The pathology of oral cancer

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Key points

- Provides an overview of the pathology of oral cancer.
- Increases awareness that oral cancer is not a simple, single disease.
- Provides understanding of the main differences between oral cancer and oropharyngeal cancer and why the distinction in important.
- Increases awareness of how the pathology of oral cancer underpins the clinical presentation.

The term 'oral cancer' describes a range of malignancies that may arise in and around the oral cavity. Over 90% of such lesions are squamous cell carcinomas, but even these may be divided into different entities based on site, aetiology and prognosis. In particular, squamous carcinomas in the oral cavity (oral cancer) should be regarded as a different disease to carcinomas arising in the oropharynx. Oropharyngeal cancer is associated with infection by human papillomavirus (HPV) and shows different clinical and histological features. This short review summarises the pathology of oral and oropharyngeal cancer, and describes some of the main prognostic factors that pathologists use to assist clinicians in planning appropriate management.

Introduction

More than 90% of malignant tumours in the oral region are squamous cell carcinomas arising from the mucosal epithelium. However, it is now apparent that these mucosal carcinomas comprise a number of different diseases that must be considered separately, due to differences in site, aetiology, prognosis and management. In particular, carcinoma of the mouth (oral cancer) should now be regarded as a different disease to carcinoma arising in the oropharynx. This is because oropharyngeal cancer is primarily associated with infection by human papilloma virus (HPV), while oral cancer is associated with the more traditional factors of tobacco and alcohol use. The site distribution of oral cancer and oropharyngeal cancer are shown in Table 1, along with the ICD (International Classification of Disease for Oncology) codes for each site.[1]

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Squamous cell carcinoma of the oral cavity (oral cancer)

Oral squamous cell carcinomas arise from the epithelial lining of the oral cavity. They have well characterised histopathological features, often referred to as 'conventional' squamous cell carcinoma. The defining criterion for a diagnosis of carcinoma is invasion of epithelial cells through the basement membrane into the superficial connective tissues. Invasion may start as small breaches by a few cells or small epithelial islands, and progress to gross infiltration of the underlying submucosa or bone by sheets and islands of malignant cells. This process of invasion gives rise to the two most classical clinical signs of cancer – the lesion is hard (induration) and is fixed to the underlying tissues (fixation). Larger lesions may outgrow their blood supply, or become

Table 1 Site distribution of oral cavity cancer and oropharyngeal cancer[1]

ICD site code	Oral cavity cancer sites	Oropharyngeal cancer sites
C00	Lips	
C01		Base of tongue
C02	Anterior tongue	
C03	Gingivae	
C04	Floor of mouth	
C05	Palate	
C06	Other areas in the mouth	
C09		Tonsil
C10		Oropharynx
C14		Pharynx, Waldeyer ring

traumatised, giving rise to a third important clinical sign – ulceration of the tumour surface. On microscopic examination, all squamous cell carcinomas therefore have an invasive component, where tumour islands can be seen deep to the surface epithelium (Fig.1). Many tumours may also rise above the surface of the mucosa, resulting in an exophytic component. This may only be at the margins of the tumour (the classic 'raised, rolled' margins) or in some cancers may predominate resulting in an exophytic hyperkeratinised surface. This exophytic pattern is most prominent in some variants of squamous cell carcinoma, including verrucous and papillary carcinomas (see below and Table 2).

