered metastasis is the clear cell renal cell carcinoma, the most common kidney carcinoma (Figure 7.24). Meticulous microscopic searching is often needed to distinguish one from another.

In most patients, swelling is the only symptom. Clear cell adenocarcinoma is a low-grade neoplasm. As of 1996, the AFIP reported that no patient is known to have died as a result of this tumor (Sicurella, et al. 2004; Ellis and Auclair 2008).

Hyalinizing Clear Cell Carcinoma

Hyalinizing clear cell carcinoma (HCCC) is a unique, low-grade salivary gland tumor that shows nests, cords, and trabeculae of clear and eosinophilic cells in a characteristic hyalinized stroma (Weinreb 2013). It primarily arises in the oral cavity but has been described at essentially all salivary gland and seromucous gland sites. The tumors raise a broad differential diagnosis, most of which are easily distinguished by light microscopy and immunohistochemistry. HCCC possess a squamous line of differentiation without true myoepithelial marker expression. Mucinous differentiation, irrespective of quantity, is not an exclusion criterion and should not lead to a diagnosis of clear cell mucoepidermoid carcinoma (Weinreb 2013). Recent evidence shows that this carcinoma harbors a recurrent and consistent *EWSR1-ATF1* fusion, which also helps link this tumor to "clear cell odontogenic carcinoma" (Bilodeau, et al. 2012; Weinreb 2013).

Cystadenocarcinoma

Cystadenocarcinoma, also known as malignant papillary cystadenoma, mucus-producing adenopapillary, or non-epidermoid, carcinoma, low-grade papillary adenocarcinoma of the palate, and papillary adenocarcinoma, is a rare malignant epithelial tumor characterized histologically by prominent cystic and frequently, papillary growth but lacking features that characterize cystic variants of several more common salivary gland neoplasms. Cystadenocarcinoma is the malignant counterpart of the cystadenoma (Ellis and Auclair 2008).

In a review of 57 cases, the AFIP found that men and women are affected equally; the average patient age was about 59 years. Approximately 65% occurred in the major salivary glands, primarily in the parotid. In addition, it is the most common salivary gland malignancy found in the sublingual gland. Most patients present with a slowly growing asymptomatic mass. Clinically, this neoplasm is rarely associated with pain or facial paralysis. Cystadenocarcinoma is considered to be a low-grade neoplasm (Ellis and Auclair 2008).

A subtype of cystadenocarcinoma is known as low-grade cribriform cystadenocarcinoma (LGCCC) and is an extremely rare neoplasm of salivary gland. LGCCC usually occurs in elderly people with a female predominance. The parotid gland is the most common site of involvement. LGCCC is characterized by the papillary-cystic or

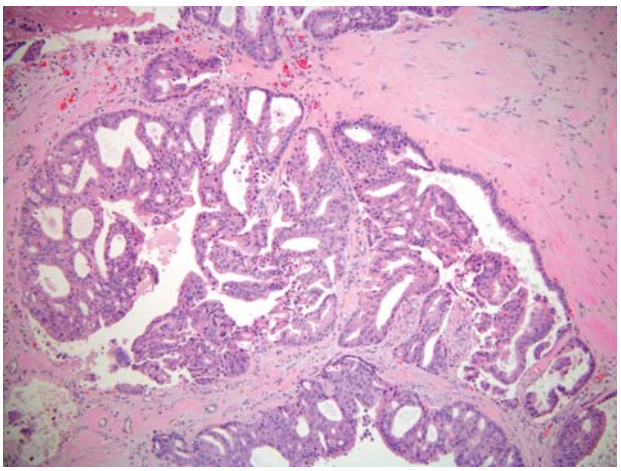


Figure 7.25. Low-grade cribriform cystadenocarcinoma, also known as the low-grade salivary duct carcinoma, is easily confused with an acinic cell carcinoma. H&E staining, 200×.

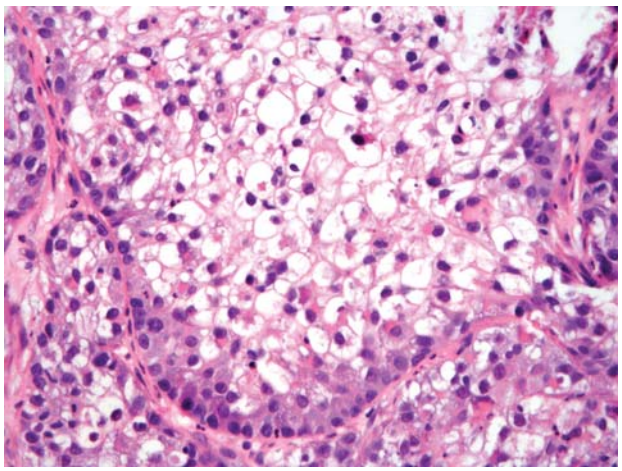


Figure 7.26. Sebaceous adenocarcinoma is characterized by sebaceous differentiation within islands of squamoid cells. H&E staining, 400×.

cribriform proliferation pattern and is similar to the low-grade ductal carcinoma in situ or atypical ductal hyperplasia of the breast in histology and biological features. LGCCC was originally designated as low-grade salivary duct carcinoma (LGSDC) in order to distinguish it from the conventional SDC. In contrast with the LGCCC, conventional SDC exhibits highly aggressive malignancy and high-grade histology similar to an invasive ductal carcinoma of the breast. However, no definite association was found between LGCCC and conventional SDC; therefore, the third WHO classification regards this neoplasm as a variant of cystadenocarcinoma due to its cystic morphology (Wang, et al. 2013a).

Histologically, LGCCC is composed of single or multiple enlarged cystic ducts accompanied by adjacent intraductal proliferation (Figure 7.25). These tumor cells are diffusely strong positive for S100. Based on the histological features, LGCCC should be distinguished with other common parotid tumors including papillary cystic variant of acinic cell carcinoma, conventional salivary duct carcinoma, cystadenocarcinoma, polymorphous low-grade adenocarcinoma (PLGA), carcinoma ex. pleomorphic adenoma, and mammary analogue secretory carcinoma (MASC) (Wang, et al. 2013a).

Sebaceous Adenocarcinoma

Sebaceous adenocarcinoma is an uncommon malignant epithelial neoplasm that is generally regarded as an intermediate grade neoplasm. The tumors have been noted to be comprised of islands and sheets of cells with areas of sebaceous differentiation (Figure 7.26). The cells of these tumors possess atypical nuclear morphology and manifest an infiltrative pattern of growth (Ellis and Auclair 2008). Clinical presentation as a painless, slow-growing, asymptomatic swelling have been reported, however, lesions may be painful or result in facial nerve involvement with paralysis. Approximately one third of these tumors have been reported to have a recurrence potential (Gnepp 1983). The vast majority of examples of this neoplasm have been limited to the parotid gland with the mean age of occurrence being 69 years (Gnepp 1983; Ellis and Auclair 2008; Wang, et al. 2010).

Microscopically, the tumor is formed of sheets and islands of malignant cells, predominately of squamous and basaloid appearance. Intermittent sebaceous differentiation is always present, but it may be minimal. Perineural invasion is relatively common.

Sebaceous Lymphadenocarcinoma

Sebaceous lymphadenocarcinoma is a particularly uncommon malignant low-grade neoplasm with a good prognosis (Gnepp and Brannon 1984). These neoplasms are believed to correspond to carcinomatous transformation of sebaceous lymphadenoma. The carcinoma portion of the tumor has been reported as sebaceous adenocarcinoma; however, other forms of salivary gland carcinomas

have been recognized (Ellis and Auclair 2008). As only four cases have been reported, all of which were associated with the parotid gland in elderly patients, there is little information available on these neoplasms (Gnepp and Brannon 1984; Ellis and Auclair 2008; Gnepp 2012).

Microscopically, this tumor consists of classic benign sebaceous lymphadenoma within lymphoid stroma. Admixed in this benign lesion are found areas of sebaceous carcinoma without the adjacent lymphoid stroma.

Oncocytic Carcinoma

Oncocytic carcinoma, also known as malignant oncocytoma or oncocytic adenocarcinoma, is a rare high-grade carcinoma, salivary neoplasm with predominantly oncocytic features. The oncocytic carcinomas constitute <1% of the cases salivary gland tumors accessioned to the AFIP files (Ellis and Auclair 2008). The majority of reported cases have been in the parotid gland where they present as painful lesions or associated with facial nerve paralysis (Sugimoto, et al. 1993). Similar to other parotid gland carcinomas, tumors that are less than 2 cm have a better prognosis than larger tumors. Thus, TNM staging correlates with the prognosis (Goode, et al. 1998). The AFIP series reports that the average age of patients with these neoplasms has been 63 years (Ellis and Auclair 2008; Zhou, et al. 2010).

As with benign oncocytomas, the oncocytic adenocarcinoma is composed of sheets of round and polyhedral cells with fine eosinophilic cytoplasm. Ultrastructurally these granules are composed of excessive numbers of atypical mitochondria. While many of the cells have no unusual features and look identical to those of the benign oncocytoma, others demonstrate atypical mitotic figures and other pleomorphic features (Figure 7.27). The finding of these two-cell groupings leads one to speculate that the oncocytic carcinoma arises from a pre-existing benign oncocytoma.

Salivary Duct Carcinoma

Salivary duct carcinoma, or salivary duct adenocarcinoma, is a high-grade malignant epithelial neoplasm comprised of elements that bear a resemblance to expanded salivary gland ducts. The AFIP files, indicate that salivary duct carcinomas represent only <1% of all epithelial salivary gland neoplasms with 75% of cases affecting the parotid

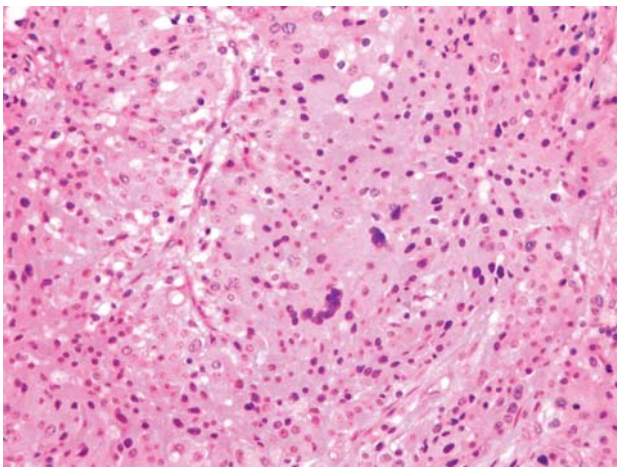


Figure 7.27. Oncocytic carcinoma demonstrating the atypical features of the oncocytes. H&E staining, 200×.

gland and with a male gender predominance of 1.5–1.0 and mean incidence occurring in the seventh and eighth decades of life (Ellis and Auclair 2008). Parotid swelling has generally been the most common presenting symptom. However, facial nerve involvement has been noted in ~25% of patients. Although a low-grade variant of this tumor has been described, high-grade variants of this neoplasm have been regarded as one of the most aggressive types of salivary gland carcinoma. One review has revealed that one third of patients with these neoplasms developed local recurrence and 46% developed distant metastasis (Ellis and Auclair 2008). The high-grade lesions are epitomized by local invasion, hematogenous and lymphatic metastasis, and a dismal prognosis (Delgado, et al. 1996; Guzzo, et al. 2002; Ellis and Auclair 2008).

The high-grade form of the salivary duct carcinoma is invariably composed of rounded solid or cystic nodules of tumor. While the smaller nodules are filled with additional tumor, the larger ones demonstrate a characteristic comedonecrosis rarely seen in other salivary gland tumors (Figure 7.28). The epithelial cells can be poorly differentiated although some show only a few atypical features. Dense fibrosis is a hallmark of salivary duct carcinoma. Within this dense fibrous stroma are small nests of malignant tumor cells (Figure 7.29).

The low-grade salivary duct carcinoma has recently been reclassified as *low-grade cribriform cystadenocarcinoma.* Even though the histology is somewhat similar to the high-grade variant the clinical behavior is vastly different. Thus the terminology has been altered allowing the treating

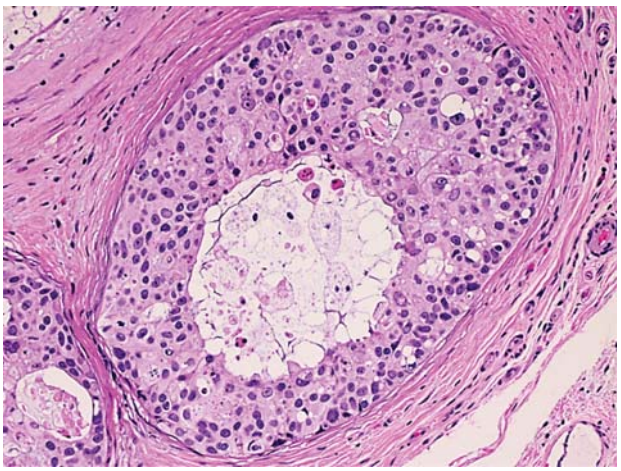


Figure 7.28. Salivary duct carcinoma containing comedonecrosis centrally within a tumor nodule surrounded by a prominent hyalinized fibrous connective tissue. H&E staining, 400×. Source: Courtesy of Dr. Mark Bernstein.

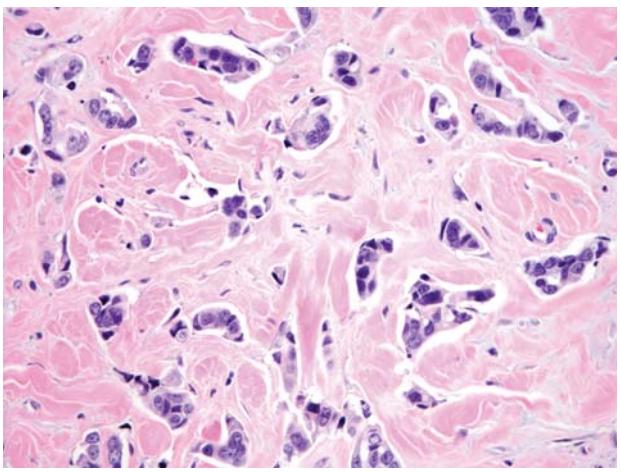


Figure 7.29. Nodules of salivary duct carcinoma embedded within a dense connective tissue stroma. H&E staining, 400×.

clinician a better understanding of the two lesions and thus decreasing the possibility of treating the patient inappropriately.

An analysis of PLAG1 and HMGA2 rearrangements in salivary duct carcinoma (SDC) has revealed that a large proportion of SDCs arise in pleomorphic adenomas (PAs), with or without residual evidence of a PA. However, a small proportion of SDCs appear to arise in low-grade cribriform cystadenocarcinoma and ductal carcinoma in situ (Bahrami, et al. 2013).

Primary Mucinous Adenocarcinoma

Primary mucinous adenocarcinoma (MAC) of salivary glands is a very rare low-grade malignant neoplasm distinguished by significant quantities of extracellular epithelial mucin. The tumors generally are organized as cords, nests, and/or appear as solitary epithelial cells. Almost all known cases of these lesions have presented with minimal symptoms and have been limited to the major salivary glands. Interestingly, the predominant site for these tumors has been the submandibular glands (Osaki, et al. 1990; Ellis and Auclair 2008). These are extremely rare lesions with no known frequency of occurrence. Comparative genomic hybridization (CGH) in a small sample of minor salivary gland tumors has revealed DNA copy number aberrations and amplification of *MDM2* (12q15) and of *AURKA* (20q13) in MAC in minor salivary glands that were different from those reported for colorectal MAC (Uchida, et al. 2010).

The histology of the mucous adenocarcinoma is unique within the realm of salivary gland malignancies. It is microscopically quite similar to the mucinous carcinoma of both the colon and the breast. Nests and groups of epithelial cells appear to float within a sea of mucous. In some cases the epithelial cells are arranged in cribriform-like branching cords.

Malignant Mixed Tumors

Carcinoma ex. pleomorphic adenoma, carcinosarcoma, and metastasizing mixed tumor have all been regarded as subtypes of malignant mixed tumors. The most common among these is the carcinoma ex. pleomorphic adenoma. On the other hand, the carcinosarcoma is a true malignant mixed tumor with both epithelial and mesenchymal elements cytologically malignant. However, the carcinosarcoma and the metastasizing mixed tumor, which demonstrate semantic inexactness, are extremely rare (Ellis and Auclair 2008).

Carcinoma Ex. Pleomorphic Adenoma

Carcinoma ex. pleomorphic adenoma, sometimes termed carcinoma ex. mixed tumor, is a malignant epithelial neoplasm that demonstrates evidence of malignancy arising primarily from or in a benign pleomorphic adenoma in one of the major salivary glands (Roijer, et al. 2002). Thus, the diagnosis necessitates that the sample contains benign tumor as well as carcinomatous elements (LiVolsi and

Perzin 1977). Only the epithelial component is malignant, not the myoepithelial as is seen in the carcinosarcoma. It appears that the longer a patient is afflicted with a pleomorphic adenoma, the more likely the transformation into the malignant form. AFIP files have indicated that carcinoma ex. pleomorphic adenoma encompasses 8.8% of all mixed tumors and 4.6% of all malignant salivary gland tumors making it the sixth most common malignant salivary gland tumor (Ellis and Auclair 2008). The most common clinical symptoms have been that of a painless mass. Although, one third of patients have been noted to present with facial paralysis (Ellis and Auclair 2008). Similar to other major salivary gland tumors, tumor stage, grade, and degree of invasion determine prognosis (Brandwein, et al. 2002).

The benign portion of this tumor makes up a variable amount of the entire mass. The malignant portion may be completely separate from the benign element (Figure 7.30) or they may be intermingled. In most tumors, the malignant portion appears most like an adenocarcinoma (Figure 7.31), NOS but other carcinoma ex. pleomorphic adenomas demonstrate area composed of mucoepidermoid carcinoma, acinic cell carcinoma, and various others. If the malignant portion of the tumor is surrounded by benign mixed tumor, it is known as *carcinoma in situ ex. pleomorphic adenoma* or *non-invasive carcinoma ex. pleomorphic adenoma*.

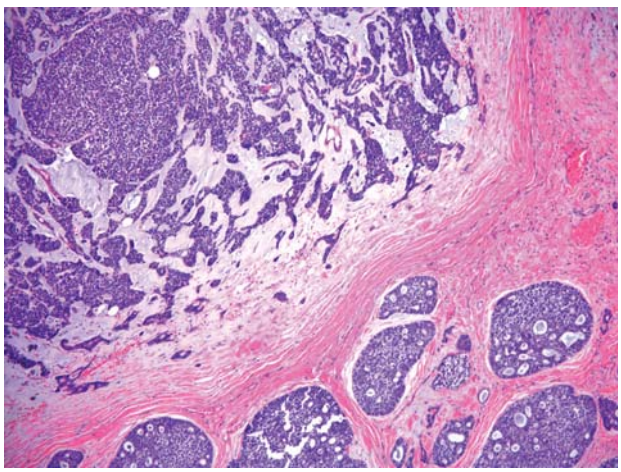


Figure 7.30. Carcinoma ex. pleomorphic adenoma demonstrating an adenoid cystic carcinoma on the right arising within a basal cell adenoma on the left. H&E staining, 100×.

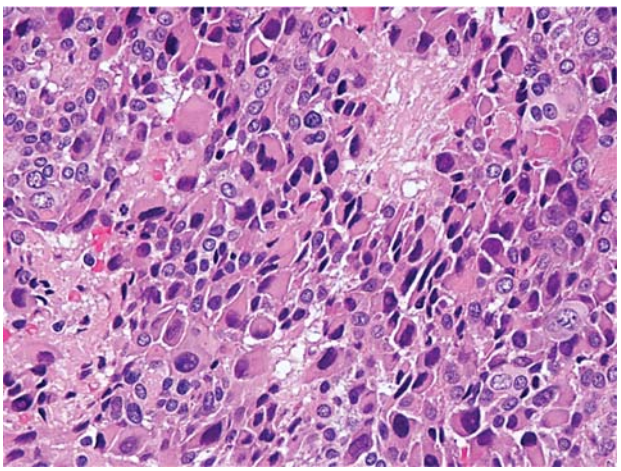


Figure 7.31. Carcinoma ex. pleomorphic adenoma exhibiting nuclear abnormalities, including pleomorphism, hyperchromatism, and large nucleoli with variations in cellularity within a pleomorphic adenoma. H&E staining, 400×. Source: Courtesy of Dr. Mark Bernstein.

Altered *PLAG1* or *HMGA2* genes have been detected in the majority of carcinoma ex. pleomorphic adenomas (CA-ex-PA). Although PLAG1 detection was specific for CA-ex-PA versus other carcinomas, its use as a standalone discriminatory test is limited by variable expression (Bahrami, et al. 2012).

Salivary Carcinosarcoma Salivary carcinoma has also been regarded and termed as a bona fide malignant mixed tumor. Consequently, these neoplasms contain elements, which are both carcinoma and sarcomatous in nature. Either or both components are expressed in metastatic lesions. Although carcinosarcomas may develop on their own, others arise in association with or within benign mixed tumors. The majority of tumors occur in the major salivary glands where patients have presented clinically with swelling, pain, nerve palsy, and/or ulceration. These tumors are extremely unusual with only a few cases being acknowledged by the AFIP (Ellis and Auclair 2008). Carcinosarcoma is an aggressive, high-grade malignancy with a survival of 3.6 years (Stephen, et al. 1986; Taki, et al. 2013).

Microscopically, carcinosarcomas always contain elements of both carcinoma and sarcoma. The sarcoma portion usually predominates over the other segment. The sarcomatous segment is usually represented by chondrosarcoma but other

types such as fibrosarcoma or osteosarcoma have been identified.

Sialoblastoma Sialoblastoma is an extremely rare neoplasm of major salivary glands with less than 20 cases identified in the literature. Tumors of the ductal or secretory epithelial cells of salivary gland are exceedingly rare in children <2 years of age. The sialoblastoma has been recognized and usually presents at birth or shortly thereafter. These tumors are composed of basaloid and myoepithelial cells that resemble the developing salivary anlage. The sialoblastoma have been reported under a variety of names such as congenital basal cell adenoma, basal cell adenoma, basaloid adenocarcinoma, and congenital hybrid basal cell adenoma-adenoid cystic carcinoma (Choudhary, et al. 2013). It has been suggested that these tumors be divided into benign and malignant lesions based on cytologic features and patterns of growth that include nerve and vascular invasion and necrosis. Brandwein, et al. (1999) suggested caution should be used in designating aggressive (malignant) and non-aggressive (benign) sialoblastoma on the basis of histomorphology alone (Batsakis and Frankenthaler 1992; Ellis and Auclair 2008).

Metastasizing Mixed Tumor Metastasizing mixed tumor is an uncommon histological benign salivary gland neoplasm that enigmatically metastasizes. Reportedly, there are long intervals occur between the diagnosis of a primary "benign" tumor and the metastases. The histological attributes of the metastatic lesions are essentially those that epitomize pleomorphic adenoma (Ellis and Auclair 2008). The majority of these benign lesions occur in the major salivary glands as a single, well-defined mass. Metastases have been described in the lung, lymph nodes, and bone. Interestingly, metastases or recurrences may occur up to 26 years after excision of the primary neoplasm (Schneider, et al. 1977; Santaliz-Ruiz, et al. 2012).

Rare Carcinomas

Primary Squamous Cell Carcinoma

Primary squamous cell carcinoma is a rare neoplasm of salivary glands. This neoplasm occurs in the parotid gland approximately nine times more frequently than in the submandibular gland; with a partiality towards males (Spitz and Batsakis 1984; Sterman, et al. 1990; Gaughan, et al. 1992; Ellis and Auclair 2008). Patients generally present with an asymptomatic mass in the parotid region. However, with progression symptoms may comprise pain and/or facial nerve palsy (Shemen, et al. 1987). Identification of these lesions requires segregating this primary carcinoma from metastatic disease originating from other head and neck or oral occurrences (Ellis and Auclair 2008). The diagnosis of primary disease probably cannot be made in minor salivary glands because of the size of the glands and proximity to mucosa that is vulnerable to develop squamous or epidermoid carcinoma (Ellis and Auclair 2008). Existing literature suggests that preceding exposure to ionizing radiation increases the risk for developing primary salivary squamous carcinoma; however, the sample size used in these studies was meager (Schneider, et al. 1977; Spitz and Batsakis 1984; Shemen, et al. 1987). The frequency of this primary salivary squamous carcinoma has ranged from 0.9 to 4.7% (Ellis and Auclair 2008). AFIP series have indicated that over a 10-year interval primary squamous cell carcinoma encompassed 2.7% of all tumors; 5.4% of malignant tumors, 2.5% of parotid neoplasms, and 2.8% of submandibular tumors; with an average age of 64 years (Ellis and Auclair 2008). Primary salivary gland squamous carcinoma is graded similar to extrasalivary squamous or epidermoid carcinomas; utilizing (low, intermediate, and high) degree of differentiation (Speight and Barrett 2002). The prognosis for these primary salivary gland cancers is dire with an 18% 10-year survival rate (Shemen, et al. 1987).

The histopathology of primary squamous cell carcinoma arising in salivary glands is not unlike those arising elsewhere (Figures 7.32, 7.33). These tumors are predominately keratin producing but several are poorly differentiated. Nerve involvement is quite common. Special stains for intracellular mucin production are often needed to rule out high-grade mucoepidermoid carcinoma masquerading as a primary squamous cell lesion.

Epithelial-Myoepithelial Carcinoma

Epithelial-myoepithelial carcinoma (EMC), also designated by some as adenomyoepithelioma, clear cell adenoma, tubular solid adenoma, monomorphic clear cell tumor, glycogen-rich adenoma, glycogen-rich adenocarcinoma, clear cell carcinoma, and salivary duct carcinoma, is an uncommon, low-grade epithelial neoplasm

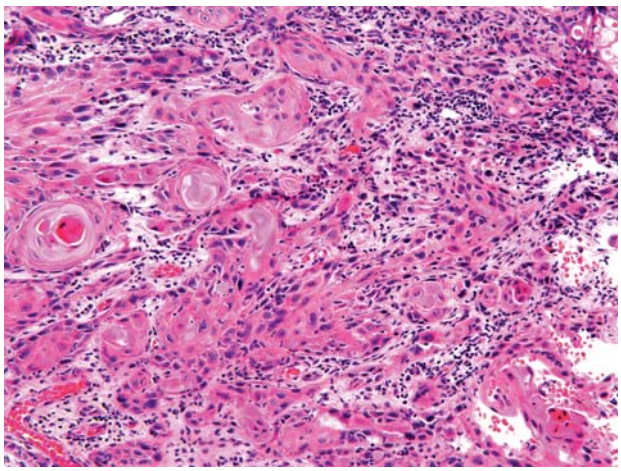


Figure 7.32. Primary squamous cell carcinoma arising within a parotid gland. Note the large amount of keratin production in this moderately differentiated tumor. H&E staining, 200×.

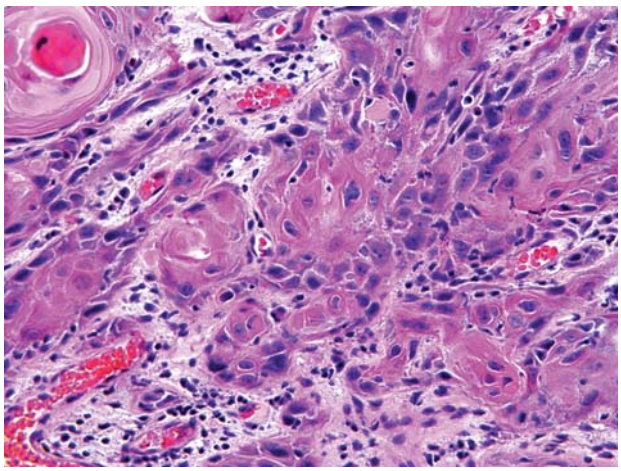


Figure 7.33. Closer view of case Figure 7.32 exhibiting atypical nuclear features. H&E staining, 400×.

composed of variable proportions of ductal and large, clear-staining, differentiated myoepithelial cells. These neoplasms make up ~1% of all epithelial salivary gland tumors (Batsakis, et al. 1992; Ellis and Auclair 2008). Epithelial-myoepithelial carcinomas are principally limited to the parotid glands. The lesions commonly present as localized painless swellings, although larger lesions maybe associated with pain or compromise of the facial muscle tone (Daley, et al. 1984; Collina, et al. 1991). The best current data indicates that the mean age of patients with these lesions is ~60 years with a gender bias of 60% towards females

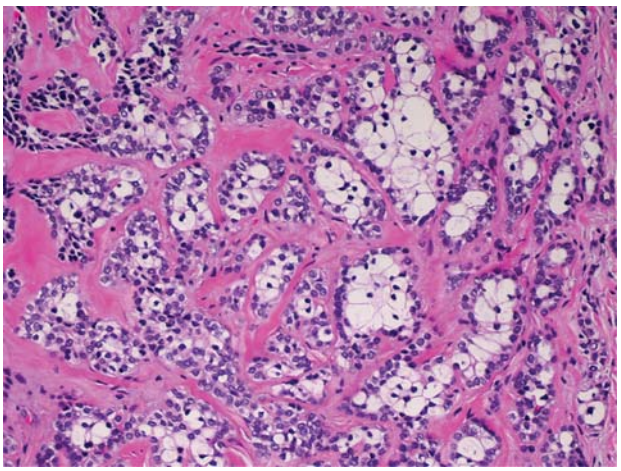


Figure 7.34. Myoepithelial carcinoma of salivary gland. Note the larger clear cells as well as the smaller epithelial cells. Each group of cells is surrounded by a dense fibrous stroma. H&E staining, 200×.

(Ellis and Auclair 2008). Although these tumors have a propensity to metastasize to parotid and cervical lymph nodes, and may on rare occasion may give rise to distant metastasis and death, these tumors are generally regarded as low-grade carcinomas with a high frequency of recurrence (Collina, et al. 1991; Batsakis, et al. 1992; Simpson, et al. 1991; Noel and Brozna 1992; Arora, et al. 2013).

The histology of the epithelial myoepithelial carcinoma is relatively unique. Most lesions are well-defined and occasionally encapsulated. The tumors themselves are made of up two cell populations: large, elongated clear cells and smaller cuboidal ductal cells (Figure 7.34). Occasionally, one encounters an EMC comprised almost completely of clear cells. Immunochemically the clear cells stain as myoepithelial cells. The majority of these tumors show little in the way of atypia with only occasional pleomorphism described.

Anaplastic Small Cell Carcinoma

Anaplastic small cell carcinoma is regarded by many as a neuroendocrine carcinoma (Gnepp and Wick 1990; Perez-Ordonez, et al. 1998; de Vicente Rodriquez, et al. 2004). These tumors often appear with the cells arranged as sheets, strands, and nests (Figure 7.35). The cells are slightly larger than a lymphocyte and possess oval, hyperchromatic nuclei, limited cytoplasm, and generally have a high mitotic index. Rarely pseudorosettes are

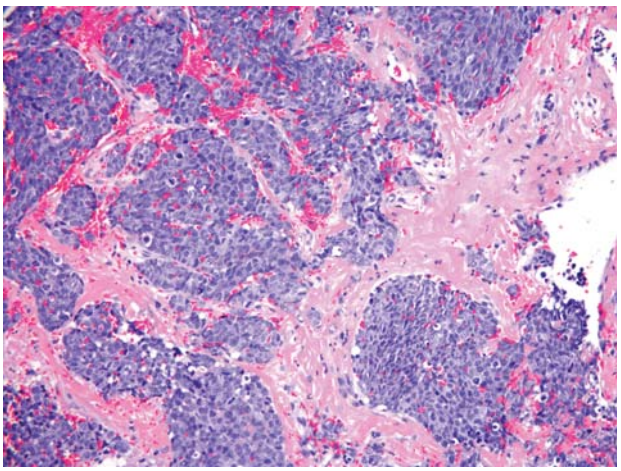


Figure 7.35. Anaplastic small cell carcinoma arranged in groups. Note the lack of cellular organization. H&E staining, 200×.

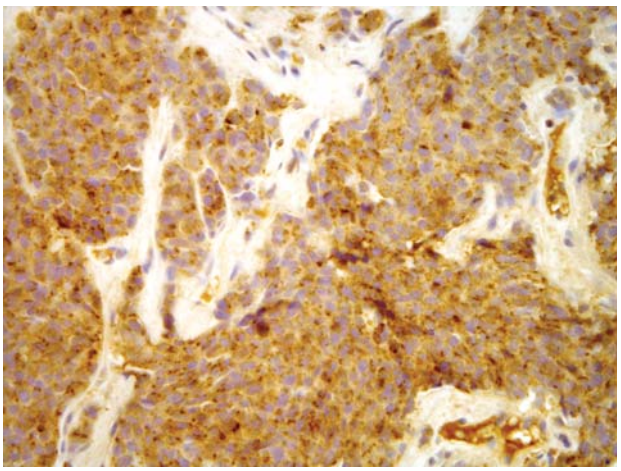


Figure 7.36. Same anaplastic small cell carcinoma as in Figure 7.35. This immunostain demonstrates the positive neuroendocrine features of these cells. Chromogranin immunostain, 200×.

encountered. The majority of these tumors stain with cytokeratins and EMA (Figure 7.36). A great number of them also stain with chromogranin, which supports their neuroendocrine origin.

Undifferentiated Carcinomas

Undifferentiated carcinomas of salivary glands are a group of rare malignant epithelial neoplasms that lack the specific light-microscopic morphologic features of other types of salivary gland carcinomas. These carcinomas are histologically similar to undifferentiated carcinomas that arise in other organs and tissues. Accordingly, metastatic carcinoma is a principal matter in the differential diagnosis of these tumors (Ellis and Auclair 2008). Three separate types are discussed arising within salivary gland; small cell undifferentiated carcinoma, large cell undifferentiated carcinoma, and lymphoepithelial carcinoma.

Small Cell Undifferentiated Carcinoma

Small cell undifferentiated carcinomas (SCUC) have also been termed extrapulmonary oat cell carcinomas. These primary malignant tumors are comprised of undifferentiated cells that do not exhibit neuroendocrine differentiation (Figure 7.37). As such, these lesions have been regarded as the undifferentiated (or non-endocrine) equivalent of the anaplastic small cell carcinoma. Small cell carcinoma has represented ~1.8% of all major salivary gland malignancies in the AFIP series. The tumors have a mean patient age of 56 years, with half of the cases presenting as asymptomatic parotid mass of only a few months duration (Perez-Ordonez, et al. 1998; Ellis and Auclair 2008). These are high-grade neoplasms with an estimated survival rate at 2 and 5 years of 70 and 46%, respectively (Gnepp, et al. 1986).

Some authorities differentiate between small cell undifferentiated carcinomas with neuroendocrine features versus those without these features. Immunostaining is the ideal way in distinguishing one from another. Chromogranin,

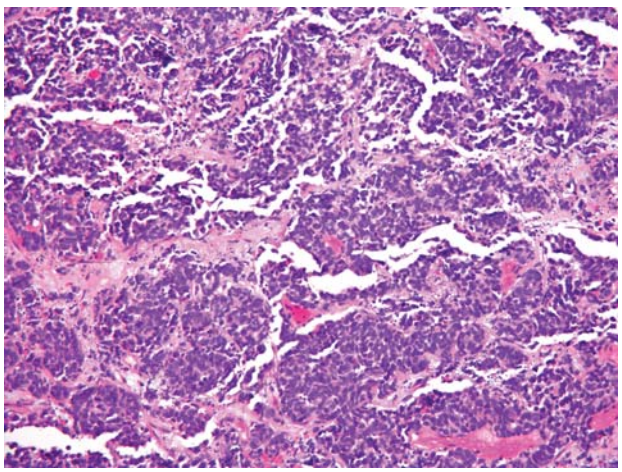


Figure 7.37. Small cell undifferentiated carcinoma of minor salivary gland. Note the complete lack of cell orientation. The cells are slightly larger than mature lymphocytes. H&E staining, 200×.

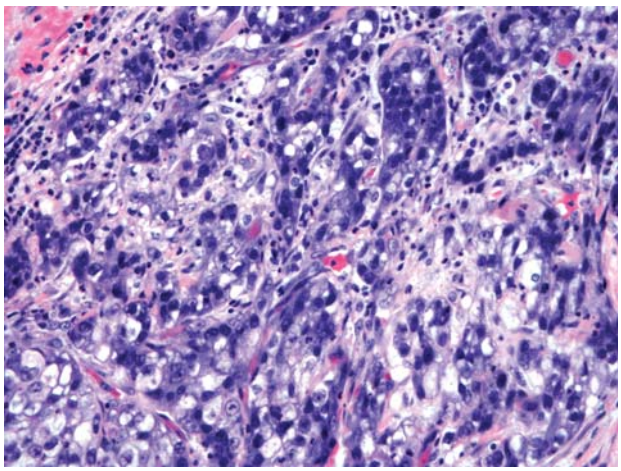


Figure 7.38. Large cell undifferentiated carcinoma of the submandibular gland. The entire tumor is composed of large, pleomorphic cells with no specific orientation. H&E staining, 200×.

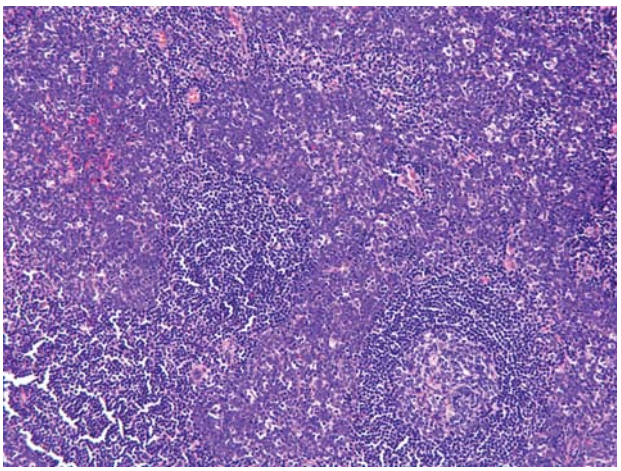


Figure 7.39. Lymphoepithelial carcinoma is composed of large malignant cells imbedded within a lymphoid stroma. Often times it is difficult to microscopically discern the malignant cells in this dense stroma. H&E staining, 100×.

synaptophysin, and NSE will all be reactive on those tumors with neuroendocrine features.

Large Cell Undifferentiated Carcinoma

Large cell undifferentiated carcinoma (LCUC) is a malignant neoplasm that lack all features of differentiation. However, in rare instances poorly formed duct-like structures have been described. Rapid growth of a parotid swelling is a common clinical presentation (Gaughan, et al. 1992). These tumors are high-grade lesions that commonly metastasize. Tumors that are T3 or greater have been noted to have a dire prognosis (Batsakis and Luna 1991). These neoplasms makes up only ~1% of all epithelial salivary gland tumors, with the vast majority of cases occurring in the parotid glands of elderly patients (Hui, et al. 1990; Batsakis and Luna 1991; Ellis and Auclair 2008).

Microscopically, these tumors lack features of acinar, ductal or myoepithelial differentiation. The cells are usually arranged in sheets separated by fibrous septae. In general, the cells of the LCUC are quite pleomorphic with many atypical mitotic figures seen (Figure 7.38). The cells of most LCUC react only with cytokeratin immunostains.

Lymphoepithelial Carcinoma

Lymphoepithelial carcinoma, which is also known as undifferentiated carcinoma with lymphoid stroma and carcinoma ex. lymphoepithelial lesion, is an undifferentiated tumor coupled with a dense lymphoid stroma; notably these lesions have been linked with Epstein–Barr virus infection (Leung, et al. 1995). Moreover, an unusually high incidence of these tumors have been identified most often in the parotid glands and to a less extend in the submandibular gland of Eskimo and Inuit populations (Bosch, et al. 1988; Ellis and Auclair 2008). Pain is a common presenting symptom; however, in 20% of patients, facial nerve involvement has been recorded (Borg, et al. 1993). Cervical lymph node metastasis has been a common finding at initial presentation and 20% of patients develop distant metastases within a 3-year period (Bosch, et al. 1988; Borg, et al. 1993).

Microscopically, this malignancy is comprised of dense lymphoid aggregates, often with germinal centers, all of which are cytologically benign. Within the lymphocytes are inconspicuous collections of large malignant epithelioid cells, many of which are arranged in a syncytial pattern (Figure 7.39). Immunochemically, these large malignant cells stain with cytokeratins and EMA but not with myoepithelial stains (Figure 7.40). Over half the cases are also EBV reactive.

Myoepithelial Carcinoma

Myoepithelial carcinoma is a very rare, malignant salivary gland neoplasm that almost entirely manifests myoepithelial differentiation. This tumor represents the malignant complement of benign

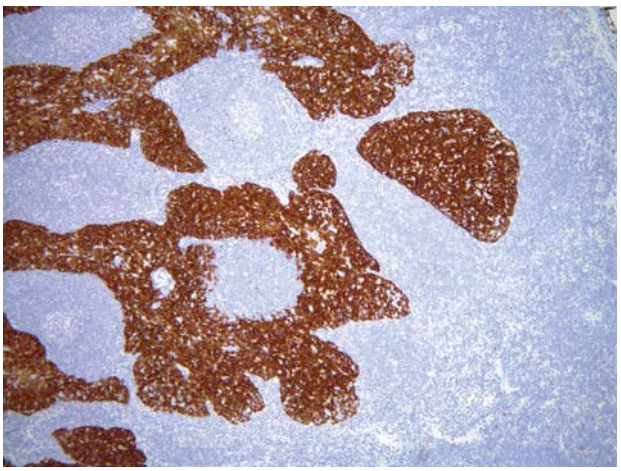


Figure 7.40. Immunohistochemistry is a great help in determining the exact tumor type in the same lesion as Figure 7.39. Note the ease with which stain depicts these large malignant cells. Pan cytokeratin (pan CK) immunostain, 100×.

myoepithelioma (Ellis and Auclair 2008; Kane, et al. 2010). The majority of patients, mean age of 55 years, present with a painless mass generally within the parotid gland (66%) (Ellis and Auclair 2008). The tumors are often intermediate-grade or high-grade carcinomas (Savera et al. 2000; Ellis and Auclair 2008). Interestingly, the histological grade of these neoplasms does not appear to correlate in a good way with clinical behavior, in that some tumors manifesting with a low-grade histologic pattern may behave in an aggressive manner (Savera, et al. 2000).

Myoepithelial carcinoma is composed of the same type cells as its benign counterpart. The cells range from clear cells to spindle cells to plasmacytoid cells and beyond. Unlike the benign variant, the malignant myoepithelioma demonstrates an invasive growth pattern which for the most part is the one distinguishing feature that is diagnostic. The majority of immunochemical stains used for myoepithelial cells are also reactive with the malignant variant, at least the better differentiated type.

Adenosquamous Carcinoma

Adenosquamous carcinoma (ASC) is an extremely uncommon malignant neoplasm that emerges concurrently from surface mucosa and salivary gland ductal epithelium. Although relatively common in other organs such as the uterus and cervix, the ASC is rare arising from salivary gland. These tumors possess histopathologic characteristics of squamous cell carcinoma and of adenocarcinoma. Analysis of the few cases reported seems to indicate that this is an extremely aggressive malignancy with a dismal prognosis (Ellis and Auclair 2008; Kusafuka, et al. 2013).

This diagnosis of adenosquamous carcinoma requires both well-defined surface squamous cell carcinoma and adenocarcinoma deeper within the specimen. These two elements do not intermingle or arise from one another, but separately. This type of cancer is easily confused microscopically with mucoepidermoid carcinoma. Other varieties of squamous cell carcinoma such as the adenoid squamous or the pseudo glanular variants can also be in the differential.

Mammary Analogue Secretory Carcinoma

Mammary analogue secretory carcinoma of salivary gland origin (MASC) resembles secretory carcinoma of the breast, which is characterized by strong S-100 protein, mammaglobin, and vimentin immunoexpression. MASCs generally are solitary, unencapsulated but well circumscribed tumors. These tumors may possess a prominent fluid-containing cystic component. MASCs are not highly infiltrative, perineural invasion is uncommon and lymphovascular invasion has not been described. MASCs often exhibit a lobulated growth pattern and are frequently composed of microcystic, tubular, and solid structures with abundant eosinophilic homogenous or bubbly secretions. Colloid-like material stains positively for periodic acid Schiff, with and without diastase, as well as for Alcian Blue. MASC has been shown to harbor a *t*(12;15) (p13;q25) translocation resulting in *ETV6-NTRK3* fusion product. Analysis for the presence of the *ETV6-NTRK3* fusion transcript has revealed positivity in both HG and low-grade components of MASC in a limited number of cases. Analysis of *TP53* and *CTNNB1* gene mutations in the HG component of MASCs, as well as detection of copy number aberration of *EGFR* and *CCND1* gene, has not revealed any abnormalities. Recognizing HG-transformed MASC and testing for *ETV6* rearrangement may be of potential value in patient treatment, because the presence of the *ETV6-NTRK3* translocation may represent a therapeutic target in MASC (Skalova 2010b, 2014; Bishop 2013). MASCs histologically may

mimic acinic cell carcinomas (ACC); recently, most non-parotid ACCs have been shown to represent MASC. However, the impact of diagnostic error is mitigated by the low-grade nature of MASCs and are not clinically aggressive (Bishop, et al. 2013).

Non-Epithelial Neoplasms

Lymphomas and Benign Lymphoepithelial Lesions

Lymphomas of the major salivary glands are typically non-Hodgkin lymphomas. AFIP reviews have indicated that non-Hodgkin lymphoma constituted 16.3% of all malignant tumors that arise in the major salivary glands. Moreover, non-Hodgkin lymphoma of the parotid gland comprised 80% of all cases (Ellis and Auclair 2008; Dispenza, et al. 2011; Shum, et al. 2014).

Patients with benign lymphoepithelial lesion and with Sjögren syndrome (Figure 7.41) are considered at an increased risk for development of non-Hodgkin lymphoma (Ihrler, et al. 2000; Abbondanzo 2001; Bernatsky, et al. 2006). The benign lymphoepithelial lesion is clinically distinguished by bilateral enlargement of the salivary and lacrimal glands (Figure 7.42). In affected glands the lesion is composed of distinctive myoepithelial islands bounded by lymphocytes, which possess germinal centers (Ellis and Auclair 2008). Immunophenotypically and genotypically, the lymphocytic component consist of polyclonal B-lymphocytes and T-lymphocytes. The B-cell lymphocytic component has been noted to result in clonal expansion and progress to a non-Hodgkin lymphoma. The majority of the non-Hodgkin lymphomas arising within benign lymphoepithelial lesions are marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT) (Ihrler, et al. 2000; Abbondanzo 2001). MALT lymphomas of the salivary glands, similar to their complement in other sites, are clinically indolent lesions (Harris 1991; Ellis and Auclair 2008). Occasionally such low-grade lymphomas can arise in other salivary gland tumors (Figure 7.43).

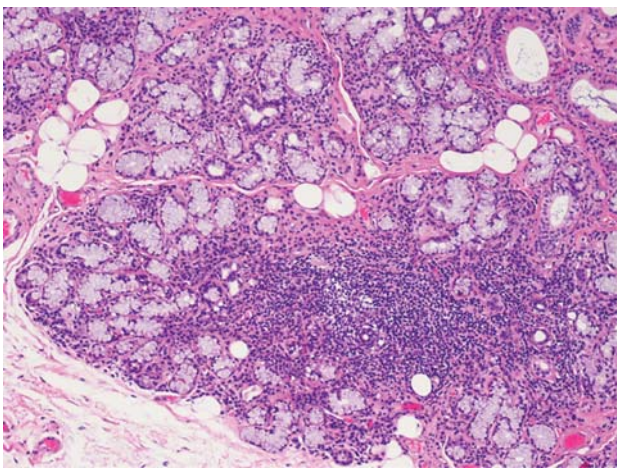


Figure 7.41. Sjogren syndrome: Lymphoid aggregate in mucous minor salivary gland in Sjogren syndrome. H&E staining, 100×. Source: Courtesy of Dr. Mark Bernstein.

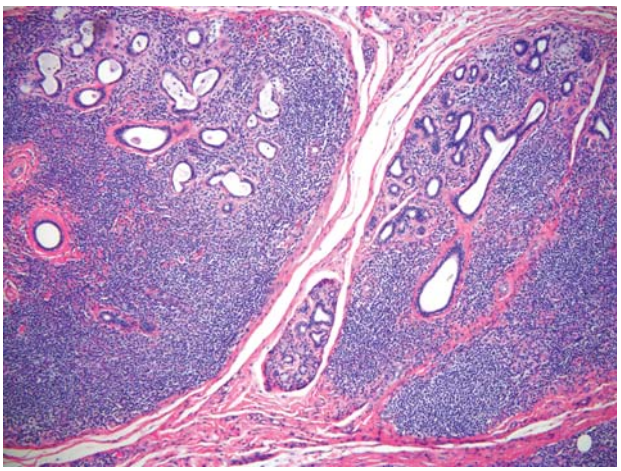


Figure 7.42. Benign lymphoepithelial lesion of the submandibular gland taken from a patient with Sjogren syndrome. Note the obliteration of normal glandular architecture by the lymphocytes. H&E staining, 100×.

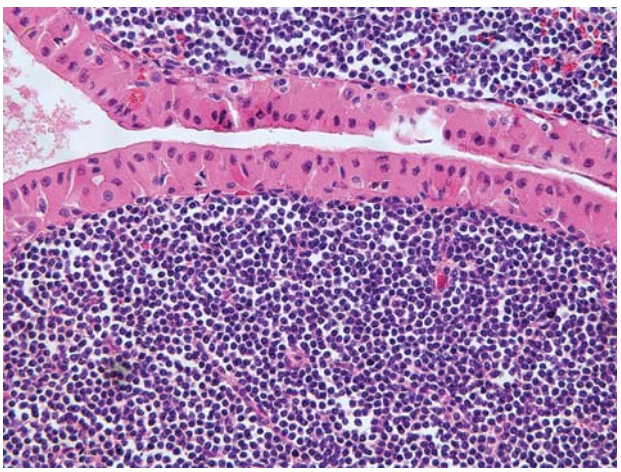


Figure 7.43. Small B-cell lymphoma arising within a Warthin tumor of major salivary gland. Note the diffuse lymphocyte pattern without germinal centers. H&E staining, 200×.

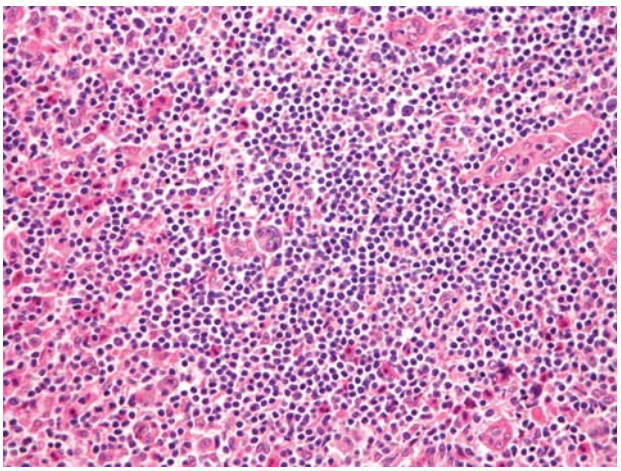


Figure 7.44. Hodgkin lymphoma within an intraparotid node. Note the classic Reed Sternberg cell in the middle of the field. H&E staining, 200×.

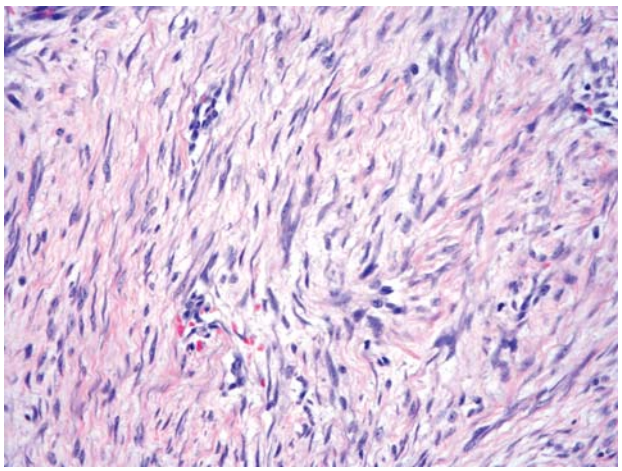


Figure 7.45. Benign spindle cell tumor of the parotid gland. After immunostaining, this lesion was determined to be an aggressive fibromatosis. H&E staining, 400×.

It is notable that primary non-MALT lymphomas of the salivary glands have been described and have a prognosis comparable to nodal lymphomas (Salhany and Pietra 1993). In contrast to non-Hodgkin lymphoma, Hodgkin lymphoma of the major salivary glands is most unusual. If present, Hodgkin lymphoma usually is contained only within the intraglandular nodes, unlike non-Hodgkin lymphoma that can efface an entire salivary gland with its malignant lymphoid cells (Figure 7.44). The majority of Hodgkin lymphomas arise in the parotid gland and manifest as either nodular-sclerosing or lymphocyte-predominant variants (Gleeson, et al. 1986; Ellis and Auclair 2008).

Mesenchymal Neoplasms

Mesenchymal neoplasms, both benign and malignant, make up 2–5% of all neoplasms that occur within the major salivary glands (Seifert and Oehne 1986).

Benign Mesenchymal Salivary Gland Tumors

The most common varieties of benign mesenchymal salivary gland neoplasms include hemangiomas, lipomas, lymphangiomas, and benign fibroblastic tumors (Figure 7.45). Treatment varies with the tumor type. Many of the vascular tumors found in the major salivary glands of infants will involute by the time the patient is 8–10 years old.

Malignant Mesenchymal Salivary Gland Tumors

Malignant mesenchymal salivary gland tumors include: malignant schwannomas, hemangiopericytomas (Figure 7.46), malignant fibrous histiocytomas, rhabdomyosarcomas, and fibrosarcomas, as well as others, and account for ~1.5% of all malignant tumors of the major salivary glands (Seifert and Oehne 1986; Luna, et al. 1991). Primary salivary gland sarcomas behave like soft tissue sarcomas in other locations; however, prognosis is governed by cell of origin, histological grade,

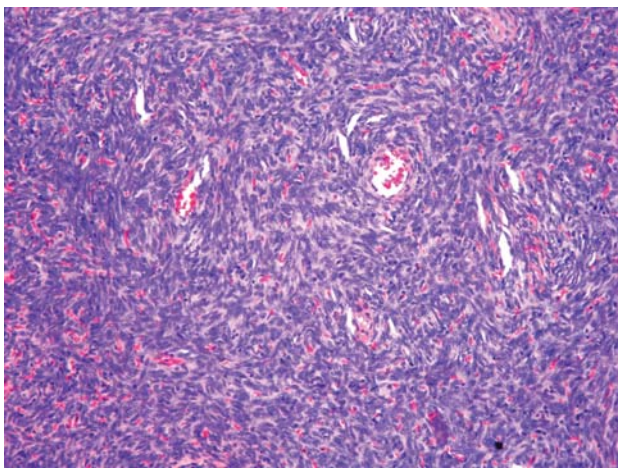


Figure 7.46. Another spindle cell tumor of the parotid gland, which was determined to represent a hemangiopericytoma. Note the high degree of cellularity. H&E staining, 200×.

tumor size, and stage (Auclair, et al. 1986; Luna, et al. 1991, Weiss 2001). The necessity to establish a primary salivary gland origin by excluding the likelihood of metastasis and direct extension from other adjacent locations cannot be overemphasized. Furthermore, the consideration of salivary gland carcinosarcoma should be considered when a sarcoma is identified within a major salivary gland (Ellis and Auclair 2008).

Malignant Secondary Neoplasms

Malignant neoplasms from primary sites outside the salivary glands may involve the major salivary glands by; (1) Direct extension from cancers that lie adjacent to the salivary glands, (2) Hematogenous metastases from distant primary tumors, and (3) Lymphatic metastases to lymph nodes within the salivary gland (Ellis and Auclair 2008). It has been estimated that ~80% of metastases to the major salivary glands are from primary tumors somewhere else in the head and neck. Direct extension into the parotid and submandibular glands is usually from squamous cell carcinomas of the skin and from melanomas. Basal cell carcinoma and Merkel cell carcinoma also involve the major salivary glands in a similar fashion though not as commonly. The parotid gland is the site for most metastases followed by the submandibular gland (Seifert, et al. 1986). The majority of metastases to the major salivary glands are squamous cell carcinomas and melanomas. More rarely, carcinomas from the lung, kidney, and breast, have been recognized presumably reaching these sites by a hematogenous route (Seifert, et al. 1986), (Batsakis and Bautina 1990). The peak incidence for metastatic tumors in the salivary glands is reported to be in the seventh decade of life (Ellis and Auclair 2008).

Grading and Staging of Salivary Gland Tumors

MOLECULAR SYSTEMATICS OF SALIVARY GLAND NEOPLASMS

One of the earliest attempts to use molecular systematics was to identify genes with altered expression in salivary adenoid cystic carcinoma (ACC). These studies observed expression of genes indicative of myoepithelial differentiation including those whose protein products are components of basement membranes and extracellular matrix (Frierson, et al. 2002). More recently, studies have indicated that the combination of copy number, gene express profiling, and identification of gene fusions and rearrangements provides an improved strategy for identification and classification of salivary neoplasms (Maruya, et al. 2004; Leivo, et al. 2005; Patel, et al. 2006).

The greatest progress in molecular systematics has been in the identification of gene fusions and rearrangements, which have led to the identification of new entities, provided insights with neoplastic entities in other organ systems, and identified potential therapeutic targets. For example, adenoid cystic carcinoma has been shown to be cytogenetically characterized by a tumor-type specific t(6;9)(q22–23;p23–24) translocation found as the sole anomaly in a subgroup of tumors. This translocation generates a fusion of the *MYB* proto-oncogene to the transcription factor gene *NFIB*. In the resulting *MYB-NFIB* fusion oncogene, which is highly overexpressed in adenoid cystic carcinoma, the 3′ part of *MYB*, including several target sites for negatively regulating microRNAs, is replaced by the last coding exon(s) of *NFIB*. The predicted *MYB-NFIB* fusion protein retains the DNA-binding and transactivation domains of wild type MYB, and is therefore expected to activate *MYB* target genes. Increased *MYB* expression reported in 17 of 20 adenoid cystic carcinomas with the *MYB-NFIB* fusion, but also in 14 of 20 fusion-negative adenoid cystic carcinomas. Collectively, these findings indicate that *MYB* over-expression, as a result of the *MYB-NFIB* fusion or through alternative mechanisms, is a significant feature of most salivary ACCs, suggesting that *MYB* may be involved in ACC development and could be a potential target to develop novel therapeutic strategies for ACC treatment (Mitani, et al. 2010).

Similarly, pleomorphic adenomas have been cytogenetically demonstrated to harbor specific chromosomal aberrations, most of which result in fusion genes involving *PLAG1* on 8q12 or *HMGA2* on 12q13–15. Several fusion partners including *CTNNB1*, *CHCHD7*, *LIFR*, and *TCEA1* fused to *PLAG1*, and *FHIT*, *NFIB*, and *WIF1* fused to *HMGA2* have been identified. *PLAG1* is subsequently activated by the reciprocal chromosomal translocations and promoter swapping/substitution,

resulting in *PLAG1* protein over-expression. All pleomorphic adenomas examined have shown constant and specific immunohistochemical expression of *PLAG1* irrespective of detectable gene rearrangements, suggesting that the immunohistochemistry for *PLAG1* is diagnostically useful, and that over-expression of the *PLAG1* protein occurs by variable mechanisms (Matsuyama, et al. 2011).

The belief that PLAG1 alterations are specific for pleomorphic adenoma and carcinomas derived thereof has been supported by the demonstration that most carcinoma ex. pleomorphic adenomas (CA-ex-PA), regardless of morphologic subtype, carry altered *PLAG1* or *HMGA2* genes, and that FISH for *PLAG1*, along with immunohistochemistry for *PLAG1*, discriminate CA-ex-PA from its de novo carcinoma counterpart (Bahrami, et al. 2012). Moreover, analysis of *PLAG1* and *HMGA2* rearrangements in salivary duct carcinoma (SDC) and examination of the role of precursor lesions have revealed that a large proportion of SDCs arise in pleomorphic adenomas (PAs), with or without residual evidence of a PA. Meanwhile, a small proportion of SDCs arise in low-grade cribriform cystadenoma (LGCCCs) or within ductal carcinoma in situ. Furthermore, utilization of *PLGA1* expression has shown that although myoepithelial tumors of the salivary glands show some parallel features with pleomorphic adenoma. These morphological similarities, and the known pathogenetic association of pleomorphic adenoma and malignant salivary gland tumors with myoepithelial differentiation, has not implicated PLAG1 in the development of salivary myoepithelial tumors since the proportion of 8q12-alterations in these tumors is very low (Friedrich, et al. 2012).

Among mucoepidermoid carcinomas (MEC) the recognition of a chromosomal translocation *t*(11;19) that generates a fusion oncogene has shown the *MECT1-MAML2* gene fusion is a highly specific genetic alteration in MEC with predominance in low-grade and intermediate-grade tumors (Miyabe, et al. 2009).

The gene fusion of *EWSR1-ATF1* fusion has been shown as a consistent finding in HCCC, with novel breakpoints described (*EWSR1* exon 11 and *ATF1* exon 3), and was the first finding of this fusion in an epithelial neoplasm. These findings allow HCCC to be distinguished from its mimics, such as epithelial-myoepithelial carcinoma and mucoepidermoid carcinoma, which have not been shown to harbor *EWSR1* (or *ATF1*) rearrangement (Antonescu, et al. 2011). Furthermore, HCCC was also negative for the POU5F1 rearrangement found in SMET, and for the *PBX1* or *ZNF444* rearrangements in other SMETs (Antonescu, et al. 2011; Thway, et al. 2012).

In that HCCCs possess mucinous features reminiscent of MEC the search for *MAML2* rearrangements led to the discovery that 82% of HCCC carry a *EWSR1* rearrangement by FISH, suggesting that HCCC is not a salivary equivalent of SMET. Subsequently, clear cell odontogenic carcinoma (CCOC) and HCCC were examined for EWSR1 rearrangement, previously having recognized that these two tumors had extensive morphologic and immunohistochemical overlap (Bilodeau, et al. 2012). Notably, a *EWSR1* rearrangement was found in 11/12 (92%) HCCCs and 5/8 (63%) CCOCs, suggesting that either CCOC represents a central example of HCCC or that CCOC represents an "odontogenic analogue" to HCCC (Weinreb 2013).

Mammary analogue secretory carcinoma of salivary gland origin (MASC) is a recently described tumor resembling secretory carcinoma of the breast characterized by strong S-100 protein, mammaglobin, and vimentin expression. This relationship was further substantiated by the demonstration that these salivary gland tumors possess a *t*(12;15)(p13;q25) translocation resulting in *ETV6-NTRK3* fusion between the ETV6 gene on chromosome 12 and the *NTRK3* gene on chromosome 15. The resulting transcript encodes and chimeric oncoprotein consisting of the helix-loop-helix (HLH) protein dimerization domain of *ETV6* fused to the protein tyrosine kinase (PTK) domain of *NTRK3* (Wai, et al. 2000).

Although molecular genomic and proteomic profiles are beginning to impact our consideration of many neoplasms, except for breast, the surgical pathologists are still guided in large part by histological grade and evidence of invasion particularly when evaluating salivary gland tumors. Histological grading of salivary gland carcinomas along

with clinical staging are the two most important considerations in determining the treatment and prognosis. Interestingly, clinical stage appears to be a more important prognostic indicator than histological grade (Speight and Barrett 2002; Ellis and Auclair 2008).

Generally, grading is used for mucoepidermoid carcinomas, adenocarcinomas, NOS, adenoid cystic carcinomas, and squamous cell carcinomas (Speight and Barrett 2002; Ellis and Auclair 2008). Whereas other salivary gland carcinomas are generally collectively categorized according histologic grade (Spiro, et al. 1978; Stephen, et al. 1986; Goode, et al. 1998; Guzzo, et al. 2002; Ellis and Auclair 2008) (Table 7.2).

Table 7.2. Grading of salivary gland tumors

Low grade
Acinic cell carcinoma
Basal cell adenocarcinoma
Clear cell carcinoma
Cystadenocarcinoma
Epithelial-myoepithelial carcinoma
Mucinous adenocarcinoma
Polymorphous low-grade adenocarcinoma
Low grade, intermediate grade, and high grade
Adenocarcinoma, NOS
Mucoepidermoid carcinoma[a]
Squamous cell carcinoma
Intermediate grade and high grade
Myoepithelial carcinoma
High grade
Anaplastic small cell carcinoma
Carcinosarcoma
Large cell undifferentiated carcinoma
Small cell undifferentiated carcinoma
Salivary duct carcinoma

[a]Some investigators consider mucoepidermoid carcinoma to be of only two grades: low grade and high grade. (Spiro, et al. 1978).

Staging of Salivary Gland Tumors

Tumors of the major salivary glands are staged according to size, extraparenchymal extension, lymph node involvement (in parotid tumors, whether or not the facial nerve is involved), and presence of metastases (Spiro, et al. 1975; Fu, et al. 1977; Levitt, et al. 1981; Kuhel, et al. 1992). Tumors arising in the minor salivary glands are staged according to the anatomic site of origin (e.g., oral cavity and sinuses).

The American Joint Committee on Cancer (AJCC) has designated staging by TNM classification (2002) (www.cancerstaging.net) (Table 7.3).

Summary

- The classification of salivary gland tumors takes into account their cellular derivation from epithelial, mesenchymal, or lymphoid origins.
- The rarity of some of these tumors, some of which display a wide spectrum of morphological patterns within the same tumor, as well as the existence of hybrid tumors results in a difficult task of differentiating benign from malignant tumors.
- For the most part, salivary gland tumors exist as benign or malignant neoplasms, with anticipated biologic behavior.
- The pleomorphic adenoma distinguishes itself as a benign tumor that may take on malignant characteristics and behavior.
- Some low-grade salivary gland malignancies represent highly curable neoplasms.
- Gene expression profiles may be used to predict biologic behavior of salivary gland malignancies. This notwithstanding, histologic grading and clinical staging remain the two most important considerations in determining the treatment of these neoplasms and their prognosis.
- Major salivary gland staging occurs according to size, extraparenchymal extension, lymph node involvement, the presence of metastases, and whether the facial nerve is involved as may occur in parotid tumors.

Table 7.3. Staging of salivary gland tumors

TNM Definitions

Major Salivary Glands

Primary Tumor (T)

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- T1: Tumor ≤2 cm in greatest dimension without extraparenchymal extension*
- T2: Tumor >2 cm but ≤4 cm in greatest dimension without extraparenchymal extension*
- T3: Tumor >4 cm and/or tumor having extraparenchymal extension*
- T4a: Tumor invades skin, mandible, ear canal, and/or facial nerve
- T4b: Tumor invades skull base and/or pterygoid plates and/or encases carotid artery

*Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.

Regional Lymph Nodes (N)

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension
- N2: Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension
  - N2a: Metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension
  - N2b: Metastasis in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension
  - N2c: Metastasis in bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension
- N3: Metastasis in a lymph node >6 cm in greatest dimension

Distant Metastasis (M)

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

AJCC stage groupings

Stage I T1, N0, M0
Stage II T2, N0, M0
Stage III T3, N0, M0
Stage III T1, N1, M0
Stage III T2, N1, M0
Stage III T3, N1, M0
Stage IVA T4a, N0, M0
Stage IVA T4a, N1, M0
Stage IVA T1, N2, M0
Stage IVA T2, N2, M0
Stage IVA T3, N2, M0
Stage IVA T4a, N2, M0
Stage IVB T4b, any N, M0
Stage IVB Any T, N3, M0
Stage IVC Any T, Any N, M1

Residual Tumor (R)

- RX-Presence of residual tumor cannot be assessed
- R0-No residual rumor
- R1-Microscopic residual tumor
- R2-Macroscopic residual tumor

Table 7.3. (*Continued*)

TNM Definitions

Minor Salivary Glands
Lip and Oral Cavity

Primary Tumor (T)
- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ
- T1: Tumor 2 cm or less in greatest dimension
- T2: Tumor more than 2 cm but ≤4 cm in greatest dimension
- T3: Tumor >4 cm in greatest dimension
- T4: (Lip) Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, i.e., chin or nose*
- T4a: (Oral Cavity) Tumor invades through cortical bone, into deep [extrinsic] muscle of tongue (genioglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face.
- T4b: Tumor involves masticator space, pterygoid plates, or skull base and/or encases internal carotid artery.

*Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify as T4.

Regional Lymph Nodes (N)
- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension
- N2: Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension
  - N2a: Metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension
  - N2b: Metastasis in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension
  - N2c: Metastasis in bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension
- N3: Metastasis in a lymph node >6 cm in greatest dimension

Distant Metastasis (M)
- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

AJCC Stage Groupings

Stage 0 Tis, N0, M0
Stage I T1, N0, M0
Stage II T2, N0, M0
Stage III T3, N0, M0
Stage III T1, N1, M0
Stage III T2, N1, M0
Stage III T3, N1, M0
Stage IVA T4a, N0, M0
Stage IVA T4a, N1, M0
Stage IVA T1, N2, M0
Stage IVA T2, N2, M0
Stage IVA T3, N2, M0
Stage IVA T4a, N2, M0
Stage IVB T4b, any N, M0
Stage IVB Any T, N3, M0
Stage IVC Any T, Any N, M1

(*Continued*)

Table 7.3. (*Continued*)

TNM Definitions

Histologic Grade (G)
- GX- Grade cannot be assessed
- G1-Well differentiated
- G2-Moderately differentiated
- G3-Poorly differentiated

Residual Tumor (R)
- RX-Presence of residual tumor cannot be assessed
- R0-No residual rumor
- R1-Microscopic residual tumor
- R2-Macroscopic residual tumor

Nasopharynx/Oropharynx

Primary Tumor (T)
- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma *in situ*

Nasopharynx
- T1: Tumor confined to the nasopharynx
- T2: Tumor extends to soft tissues
- T2a: Tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension.
- T2b: Any tumor with parapharyngeal extension
- T3: Tumor involves bony structures and/or paranasal sinuses
- T4: Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit, or masticator space.

Oropharynx
- T1: Tumor 2 cm or less in greatest dimension
- T2: Tumor more than 2 cm but ≤4 cm in greatest dimension
- T3: Tumor >4 cm in greatest dimension
- T4a: Tumor invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible.
- T4b: Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

Regional Lymph Nodes (N)

Nasopharynx
- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Unilateral metastasis in lymph node 9s), 6 cm or less, above the supraclavicular fossa
- N2: Bilateral metastasis in lymph node 9s), 6 cm or less, above the supraclavicular fossa
- N3: Metastasis in lymph node (s) 6 cm or greater and/or to supraclavicular fossa
  - N3a: Greater than 6 cm in dimension
  - N3b: Extension to the supraclavicular fossa

Oropharynx/Hypopharynx
- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension
- N2: Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension

Table 7.3. (*Continued*)

TNM Definitions

• N3: Metastasis in a lymph node >6 cm in greatest dimension
  ◦ N2a: Metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension
  ◦ N2b: Metastasis in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension
  ◦ N2c: Metastasis in bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension

Distant Metastasis (M) • MX: Distant metastasis cannot be assessed • M0: No distant metastasis • M1: Distant metastasis
AJCC Stage Groupings Nasopharynx
Stage 0 Tis, N0, M0 Stage I T1, N0, M0 Stage IIa T2a, N0, M0 Stage IIb T1, N1, M0 Stage IIb T2, N1, M0 Stage IIb T2a, N1, M0 Stage IIb T2b, N0, M0 Stage IIb T2b,N1, M0 Stage III T1, N2, M0 Stage III T2a, N2, M0 Stage III T2b, N2, M0 Stage III T3, N0, M0 Stage III T3, N1, M0 Stage III T3, N2, M0 Stage IVA T4, N0, M0 Stage IVA T4, N1, M0 Stage IVA T4, N2, M0 Stage IVB Any T, N3, M0 Stage IVC Any T, Any N, M1
Oropharynx/Hypopharynx
Stage 0 Tis, N0, M0 Stage I T1, N0, M0 Stage II T2, N0, M0 Stage III T3, N0, M0 Stage III T1, N1, M0 Stage III T2, N1, M0 Stage III T3, N1, M0 Stage IVA T4a, N0, M0 Stage IVA T4a, N1, M0 Stage IVA T1, N2, M0 Stage IVA T2, N2, M0 Stage IVA T3, N2, M0 Stage IVA T4a, N2, M0 Stage IVB T4b, Any N, M0 Stage IVB Any T, N3, M0 Stage IVC Any T, Any N, M1 Stage IVC Any T, Any N, M1

(*Continued*)

Table 7.3. (*Continued*)

TNM Definitions

Histologic Grade (G)
- GX-Grade cannot be assessed
- G1-Well differentiated
- G2-Moderately differentiated
- G3-Poorly differentiated

Residual Tumor (R)
- RX-Presence of residual tumor cannot be assessed
- R0-No residual rumor
- R1-Microscopic residual tumor
- R2-Macroscopic residual tumor

Nasal Cavity and Paranasal Sinsuses: Maxillary Sinus

Primary Tumor (T)
- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma *in situ*
- T1: Tumor confined to the maxillary sinsus with no erosion or destruction of bone
- T2: Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to the posterior wall of the maxillary sinus and ptygeroid plates
- T3: Invades any of the following: bone of the posterior wall of the maxillary sinus, subcutaneous tissues, floor of medial wall of orbit, ptyergoid fossa, ethmoid sinuses
- T4a: Tumor invades anterior orbital contents, skin of cheek, ptergoid plates, infratemporal fossa, cribiform plate, sphenoid or frontal sinuses
- T4b: Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of the trigeminal nerve V_2, nasopharynx, or clivus

Nasal Cavity and Ethmoid Sinus

Primary Tumor (T)
- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ
- T1: Tumor restricted to any one subsite, with or without bony invasion
- T2: Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
- T3: extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribiform plate
- T4a: Tumor invades any of the following: anterior orbital contents, skin of nose, or cheek, minimal extension to anterior cranial fossa, ptygeroid plates, sphenoid, or frontal sinuses
- T4b: Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V_2, nasopharynx, or clivus

Regional Lymph Nodes (N)
- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis

Table 7.3. (*Continued*)

TNM Definitions

- N1: Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension
- N2: Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension
  - N2a: Metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension
  - N2b: Metastasis in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension
  - N2c: Metastasis in bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension
- N3: Metastasis in a lymph node >6 cm in greatest dimension

Distant Metastasis (M)

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

AJCC Stage Groupings

Stage 0 Tis, N0, M0
Stage I T1, N0, M0
Stage II T2, N0, M0
Stage III T3, N0, M0
Stage III T1, N1, M0
Stage III T2, N1, M0
Stage III T3, N1, M0
Stage IVA T4a, N0, M0
Stage IVA T4a, N1, M0
Stage IVA T1, N2, M0
Stage IVA T2, N2, M0
Stage IVA T3, N2, M0
Stage IVA T4a, N2, M0
Stage IVB Any T, N3, M0
Stage IVB T4b Any N, M0
Stage IVC Any T, Any N, M1

Histologic Grade (G)

- GX- Grade cannot be assessed
- G1-Well differentiated
- G2-Moderately differentiated
- G3-Poorly differentiated

Residual Tumor (R)

- RX-Presence of residual tumor cannot be assessed
- R0-No residual rumor
- R1-Microscopic residual tumor
- R2-Macroscopic residual tumor

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Chapter 8

The Molecular Biology of Benign and Malignant Salivary Gland Tumors

Randy Todd DMD, MD, DMSc

Outline

Introduction: The Puzzle and the Promise

At present, the molecular biology of head and neck neoplasms is poorly understood. The vast majority of malignancies in this region originate from the squamous epithelium; therefore, the primary research focus has been on squamous cell carcinoma. Far less is known regarding the molecular mechanisms governing benign and malignant salivary gland tumors (Kaye 2006). Salivary gland tumors account for 0.4–13.5 cases per 100,000 (1–3% of head and neck carcinomas and 0.3% of all malignancies) in the United States (Eveson, et al. 2005; Vander Poorten, et al. 2012). Proposed risk factors include diet, history of radiation, genetic predisposition, nickel, tobacco use (Warthin tumor), and certain occupational exposures (rubber manufacturing, beauty shop workers) (Carlson, et al. 2013). How these risk factors translate into the molecular events that govern salivary gland tumor progression largely remains unclear. However, themes from the hallmarks of neoplasia found with tumors at other anatomic sites are proving true in salivary gland tumors. Therefore, by identifying molecular events observed in other tumors that are common in salivary gland neoplasms, we can begin to unravel some of the puzzle of these complex lesions and appreciate the promise of translating benchwork success into novel, biologically-based diagnostic and therapeutic strategies.

What are some of the challenges of studying the molecular biology of benign and malignant salivary gland tumors? First, salivary gland tumors are relatively uncommon. As stated earlier, salivary gland tumors account for a small percentage of head and neck neoplasms (Bansal, et al. 2012). Squamous epithelial lesions account for greater than 90% of tumors in this region. Second, a great deal of heterogeneity exists in the origin (by location and histology) of salivary gland tumors. Location is associated with certain predilections. The majority of tumors occur in the major salivary glands (parotid, submandibular, and sublingual) (Prenen, et al. 2008). Seventy percent of salivary gland tumors occur in the parotid gland, with 85% of those tumors being benign (Adelstein, et al.

Salivary Gland Pathology: Diagnosis and Management, Second Edition. Edited by Eric R. Carlson and Robert A. Ord.

2012). Yet 50–90% of minor salivary gland tumors are malignant (Lopes, et al. 1998). How certain salivary glands are more predisposed to malignant transformation is unclear. In addition to location, the cellular etiology of salivary gland neoplasms varies greatly. Salivary gland tumors are the most complex and diverse of all tumors (Bell and Hanna 2012). There is a great overlap in cell/tissue types (as well as variety in production/distribution of extracellular material) involved, leading to constant reclassification of these tumors (Adelstein, et al. 2012) (Figure 8.1). Furthermore, there is a great deal of heterogeneity with respect to clinical behavior. Aggressive behavior is inversely correlated with the fraction of myoepithelial cells (Batsakis, et al. 1989). High grade lesions have a greater tendency for lymphatic spread. Distant hematogenous metastases (primarily to the lungs, bones or liver) are more common in adenoid cystic carcinoma, adenocarcinoma not otherwise specified, carcinoma ex. pleomorphic adenoma, small cell carcinoma, and ductal carcinoma than other salivary gland cancers. Adenoid cystic carcinoma and polymorphous low grade carcinoma have a higher predilection for neurotropism. Third, salivary gland tumors tend to be very indolent: adenoid cystic carcinoma patients can live 10–20 years after diagnosis of malignant disease (Prenen, et al. 2008). Therefore, salivary tumors represent a significant challenge to study at the molecular level. Because they are uncommon, salivary gland tumors are very difficult to collect in sufficient numbers to validate target molecule findings. In addition, the histologic spectrum in the etiology of these tumors clouds direct comparisons: do tumor specimens within the same study set have similar clonal origin? As a result of being so rare and complex, understanding the molecular basis of these tumors suffers from lack of databases, materials, cell lines and animal models, as well as robust clinical studies (Bell and Hanna 2012). However, understanding the precise molecular underpinnings of salivary gland tumor progression promises novel, powerful modalities for patient management.

Advances in our understanding of the molecular events that govern human disease promise a personalized approach to medicine. Individual tumor biology will allow disease progression/response to be better predicted and offer

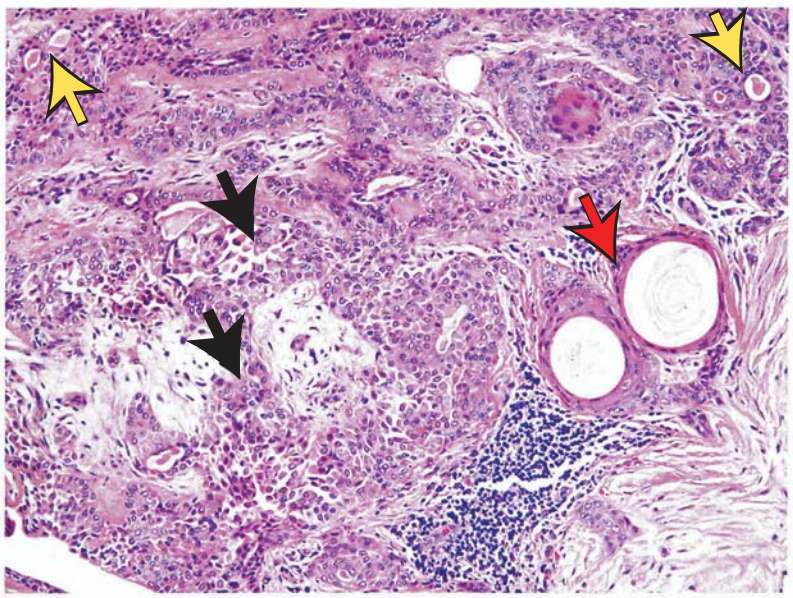


Figure 8.1. Why are salivary gland tumors so hard to study? Among the most important characteristics that make salivary gland tumors extremely difficult to study at the molecular level is the heterogeneity of the cellular and extracellular matrix composition and distribution. For example, pleomorphic adenoma, the most common benign salivary gland tumor, shows a wide array of normal and neoplastic cell types, as will a variety of cell products. In this view, the tumor is composed of a proliferation of glandular epithelium and myoepithelial cells (black arrows) within a variably hyalinized and myxoid stroma. Discrete ductal elements cuffed by myoepithelial cells are appreciated throughout (yellow arrows). Focal squamous differentiation/cystic degeneration is also appreciated (red arrow). Understanding the role and interactions of each cell type in the biology of the developing tumor is a complex task. (*Source*: Courtesy of Dr. Vikki Noonan, Division of Oral Pathology, Boston University Henry M. Goldman School of Dental Medicine, Boston, MA.)

novel treatment targets with fewer side effects (Dietel, et al. 2013). Diagnostic information will be obtainable not only from biopsy tissue, but blood and saliva (Sidranski 2002; Yoshizawa, et al. 2013). Molecular markers will be able to better diagnose and differentiate between salivary gland tumors (Dietel, et al. 2013). Identification of the molecular determinants of salivary gland tumor progression will better guide existing treatment protocols by ensuring prediction of treatment response and prognosis will be more reliable. Therapeutic options for salivary gland tumor patients will also be improved. Molecular events underlying disease progression will serve as novel therapeutic targets, alone or in combination. Both conventional and biologically-based treatment protocols will also be improved by reducing side effects, earlier identification of recurrent disease and reducing recurrent disease (Sidranski 2002; Kolch, et al. 2005; Taube, et al. 2005). Before exploring these exciting new possibilities, a review of salivary gland tumor cellular and molecular biology is necessary.

Salivary Gland Tumor Cell Biology

Today, the most clinically significant attributes of salivary gland tumors include the stage, histologic grade, anatomic site, patient age, and adequacy of tumor margin (Zarbo 2002). Over the last half century, the diversity of salivary gland neoplasms has been more greatly appreciated. Since 1954, there has been a doubling of benign (6 to 13) and malignant (10 to 23) salivary gland neoplasm categories (Nagao, et al. 2012). Two important classification schemes have emerged to define the origin/development, identification and behavior/prognosis of salivary gland tumors: histogenesis and morphogenesis. Both schemes explain salivary gland tumorigenesis in terms of stem cells (undifferentiated cells endowed with limitless capacity for self-renewal) and progenitor cells (stem cell daughter cells with a committed differentiation program and limited replication ability) emerging from the basic cellular framework of the salivary gland (excretory duct, striated duct, intercalated duct, and acinus) (Dardick and Burford-Mason 1993) (Figure 8.2). The newly identified salivary gland tumors (such as basal cell adenoma, polymorphous low-grade adenocarcinoma, epithelial-myoepithelial carcinoma, and salivary duct carcinoma) reflect a trend in pathology to look beyond the histogenesis of the disease and focus on morphogenesis (Zarbo 2002).

Histogenetic classification categorizes tumors based on the cell type within the normal salivary gland unit that is involved in tumor induction (Batsakis, et al. 1989; Sreeja, et al. 2014). According to histogenetic classification schemes, salivary gland tumors with terminal ductal, myoepithelial, and acinar differentiation were believed to originate from distal intercalated duct reserve cells (Figure 8.2a). Salivary gland tumors with large duct, squamous or mucinous cell differentiation originate from an excretory duct reserve cell. The dichotomy between cells of origin is believed to have clinical significance: tumors derived from the main ductal segments tend to be high grade and more aggressive, whereas tumors from the terminal ductal segments are low grade or benign (Bell and Hanna 2012). Myoepithelial cells in the terminal duct have been postulated to have "tumor suppressor" effects, leading to indolent and protracted behavior (Dardick, et al. 1982). Loss of myoepithelial cells coincides with more aggressive behavior. Several theories have been proposed as to the role of stem cells and progenitor cells: basal reserve theory, pluripotent unicellular theory, semipluripotent bicellular reserve cell theory, and the multicellular theory (Cheuk and Chan 2007). Central to all the histogenetic classification schemes is, (1) tumorigenesis does not originate in the acinus and (2) salivary gland tumor cell biologic behavior arises from either de-differentiation (loss of specialized features) or transdifferentiation (acquisition of another differentiated cell phenotype) (Dardick and Burford-Mason 1993). Due to difficulties clinically classifying certain tumors, as well as some inconsistencies with current cellular and molecular biology findings, an alternative classification scheme has been proposed (Dardick and Burford-Mason 1993).

Morphogenetic classification, a newer approach to salivary gland neoplasm classification, explains tumor anatomy based on three primary criteria: types of cell differentiation, patterns of tumor cell organization and synthesis/distribution of extracellular materials (Dardick, et al. 1982; Dardick and Burford-Mason 1993; Sreeja, et al. 2014) (Figure 8.2b). Two models exist in the morphogenesis classification scheme. The linear model proposes that stem cells give rise to two distinct progenitors: epithelial and myoepithelial. The stochastic model is a bidirectional pathway

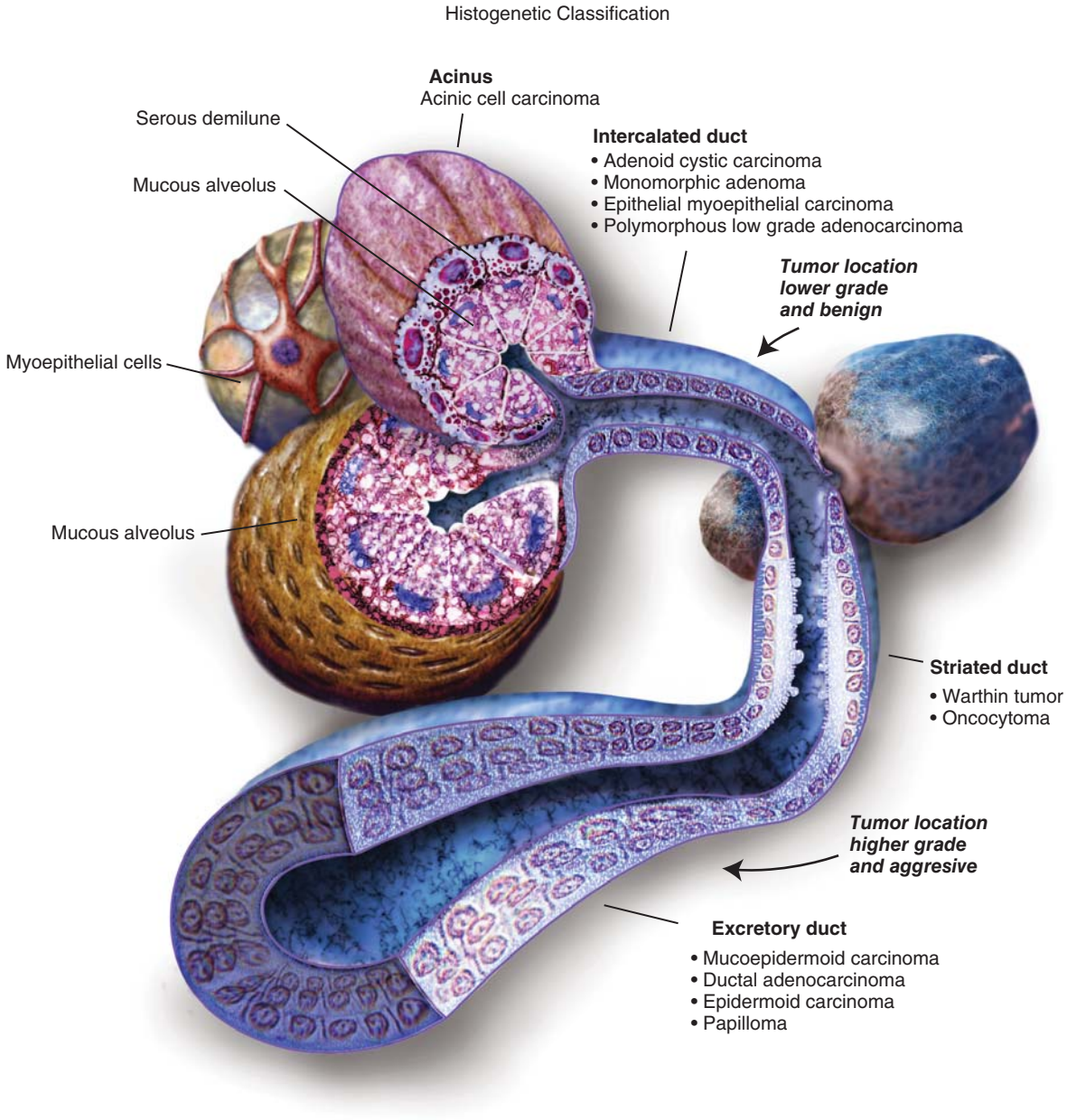


Figure 8.2. Histogenetic versus morphogenetic classification: How do salivary gland tumors arise? (a) Based on related histology between normal salivary gland development and salivary gland tumors, histogenetic classification proposes that heterogeneity is dependent on the location of the stem/progenitor cells. (b) Morphogenetic classification is based on (i) cell type (luminal cells, myoepithelial-like cells, basal-like cells), (ii) type and distribution of extracellular material, and (iii) pattern of cellular organization. Both schemes are important attempts at understanding the biology of salivary gland tumor development to better identify and predict the behavior of this heterogeneous group of neoplasms.

where two separate epithelial and myoepithelial progenitors are generated (Bell and Hanna 2012). In the salivary gland tumor, three morphogenetic tumor forms arise: luminal and myoepithelial cells; only luminal cells; only myoepithelial/basal cells (Dardick and Burford-Mason 1993). Salivary gland tumors differ based on variations of cell type (cuboidal/columnar sheets, islands, and

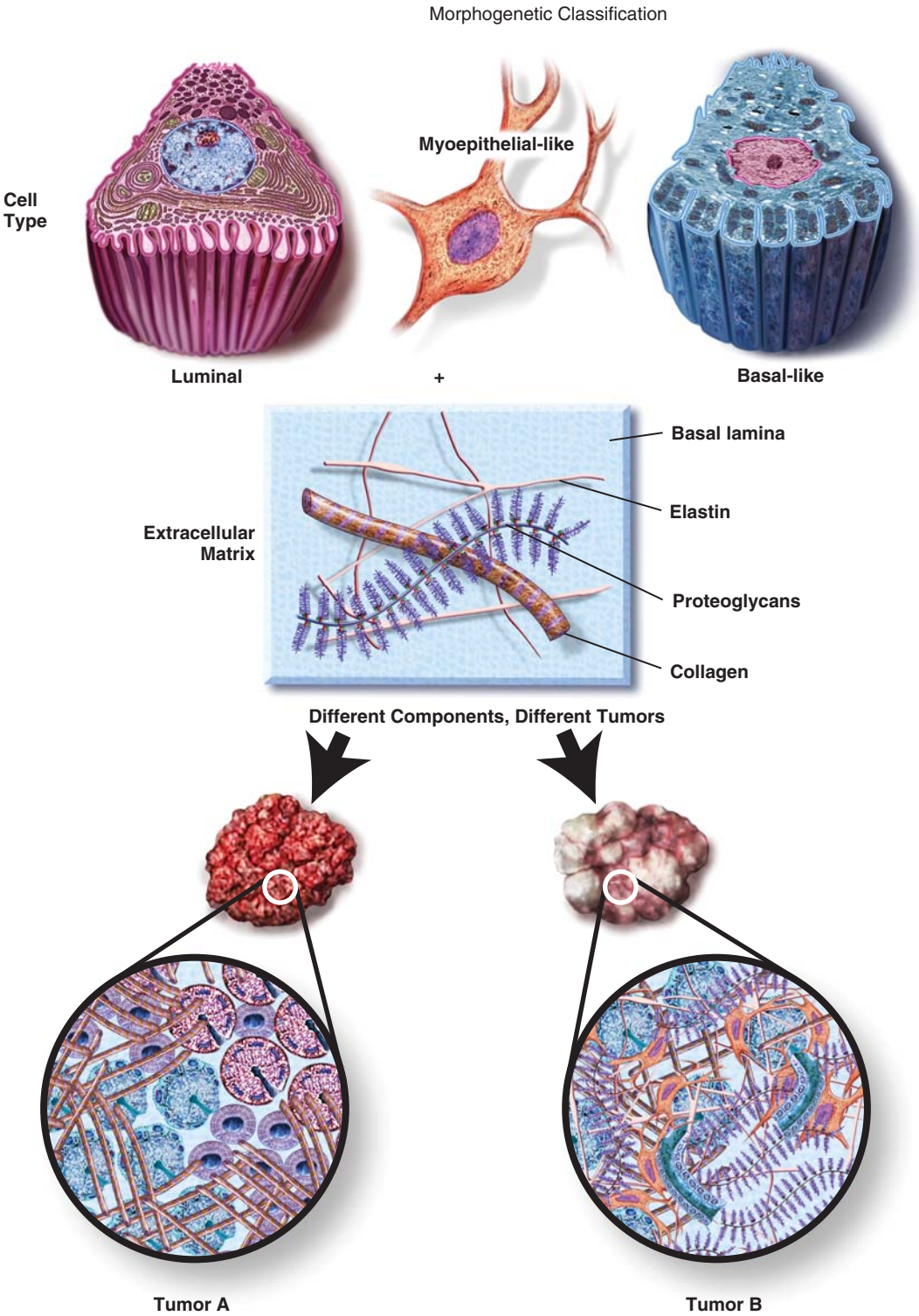


Figure 8.2. (*Continued*)

duct-like structures), myoepithelial cell type (spindle, plasmacytoid, clear), ductal:myoepithelial cell ratio, and presence/absence/type of extracellular material (Sreeja, et al. 2014). While histogenetic classification suggests de-differentiation occurs, morphogenesis classification proposes stem cell/progenitor cell inhibition of differentiation. In addition to the clinical importance of these two theories, the application of the histogenetic and morphogenetic models has important implications into the molecular events governing salivary gland tumorigeneis. The histogenetic classification is a more taxonomic approach. The morphogenetic approach is a more working classification that seeks to unravel overlapping histologic patterns using the biologic features of the tumor (Dardick, et al. 1985).

While hematoxylin-eosin staining remains the gold standard for salivary gland tumor diagnosis, immunohistochemistry (IHC) is more commonly being used to better understand the morphogenesis of the disease and enhance diagnostic accuracy (Nagao, et al. 2012). While few tumor type-specific markers are available, IHC marker panels can support and enhance the histological assessment. At present, most IHC markers target differentiation-related proteins (Nagao, et al. 2012). For example, markers of luminal/acinar epithelial differentiation might include the epithelial membrane antigen, carcinoembryonic antigen and low molecular weight keratins. Myoepithelial IHC markers include S-100, GFAF, vimentin, and high molecular weight keratins. More specific myoepthelial markers include calpontin, caldesmon, and alpha-smooth muscle actin. Tumor matrix production can be assessed by IHC detection of amylase, type IV collagen, and laminin. Organelle IHC staining can also help identify certain tumor types: mitochondria staining of oncocytic tumors and lysozyme staining for tumors with acinar differentiation. Differential diagnosis of salivary gland tumors with certain structural/architectural histological patterns can be aided by IHC examination using these marker panels (Zarbo 2002). Several salivary gland tumors exhibit a cribriform pattern. Clear cell salivary gland tumors not only can be distinguished from each other using EMA and calpontin, but from metastatic tumors such as renal cell carcinoma (by RCC or CD10) and melanoma (by Melan-A). Specimens with limited sample can be differentiated as either benign or malignant using proliferation markers such as Ki-67 and certain tumor-related proteins (discussed next). Lastly, salivary "undifferentiated carcinoma" (small cell carcinoma, large cell carcinoma, and lymphoepithelial carcinoma) can be distinguished from lymphoma if they stain positive for pan-CK and negative for leukocyte common antigen. While a more accurate classification of salivary gland tumors may improve diagnosis and provide a more precise therapeutic protocol, these biomarkers target differentiation proteins that can be used to separate one cell type from another. However, in addition to considering the biology of salivary gland cell types, it is important to view salivary gland tumor biology in the context of general tumor biology.

Molecular Biology of Salivary Gland Neoplasms

While identifying certain differentiation and matrix-associated molecules has aided in the classification and diagnosis of salivary gland tumors, the molecular mechanisms underlying salivary gland tumor progression are poorly understood. However, like in neoplasms at other anatomic sites, an understanding of the biologic determinants governing salivary gland tumors can better direct the classification, diagnosis, and management of the disease. Therefore, several lines of investigation regarding salivary gland tumor molecular biology are best appreciated in the general context of cancer molecular and tumor biology.

The fundamental paradigm of molecular biology is that deoxyribonucleic acid (DNA) is transcribed into messenger ribonucleic acid (mRNA), which is translated into protein (Figure 8.3a). Genes are the coding units within chromosomal DNA. The code is transferred from the nucleus to the cytoplasm via mRNA. There, the mRNA is used as a template to create proteins that are responsible for cellular structure and function. Therefore, while "disease genes" do refer to chromosomal DNA regions that are associated with a pathologic process, it is the alteration of the protein function that is the primary molecular/biochemical determinant. In cancer, "oncogenes" are normal genes altered in order to support tumorigenesis; "tumor suppressor genes" are inactivated regulatory genes that block tumor formation. However, it is really the overactive oncoproteins and inhibited tumor suppressor proteins that ultimately lead to tumor development. DNA, mRNA and proteins associated with tumor progression can also serve as diagnostic

and therapeutic targets. The following sections will consider the contribution DNA, mRNA, and proteins identified to be altered during tumorigenesis in general and salivary gland neoplasms, as well as how these events might be exploited clinically.

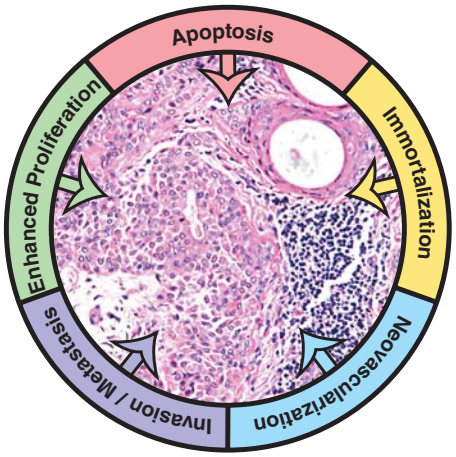
PROTEIN DYSREGULATION AND SALIVARY GLAND NEOPLASM PHENOTYPES

Proteins associated with tumor development are dysregulated through two primary mechanisms. First, a structurally intact ("normal" or "wild type") protein can be produced in altered quantities (or temporally and/or anatomically ectopic production or reduced/absent product). Second, an altered protein can be produced that may be overactive (or constituently active), inactive or abnormally interact with/sequester other proteins. With regard to tumor development, qualitatively or quantitatively altered proteins are often growth factors/extracellular ligands, cell surface receptors, cytoplasmic/nuclear secondary messengers, and transcription factors. Each of these proteins forms interconnecting signal transduction networks that control function in both heath and disease.

Tumor cells share several traits or phenotypes. Each contributes to a behavior that allows the tumor cell to outcompete its normal counterpart. These phenotypes do not appear simultaneously but accumulate in a preferred, but not absolute, order over time (Vogelstein and Kinzler 1998). Cellular behaviors commonly seen in tumor cells include enhanced proliferation, escape of apoptosis, immortalization, neovascularization, and, in the case of malignant tumors, invasion/metastasis (Figure 8.3b). While the mechanisms contributing to these phenotypes are much less defined than tumors at other anatomic sites, certain themes are emerging.

Enhanced Proliferation

Tumor cells can grow faster than their normal counterparts (Catalano, et al. 2013). Two fundamental mechanisms support this phenotype. First, tumor cells do not have to wait for a signal to start cell division due to the overactivity of growth promoting networks. Second, growth constraints are bypassed or inactivated in a tumor cell. Growth signals are overactivated in a tumor cell by generating its own proliferation signals through several different mechanisms, including production of its own growth factors, amplification of extracellular signals using over expressed (or constituently active) cell surface receptors, dependence on overactive intracellular messengers, or alteration of transcription factors that regulate the production other proteins (Black and Dinney 2008; Grandal



(a)

Figure 8.3. Paradigms in tumor biology: What are the cellular and molecular alterations of a cancer cell? (a) Neoplastic cells acquire several phenotypes that provide a selective advantage to their normal counterparts. These important characteristics include enhanced proliferation (due to overactive growth promoters and inactivated/suppressed growth inhibitors), failure to undergo apoptosis, immortalization, neovascularization (allowing tumors to increase in size and spread), and invasion/metastasis (allowing malignant cells to grow at sites remote from the primary tumor). These phenotypes are regulated by networks of signal transduction pathways. (b) Deregulation of these cell traits can occur through alterations in the fundamental molecular mechanisms governing normal cell behavior. Elements of signal transduction pathways include protein ligands (cytokines, growth factors, matrix molecules), cell surface ligand receptors, cytoplasmic secondary messengers, and nuclear transcription factors (*left panel*). In neoplastic salivary gland cells, large scale and small scale damage to chromosomal DNA (as well as epigenetic alterations) can lead to quantitative or qualitative changes in messenger RNA which carries the blueprint of the signal transduction proteins for production. Synthesis of quantitatively or qualitatively altered regulatory proteins can, in turn, lead to the phenotypes observed in tumor cells (*right panels*).

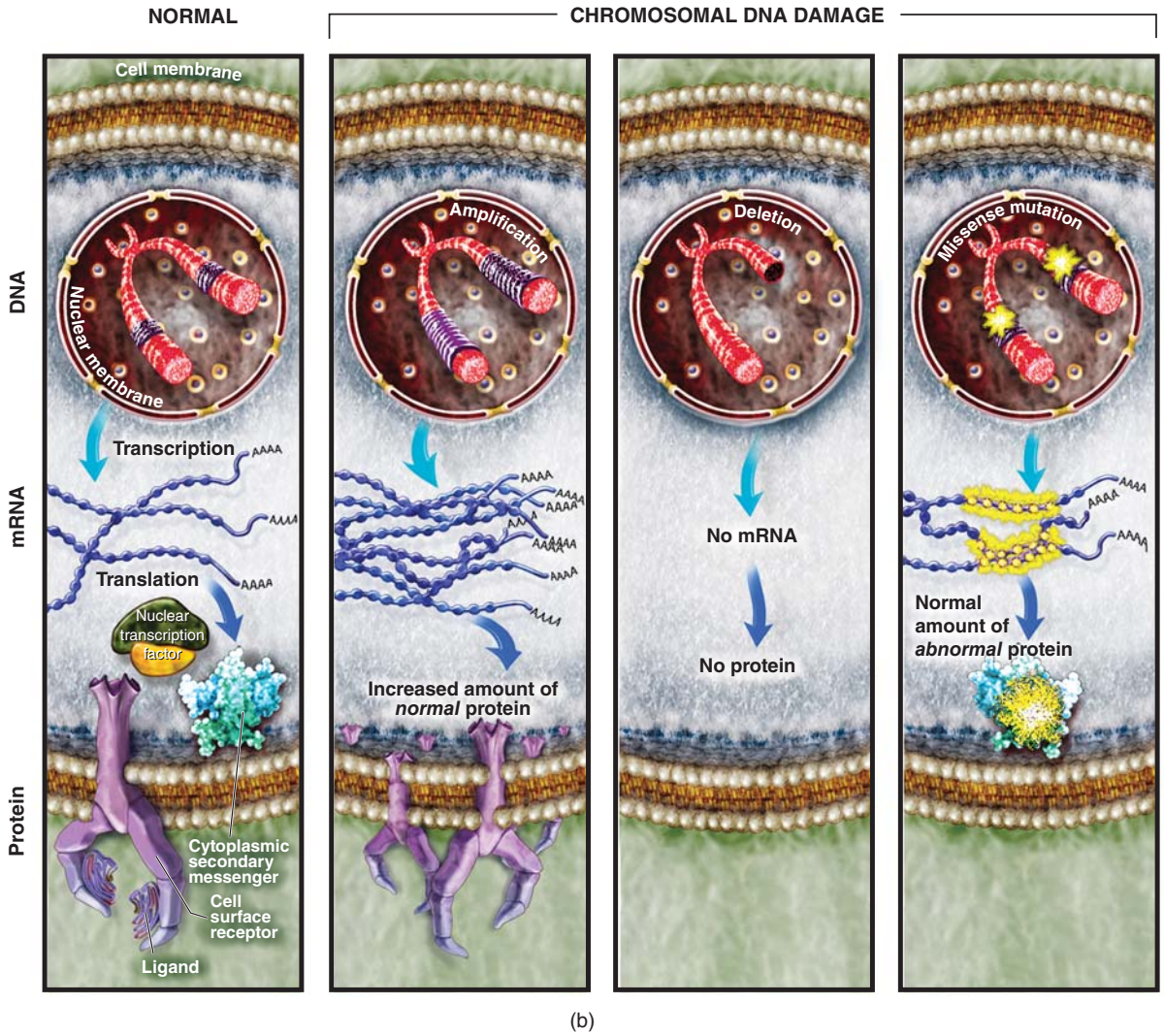


Figure 8.3. (*Continued*)

and Madshus 2008; Lee and Muller 2010; Smith, et al. 2010; Brognard and Hunter 2011).

Proliferation-associated proteins, which include extracellular ligands/ligand receptors, constituently functioning secondary messengers and nuclear transcription factors, have been shown to be overactive in various salivary gland neoplasms (Skalova and Leivo 1996) (Figure 8.4). Extracellular ligands and their receptors, such as the epidermal growth factor (EGF) and its receptor (EGFR), are aberrantly expressed in a variety of salivary gland cancers, such as adenoid cystic carcinoma and high grade mucoepidermoid carcinoma (Liu, et al. 2012; Ach, et al. 2013; Cros, et al. 2013; Nakano, et al. 2013). Part of the human epidermal growth factor receptor (HER) superfamily, EGFR (or HER-1) is joined by HER-2/NEU and HER-3 as receptors commonly overexpressed by adenoid cystic carcinomas (Todd and Wong 1999; Gibbons, et al. 2001). Expression of HER-4 in salivary gland tumors is less clear. A secondary messenger pathway downstream from EGF-EGFR binding, the PI3K-AKT pathway, is also dysregulated in acinic cell carcinoma (Diegel, et al. 2010). The Wnt/β-catenin pathway is also overactive due either to direct alteration of factors within the cascade or indirectly through loss of pathway inhibitors (WNT inhibitory factor-1) (Liu, et al. 2012). The SOX 4 transcription factor is also highly overexpressed in adenoid cystic carcinoma (Frierson, et al. 2002). In short, aberrantly

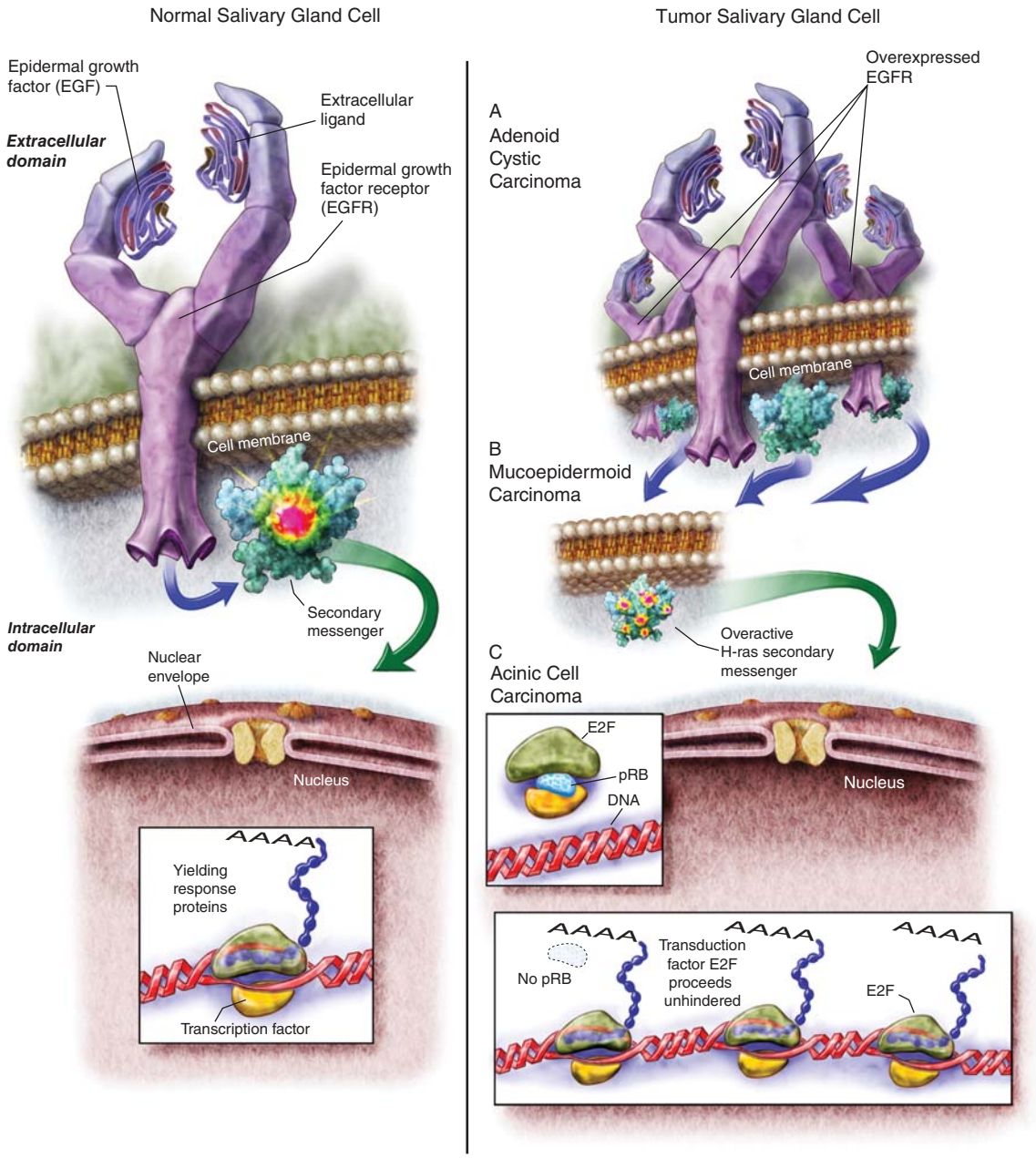


Figure 8.4. Enhanced cellular proliferation: How does protein deregulation lead to salivary gland tumor cell behavior? (*Left panel*) Important signal transduction pathways that regulate cellular proliferation are abrogated in salivary gland tumors. In normal cells, extracellular ligands bind to cell surface receptors. Ligand-receptor binding activates secondary messengers that regulate several functions, including the production of response proteins via nuclear transcription factors. (*Right Panel*) Qualitative or quantitative alteration of signal transduction proteins leads to a release from pathway regulation. (A) In adenoid cystic carcinoma, the epidermal growth factor receptor (EGFR) is overexpressed, leading to hypersensitivity of the cell to the many ligands that bind to EGFR. (B) The secondary messenger H-ras is constituently active (or activated independent of upstream stimuli) in mucoepidermoid carcinomas. (C) The cell cycle regulator pRb is downregulated in acinic cell carcinoma. Without pRb, the transcription factor E2F proceeds unhindered, thereby enhancing cellular proliferation programs. While there are many regulators within each signal transduction pathway, only one element needs to be altered to potentially change a phenotype like enhanced proliferation. However, networks of other pathways may limit some alterations from causing an overall cellular change.

expressed/active growth promoters appear to contribute to salivary gland neoplastic progression. While the important proliferation pathways are not fully defined for any particular salivary tumor, these pathways appear to be able to be disrupted by signals appearing in the microenvironment, at the cell surface, within the cytoplasmic signaling cascades, as well as through transcription factors that regulate other growth promoting molecules.

The second fundamental mechanism supporting enhanced proliferation is the loss of proteins that inhibit cell division (Lee and Muller 2010; Blanpain 2013). Proliferation is governed by an internal cell cycle clock that runs through four phases: a G1 or gap phase, an S phase where the cell duplicates its genetic material, a second gap phase (or G2), then an M phase where the cell divides (Vermeulen, et al. 2003). While each phase is tightly regulated, the primary checkpoint where the cell commits to cell division is at the restriction (or R) point at the end of G1 (Vermeulen, et al. 2003). Cells that do not pass R-point enter differentiation/senescence programs (Chandler and Peters 2013). The key regulator of R-point is the retinoblastoma protein (pRb) (Henley and Dick 2012). Cells that pass through R-point move irreversibly towards S phase due to the activity of the transcription factor E2F (Classon and Harlow 2002). Cell cycle progression is blocked at R-point when pRb binds E2F, thereby preventing the activation of the E2F-mediated pathways that ultimately lead to cell division (Dyson 1998). Loss of pRB activity allows progression through R-point/activation of E2F pathways unhindered. Many tumor cells suffer a reduction or loss of pRb (Manning and Dyson 2012). Neoplastic cells that have normal pRB levels frequently have a disruption upstream or downstream of pRb. In salivary gland tumors, the presence of pRB is variable. As expected, pRb is present in higher levels in normal verses benign and malignant salivary gland tumors (Liu, et al. 2005). However, downregulation of pRb appears to be more important in some salivary gland neoplasms more than others: pRb is infrequently altered in adenoid cystic carcinoma but abnormally expressed in acinic cell carcinoma, as well as many benign and malignant myoepithelial tumors (Yamamoto, et al. 1996; Shintani, et al. 2000; Etges, et al. 2004; Liu, et al. 2005; Vekony, et al. 2008).

Unregulated proliferation is not enough to generate a tumor. Other cellular checkpoints exist that inhibit rapid cellular division. A rapidly expanding cell mass can quickly outgrow its nutrient supply. Cells also have an inherent limit to the number of times it can divide, independent on the rate of that division. Lastly, the cell has a program to eliminate aberrant cells: apoptosis.

Evasion of Apoptosis

An important mechanism to remove damaged cells is apoptosis (Hanahan and Weinberg 2011). Key triggers of apoptosis include growth factor withdrawal, ionizing radiation, chemotherapy cytokine exposure, high calcium concentrations, nitric oxide, or oxidative stress (Fadeel and Orrenius 2005; Cheung, et al. 2006). An apoptotic cell is dismantled, condensed, and eventually eliminated by phagocytosis (Cheung, et al. 2006). Apoptosis can be initiated through external stimuli, as well as internal factors (Ouyang, et al. 2012). Cells with damaged proliferative regulatory pathways would normally be eliminated through apoptosis (Cheung, et al. 2006). Therefore, the pathways leading to apoptosis also have to be inactivated during tumorigenesis.

A major regulator of apoptosis is p53. In response to extracellular (such as UV radiation, ionizing radiation, hypoxia) and intracellular insults (such as DNA damage, oncogene signaling, transcriptional abnormalities), p53 induces cell growth arrest and DNA repair (Golubovskaya and Cance 2013). If the damage is too profound, p53 initiates apoptosis (Vogelstein and Kinzler 1992). Tumor cells can evade apoptosis by eliminating p53 function, either by reducing p53 quantitatively or altering p53 structure. Mutated p53 acts in a dominant negative manner, sequestering wild-type (or normal) p53 (Nag, et al. 2013). Like pRb, most human cancers subvert p53 directly or by abrogating upstream or downstream mediators in its pathway (Vogelstein and Kinzle 1992). Salivary gland tumor cells, particularly malignancies, do subvert apoptosis (Ben-Izhak, et al. 2007). In fact, in many cases, apoptosis assays, as well as specific apoptosis mediators, are believed to be useful in separating salivary gland cancers from their benign counterparts (Nagao, et al. 1998; Weber, et al. 2002), though this is not a universal finding (Karja, et al. 1997; Rosa, et al. 1997). While mutated p53 has been identified in a wide variety of salivary gland neoplasms, variations in findings are likely the result of varied experimental approach and specimen procurement (Deguchi, et al. 1993; Felix,

et al. 1996; Yin, et al. 2000; Kiyoshima, et al. 2001; Nagler, et al. 2003; Marques, et al. 2008; Ben-Izhak, et al. 2009). Like the pRb pathway, upstream and downstream elements of the p53 pathway (including c-MYC, MDM2, pAKT, and BCL-2) have been shown to be altered in various salivary gland neoplasms (Deguchi, et al. 1993; Rosa, et al. 1997; Nagao, et al. 1998; Nagler, et al. 2003; Marques, et al. 2008; Jin, et al. 2012).

Immortalization

Cells that can rapidly proliferate without being cleared through apoptosis still face another challenge: senescence. Under normal conditions, cells can divide a fixed number of times before they stop or senesce (Hayflick 1965). The major underlying mechanism for the halt is that chromosome caps or telomeres are exhausted. Loss of telomeres leads the ends of the chromosomes to stick to adjacent chromosomes if the cell is allowed to divide; therefore, cell division is halted (Shay and Wright 2005). The majority of tumor cells avoid senescence by synthesizing the enzyme telomerase that restores the chromosomal cap (Xu, et al. 2013). Initial reports suggest that malignant salivary gland cells exhibit telomerase activity, whereas expression in their benign counterparts is variable (Shigeishi, et al. 2011). EGFR may be an upstream positive regulator of telomerase in these tumors. Overexpression of pleomorphic adenoma gene-1 (PLAG-1) in salivary gland tumors also leads to a capacity for limitless cellular replication via the IGF-2 pathway (Declercq, et al. 2008).

Neovascularization

Cells require nutrients to fuel growth and a means to eliminate waste. Both processes cannot cross a gradient greater than 3–4 cell layers thick (Folkman 2006). Therefore, even cells with enhanced proliferative capability, absent apoptotic activity, and immortality will remain dormant unless a new blood supply arises to support that growth (Gimbrone, et al. 1972). Tumor cells must develop an "angiogenic switch" that supports new endothelial growth (Gimbrone, et al. 1972). Few incipient tumor masses develop this switch (Auguste, et al. 2005).

Like tumors at other anatomic sites, angiogenesis appears to be an important event in salivary gland tumor progression. Microvascular density increases in association with salivary gland tumors, though some controversy remains whether neovascularization is greater in malignant versus benign disease (Shieh, et al. 2009; Vidal, et al. 2013). Increased densities of mast cells and tumor-associated macrophages appear to be a cellular source of pro-angiogenic factors in salivary gland neoplasms (Shieh, et al. 2009; Vidal, et al. 2013). Vascular endothelial growth factor (VEGF) and NOTCH are important signaling pathways that support neovascularization in salivary gland tumors (Liu, et al. 2012; Andisheh Tadbir, et al. 2013; Margaritescu, et al. 2013; Bell et al. 2014). A significant number of salivary gland carcinomas (65%) express VEGF (Lim, et al. 2003). Tumor hypoxia leads to HIFα-HIFβ dimerization that, in turn, induces VEGF overexpression (Lim, et al. 2003). The activity of angiogenesis inhibitors is less defined. Thrombospondin-1 appears to be downregulated in salivary gland carcinomas while TIMP-2 is highly active in the stroma of pleomorphic adenomas (Kishi, et al. 2003; Zhang, et al. 2009b). Factors supporting angiogenesis, such as VEGF, are believed to correlate with tumor aggressiveness (Demasi, et al. 2012). In fact, angiogenesis and another important tumor phenotype, invasion and metastasis, share many overlapping cellular and molecular mechanisms of disease (Lequerica-Fernandez, et al. 2007; de Faria, et al. 2011).

Invasion and Metastasis

Tumor invasion is the primary phenotype that demarks benign from malignant disease (Comoglio and Trusolino 2002). While locally aggressive benign tumors may displace or destroy surrounding tissue, invasion marks the escape of the cancer cell into the surrounding "normal" stroma. Invasion is instigated by the cancer cell but is supported by underlying stromal cells (Talmadge and Fidler 2010). At the lead edge of invasion, enzymes are released to break down the basement membrane (Willis, et al. 2013). In the early stages of invasion, the cancer cell undergoes an epithelial-mesenchymal transition (EMT). Several cellular phenotypes are lost during EMT, including cell proliferation, certain differentiation genetic pathways, and altered E-cadherin expression (Cavallaro and Christofori 2004; Berx and van Roy 2009). However, EMT cells gain other phenotypes,

such as increased mobility, a fibroblast-like morphology, upregulation of stem cell-like programs and expression of N-cadherin (Mani, et al. 2008). Tumor stimulated neovasculature not only helps support cancer cell growth, but allows escape routes for the tumor to spread to remote sites (Samples, et al. 2013). Metastasis involves the intravasation of the cancer cell into the blood or lymphatic vessels; thereafter, the cancer cell extravasates into a distant organ site (Klymkowsky and Savagner 2009). The disseminated cancer cell then undergoes a second transformation, a mesenchymal-epithelial transition (MET), reverting the cell back to more static cellular programs leading to basement membrane synthesis, a return of cell polarity and restoration of differentiated functions (Ahmad and Hart 1996). The cascade(s) leading to the timing, mechanisms and tropism of metastasis are poorly understood (Hanahan and Weinberg 2011).

Invasion and metastasis are important (but very variable) themes in salivary gland tumor biology. Neoplasms like adenoid cystic carcinoma are not only locally invasive, but have a tropism for neural spread and a predisposition for late metastasis. Mucoepidermoid carcinoma tends to be locally invasive alone. Pathways leading to these invasion/metastatic phenotypic variations between salivary gland neoplasms are beginning to emerge. Like other cancers, matrix metalloproteinases appear to be an important event contributing to basement membrane destruction and invasion in a variety of salivary gland cancers (Nagel, et al. 2004; Luukkaa, et al. 2008; Luukkaa, et al. 2010a,b; Yang, et al. 2012). Transforming growth factor-β and E-cadherin alterations contribute to EMT in the early stages of salivary gland cancer invasion (Prabhu, et al. 2009; Ghahhari, et al. 2012; Jia, et al. 2012; Sun, et al. 2012; Dong, et al. 2013; Zhao, et al. 2013). Perineural invasion appears to be supported by nerve growth factor, brain-derived neurotropic factor, EMMPRIN, and tyrosine kinase A (Wang, et al. 2006; Shang, et al. 2007; Liu, et al. 2012; Yang, et al. 2012). The tyrosine kinase receptor pathway c-KIT and an associated factor SLUG appear to regulate important cellular phenotypes of the invasive cell (Jeng, et al. 2000; Andreadis, et al. 2006; Lee, et al. 2012; Liu, et al. 2012; El-Nagdy, et al. 2013). Ultimately, the salivary gland cancer cell is allowed to escape via vascular channels induced by factors such as VEGF (Jia, et al. 2012). Lastly, N-cadherin appears to be an important extracellular molecule contributing to both perineural invasion and metastasis (Jia, et al. 2012). Factors inhibiting invasion and metastasis, such as maspin and MCM2, are also suppressed during salivary gland carcinogenesis (Martins, et al. 2005; Ghazy, et al. 2011).

NUCLEIC ACID DYSREGULATION IN SALIVARY GLAND NEOPLASMS

Thus far, the genesis of salivary gland neoplastic cellular behavior has been presented in terms of aberrant protein function. Enhanced proliferation, apoptosis evasion, immortalization, angiogenesis, and invasion/metastasis have been explained by upregulated proteins, absent inhibitory protein function, and altered function (such as constituent activation, dominant-negative sequestration, etc.). These changes occur at the cell surface, the cytoplasm, and the nucleus. Behind the alteration of these regulatory proteins are often important mutations in the nucleic acids encoding them. Both major and subtle changes in the structure of chromosomal DNA can lead to important changes in these regulatory proteins. Furthermore, epigenetic activity can also result in perturbations in gene expression (or mRNA levels) that can also disrupt these important regulatory pathways.

Genetic Alterations in Salivary Gland Tumors

Abrogation of key cellular regulatory pathways often begins with alterations of the genes encoding factor[s] that govern those pathways. Genes are coding regions within the cell's chromosomal DNA (Todd, et al. 2000). Structurally, genes are composed of promoter/enhancer regions (that control the timing and amount of gene activity), introns and exons (that carry the protein code separated by "spacers") and a termination codon (that stops transcription) (Kim, et al. 2002b). Chromosomal DNA is composed of protein (principally histone proteins) and four nucleic acids (adenine, thymine, guanine, and cytosine) (Todd, et al. 2000; Kim, et al. 2002a). The integrity of these regions is closely protected by structural and chemical elements (Chao and Lipkin 2006). Neoplastic cells suffer from genomic instability that can lead to up- or downregulation of genetic activity, as well as alterations of the genetic code (Abbas, et al. 2013).

Many tumor phenotypes support the generation of genetic errors: enhanced proliferation increases the rate of genetic errors; evasion of apoptosis protects cells harboring mutations from being eliminated; immortalization allows genetic errors to be inherited for a longer period of time. Cancer itself is considered a genetic disease resulting from an accumulation of mutations that occur in a preferred but not absolute order (Vogelstein and Kinzler 1998). These genomic alterations occur at vastly different scales, from whole chromosomes to a single nucleotide.