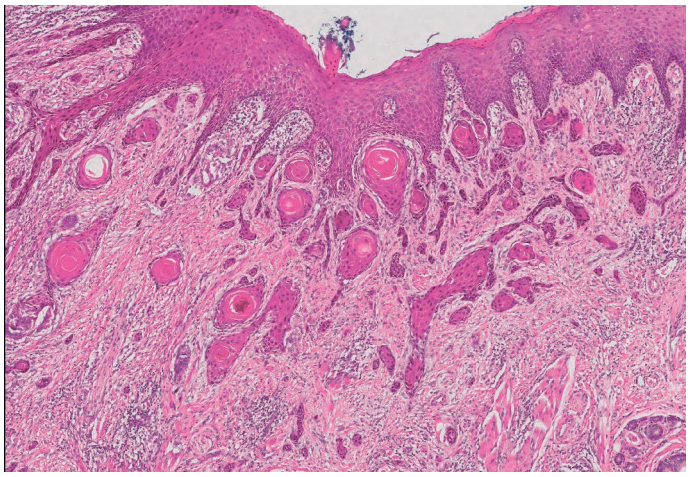

Fig. 1 Squamous cell carcinoma of the oral cavity. Tumour islands can be seen infiltrating the connective tissues deep to the overlying oral epithelium. This carcinoma is moderately differentiated with a non-cohesive invasive pattern

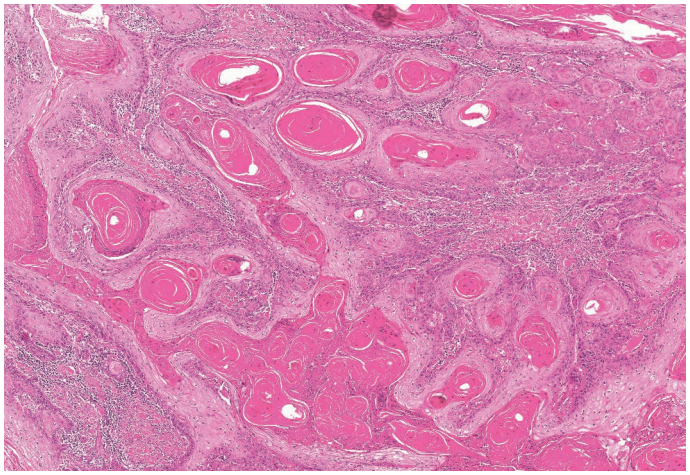

Fig. 2 Well differentiated squamous cell carcinoma. Tumour islands have a visible basal layer and there is prominent central keratinisation with formation of 'keratin pearls'

Histologic grading of oral squamous cell carcinoma

When a pathologist examines a carcinoma, they will always grade the lesion, since the grade is associated with prognosis and can help the clinician plan appropriate management. It is usually easy to identify an epithelial origin for a conventional oral squamous cell carcinoma since, to some degree, the tumour resembles the normal squamous epithelium from which it arises. The degree of resemblance provides the basis for the most widely used grading scheme for squamous cell carcinoma, which was first suggested by Broders in 1920[2] and is advocated by the World Health organisation (WHO).[3] Tumours are classified as well, moderately or poorly differentiated depending on how closely the tumour resembles normal oral epithelium. Overall, most mouth cancers are moderately differentiated (60%), with about 30% being well differentiated and only 10% poorly differentiated.

In a well differentiated carcinoma it is easy to identify that the tumour originates from squamous epithelium (Fig. 2), since it shows a considerable amount of keratin production, with evidence of stratification and a quite well formed basal cell layer surrounding the tumour islands. Often, the islands of tumour contain central 'eddies' of keratin referred to as keratin pearls. The tumour islands are usually well defined and

Table 2 Variants of oral cavity squamous cell carcinoma, with a summary of the key histological and clinical features. Prognosis is described as relative to conventional oral lesions

Variant	Histological features	Clinical features
Verrucous carcinoma	Well differentiated. Cohesive 'pushing' invasive front with wide rete pegs. Heavily keratinised.	Most common on buccal mucosa. Exophytic verruciform surface. Good prognosis. Rarely metastasises.
Basaloid squamous cell carcinoma	Islands of dark basaloid cells with peripheral palisading. Areas of conventional squamous carcinoma also present. Prominent pleomorphism and mitoses. Areas of 'comedo' necrosis	Most common on the tongue. Poor prognosis
Spindle cell carcinoma	Sheets of malignant spindle cells resembling sarcoma. Areas of conventional carcinoma, or overlying dysplasia can be found	Lesions may be pedunculated or polypoid (especially on the larynx). Oral lesions most common on the tongue. Poor prognosis
Adenosquamous carcinoma	Shows features of both squamous carcinoma and adenocarcinoma	Most common on the tongue, then floor of mouth. Poor prognosis
Papillary squamous cell carcinoma	An exophytic lesion resembling a benign squamous papilloma, but with evidence of stromal invasion	Most common in the larynx. When it occurs in the oral cavity the commonest sites are the gingivae or tongue. Has a good prognosis

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are often continuous with the surface epithelium. There is a cohesive invasion pattern with intact large branching rete pegs 'pushing' into the underlying connective tissues. Cytological atypia or dysplasia may not be prominent.

Moderately differentiated carcinomas show a greater degree of cellular atypia and less evidence of keratinisation, with fewer keratin pearls (Figs.1 and 3). Lesions may have a less cohesive invasive front, often with small islands or cords of cells permeating the underlying tissues (Fig. 1). Cytological atypia, with nuclear and cellular pleomorphism, and hyperchromatic nuclei, is always seen and may be extensive.

Poorly differentiated squamous cell carcinomas show little resemblance to a normal squamous epithelium, but it is still possible to recognise that the cells are of epithelial origin (Fig. 4). They usually show considerable atypia, often with bizarre pleomorphic cells, and they invade in a non-cohesive pattern with fine cords, small islands and single cells infiltrating widely through the connective tissues. Mitotic figures are prominent and many may be abnormal. At the worst end of the spectrum a tumour may be so poorly differentiated that it is not possible to recognise that it is of epithelial origin, and it is then called anaplastic or undifferentiated. Immunocytochemical stains are needed to confirm an epithelial origin.

The degree of differentiation is widely used to predict prognosis and shows a significant correlation to survival.[4] In a UK study, the five-year disease specific survival for patients with well differentiated carcinomas was 89%, compared to 68% and 45% for moderately or poorly differentiated carcinomas respectively.[5] However, the grading scheme is subjective and, since 60% of cases are moderately differentiated, the system lacks discriminatory power for prediction of prognosis for individual patients. In practice, therefore, tumour grading often includes a number of other more refined histological features, which help predict prognosis for individual patients and support their management. The most often used histological prognostic factors are discussed in this article.

There are also a number of variants of squamous cell carcinoma that may be encountered within the oral cavity. All are rare, but the most commonly encountered are summarised in Table 2. The clinical presentation of the variants is similar to conventional squamous cell carcinoma, with the exception of verrucous and papillary carcinomas, which are quite distinctive. These are heavily keratinised, white verruciform or papillary lesions that present as exophytic swellings, most commonly on the buccal mucosa or upper alveolus.

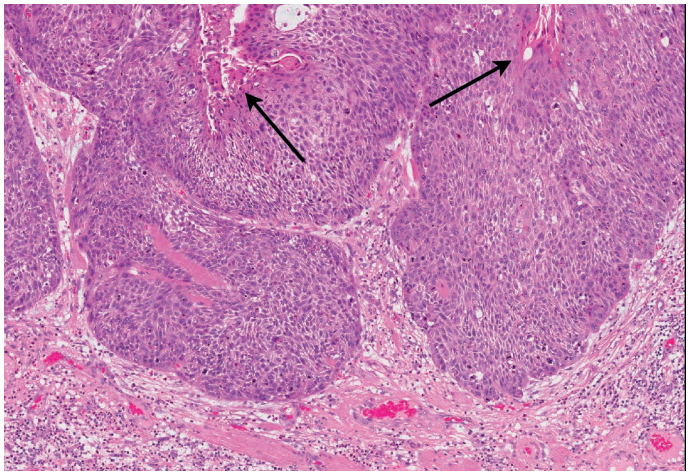

Fig. 3 Moderately differentiated squamous cell carcinoma. Tumour islands are clearly epithelial in origin and a basal layer can be seen in places. Only small areas of keratinisation are visible (arrows). This example has a 'pushing' cohesive invasive front