Important genome guardian pathways are altered in salivary gland tumors. The MDM2-p14^{ARF}-p53 regulatory pathway functions to protect the genome from environmental mutagens, such as radiation and various chemical agents. This pathway has been found to be altered in salivary gland carcinoma (Jin, et al. 2012). In fact, it has been suggested that p53 mutation may be an important early event in the transition from benign to malignant salivary gland disease (Ohki, et al. 2001). Other mismatch repair systems, such as hMSH1/2, have not been found to be important to salivary gland tumor progression (Ohki, et al. 2001; Castrilli, et al. 2002).

Some genetic alterations are so large that they can be observed directly under a microscope. Many tumor cells have an abnormal chromosome number (aneuploidy) (Meltzer, et al. 2001). Other damage involves large chromosomal regions. Translocation results in two chromosomes swapping DNA regions (Todd and Munger 2003). If these breaks occur near a gene promoter, a quantitative alteration of gene expression can result. If the break occurs in a coding region, a protein with altered function might be generated. Gene amplification occurs when DNA region is duplicated multiple times, often 50–100-fold (Todd and Munger 2003). Chromosomal deletion results in the complete loss of genetic material (Todd and Munger 2003). The loss of several key regulatory proteins has been associated with deletion of one or both gene copies.

Large scale chromosomal alterations occur both in benign and malignant salivary gland tumors (Giefing, et al. 2008; Gouveris, et al. 2011). Like in hematologic malignancies and sarcomas, several chromosomal translocations have been observed in salivary gland tumors, some appearing to be tumor-specific (Stenman 2005; Bhaijee, et al. 2011). A fusion protein of the MYB oncogene

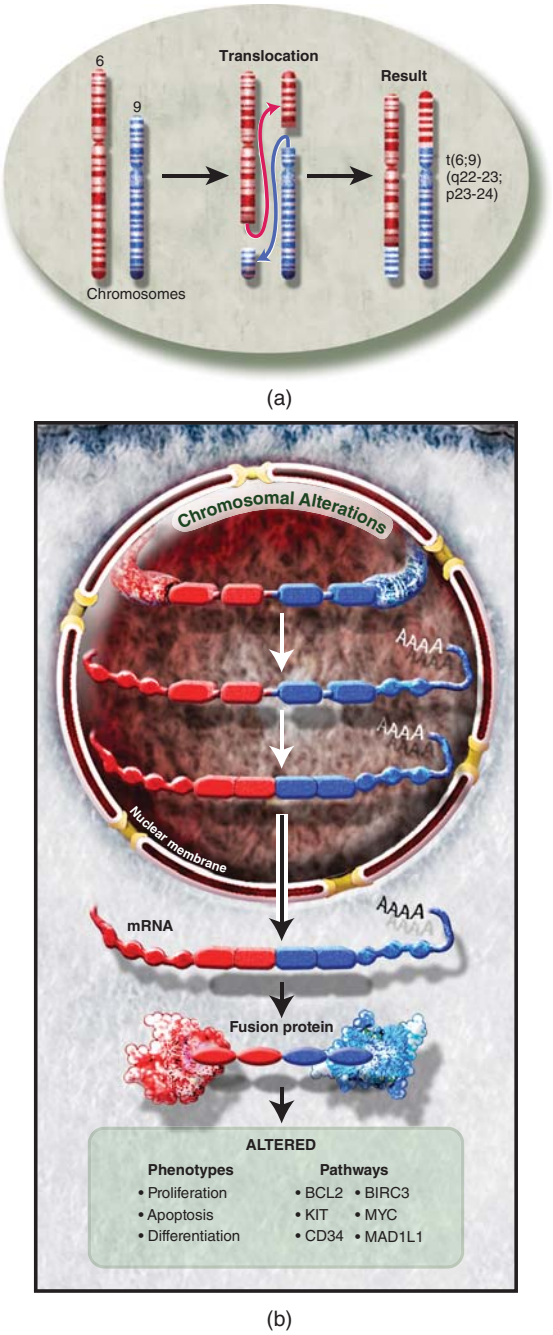


Figure 8.5. How chromosomal alterations lead to phenotypes in salivary gland tumors. The MYB-NFIB gene fusion is a molecular hallmark of adenoid cystic carcinoma. (a) A translocation of genetic material occurs between chromosomes 6 and 9 (t(6;9)(q22–23;p23–24). (b) The fusion of genetic material leads to a modification of both genes. This fused gene is then transcribed into modified mRNA that is later translated into a highly overexpressed fusion protein that leads to the deregulation of several signal pathways involved in cell proliferation, apoptosis and differentiation, including BCL2, KIT, CD34 BIRC3, MYC, and MAD1L1.

and NFIB transcription factor through a translocation between chromosomes 6 and 9 [t(6;9)(q22–23;pq23–24)] (Brill, et al. 2011) (Figure 8.5). Approximately 80% of adenoid cystic carcinomas share the MYB-NFIB gene fusion oncoprotein (Persson, et al. 2009). The fusion product results in an overactive MYB fusion protein that targets genes involved in apoptosis, cell cycle regulation, and cell adhesion in adenoid cystic carcinoma (Liu, et al. 2012). The translocation between chromosomes 11 and 19 [t(11;19)(q21–22;p13)] results in the CRTC1/MAML2 fusion gene frequently observed in mucoepidermoid carcinoma (Adelstein, et al. 2012). The fusion oncoprotein replaces the NOTCH binding domain of MAML2 with the CREB-binding domain of CRTC1, creating a mutant transcription factor that activates several growth promoting signal pathways. Tumors harboring this translocation tend to be less aggressive (Behboudi, et al. 2006; Adelstein, et al. 2012). Gene fusion between PLAG1 and CTNNB1 appears to be specific for pleomorphic adenoma [t(3;8)(p21;q12) (Matsuyama, et al. 2011; Stenman 2013). This translocation results in β-catenin promoter swapping, thereby deregulating PLAG-1 target genes via the IGF2/IGF1R mitogenic pathway (Declercq, et al. 2008). Lastly, mammary analogue secretory carcinoma of the salivary glands harbor the ETV6-NTRK3 gene fusion [t(12;15)(p13;q25)] (Skalova, et al. 2010). ETV6-NTRK3-induced transformation appears to be mediated through the IGF1R pathway (Fehr, et al. 2011). Currently, almost 400 gene fusions have been identified in about 20% of human cancers (Bell and Hanna 2012).

Other large scale chromosomal alterations include gene amplification and deletions. Several genes are amplified in salivary gland tumors. MET, an important gene for invasion and metastasis, is amplified in salivary gland carcinoma and has been found as a predictor of poor prognosis (Ach, et al. 2013). The HER-2/NEU gene amplification has been associated with high-grade transformation in several salivary gland carcinoma, including acinic cell carcinoma, adenoid cystic carcinoma, myoepithelial carcinoma, salivary duct carcinoma, and mucoepidermoid carcinoma (Glisson, et al. 2004; Cornolti et al. 2007; Hashimoto, et al. 2012; Nagao 2013). In a subset of adenoid cystic carcinoma, the c-KIT oncogene is amplified in a subcentromeric region of chromosome 4q (Rao, et al. 2008). Adenoid cystic carcinoma can also harbor several gene amplifications, including ERB-B1, CCND1, and PIK3CA (Sequeiros-Santiago, et al. 2009). Amplification patterns of these oncogenes have clinicopathologic correlations: CCND1 (advanced tumor stage), ERBB1 (distant metastasis), and ERTT1/CCND1/PIK3CA (reduced survival) (Sequeiros-Santiago, et al. 2009). Amplification of the HER2, MDM2, and HMGA2 genes are believed to be important in the malignant transformation of pleomorphic adenoma (Carlson, et al. 2013). Several chromosomal deletions have been associated with salivary gland tumors. Activity of the tumor suppressor gene PTEN is reduced due to a chromosomal deletion (often in association with amplification of the EGFR and HER2 genes) (Ettl, et al. 2012a). Deletion of a portion of the short arm of chromosome 1 (1p32–p36) is one of the most frequent genomic alterations in adenoid cystic carcinoma, though which gene at this locus is important for disease progression is unclear (Rao, et al. 2008). Furthermore, a loss of genetic material at the end of chromosome 6q is frequently combined with a reciprocal translocation between chromosome 6q and chromosome 9p (or some other chromosome) in adenoid cystic carcinoma (El-Naggar, et al. 1999). The deleted portion of chromosome 6q is believed to harbor a tumor suppressor gene. The combination of an activated oncogene and inhibition of a tumor suppressor supports the hypothesis of a multistep accumulation of genetic alterations during tumorigenesis.

Small scale changes in the nucleotide sequence of DNA can have profound changes to the proteins they encode (Arana and Kunkel 2010; Kim and Mirkin 2013). Single nucleotide changes are referred to as point mutations (Kim, et al. 2002a). These changes can result in the alteration of a protein structure/function (missense mutation) or failure to the protein to synthesize (nonsense mutation). Furthermore, addition or subtraction of nucleotide[s] leads to frame shift mutations which can alter how an entire protein is translated (Kim, et al. 2002a). Point mutations in a number of regions of c-KIT have led to overactivity in adenoid cystic carcinoma (Vila, et al. 2009). In animal and human studies, altered function of p53 has been attributed, in part, to point mutations that cause mutated p53 to sequester and inactivate wild type p53 (Papadaki, et al. 1996; Turgut, et al. 2006). Activating point mutations in the H-RAS oncogene have been found in benign and malignant salivary gland tumors, including pleomorphic adenoma, carcinoma ex. pleomorphic adenoma,

adenocarcinoma, and mucoepidermoid carcinoma (Milasin, et al. 1993; Okutsu, et al. 1993; Yoo and Robinson 2000).

Epigenetic Alteration of Gene Expression in Salivary Gland Tumors

While large and small scale structural alterations can lead to gene expression changes (as well as quantitative and/or qualitative gene product alterations), non-structural regulatory mechanisms can be abrogated in salivary gland tumorigenesis. Gene expression is, in part, regulated by conformational changes in the DNA. Acetylation of the histone proteins in the chromosomal DNA can lead to the activation or suppression of gene expression (Verdone, et al. 2005). Addition or removal of methyl groups within the gene promoter can also activate or suppress gene activity (Baylin 2005). Furthermore, mRNA already transcribed can be further regulated. For example, micro RNAs, usually 22 nucleotides in length, can sequester mRNA, thereby blocking translation and promoting degradation (Bora, et al. 2012).

Methylation/de-methylation of a gene promoter can activate or suppress gene activity. Therefore, aberrant promoter methylation can lead to overexpressed oncogenes or inactivation of tumor suppressor genes without an alteration in the genetic code (Kishi, et al. 2005; Williams, et al. 2006). In the case of tumor suppressor genes, one gene may be structurally altered while the other suffers an alteration in the methylation status of its promoter. For example, in salivary gland carcinoma, $p16^{INK4a}$ and $p14^{ARF}$ often suffer a deletion in one gene copy and hypermethylation of the promoter in the other (Suzuki and Fujioka 1998; Nishimine, et al. 2003; Li, et al. 2005; Guo, et al. 2007). Over 40 genes, including MYB, E-cadherin, suprabasin, and PTEN, have been shown to be up- or downregulated during salivary gland tumorigenesis based on promoter methylation (Zhang, et al. 2007; Lee, et al. 2008; Fan, et al. 2010; Bell, et al. 2011; Shao, et al. 2011a; Shao, et al. 2012). Though there is a great deal of heterogeneity in promoter methylation, the methylation status of several genes has been correlated with several clinical observations, including transformation of benign to malignant, diagnosis of specific tumors, local/perineural invasion, and metastatic spread (Williams, et al. 2006; Lee, et al. 2008; Durr, et al. 2010; Fan, et al. 2010; Schache, et al. 2010; Hu, et al. 2011; Shao, et al. 2011b, 2012). Large scale or high throughput gene expression analysis can uncover pathways/pathway elements leading to certain tumor phenotypes. For example, the overexpression of SOX-4, the most significantly overexpressed oncogene in adenoid cystic carcinoma, likely contributes to malignant progression by downregulating NFκB inhibitors (such as IκB) and upregulating apoptosis inhibitors (such as survivin) (Pramoonjago, et al. 2006).

Aberrant post-transcriptional regulation also contributes to salivary gland tumorigenesis. mRNA signatures have been associated with a number of clinical characteristics in salivary gland tumors, including growth and invasion, cell cycle deregulation, and aggressiveness/poor outcome (Zhang, et al. 2009a; He, et al. 2013; Liu, et al. 2013; Mitani, et al. 2013; Shin, et al. 2013). Recently, evidence that mutations in SPEN, an RNA binding protein, contribute to transcriptional reprogramming in adenoid cystic carcinoma has been demonstrated (Frierson and Moskaluk 2013).

Summary and Clinical Applications

Our understanding of the molecular determinants governing salivary gland neoplasia is very preliminary. Salivary gland tumors are uncommon lesions that are composed of over 30 different pathologic entities, many with several subtypes according to the second revision of the World Health Organization Histological Classification of Salivary Gland Tumors (Eveson 1992). Furthermore, within each lesion, there is a vast histologic heterogeneity with each "normal" and neoplastic cell type contributing to disease progression. Chromosomal large scale (translocations, amplifications, and deletions) and small scale (point mutations) alterations, as well as epigenetic changes (such as methylation changes in gene promoters) lead to quantitative and qualitative changes in gene expression. These alterations in gene expression result in important changes in the quantity and/or activity of important regulatory proteins. These proteins, extracellular ligands, receptors, secondary messengers, and transcription factors, serve in a network of signal transduction pathways that control critical cellular functions such as proliferation, apoptosis, senescence/differentiation, angiogenesis, and invasion/metastasis. The abrogation of these regulatory pathways is not completely

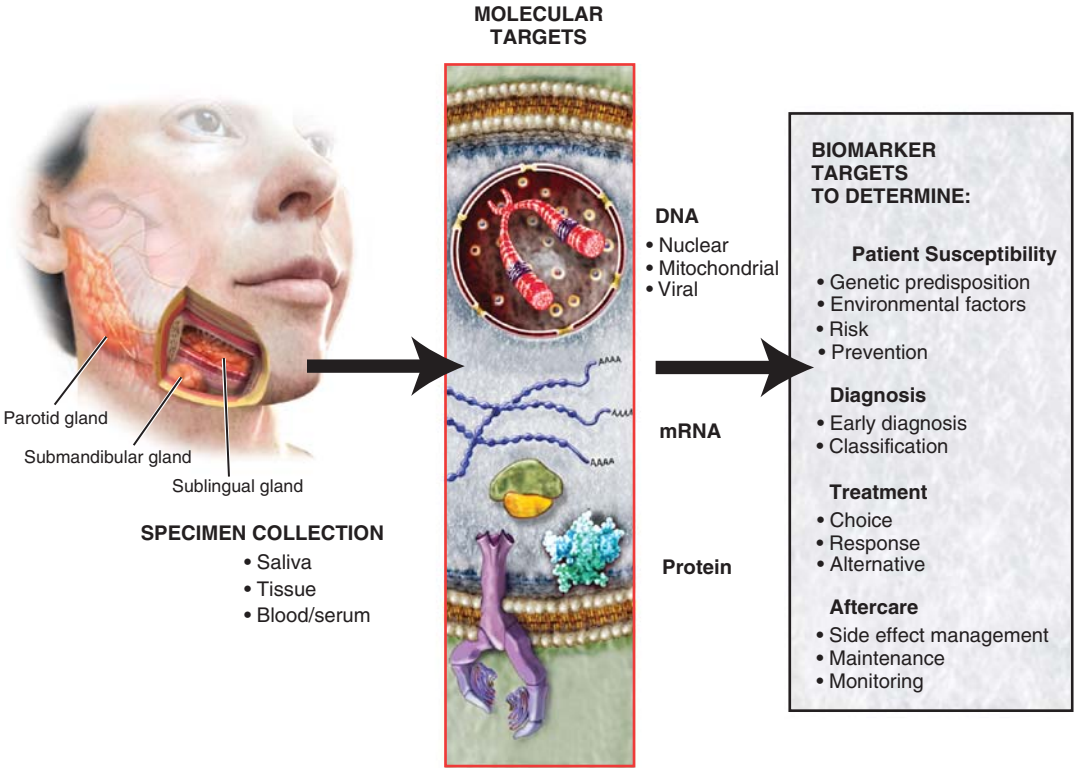
understood for any salivary gland tumor. However, with the data available to date, translation of these bench-top findings into the clinical setting has begun.

DIAGNOSTIC APPLICATIONS

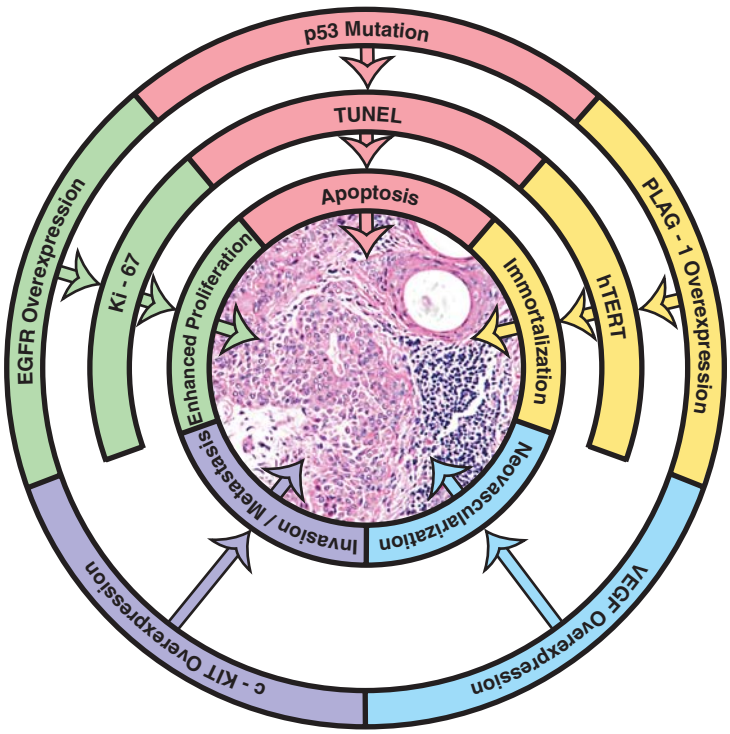
At present, diagnosis of salivary gland tumors involves physical examination, imaging and fine needle aspiration cytology (FNAC) (Carlson, et al. 2013). The sensitivity of FNAC of benign and malignant salivary neoplasms ranges from 73 to 86%, whereas the specificity is 97% for benign tumors and 85% for malignant tumors (Schindler, et al. 2001; Carlson, et al. 2013; Turk and Wenig 2014). When possible, immunohistochemistry can further refine the diagnosis (Nagao, et al. 2012). While treatment of salivary gland neoplasms almost always involves surgical excision, an accurate pre-operative diagnosis will aid therapeutic planning (Schindler, et al. 2001). At present, primary clinicopathologic parameters (such as patient age, histiotyping, grade, and disease stage) guide treatment (Vander Poorten, et al. 2012). There is often a poor correlation between tumor histology and biological aggressiveness (Leivo 2006). Along with histiotyping, optical grading, and clinical staging are currently the primary determinants in treatment planning (Vander Poorten, et al. 2012). Low-grade/low stage tumors are treated with excision alone while high-grade/high stage tumors may include neck dissection and radiation/chemo-radiation (Bell and Hanna 2012). However, grading schemes have a great deal of variability and poor reproducibility, leading to difficulties in treatment planning and determination of patient prognosis (Seethala 2011). Therefore, exploiting molecular biomarkers of neoplastic progression should result in a more personalized management.

Advances in diagnostic methods promise a better understanding of the disease (Figure 8.6a). Molecular markers can be identified not only in FNAC and open biopsy samples, but other specimens such as blood/serum and saliva. Furthermore, not only is the gene product a potential marker, but DNA and mRNA are as well (Sidranski 2002; Yoshizawa, et al. 2013). While DNA only contributes to neoplastic phenotypes if a gene is active, several robust single and high-throughput analyses exist to identify tumor-associated alterations (Liu, et al. 2012; Watson, et al. 2013). While lacking the stability of DNA, mRNA is a direct reflection of gene activity. Analytic techniques are available that allow for detection of mRNA in small quantities, as well as high throughput detection of gene expression signatures (Golub, et al. 1999; Buckhaults 2006). In addition to immunohistochemistry, novel proteomic approaches allow identification of protein targets in multiple samples, as well as multiple modifications of the same protein target (Donadio, et al. 2013; Ellis, et al. 2013; Paiva-Fonseca, et al. 2013). DNA, mRNA, and protein biomarkers can target either: (1) the result of a signal transduction network, such as the tumor phenotypes of enhanced proliferation (Ki-67 immunostaining), apoptosis (TUNEL assay) or immortalization (hTERT assay) or (2) the specific elements of those pathways (growth factors/receptors, secondary messengers, transcription factors) (Figure 8.6b). While the use of individual pathway elements as biomarkers is self-evident, molecules indicating the result of a signaling network may be a direct or indirect byproduct of that pathway. For example, enhanced proliferation is a phenotype regulated by several separate pathways. Ki-67, an anti-apoptotic protein, is present in the G1, S, and G2 phases of the cell cycle; therefore, counting the number of cells that stain positive for Ki-67 is an indicator of how rapidly a tumor is proliferating (Murakami, et al. 1992). To date, Ki-67 may be the most important supplement to optical grading as a prognostic indicator for adenoid cystic carcinoma, acinic cell carcinoma, mucoepidermoid carcinoma, and salivary duct carcinoma (Vander Poorten, et al. 2012). These biologically-based markers promise earlier diagnosis, more precise disease stratification, more accurate prediction of disease response (and selection of alternative treatment), more sensitive disease monitoring, ability to predict/mitigate treatment side effects, and prevention of disease recurrence (Sidranski 2002).

While the immunohistochemical detection of protein targets is aiding diagnosis and classification of salivary gland tumors today, molecular alterations are emerging as a means to more precisely define these neoplasms. Given the prominence of chromosomal translocations in salivary gland tumorigenesis, the resultant gene fusions serve as an attractive biomarker. The MYB-NFIB fusion tends to appear exclusively in adenoid cystic carcinoma while the majority of mucoepidermoid carcinoma is associated with the CRTC1-MAML2 translocation (Behboudi, et al. 2006; Persson,



(a)



(b)

Figure 8.6. How can biomarkers aid in salivary gland tumor diagnosis? Biomarkers of neoplasia are already being explored to augment the current diagnostic work-up of salivary gland tumor patients. (a) In addition to utilizing biopsy and fine needle aspiration samples, investigators are testing biomarker availability in saliva and the bloodstream. Diagnostic targets may be DNA, mRNA or proteins. The purpose of these targets would be to better understand patient risk/predisposition, identify/classify disease earlier, guide treatment choice and improve patient monitoring. (b) Tumor biomarkers can target specific neoplastic phenotypes (middle circle) or individual molecular events (outer circle).

et al. 2009). In fact, mucoepidermoid carcinoma harboring the CRTC1-MAML2 translocation show a significantly better survival rate (Behboudi, et al. 2006). Over 90% of mammary analogue secretory carcinoma contain the ETV6-NTRK3 gene fusion (Skalova, et al. 2010; Fehr, et al. 2011). Interestingly, carcinoma ex. pleomorphic adenomas contain translocations containing either PLAG1 or HMGA2, but pleomorphic adenomas do not (Persson, et al. 2009). Gene amplifications have also been tested as biomarkers. Amplifications of ERBB1, CCND1, and PIK3CA in adenoid cystic carcinoma indicate reduced survival (Sequeiros-Santiago, et al. 2009). HER2/NEU amplification may be an efficacy predictor for salivary gland tumors treated with lapatinib, as well as a marker for carcinoma ex. pleomorphic adenoma (versus pleomorphic adenoma) (Vidal, et al. 2009; Hashimoto, et al. 2012). Chromosomal deletions are also being explored as biomarkers. Deletion of 1p32–p36, the most frequent genetic change in adenoid cystic carcinoma, may be an indicator of poor prognosis (Rao, et al. 2008). Deletion mutations in exon 19 of EGFR appear to indicate improved clinical response when treated with the tyrosine kinase inhibitors gefitinib and erlotinib (Dahse and Kosmehl 2008). Deletion in the CDKN2A gene, combined with the MECT1-MAML2 fusion gene indicate poor prognosis in mucoepidermoid carcinoma patients, suggesting an important step in tumorigenesis (Anzick, et al. 2010). Deletion of the long arm of chromosome 6 is a consistent finding in adenoid cystic carcinoma (Bell and Hanna 2012).

Epigenetic alterations of gene expression have also been explored as biomarkers. Benign and malignant, as well as high grade versus low grade tumors, show distinct methylation patterns (Williams, et al. 2006). Promoter methylation of p16 correlates with the malignant transformation of pleomorphic adenoma (Schache, et al. 2010; Hu, et al. 2011). Hypermethylation of EN1 appears to be specific early event in adenoid cystic carcinoma development (Bell, et al. 2011). The hypomethylated Suprabasin gene in adenoid cystic carcinoma is associated with metastasis (Shao, et al. 2012). Lastly, emerging studies support marker panels, rather than single biomarkers. Identification of multiple genetic changes, as well as alterations of gene expression and protein, has been explored as biomarkers to help direct patient treatment (Ettl, et al. 2012b; Nardi, et al. 2013).

DNA, mRNA, and protein biomarkers, alone and in combination, are being explored to aid in identifying clinically relevant salivary tumor phenotypes. First, as alluded to earlier, molecularly based markers are being used to identify malignant transformation (Schneider, et al. 2013). Expression of hTERT/EGFR, MSF, and VEGF, as well as polymorphisms in MDM2 and $p14^{ARF}$, has been correlated with malignant transformation (Aljorani, et al. 2011; de Faria, et al. 2011; Shigeishi, et al. 2011; Jin, et al. 2012). Both c-KIT and SLUG expression correlates with invasion (and metastasis) of adenoid cystic carcinoma (Tang, et al. 2010). Biomarkers have been identified demarking the malignant transformation of benign tumors. In addition to the studies cited previously separating pleomorphic adenoma from carcinoma ex. pleomorphic adenoma, aberrant expression of p53, BCL-2, and EGFR have been found to useful in distinguishing salivary basal cell adenoma from adenocarcinoma (Nagao, et al. 1998).

Second, biomarkers are being used to better differentiate tumors (as well as sub-classify histologically similar tumors) (Donadio, et al. 2013; Paiva-Fonseca, et al. 2013). Given the heterogeneous (as well as overlapping) histology of salivary gland tumors and often limited tissue specimen for diagnosis, biomarkers not only might identify malignant tissue, but be able to discriminate between histologically similar salivary gland tumors and tumors from remote anatomic sites. Immunohistochemical detection of p63 can differentiate between salivary gland oncocytoma and oncocytic carcinoma from metastatic renal cell carcinoma (McHugh, et al. 2007). Gene expression and immunohistochemical panels have been identified separating pleomorphic adenoma and adenoid cystic carcinoma from other salivary gland tumors, as well as histological overlap of adenoid cystic carcinoma from polymorphous low-grade adenocarcinoma (Skalova and Leivo 1996; Maruya, et al. 2004; El-Nagdy, et al. 2013). The oncogene c-KIT is found in 100% of myoepitheilial carcinomas (and lymphoepithelial carcinomas) and 80–94% of adenoid cystic carcinomas (Jeng, et al. 2000; Mino, et al. 2003). Lastly, p63 expression might be helpful separating acinic cell carcinoma from mucoepidermoid carcinoma (Sams and Gnepp 2013).

Third, biomarkers are being explored as patient management guideposts. Several studies have correlated specific biomarkers with aggressive behavior and invasive phenotypes.

For example, NCAM has been implicated in perineural invasion (Shang, et al. 2007; Kehagias, et al. 2013). In adenoid cystic carcinoma and mucoepidermoid carcinoma, mutant p53, VEGF, aniopoietins, and c-KIT/SLUG expression have been associated with aggressive/invasive growth and metastasis (Papadaki, et al. 1996; Tang, et al. 2010; Demasi, et al. 2012). Various marker/marker panels have been explored as prognostic indicators: PTEN loss/EGFR/HER2 overexpression;, BCL-2/p53/Ki-67, MMP-1/7/9/13, EBFR/p53/E-cadherin (mucoepidermoid carcinoma), and 1p32–p36 deletion (adenoid cystic carcinoma) (Yin, et al. 2000; Nagler, et al. 2003; Hoyek-Gebeily, et al. 2007; Luukkaa, et al. 2008, 2010a; Rao, et al. 2008; et al. Ettl, et al. 2012a; Stenner, et al. 2012). Deregulation of p16 and p53 pathways has been implicated with recurrence (Vekony, et al. 2008; Byrd, et al. 2013). Survival has been correlated with several marker/marker panels: $p27^{Kip1}$, Ki-67/CRTC1-MAML2 (mucoepidermoid carcinoma); EGFR/HER2/survivin/pSTAT3 loss; p53/Ki-67/TUNEL; MET/EGFR/PTEN loss; and ERBB1/CCND1/PIK3CA (Ben-Izhak, et al. 2007, 2008; Miyabe, et al. 2009; Sequeiros-Santiago, et al. 2009; Stenner, et al. 2011; Ettl, et al. 2012a; Ach, et al. 2013). Lastly, individual markers and marker panels are being studied to determine tumor-associated alterations that might direct current therapeutic protocols (Dahse and Kosmehl 2008; Vidal, et al. 2009; Nardi, et al. 2013).

THERAPEUTIC APPLICATIONS

While patient assessment might improve the efficacy of current treatment protocols, novel, biologically-based treatment approaches can also be developed based on molecular defects leading to salivary gland tumorigenesis. At present, surgical excision is the primary treatment of salivary gland tumors. In addition, radiation alone or in combination with chemotherapy may play an important role in local control administered either postoperatively or as a definitive treatment (Carlson, et al. 2013). However, for patients where obtaining a surgical margin is impossible, perineural spread is noted or locally advanced, recurrent, or metastatic spread is discovered, the present therapeutic options are limited and often palliative (Bell and Hanna 2012). To date, several therapeutic strategies have been developed to exploit a better understanding of how tumors develop.

The goal of a biologically-based therapeutic strategy is to tailor treatment to the specific molecular defects resulting in tumor behavior (Figure 8.7a). An additional benefit of this molecular approach is to limit side effects of treatment, though associated toxicities do exist (Dy and Adjei 2013). Targets of this designer therapy can be any member of the molecular paradigm: DNA, RNA, or protein. Many DNA-based strategies simply replace damaged genes with "normal" ones. Other strategies include activation of cancer cell-clearing immune response, enhancement of DNA repair enzyme activity, drug resistance gene inactivation, or enzymatic destruction of viral/oncogenic material (Kelley and Fishel 2008; Ortiz, et al. 2012). Delivery approaches of these therapeutic genes include microorganisms (principally viruses) and nanocarrier methods (Mohit and Rafat 2013; Thakor and Gambhir 2013). Gene expression or mRNA can also serve as a target. Two major approaches are RNA interference and manipulation of gene expression through changes in methylation (Morris 2006; Gallinari, et al. 2007). Lastly, the gene products (proteins) themselves can serve as targets. The two principle approaches employ either monoclonal antibodies or low molecular weight proteins (Gibbs 2000; Sliwkowski and Mellman 2013). Biologically-based molecular targets, used alone or in tandem, attack aberrant neoplastic cell behavior at the very defects responsible.

To date, the advent of biologically-based therapies directed at salivary gland tumors has been modest. Experimental and clinical strategies fall primarily into three broad categories; monoclonal antibodies, RNA interference, and small molecule inhibitors. Studies using monoclonal antibodies to EGFR gene family members have been performed with limited success (Figure 8.7b). The EGFR (HER1/ErbB1) family of transmembrane tyrosine kinase receptors has been an attractive therapeutic target for tumors at a variety of anatomic sites. Therefore, several monoclonal antibodies to EGFR family members are available. Trastuzumab targets the HER-2/NEU receptor noted in a significant portion of breast cancers. A recent study of three mucoepidermoid carcinoma patients administered trastuzumab showed a partial response in one patient and stabilization of the disease in two others (Haddad, et al. 2003). A larger study of adenoid cystic carcinoma patients treated with Gefitinib (an ErbB1 monoclonal antibody) showed disease stabilization in 53% of patients that extended for

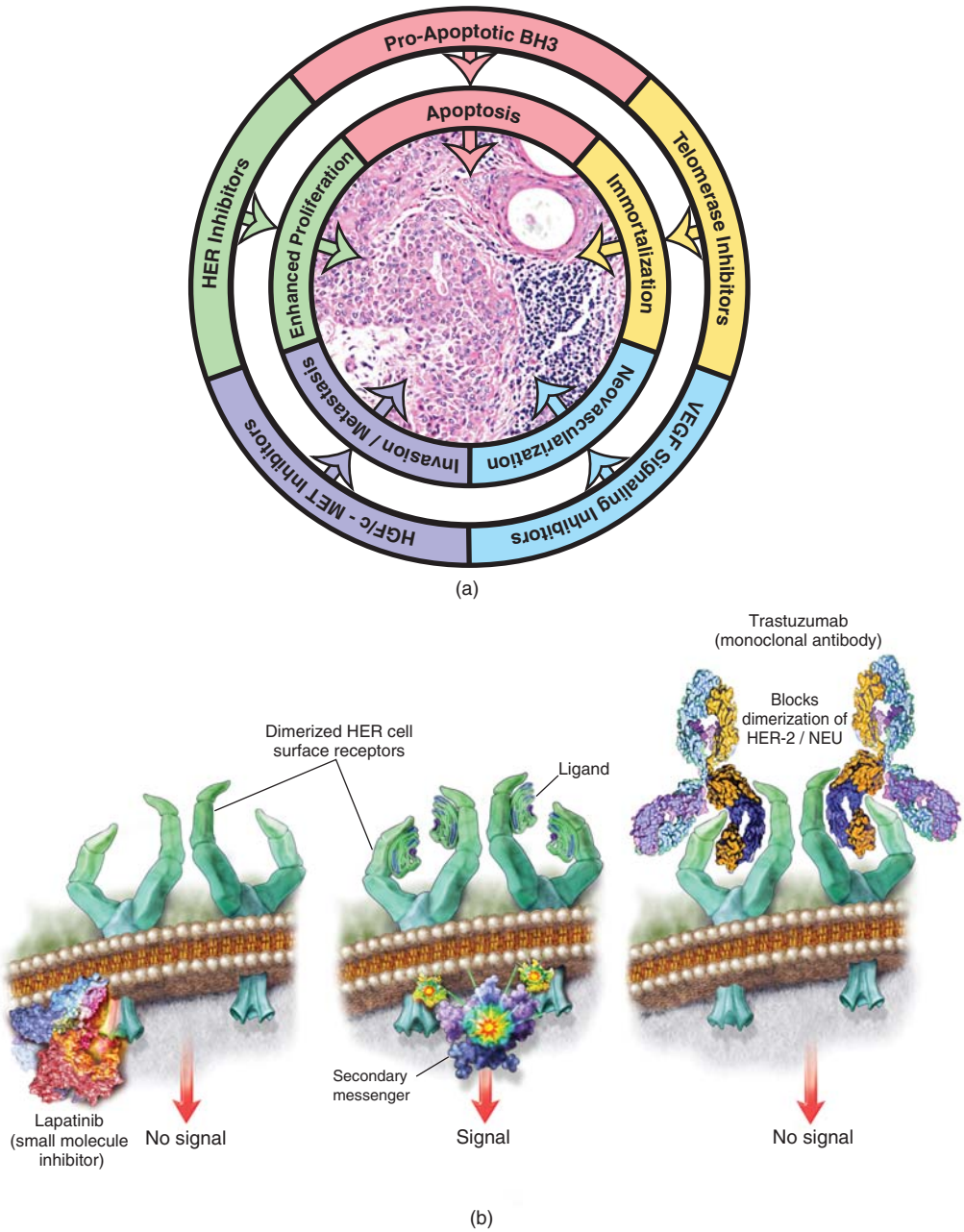


Figure 8.7. How can an understanding of salivary gland tumor biology lead to targeted therapeutic options? At present, several biologically-based tumor therapies are in clinical trials. (a) The cellular phenotypes that salivary gland tumors share with other forms of neoplasia are potential targets. (b) The HER cell surface receptors are deregulated in several tumors, including salivary gland tumors. After binding a ligand, these receptors dimerize and activate secondary messengers, which support cellular proliferation (middle). Aberrant activity of HER-1/EGFR secondary messenging can be blocked using the small molecule inhibitor Lapatinab (*left*). Dimerization of HER-2/NEU can be blocked using the monoclonal antibody Trastuzumab, thereby preventing any downstream signaling.

16 weeks in 26% (Vattemi, et al. 2008). Thirty salivary gland cancer patients with either recurrent or metastatic disease were treated with Cetuximab, another ErbB1 antibody, and, of the 23 who were available at 3 months, 11 showed stabilization of the disease (Vattemi, et al. 2008). Monoclonal antibodies have also been used in combination with conventional chemotherapy (Kaidar-Person, et al. 2012; Caballero, et al. 2013). Small molecule inhibitors have also been tested. Lapatinib, an orally administered reversible inhibitor of ErbB1/2 tyrosine kinase activity, was tested in adenoid cystic carcinoma patients that showed expression of one or both receptors: of 14 patients, 9 had stable disease (Agulnik, et al. 2007). The tyrosine kinase inhibitor Imatinib mesylate, a potent blocker of c-KIT activity, was tested in two separate studies of adenoid cystic carcinoma patients; however, no objective response was noted in either study (Hotte, et al. 2005; Pfeffer, et al. 2007). As part of a greater study, the small molecule inhibitor of VEGF/c-KIT/PDGFR tyrosine kinase activity showed partial response in an adenoid cystic carcinoma patient after three treatment cycles (Rugo, et al. 2005). In experimental models of mucoepidermoid carcinoma and adenoid cystic carcinoma, RNAi targeting the gene fusions MECT1-MAML2 and MYB-NFIB, as well as MAPK and EGFR, has shown promise in reversing important malignant phenotypes (Komiya, et al. 2006; He, et al. 2013; Liu, et al. 2013; Stenman 2013). While not exhaustive, this survey reinforces themes introduced earlier regarding the difficulty targeting treatment in these patients. Few robust clinical trials contain a translational component. Biologically based therapy necessitates that the study subjects carry the proper genetic defect. Furthermore, failure to respond may not be the result of conventional causes of treatment failure, such as improper dosing, but the failure to recognize the multiple genetic defects critical to address these tumors (Locati, et al. 2009). Just as salivary gland tumorigenesis is a multi-step accumulation of genetic errors, the successful treatment of salivary gland tumors will necessitate the identification and remedy of critical genetic defects.

Summary

- Salivary gland tumors are complex, heterogeneous tumors.
- Neoplastic salivary gland cells share several phenotypic traits, including enhanced proliferation, evasion of apoptosis, immortalization, neovascularization, and invasion/metastasis.
- Traits of salivary gland neoplastic cells result from quantitatively or quantitatively altered signal transduction regulatory proteins. Regulatory factors include extracellular ligands, cell surface receptors, secondary messengers, and transcription factors.
- Signal transduction regulatory proteins can be altered genetically and epigenetically.
- Large-scale genetic changes include chromosomal translocations, amplifications, and deletions. Point mutations are an example of small-scale genetic changes. Large- and small-scale changes can lead to either up- or downregulation of gene expression or transcriptional errors leading to the production of proteins with altered functions.
- Epigenetic changes include important transcriptional and post-transcriptional changes of signal transduction proteins.
- The molecular alterations supporting salivary gland tumorigenesis are poorly understood. Defining universal and tumor-specific signal transduction pathway alterations will generate a fingerprint for each salivary gland tumor. These biomarkers will likely be panels of DNA, mRNA, and protein alterations. A precise understanding of the genetic make-up of individual tumors will allow personalized patient management.
- Advantages of personalized salivary gland diagnostic applications include better tumor diagnosis/classification, screening and risk assessment, identification of lifestyle modifications for risk reduction, and prognosis determination.
- Advantages of personalized salivary gland therapeutic applications include improved prediction of treatment efficacy/treatment planning, more precise dose modulations, stratification of patients for targeted therapy, and better post-surgical follow-up for early detection of recurrent tumors.
- Improvements in specimen acquisition, high throughput analysis, and bioinformatics should help overcome many of the difficulties in understanding these rare, complex tumors.

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Chapter 9

Tumors of the Parotid Gland

Outline

Introduction

This chapter will discuss the diagnosis and management of parotid tumors arising from epithelial cells, that is, salivary derived parotid tumors. Non-epithelial tumors will be discussed in Chapter 14. Although the commonest tumor is the benign pleomorphic adenoma, there is currently much controversy in the literature about the surgical management of this tumor regarding the role of extracapsular dissection versus the traditional parotidectomy and this controversy will be discussed at length. Changing approaches to neck dissection and adjuvant radiotherapy in malignant parotid tumors will also be highlighted.

Etiology and Epidemiology

The etiology of salivary gland tumors is largely unknown. There is an increase in salivary tumors from exposure to radiation documented from Hiroshima and Nagasaki (Saku, et al. 1997). An increase in poorly differentiated carcinoma of the parotid that may be associated with Epstein–Barr Virus is reported in Inuit people. It is thought that Warthin tumors arise from salivary duct remnants enclaved in lymph nodes during embryologic development and that irritation from tobacco smoke may cause these ducts to proliferate (Lamelas, et al. 1987). At the present time, data does not show any connection between cell phone use and increased risk of parotid tumors (Lonn, et al. 2006). There is a reported increase in other solid tumors, particularly breast cancer in conjunction with salivary malignancies (In der Maur, et al. 2005). There is a racial predilection with high incidence in Asians (particularly Chinese) and Inuit people associated with lymphoepithelial carcinoma of the parotid gland. An association with Epstein–Barr Virus (EBV) is common and has treatment implications (Anantharajan, et al. 2013).

Salivary gland tumors are rare 1.5–2 per 100,000 in the USA and they comprise approximately 3% of head and neck malignancies. Eighty percent of all salivary tumors are located in the parotid gland and of these tumors approximately 80% will be benign. The "rule of 80s" also states that 80% of parotid tumors are located in the superficial lobe and that 80% of these will be pleomorphic adenomas (PAs). This chapter will discuss the epithelial derived salivary tumors of the parotid.

Diagnosis

The diagnosis of a tumor of the parotid gland will be dependent upon the history, clinical examination, imaging, and fine needle aspiration biopsy

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(FNAB). In most cases the history will be of a painless slow growing lump that the patient had been aware of for some months, or even years, and that was noticed initially when shaving, washing, or applying make-up. Occasionally, the patient will report a rapidly growing mass but this is not always a malignancy, as a long standing retromandibular tumor that can no longer be accommodated in this space may have "popped out" and become prominent. Pain in a parotid mass is usually an ominous sign and can be an indication of adenoid cystic carcinoma. A history of facial nerve weakness, numbness of the ear or facial skin, or enlarged nodes in the neck, are all signs of malignancy.

Clinical examination will begin with the cervical nodes and palpation of the parotid. The facial nerve and muscles of facial expression are tested and intra-oral examination of the soft palate and lateral pharynx is done to exclude deep lobe tumors extending into the parapharyngeal space. Most parotid tumors will present as smooth sometimes lobulated, firm, or hard non-tender masses in the superficial lobe. Most are discrete and mobile. Fixation to the skin, ulceration, or deep muscle fixation are all signs of malignancy. Facial nerve palsy and associated hard lymph nodes are also signs of parotid cancer. However, only 2.6–22% of parotid cancers will have VII nerve palsy (Ord 1995). Overall 30% of malignancies are diagnosed on clinical features with palpable cervical nodes, facial nerve palsy, deep fixation, and rapid enlargement being significant signs (Wong 2001). The majority of cancers present clinically as benign tumors.

The differential diagnosis of parotid tumor includes lesions arising outside the parotid as well as intra-parotid masses. Skin lesions such as sebaceous or dermoid cysts are usually distinguished by their superficial origin in the overlying skin. Neoplasms of the masseter and masseteric hypertrophy will become fixed and more prominent on clenching the jaws. Condylar masses usually move with jaw opening and jaw lesions are usually bony hard to palpation. Intra-parotid masses that mimic parotid tumors include enlarged parotid nodes and, as these may be metastatic, clinical examination of the parotid mass should always include the ear and the scalp for skin cancers. Parotid cysts may be difficult to distinguish from common parotid tumors such as PAs and low-grade mucoepidermoid carcinoma that can present as fluctuant cysts. Tumors arising in the parotid tail may be mistaken for submandibular or neck masses (Figure 9.1) while those arising in the accessory gland may be thought to arise in the cheek itself (Figure 9.2).

In imaging the parotid gland, technetium scans may confirm a diagnosis of Warthin tumor or oncocytoma but are largely of historical interest. The same is true for sialography, which is no longer used for tumor diagnosis but is useful in diseases of the ductal system (see Chapter 2). Ultrasound can distinguish cystic from solid masses and may be helpful to guide FNAB. As a diagnostic tool it has a 72% sensitivity and 86% specificity for detecting malignant tumors (Schick, et al. 1998). In the assessment of benign disease and pleomorphic adenomas, sensitivities of 80% and specificity of 86% with an accuracy of 84% are reported (Bialek, et al. 2003; Bozzato, et al. 2007). However, CT scanning or MRI are the imaging modalities of choice if the clinician feels the information gained is worth the financial cost. Little is added to the diagnosis when imaging tumors in the superficial lobes, however, imaging deep lobe tumors particularly those with parapharyngeal extension gives the surgeon useful information. Recent papers have claimed that high resolution MRI using a surface coil may allow imaging of the facial nerve and its relationship to the tumor (Takahashi, et al. 2005). Other methods of predicting facial nerve position have been to use anatomic lines drawn on the images, such as the facial nerve line that connects the lateral surface of the posterior belly of the digastric muscle with the lateral surface of the cortical bone of the ascending ramus of the mandible and has been assessed as 88% accurate in determining the location of the tumor in relation to the nerve (Ariyoshi and Shimahara 1998). Another proposed guideline is the Utrecht line connecting the most dorsal point visible of C1 or C2 vertebra to the retromandbibular vein (RMV) (de Ru, et al. 2002). Magnetic resonance imaging may be helpful in distinguishing benign PAs from malignant tumors, by post contrast enhancement, a higher T2 signal and lack of invasion (Figure 9.2). However, Fee and Tran (2003) suggest that neither MRI or ultrasound is accurate enough to be routinely used in the work up of parotid masses and that careful history and examination is sufficient for most cases. This conclusion was echoed by de Ru, et al. (2007), who concluded that MRI and palpation are almost equally accurate for assessing tumor location and both are superior to ultrasound. They recommend the use of FNAB as an accurate method of assessing whether a tumor is malignant

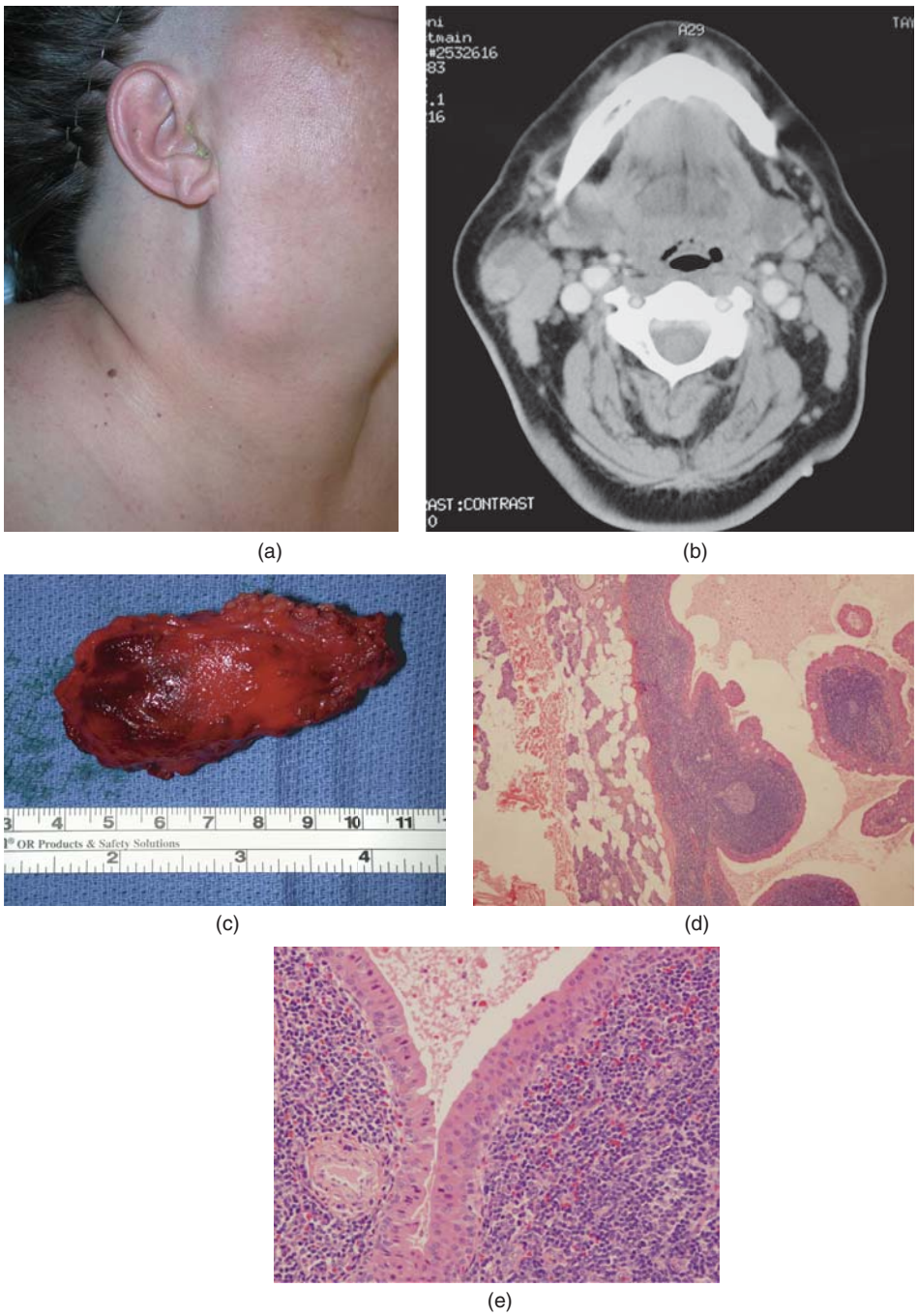


Figure 9.1. (a) A woman with a Warthin Tumor in the right parotid tail presenting as a neck mass.(b) CT scan confirms the mass to be present in the parotid tail. (c) Surgical specimen following partial parotidectomy of parotid tail with tumor (see also Figure 9.11). (d) and (e) Low and high-power microscopic views of the specimen that identified a Warthin tumor.

and MRI only for tumors in the deep lobe or malignant tumors. PET scan and fused PET/CT has so far not been shown to reliably differentiate between benign and malignant parotid tumors (Rubello, et al. 2005). In examining only malignant salivary tumors for staging and restaging, PET-CT was found to show no significant difference in accuracy between conventional imaging but was more specific (73% vs 43%), (Sharma, Jain, Singh et al. 2013).

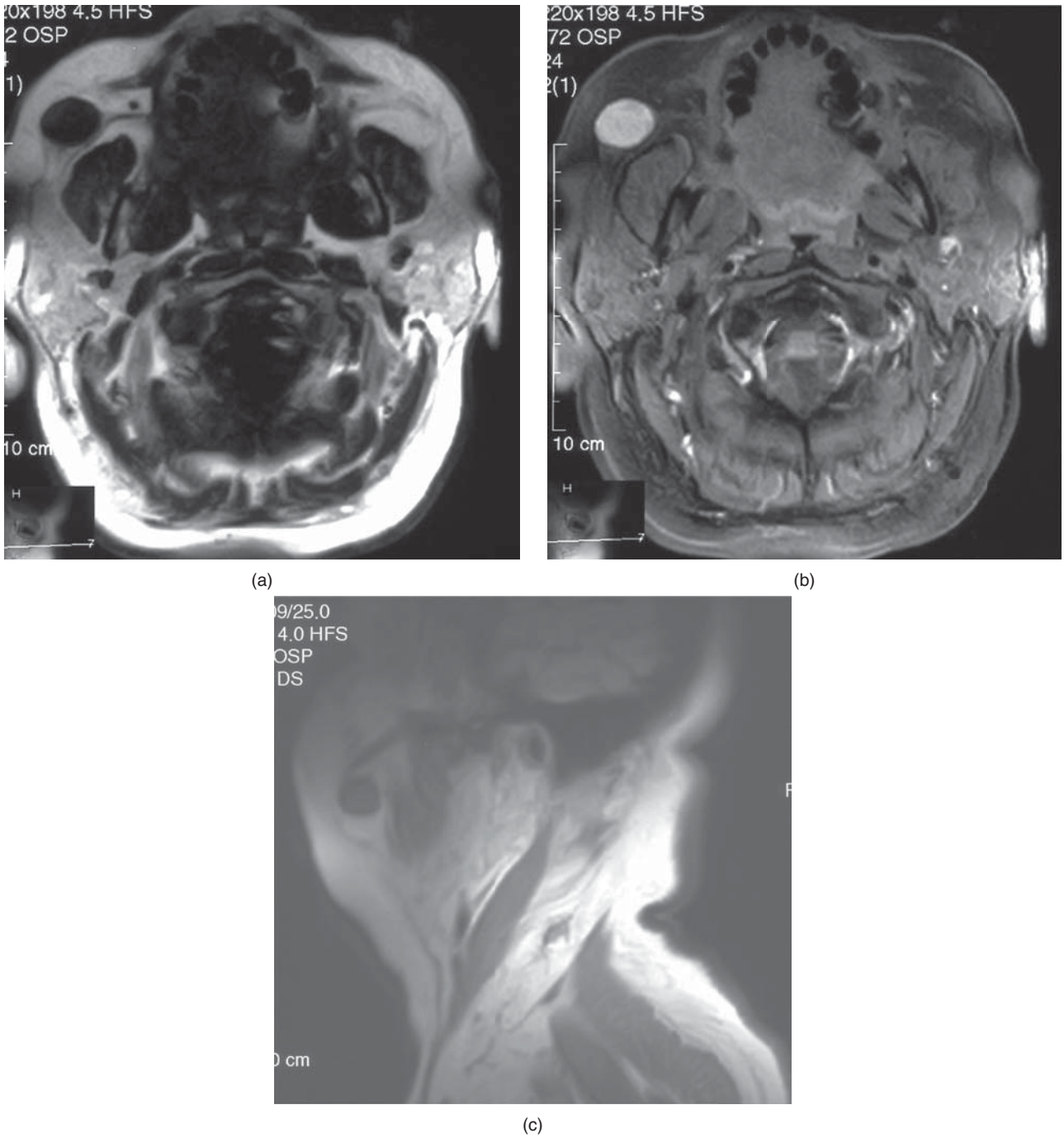


Figure 9.2. (a and b) MR T1 and T2 weighted images of a cystic pleomorphic adenoma deep in the cheek is a diagnostic challenge as to whether this is a minor salivary gland tumor or an accessory parotid tumor. (c) Clinically this lesion appears to be inferior to the parotid duct as seen in the sagittal view which would make an accessory lobe tumor unlikely.

FNAB may be utilized to give a preoperative cytologic diagnosis. Open biopsy is contraindicated as it will cause spillage and seeding of benign PAs and lead to increased recurrence (Figure 9.3). Although FNAB will not usually change the proposed treatment plan of parotidectomy, a malignant diagnosis may allow better presurgical counseling for possible facial nerve sacrifice. In

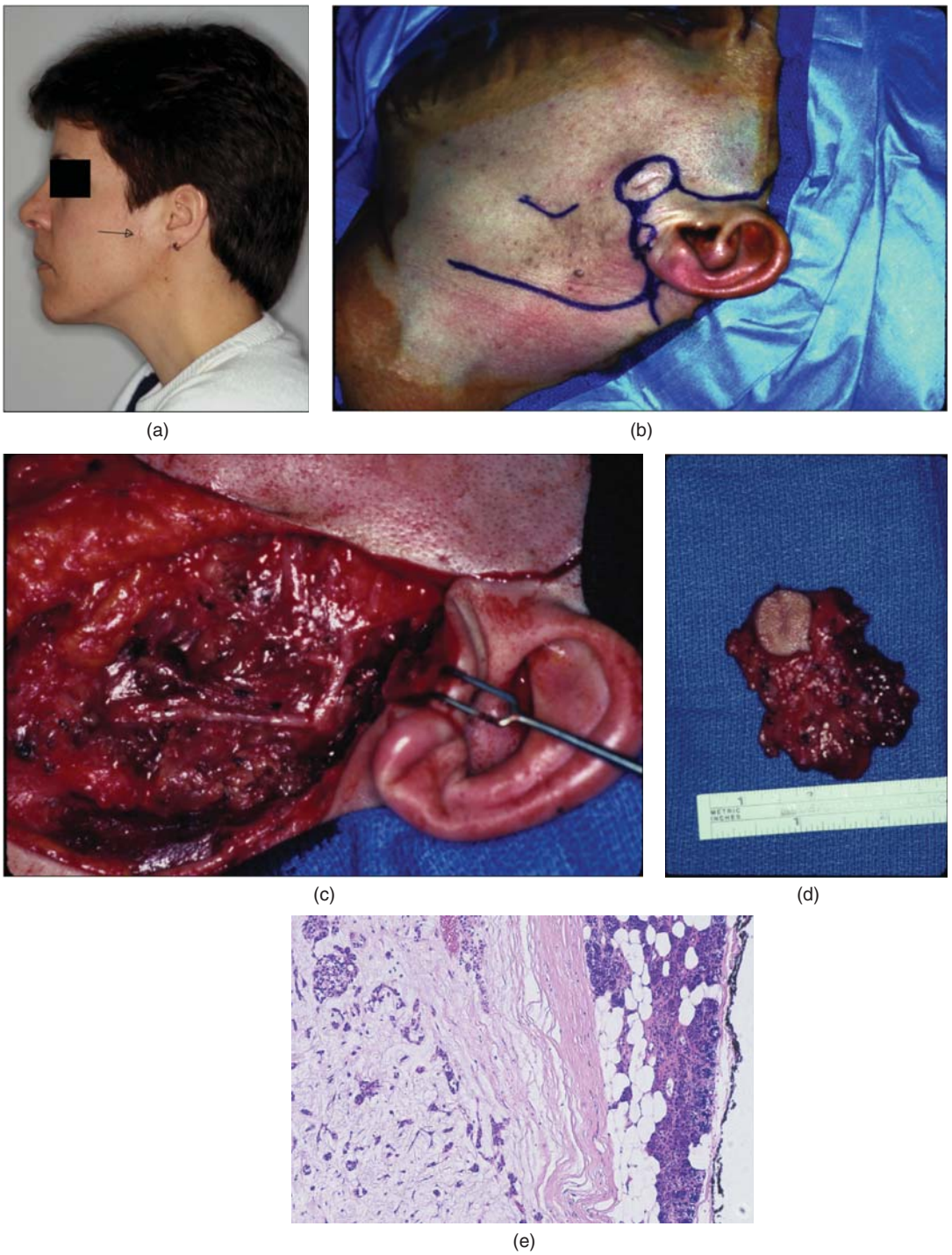


Figure 9.3. (a) A 45-year-old woman with parotid pleomorphic adenoma biopsied through the cheek. The arrow points to the biopsy scar. (b) Surgical incision marked out and includes a skin paddle 1cm. around the biopsy scar. (c) Following superficial parotidectomy with complete nerve dissection. (d) Surgical specimen of parotid with overlying skin. The patient is disease free 10+ years post-surgery. (e) Histopathology confirms the diagnosis of pleomorphic adenoma. Note the marked pseudocapsule of collagenous tissue. The patient is disease free greater than 10 years postoperatively.

addition when extra-capsular dissection (ECD) or limited superficial parotidectomy is contemplated (see the following) it is best to have confirmation of the benign nature of the tumor (O'Brien 2003). There is still controversy as to whether FNAB is mandatory as part of the diagnostic work up for a presumed parotid tumor. Although Schröder, et al. (2000) report a sensitivity of 93.1%, specificity of 99.2% and accuracy of 98.2%, other papers have shown lower figures; sensitivity 81.5% and specificity 97.5% (Longuet, et al. 2001).

Zbären, et al. (2001) recommended FNAB as a valuable adjunct to preoperative diagnosis reporting 86% accuracy, 64% sensitivity and 95% specificity. However, in a study of 6249 participant responses from the database of the College of American Pathologists Inter-laboratory Comparison Program in Non-gynecologic Cytology, the sensitivity and specificity for interpreting salivary tumors as benign or malignant was 73 and 91%. Benign cases with the commonest false positive rates were monomorphic adenoma 53% and intra-parotid lymph node 36%. Malignant salivary gland tumors with the highest false negative rate were acinic cell carcinoma (49%), low grade mucoepidermoid carcinoma (43%), and adenoid cystic carcinoma 33%. It was felt the data confirmed the difficulty inherent in FNAB of salivary glands (Hughes, et al. 2005). A paper from the Memorial Sloan Kettering Hospital concluded that a FNAB biopsy result positive for a malignant or neoplastic process is generally predictive of the final histologic diagnosis, whereas the predictive value of a negative FNAB is low (Cohen, et al. 2004). Combining FNAB with ultrasound guidance can improve accuracy and diagnostic yield especially in difficult tumors such as carcinoma ex pleomorphic adenoma where sampling error is a problem. In the diagnosis of pleomorphic adenomas with ultrasound guided FNAB, sensitivities of 97% and specificity of 98% are published (Carrilo, et al. 2009).

Surgical Management

The basic surgical procedure is the superficial parotidectomy in which the superficial lobe of the parotid is removed preserving the facial nerve unless it is directly infiltrated by tumor. The author's usual incision is the modified Blair or "lazy S." The skin flap is elevated in a plane through the subcutaneous fat superficial to the parotid capsule (Figure 9.4). Recently, the use of a face-lift incision has been advocated to improve esthetic results of the scar (Honig 2005; Meningaud, et al. 2006). These authors have also combined face lift incisions with a separate SMAS (superficial musculoaponeurosis) dissection to eliminate hollowing and reduce Frey syndrome. Concerns regarding access to anteriorly sited tumors when using a face lift approach for parotidectomy do not appear to be borne out in anatomic studies (Nouraei, et al. 2006) (Figures 9.5 and 9.6).

Once the skin flap is elevated the sternocleidomastoid muscle (SCM) is identified with the overlying greater auricular nerve whose branch to the earlobe may be preserved if it does not compromise tumor resection (Figure 9.4e). The anterior border of the SCM is dissected free of the posterior parotid gland, which is retracted anteriorly. Deeper dissection at the superior end of the SCM will allow identification of the posterior belly of the digastric muscle. The facial nerve trunk lies 4 mm superior to the digastric and at the same depth and is an important landmark (Figure 9.7). Next, attention is turned to the preauricular region with sharp and blunt dissection down the cartilage of the external auditory meatus to the bony portion of the meatus. A strip of parotid tissue remains, which separates the cervical from the preauricular dissection and this tissue is carefully dissected away to the depth of the digastric muscle. Some troublesome bleeding has to be controlled with bipolar diathermy under direct vision superficial to where the facial nerve will be identified. The facial nerve trunk can be confirmed with a nerve stimulator and the nerve braches are dissected out peripherally to mobilize and remove the superficial parotid. It is usually best to dissect either the frontal or mandibular branches first depending on the site of the tumor and then proceed stepwise inferiorly or superiorly dissecting the branches in order and staying superficial to the nerves.

If the tumor directly overlies the facial nerve trunk making it impossible to access safely then the peripheral branches can be identified and followed backwards as a retrograde parotidectomy, although this is more tedious. The mandibular branch of the facial nerve, where it crosses the anterior facial vein, or the buccal branch with its close relationship to the parotid duct (Pogrel, et al. 1996), can be found initially. Despite a 66% incidence of weakness 1 week post parotidectomy, normal facial nerve function was present in 99% of 136 retrograde parotidectomies in one series (O'Regan, et al. 2007).

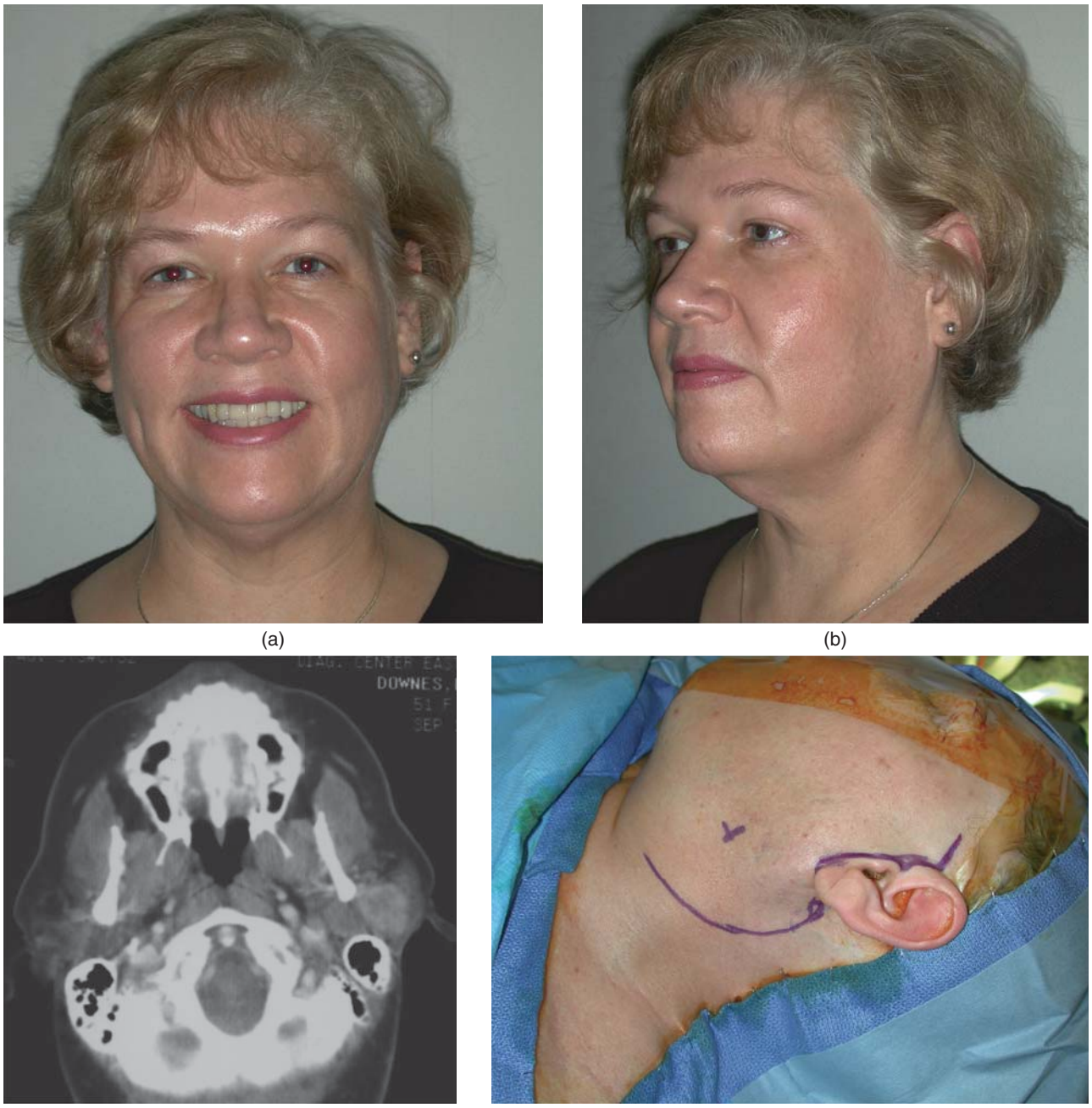
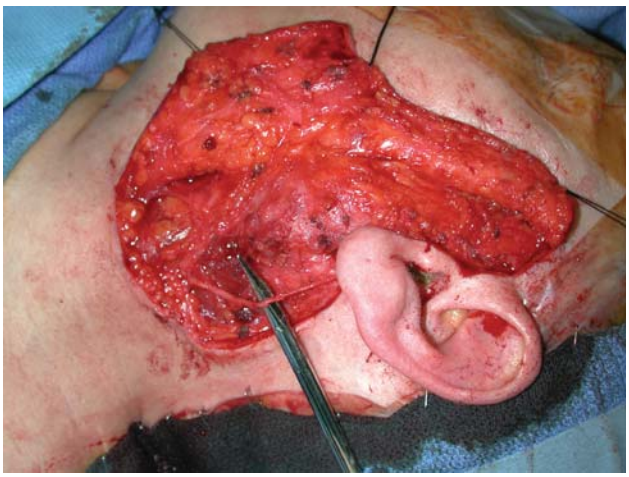


Figure 9.4. (a and b) Patient with pleomorphic adenoma of the left parotid gland, preoperatively. (c) CT scan of left parotid showing superficial lobe tumor. (d) Modified Blair incision. (e) Skin flap raised, the instrument indicated the sensory branch of the greater auricular nerve to the ear which was preserved in this case. (f) The parotidectomy has been performed from inferiorly and the superficial lobe is being retracted superiorly. The arrow indicated the deep surface of the tumor which was adjacent to the nerve bifurcation and has no normal parotid tissue covering the tumor capsule. (g) The surgical specimen the tumor is seen superiorly with no good surrounding "cuff" of tissue. (h) The surgical site post-parotidectomy with complete dissection of the facial nerve. (i) A free abdominal fat graft is placed to reduce "hollowing" which was a concern of the patient. (j and k) 6 months postoperative.



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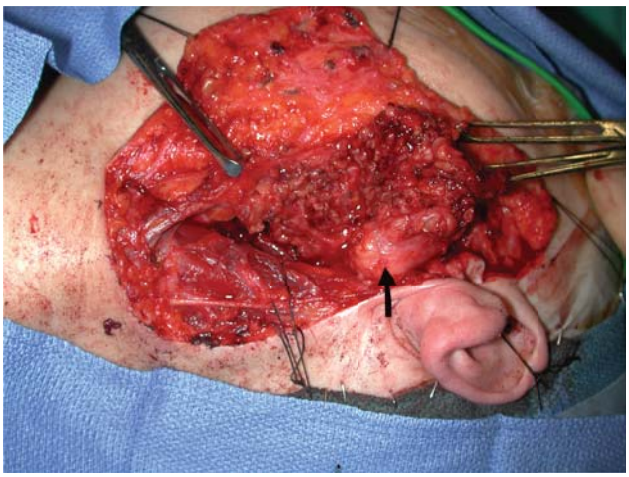

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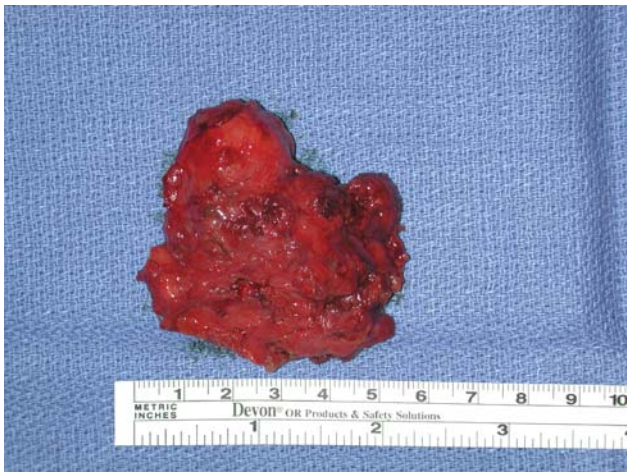
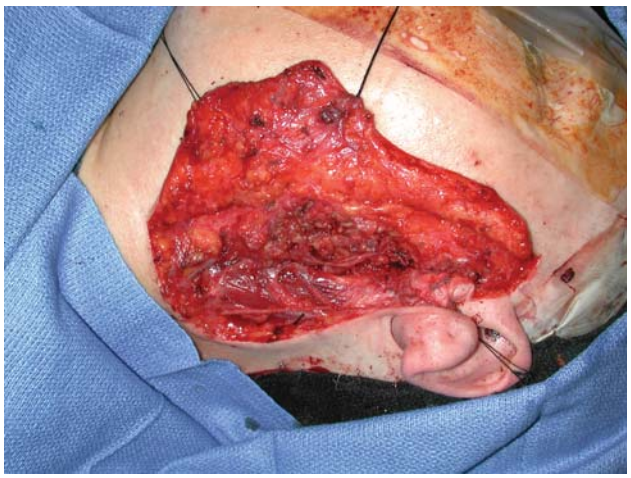


(g)

Figure 9.4. (*Continued*)

In tumors of the deep lobe it is usually necessary to undertake a total parotidectomy. The superficial parotidectomy is performed preserving the facial nerve and dissecting the superficial lobe from superiorly so that it remains attached to the deep lobe inferiorly and at the tail. Most deep lobe tumors will be retromandibular and lie inferior to the trunk of the nerve. The space inferiorly is larger and by gentle retraction of the nerve trunk and blunt dissection around the tumor it can usually be delivered into the neck. In larger tumors the neoplasm may be impacted between the mandible and the mastoid with no means of mobilizing it without either dislocating the mandible forward or a subsigmoid or "C" osteotomy to give more space. As contemporary surgery has evolved more emphasis has been placed on reducing morbidity. Deep lobe tumors may be removed without removing the superficial lobe but leaving it attached anteriorly and then replacing it after excising the deep lobe tumor (Coleela, et al. 2007). This technique preserves facial contour and 84% of glandular function compared to the contralateral parotid.

In those tumors with parapharyngeal extension blind finger enucleation may lead to capsular rupture or cause brisk hemorrhage. In order to visualize and safely remove these tumors an osteotomy of the mandible with or without lip split is utilized (Kolokythas, et al. 2007) (Figures 9.8 and 9.9). Under such circumstances, some patients develop what has been described as first bite



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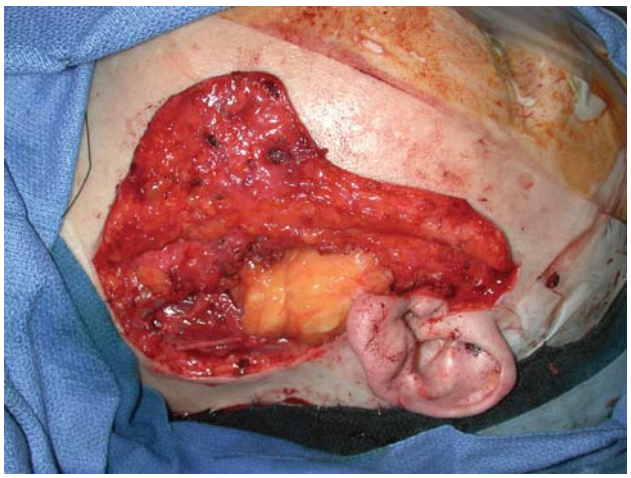

(i)

(j)

(k)

Figure 9.4. (*Continued*)

syndrome, where severe cramping or spasm in the parotid region is experienced by the patient with the first bite of each meal that diminishes over the next several bites (Linkov, et al. 2012). The mechanism is thought to be due to a loss of sympathetic innervation of the parotid gland, specifically related to sacrifice of the sympathetic chain during surgery of the parapharyngeal space. Treatment involves the use of pain medication, acupuncture, and Botox injections.

ACCESSORY PAROTID TUMORS

The accessory parotid gland is closely related to Stenson duct as it curves deep to the anterior border of the masseter muscle. It is present in 21–65% of patients (Frommer 1977; Toh, et al. 1993) and tumors in this gland, which are rare, will present as a cheek mass anterior to the main parotid and may be thought erroneously to be arising in the buccal minor salivary glands. It is important to differentiate between these two as an

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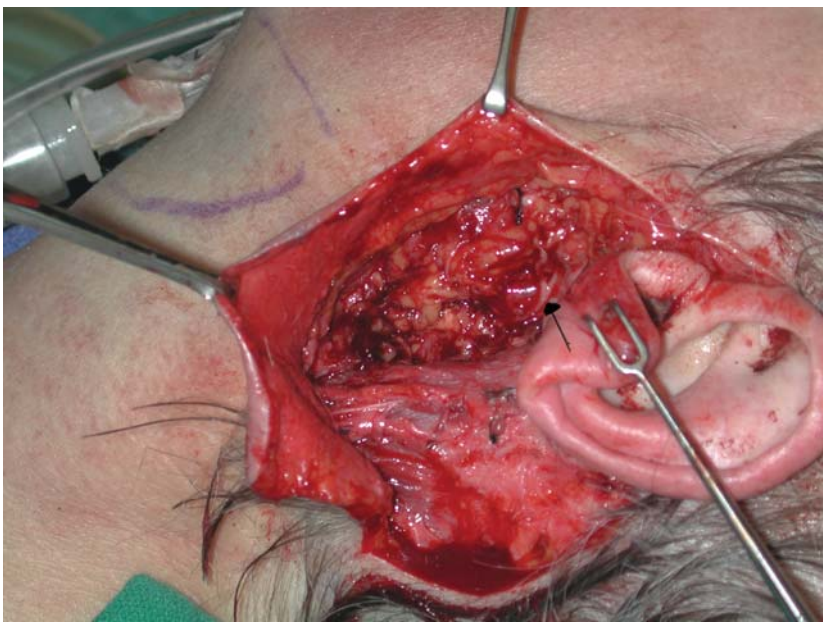
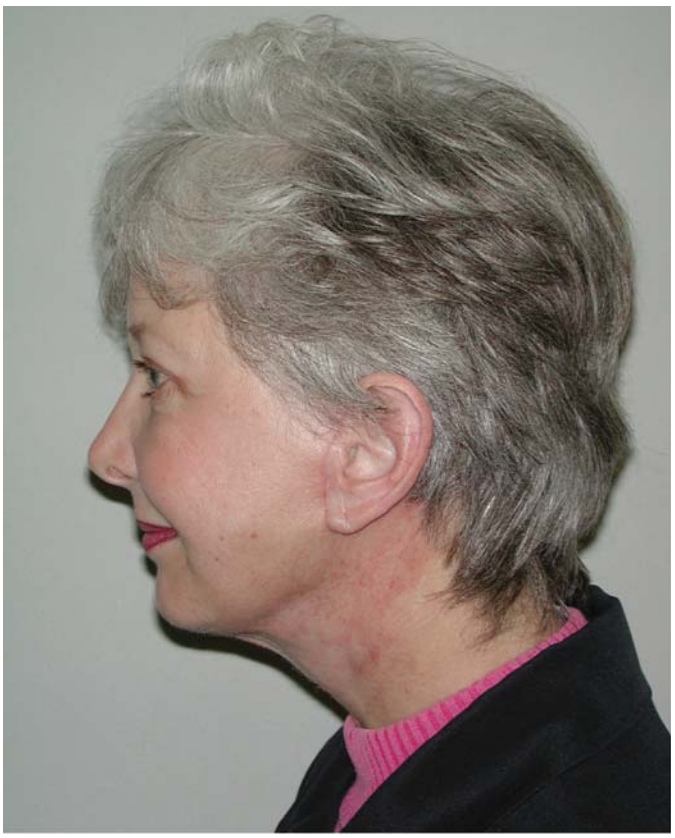
(b)



(c)

Figure 9.5. (a and b) Pre-operative facial views of patient with left parotid pleomorphic adenoma. Patient requests bilateral face lift at the same time as parotidectomy. (c) Surgical access through face lift incision running into occipital hair line. Arrow shows facial nerve trunk being dissected. (d and e) 6 months postoperative notice absence of neck incision. (Esthetic portions of this case undertaken by Dr. A Pazoki DDS MD.)

(d)



(e)

Figure 9.5. (*Continued*)

intra-oral approach is contraindicated for accessory lobe tumors due to the vicinity of buccal branches of the facial nerve and a higher propensity for malignant neoplasm in the accessory gland (Yang, et al. 2011). In one recent review of 152 cases of accessory parotid gland tumors, 30% were found to be malignant (Newberry, et al. 2014).

It is our practice to use an extended parotidectomy approach tracing the buccal nerves distally to protect them (Figure 9.10). There is currently a controversy between surgeons regarding superficial parotidectomy or extracapsular dissection. This important topic will be discussed later in the section on pleomorphic adenomas.

BENIGN TUMORS

Pleomorphic Adenoma (PA)

The PA is the commonest benign salivary gland tumor and the commonest salivary tumor overall, although it is comparatively rare in young children. It is slow growing and can reach giant proportions if neglected, and there is a 2–4% malignant change. PA will recur if the tumor is inadequately removed. Although PAs have a pseudo-capsule of compressed fibrous tissue, the buds and pseudopodia from the tumor involve the capsule so that simple enucleation will leave tumor remnants and lead to multifocal recurrence. The concept of whether the capsule is incomplete and whether pseudopodia of tumor involve the parotid tissue is currently being questioned and with it the need for complete superficial parotidectomy. Although parotidectomy is supposed to remove PAs with a cuff or margin of normal tissue to prevent recurrence, the tumor's proximity to the facial nerve frequently means that the dissection at some points leaves no tissue around the capsule. In a recent histologic analysis of the capsular form in PAs, 81% showed capsular exposure following parotidectomy or submandibular gland excision (Webb and Eveson 2001) (Figure 9.4f). This paper also showed 57% bosselations, 33% enveloping

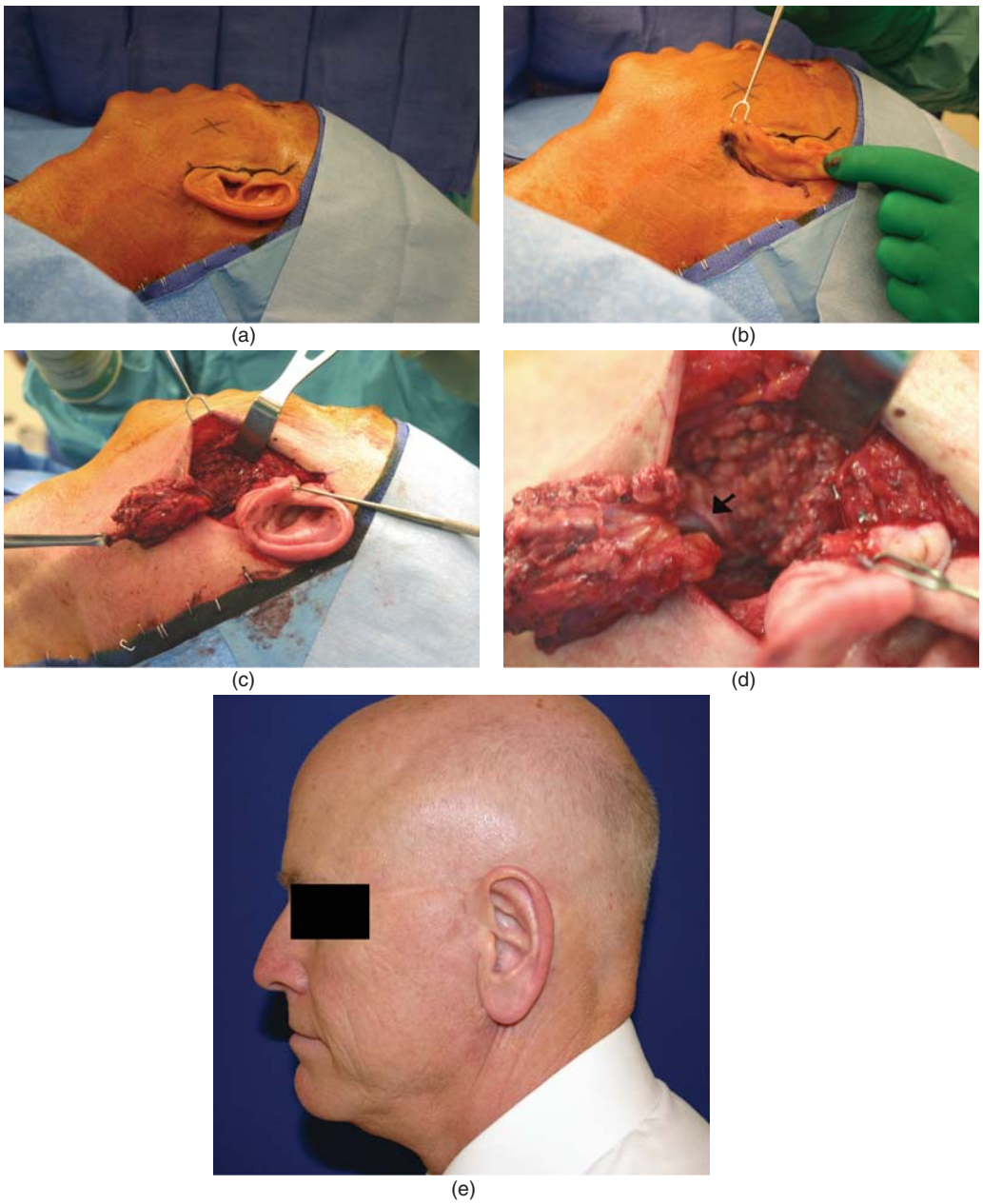


Figure 9.6. (a) Preauricular portion of omega face lift incision for parotidectomy for benign cystic lesion in the retromandibular portion of the superficial lobe of the left parotid gland. (b) Post-auricular portion of omega incision funs in the post-auricular sulcus. (c) A partial parotidectomy of the retroauricular portion of the superficial lobe is almost completed. The specimen is pedicled to the remains of the parotid tail. (d) Close-up of the dissection. Arrow points to the mandibulo-cervical trunk, which was the only branch of the facial nerve that required dissection, as it crosses superficial to the retromandibular vein. (e) The patient is noted 3 months postoperatively with no visibile scar.

of the capsule with 42% microinvasion, and 12% "tumor buds" in the capsule; and large >25 mm hypocellular tumors had thinner capsules possibly easier to rupture at surgery. This article suggested that a minimum of 1 mm of normal tissue around PSA was required as a margin. However, in an article reviewing 475 PAs of the superficial lobe of the parotid, 380 treated by extracapsular dissection and 95 by superficial parotidectomy, there was no difference in recurrence rate or permanent facial

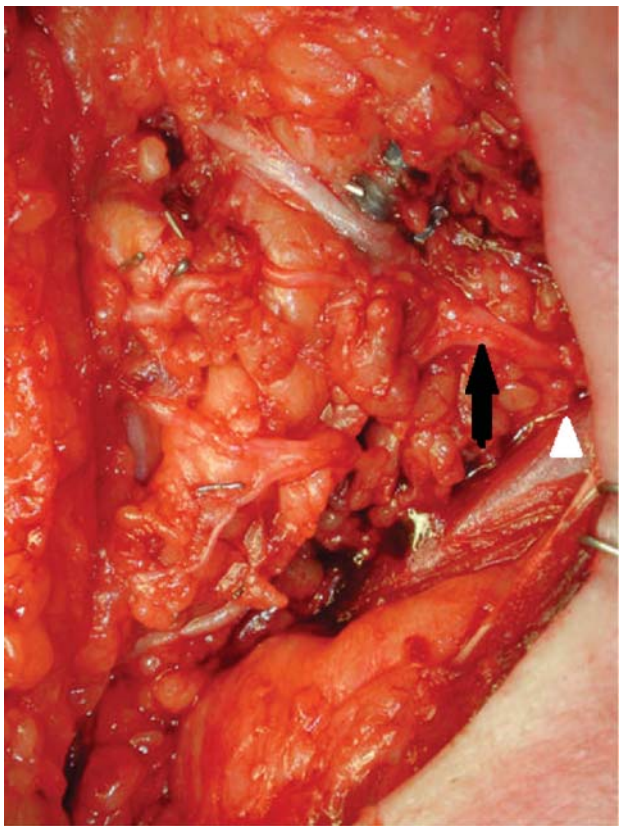
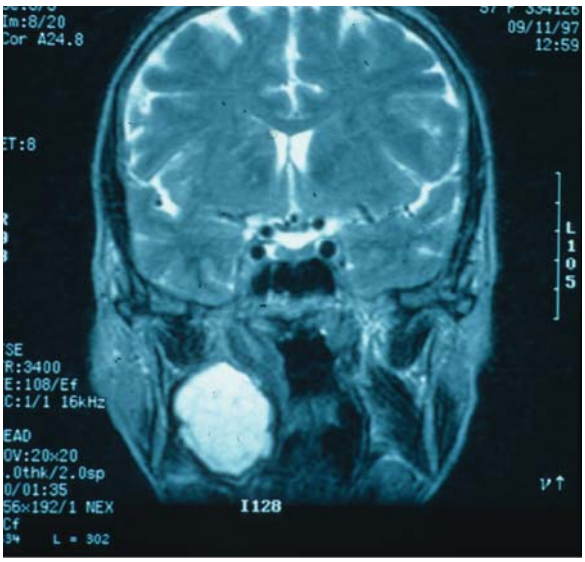


Figure 9.7. The facial nerve trunk (large arrow) is noted 4 mm superior to and at the same depth as the upper border of the posterior belly of the digastric muscle (indicated by apex of triangle).

nerve palsy (McGurk, et al. 1996). These surgeons postulated that tumor buds or micro-invasion into the capsule had little significance and that extracapsular dissection could be done safely. In 1999, a series of 59 partial parotidectomies with selective nerve dissection for benign and low-grade malignant tumors reported a zero incidence of permanent facial nerve paralysis or paresis and zero recurrence (Witt 1999). Although Witt in a later paper confirmed that capsular exposure occurred in virtually all types of parotid surgery and could find no difference in recurrence, capsular rupture, tumor-facial nerve interface, and permanent facial palsy between total parotidectomy, superficial parotidectomy, and extracapsular dissection, he recommended against minimum margin resection in extra capsular dissection (Witt 2002). Further evidence for extracapsular dissection is provided by a series of 83 cases in which the overall recurrence rate was 6%, but 17.6% when tumor itself was at the margins, however, cases with margins of <1 mm had a recurrence of only 1.8% (Ghosh, et al. 2003). They also reported that intra-operative capsular rupture and microscopic invasion of the capsule had no influence on recurrence suggesting that a fraction of a millimeter of normal tissue was an adequate margin and that only tumors that actually involved the margin were at risk for recurrence. These authors recommend that preservation of vital structures is a more important consideration than preserving a cuff of normal tissue.

In contrast, Piekarski, et al. (2004) found a recurrence rate of 8.2% and an unacceptable rate of complications with extra capsular dissection (ECD), and did not recommend the technique as too "technically demanding." In a separate publication with 213 patients who were operated for pleomorphic adenoma of the parotid, five of nine primary tumors (56%), which recurred, were found to have pseudopodia extending outside the capsule on histologic review. This was statistically higher than the examined cases that did not recur (8%) and the authors concluded that pseudopodia extending outside the capsule were a significant risk for recurrence (Henriksson, et al. 1998). Interestingly, in the same study only 2 of 28 cases that ruptured during surgical removal recurred (7.1%), which was not significantly different to the 4.1% recurrence rate for the tumors that had no rupture. A further cautionary note is raised by the histologic analysis of (Zbären and Stauffer 2007) in which 160 of 218 (73%) of PAs were found to have adverse capsular characteristics; 33% with an incomplete capsule and 13% with satellite nodules. These were most frequently seen in the stroma rich myxoid subtype. Similar findings with stroma rich PAs showing 71% of focal absence of a capsule and 33% of satellite nodules have been reported with recommendations against local dissection (Stennert, et al. 2004.)

It does not appear that extracapsular dissection is just a "euphemism for enucleation" as some have claimed, as recurrence rates are comparable to parotidectomy and most papers show lower morbidity. The exact margin required for complete removal of PA remains controversial. A criticism of extracapsular dissection has been that even if this technique is suitable for a presumed benign PA, what should the surgeon do if the final histopathologic diagnosis turns out to be malignant? In a review of 662 clinically benign parotid tumors 503 treated by extra-capsular dissection and 159 by superficial parotidectomy, 5% were malignant and



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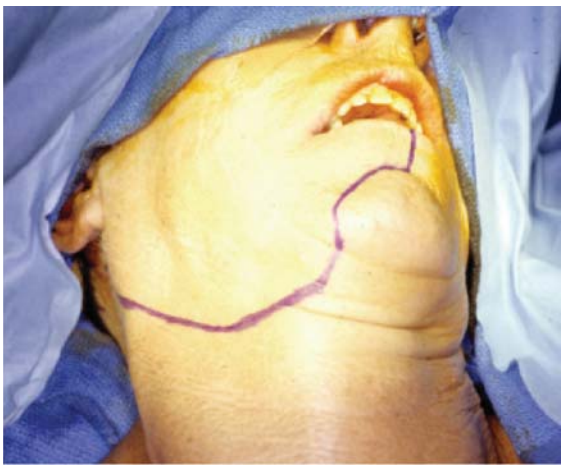

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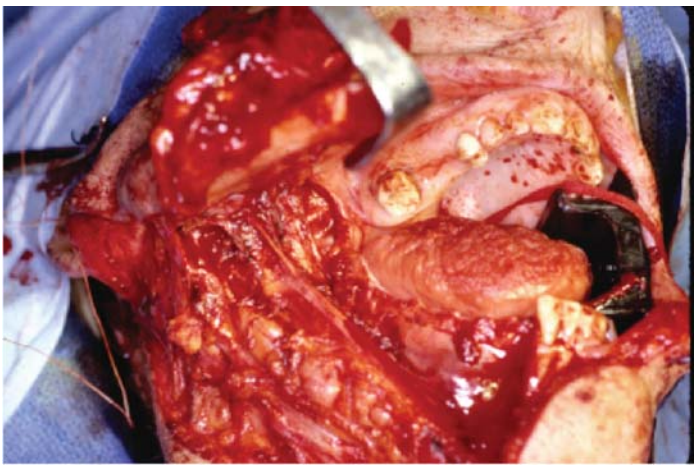


(c)

Figure 9.8. (a) MR shows parapharyngeal pleomorphic adenoma. (b) Standard lip split incision for mandibulotomy. (c) Mandible is retracted out of the field and the PSA is dissected preserving the overlying lingual nerve.

there was no difference in 5- or 10-year survival or recurrence rates between the malignant tumors in the two surgical groups, although morbidity was significantly lower in the extra-capsular dissection group (McGurk, et al. 2003).

The current evidence is not conclusive but two large meta-analyses published recently comparing ECD to superficial parotidectomy for benign tumors have both concluded that ECD is a viable treatment option. In 2012, Albergotti, et al. performed a meta-analysis on nine studies (1882 patients), and found no significant difference between the ECD and parotidectomy groups in terms of recurrence. There was a significantly lower transient facial nerve paresis but not for permanent palsy and less Frey syndrome in the ECD cohort. In 2014 Foresta, et al. reviewed 1152 articles and 123 studies were included in their meta-analysis. Their conclusions were very similar to the previous analysis with parotidectomy having a higher recurrence rate, incidence of facial nerve paralysis, and Frey syndrome. Their conclusion was that ECD was a good surgical treatment for

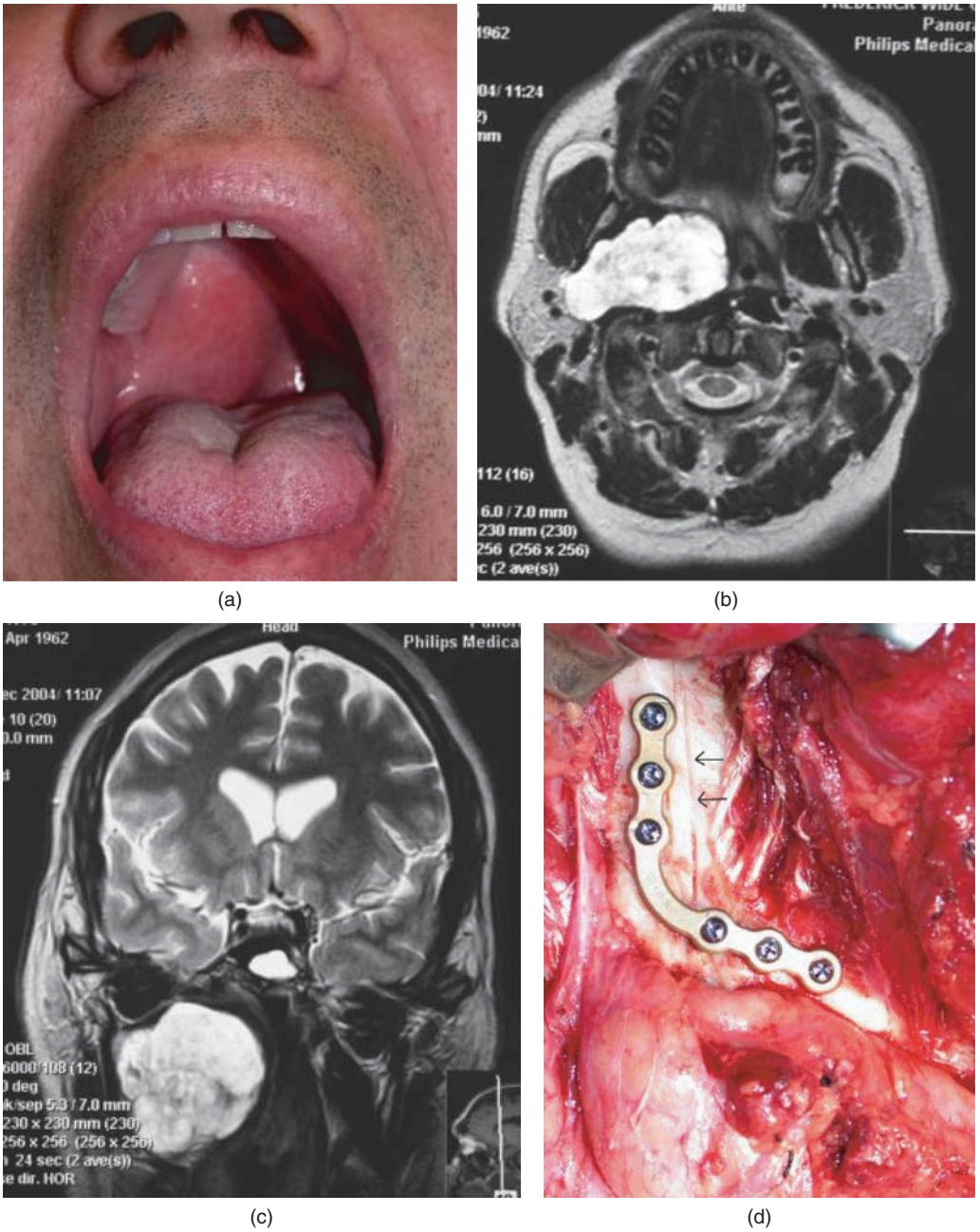
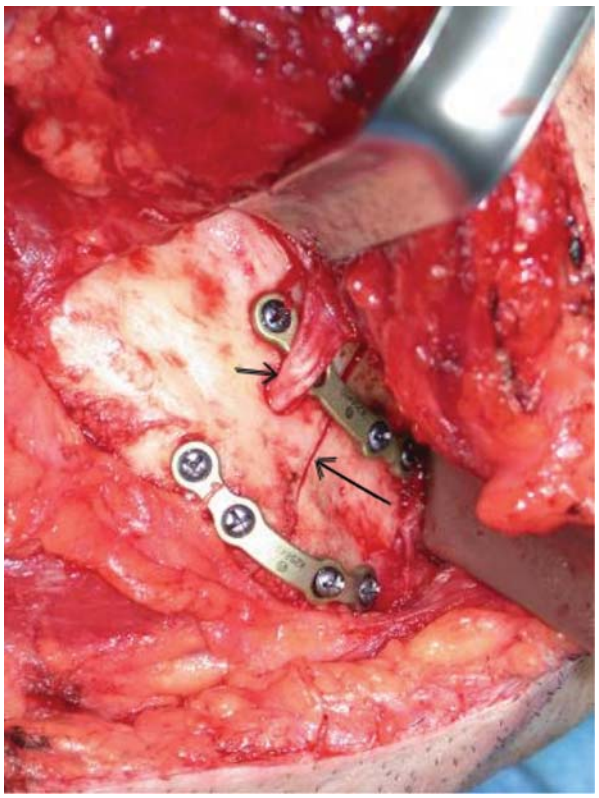


Figure 9.9. (a) Deep lobe parotid tumor with parapharyngeal extension presenting as a palatal mass. (b and c) MR axial and coronal scans show the tumor in the lateral pharyngeal space. (d) The mandible is accessed via a cervical incision from mastoid to chin without lip split. Subsigmoid osteotomy cut marked with saw through buccal cortex only (arrows) and plate has been applied prior to completing the osteotomy. (e) Osteotomy marked with a saw through the buccal cortex (long arrow) anterior to the mental nerve (short arrow). Two miniplates applied prior to completing the osteotomy. (f) The plates are removed and the double osteotomy is completed and the osteotomized hemi-mandible retracted upward and rotated to expose the lateral pharyngeal space and the tumor is being delivered under direct vision. (g) The final specimen, which was PA seen in relation to the mandible. (h) The post-resection tumor bed. The plates are reapplied to reconstruct the original position and occlusion for the mandible.



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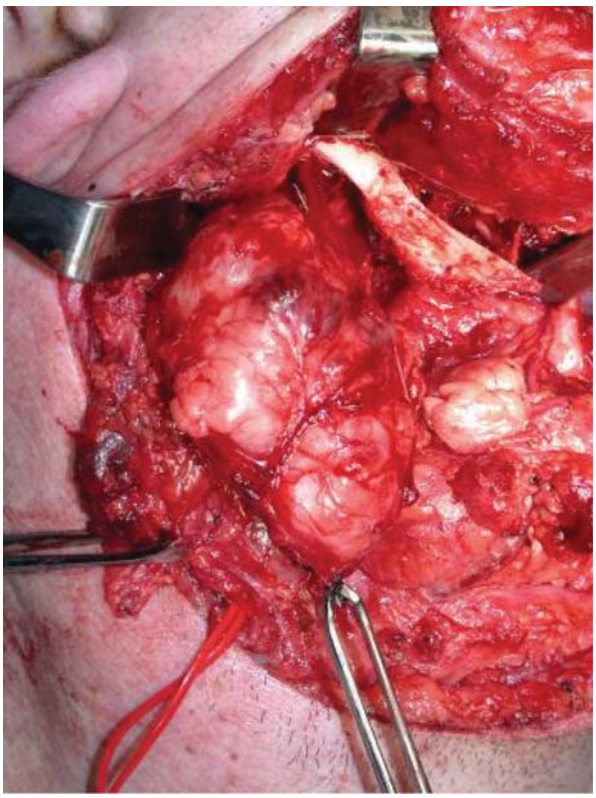

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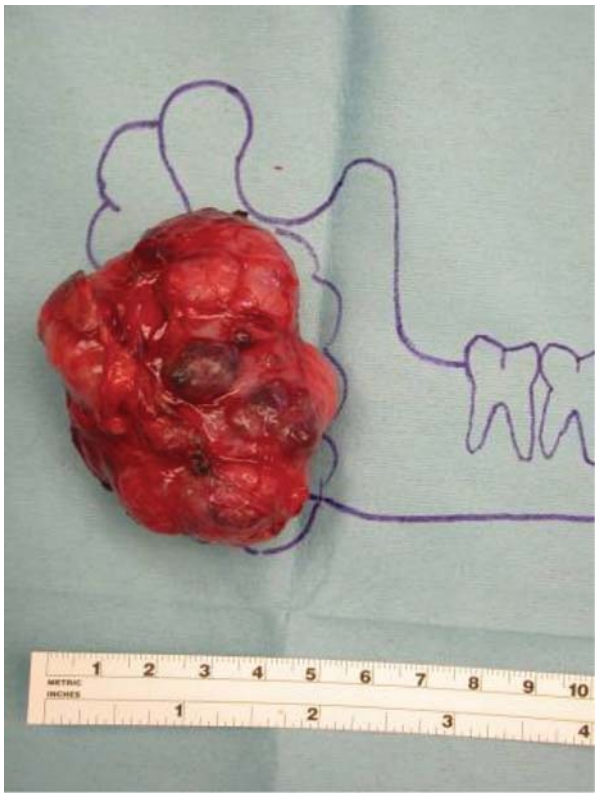

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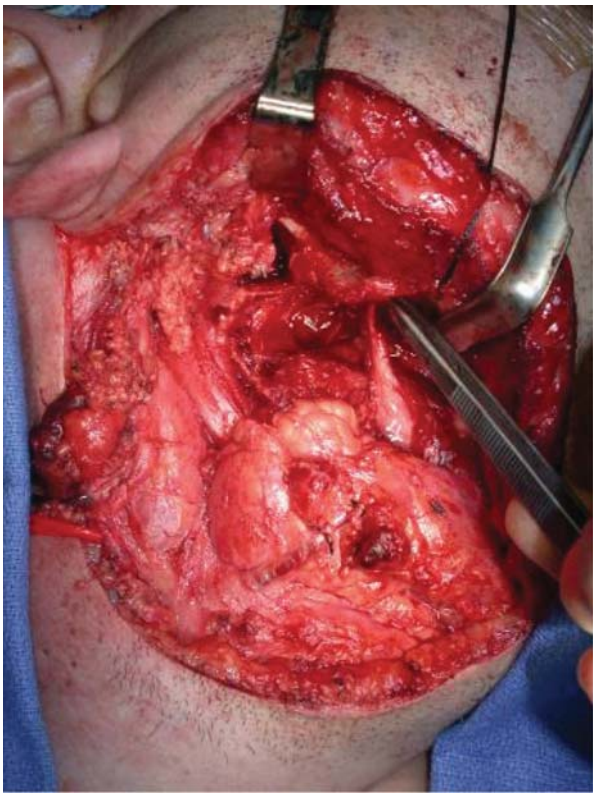


(h)

Figure 9.9. (*Continued*)

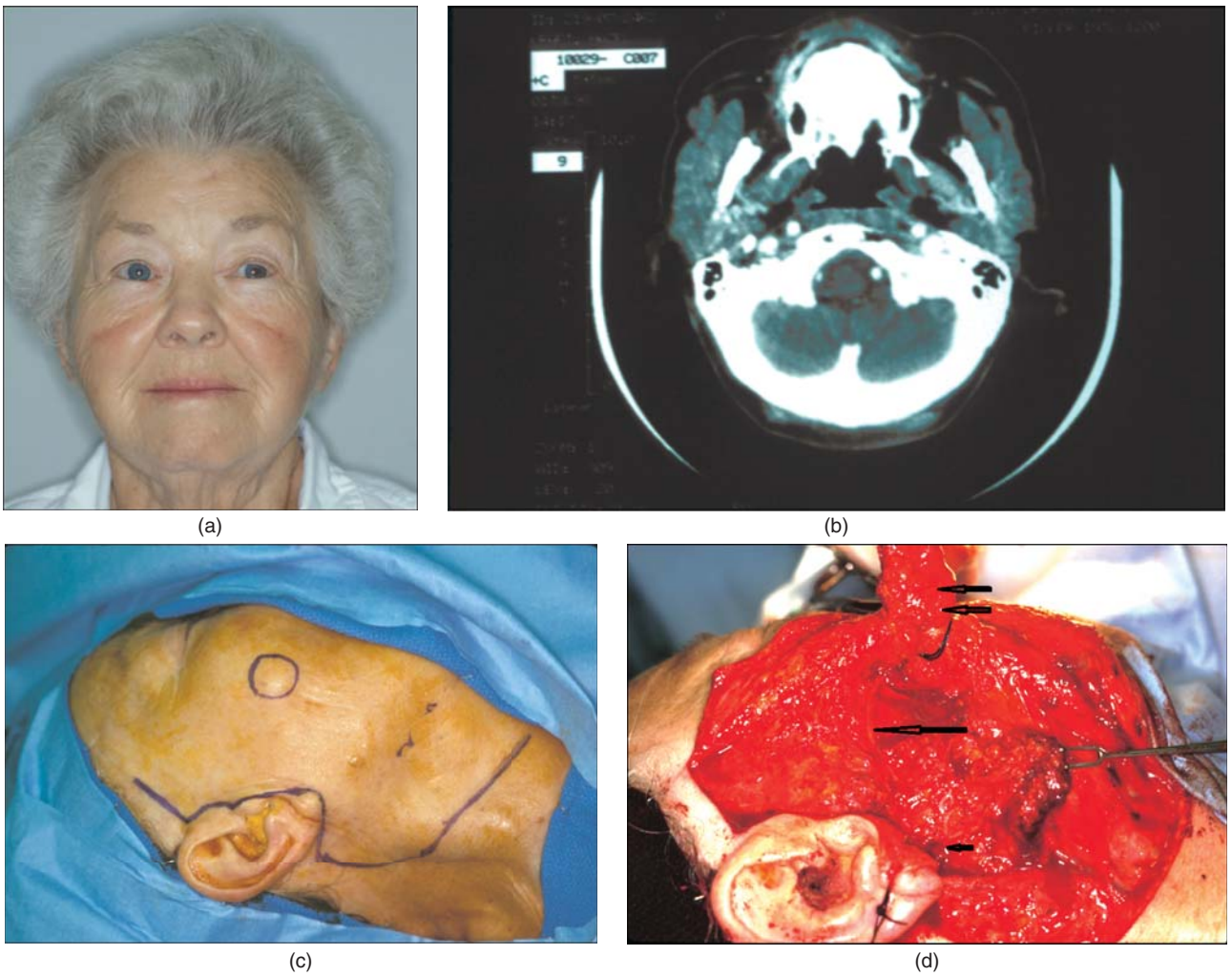


Figure 9.10. (a) Female patient with fullness and mass in anterior right cheek. (b) Axial CT shows a mass in the accessory parotid gland. (c) Proposed extended Blair incision to allow access anteriorly. (d) Intraoperative view shows facial nerve trunk, and by dissecting the facial nerve branches anteriorly a strip of superficial parotid has been elevated along with the accessory parotid gland and tumor. The buccal branches are preserved and the long single arrow shows the superior buccal branch.

benign parotid tumors <4 cm in the superficial lobe with no facial nerve involvement.

Despite these studies, it should be noted that Witt and Rejto (2009), in a 38-year Ovid Medline search (1970–2008) with statistical analysis, demonstrated the complete opposite results. These authors concluded that ECD had a significantly higher recurrence rate and permanent facial nerve palsy than parotidectomy.

It does appear that ECD has a place in the surgical management of smaller benign superficial lobe tumors of the parotid gland; however, it is not a procedure for the inexperienced parotid surgeon.

A superficial lobe parotid tumor that is clinically benign and diagnosed as a PA on FNAB may also be treated with a limited superficial parotidectomy (without complete dissection of the facial nerve) and may not require a complete superficial parotidectomy for cure (O'Brien 2003). This is probably most commonly undertaken for tumors in the parotid tail. In their 2013 review Zbären, et al. concluded that formal parotidectomy is not mandatory, and that ECD in the hands of a novice/occasional parotid surgeon may result in higher recurrence. These authors recommend partial superficial parotidectomy as removing a

better cuff than ECD to minimize recurrence but less healthy tissue than formal parotidectomy thus reducing complications (Zbären, et al. 2013) (Figure 9.11).

Deep lobe PAs are usually larger and frequently will have less surrounding parotid tissue especially deeply where they abut the prevertebral muscles of the neck. However, the inability to obtain a surrounding cuff of parotid does not seem to lead to increased recurrence. Harney et al. (2003) found that the capsules of deep lobe tumors were significantly thicker and that there was less extra-capsular extension of tumor in the deep lobe tumors (58% vs 79%), which may explain this phenomena.

If the capsule of the tumor is ruptured during surgery then recurrence is not inevitable and perhaps liberal irrigation with sterile water

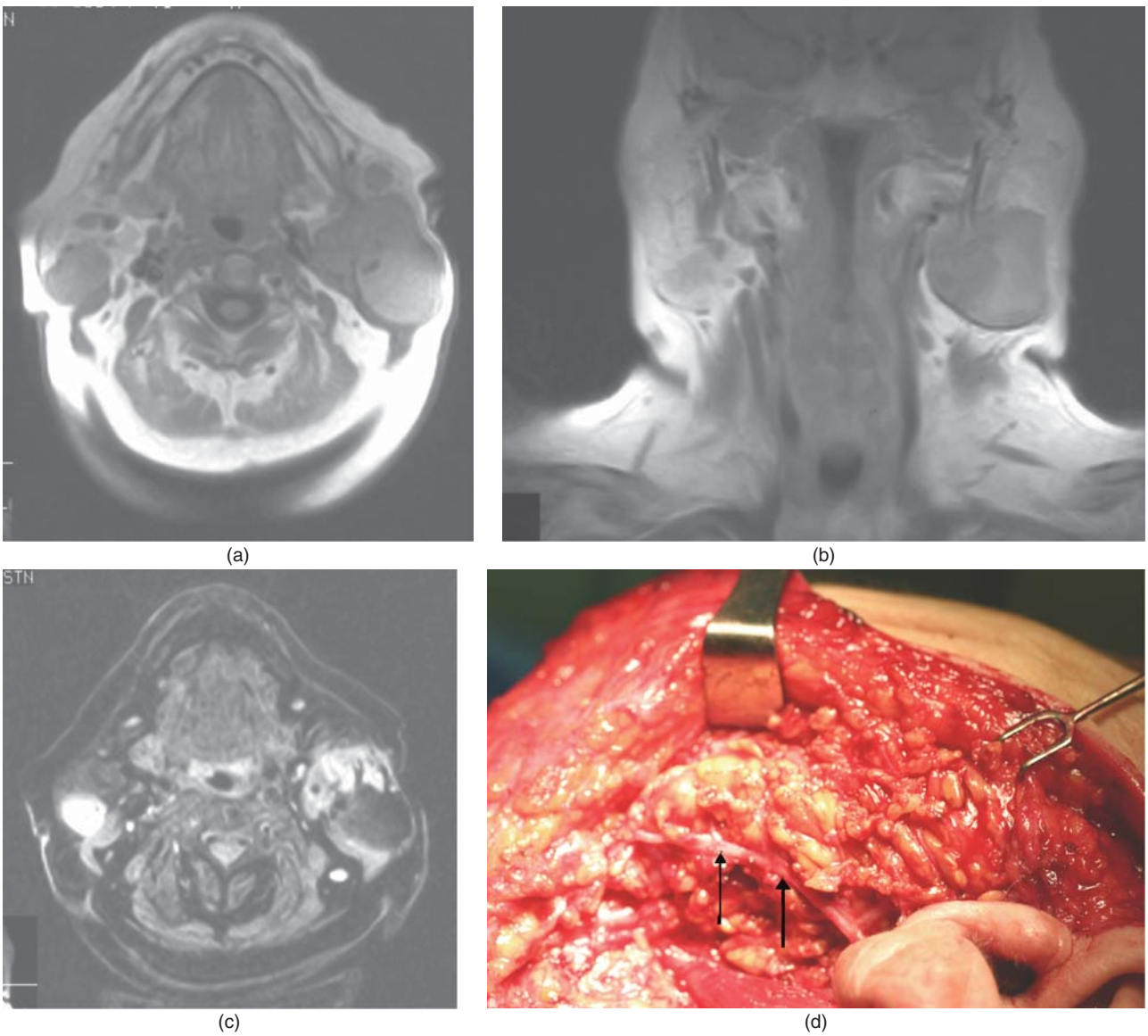
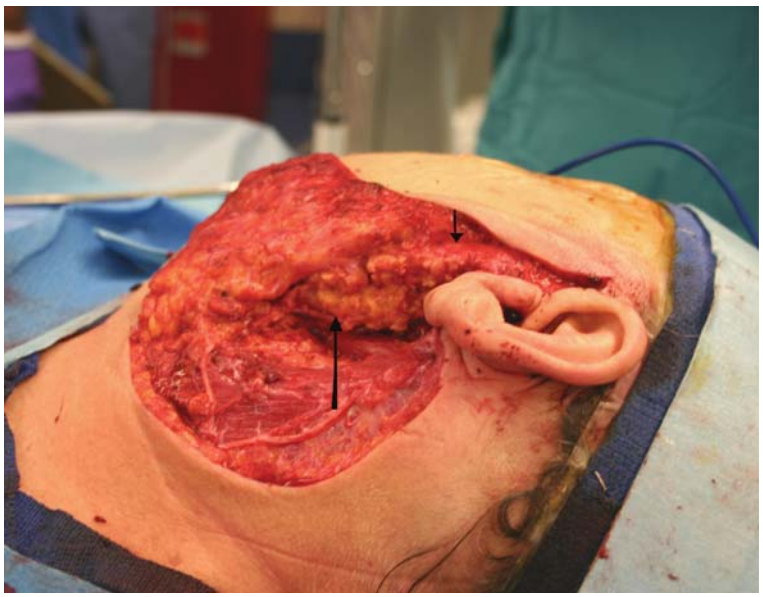


Figure 9.11. (a–c) MR images of large cystic benign tumor in the parotid tail. (d) Following partial parotidectomy the two arrows point to the dissected cervico-mandibular branch of the facial nerve, the parotid tail tumor have been resected inferior to this nerve branch. The upper branches of the facial nerve have not been dissected in this case. (e) The long arrow points to the resected parotid tail region while the shorter arrow points to the remaining superficial parotid lobe preserved intact. (f) Surgical specimen.



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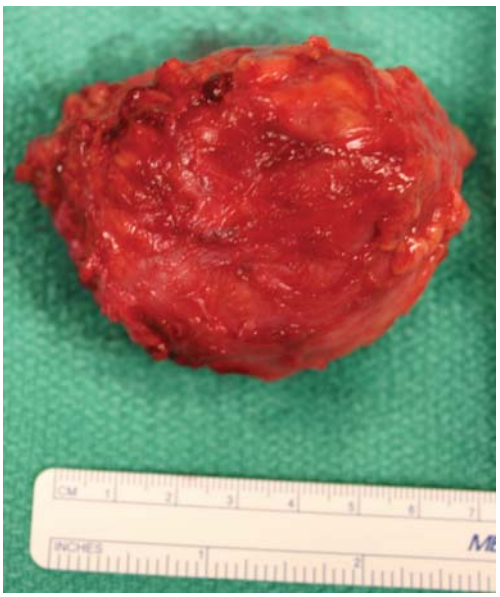
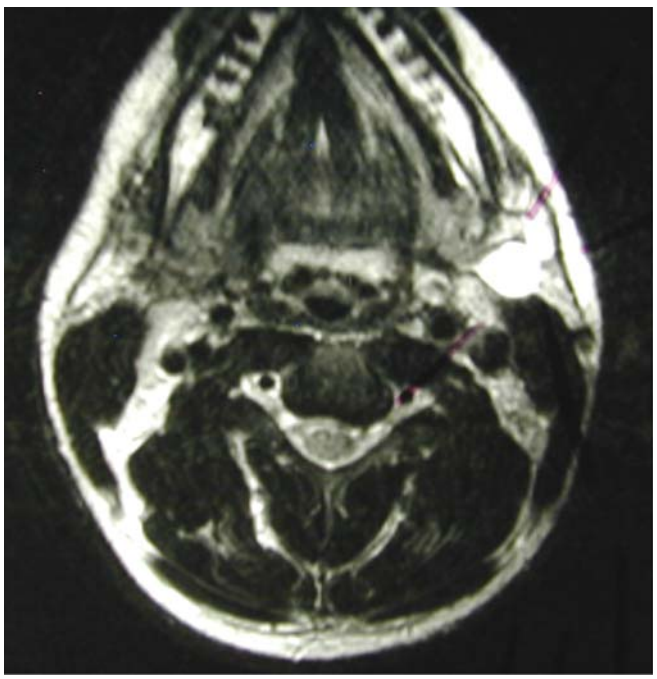


(f)

Figure 9.11. (*Continued*)

followed by normal saline may be tumoricidal (Webb and Eveson 2001). When recurrence occurs it is frequently multinodular (Figures 9.12 and 9.13) and requires more radical en bloc surgery with excision of the previous scar, muscle, overlying skin, and facial nerve if they are involved. Maxwell, et al. (2004), in a retrospective study of 35 patients treated with surgery alone, found a locoregional



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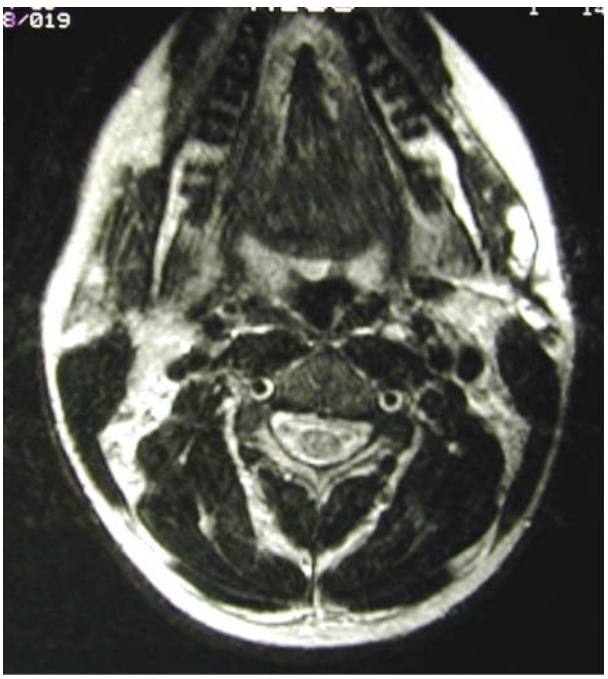
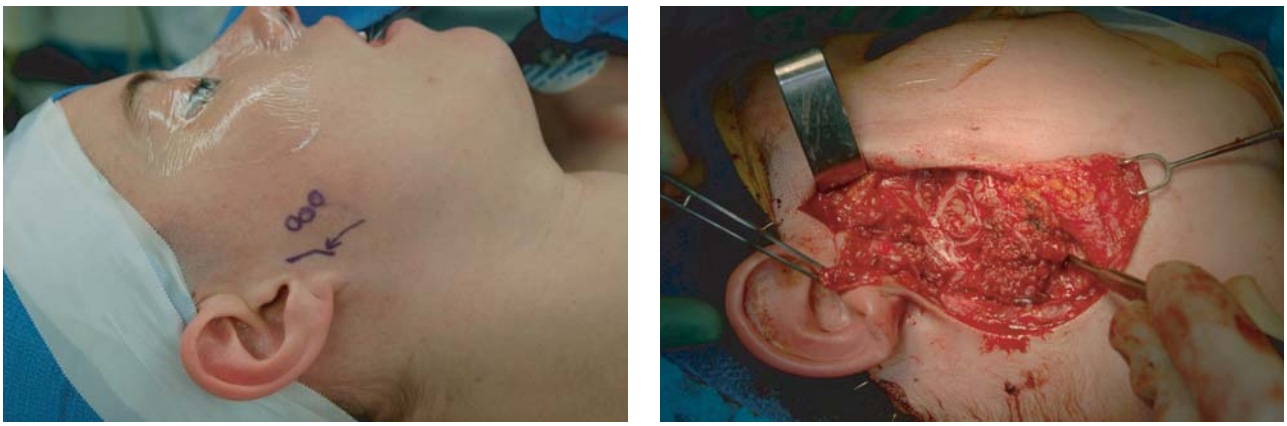


(b)

Figure 9.12. (a) Two large nodules of recurrent pleomorphic adenoma exist in the left parotid gland. (b) Two smaller nodules are seen in the parotid tail.



(a) (b)

Figure 9.13. (a) A 20-year-old woman who previously had a "cyst" enucleated now presents with multinodular recurrence of pleomorphic adenoma in the superficial parotid. The surgical marking pen delineated three palpable nodules and arrow points to the 1.5 cm incision in front of the ear lobe used for the original surgery. (b) Surgery consists of parotidectomy with excision of the previous skin incision. The superficial lobe is being retracted inferiorly. The instrument points to one of the tumor nodules.

control of 77% with a malignant transformation of 5.7%. In a separate study of 42 cases of multi nodular recurrence (6 with prior radiation) there were 2 patients with malignant transformation who died of distant metastases. Twelve patients had subtotal parotidectomy, 25 total parotidectomy, 5 subtotal petrosectomy and 14 had facial nerve resection. Seven patients of 36 who were followed developed further recurrences (19.4%), all of whom had only undergone subtotal parotidectomy (Leonetti, et al. 2005). In a further series of 33 patients, 73% multifocal, 9% with malignant transformation, treated surgically; 6 (18%) recurred at an average of 9 years, and 23% of patients with initial enucleation and 14% with initial superficial parotidectomy, had permanent partial facial nerve injury (Zbären, et al. 2006b). Renehan, et al. (1996) reviewed 144 cases of recurrent PA and suggested a role for radiation in multi nodular cases. A recent paper of 34 cases of recurrent PSA with radiation therapy post gross resection shows a 20-year actuarial control rate of 94% (Chen, et al. 2006).

WARTHIN TUMOR

The Warthin tumor is the second commonest benign tumor of the parotid. If it is diagnosed when small and asymptomatic it may not require treatment in an elderly or infirm patient. There is a 12% incidence of multiple ipsilateral or bilateral tumors. There appears to be a link to heavy smoking and bilateral Warthin tumors (Klussman, et al. 2006). Eight percent of these tumors occur in extra-parotid cervical lymph nodes and may be found at the time of parotidectomy or serendipitously in neck dissection specimens. Treatment is as for PA. Warthin tumors have a tendency to occur in the parotid tail where the majority of parotid lymph nodes occur so partial parotidectomy is often all that is required.

MALIGNANT TUMORS

Principles of Management of Parotid Carcinoma

There is no universally agreed method for managing parotid cancer; however, prognosis and management are related to two variables; the histologic classification/grade of the tumor and the staging. In reviewing 2465 patients with carcinoma of parotid and submandibular glands Wahlberg, et al. (2002) found 10-year survival rates of 88% acinic cell carcinoma, 80% mucoepidermoid carcinoma (MEC), 74% adenoid cystic carcinoma (ACC), but only 55% adenocarcinoma unspecified, and 44% undifferentiated carcinoma. It should be noted that 5-year survival figures for ACC will give an artificially high value as late local recurrence and distant metastasis continues over a 20+ year period. Harbo, et al. (2002) also found acinic cell carcinoma to have the best 10-year survival, but

in their Cox hazard regression analysis found T stage, N stage, M stage, and histologic differentiation to be significant in predicting prognosis and recommended the use of both staging and histologic diagnosis to assess prognosis. In other series, significant factors include extraglandular extension, aggressive histology, and nodal disease (Bhattacharyya and Fried 2005), histologic grade, T stage, N stage, and facial nerve dysfunction (Lima, et al. 2005), and N stage and perineural involvement (Hocwald, et al. 2001).

The only other predictor of adverse prognosis reported in several series was advancing age, (Bhattacharyya and Fried 2005; Lima, et al. 2005; Kirkbridge, et al. 2001).

The reported survival related to stage varies between authors, which may reflect differences in therapy as well as different patterns of histopathology. Luukkaa, et al. (2005) found 5-year survival Stage I–IV to be 78, 25, 21, and 23%, while Lima, et al. (2005) found 10-year disease specific survival Stage I–IV to be 97, 81, 56, and 20%.

In considering management, Kaplan and Johns (1986) divide parotid cancers into four groups to recommend treatment. Group I T1–2 low-grade tumors are treated by parotidectomy with preservation of the facial nerve (Figures 9.14 and 9.15). Group II T1–2 high grade are treated with parotidectomy, plus first echelon nodes removal and post-operative radiation therapy (RT) (Figure 9.16). Group III T3 tumors any positive nodes and recurrent tumor not in group IV, are treated with radical parotidectomy with sacrifice of the facial nerve if necessary and radical neck dissection plus postoperative RT. Group IV includes T4 and tumors with significant local extension and are treated by radical parotidectomy plus skin, muscle, and bone as indicated with radical neck dissection and postoperative radiation therapy (see Figure 14.16).

Controversy exists in the exact indications for RT and adjuvant therapy, neck dissection, and facial nerve sacrifice. The majority of recent papers do show that RT is indicated for advanced parotid carcinoma and confers a survival benefit (Bhattacharyya and Fried 2005), or longer disease free survival (Hocwald, et al. 2001). However, there is a move towards suggesting RT for earlier stage disease. Zbären, et al. (2006a) retrospectively analyzed T1–2 carcinomas with and without postoperative RT and found local recurrence rates of 3 and 33%, respectively and actuarial and disease free survival of 93 and 92% with, and 83 and 70% without RT. In an earlier publication from the same unit RT was suggested not just for high-grade tumors but low-grade T2–4 (Zbären, et al. 2003). So perhaps RT is indicated for earlier stage disease than was previously recommended. The latest data regarding fast neutron therapy in the management of advanced salivary cancer with gross residual disease shows a 6-year local-regional control of 59%, and 100% with no evidence of gross residual disease (Douglas, et al. 2003).

Benefits of chemotherapy have not been clearly demonstrated for parotid cancer (see Chapter 13). A recent critical literature review found a very low evidence of evidence to support the addition of chemotherapy to radiation in salivary gland cancer (Cerda, et al. 2014). However, high grade salivary duct cancer that is HER-2 positive may be treated with trastuzumab as targeted therapy (similarly to ductal carcinoma of the breast). Although most papers are case reports, in one series of 13 patients, 8 adjuvant and 5 palliative with metastatic disease, there was a 62% response rate for adjuvant patients with 5/8 disease free at 2 years. All five of the metastatic patients responded, with a median duration of response of 18 months and one patient had no evidence of disease 52 months following treatment (Limaye, et al. 2013). We have successfully treated one patient with metastatic salivary duct carcinoma.

Similarly, although lymph node dissection is recommended for positive nodes and high-grade tumors, there is an increasing interest in the N0 neck. Occult metastasis rates of 22–45% (Zbären, et al. 2003; Stennert, et al. 2003) led these authors to recommend an elective neck dissection in the N0 neck for parotid cancer (Figure 9.17). Elective neck dissection for high-grade tumors and >T2 low grade tumors should encompass levels I-III and upper V (Teymoortash and Werner 2002). In comparing elective neck dissection for the N0 neck against observation, Zbären, et al. (2005) found an actuarial and disease free survival of 80 and 86% for the elective neck dissection patients versus 83 and 69% for the observation group in a retrospective study. In squamous cell carcinoma of the parotid gland, elective neck dissection in N0 cases showed a significant increase in DSS 51.1% versus 78.3% (Pfisterer, et al. 2014).

Regarding the facial nerve, Spiro and Spiro (2003) have recommended preservation unless the nerve is adherent to/embedded in the tumor.

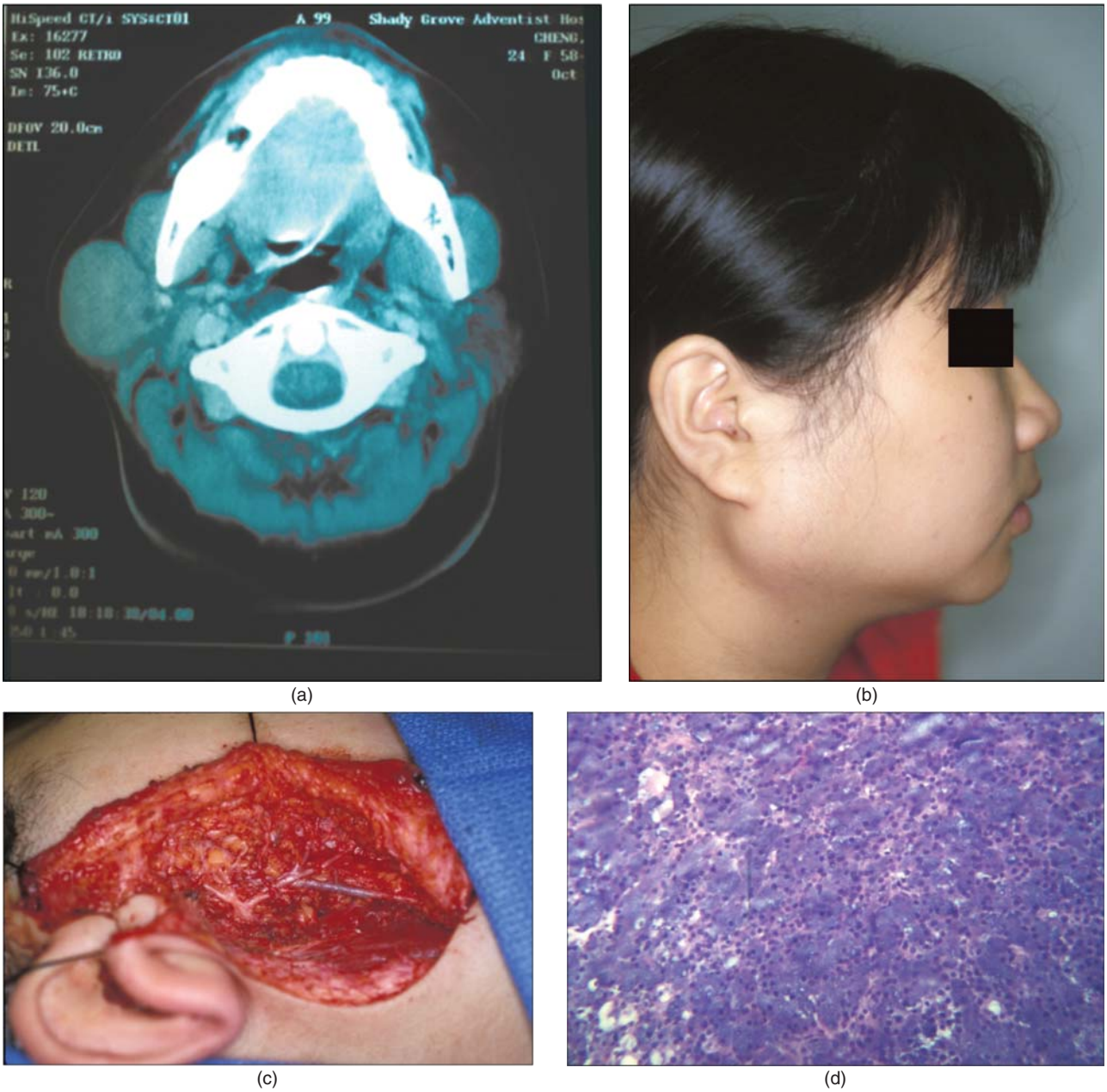


Figure 9.14. (a) CT scan of large superficial lobe tumor in 22-year-old woman. (b) Clinical appearance, the tumor has no signs of malignancy. (c) Complete parotidectomy the facial nerve was not involved. (d) Histopathology showed acinic cell carcinoma. The patient is alive and without evidence of disease more than 8 years postoperatively.

They feel that close margins to the nerve can be treated successfully by radiation therapy. This view is supported by the work of Carinci, et al. (2001), who found that sacrifice of the nerve was not always able to improve survival rate. In a series of 107 patients with parotid cancer, 91 had normal nerve function preoperatively and facial nerve preservation was possible in 79 patients. The 5-year disease free rate and 5- and 10-year survival rates were 65, 83, and 54% in the preserved nerve cohort, and 56, 62, and 42% in the patients with nerve sacrifice. The authors felt that preservation of the facial nerve by careful dissection gave favorable oncologic results (Guntinas, et al. 2004).

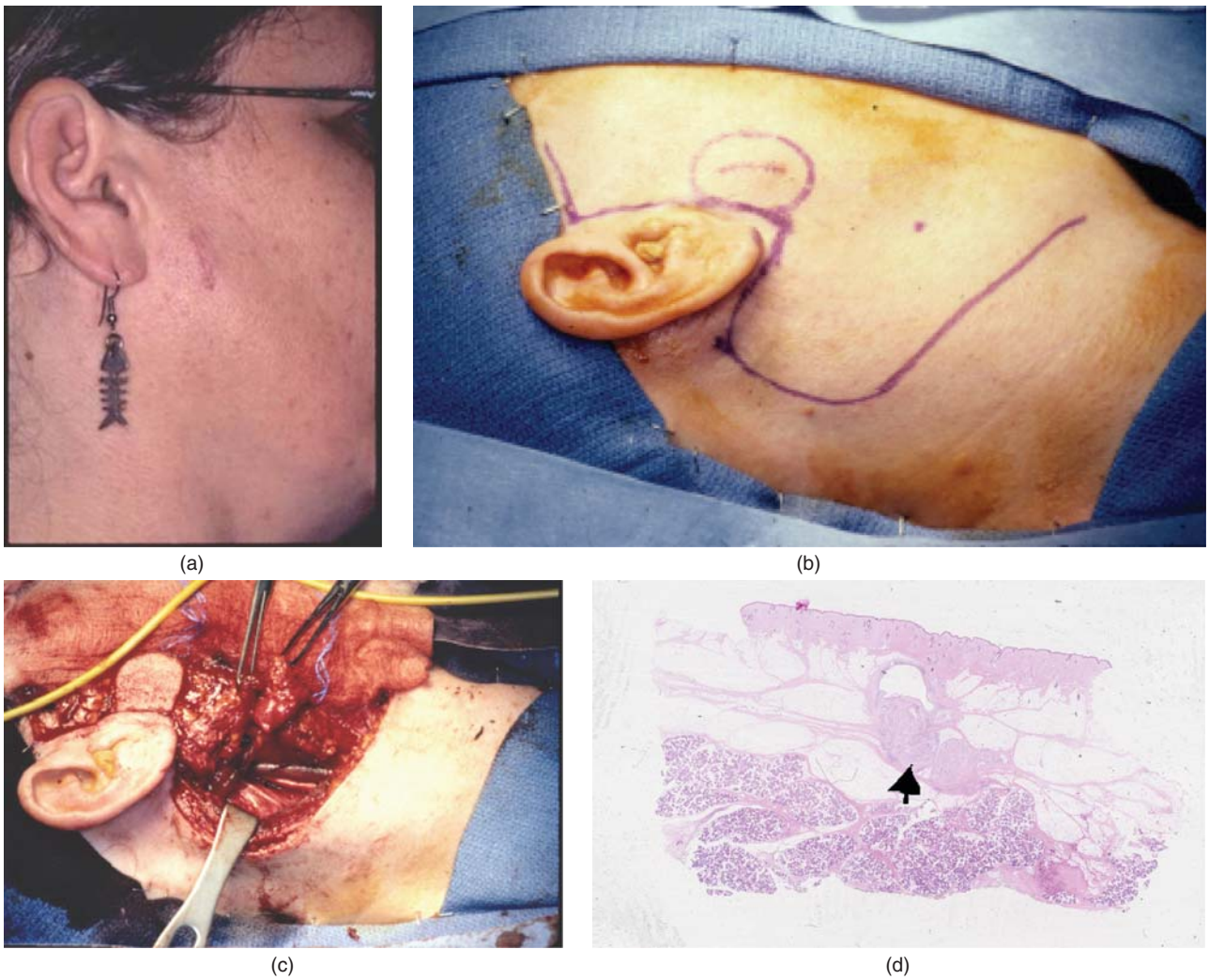
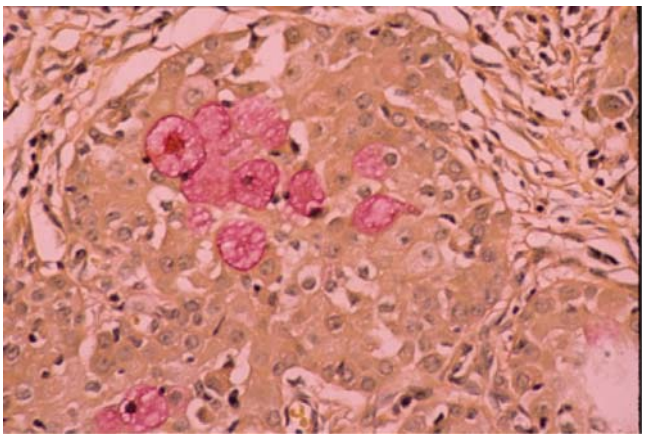


Figure 9.15. (a) Patient who had "skin cyst" biopsied which was histologically a parotid low grade mucoepidermoid carcinoma. Note preauricular biopsy scar. (b) Operative image shows Blair incision incorporating 1 cm around the biopsy. (c) The level II nodes (first echelon nodes) will be taken in continuity in this case. (d) Histologic slide shows focus of mucoepidermoid carcinoma (arrow) in the biopsy scar between the skin and parotid showing the importance of excising "seeded skin. (e) Mucicarmine stain confirms intracellular mucous. (f) Surgical specimen. (g) Patient is alive and disease free 14 years post-surgery.

Finally, a disease free survival in patients with normal, partially and completely impaired facial nerve function preoperatively of 69, 37, and 13%, despite the use of facial nerve sacrifice and postoperative RT indicates what a poor prognosis invasion of the nerve confers (Terhaard, et al. 2006).

In specific histologic tumor types, variable results for different treatments have been reported. Mucoepidermoid carcinoma is the commonest salivary malignancy and most cases, are fortunately low or intermediate grade. A series of 89 cases at the Mayo clinic, 69 T1–2, 85 N0, and 83 low/intermediate grade were treated by parotidectomy with "appropriate" neck dissection and only 7 had RT. Kaplan-Meier estimated cancer–specific survival rates at 5, 15, and 25 years were 98.9, 97.4, and 97.4% (Boahene, et al. 2004). Using a point grading system for histopathologic features in a series of 234 mucoepidermoid carcinomas of the major salivary glands, cystic component <20%, four or more mitotic figures per 10 high power fields, neural involvement, necrosis, and anaplasia



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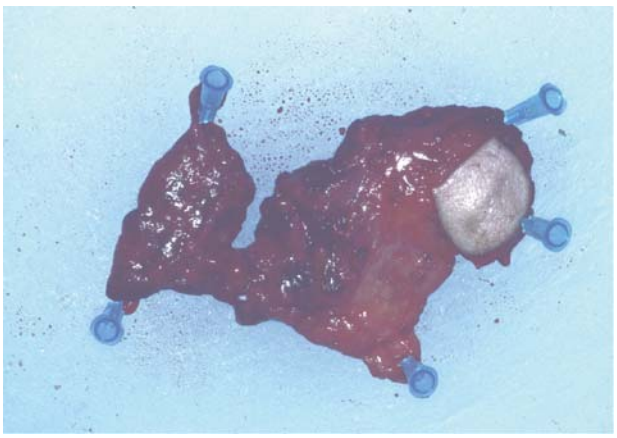

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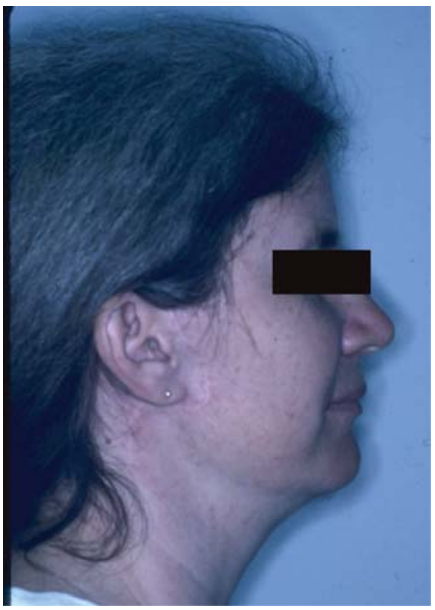
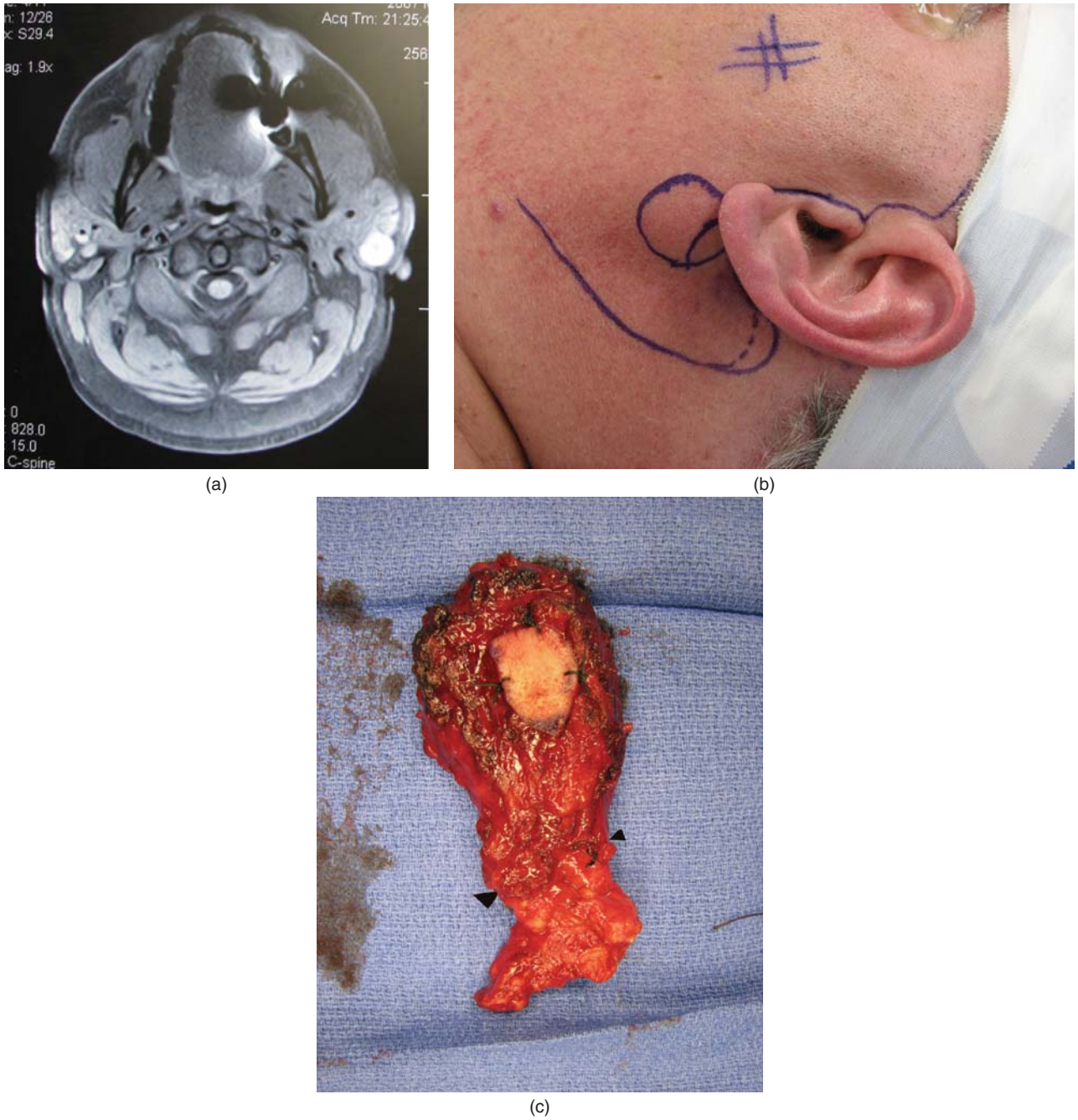


(g)

Figure 9.15. (*Continued*)

were found to have prognostic significance for parotid MECA (Goode, et al. 1998). Intermediate grade MECAs tend to behave more like low grade MECAs, while high grade MECAs behave aggressively with local recurrence, regional, and distant metastases in the majority of cases. Other low-grade tumors, such as acinic cell carcinoma, epimyoepithelial carcinoma, and low grade adenocarcinoma, all can be treated like low grade MECAs. Polymorphous low-grade adenocarcinoma is rare in the major glands being seen mostly in the minor salivary glands of the oral cavity.

On the other hand, results for high-grade cancers, such as primary squamous carcinoma of the parotid, are poor; in one published series two thirds were treated with radical surgery and RT and one third with radiation therapy alone but 5-year actuarial survival and disease free survival was 31 and 33%, respectively (Lee, et al. 2001). A 2014 study of 2545 cases of primary squamous cell carcinoma of the parotid, however, showed a 5-year DSS survival of 54.4%. Poor prognostic factors included black race, age >75 years, T3 or greater, and high stage. (Pfisterer, et al. 2014). Malignant change in PSA is most commonly seen as carcinoma ex. pleomorphic adenoma and prognosis will depend on the histologic type of malignancy and whether the malignancy has spread outside the capsule.



(a) (b)

(c)

Figure 9.16. (a) MR of parotid tumor which radiologically was diagnosed PSA, but FNAB diagnosis Adenoid cystic carcinoma. (b) In view of cytologic diagnosis proposed treatment includes resection of overlying skin (tethered) and level II cervical nodes. (c) Surgical specimen shows parotid with skin. The arrows show where level II nodes and fat are in continuity with the parotid tail. Final diagnosis was cellular PSA with the FNAB diagnosis being a false positive.

In carcinoma ex. pleomorphic adenoma the use of postoperative RT improved 5-year local control from 49 to 75% and improved survival in patients without cervical metastasis (Chen, et al. 2007). Two other forms of malignant PSA occur that are both rare, the "true" malignant mixed tumor or carcinosarcoma where malignant change is seen in both the epithelial and myoepithelial component of

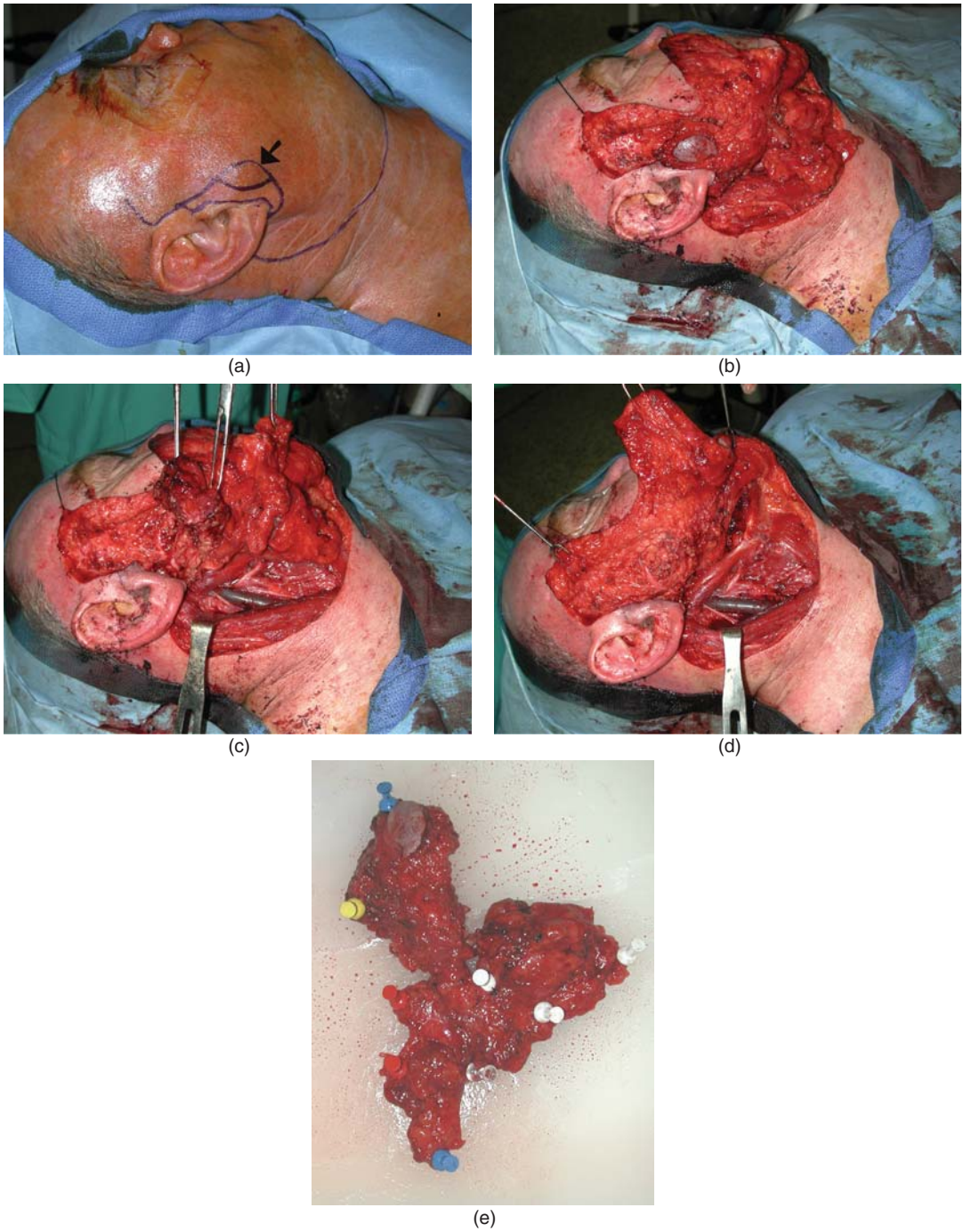


Figure 9.17. (a) High grade parotid malignancy with skin fixity and N0 neck. Incision modified to include skin excision (arrow), and cervical incision extended to allow supraomohyoid neck dissection. (b) The skin flaps developed with the skin overlying the tumor left on the parotid gland. (c) The selective neck dissection is complete with the specimen in continuity with the parotid gland. The facial nerve trunk has been exposed and the superficial parotidectomy is being performed. (d) The surgical site following parotidectomy and selective neck dissection. (e) The surgical specimen with the parotid superiorly and level I nodes pinned out with white pins.

the PA; and the benign metastasizing PSA, which as its name suggests retains a benign histologic appearance despite the presence of metastases.

It is hard to interpret adenoid cystic carcinoma survival figures in some series as ACC is very slow growing and 5-year survival is less meaningful in this neoplasm as survival continues to fall on 20-year follow up. Thus, in series with short follow up ACC will erroneously be thought to have a good prognosis. Typical long term survival figures are; 84.3% after 2 years, 75.9% after 5 years, 50.49% after 10 years, and 20.11% after 20 years (Issing, et al. 2002). The type of histologic appearance, solid versus cylindrical and the presence of perineural invasion are important prognostic factors. Even with documented lung metastases patients can live 5+ years, the average survival between the appearance of lung metastases and death being 32.3 months in one series (van der Waal, et al. 2002). Wide field adjuvant RT post radical surgery is usually recommended for ACC.

The histologic grade of the tumor must be taken into account as well as TNM staging when interpreting survival results in reported series. Every parotid cancer will be unique and the decision for what is the correct surgery will be made on an individual basis for each patient.

Summary

- 80% of parotid tumors are benign most commonly pleomorphic adenomas.
- Less than one third of malignant tumors will have obvious clinical signs of malignancy, for example facial nerve palsy, ulceration, fixation, or lymphadenopathy.
- Routine use of CT or MRI does not appear justified and should be used selectively for malignant neoplasms and deep lobe tumors.
- Preoperative open biopsy is contraindicated and FNAB is the modality of choice for preoperative histologic diagnosis.
- Although superficial parotidectomy remains the basic surgical procedure, there is currently much debate regarding the roles of partial parotidectomy and extracapsular dissection in the management of PA. The role of the capsule and the acceptable margin for PA remains undefined.
- Recurrent PSA will frequently require en bloc resection due to its infiltrative and multinodular nature. Cure in this situation is probably achieved in approximately two thirds of cases.
- Management of malignant parotid tumors will depend on both the histologic diagnosis and the staging of the tumor.
- Radiation therapy may be helpful in earlier stage disease and lower grade tumors that previously advocated.
- Selective neck dissection for the N0 neck may be justified in early stage disease given the high reported rate of occult nodes.
- The facial nerve should be preserved in parotid cancer unless it is directly infiltrated by tumor.

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Chapter 10

Tumors of the Submandibular and Sublingual Glands

Outline

Introduction

This chapter will discuss the diagnosis and management of epithelial derived tumors of the submandibular and sublingual glands. These tumors are much less common than tumors of the parotid gland and long series of cases from which to apply evidence based medicine treatment protocols is lacking particularly with regard to the sublingual gland neoplasms. Current approaches are highlighted although the diversity of histologic types, paucity of cases, and lack of long-term followup results in many of these cases being treated empirically based on oncologic principles derived from other tumors and sites in the head and neck region.

Epidemiology and Etiology

The etiology of tumors of the submandibular and sublingual glands is the same as discussed in relation to salivary gland tumors of the parotid gland (see Chapter 9). At a molecular level, in a study that examined PCNA, Ki-67, and p53 in pleomorphic adenomas (PAs), mucoepidermoid carcinomas (MECA) and adenoid cystic carcinoma (ACC); PCNA, Ki-67, and p53 expression for PA and ACC in the submandibular gland was similar to that reported for tumors of the parotid gland and minor salivary glands. However, there was a higher expression of these markers in MECA of the submandibular gland (Alves, et al. 2004). This may indicate that MECA of the submandibular gland is potentially more aggressive.

Approximately 10–15% of all salivary gland tumors will occur in the submandibular gland, and only 0.5–1% in the sublingual gland. As such, sublingual tumors are very rare. In the submandibular gland approximately 50% of these tumors are benign. Series vary in their percentages, 657 of 1235 tumors (53%) benign (Auclair, et al. 1991), 55% benign (Oudidi, et al. 2006), which included nonepidermoid cancers, to 39.2% benign (Rapidis, et al. 2004).

Pleomorphic adenoma is the commonest benign tumor in the submandibular gland while ACC predominates for malignant tumors. In examining malignant tumors, Bhattacharyya (2004) analyzed 370 cases from the Surveillance, Epidemiology, and End Results (SEER) database, finding ACC 42.2% and MECA 22.2%, while Rapidis, et al.'s (2004) literature review of 356 cases showed ACC 45.3%, adenocarcinoma 14.3%, MECA 12.9%, and carcinoma ex. pleomorphic adenoma 11.2%, and Auclair, et al. (1991) found ACC 24% and MECA 19% in 578 cases.

Salivary Gland Pathology: Diagnosis and Management, Second Edition. Edited by Eric R. Carlson and Robert A. Ord.

Although sublingual gland tumors are rare they are important to recognize as they have an extremely high rate of malignancy. In a review of approximately 4000 patients with salivary tumors collected over a 55-year period, only 18 (0.5%) had sublingual gland tumors all of which were malignant (Spiro 1995). There are very few other large series of sublingual gland tumors in the literature, Yu, et al. (2007) reported 30 cases collected over a 50 year period all of which were malignant. Yamazaki, et al. reviewed the literature in 1987 and found 83 cases of sublingual gland tumors of which 72 (87%) were malignant. In the combined experience of the authors, of 821 epithelial salivary gland tumors treated between 1990 and 2014 at our respective medical centers, 15 (1.8%) were sublingual gland tumors and all were malignant (Table 10.1). Adenoid cystic carcinoma appears to be the commonest histologic type, followed by MECA; ACC 50%, MECA 28% (Spiro 1995), ACC 56.7% (Yu, et al. 2007), ACC 66%, and MECA 33% (Perez, et al. 2005). Zdanowski, et al. (2011) found 66.7% of their sublingual gland tumors were adenoid cystic carcinomas but also comment that 83.3% of their series presented late with stage III or IV disease.

Diagnosis

SUBMANDIBULAR GLAND TUMORS

Most submandibular gland tumors present with a slow growing, painless mass inferior to the mandible (Figure 10.1). In a series of 87 submandibular gland carcinomas, 94% presented with a palpable mass, and 39% with pain (Kaszuba, et al. 2007). As tumors of the gland are rare and inflammatory swelling secondary to sialolithiasis is seen more often, they may not be initially diagnosed and can present with late disease. In one series, 50% of all referred patients with submandibular gland tumors had already had their submandibular gland removed on the presumption that the involved process was benign (Camilleri, et al. 1998). The average tumor size in 370 cases of cancer of the submandibular gland was 2.9 cm (Bhattacharyya 2004). Inflammatory disease, however, is often painful and usually characterized by exacerbations and resolutions of the swelling in relation to eating. In a series of 258 submandibular gland excisions 119 (46%) had sialolithiasis, 88 (34%) sialadenitis, and 51 (20%) tumors (Preuss, et al. 2007).

Table 10.1. Sublingual gland tumors 1990–2014

Patient	Age	Race	Gender	Pathology	Stage
1	45	B	M	Int. MECA	IV
2	85	W	F	PLGA	I
3	57	W	F	Int. MECA	I
4	46	W	M	Adeno Ca NOS	IV
5	69	W	M	Comedo Adeno Ca	X
6	67	W	F	ACC	II
7	47	B	F	HG MECA	IV
8	54	A	M	LG MECA	I
9	68	W	F	ACC	I
10	70	W	F	LG MECA	III
11	70	B	F	ACC	II
12	58	W	M	LG MEC	I
13	47	W	F	Int. MECA	II
14	56	B	F	ACC	I
15	48	W	F	Int. MECA	I

Key: B = Black, W = White, A = Asian. M= Male, F = Female, MECA = Mucoepidermoid carcinoma. ACC = Adenoid cystic carcinoma, Adeno Ca = adenocarcinoma, PLGA = polymorphous low grade adenocarcinoma. LG = low grade, Int. = intermediate grade, HG = High grade, NOS = not otherwise specified.

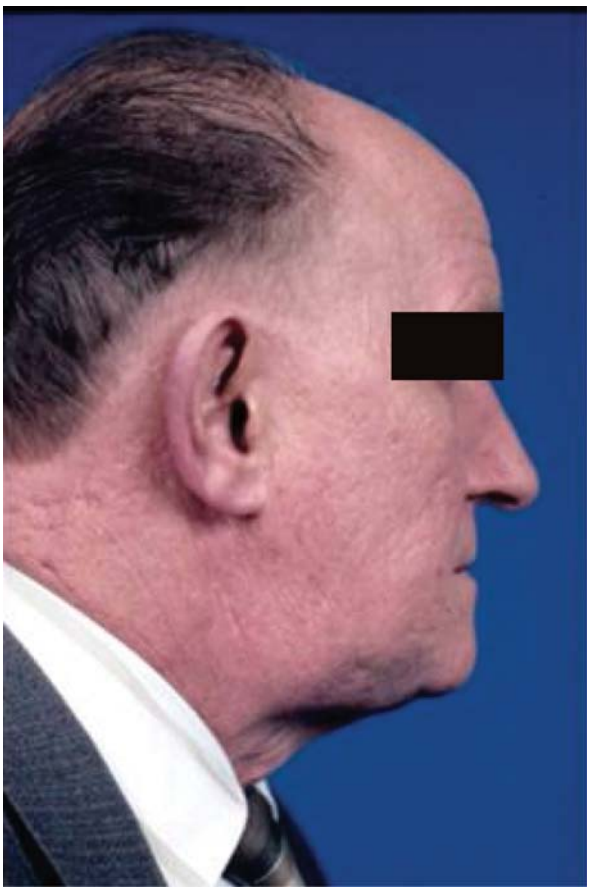


Figure 10.1. A 64-year-old man with a painless submandibular mass.

Examination usually reveals a smooth, firm to hard mass in the submandibular triangle that is most commonly discrete and mobile. Fixation of the mass to the skin or underlying mylohyoid muscle is a sign of malignancy with advanced extracapsular infiltration (Figure 10.2). Neural involvement of the mandibular branch of the facial nerve with ipsilateral lower lip palsy, the lingual nerve with ipsilateral anesthesia/paresthesia of the tongue or the hypoglossal nerve with ipsilateral palsy of the tongue muscles are also signs of cancer. Associated hard cervical nodes due to regional metastasis may also be present in malignant tumors. However, it may be more difficult to clinically assess whether a submandibular gland tumor is benign or malignant compared to a parotid tumor, as clinical judgment for these tumors has been said to be unreliable (Lee, et al. 2013.)

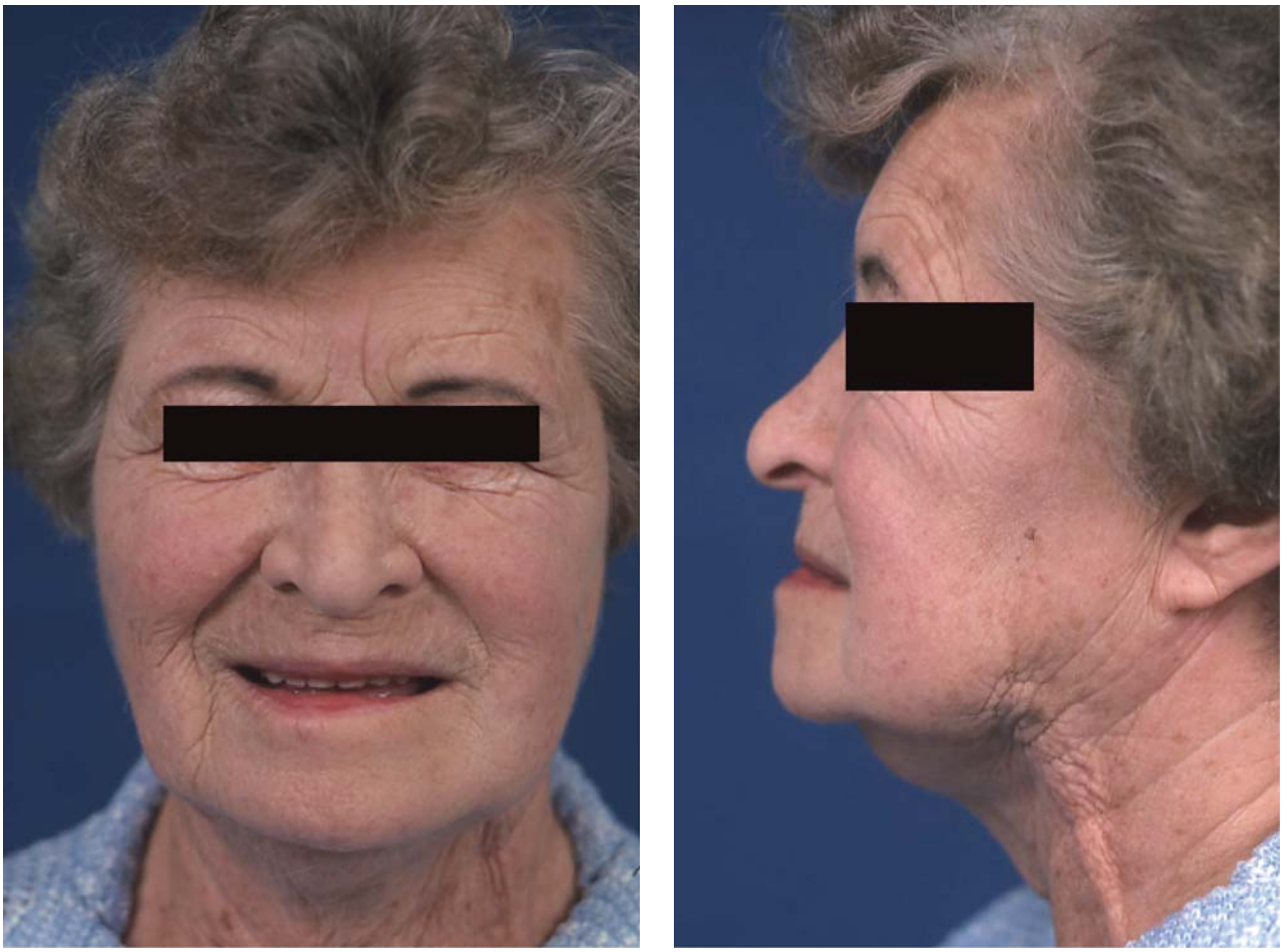
The differential diagnosis of a solitary mass in the submandibular triangle with no overt signs of malignancy will include lymphadenopathy, plunging ranula, vascular malformation and branchial cysts. It may be difficult to differentiate a lymph node from the enlarged gland on clinical examination alone. If the mass is bimanually palpable from within the floor of mouth it is more likely to be a submandibular gland mass, and if it can be "rolled" over the lower border of the mandible on palpation it is a lymph node. The plunging ranula is usually soft-cystic in consistency but can become firm if chronically encysted. Vascular lesions are also soft, may "pit" on firm pressure or have thrills and murmurs. Branchial cysts lie more posterior and are partially beneath the anterior border of the sternocleidomastoid muscle.

Imaging techniques to delineate submandibular gland lesions include ultrasound, CT and MR. As the submandibular gland is superficial in the neck high resolution ultrasound can distinguish intraglandular from extraglandular masses and can differentiate benign tumors from those that are malignant (Alyas, et al. 2005) (Figure 10.3). CT scanning may be useful in detecting early cortical erosion of the mandible and identifying cervical nodes in malignant cases (Figure 10.4). In a study to identify whether a submandibular mass was intra or extraglandular, the accuracy of contrast enhanced CT was 87%, CT sialography 85% and MR 91% (Chikui, et al. 2004). These authors did not find displacement of the facial vein and its relationship to the mass a helpful guide.

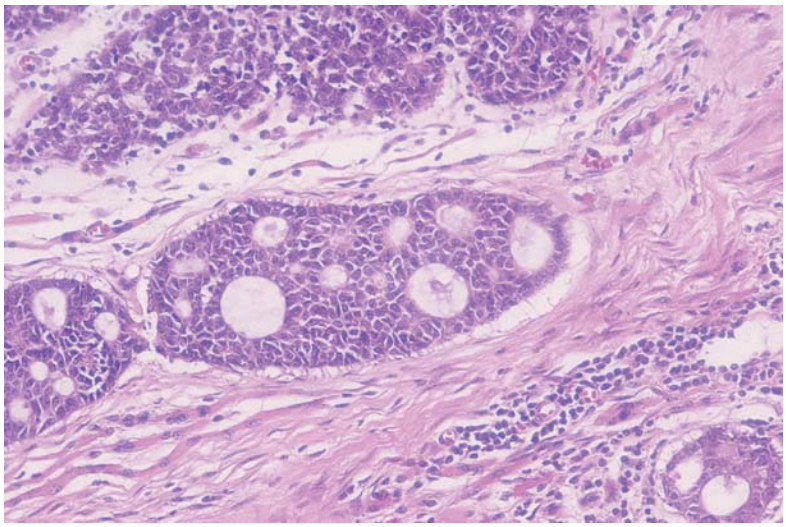
Open biopsy of the submandibular gland mass is contraindicated for similar reasons that were discussed in relation to the parotid (see Chapter 9). Fine needle aspiration biopsy (FNAB) is the method of choice for these tumors, one literature review finding an overall accuracy of greater than 80% in skilled hands, which is comparable with the accuracy of frozen section (Pogrel 1995). A further review of submandibular swellings of all types including sialadenitis assessed preoperatively using FNAB cytology/core biopsies showed an accuracy of 88% with sensitivity of 71.4% and specificity of 94.4% (Taylor, et al. 2011). We have used ultrasound guided FNAB for difficult cases with success.

SUBLINGUAL GLAND TUMORS

Tumors of the sublingual gland present as a mass in the floor of mouth usually painless and slow



(a) (b)



(c)

Figure 10.2. (a) Elderly woman with a hard submandibular mass (adenoid cystic carcinoma on fine needle aspiration biopsy) who presented with a palsy of the marginal mandibular branch of the facial nerve. (b) Lateral facial view shows skin fixation and tethering. (c) Histopathology of adenoid cystic carcinoma of submandibular gland.

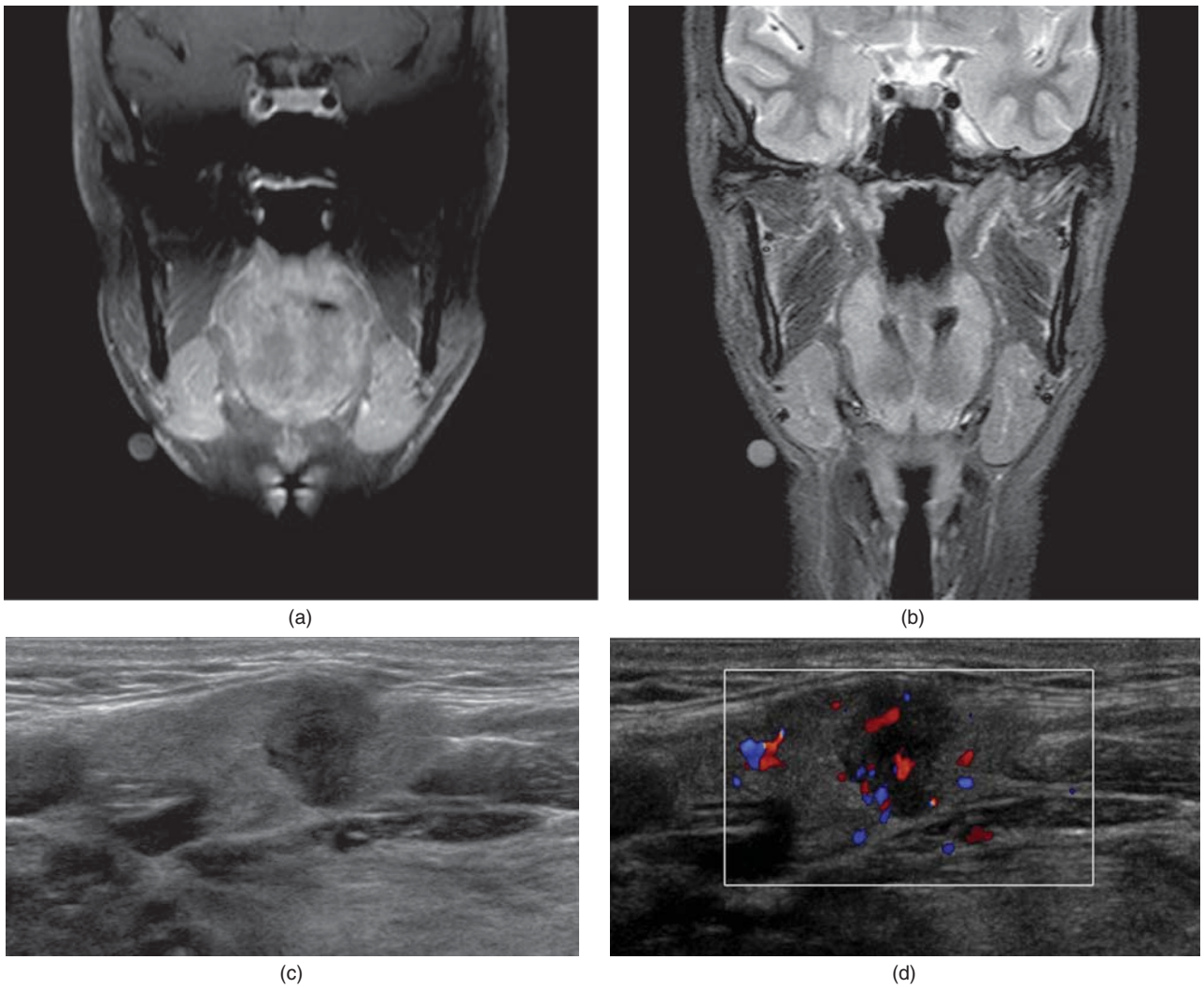
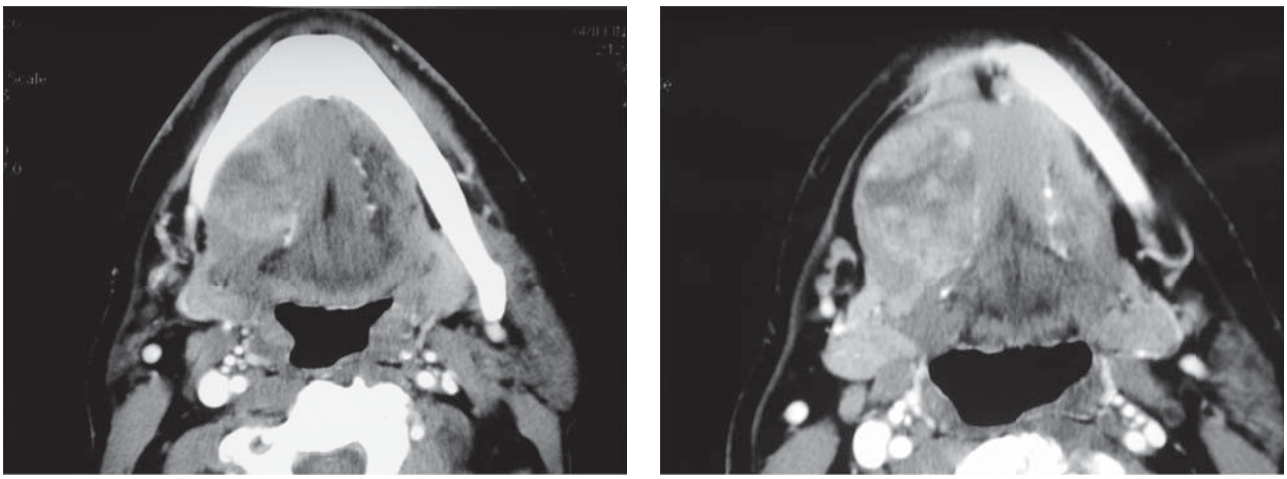


Figure 10.3. Imaging studies of a 27-year-old woman with a palpable mass in the right submandibular gland region. The coronal cuts of the MRI (a and b) identified a mass of the right submandibular gland. High resolution ultrasound (c) and color Doppler ultrasound (d) confirmed the presence of the mass. An ultrasound guided fine needle aspiration biopsy was performed that showed epithelial cells consistent with a mucoepidermoid carcinoma. The patient underwent a supraomohyoid neck dissection that showed a 6 mm focus of mucoepidermoid carcinoma within the right submandibular gland.

growing. They may be large enough to impair tongue movement with speech difficulty or to prevent wearing a lower denture (Figure 10.5). Occasionally, they may cause obstruction of Wharton duct, either due to pressure or malignant infiltration and present with a submandibular swelling. Virtually 100% of these tumors are malignant and involvement of the lingual nerve or hypoglossal nerve with ipsilateral anesthesia or weakness of the tongue may be seen. Examination by palpation reveals a firm to hard mass, which may be tender and fixed to the lingual periosteum. Infiltration of the tongue muscles with slurring of speech or dysphagia can occur.

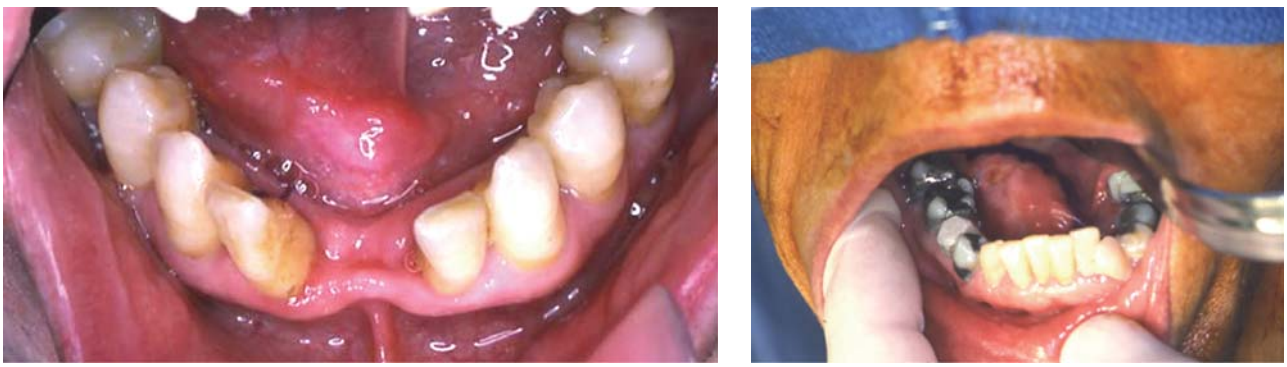
The only other entity on the differential diagnosis is a ranula, which can resemble a cystic tumor.

Imaging is usually by CT or MRI. CT scans will be more accurate for early cortical bone invasion (Figure 10.6). In MRI, T1 weighted signal intensity of carcinomas in and near the sublingual gland is lower than the gland, whereas T2 weighted signal intensity of carcinomas exceeds that of the gland (Sumi, et al.1999).



(a) (b)

Figure 10.4. (a, b) CT scans showing submandibular mass with differing regions of radiolucency and opacity. Histopathology showed pleomorphic adenoma.



(a) (b)

Figure 10.5. (a) Adenocarcinoma of right sublingual gland. (b) Polymorphous low grade adenocarcinoma of the sublingual gland. Re-published with permission from: Blanchaert RG, Kumar D, Ord RA: Polymorphous low-grade adenocarcinoma of the sublingual gland. *Int J Oral Maxillofac Surg* 27:115–117, 1998.

In the sublingual gland, histologic diagnosis is accomplished by incisional biopsy through the overlying oral mucosa.

Management

SUBMANDIBULAR GLAND TUMORS

As in all salivary gland tumors surgery is the primary modality of treatment. When the diagnosis is established preoperatively as benign PA by FNAB then an extra capsular excision of the submandibular gland is indicated (Figures 10.7 and 10.8). Pleomorphic adenoma should be treated in the same manner as for the parotid gland (see Chapter 9). There is some evidence that the capsule of PAs in the submandibular gland is thinner than in the parotid (Webb and Eveson 2001) and it is important to maintain a margin of normal tissue around the tumor. If the entire gland and tumor is not removed but the PA merely enucleated, there is a higher risk of recurrence (Laskawi, et al. 1995). In this dissection, it is easy to maintain a little extra fat and connective tissue over areas where the PA may approach the surface of the gland (Figure 10.9). In a series of 15 PAs of the submandibular gland, 20% were in the surface of the gland (Laskawi, et al. 1995) (Figure 10.10). The marginal mandibular branch of the facial nerve

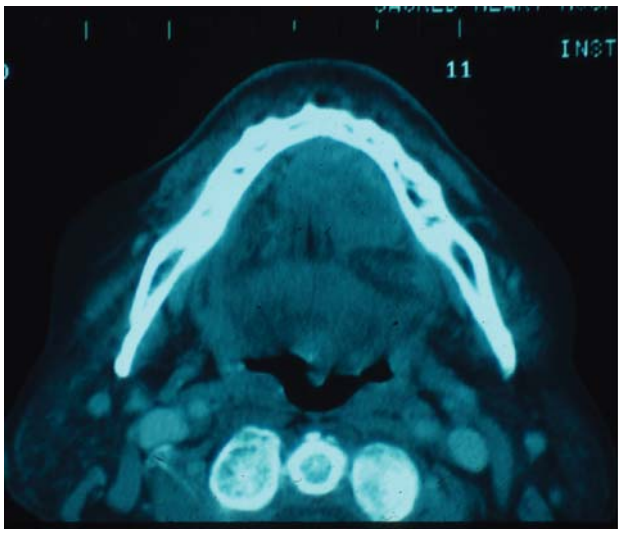
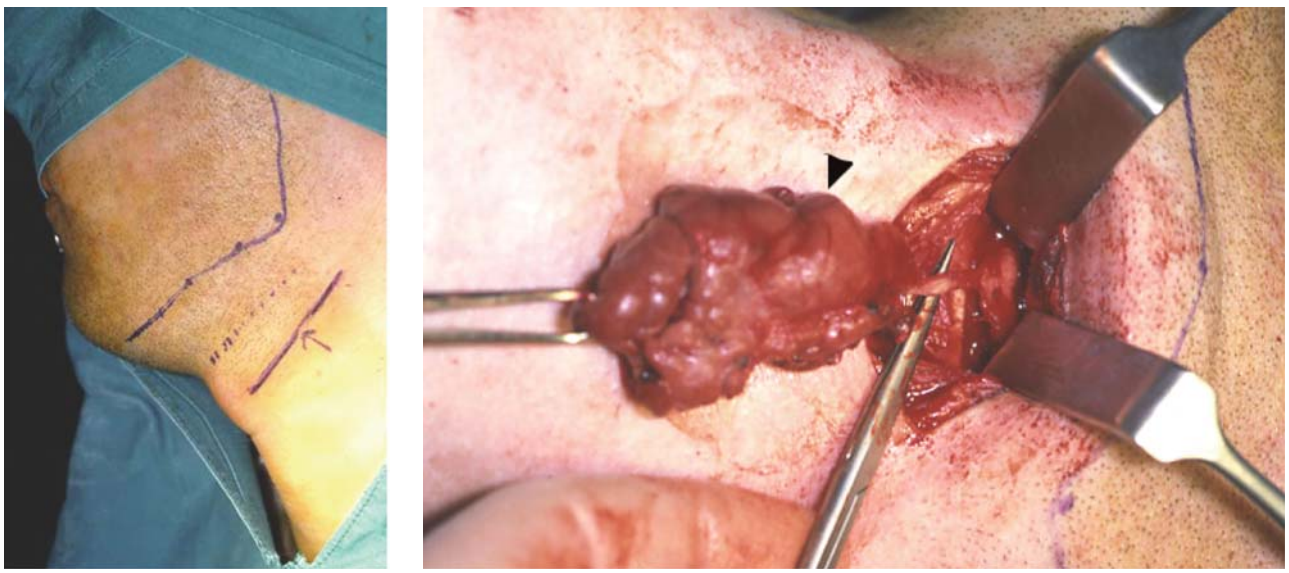


Figure 10.6. CT scan of large malignant tumor of the left sublingual gland.

lies between the platysma superficially and the capsule of the submandibular gland (superficial layer of the deep cervical fascia) deeply and can be preserved either by dissecting it along its course and retracting it superiorly or by ligating and cutting the anterior facial vein inferior to the nerve and using traction on the tied distal end of the vessel to retract the nerve out of the field (the Hayes–Martin maneuver). The incidence of transient palsy of the marginal mandibular branch of the facial nerve is 7% in excising benign tumors and 21% in excising malignant tumors, with only 1 case (<1%) of permanent palsy in this series (Preuss, et al. 2007). The facial artery is sacrificed if it passes through the gland itself but if not, its numerous small branches including the submental branch can be clipped and the main vessel preserved.

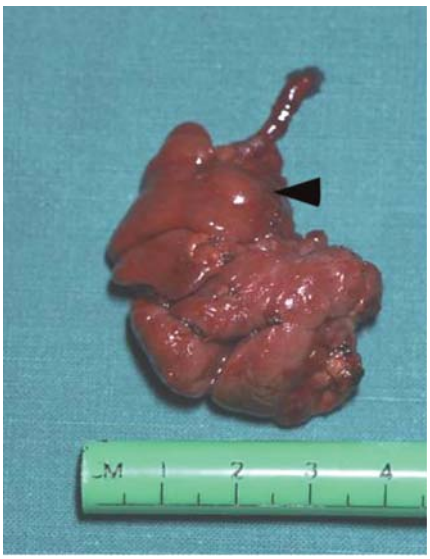
In recurrent PA, the disease will frequently be multi nodular as in the parotid and as 45% of these cases involve the subcutaneous tissue under the previous operative scar, excision of the scar with a margin of the surrounding skin is recommended as part of the en bloc excision (Laskawi, et al. 1995).

Where a definite diagnosis of benign tumor is not established preoperatively, or when a low grade malignant tumor is diagnosed, an en bloc resection of level I is safest. If the final histologic diagnosis is benign, no important structures have been sacrificed, only the gland and tumor plus fat with lymph nodes. If the tumor is a low grade malignancy then no further surgery is indicated. In the case of a high grade tumor a selective or radical neck dissection can be completed at the same time (Figure 10.11).



(a) (b)

Figure 10.7. (a) The incision for submandibular gland tumor removal lies approximately 1–2 finger-breadths below the lower border of the mandible and is placed in a natural skin crease. (b): The submandibular gland is pedicled on its duct, which is indicated by the sharp scissors. The arrow points to the tumor in the hilum. (c) Surgical specimen with arrow indicating PA. (d) Histopathology shows pleomorphic adenoma of submandibular gland.



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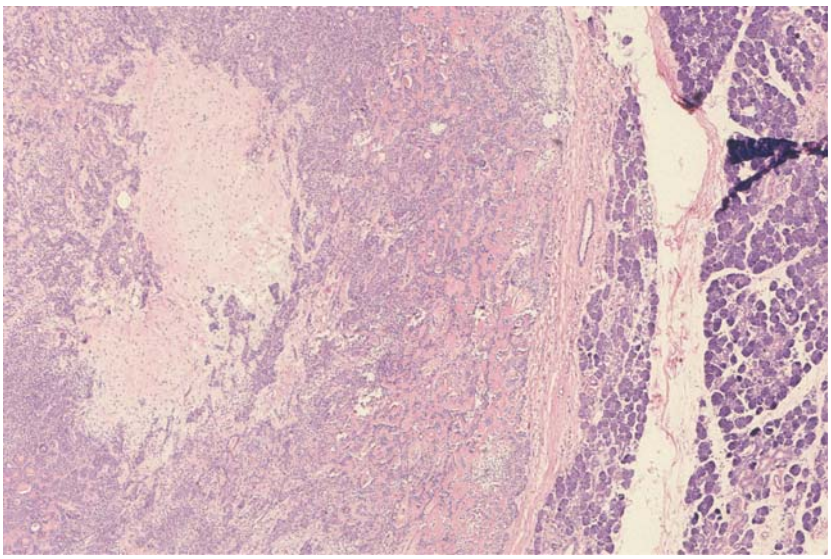


(d)

Figure 10.7. (*Continued*)

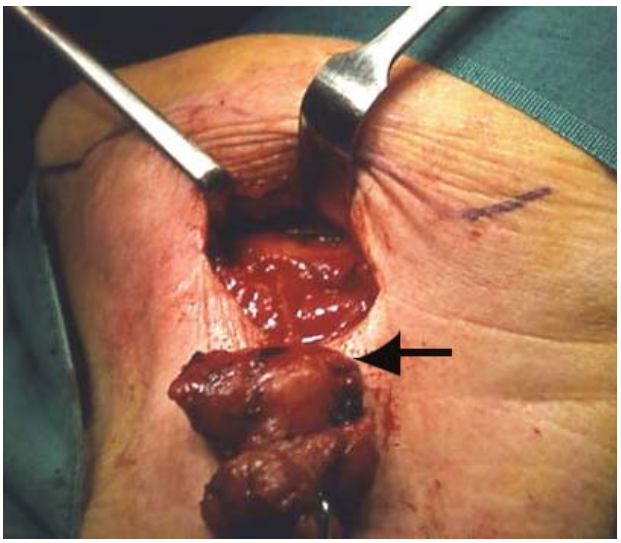


Figure 10.8. Another case of submandibular pleomorphic adenoma, the specimen is pedicled on the duct. The larger tumor at the hilum is indicated by the arrow.

In undertaking the level I dissection the cervical skin flap is lifted in a subplatysmal plane and the marginal mandibular branch of the facial nerve is preserved. The anterior belly of the digastric muscle is identified and its fascia dissected free. The fascia is dissected off the mylohyoid muscle freeing the fat and nodes from the digastric, mylohyoid, and inferior border of the mandible. The posterior edge of the mylohyoid muscle is retracted to identify the lingual nerve, which is preserved if it is uninvolved by cutting its branch to the gland and allowing the nerve to retract into the mouth. The duct is sectioned and the facial vein and artery tied off or dissected free as indicated to release the specimen. In low grade N0 tumors, a neck dissection is usually not indicated but the excision can be extended to encompass lymph node levels II and III as a supraomohyoid neck dissection. If lymph nodes are clinically involved then a type I modified radical neck dissection is required.

In high grade tumors or advanced low grade tumors with extracapsular infiltration and involvement of the skin, muscle, or mandible, extended resections with incorporation of these structures will be necessary to obtain clear margins. These resections will be dictated by the size and extent of the tumor. In N0 cases, selective neck dissection levels I–III or I–IV will be used and modified radical neck dissections for clinically positive necks. In the case of ACC, widespread infiltrative growth beyond the palpable tumor makes obtaining clear margins challenging. The propensity for perineural invasion with ACC will necessitate sacrifice of involved nerves, for example lingual, hypoglossal, and facial, tracing the nerves proximally using frozen section guidance to determine clearance. Unfortunately "skip" metastases can occur along the nerve and a negative frozen section is no guarantee of success. ACC is more prone to metastasize hematogenously than through lymphatics

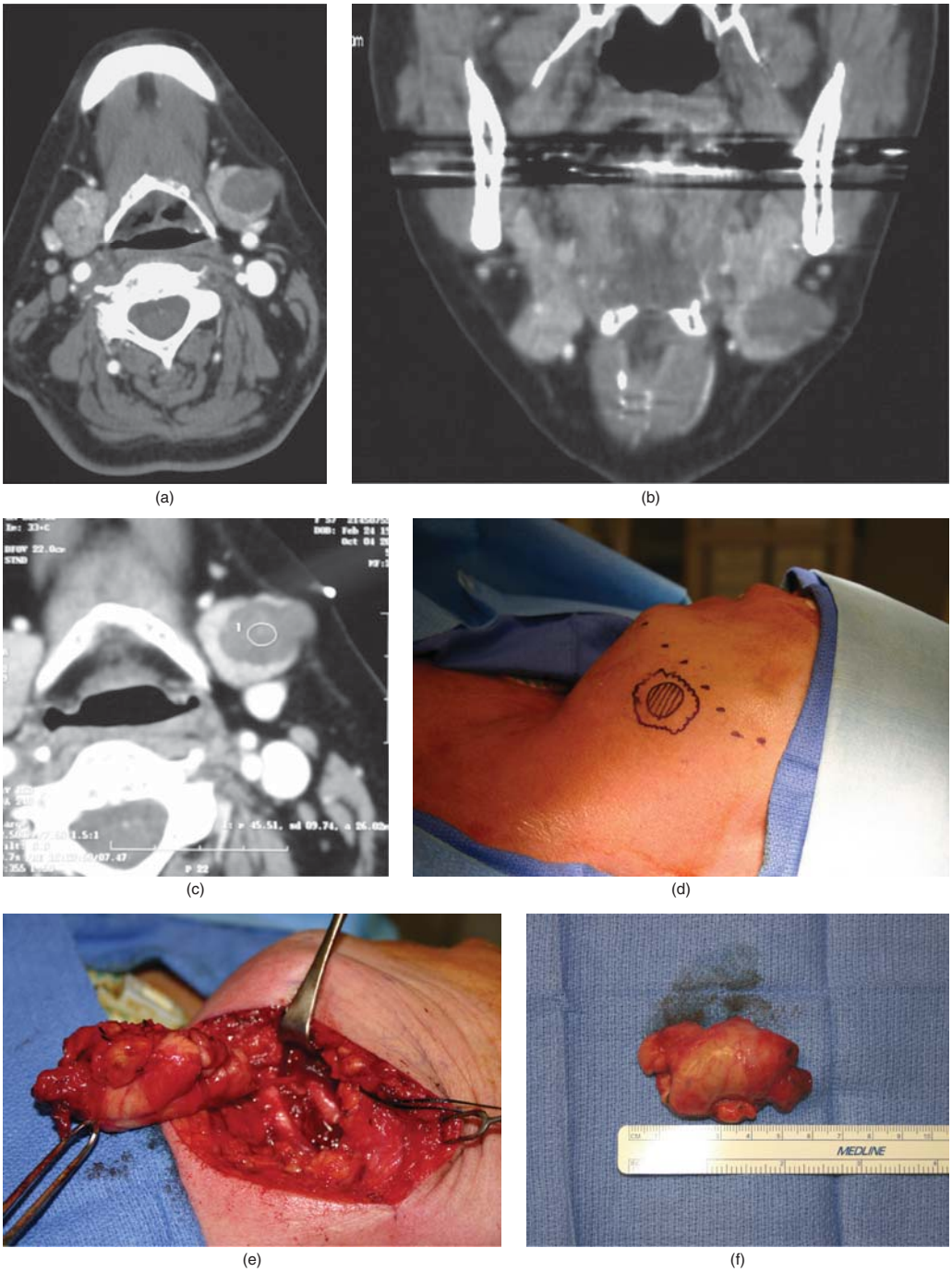
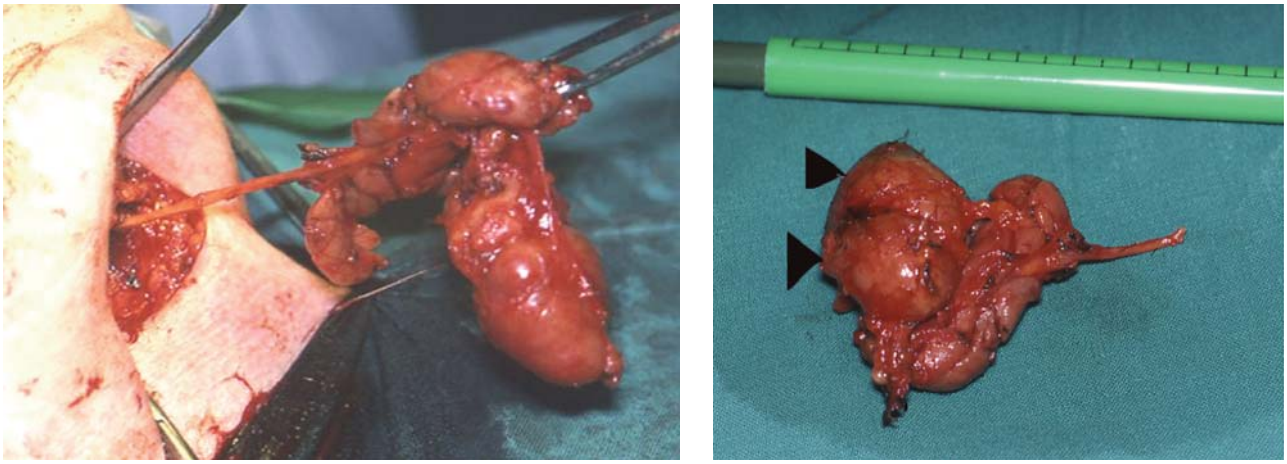
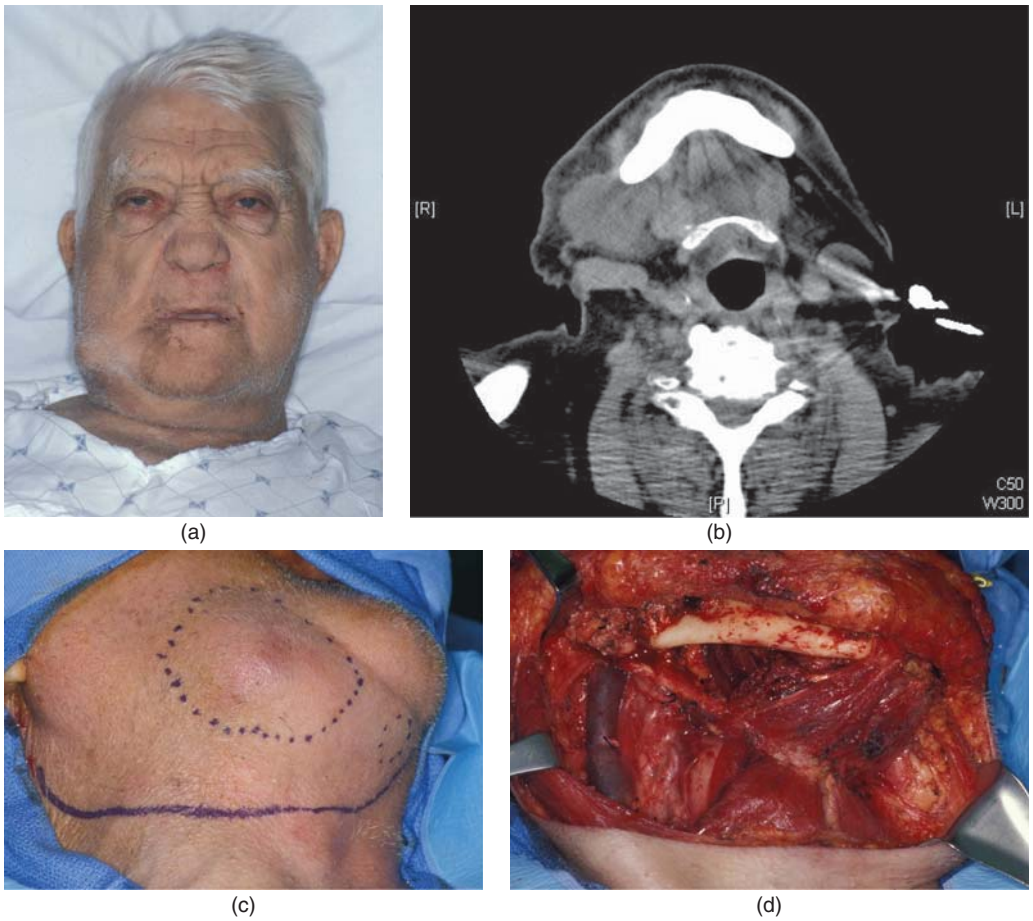


Figure 10.9. (a) Axial CT shows tumor projecting beyond the gland surface. (b) Coronal CT confirms the surface involvement. (c) High power axial CT scan shows the tumor marked with a circle. (d) Operative picture showing the tumor marked by palpation. (e) Intraoperative view of extracapsular dissection preserving soft tissue over the tumor surface. (f) Surgical specimen.



(a) (b)

Figure 10.10. (a) Submandibular gland attached only by its duct. The pleomorphic adenoma is large and hangs beneath the gland attached only by the enveloping fascia of the capsule.(b) Surgical specimen with arrows pointing to the large PA, which has no real attachment to the gland.



(a) (b)

(c) (d)

Figure 10.11. (a) A 82-year-old man with pain and swelling of the right submandibular region. (b) CT scan confirms a right submandibular gland mass diagnosed as malignant on fine needle aspiration biopsy. (c, d) Intra-operative figures views showing level I excision combined with a selective neck dissection in view of high grade cytology. (e) Operative specimen. (f, g) Hematoxylin and eosin stain (f) and Alcian Blue stain (g) confirm a diagnosis of high grade mucoepidermoid carcinoma. (h) One year postoperative view of the patient. He died 3 years postoperatively with distant metastases of the lung.

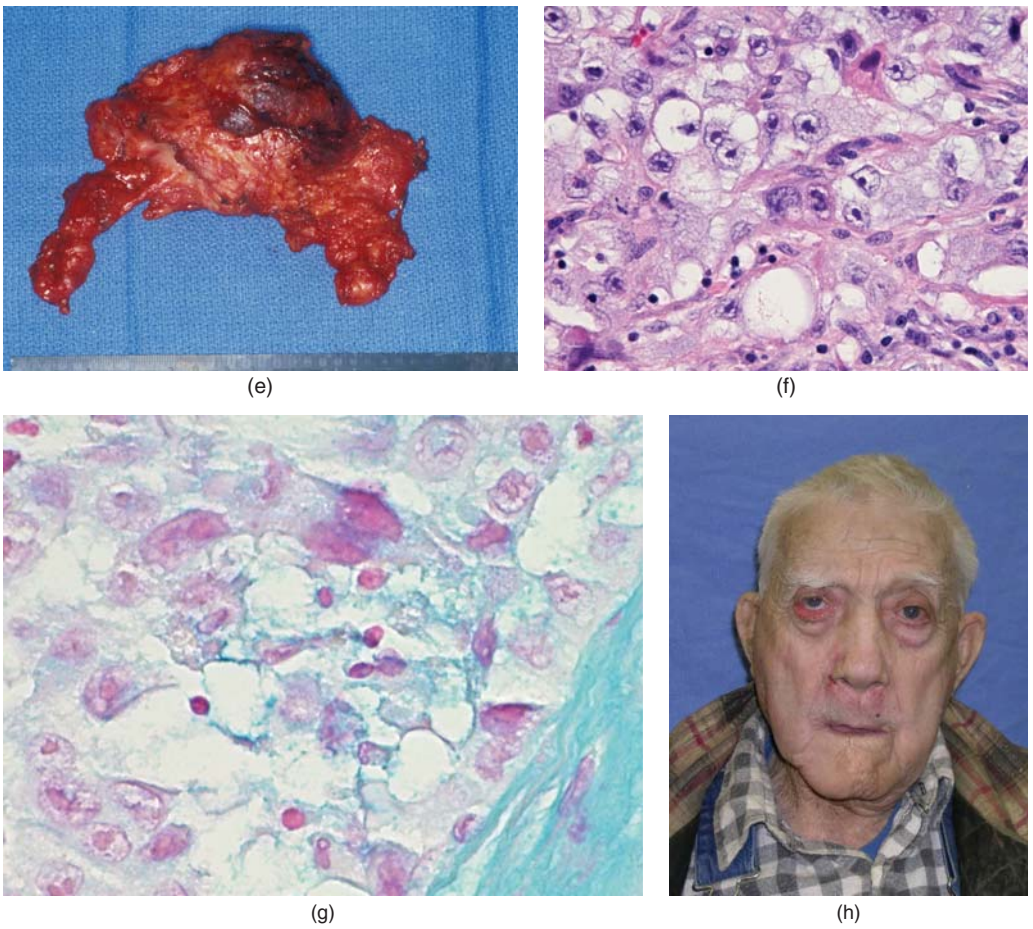


Figure 10.11. (*Continued*)

such that a selective neck dissection is usually sufficient.

Postoperative radiation therapy is administered for high grade tumors, positive margins, positive nodes, and perineural spread if re-resection is not possible. Chemotherapy has not been shown to improve survival in salivary gland cancer.

Prognosis will depend on the histologic grade and the stage of the tumor. Some authors (Anderson, et al. 1991) have found a crude 10-year survival of 50%, with 10% local recurrence and 39% of cases having metastasized at the time of diagnosis. In the series reported by Rapidis et al. (2004), 8 of 14 patients died during followup with a survival rate of 38.5%, but 11 of 14 of these patients presented with stage III or IV disease. Bhattacharyya (2004) analyzed 370 cases of submandibular gland cancer from the SEER database and reported a 59.7% 5-year survival; however, this figure is high as 42.2% of his cases were ACC with a mean survival of 99 months. In the same series, the patients with squamous cell carcinoma had a mean survival of 52 months. Younger age, low-grade histology and the use of radiation therapy were factors in improving survival. Weber, et al. (1990) found a 69% 5-year survival, with extracapsular infiltration and lymph node metastases, indicating a poor prognosis. Stages TI-TIVA had a case specific 5-year survival of 88% compared to 55% for T4b, and 5-year survival of 86% for negative nodes compared to 30% for positive nodes.

More recent papers have confirmed the propensity for submandibular gland tumors to have a higher failure rate related to distant metastases. In a Brazilian study of 255 major salivary carcinomas, the percentage of distant metastasis seen was 42% for the submandibular gland, 20% for the parotid gland, and 17% for the sublingual gland (Mariano, et al. 2011). Again, this may be

due to the high percentage of adenoid cystic carcinomas found at this site. However, in an interesting study that compared parotid and submandibular adenoid cystic carcinomas and their propensity for earlier systemic dissemination, the authors found more abundant tumor-associated blood vessels in the submandibular gland microenvironment. This study postulates a true site difference in the behavior of adenoid cystic carcinomas (Shin, et al. 2014).

Actuarial 5-year locoregional control, distant metastasis free survival, disease free, and overall survival rates were 69.7, 65.8, 52.8, and 56.8%, respectively (Roh, et al. 2008). In multivariate analysis, T category and histological grading were prognostic for disease free survival and T category and resection margins for loco-regional control. Of this series, 33.9% initially had or developed distant metastases. Another series showed actuarial 5-year locoregional control, distant metastasis-survival, and disease free survival of 80.5, 86.1, and 71.85%, respectively (Mallik, et al. 2010). In this study, overall stage grouping, perineural invasion, and radiotherapy dose were significant predictors of loco-regional control. In addition overall stage grouping and T stage affected disease free survival, with a non-significant trend for worse outcomes with extraglandular involvement.

Most published series have found a survival benefit conferred by radiation therapy with 75% of patients receiving adjuvant radiation in one study (Camilleri, et al. 1998). Storey, et al. (2001) report actuarial locoregional control of 88% at 5 and 10 years; however, the corresponding disease free survival rates were 60 and 53% due to 36% of patients with locoregional control developing distant metastases. Nonetheless, the median survival time for patients with locoregional control was 183 months compared to 19 months for those patients without locoregional control. In a similar study of adjuvant radiation therapy, cancer specific survival was 79 and 57% at 5 and 10 years, respectively, with local control of 85 and 74%, respectively. Twenty percent of their patients (all ACC) developed distant metastases (Sykes, et al. 1999). A retrospective study of 87 patients that compared patients who received either initial enucleation of the gland (subcapsular dissection) with no evidence of residual primary or nodal disease followed by postoperative radiation therapy; or patients who had evidence of gross residual primary or nodal disease, grossly positive margins, or piecemeal removal following initial treatment who underwent definitive surgical resection followed by postoperative radiation therapy, found no difference in locoregional control, disease specific survival, or overall survival (Kaszuba, et al. 2007). This suggests patients without evidence of gross residual disease post enucleation might be satisfactorily treated with radiation therapy without further surgery.

In a series of 22 patients with ACC of the submandibular gland, disease free survival at 5 years of 57% and 10 years of 41% and overall survival of 70 and 37%, respectively, were found (Cohen, et al. 2004). These authors concluded that early diagnosis, wide surgical intervention and postoperative radiotherapy were associated with a favorable prognosis while not surprisingly large tumor size, positive surgical margins, perineural invasion, and local recurrence were negative prognostic factors.

In comparing submandibular gland cancers to parotid cancer, a poorer overall prognosis was associated with submandibular gland tumors (Hocwald, et al. 2001). In addition, the likelihood of developing distant metastasis is greater in the submandibular gland than the parotid (Schwenter, et al. 2006); however, this may be due to the higher percentage of ACC. In one large series of 370 cases only 12 (2.9%) presented with distant metastases, but 24.9% were found to have positive regional nodes (Bhattacharyya 2004). Interestingly, in this retrospective review extraglandular extension and nodal positivity did not affect survival. Goode, et al. (1998) in a study of 234 cases of MECA of the major salivary glands stated that MECAs with equal histopathologic grade had a better prognosis when their tumors were in the parotid gland rather than in the submandibular gland. This finding was confirmed in a Swedish study of 2465 major salivary gland tumors (Wahlberg, et al. 2002). High grade MECA is also more common in the submandibular gland, with 32 of 82 cases (39%) occurring in this gland (Bhattacharyya 2004).

SUBLINGUAL GLAND TUMORS

Virtually all sublingual gland tumors will be malignant and, as for all salivary tumors, primary surgery is the treatment of choice. Prognosis will be determined by the histologic grade and the stage of the tumor. In the very rare benign tumor, or with small low grade carcinomas, a transoral wide local resection may be successfully performed

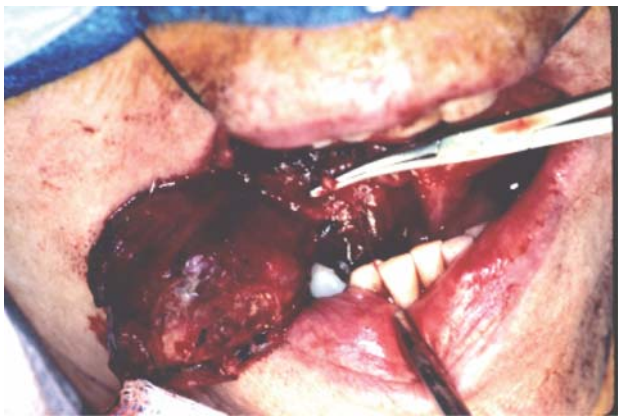
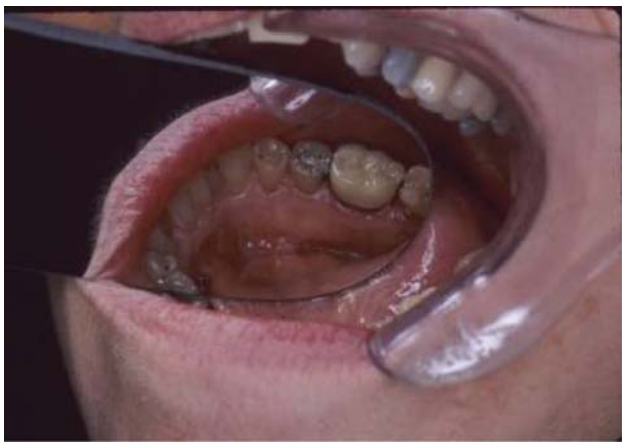


Figure 10.12. Delivering sublingual gland with low grade malignant tumor via an intraoral wide local excision. Re-published with permission from: Blanchaert RG, Kumar D, Ord RA: Polymorphous low-grade adenocarcinoma of the sublingual gland. *Int J Oral Maxillofac Surg* 27:115–117, 1998.

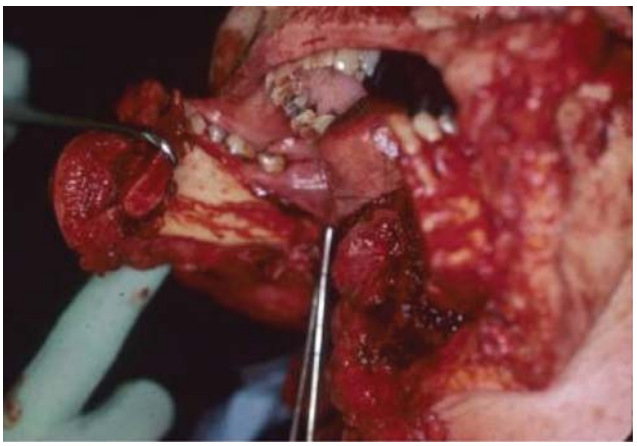
(Blanchaert, et al. 1998). This will be easier to undertake in edentulous patients and the Wharton duct will require a sialodochoplasty procedure (Figure 10.12). In most cases due to grade, tumor size, the presence of teeth, and involvement of mandibular periosteum/bone, a wider access will be required. If the periosteum is uninvolved and can be safely peeled from the lingual bone a standard "pull through" approach or a lip split with mandibulotomy can be used (Figure 10.13). The functional result of the lip split/mandibulotomy is better than the pull through (Devine, et al. 2001). As both of these methods of access involve entering the neck, a supraomohyoid neck dissection is usually carried out in the N0 neck, even for low grade tumors (Figure 10.14).

Most malignant tumors of the sublingual gland are adenoid cystic carcinomas, which have a low incidence of lymph node metastasis (10%, but selective neck dissection is recommended: Sun, et al. 2010). Due to local infiltration of the lingual nerve, submandibular duct, and the oral portion of the submandibular gland, the submandibular gland and neck dissection are usually removed in continuity (Figure 10.15).

When positive nodes are present, type I modified radical neck dissection is required. Both lingual and hypoglossal nerves can be involved by these tumors at an early stage, particularly the ACC. Sacrifice of the nerve with proximal tracing and frozen section guidance as described for the submandibular tumors may be needed. In tumors fixed to periosteum, or where minimal cortical erosion is present, an oblique marginal mandibular resection angling the cut to take a greater height of the lingual plate will be utilized. The marginal mandibular resection can be performed with the pull through or mandibulotomy approach. Where the medullary bone is invaded, a segmental mandibular resection with a composite en bloc resection of the floor of mouth is safest and will provide excellent access (Figure 10.16). In these larger soft tissue resections, a thin pliable

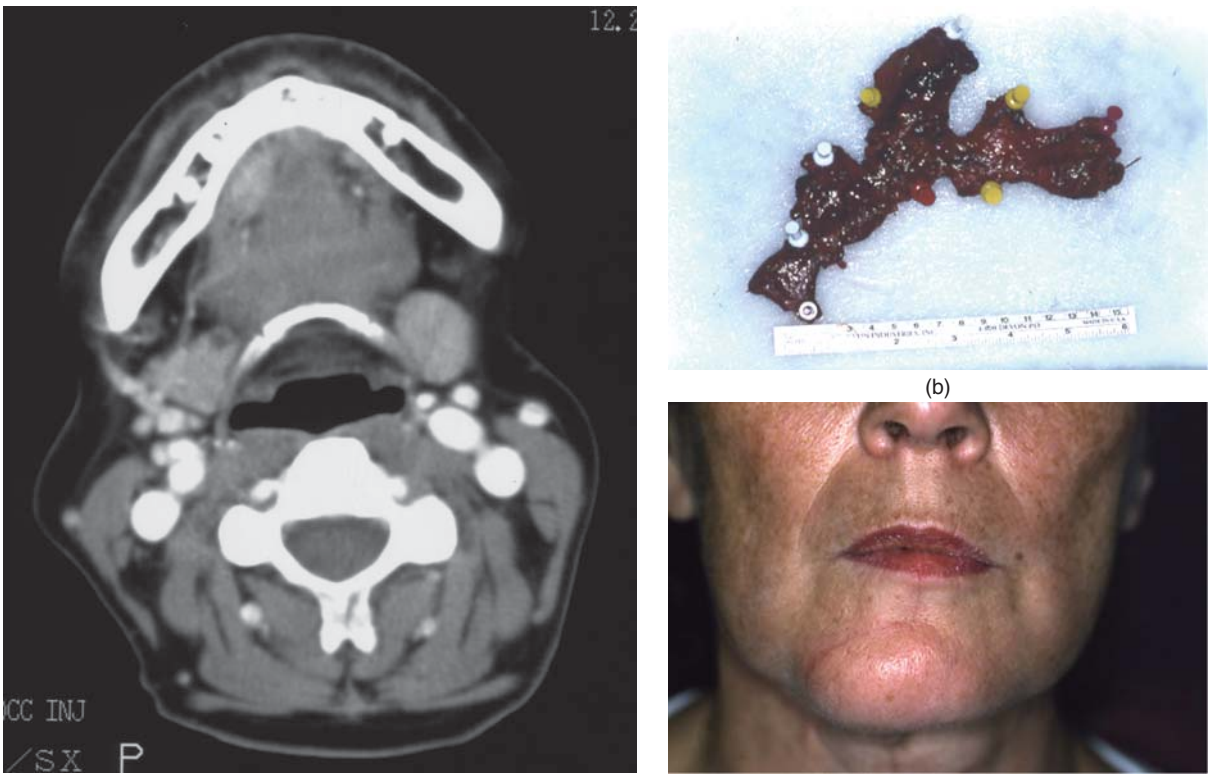


(a)



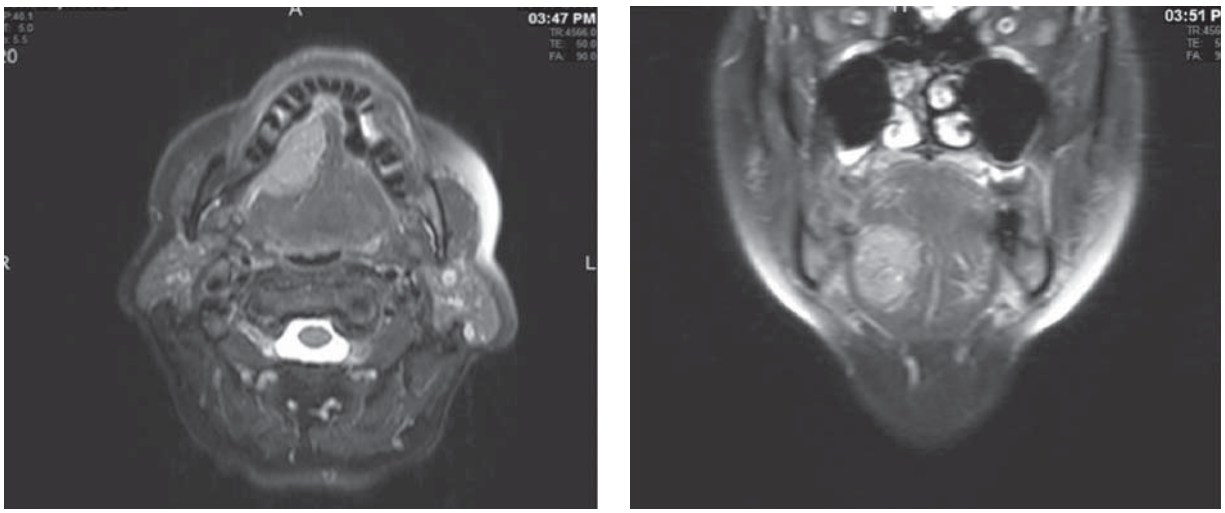
(b)

Figure 10.13. (a) Adenoid cystic carcinoma of sublingual gland closely approximated to the mandible (seen via an intraoral mirror photograph). (b) Following lip split and mandibulotomy the periosteum is found to be uninvolved and is stripped from the mandible, which is preserved.



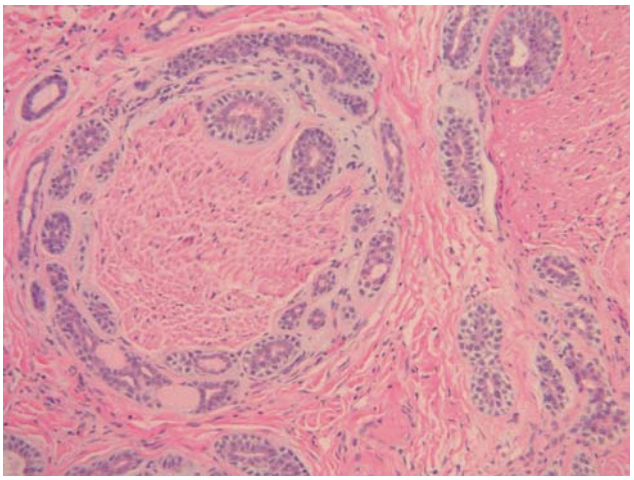
(a) (b) (c)

Figure 10.14. (a) CT scan shows low grade mucoepidermoid carcinoma of the right sublingual gland. (b) This tumor was accessed via a lip split incision and mandibulotomy. Bilateral supraomohyoid neck dissections were undertaken as can be seen in the surgical specimen. (c) Cosmetic result of lip split incision. Patient is alive and tumor free greater than 13 years postoperatively.



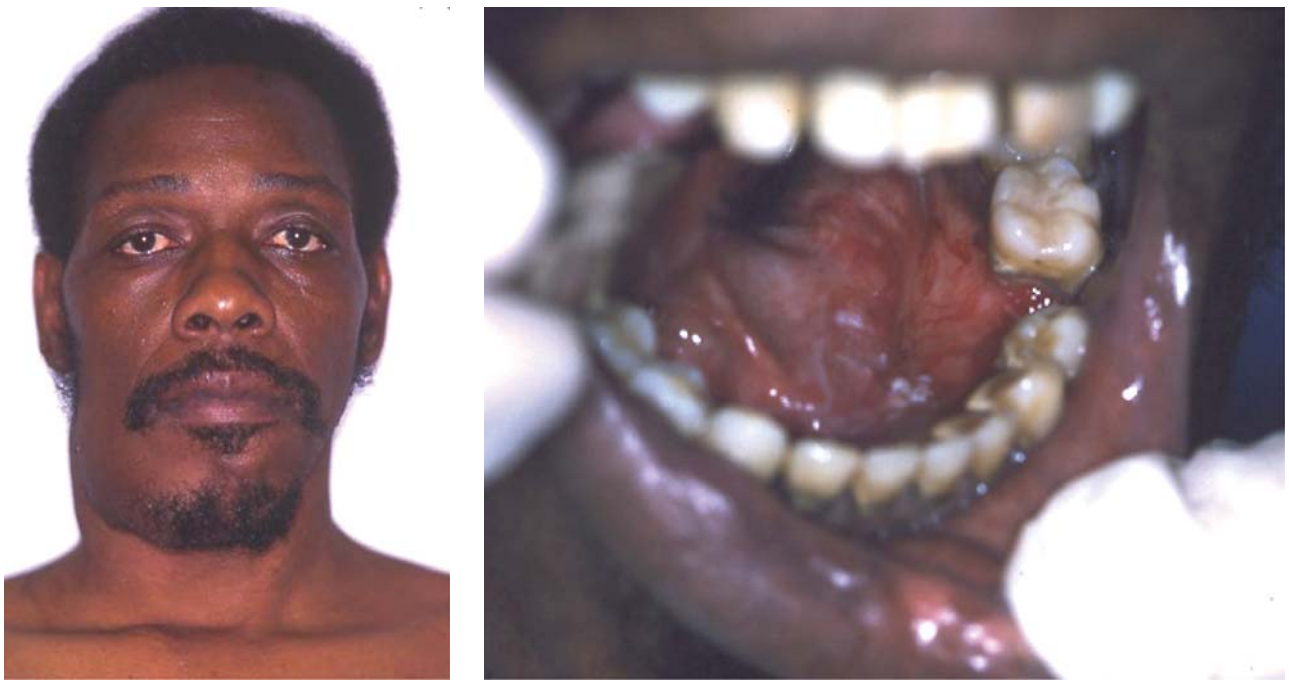
(a) (b)

Figure 10.15. (a and b) Axial and coronal MR show right sublingual gland tumor. Note proximity anatomically to the tongue, mandible, lingual nerve, submandibular duct, and oral extension of submandibular gland. (c) Histopathology of adenoid cystic carcinoma of right sublingual gland in a 70-year-old African American woman complaining of floor of mouth pain for 2 years. Slide shows perineural and intraneural invasion of the lingual nerve. Source: Dr John C. Papadimitriou, Professor of Pathology, Department Pathology University of Maryland. Reproduced with permission of Dr Papadimitriou.



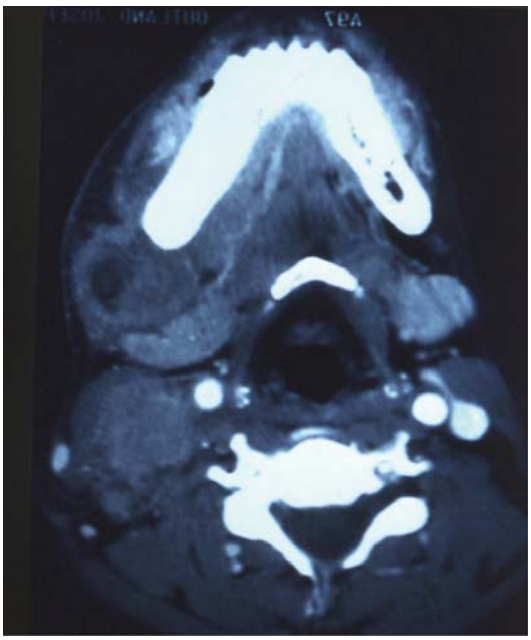
(c)

Figure 10.15. (*Continued*)



(a) (b)

Figure 10.16. (a) A 46-year-old African American man with right cervical lymphadenopathy. (b) Intra oral view of high grade mucoepidermoid carcinoma fixed to the right mandible. (c) CT scan confirms necrotic node. (d) A modified radical neck dissection and hemimandibulectomy with lip split was performed. (e) Postoperative panoramic film showing the reconstruction plate. (f) Immediately post-chemoradiation. (g) Mass in anterior mediastinum eroding sternum and manubrium. (h) Close up view of manubrial mass. The patient died shortly thereafter due to lung metastases. Re-published with permission from: Ord RA, Salivary gland disease. In: Fonseca R (ed.), *Oral and Maxillofacial Surgery, Volume 5, Surgical Pathology*, Ch. 10, Philadelphia, WB Saunders Co., pp. 288–289, 2000 (Figures 10–21 a, b, c, d, e, f, g).



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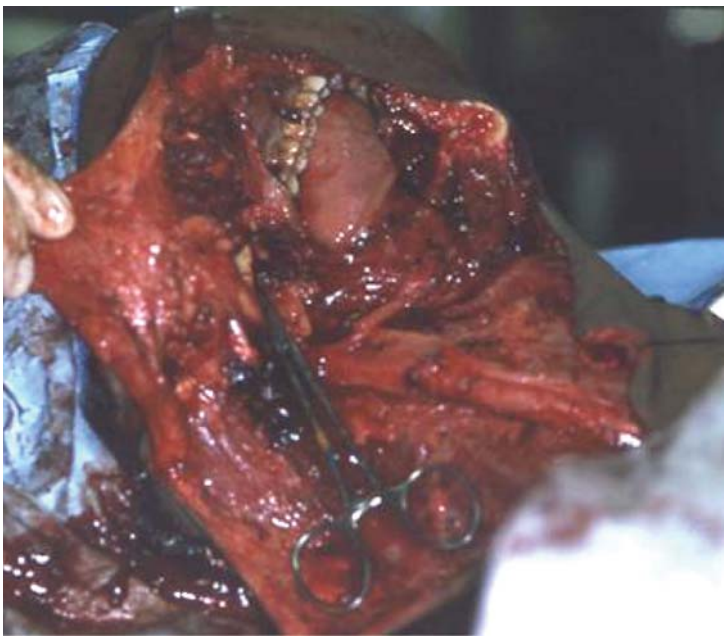

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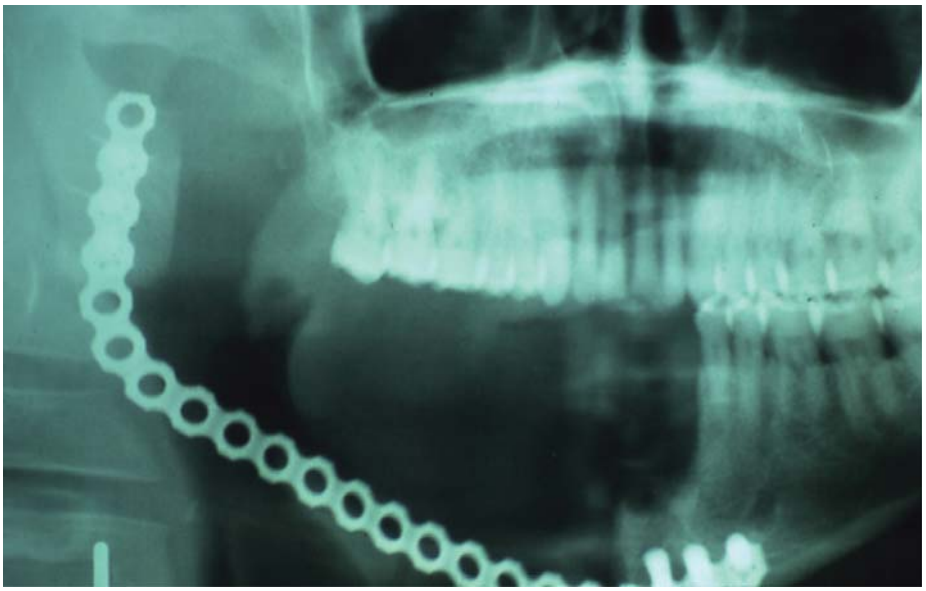


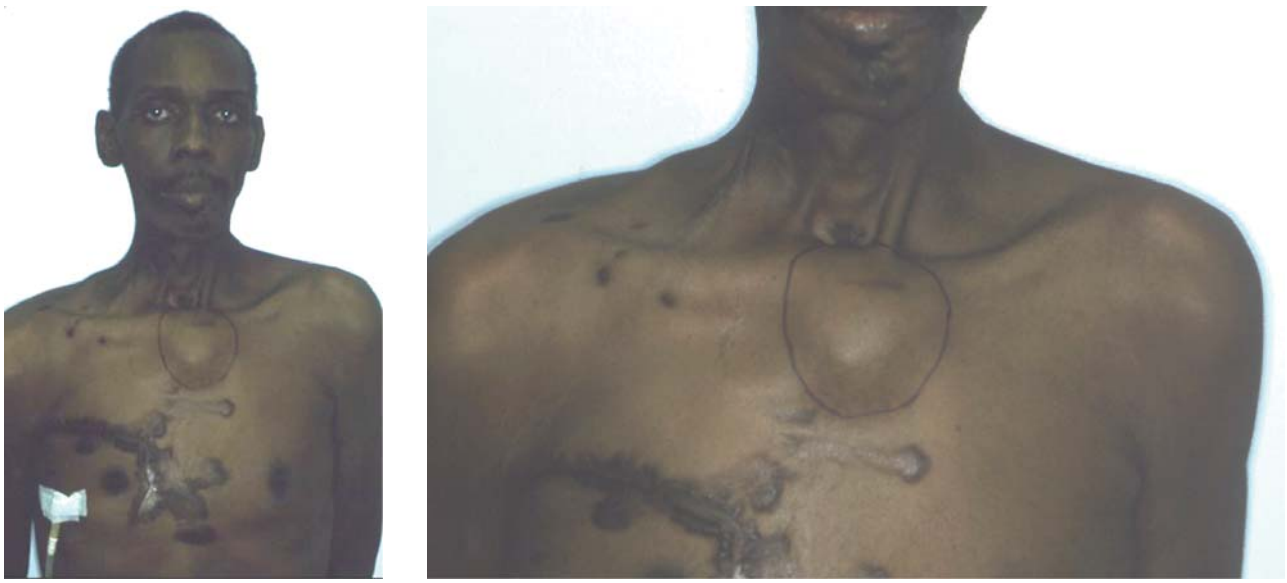
(e)

(f)

Figure 10.16. (*Continued*)

flap such as the radial forearm flap probably gives the best results in maintaining tongue mobility. Where the mandible has been resected, a fibular flap (Rinaldo, et al. 2004) or deep circumflex iliac artery (DCIA) flap is appropriate.

Adjuvant radiation therapy is indicated for positive nodes, perineural invasion, extracapsular nodal spread, positive margins, and high grade histology. Prognosis for these tumors is difficult to assess as the literature is mostly composed of case reports and small series. Spiro (1995) reported only 3 of 18 patients (16.6%) dying of their tumor with a median followup of 74 months. However, Yu, et al. (2007) reported distant metastases and local recurrence as the main cause of death with local recurrence rates of 30% and distant metastases,



(g) (h)

Figure 10.16. (*Continued*)

26.7%. In this series, 56.7% of tumors were stage III.

It is reasonable to conclude that, although 5-year survival from submandibular and sublingual gland cancer is reasonable, the high percentage of ACC found in these glands leads to continuing decrease in survival at 10 years and beyond due to late local recurrence and distant metastases.

Summary

- Submandibular gland tumors comprise only 10% of salivary tumors.
- Most submandibular swellings are inflammatory in etiology.
- 50% of submandibular tumors will be malignant.
- Open biopsy should not be used for submandibular gland tumors. FNAB is the preoperative diagnostic method of choice.
- Sublingual gland tumors comprise <1% of salivary tumors.
- 90% of sublingual gland tumors are malignant.
- ACC followed by MECA are the commonest cancers in both the submandibular and sublingual glands.
- Surgical management is based on both histologic diagnosis and stage.

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Chapter 11

Minor Salivary Gland Tumors

Outline

Introduction

The evaluation, diagnosis, and treatment of a patient with a mass occupying the territory of minor salivary gland tissue in the palate, buccal mucosa, or lips, represent intellectually stimulating disciplines. This statement is clearly derived from the relative paucity of lesions in these anatomic areas. Salivary gland tumors in general are quite rare, accounting for only 0.2–6.6% of all human tumors (Chidzonga, et al. 1995). Both geographic and racial factors may explain the relative paucity of these tumors (Ansari 2007). The average annual incidence of salivary gland tumors per 100,000 population is 4.7 for benign tumors and 0.9 for malignant tumors (Ansari 2007). Both neoplastic and non-neoplastic entities are diagnosed in the salivary glands, including the minor salivary glands, thereby adding to the stimulating nature of the differential diagnosis, microscopic diagnosis, and treatment of minor salivary gland tumors. Data regarding the incidence of salivary gland tumors in general may be difficult to obtain. This is not only due to the rarity of these tumors, but also to the previous non-routine nature of reporting of these diagnoses to hospital tumor registries, and the occasional treatment of these lesions in office settings (Melrose 1994). It has been estimated that minor salivary gland tumors account for only 2–5% of all head and neck tumors, with malignant minor salivary gland tumors accounting for only 2–4% of all head and neck cancers (MacIntosh 1995). In 1985, Regezi, et al. reported on 238 minor salivary gland tumors amongst 72,282 (0.33%) total oral biopsy specimens diagnosed over a 19-year period (Regezi, et al. 1985). Similarly, Rivera-Bastidas, et al. reported 62 minor salivary gland tumors from a total of 9000 oral biopsies (0.7%) during a 24-year period (1996). A review of 40,000 head and neck tumors over a 40-year period of time revealed 196 (0.5%) minor salivary gland tumors. Approximately 10% of all salivary gland tumors arise in the minor glands (Ord 1994). Of these minor salivary gland tumors, 70% occur in the oral cavity, 25% in the nasal cavity/sinuses/nasopharynx, and 3% occur in the larynx (MacIntosh 1995). Of the oral minor salivary gland tumors, at least 50% have been diagnosed in the palate, according to

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most large series (Eveson and Cawson 1985; Spiro 1986). In addition to relatively low numbers of minor salivary gland tumor diagnoses, there are controversies regarding the precise microscopic diagnosis of these tumors. In Waldron et al.'s review of 426 oral minor salivary gland tumors (Waldron, et al. 1988), each of these cases were reviewed by the three authors and complete concurrence of the microscopic diagnoses was reached in 346 cases (81.2%). In 49 cases, there were minor disagreements as to the diagnoses, mainly related to the subclassification of the tumors. Significant disagreement, regarding a benign versus malignant diagnosis of the neoplasm, was noted in 21 cases (5%). Moreover, following the authors' review, their diagnoses were compared to those of the contributing pathologists. There was complete agreement in 374 cases (87.8%). These statistics exemplify the complex nature of intraoral minor salivary gland tumors, thereby questioning the exact incidence of these neoplasms as a whole as well as specific diagnoses in particular.

Minor salivary gland tumors occur not only as benign and malignant entities, but also as a spectrum of cell types within these glands (Carlson 1998). The frequency of benign versus malignant tumors occurring throughout the minor glands in the oral cavity is one feature that distinguishes these tumors from their counterparts in the major glands. One series reported 15% of parotid gland tumors and 37% of submandibular gland tumors to be malignant (Eveson and Cawson 1985). In general terms, published series record that approximately 20–70% of minor salivary gland tumors are malignant (Ord 1994; Epker and Henny 1969) (Table 11.1). It seems that the center that reports the incidence of benign versus malignant minor salivary gland tumors of the oral cavity is the primary bias in these reports. For example, tertiary care referral centers with a cancer initiative may be preferentially referred patients with malignant diagnoses. Spiro's report of his 35 year experience with salivary gland neoplasia at Memorial Sloan Kettering Cancer Center is a case in point. He reported on 2807 patients, 607 of whom had minor salivary gland tumors. The frequency of malignant tumors in this report was 87%. The Armed Forces Institute of Pathology reported 2945 cases of minor salivary gland tumors in 1991. By contrast, 49% of these cases were malignant. Numerous other series have reported similar figures, such that it has become reasonably well accepted that approximately 50% of minor salivary gland tumors of the oral cavity are benign and 50% are malignant.

Etiology of Minor Salivary Gland Tumors

Risk factors for salivary gland tumors have been studied extensively. Carcinoma of the major salivary glands, for example, has identified a relationship with prior radiation therapy and previous skin cancer (Spitz, et al. 1984). Another study reported 31 patients who had both a newly diagnosed salivary gland tumor and a history of radiation therapy to the head and neck region (Katz and Preston-Martin 1984). Radiation therapy had been administered with a range of 11–66 years prior to the development of the salivary gland tumors. No course of radiation therapy was administered for a malignant condition, but rather for acne, hypertrophied tonsils, keloids, and other benign conditions. As such, it is reasonable to assume that a low dose of radiation therapy was administered. Only three cases of minor salivary gland tumors were identified among these 31 cases, including two adenoid cystic carcinomas and one mucoepidermoid carcinoma. One of the tumors was located in the palate and two were located in the cheek/retromolar region.

Benign and malignant salivary gland tumors have also been linked to exposure to ionizing radiation related to the atomic bombings in Hiroshima and Nagasaki during World War II. One hundred and forty-five salivary gland tumors have been studied in survivors of these bombings (Saku, et al. 1997). One hundred and nineteen major gland tumors (27 malignant tumors, 82 benign tumors, 10 undetermined tumors) and 26 minor gland tumors (14 malignant tumors, 12 benign tumors) were identified. Among the 41 malignant tumors, the frequency of mucoepidermoid carcinoma was disproportionately high, and among the 94 benign tumors, the frequency of the Warthin tumor was high.

The association between first primary benign and malignant neoplasms of the salivary glands and the subsequent development of breast cancer has also been investigated (Abbey, et al. 1984). This study identified a fourfold to fivefold increased risk of a second primary breast cancer subsequent to the first salivary gland tumor. Of note is that all of the primary salivary gland tumors were of the major glands and three of the four patients

Table 11.1. Incidence of minor salivary gland tumors

Authors	Year	Location	Number of Cases	Histology
AFIP (Ellis and Auclair 1991a)	1991	USA	2945	Benign 51% Malignant 49%
Ansari	2007	Iran	18	Benign 11.1% Malignant 88.9%
Chau and Radden	1986	Australia	98	Benign 62% Malignant 38%
Chidzonga, et al.	1995	Zimbabwe	282	Benign 80% Malignant 20%
Dhanuthai, et al.	2009	Thailand	311	Benign 47.3% Malignant 52.7%
Eveson and Cawson	1985	England	336	Benign 54% Malignant 46%
Isacsson and Shear	1983	Sweden	201	Benign 28% Malignant 72%
Ito, et al.	2005	Brazil	113	Benign 37% Malignant 63%
Jabar	2006	Libya	75	Benign 39% Malignant 61%
Lopes, et al.	1999	Brazil	196	Benign 35% Malignant 65%
Potdar and Paymaster	1969	India	110	Benign 49% Malignant 51%
Regezi, et al.	1985	USA	238	Benign 65% Malignant 35%
Rivera-Bastidas, et al.	1996	Venezuela	62	Benign 55% Malignant 45%
Satko, et al.	2000	Slovakia	31	Benign 48% Malignant 52%
Spiro	1986	USA	607	Benign 13% Malignant 87%
Stuteville and Corley	1967	USA	80	Benign 10% Malignant 90%
Toida, et al.	2005	Japan	82	Benign 67% Malignant 33%
Waldron, et al.	1988	USA	426	Benign 58% Malignant 42%

described had benign salivary gland tumors. While no association between minor salivary gland neoplasia and breast cancer was established, the study nonetheless attempted to develop a relationship between salivary gland neoplasia and breast cancer. Moreover, the study investigated subsequent breast cancer in patients with a history of salivary gland neoplasia, rather than vice versa. As such, a risk factor for salivary gland tumor development would not be established in patients with breast cancer. In addition, minor salivary gland neoplasia was not represented in this cohort of patients.

In the final analysis, there is some evidence to identify risk factors for the development of minor salivary gland tumors, yet not as much evidence as exists for the development of major salivary gland tumors.

Diagnosis of Minor Salivary Gland Tumors

The diagnosis of a minor salivary gland tumor begins with the establishment of a differential diagnosis. This differential diagnosis should be classified categorically and in order of decreasing likelihood (Carlson 1998). The evaluation of a lesion of the palate, lip, or buccal mucosa might suggest inflammatory, neoplastic, and non-neoplastic entities. Ultimately, the differential diagnosis is based on the patient's history, physical examination, and the anatomic location of the pathologic entity under scrutiny. Generally speaking, benign and malignant minor salivary gland tumors present as painless, slowly enlarging intraoral masses. When present, ulceration predicts a malignant diagnosis, although many minor salivary gland malignancies do not create ulceration of the oral mucosa. Pain is an ominous sign and is associated with perineural invasion, typically by adenoid cystic carcinoma. A painful enlargement of the minor salivary glands is malignant until proved otherwise. The presence or absence of pain therefore represents an important element of the patient's history. Special imaging studies may be obtained prior to performing the biopsy, if required at all, or they may be obtained after the establishment of a diagnosis based on incisional biopsy. Experience shows, however, that their purpose is to anatomically delineate the extent of the tumor rather than to assist in the establishment of the diagnosis. The experienced salivary gland surgeon may detect nuances on imaging studies that favor various diagnoses on the differential diagnosis. While fine needle aspiration biopsy is an essential part of the diagnosis of parotid neoplasms, it has no practical role in the diagnosis of minor salivary gland neoplasms. Rather, an incisional biopsy should be routinely performed, for example, when planning treatment of palatal tumors due to the diverse nature of possible histopathologic diagnoses, as well as the diverse nature of surgical treatment plans based on these diagnoses.

Other minor salivary gland tumor sites, such as the buccal mucosa and upper lip require greater attention to the differential diagnosis in order to determine whether incisional or excisional biopsy best serves the needs of the patient. In many instances, the differential diagnosis may strongly support a benign neoplasm such that proceeding directly to excision is the most appropriate therapy. For example, a tumor in the upper lip that is freely moveable and associated with normal overlying mucosa indicates that an excisional biopsy may be performed in most instances due to the high likelihood of a benign tumor. A minor salivary gland tumor of the buccal mucosa, similar to the palate, has a diverse number of possibilities on the differential diagnosis such that an incisional biopsy should be considered to establish the diagnosis (Table 11.2). There are instances, however, where a freely moveable buccal mucosal tumor may be excised without preceding incisional biopsy, similar to the upper lip tumor previously described.

Treatment of Minor Salivary Gland Tumors

GENERAL PRINCIPLES OF SURGERY FOR MINOR SALIVARY GLAND TUMORS

The treatment of minor salivary gland tumors is distinctly surgical. The specific type of surgery is a function of the anatomic site of the tumor, the invasion of surrounding structures, and the histopathologic diagnosis provided that an incisional biopsy has been performed. In general terms, a palatal minor salivary gland tumor requires an incisional biopsy so as to definitively establish the histopathologic diagnosis prior to the tumor surgery. This biopsy should be performed in the center of the mass so as to not seed the surrounding normal tissue (Freedman and Jones 1994). The decision as to whether to perform an incisional biopsy of buccal mucosal and lip masses thought to represent minor salivary gland tumors rests on the surgeon's intuition as to the benign versus malignant nature of the mass. Smooth, freely moveable submucosal masses without fixation to the overlying mucosa are likely benign and may be treated with excisional biopsies without first performing an incisional biopsy due to the high likelihood of a benign process. By contrast, sizeable masses with mucosal fixation in these areas should probably

Table 11.2. Incidence of benign and malignant minor salivary gland tumors at various sites

Authors	Year	Palate	Lip	Cheek
AFIP (Ellis and Auclair 1991a)	1991	Benign 53% Malignant 47%	Benign 73% Malignant 27%	Benign 50% Malignant 50%
Chau and Radden	1986	Benign 67% Malignant 33%	Benign 77% Malignant 23%	Benign 64% Malignant 36%
Dhanuthai, et al.	2009	Benign 56% Malignant 44%	Benign 87% Malignant 13%	Benign 65% Malignant 15%
Eveson and Cawson	1985	Benign 53% Malignant 47%	Benign 73% Malignant 27%	Benign 50% Malignant 50%
Isacsson and Shear	1983	Benign 78% Malignant 22%	Benign 71% Malignant 29%	Benign 89% Malignant 11%
Jabar	2006	Benign 58% Malignant 42%	Benign 46% Malignant 54%	Benign 46% Malignant 54%
Lopes, et al.	1999	Benign 42% Malignant 58%	Benign 60% Malignant 40%	Benign 0% Malignant 100%
Potdar and Paymaster	1969	Benign 49% Malignant 51%	Benign 67% Malignant 33%	Benign 78% Malignant 22%
Regezi, et al.	1985	Benign 30% Malignant 70%	Benign 88% Malignant 12%	Benign 43% Malignant 57%
Rivera-Bastidas, et al.	1996	Benign 56% Malignant 44%	Benign 18% Malignant 82%	Benign 50% Malignant 50%
Spiro	1986	Benign 26% Malignant 84%	Benign 18% Malignant 82%	
Stuteville and Corley	1967	Benign 4% Malignant 96%	Benign 33% Malignant 67%	Benign 27% Malignant 73%
Toida, et al.	2004	Benign 69% Malignant 31%	Benign 67% Malignant 33%	Benign 60% Malignant 40%
Waldron, et al.	1988	Benign 58% Malignant 42%	Benign 75% Malignant 25%	Benign 54% Malignant 46%

be subjected to incisional biopsy so as to establish the diagnosis due to the concern for malignant disease. As with tumor surgery for other diagnoses, minor salivary gland tumor surgery requires a pre-operative assessment of the anatomic barriers. Physical examination and imaging studies serve to delineate invasion of surrounding anatomic barriers by the tumor. In the palate, for example, it is important to determine whether the palatal bone has been invaded by the tumor. Benign tumors typically do not invade bone, but may "cup it out." In such situations, it is not necessary to resect bone. Malignant tumors of the palate display variable involvement of the palatal bone. Imaging studies, particularly coronal bone windows, must be obtained so as to assess the involvement of the anatomic barrier of palatal bone. Minor salivary gland tumors of the upper lip and buccal mucosa exhibit different behavior regarding their invasion of the anatomic barrier of the surrounding mucosa. In general terms, it is appropriate to preserve the mucosa surrounding a benign minor salivary gland tumor of these sites, while a malignant tumor surgery in these sites requires sacrifice of the surrounding mucosa (Table 11.3).

Treatment of minor salivary gland tumors becomes predicated on the histopathologic diagnosis, which largely translates to the known biologic

Table 11.3. Management of the anatomic barriers in minor salivary gland tumor surgery

	Site		
Histology	Palate	Lip	Buccal mucosa
Benign	– Mucosal sacrificing – Periosteal sacrificing – Bone sparing	– Mucosal sparing – Muscle sparing – Skin sparing	– Mucosal sparing – Muscle sparing – Skin sparing
Malignant	– Mucosal sacrificing – Periosteal sacrificing – Bone sacrificing (variable)	– Mucosal sacrificing – Muscle sacrificing – Skin sparing (variable)	– Mucosal sacrificing – Muscle sacrificing – Skin sparing (variable)

behavior of the neoplasm. Descriptive surgical terms may describe the sacrifice of surrounding soft and hard tissues as a matter of convenience (Carlson 1998). For example, surgical management of palatal tumors may be as straight forward as a periosteal sacrificing, bone sparing wide local excision with split thickness dissection of the soft palate. This specific surgical procedure is the main procedure performed for benign palatal tumors and also has a role to play in some low-grade malignancies (Carlson 1998). The bone sparing, periosteally sacrificing wide local excision with full thickness sacrifice of the soft palate is reserved for deeply infiltrative low-grade malignancies of the palate. The most aggressive surgery for palatal minor salivary gland tumors is the maxillectomy, specifically reserved for the highly aggressive minor salivary gland malignancies of the palate.

SURGICAL TREATMENT OF BENIGN MINOR SALIVARY GLAND TUMORS

The treatment of benign tumors of the minor salivary glands centers on the pleomorphic adenoma, with a brief discussion of the surgery for the canalicular adenoma. The three most common minor salivary gland anatomic sites will be considered, including the palate, the lip, and the buccal mucosa.

Pleomorphic Adenoma

The terms pleomorphic adenoma and mixed tumor are equally satisfactory and interchangeable when describing this common minor salivary gland tumor. The designation mixed is based on the tumor's mixtures of neoplastic elements such that each mixed tumor has unique features (Melrose 1994). It has also been pointed out that the designation refers to the tumor showing combined features of epithelioid and connective tissue-like growth (Waldron 1991). There is universal agreement that the pleomorphic adenoma is the most common salivary gland tumor. The Armed Forces Institute of Pathology data of 13,749 salivary gland tumors showed 6880 cases of pleomorphic adenoma of which 4359 were located in the parotid gland and 1277 were located in minor salivary gland tissue (Auclair, et al. 1991). The palate accounted for 711 of these 6880 cases of pleomorphic adenoma (10.3%) and was the second most common site for this tumor in the AFIP data. The 711 cases in the palate represent 56% of cases located in the minor salivary glands. Interestingly, the AFIP data subclassified palatal pleomorphic adenomas into those occurring on the hard palate (118 cases) and those occurring in the soft palate (110 cases). There were 483 cases that were not specified as to location in the palate. The subclassification of specific anatomic location in the palate is of significance when working up these cases and planning surgical treatment for these patients. Those pleomorphic adenomas located primarily in the soft palate require investigation as to involvement of the parapharyngeal space.

Treatment of the palatal pleomorphic adenoma is based on the realization that this tumor does not possess a capsule. This notwithstanding, the tumor does exhibit a "pseudocapsule" represented by a loose fibrillar network surrounding the tumor. In addition, the periosteum on the superior aspect of the tumor does serve as a very competent anatomic barrier such that palatal bone may be preserved in this tumor

surgery, even when the bone has been "cupped out" clinically and radiographically. Under such circumstances, the pleomorphic adenoma does not invade bone histologically such that bone resection is not warranted. In fact, it is reasonable to proceed with surgery without obtaining CT scans pre-operatively. A periosteally sacrificing wide local excision is performed, observing at least a 5 mm linear margin surrounding the clinically apparent tumor (Figure 11.1). While these tumors are submucosal in nature, the mucosa must be sacrificed with the tumor due to the close proximity of the tumor and the overlying mucosa (Yih, et al. 2005). The most appropriate linear margin of uninvolved soft tissue included at the periphery of the tumor seems to be a source of controversy (Carlson 1998; Ord 1994; Pogrel 1994). The soft palate musculature is dissected in a split thickness fashion so as to prevent an oral-nasal communication. A preoperatively fabricated palatal stent protects the exposed bone in the postoperative period until granulation tissue appears on the bone surface of the palate. There is no need to provide reconstruction of this exposed bone surface, as mucosalization ultimately occurs predictably. Negative soft tissue margins in the specimen predict a curative surgery without recurrence of the tumor (Beckhardt, et al. 1995).