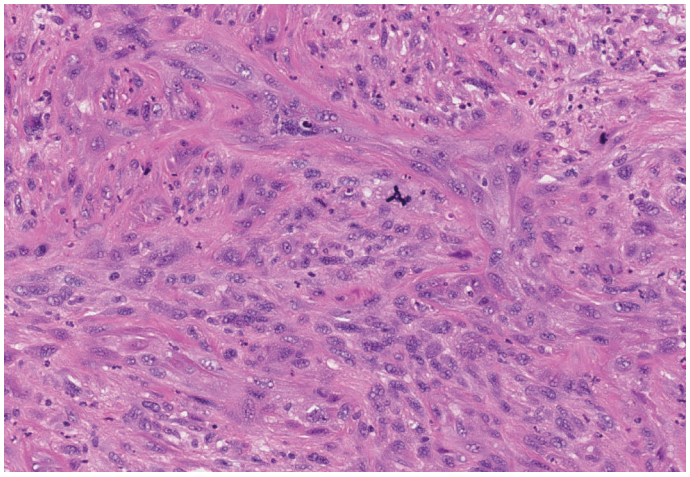

Fig. 4 Poorly differentiated squamous cell carcinoma. Although the lesion can still be seen to be epithelial, there is no evidence of differentiation or keratinisation. There is considerable pleomorphism and an abnormal mitosis can be seen centrally. The invasive pattern is non-cohesive, with individual cells permeating the connective tissues

Histological prognostic factors

Pattern of invasion

The pattern of invasion has been mentioned above, and although it is associated with differentiation, a number of workers have developed more refined grading schemes that score different parameters with an emphasis on pattern of invasion.[2,6] These have been shown to have a high prognostic value.[7–9] Four patterns of invasion have been described. Type I pattern is cohesive in the form of 'pushing' bulbous rete pegs which tend to infiltrate at the same level (Fig. 3). The type II pattern shows infiltrating cords, strands or large islands which tend to be branching and continuous with the main tumour mass. Type III pattern shows small islands and cords which are separated from the main tumour (Fig. 1), and the type IV pattern is characterised by widely infiltrating small islands and single cells (Fig. 4). In clinical practice, the UK Royal College of Pathologists[10] recommends that oral squamous cell carcinomas can be graded simply into two patterns: cohesive (Types I and II) and non-cohesive (Types III and IV). Odell *et al.*[7] studied 47 carcinomas of the anterior tongue and showed that 74% of those with a non-cohesive pattern metastasised, compared to only 16% of cohesive lesions.

Table 3 Definition of T categories for oral cavity cancer[14]

T category	Maximum diameter	Depth of invasion
T1	≤ 2 cm	≤ 5 mm
T2	≤ 2 cm	5–10 mm
or	2–4 cm	≤ 10 mm
T3	> 4 cm	
or		> 10 mm
T4	Advanced disease invading bone or adjacent structures	

Depth of invasion

The depth of invasion of a tumour can be measured from the adjacent normal epithelium to the deepest point of the invading cells.[10] The depth has been shown to be a good predictor of lymph node metastases and overall survival. Unfortunately, there is no international agreement over the significance of different depths, and there is good evidence that a prognostically significant depth may vary by site.[11] Nevertheless, a meta-analysis showed that a cut-off depth of 4 mm was the optimal value for prediction of lymph node metastases[12] and this depth is recommended in the UK guidelines.[10] Some studies have shown that the risk of metastasis for a tumour greater than 4 mm was four times greater than for a tumour less than 4 mm.[13] The new edition of the UICC manual for staging for cancer now includes depth of invasion as one of the criteria for the T stage for oral cavity cancers, but uses 5 mm and 10 mm as the cut off values (Table 3).[14,15] Previously, any cancer less than 2 cm in diameter was categorised as T1, but in the new edition the tumour must also have a depth of invasion of 5 mm or less. A tumour with a depth greater than 5 mm and up to 10 mm is categorised as T2, whereas any tumour greater than 10 mm deep is category T3 regardless of diameter. It should be noted that staging for oropharyngeal cancer is different and does not include depth of invasion.[14]

Perineural invasion

Spread of a carcinoma along nerves has been shown to correlate with disease recurrence and survival.[16] Perineural invasion is seen in up to 60% of oral squamous cell carcinomas,[16,17] but it is most significant when a tumour is seen within a large nerve at a site some distance from the main tumour mass. Although perineural invasion has been shown to be an independent factor, it is usually also associated with large carcinomas which are moderately or poorly differentiated and also show bone or lymphovascular invasion.