As previously mentioned, the pleomorphic adenoma that develops in the soft palate may be different from the pleomorphic adenoma of the hard palate, in so far as its anatomic progression is concerned. Tumors located on the hard palate will grow into the oral cavity (Figure 11.2), whereas tumors of the soft palate (Figure 11.3) may descend into the parapharyngeal space (Carlson 1998). As such, when considering the surgical treatment for a pleomorphic adenoma of the soft palate, the surgeon should obtain CT scans preoperatively so as to determine possible involvement of the parapharyngeal space. When dissection of the parapharyngeal space by the tumor is noted, a combined transoral/transcutaneous approach to tumor extirpation is indicated. A mandibular osteotomy for effective dissection of the tumor bed and protection of the great vessels in the neck may be indicated.

Pleomorphic adenomas are known to occur in other minor salivary gland sites, including the lip, buccal mucosa, and tongue. Lip tumors accounted for 297 cases in the AFIP files, of which a majority occurred in the upper lip. Lower lip pleomorphic adenomas are very rare. The buccal mucosa accounted for 126 cases in the AFIP series. The surgery required for removal of pleomorphic adenomas in the lip and buccal mucosa involves an excision of the tumor and associated minor salivary gland tissue. The plane of dissection is "peri-pseudocapsular" in nature. This ensures an anatomic barrier of fascia surrounding the tumor. These tumor surgeries are curative as long as tumor spillage does not occur intraoperatively. Subtherapeutic ablation of these tumors in the form of an enucleation will certainly predispose the patient to persistent disease. Such recurrences were noted to be multifocal in nature as originally described in the major salivary glands (Foote and Frazell 1953).

Malignant pleomorphic adenomas of salivary gland origin are uncommon neoplasms. The broad heading, malignant mixed tumor, includes three different clinical and pathologic entities: *carcinoma ex. pleomorphic adenoma*, *carcinosarcoma*, and *metastasizing pleomorphic adenoma*. Carcinoma ex.pleomorphic adenoma, perhaps the most commonly referenced malignant pleomorphic adenoma, is a pleomorphic adenoma in which a second neoplasm develops from the epithelial component that fulfills the criteria for malignancy. These features include invasiveness, destruction of normal tissues, cellular anaplasia, cellular pleomorphism, atypical mitoses, and abnormal architectural patterns (Gnepp and Wenig 1991). The Armed Forces Institute of Pathology data showed 326 cases of carcinoma ex-pleomorphic adenoma which accounted for 2.4% of their 13,749 cases. A significant majority of these tumors were located in the parotid gland (64.4%); however, these malignancies occurred in the minor salivary glands, as well. The palate accounted for 36 of 57 cases in the minor glands, with the upper lip (6 cases), tongue (4 cases), and cheek (4 cases) also represented. A review of this tumor shows that preoperative duration of a benign pleomorphic adenoma is the main determining factor regarding malignant transformation. Specifically, the incidence of malignancy progressively increases from 1.6% for tumors present for less than 5 years to 9.4% for tumors present for periods longer than 15 years (Auclair, et al. 1991). The other predisposing condition for the development of this malignancy is recurrence of a benign pleomorphic adenoma. This fact supports a curative approach to the pleomorphic adenoma from the outset, with

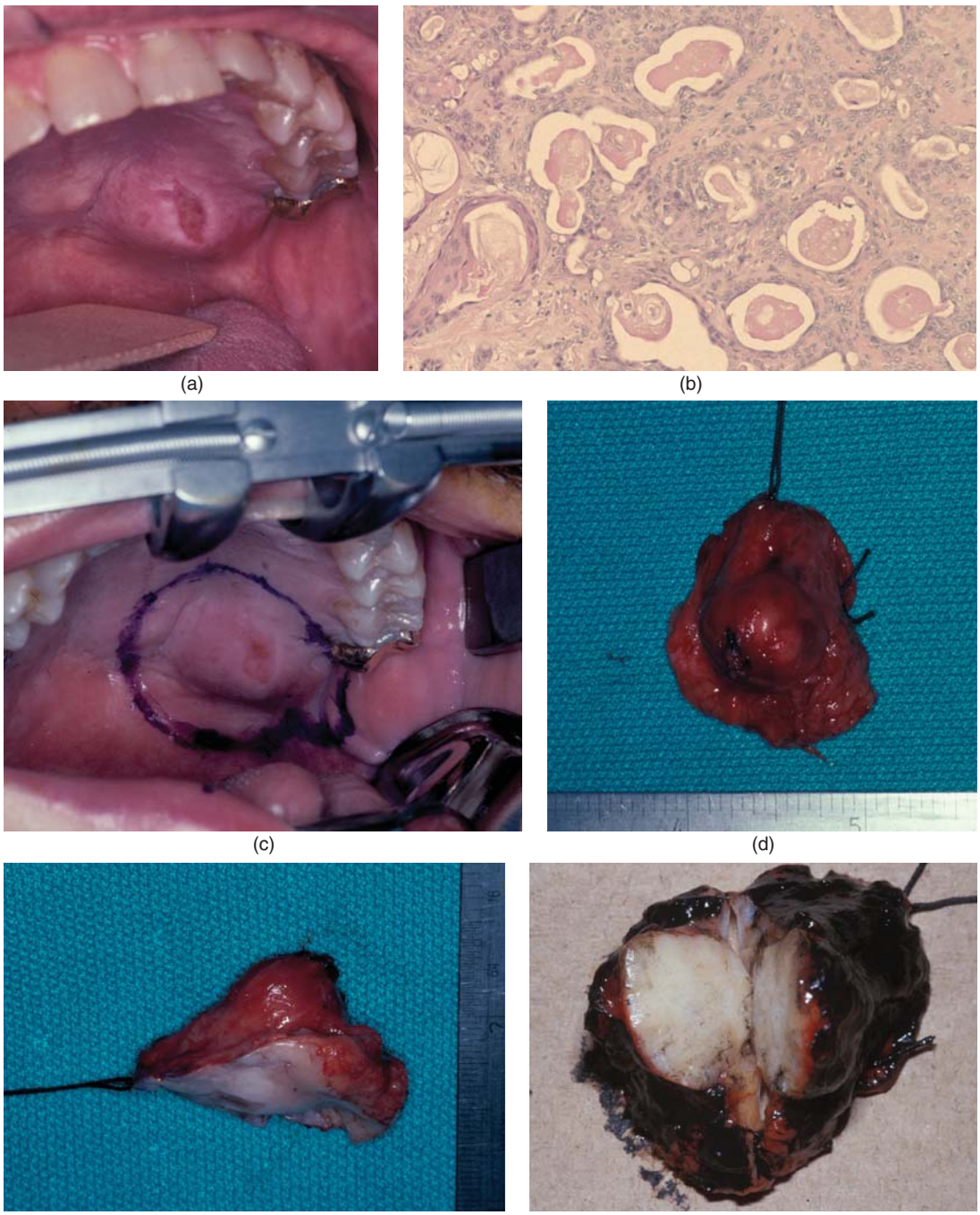


Figure 11.1. The clinical appearance of a pleomorphic adenoma of the palate (a). An incisional biopsy was performed, and showed an acanthomatous variant of this tumor (b). A periosteal sacrificing, bone sparing wide local excision with split thickness sacrifice of the soft palate was performed with a 5–10 mm linear mucosal margins (c). In so doing, the periosteum serves as the superior anatomic barrier on the specimen (d, e). The cut specimen (f) shows the characteristic appearance of a pleomorphic adenoma. The histopathology of the tumor specimen (g) shows the tumor approaching, but well contained within the pseudocapsule. The remaining tissue bed (h) is covered with a surgical stent and allowed to heal with tertiary intention. No tissue coverage of the palate is required. The tissue bed is noted at 3 months (i) and 12 months (j) postoperatively. Effective mucosalization of the exposed bone surface of the hard palate and exposed muscle surface of the soft palate has occurred.

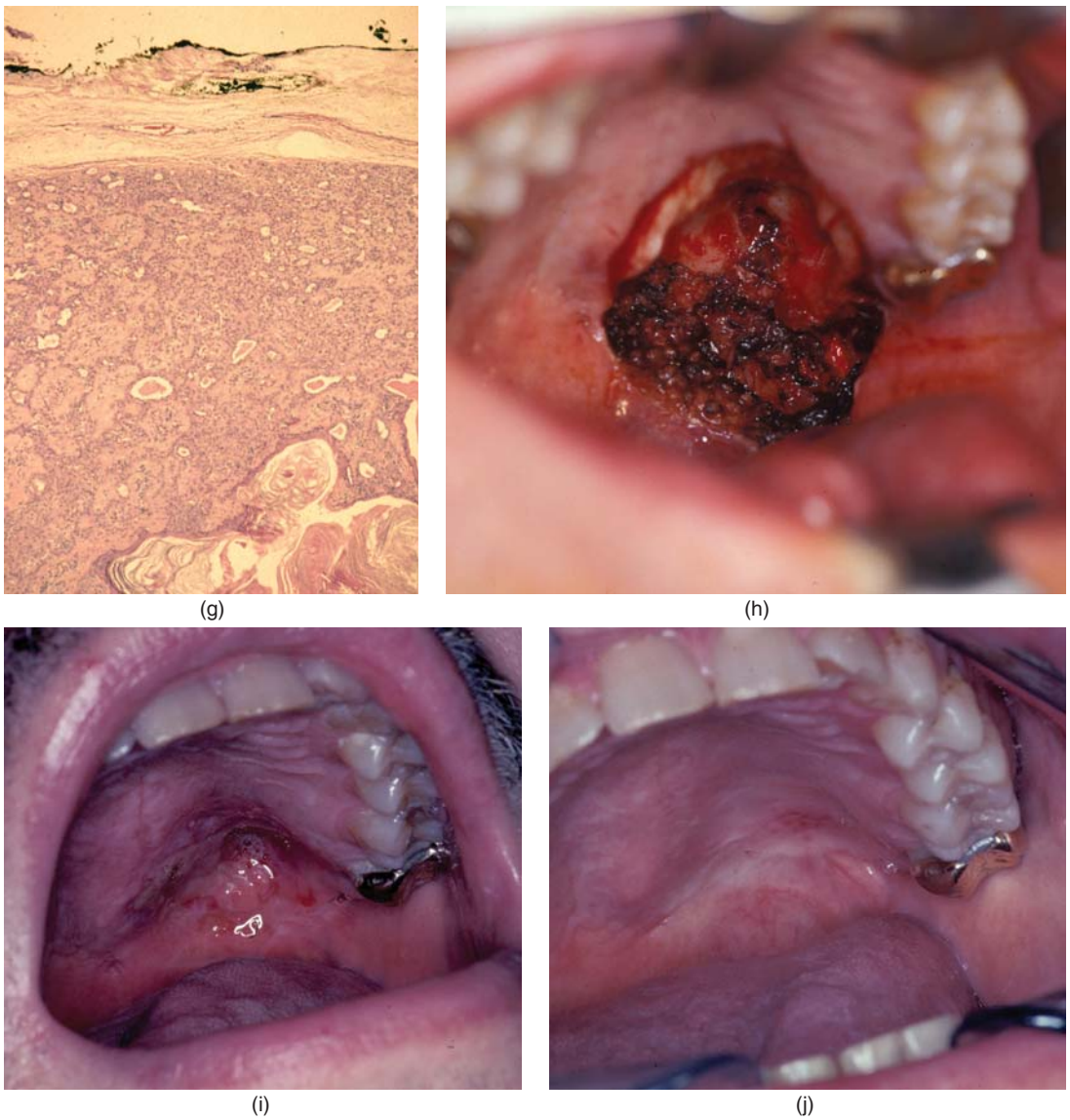


Figure 11.1. (*Continued*)

abandonment of the subtherapeutic enucleation of these tumors in the parotid gland or minor salivary gland tissues. The prognosis for this malignancy is generally considered dismal, with 71% of patients exhibiting metastatic disease during the course of their disease.

Carcinosarcoma, also known as true malignant pleomorphic adenoma, is a tumor defined by histologic evidence of malignancy in both the epithelial and stromal elements of the tumor. These tumors are rarer than the carcinoma ex. pleomorphic adenoma, accounting for only eight cases in the AFIP registry, and none occurred in the minor salivary glands. Other cases presented in the literature do identify the existence of this diagnosis in the minor salivary glands.

Metastasizing mixed tumor is a histologically benign pleomorphic adenoma, but located in distant sites. The pleomorphic adenomas are known to arise in major as well as minor salivary glands, and the metastatic foci have been identified in the cervical lymph nodes, spine and liver (Auclair, et al. 1991). Data on the interval from removal of the primary tumor to the identification of the first metastasis is 1.5–51 years, with an average of 16.6 years.

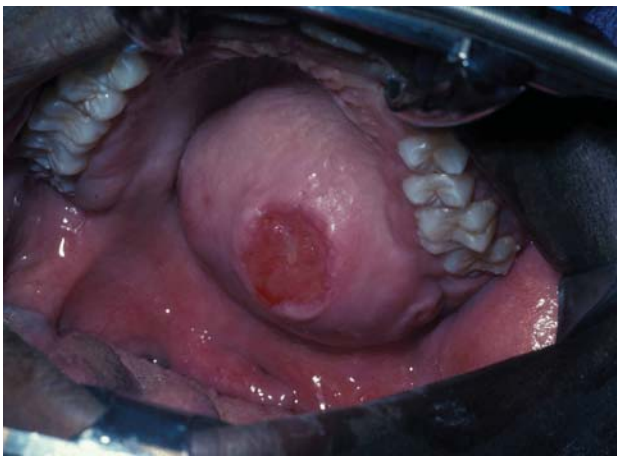


Figure 11.2. A large pleomorphic adenoma that is primarily located over the hard palate. As such, it is permitted to grow in an exophytic fashion, with cupping out of the palatal bone, but no involvement of the parapharyngeal space. Reprinted with permission from: Carlson ER: Salivary gland pathology – Clinical perspectives and differential diagnosis, In: *The Comprehensive Management of Salivary Gland Pathology, Oral and Maxillofacial Surgery Clinics of North America* 7, 361–386, WB Saunders Co., 1995.

Canalicular Adenoma

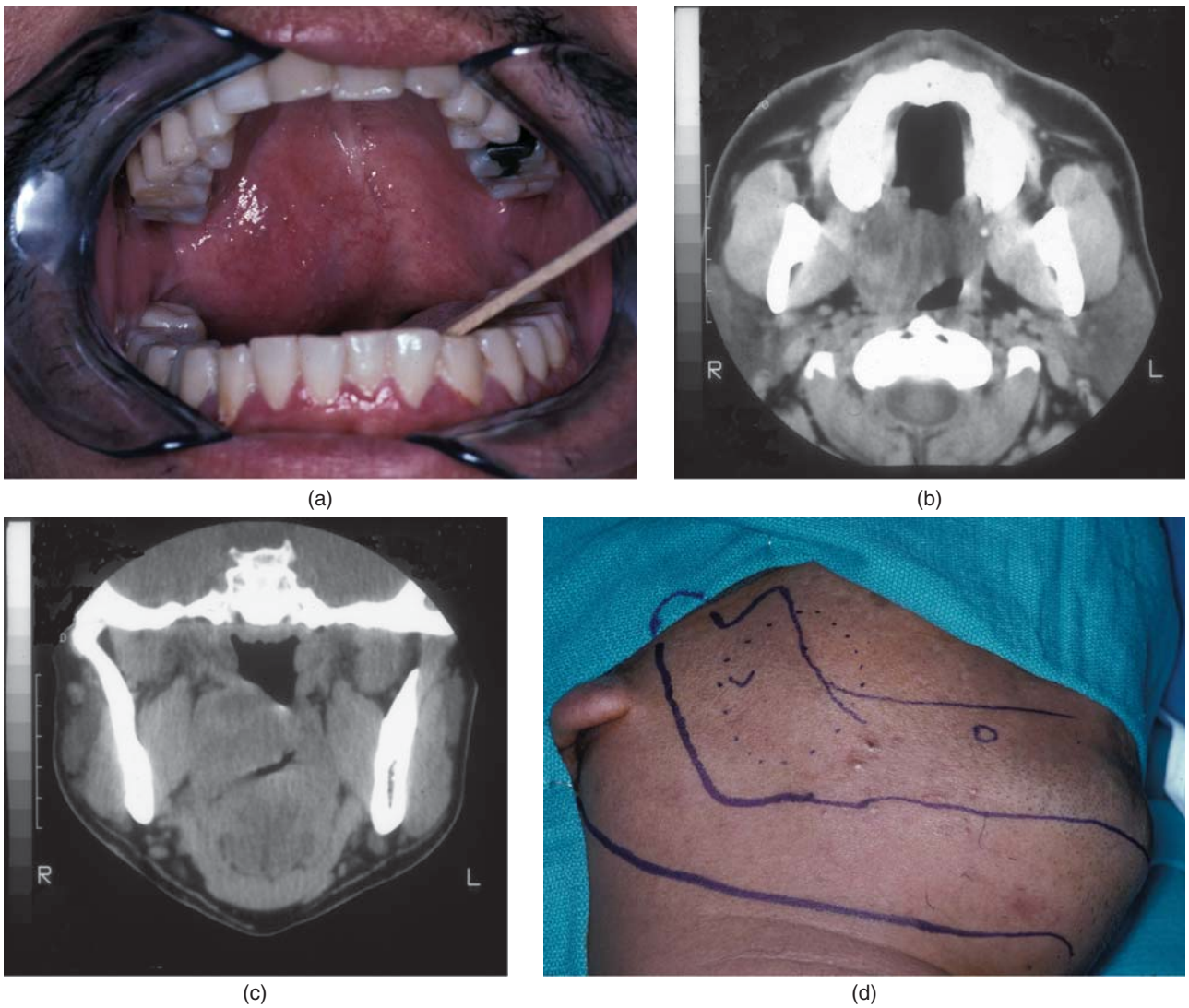
The canalicular adenoma is a benign tumor that has a significant predilection for the upper lip (Figure 11.4). In the past, this tumor was more commonly referred to as a monomorphic adenoma. Gardner recommended that the term monomorphic adenoma be used as a nosologic group of epithelial salivary gland tumors that are not pleomorphic adenomas (Gardner and Daley 1983). The canalicular adenoma and basal cell adenoma identify specific forms of monomorphic adenomas (Daley, et al. 1984). The canalicular adenoma classically occurs in the upper lip in elderly women (Kratochvil 1991). In fact, canalicular adenomas typically affect an older population compared to pleomorphic adenomas (Ord 1994). The canalicular adenoma is typically an asymptomatic, slow-growing, and freely moveable mass that uncommonly exceeds 2 cm in widest diameter. They may resemble mucoceles which are uncommonly located in the upper lip. Of the 121 canalicular adenomas in the AFIP files, 89 of them occurred in the upper lip. The second most common site was the buccal mucosa (Auclair, et al. 1991). The tumor is encapsulated such that an excision of the tumor in any anatomic site in a pericapsular fashion represents a curative surgery provided that tumor spillage does not occur (Figure 11.5). The canalicular adenoma is multifocal in 20% of cases (Ord 1994). If recurrence is believed to have occurred, it might actually represent a new primary tumor (Melrose 1994).

SURGICAL TREATMENT OF MALIGNANT MINOR SALIVARY GLAND TUMORS

The malignant diagnoses in the minor salivary glands are more diverse than their benign counterparts. These malignant diagnoses may be low-grade or high-grade, and most represent histopathologic diagnostic challenges. As with the benign minor salivary gland tumors, surgery represents the hallmark of therapy for malignant minor salivary gland tumors, and the principles of surgery have not changed significantly over the past several decades (Bell, et al. 2005). In addition to eradication of the primary malignancy, consideration should be given for neck dissection in very specific circumstances, as well as postoperative radiation therapy in this cohort of patients.

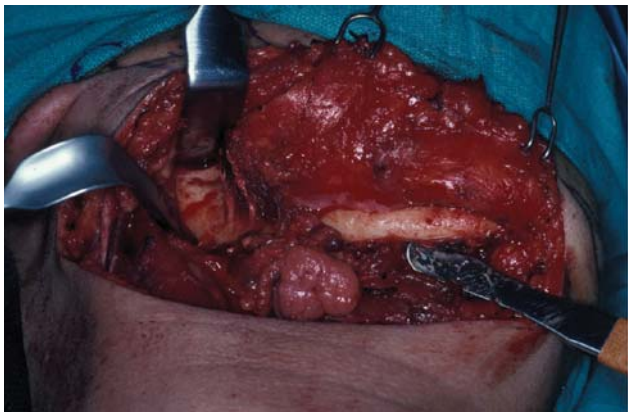
Mucoepidermoid Carcinoma

The mucoepidermoid carcinoma is the second most common tumor of the salivary glands overall, the most common salivary gland malignancy overall, and the most common minor salivary gland malignancy (Auclair and Ellis 1991). During the greater than 70 years since its first description, this neoplasm has generated significant debate regarding the possible existence of a benign variant, the optimal number of grades, and the proper treatment for certain minor salivary gland lesions. The term *mucoepidermoid tumor* was first introduced by Stewart, Foote, and Becker in 1945 in their publication of 45 cases (Stewart, et al. 1945). In this report, only two grades were utilized, including relatively favorable (benign) and highly unfavorable (malignant) tumors. The authors indicated that the adjective benign was rarely ever applicable in an absolute sense and as used in their report did not imply innocent behavior. It did indicate, however, that the authors had not observed metastasis from these tumors. The designation malignant indicated a histologic structure that was associated with the ability to produce regional lymph node and distant metastases. This notwithstanding, the authors



(a) (b) (c) (d)

Figure 11.3. The clinical appearance of a pleomorphic adenoma that is located primarily in the soft palate (a). Its chronic growth permitted entry into the parapharyngeal space, as noted on CT scans (b, c). Due to the relative inability to dissect this tumor bed entirely transorally, a decision was made to perform a combined transcutaneous and transoral approach to the tumor ablation with an Attia double osteotomy of the mandible. Wide transcutaneous access was accomplished for this tumor surgery (d). Dissection of the mandible was performed in a subperiosteal fashion, while maintaining as much periosteum and muscle as possible on the lateral surface of the mandible (e). Bone plates were placed on the mandible in preparation for the osteotomy (f). The plates were then removed and an Attia double osteotomy of the mandible was performed that involved a horizontal resection of the mandible superior to the mandibular foramen and a vertical resection of the mandible anterior to the mental foramen. Superior reflection of the mandibular segment was then able to be accomplished (g). Reflection of the medial surface of the medial pterygoid muscle permitted entry into the parapharyngeal space with identification of the tumor (h). With the great vessels of the neck protected, the tumor ablation continued intraorally with development of the tumor dissection surrounding the pseudocapsule (i). The combination of transcutaneous access and transoral access permitted safe delivery of the specimen (j). Histopathology identified a pleomorphic adenoma with tumor present in the pseudocapsule, but with negative margins (k). Following delivery of the specimen, the plates are replaced on the mandible and closure occurred (l). The 6-month postoperative view of the palate is noted (m). This surgery provided curative surgery for this patient's tumor. Reprinted with permission from: Carlson ER, Schimmele SR: The management of minor salivary gland tumors of the oral cavity, In: *Surgical Management of Salivary Gland Disease, The Atlas of the Oral and Maxillofacial Surgery Clinics of North America* 6:75–98, WB Saunders Co., 1998.



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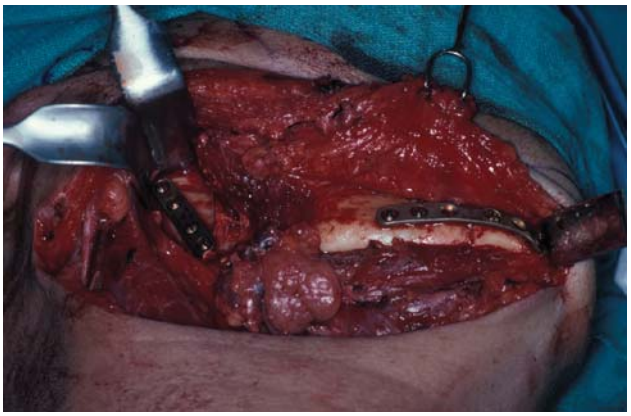

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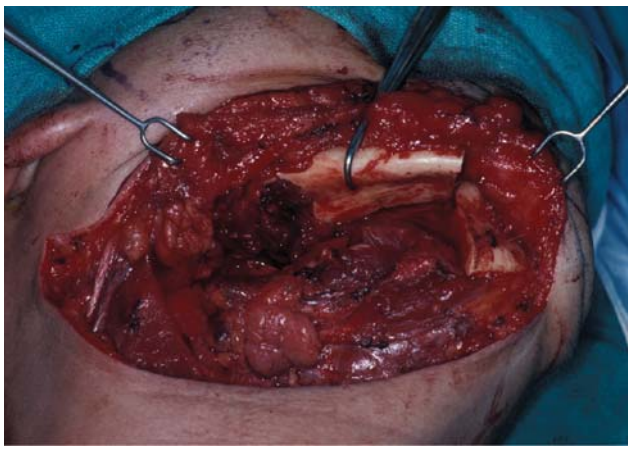

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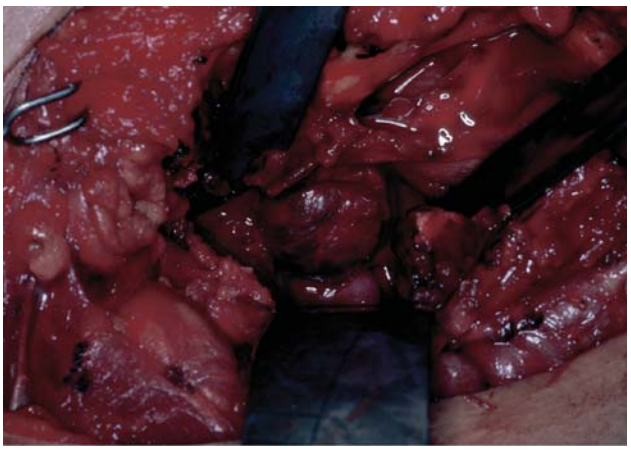

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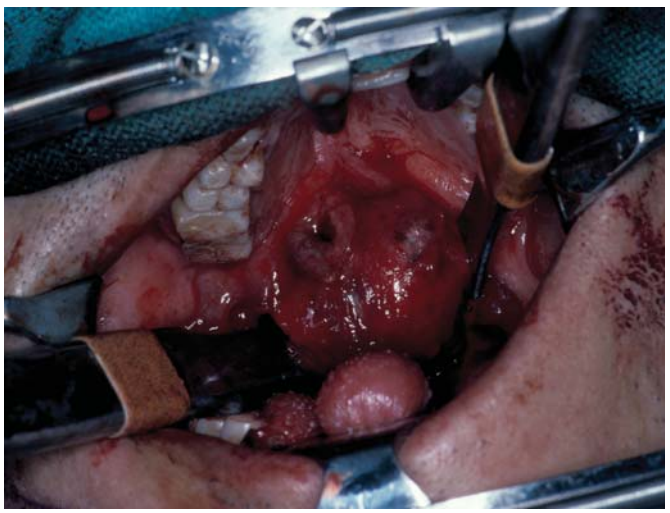

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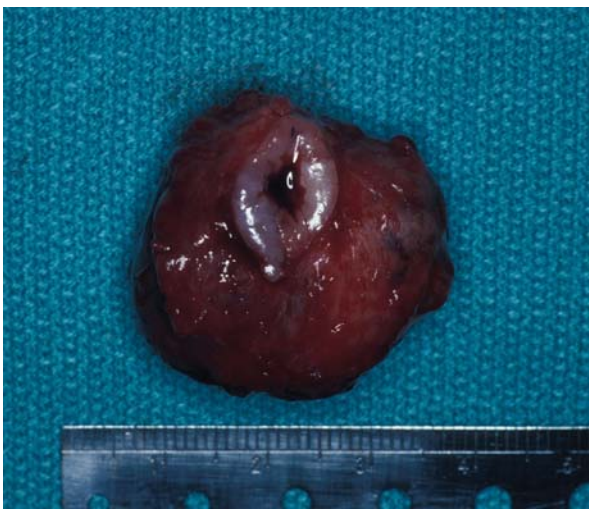
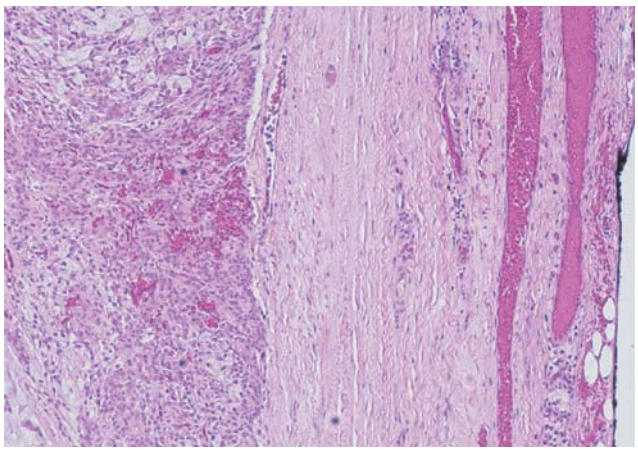


(j)

Figure 11.3. (*Continued*)



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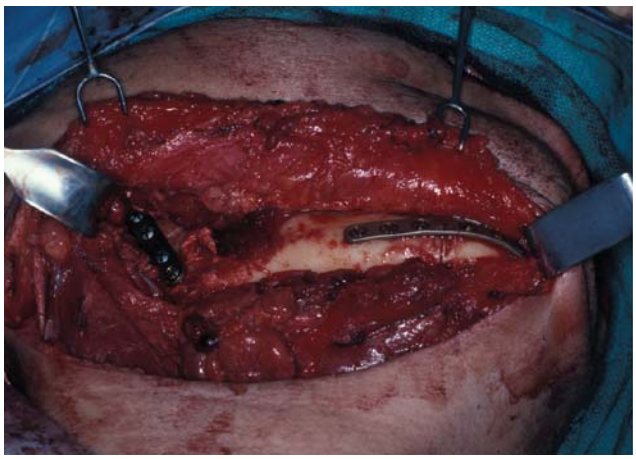

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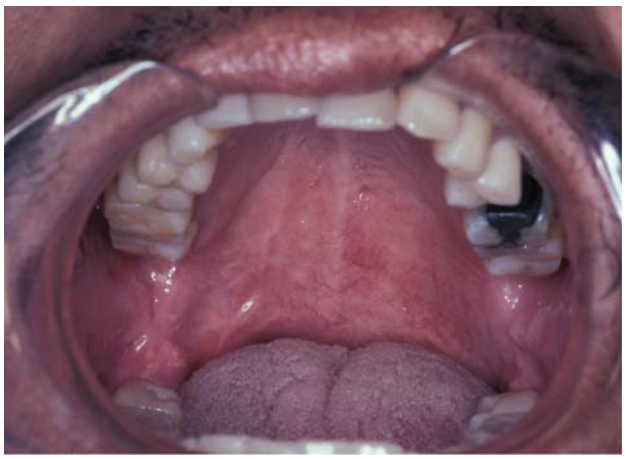
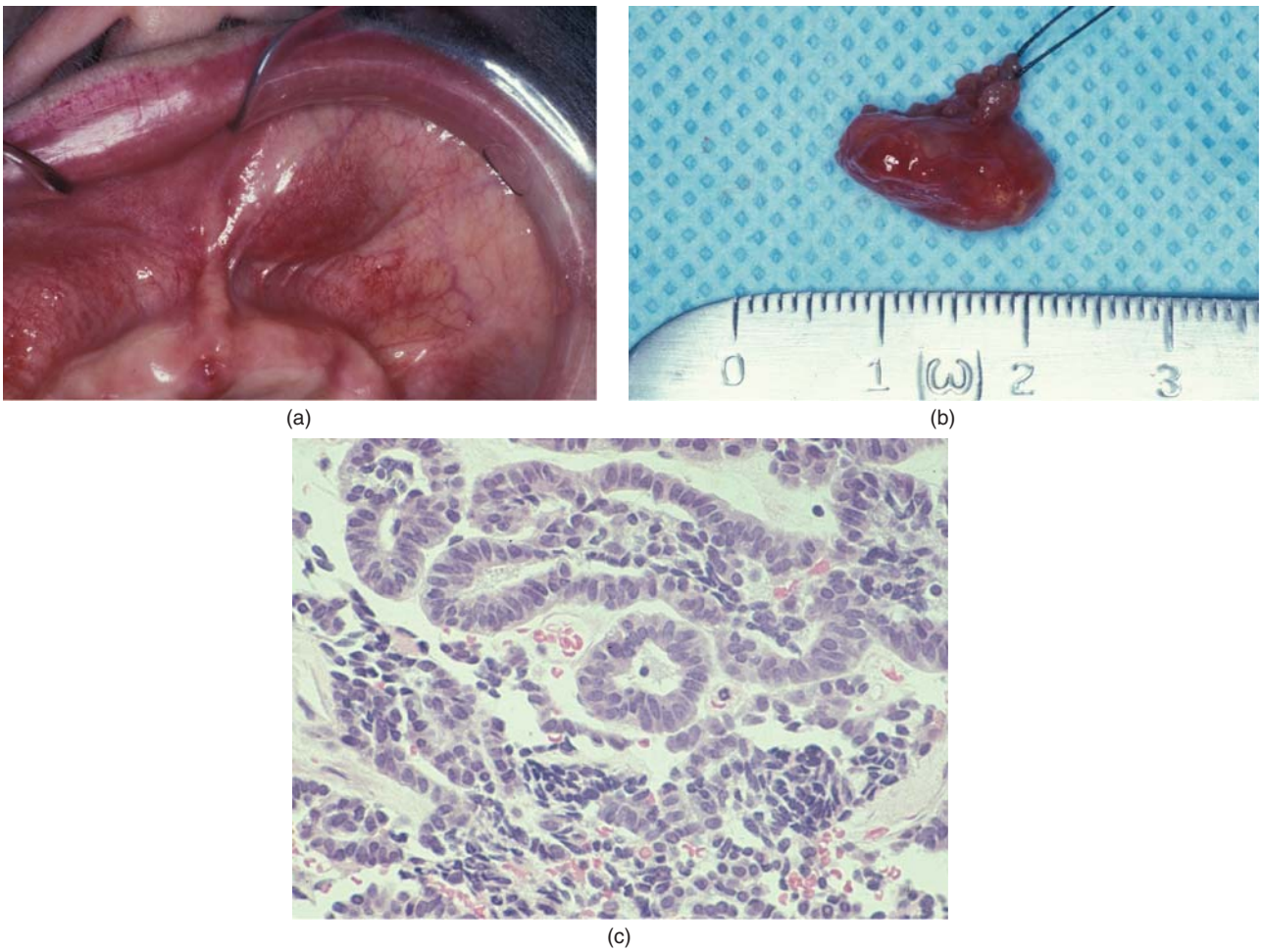


(m)

Figure 11.3. (*Continued*)

explicitly referred to and separated the benign and malignant tumors in their series of 45 cases in this report, of which there were 26 "benign" tumors and 19 "malignant" tumors. In 1953 this grading scheme was modified to include three grades due to the development of metastases related to tumors previously referred to as benign (Foote and Frazell 1953). These investigators accepted all of these tumors as malignant, and clinical and pathologic correlation suggested that separation into low, intermediate, and high grade malignant subgroups might be useful, mainly due to histologically overlapping qualities. The designation of intermediate grade was recognized as behaving more like the low-grade tumors than the high-grade tumors. Interestingly, despite the authors' recognition that all of these tumors were malignant, the designation *mucoepidermoid tumor* persisted throughout their paper. Subsequent studies were undertaken to more objectively determine if a benign variant existed. One such study investigated 23 mucoepidermoid carcinomas with a malignant course, such as evidence of local extension of tumor outside the capsule, local recurrences, histologically verified metastases, or death due to the tumor (Eneroth, et al. 1972). Fifteen patients showed local recurrences, 13 showed histologically verified metastases, and 22 patients died of their disease. In 7 of the 23 cases the histology revealed highly or moderately differentiated structures, and in 3 of these cases the primary tumor as well as the lymph node metastases were highly differentiated. Six of the 23 patients had tumors in the palate with 2 of these patients developing recurrences, 1 with lymph node metastases, and 5 of the patients died due to their disease. The authors concluded



(a) (b)

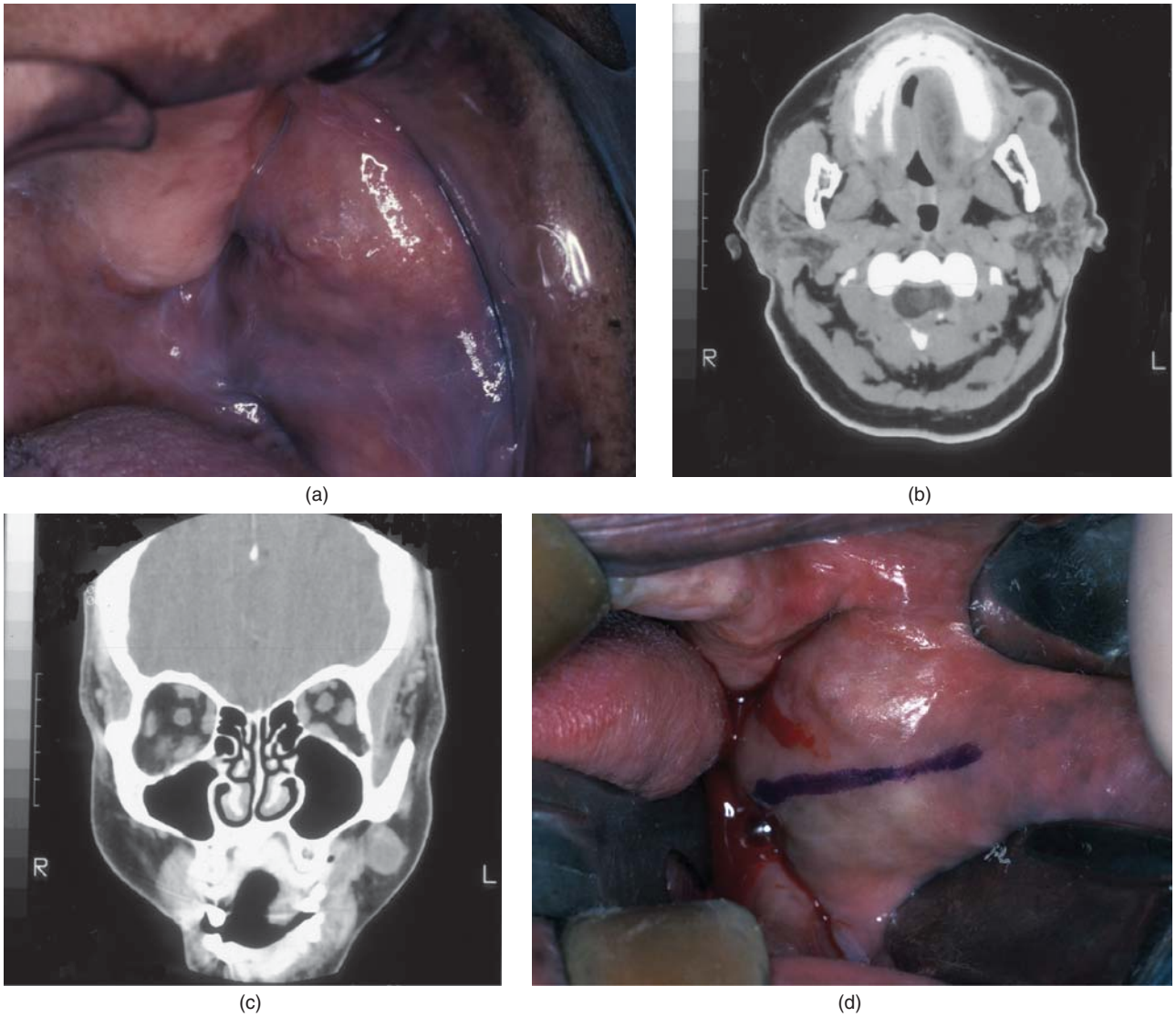
(c)

Figure 11.4. A freely moveable, indurated, submucosal mass of the upper lip in an elderly woman, highly suggestive of a canalicular adenoma (a). Based on this assumption, an incisional biopsy is not required. A pericapsular dissection of this mass was performed in association with surrounding minor salivary gland tissue, thereby allowing for delivery of the specimen (b). The histopathology of the specimen confirms the clinical impression of canalicular adenoma (c). Reprinted with permission from: Carlson ER, Schimmele SR: The management of minor salivary gland tumors of the oral cavity, In: *Surgical Management of Salivary Gland Disease, The Atlas of the Oral and Maxillofacial Surgery Clinics of North America* 6:75–98, WB Saunders Co., 1998.

by stating that well differentiated metastases in cases with a malignant course contradicted the existence of a benign variety of mucoepidermoid carcinoma, such that all of these neoplasms should be considered cancers (Eneroth, et al. 1972).

Of the 712 mucoepidermoid carcinomas occurring in the minor salivary glands in the AFIP registry, 305 (43%) of these tumors were located in the palate, 93 (13%) in the buccal mucosa, and 58 (8%) in the lip, with 37 specifically designated as the upper lip and 12 specifically designated as the lower lip (Auclair, et al. 1991). While the AFIP data is generally recognized as being representative of the incidence of most salivary gland tumors, some authors have identified the mucoepidermoid carcinoma to be more common in minor salivary gland sites than in major salivary gland sites (Plambeck, et al. 1996).

Histologic grading of mucoepidermoid carcinomas is an important exercise. Histologic grade connotes biologic aggressiveness, prognosis, and also provides the surgeon with important information with which to plan surgical treatment (Evans 1984; Brandwein, et al. 2001). Mucoepidermoid carcinomas are composed of three cell types: mucous secreting, epidermoid, and intermediate.



(a) (b) (c) (d)

Figure 11.5. A freely moveable, indurated, submucosal mass of the buccal mucosa is noted in this patient (a). The CT scans (b, c) show a well circumscribed mass of this region. A benign neoplastic process occupies a high position on the differential diagnosis such that a mucosal sparing excision of the mass with transoral access is able to be performed without first obtaining an incisional biopsy (d). A pericapsular dissection is performed (e), thereby permitting delivery of the specimen (f). Stenson duct was intimately attached to the tumor and therefore sacrificed with the tumor. Histopathology identified canalicular adenoma (g) with an uninvolved capsule (h). The appearance of the site is noted to be well healed at 9 months postop (i). Reprinted with permission from: Carlson, ER, Salivary gland pathology – Clinical *Perspectives and Differential Diagnosi*s, In: The *Comprehensive Management of Salivary Gland Pathology, Oral and Maxillofacial Surgery Clinics of North America* 7, 361–386, WB Saunders Co., 1995.

The intermediate cell is appropriately named because it is likely the progenitor of the two other cells (Batsakis and Luna 1990). Three grading schemes have found general acceptance among pathologists, and differences in biologic behavior could be demonstrated as a function of grade, even though the clinical stage has also been considered an important prognosticator. Indeed, Brandwein, et al. found that only 5% of low-grade mucoepidermoid carcinomas of the major glands, and only 2.5% of low-grade mucoepidermoid carcinomas of the minor glands metastasized to regional lymph

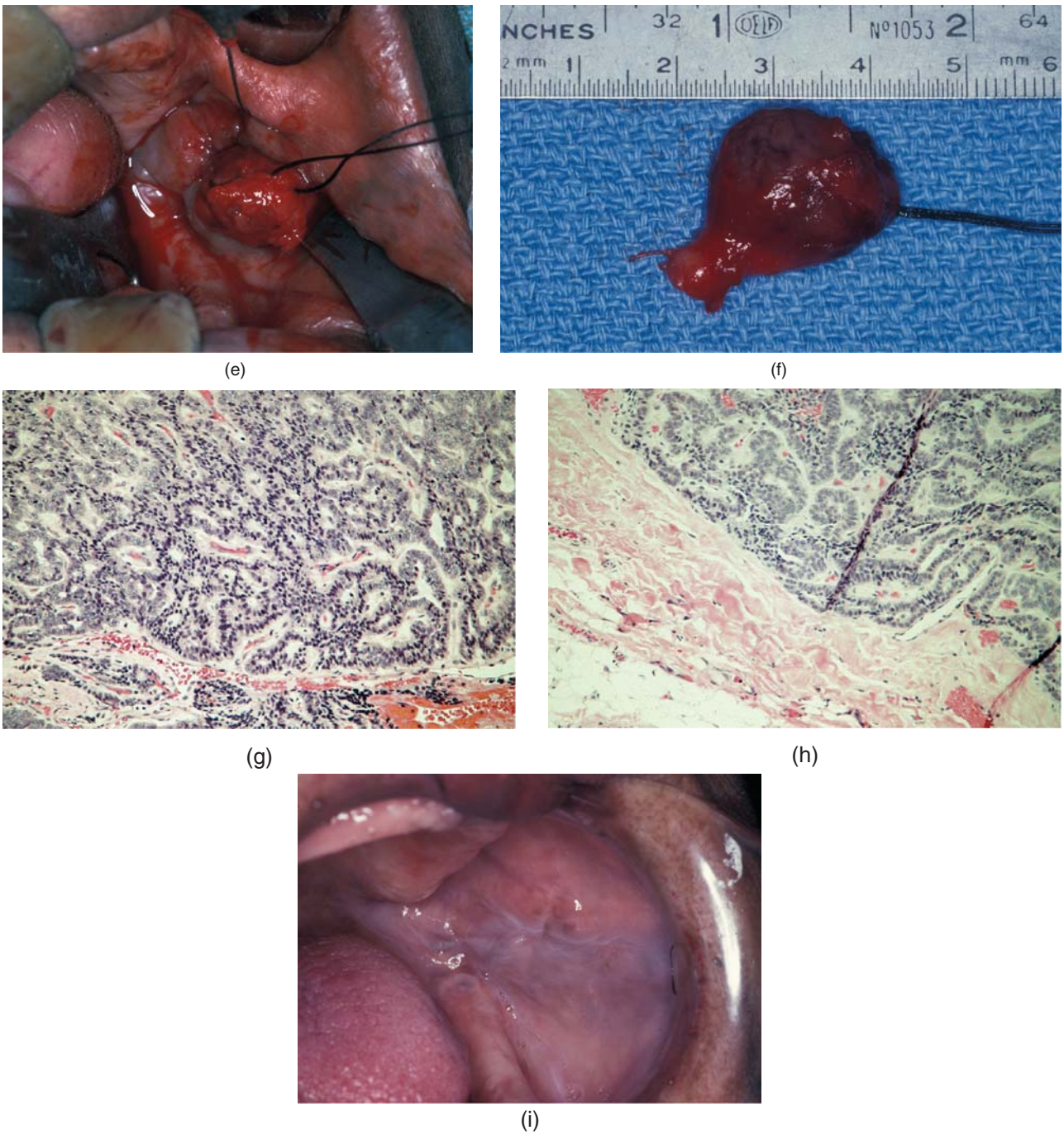


Figure 11.5. (*Continued*)

nodes or resulted in death. Spiro indicated that survival of patients with minor salivary gland carcinoma is significantly influenced by the clinical stage and the histologic grade, but the applicability of grading to survival was limited to patients with mucoepidermoid carcinoma or adenocarcinoma in their study (Spiro, et al. 1991). They determined that staging was important in all patients regardless of the histologic diagnosis.

The mucoepidermoid carcinoma is the most common salivary gland malignancy in children (Auclair, et al. 1991; Luna, et al. 1991; Ord 1994;

Rogerson 1995). Although most of these tumors are noted in the parotid gland, the palate is the second most common site of involvement. Most appear to occur in teenagers and the majority are of low-grade or intermediate-grade histology. Mucoepidermoid carcinoma in children appears to follow a more favorable course with cure rates of 98–100% (Ord 1994).

Surgical treatment of the mucoepidermoid carcinoma of minor salivary gland origin is primarily a function of the anatomic site of the tumor and its histologic grade. Those arising in the palate are not only the most common, but also the most variable in so far as surgical treatment is concerned. It is the histologic grade that is of utmost importance when determining treatment in the palate. Large series show that the low grade cancer is most common in this anatomic site (Pires, et al. 2007). Incisional biopsy is clearly essential to establish the histopathologic diagnosis, as previously described. Computerized tomograms are essential in planning surgical treatment of palatal mucoepidermoid carcinomas as they assess the involvement of the underlying palatal bone. When the palatal bone does not appear to be involved by the cancer, a bone sparing, periosteal sacrificing wide local excision with split thickness sacrifice of the soft palate musculature is the surgical treatment of choice (Figure 11.6). Similar to the surgery for the palatal pleomorphic adenoma, the periosteum serves as the anatomic barrier on the superior aspect of the tumor specimen, and tumor-free periosteal frozen and permanent sections should be obtained so as to confirm this concept. When the periosteum has not been invaded by the cancer and all radial soft tissue margins are free of tumor, this surgery has a high frequency of cure. When the palatal bone is noted to be invaded by tumor on preoperative CT scans, however, its sacrifice is indicated as part of a traditional partial maxillectomy (Figure 11.7). Ord and Salama (2012) reviewed their series of 18 mucoepidermoid carcinomas of the palate, 17 of which were low-grade. Sixteen patients underwent soft tissue excision only of their tumors with periosteum serving as the deep anatomic barrier on the specimen due to the absence of bone erosion on preoperatively obtained CT scans. One patient required bone sacrifice due to intraoperative suspicion for bone erosion and one patient underwent bone sacrifice due to preoperative CT suspicion for bone erosion. Interestingly, only the patient with CT evidence of bone erosion demonstrated microscopic evidence of bone invasion by the tumor. No local recurrences were identified in these 18 patients with a mean follow-up period of 44 months. The authors concluded that the periosteum represents an effective anatomic barrier margin for palatal mucoepidermoid carcinomas.

The designation of an intermediate mucoepidermoid carcinoma of the palate may change the recommended surgical treatment of the tumor in this, and other anatomic sites, with a more aggressive surgical procedure required for curative intent (Figure 11.8). This is particularly true if the designation of intermediate grade is made by the pathologist based on the worst microscopic pattern observed in the tumor. For example, a mucoepidermoid carcinoma that is predominantly low grade, but that shows a component of intermediate-grade cancer, will likely be designated intermediate grade. This notwithstanding, the behavior of such a tumor is likely to be low grade in nature. This scenario is different from a cancer that is designated intermediate-grade that shows a predominantly intermediate grade pattern with intermixed low-grade cancer. The surgeon may wish to offer more aggressive surgical therapy in the form of a partial maxillectomy for the mucoepidermoid carcinoma of the palate that is predominantly intermediate grade on microscopic sections. While rare, a high grade mucoepidermoid carcinoma of the palate would require a partial maxillectomy, and prophylactic surgical removal of the cervical lymph nodes in the case of an N0 neck, or a therapeutic neck dissection in the case of an N+ neck. Postoperative radiation therapy would also be administered in such circumstances.

Mucoepidermoid carcinoma of the buccal mucosa is the second most common minor salivary gland site affected. In contrast to benign neoplasms of this anatomic site, a mucosal sacrificing tumor surgery is required, with attention to the sacrifice of surrounding submucosal anatomic barriers. The same is true of the lip (Figure 11.9).

Survival of patients with mucoepidermoid carcinomas of the minor salivary glands is clearly related to grade. Five-year survival rates have been estimated at 90% and 15-year survival rates have been estimated at 82% for low-grade mucoepidermoid carcinomas (Ord 1994). In their study of 37 patients with mucoepidermoid carcinoma of the palate, Li, et al. (2012) identified an overall survival of 84.4% at 5 years and 10 years.

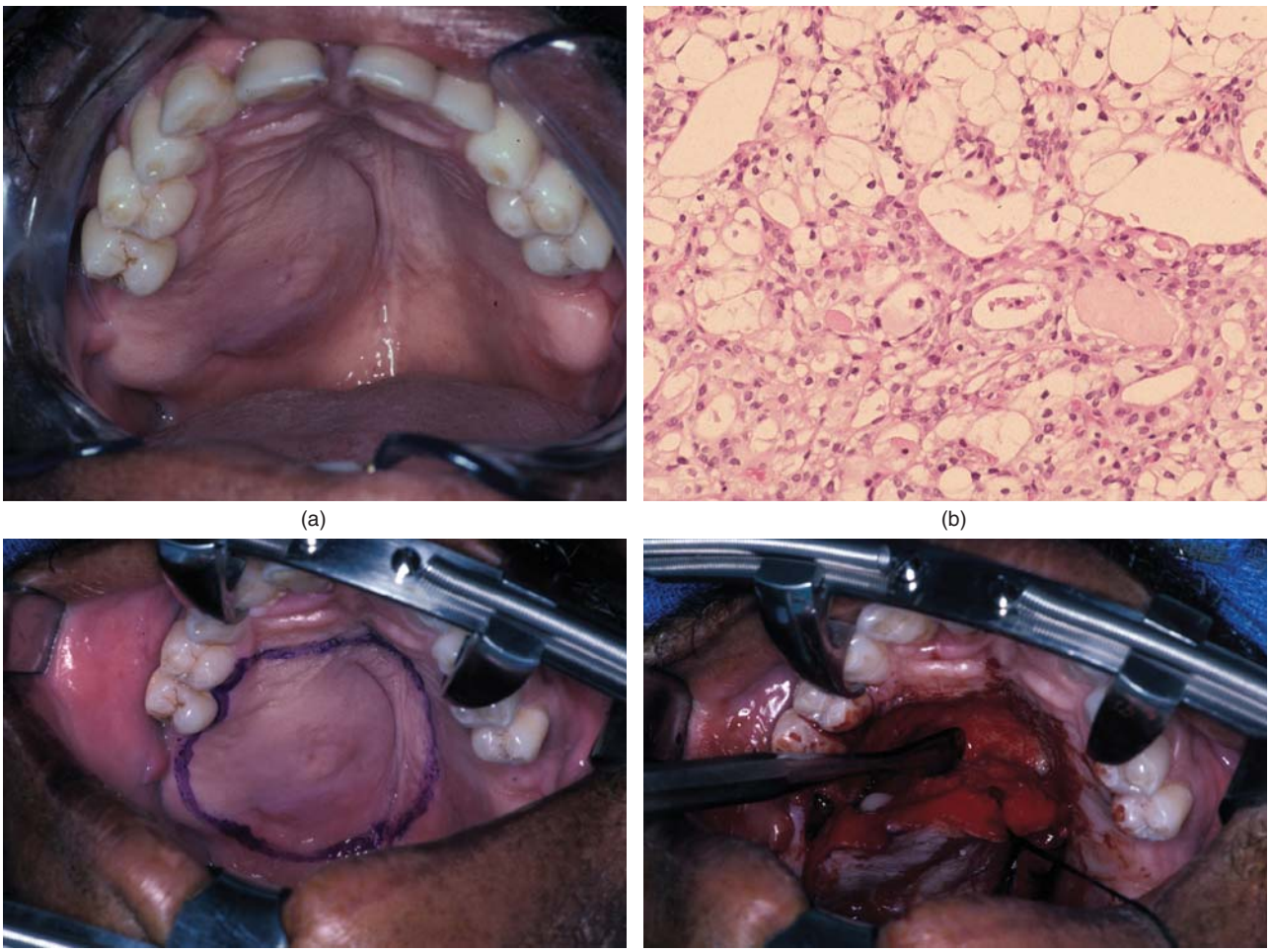
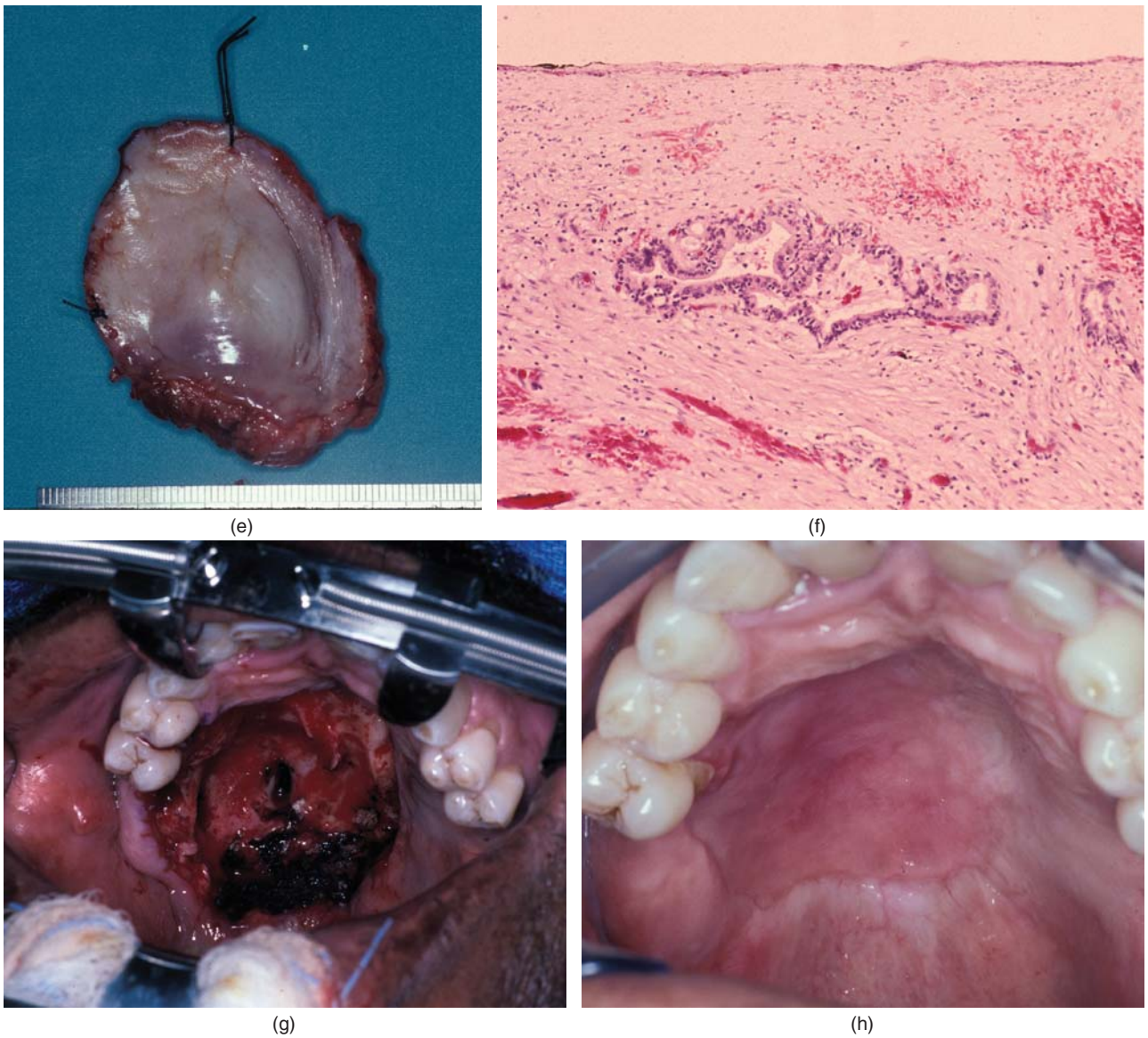


Figure 11.6. A mass of the palate in a 45-year-old man (a). The extensive differential diagnosis, including benign and malignant entities requires an incisional biopsy for diagnosis prior to performing definitive tumor surgery. The biopsy identifies low-grade mucoepidermoid carcinoma (b). A periosteal sacrificing, bone sparing wide local excision with split thickness sacrifice of the soft palate is planned with 1 cm mucosal linear margins (c). A sharp dissection is performed with a periosteal elevator between the periosteum on the superior aspect of the tumor specimen and the overlying palatal bone (d). The specimen is delivered (e). Histopathology shows low-grade mucoepidermoid carcinoma with negative margins. The association of the superior aspect of the tumor and the periosteum is noted (f). The remaining tissue bed (g) is temporarily covered with a palatal stent. Mucosalization of the exposed bone and soft palate musculature is noted at 9 months postoperatively (h). This surgery provided curative care for this patient's tumor. Reprinted with permission from: Carlson ER, Schimmele SR, The management of minor salivary gland tumors of the oral cavity, In: *Surgical Management of Salivary Gland Disease, The Atlas of the Oral and Maxillofacial Surgery Clinics of North America* 6:75–98, WB Saunders Co., 1998.

Central Mucoepidermoid Carcinoma

Salivary gland cancers of the jaws most frequently involve direct intraosseous extension of primary malignancies arising from the major or minor salivary glands (Woolgar, et al. 2013). Centrally occurring malignant salivary gland tumors are very rare. While academic understanding and the international literature would primarily point to the identification of mucoepidermoid carcinoma of the jaws in this category of tumor, other malignant salivary gland tumor diagnoses have been identified in the jaws (Li, et al. 2008). Adenoid cystic carcinoma seems to be the second most common central salivary gland malignancy of the jaws (Woolgar, et al. 2013). Central mucoepidermoid carcinoma is considered an exceedingly rare



(e) (f)

(g) (h)

Figure 11.6. (*Continued*)

subgroup, accounting for approximately 2–4% of all cases of mucoepidermoid carcinoma (Chiu, et al. 2012). This primary malignancy occurs most frequently in the fourth and fifth decades of life with a male to female ratio of 1:1.4 (Zhou, et al. 2012). These malignancies are most commonly located in the mandible, and specifically in the molar/ramus region, and a predominantly unilocular or multilocular radiographic character is noted (Zhou, et al. 2012) (Figure 11.10a). Most cases are classified as low-grade malignancies. The exact pathogenesis is uncertain, however, several hypotheses have been documented in the literature including ectopic salivary gland tissue resulting from entrapment during embryonic development of minor salivary glands, inclusions of embryonic rests of submandibular or sublingual glands, or seromucinous glands displaced from the maxillary sinus into the maxilla; development in a submucosal gland with intraosseous extension; and neoplastic transformation of the epithelial lining of odontogenic cysts (Chiu, et al. 2012). The latter possibility is most favored as transition of cyst lining to carcinoma is evident in some

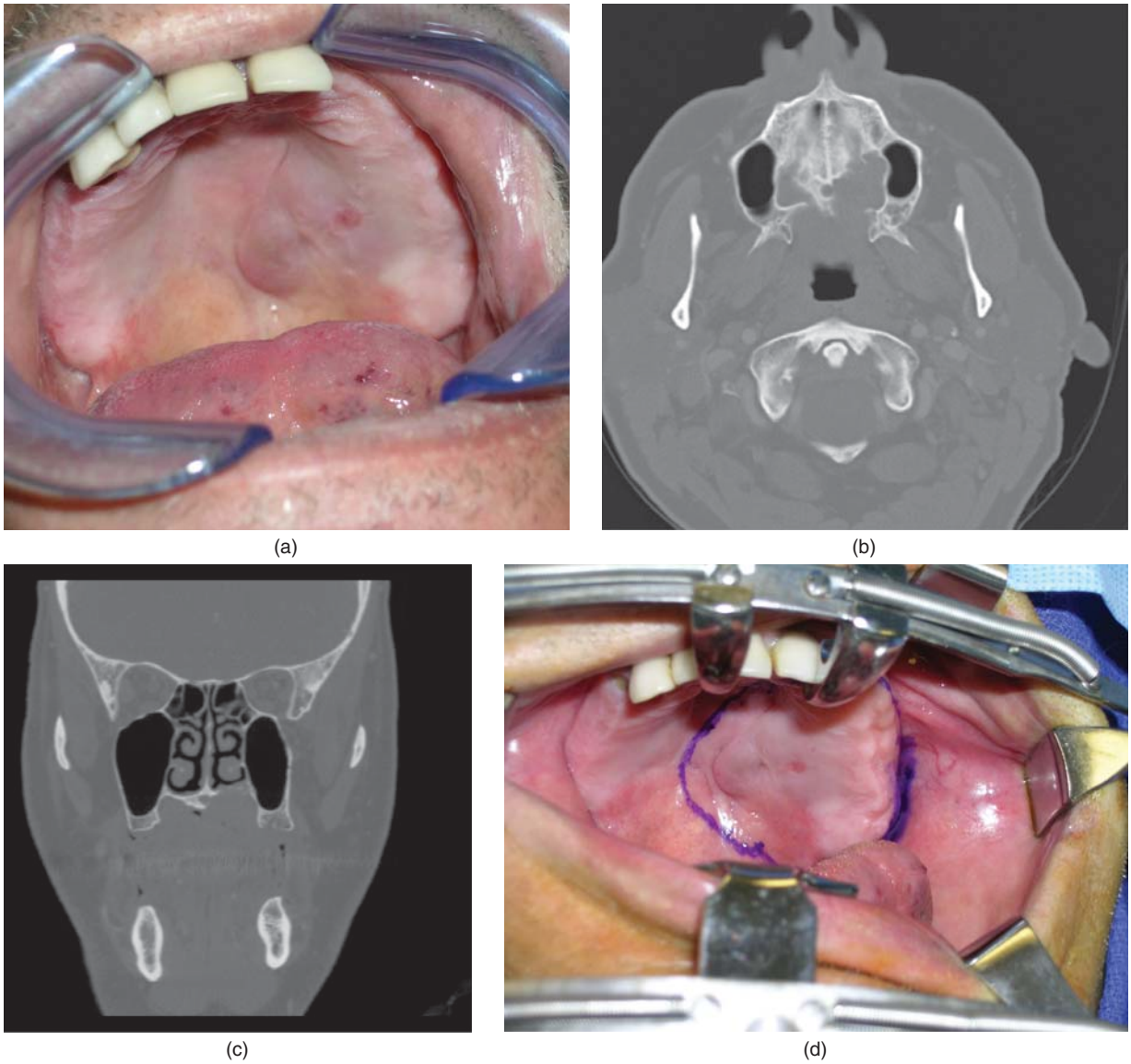
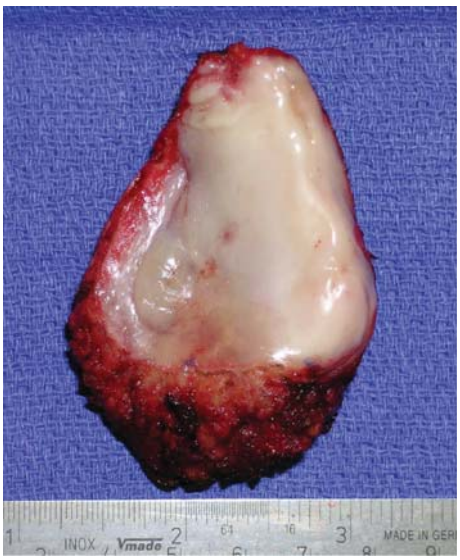


Figure 11.7. A mass of the left palate (a) that demonstrated low-grade mucoepidermoid carcinoma on incisional biopsy. Axial (b) and coronal (c) CT scans demonstrated bone invasion by the tumor such that a partial maxillectomy was planned. One centimeter linear margins in bone and soft tissue were included at the periphery of the resection (d and e). Decalcified histopathologic sections (f – hematoxylin and eosin, original magnification ×140) confirmed the destruction of bone by the tumor. The defect (g) underwent obturation and showed no evidence of disease at 2 years postoperatively (h).

cases (Zhou, et al. 2012; Spoorthi, et al. 2013). Preferred treatment is radical resection of the tumor (Figure 11.10). The value of neck dissection for N0 disease is debatable as cervical lymph node metastases seem to occur in fewer than 10% of cases (Chiu, et al. 2012; Takano, et al. 2012). Patients require therapeutic neck dissections when cervical lymph node metastases are apparent on clinical examination and or on imaging studies (Figure 11.10). Distant metastasis is rare but has been reported in the lungs, brain and clavicle (Chiu, et al. 2012; Zhou, et al. 2012).

Adenoid Cystic Carcinoma

Like the mucoepidermoid carcinoma, the adenoid cystic carcinoma is a very diverse tumor with three histologic variants. These have been described



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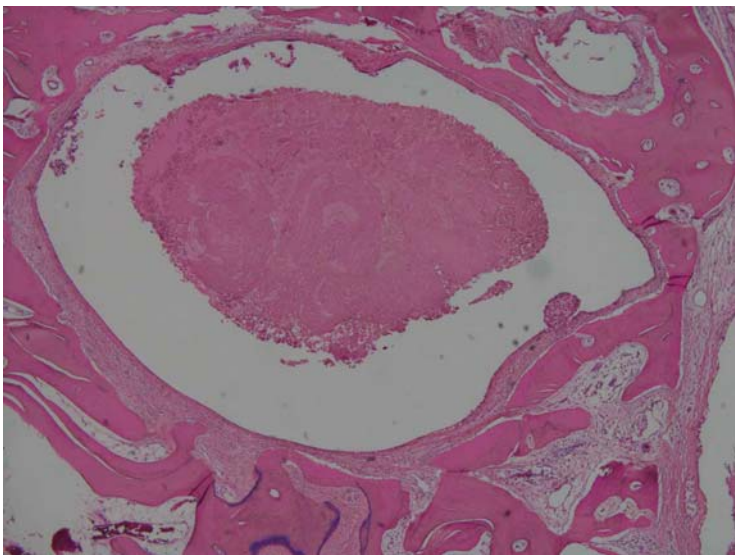

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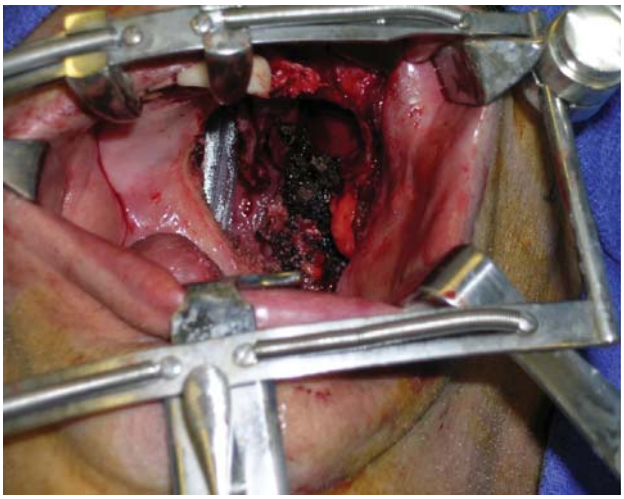

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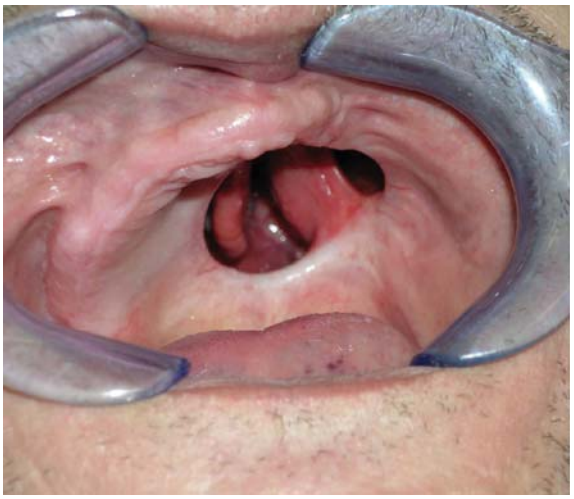

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Figure 11.7. (*Continued*)

morphologically, rather than by grade as is the case with the mucoepidermoid carcinoma, and include the tubular, cribriform, and solid variants. The adenoid cystic carcinoma is characteristically slow-growing, with a high propensity for recurrent disease. It is highly infiltrative, exhibits profound neurotropism, and is associated with a dismal long-term survival rate. This malignancy was first described by Theodor Billroth in 1859 and referred to as cylindroma (Tomich 1991). In 1953 Foote and Frazell proposed the currently accepted nomenclature, adenoid cystic carcinoma. Of the 600 cases of adenoid cystic carcinoma in the AFIP files, 312 were noted in the major salivary glands, and 288 were noted in the minor salivary glands. The palate was the most common site affected in the minor salivary glands, followed by the tongue. Adenoid cystic carcinoma accounts for 8.3% of all palatal salivary gland tumors and 17.7% of all malignant palatal salivary gland tumors in the AFIP series (Tomich 1991).

From a surgical standpoint adenoid cystic carcinoma is probably the most challenging salivary gland tumor for the surgeon (Ord 1994). While straightforward to perform in most cases, radical resection is fraught with recurrences and ultimate distant metastases. This notwithstanding, palatal tumors should be managed with radical

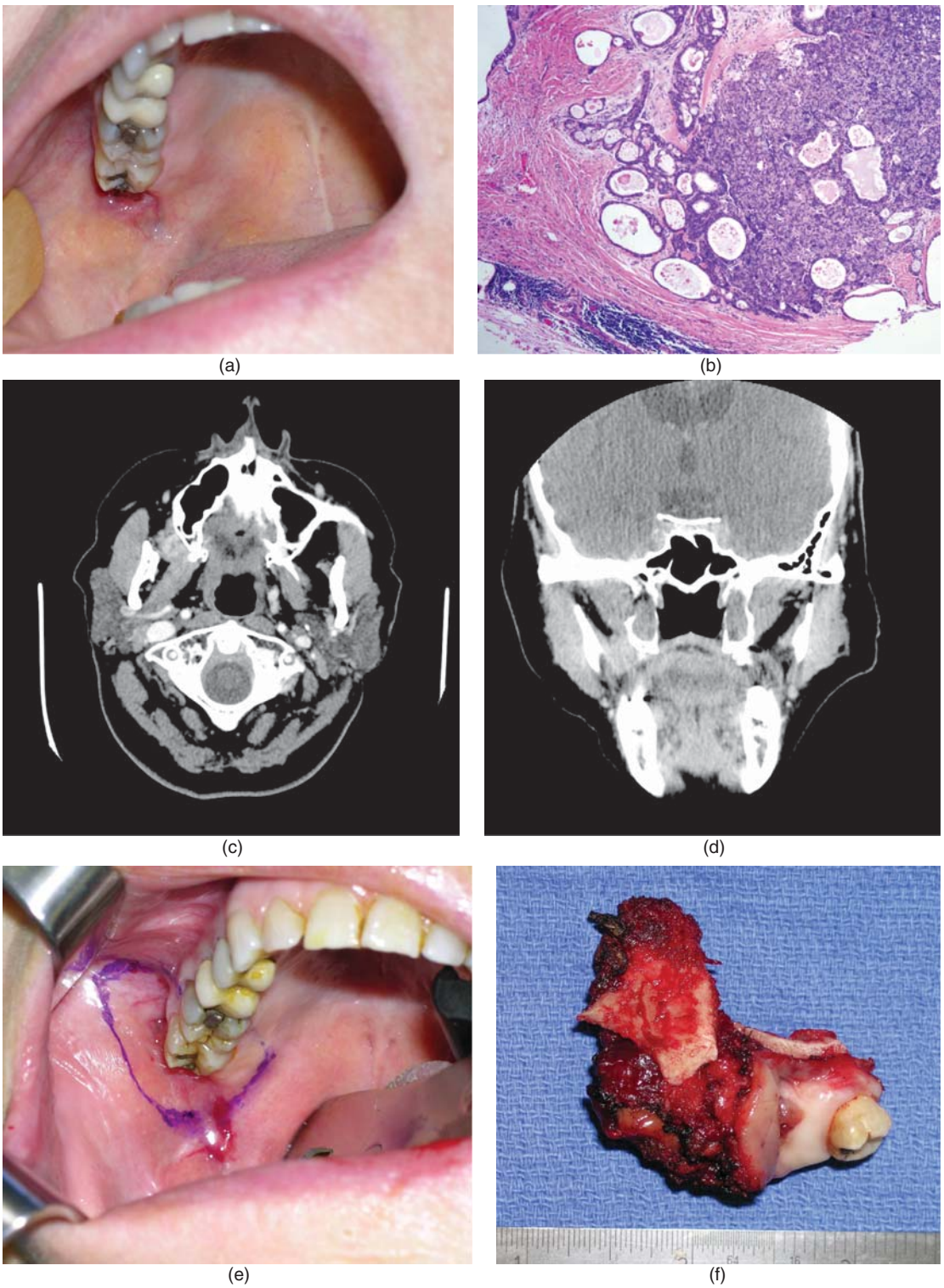
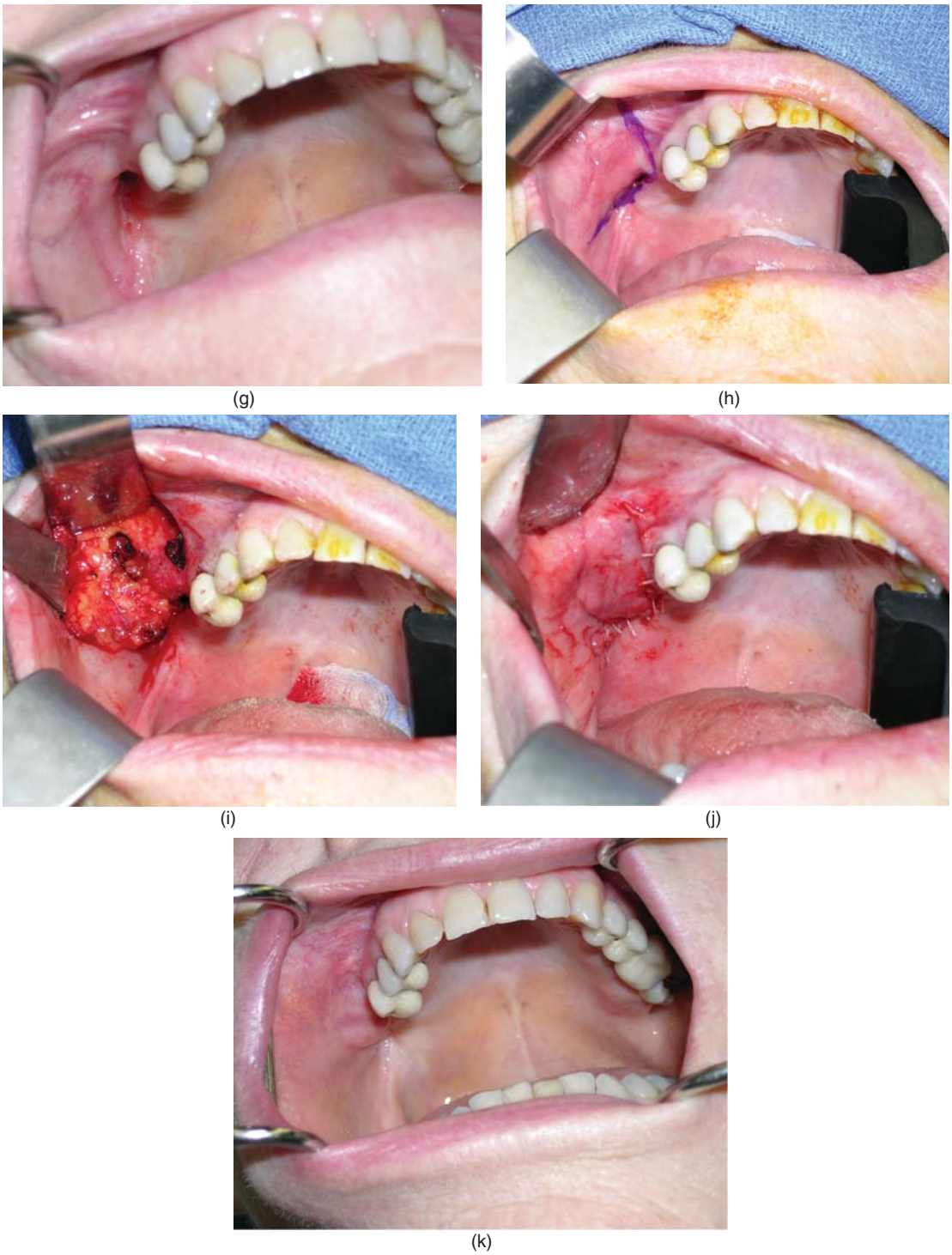


Figure 11.8. A lesion of the right tuberosity region (a). Biopsy of the lesion showed intermediate-grade mucoepidermoid carcinoma (b). Computerized tomograms identified an enhancing mass located lateral to the right tuberosity, and in close proximity to the coronoid process (c, d). Definitive tumor surgery involved a transoral partial maxillectomy and coronoidectomy en bloc (e), which permitted effective removal of the cancer (f). The resultant defect was obturated and allowed to contract significantly over time (g). Soft tissue reconstruction was accomplished with a buccal fat flap and advancement of the mucosa (h, i, j). The reconstruction healed well as noted at 6 years postoperatively (k).



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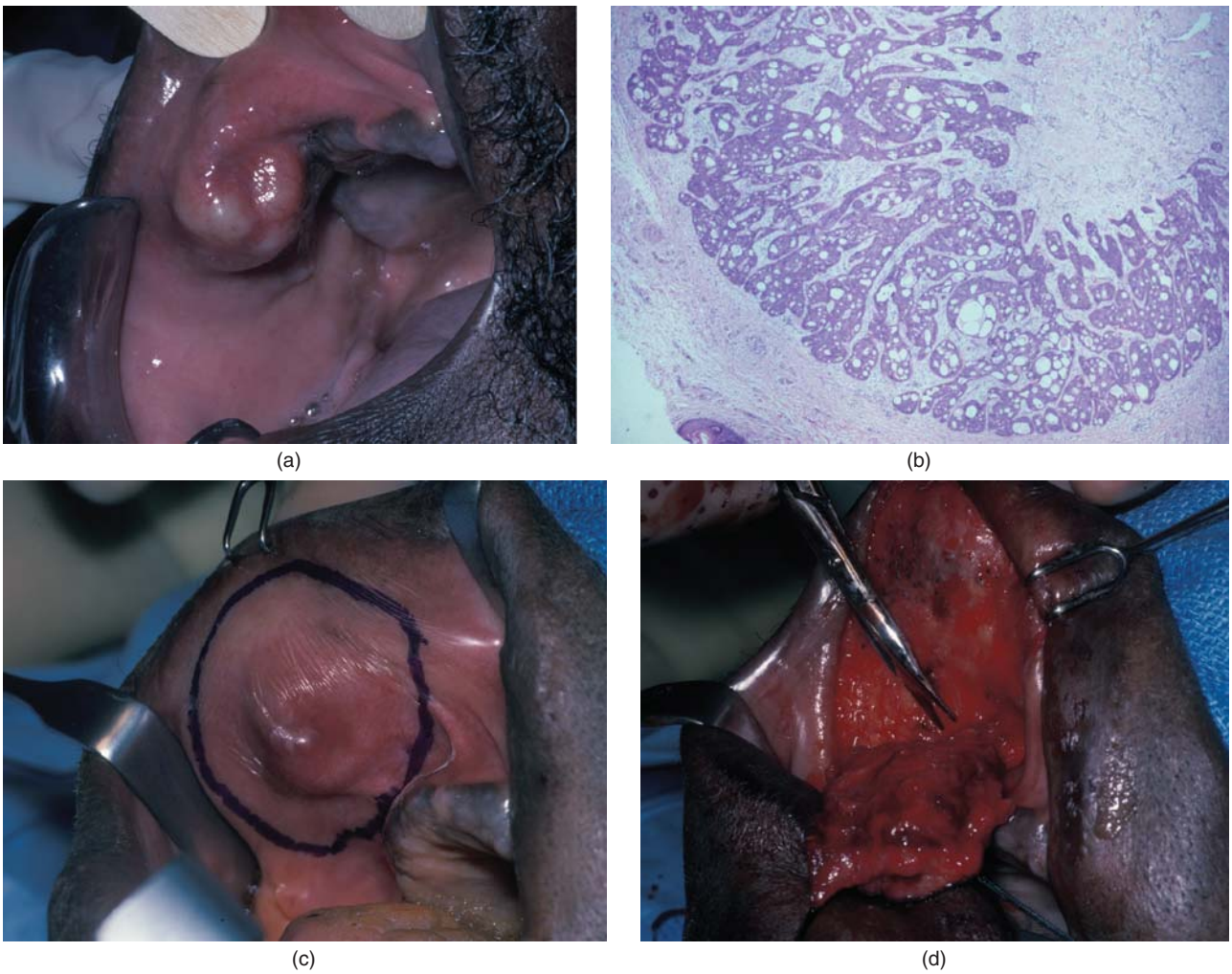
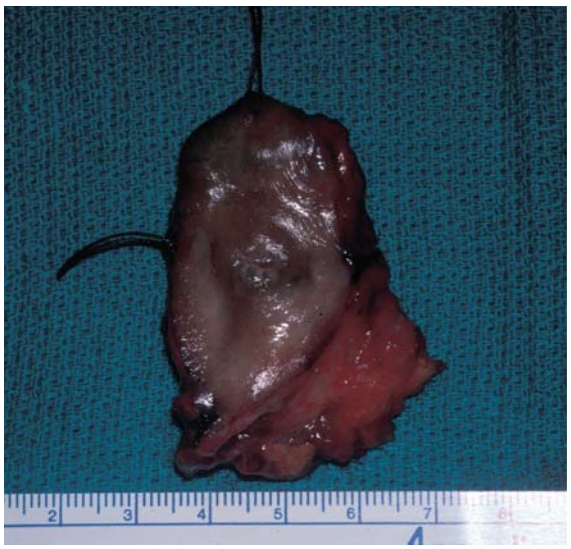


Figure 11.9. An indurated upper lip mass that was fixed to surrounding mucosa (a). Due to the likely, but equivocal malignant nature of the mass, incisional biopsy is essential for the establishment of the diagnosis prior to definitive surgical therapy. The histopathology identified intermediate-grade mucoepidermoid carcinoma (b). A wide local excision of the mass with oral mucosal sacrifice was planned (c). A surgical plane was developed between the dermis of the upper lip and the musculature on the deep aspect of the tumor specimen (d). The specimen was delivered and oriented for the pathologist with sutures (e). Final histopathology identified intermediate-grade mucoepidermoid carcinoma with perineural invasion (f). The defect was reconstructed immediately with a full thickness skin graft (g). A prophylactic neck dissection was not performed as part of this cancer surgery due to the low concern for occult neck disease associated with this diagnosis. The patient underwent postoperative radiation therapy and the surgical site was noted to be well healed at 1 year postoperatively without signs of recurrent disease (h). Reprinted with permission from: Carlson, ER, Salivary gland pathology – Clinical perspectives and differential diagnosis, In: The *Comprehensive Management of Salivary Gland Pathology, Oral and Maxillofacial Surgery Clinics of North America* 7:361–386, WB Saunders Co., 1995.

maxillectomy, observing 1–2 cm linear margins, and with resection of the greater palatine neurovascular bundle to foramen rotundum with frozen section guidance (Figure 11.11). The presence or absence of tumor in association with this nerve should be documented as far superior as possible. Cervical lymph node metastases are considered to be rare such that prophylactic neck dissection is not required in the patient with an N0 neck associated with a palatal adenoid cystic carcinoma as the incidence of cervical metastases is approximately 10% (Min, et al. 2012). Prophylactic neck dissection



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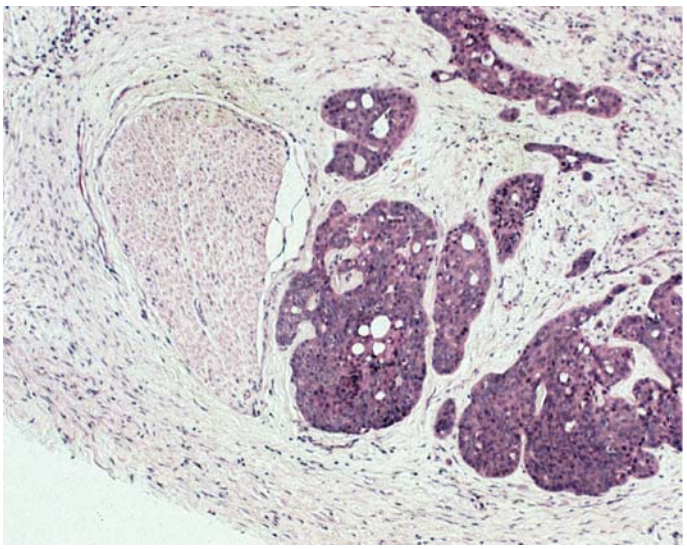

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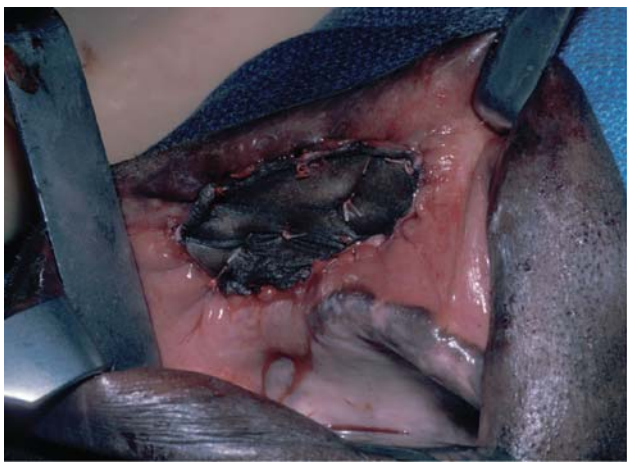

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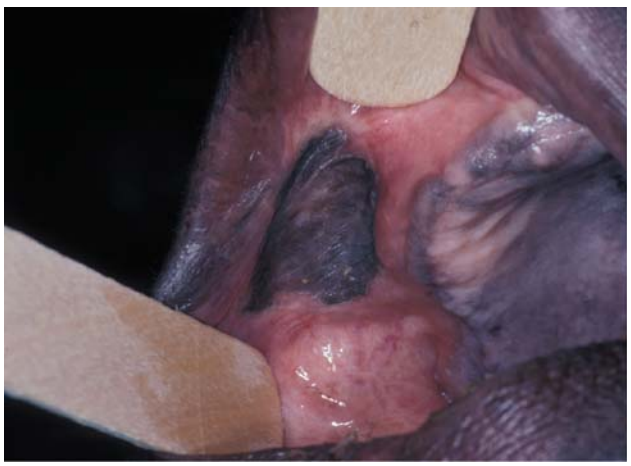

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Figure 11.9. (*Continued*)

should be considered due to the proximity to lymphatic vasculature associated with adenoid cystic carcinoma at other sites (Figure 11.12). Min, et al. (2012) identified the base of tongue, mobile tongue, and floor of mouth as the most frequent sites of lymph node metastases, with incidences of 19.2, 17.6, and 15.3%, respectively. Postoperative radiation therapy is generally considered advisable for all patients with adenoid cystic carcinoma of the minor salivary glands, regardless of the adequacy of the resection (Dragovic 1995; Ord 1994; Triantafillidou, et al. 2006). The prognosis associated with adenoid cystic carcinoma of the minor salivary glands is inferior to that of the major salivary glands (Ampil and Misra 1987; Nascimento, et al. 1986). In addition, it has been found that the best prognosis for the adenoid cystic carcinoma is associated with the tubular variant, while the solid variant (Figure 11.13) is associated with the worst prognosis (Perzin, et al. 1978). It has also been pointed out that perineural invasion of major nerves and positive margins at surgery, in addition to the solid variant of adenoid cystic carcinoma, are associated with increased treatment failures (Fordice, et al. 1999). Typical survival statistics for adenoid cystic carcinoma in general include 60% for 5-year survival, 30% for 10-year survival, and 7% for survival at 20 years (Ord 1994). It has been pointed out that adenoid cystic carcinoma of minor salivary gland sites has

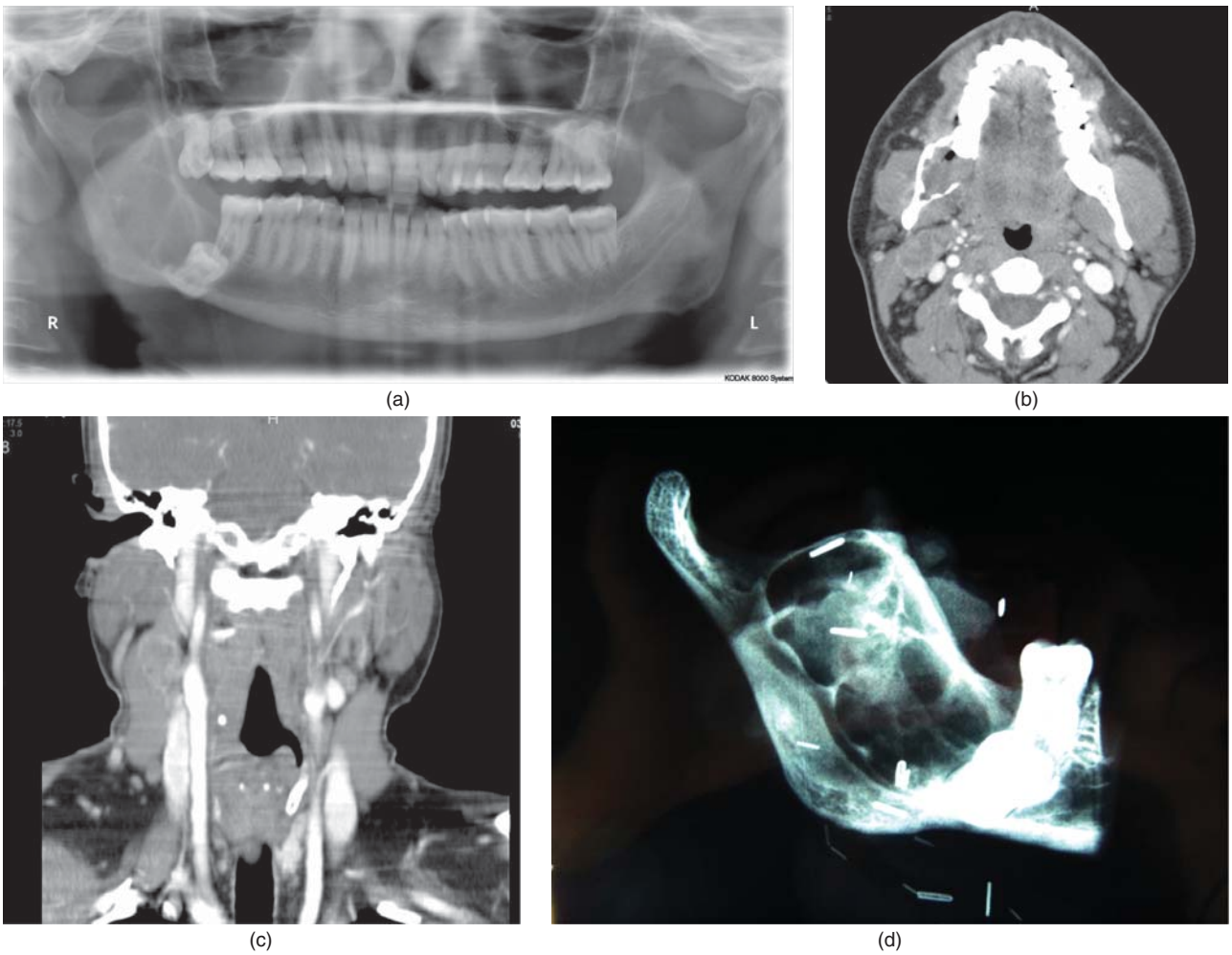


Figure 11.10. A central mucoepidermoid carcinoma of the right mandibular ramus. The panoramic radiograph demonstrates a multilocular radiolucency (a). The patient demonstrated an enlarged right level II lymph node that is also apparent on the MRI study (b and c). The patient underwent a composite resection including a disarticulation resection of the right mandible and type I modified radical neck dissection. The specimen radiograph is noted in (d).

a worse prognosis, with a 0% survival at 20 years (Ord 1994). The presence of perineural spread has a significant impact on survival. Five-year survival rates of patients with perineural spread have been found to be 36.9% while 5-year survival rates have been found to be 93.8% in patients without perineural spread (Ord 1994). In their review of 26 cases of adenoid cystic carcinoma of the intraoral minor salivary glands, Luksic, et al. (2014) found disease specific survival rates of 62% at 5 years, 53% at 10 years, and 27% at 15 years for patients with perineural invasion compared with 90% for those patients who did not have invasion at the same follow-up intervals. These authors found that perineural invasion was associated with a higher incidence of distant metastases. The lungs are the most common site of distant metastatic spread of adenoid cystic carcinoma, typically with multiple lobe involvement (Figure 11.14).

Polymorphous Low-Grade Adenocarcinoma

In 1983 two separate investigations reported on low-grade adenocarcinomas of minor salivary glands referred to as terminal duct carcinoma (Batsakis, et al. 1983) and lobular carcinoma (Freedman and Lumerman 1983). Terminal duct carcinoma was suggested to specify the histogenesis of the tumor which was thought to be

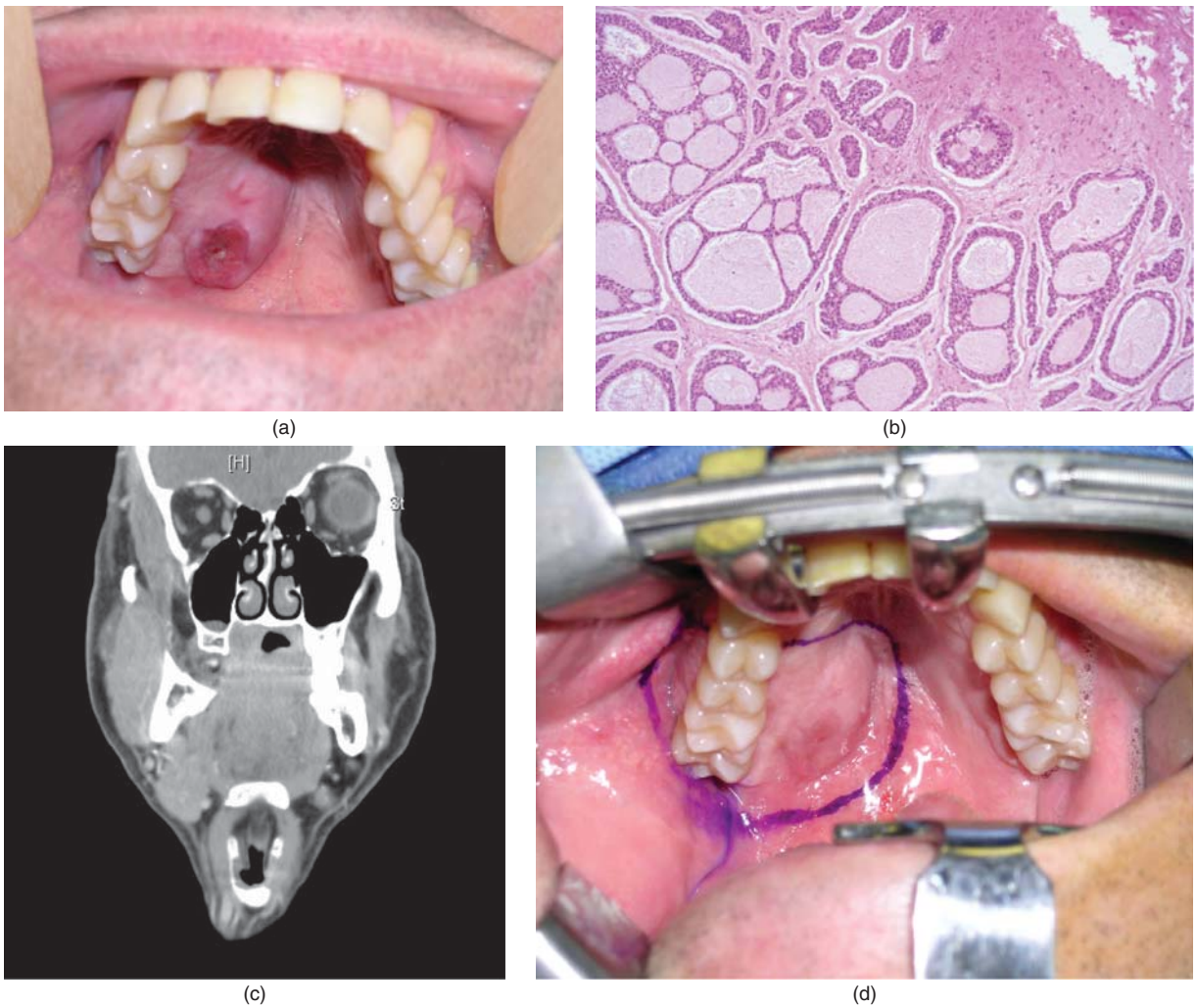
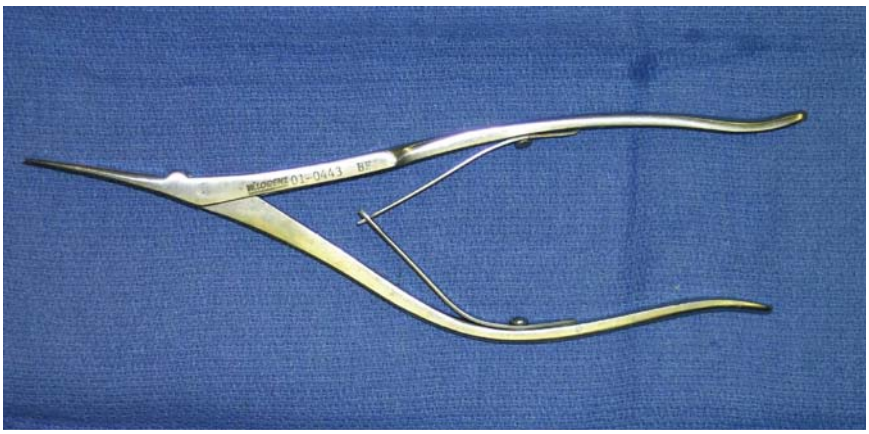


Figure 11.11. A 52-year-old man with a 6-month history of a palatal mass (a). Incisional biopsy showed adenoid cystic carcinoma (b). Computerized tomograms identified a soft tissue mass and minimal invasion of the palatal bone (c). A maxillectomy was planned for this patient observing 1 cm linear margins in bone and soft tissue (d). The bony cuts were created throughout the maxilla and the Smith splitter (e) was utilized to separate the specimen from the remaining facial skeleton (f). The specimen was delivered and inspected from the palatal side (g) and the nasal/sinus side (h) so as to clinically confirm the efficacy of the resection. Frozen sections were obtained to microscopically examine the soft tissue margins as well as a segment of greater palatine nerve in the superior aspect of the defect. All frozen sections were negative thereby not requiring additional sampling of the nerve or mucosa. Final histopathology identified adenoid cystic carcinoma invading the maxillary bone (i). The patient underwent postoperative radiation therapy and was without evidence of cancer at 1 year postoperatively (j). This view provides anatomic delineation of the eustachian tube in the defect. He successfully underwent soft tissue reconstruction with a temporalis muscle flap 1 year postoperatively and healed uneventfully as noted at 4 years postoperatively (k). He was doing well until 7 years postoperatively when back pain led to an MRI (l) that identified a compression fracture of T1 with loss of vertebral bone height and osseous retropulsion. A biopsy was performed that identified metastatic adenoid cystic carcinoma of T1.

the progenitor cell of the terminal duct. Lobular carcinoma was suggested due to the morphology of the tumor resembling lobular carcinoma of the breast. A review of these reports indicates that the authors were independently describing the same neoplasm (Wenig and Gnepp 1991). It is thought that, prior to this time, these neoplasms were classified as either adenoid cystic carcinoma or



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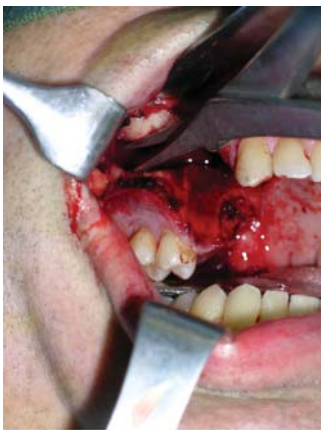

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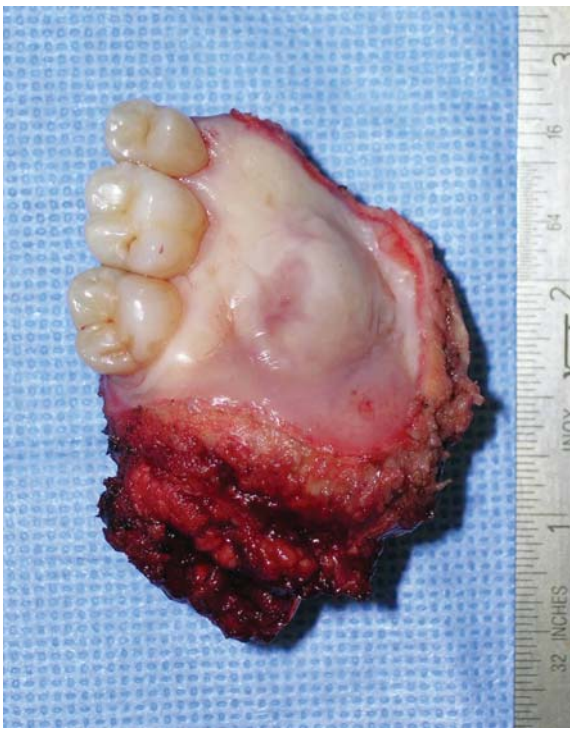

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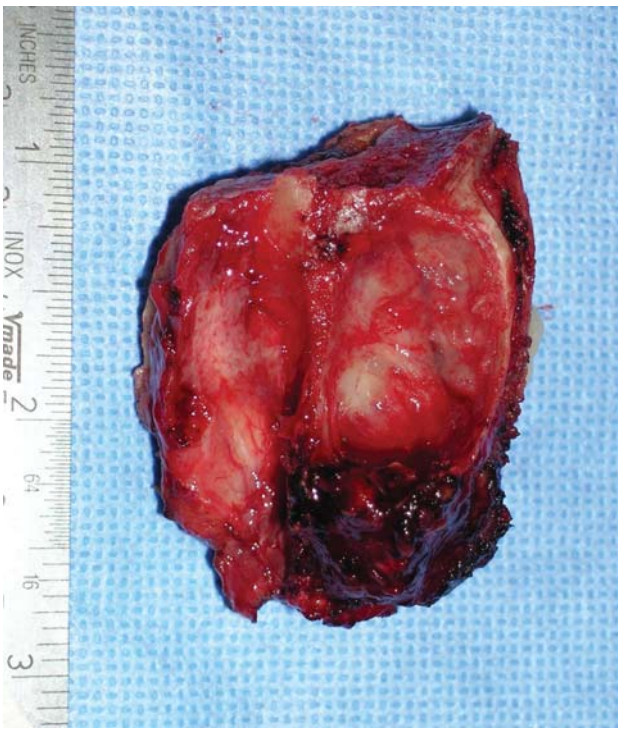

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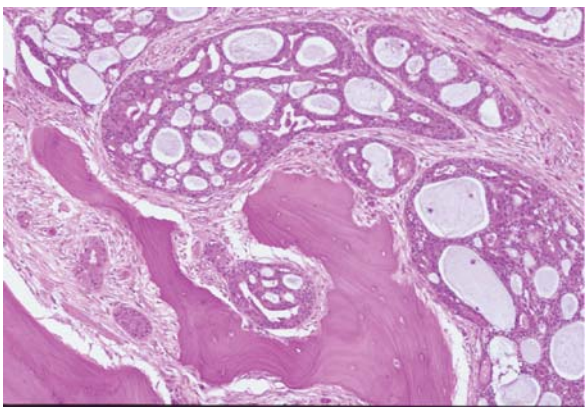

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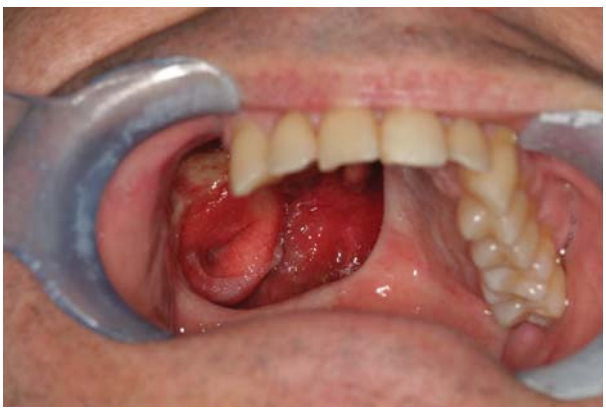

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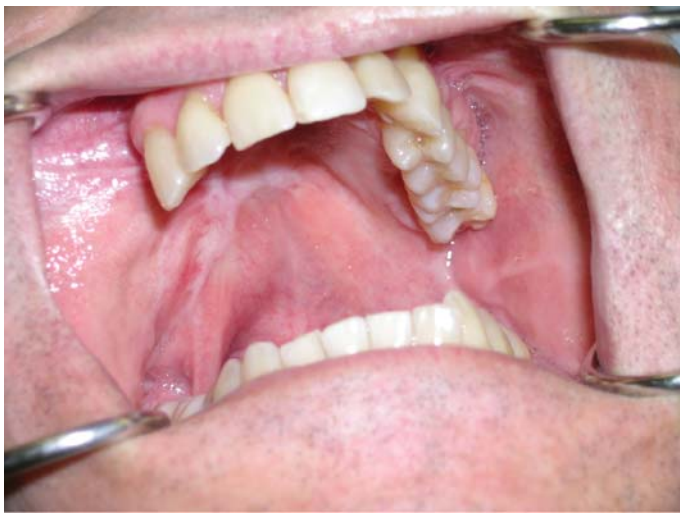

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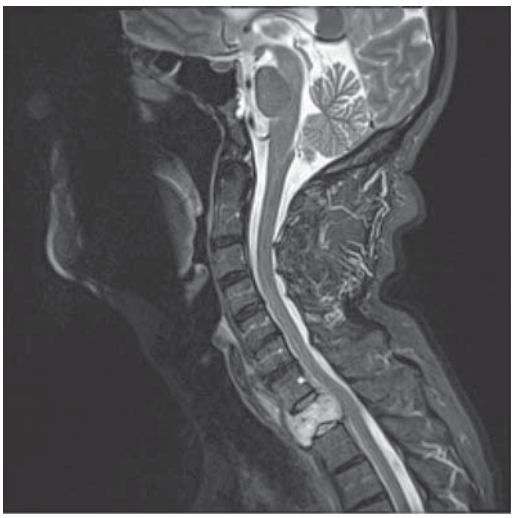

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adenocarcinoma (Regezi, et al. 1991). High power evaluation of polymorphous low-grade adenocarcinoma and adenoid cystic carcinoma may permit the distinction between the two malignancies as adenoid cystic carcinoma shows ductal type structures lined by multiple cells in thickness, while polymorphous low-grade carcinoma shows ductal type structures more commonly lined by single cell layers (Figure 11.15). An Indian filing pattern is also seen in polymorphous low-grade adenocarcinoma. The common morphologic features of polymorphous low-grade adenocarcinoma and adenoid cystic carcinoma have led researchers to investigate methods of distinguishing these diagnoses (Beltran, et al. 2006). In 1984, Evans and Batsakis described 14 cases of a distinctive minor salivary gland neoplasm that they named polymorphous low-grade adenocarcinoma. This term emphasized the features of this neoplasm, including their cytologic uniformity and histologic diversity, variable growth patterns from solid to papillary to cribriform to fascicular, and relative lack of nuclear atypia (Evans and Batsakis 1984). Mitotic figures were infrequent and tumor necrosis was only seen in one case. Perineural invasion is commonly noted in this malignancy. The tumors were distinctly unencapsulated and deeply infiltrative of bone and surrounding soft tissues. Radical surgical procedures were required for tumor control, but no distant metastases were noted. The authors judged from their survey of adenocarcinomas of the major salivary glands that the polymorphous low-grade adenocarcinoma was at least primarily an oral neoplasm. Since this report, Batsakis and El-Naggar have subclassified polymorphous low-grade adenocarcinomas (terminal duct adenocarcinomas) into papillary and nonpapillary forms. The papillary form was found to exhibit a more aggressive course with a higher rate of recurrence at the primary site, metastasis to cervical lymph nodes, and distant metastasis (Batsakis and El-Naggar 1991). The AFIP registry identified 75 cases of this neoplasm, and all were located in the minor salivary glands (Wenig and Gnepp 1991). Forty-four of these cases were located in the palate (58.6%), with the upper lip and buccal mucosa showing 12 cases each. Involvement of other oral minor salivary gland sites has been reported, however, this is quite rare (Kennedy, et al. 1987; de Diego, et al. 1996).

Since its original description in minor salivary gland sites, cases of polymorphous low-grade adenocarcinoma have been reported in all of the major salivary glands such that this tumor cannot be stated to be exclusive to minor salivary gland tissue (Merchant, et al. 1996; Barak, et al. 1998; Nagao, et al. 2004; Blanchaert, et al. 1998).

Treatment of polymorphous low-grade adenocarcinoma should involve surgery with curative intent. The specific surgical procedure is based on the anatomic site. Surgical removal of these tumors in the palate requires a thorough assessment of the palatal bone with computerized tomograms. Bone involvement by this tumor is not an inherent property of this neoplasm, but rather seems to be

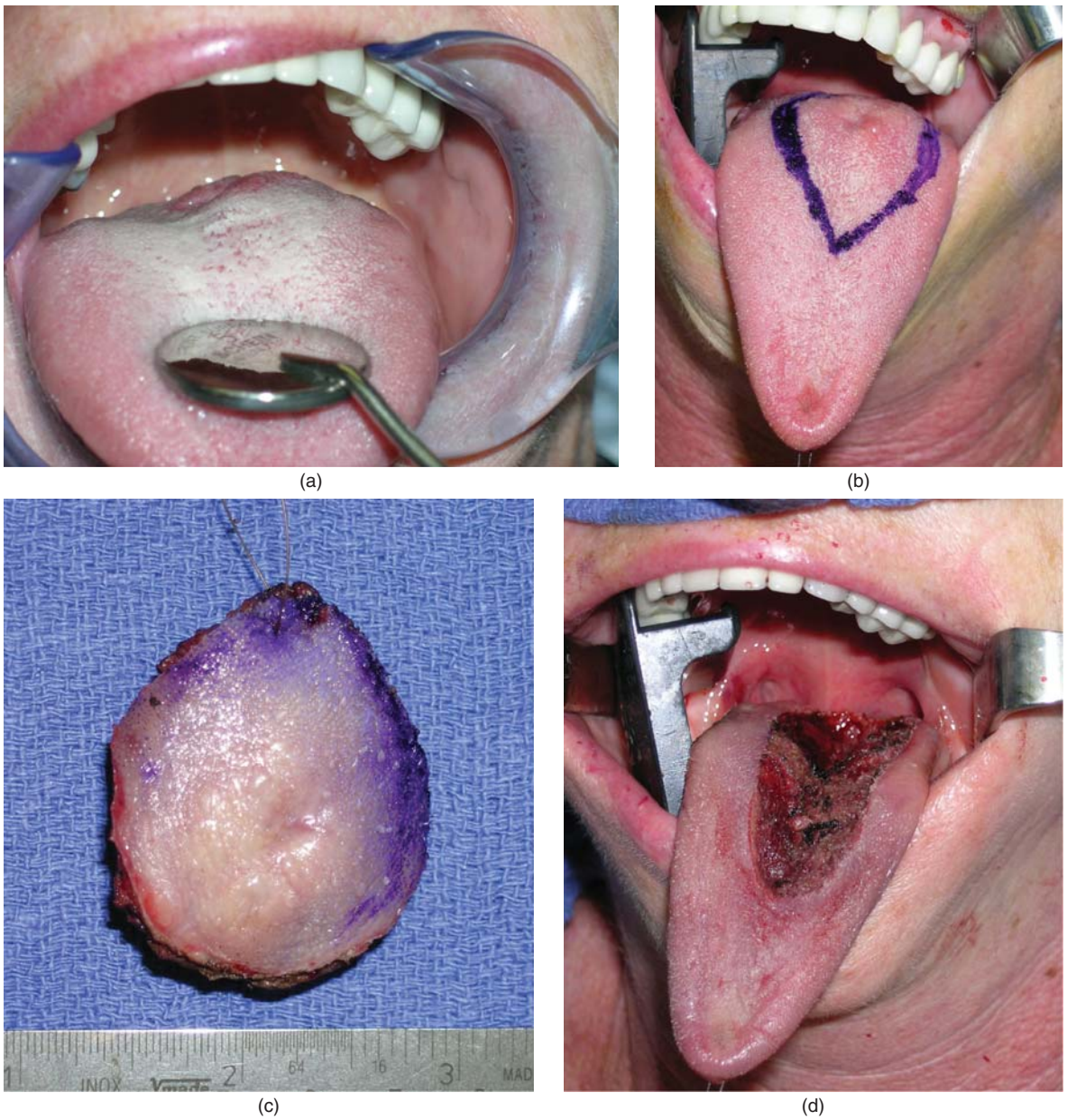
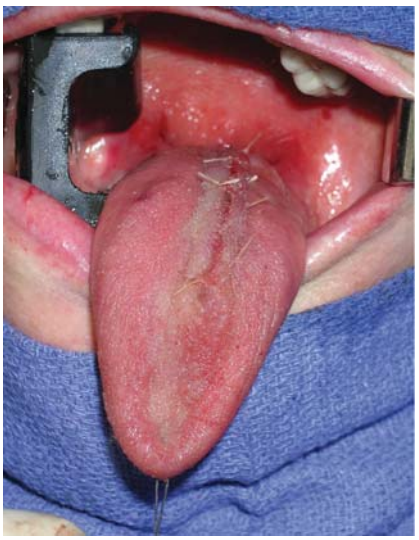


Figure 11.12. A mass of the dorsum of the tongue (a) that demonstrated adenoid cystic carcinoma on incisional biopsy. A wide excision of the dorsum of the tongue, observing one centimeter linear margins (b and c) was performed with primary closure of the tongue defect (d, e). The tongue specimen showed classic cribriform architecture associated with the adenoid cystic carcinoma (f; hematoxylin and eosin, original magnification ×40). Bilateral supraomyohyoid neck dissections were performed (g, h). One lymph node with metastatic adenoid cystic carcinoma was identified (i). The patient underwent postoperative radiation therapy and showed no evidence of disease at 5 years postoperatively (j, k, l).

a function of chronicity of the tumor. Since these malignancies are not fast growing, many patients have long histories of their presence, such that palatal bone infiltration by the tumor may occur over time. In addition, the characteristically deeply infiltrative nature of these tumors into surrounding soft tissues, regardless of the chronicity of the tumor, is such that the soft palate typically requires full thickness sacrifice in most cases. These features are clearly a departure from the treatment of



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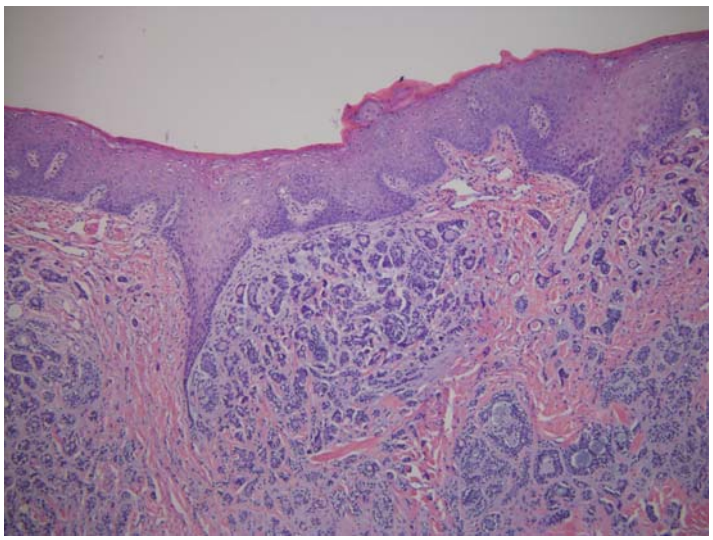

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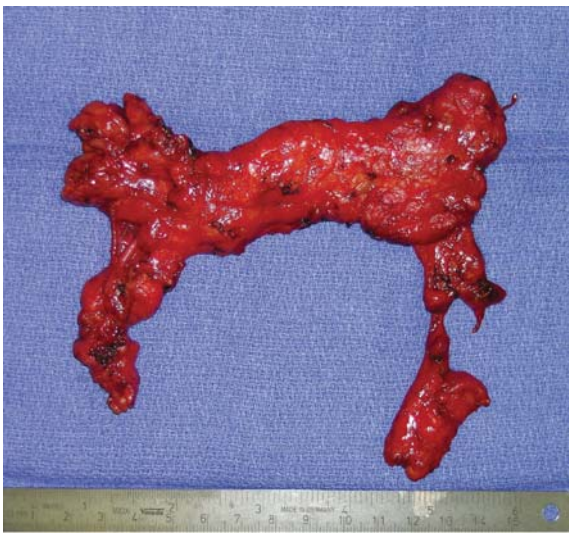

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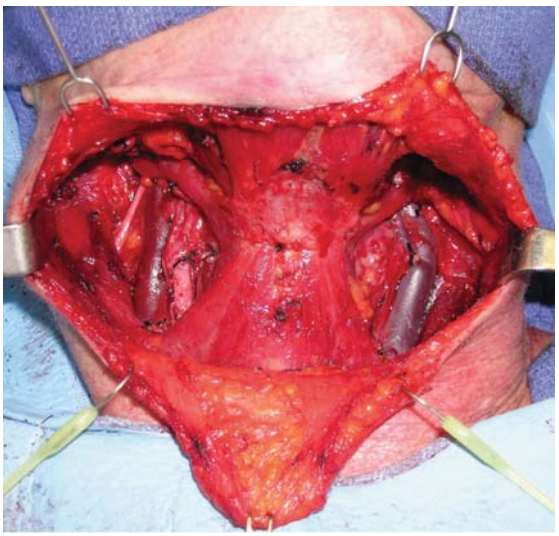

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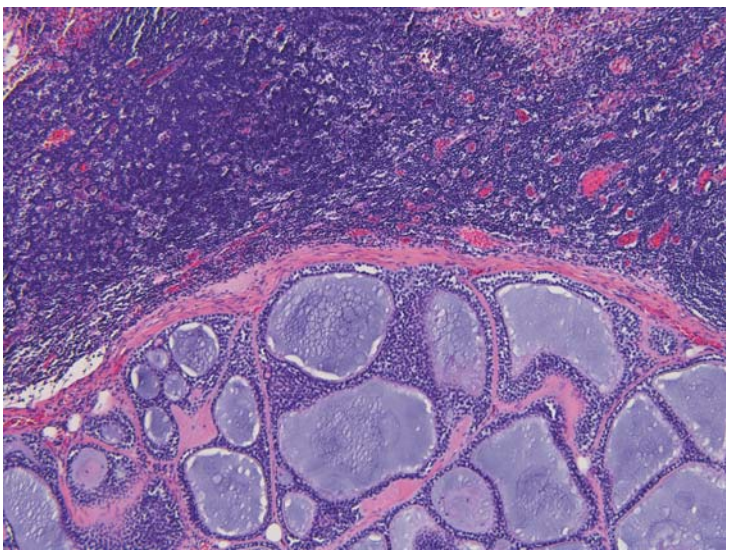

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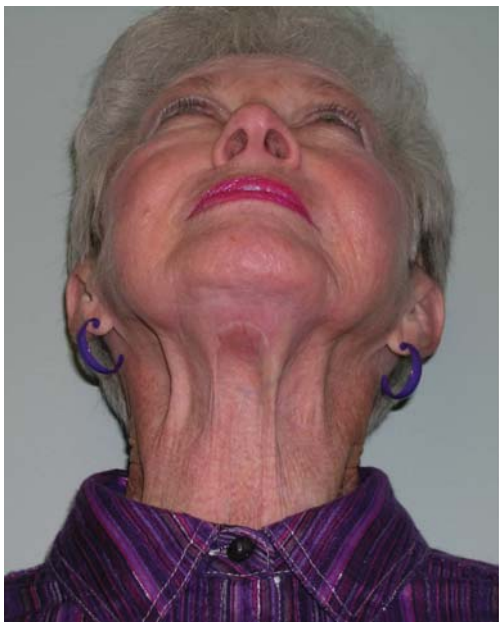

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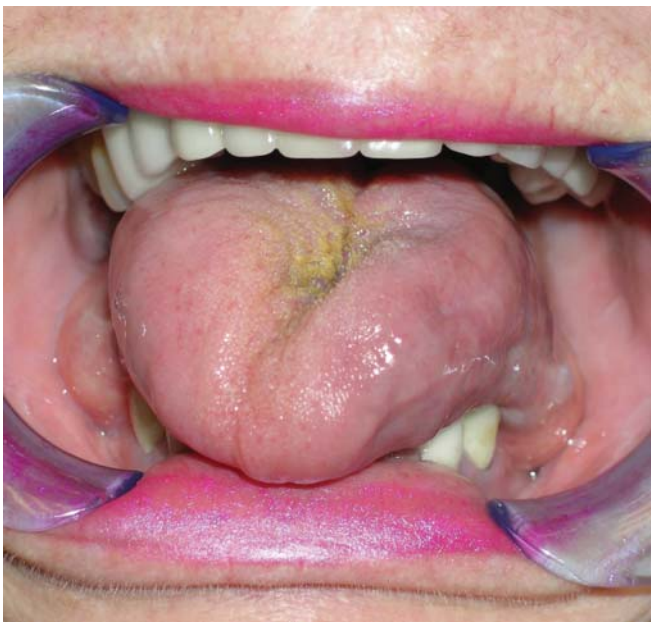

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mucoepidermoid carcinoma of the palate where grade is the main determining factor in planning surgical treatment. Once a biopsy diagnosis of polymorphous low-grade adenocarcinoma of the palate has been established, therefore, CT scans should be obtained to examine the quality of the palatal bone. If the bone is unaltered by the tumor, a bone sparing, periosteal sacrificing wide local excision with full thickness sacrifice of the soft palate may be performed (Figure 11.16). Due to the tumor's neurotropism, the greater palatine neurovascular bundle should be sampled for frozen sections superiorly. Since perineural spread is not characteristic of this tumor, it is unlikely to find tumor tracking along the nerve, in contradistinction to adenoid cystic carcinoma where tumor may be found surrounding this nerve at foramen rotundum. An immediate surgical obturator is fabricated preoperatively for insertion at the time of ablative surgery so as to permit the patient to begin taking a diet on the day of surgery. If the bone is eroded by the tumor, a traditional maxillectomy is necessary, also resulting in a full thickness sacrifice of the soft palate (Figure 11.17). An immediate surgical obturator must also be fabricated preoperatively for insertion at the time of surgery when a maxillectomy is planned for this diagnosis.

The surgical treatment of polymorphous low-grade adenocarcinoma of the upper lip or buccal mucosa is similar to that of a mucoepidermoid carcinoma of these regions. The basic approach involves a mucosal sacrificing wide local excision with attention to submucosal anatomic barriers being included on the specimen so as to ensure tumor free margins (Figure 11.18).

The use of radiation therapy has been assessed in the management of polymorphous low-grade adenocarcinoma. In a clinicopathologic study of 164 cases of this malignancy, 17 patients underwent incisional, excisional, or wide local excision followed by radiation therapy (Castle, et al. 1999). Adjuvant radiation therapy did not affect survival. Their study showed that patients who were treated with radiation therapy were more likely to have evidence of disease at last follow up when compared with patients who did not have radiation therapy. Furthermore, there was no statistically significant difference in the overall patient outcome based on the type of initial treatment given or for any additional treatment rendered, whether it is additional surgery, radiation therapy, or chemotherapy. Based on this report and others (Crean, et al. 1996), the treatment for polymorphous low-grade adenocarcinoma of minor salivary glands remains surgical. It has been estimated that

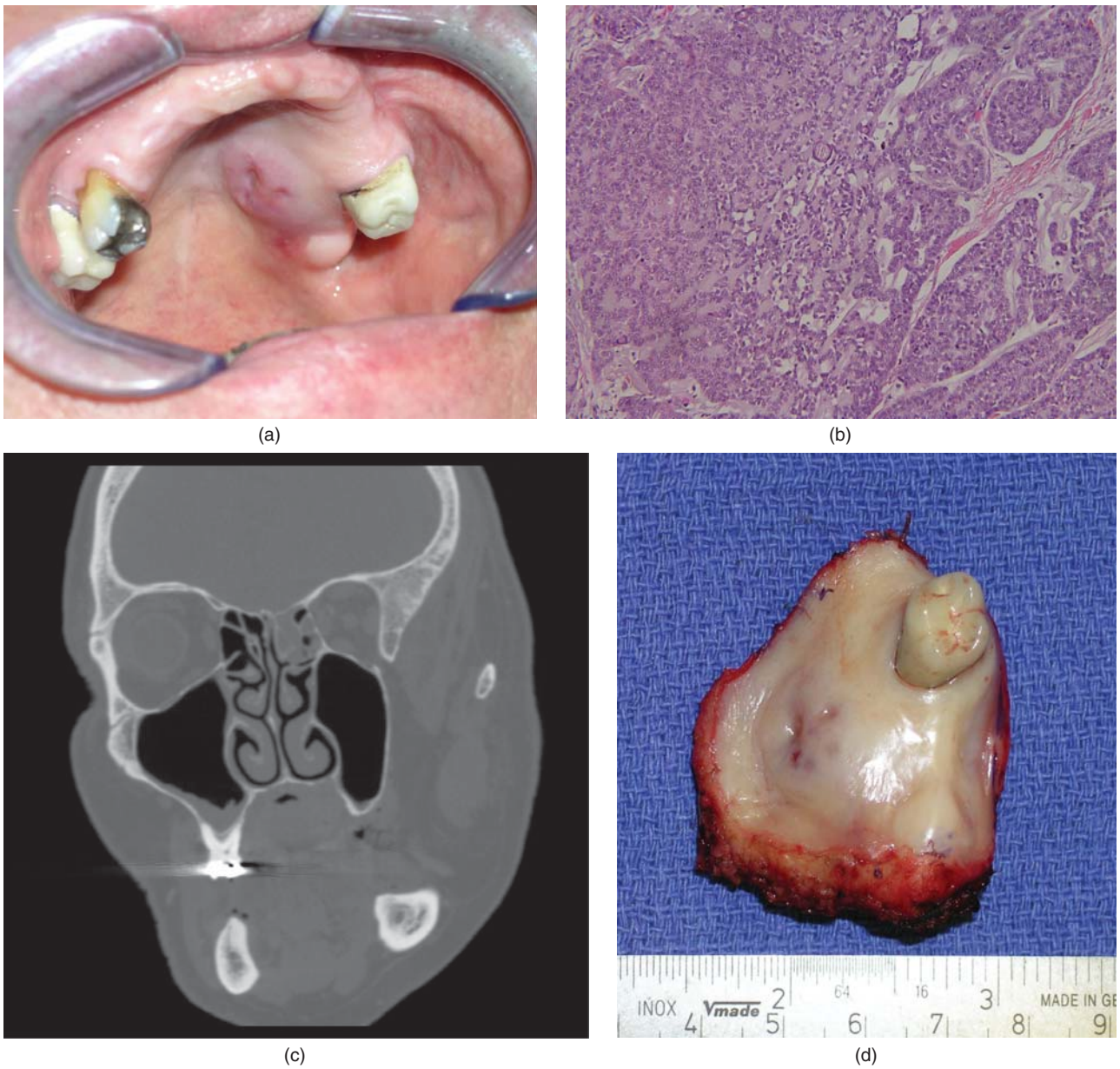
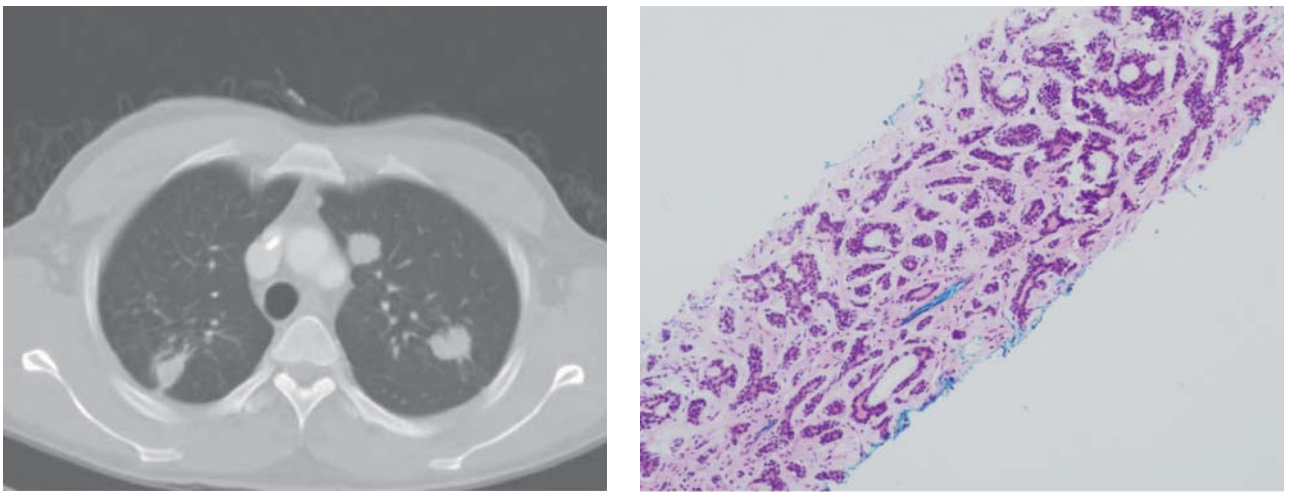


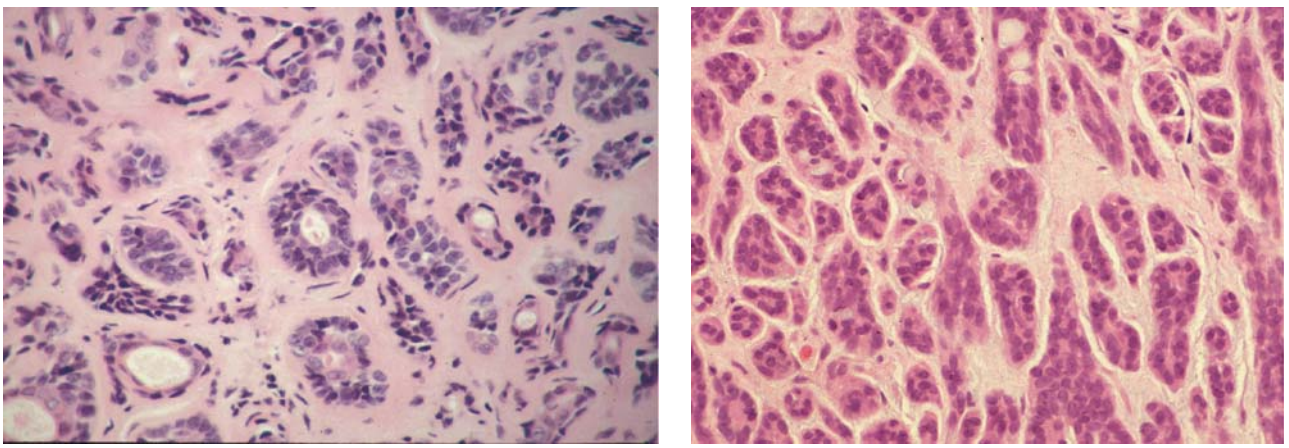
Figure 11.13. A mass of the left palate (a) whose incisional biopsy identified solid adenoid cystic carcinoma (b; hematoxylin and eosin, original magnification ×100). Coronal CT images identified subtle erosion of the palatal bone (c). A partial maxillectomy was performed observing 1 cm linear margins in bone and soft tissue (d).

approximately 80% of patients survive their disease without evidence of tumor at periods from between several months to 25 years after removal (Wenig and Gnepp 1991). One case has been reported where death occurred as a result of this neoplasm with direct extension to vital structures of the head (Aberle, et al. 1985). In addition, while rare, metastasis to cervical lymph nodes (Kumar, et al. 2004) and to distant organs (Hannen, Bulten, Festen et al. 2000) have been reported from polymorphous low-grade adenocarcinomas originating in the palate. These reports indicate that cervical lymph node involvement should be suspected in patients with papillary cystic change in the tumor and that periodic chest X-ray examination should be performed postoperatively when this variant of tumor is diagnosed. In addition, while regional and distant metastases are rare related to this tumor,



(a) (b)

Figure 11.14. A representative axial cut of a chest CT (a) of a patient with multiple pulmonary metastases related to recurrent adenoid cystic carcinoma of the palate. A CT guided core biopsy of one of the nodules identified metastatic adenoid cystic carcinoma (b) hematoxylin and eosin, original magnification ×40).



(a) (b)

Figure 11.15. Subtle differences between the adenoid cystic carcinoma (a) and the polymorphous low-grade adenocarcinoma (b). The adenoid cystic carcinoma characteristically shows multiple cell layered ductal structures, while the polymorphous low-grade adenocarcinoma shows single cell layered ductal structures. Figure 11.15(b) reprinted with permission from: Carlson ER: Salivary gland pathology. Clinical perspectives and differential diagnosis. In: *The Comprehensive Management of Salivary Gland Pathology, Oral and Maxillofacial Surgery Clinics of North America* 7:361–386, 1995. Figures 11.15 (a and b) = hematoxylin and eosin, original magnification ×100.

long-term follow up is recommended due to the possibility for late recurrences (Fife, et al. 2013).

Acinic Cell Adenocarcinoma

Acinic cell adenocarcinoma is a very rare malignancy of the minor salivary glands. It has been estimated to represent approximately 2.5–3% of salivary gland tumors in general (Spiro 1986; Guimaraes, et al. 1989) and about 4% of minor salivary gland tumors (Castellanos and Lally 1982). Indeed, acinic cell adenocarcinoma is not represented in many studies of minor salivary gland tumors (Isacsson and Shear 1983; Chau and Radden 1986; Jabar 2006) and other studies show only a very limited number of these cases

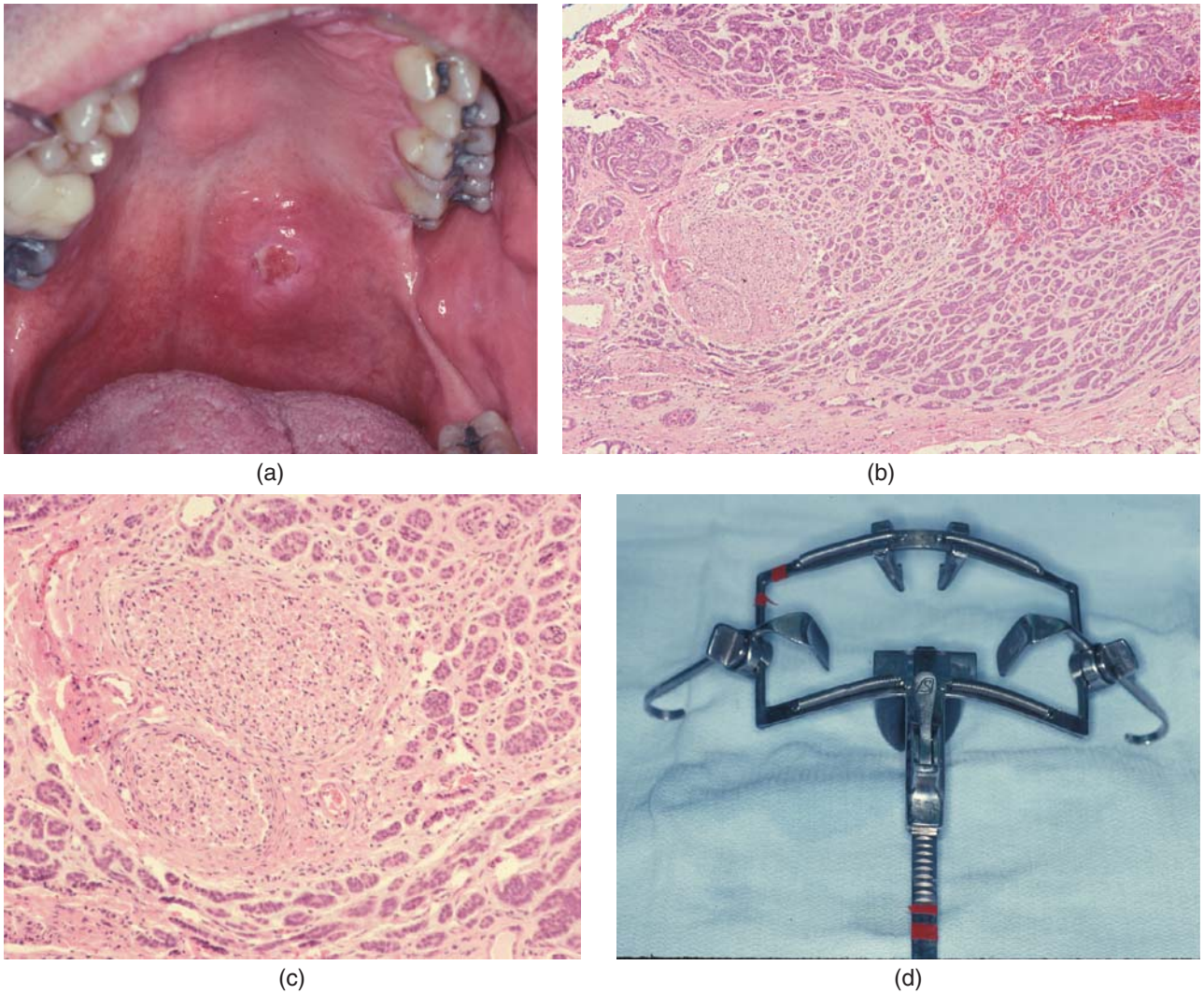
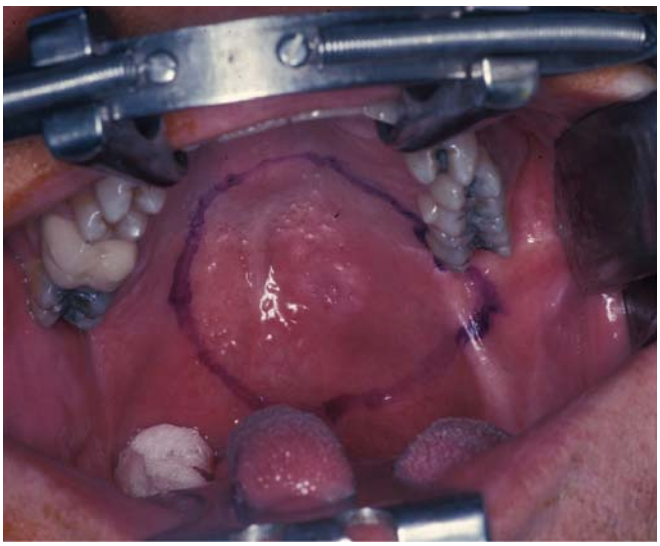


Figure 11.16. A 51-year-old man with a mass of the soft palate that had been reportedly present for only 2 months (a). Incisional biopsy showed a microscopically cribriform tumor with obvious perineural invasion (b, c). A diagnosis of polymorphous low-grade adenocarcinoma was made. Computerized tomograms did not reveal involvement of the palatal bone such that a periosteal sacrificing, bone sparing wide local excision with full-thickness sacrifice of the soft palate was performed. A Dingman mouth gag was utilized so as to provide acceptable retraction to perform this surgery (d). One centimeter linear margins in mucosa were planned (e). The specimen is delivered (f). Final histopathology ultimately identified a negative periosteal surface, thereby justifying the preservation of palatal bone (g). The greater palatine neurovascular bundle was clamped prior to delivery of the specimen so as to procure a 1-cm segment of nerve for frozen section analysis (h). The hemostat remained on the nerve stump while the frozen section was being evaluated. If the nerve was positive for cancer, the nerve would be pulled down to procure additional frozen sections so as to clear the cancer. The defect (i) was addressed with an immediate obturator that had been fabricated preoperatively (j, k). The exposed palatal bone is covered with immature granulation tissue at 1 month postoperatively (l), that undergoes maturation by 3 months postoperatively (m). At 1 year postoperatively, the patient's defect has demarcated well (n), and a definitive obturator has been fabricated (o). The patient is free of disease at 24 years postoperatively. Reprinted with permission from: Carlson, ER, Salivary gland pathology – Clinical perspectives and differential diagnosis, In: *The Comprehensive Management of Salivary Gland Pathologyn Oral and Maxillofacial Surgery Clinics of North America* 7:361–386, WB Saunders Co., 1995.



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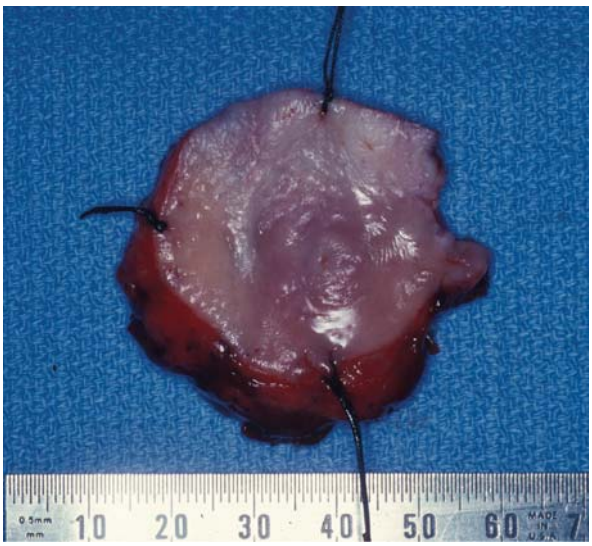

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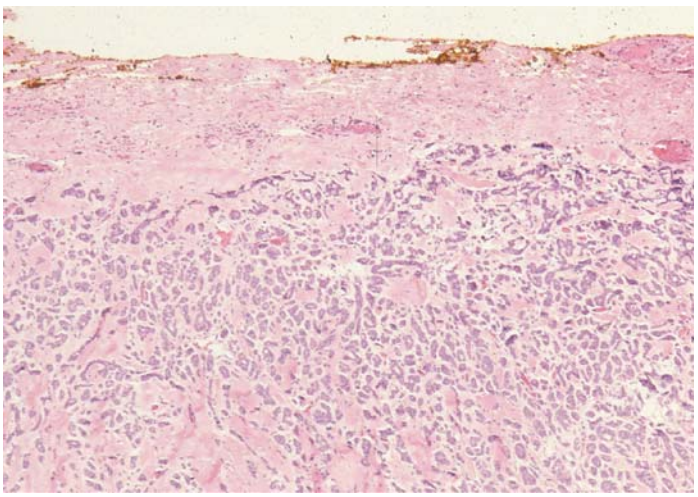

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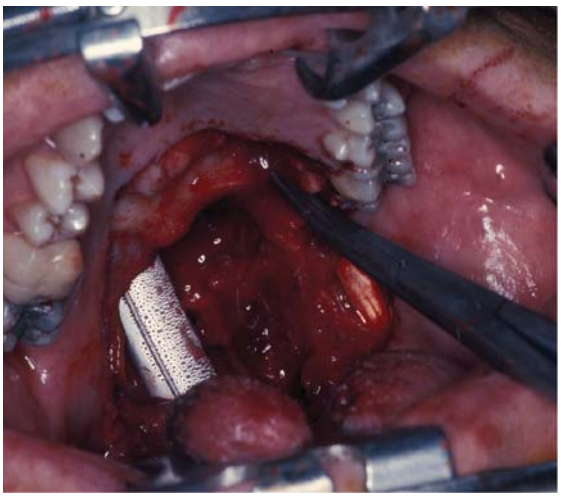

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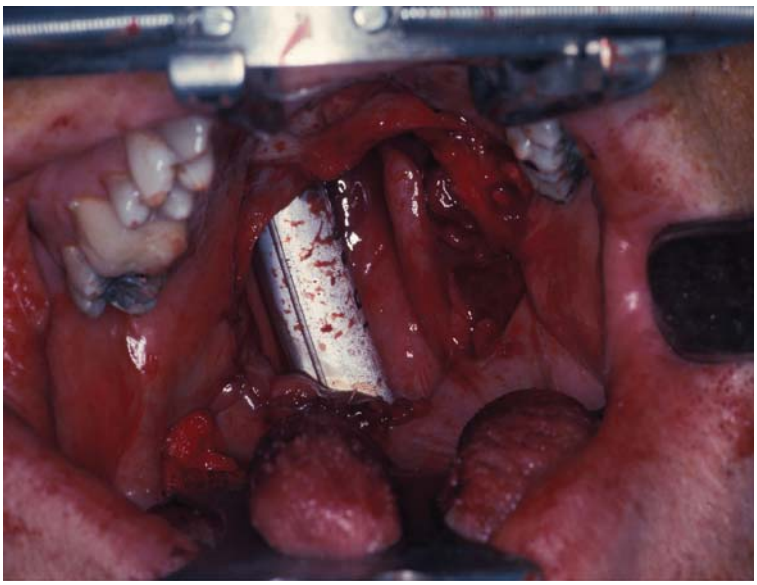

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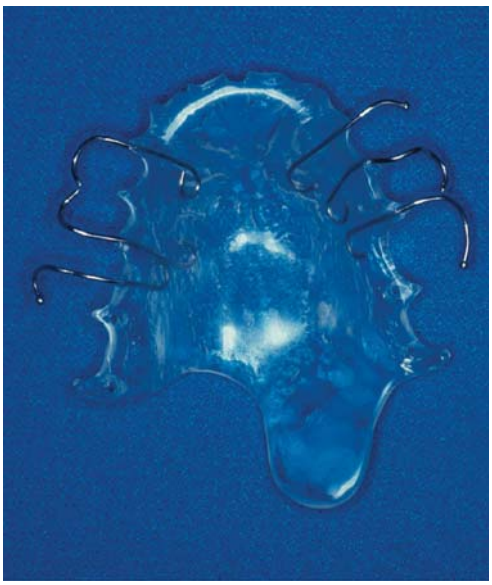
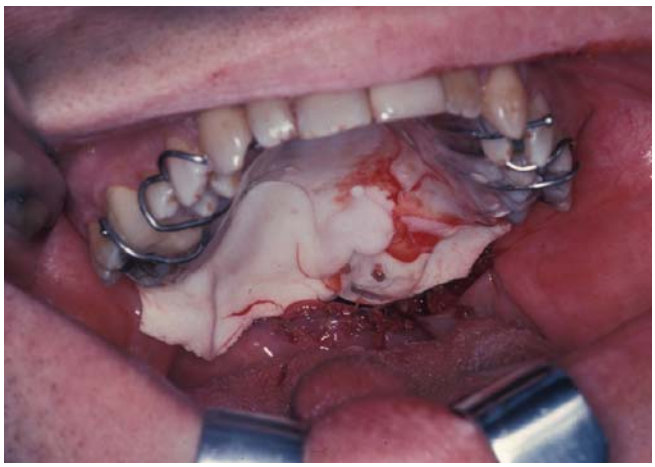


(j)

Figure 11.16. (*Continued*)



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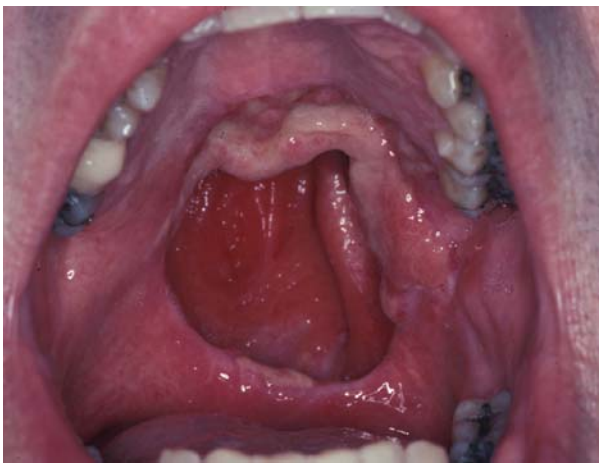

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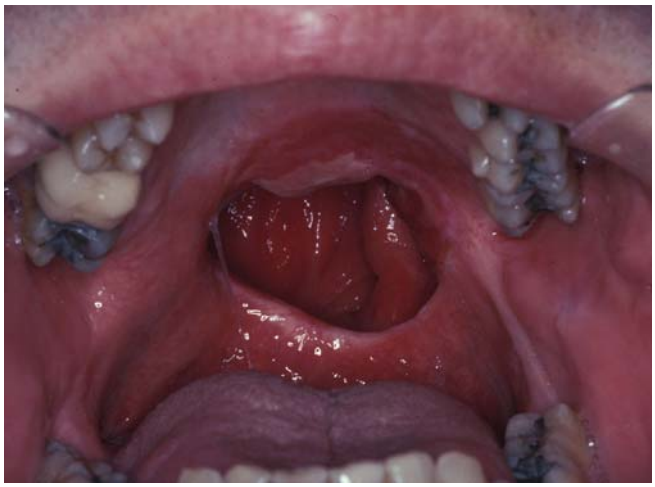

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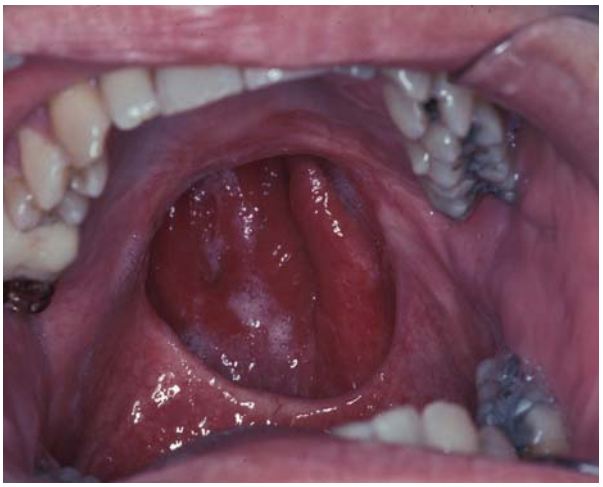

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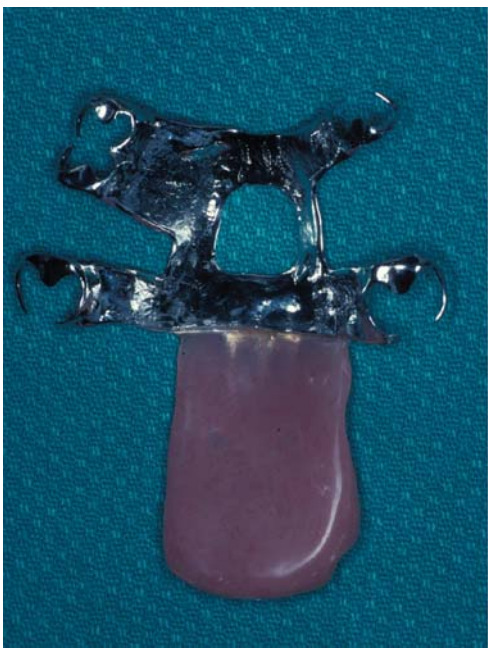

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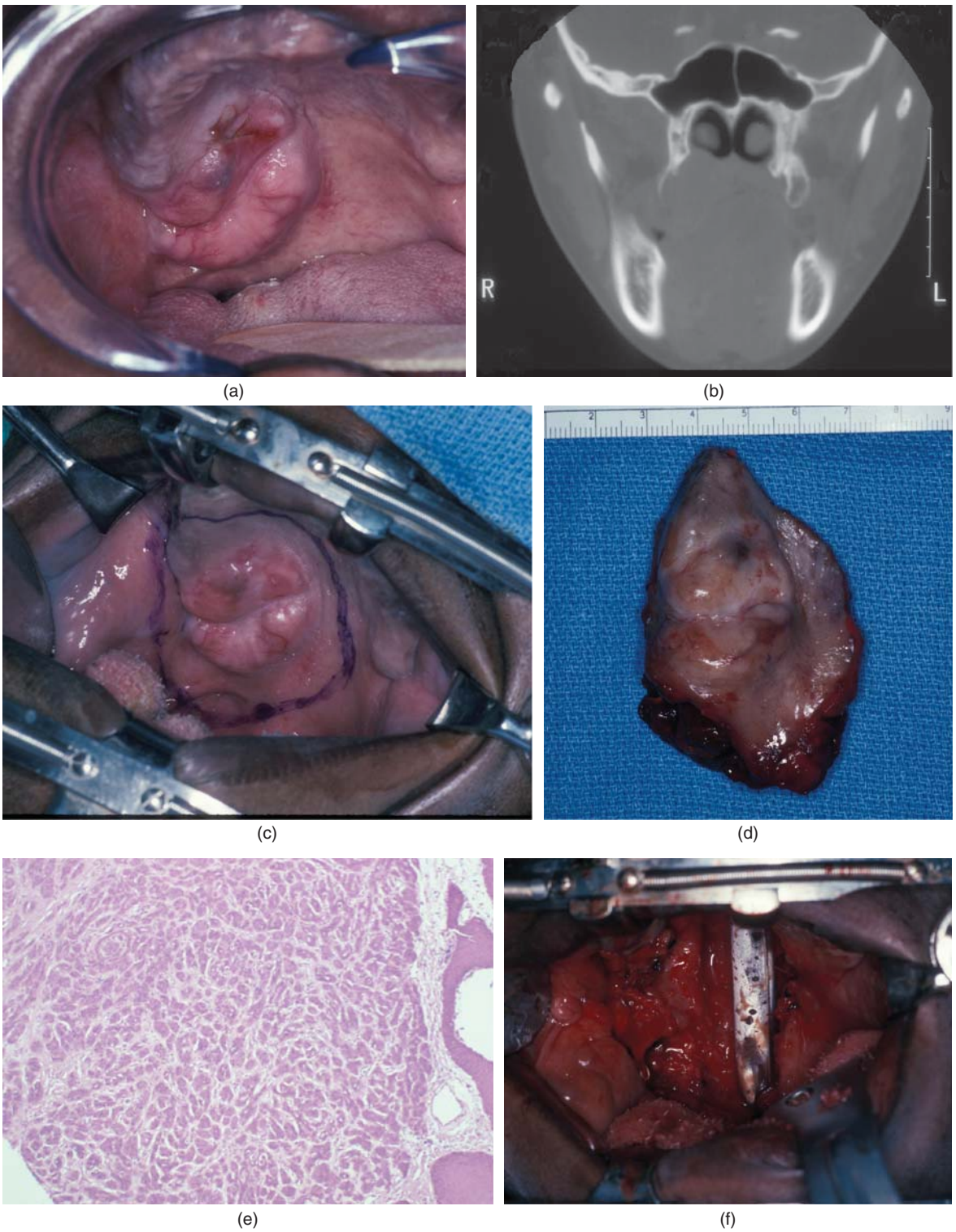
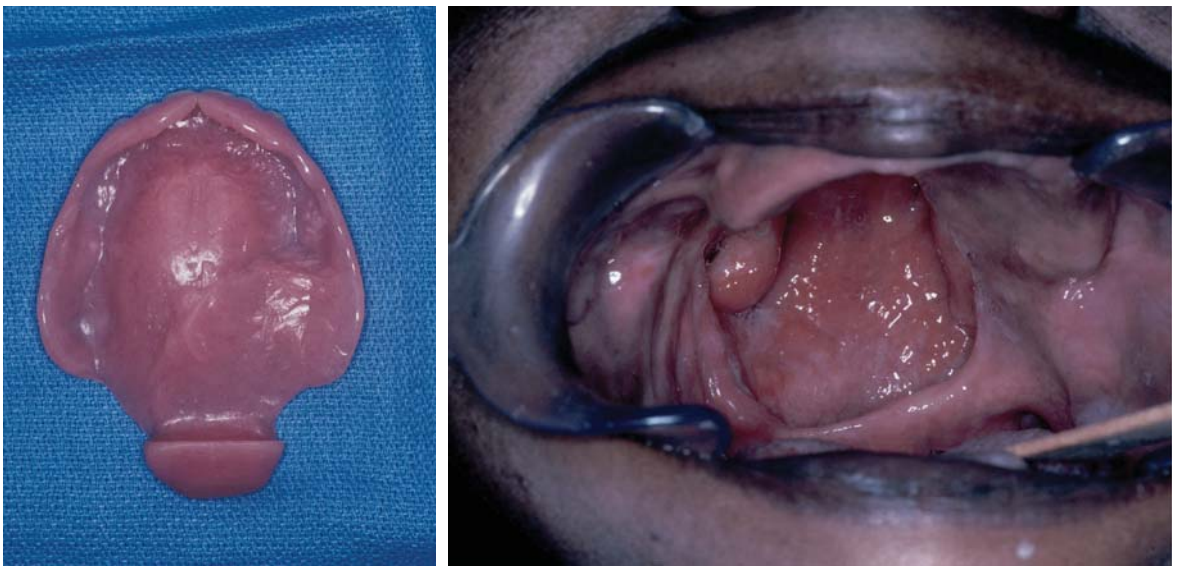


(a) (b) (c) (d) (e) (f)

Figure 11.17. A biopsy proven polymorphous low-grade adenocarcinoma of the palate in a 53-year-old woman that had been present for several years according to the patient (a). Computerized tomograms were obtained that identified destruction of bone by the cancer (b). As such, a maxillectomy was performed, observing 1-cm linear margins in bone and soft tissue (c). The maxillectomy specimen delivered (d). The histopathology confirmed the involvement of the maxillary bone by the tumor (e). The large ablative defect (f) was addressed with an immediate obturator (g). At 1 year postoperatively, the patient showed no signs of recurrent disease (h).



(g) (h)

Figure 11.17. (*Continued*)

(Toida, et al. 2005; Lopes, et al. 1999). The acinic cell adenocarcinoma behaves most similarly to the low-grade mucoepidermoid carcinoma (Ord 1994). In fact, like the low-grade mucoepidermoid carcinoma, the acinic cell adenocarcinoma was originally purported to be a benign neoplasm (Ellis and Auclair 1991a). For the first half of the twentieth century, these tumors were thought to be benign. In 1953, Buxton and his group were the first to ascribe a malignant character to many of these tumors (Buxton, et al. 1953). These were identified as serous cell adenocarcinomas, after which time Foote and Frazell classified these tumors as acinic cell adenocarcinomas (Foote and Frazell 1953).

The AFIP registry shows 886 acinic cell adenocarcinomas, of which 753 were located in the major salivary glands (85%), and 133 (15%) in the minor salivary glands. The most common site of minor salivary gland involvement was the buccal mucosa, accounting for 43 cases (32%), followed by the lip (38 cases = 29%). Tumors in the upper lip were three times more common than tumors in the lower lip. The palate was the only other significant anatomic site to be affected by this tumor, and accounted for 22 cases (17%). A female preponderance was noted, with a mean age of 44 years. In their series of 21 cases of acinic cell carcinoma of minor salivary glands, Omlie and Koutlas (2010) identified seven cases in the buccal mucosa, six in the palate, five in the upper lip, one in the lower lip, and two in the retromolar mucosa. Fifteen of the 21 patients were men.

Surgery for acinic cell adenocarcinoma is performed in a similar fashion as that of low-grade mucoepidermoid carcinoma. Tumors of the buccal mucosa and upper lip are treated with mucosal sacrificing wide local excisions, including 1-cm linear margins, with attention to the necessary sacrifice of surrounding anatomic barriers (Figure 11.19). Tumors of the palate can be treated with bone sparing, periosteally sacrificing wide local excisions with split thickness sacrifice of the soft palate. Computerized tomograms may be obtained preoperatively to confirm the lack of bone erosion. Cure is most commonly realized and recurrences and regional and distant metastases are rare when these malignancies are treated with curative intent (Omlie and Koutlas 2010). Cervical lymph node metastases are rare such that prophylactic neck dissections are not recommended. Distant metastatic spread of the acinic cell carcinoma of minor salivary gland origin is also uncommon, although metastases have been identified in the lungs, liver, brain and bone (Triantafillidou, et al. 2010). Five- and 10-year survival rates are generally quite favorable, and reported as 82 and 68%, respectively (Hickman, et al. 1984).

Epithelial-Myoepithelial Carcinoma

The epithelial-myoepithelial carcinoma is very rare, representing approximately 1% of all salivary gland tumors (Angiero, et al. 2009). It most commonly occurs in the parotid gland but has been noted in

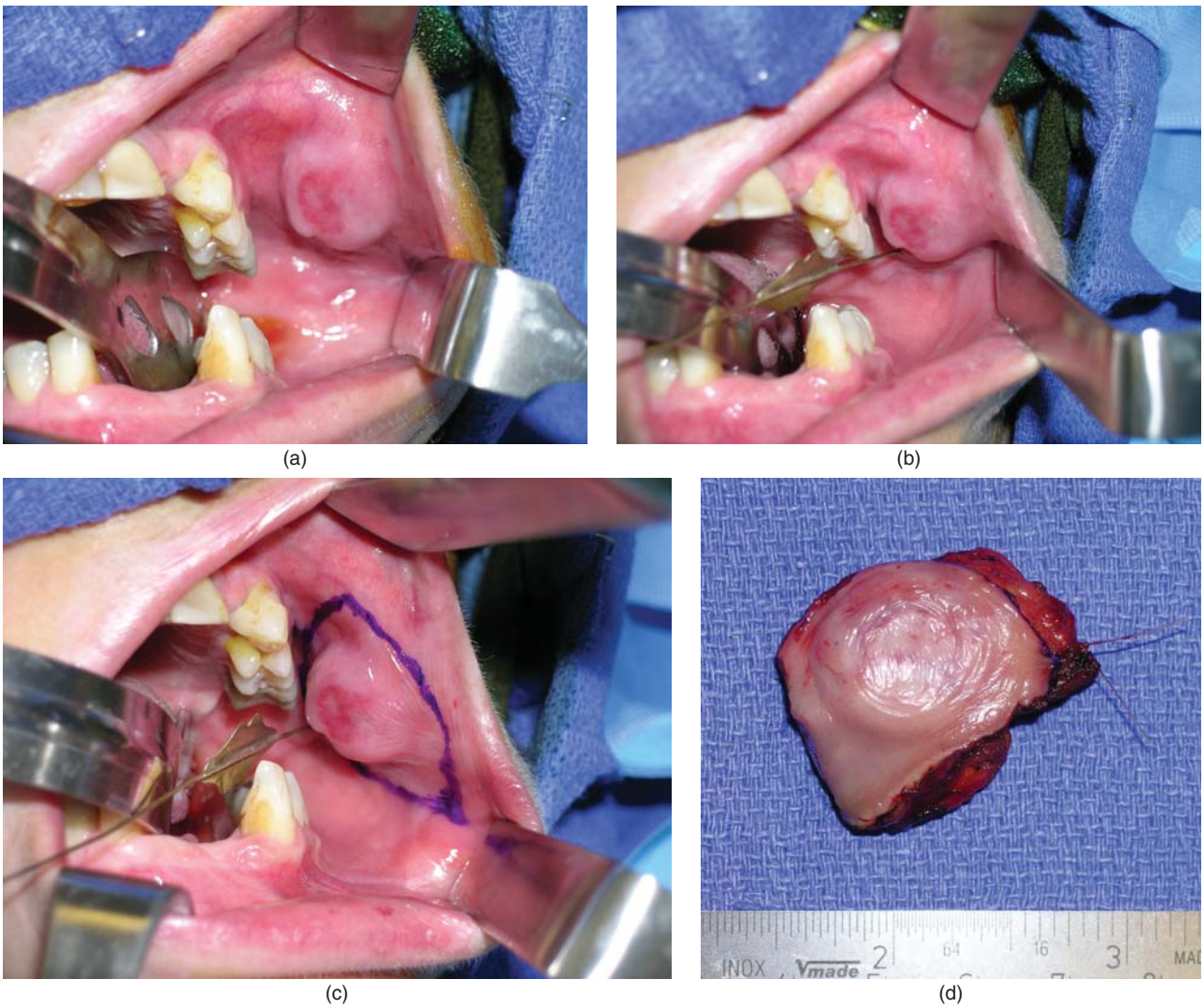
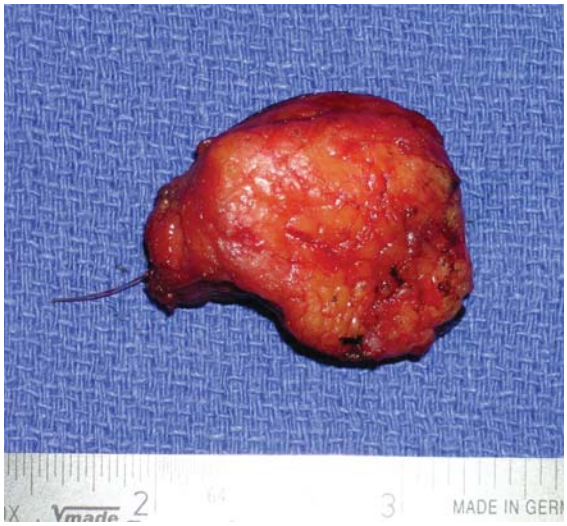


Figure 11.18. A biopsy proved polymorphous low-grade adenocarcinoma of the buccal mucosa in a 53-year-old woman with a 5-year history of this mass (a). The characteristically thick tumor blocked immediate visualization of the Stenson duct that is able to be cannulated and is free from the margin of the tumor (b). A mucosal sacrificing wide local excision with 1-cm linear margins and isolation of the Stenson duct was performed (c). The specimen was able to be delivered without tumor spillage and with a deep anatomic barrier margin of fat within the cheek (d, e). Microscopic analysis of the tumor identified a 3.5 cm thick PLGA (f) with negative margins and perineural invasion (g). The defect was reconstructed with a buccal fat flap (h). There was no need for radiation therapy postoperatively. Acceptable healing is noted without tumor recurrence at 12 months postoperatively (i). Figure 11.18(f); hematoxylin and eosin, original magnification ×10. Figure 11.18(g); hematoxylin and eosin, original magnification ×40.

the minor salivary glands. This malignancy has been categorized as an intermediate grade malignancy according to the AFIP classification (Ellis and Auclair 1991b) although Angiero et al. (2009) have classified this malignancy as primarily low-grade. Only 57 cases were identified in their series, with 50 cases diagnosed in the major salivary glands (88%), and 7 cases (12%) in the minor salivary glands (Corio 1991). Of the 7 cases in the minor salivary glands, 4 were located in the palate, 1 in the tongue, and 2 cases were not specified as to anatomic location. A mean age of 59 years was noted in these 57 cases. This tumor is known to be highly differentiated, yet it is malignant due



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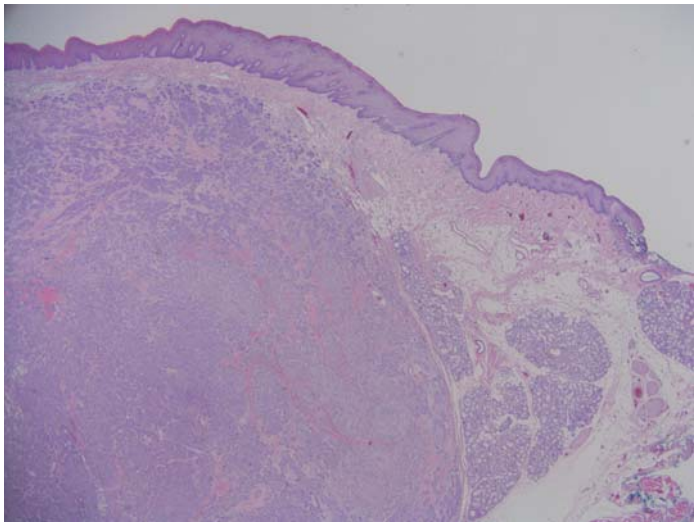

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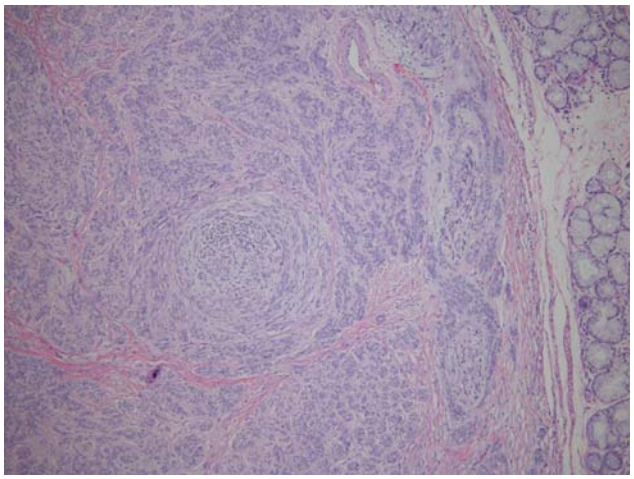

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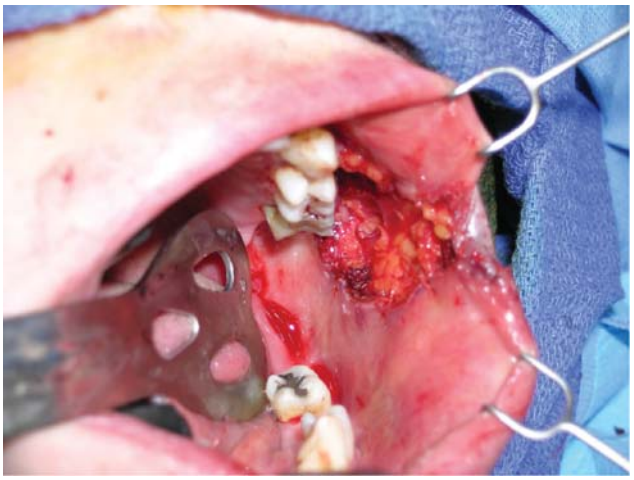

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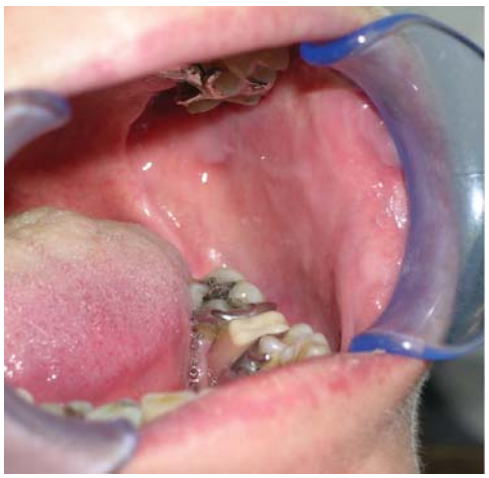

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Figure 11.18. (*Continued*)

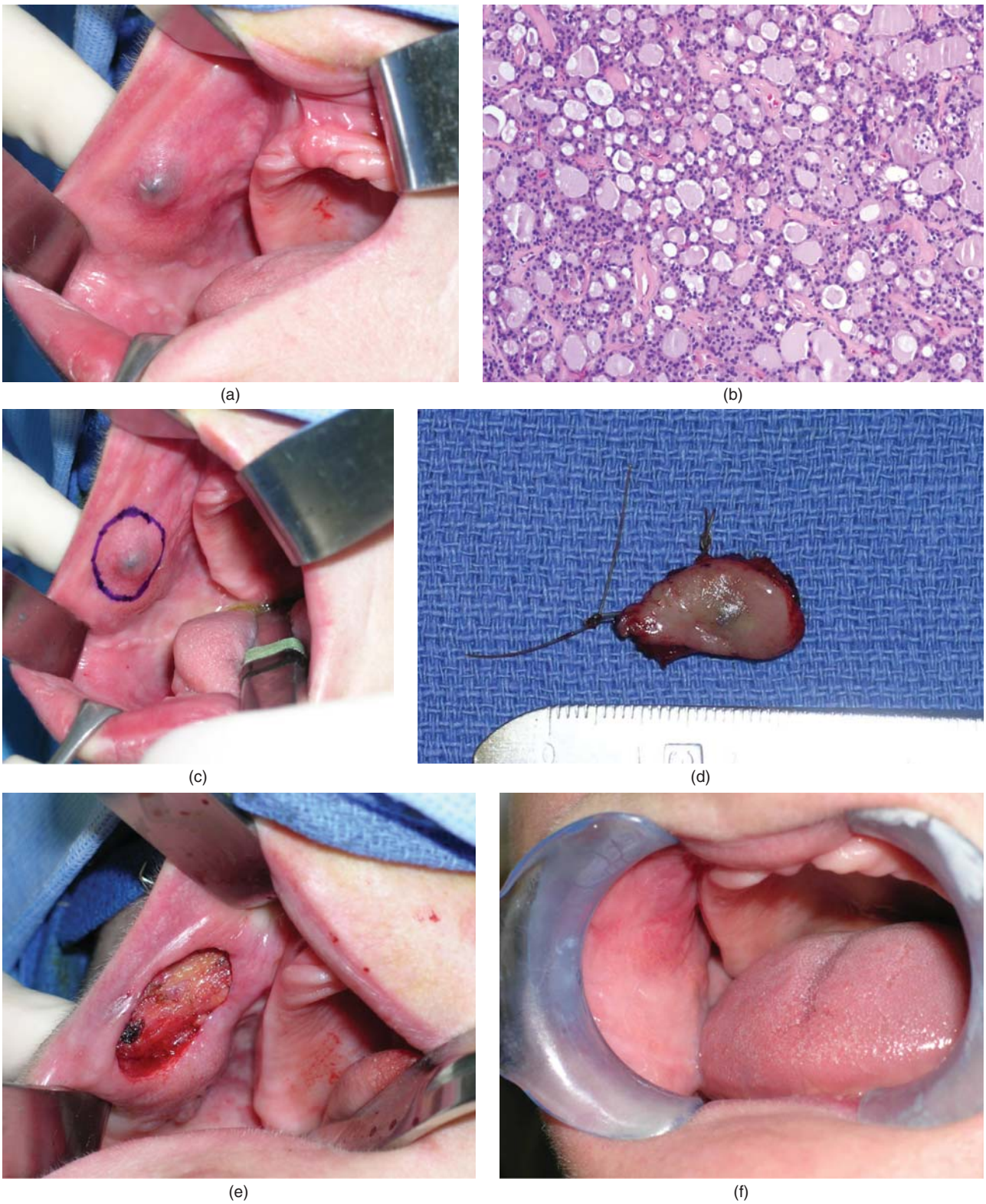


Figure 11.19. An acinic cell adenocarcinoma of the buccal mucosa in a 52-year-old woman (a, b). A mucosal sacrificing wide local excision observing 1-cm linear margins was performed (c). Excision of the specimen (d) occurred without tumor spillage. The defect (e) was reconstructed with mucosal flaps so as to not distort the appearance of the upper lip. Acceptable healing without tumor recurrence is noted at 6 years postoperatively (f).

to infiltrative and destructive growth patterns, the presence of necrosis, perineural involvement and metastases (Corio, et al. 1982). Corio et al. presented 16 cases of this neoplasm and found 12 cases to involve the parotid gland, 3 cases in the submandibular gland, and 1 case in the buccal mucosa (Corio, et al. 1982).

Standardized recommendations for surgery for the epithelial-myoepithelial carcinoma are difficult to make due to the rare nature of this malignancy. Nonetheless, evaluation of involved anatomic barriers with physical examination and CT scans generally permits an effective approach to eradication of these malignancies in various minor salivary gland sites (Figure 11.20). In such circumstances, the surgeon respects well established principles of linear and anatomic barrier margins when operating salivary gland tumors, while also relying on past experience with other low and intermediate grade minor salivary gland malignancies. In so doing, tumor free margins are able to be obtained while performing surgery similar to that for a diagnosis of low or intermediate grade mucoepidermoid carcinoma. Recurrences have been reported (Corio 1991), but appropriate surgical management of epithelial-myoepithelial carcinomas of the minor salivary glands should be performed with curative intent. Quantitative survival statistics are not published in the literature.

SURGICAL MANAGEMENT OF THE NECK FOR MINOR SALIVARY GLAND MALIGNANCIES

Surgical management of the neck is a controversial and intriguing concept for surgeons managing oral/head and neck malignant disease. At the core of this discipline is an assessment of occult disease in patients with clinically negative necks. To this end, there seems to be a consensus in the literature that occult neck disease is relatively uncommon related to minor salivary gland malignancies compared to squamous cell carcinoma of the oral/head and neck. Moreover, it is also uncommon for patients with minor salivary gland malignancies to present with clinically palpable neck disease related to these tumors. Spiro found 53 patients presenting with cervical metastases amongst 378 patients (14%) with minor salivary gland malignancies (Spiro, et al. 1991). Another 26 patients (7%) developed subsequent cervical metastases for an overall rate of nodal involvement of 21%. Interestingly, nine patients underwent an elective neck dissection, all of whom showed histologically confirmed metastatic disease. The authors do not, however, discuss the incidence of occult and clinically apparent metastases as a function of anatomic site of the primary minor salivary gland malignancy. Sadeghi, et al. identified nine patients presenting with cervical metastases related to minor salivary gland malignancies, fiveof which were present in the tongue base (Sadeghi, et al. 1993). Beckhardt, et al. found N+ necks in only 3% of their patients with malignant minor salivary gland tumors of the palate, while Chung, et al. identified only 2 out of 20 patients with malignant salivary gland tumors of the palate presenting with cervical metastases (Chung, et al. 1978; Beckhardt, et al. 1995). The latter three studies only discussed clinical staging of the neck without comments regarding their histology such that limited information is available regarding the true rate of metastasis to the cervical lymph nodes. In the final analysis, it seems that the incidence of occult neck disease related to a minor salivary gland malignancy of the oral cavity is sufficiently low to negate the need for elective neck dissection. Indications for neck dissection in these patients, therefore, are limited to patients who present with cervical metastases; those patients whose preoperative imaging studies document changes in the cervical lymph nodes consistent with metastatic disease; and those patients with high-grade malignancies, regardless of the clinical and radiographic imaging results.

THE ROLE OF RADIATION THERAPY IN THE MANAGEMENT OF MINOR SALIVARY GLAND MALIGNANCIES

It was once thought that salivary gland malignancies were radioresistant (Dragovic 1995). This previously stated misconception can no longer be considered valid. As such, radiation therapy is indicated in the postoperative management of all high-grade malignant minor salivary gland tumors, as well as in patients with positive surgical margins, positive regional lymph nodes, and recurrent tumor (Dragovic 1995). This being the case, it is important to remember that surgery is the primary therapy for minor salivary gland malignancies. Shingaki et al.'s review of the role of radiation

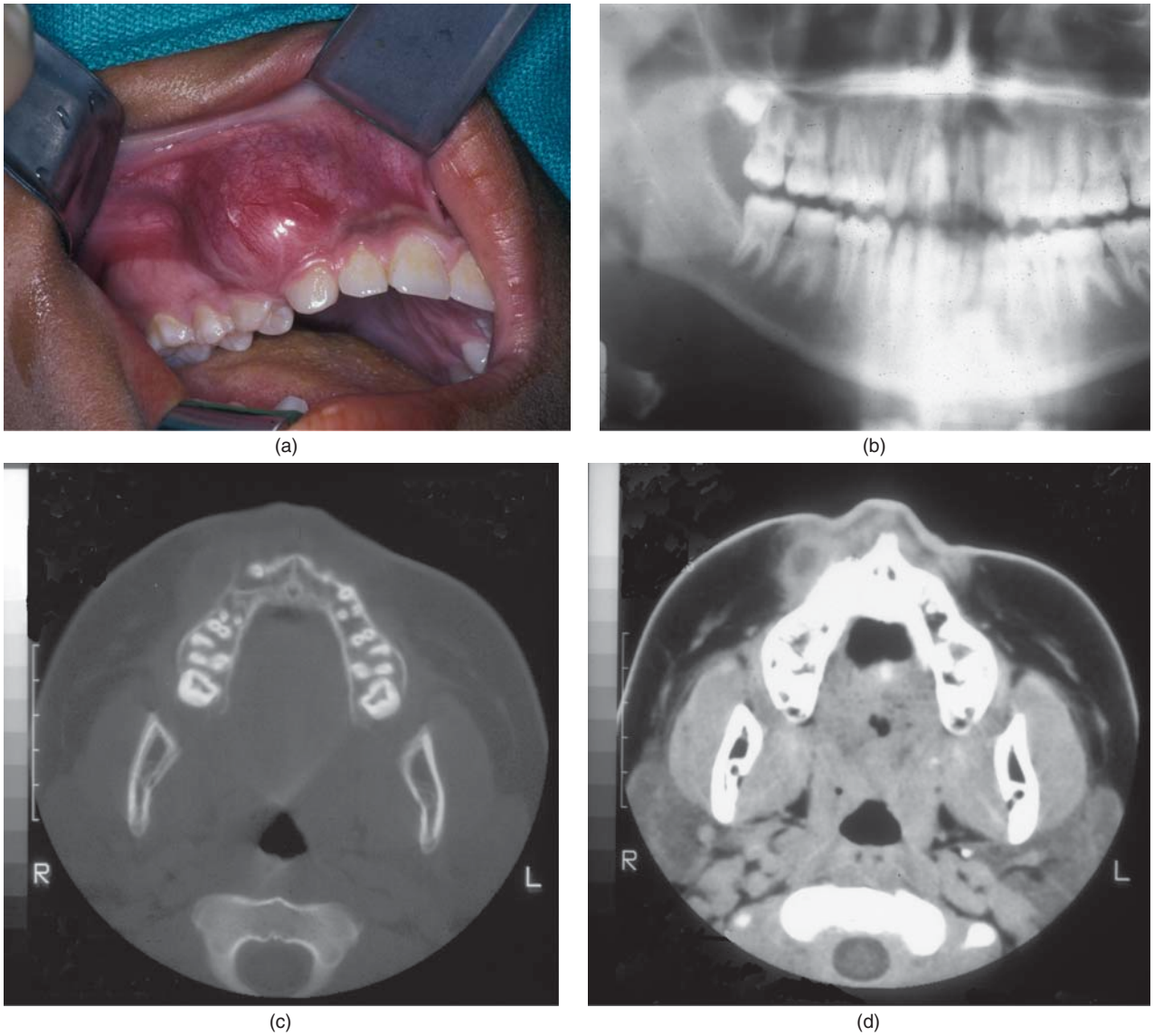
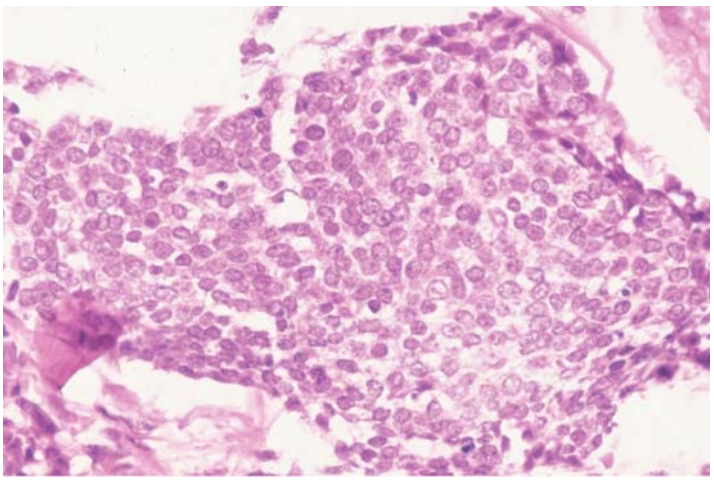


Figure 11.20. A mass of the right maxillary gingiva in a 12-year-old girl (a). Panoramic radiograph demonstrates alteration of the bone between the first premolar and canine teeth with divergence of the roots of these teeth (b). Computerized tomograms demonstrate a soft tissue mass with involvement of the maxillary bone (c, d). Incisional biopsy showed epithelial-myoepithelial carcinoma (e). A partial maxillectomy observing 1-cm linear margins in bone and soft tissue was performed (f). The specimen was able to be removed without tumor spillage (g, h). Final histopathology showed destruction of bone by the cancer (i). The specimen radiograph demonstrated acceptable bone margins in the specimen (j). The resultant ablative defect of the maxilla (k) was reconstructed with an immediate obturator device (l). The use of the obturator permitted contracture of the defect as noted at 1 month postoperatively (m). By 3 months postoperatively, the defect had demarcated significantly (n). An interim obturator was fabricated that allowed for better seal of the defect (o, p). The patient functioned well with a definitive obturator (q) until soft tissue reconstruction was planned with a buccal fat flap and advancement of the buccal mucosa (r, s, t). The appearance of the healed flap is noted at 1 year postoperatively (u).



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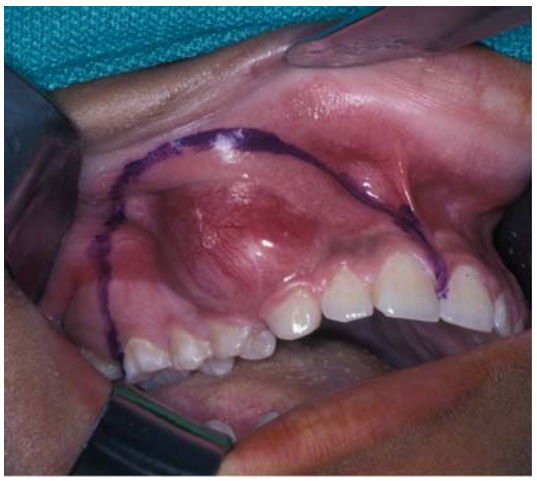

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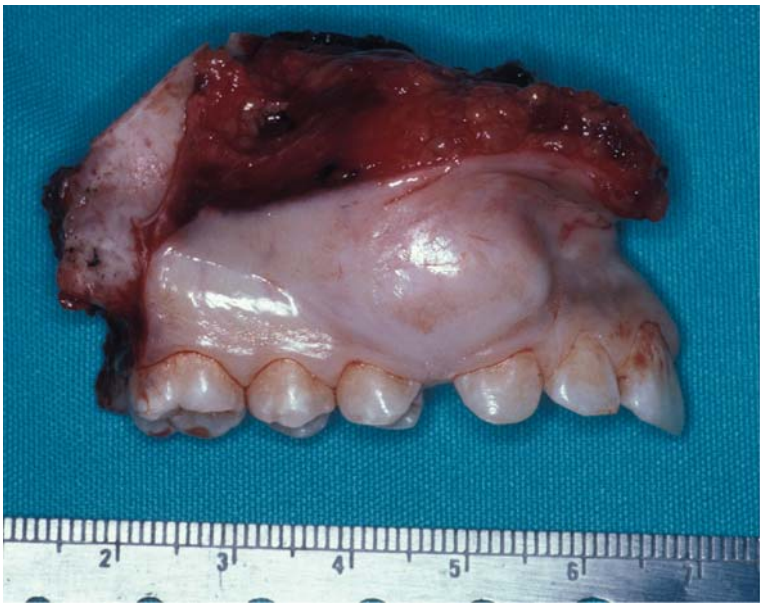

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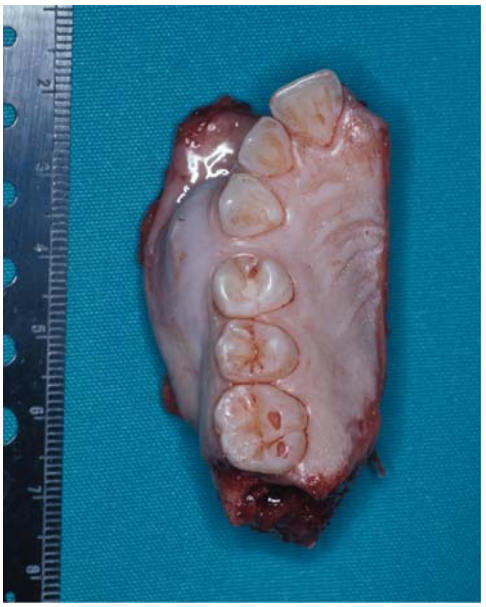

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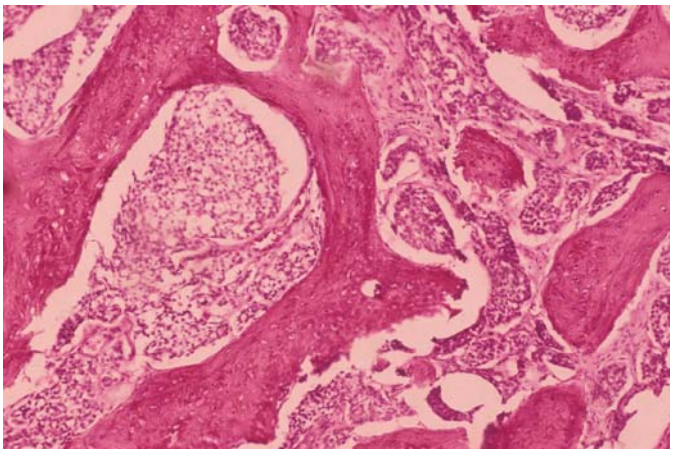

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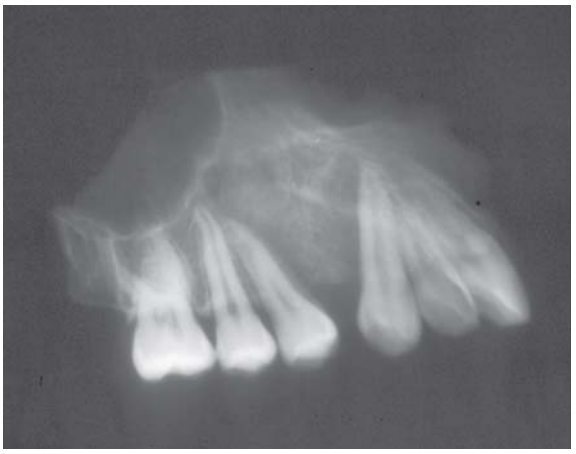

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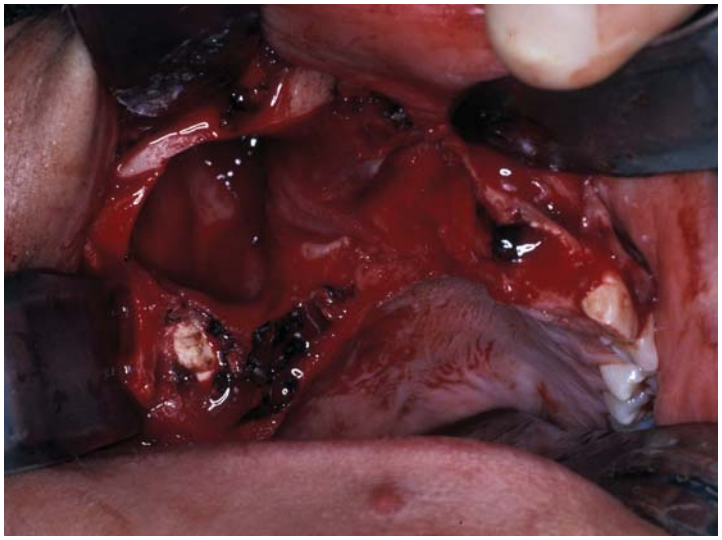

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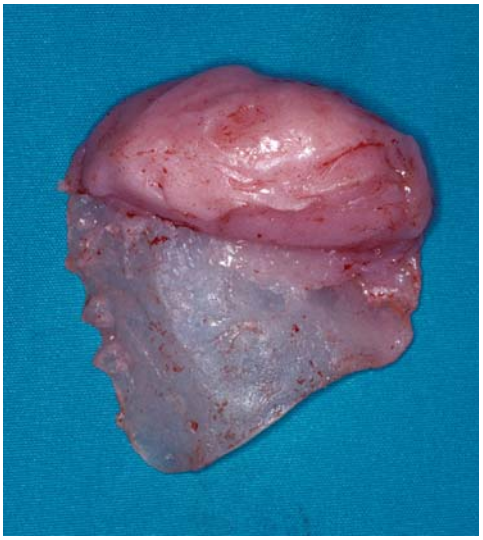

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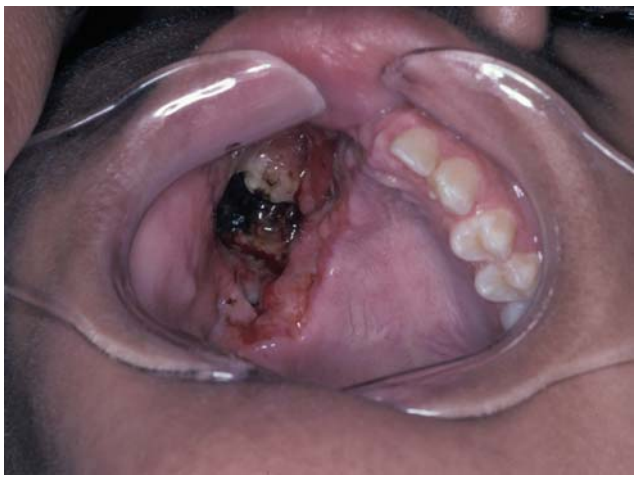

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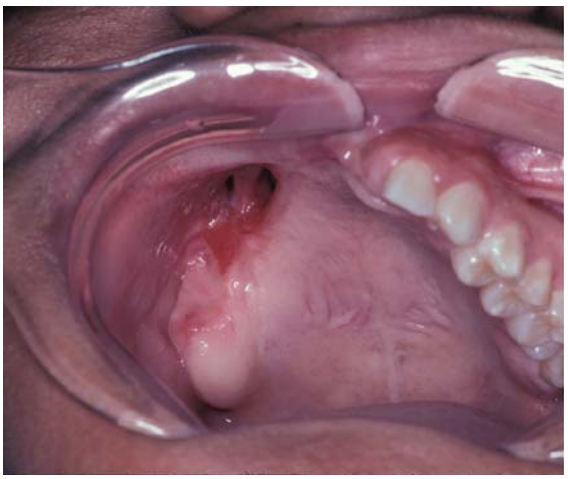

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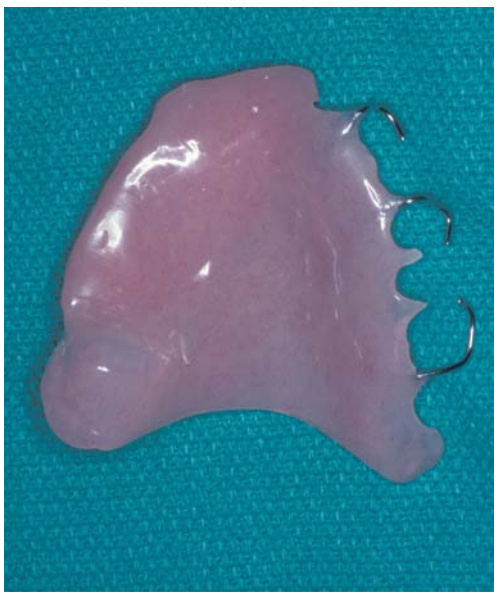

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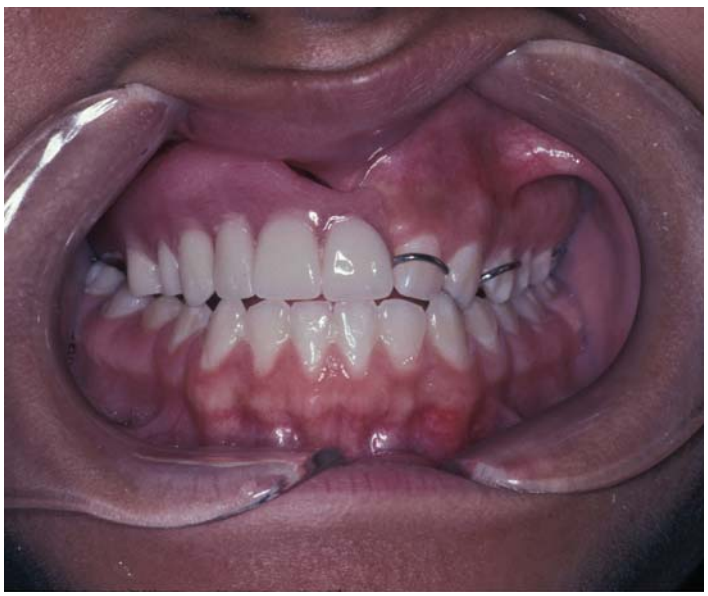

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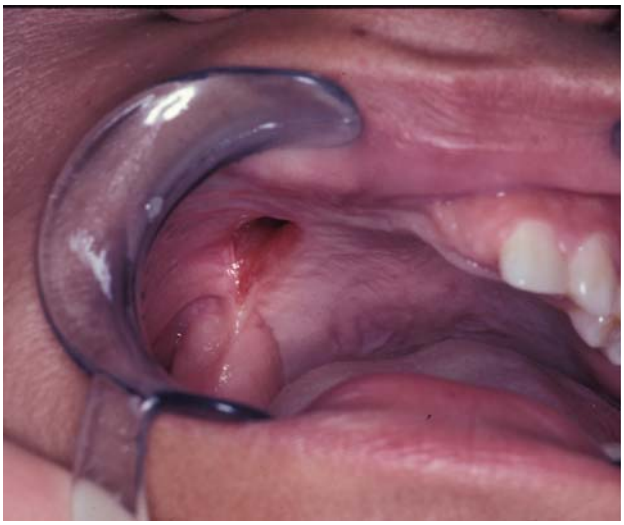

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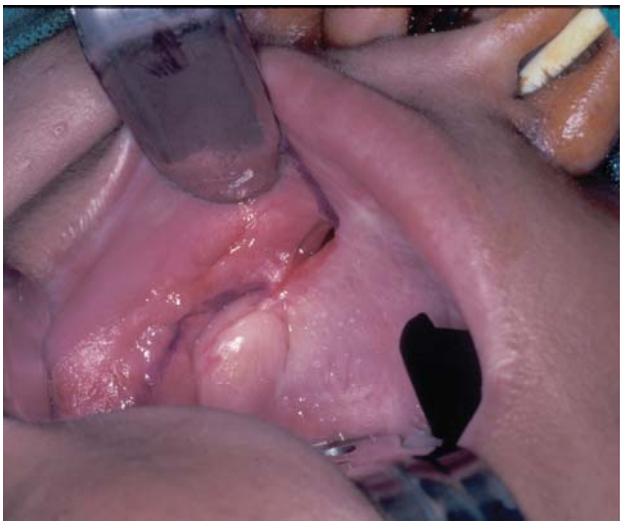

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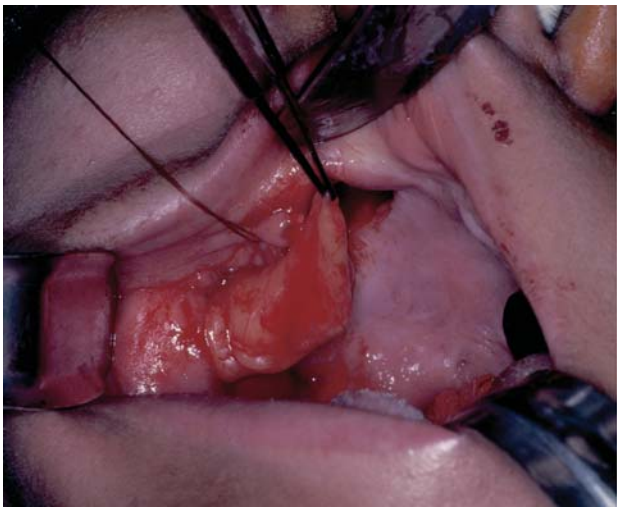

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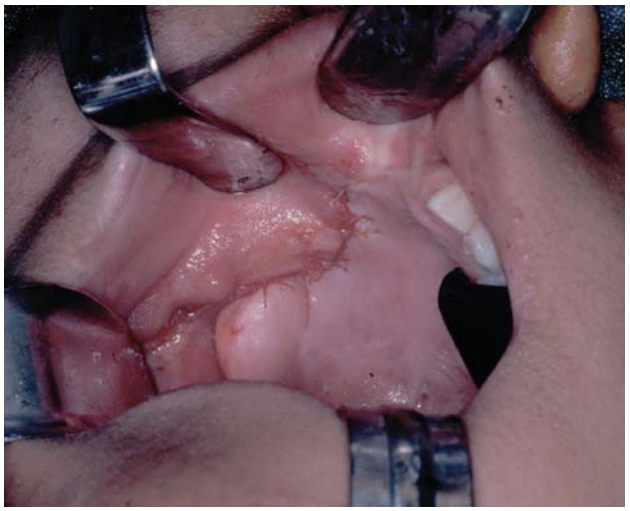

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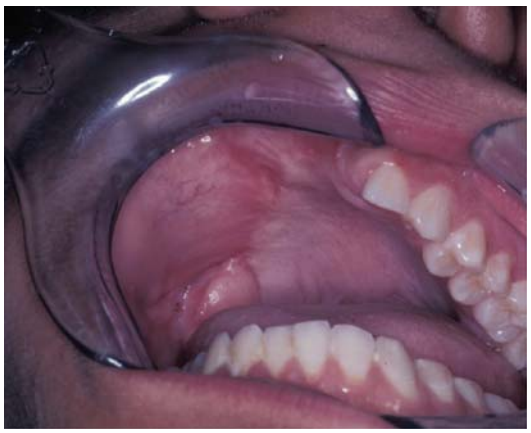

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Figure 11.20. (*Continued*)

therapy in 44 patients with salivary gland cancers, 34 of whom were treated for minor salivary gland cancers, examined the results of surgery versus surgery and postoperative radiation therapy in these patients (Shingaki, et al. 1992). Interestingly, no patients experienced recurrent disease when negative surgical margins were found in the specimen, regardless of whether surgery or surgery and postoperative radiation therapy was performed. All patients with positive surgical margins developed recurrent disease when surgery was the modality of treatment, and 8 of 15 patients (53%) with positive surgical margins developed recurrent disease when their salivary gland cancer was treated with a combination of surgery and postoperative radiation therapy. While not broken down to major versus minor salivary gland primary sites, these results do point to the significant benefit of obtaining negative margins in the resected specimen. The reader is directed to Chapter 12 for more details regarding the use of radiation therapy in the management of salivary gland tumors.

THE ROLE OF CHEMOTHERAPY IN THE MANAGEMENT OF MINOR SALIVARY GLAND MALIGNANCIES

There are few reports on the benefit of systemic chemotherapy in the management of salivary gland cancers. Chemotherapy is generally reserved for the palliative management of advanced, non-resectable disease where radiation therapy has already been administered. Most patients for whom chemotherapy is considered will have diagnoses of mucoepidermoid carcinoma, adenoid cystic carcinoma or high-grade adenocarcinoma (Laurie and Licitra 2006). The expression of c-kit in adenoid cystic carcinoma, overexpression of her-2 in mucoepidermoid carcinoma, overexpression of epithelial growth factor receptor in adenocarcinoma, and androgen receptor positivity in salivary duct carcinoma makes the use of imatinib, trastuzumab, cetuximab, and antiandrogen therapy, at least theoretically beneficial (Laurie and Licitra 2006). While these agents may be of value in treating difficult cases of minor salivary gland malignancies, there is a need to conduct high-quality clinical trials in patients with these cancers. The reader is directed to Chapter 13 for more details regarding the use of chemotherapy in salivary gland malignancies.

Summary

- Approximately 10% of all salivary gland tumors arise in the minor glands.
- Approximately 1% of head and neck tumors occur within the minor salivary glands, although some authors believe that this figure is somewhat higher.
- 70% of minor salivary gland tumors arise in the oral cavity.
- 50% of oral minor salivary gland tumors are found in the palate.
- 50% of oral minor salivary gland tumors are benign and 50% are malignant.
- Inconclusive evidence exists for cause and effect relationships with minor salivary gland tumors.
- An incisional biopsy is almost always indicated prior to definitive management of a palatal minor salivary gland tumor due to the near equal distribution of benign and malignant diagnoses.
- An excisional biopsy of a buccal mucosal or upper lip minor salivary gland tumor may be acceptable without first obtaining the histopathologic diagnosis provided signs of benign disease exist.
- Benign tumors of the palate, buccal mucosa, and upper lip may be excised without special imaging studies.
- When present, ulceration predicts a malignant diagnosis, although many minor salivary gland malignancies do not create ulceration of the oral mucosa.
- Pain is associated with perineural invasion, most commonly seen with adenoid cystic carcinoma.
- Malignant tumors of the palate should undergo special imaging studies so as to determine involvement of the palatal bone.
- Malignant tumors of the buccal mucosa and upper lip do not require imaging prior to ablative surgery.
- Surgery represents the primary treatment of minor salivary gland tumors.
- Surgical removal of minor salivary gland tumors requires a scientific approach to the surrounding anatomic barriers.
- High cure rates are anticipated following removal of pleomorphic adenomas and canalicular adenomas of minor salivary gland sites.

- High cure rates are anticipated following removal of low-grade mucoepidermoid carcinomas and polymorphous low-grade adenocarcinomas of minor salivary gland sites.
- Variable cure rates are associated with surgery for intermediate and high-grade mucoepidermoid carcinomas and adenoid cystic carcinomas of minor salivary glands.

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Chapter 12

Radiation Therapy for Salivary Gland Tumors

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Outline

Introduction

Tumors of the salivary glands represent an uncommon but complex challenge in the field of head and neck cancer. Salivary gland tumors account for only 3–5% of all head and neck cancers but comprise more than 30 morphologically distinct neoplasms with varying natural histories, treatment approaches and clinical outcomes. In the past these neoplasms were thought resistant to radiation therapy. However, over the past 10 years there have been dramatic improvements in radiation techniques and modern clinical trials show that salivary gland tumors are highly responsive to radiation therapy. A recent trial showed a 60% improvement in local control of salivary gland tumors after radiation therapy (Terhaard, et al. 2005). Other studies have confirmed this improvement in local control and documented a survival advantage for radiation therapy (Pohar, et al. 2005, Herman, et al. 2013).

Histology is the strongest predictor of clinical outcome in salivary gland tumors. The biology of the malignancy predicts its risk of spread to the nodes and nerves thus determining the optimal treatment approach. The wide variety of histologies found in salivary gland tumors gives a wide range of clinical outcomes. This has made it difficult to determine the optimal treatment approach in these rare tumors. Efforts to combine patients with different cell types give larger numbers of these rare tumors on trial but blur the risk of disease in patients and obscure the benefits of treatment. It is more useful to segregate salivary gland tumors by their inherent biology. This gives a better indication of the risk of spread, required treatment, and expected outcomes. Adenoid cystic carcinoma displays a unique growth pattern and requires a treatment approach quite distinct from the other histologies. Even though adenoid cystic carcinoma is the second most common malignancy it should not be combined with other cell types and will be addressed last in this chapter to highlight its different risk of spread and radiation therapy technique. The remaining salivary gland tumors can be divided into three risk groups based on their risk of local recurrence, nodal spread, and survival. This chapter will explore low-, moderate-, and high-risk groupings and discuss the variations in radiation technique required for each cohort.

Low risk salivary gland tumors include acinic cell carcinoma and pleomorphic adenomas, along with small, well differentiated mucoepidermoid carcinoma. These tumors have a low rate of local

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Low risk	Moderate risk	High risk
Well differentiated mucoepidermoid carcinoma	Well differentiated mucoepidermoid carcinoma with adverse features*	Poorly differentiated mucoepidermoid carcinoma
Acinic cell carcinoma	Moderately differentiated mucoepidermoid carcinoma	Undifferentiated carcinoma Adenocarcinoma Salivary duct carcinoma Squamous cell carcinoma
Pleomorphic adenoma	Carcinoma ex-pleomorphic adenoma	
	*Adverse features with moderate risk: Lymphovascular invasion, Perineuralinvasion, T3/T4 tumor, Margin positive, margin close (< 5mm)	*Adverse High Risk Features Facial nerve involvement Histologically node positive Unresectable disease

Figure 12.1. Salivary gland tumors can be divided into three risk groups based on histology, tumor size, and margin status.

Low RiskTumors	Moderate Risk Tumors	High Risk Tumors
Resect and Observe	Adjuvant Radiation Target Tumor Bed Radiation Dose 60Gy	Adjuvant Radiation Target Tumor Bed Radiation Dose 60-70Gy
	Consider Cervical Node I-III Radiation Dose 50-54Gy	Cervical Nodes Levels I-V Radiation Dose 50-60Gy

Figure 12.2. A basic treatment algorithm for salivary gland tumors based on risk grouping. Low risk tumors can often be observed. Moderate risk tumors benefit from adjuvant radiation to the operative bed. High risk salivary gland tumors require radiation therapy to the resection bed and regional lymph nodes.

recurrence and an exceeding low rate of nodal spread. As a result, local excision is curative and adjuvant radiation is not usually required. Moderate risk salivary gland tumors include large T3/T4 tumors and smaller mucoepidermoid carcinomas that are moderately differentiated or that contain lymphovascular space invasion or perineural invasion. Patients in the moderate risk group carry a low risk of nodal spread but a significant risk for local recurrence. They benefit from adjuvant radiation therapy to the surgical bed and may occasionally require treatment of the first level of regional nodes. High risk salivary gland tumors include poorly differentiated mucoepidermoid carcinoma, adenocarcinoma, salivary duct carcinoma, undifferentiated carcinoma, and the rare squamous cell carcinoma that is not the result of a cutaneous lesion spread to the parotid gland. These high risk patients frequently develop local recurrence and have a significant risk of occult spread to regional lymph nodes. Some studies have found that up to 50% of high risk patients are node positive at time of neck dissection (Regis De Brito Santos, et al. 2001). As a result, the best treatment for high risk salivary gland tumors is resection followed by adjuvant radiation to the surgical bed and ipsilateral lymph nodes. A description of these three risk groups of salivary gland tumors is shown in Figure 12.1. A treatment algorithm based on these three risk groups of salivary gland tumors is shown in Figure 12.2 and will be discussed throughout this chapter.

Radiation technique has improved over the past decade just as our understanding of salivary gland tumor biology has improved. In the past, classical radiation techniques used a large simple field to ensure coverage of the region of risk. This resulted in radiation to a large volume of normal tissue that limited the dose to tumor while causing toxicity to a large area. Improvements in radiation technique such as intensity modulated radiation therapy (IMRT) now results in better sparing of uninvolved normal tissue while at the same time increasing dose to the tumor and at risk nodes. This chapter will examine these improvements in radiation technique as they relate to salivary gland tumors and discuss the outcomes seen in modern studies of radiation therapy.

Low Risk Salivary Gland Malignancies

Acinic cell carcinoma and pleomorphic adenomas along with small, well differentiated mucoepidermoid carcinoma comprise a low risk category of salivary gland tumors (Figure 12.1). These tumors have a low rate of local recurrence and low rates of nodal involvement. They are often cured by surgical resection and do not normally require adjuvant radiation therapy.

Acinic cell carcinoma is a slowly growing low grade lesion that often affects the parotid gland. A recent SEER review found 1129 cases of acinic cell carcinoma in the US from 1973–2009 (Patel, et al. 2009). The tumor was more common in women who along with young patients (<45 yo) have a better prognosis. Male patients had a lower survival and patients with larger tumors (>3 cm) show a decrease in survival. Small (T1/ T2), low grade acinic cell carcinomas that are resected with negative margins can be observed after surgery with very low rates of local or nodal failure (Chen, et al. 2007). Not all acinic cell carcinomas are indolent, however. Perineural invasion, lymphovascular invasion, and extension beyond the parotid gland are all indications for postoperative radiation to the tumor bed. In addition, a review from the Mayo clinic found several cases of acinic cell carcinoma that recurred at the base of skull. These patients with skull base involvement had a poor prognosis marked by multiple recurrences often over a decade despite aggressive surgery and radiation (Breen, et al. 2012). Gomez showed that some poorly differentiated acinic cell tumors can behave like an undifferentiated carcinoma with spread to the lymph nodes and a poor prognosis (Gomez, et al. 2009). These rare high grade acinic cell carcinomas require aggressive adjuvant radiation like other high risk salivary gland tumors.

Pleomorphic adenoma is the most common benign salivary gland tumor. These tumors normally develop in the parotid gland but may arise in submandibular, sublingual, or minor salivary glands. Most pleomorphic adenomas are found in the parotid and the preferred treatment is superficial parotidectomy with facial nerve preservation. Local control remains excellent at around 95% and adjuvant radiation is not commonly required (O'Brien, 2003, Mendenhall, et al. 2008). Postoperative radiation is advised in the small subset of patients with positive margins or multifocal recurrences. Ravasz reported local control in 77 of 78 patients (99%) when tumor spillage or positive margins were treated with conventional radiation to a dose of 60–75 Gy (Ravasz, et al. 1990). Radiation can also be effective in the setting of recurrence pleomorphic adenoma. Chen reported on 34 patients at the University of California San Francisco with recurrent pleomorphic adenomas treated to a low median dose of 50 Gy (range 45–60 Gy) and still saw excellent results with local control in 94% of patients (Chen, et al. 2006b). Thus surgery is the mainstay of treatment for pleomorphic adenoma but adjuvant radiation improves outcomes in patients with positive margins or in patients who develop multinodular recurrence.

In summary, low risk salivary gland tumors represent a local threat. With adequate surgical resection these tumors show low rates of local recurrence or nodal spread and no adjuvant radiation therapy is required. Terhaard, et al. showed a local control rate as high as 95% at 5 years in low risk patients treated with surgery alone (Terhaard, et al. 2005). Another trial found only two patients with occult nodal disease out of 53 neck dissections (Armstrong, et al. 1992). As a result, low risk salivary gland tumors have an excellent prognosis with overall survival at 5 years of 97% and 10-year survival of 94% (Patel, et al. 2014).

Moderate Risk Salivary Gland Malignancies

Moderate risk salivary gland tumors include mucoepidermoid carcinoma with moderate differentiation or low grade tumors that contain either lymphovascular space invasion or perineural invasion (Figure 12.1). Larger tumors and tumors with bone involvement (Stage T3 or T4) also fall within the moderate risk group. Patients with positive margins or "close margins" can also be placed in the moderate risk group. These moderate risk salivary gland tumors have a significant risk of local recurrence and benefit from adjuvant radiation therapy to the postoperative tumor bed.

Surgery is the primary treatment for salivary gland tumors. Patients with gross residual disease should be considered for re-resection at a high volume center. If additional surgery is not possible then patients benefit from radiation therapy targeting the region of gross residual disease to 70

Gy. A clear dose response has been seen in these patients. Salivary gland tumors with microscopically positive margins should also be evaluated for additional surgery. If not completely resected, then microscopic residual disease is recommended to a radiation dose of 60–66 Gy. Patients with close resection margins (<5 mm) also have increased rates of local recurrence. As a result, close margin is an adverse risk factor that can place a patient in the moderate risk category. One study found 55% recurrence in close margin patients with surgery alone but control in 95% of patients after adjuvant radiation (Terhaard, et al. 2005).

The biology of the salivary gland tumor predicts its rate of local recurrence and hence benefit from radiation therapy. Salivary gland tumors that demonstrate lymphovascular space invasion or perineural invasion have a higher tendency for microscopic spread. As a result these two characteristics are adverse features that may cause a tumor to fall within the moderate risk category. In a large study of more than 500 patients, 10-year tumor control in salivary gland tumors with perineural invasion was only 60% after surgery alone but increased to 88% with adjuvant radiation (Terhaard, et al. 2005). The size of a tumor also indicates the risk of subclinical disease and the benefit for adjuvant radiation therapy. A review of patients at UCSF showed that T1/T2 salivary gland tumors showed good local control at 10 years with 81% controlled by surgery alone. However, T3 or T4 tumors had a higher recurrence rate with a local control at 10 years of only 39% (Chen, et al. 2006a). Bone invasion also significantly increases the recurrence risk following surgery. The Dutch Head and Neck Oncology Cooperative Group found local control of only 54% with surgery alone in the presence of bone invasion with adjuvant radiation improving outcome to a local control of 86% (Terhaard, et al. 2005). As a result, most authors place T3 and T4 tumors in a moderate risk group that requires adjuvant radiation.

Location of the salivary gland tumor is a matter of debate in its risk for tumor recurrence and hence benefit from radiation. Some authors recommend adjuvant radiation for all submandibular gland tumors and for all salivary gland tumors involving the minor glands. However, the location of a salivary gland tumor may not be as significant a predictor for risk of recurrence as was once thought. A recent SEER review of 2667 patients with minor salivary gland tumors showed that biology of the tumor was most predictive of risk (Lloyd, et al. 2010). A predictive index was identified based on male sex, T3/T4 tumors, and pharyngeal site of tumor but the most predictive factor was high risk histology. Minor salivary gland tumors with only one of these factors showed node involvement in only 2% of patients. Patients with three of these risk factors showed 41% node positivity and patients with all four risk factors developed nodal disease in 70% of cases (Lloyd, et al. 2010).

Researchers in the Netherland have carefully examined risk factors associated with salivary gland tumors and developed a simple predictive treatment algorithm (Al-Mamgani, et al. 2012). Patients with incomplete or close resection margins, perineural invasion, and T3–4 tumors are treated with adjuvant radiation. The risk of nodal recurrence is assigned based on points given for T-stage, histology, and location of tumor. Patients with a low score (T1 acinic cell carcinoma of the parotid gland) show recurrence rates after surgery alone of less than 5%. Salivary gland tumors with a moderate score (T2 mucoepidermoid carcinoma of the oral cavity or parotid) carry a 12–33% risk or nodal recurrence and benefit from adjuvant radiation to the resection bed along with cervical node levels I-III. Patients with four or five risk factors show high recurrence rates of 50–60% and require comprehensive radiation to the tumor bed and neck nodes. In a trial of 186 patients no patient developed a local recurrence following the Dutch treatment guidelines and the cause specific survival was an impressive 80% (Al-Mamgani, et al. 2012).

High Risk Salivary Gland Malignancies

Patients with salivary gland tumors are placed in the high risk group based on histology, involvement of the facial nerve, bulky clinically positive neck disease, or unresectable disease. High risk salivary gland tumors include aggressive histologies such as adenocarcinoma, undifferentiated carcinoma, high-grade mucoepidermoid carcinoma, salivary duct carcinoma, and squamous cell carcinoma (Figure 12.1). These tumors frequently develop microscopic invasion beyond the salivary gland and unfortunately have a tendency to spread to the regional nodes even at an early stage. Patients with

these histologies demonstrate frequent local recurrence even after optimal surgical resection and commonly show occult nodal disease in the setting of a clinically and radiographically negative neck.

Many reports have found frequent involvement of the cervical nodes in patients with high risk histologies. Classic studies at Memorial Sloan-Kettering showed occult nodal disease in 18% of adenocarcinomas, in 14% of high-grade mucoepidermoid carcinomas, and in as many as 41% of squamous cell carcinomas (Armstrong, et al. 1992). Lau, et al. reported on patients with clinically negative necks treated between 1999–2013 with elective node dissection and found 35% node positivity in adenocarcinoma and poorly differentiated mucoepidermoid carcinoma with cervical neck levels II and III most frequently involved (Lau, et al. 2013). Other studies of high risk patients demonstrate node involvement at time of neck dissection in more than 50% of cases (Regis De Brito Santos, et al. 2001, Stennert, et al. 2003). Salivary gland tumors with both high-risk histology and T3 or T4 stage are found to be node positive in 76% of neck dissections. Despite these high rates of nodal spread in high-risk patients, salivary gland tumors remain almost exclusively a unilateral disease. Rates of involvement on the contralateral cervical nodes are extremely rare. A review of 251 salivary gland tumors found no instances of contralateral neck failures (Chen, et al. 2007) and another study from MSK found that treatment for the opposite neck was unnecessary (Harrison, et al. 1990). As a result, patients with high risk tumors are commonly treated by surgical resection of the primary tumor along with an ipsilateral neck dissection followed by adjuvant radiation.

The treatment of the clinically negative neck in high risk patients has become controversial. Despite neck dissection, high risk patients continue to develop recurrences. An older review of patients at MSK showed that resection alone yielded a local control of only 17% in high risk patients (Armstrong, et al. 1990). Adjuvant radiation to the tumor bed and ipsilateral neck decreases local recurrence and increases survival in high risk salivary gland tumors, and some authors now suggest that radiation alone can control clinically negative occult nodal disease in these patients. A review of patients at the University of California San Francisco showed that adjuvant radiation controlled high risk salivary gland tumors without the need for neck dissection. This group of high risk histologies showed perineural invasion in 74% of patients and had a 56% rate of margin positivity. In these patients elective nodal irradiation in place of neck dissection showed no nodal failures in more than 250 treated patients and gave a 5-year survival rate of 81% (Chen, et al. 2007). Herman, et al. examined elective node dissection compared with elective nodal irradiation at the University of Florida. In their study all patients underwent resection of the primary tumor followed by post-operative radiation. Clinically N0 patients treated with elective node dissection showed a 10% recurrence in the neck at 5 years with no neck recurrences in the group treated with elective neck irradiation (ENI). The resulting cause-specific survival in patients with neck dissection was 84% compared with 94% in the ENI group leading the authors to conclude that high risk patients do not benefit from a planned neck dissection (Herman, et al. 2013).

There may be controversy associated with the optimal treatment of clinically node negative patients, but patients with bulky or unresectable salivary gland tumors clearly benefit from comprehensive neck dissection and adjuvant radiation therapy. A review from UCSF examined this treatment approach in high risk patients. Salivary gland tumor patients who were medically inoperable, who refused surgery or those who were deemed inoperable due to the location and extensiveness of the primary tumor were treated with definitive radiation. A clear dose response was seen in these high risk patients. Those treated with radiation to a total dose of less than 66 Gy had a local control at 5 and 10 years of 53% and 40%. If, however, unresectable salivary gland tumors were treated with modern radiation technique to more than 66 Gy, then the resulting local control at 5 years was 92% and control at 10 years remained high at 81% (Chen, et al. 2006b).

Thus, surgery and adjuvant radiation benefit unresectable salivary gland tumors and this approach is also favored when the facial nerve is involved by parotid tumors. Involvement of the facial nerve remains one of the worst prognostic factors in salivary gland tumors. A review of patients at Johns Hopkins treated by surgery and adjuvant radiation showed an overall local control at 10 years of 90% with an overall survival at 5 years of 74%. However, if patients presented with facial nerve paresis then control was poor with local control in only 50% and a dismal 5-year

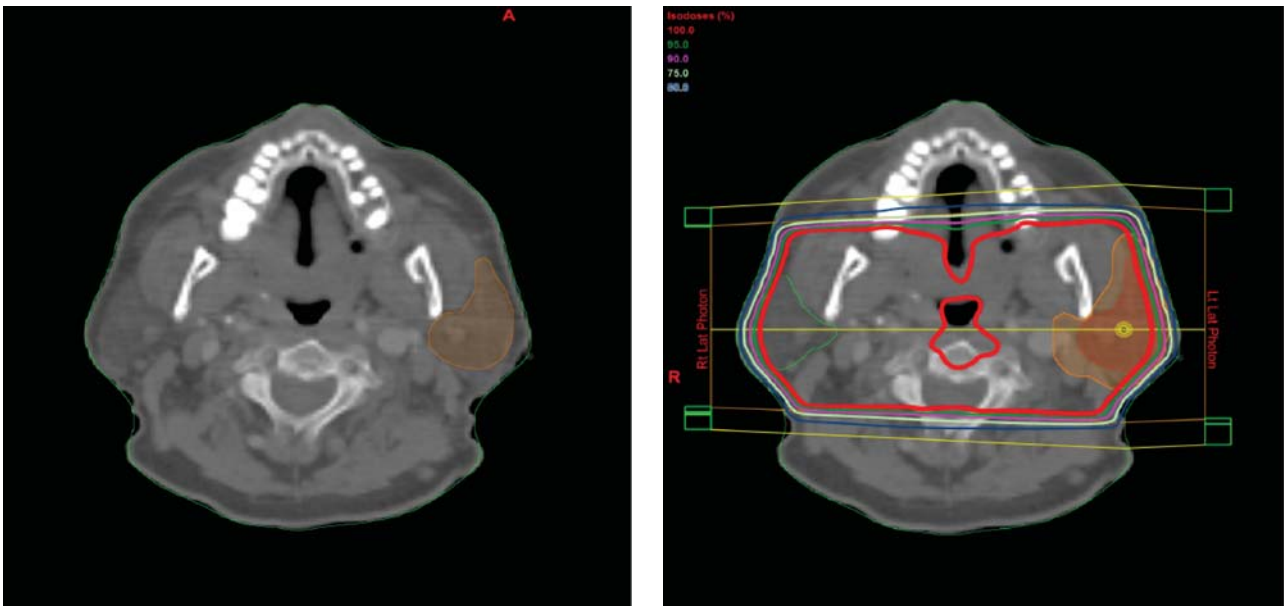
survival rate at less than 10% (North, et al. 1990). As a result, patients presenting with facial nerve palsy are recommended for en bloc resection with sacrifice of the seventh nerve and then require high dose adjuvant radiation.

The outcomes for patients with high risk salivary gland tumors are increasing. The previously mentioned studies show that these tumors are sensitive to radiation and with optimal surgical care and carefully delivered radiotherapy local control even in high risk patients is excellent. Unfortunately, these patients still suffer from distant metastatic disease and the overall survival has not kept pace with local control. This argues for concurrent chemotherapy along with radiation or adjuvant chemotherapy in high risk patients. This combined chemo-radiation approach is a standard of care in other head and neck cancers and is the clear trend in treatment for lung and GI malignancies. The current RTOG 1008 trial is addressing concurrent chemotherapy in high risk salivary gland tumors. Patients with high grade mucoepidermoid, adenocarcinoma, salivary duct carcinoma, and high-grade adenoid cystic carcinoma are being randomized to surgery followed by IMRT to 60–66 Gy in a control arm and IMRT with concurrent weekly cisplatin in the experimental arm. The results of this trial are anticipated to show a further benefit in local control and hopefully will translate into a survival benefit for high risk salivary gland patients.

Evolution of Radiation Techniques in Salivary Gland Malignancies

Over the past 10 years, there have been dramatic improvements in radiation therapy for salivary gland tumors. Early radiation techniques were limited to a few treatment portals and simple dose calculation. These early treatments also suffered from a relatively large uncertainty in daily patient setup on the radiation machines. As a result, treatment was delivered to the salivary gland tumor and a large amount of the surrounding normal tissues. This approach limited the dose of radiation that could be safely delivered and resulted in poor tumor control. At the same time the large volume of irradiated normal tissue caused frequent acute and late toxicity.

Some of the earliest radiation treatment for salivary gland tumors was delivered with two opposed lateral photon beams. This resulted in a square or rectangular box of radiation that was delivered to the salivary gland tumor and also to the



(a) (b)

Figure 12.3. Axial images of a patient with mucoepidermoid carcinoma of the left parotid gland are shown in panel (a). The parotid gland is contoured as a clinical treatment volume (CTV) and shown in orange. Part (b) shows a simple radiation treatment targeting the CTV with two opposed lateral beams. The target region is covered with full dose but the contralateral parotid and oropharynx receive full dose.

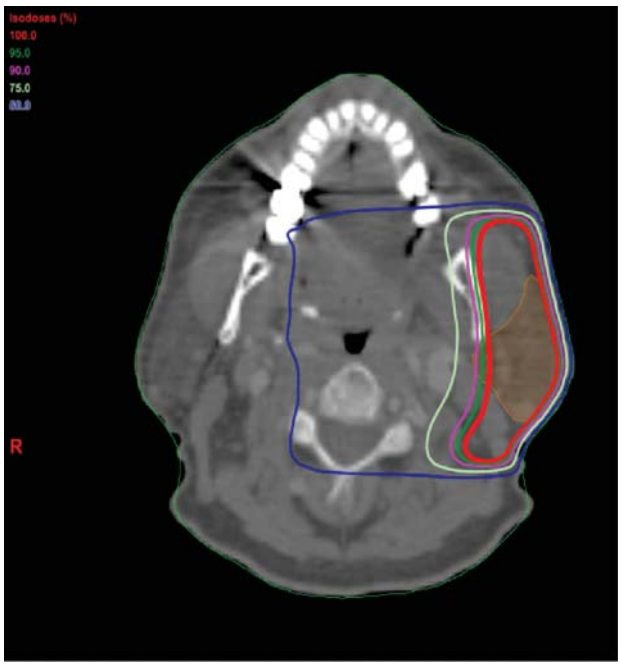


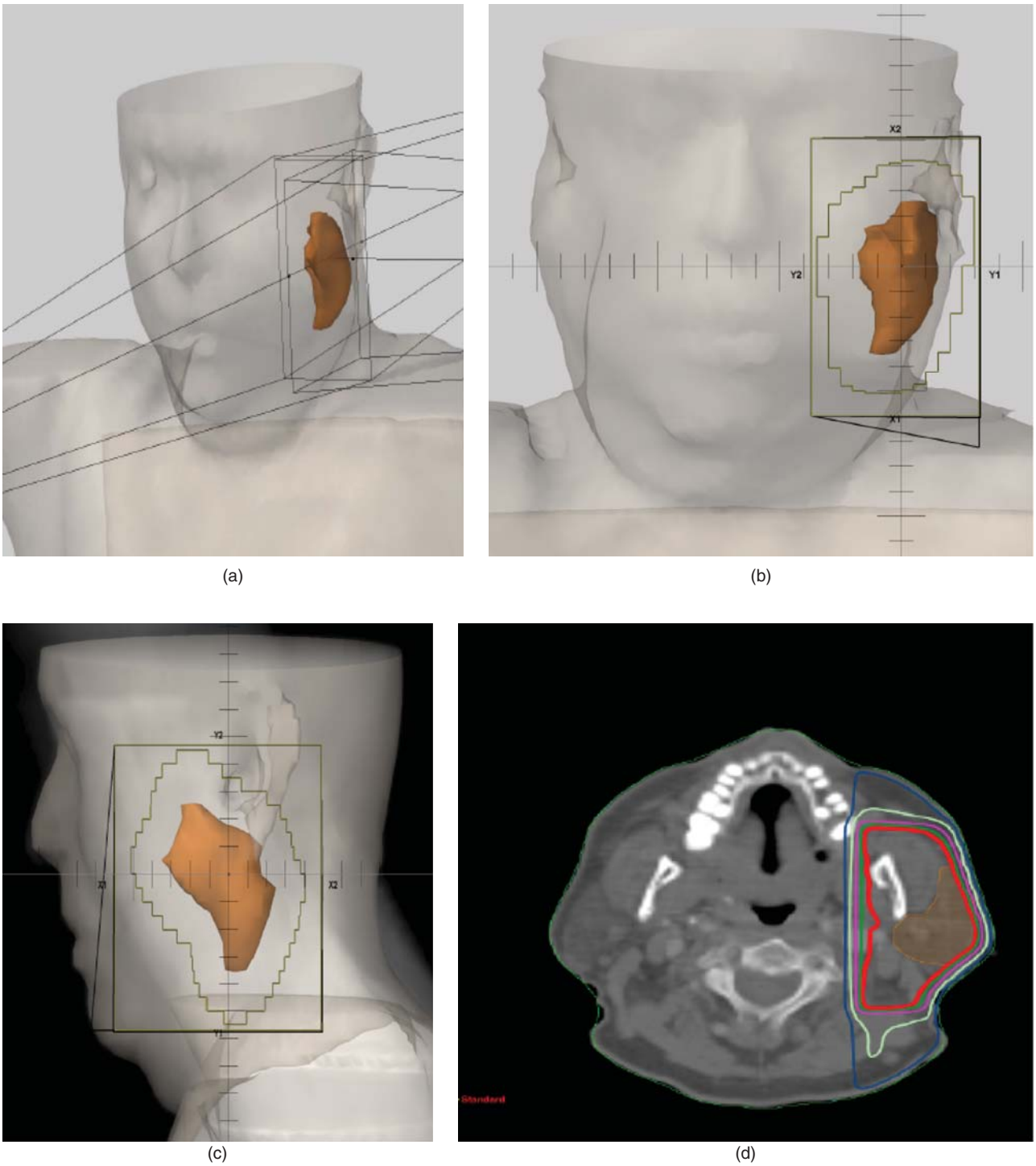
Figure 12.4. A mixed beam of photon and electron energy can be used to treat salivary gland tumors. Here, the Clinical Target Volume (CTV) is shown in orange. A combined photon-electron radiation plan targets the CTV while providing some protection to the oropharynx and contralateral parotid gland. The radiation prescription dose is shown in red. The 95% isodose line is shown in dark green. The 90% isodose line is shown in purple. The 75% isodose line is shown in light green. The 50% isodose line is shown in blue.

uninvolved side of the patient (Figure 12.3). This technique covered the target region but resulted in severe skin erythema and oral mucositis and led to high rates of xerostomia. As radiation treatment machines improved, simple opposed lateral fields were abandoned and replaced by radiation treatment using a mixture of photons and electrons. Photons of radiation provide deep penetration of energy to cover the deep lobe of the parotid gland and lymph nodes. Electron radiation therapy delivers a superficial dose of energy that provides good coverage for the skin and superficial parotid gland. A combination of photons and electrons allowed the radiation oncologist to tailor treatment to the target depth of individual patients. Superficial tumors were treated with a greater proportion of electron beams while deeper tumor sites or larger patients were treated with a greater percentage of photon energy. This photon-electron technique was one of the first attempts at conformal radiation for salivary gland tumor radiation therapy (Figure 12.4).

Photon-electron therapy was effective in targeting the salivary tumor bed but it was limited to relatively simple fields and was often not capable of dealing with the complex geometry of many head and neck cancer patients. This led to the development of computer generated three dimensional conformal radiation therapies (3-D conformal radiation). In this approach a radiation target was defined on a planning CT scan and then radiation portals were generated using different angles and energies of photon radiation to cover the area of risk with dose (Figure 12.5). This 3-D conformal radiation therapy provided adequate coverage of head and neck anatomy and became a common method for treating salivary gland tumors.

Improvements in computer planning and radiation treatment machine design allowed 3-D conformal radiation planning to develop into modern intensity modulated radiation therapy (IMRT) the current standard of care for patients with head and neck cancer. IMRT focuses many beams of radiation onto the tumor target. A computer generated plan then modulates the dose of energy that is delivered by each beam in order to provide the maximal coverage of the tumor while protecting the surrounding normal tissues. In this approach typically between five and nine beams are focused on the patient (Figure 12.6). Typically each radiation portal in an IMRT treatment plan is shaped by a multi-leaf collimator (MLC). This device contains several small strips or leaves of metal that block a portion of the radiation beam to allow differential dose delivery (Figure 12.7). At a given angle, some of the MLC leaves will deploy to block energy from a critical structure such as the mandible. At another angle the MLC leaves retract to allow dose to be delivered to the tumor. The resulting IMRT plan generates a highly conformal radiation treatment to the areas at risk while protecting the uninvolved salivary glands, oral cavity, mandible, and spinal cord. This modern IMRT approach has become the standard method for treating salivary gland tumors (Figure 12.8).

IMRT allows delivery of a high dose of radiation to salivary gland tumors and regional neck nodes. The improved normal tissue sparing of this technique dramatically reduces acute and late radiation toxicity. Consequently, radiation therapy



(a) (b)

(c) (d)

Figure 12.5. A 3-D conformal radiation treatment plan was generated using three beams of radiation each targeting the left parotid gland from a different angle (a–c). Radiation blocks are used to protect surrounding normal tissue from radiation damage. The anterior beam is shown in (b). The left lateral beam is shown in (c). The 3-D conformal radiation plan provides better coverage of the parotid gland as shown in (d). Here, the CTV is shown in orange. The radiation prescription dose is shown in red. The 95% isodose line is shown in dark green. The 90% isodose line is shown in purple. The 75% isodose line is shown in light green. The 50% isodose line is shown in blue.

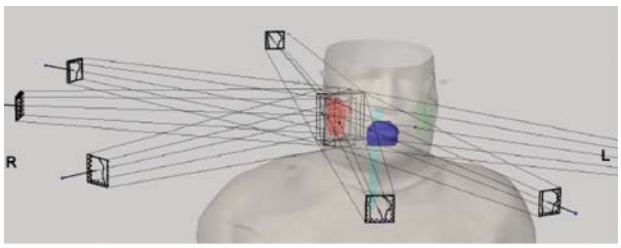


Figure 12.6. Intensity modulated radiation therapy (IMRT) targets the salivary gland tumor from multiple directions. This approach allows radiation to focus on the tumor site while protecting normal tissues from injury.

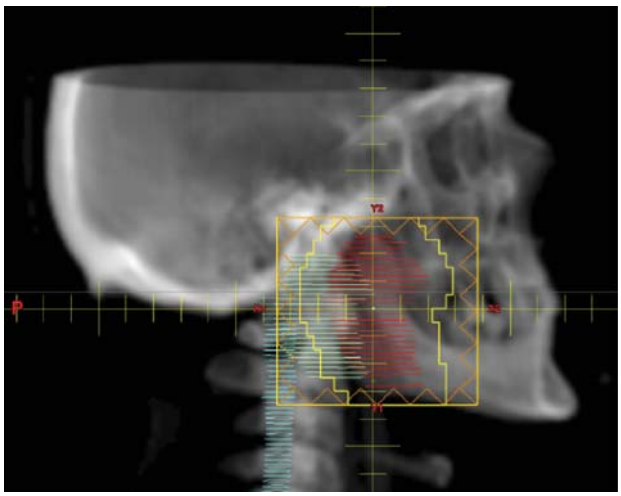


Figure 12.7. A multi-leaf collimator (MLC) is shown. Each individual leaf can be inserted into or removed from the beam of energy to modulate the radiation dose. This allows precise coverage of the salivary gland tumor and areas at risk for microscopic disease while protecting the surrounding normal tissues.

to higher doses can now be safely delivered and a clear dose response has been seen in salivary gland tumors. A recent trial at UCSF showed that salivary tumors treated to less than 66 Gy showed a local control at 5 and 10 years of 53 and 40%, respectively. However, if salivary gland tumors were treated to doses above 66 Gy, then local control at 5 years was 92% and control at 10 years remained at 81% (Chen, et al. 2006b).

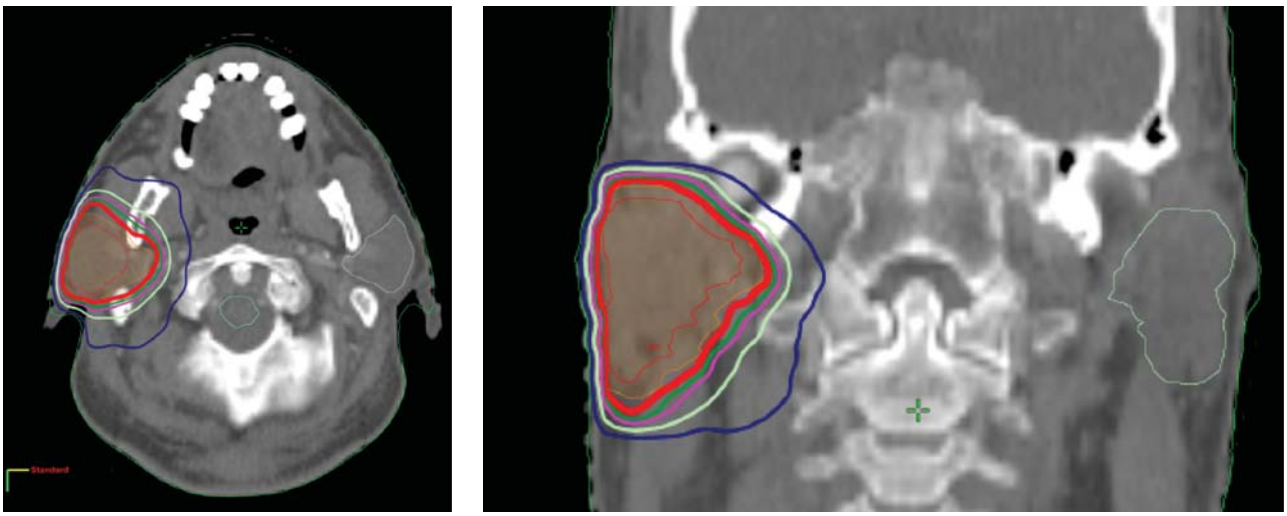
In addition to improved tumor control IMRT also results in lower rates of xerostomia and osteoradionecrosis. Studies have found that salivary glands are exquisitely sensitive to radiation. Mild xerostomia begins to develop in patients during the second or third week of radiation therapy. Xerostomia worsens as radiation therapy progresses and can become a severe, permanent, adverse effect to treatment if excessive dose is delivered to the uninvolved parotid glands. Long term xerostomia causes a dramatic decline in patient quality of life and can result in osteoradionecrosis. Clinical experience with opposed lateral fields and early 3-D conformal radiation found high rates of late effect toxicity.

Careful review of radiation treatment plans revealed a threshold for parotid gland damage from radiation. In patients where the mean parotid radiation dose was less than 26 Gy rates of xerostomia were significantly reduced. Recent studies of IMRT for head and neck cancer find that long term xerostomia is now uncommon. A review from the University of California Los Angeles looked at 158 patients with head and neck cancer treated with IMRT and found long term xerostomia in only 17% of patients. None of the patients in this study developed osteoradionecrosis (Duarte, et al. 2014). Another trial of patients treated with IMRT to doses of 65–70 Gy followed patients for 34 months and saw no cases of osteoradionecrosis in 176 treated patients (Ben-David, et al. 2007).

Radiation Technique for Low and Moderate Risk Salivary Gland Tumors

The improvements in radiation technique that we have discussed now allow adjuvant radiation to be both well tolerated and effective in treating salivary gland tumors. Patients with low risk salivary gland tumors, such as acinic cell carcinoma or small, low grade mucoepidermoid carcinoma, are often surgically cured when resected with adequate margins. These low risk patients have only a slight risk of local recurrence and adjuvant radiation is not usually required. However, in the presence of a positive margin or multi-nodular recurrence of a pleomorphic adenoma low grade tumors should be treated with radiation focused on the operative bed as shown in Figure 12.9.

Moderate risk patients carry a significant risk of local recurrence within the resection bed even after the best surgical management. As a result, adjuvant radiation to the tumor bed improves local control (Figure 12.2). A typical radiation treatment



(a) (b)

Figure 12.8. (a and b) An IMRT treatment plan is shown targeting the parotid gland and tissue at high risk of microscopic tumor involvement. The full dose of radiation is focused around the target region with rapid dose fall off protecting the surrounding normal tissues. Here, the Clinical Treatment Volume (CTV) is shown in orange. The radiation prescription dose is shown in red. The 95% isodose line is shown in dark green. The 90% isodose line is shown in purple. The 75% isodose line is shown in light green. The 50% isodose line is shown in blue.

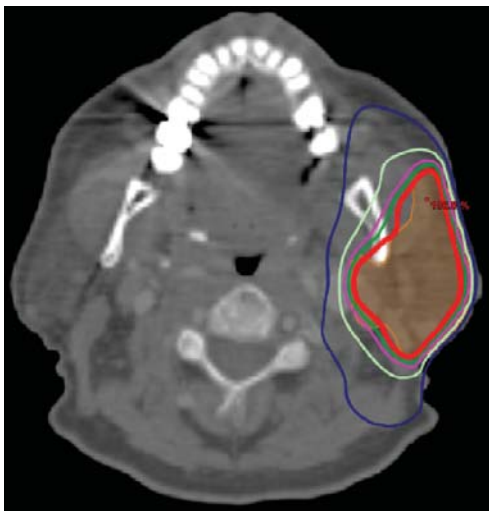
for a moderate risk patient begins by contouring the tumor or resection bed on a post-operative CT scan and defining this region as the clinical treatment volume (CTV). This CTV region accounts for the pre-operative tumor location and may extends for one to two centimeters to account for microscopic residual disease. A typical moderate risk parotid gland tumor CTV is shown in Figure 12.9. The CTV is then expanded by 3–5 mm to account for patient setup error and defined as the planning target volume (PTV). An IMRT plan is generated to cover the PTV while limiting dose to the contralateral parotid gland, mandible, oropharynx, oral cavity, and spinal cord. The PTV in a moderate risk patient is typically treated with daily radiation therapy over a period of 6 weeks to a dose of 50–60 Gy. Patients with close or involved margins may be treated to a slightly higher dose of 60–66 Gy.

Some patients with moderate risk salivary gland tumors harbor a risk of involvement of the first level of draining lymph nodes. They should be treated to the tumor bed along with cervical neck levels IB, II, and III. The following patient presented with a 2-cm moderately differentiated tumor of the right parotid gland. The margin was negative but close at only 3 mm and the tumor contained lymphovascular space invasion. The patient was treated with IMRT to the resection bed along with cervical neck levels II and III at 2 Gy per fraction to 50 Gy. The tumor bed was boosted to a final dose of 60 Gy. The isodose curves and a dose volume histogram are shown in Figure 12.10. The patient tolerated the treatment well developing mild sore throat and dysphagia during the last 2 weeks of radiation and quickly recovered full swallow function with no evidence of significant xerostomia or other complications.

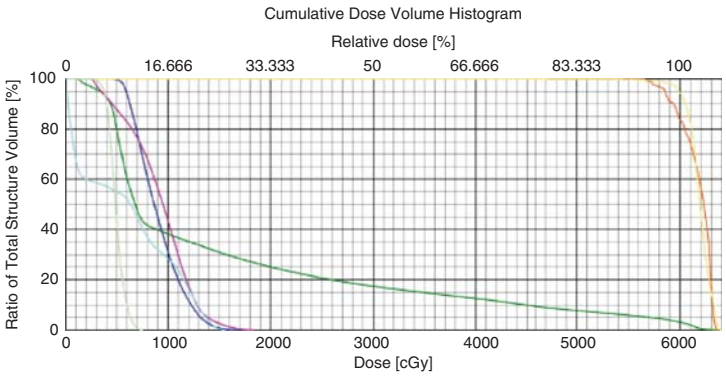
Radiation Technique for High Risk Salivary Gland Tumors

Radiation therapy has an even greater role in high risk salivary gland patients. High risk patients are commonly node negative on physical exam and by radiographic studies but these patients harbor high rates of occult spread to the regional lymph nodes. These tumors unfortunately carry a high risk of local recurrence even after optimal resection. As a result, adjuvant radiation decreases local and regional recurrence and dramatically improves survival in high risk salivary gland tumors. A treatment algorithm for high risk salivary gland tumors is shown in Figure 12.2.

After surgical resection, high risk patients are simulated for radiation therapy using a standard



(a)



(b)

Figure 12.9. A typical IMRT plan is shown for the treatment of a low or moderate risk salivary gland tumor. The operative bed in moderate risk tumors carries a significant risk of residual disease. In this case the parotid gland with expansion into the surrounding tissues is contoured as a Clinical Treatment Volume (CTV). (a) Radiation beams are focused on the CTV and the dose is modulated from each beam in order to cover the target region while minimizing dose to uninvolved tissues. The axial view of the isodose coverage is shown. (b) A dose volume histogram is also included indicating full coverage of the target CTV and PTV shown in orange and yellow, respectively. The dose to normal tissues is as follows: contralateral parotid in light green, spinal cord in cyan, mandible in dark green, oral cavity in dark blue, and oropharynx in purple.

immobilization device. The resection bed is then defined as a high risk clinical treatment volume (CTV). The ipsilateral regional lymph nodes are then defined as a low risk CTV. A typical radiation treatment would deliver 50 Gy to the ipsilateral cervical nodes in level IB, II, and III. The tumor bed would then be boosted with an additional 10 Gy to a total dose of 60 Gy. Alternatively, the clinically negative nodal regions may be treated at 1.8 Gy per fraction to a dose of 54 Gy, while the higher risk CTV comprised by the resection bed is treated at 2 Gy per fraction to 60 Gy. A representative plan of radiation treatment for a patient with a clinically node negative high risk salivary gland tumor is shown in Figure 12.11.

Patients with bulky or unresectable salivary gland tumors present the hardest challenge for radiation therapy. The following patient presented with a large, poorly differentiated adenocarcinoma of the submandibular gland. At presentation, multiple ipsilateral level II and III lymph nodes were enlarged and hypermetabolic on PET imaging. Given multiple medical comorbidities the patient was felt medically inoperable and was treated with definitive radiation. The tumor and cervical node levels I–V were treated with IMRT to 50 Gy (Figure 12.12). The tumor and enlarged nodes were treated to 60 Gy. The primary tumor itself was then boosted to a total dose of 70 Gy. The patient was able to return to a soft diet after 2 months and was maintaining her weight with a normal diet after 3 months. Her local tumor was controlled at 1 year but she unfortunately developed lung metastasis.