Invasion of vessels

Invasion of lymphatic or blood vessels is also common (Fig. 5) and is widely thought to be associated with lymph node metastases and a poor prognosis.[9] However, as with perineural invasion, it is also associated with poorly differentiated carcinomas, a non-cohesive invasion pattern and larger tumours.

The tumour stroma

The tumour microenvironment represents a complex dynamic interaction between the malignant cells of the carcinoma and normal host cells, including cells of the connective tissues and of the host immune and inflammatory responses. It has long been known that a prominent host response, may be associated with a better prognosis and the presence of dense infiltrates of inflammatory cells is included in some histological multifactorial grading schemes.[2] However, there is also evidence that inflammation may drive cancer progression and some specific inflammatory cells, especially tumour-associated-macrophages, are associated with a poor prognosis.[18,19] Understanding these interactions is an area of much intensive research which may result in new therapeutic interventions.[19] For example, epithelial-mesenchymal interactions promote the formation of cancer-associated-fibroblasts (CAF), which are a heterogeneous population derived in part from resident fibroblasts, but also from a range of other cell types including cancer cells themselves, by a process of EMT (epithelial-mesenchymal-transition).[19,20] CAF have tumour-promoting properties, including stimulation of cancer cell growth, migration and invasion. They resemble myofibroblasts and can be identified by staining for smooth muscle actin (SMA) by immunohistochemistry.

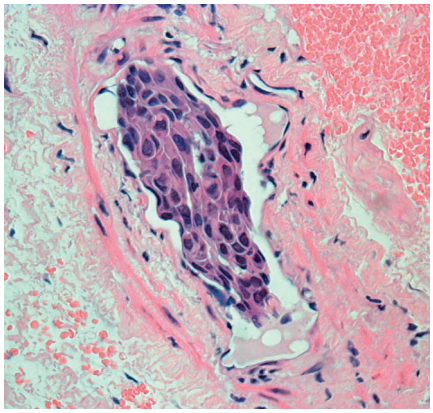

Fig. 5 An island of squamous cell carcinoma within a lymphatic vessel

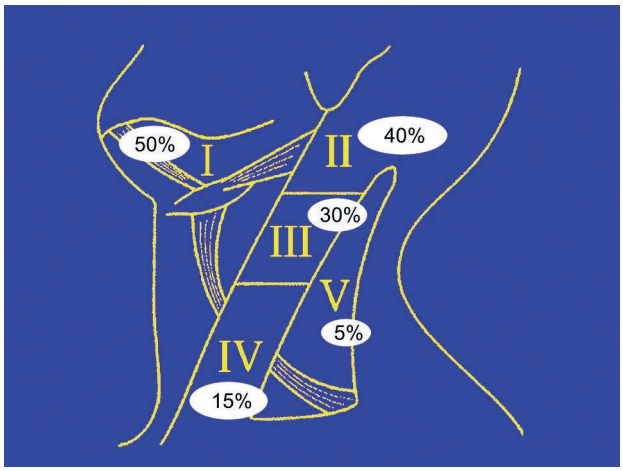

Fig. 6 A lateral view of the neck illustrating the five anatomical levels. The vast majority of oral cancers metastasise to level I (50%) (just below the mandible in the submandibular triangle) or to level II (40%) (in the region of the upper aspect of the sternomastoid muscle). Metastases are often multiple, so proportions shown add to more than 100%

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Table 4 Definition of N categories for oral cavity cancer[14]

N category		Size of metastasis	ENE
N0	No nodal metastasis		
N1	Metastasis in a single ipsilateral node.	≤3 cm	No
N2			
N2a	Metastasis in a single ipsilateral node	3-6 cm	No
N2b	Metastasis in multiple ipsilateral nodes	≤6 cm	No
N2c	Metastasis in bilateral or contralateral nodes	≤6 cm	No
N3			
N3a	Metastasis in any lymph node	>6 cm	No
N3b	Metastasis in any lymph node	Any	Yes

ENE: extranodal extension

A recent systematic review analysed twenty publications that had studied the prognostic value of SMA-positive CAF in oral cancer, and found that high levels of CAF in the stroma predicted an overall decrease in survival, and was associated with aggressive tumour characteristics, including late stage, high grade, depth of invasion and perineural and vascular invasion.[21] Although more research is needed, the evidence suggests that CAF may be a useful prognostic biomarker and have potential as a therapeutic target.