ADENOID CYSTIC CARCINOMA

Adenoid cystic carcinoma (ACC) is an unusual tumor with a distinct natural history, route of

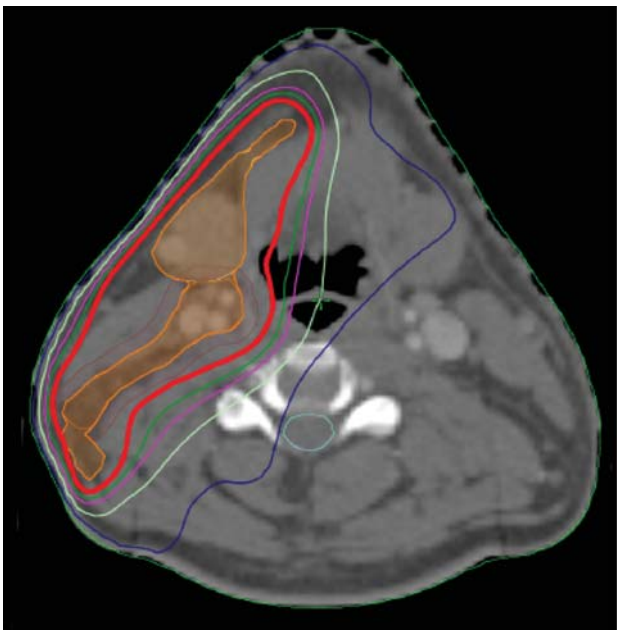


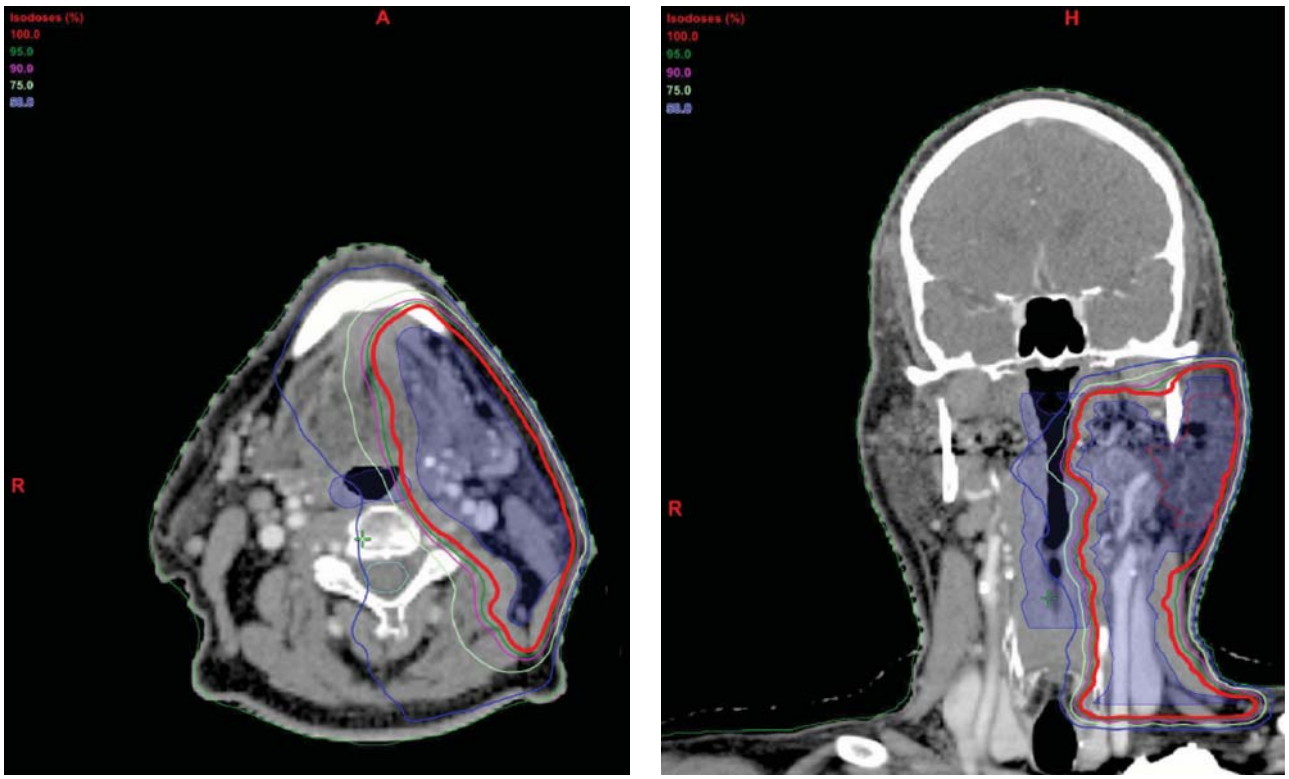
Figure 12.10. An IMRT plan is shown targeting the parotid bed along with the lymph nodes in levels IB, II, and III. The low risk CTV (orange) was treated at 2 Gy per fraction to 50 Gy. The CTV at highest risk was boosted to a total dose of 60 Gy. The radiation prescription dose is shown in red. The 95% isodose line is shown in dark green. The 90% isodose line is shown in purple. The 75% isodose line is shown in light green. The 50% isodose line is shown in blue.

spread and pattern of local recurrence. As a result, these tumors should be thought of and treated differently from the other histologies involving the salivary glands. Adenoid cystic carcinomas often involve the minor salivary glands at the junction of the hard and soft palate but can occur throughout the head and neck. They often present as indolent tumors with a low mitotic rate making them resistant to treatment. Many adenoid cystic carcinomas demonstrate a slow, relentless pattern of local and distant recurrence decades after initial diagnosis.

Adenoid cystic carcinoma differs from other salivary gland tumors in terms of its treatment. Despite their high risk of local recurrence these tumors do not carry a high risk of node involvement. Classic texts report nodal involvement by adenoid cystic carcinoma in only 15% of cases in contrast to adenocarcinoma or squamous cell carcinomas, which involve the nodes in 40–50% of cases. Given their propensity for recurrence and general poor outcomes, some authors advocate a neck dissection in all adenoid cystic carcinomas. Other groups have shown that a neck dissection is not required. A recent international review examined 495 patients with adenoid cystic carcinoma treated at nine different centers (Amit, et al. 2014). Roughly half of these patients were treated with a neck dissection and 16% were node positive. Patients not treated with neck dissection did not suffer from increased rates of recurrence in the neck and the 5-year disease specific survival for the entire cohort was 80%. Most failures were local or distant not within the regional nodes. Other studies have found the same low rate of nodal recurrence in the absence of neck dissection. Chen, et al. reported on 84 patients with adenoid cystic carcinoma and found no cases of nodal relapse (Chen, et al. 2007). Pommier, et al. reported on 24 patients with aggressive adenoid cystic carcinoma involving the skull base treated at the Massachusetts General Hospital between 1991 and 2002 (Pommier, et al. 2006). None of these patients received a neck dissection and with a median duration of follow up of 62 months none of the patients developed recurrence of disease in the neck.

Instead of spreading to regional nodes, adenoid cystic carcinoma grows along nerves. Perineural invasion is pathognomonic for this histology and these tumors often spread along the track of main named cranial nerves. As a result radiation therapy should target the tumor bed and follow major cranial nerves from the site of primary tumor up to the neural foramen at the base of skull (Figure 12.13). This pattern of radiation is opposite to the treatment of other high risk salivary gland tumors. Most high grade salivary gland tumors require radiation to track down from the tumor into the regional nodes. Adenoid cystic carcinoma however, requires adjuvant radiation treatment that tracks up along the nerves.

In the past, adenoid cystic carcinoma was difficult to control with radiation and was though resistant to treatment. This was a result of inferior radiation techniques and lower doses of radiation more than a result of intrinsic resistance on the part of adenoid cystic carcinoma. A large Dutch trial indicated that there is a clear dose response effect with adenoid cystic carcinoma. When patients were treated to doses of less than 60 Gy tumor recurrence was common, but at doses greater than 66 Gy local control of ACC was excellent (Terhaard et al. 2005). Another review of patients treated at the University of Florida with surgery and 66Gy of adjuvant radiation showed local control at 5 and



(a) (b)

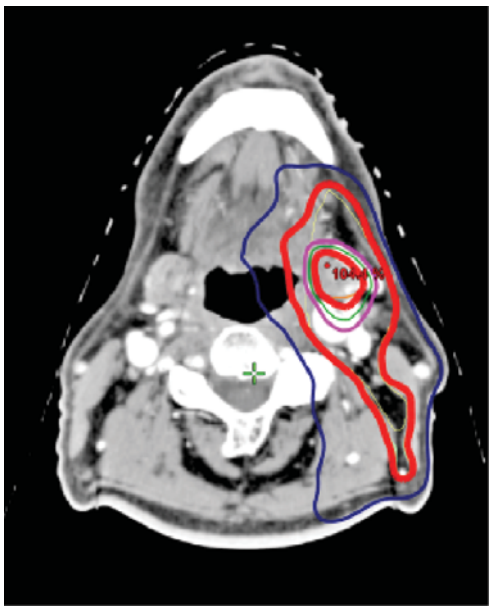
Figure 12.11. A representative plan is shown treating a patient with a high risk salivary gland tumor and a clinically negative neck. The regional nodes were treated at 1.8 Gy per fraction to 54 Gy. The tumor bed was treated to a slightly higher dose of 2 Gy per fraction to 60 Gy. The radiation prescription dose is shown in red. The 95% isodose line is shown in dark green. The 90% isodose line is shown in purple. The 75% isodose line is shown in light green. The 50% isodose line is shown in blue. Part (a) shows an axial isodose and (b) shows a coronal image of the radiation treatment plan.

10 years as high as 90% (Mendenhall, et al. 2005). Overall survival in these patients was low, however, at only 48% at 10 years with many patients developing distant metastatic disease. This suggests that improvement in systemic therapy will be needed before increases in survival can be shown in adenoid cystic carcinoma.

Advanced Radiation Therapy Techniques: Fast Neutron and Proton Therapy

Neutron therapy was studied as a means of increasing radiation dose and thus local control for salivary gland tumors. Neutron radiation therapy differs from traditional photon beam radiation. All radiation therapy is thought to function by inducing DNA damage within tumor cells. The neutron particle has mass and as a result it interacts with tumor cell DNA differently than a weightless photon of X-rays from IMRT or traditional radiation treatment. The neutron beam causes a higher rate of DNA damage over a short path length compared to photon DNA damage. This is referred to as a high linear energy transfer (LET) and allows a neutron beam to have a much higher biologically effective dose than photon radiation.

It was hoped that the higher biological effect of neutron radiation would improve outcomes in salivary gland tumors. The University of Washington has extensively studied neutron therapy for salivary gland tumors, treating more than 300 consecutive patients with neutron therapy. More than 94% of these patients harbored gross residual disease and 42% of them had T4 lesions. Despite these very high risk factors neutron therapy resulted in local control at 6 years of 59% and a cause-specific survival of 67% (Douglas, et al.



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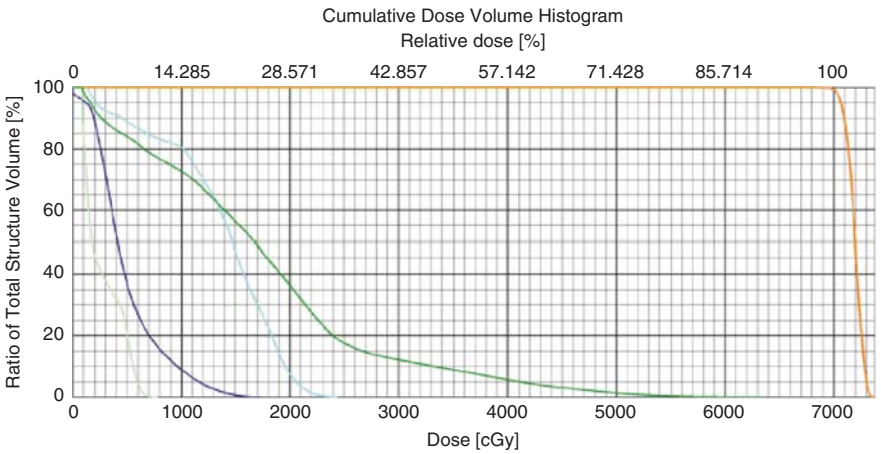
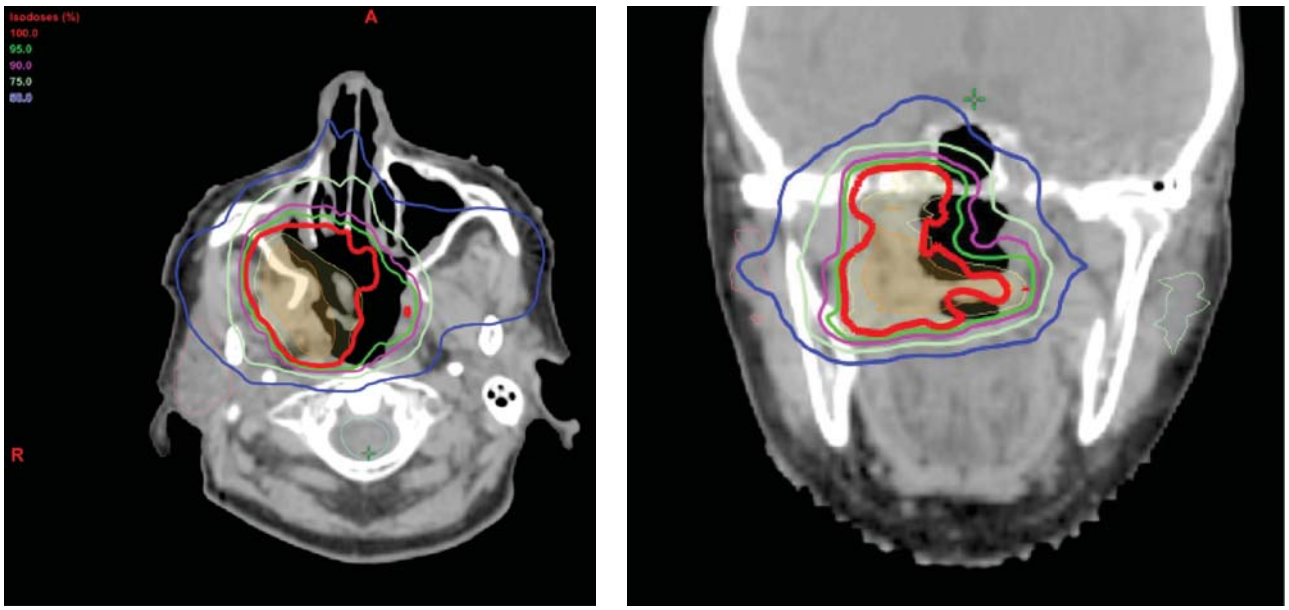


(b)

Figure 12.12. A radiation treatment plan is shown treating a patient with an unresectable high risk adenocarcinoma of the submandibular gland. Cervical levels IV and V were treated with IMRT to 50 Gy. Levels II and III were treated to 60 Gy. The gross tumor volume (GTV) was treated to 70 Gy. (a) The radiation prescription dose is shown in red. The 95% isodose line is shown in dark green. The 90% isodose line is shown in purple. The 75% isodose line is shown in light green. The 50% isodose line is shown in blue. (b) A dose volume histogram is also included indicating full coverage of the target CTV shown in (a). The dose to normal tissues is as follows: contralateral parotid in light green, spinal cord in cyan, mandible in dark green, and the oral cavity in dark blue.

2003). Unfortunately neutron therapy also resulted in higher rates of toxicity with 10% of patients developing late effect grade 3 or 4 adverse effects. Four patients developed central nervous system necrosis, three patients developed blindness, and four patients developed osteoradionecrosis. As a result neutron therapy is no longer commonly used.

Proton therapy is one of the newest technological advances in radiation therapy and offers the hope of improved dose distributions with resulting better local control and decreased toxicity. Protons are positively charged particles that have mass. As a result, when a beam of proton energy strikes a tumor target it has a characteristic interaction that differs substantially from an X-ray beam (Figure 12.14). The photon of X-ray energy deposits some dose when it initially enters the tissue and then continues to give a low dose of irradiation as it travels through the target. Much of the deposited dose is given beyond the intended target and is terms "exit dose." A proton beam, however, gives a low amount of deposited dose as it enters the tumor. Then the proton beam slows down and delivers the vast majority of its dose over a very short region termed the Bragg peak. Proton beams display a rapid fall off in dose beyond the Bragg peak with no "exit dose" beyond the target.



(a) (b)

Figure 12.13. (a and b) An IMRT plan is shown treating a patient with an adenoid cystic carcinoma located at the junction of the soft and hard palate. The tumor was resected with a negative but close margin and contained lymphovascular space invasion. Due to the inherent biology of adenoid cystic carcinoma there is a risk of recurrence within the operative site and along the tract of the V2 cranial nerve. A radiation treatment plan was generated to target the clinical treatment volume (CTV). The patient was treated at 2 Gy per fraction to a dose of 66 Gy. The radiation prescription dose is shown in red. The 95% isodose line is shown in dark green. The 90% isodose line is shown in purple. The 75% isodose line is shown in light green. The 50% isodose line is shown in blue.

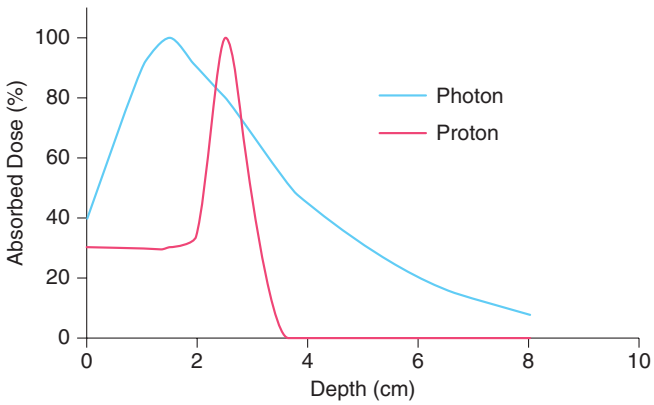


Figure 12.14. The figure demonstrates the difference in dose distribution between a beam of photon energy and a beam of proton energy. The typical behavior of an IMRT photon beam is shown in blue. Note the rapid rise in dose as the beam of energy interacts with the tissue and also note the low level of dose that continues through the entire width of tissue. This tail of deposited energy beyond the maximal point is termed "exit dose." In contrast, a proton beam delivers a moderate dose of energy as it enters the tissue and then deposits a large amount of dose at its maximal point. This point of rapid dose delivery is termed the Bragg peak. The sudden fall off of dose beyond the Bragg peak has an obvious theoretical advantage in limited exit dose to normal tissues that surround the tumor.

This has an obvious theoretical advantage in focusing the radiation dose on the tumor while further protecting normal tissue beyond the target area.

In the past proton therapy was limited to only a few centers around the world but recently there has been a dramatic increase in the availability of proton beam radiation centers. Few studies have examined the effect of proton radiation therapy on salivary gland tumors but the initial reports are promising. Pommier et al. reported on the Massachusetts General Hospital experience with adenoid cystic carcinoma treated with proton therapy in a twice daily fashion to a median dose of 75.9 Gy equivalents. Despite a very high risk cohort with positive margins and skull base involvement they found five year local control in 93% of patient

and 8-year local control in 82% (Pommier, et al. 2006). Disease free survival was 77 and 59% at 5 and 8 years, respectively. Further study is needed to ensure that proton therapy does not fall victim to the same increase in late toxicity that limited neutron therapy for this and other diseases.

Summary

- Salivary gland tumors are a complex mixture of different histologies with varied natural histories, risk of spread, and treatment techniques.
- A better understanding of salivary gland tumor biology allows these patients to be divided into risk groups.
- Low risk salivary gland tumors are often cured by adequate surgical resection and do not frequently require adjuvant therapy.
- Moderate risk salivary gland tumors have a significant risk of local recurrence even after optimal surgery and benefit from adjuvant radiation therapy to the tumor bed and occasionally to the first echelon of lymph nodes.
- High risk salivary gland tumors have high rates of local recurrence and suffer from frequent involvement of the regional lymph nodes. These high risk patients require postoperative radiation to the ipsilateral neck with high doses of radiation to the tumor bed.
- Adenoid cystic carcinoma frequently spreads along nerves resulting in a different radiation technique.
- Advances in radiation technique allow for much better outcomes in salivary gland tumors. IMRT delivers a higher dose to the tumor improving local control and avoiding aggressive surgery in many patients. More accurate radiation therapy protects critical structures of the head and neck decreasing adverse effects of treatment.
- Newer advanced radiation techniques such as the growing availability of proton therapy hold the promise to further improve the outcome of our patients.
- Clinical trials are ongoing to examine combination chemotherapy and radiation in management of high risk salivary gland malignancies. It is hoped that better integration of systemic therapy will decrease distant metastatic recurrence and, hence, improve survival.

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Chapter 13

Systemic Therapy for Salivary Gland Cancer

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Outline

Introduction

Salivary gland tumors are a group of heterogeneous neoplasms that constitute less than 1% of all cancers diagnosed globally (WHO 2005). The behavior of these tumors varies widely depending on their location, histology, and tumor biology. The tumors can involve both the major salivary glands (parotid, submandibular, and sublingual) and the minor salivary glands. The most common location is the parotid gland, which accounts for approximately 80% of all the salivary gland tumors (Guzzo, et al. 2010). Tumors involving the minor salivary glands are rare but are also more likely to be malignant. Salivary gland tumors include both benign and malignant neoplasms and they are classified according to the World Health Organization (WHO) system (WHO 2005). This chapter will focus on the use of systemic therapy in the treatment of salivary gland cancers.

Epidemiology and Risk Factors

The global annual incidence rates for salivary gland cancers (SGC) vary between 4 and <0.05 per 100,000 (Parkin, et al. 2002). It has been suggested that radiation exposure, viral infections, diet, and genetic predisposition may play a role in the development of these rare cancers. The association between radiation exposure and SGC was first identified in atomic bomb survivors in Hiroshima (Saku, et al. 1997). Subsequently SGC has been reported in patients receiving radiation to the head and neck region for both cancers and benign conditions (Schneider, et al. 1998).

Viral infections have been shown to be associated with the development of SGCs. Lymphoepithelial carcinoma is an SGC that is strongly associated with Epstein–Barr Virus (EBV) infection in areas endemic to the virus (WHO 2005). Epidemiologic studies have shown that patients with the human immunodeficiency virus (HIV) are also more likely to develop SGCs (Serraino, et al. 2000). The human papillomavirus (HPV) has been identified in some mucoepidermoid carcinomas (Brunner, et al. 2012, Isayeva, et al. 2013); however, this has not been a consistent finding (Jour, et al. 2013). Similarly, HPV has been rarely identified in other SGCs (Hafed, et al. 2012). At this time, it is not clear if there is a significant association between HPV and SGCs.

Environmental carcinogens have also been shown to be associated with SGCs. Tobacco smoke exposure has been associated with the

Salivary Gland Pathology: Diagnosis and Management, Second Edition. Edited by Eric R. Carlson and Robert A. Ord.

development of Warthin tumor (Pinkston and Cole 1996, WHO 2005). Exposure to nickel and rubber manufacturing have been reported to be risk factors for SGCs (Horn-Ross, et al. 1997). In addition, professionals such as hair dressers and beauticians are reported to have higher risk of developing SGCs (Swanson and Burns 1997).

Molecular Biology of Salivary Gland Tumors

SGCs consist of variety of different tumors and there is considerable variation in the type of molecular changes identified in these tumors. These molecular changes include fusion genes, oncogenic mutations, and alterations in gene amplification or expression. Some of these molecular alterations are specific to the tumor type and could help establish the diagnosis in the absence of a histologic diagnosis; others have been identified as potential therapeutic targets.

Fusion genes are relatively rare molecular events in malignant epithelial tumors. The *MYB-NFIB* fusion gene has been identified in adenoid cystic carcinoma (ACC) and appears to be specific to this tumor type (Persson, et al. 2009). The *MYB-NFIB* fusion gene activates the transcription of a variety of genes downstream to *MYB*, which includes *BCL2*, *KIT*, *CD34*, *BIRC3*, and *MYC* (Stenman 2013). These genes are important in activation of cell proliferation, differentiation, and apoptosis. The *MYB* gene has been reported to be activated in the vast majority (80%) of all ACCs either by gene fusion or by other mechanisms. Mucoepidermoid carcinoma (MEC) is characterized by the *CRTC-MAML2* fusion gene and both constituent genes have role in cell cycle (Enlund, et al. 2004). The *CRTC1* is a cAMP response element binding protein (CREB) co-activator that regulates genes involved in cell proliferation and differentiation in response to stimulus from growth factors and cytokines (Coxon, et al. 2005). The *MAML2* gene is a co-activator for the *NOTCH* gene which also plays a major role in cell cycle as well as in oncogenesis. The oncoprotein resulting from this gene fusion has transforming activity in both in-vitro and in-vivo experiments. Recently the *ETV6-NTRK3* gene fusion was identified in mammary analogue secretory carcinoma (MASC) and the chimeric tyrosine kinase resulting from this fusion has shown transforming activity as well (Skalova, et al. 2010). Targeting the IGF1R pathway has been shown to effectively inhibit the transforming activity of this fusion kinase (Tognon, et al. 2011).

Over-expression of the epidermal growth factor receptor (*EGFR)* gene is the most common genomic abnormality reported in SGCs, it is identified in approximately 70% of all SGCs (Locati, et al. 2009b). However, activating mutations involving the tyrosine kinase domain of the *EGFR* gene are rare. Other genes that have been reported to be over expressed or amplified in SGC include *HER2*, *VEGF*, and *C-KIT* (Press, et al. 1994, Lim, et al. 2003, Skalova, et al. 2003, Dagrada, et al. 2004, Freier, et al. 2005). VEGF expression is an independent prognostic factor and high expression is associated with inferior outcomes. C-Kit expression is found in the majority of high grade ACCs (90%). Expression of estrogen and progesterone receptors has been reported in some SGCs, though this is a rare finding.

Clinical Presentation

The clinical presentation for SGC depends on the site of origin and involvement of adjacent structures. Approximately half of all major SGCs arise in the parotid gland and they usually present as a painless mass arising in the parotid, submandibular, or sublingual gland. Around 90% of all salivary gland tumors arise in the parotid gland and about 25% of them are malignant (2005). In the case of submandibular salivary gland, the proportion of SGCs is about 45%, 70–90% in sublingual gland tumors and 50–75% in minor salivary gland tumors (Guzzo, et al. 2010). If the mass is associated with facial nerve palsy then it is likely to be a malignant SGC. Similarly presence of associated lymphadenopathy also indicates malignant SGC.

Tumors arising from minor salivary glands are more likely to be malignant than tumors arising in major salivary glands. More than half of all minor salivary gland tumors arise within the oral cavity. Symptoms for minor SGCs vary according to the location. Oral tumors may present as a painless submucosal tumor, minor SGCs in the nasopharynx can cause facial pain, nasal obstruction, and bleeding, and tumors in the hypopharynx can result in hoarseness of voice and dyspnea. Minor SGCs in the nasopharynx are also more likely to present at an advanced stage with invasion of the skull

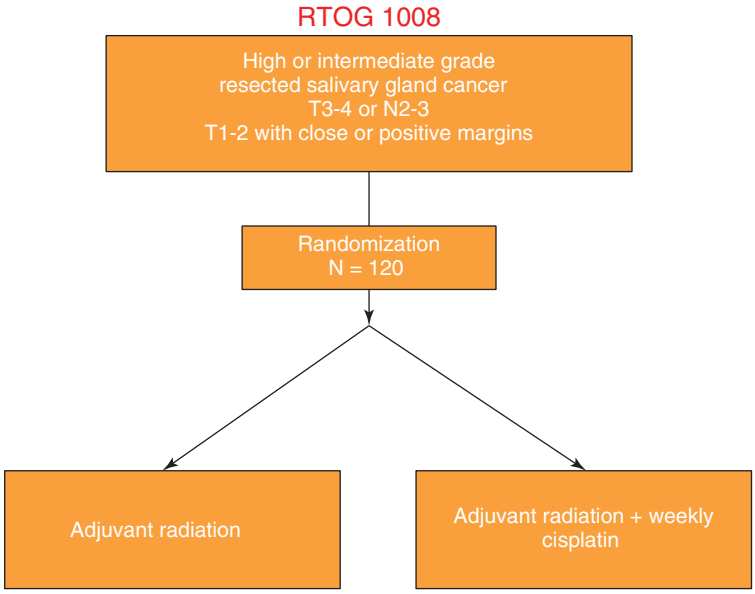

Figure 13.1. The role for concomitant chemotherapy with adjuvant radiation is being evaluated by the RTOG 1008 clinical trial.

base, intracranial and cranial nerve involvement (Schramm and Imola 2001). A thorough initial assessment with history and physical exam could help estimate the extent of the disease and the likelihood of it being a malignant tumor. Tissue diagnosis will have to be established and this can achieved in most cases with fine needle aspiration cytology. Imaging scans such as computerized tomography (CT) and/or magnetic resonance imaging (MRI) may be needed to establish the TNM stage of the disease.

Treatment

Treatment of SGCs depends on the location, tumor histology, and the extent of disease involvement. Whenever possible, a complete surgical resection with clear margins is the preferred treatment approach for SGCs. In patients with SGCs that are unresectable or medically inoperable, definitive radiation remains the treatment of choice. Concurrent chemotherapy with a platinum agent can be considered in patients with good performance status; however, there is insufficient evidence to support this approach over definitive radiation alone.

ADJUVANT TREATMENT

There is no established role for adjuvant chemotherapy alone in patients with resected SGCs, though this approach may be considered with concomitant adjuvant radiation. Adjuvant radiotherapy is indicated in patients with high risk features such as high grade tumors, advanced disease stage, adenoid cystic carcinoma histology, and skin or nerve invasion. In addition, patients with T2 or greater SGCs involving the submandibular, sublingual, and minor salivary glands are potential candidates for adjuvant radiotherapy. The role for concomitant chemotherapy with adjuvant radiation has not been established but is currently being evaluated by the RTOG 1008 clinical trial (Figure 13.1) (Rodriguez, et al. 2008). This randomized phase II trial will compare adjuvant radiotherapy with concurrent cisplatin chemotherapy to adjuvant radiotherapy alone in patients with resected SGCs. Results from this trial are expected to be available soon.

TREATMENT OF METASTATIC DISEASE

Cytotoxic chemotherapy is primarily used in the treatment of advanced stage disease that cannot be treated with definitive surgical resection or radiation. However, the optimal chemotherapy regimen in the treatment of SGCs has not been established. Given the rarity of these tumors there have been no large randomized trials to establish the survival benefit from cytotoxic chemotherapy treatment. The primary role for chemotherapy treatment is to palliate symptoms in patients with metastatic SGC. Small phase II trials and case series have

studied the use of both monotherapy and combination chemotherapy in the treatment of SGCs. In addition tumor histology in SGCs appears to determine sensitivity to chemotherapy treatment. Treatment with single agent paclitaxel appears to be effective in patients with mucoepidermoid carcinomas and adenocarcinoma but it has not shown activity against ACC (Gilbert, et al. 2006, Laurie, et al. 2011). Similarly, treatment with cisplatin was shown to be associated with increased toxicity but no better efficacy than mitoxantrone, epirubicin, or vinorelbine in patients with ACCs (Table 13.1).

Single agent paclitaxel, cisplatin, doxorubicin, mitoxantrone, vinorelbine, and methotrexate have all shown activity in the treatment of SGCs. The response rate is modest and ranges between 10 and 40% (Schramm, et al. 1981, Licitra, et al. 1991, Vermorken, et al. 1993, Verweij, et al. 1996, Airoldi, et al. 2001). The choice of agent will depend on the tumor histology and the patient's ability to tolerate the agent. In general, any one of these agents can be considered for the treatment of SGCs, except in the case of ACCs where paclitaxel is not particularly effective.

Combination chemotherapy is generally associated with better tumor response rate compared to single agent chemotherapy but it is also associated with a higher incidence of adverse effects (Table 13.1). Several different combinations of platinum, anthracycline with or without other agents including cyclophosphamide, and 5-fluorouracil have been evaluated in the treatment of advanced stage SGCs. The most common regimen being

Table 13.1. Chemotherapy in the treatment of metastatic or recurrent salivary gland cancers.

Agent(s)	ACC		MEC		ADC	
	N	No of objective responses	N	No of objective responses	N	No of objective responses
Cisplatin (Schramm et al. 1981, Suen and Johns 1982, Kaplan et al. 1986, Licitra et al. 1991, de Haan et al. 1992, Jones et al. 1993)	66	28	7	2	8	0
Paclitaxel (Gilbert et al. 2006)	14	0	14	3	17	5
Gemcitabine (van Herpen et al. 2008)	21	0	–	–	–	–
Vinorelbine (Airoldi et al. 2001)	13	2	–	–	5	2
Mitoxantrone (Mattox et al. 1990, Verweij et al. 1996)	50	5	–	–	–	–
Epirubicin (Vermorken et al. 1993)	20	2	–	–	–	–
CAP (Alberts et al. 1981, Kaplan et al. 1986, Dreyfuss et al. 1987, Belani et al. 1988, Creagan et al. 1988, Licitra et al. 1996)	36	9	16	8	29	19
CAP + 5FU (Dimery et al. 1990)	7	3	1	1	9	4
Carboplatin/paclitaxel (Ruzich et al. 2002)	10	2	1	0	2	1
Cisplatin/vinorelbine (Airoldi et al. 2001)	9	4	1	0	4	3
Cisplatin/gemcitabine (Laurie et al. 2010)	10	2	4	1	8	3
Cisplatin/5FU (Hill et al. 1997)	11	0	—	–	–	–

ACC = Adenoid cystic carcinoma
MEC = Mucoepidermoid carcinoma
ADC = Adenocarcinoma

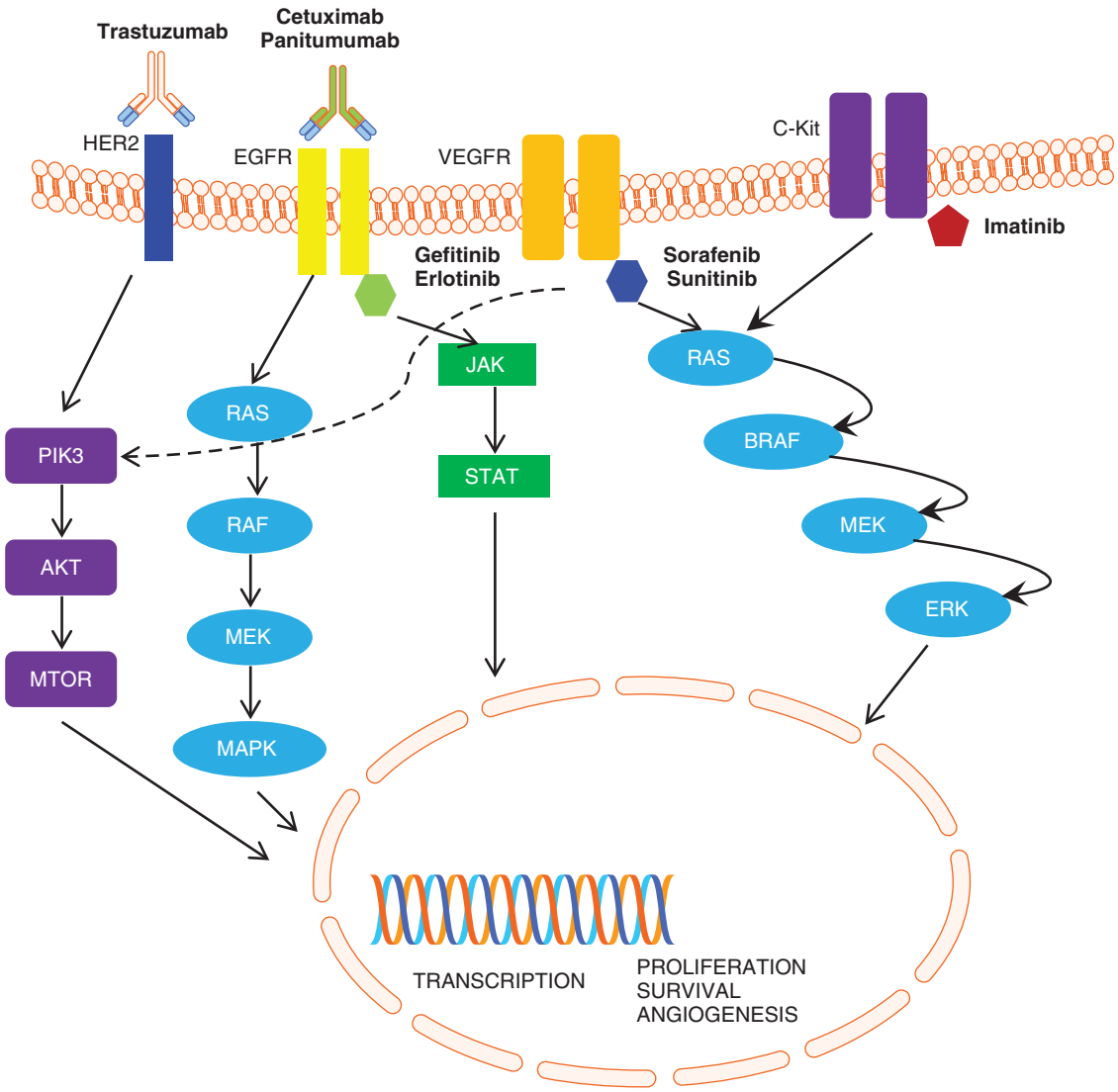

Figure 13.2. Activated signaling pathways and their inhibitory agents in advanced salivary gland cancers.

cyclophosphamide, doxorubicin, and cisplatin (CAP) given on day 1 of a 28-day cycle (Dreyfuss, et al. 1987, Licitra, et al. 1996). The overall response rate ranges between 30 and 40% for all patients with advanced stage SGCs. In addition, the response rates may vary according to the histologic type with some histologic types such as adenocarcinomas showing a better response rate of approximately 60%.

In general, our approach has been to use combination chemotherapy in patients who are symptomatic from the disease and single agent chemotherapy in all other patients. In patients who have an indolent disease that is asymptomatic, close monitoring without any systemic therapy would be appropriate.

TARGETED THERAPY

The field of oncology has been revolutionized by the advent of molecularly targeted therapy (Figure 13.2). Some of these agents have been evaluated in patients with SGC. The majority of these studies involve agents targeting receptor tyrosine kinases in advanced stage salivary gland cancers. So far, molecularly targeted treatment approaches have not shown any significant activity or improvement in survival outcomes (Table 13.2).

Table 13.2. Targeted therapy in the treatment of metastatic or recurrent salivary gland cancers.

Agent	Molecular Target	N	Tumor type	Response rate	Comment
Imatinib (Pfeffer et al. 2007)	CKIT	26	ACC	–	No significant activity
Gefitinib (Jakob et al. 2014)	EGFR	29	SGC	–	No significant activity
Cetuximab (Locati et al. 2009a)	EGFR	30	SGC	–	No significant activity
Trastuzumab (Haddad et al. 2003)	HER2	15	SGC	–	No significant activity
Lapatinib (Agulnik et al. 2007)	HER2	40	SGC	–	No significant activity
Sorafenib (Thomson et al. 2013)	VEGFR	23	ACC	8.3%	Significant toxicity
Sunitinib (Chau et al. 2012)	VEGFR	14	ACC	–	No significant activity
Bortezomib (Argiris et al. 2011)	Proteasome	25	ACC	–	No significant activity

ACC = adenoid cystic carcinoma
MEC = mucoepidermoid carcinoma
ADC = adenocarcinoma
SGC = salivary gland cancer

Targeting *C-KIT*

ACCs have been reported to have C-kit expression and individual case studies have reported response to treatment with imatinib (Mino, et al. 2003). Phase II trials evaluating single agent imatinib for the treatment of ACCs did not report any significant treatment response (Pfeffer, et al. 2007). The combination of imatinib with cisplatin in a phase II trial was reported to have a partial response in 5 out of 28 evaluable patients with ACC and 19 had stable disease (Ghosal, et al. 2011). Overall, prospective studies have not shown any significant treatment benefit with imatinib for patients with ACC.

EGFR Inhibition

Gefitinib is an EGFR tyrosine kinase (TK) inhibitor and has shown activity in patients with lung and pancreatic cancers. EGFR over-expression has been reported in patients with MEC and ACCs. Treatment with gefitinib in a phase II trial did not report any significant objective response in patients with advanced stage SGCs. Stable disease was reported in 10 (34%) patients (Jakob, et al. 2014).

EGFR inhibition can also be achieved by cetuximab which is an anti-EGFR monoclonal antibody. Treatment with cetuximab was not associated with treatment response in a phase II trial with 30 patients with SGCs (Locati, et al. 2009a). Disease stabilization was reported in 24 (80%) patients and 15 (50%) patients had disease stabilization for at least 6 months.

HER2 Inhibition

Her2 expression has been reported in MEC and salivary duct cancers (Glisson, et al. 2004, Jaehne, et al. 2005). A phase II trial was initiated to evaluate trastuzumab, a monoclonal antibody targeting HER2 for patients with HER2 expression positive SGCs (Haddad, et al. 2003). The study closed early due to low rates for HER2 expression positive tumors. In one patient with Her2 positive MEC, partial response was reported, which lasted for over 2 years. In addition, there have been case studies reporting benefit from trastuzumab in combination with chemotherapy for patients with salivary duct carcinomas.

Lapatinib is a small molecule dual kinase inhibitor for *HER2* and *EGFR* that was evaluated in a phase II trial for patients with metastatic SGCs (Agulnik, et al. 2007). Of the 40 patients enrolled in the multicenter phase II trial, none of them had a treatment response, 15 patients with ACC had stable disease, and 8 patients with non ACC had stable disease. The treatment outcomes did not correlated with either EGFR or HER2 expression in this study.

Multi Kinase Inhibition

Sorafenib and sunitinib are multi kinase inhibitors that have been evaluated in patients with advanced stage ACCs. Sorafenib was evaluated in 23 patients with ACC and 2 patients had partial response with a median progression free survival of 13 months (Thomson, et al. 2013). In another study, 14 patients with ACC were treated with sunitinib and

no treatment responses were reported but 5 patients had disease stabilization (Chau, et al. 2012).

Both of these treatments were difficult to tolerate, more than half the patients receiving sorafenib developed grade 3 or higher toxicity. The authors did not recommend further evaluation of sorafenib in this patient population. Similarly sunitinib also had a significant toxicity profile with 3 patients removed from the study due to toxicity and 10 patients required dose reductions.

Proteasome Inhibition

Bortezomib is a 26S proteasome and *NF-κB* inhibitor that had shown pre-clinical activity against ACC tumors in combination with doxorubicin. A phase II trial evaluated treatment with both single agent bortezomib and in combination with doxorubicin in the treatment of patients with incurable ACC (Argiris, et al. 2011). Of the 24 patients treated with single agent bortezomib, none had an objective response and stable disease was reported in 15 patients. One patient out of 10 receiving the combination therapy had a partial response.

Summary

- Systemic therapy in the treatment of SGCs is primarily limited to patients with metastatic or recurrent disease.
- The role for chemotherapy in the adjuvant setting is unclear and could be considered in patients with high risk features after tumor resection. The RTOG 1008 trial may help shed more light on this issue when results from this study become available.
- In patients with metastatic or recurrent SGCs the choice of chemotherapy is dependent on several factors including clinical course and histology. Some patients have an indolent course and can be observed without any systemic therapy. In patients with symptomatic and/or progressive disease both combination and single agent cytotoxic chemotherapy can be considered.
- In patients with ACC both paclitaxel and gemcitabine have not shown activity and should be avoided.
- The CAP regimen has shown activity against ACC, acinic cell carcinoma, adenocarcinomas, and malignant mixed tumors.
- Agents such as cisplatin, 5-FU, and methotrexate seem to provide better response in patients with MEC and undifferentiated tumors.
- Molecularly targeted therapy holds significant promise in the treatment of SGCs but so far, none of the available agents have shown any significant activity.
- A better understanding of the molecular biology of salivary gland cancers could lead to better treatment options in the future. The rarity and heterogeneity of SGCs pose major challenges to achieving this goal but persistent efforts are needed to achieve better outcomes for the patients.

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Chapter 14

Non-salivary Tumors of the Salivary Glands

Outline

Introduction

This chapter will discuss the non-salivary tumors that occur in the major salivary glands. (Salivary gland tumors have been discussed in Chapters 9, 10, and 11.) Essentially, the chapter will be divided into primary benign and malignant mesenchymal tumors and metastatic lesions mostly epithelial in the lymph nodes or substance of the major glands. As the epidemiology and etiology of these tumors is very variable, it will be discussed in relation to individual tumors and groups of tumors.

Mesenchymal Tumors

BENIGN MESENCHYMAL TUMORS

Hemangiomas

Hemangiomas and hemangioendotheliomas are most commonly seen in the parotid gland and in children where they account for up to 35% of salivary tumors (Ord 2004). These tumors are most commonly seen under the age of 1 year and may be present at birth where they may exhibit aggressive growth. Hemangioendotheliomas are more aggressive and rapidly growing and occur in the <6 month infant, while older children tend to present with the slower growing cavernous lesions (Figure 14.1). In the past, surgical removal was advocated but as the majority of tumors involute over time, and because of the morbidity of surgery in infants, this has largely been abandoned in favor of medical therapy. Previous papers have indicated that vascular malformations of the parotid respond poorly to medical therapy, however, this has been disproven in a recent paper (Greene, et al. 2004). These authors reviewed 100 consecutive children with a 4.5:1 female to male ratio with 59% of tumors ulcerating during the proliferating phase and 89% involving nearby structures. Seventy of the patients were treated medically; 67 primarily with corticosteroids and 3 with interferon. Initially, 56/67 of the patients treated with steroids showed regression or stabilization but 18 required further treatment with interferon. The overall response to steroids/alfa-2a or -2b interferon was 98% and the authors concluded that parotid gland vascular tumors respond in the same way as hemangiomas elsewhere. Interestingly, 66% of the children

Salivary Gland Pathology: Diagnosis and Management, Second Edition. Edited by Eric R. Carlson and Robert A. Ord.

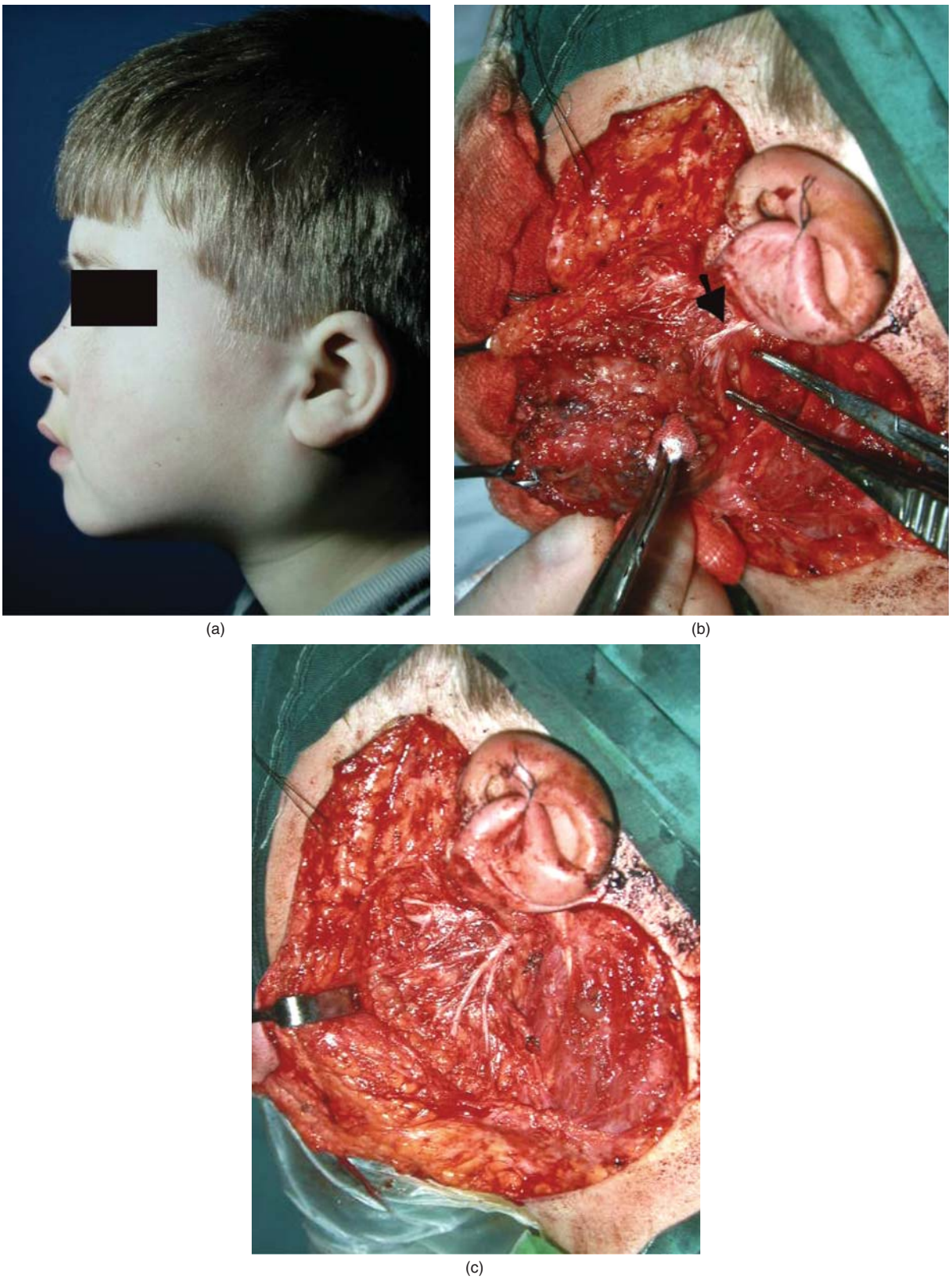


Figure 14.1. (a) A 3-year-old boy with prominent cavernous vascular neoplasm of the parotid gland. (b) Operative sequence shows the neoplasm is mobilized forward after tying off feeding vessels and is being peeled of the trunk of the facial nerve (arrow). (c) The vascular neoplasm is removed in total with the superficial lobe of the parotid gland after complete facial nerve dissection.

required some form of reconstructive surgery during the involuted phase.

Increased interest has developed in the use of oral propranolol for head and neck hemangiomas in children. In one study of 39 children (all head/neck sites) including parotid, propranolol therapy resulted in lightening and reduction of the hemangioma in 37 of 39 cases. There were no complications but in five patients acebutolol was substituted due to sleep disturbance with propranolol (Fuchsmann, et al. 2011). In a retrospective review of 56 patients treated for parotid hemangiomas, 22 patients had steroid therapy and initially responded but 68% rebounded after steroid cessation. Overall, 16 patients had good results with surgery. Ten patients had oral propanolol, and 8 of 10 had significant shrinkage within the first month with no side effects. The authors concluded that propranolol seemed a promising new modality for managing parotid hemangiomas (Weiss, et al. 2011). Mantadakis, et al. (2012) reviewed the current literature and concluded that oral propranolol at therapeutic doses of 2–3 mg/kg per day in divided doses was safe for the management of children with symptomatic hemangiomas, and felt it should be considered as the first line agent in all infants with symptomatic hemangiomas who do not have a pulmonary or cardiovascular contraindication to it.

In adults, vascular lesions of the parotid are less common but intramuscular hemangiomas of the masseter muscle can be a diagnostic challenge (Figure 14.2). High resolution ultrasound and MRI have been suggested for accurate diagnosis of vascular lesions of the parotid in adults (Wong, et al. 2004).

Vascular lesions of the submandibular gland are seen rarely and like vascular lesions elsewhere will be treated depending on their flow characteristics and the vessel(s) affected (Figure 14.3).

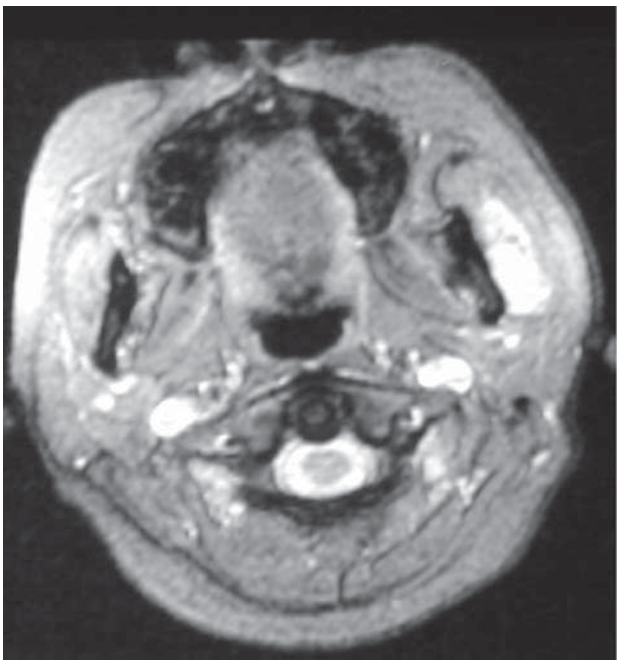


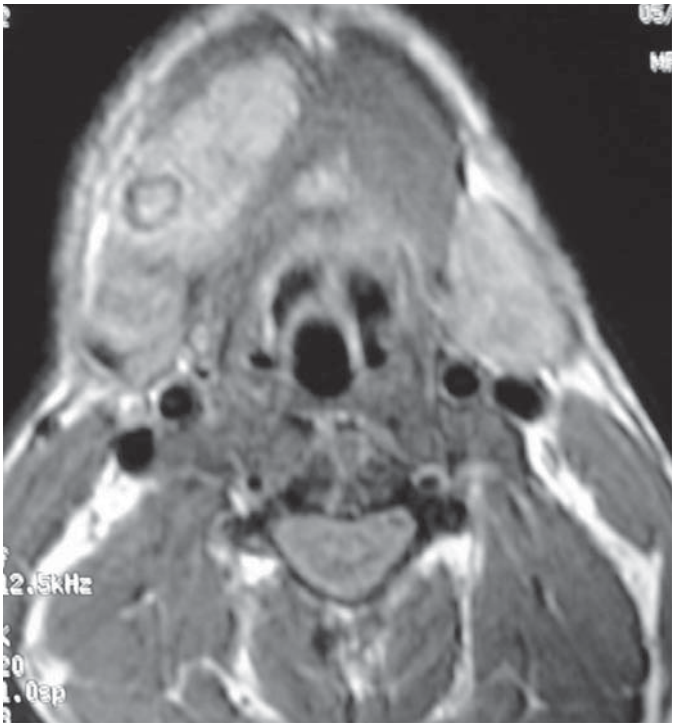
Figure 14.2. The magnetic resonance scan shows the vascular malformation is located intramuscularly in the masseter muscle deep to the parotid.

Lymphangiomas

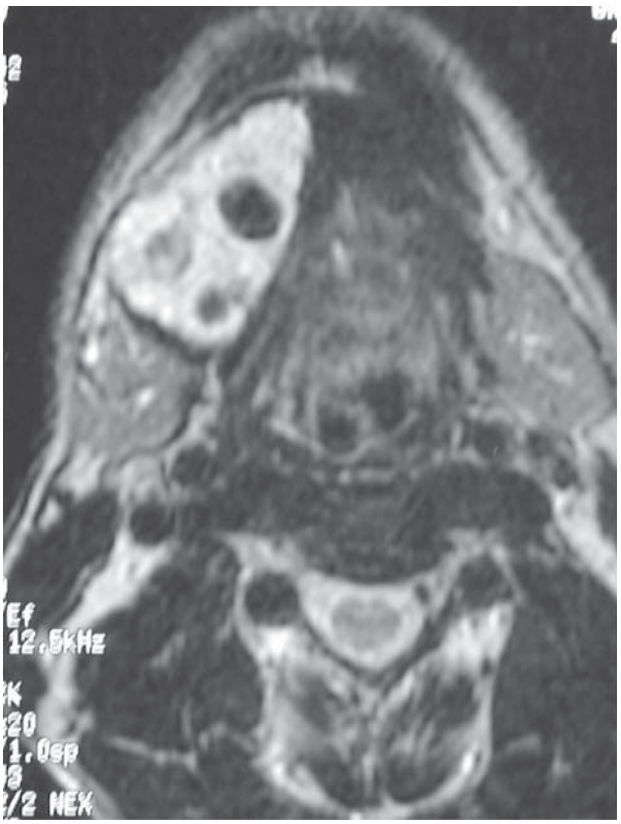
Lymphangiomas may be capillary or cavernous (and associated with vascular malformations) or be cystic in nature. They are common in the neck and seen more in the submandibular (37%) than parotid glands (31%) (Orvidas and Kasperbauer 2000). They may be prominent at birth as cystic hygromas and may pose a threat to the airway (Figure 14.4). In children, they can increase considerably in size during upper respiratory tract infections. Some authors have documented the posterior triangle to be a more common site in the neck than the submandibular space; 54% versus 17%, respectively (Fageeh, et al. 1997). In 25 cases of cystic hygroma reported in 2012, 12 (48%) were in the posterior triangle, 7 (28%) submandibular, and 3 (25%) in the parotid (Zainine, et al. 2012). In a series of 324 pediatric patients with salivary gland masses, 89 (27.5%) were lymphangiomas compared to 192 (59.2%) of hemangiomas (Bentz, et al. 2000). Many of these lesions are treated surgically but persistence and recurrence is problematic (Orvidas and Kasperbauer 2000). Especially in the infiltrating lesions, complete excision may be impossible and debulking is performed. Surgery can be combined with sclerosing injections or these can be used as a single modality. Sclerosants are most effective in macrocystic lymphangiomas and in 54 of these cases 49% had excellent results, 35% good, and 16% poor using the sclerosant injection (Emran, et al. 2006).

Neural Tumors

In Siefert and Oehne's (1986) review of 150 benign mesenchymal tumors of the salivary glands 16% were neurogenic in origin distributed over the



(a)



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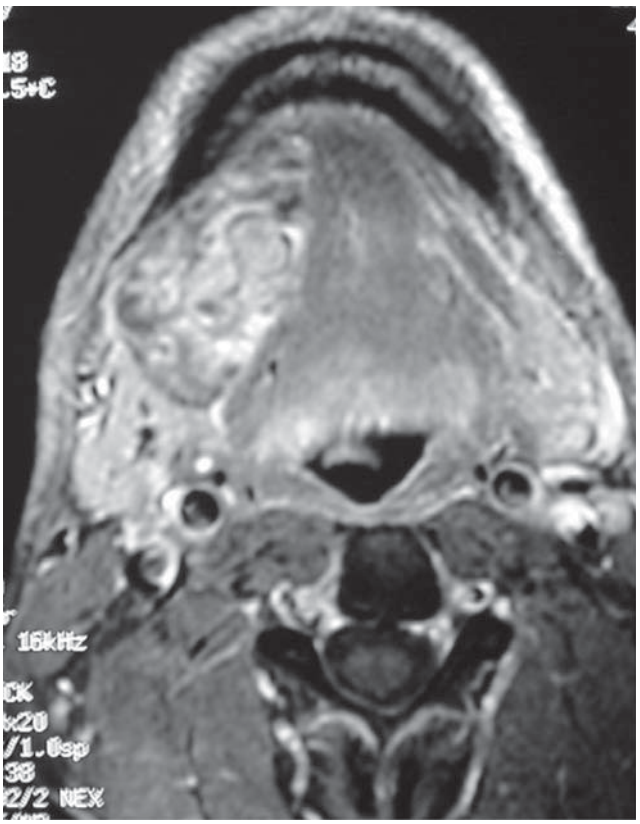


(c)

Figure 14.3. (a, b c) Vascular malformation in the submandibular region. At the time of surgery this was found to be cavernous and primarily venous.

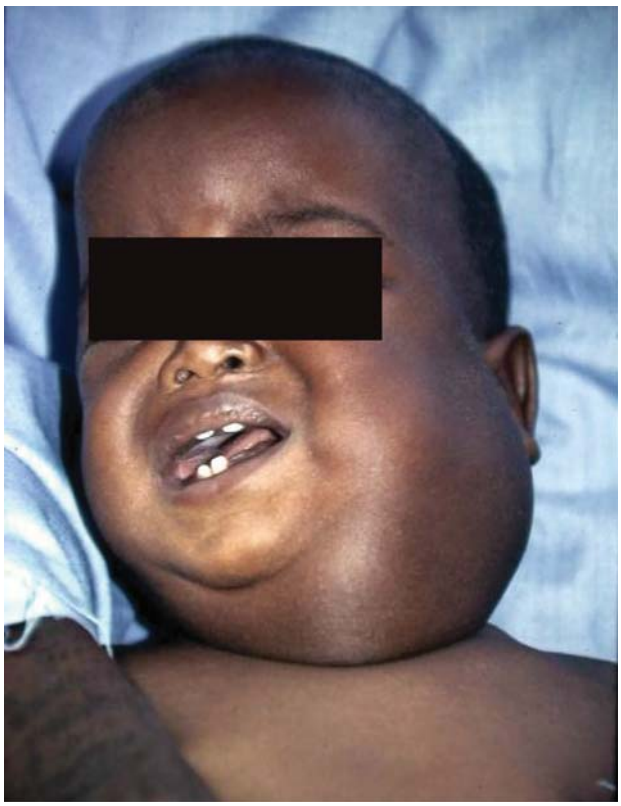


Figure 14.4. Lymphangioma involving both parotid and submandibular glad in an 8-month-old infant.

fourth to seventh decades. These were divided into neurilemmomas (neurinomas) in 12 of 27 cases, neurofibromas in 12 of 27 cases, and neurofibromatosis in 3 of 27 cases. There was a predominance of males (75%) for neurofibromas and for females (65%) for neurilemmomas. Both MRI and CT scans may be useful in imaging. In the parotid gland, extension of the tumor in the gland and in the petrous bone is well defined by MRI, while a CT scan shows bone erosion and relationship to the inner ear. A combination of CT and MRI is recommended when surgical resection is planned (Martin, et al. 1992).

Complete removal of these lesions especially the plexiform neurofibroma can be extremely difficult due to their infiltrating nature and often increased vascularity (Figure 14.5).

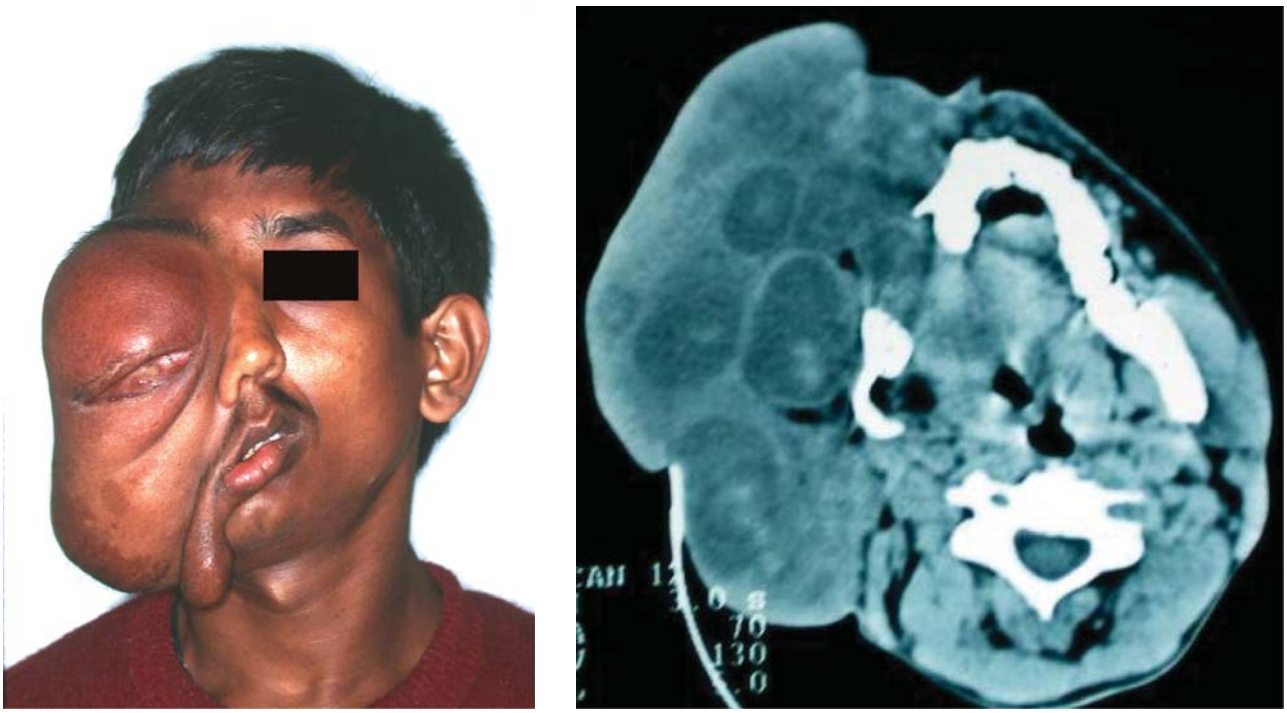
Although approximately one third of neurilemmomas occur in the head and neck (Almeyda, et al. 2004), they are comparatively rare in the salivary glands, usually published as isolated case reports. However, as they may be mistaken for a malignant parotid tumor due to facial nerve dysfunction, for example, progressive weakness, sudden facial paralysis, hemifacial spasm, and pain (Balle Greisen 1984), it is important to make the diagnosis to avoid inappropriate radical surgery. Regarding intra parotid neurofibromas, a "conservative course of treatment with limited tumor excision and emphasis on retaining facial nerve function" is advocated (McGuirt, et al. 2003). Indeed, once the histologic diagnosis is made because of the slow growth of the tumor and the unlikelihood of malignant change, conservative treatment of leaving the tumor in situ to preserve the nerve has been recommended (Fierke, et al. 2006).

Lipomas

Approximately 15–20% of lipomas occur in the head and neck region (Weiss and Goldblum 2001), and in reviewing 125 lipomas in the oral and maxillofacial region, 30 (24%) were parotid and 17 (13.6%) were submandibular (Furlong, et al. 2004). In this series, there was a 3:1 male to female gender ratio and a mean age of 51.9 years. Histologically, almost half (62/125) were classic lipomas, while 59 were spindle cell/pleomorphic, 2 were fibrolipomas, and 2 chondroid lipomas. Spindle cell lipomas comprised the majority of parotid lipomas. In a review of 167 mesenchymal salivary gland tumors, Seifert and Oehne (1986) found lipomas comprised 22.5% of 150 benign tumors and 95% were in the parotid. Again, 85% occurred in males. A recent report of 660 parotid neoplasms found only 8 patients had lipomatous tumors (1.3%); 5 with focal lipoma and 3 with diffuse lipomatosis (Ethunandan Vura Umar, et al. 2006). Only one tumor of the eight was in the deep lobe but a small series of parotid lipomas in the deep lobe were reported (Gooskens Mann 2006). The largest series of 70 lipomas of the parotid showed 70% male, with 63.2% intraparotid and 36.8% periparotid (Starkman, et al. 2013).

Lipomas are comparatively rare in the oral cavity, but in one paper with 46 cases, 2 patients were classified as having minor salivary gland lipomas (Fregnani, et al. 2003).

Salivary lipomas usually present as slow growing painless masses and their appearance on CT or MRI is diagnostic (Figure 14.6). Surgical excision is the treatment of choice and although easy in a classic lipoma, it can be challenging in the infiltrating variety (Figure 14.7).



(a) (b)

Figure 14.5. (a) Massive plexiform neurofibroma involving the parotid and orbit. (b) CT scan shows extensive soft tissue involvement.

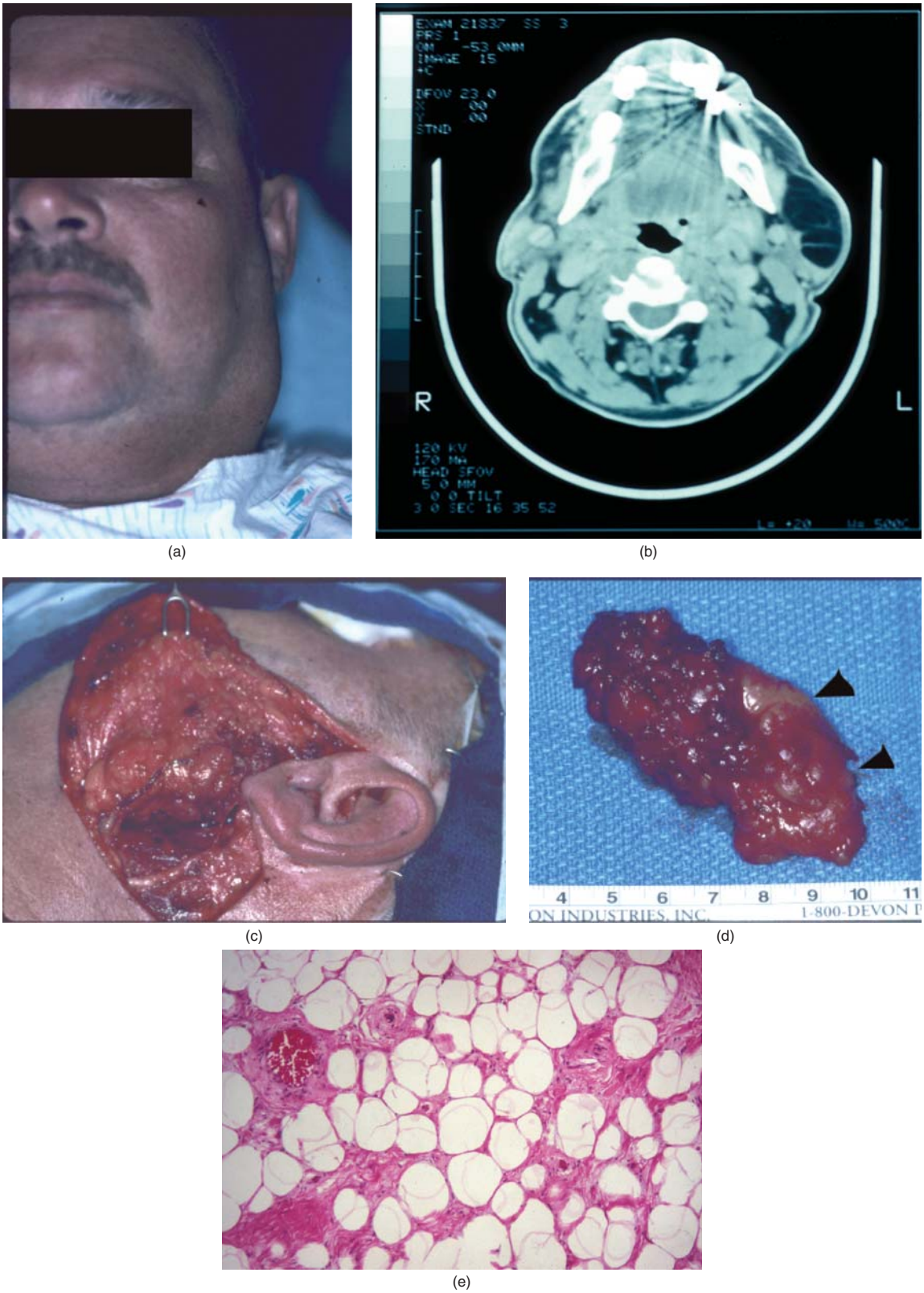
Recently, a designation of sialolipoma has been proposed for lipomas containing glandular elements, for example, ductal or acinar tissue (Nagao, et al. 2001). In their series of 2051 salivary tumors, 7 sialolipomas (5 in the parotid and 2 palatal) were reported. Excision of sialolipoma as for classic lipoma is curative. Since the initial report, other cases both in major and minor glands have been published (Lin, et al. 2004; Michaelidis, et al. 2006). A 2013 review of 31 lipomatous lesions of the parotid/submandibular gland found 20 ordinary lipomas, 6 oncocytic lipomas, 4 non-oncocytic sialolipoma, and 1 microcystic lipoadenoma (Agaimy, et al. 2013).

MALIGNANT MESENCHYMAL TUMORS

Sarcomas

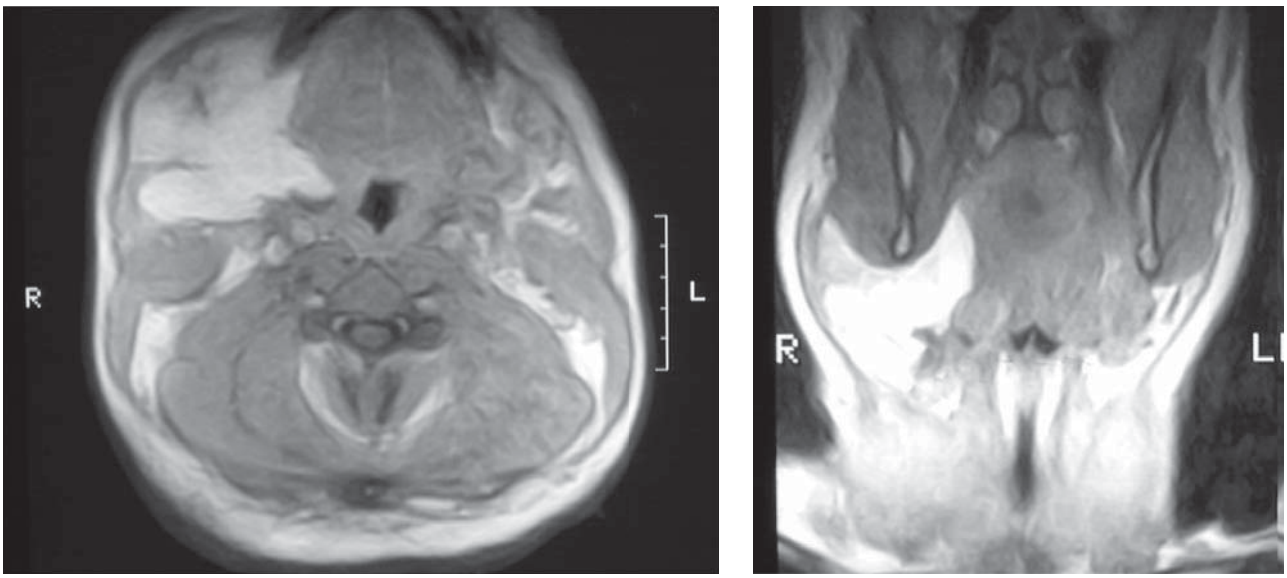
Sarcomas of the salivary glands are very rare and case reports of virtually all histologic types have been reported. In Siefert and Oehne's 1986 review of 167 mesenchymal tumors of the salivary glands, only 17 were sarcomas (10%). In this series, five cases were malignant fibrous histiocytomas, five cases malignant schwannomas, four cases embryonal rhabdomyosarcoma, and there were single cases of myxoid liposarcoma, leiomyosarcoma, and malignant hemangioendothelioma. An 18-year retrospective study from the MD Anderson found only 17 cases, primarily T1, in the parotid. All cases were treated surgically primarily and 76% had adjuvant therapy, 41% of cases recurred, and 5-year and 10-year survival was 42 and 20%, respectively. The authors reviewed the literature and found 187 cases of salivary gland sarcoma reported. The commonest sarcomas identified were rhabdomyosarcoma 12.8%, hemangiopericytoma 8.5%, angiosarcoma 7.5%, liposarcoma 7.5%, malignant fibrohistiocytoma 7.5%, and synovial sarcoma 5.3% (Cockerill, et al. 2013).

In reviewing salivary masses in children, rhabdomyosarcomas were the most common malignant mesenchymal tumor at 7% (Bentz, et al. 2000) and in 137 children with rhabdomyosarcomas of the head and neck the parotid was the site for 6% of these tumors (Hicks and Flaitz 2002). Obviously, treatment plans will be dictated by the individual sarcoma type with initial chemotherapy for rhabdomyosarcoma in children followed by radiation therapy or surgery for residual disease.



(a) (b) (c) (d) (e)

Figure 14.6. (a) Lipoma in tail of the left parotid gland. (b) The CT scan is diagnostic of lipoma. (c) Intraoperative view of partial parotidectomy with parotid tail lipoma. (d) The specimen with arrows pointing to the lipoma. (e) Histopathology of the specimen confirmed the presence of lipoma.



(a) (b)

Figure 14.7. (a and b) MR images of infiltrating lipoma of submandibular region.

Rhabdomyosarcoma of the salivary glands appears locally aggressive with a poor prognosis (BenJelloun, et al. 2005). In malignant fibrous histiocytoma, clear surgical margins appear to be the most important prognostic factor (Sachse, et al. 2006). Angiosarcoma may affect the parotid as a primary or metastatic tumor and in a series of 29 angiosarcomas of the oral and salivary gland region, there were 4 primary parotid and 3 primary submandibular gland angiosarcomas, with a further 3 metastatic to the parotid (Fanburg-Smith, et al. 2003).

All of the metastatic patients died but patients with primary salivary gland angiosarcoma appear to have a better prognosis than cutaneous or deep tissue angiosarcomas. Malignant neural sarcomas are treated with wide excision and facial nerve grafting or reanimation (McGuirt, et al. 2003). Other sarcomas of the salivary glands are rare. Chadan, et al. (2004) found only 11 reported cases of salivary gland liposarcoma in the literature.

Sarcomas can involve any of the major salivary glands although parotid is most common and due to their rarity, treatment is usually on an individual and empiric basis (Figure 14.8).

Epithelial Non-salivary Tumors

The major salivary glands may be infiltrated by squamous cell carcinoma from the overlying skin or be primarily involved by melanoma. Surgical resection with a margin of normal tissue preserving the facial nerve and utilizing neck dissection and adjuvant radiotherapy as indicated by the tumor stage is the appropriate treatment (Figure 14.9).

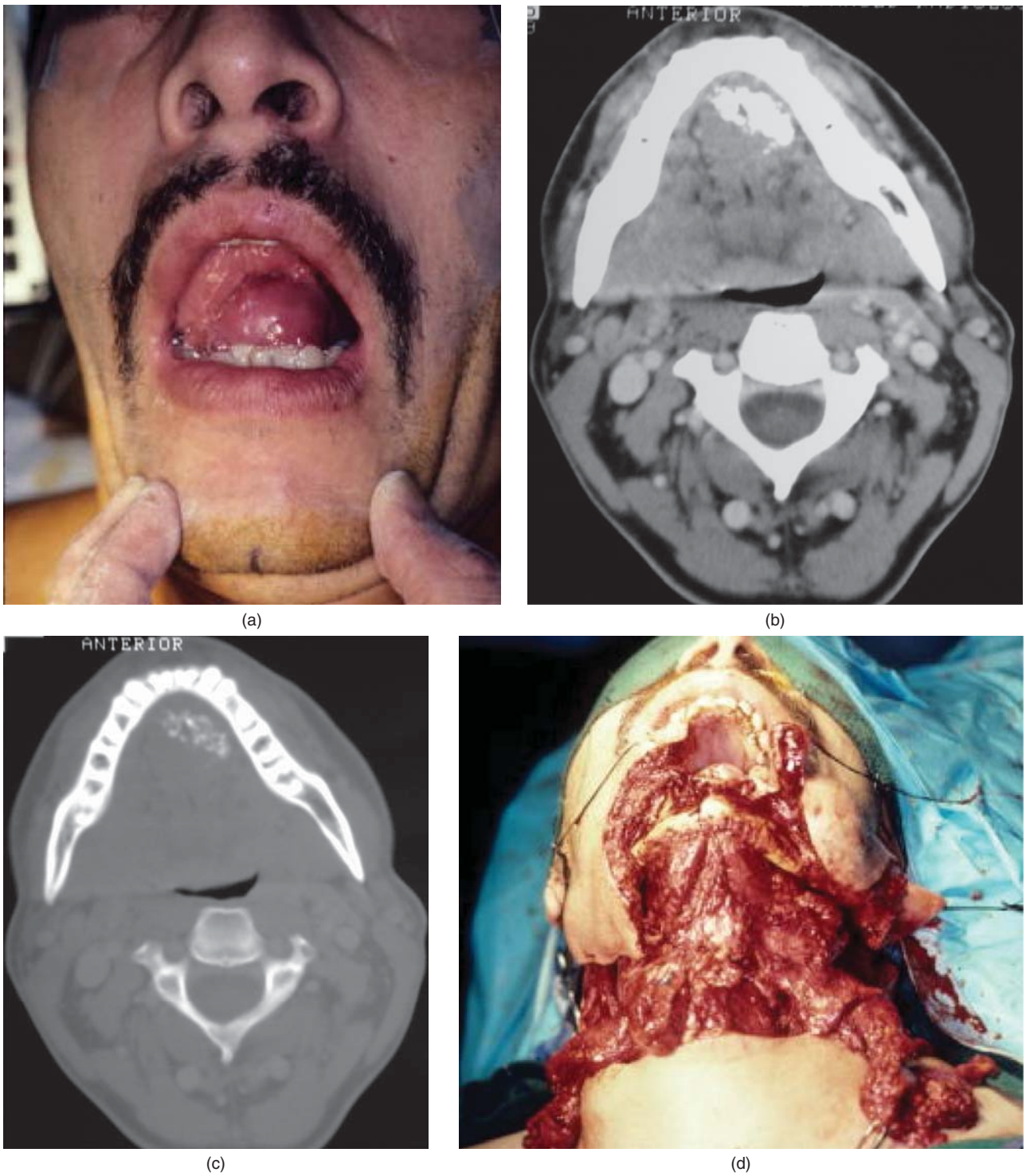
Tumors of Salivary Gland Lymph Nodes

PRIMARY LYMPH NODE TUMORS

Lymphomas

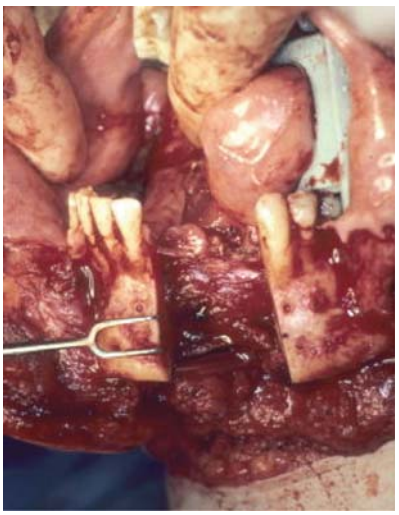
Primary lymphoma of the salivary glands is rare. Eighty percent of lymphomas of the salivary glands are found in the parotid gland and 20% in the submandibular gland, with only case reports of sublingual and minor gland involvement (Eraso, et al. 2005) (Figure 14.10).

Other authors have found a higher incidence of submandibular involvement (39%) (Dunn, et al. 2004). In 121 parotid tumors 8.3% were lymphomas (Shine, et al. 2006) and in 51 submandibular tumors 14% were lymphomas (Preuss, et al. 2007). Patients with Sjogren syndrome, AIDS, and hepatitis C have an increased risk of developing salivary lymphomas. In a review of 463 cases of Sjogren syndrome, 27 patients had a diagnosis of lymphoma (5.8%) (Tonami, et al. 2003). In this



(a) (b) (c) (d)

Figure 14.8. (a) Rapidly growing sublingual gland tumor diagnosed as synovial cell sarcoma on biopsy and immunohistochemistry. (b and c) CT images reveal calcification in the mass leading to an initial clinic diagnosis of a high grade malignant carcinoma ex. pleomorphic adenoma. (d) Access was accomplished via a lip split and mandibulotomy. Bilateral neck dissections were performed. (e) A paramidline mandibulotomy was required prior to excision of the floor of mouth and ventral tongue. (f) Surgical specimen. (g) Post resection: the reconstruction will be accomplished with a microvascular forearm flap. (h) Four weeks post-surgery. (i) Intraoral view showing the forearm flap reconstruction of the floor of mouth.



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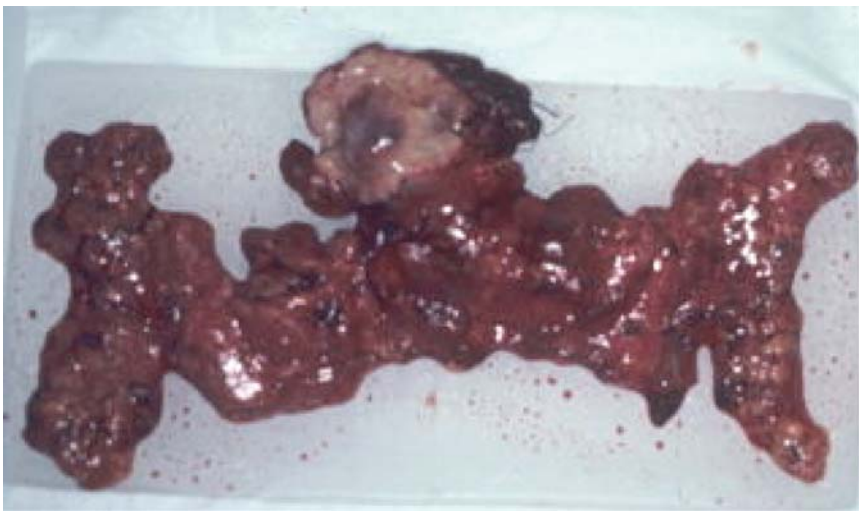

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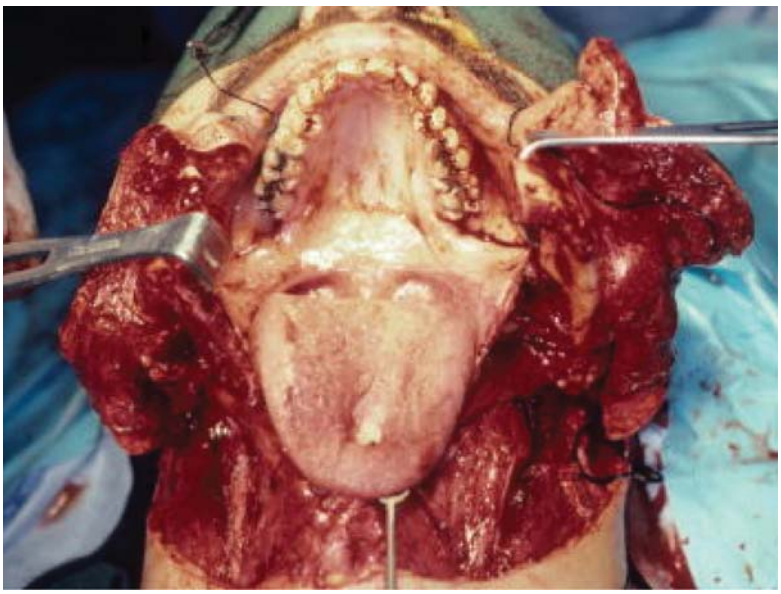

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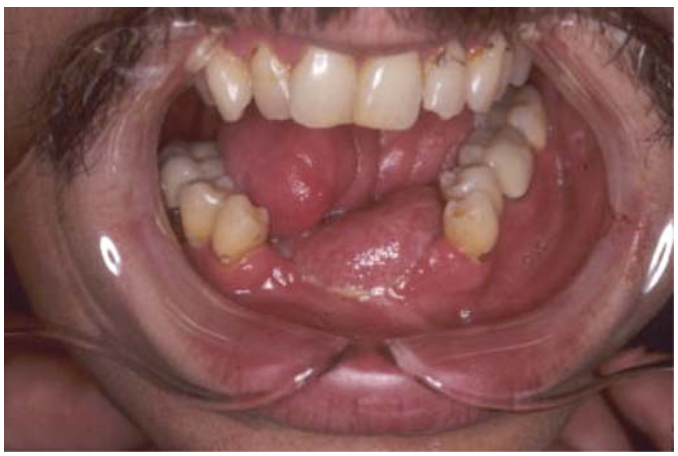


(i)

Figure 14.8. (*Continued*)

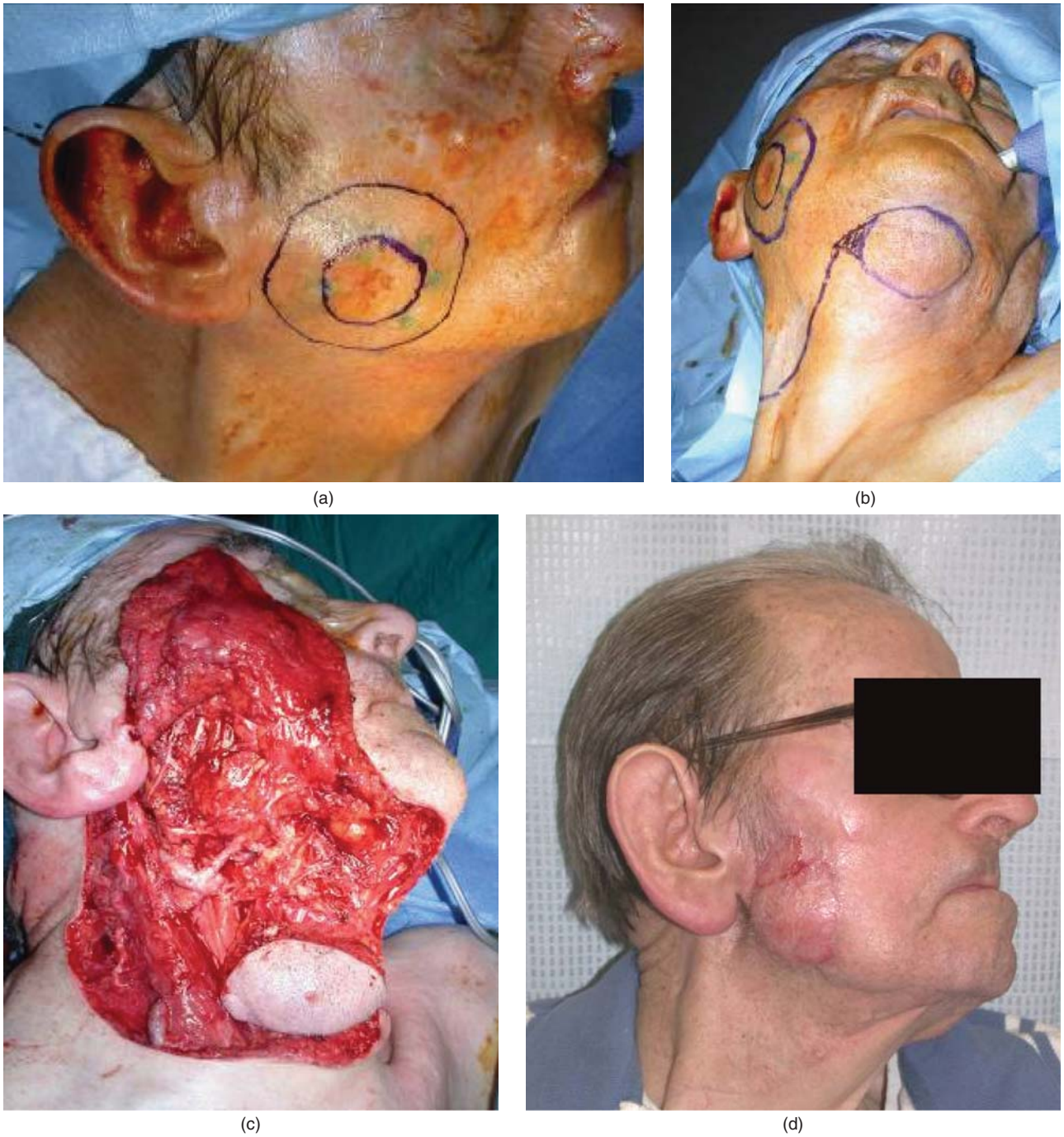
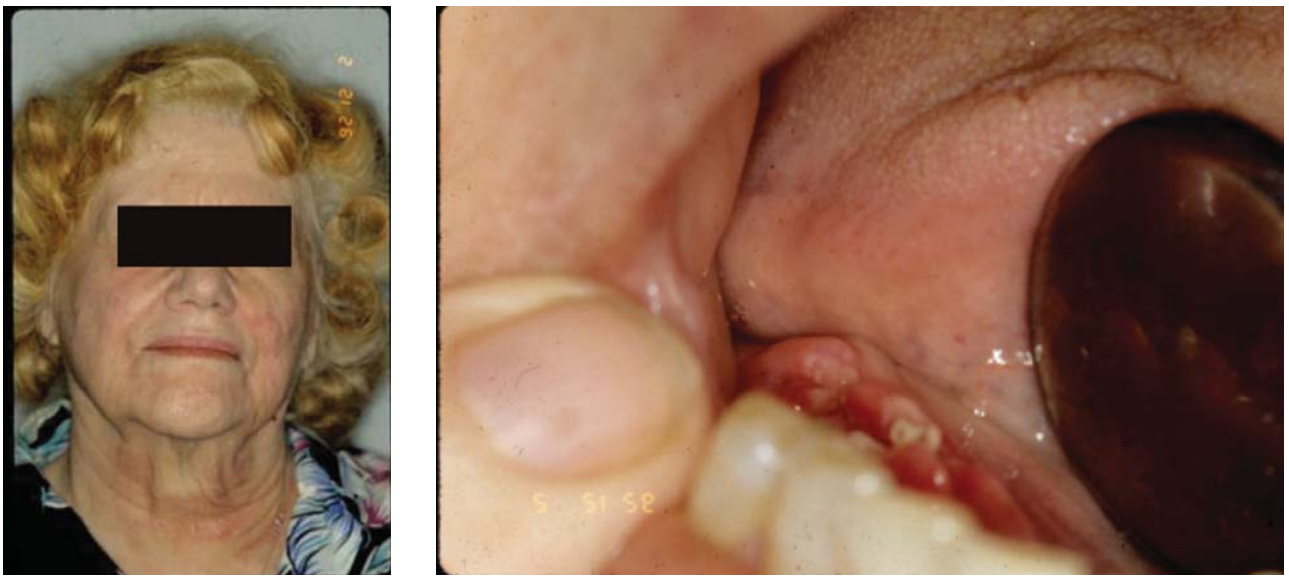


Figure 14.9. (a) Elderly man with primary desmoid melanoma of the parotid. A 2-cm margin is marked, the light blue staining of the skin around the lesion is from dye injection for sentinel node biopsy (patient has had lymphoscintigraphy immediately preoperative). (b) Markings for the proposed surgery, which is a total parotidectomy with left supraomohyoid neck dissection (unless sentinel nodes are found at Levels IV or V). Reconstruction with a submental flap based on the submental vessels. (c) The neck dissection and parotidectomy with preservation of the facial nerve is complete, the submental flap is pedicled on its vascular supply prior to be rotated into the defect. (d) Three months postoperative view of the patient.



(a) (b)

Figure 14.10. (a) Elderly woman with itchy facial and neck rash who complains of an intraoral swelling. (b) The patient's finger is retracting the commissure and the mouth mirror the tongue and a red fleshy swelling of the sublingual gland can just be appreciated. Biopsy showed a non-Hodgkin lymphoma of the sublingual gland.

series, 26 of the 27 patients had non-Hodgkin lymphoma, including 6 mucosal-associated lymphoid tissue (MALT lymphomas), and only 1 patient had Hodgkin lymphoma. At the initial presentation, 14 (52%) of patients had extranodal disease, with 9 of 27 (33%) in the salivary glands. However, 21 patients (78%) had nodal involvement mostly in the cervical nodes. Masaki and Sugai (2004) also give a figure of 5% of stage III Sjogren patients developing lymphomas, which are thought to arise from lymphoepithelial lesions. The B-cells in these lesions become activated by interactions between CD40L and CD40, with progression from polyclonal lymphoproliferation to monoclonal lymphoproliferation to MALT lymphoma, and finally to high grade lymphoma as a multistep process. Other authors have highlighted the difficulty diagnosing true lymphoma from the other lymphoproliferative disorders occurring in Sjogren syndrome, although there is a 40-fold increased risk in developing B-cell lymphomas (Prochorec-Sobieszek and Wagner 2005). Clinical features associated with lymphoma include persistent major salivary enlargement (>2 months), persistent lymphadenopathy or splenomegaly, monoclonal gamopathy, and type II mixed cryoglobulinemia.

Hepatitis C is also associated with MALT lymphomas of the salivary glands. In a series of 33 cases of primary salivary MALT lymphomas, 15 patients had a history of Sjogren syndrome (42%), 2 (6%) other autoimmune disease, and 7 (21%) hepatitis C infection (Ambrossetti, et al. 2004). There is an increase in lymphoma in AIDS, however, although 51% of patients in a study of 100 patients who died with AIDS with no salivary gland symptoms showed histologic signs of parotid disease, only one case of lymphoma was found (Vargas, et al. 2003) (Figure 14.11).

Not all primary salivary lymphomas fall into the MALT group and follicular lymphomas comprise 30 and 22% of two recently published series (Kojima, et al. 2001; Nakamura, et al. 2006) (Figure 14.12). These lymphomas have a younger age of onset than MALT lymphomas, do not occur in patients with autoimmune disease, and appear relatively more common in the submandibular gland.

Most salivary lymphomas present as unilateral, painless masses, usually with a history of <4 months and, although CT scans show poorly defined indistinct margins, there is no pathognomic sign for salivary lymphoma (Shine, et al. 2006; Shum, et al. 2014). The lesions may be multiple in the ipsilateral gland and lymphadenopathy can be associated. The use of FNAB in diagnosing salivary lymphoma is questioned as inaccurate with high

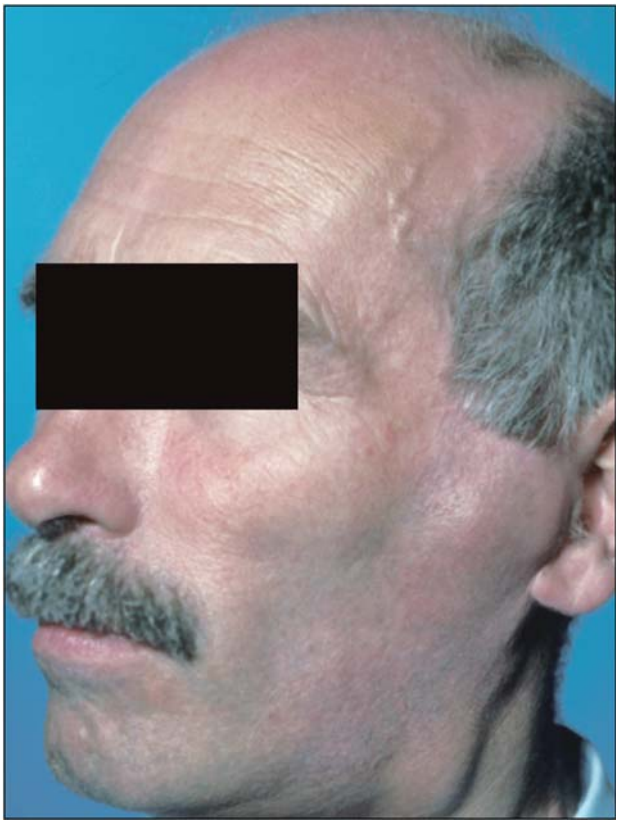


Figure 14.11. A 52-year-old man with left parotid mass and firm level II node who has a salivary lymphoma as a presenting sign of previously undiagnosed AIDS.

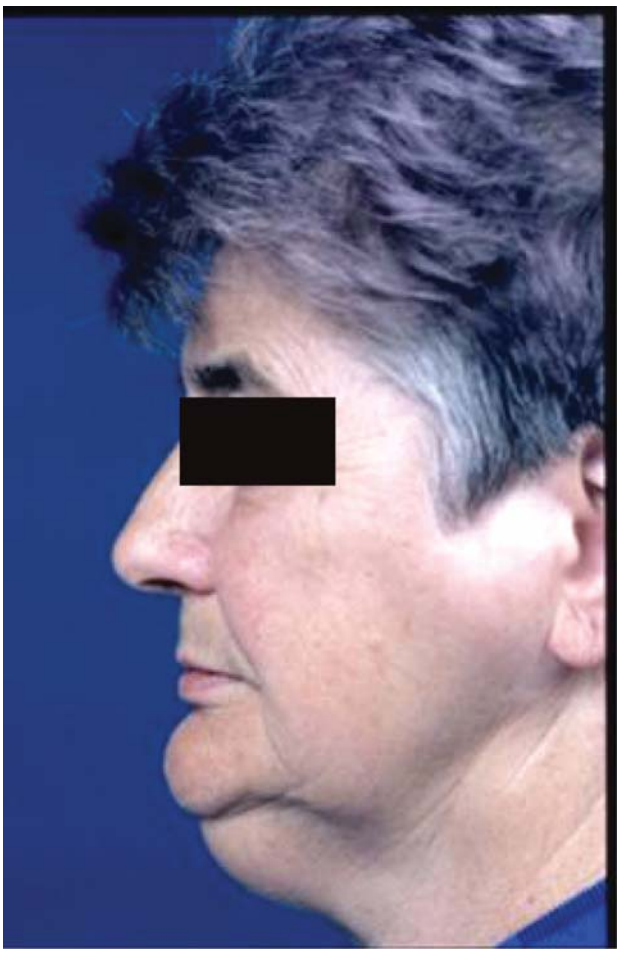


Figure 14.12. Non-Hodgkin lymphoma of the left parotid and submental nodes.

rates of false negative results (Zbären, et al. 2001). Zurrida, et al. (1993) were only able to identify two of seven lymphomas (28.6%) and Hughes, et al. (2005) found a 57% false negative rate in salivary lymphomas in reviewing the data from the College of American Pathologists Interlaboratory Comparison Program in Nongynecologic Cytology. In the absence of Sjogren syndrome or clinical suspicion of lymphoma, these lesions are frequently diagnosed following surgical removal.

Treatment is by chemotherapy, medical therapy, and radiation therapy, depending on the histologic diagnosis and the clinical staging. MALT lymphomas of salivary gland appear to have a low grade indolent course with 5-year overall survival, cause specific survival, and progression free survival of 85% (+/− 8%), 94% (+/− 6%), and 65% (+/−10%), respectively (Ambrossetti, et al. 2004). These results were the case despite 42% of their patients being stage IV and local therapy was often adequate (Figure 14.13). Dunn, et al. (2004) in 23 primary salivary lymphomas, 19 MALT, 3 diffuse large cell, and 1 follicular, found overall 5-year survival of 94.7% and relapse free survival of 51.4%. Only two patients died; one patient had a MALT lymphoma that transformed into a diffuse large cell lymphoma. In a series of 63 patients with MALT lymphoma involving the salivary glands, 41 received multimodal therapy (37 with surgery as a treatment) and 9 by surgery alone. Five-year disease free survival was 54.4%, disease specific survival 93.2%, and overall survival 81.7%. Factors significant for disease free survival were the use of radiation therapy, stage, and residual tumor. Factors significant in disease specific survival were stage, recurrence, and residual tumor. The authors concluded that recurrence can occur in up to 35% at 5 years, although survival is not affected and that radiotherapy is the only modality that improves disease specific survival (Anacak, et al. 2012).

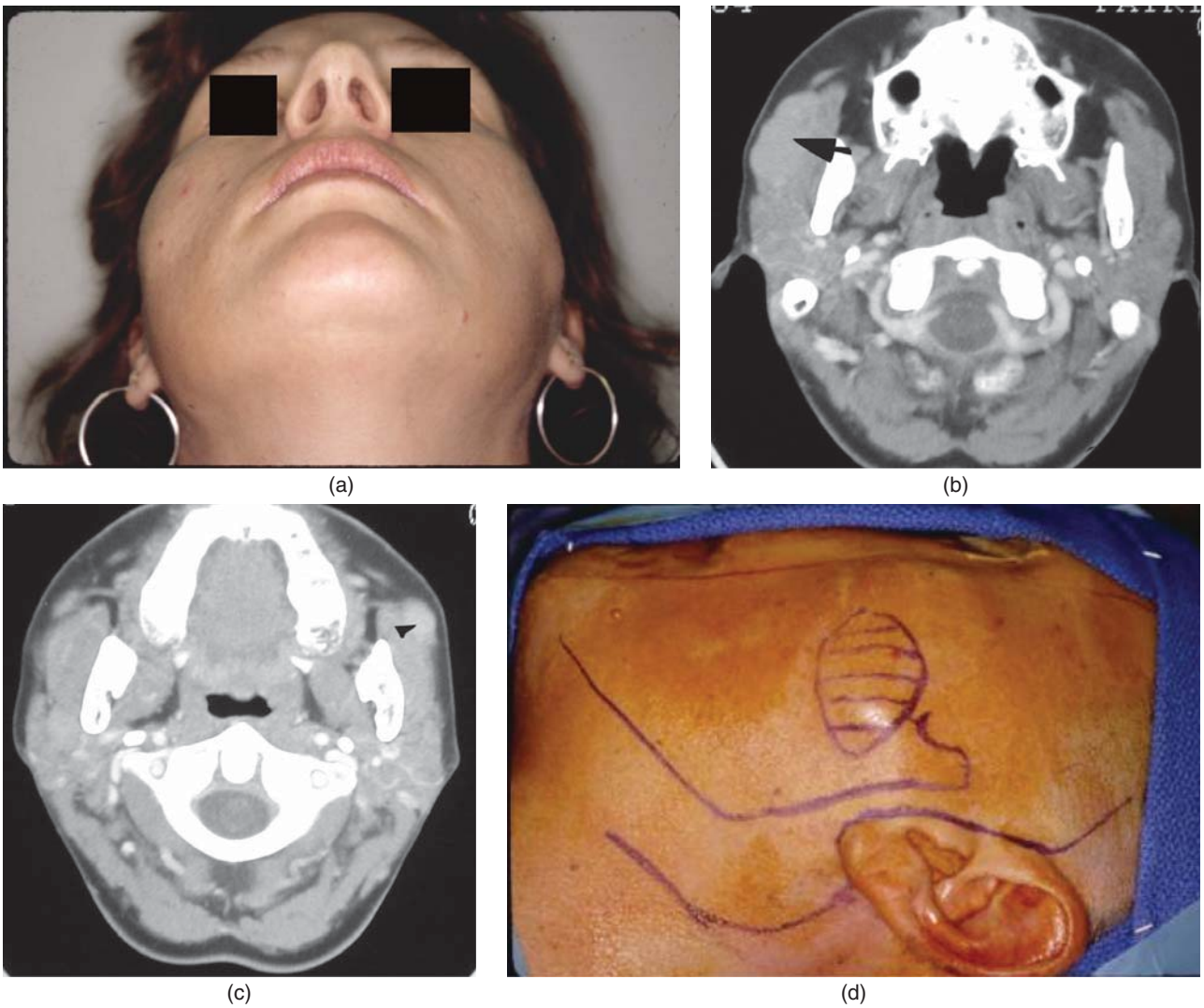


Figure 14.13. (b) A 35-year-old woman with MALT lymphoma of the Waldeyer ring controlled by chemotherapy. Now has bilateral parotid involvement, which is not responding to medical therapy and is concerned regarding her appearance. (b and c) CT scans show bilateral parotid involvement (arrows), which has slowly increased in size over a 3-year period. (d) Proposed parotidectomy and excision of MALT lymphoma.

The largest study of extranodal marginal zone MALT lymphoma of the salivary glands is from the Surveillance Epidemiology and End Results (SEER) data base with 577 cases available for frequency/incidence analysis and 712 for relative survival. The parotid gland was the site of 80.9% of cases and 73% of patients were female. Fifteen-year relative survival was 78.45%, worse in blacks and advanced stage disease. There was no survival difference between cases treated with surgery, radiation therapy, or both. The study concludes that early stage disease could be treated by unimodality therapy and that even advanced stage disease has a relatively high survival (Vazquez, et al. 2013). Kojima, et al. (2001) noted that follicular lymphomas arising from salivary glands appeared to share some of the characteristics of MALT lymphoma with an indolent prognosis.

SECONDARY LYMPH NODE TUMORS

Regional Metastases

The lymph nodes associated with the major glands may all be involved by regional metastases. In the

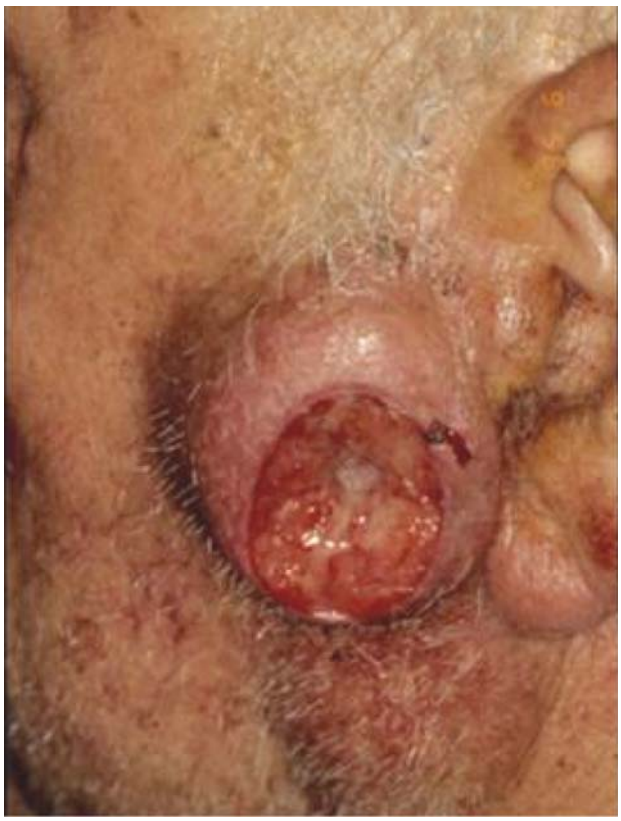


Figure 14.14. Malignant syringoma of forehead metastatic to left parotid and fungating through preauricular skin.

parotid gland, skin cancer, particularly squamous cell carcinoma (SCC) and malignant melanoma (MM) of the scalp, forehead, temple, upper lip, cheek, and ear, is most common; although Merkel cell tumors, malignant syringomas, and other more unusual skin cancers can be seen (Figure 14.14).

The largest experience with these tumors is in Australia where squamous cell carcinoma and melanoma of the facial skin is epidemic and metastatic cutaneous cancer is the commonest parotid malignancy (O'Brien, et al. 2002). Although fewer than 5% of patients with cutaneous SCC do metastasize to lymph nodes, certain features may place these tumors at increased risk of metastasizing. In a review of 266 patients, 61% having parotid lymph node involvement +/− cervical involvement, tumor thickness >4–5 mm, and proximity to the parotid (temple/forehead, cheek, or ear) were high risks, and increasing tumor size and recurrence contributed to an increased risk (Vaness, et al. 2006) (Figure 14.15). In 2002, O'Brien, et al. suggested that the TNM system of designating all nodal metastases from cutaneous cancer N1 was limited and did not accurately delineate the extent of disease. They suggested separating disease in the parotid P1 <3 cm, P2 >3 cm, and <6 cm, P3 >6 cm from neck disease: N0 no nodal disease, N1 a single node <3 cm, N2 multiple nodes, or any node >3 cm for staging. In a multivariate analysis of 87 patients, they found that increasing P stage, positive margins, and lack of adjuvant radiation therapy independently predicted for decreased local control in the parotid. Clinical and pathologic N stage both significantly impacted survival. They concluded that patients with positive nodes in both parotid and neck had the worst prognosis, and that prognosis was worse for nodal disease >N1 (Figure 14.16). A much smaller study from Israel showed a zero overall survival rate for patients with both parotid and cervical nodes positive for metastatic cutaneous SCC (Barzilai, et al. 2005) Using the separate staging system for parotid disease (P) and neck disease (N) proposed by O'Brien, et al. (2002), two recent studies have been published. One series of 67 patients from New Zealand found again that the extent of parotid disease was an independent prognostic factor and those patients with both parotid and neck disease did worst, although interestingly adjuvant radiation therapy did not influence survival in their data (Ch'ng, et al. 2006). The second paper was a retrospective multi-center trial from three Australian and three US centers, with 322 patients with metastatic cutaneous SCC to the parotid and/or neck. Results from this study show a significantly worse 5-year survival for patients with advanced P stage 69% versus 82% for early P stage; and 61% with parotid plus neck disease versus 79% for parotid alone. This study supported the adoption of the new staging system separating parotid and neck disease (Andruchow, et al. 2006).

In terms of treatment of metastatic cancer to the parotid, Bron, et al. (2003) reviewed 232 cases of which 54 were primary parotid cancers, 101 were metastatic cutaneous SCC, 69 MM, and 8 with other metastatic cancers. Patients were treated with primary surgery sparing the facial nerve where indicated, with 54 therapeutic and 110 elective neck dissections, and 78% of the patients had adjuvant radiation therapy. Five-year survival rates were 77% for primary cancers, 65% for metastatic SCC, 46% for MM, and 56% for other metastatic cancers. As expected, local failure was highest in metastatic SCC and distant failure in MM.

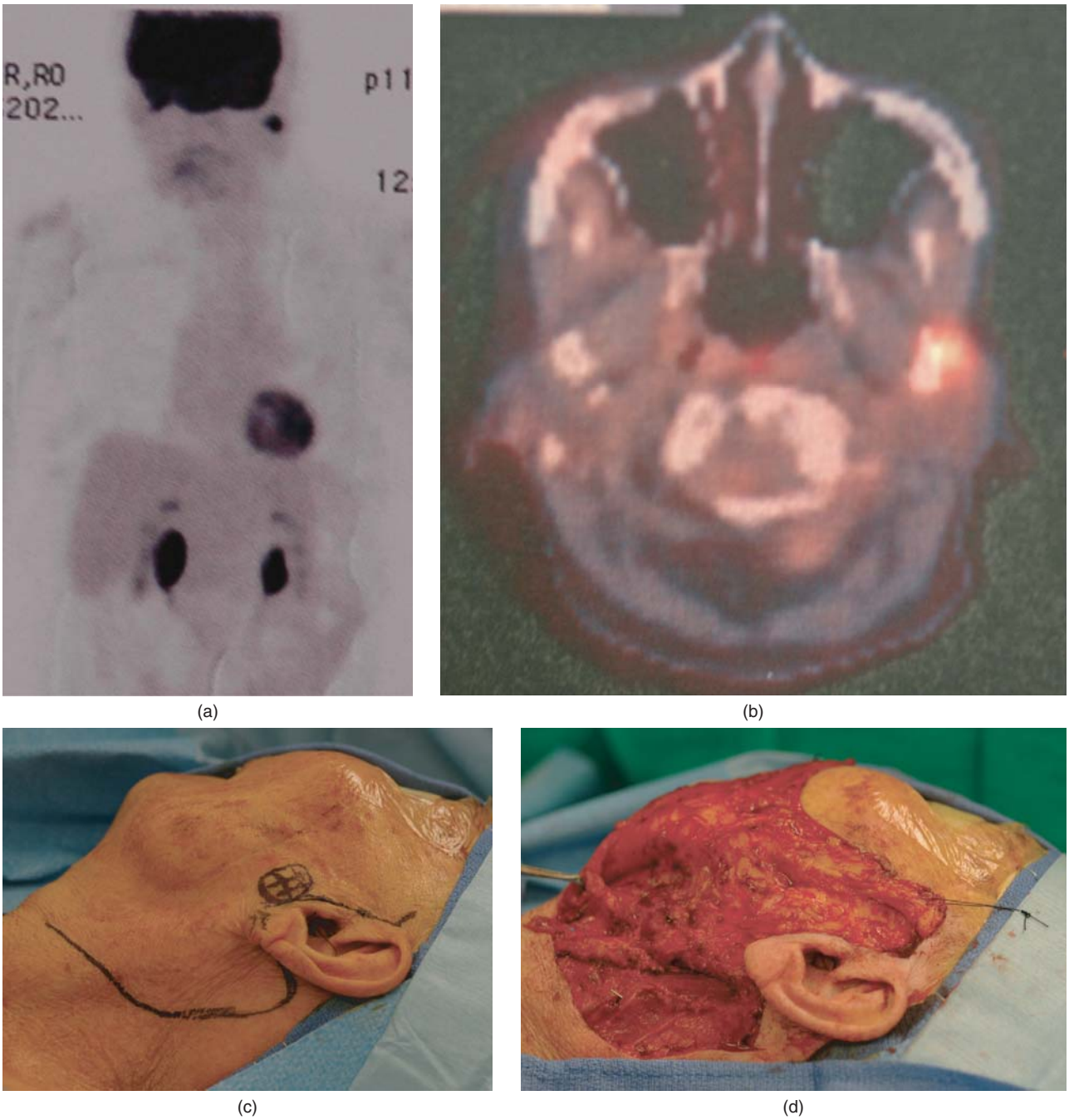
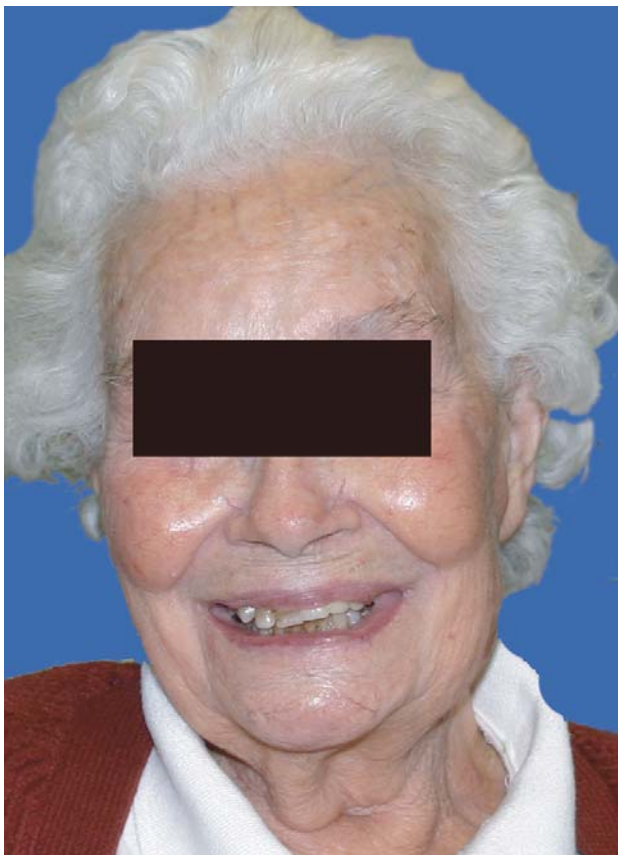


Figure 14.15. (a) PET scan of an elderly woman with left preauricular mass post resection of SCC of cheek. Scan shows a hot spot SUV 6.7. (b) Fused PET/CT confirms positive node in the parotid. (c) Proposed surgery of superficial parotidectomy with extended Blair incision to allow for supraomohyoid neck dissection. (d) Incision allows wide access down to level III. (e) Postoperative patient has no nerve weakness.



(e)

Figure 14.15. (*Continued*)

In treating patients with nodal involvement of the parotid, superficial parotidectomy with wide excision to obtain negative margins is indicated with facial nerve sacrifice if it is infiltrated. When the neck is also involved, level II is the commonest site and in these cases a comprehensive neck dissection is recommended. If the neck is clinically uninvolved (N0), and the primary cancer anterolateral to the parotid, then a supraomohyoid neck dissection including the external jugular nodes is indicated (Figure 14.15). With positive cervical nodes, a modified radical or radical neck dissection is indicated (Figure 14.16) and with a posterior primary, level V should be dissected as well (Figure 14.17) (Vauterin, et al. 2006). Adjuvant RT is given in node positive necks for close margins or perineural invasion. In the case of MM where sentinel lymph nodes are identified in the parotid by scintigraphy, intraparotid sentinel lymph node biopsy is a reliable, accurate, and safe procedure (Loree, et al. 2006) (Figure 14.9).

In two recent comprehensive reviews of the management of regional lymph nodes from squamous cell carcinoma and malignant melanoma of the skin, the authors examined the role of surgery in the neck and parotid gland (Gurney and Newlands 2014; Newlands and Gurney 2014). In malignant melanoma for P0/N0 the authors recommend sentinel node biopsy rather than elective neck dissection. Even in positive sentinel node biopsy the authors provide evidence that a completion neck dissection does not confer a 5-year survival benefit over a watch and wait policy. In P+ N0 therapeutic parotidectomy and neck dissection levels I-V is recommended, and in P0 N+ if the cutaneous primary is likely to have drained through the parotid then superficial parotidectomy should be performed with an I-V neck dissection. Similarly for cutaneous squamous cell carcinoma the authors recommend no role for elective neck dissection in P0 N0 disease. Whether sentinel node biopsy is useful for high risk cutaneous SCC is currently under investigation. In P+/N0 disease parotidectomy and selective regional approach to the elective neck is recommended (Gurney and Newlands 2014; Newlands and Gurney 2014). Different recommendations in the elective management of cervical and parotid lymph nodes in N0 cutaneous SCC were given following a decision analysis approach. In this study, the authors concluded, using a decision tree and probabilities of recurrence and salvage from the literature, that a wait-and-see approach is justified when the probability of occult metastasis is <19%. When the probability of metastasis exceeds 25%, elective neck dissection has a higher utility than observation (Wong and Morton 2013).

In addition to regional metastasis from cutaneous primary cancers, metastasis can occur from non-cutaneous head and neck carcinomas. Metastasis to the parotid from other head and neck sites, for example the oral cavity, is more common if the usual lymphatic drainage pattern has been disrupted by previous neck dissection or radiation therapy (Ord, et al. 1989). It is also possible for mucosal melanoma to metastasize to the parotid region (Figure 14.18).

There are fewer reports of involvement of the submandibular gland being directly involved by lymph node metastases, although it is routinely removed during neck dissection. The lymph nodes are not usually found within its capsule; however, Preuss, et al. (2007) found that in

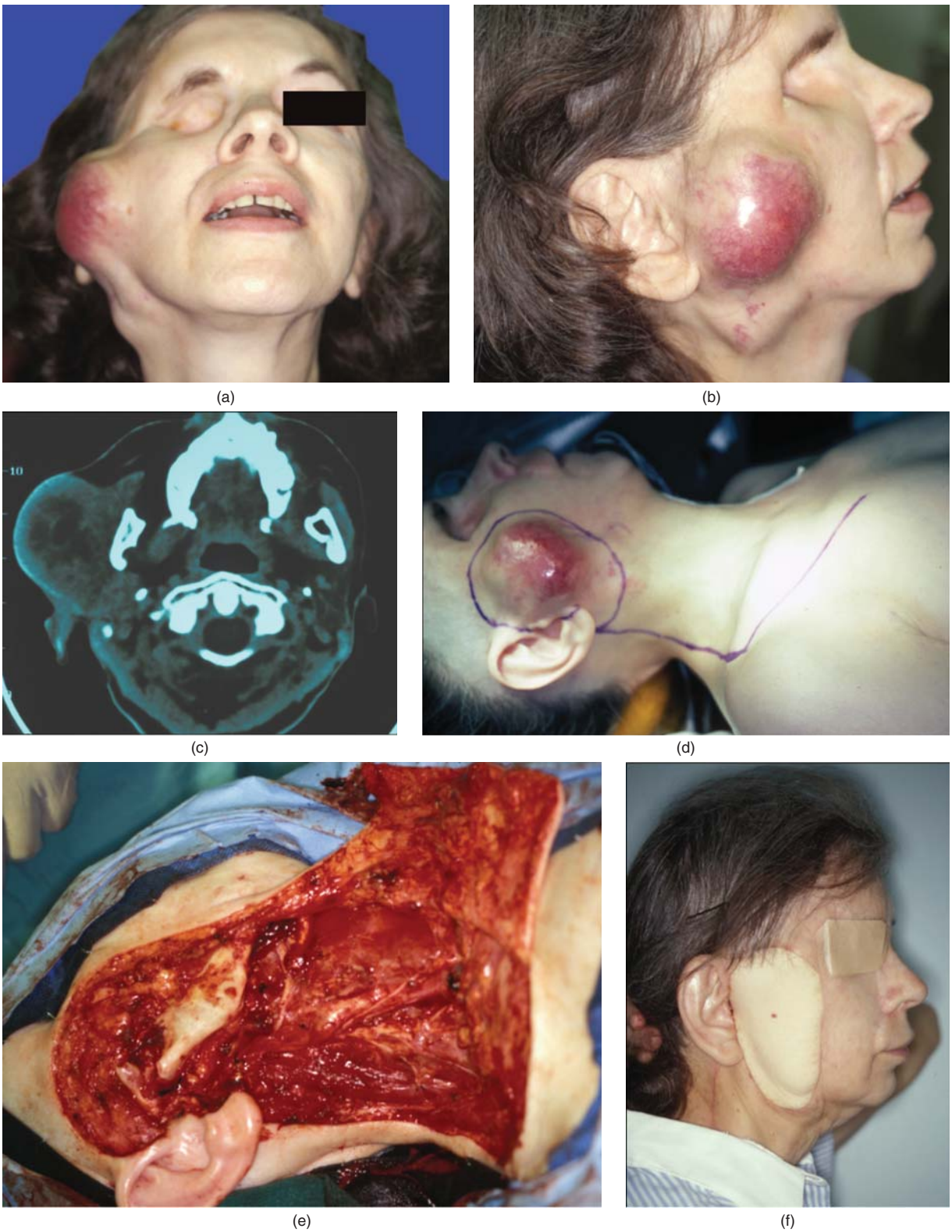
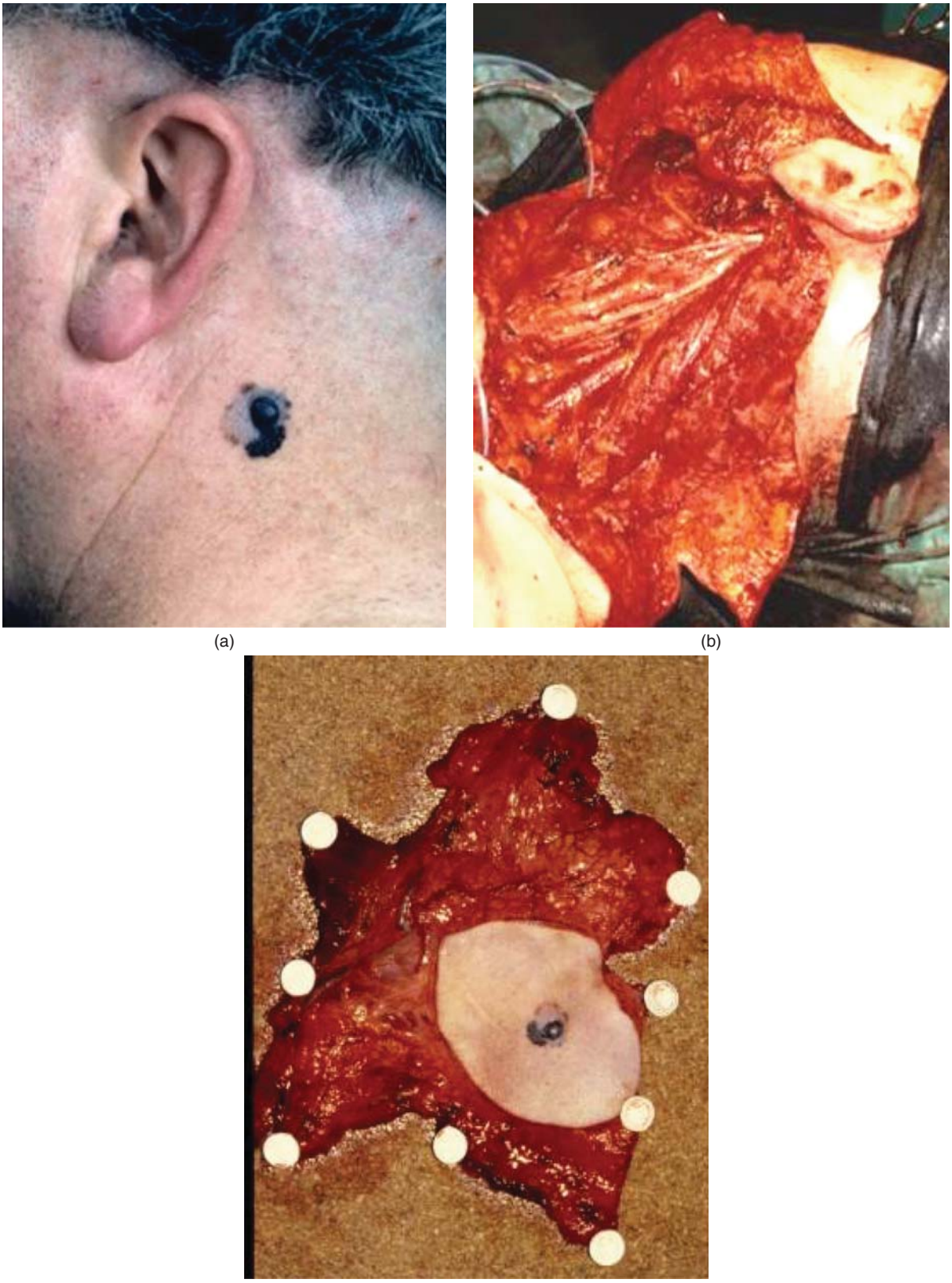


Figure 14.16. Full face (a) and lateral (b) view of an elderly woman who had excision of right eyelids and right orbital exenteration for advanced squamous cell carcinoma of the lids. (c) She was lost to followup and now presents with massive disease in the parotid nodes (P3) and Level II neck nodes (N2). (d) Proposed surgery with radical parotidectomy and radical neck dissection. (e) The masseter muscle is sacrificed along with the facial nerve and a total parotidectomy. The mandible was uninvolved by tumor and was preserved. (f) Reconstruction is accomplished with a latissimus dorsi flap. Patient developed chest metastases 18 months post-surgery.



(a) (b) (c)

Figure 14.17. (a) Patient with nodular melanoma of posterior neck with palpable parotid lymph nodes. (b) Post total parotidectomy and radical neck dissection. (c) Surgical specimen with 5-cm skin margin. Patient developed lung metastases within 6 months and died of disease.

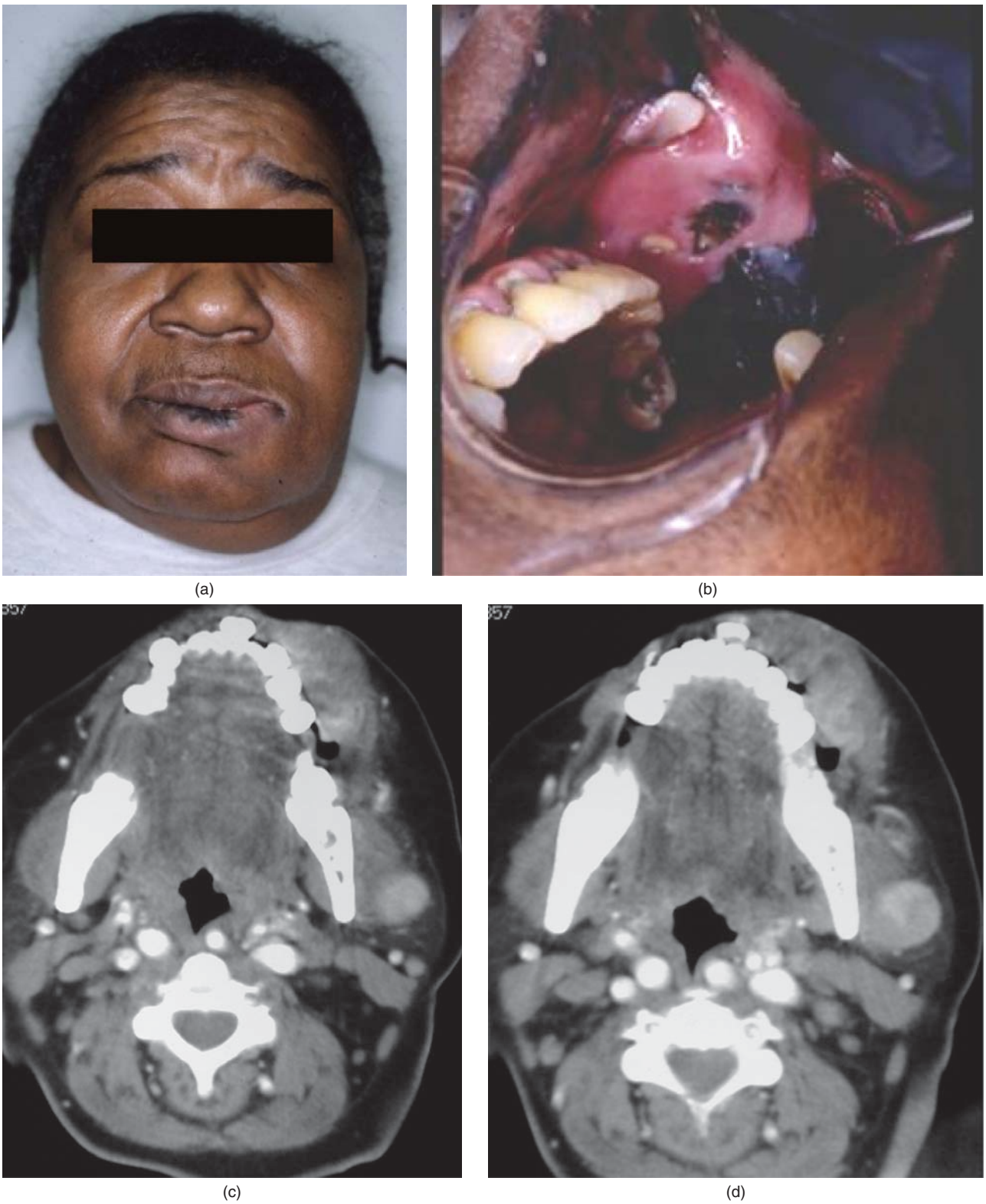
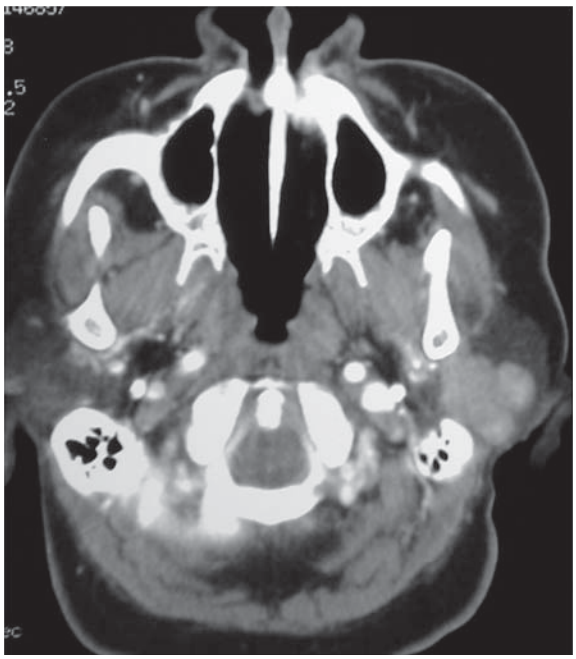


Figure 14.18. (a) Patient with large lymph node swelling at level I and pigmented melanoma of lower lip. (b) Intra oral exam shows deeply pigmented melanoma involving the buccal mucosa and extending to the retromolar region. (c and d) CT scans show primary melanoma as thickening of the left cheek and lip with nodal involvement of the parotid. (e) CT scan at a more cephalad level now shows multiple positive nodes in the parotid gland. (f and g) Hematoxylin and eosin stain of the tumor (f), and HMB-45 stain (g) confirming the diagnosis of melanoma.



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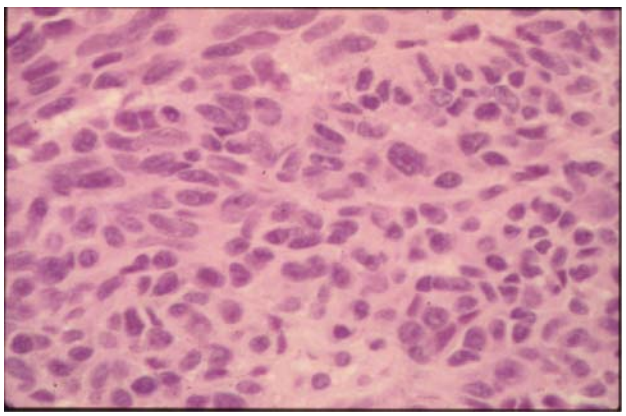

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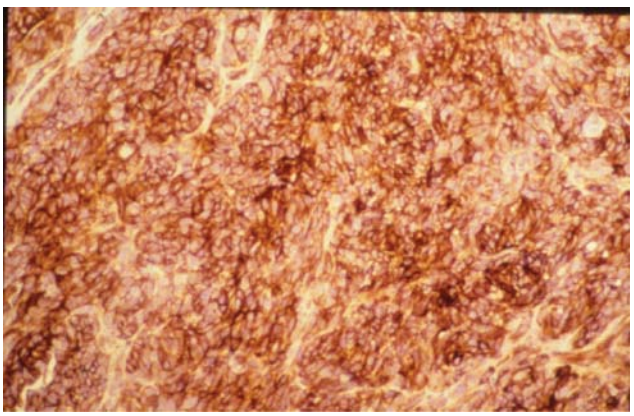
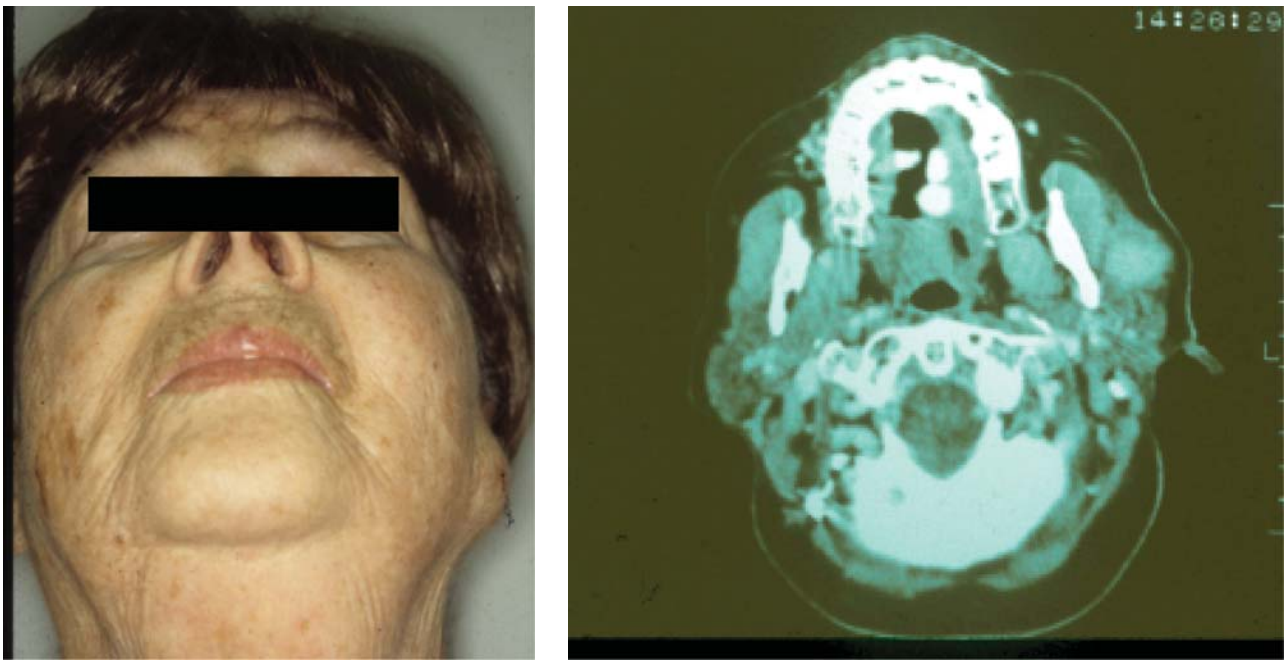


(g)

Figure 14.18. (*Continued*)

24 malignant submandibular gland tumors (30%) were metastatic, 3 from the oropharynx, 2 from the nasopharynx, and 2 with unknown primaries.

In the sublingual gland metastatic spread from tongue cancer to sublingual nodes is not common and was first reported in three cases in 1985 (Ozeki, et al. 1985). In one study of 253 patients with 326 neck dissections, 5 cases of lingual lymph node metastases were found and in all these cases bilateral cervical nodes were found (Woolgar 1999). In a combined study between the University of Maryland and Peking Union Medical College, we were only able to identify two cases (Zhang, et al. 2011). Whether these may explain some cases of "local" recurrence with previous negative margins is unclear. Certainly these lingual nodes would be removed in composite or "commando" resections where the tongue primary is removed in continuity with the neck dissection, but they may be left in cases where the primary is resected from an intraoral approach and the neck dissection is performed separately. One study reports a 5-year actuarial survival of 80% for patients treated with incontinuity neck dissection compared to 63% for those with discontinuity dissection (Leemans, et al. 1991). However, these



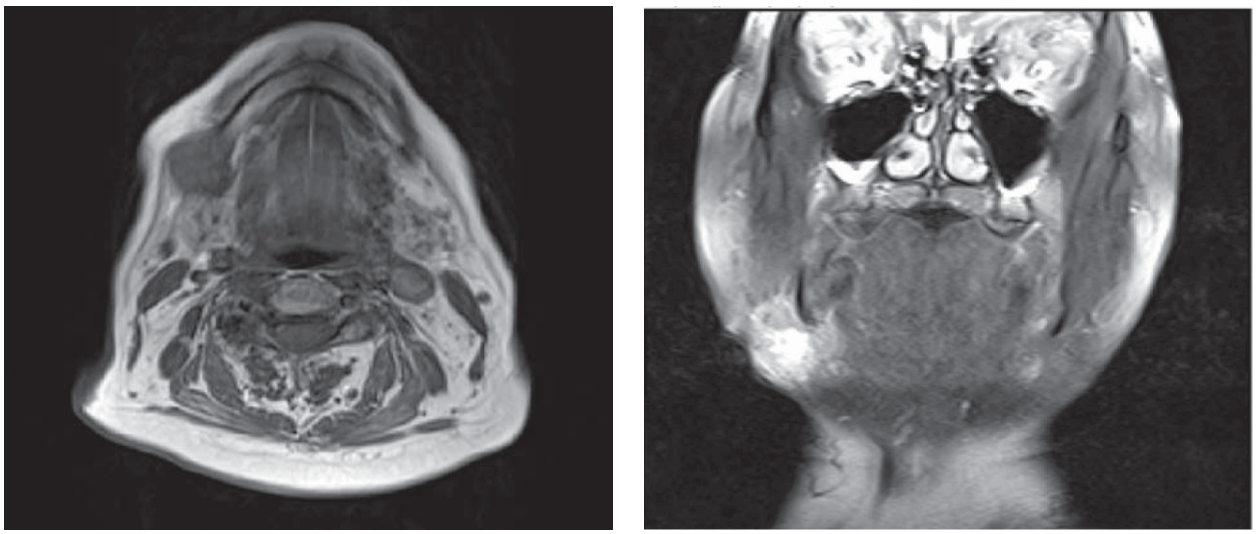
(a) (b)

Figure 14.19. (a) An 80-year-old woman with known small cell carcinoma of the lung presenting with a metastatic mass in the left parotid gland. (b) CT scan of the patient in (a).

findings were contradicted in a later study that retrospectively studied 193 patients grouped into three cohorts of incontinuity, discontinuous resection, and delayed discontinuous neck dissection. There was no difference in disease free survival, cancer specific survival, or between early stage and late stage disease (Tesseroli, et al. 2006). Whether some of this difference in survival is attributable to involvement of sublingual gland nodes is unknown.

Distant Metastases

The major salivary glands can also be a site for distant metastatic disease, especially the parotid gland, although these cases are rare. In a literature review of over 800 patients with metastatic disease in the parotid 80% were from cutaneous SCC or melanoma (as described previously), while 66 were non cutaneous head and neck tumors, and 87 from a distant primary site (Pisani, et al. 1993). In their personal series of 38 patients, 10 had non-cutaneous head and neck cancers while 4 were from distant sites (2 renal and 2 lung). Nuyens, et al. (2006) found 34 of 520 parotid tumors to be metastatic; 31 from cutaneous primaries, 2 from ductal breast cancer, and 1 from a limb rhabdomyosarcoma. Although rare, these distant metastases can provide a diagnostic challenge as the two commonest primary sites appear to be lung and kidney. Small cell lung cancer is very difficult to differentiate from primary small cell carcinoma of the salivary gland so CT scan of the lungs is an essential part of the work up (Figure 14.19). Primary small cell neuroendocrine carcinomas of the salivary glands are rare comprising 1.85–2.8% of salivary gland tumors (Gnepp and Wick 1990; Baca, et al. 2011) (Figure 14.20). In a small series of five cases of neuroendocrine and small cell carcinomas of the parotid, one of the authors (RAO) found only one primary parotid cancer. Salivary glands are the second commonest head and neck site for primary small cell carcinomas (larynx being the most common) and they are aggressive tumors with an overall poor prognosis (Renner 2007). They are divided into neuroendocrine and ductal types, and according to cytokeratin 20 immunoreactivity the ductal sites can be subdivided into pulmonary and Merkel types (Nagao, et al. 2004). This study indicated that negative immunostain for cytokeratin 20 could be a marker for poor prognosis and also that salivary gland small cell carcinoma



(a) (b)

Figure 14.20. (a) Axial MR shows right submandibular gland mass approximating the lower border of mandible. (b) Coronal MR shows enhancement of mass, cortical bone of mandible appears intact. (c) FNAB cytology reported as small blue round cell tumor with neuroendocrine features. (d) Hematoxylin and eosin stain of final specimen, post selective neck dissection and marginal mandibular resection of the inferior mandible, shows squamous cell carcinoma with neuroendocrine features. (e) (Synaptophysin stain) and (f) (CD56 immunohistochemical stain) showing positivity and confirming neuroendocrine nature of this tumor. Source: Figures 14.20 (c–f) Dr John C. Papadimitriou, Professor of Pathology, Department Pathology University of Maryland. Reproduced with permission of Dr Papadimitriou.

may have a better prognosis than extra-salivary sites. A later study has shown absence of Merkel cell polyoma virus in these parotid tumors, irrespective of the cytokeratin 20 status (Chernock, et al. 2011).

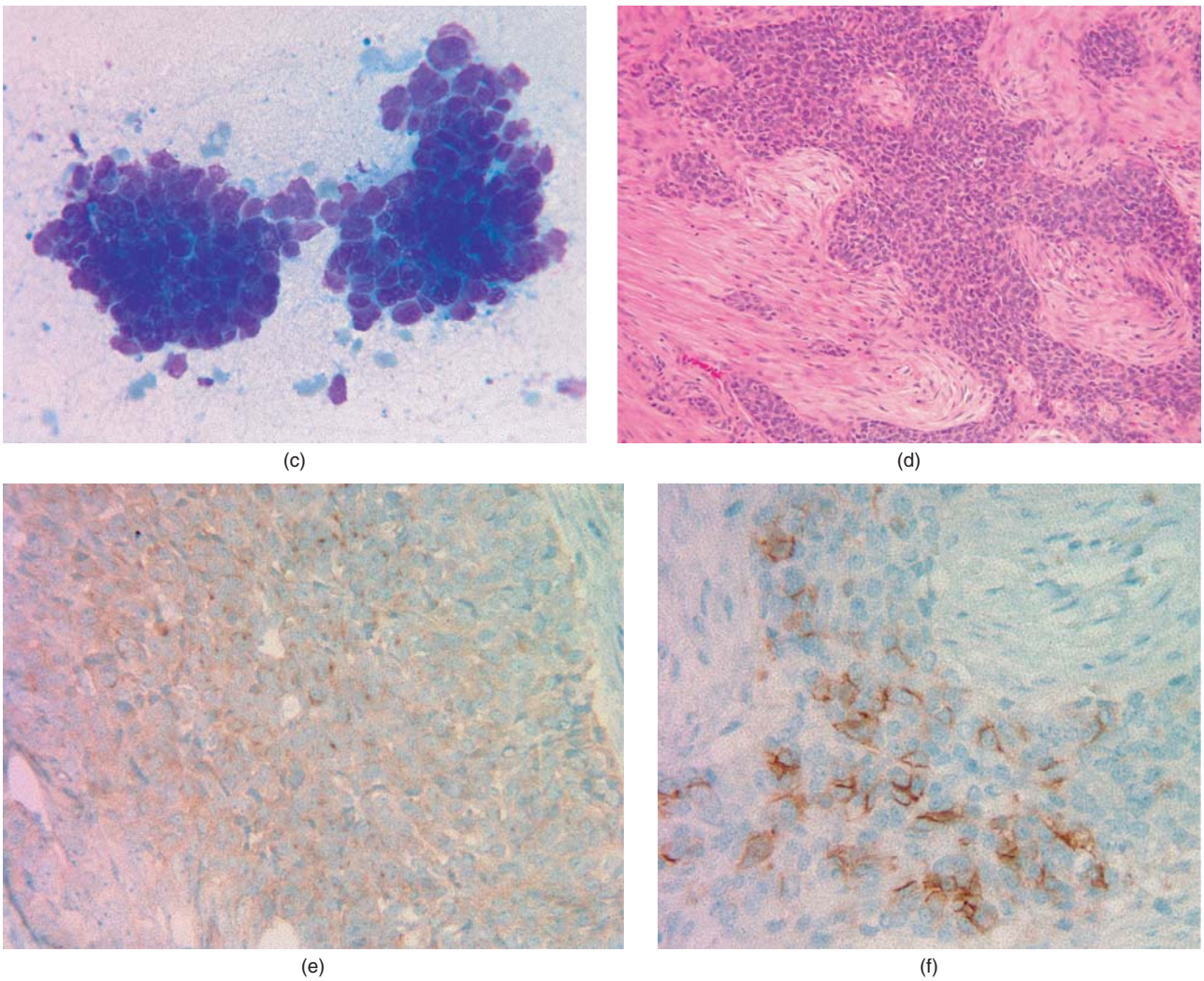
In a single case report, immunohistochemical study of estrogen receptors was used to identify a parotid tumor as a breast metastasis (Perez-Fidalgo, et al. 2007).

Regarding distant metastases from renal cell cancer the same problem is found. Most of these will be from clear cell renal carcinoma and mimic the salivary clear cell adenocarcinoma or clear cell variant of mucoepidermoid carcinoma, which are both primary salivary gland cancers. In a case report and review of the literature, Park and Hlivko (2002) were able to find 25 cases of metastatic renal cell carcinoma to the parotid gland. In 14 of these cases (56%), the metastasis was the initial presenting sign of a previously undiagnosed renal carcinoma. None of the cases presented with facial paralysis and the authors were able to make the diagnosis in three of six cases with FNAB. In a small series of our own patients, we were able to differentiate renal cell carcinoma from monomorphic clear cell salivary adenocarcinoma by immunohistochemistry and electron microscopic ultrastructural differences (Rezende, et al. 1997).

Distant metastasis to salivary glands other than the parotid gland appears to be extremely unusual, although a unique case of bilateral submandibular gland metastases from breast carcinoma was published in 2001 (Cain, et al. 2001).

Miscellaneous

It is difficult to include every disease process that can present rarely in the parotid gland. We recently published a case of unicentric Castleman disease in the parotid gland that we surgically resected (Reece, et al. 2012). It appears that the unicentric type is benign in nature and can be cured by simple excision or parotidectomy. An analysis of 10 cases of Castleman disease in the parotid and neck also concluded that surgical resection is the choice of treatment with excellent results (Zhong, et al. 2009).



(c) (d)

(e) (f)

Figure 14.20. (*Continued*)

Summary

- The commonest parotid tumors in children are hemangiomas and hemangioendotheliomas.
- In vascular parotid lesions in children, medical therapy with steroids, alpha/beta interferon, or oral propranolol is preferred.
- In salivary lymphangiomas, a combination of debulking and sclerosing injections to macrocystic areas is used for management.
- Parotid lymphomas are usually associated with Sjogren syndrome, hepatitis C, or AIDS.
- Most salivary lymphomas are MALT lymphomas, which follow a fairly indolent course.
- The parotid lymph node bed may be the first echelon nodes for cutaneous cancers of the cheek, ear, scalp, forehead, and temple.
- Metastatic parotid nodes (P) and neck nodes (N) should be staged separately when involved by primary cutaneous cancers.
- Patients with both neck nodes and parotid nodes have the worst prognosis.
- Radiation therapy is given for close margins, perineural spread, and more than one positive node.
- In small cell carcinomas of the salivary gland, a full work up must be done to determine whether the tumor is a salivary primary or metastatic from a distant site.

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Chapter 15

Pediatric Salivary Gland Pathology

Outline

Introduction

Diseases of the salivary glands are rare in the pediatric population. At the time of their 1972 study of 9983 salivary gland lesions accessioned in their system, the Armed Forces Institute of Pathology (AFIP) identified 430 salivary gland lesions in children younger than the age of 15 years, accounting for only 4.3% of the total (Krolls, et al. 1972). This series included 262 non-neoplastic lesions (61%), of which there were 185 mucoceles and 67 inflammatory lesions. There were 168 cases of salivary gland tumors, (39%) of which 114 were benign (68%) and 54 were malignant (32%). Sixty of the 114 (53%) benign tumors in this series were epithelial in nature and 39 (34%) represented vascular proliferations. The most common benign tumor in this series was the pleomorphic adenoma and the most common malignant tumor was the mucoepidermoid carcinoma. Ellis, et al. (1991) reviewed benign and malignant salivary gland tumors in patients under the age of 17 years and compared these numbers to patients of all ages. Children accounted for 4.5% of all patients with salivary gland lesions in their series. A total of 494 salivary gland tumors were reviewed, of which 223 were malignant (45%), with 212 (95%) malignant epithelial tumors, and 11 (5%) malignant mesenchymal tumors. There were 271 total benign tumors (55%), of which 210 (78%) were benign epithelial tumors and 61 (22%) were benign mesenchymal tumors. Pleomorphic adenomas accounted for 193 cases (39%) occurring in this age group and 71% of all benign tumors in this series. The pleomorphic adenomas represented only 3.9% of these tumors occurring in all age groups, owing to the greater percentage of other benign tumors occurring in patients younger than 17 years of age. Mucoepidermoid carcinoma accounted for 123 cases (25%) occurring in this age group and 55% of all malignant tumors in this series. Similarly, the mucoepidermoid carcinomas represented only 7.7% of these tumors occurring in all age groups owing to the greater percentage of other malignant tumors occurring in patients younger than 17 years of age.

Craver and Carr (2012) reviewed their 17-year experience with 213 pediatric salivary gland lesions and identified 173 non-neoplastic lesions (81%) of which there were 137 mucoceles (64% of total in series) and 26 inflammatory lesions (12% of total in series). There were 40 neoplasms, of which 36 (90%) were benign and 4 (10%) were malignant.

In the African pediatric population, mumps is the most common inflammatory salivary gland lesion, but in the developed world, only sporadic

Salivary Gland Pathology: Diagnosis and Management, Second Edition. Edited by Eric R. Carlson and Robert A. Ord.

cases of mumps are now reported (Ajike and Lakhoo 2015). These authors also reported that salivary gland neoplasms constituted 10% of all pediatric neoplasms. The majority are reported to be benign with the most common benign neoplasm being the pleomorphic adenoma.

In a series of 2135 patients with tumors of the major salivary glands from 1930–1964, 38 patients (1.7%) 16 years of age and younger were observed to have epithelial tumors (Castro, et al. 1972). Thirty three (87%) of the tumors were located in the parotid gland and five tumors (13%) were located in the submandibular gland. The most common malignant tumor was the mucoepidermoid carcinoma and the most common benign tumor was the pleomorphic adenoma. Lack and Upton (1988) reported 80 salivary gland tumors in patients 18 years of age or younger during a 58 year period from 1928–1986. Twenty-five (31%) epithelial tumors were diagnosed and 55 (69%) non-epithelial tumors were diagnosed. The capillary hemangioma was the most common tumor diagnosed in this series, accounting for 27 (34%) of the 80 cases, followed by 19 cases of lymphangioma (24%), 10 cases (12.5%) of pleomorphic adenoma, and 6 cases (7.5%) of mucoepidermoid carcinoma.

Non-Neoplastic Salivary Gland Lesions

Non-neoplastic salivary gland lesions in children are associated with a wide spectrum of etiologies (Table 15.1). Congenital abnormalities (see Chapter 17), acute and chronic suppurative infections, and other inflammatory disorders, obstruction, neoplastic disease, and degenerative disorders should be considered as part of a differential diagnosis for a child with salivary gland swelling (Figure 15.1). These pathologic entities are less common and have a different incidence in children compared to adults (Tasca and Clarke 2011). Inflammatory disorders of the salivary glands in children may be infectious or non-infectious. Infectious disorders may involve the parenchyma of the salivary gland as a sialadenitis, or the intrasalivary gland lymph nodes as occurs in mycobacterium tuberculosis or non-tuberculous mycobacteria. Non-infectious inflammatory disease tends to involve multiple salivary glands as occurs in Sjogren syndrome and sarcoidosis as a pan-sialadenitis. Infectious disorders more commonly involve a single gland as occurs in an acute suppurative parotitis, or a pair of major glands as most commonly occurs in mumps parotitis.

Table 15.1. Inflammatory and infectious diseases of the salivary glands in children.

Bacterial infections
Acute pyogenic infection
Recurrent parotitis
Intraparotid lymphadenopathy
Mycobacterium tuberculosis
Non-tuberculous mycobacteria
Cat-scratch disease (*Bartonella henselae*)
Actinomycosis
Viral infections
Paromyxovirus (mumps)
Coxsackie A and B
Echovirus
Influenza A
Cytomegalovirus (CMV)
Epstein–Barr virus (EBV)
Human immunodeficiency virus (HIV)
Non-infectious disorders
Sarcoidosis
Sjogren syndrome
Pseudolymphomas

MUCOUS ESCAPE REACTION

The diagnosis and treatment of mucoceles and ranulas have been discussed in detail in Chapter 4. That notwithstanding, there are some additional comments that can be made about these lesions in pediatric patients. In terms of their peak incidence of occurrence, studies have identified that the mucocele and ranula are most commonly diagnosed in the first and second decades of life. Specifically, the report by Hayashida, et al. (2010) analyzed 173 cases of mucocele and found that 132 cases (76%) occurred in the first or second decades of life with 49% of the mucoceles occurring in the second decade of life. Bhargava, et al. (2014) have presented a case of a mucocele of the lower lip in an 11-month-old patient. Syebele and Butow (2010) reviewed 50 cases of mucoceles and noted that 62% were diagnosed in the first two decades of life. Of particular interest in this paper, is that 48 of 50 patients were tested for HIV infection, 33 patients (68%) were HIV positive, and 10 of these patients were younger than 10 years of age.

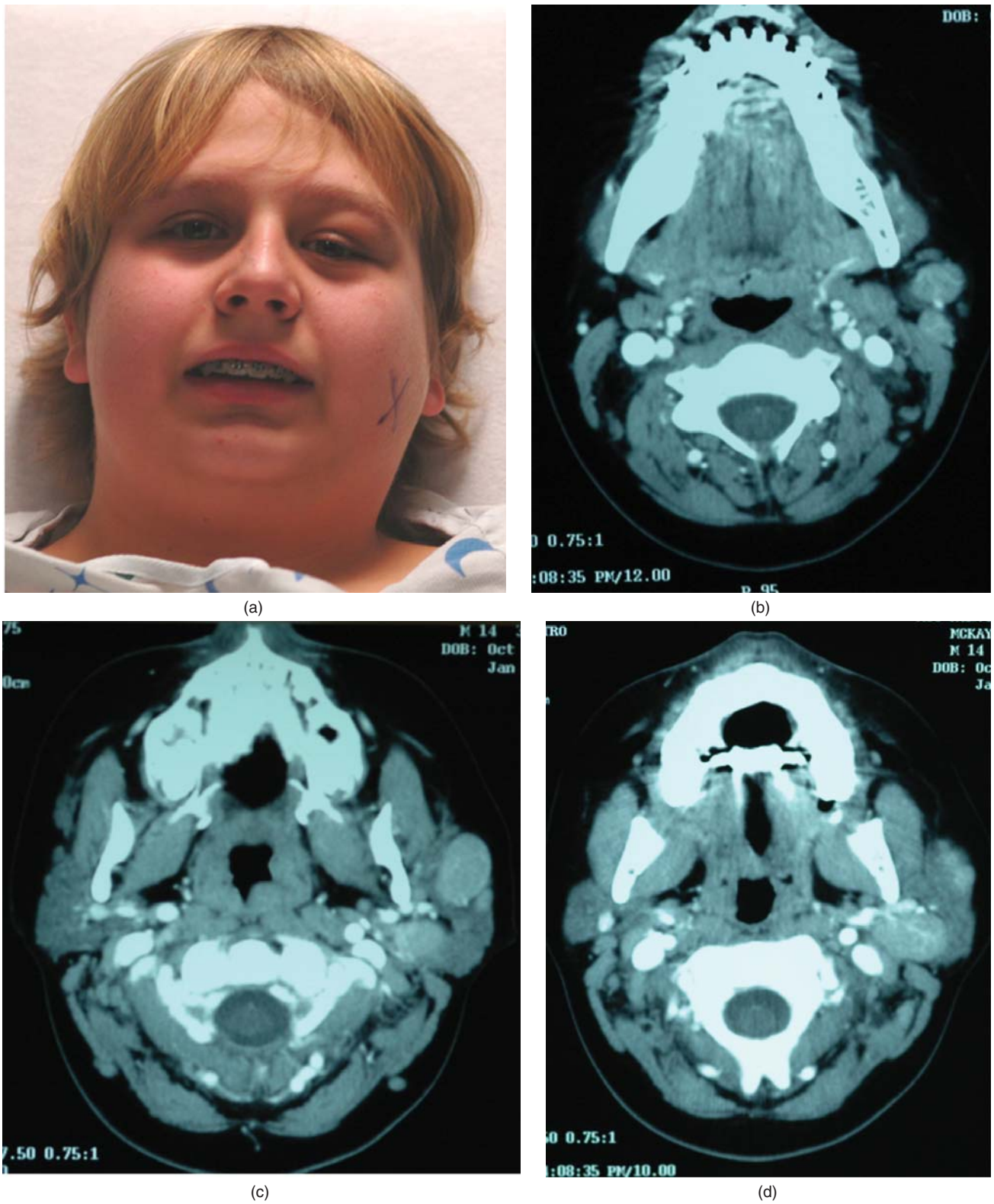
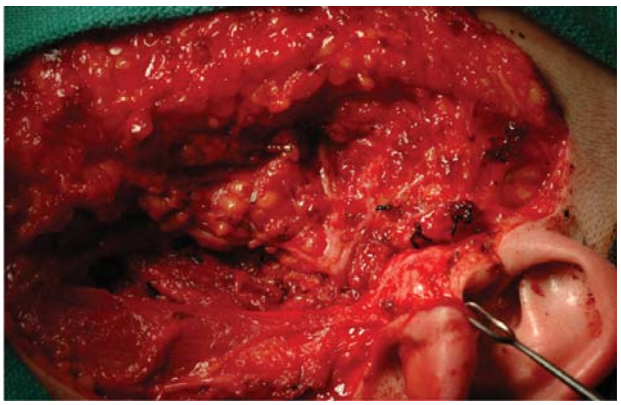


Figure 15.1. A 14-year-old boy with a 9-month history of left parotid swelling (a). CT scans (b, c, and d) identified separate masses of the superficial and deep lobes of the left parotid gland. The patient underwent total parotidectomy with dissection and preservation of the facial nerve (e). Final pathology identified reactive lymph nodes consistent with cat scratch disease.



(e)

Figure 15.1. (*Continued*)

In terms of treatment, some authors have historically recommended a 5–6 month observation period for the ranula in pediatric patients after which time patients should undergo surgical intervention (Pandit and Park 2002; Zhi, et al. 2008). Seo, et al. (2010) reviewed 17 pediatric patients with symptomatic ranulas that exceeded 2 cm in diameter, who underwent surgical excision of the ranula and offending sublingual gland. All patients had been observed for 3–14 months prior to being offered surgical intervention and none of the cases underwent spontaneous resolution. In fact, in two cases, the ranula increased in size. The authors concluded that a lengthy presurgical observation period is not necessary in terms of surgical decision making for pediatric patients with ranulas.

BACTERIAL SIALADENITIS

Bacterial sialadenitis is a relatively rare disease in children. It most frequently involves the parotid gland. Newborn children, those with pre-existing immunodeficiency such as those receiving chemotherapy, and children with severe dental and gingival infections are particularly at risk. Physical examination will reveal pain and swelling in the affected salivary gland. In a retrospective review of 118 patients aged 18 years and younger with parotid swellings, 75 patients (64%) had neoplasms and 43 patients (36%) had infectious or inflammatory lesions (Orvidas, et al. 2000). Overall, 84% of the lesions in this series were benign. The ratio of neoplastic lesions to non-neoplastic swellings of the parotid gland of 1.74:1 in this pediatric population is noticeably different from that of most adult populations of 2.68:1 (Gallia and Johnson 1981). Parotid swellings in children, therefore, are more likely to be infectious/inflammatory compared to parotid swellings in adults that are more likely to be neoplastic.

Acute Submandibular Sialadenitis

Acute submandibular sialadenitis is a rare condition in pediatric patients (Figure 15.2). In their 30-year study of sialadenitis in patients up to 16 years of age, Kaban, et al. (1978) identified 49 patients requiring 67 hospitalizations. Four distinct types of sialadenitis were diagnosed, including 18 patients with acute suppurative parotitis, 14 patients with recurrent parotitis, 9 patients with chronic parotitis, and 8 patients with acute submandibular sialadenitis. Obstruction of the Wharton duct was the etiology of all eight cases of acute submandibular sialadenitis, seven of which involved sialolithiasis, and one of which involved a congenital ductal stenosis. All patients with sialolithiasis underwent submandibular gland excision and the one patient with congenital stenosis underwent a reconstructive duct procedure. As in adult patients, submandibular sialadenitis in pediatric patients should be first evaluated with radiographs to rule out the presence of a sialolith. If present, expedient removal should be undertaken. In a review of pediatric sialoliths versus adult sialoliths, Chung, et al. (2007) found that stones were more likely to be smaller and in the distal duct in children. They recommended careful bimanual palpation for diagnosis and intraoral stone removal in the majority of children. Similar findings in radiological imaging of pediatric patients with salivary stones have been reported (Salerno, et al. 2011). The long term outcome for children who had intraoral stone removal is excellent with 82.4% "symptom free" (Woo, et al. 2009).

An alternative to surgery is lithotripsy which has been undertaken in children with sialolithiasis. In one series of seven children extracorporeal electromagnetic shock wave lithotripsy achieved complete stone disintegration in five cases and in two cases a residual fragment <2 mm was seen on US monitoring. The mean number of sessions to achieve this result was five (Ottaviani, et al. 2001). Sialoendoscopy has also been used both as a diagnostic and therapeutic procedure in children with salivary stones (Nahieli, et al. 2000).

If a sialolith is not identified, medical management should be performed, including proper hydration and empiric antibiotic therapy. Severe

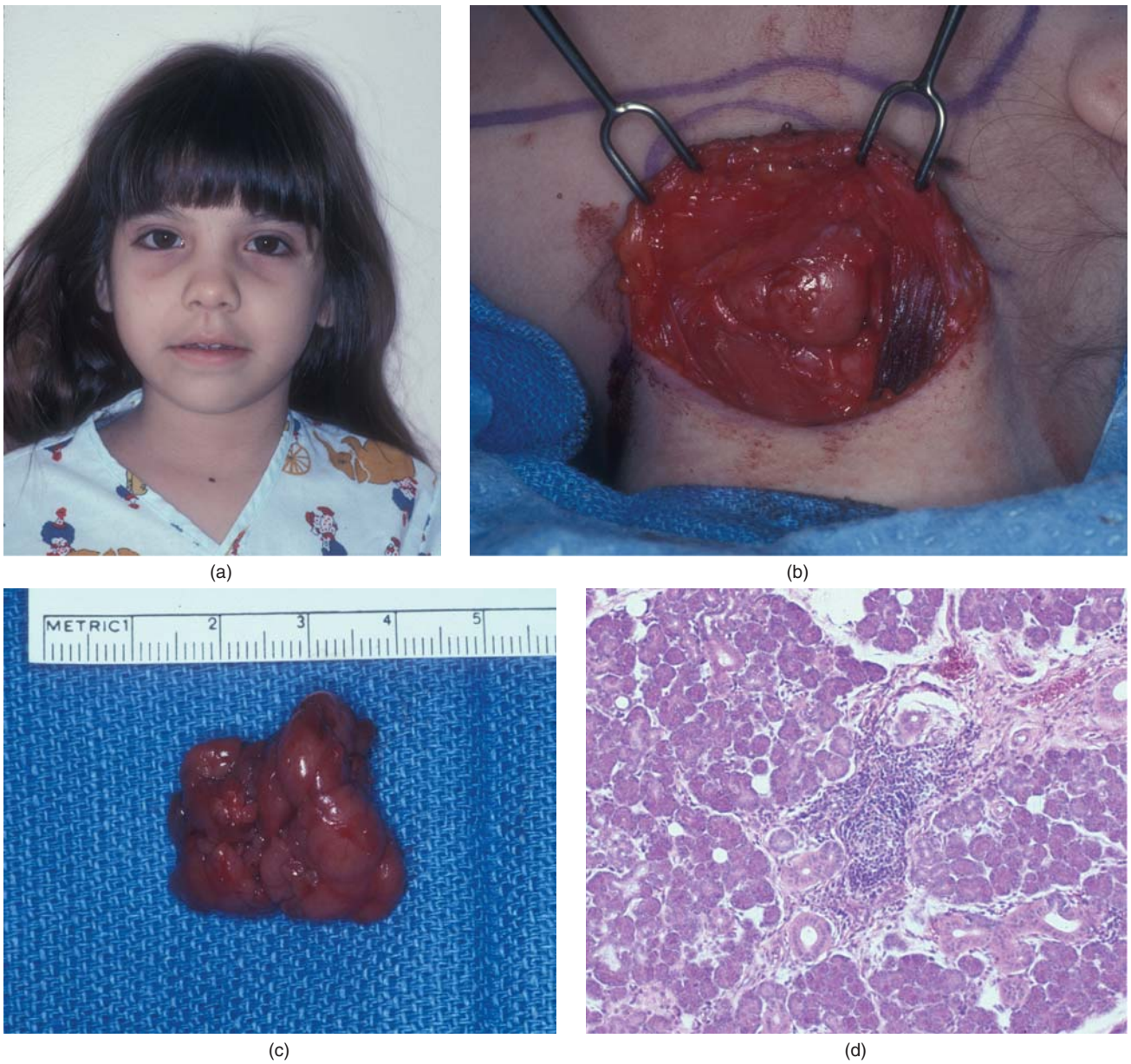


Figure 15.2. A 7-year-old girl (a) with recurrent swellings of the left submandibular gland. Conservative measures were undertaken initially without success. She was therefore subjected to excision of the left submandibular gland (b and c). Histopathology identified mild sialadenitis of the submandibular gland (d).

cases of sialadenitis, those cases where questionable parental compliance exists, or immunocompromised patients will require inpatient therapy. Mild cases in otherwise healthy patients with effective parental support can be effectively managed on an outpatient basis. The development of chronic submandibular sialadenitis is not anticipated in pediatric patients as commonly occurs in adults.

Acute Suppurative Parotitis

Acute parotitis in children and infants (Figure 15.3) is primarily due to salivary stasis and the most common responsible organisms are *Staphylococcus aureus* and *Streptococcus viridans*. As with adults, treatment of acute parotitis in children is primarily medical and involves hydration, sialogogues, and gentle massaging of the gland. In severe cases,

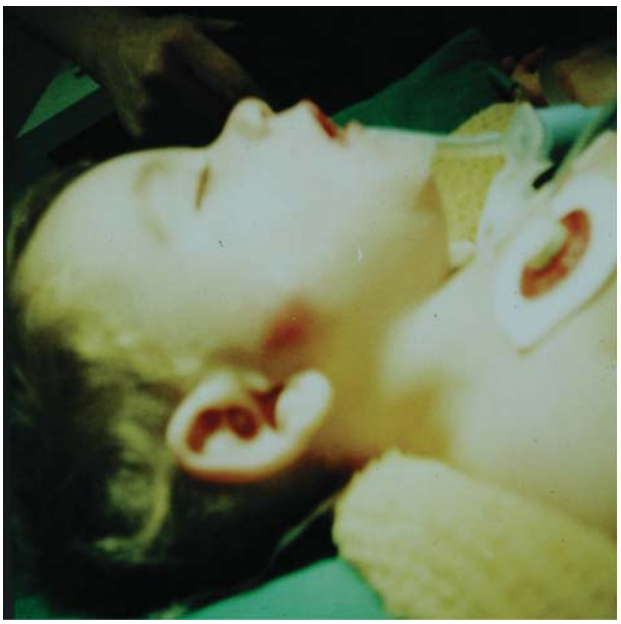


Figure 15.3. A baby with an acute suppurative infection of the right parotid gland. It was thought that this infection represented hematogenous spread of a distant infection to an intraparotid lymph node.

intravenous antibiotics are required and surgical drainage may be necessary.

Chronic Recurrent Parotitis

Chronic recurrent parotitis, also known as juvenile recurrent parotitis, is defined as recurrent parotid inflammation and is generally associated with non-obstructive sialectasia of the parotid gland (Chitre and Premchandra 1997). Next to mumps, chronic recurrent parotitis is the most common inflammatory salivary gland disease in childhood and adolescence (Ellies and Laskawi 2010). The disease is more common in males, characterized by recurring episodes of swelling and/or pain in the parotid gland and is commonly accompanied by fever and malaise (Figure 15.4). There is typically an absence of pus and the swelling lasts from several days to 2 weeks with spontaneous resolution. The number of attacks varies although the most common pattern is an attack every 3–4 months. The frequency rate peaks during the first year at school, and commonly symptoms usually subside or completely disappear after puberty (Chitre and Premchandra 1997). Clinical diagnosis can be confirmed by ultrasound that shows sialectasis or sialography showing sialectasis and ductal kinking

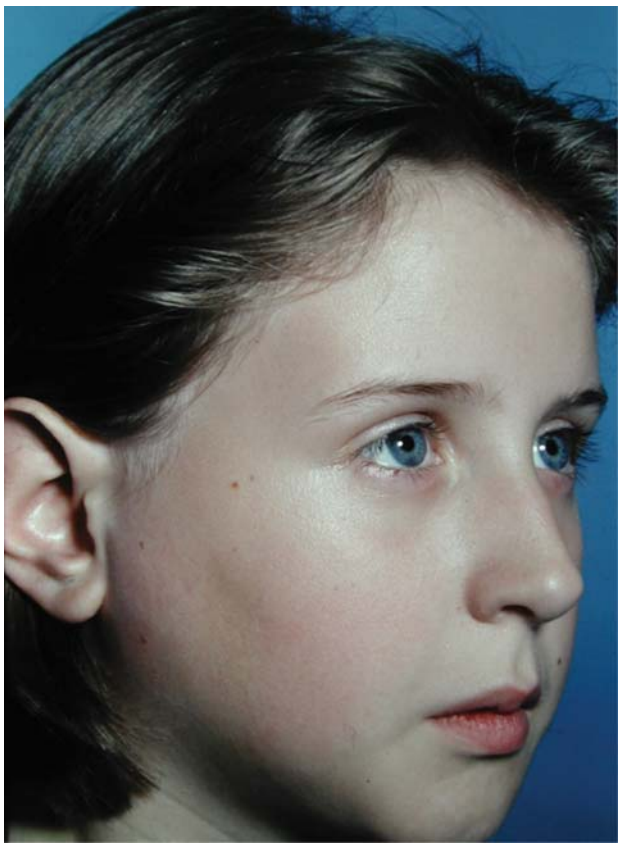


Figure 15.4. A 6-year-old girl with recurrent right parotid swelling indicative of chronic recurrent parotitis.

(Nahlieli, et al. 2004). In the acute phase, serum amylase can be a marker for the disease (Saarinen, et al. 2013).

Treatment for this condition has historically been without universal acceptance primarily due to the uncertainty regarding its etiology as well as the rarity of the disease. As such, treatment of the acute episode has been centered on relief of pain and an attempt at preventing damage to the parenchyma of the gland. Antibiotics have been found to result in rapid decrease in swelling. Sialoendoscopy is also of benefit in the management of chronic recurrent parotitis in children. Hackett, et al. (2012) reported on 18 pediatric patients who underwent a total of 33 sialoendoscopic procedures on 27 glands. Chronic recurrent parotitis was the most frequent indication for surgery, with 12 children represented (67%) and 19 glands involved. Three patients had recurrent symptoms after the first sialoendoscopy. Eight patients required only one procedure to address their symptoms, two patients required two procedures, one patient required

parotidectomy, and one patient was lost to followup. The authors concluded that sialoendoscopy is both diagnostic and therapeutic for a clinical diagnosis of chronic recurrent parotitis. Shacham, et al. (2009) reported on 70 children with chronic recurrent parotitis and five adult patients who had chronic parotitis similar to the children in this study. All patients underwent sialoendoscopy with lavage and dilatation and endoscopic injection of hydrocortisone into the gland. In 93% of patients a single endoscopic evaluation resulted in resolution of this disease and prevented its recurrence.

In a comprehensive review of the literature on the use of sialoendoscopy in the management of juvenile recurrent parotitis, Canzi, et al. (2013) identified 10 research series that they included in their review with a total of 179 children average age of 7.8 years and 109 were male. The most relevant diagnostic finding with sialoedoscopy was white wall appearance of the duct with absent vascularity (75%). In all reports the treatment was effective, with complete cure in 78% of cases or improvement with frequency reduction in 22%. Only 14% of children had a second or further procedures. Followup time for these reports was short, with a range of 4–36 months.

While the cause of chronic recurrent parotitis remains unclear, genetic, infectious (recurrent viral), allergic, and immune mediated are all possible etiologies. Maynard (1965) proposed that a low salivary flow rate due to dehydration results in a low grade inflammation of the gland and duct epithelium. This in turn results in distortion and stricture of the distal ducts and metaplasia of the duct epithelium. Thereafter, the metaplasia results in excessive mucous secretion. These changes, along with a further reduction in salivary flow rate, then predispose the gland to recurrent inflammation. A reduced salivary flow rate may result from glandular damage caused by a primary infection in the gland. That notwithstanding, the reduced salivary flow rate may be the primary factor in the pathogenesis of the disease. Maynard (1965) pointed out that the salivary flow rate was reduced in even the unaffected parotid gland in patients with unilateral disease.

Neoplastic Salivary Gland Disease

Salivary gland tumors are rare in children and include epithelial and mesenchymal, benign, and malignant neoplasms. A review of their incidence is noted in Table 15.2 that demonstrates significant differences in the incidence and anatomic distribution of tumors in adult and pediatric populations. The 1991 AFIP data showed that children accounted for only 4.5% of all patients with salivary gland tumors. Mixed tumors, mucoepidermoid carcinomas, and acinic cell adenocarcinomas accounted for over 92% of all epithelial tumors and about 77% of all tumors in this age group. In this series, and those of others (Krolls, et al.

Table 15.2. Comparison of the reported incidence of epithelial salivary gland neoplasms in pediatric and adult populations.

Incidence	Pediatric 3–4/million/year	Adult 80/million/year
Percentage of all salivary tumors	5%	90%
Benign	50%	80%
Malignant	50%	20%
Percentage of all salivary gland tumors occurring in the parotid gland	85%	82%
Benign	48%	90%
Malignant	52%	10%
Percentage of all salivary gland tumors occurring in the submandibular gland	11%	8%
Benign	33%	67%
Malignant	67%	33%
Percentage of all salivary gland tumors occurring in the sublingual gland	3%	1%
Benign	85%	2%
Malignant	15%	98%
Percentage of all salivary gland tumors occurring in the minor salivary glands	1%	8%
Benign	50%	60%
Malignant	50%	40%

Adapted from: Bradley PJ, Hartley B. Salivary gland neoplasms. In: Bradley PJ, Guntinas-Lichius O (eds). *Salivary Gland Disorders and Diseases: Diagnosis and Management*. Stuttgart, Thieme, p. 94, 2011.

1972; Lack and Upton 1988; Laikui, et al. 2008; Yoshida, et al. 2014), mucoepidermoid carcinoma is the most common salivary gland malignancy in children. The mixed tumor is the most common benign salivary gland tumor in children in large series (Krolls, et al. 1972; Ellis, et al. 1991). The benign and malignant epithelial salivary gland tumors together account for approximately 85% of all salivary gland tumors reported in children (Ellis, et al. 1991). The slight preponderance of benign tumors (55%) in pediatric patients is lower than the 63% incidence of benign salivary gland tumors in all patients in the AFIP data (Ellis, et al. 1991). This observation that malignant tumors are relatively more common than benign tumors in pediatric patients suggests that the pathogenesis of salivary gland tumors in pediatric patients might be different from that of adults. A genetic predisposition for cancer may be seen as in one series 4 of 17 pediatric salivary cancers (23.5%) were second cancers occurring 6–9 years after the first primary cancer (Chiaravali, et al. 2014).

EPITHELIAL TUMORS

Malignant epithelial salivary gland tumors are relatively more common in children (40–60% of total) than in adults (20–30%). In the series of 494 total salivary gland tumors in children by Ellis, et al. (1991), 422 (85%) were epithelial in nature and 72 (15%) were mesenchymal. This series included 271 benign tumors of which 210 (78%) were epithelial, and 223 malignant tumors of which 212 (95%) were epithelial. In these pediatric patients, the pleomorphic adenoma was the most common tumor overall, accounting for 193 (39%) of the 494 pediatric tumors and 3.9% of all similar tumors occurring in all age groups, owing to the greater frequency of the diagnosis of the pleomorphic adenoma in adult patients. These 193 pleomorphic adenomas represented 92% of the 210 benign epithelial tumors and 71% of the total combined benign epithelial and benign mesenchymal tumors. The Warthin tumor was the second most common benign epithelial tumor, accounting for only five cases (2.4% of benign epithelial tumors).

The mucoepidermoid carcinoma was the most common malignant tumor in the AFIP series (Ellis, et al. 1991), accounting for 123 cases. These represented 58% of the total 212 number of malignant epithelial tumors and 55% of the total 223 number of malignant tumors in this series. The acinic cell adenocarcinoma was the second most common epithelial malignancy in this series (31%) and the third most common tumor overall in this series (25%).

In their series of 80 salivary gland tumors in children, Lack and Upton (1988) identified 25 epithelial tumors (31%), of which 10 were pleomorphic adenomas (40%), 6 were mucoepidermoid carcinomas (24%), and 5 were acinic cell carcinomas (20%). The pleomorphic adenomas were located in the parotid gland in five cases, in the submandibular gland in four cases, and in the soft palate in one case. The mucoepidermoid carcinomas were located in the parotid gland in five cases and in the premaxillary soft tissues in one case. The acinic cell carcinomas were located in the parotid gland in all five cases. In China, pleomorphic adenoma was 91.45% of benign childhood tumors and mucoepidermoid carcinoma 47.1% of malignant tumors (Fang, et al. 2013).

Regarding survival, using SEER data (763 patients <30 years old) and a Kaplan–Meier analysis, the relative 5-year survival was 100% for <1-year-old patients (only 1 patient), 50% in the 1–4 year group, 87.2% in the 5–9-year-olds, 97% among the 10–14-year-olds, and 95% among 15–19-year-olds (Rutt, et al. 2011). Favorable outcomes were also reported by Kuperman, et al. (2010). In his series of 61 patients, 83% were parotid tumors and 46% were mucoepidermoid carcinomas. Cervical metastases were found in 37% of children and 75% underwent surgery with radiation given in 45% of cases. The overall 5-year survival rate was 93% and 26% developed a recurrence. Predictors for poor outcome were margin status, tumor grade, and neural involvement. In a population based study comparing adult and pediatric salivary cancers, the commonest tumor was mucoepidermoid carcinoma in each group. However, children had tumors with more favorable features and staging (76% vs 50%), better differentiated tumors (88% vs 49%) and a 5-year overall survival of 95% +/− 1.55 compared to 59% +/− 0.55 for adults (Sultan, et al. 2011).

MESENCHYMAL TUMORS

Mesenchymal salivary gland tumors are much more commonly noted in children than in adults. Ellis, et al. (1991) found 40 hemangiomas amongst 61 benign mesenchymal tumors (66%) and 72 benign and malignant mesenchymal tumors (56%). Lack

and Upton (1988) found 27 hemangiomas in their series of 80 pediatric salivary gland tumors (34%) that represented 49% of their 55 mesenchymal tumors.

Vascular Tumors

Vascular salivary gland tumors in children typically occur in the parotid gland, are most commonly noted at or soon after birth, and are more frequent in females (Lack and Upton 1988; Ord 2004). In general, vascular tumors are classified as hemangioendotheliomas that occur in patients younger than 6 months of age with rapid growth and aggressive behavior (Figure 15.5). Hemangiomas are slower growing processes that occur in older children. Krolls, et al. (1972) described the hemangioendothelioma as an immature hemangioma. Such tumors are characterized by a unique tripartite growth cycle of proliferation, plateau, and involution. Although most involute without intervention, many require medical or surgical treatment. Krolls, et al. (1972) reported that the parotid gland was involved in 37 of their 39 vascular lesions. In Lack and Upton's (1988) series of 27 cases of hemangioma, all of which occurred in the parotid gland, 19 occurred in females and 8 occurred in males. A decided left side laterality was realized with a five times greater occurrence of the hemangioma of the left parotid gland compared to the right parotid gland. A median age of 4 months with the oldest child being 16 months of age was noted in this series. Clinical findings include a soft, compressible mass with a bluish hue to the skin. Regression and involution of rapidly growing infantile hemangioendotheliomas of the parotid gland has been reported (Scarcella, et al. 1965) although parotid lesions may be associated with slower involution or scarring (Drolet, et al. 1999). Following involution, phleboliths may develop and can be seen radiographically in older children (Figure 15.6).

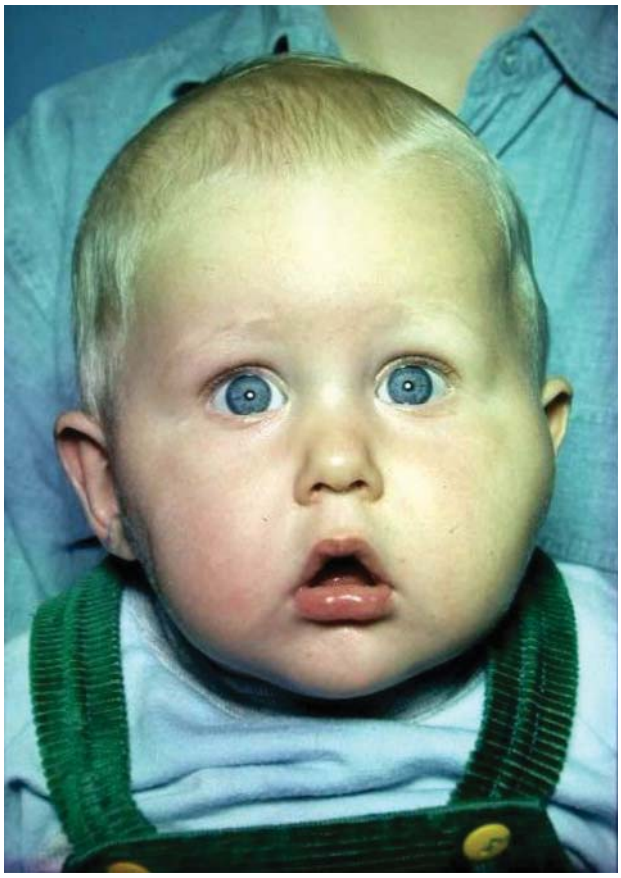
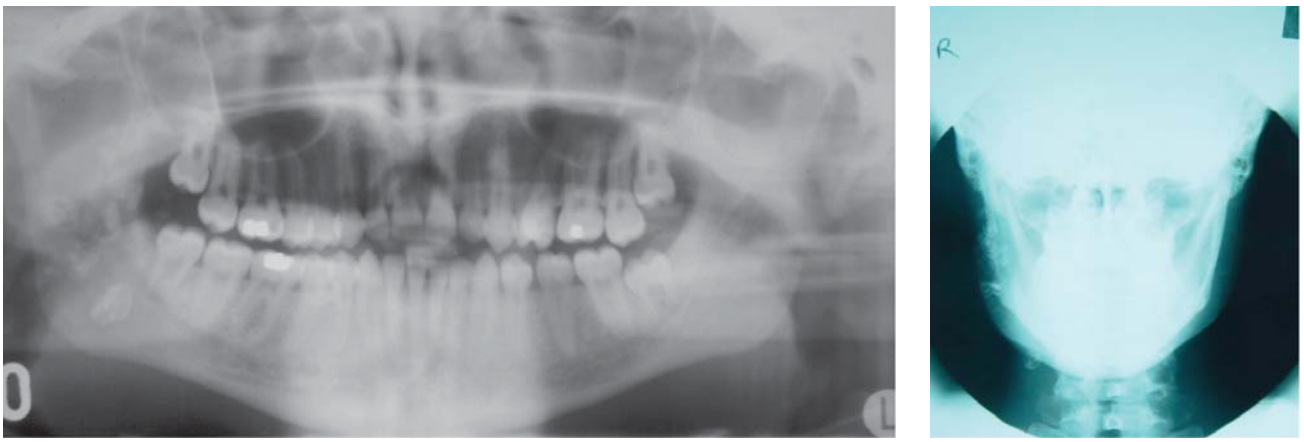


Figure 15.5. A 4-month-old infant with left parotid swelling related to a hemangioendothelioma. With permission from Kaban LB, Troulis MJ (eds): Pediatric Oral and Maxillofacial Surgery, 2nd edition, chapter 14, Saunders, 2004.

Management of parotid hemangioendotheliomas has evolved as natural history and behavior have both become better understood. Radiation therapy was once used successfully for rapidly growing tumors in infants, however, the observation of late secondary malignancies in irradiated children has resulted in the abandonment of this modality of treatment. Surgical excision became the mainstay of treatment for many years and is occasionally still required. Excision of these lesions in infants and young children incurs a high risk for complications including death, facial nerve palsy, and recurrence of the tumor. As such, most authors now recommend non-operative management for infants based on the anticipated spontaneous regression of these tumors.

In childhood hemangiomas the efficacy of systemic corticosteroid therapy is well documented (Enjolras, et al. 1990; Gangopadhyay, et al. 1997) and interferon alfa-2a and alfa 2b have been used successfully (Ezekowitz, et al. 1992; Soumekh, et al. 1996). That said, a shift towards the use of beta-blockers in infantile hemangiomas has occurred as a standard of care (Puttgen 2014). Propranolol is widely accepted to be a safer and better tolerated drug than oral corticosteroids. There is evidence that the use of propranolol is also distinguished from oral corticosteroids in its effectiveness in treating infants who are beyond the proliferative phase of growth. The proposed



(a) (b)

Figure 15.6. An 18-year-old patient with calcifications superimposed over the right mandibular ramus on panoramic (a) and posterior-anterior (b) radiographs. The radiographs confirm the presence of phleboliths of the right parotid gland, indicative of a hemangioma of this gland. With permission from Kaban LB, Troulis MJ (eds): Pediatric Oral and Maxillofacial Surgery, 2nd edition, chapter 14, Saunders, 2004.

mechanism of action of propranolol includes rapid vasoconstriction of the lesion. Inhibition of angiogenesis by downregulation of proangiogenic growth factors vascular endothelial growth factor, basic fibroblast growth factor, and matrix metalloproteinases 2 and 9 seems to correspond to growth arrest. Finally, the hastening of the induction of apoptosis of endothelial cells has been proposed to result in the stimulation of regression of infantile hemangiomas. Surgical resection is reserved for those tumors that do not respond to medical therapy (Figure 15.7).

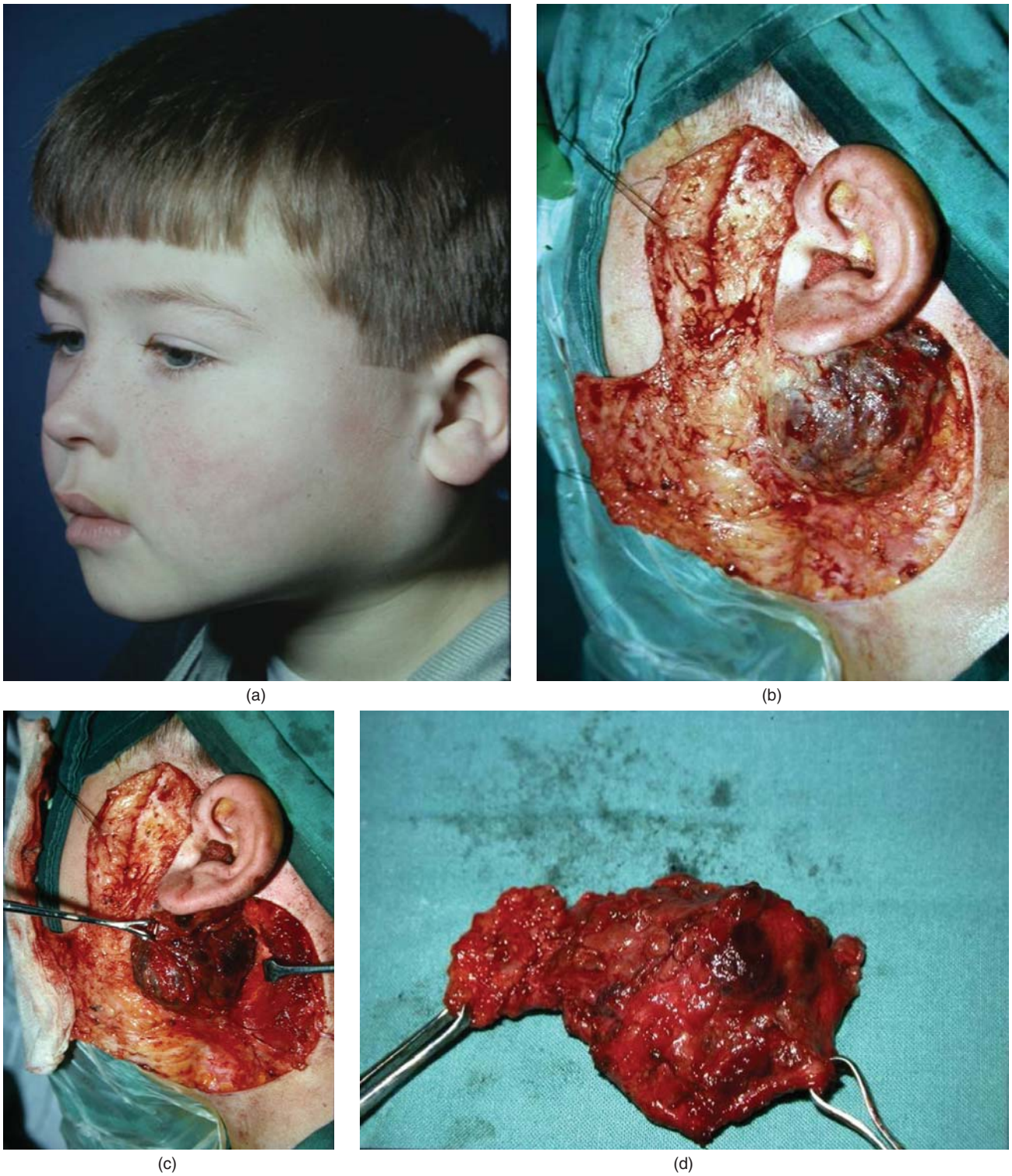
Lymphatic Malformations

Lack and Upton (1988) reported 19 children with a diagnosis of lymphangioma involving salivary glands. These presented occasionally as a primary focus of involvement, but more commonly with more extensive involvement of juxtaglandular soft tissues and secondary enclavement of the salivary gland (Figure 15.8). These 19 lymphangiomas were the second most common mesenchymal tumor in their series of which 27 cases of hemangioma were most commonly noted. The lymphangiomas were six times more common in females with a median age of 6 years and equal distribution on each side of the neck. In their series of 494 pediatric salivary gland tumors, Ellis, et al. (1991) identified only 5 cases of lymphangioma amongst 61 total benign mesenchymal tumors that also included 40 cases of hemangioma.

Treatment recommendations of the salivary lymphangioma have included observation, injection of sclerosing agents, and conservative surgery. Sclerosing agents are most successful in those lesions that have large cystic spaces. Surgical excision with preservation of the facial nerve in the case of a parotid lymphangioma will likely not completely remove the abnormal lymphatic channels and microcysts. This notwithstanding, this debulking procedure proves to be clinically effective in controlling the disease (Ord 2004).

Neural Tumors

Neural tumors of the salivary glands can be categorized as neurofibromas, neurilemmomas, and manifestations of neurofibromatosis (Ord 2004). Lack and Upton (1988) reported six patients with neural tumors involving the major salivary glands, four tumors involving the parotid gland, and one case each involving the submandibular gland and sublingual gland. The most common clinical setting was neurofibromatosis with the corresponding neural tumor being a plexiform neurofibroma. Ellis, et al. (1991) reported 10 neural tumors, 7 cases of neurofibroma, and 3 cases of schwannoma. Complete removal of neurofibromas can be very difficult due to their highly infiltrative nature such that debulking with preservation of normal anatomy is preferred (Figure 15.9).

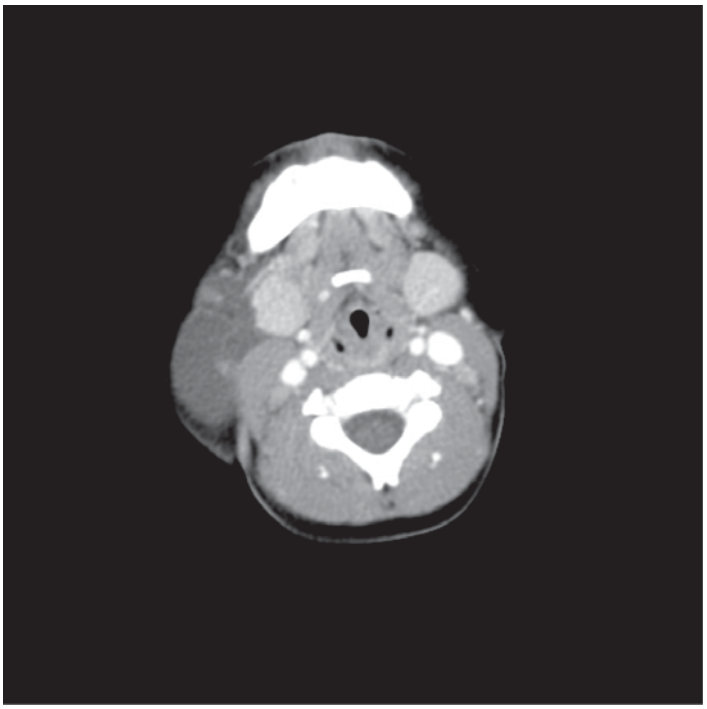


(a) (b)

(c) (d)

Figure 15.7. A 3-year-old boy (a) with left parotid swelling that is soft and compressible. The overlying skin has a subtle blue hue, indicative of a hemangioma. The angiogram supported this diagnosis. The patient underwent left superficial parotidectomy (b and c). The specimen is noted in (d). With permission from Kaban LB, Troulis MJ (eds): Pediatric Oral and Maxillofacial Surgery, Saunders, 2nd edition, chapter 14, 2004.

(a)



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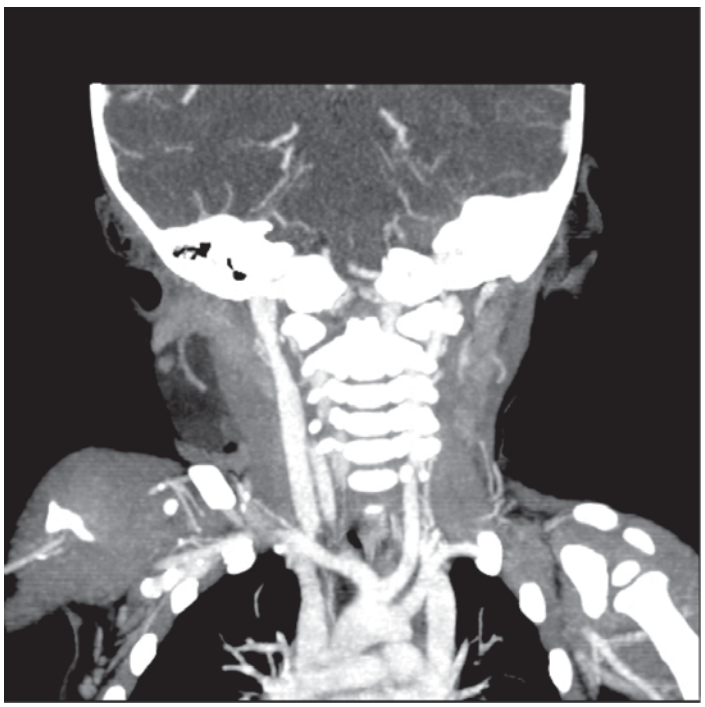
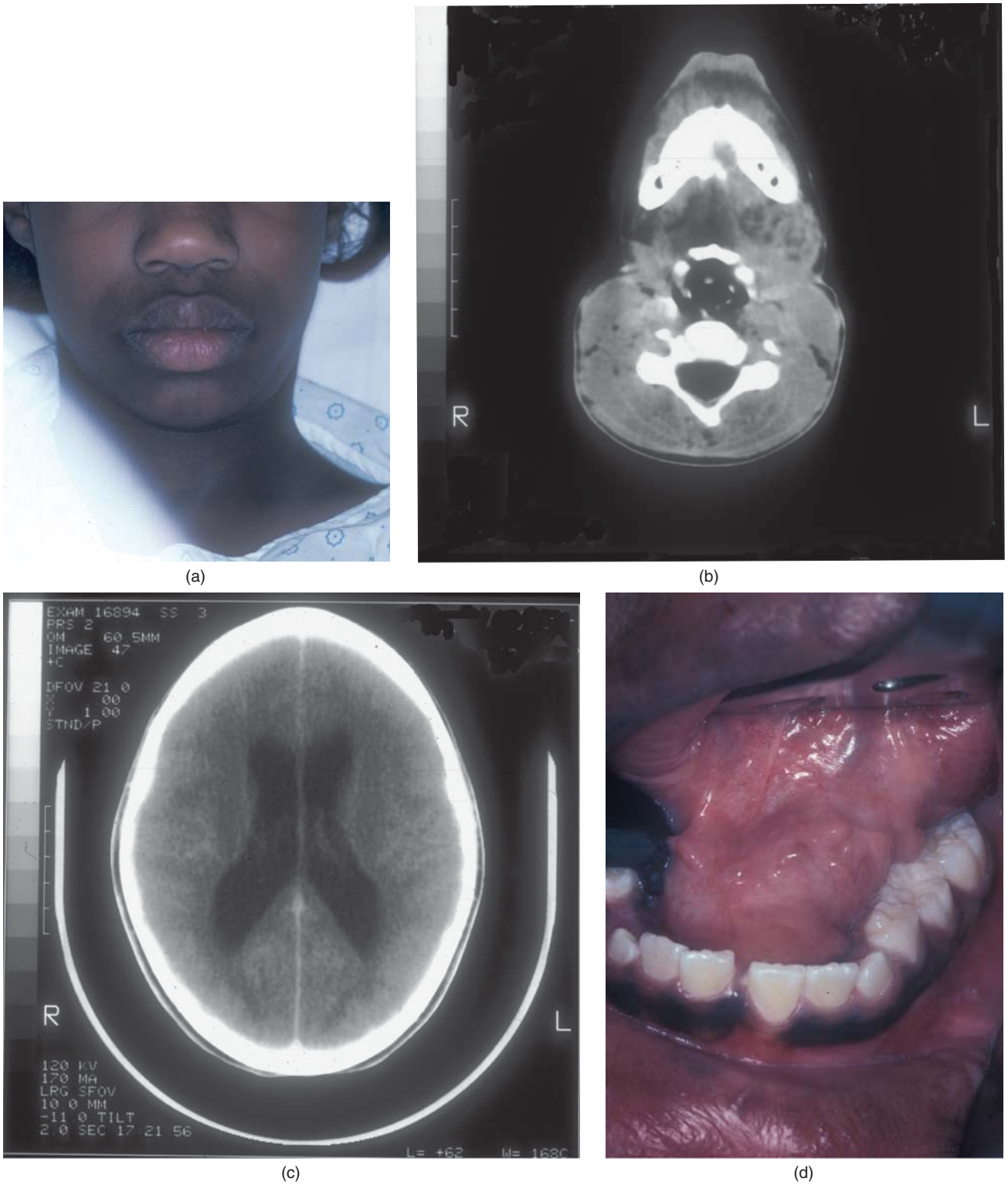


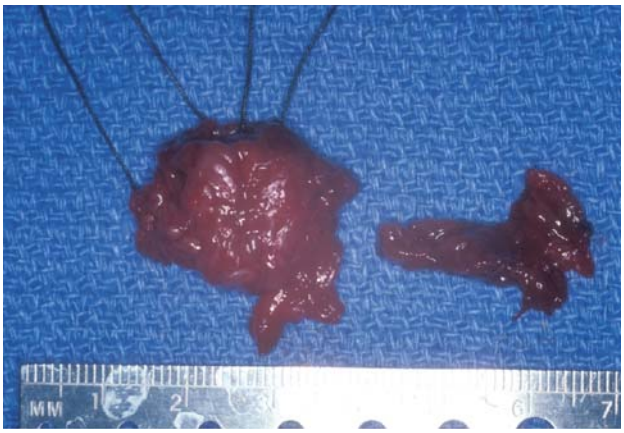
(c)

Figure 15.8. An 11-month-old boy with a right facial/upper neck swelling that has been present for two weeks (a). Imaging with CT (b and c) identified a 4-cm mass with intimate association with the submandibular and parotid glands. The patient underwent excision of the mass and lymphangioma was diagnosed.



(a) (b) (c) (d)

Figure 15.9. An 8-year-old girl (a) with left submandibular swelling that had been present for 6 months. Imaging with CT identified an ill-defined mass of the submandibular gland region (b) as well as hydrocephalus (c). Oral examination (d) showed fullness in the left sublingual space. With a differential diagnosis of neurofibroma the patient underwent a debulking of this lesion (e and f). Histopathology identified a plexiform neurofibroma (g), indicative of neurofibromatosis. The patient did well postoperatively as noted at her 2-year visit (h and i). No reaccumulation of the tumor was noted on physical examination.



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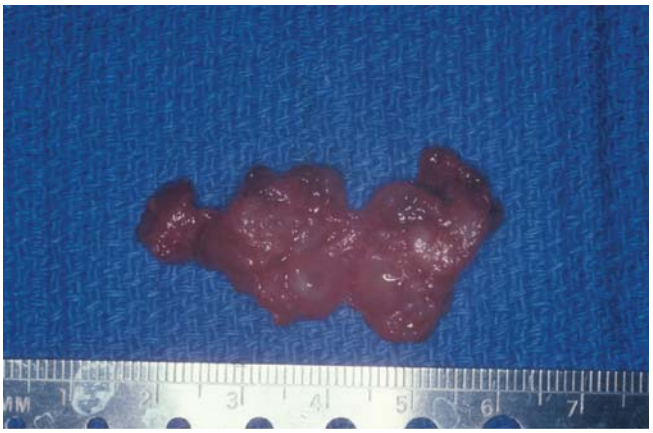

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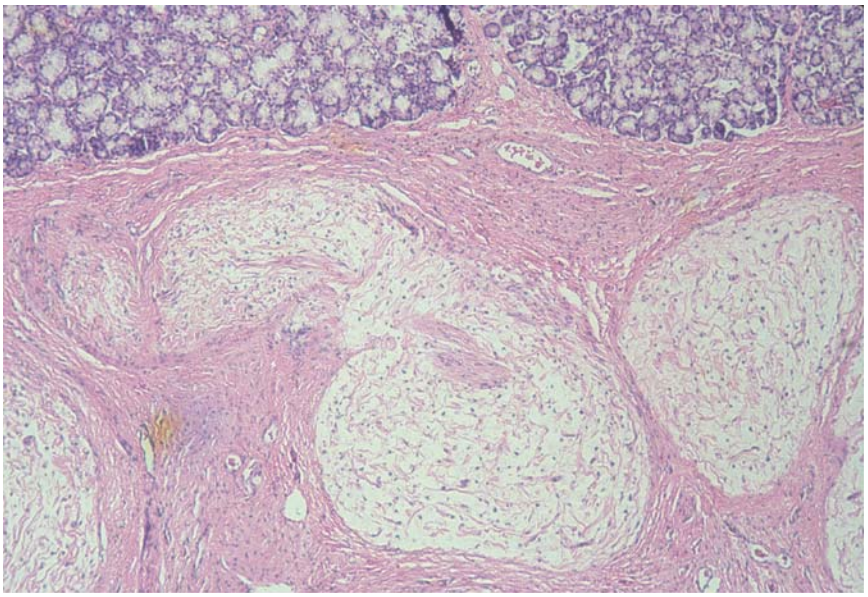
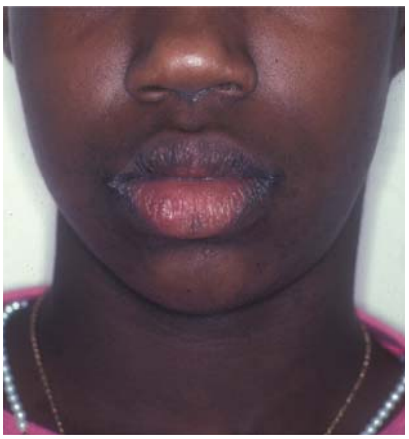
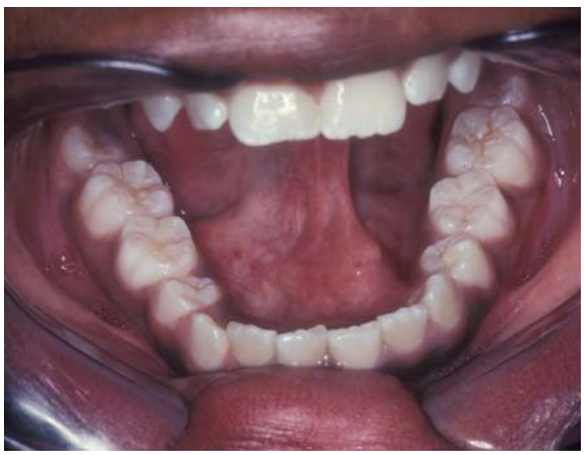


(g)



(h)



(i)

Figure 15.9. (*Continued*)

PAROTID TUMORS

In their review of the Salivary Gland Register from 1965–1984 at the University of Hamburg, Seifert, et al. (1986) reported on 9883 cases of salivary gland pathology, including 3326 neoplasms, 80 of which occurred in children. Fifty-seven (71%) of these tumors developed in the parotid gland. Pleomorphic adenoma accounts for virtually all of the benign pediatric neoplasms occurring in the parotid gland with the Warthin tumor representing

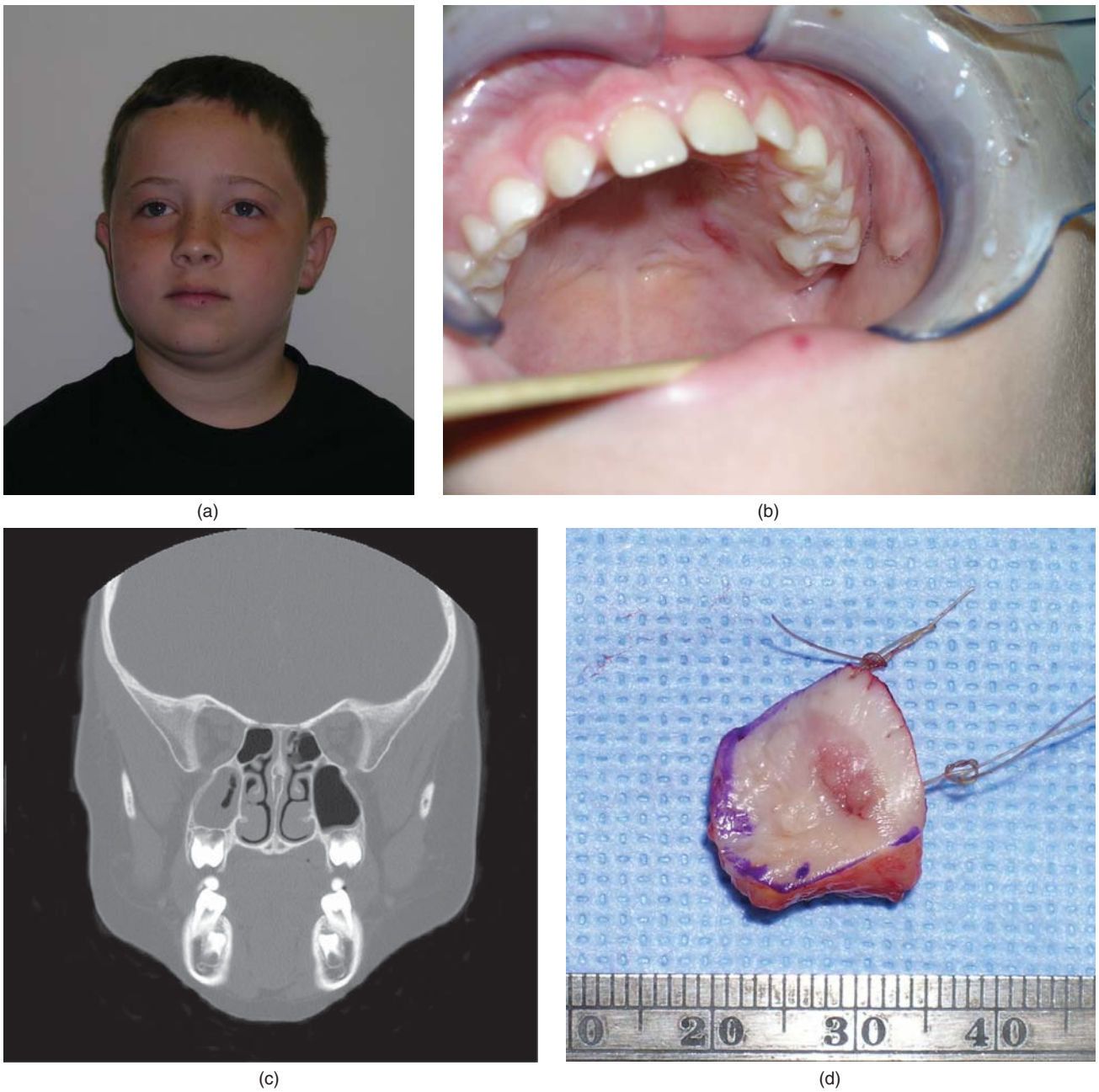
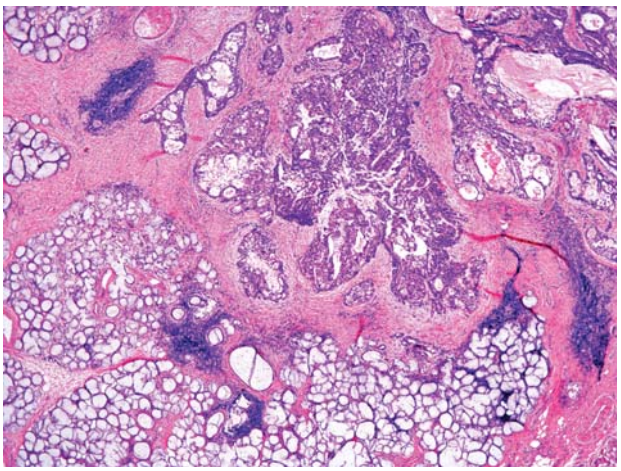


Figure 15.10. A 9-year-old boy (a) with a mass of the left hard-soft palate junction (b). Incisional biopsy identified low-grade mucoepidermoid carcinoma. Imaging with CT (c) showed no bone erosion of the hard palate such that the patient underwent wide local excision of his cancer (d). Final histopathology (e) identified intermediate grade mucoepidermoid carcinoma. (Hematoxylin and eosin, original magnification ×100.)



(e)

Figure 15.10. (*Continued*)

a minor contribution at this anatomic site. In 166 children with epithelial parotid tumors, 93 (55%) were benign and 73 (45%) were malignant (Ord 2004). Of the 73 malignancies, 47 (64%) were mucoepidermoid carcinomas and 17 (23%) were acinic cell carcinomas. This relative incidence of mucoepidermoid carcinomas and acinic cell carcinomas of the parotid gland in children is distinguished from the near equal incidence of these malignancies in the parotid gland in adult patients in the AFIP data (Ellis, et al. 1991). Finally, although the parotid gland is a less common site for salivary gland tumors in children compared to adults, there is a greater chance for malignancy in children.

The workup of a child with a parotid swelling does not differ significantly from that of an adult. Once inflammatory disease has been ruled out, a fine needle aspiration biopsy of a discrete parotid mass in a child is useful to establish its cytologic character. Structural imaging is also valuable so as to establish the anatomic extent of the tumor. Superficial parotidectomy or partial superficial parotidectomy with facial nerve identification and preservation are the procedures of choice for pediatric parotid tumors. Facial nerve sacrifice is only performed when preoperative palsy is noted to exist or when nerve invasion is appreciated intraoperatively. The facial nerve is more superficial in infants younger than 4 months of age compared to older children due to the lack of development of the mastoid process (Ord 2004). Neck dissection is performed for high-grade malignancies or when evidence of metastatic adenopathy is present.

SUBMANDIBULAR GLAND TUMORS

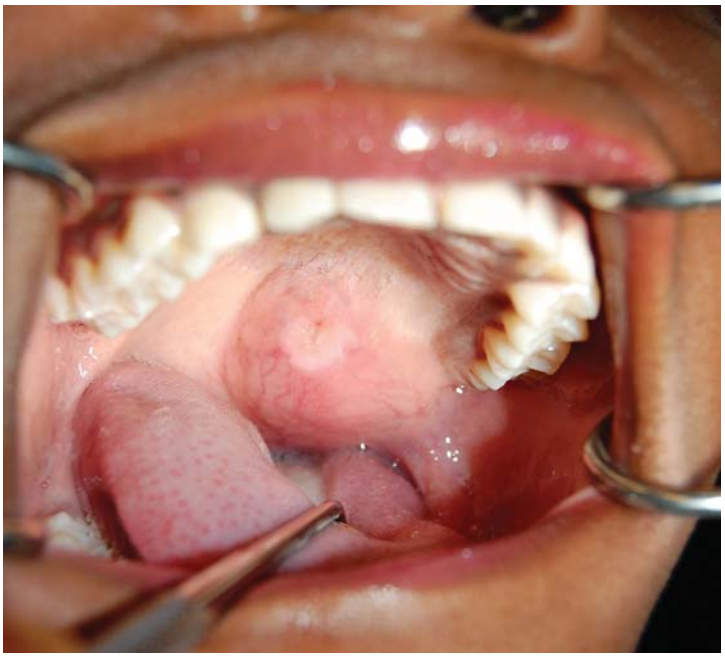
As in adults, submandibular gland tumors are very uncommon in pediatric patients. Of 168 salivary gland tumors in the series of Krolls, et al. (1972), submandibular gland tumors included 3 lymphomas, 4 mucoepidermoid carcinomas, and 10 benign tumors. While there were 12 acinic cell carcinomas in this series, none occurred in the submandibular gland. Lack and Upton (1988) similarly identified their five cases of acinic cell carcinoma exclusively present in the parotid gland, but they identified no cases of mucoepidermoid carcinoma in the submandibular gland. These authors identified 4 of 10 cases of pleomorphic adenoma occurring in the submandibular gland. In Castro's series of 38 major salivary gland tumors, 5 were noted to occur in the submandibular gland. These included four cases of pleomorphic adenoma and one case of malignant mixed tumor. The treatment of submandibular gland tumors in children includes excision of the submandibular gland and tumor en bloc.

MINOR SALIVARY GLAND TUMORS

Minor salivary gland tumors in children are rare. Population studies have demonstrated that only 5% of minor salivary gland tumors occur in children, with a near equal distribution of benign and malignant tumors (Galer, et al. 2012). In their study of 35 minor salivary gland tumors in children, Galer, et al. (2012) identified 22 cases of mucoepidermoid carcinoma, 9 cases of adenoid cystic carcinoma, and 4 cases of adenocarcinoma. Thirty-one of the malignancies were low-intermediate grade. Twenty of the tumors were classified as occurring in the oral cavity and 13 were classified as occurring in the hard palate. These authors found an excellent prognosis for their patients with an overall survival of 88.4% and disease free survival of 89.3% at 5 years. Preferred treatment is identical to that of adult's diagnosis for diagnosis. In the author's unpublished series of 275 minor salivary gland tumors, 12 (4.3%) were pediatric cases (age 9–19). Ten cases were malignant (83.3%), of which 7 (70%) were mucoepidermoid carcinomas and 9 of the 12 tumors was located in the palate (75%).

A mucoepidermoid carcinoma of the palate in a child should undergo structural imaging and excision of the tumor with appropriate anatomic barrier inclusion on the deep aspect of the tumor (Figure 15.10). Unless the bone is clinically or

(a)



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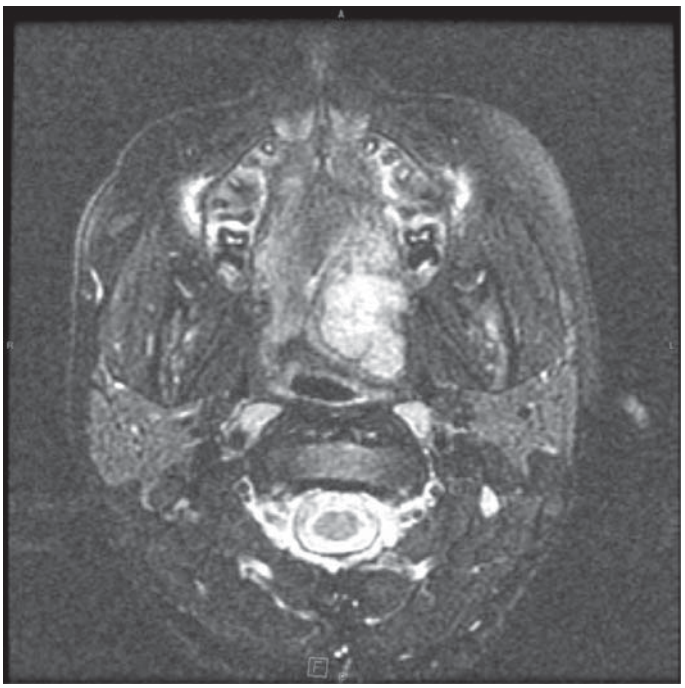

(c)

Figure 15.11. A 12-year-old girl (a) with a long history of a slowly growing mass of the palate (b). Axial T2 weighted MRI (c) identifies a hyperintense multilobulated mass consistent with a pleomorphic adenoma that was confirmed by incisional biopsy. Source: Reproduced with permission of John Caccamese.

radiologically involved the bone does not require resection for low grade mucoepidermoid carcinoma in children (Caccamese and Ord 2002). The periosteum appears to be an effective oncologic barrier and its inclusion on the deep surface of the tumor permits a margin-free cancer surgery with high rates of cure.

The surgical management of benign palatal salivary gland tumors, like that of malignant salivary gland tumors is identical to those surgeries performed in adult patients (Figure 15.11). Specifically, the inclusion of the periosteum on the deep surface of the tumor provides effective cure of these benign tumors. The superiorly located maxillary bone need not be included with the tumor specimen.

Summary

- Salivary gland lesions are rare in the pediatric population that is variably defined in terms of age.
- The mucocele is the most common salivary gland lesion encountered in pediatric patients.
- Mumps has historically been the most common form of sialadenitis diagnosed in children.
- Chronic recurrent parotitis is the second most common form of sialadenitis in children.
- The pleomorphic adenoma is the most common pediatric salivary gland tumor and the most common benign tumor in children. Together with the hemangioma, these benign tumors account for nearly 90% of all benign salivary gland tumors in children.
- The mucoepidermoid carcinoma is the most common malignant pediatric salivary gland tumor. Together with the acinic cell carcinoma, these two malignant tumors account for approximately 60% of malignant salivary gland tumors in children.

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Chapter 16

Trauma and Injuries to the Salivary Glands

Outline

Introduction

The salivary glands may be subjected to a number of injuries and insults. Trauma to the parotid is relatively rare, 0.21% of patients in a trauma unit (Lewis and Knottenbelt 1991). Penetrating trauma may be truly uncontrolled or accidental in nature; however, identical complications and injuries are seen after the intentional controlled trauma of surgery. This chapter will therefore deal with the complications of both salivary gland surgery and true traumatic injury. In addition, the injurious effects of radiation and barotraumas will be reviewed.

Penetrating Injuries

TRAUMA TO THE GLAND

Salivary Fistula

Penetrating injury to the substance of a major gland, for example the parotid or submandibular gland will cause direct damage to the gland and possible related structures and may lead to the formation of an external salivary fistula to the skin (Figure 16.1). When the substance of the gland is injured suture of the parenchyma is recommended (Lewkowicz, et al. 2002). In addition to direct closure of the parotid capsule, a pressure dressing is applied for 48 h to reduce the chances of sialocele formation. In 51 cases of parotid complications following trauma, 15 (30%) developed parotid fistula, treated by intravenous fluids and nil by mouth, with faster healing of parenchymal injuries alone than when the ductal system was involved (Parkeh, et al. 1989). Similarly, Ananthakrishnan and Parkash (1982) reported that their three cases of fistula from the parotid gland parenchyma resolved without treatment, unlike the 14 fistulas related to parotid ductal injury. In a study of 13 patients with traumatic parotid fistulas, 54% resolved with conservative management within 3 weeks and the remaining patients were cured by internal drainage with a catheter (Cant and Campbell 1991). Landau and Stewart (1985) advocated conservative management of post traumatic parotid fistulas and sialoceles found that parenchymal injuries alone resolved in 5 days whereas ductal injuries took 14 days. While

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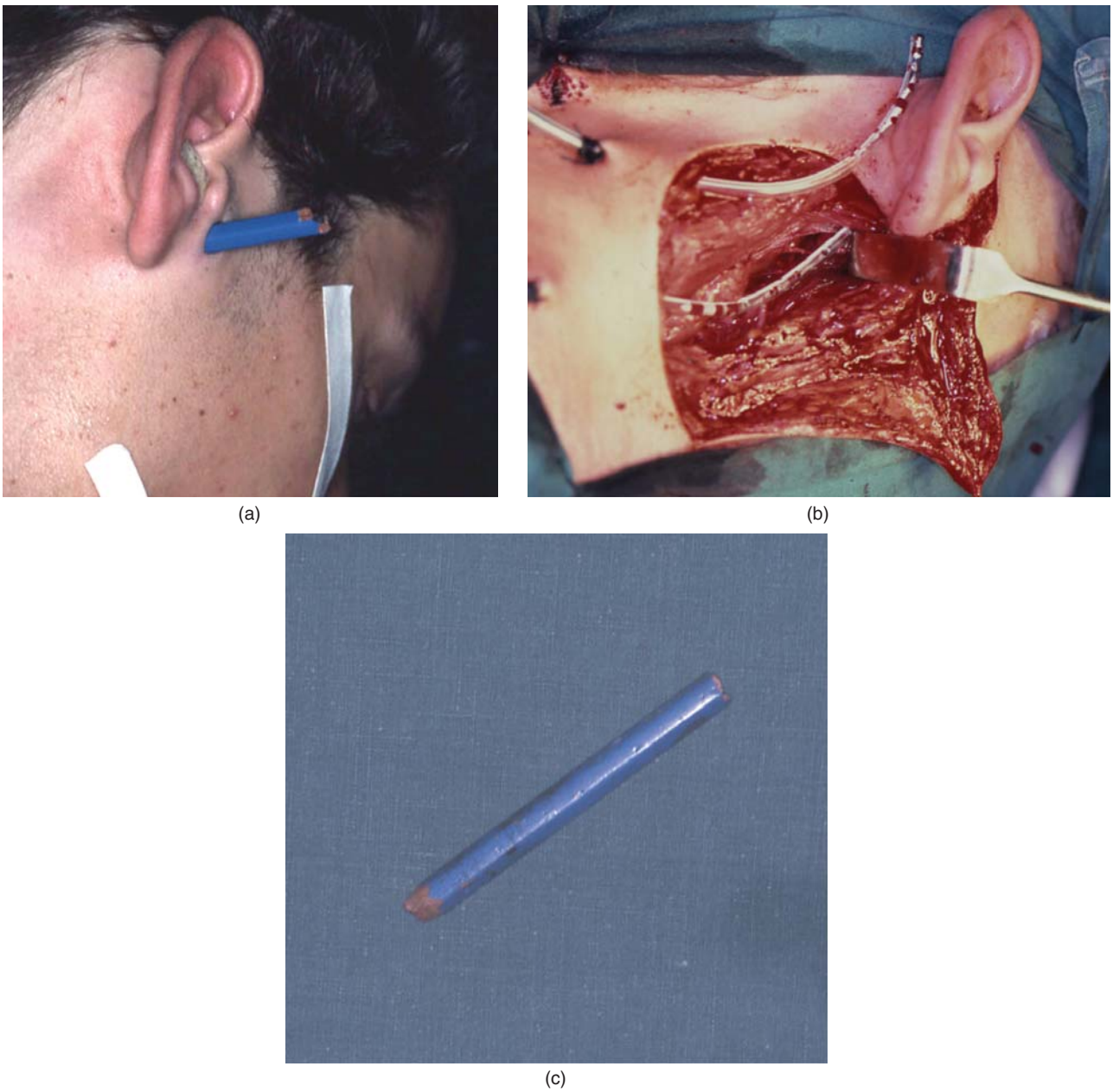


Figure 16.1. (a) Penetrating injury of the parotid after being stabbed with a pencil. (b) Exploration via a modified Blair incision to check for damage to the external carotid artery, facial nerve and suture the capsule. (c) The length of the recovered pencil illustrates the depth of the wound.

Morestin (1917), in a series of 62 war injuries with parotid fistula, 30 glandular and 32 ductal, reported good successes with the creation of an intraoral fistula. In more extensive avulsive injuries with gross scarring, conservative treatment may be less successful (Figure 16.2) and established epithelialized fistulas require excision with repair of the parotid capsule and closure.

The submandibular gland is less liable to be involved in the development of traumatic fistulas perhaps because it is protected by the mandible and its smaller size. Few cases are reported and in

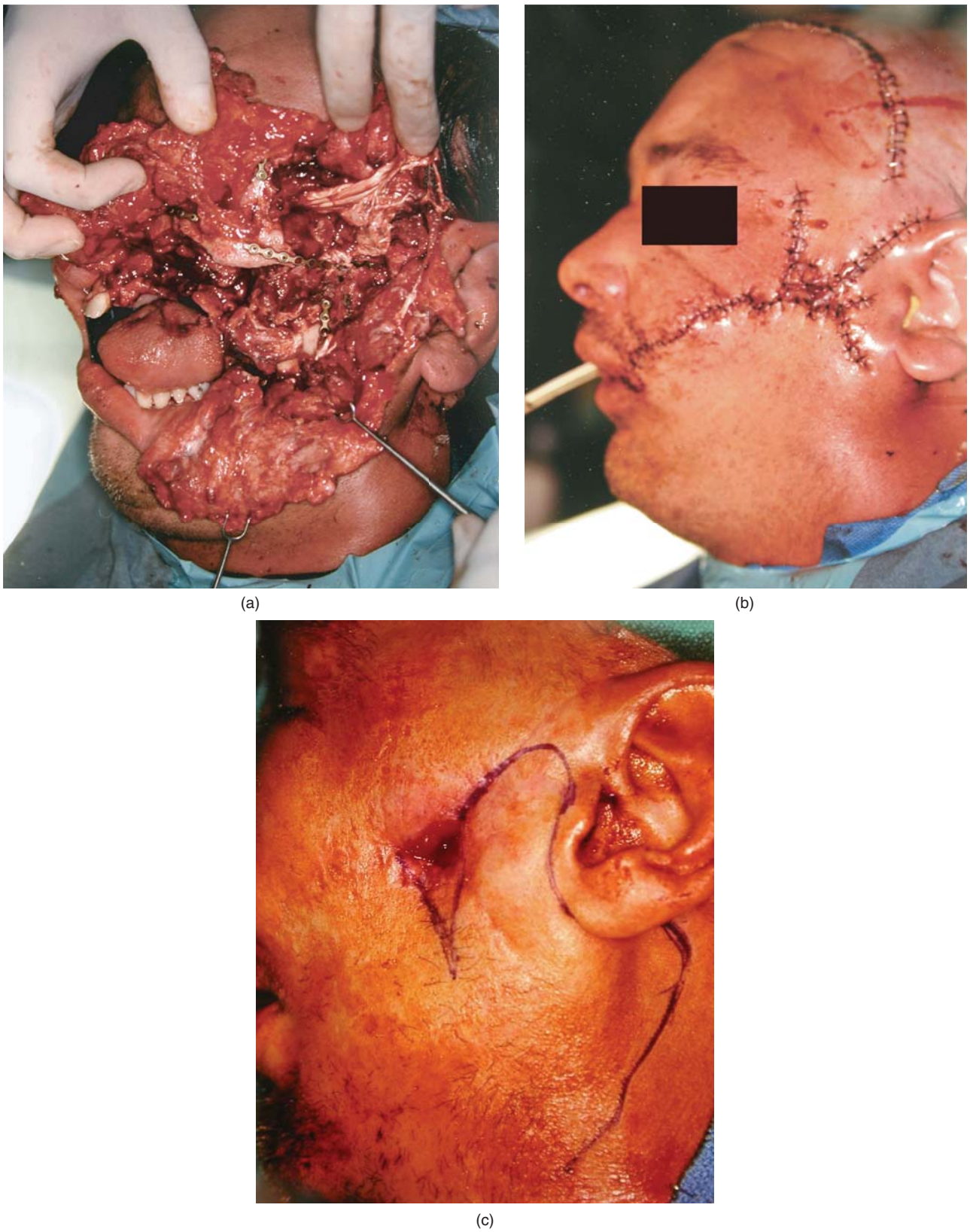


Figure 16.2. (a) Extensive avulsive injury from self-inflicted shotgun wound. (b) Post-surgical reduction of facial fractures and wound closure. (c) The patient developed a salivary fistula, which was treated by excision resuturing and a rotation flap as outlined.

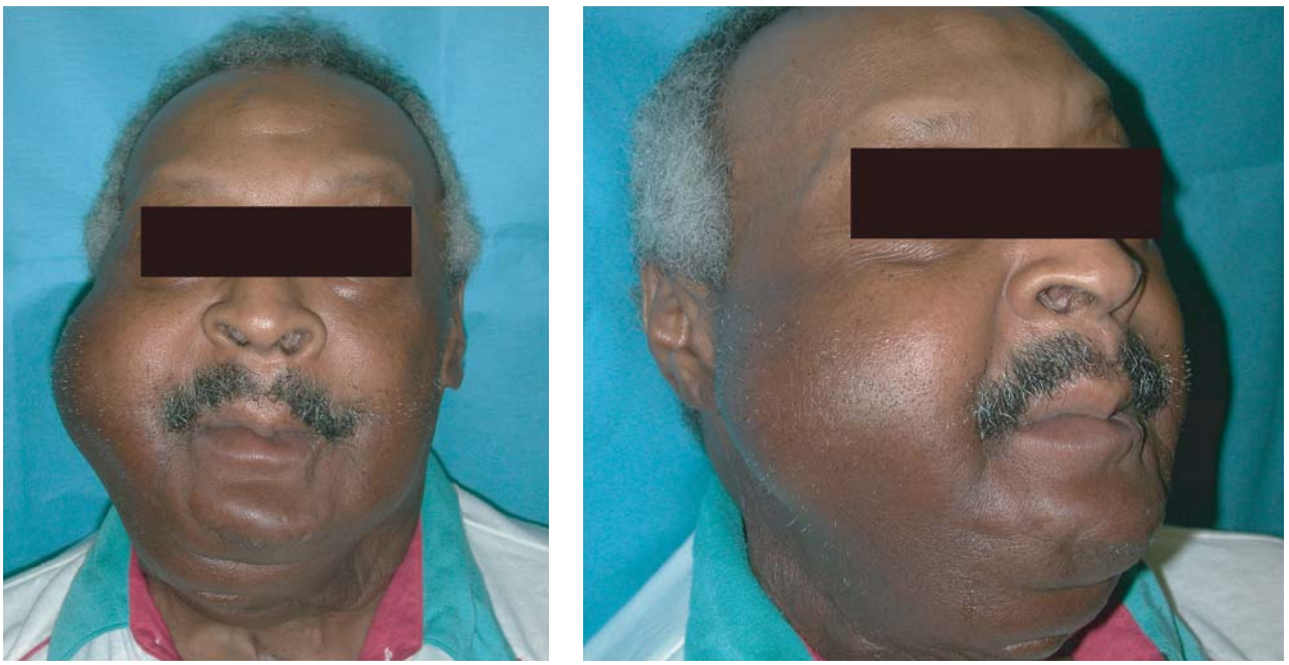
1995 a published case report of a submandibular gland fistula secondary to a gunshot wound, which reviewed the literature found only one other case from 1976 (Singh and Shaha 1995). In their case, the fistula resolved without active treatment in 10 days.

Rarely internal parotid fistulas can occur presenting as rhinorrhea or rhinorrhea related to food usually as a result of maxillary fracture with parotid fistula into the maxillary antrum (Scher and Poe 1988; Faussat, et al. 1993). In a recent report of parotid fistula into the maxillary antrum (and a very rare case of a sublingual gland fistula to the skin), excellent results were achieved with botulinum toxin injection (Breuer, et al. 2006). Although the authors state that primary surgical repair should be carefully considered, they found the injection of botulinum toxin to be effective, shorten fistula closure time, and be minimally invasive.

The current management of fistulas from the parotid gland parenchyma is therefore conservative, as cases that do not involve the duct will resolve. In recalcitrant cases botulinum toxin appears a good option. True fistula post-surgery, for example, superficial parotidectomy, is not common but may occur through the surgical skin incision. Usually management with antisialogogues, nil by mouth or botulinum toxin will lead to resolution. In a report of three cases post-parotidectomy treated with injection of botulinum toxin under electromyographic control, all resolved with no recurrence 14–21 months after therapy (Marchese-Ragona, et al. 2006).

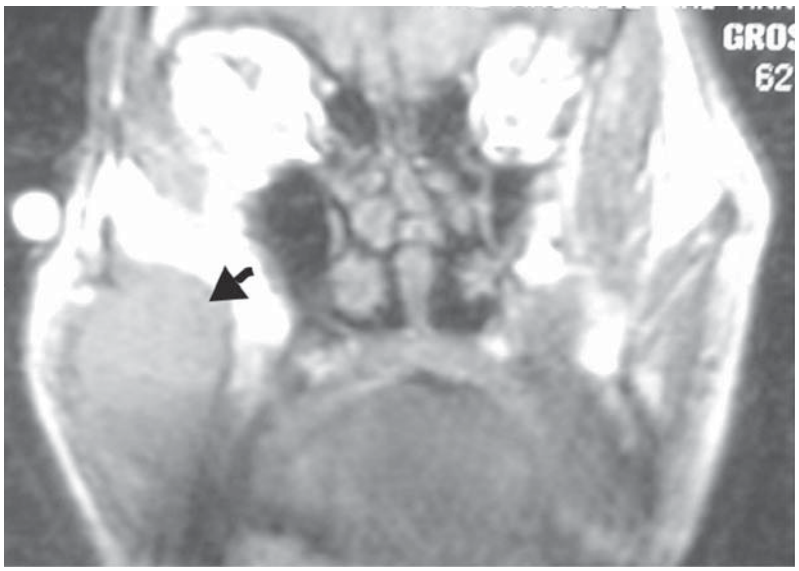
Sialocele

A sialocele is formed by the extravasation of saliva into glandular or periglandular tissues due to disruption of the parenchymal or ductal structures of the saliva gland. This is most commonly seen following trauma and the usual sites are the sublingual gland (ranula) or minor salivary glands (mucocele). Ranulas and mucoceles have been discussed in Chapter 4 and this section will concentrate largely on parotid sialocoeles. Parotid sialocoeles are usually seen after penetrating trauma to the parotid region and will present as painless, cystic swellings which are gradually increasing in size. Aspiration of the sialocele with fluid positive for amylase >10,000 units/liter will confirm the diagnosis. CT scan will show a cystic mass with smooth



(a) (b)

Figure 16.3. (a and b) Frontal and three-quarters views of patient with right parotid sialocele post-surgery. (c, d and e) MRI views of sialocele with enhancing capsule.



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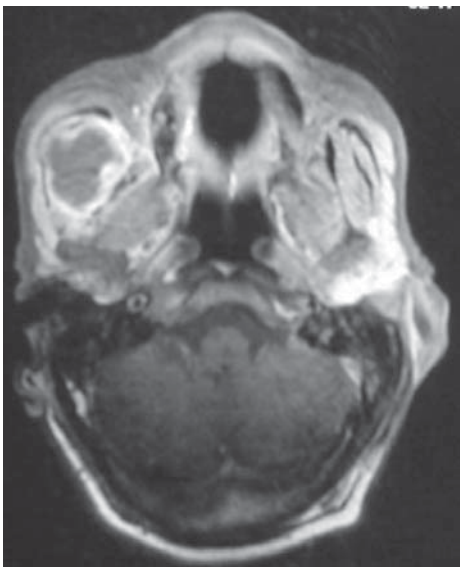

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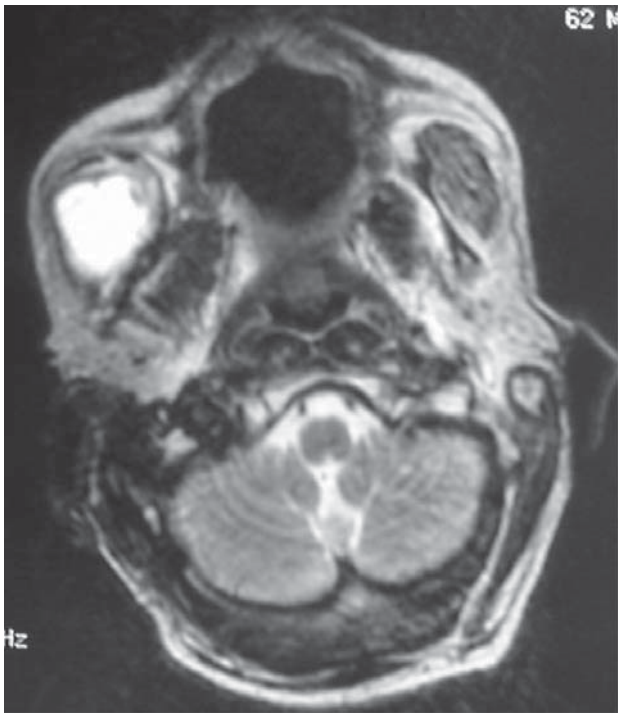
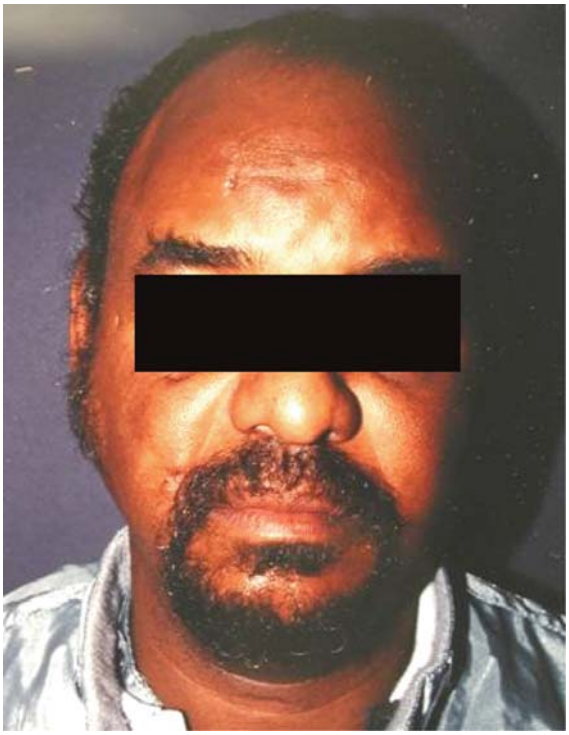


(e)

Figure 16.3. (*Continued*)

margins and a density lower than the surrounding tissues. After 2 weeks there will be enhancing borders due to the development of a capsule (Cholankeril and Scioscia 1993) (Figure 16.3).

Traditional management has been conservative the same as for parotid parenchymal fistulas (Landau and Stewart 1985; Parkeh, et al. 1989; Cant and Campbell 1991) with resolution reported in approximately the same time period as for fistulas. Most sialoceles develop 8–14 days post-injury and the development of a late capsulated sialocele is more difficult to treat. Literature reviews



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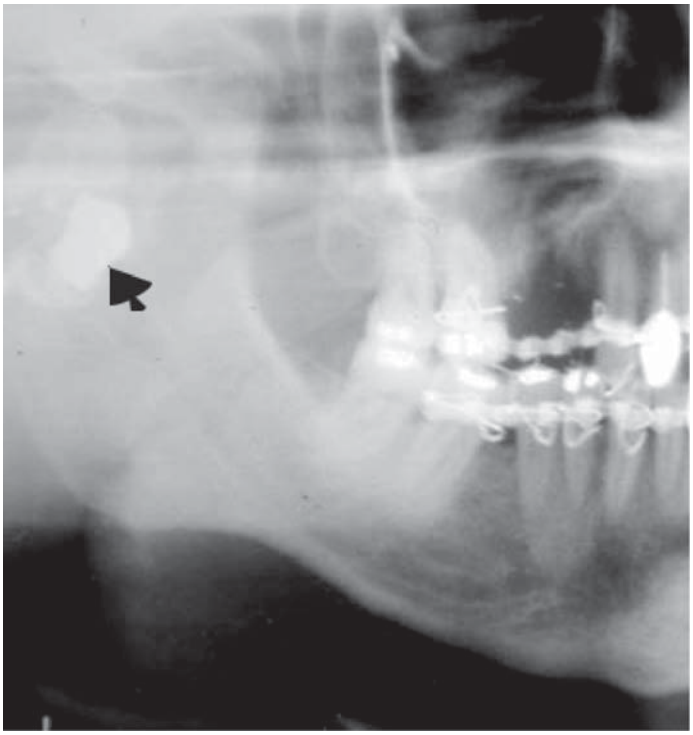

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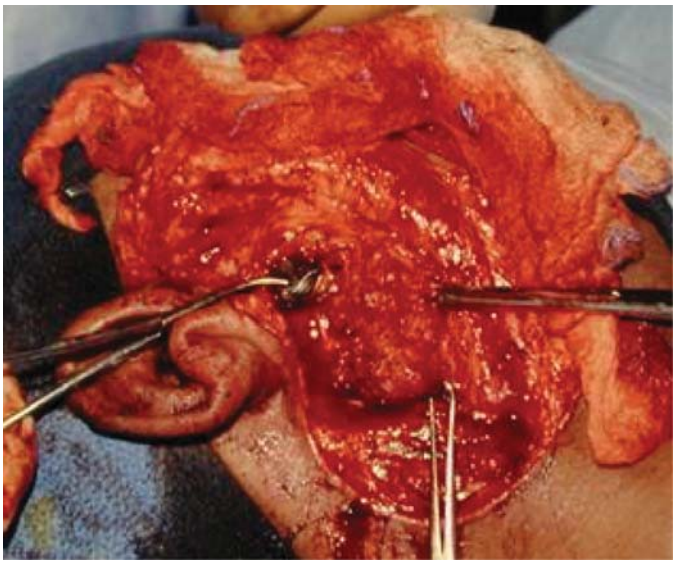


(c)

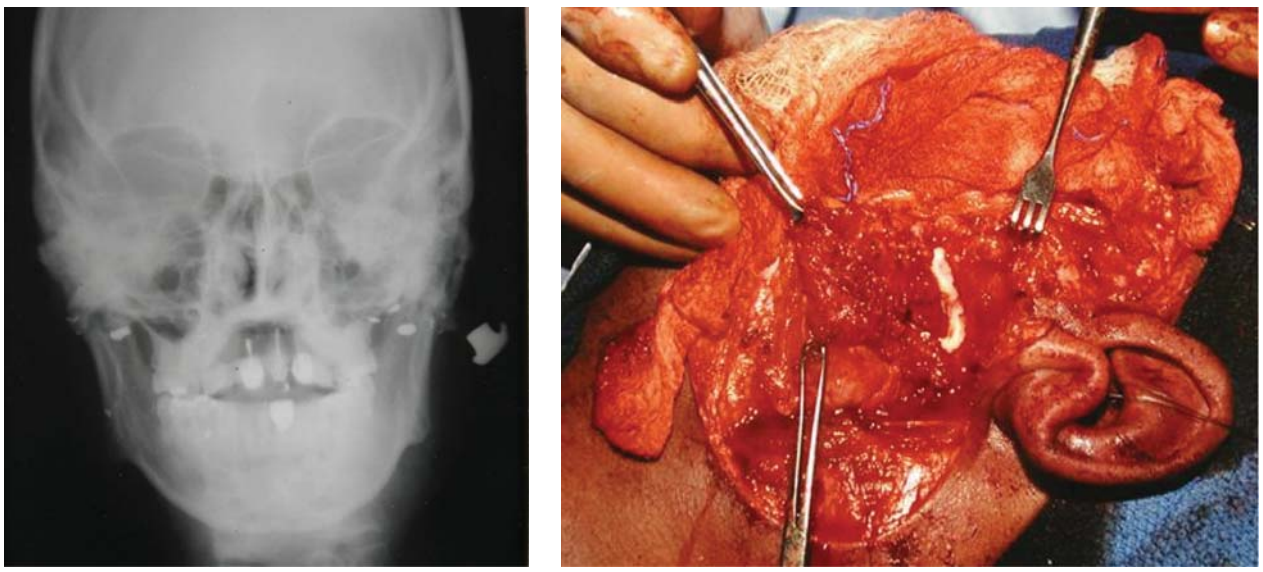
Figure 16.4. (a) A 41-year-old male post a gunshot wound that entered in the left parotid region and traversed to the right parotid region, with fracture of both left and right condyles developed an increasing sialocele in the right parotid gland. (b) Panoramic film shows the retained bullet in the right parotid gland (arrow). (c) Modified Blair incision and partial parotidectomy, with mosquito forceps indicating the bullet. The bullet was located between the superior and inferior branches of the facial nerve which was intact with no weakness. The capsule of the parotid was repaired and the sialocele resolved.

show that treatments proposed include multiple aspirations, pressure dressings, secondary duct repair if this is the etiology, creation of an intraoral fistula, sectioning the auriculotemporal nerve, the use of antisialogogues (atropine, probanthine, glycopyrrolate), duct ligation, and even radiation or parotidectomy (Canosa and Cohen 1999; Lewkowicz, et al. 2002) (Figures 16.4 and 16.5).

In recent years, the use of botulinum toxin has caused a paradigm shift in the way these injuries can be managed. In 1999, Ragona, et al. reported a case of post traumatic parotid sialocele resistant to conservative therapy that was successfully cured using botulinum injection. These authors used *Botulinum F.* due to its earlier and shorter efficacy compared to *Botulinum A* and injected the gland with electromyographic control. Botulinum toxin works by causing a chemical denervation of the gland by blocking the cholinergic neurotransmitter. Following this paper, a report on four cases of recurrent post-parotidectomy sialoceles treated with *Botulinum A.* toxin injected subcutaneously with 100% success was published (Vargas, et al. 2000) as well as other case reports (Chow and Kwok 2003). There is a single case of a submandibular sialocele treated with resolution using botulinum toxin A (Capaccio, et al. 2007).

Nerve Injuries

The facial nerve is at risk from penetrating injury to the facial region both in the parotid and in the distribution of its peripheral branches to the facial musculature. It is stated that damage to branches distal to a line drawn from the lateral canthus to the commissure does not require repair and may be managed expectantly. All patients with facial wounds should have a careful clinical examination of the facial nerve function. Where this is not possible, for example, in the unconscious patient or the uncooperative infant (Figure 16.6), the wound should be carefully explored at the time of surgery to exclude transaction of the branches of the facial nerve. Primary repair soon after the injury with end to end anastomosis is the ideal scenario, as paralysis of the facial nerve is a devastating injury for the patient, and even when "successful" nerve repair has been carried out with satisfying results (based on the House-Brackmann, Stennert, and May grading), patients experienced a reduced quality of life (Guntinas-Lichius, et al. 2007) (Figures 16.7 and 16.8). This section will discuss the management of the primary nerve injury and will not discuss the techniques for facial reanimation or static slings, which are beyond the scope of this text. The interested reader will find many recent review articles addressing these topics (Malik, et al. 2005; Guntinas-Lichius, et al. 2006).



(a) (b)

Figure 16.5. (a) Plain film of 20-year-old man following a gunshot wound shows bullet "floating" in parotid. sialocele. (b) Surgical exploration to remove the bullet revealed an abscess cavity where the bullet had lodged. Note pus draining.

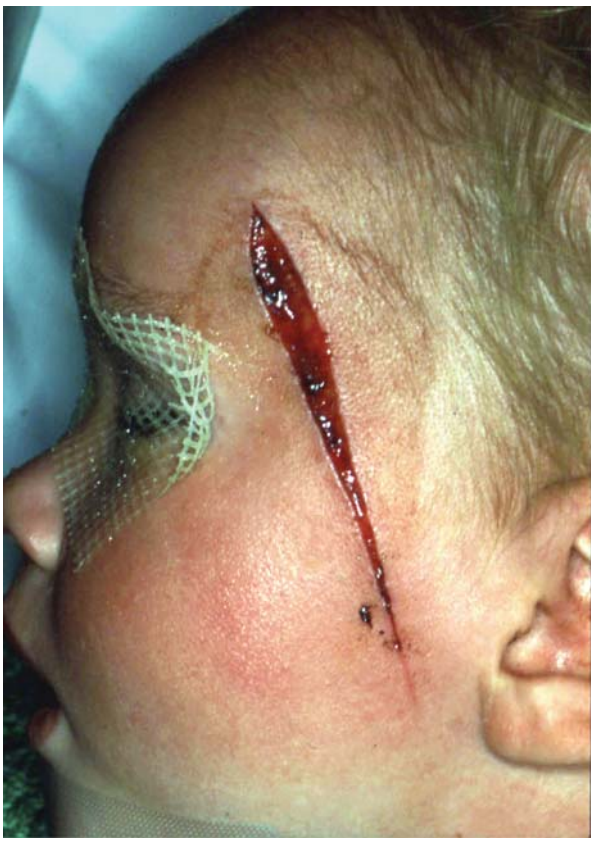


Figure 16.6. Infant with laceration from broken glass. No facial nerve damage.

Classically the nerve is sutured under the microscope using 9-O or 10-O nylon sutures attempting to coapt the nerve ends without tension (Figure 16.9). The suturing can be epineural or fascicular. In epineural suturing less damage is caused to the neural bundles with less foreign body reaction in the fascicles due to the suture materials; however, fascicular suturing should allow better adaptation of the fascicles and trimming back the epineurium to prevent fibrous tissue in-growth. However, anatomic studies have shown the fascicular and connective tissue anatomy of the facial nerve to be complex with the number of fascicles increasing in a proximo-distal way from the geniculate ganglion with diminishing diameter (Figure 16.10). This variability in number of fascicles and structure along the extratemporal facial nerve constitute a difficulty in facial nerve repair (Captier, et al. 2005). The use of tubes, for example collagen, to support the anastomosis and prevent connective tissue ingrowth and also tissue glues, for example fibrin, to replace sutures and their foreign body reactions have been advocated. However, the tubes can themselves cause foreign body reactions and possible compression. Regarding the tissue glues animal experiments appear to show sutures to be superior. In the rabbit model, axonal growth was faster and greater with epineural suture than fibrin adhesive (Junior, et al. 2004) Although the rate and amount of reduction in conduction velocity was equivalent between the two methods the authors concluded that epineural suture appears the method of choice. In another study in the rat model looking at suture and the effects of platelet rich plasma (PRP) and fibrin sealant, the best return of function for the facial nerve was again with suture (Farrag, et al. 2007). The authors did note a favorable neurotropic effect for the PRP but no benefit for the fibrin sealant.

As it is vital that the anastomosis be tension free, difficulty is encountered when a gap between the nerve ends exists. In a cadaver study, Gardetto, et al. (2002) showed that removal of the superficial part of the parotid gland could allow overlap of the cut branches of the facial nerve. They found it possible to bridge gaps of 15 mm in the temporo-zygomatic branches, 23 mm in the buccal-mandibular branches, and 17 mm in the nerve trunk. Following this experimental work the authors reported successful clinical results on three patients recommending the technique for gaps up to 15 mm but cautioning against its use in the presence of infection or nerve defects (Piza-Katzer, et al. 2004). In another approach the use of a rapid nerve expander (2 cm/30 min) was used to bridge gaps up to 3 cm (Ya, et al. 2007). In nine patients, five achieved good results with EMG peak value of mimetic muscles 82–95% of the normal side, three cases were fair with EMG 60–90%, and 1 case with poor EMG 55%. Other surgical options in this situation are the use of a tube as a conduit and grafting. In seven patients with post-traumatic defects up to 3 cm, the use of a bioabsorbable polyglycolic acid tube was reported as giving very good results in one case, good in four and fair in two (Navissano, et al. 2005). The two commonest sites for donor nerves for the facial nerve are the greater auricular, which is adjacent to the surgical field, and the sural nerve. Surgical principles for repair follow those for direct anastomosis. As expected facial function from cable nerve graft interposition is not as good as end to end anastomosis (Malik, et al. 2005). If there is widespread destruction of multiple branches from an injury

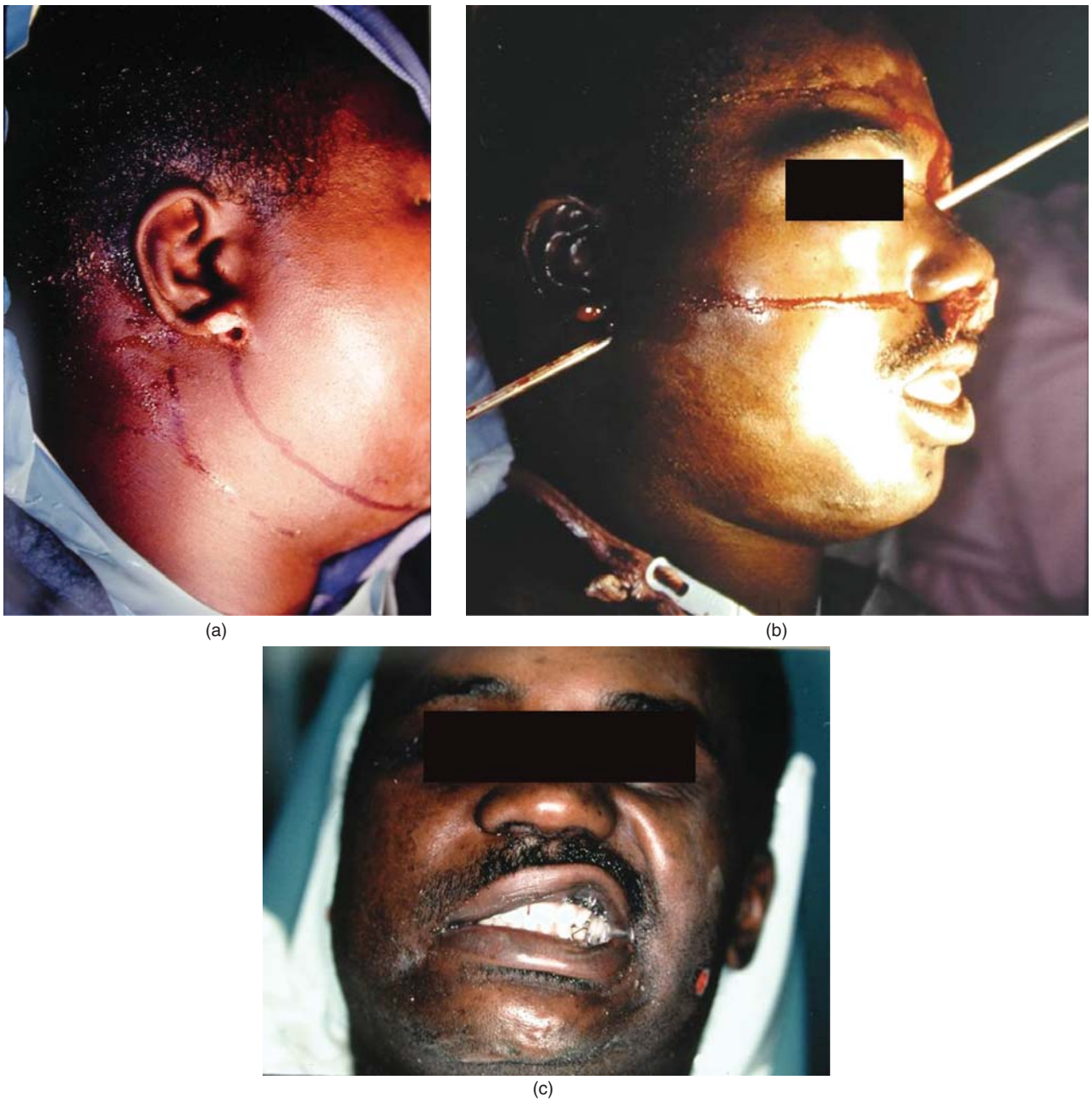


Figure 16.7. (a) Entrance wound for bullet below ear lobe. (b) Bougie placed through track of bullet to demonstrate entrance and exit. (c) Frontal and buccal facial nerve paralysis.

such as a gunshot, the entire superficial cervical plexus can be used to supply multiple grafts.

Frey Syndrome

Although Frey syndrome is now most commonly seen in relation to parotid surgery it was originally described after a shotgun injury to the parotid gland (Frey 1923), however, despite Frey's landmark paper, gustatory sweating was probably first described by Baillarger in 1853 (Dulguerov, et al. 1999). In the trauma arena the obvious problem is management and treatment of the condition,

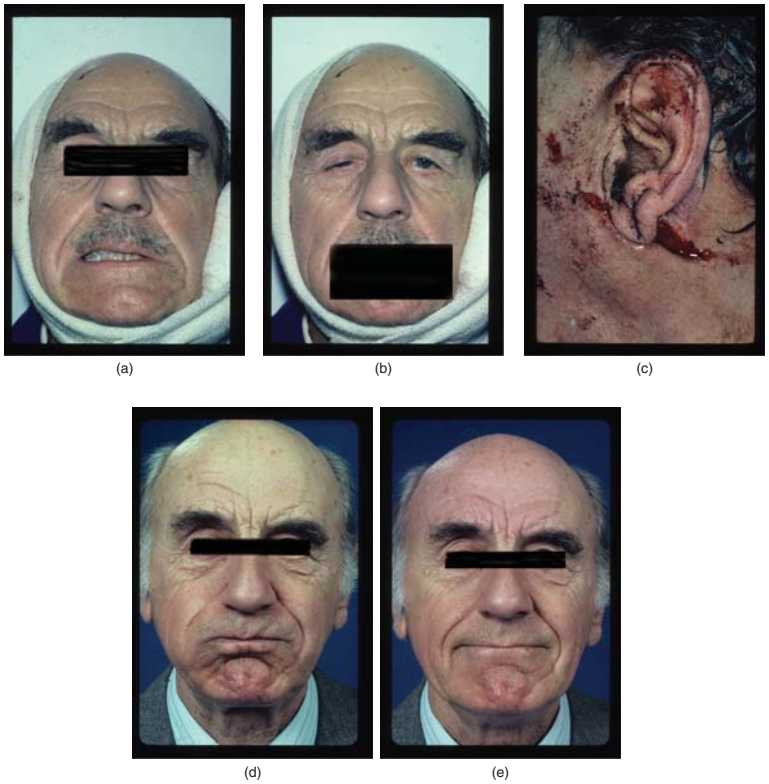


Figure 16.8. (a and b) A 72-year-old man diagnosed with a stroke in the ER after falling through a plate glass window. The diagnosis was made due to the dense facial nerve palsy. (c) After removing the dressings the deep penetrating wound in the region of the facial nerve trunk is appreciated. (d and e) One-year post-repair of nerve trunk and microneural suture, the patient still has some weakness of the upper lid and cannot "blow out" his cheek on the left side, but has good facial symmetry and function.

whereas in post-parotidectomy cases much work has been done on prevention.

Previously reported treatments of Frey syndrome have included topical and systemic anticholinergics, tympanic neurectomy, sectioning of the auriculotemporal or glossopharyngeal nerves, or interposition of fascia lata between the parotid bed and overlying skin. Currently the use of botulinum toxin is the most frequently reported therapeutic modality for Frey syndrome. A report of 33 patients with Frey syndrome treated by intracutaneous injection of 16 to 80 IU of botulinum toxin A showed all symptoms to resolve within a week (Eckardt and Kuettner 2003). In a prospective non-randomized, non-blinded study of 11 patients treated with botulinum toxin A with followup at 6–23 months, only one patient recurred and was successfully retreated (Kyrmizakis, et al. 2004). A prospective randomized trial to establish the ideal dosage and length of effect of botulinum toxin A was carried out on 20 patients divided into two groups receiving either 2 MU/cm or 3 MU/cm. In the 3 MU/cm group, a single injection resulted in nearly complete absence of gustatory sweating during the 12-month followup period. In the 2 MU/cm group, 44% of the total skin areas were still sweating and required a second injection, and the authors concluded that 3 MU/cm^2 is the recommended dose (Nolte, et al. 2004). Some authors have cautioned that the effect of botulinum in Frey syndrome is often temporary and further injections may be necessary depending upon the initial dose and the length of time followed (Ferraro, et al. 2005).

In regards to parotidectomy patients, probably 100% of patients will have gustatory sweating if tested with starch and iodine (Laage-Hellman 1957) (Figure 16.11). However, few patients clinically notice this problem and most do not wish for treatment so that this condition will be underestimated in clinical reports. Frey syndrome is rarely reported after submandibular gland removal. Berini-Aytes and Gay-Escoda (1992) reviewed 206 submandibular gland excisions and found only one case of Frey syndrome, while Teague, et al. (1998) reviewed the literature and found seven reported cases since 1934.

The techniques described for prevention of Frey syndrome depend upon placing a barrier between the parotid bed and skin to prevent the

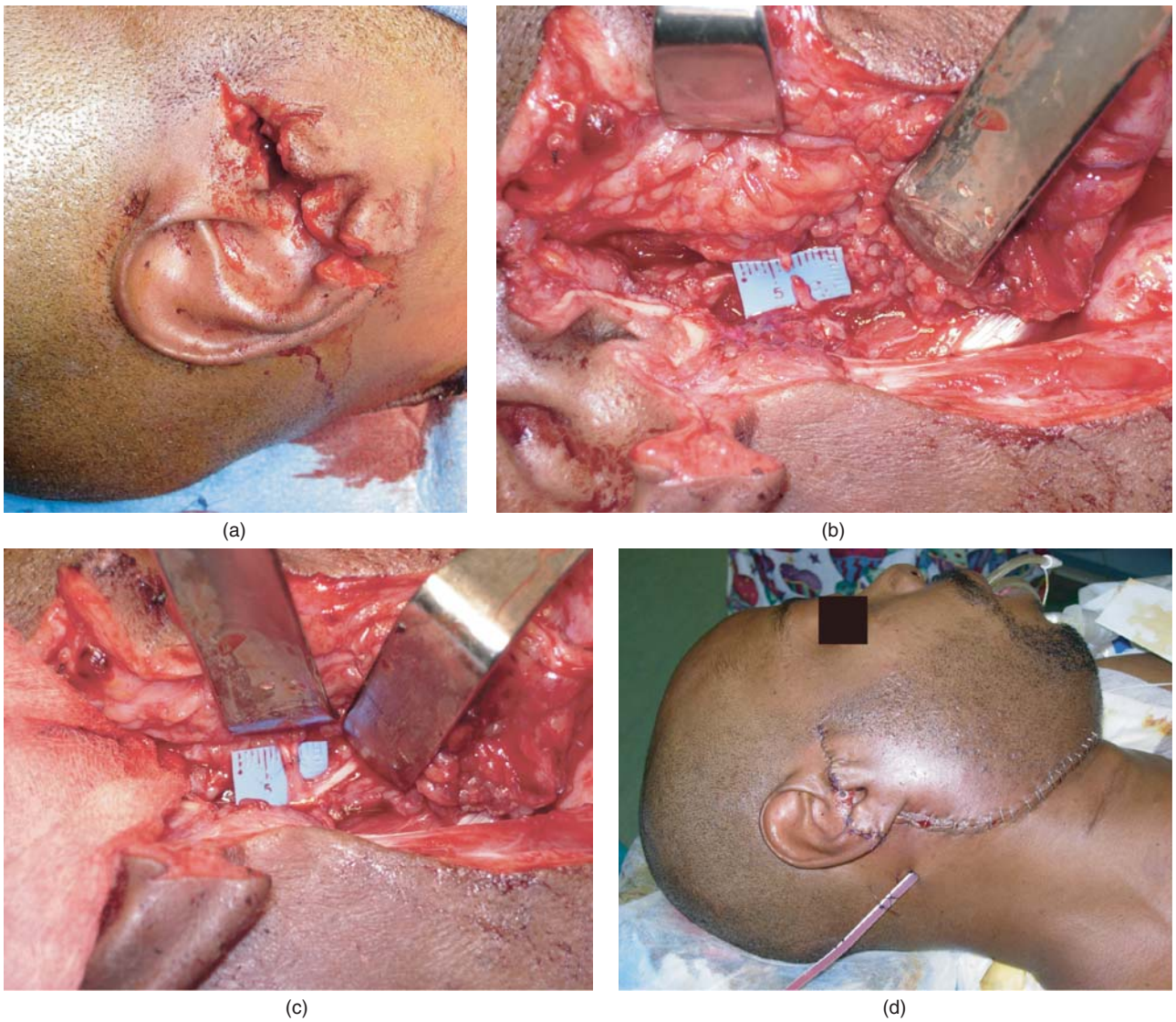


Figure 16.9. (a) Penetrating wound through ear and parotid. (b) Exploration of wound reveals transaction of the superior branch of the facial nerve. (Ruler from surgical marker makes a good background for microsuture if custom microsurgical background material is unavailable.) (c) Post microsurgical repair. (d) Post-suturing of wounds. This case was treated by Dr. J Caccamese, Dept OMS, University of Maryland.

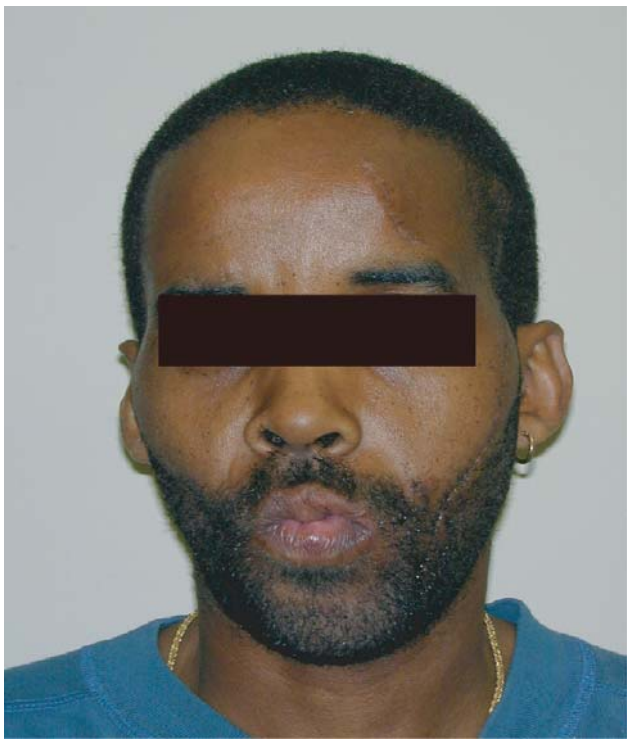
growth of the secretory parasympathetic nerves from the parotid into the sweat glands causing a paradoxical innervation. Acellular dermis has been used with success but a higher complication rate (Govindaraj, et al. 2001). Temporoparietal flaps and the superficial musculoaponeurotic system (SMAS) have been used with good outcomes in 146 parotidectomy patients (Cesteleyn, et al. 2002). No cases of Frey syndrome were encountered in reviewing 160 patients followed from 5–22 years treated with an interpositional SMAS layer at the time of parotidectomy and tested with starch/iodine during follow up (Bonanno, et al. 2000). Other reported barriers have been the use of parotid gland fascia (Zumeng, et al. 2006) and sternocleidomastoid flaps, with mixed results (Kerawala, et al. 2002; Filho, et al. 2004).

It would appear that Frey syndrome is preventable in most cases and perhaps the use of the SMAS layer is the most convenient for the surgeon.

Figure 16.10. (a) Extensive penetrating wound anterior to the parotid gland, which involves the peripheral branches of the nerve. (b) Nerve branches identified for microneural repair. (c) High power view of completed repair. (d, e, f, and g) Post repair note, upper branch weakness persists. This case was treated by Dr. J Caccamese, Dept OMS, University of Maryland.

Hollowing

This is a complication seen in patients following parotidectomy rather than trauma and can be managed in a variety of ways. Reconstruction at the time of surgery to prevent the defect occurring is preferable to secondary reconstruction when scarring and the superficial position of the facial nerve post-parotidectomy increase the risk of nerve damage. Various techniques have been used some of which have been discussed in this chapter in relation to Frey syndrome and in Chapter 9. Techniques include the use of layered acellular dermis, free fat grafts (Figure 9.4), use of the SMAS layer, temporalis, and sternocleidomastoid flaps, as well as microvascular free flaps including fascial forearm flaps for larger defects. Choice of technique will depend on the size of the defect, the surgeon's own experience, and the wishes of the patient.



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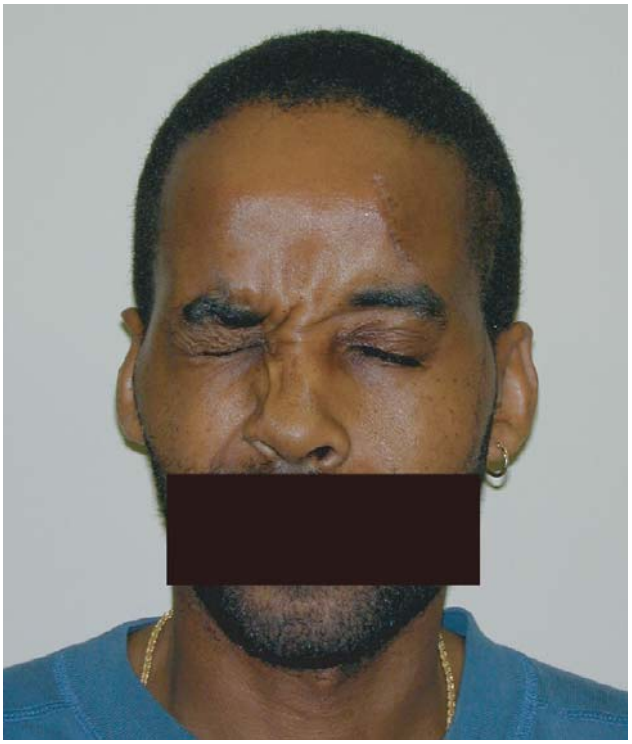

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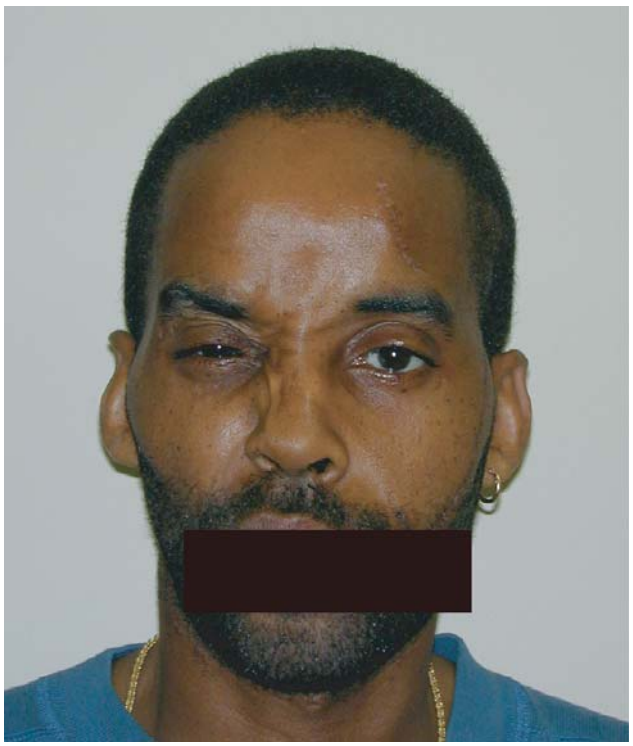

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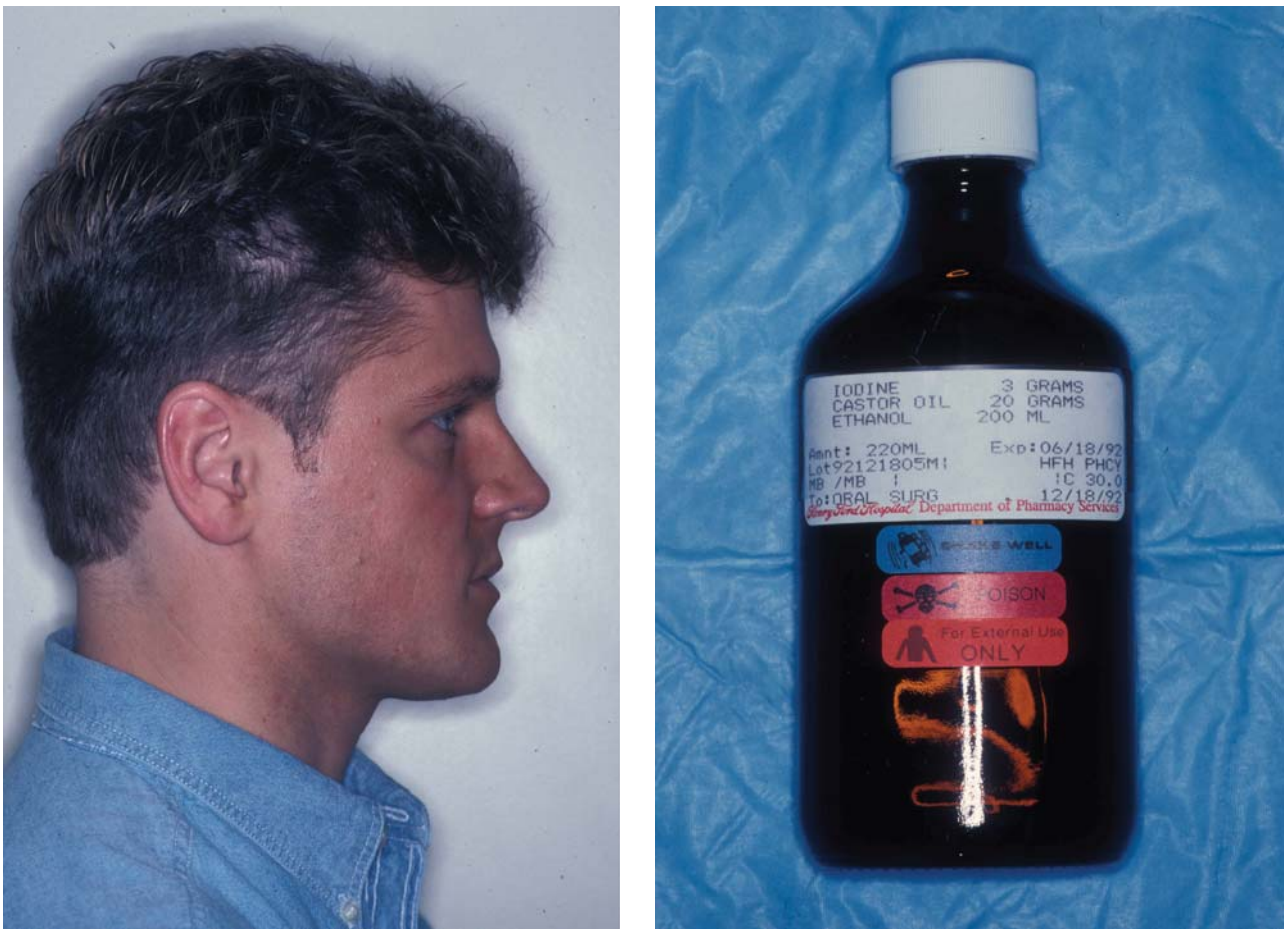
Figure 16.10. (*Continued*)

TRAUMA TO SALIVARY GLAND DUCTS

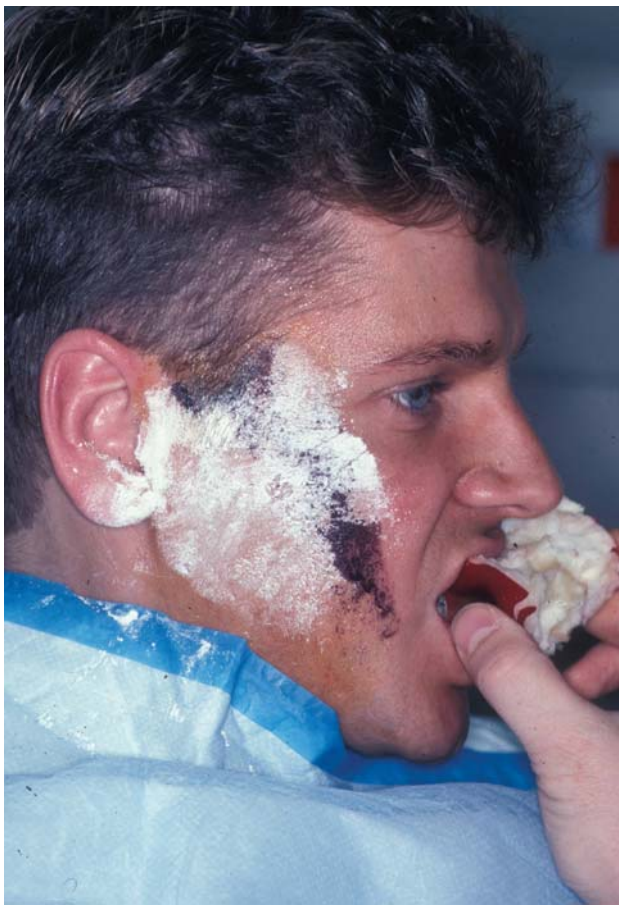
Transection

As has already been discussed previously in the sections on fistulas and sialoceles related to parenchymal trauma, conservative management is usually satisfactory except in those cases where the injury involves partial or complete transaction of the duct. Under these circumstances most papers have indicated that resolution is less certain and takes longer with active management frequently required. There are studies that support conservative measures in duct injuries and in one report, of 19 patients with duct injury confirmed by methylene blue dye injection in a retrograde fashion through the Stenson duct who were treated non-operatively, 9 (47%) healed without complications. Although seven patients (36.8%) developed salivary fistulas and four (21.4%) developed sialoceles, these were described as short term and resolved without the need for surgery (Lewis and Knottenbelt 1991). Van Sickels (1981), divided the parotid duct anatomically into three sites of injury, based on implications for treatment. Site A is the intra-glandular portion of the duct and ductal injuries in this location are treated as described previously for parenchymal trauma. Site B represents the duct as it overlies the masseter muscle and site C is the duct's course anterior to the masseter muscle through the deep tissues of the cheek into the mouth. Injuries at both these sites require exploration and direct repair of the



(a) (b)

Figure 16.11. (a) Lateral view of face of patient complaining of gustatory sweating (Frey syndrome). (b) Bottle of iodine solution that is painted on the face and then covered with corn starch. (c) While the patient eats an apple the corn starch is colored blue-black, indicative of gustatory sweating.



(c)

Figure 16.11. (*Continued*)

duct if possible. If repair is impossible, creating a direct fistula into the mouth is the treatment of choice for site C injuries (Lazaridou, et al. 2012).

However, in most cases current management is directed toward primary repair and the clinician must therefore have a high level of suspicion for injuries involving the region of the parotid duct. The classic anatomic surface markings of the duct are illustrated in Figure 16.12. However, an ultrasound study has shown that 92% of ducts were below the classic anatomic surface markings, although 93% of the ducts were within 1.5 cm of the middle half of a line between the tragus and the cheilion (Stringer, et al. 2012). In this study, the mean internal caliber of the duct was 0.6+/−0.2 mm. Confirmatory evidence for transaction is obtained by cannulating the distal portion of the duct through the Stenson papilla and observing the catheter in the wound (Figure 16.13) or by injecting saline or a small (1 cc) amount of methylene blue through the Stenson papilla. Van Sickels (2009) cautions against injecting too much dye which can stain the tissues and increase the difficulty of the dissection. Identification of the proximal end may be technically difficult as it can retract into the gland substance. Milking the gland to obtain salivary flow is helpful in these circumstances and the anesthesiologist must be cautioned preoperatively against the use of anti-parasympathetic agents. If the proximal and distal ends of the duct are identified and can be coapted, then microsurgical repair can be carried out (Hallock 1992) (Figure 16.14).

The use of stents (usually indwelling catheters) for 10–14 days to prevent stenosis is advocated by some and appears a reasonable hypothesis, although no long term studies of these injuries with and without stenting has been published. A technique of using a 4F Foley

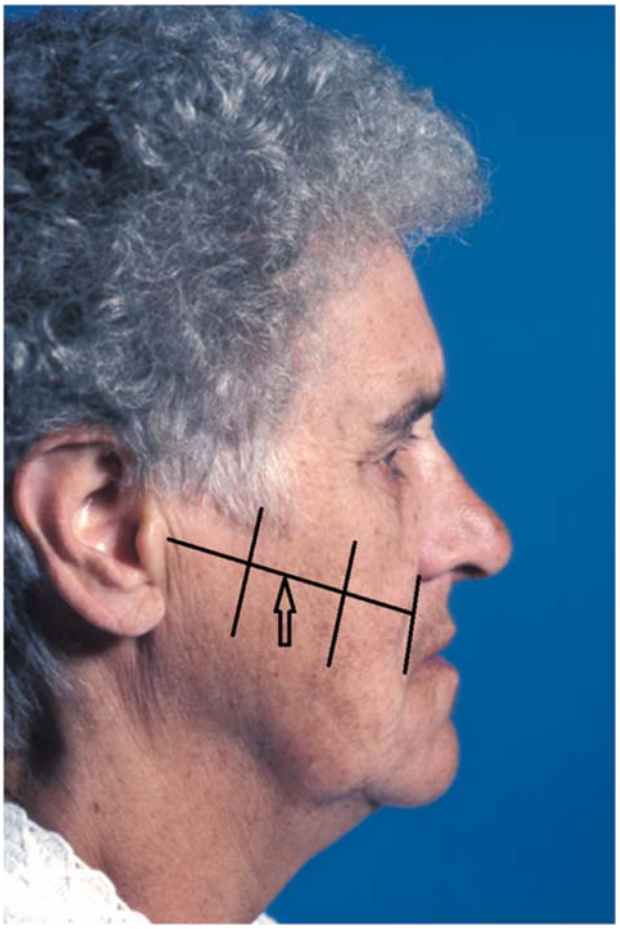


Figure 16.12. Surface markings of the parotid duct are shown by a line drawn from the tragus of the ear to bisect a line drawn from the alar base to the commissure. The middle third of this line (arrow) is surface marking of the parotid duct.

embolectomy catheter for identification of the transaction and then left in place as a stent is described (Etoz, et al. 2006). When the proximal and distal ends of the duct cannot be coapted due to tissue loss, repair using a vein graft has been reported (Heymans, et al. 1999). Steinberg and Herréra (2005) recommended the use of sialography postoperatively to assess the result of duct repair, stating this technique may not always be practical or possible in the acute setting. However, we have used sialography intraoperatively (Figure 16.13). A further development in the repair of ductal injuries has been the utilization of the sialendoscope in some centers, for both repair and followup assessment (Koch, et al. 2013; Kopeć, et al. 2013).

When the injury is too proximal, the wound is avulsive or the duct cannot be identified, the clinician can either create an intraoral fistula or ligate the proximal duct. A controlled fistula can be created by suturing the proximal duct through the buccinator into the oral cavity if enough length is present, or by placing a catheter or drain from the area of the wound into the mouth and leaving it to fistualize (Figure 16.15). Although tying off the proximal duct to cause eventual atrophy has been proposed (Van Sickels 1981), in the author's experience this is unpredictable and, even with the use of pressure and antisialogogues, these patients can have considerable swelling and pain. Chemical denervation using botulinum toxin A may be used to achieve a good outcome in these circumstances (Arnaud, et al. 2006).

In the case of the submandibular duct transection is usually iatrogenic as a result of surgery on the sublingual gland, sialolithotomy from Wharton duct, or resection of floor of mouth cancer. In this case sialodochoplasty with repositioning of the duct posteriorly is all that is required. A catheter has been used as a stent (Ord and Lee 1996), following reposition of Wharton duct in floor of mouth cancer; however, now the duct lumen is identified, one blade of a sharp iris scissors is inserted and a vertical cut through one wall of the duct carried out. The duct is now "fish-tailed" and sutured to a newly created hole in the oral mucosa with 6o nylon sutures. Stenosis and stricture has not been a problem with this technique.

Stenosis of the Duct

When ductal injuries are not surgically repaired immediately complications, such as fistulas and sialoceles, may arise and their management has been discussed. If the duct has not been surgically repaired by 72 h conservative or medical therapy is recommended (Arnaud, et al. 2006). In the long term stricture of the duct may occur, although most strictures are secondary to inflammatory or infective conditions. In cases of intra-ductal salivary gland obstruction 22.6% of 642 cases were due to strictures, which were more common in females (Ngu, et al. 2007) (Figure 16.16). When this occurs at the distal end of the Stenson duct, excision and diversion of the duct into the oral cavity may be feasible. When the main duct is involved with strictures, sialendoscopy may be useful to dilate the strictures using saline

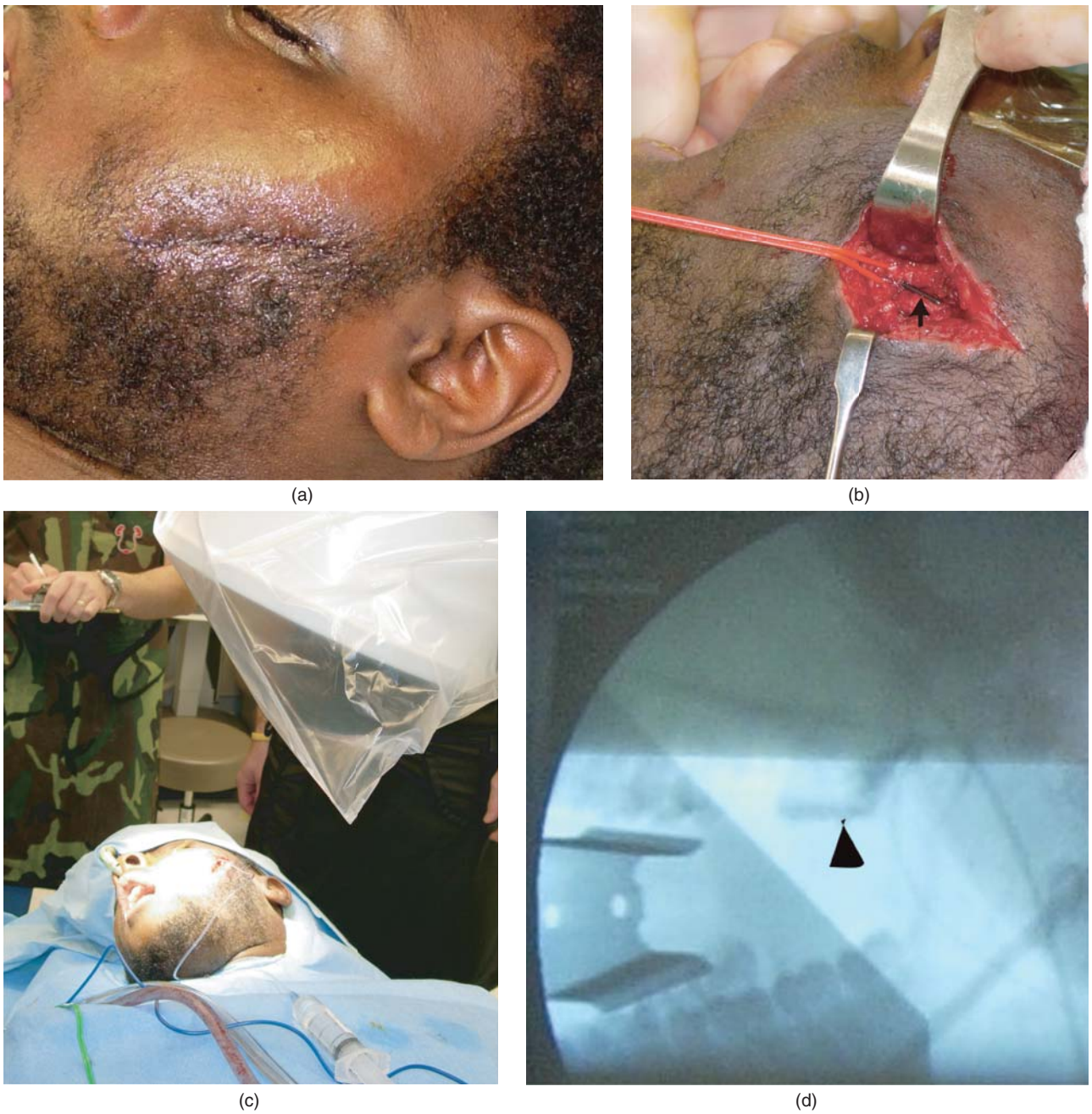


Figure 16.13. (a) Patient with cheek laceration that was primarily sutured now has developed sialocele due to missed duct injury. (b) Wound reopened for re-exploration. The duct is discovered to be transected. Vessel loop around distal end of duct. Lacrimal probe passed from intra-oral through the Stenson duct into the wound (short arrow). (c) After finding the proximal end of the duct by milking the gland the duct is approximated. The duct is cannulated and contrast dye injected for intra-operative sialogram. (d) Fluoroscopic image of intra-operative sialogram with repaired duct (arrow).

pressure, balloon dilatation, or the miniforceps grasper, and even the insertion of a stent to the duct lumen (Nahliel, et al. 2004). Simple balloon angioplasty was successful in 7/9 patients and five of these patients remained asymptomatic on followup (Salerno, et al. 2007). If this is unsuccessful and the patient continues to have recurrent swelling and sialadenitis, denervation with

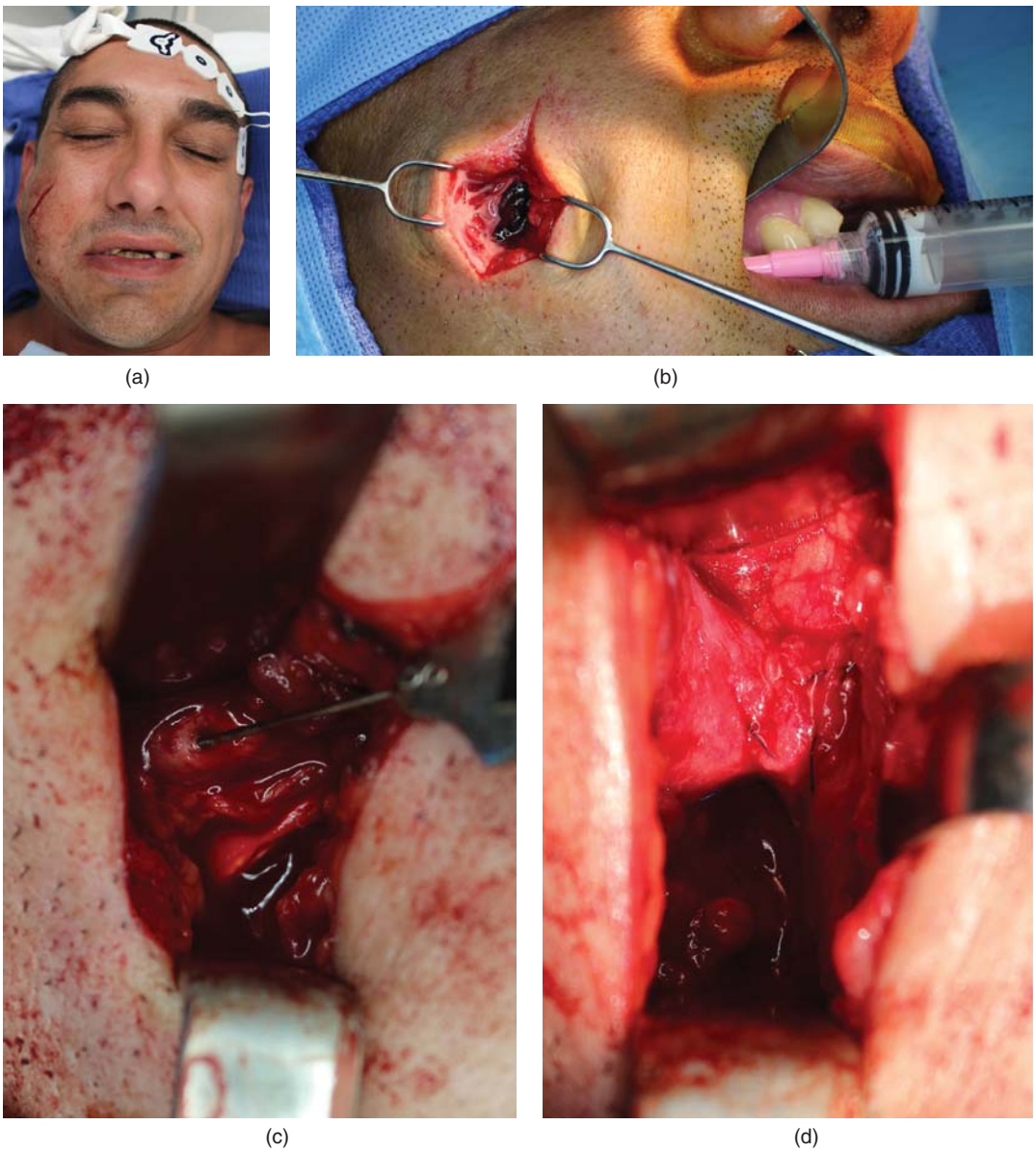
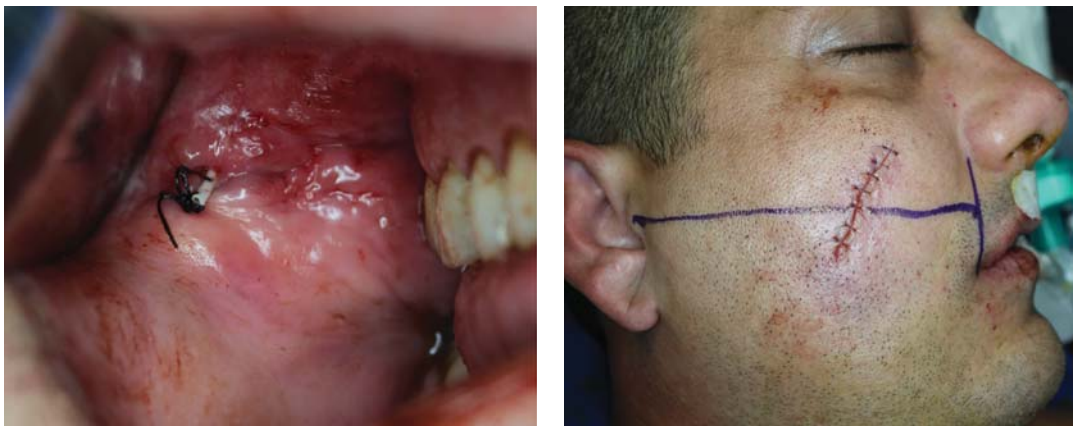


Figure 16.14. (a) A 38-year-old man with a laceration of the right cheek in the operating room in preparation for primary closure and exploration of Stenson duct due to the depth and anatomic location of the laceration. (b) Sterile milk was injected in the distal aspect of Stenson duct that permitted the identification of its laceration. (c) The proximal end of the lacerated Stenson duct is able to be cannulated with a lacrimal probe. (d) The proximal and distal ends of the Stenson duct are primarily closed with 6-0 Prolene sutures with an indwelling catheter in place. (e) The catheter is sutured to the oral mucosa and maintained in place for 2 weeks. (f) The cheek wound is primarily closed in anatomic layers. The location of the laceration is appreciated to exist along the middle third of the line denoting the surface marking of the Stenson duct. Source: Courtesy of Dr. J. Greg Anderson and Dr. Michael Foster, University of Tennessee Medical Center Department of Oral and Maxillofacial Surgery. Reproduced with permission of Dr. Anderson.



(e) (f)

Figure 16.14. (*Continued*)

botulinum toxin or even parotidectomy may be required.

In the submandibular gland the stricture can be excised and sialodochoplasty performed as described earlier.

Radiation Injury

EXTERNAL BEAM

Radiotherapy is commonly administered to patients with head and neck cancer, however, the injurious effect that this treatment modality has on the salivary glands leading to profound xerostomia, which may be permanent, is well known. The serous cells found in the parotid gland are extremely sensitive to apoptotic death following even moderate doses of radiation. Indeed, permanent loss of salivary function is seen after doses approximately larger than 3500 cGy with little in the way of measurable parotid saliva and 5% of patients will demonstrate a sialadenitis with gland swelling and raised amylase within 12 h of their first treatment (Parsons 1994). However, although it is known that damage to the salivary glands will increase with radiation dose and volume of gland irradiated there is no universal agreement over the dose required to produce xerostomia. Someya, et al. (2003) found gradual recovery of function over time with doses of 5000 cGy, while no significant recovery was seen in patients who had >5800 cGy (Figure 16.17). The minor salivary/sublingual glands do not seem to play much of a role in the development of xerostomia, which seems to depend mainly on the mean dose to both the parotid and submandibular glands (Jellema, et al. 2005). These authors also found that the stickiness of saliva post-radiation depended mainly on the mean dose to the submandibular glands.

The exact pathogenesis and mechanism of injury to the saliva glands as a result of radiation therapy is also controversial with no universal agreement as to cause. Based on animal studies on the rat model, a mechanism of delayed serous cell death due to sublethal DNA damage, which results in death during a reproductive phase due to highly redox-reactive metal ions, for example iron and copper associated with secretion granules has been proposed (Nagler 2002, 2003). Another study showed significant increase in cytotoxic T-cells in irradiated submandibular glands, suggesting cell mediated mechanisms may be responsible for the sialadenitis with subsequent acinar cell destruction/atrophy (Teymoortash, et al. 2005). The use of FDG-PET-CT to measure fractional loss of parotid FDG uptake has been proposed as a means to predict post-radiation therapy parotid toxicity (Cannon, et al. 2012).

Obviously, once established, the effects of radiation damage are difficult to treat or reverse so much effort has been aimed at prevention. Important advances in delivery of radiation therapy using 3-D conformal planning and intensity-modulated radiation therapy (IMRT), combined with drugs such as growth factors, cholinergic agonists, and cytoprotective agents (Amifostine) are currently the preferred modalities of prevention (Garden, et al. 2006).

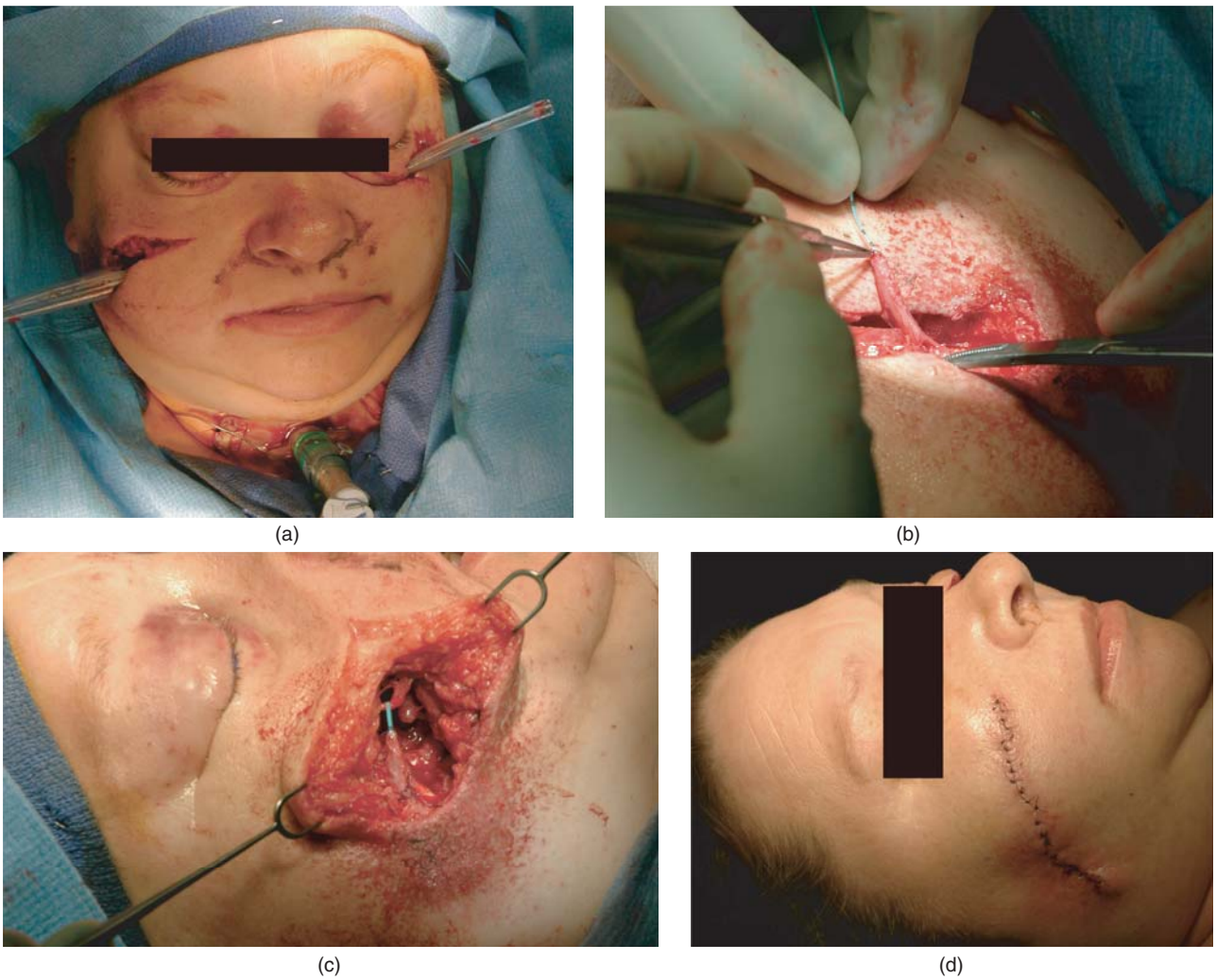
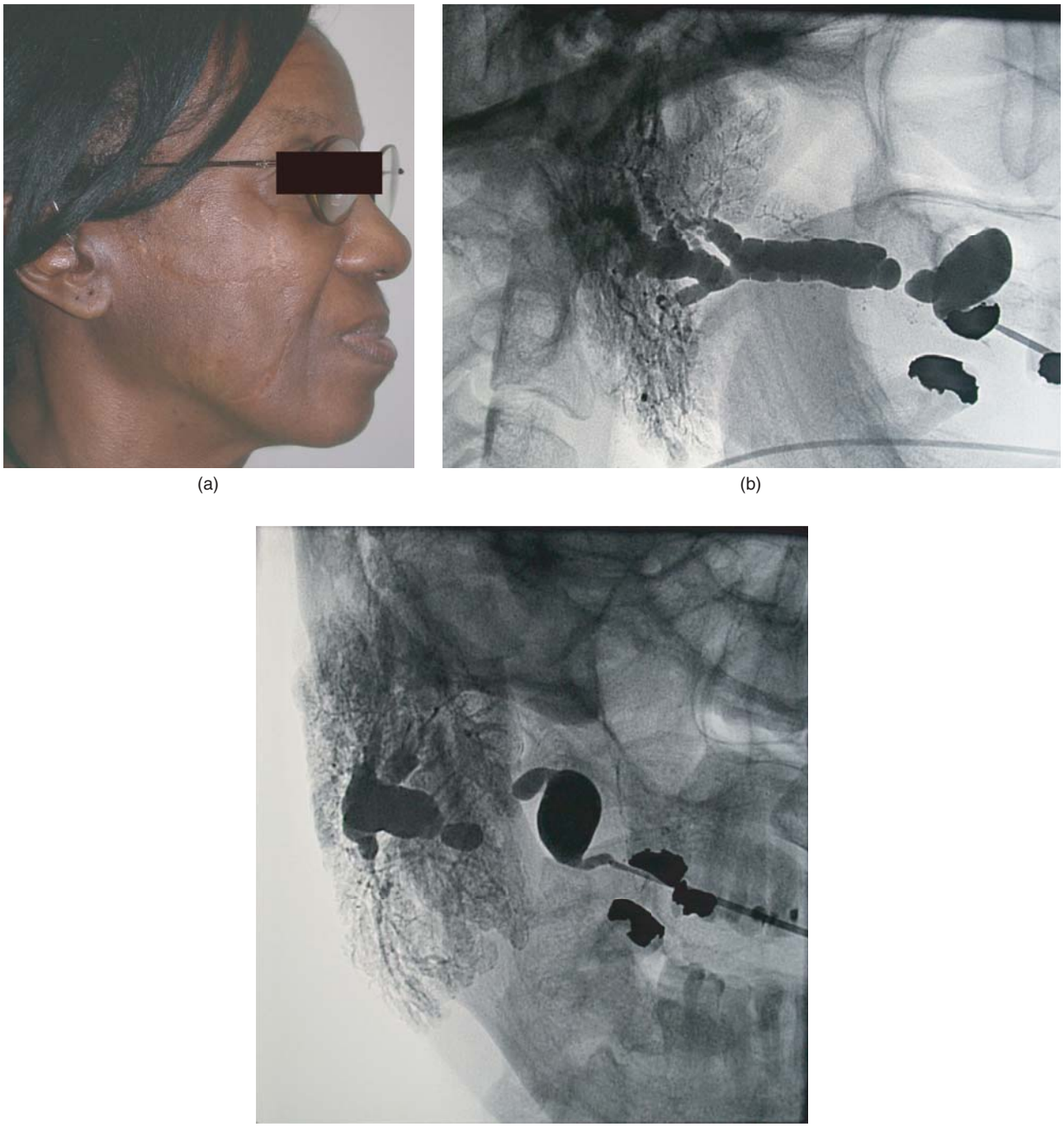


Figure 16.15. (a) Gunshot wound entering at right parotid region with exit at left infraorbital region as indicated by suction tubing. (b) The parotid duct is identified and dissected from the wound to be cannulated as shown. (c) The duct is diverted intraorally via the cannula. Note powder burn at entrance wound. (d) Final repair. This case was treated by Dr. J. Caccamese, Department of Oral and Maxillofacial Surgery, University of Maryland.

It has been shown with conventional radiation therapy that the ability to spare the contralateral major salivary glands or to spare the parotid by positioning of the portals can significantly increase salivary flow and reduce xerostomia (Beer, et al. 2002; Malouf, et al. 2003). The sophistication of 3-D conformal planning and IMRT allows the radiotherapist to give more radiation to the tumor target with increased sparing of normal tissue. In one study only 12% of patients developed xerostomia following IMRT for head and neck cancer and there were no locoregional recurrences with a median follow up of 24 months (Saarilahti, et al. 2005). Jen, et al. (2005) compared 108 patients treated with conventional RT to 72 treated with 3-D conformal radiation therapy, finding that 3-D conformal radiation therapy delivered a higher dose to the tumor with better local control in T4 patients and improved survival with significantly better parotid function. IMRT has also been used to spare the submandibular glands to prevent radiation induced xerostomia (Saarilahti, et al. 2006). The ability to use 3-D conformal RT and IMRT to spare the opposite parotid by excluding the contralateral level II nodes from the field was not shown to be associated with any loco-regional recurrence and



(a) (b) (c)

Figure 16.16. (a) Patient with soft tissue scarring from penetrating wounds caused by a road traffic accident 10 years previously. She now has a 7-year history of parotid and cheek swelling. (b and c) Sialogram shows stricture of duct with proximal dilatation of Stenson duct and secondary ducts and a large cystic swelling distal to the structure.

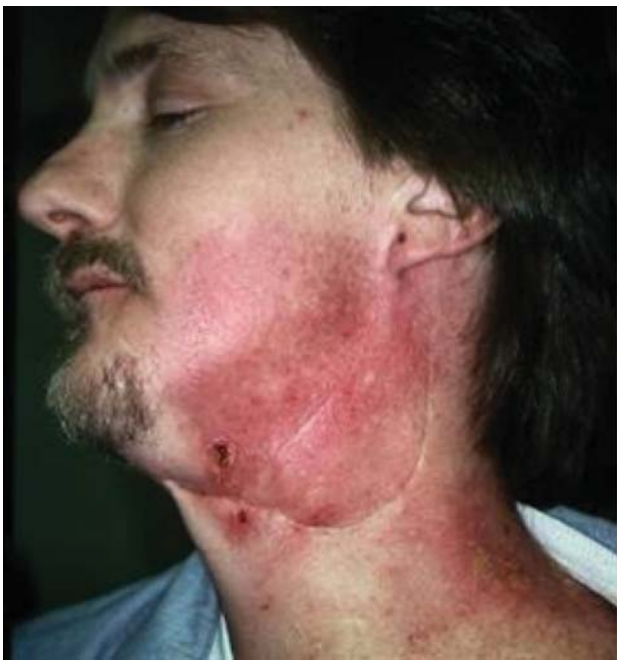


Figure 16.17. Marked skin reaction over parotid region following 65 Gy external beam radiation given postoperatively.

no recurrence occurred in the spared area (Bussels, et al. 2004).

Several studies have shown that IMRT is superior to 3-D conformal radiotherapy in regards to late toxicity from xerostomia (Kouloulias, et al. 2013; Lambrecht, et al. 2013). In both these studies there was no difference in tumor control.

A number of drugs have been investigated for preventing radiation damage. A phase III prospective randomized trial of Amifostine (Ethyol) with 315 patients showed significant reduction in grade 2 or greater xerostomia and chronic xerostomia with no effect on locoregional control, disease free survival or overall survival. In this study, however, 53% of patients experience nausea and/or vomiting (Brizel, et al. 2000). A followup study to review results of this study after 2 years, found the significant decrease in grade 2 or greater xerostomia had been maintained as well as an increase in the proportion of patients with meaningful unstimulated saliva and reduced mouth dryness. There was no compromise of locoregional control, progression free, or disease free survival (Wasseman, et al. 2005). In this study, the Amifostine was given intravenously, and a recent phase II study has shown a similar radioprotective benefit for Amifostine given subcutaneously as a simpler alternative (Anne, et al. 2007). Another approach has been to use pilocarpine, which has been used to treat xerostomia during radiotherapy as a chemopreventive agent. A randomized, double blind, placebo controlled trial of pilocarpine on 60 patients, only 39 of whom were evaluable, indicated that pilocarpine used with radiotherapy could lead to significant diminishment in subsequent xerostomia (Haddad and Karimi 2002). Another randomized trial with 66 patients also concluded that patients with stimulated glands from pilocarpine during radiation had less decrease in salivary flow, which reduced radiation side-effects (Nyarady, et al. 2006). However, the RTOG study 97–09, which was a phase III trial with 245 patients, showed that although there was a significantly increased unstimulated salivary flow in the pilocarpine group, there was no difference in parotid stimulated salivary flow in the amelioration of mucositis or quality of life between the two groups (Scarantino, et al. 2006). Other novel approaches to the problem have been the use of gene therapy, which has yielded promising results in animal models (Thula, et al. 2005; Cotrim, et al. 2006). Future directions may lie in the use of stem cells to regenerate damaged salivary glands (Stiubea-Cohen, et al. 2013).

Finally, a surgical approach to prevention of xerostomia has been the transfer of the submandibular glands into the submental triangle out of the radiation field prior to the commencement of radiation therapy. In a phase II trial of patients who had primary surgery for oropharyngeal cancer followed by adjuvant RT, with or without submandibular gland transfer, 24 of 51 patients were evaluated for swallowing. The cohort with preservation of one gland (13 patients) had significantly increased saliva and swallowing function (Rieger, et al. 2005). Similar results are reported in a small series of patients undergoing chemoradiation (Al-Qahtani, et al. 2006). Regarding long term results in 26 patients followed for 2 years, normal amounts of saliva were reported in 83% (Seikaly, et al. 2004) A further study by the same group showed this surgical technique of submandibular gland transfer to be reproducible in a multicenter setting with 74% of patients prevented from XRT-induced acute xerostomia (Jha, et al., 2012). In a Chinese study of 38 patients, 92.3% of patients had no or minimal xerostomia 2 years post radiation therapy (Zhang, et al. 2012).

RADIOACTIVE IODINE

Radioactive iodine is used in the treatment of thyroid cancer but is also concentrated in the salivary glands particularly the parotid and may cause sialadenitis, which is immediate or begins a few months after treatment (Mandel and Mandel 2003). In a prospective study of 76 patients receiving radioactive iodine, 20 (26%) developed salivary gland toxicity, 11 developed toxicity within 48 h, and 9 not until 3 months post-therapy. A total of 16 patients had chronic toxicity typically xerostomia at 12 months (Hyer, et al. 2007). In seeking to quantitate salivary gland dysfunction using scintigraphy in 50 patients, 46 and 42% were found to have decreased maximum secretion and uptake ratio, respectively (Raza, et al. 2006). The damage was seen more in the parotid and was dependent on the radioiodine dose. The damage and symptoms may be permanent (Mandel and Mandel 1999). The damage is most likely related to an oxidation injury indicated by an increase in prostaglandin levels (Wolfram, et al. 2004).

A randomized placebo controlled study using vitamin E found a significant protective effect against radiation induced dysfunction in salivary glands. In this trial, salivary function was assessed using salivary gland scintigraphy and, although the control group had significantly reduced salivary secretion following the radioactive iodine, the group receiving Vitamin E had no reduced function (Fallahi, et al. 2013).

Current management is symptomatic as for sialadenitis and xerostomia from other causes. Animal studies using the rabbit model indicate that Amifostine can significantly reduce radioiodine induced parenchymal damage (Kutta, et al. 2005). The use of sialendoscopic treatment in this condition for patients with partial duct stenosis has also been reported (Kim, et al. 2007). In one series of sialendoscopy with dilation and irrigation, 54% of patients reported complete resolution of

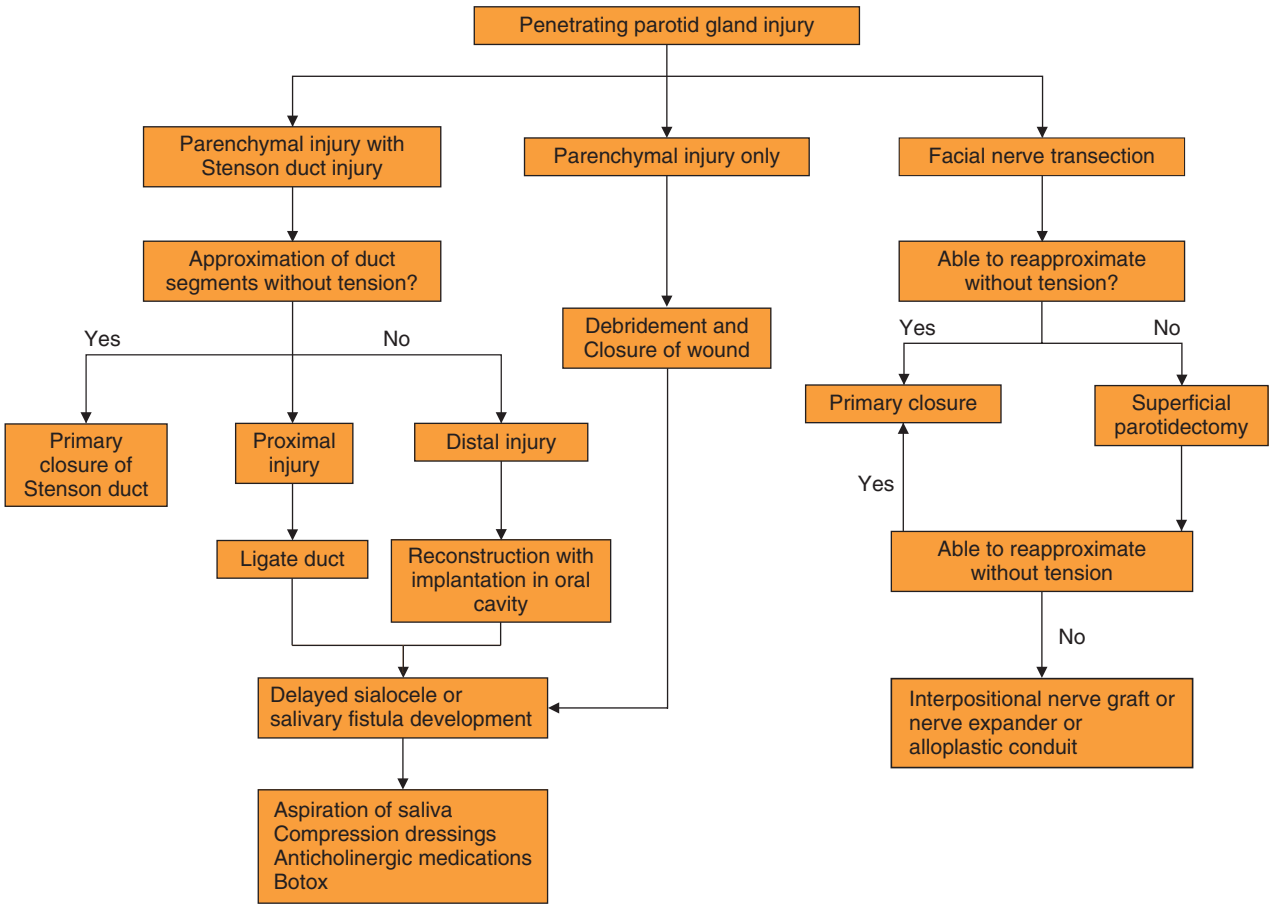


Figure 16.18. Algorithm for management of penetrating trauma to the parotid gland.

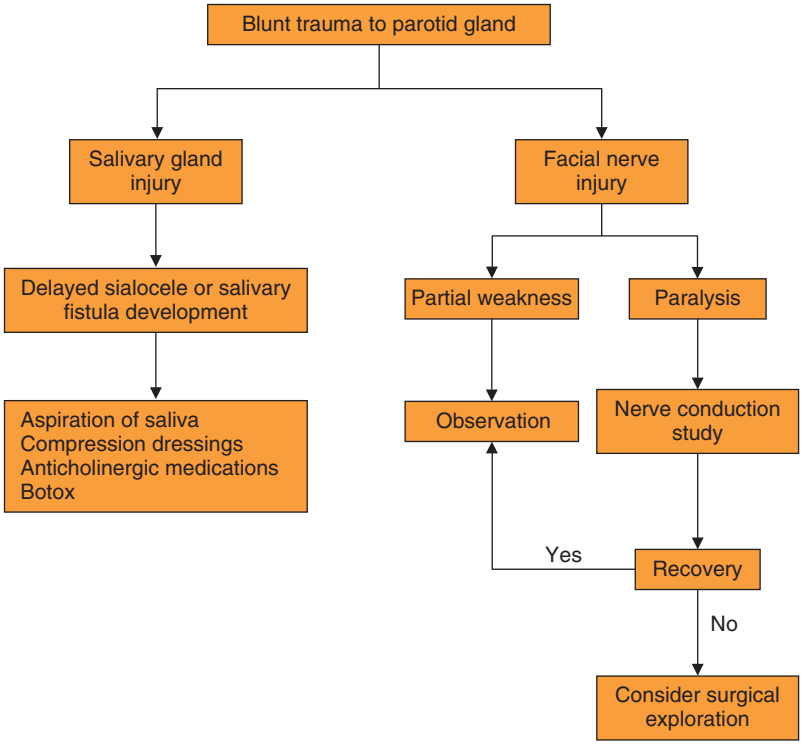


Figure 16.19. Algorithm for management of blunt trauma to the parotid gland.

symptoms, 36% partial improvement, and 10% no improvement at a mean follow up of 18 months (Prendes, et al. 2012).

Barotrauma

Air can be forced in a retrograde fashion into the parotid duct by a rise in intraoral pressure and cause parotid emphysema or pneumoparotid. This condition may occur in glass blowers and musicians who play woodwind or brass instruments. It is usually a benign condition but can cause recurrent sialadenitis or even progress to subcutaneous emphysema. The condition has also been reported in conjunction with the use of an air syringe during routine dentistry (Takenoshite, et al. 1991), secondary to coughing with chronic obstructive airways disease (Cook and Layton 1993), and self-induced in children and adults (Goguen, et al. 1995; Gudlaugsson, et al. 1998). The condition can be diagnosed by palpation of emphysema in the parotid and the escape of frothy saliva from the duct. Sialography, and CT scans have been used for diagnosis (Gudlaugsson, et al. 1998; Maehara, et al. 2005). In one case with subcutaneous emphysema extending to the mediastinum, parotid duct ligation was used for cure (Han and Isaacson 2004).

Summary

See Figures 16.18 and 16.19 for algorithms for management of trauma.

- Most parenchymal penetrating injuries of the parotid gland will resolve with conservative treatment.
- Parotid fistulae and sialocele due to parenchymal injury will also resolve with conservative therapy.
- Chemical denervation of the gland with *Botulinum A* toxin injected subcutaneously appears a safe way of treating fistulas and sialoceles.
- It is important to recognize the possibility of duct injury early as immediate repair is indicated.
- Microneural repair of facial nerve injuries primarily without tension is the ideal management for a transected facial nerve or its branches.

- At present, the use of tissue glues for nerve repair does not appear to improve results.
- Most cases of Frey syndrome following parotidectomy are subclinical.
- Botulinum toxin is useful in the treatment of Frey syndrome.
- A variety of barrier techniques to prevent Frey syndrome have been described with the use of the SAMAS layer appearing to give good results.
- IMRT and 3-D conformal planning show great promise in preventing radiation damage to the salivary glands.
- Amifostine and pilocarpine used during radiation may act as radioprotectants.

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Chapter 17

Miscellaneous Pathologic Processes of the Salivary Glands

Outline

Introduction

This chapter will review a heterogenous group of salivary diseases that are not covered in other sections of this book. Hereditary and developmental conditions of the glands are rare such that the most common branchial arch anomalies will be emphasized. Under the heading of saliva, most clinical emphasis will be given to the treatment of drooling. This condition is not uncommon and there are a wide variety of treatment approaches which will be discussed.

Hereditary and Congenital Conditions

APLASIA

Aplasia of one or all of the major salivary glands is a rare condition, which may present with severe xerostomia, rampant caries, candidiasis, pharyngitis, and laryngitis. In addition "dental chipping" (Mandel 2006) and recurrent herpes labialis (Heath, et al. 2006) has been described as a presenting sign of salivary gland aplasia. It is said to be more common in males (Frydrych and Koong 2014). MRI may be used to confirm the clinical diagnosis of salivary gland aplasia (Mohan, et al. 2013).

The condition may occur as part of a recognized syndrome, including Down syndrome (Odeh, et al. 2013), associated with other congenital anomalies, or as an isolated phenomena. In one series of 21 Treacher Collins patients, 19% had aplasia and 29% dysplasia diagnosed on ultrasound and salivary gland function tests (Østerhus, et al. 2012). Aplasia of the lacrimal and salivary glands (ALSG) presenting with irritable eyes and xerostomia is an autosomal dominant condition, which appears to be related to mutations in FGF10 (Entesarium, et al. 2007). In lacrimo-auriculo-dento-digital syndrome (LADD) agenesis of salivary glands as well as lacrimal glands can be seen and is an autosomal dominant condition with variable expressivity (Inan, et al. 2006). A case of submandibular agenesis with parotid gland hypoplasia in association with ectodermal dysplasia is reported

Salivary Gland Pathology: Diagnosis and Management, Second Edition. Edited by Eric R. Carlson and Robert A. Ord.

(Singh and Warnakulasuriya 2004). In addition aplasia in association with hypoplasia of the thyroid (D'Ascanio, et al. 2006), accessory parotid tissue (Antoniades, et al. 2006) and cleft lip and palate (Reija, et al. 2013) is described.

In a comprehensive review of the literature in 2010 (Pham Dang, et al.), 35 cases of bilateral major gland aplasia were identified. These authors also document 10 cases of unilateral submandibular agenesis, 10 cases of aplasia of the salivary glands with absent lacrimal puncta with no family history, and 2 familial forms of this condition have also been studied.

Management of these cases is symptomatic and directed towards the xerostomia and other oral health care issues.

DUCT ATRESIA

Duct atresia is rare and in a 2001 review (Hoffrichter, et al. 2001) only eight previous case of submandibular duct atresia were found with six unilateral and two bilateral. The condition usually presents in babies or infants as a "ranula" (Aronovitch and Edwards 2014) and is thought to be due to failure of the duct to penetrate the oral mucosa during development, known as an imperforate Wharton duct (Figure 17.1). The diagnosis can be made by the presence of dilated Wharton duct(s) on CT scan. Management is by sialodochoplasty to create a new duct orifice.

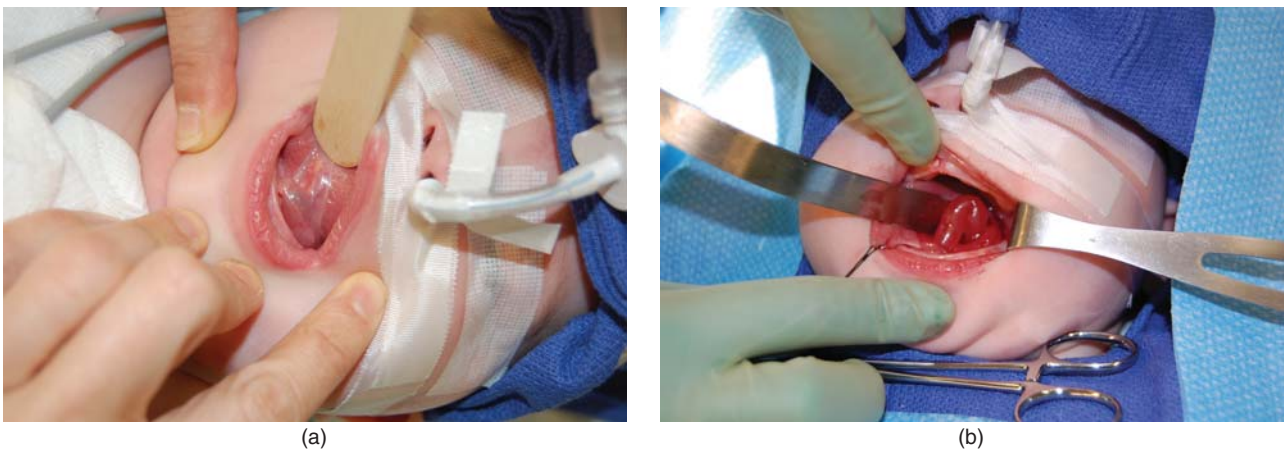
ABERRANT GLANDS

Accessory glands are ectopic in position but possess a duct that usually opens into another main duct, for example the accessory parotid gland whereas aberrant glands have no duct system. Some of these aberrant glands can form fistulas and secrete while the patient is eating others do not secrete but form choristomas. The commonest sites for these aberrant glands is the lateral neck, pharynx, and middle ear (Enoz and Suoglu 2006), presumably from their proximity to the first two branchial arches during development. These aberrant glands may be involved in neoplastic change and may account for the central salivary tumors of the jaws (usually the mandible).

A case of ectopic parotid in conjunction with CHARGE syndrome (coloboma of the eye, heart defects, atresia of the nasal choanae, retardation of growth, genital abnormalities, and ear abnormalities/deafness) has been reported (Ormitti, et al. 2013).

POLYCYSTIC DISEASE OF THE SALIVARY GLANDS

This is a rare disease, which may be a hereditary condition as familial cases have been reported (Smyth, et al. 1993). It is thought to be due to a developmental abnormality of the intercalated duct system. Seifert, et al. (1981) reviewed 5739 cases of salivary gland disease and found 360 cases of cystic



(a) (b)

Figure 17.1. A 3-month-old baby with swelling of the floor of mouth (a) for whom a clinical diagnosis of congenital ranula was made. Intraoperative exploration identified a significantly dilated Wharton duct (b) with no opening of the duct to the oral mucosa. An imperforate duct was therefore diagnosed and a sialodochoplasty was performed for correction. Source: John Caccamese, Reproduced with permission of John Caccamese.

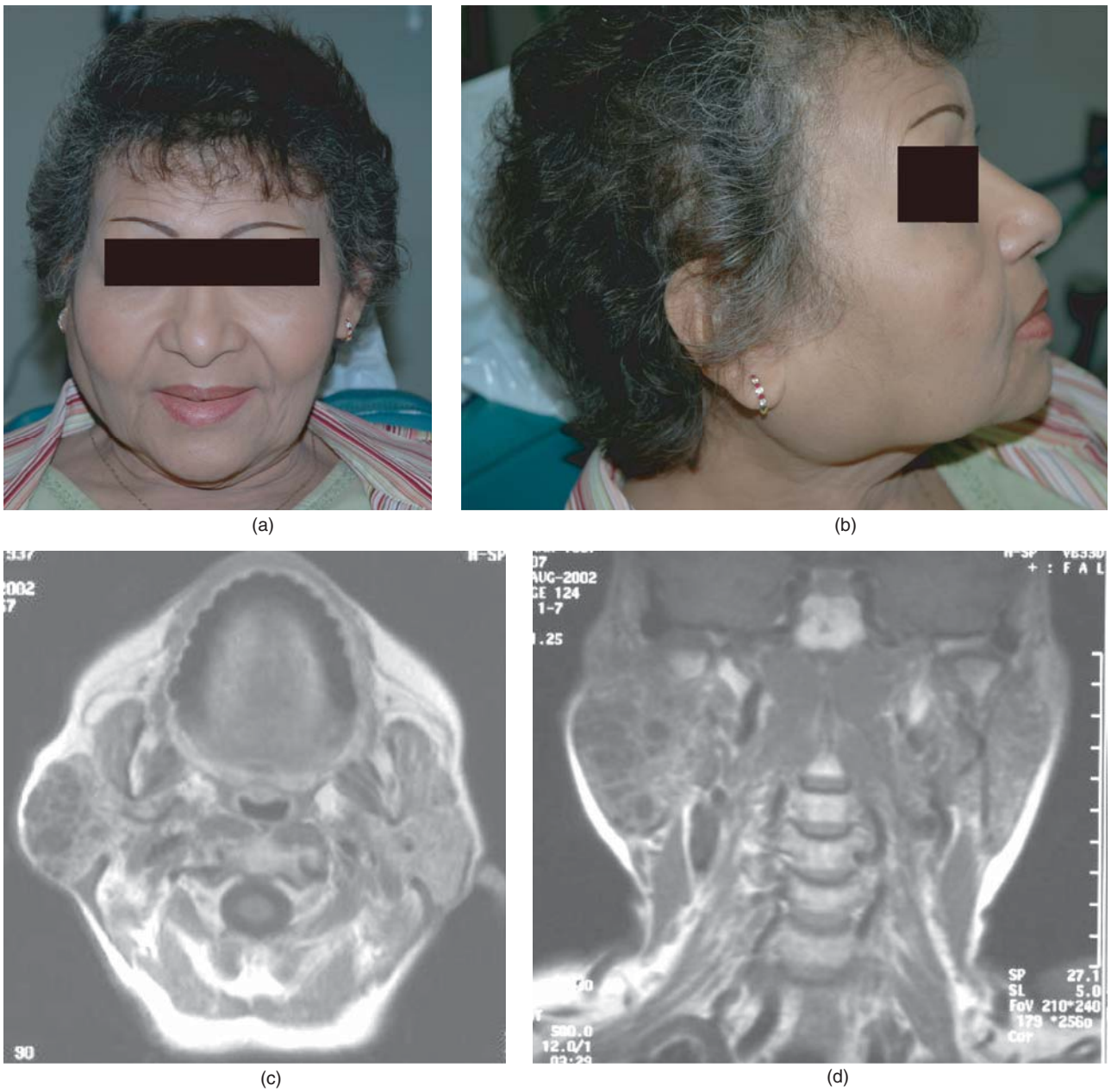
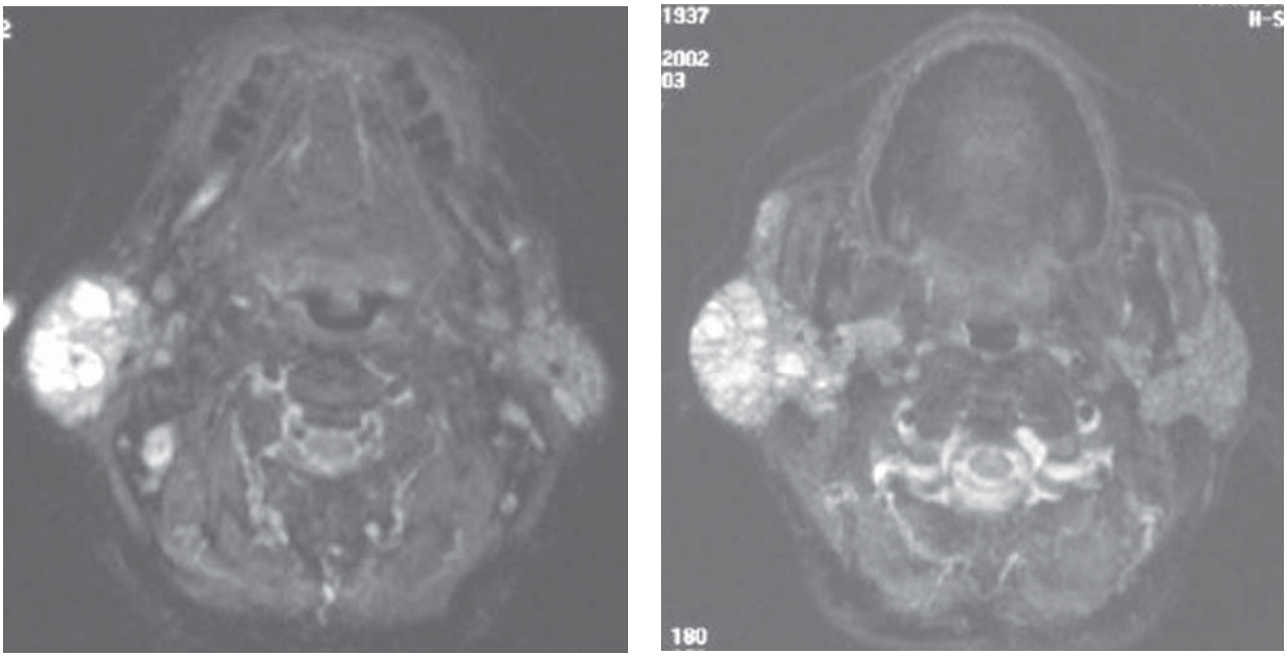


Figure 17.2. (a and b) Middle-aged woman with right parotid swelling for "many" years. Patient is concerned regarding her appearance as she has no symptoms. (c, d, e, and f) MRI films show multiple cysts within the gland. At the time of surgery multiple microliths were seen.

disease, of which 2 patients were classified with dysgenetic polycystic parotid disease. Although it is usually bilateral, unilateral cases have been described (Seifert, et al. 1981) (Figure 17.2). It is said to be always seen in females, however, a case of the condition in the submandibular glands in a male patient is reported (Garcia, et al. 1998). Histologically, the gland is replaced with multiple cysts that may contain spheroliths or microliths. There is a marked absence of inflammatory change. Parotidectomy may be carried out for esthetic reasons.



(e) (f)

Figure 17.2. (*Continued*)

FIRST BRANCHIAL CLEFT CYSTS, FISTULAS, AND SINUSES

Anomalies of the first brachial arch are intimately associated with the parotid gland and the periauricular structures. They are less common than second branchial arch anomalies. In a survey of 183 patients with branchial cleft cysts and fistulas, 148 patients (80.8%) had branchial cysts of which 35 (23.6%) arose from the first arch and 35 (23.6%) had fistulas of which 11 (31.4%) arose from the first arch (Agaton-Bonilla and Gay-Escoda 1996). The usual figure for the incidence of first branchial arch anomalies is 10% (Olsen, et al. 1980).

Although Work (1972) classified type I cystic lesions containing only squamous epithelium and type II lesions that contained squamous epithelium with adnexal skin structures plus cartilage, the presence of infection may make it impossible to classify these lesions using these criteria. Olsen, et al. (1980) simplified this classification dividing the type II anomaly into cysts, fistulas, and sinuses. Cysts are tracts with no opening, sinuses are a tract with a single opening usually from the external auditory canal, and fistulas are tracts with two openings usually from the external auditory meatus to the anterior neck above the hyoid bone. In their series of 39 cases, Triglia, et al. (1998), found 20 (51%) sinuses, 11 (28%) fistulas, and 8 (21%) cysts. Similarly, in the series of 10 patients by Solares, et al. (2003), 5 (50%) were sinuses, 3 (30%) fistulas, and 2 (20%) cysts.

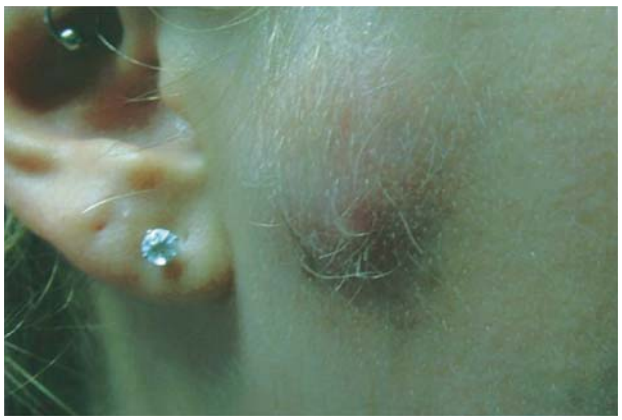


Figure 17.3. A 20-year-old girl with recurrent localized infection of the parotid and a periparotid sinus.

Presentation is usually with recurrent infection, with discharge of pus or an abscess in the anterior neck, a chronic purulent discharge from the ear or an infected swelling of the parotid region (Figure 17.3). The usual age of presentation is between birth and twenty years with most cases diagnosed at age of 2-and-a-half years.

Unfortunately, the infection is often not recognized as a manifestation of a first branchial arch abnormality and is treated with drainage or inadequate limited exploration, which will complicate subsequent surgery. In the series by Triglia, et al. (1998), 44% of patients had undergone prior surgery, while 65% of patients had incomplete surgery before referral in another paper (Martinez, et al. 2007). According to Maddy and Ashram (2013) 50% of their patients had prior abscess drainage and 2 of 18 cases unsuccessful previous excisions. As the fistulas and sinuses communicate with the external auditory canal and their relationship to the facial nerve is variable a wide parotidectomy exposure with dissection of the nerve is essential for complete removal. In fistulas to the auditory meatus removal of the cartilage surrounding the fistulous tract is recommended (Figure 17.4). Rarely, defects of the tympanic membrane in association with first branchial arch fistulas are reported (Pradhu and Ingrams 2011). If the fistula or sinus tract is not completely removed the lesion will recur and, although the recurrence rate is small, 3–5% (Stulner, et al. 2001), this may increase in patients with previous infection or inadequate surgery. Computed tomography fistulography is best to demonstrate the complete course of the tract if there is a cutaneous opening (Goff, et al. 2012). Branchial cysts will usually appear as parotid masses and are usually clinically diagnosed as cystic parotid tumors (Figure 17.5).

The first branchial lesions are usually superficial to the nerve and Triglia, et al. (1998) reviewed 73 cases, including their 39, and found that 63% were superficial, 29% deep, and 8% between the nerve. In the small series by Solares, et al. (2003), however, 7 of 10 lesions were deep to the nerve and 1 lay between the branches. A recent review showed 72% of cases superficial to the nerve but sometimes adherent, deep to the nerve in 17%, and between the nerve branches in 11% (Maddy and Ashram 2013) (Figure 17.6). Larger cysts deep to the nerve may be difficult to remove as the nerve may be adherent to them (Figure 17.7) and dissection can be slow and tedious.

It is very important to recognize the first arch abnormality as its complexity and anatomical variety necessitates wide exposure through a parotidectomy incision and dissection of the facial nerve to minimize the chances of subsequent facial nerve damage.

CYSTIC FIBROSIS

The composition of saliva is changed in cystic fibrosis and the formation of viscous mucus may lead to cystic dilations of the ducts and acini especially in the sublingual gland. The calcium concentration in saliva is also raised and microliths of calcium complexes with the viscous mucous can be seen.

Saliva

SALIVA AS A DIAGNOSTIC FLUID

In many ways saliva represents an ideal fluid for diagnostic analysis being readily available and not requiring invasive techniques. Currently, there is much interest in developing technologies to use saliva to diagnose, monitor progress, and assess treatment and recurrence of oral cancer. However, its mucus nature has made it difficult to analyze. In addition there is evidence to suggest that the methods of processing saliva prior to analysis may have a significant effect on the results obtained for proteins in proteome analysis (Oshiro, et al. 2007). In seeking to analyze the proteome of saliva, researchers are hoping to find specific diagnostic biomarkers and develop techniques to discriminate between these biomarkers using proteomic and genomic technologies (Wong 2006). Several different research groups have examined varying aspects of salivary composition and have demonstrated significant differences between saliva in healthy subjects and those with oral cancer. Studies have examined biochemical and immunological parameters (Shpitzer, et al. 2007), salivary endothelin levels (Pickering, et al. 2007), and reactive nitrogen species and antioxidant profile (Bahar, et al. 2007). Using genomic analysis, four mRNAs (OAZ, SAT, IL8, IL1b) were identified that collectively had a discriminatory power of 91% sensitivity and specificity for detecting oral cancer (Zimmerman, et al. 2007). Nonetheless, despite these promising initial results this technique remains a research tool at the present time. An update review on the current status of salivary markers for interested readers is provided by Yakob, et al. (2014).

Another area of current interest in diagnosis utilizing saliva is the detection of HPV given its now proven status as a causative etiology in oro-pharyngeal cancer (OPC). It is not as clear whether HPV associated with oral cancer has a causative role as seen in OPC. In areas of high

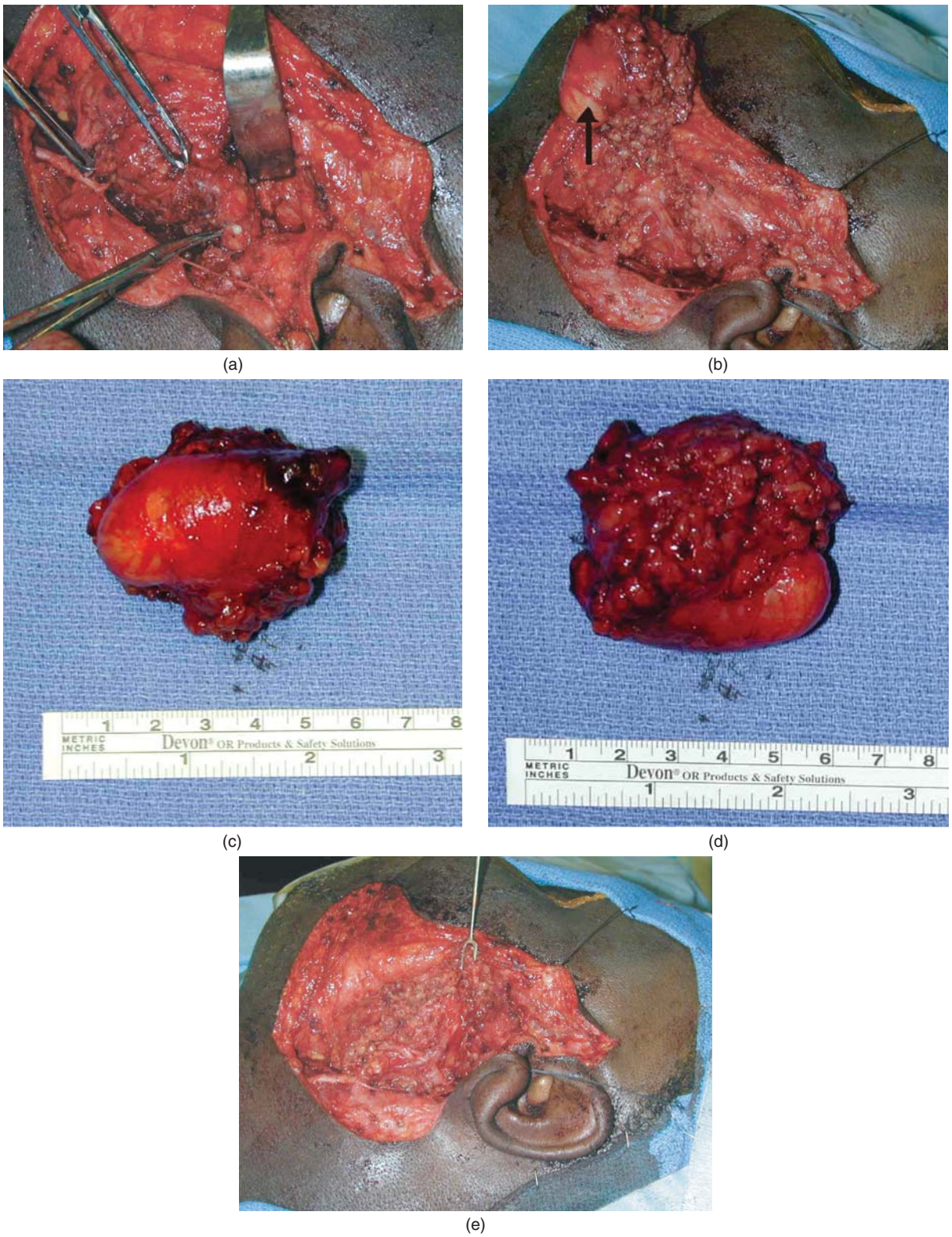


Figure 17.4. (a) Operative photograph of patient with a discrete mass thought to be a parotid tumor. (Patient's ear at lower right of image). While dissecting down the external auditory meatus a fistulous tract to the cartilage was identified and the clamp points to a bead of pus from the fistulous tract. (b) The fistula was removed with a rim of the cartilage from the ear canal and a superficial parotidectomy carried out to remove the branchial cyst (arrow). (c and d) The parotidectomy specimen shows the cyst deep in the parotid but it was lying superficial to the facial nerve. (e) Following superficial parotidectomy (the ear lobe is sutured up for surgical retraction).

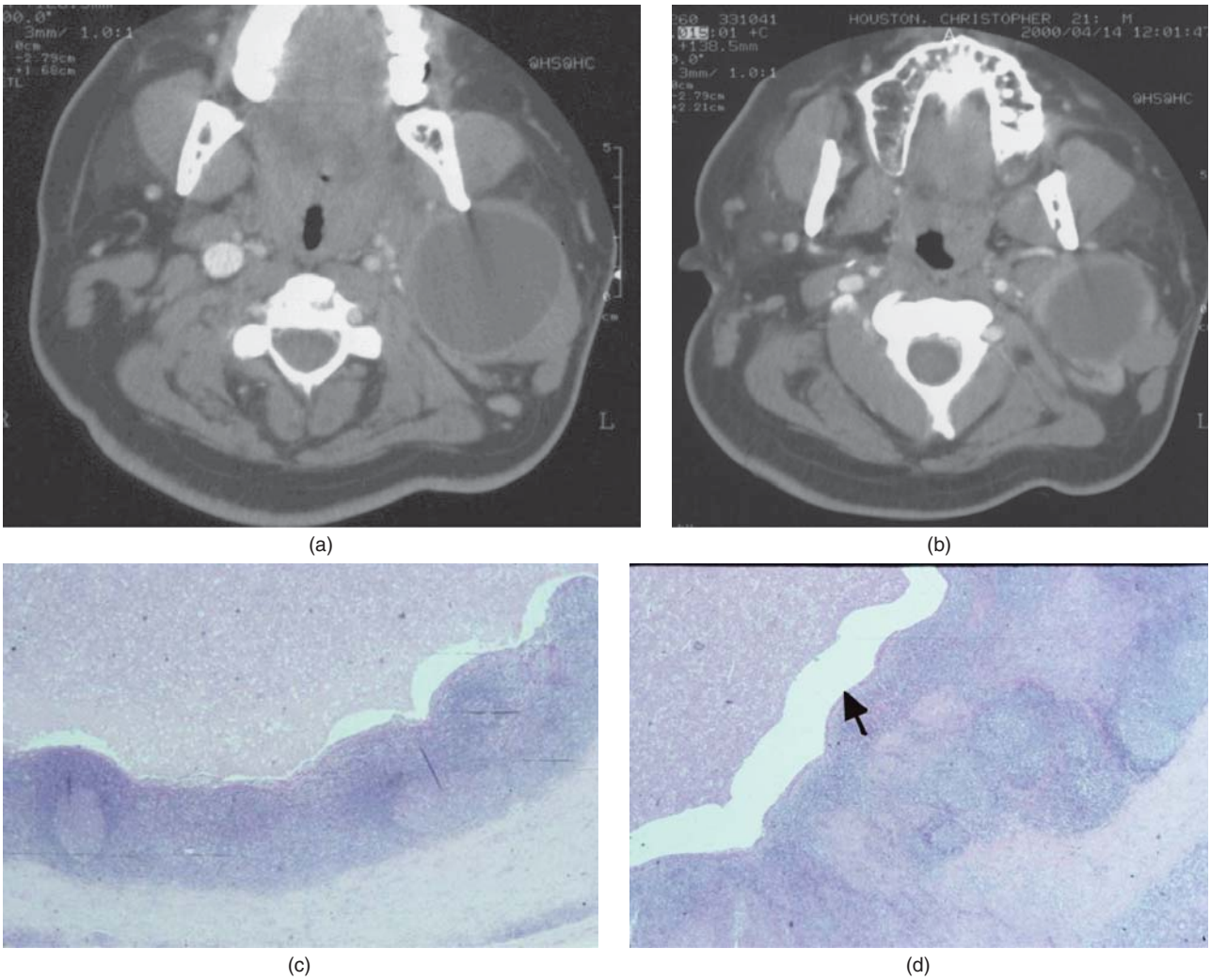


Figure 17.5. (a and b) CT scans of large branchial cyst in the parotid gland. (c and d) Histology of the branchial (lymphoepithelial cyst). The proteinaceous cyst contents are superior and the arrows point to the squamous epithelial lining and its associated lymphoid follicles.

rates of oral cancer such as India, high levels of HPV 16 and 18 have been found in women with cervical cancer and oral cancer (Kulkami, et al. 2011). Studies have shown the feasibility of detecting HPV 16 by saliva screening in healthy patients (Turner, et al. 2011) and those with genital HPV (Peixoto, et al. 2011). It is hard at the current time to see what a positive HPV saliva test means and what diagnostic or therapeutic implications it may have for the patient. In view of the higher risk for asymptomatic oral infection in women with genital HPV-infection some authors have postulated that prophylactic HPV vaccination may reduce the burden of HPV related diseases (Adamopoulou, et al. 2013).

DROOLING

The term drooling is often used synomonously with sialorrhea; however, virtually all patients who drool do not have an increase in the amount of saliva they produce. Patients with Parkinson's disease with a reduced saliva production can often suffer from drooling. Drooling is the result of a lack of coordinated swallowing with pooling of saliva in the anterior floor of mouth with subsequent

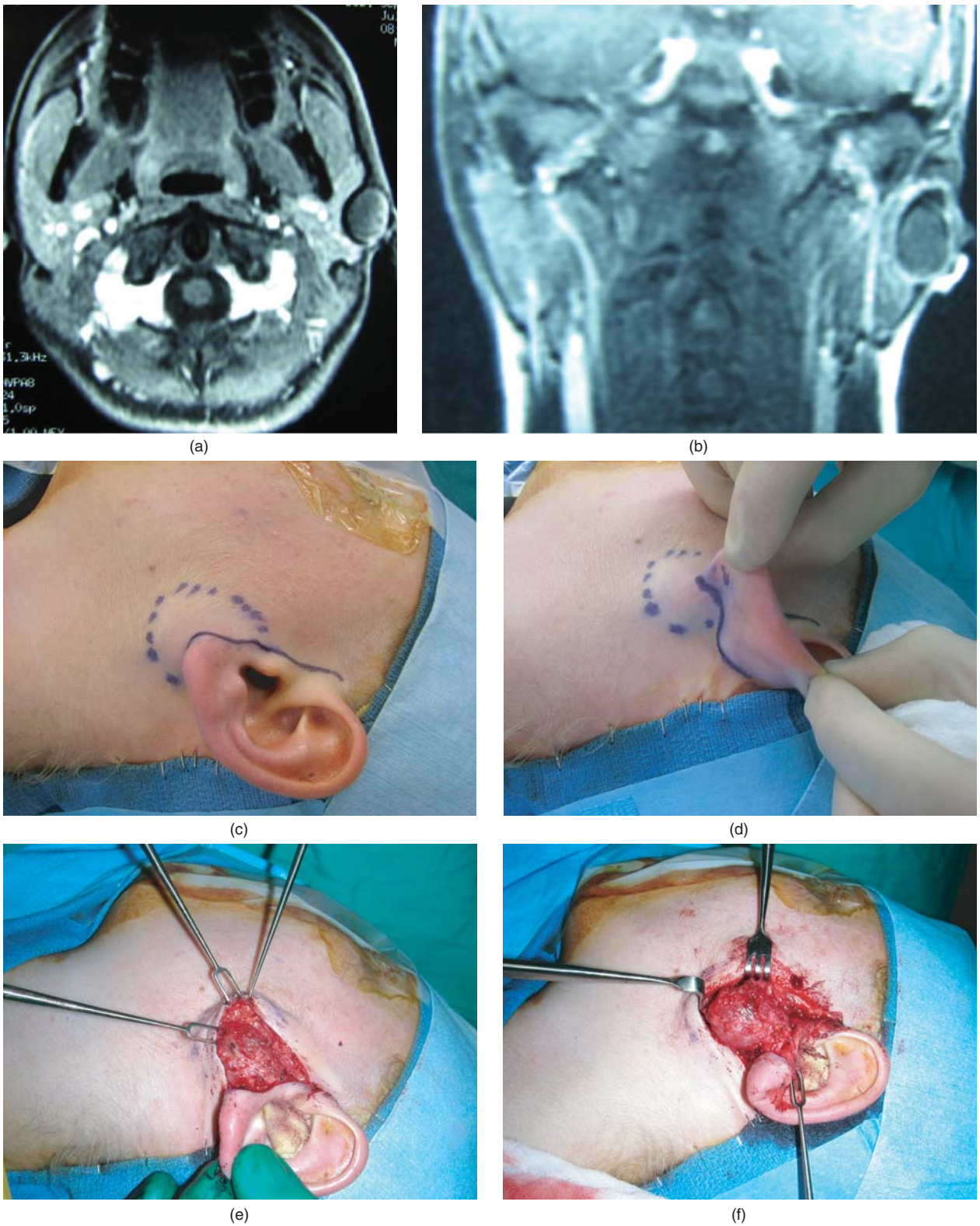
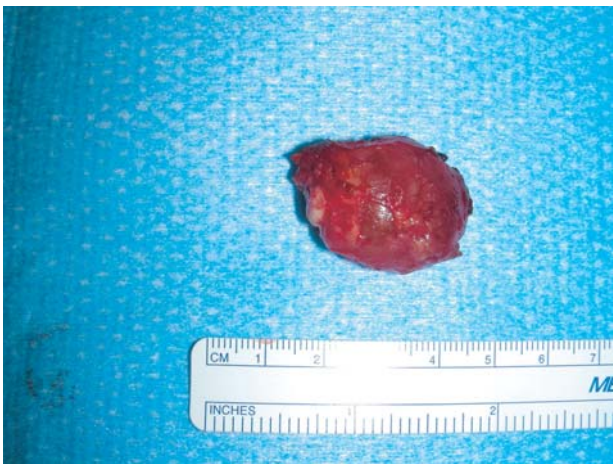
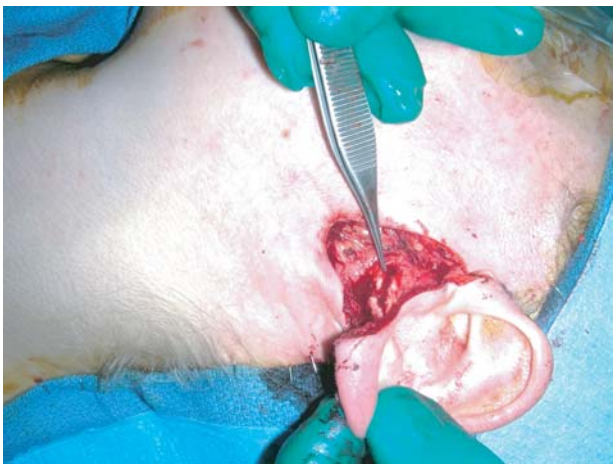


Figure 17.6. (a and b) Axial and coronal MR showing a superficial subcutaneous cyst in the left parotid gland in a 14-year-old girl. (c and d) The extent of the cyst is outlined by dotted line: an omega incision will be used for excision. The pre-auricular limb of the proposed incision is seen in (c) and the retroauricular portion is seen in (d). (e) The cyst lies superficial to the parotid gland. (f) After further dissection the fistulous attachment of the cyst to the cartilaginous external auditory meatus is revealed. (g) The 3-cm cyst was removed intact with a portion of the cartilaginous meatus to prevent recurrence. (h) The instrument points to the area where cartilage was removed from the external auditory meatus with the fistula. (i) Closure is performed with subcuticular sutures.



(g)



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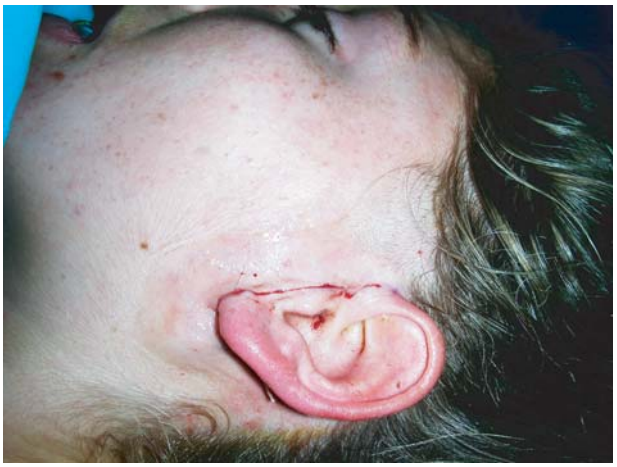


(i)

Figure 17.6. (*Continued*)

drooling as exemplified in conditions such as cerebral palsy and amyotrophic lateral sclerosis. This condition can have a severe impact on the patient's quality of life. Many different methods of managing this condition have been proposed and are summarized in an excellent review by Meningaud, et al. (2006). These patients benefit from a multidisciplinary team approach, and both medical and surgical treatments are used in their management. Medical therapy includes oral motor therapy, orofacial regulation therapy and behavioral modification via biofeedback. In an analysis of studies from 1970–2005 of behavioral treatments of drooling, only 17 articles with 57 patients met the inclusion criteria. The evidence base found 15 studies that used a single participant design and 2 that used an experimental comparison group design. Some studies were poorly designed and methodological flaws identified. Conclusions were that it was not possible to assess the efficacy of behavioral therapy and that further research is needed (Van der Burg, et al. 2007). Drug therapy may be by the use of anticholinergics given orally or by botulinum toxin injections. Certain conditions such as glaucoma preclude the use of these oral drugs and side effects are not uncommon. In a systematic review of the literature, only seven papers were found to meet the inclusion criteria and the authors concluded that there was some evidence benztropine, glycopyrrolate, and benzhexol hydrochloride were effective in children with drooling (Jongerius, et al. 2003). Botulinum toxin A has been injected into the parotid glands solely or with the submandibular glands with good results.

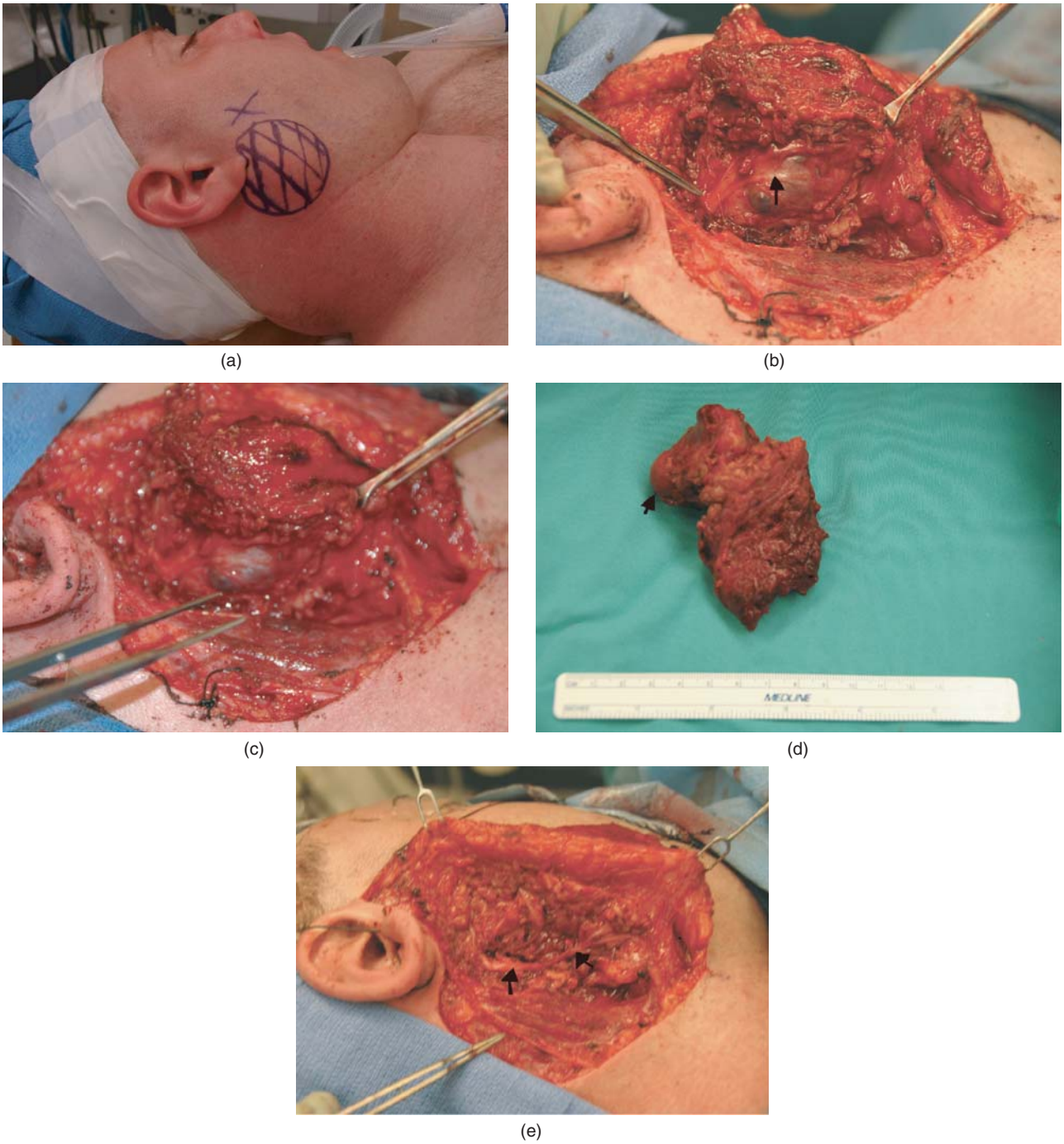


Figure 17.7. (a) A 27-year-old man with a large cystic lesion in his right parotid. The FNAB showed benign disease. (b) Initial superficial parotidectomy (superficial lobe retracted by an Allis clamp) reveals the cyst lying deep to the cervico-mandibular branch of the facial nerve (arrow). (c) The cervico-mandibular branch is carefully dissected off the cyst capsule and retracted towards the ear. (d) Parotidectomy specimen with deep lobe branchial cyst. (e) The cervico-mandibular trunk (arrow) is stretched over the defect that the deep lobe brachial cyst occupied.

However, the effect is only temporary. In a double blind placebo controlled study on 20 patients with Parkinsonism, botulinum toxin A injection into the parotid and submandibular glands was found to be an effective and safe treatment for drooling (Mancini, et al. 2003). In another prospective, double blind placebo controlled trial of different doses of botulinum toxin A (18.75, 37.5, and 75 MU per parotid) the primary end point was achieved with the highest dose of 75 MU without side effects (Lipp, et al. 2003). Similarly in a controlled trial of botulinum against scopolamine in children with cerebral palsy and drooling botulinum toxin was found to have a significant effect (Jongerius, et al. 2004). Although botulinum showed fewer and less severe side effects than transdermal scopolamine, general anesthesia was required for the injections. Despite the fact that treatment by botulinum toxin A can improve drooling for up to 6 months, there is currently no data in the literature for optimum or maximum dosage, frequency of injections, and duration of action (Lal and Hotaling 2006). In some syndromes (e.g., CHARGE syndrome), excess salivation may be associated with aspiration and intermittent and prospective botulinum injections have proven helpful in managing aspiration (Blake, et al. 2012).

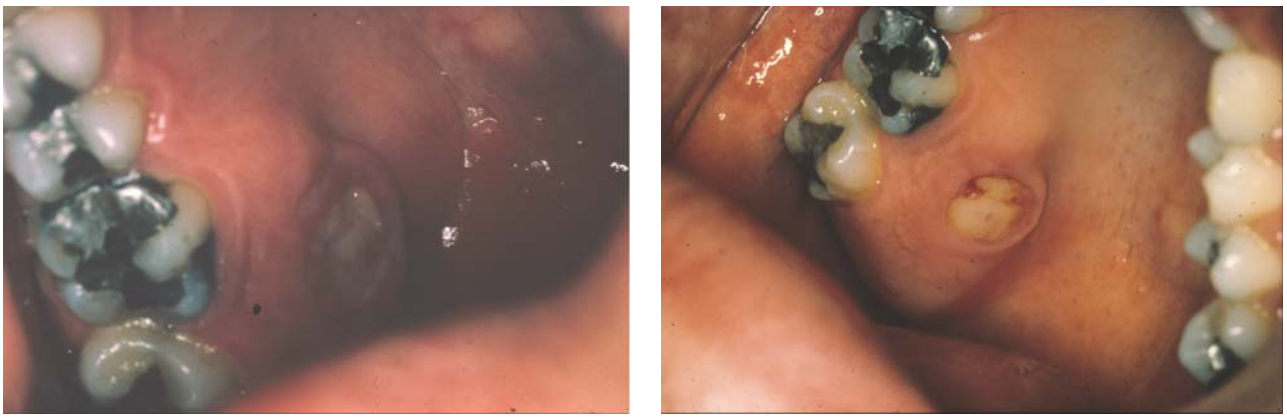
Radiation therapy has been used to reduce saliva production but is obviously contraindicated in children due to its effects on growth and the possibility of radiation induced sarcoma. Even in adults its long term side effects preclude its use. An exception may be in patients such as those with poor life expectancy, including those with as amyotrophic lateral sclerosis, where radiation may be of benefit in reducing salivary production.

Surgery encompasses both sectioning of secretory nerves and also operations on the glands and ducts. Sectioning of the Jacobson nerve in the middle ear has fallen out of favor and sectioning of the chorda tympani will cause loss of taste. Many different surgical techniques have been described since Wilkie's classic paper advocating excision of the submandibular glands combined with posterior positioning of the parotid ducts (Wilkie 1967). These methods have included duct ligation, duct repositioning, and gland excision of one or more of the major glands. At the present time, excellent permanent results have been reported with submandibular duct repositioning and sublingual gland excision. Although submandibular gland excision with parotid duct ligation has been reported as 87% successful (Manrique, et al. 2007), it does give rise to temporary parotid edema, which can be significant, and Greensmith, et al. (2005) reported that bilateral submandibular duct repositioning gland with sublingual gland excision was superior to this technique. However, some authors have questioned the need for excision of the sublingual glands. In a study to assess submandibular duct reposition alone against duct reposition and sublingual gland removal, a 3% postoperative hemorrhage and 12% of parents expressing concerns of pain was found for the duct reposition only procedure, while 13.7% hemorrhage and 36% concern over postoperative pain was found in the group with sublingual gland excision (Glynn and O'Dwyer 2007). As both procedures were equally effective in controlling drooling, the authors state that they no longer carry out sublingual gland excision.

Due to the number of different causes of drooling and the multiple treatment choices available these patients are best assessed by a multidisciplinary team. As in many other aspects of pediatrics and medicine simple noninvasive methods of management are attempted first before suggesting surgical management.

SALIVA IN THE MANAGEMENT OF XEROPHTHALMIA

Although dry eyes may occur in relation to dry mouth in conditions such as Sjogren syndrome, keratoconjunctivitis sicca can occur in isolation. Isolated keratoconjunctivitis sicca is not an uncommon condition and currently there is no satisfactory treatment. Transfer of the submandibular gland duct into the lacrimal basin was first undertaken in 1986 (Murube-Del-Castillo 1986). The largest series of 38 cases with micro-anastomosis of the submandibular gland vessels to the temporal vessels in the temporal fossa and insertion of the Wharton duct into the upper eyelid is 38 (Yu, et al. 2004). In this series, only five cases failed, eight cases had epiphora that required reduction of the size of the submandibular gland and two cases had ductal reconstruction secondary to blockage. The authors stress the use of scintigraphy preoperatively to assess the salivary glands function and rule out a Sjogren disease, and also postoperatively, to assess revascularization and function. Paniello (2007) reported success in six



(a) (b)

Figure 17.8. (a) Necrotizing sialometaplasia of palate with rolled edge and granular base clinically resembling squamous cell carcinoma. (b) Necrotizing sialometaplasia at a later stage with exposed palatal bone.

out of seven transfers (86%). Four out of five patients had keratoconjunctivitis sicca secondary to Stevens–Johnson syndrome. Note that it will be important in the future to test these patients for IgG(4) related disease (see later section) as steroid therapy may be indicated rather than surgery in these cases.

Ischemic/degenerative Changes

NECROTIZING SIALOMETAPLASIA

Necrotizing sialometaplasia can be seen in any of the salivary glands but is most commonly diagnosed in the minor salivary glands of the palate (Figure 17.8)

It is thought to be secondary to local ischemia with secondary necrosis of the gland and may be secondary to trauma or surgery, but is usually spontaneous. Initially, there is swelling quickly followed by ulceration, which may be deep down to the bone. Healing may take 2–3 months. Biopsy may be necessary to distinguish this lesion from a malignancy and the histology may be misinterpreted. There is lobular necrosis of the salivary gland with squamous metaplasia of the ducts and this can be misdiagnosed as mucoepidermoid carcinoma or squamous cell carcinoma. In addition, the epithelium adjacent to the ulcer can display pseudo-epitheliomatous hyperplasia, which can also be mistaken for squamous cell carcinoma. If the patient keeps the lesion clean with mouthwashes, healing will occur and recurrence is not seen. Biopsy will often be required to rule out malignancy and histologic interpretation by an experienced pathologist is essential.

AGE CHANGES IN SALIVARY GLANDS

Generalized acinar atrophy can occur in the major salivary glands with age. Frequently, the glandular tissue is replaced with fat. In addition, oncocytic metaplasia increases in older patients. Oncocytes are large granular eosinophilic cells. Their granular cytoplasm appears to be secondary to numerous mitochondria. A diffuse oncocytosis of the salivary glands can occur. These changes are not clinically relevant although oncocytes can give rise to an oncocytoma, which is usually benign but may occasionally be a malignant type. Oncocytomas are of interest as they are similar to a Warthin tumor in appearing as “hot” spots on technetium scans.

Küttner Tumor

In the 1992 new WHO classification, the Küttner Tumor (chronic sclerosing sialadenitis of the submandibular gland) was included in the new designation of tumor-like lesions to be distinguished from true tumors (Seifert 1992). Clinically, the “tumor” described by Küttner in 1896 cannot be distinguished from a true neoplasm (Williams, et al. 2000). Early work by Seifert and Donath in 1977, reviewing 349 cases of chronic sialadenitis,

had caused them to postulate that two factors were important in the etiology of Küttner tumor. There was an initial disturbance of secretion with an obstructive electrolyte sialadenitis and an immune reaction of the salivary duct system with the final phase of an obstructive progressive immunosialadenitis. By 2003, a number of studies emphasized that this was an under recognized entity as a specific entity with a possible immunologic background (Blanco, et al. 2003). In 2008, Machado de Sousa, et al., using immunohistochemical markers concluded that Küttner tumor was more in keeping with an inflammatory induced degenerative disease.

However, by 2010, after the recognition of Mikulicz disease as being an IG(4) related disease, comparison to Küttner tumor also revealed serologic and histopathologic findings implicating Küttner tumor as an immunoglobulin G(4) disease (Takano, et al. 2010). These findings have been validated and the high expression of IgG(4) confirms it belongs in the spectrum of immunoglobulin G(4) diseases and differentiates it from Sjogren syndrome, lymphoepithelial sialadenitis, and non-specified chronic sialadenitis (Gever, et al. 2010). This has led to the realization that Küttner tumor is not just a solitary tumor of the submandibular gland seen in the fifth to seventh decades of life, but represents a more systemic disease. This disease has now been reported in children and the importance of recognition is due to the fact that it may be treated by steroids to prevent other IgG(4) complications (Melo, et al. 2012.) Not surprisingly, reports of Küttner tumor with involvement of lacrimal glands have now begun to appear (Shin, et al. 2012).

At the present time, the spectrum of IgG(4) related diseases in the head and neck is thought to include idiopathic orbital inflammatory syndrome (inflammatory pseudotumor), orbital lymphoid hyperplasia, Mikulicz disease, Küttner tumor, Hashimoto's thyroiditis, Reidel thyroiditis, and pituitary hypophysitis. Because multiple site involvement is common in IgG(4) related disease, the pancreas, bile ducts, gallbladder, kidneys, retroperitoneum, mesentery, lungs, GI tract, and blood vessels all may show manifestations. Diagnosis is important as IgG(4) disease may show a dramatic response to corticosteroid therapy and radiologic diagnosis may be possible (Fujita, et al. 2012) Salivary gland enlargement, with marked enhancement and restricted diffusion have been suggested as MR features favoring this diagnosis (de Cocker, et al. 2014)

Summary

- Fistulas and sinuses above the hyoid bone in the periparotid region should be suspected of being first arch anomalies.
- In managing first branchial arch anomalies, wide exposure with complete dissection of the facial nerve is mandatory because of the complex and unpredictable relationship of the sinuses, fistulas, and cysts to the nerve.
- In managing drooling a multidisciplinary team is optimum.
- Surgery for drooling is used when other less invasive therapies have been tried and failed. Posterior repositioning of the submandibular ducts with or without sublingual gland excision appears to give good results.
- Necrotizing sialometaplasia should be considered in the diagnosis of ulcerative palatal lesions and may be mistaken clinically and histologically for a malignancy.

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