Lymph node metastases

Approximately 50% of patients with oral or oropharyngeal cancer will present with evidence of tumour in a cervical lymph node, and in many cases this may be the first presentation. Examination of the neck therefore may give the dentist an opportunity to effect an early diagnosis. This is especially the case in oropharyngeal carcinomas where the primary tumour may not be easily visible on clinical examination. The lymph nodes of the neck can be simply divided into five regions or levels (Fig. 6) and tumours often metastasise to nodes at multiple levels. Overall, positive lymph nodes are most commonly detected at levels I and II which are the sites of metastasis of about 90% of oral and oropharyngeal cancers.[22,23] In 30%, level III may also be involved, but positive nodes are less frequently encountered at levels IV and V (Fig. 6). The distribution of nodal metastases also varies by site of the primary tumour. For example, tumours in the cheek or floor of mouth more frequently involve level I, while tongue and oropharyngeal tumours tend to involve levels II and III. Level V is rarely involved, but when nodes are found at this site, the primary lesion is likely to be in the tongue or oropharynx.[23] The presence of nodal metastases is an important component of the TNM staging scheme.

Tumour size and stage

The maximum diameter of a carcinoma is used as the T component of the TNM (tumour, node, metastasis) classification scheme that is used to stage malignant tumours.[14] The size is measured by the pathologist on the surgical specimen to provide a pT value for final staging along with imaging to determine the presence or absence of nodal (N) or distant metastases (M). In the latest edition of the UICC staging manual,[14,15] oral cavity and oropharyngeal cancer are considered separately and are given different criteria for T and N values. Of special note, as discussed previously, is that the size (T) value for tumours of the oral cavity is now defined by the diameter as well as by the depth of invasion (Table 3). In the N category, the classification depends on the site of the metastases (ipsilateral or contralateral) as well as the size (Table 4). If tumour extends or ruptures beyond the capsule of the node (extranodal extension, ENE), this is regarded as an indicator of poor prognosis and places the cancer into category N3b regardless of size. For carcinomas of the oral cavity, a T1 carcinoma without metastases is classified as Stage I, and a T2 carcinoma without metastases is classified as Stage II. Larger tumours, and tumours with nodal or distant metastases are classified into Stages III or IV. It can be seen therefore that the size of the lesion is important in determining the final stage of the cancer.

Tirelli *et al.*[24] determined the effects on survival of the new UICC staging scheme and showed that five-year disease-specific survival for T1 tumours was 95.7% compared to 80.5%, 69.1% and 60% for T2, T3 and T4 tumours, respectively. Tumours without nodal metastases (No) showed 89.6% five-year disease specific survival compared to 58.8% for N1 tumours and 57.1% and 56.5% for N2 and N3 tumours, respectively. From these data it can be seen that the five-year survival for tumours in Stages I and II may be over 80%, but survival for patients with later stage tumours (III and IV) is less than 60%. The presence of distant metastases is categorised as Stage IVc and has a poor prognosis of less than 20% five-year survival.

Squamous cell carcinoma of the oropharynx

It is now well established that oropharyngeal cancer should be regarded as a distinct and separate entity to oral cavity cancer. This is based on its association with HPV as a causative agent and the distinctive biological and histological features. Oropharyngeal cancer arises in those areas of the oropharynx where tonsillar tissue is present (Table 1), primarily the palatine tonsils of the fauces and tonsillar tissue of the base of the tongue. Oropharyngeal cancer is also defined by the presence of high risk HPV (usually HPV 16),[25] and HPV must be demonstrated in the lesion to confirm the diagnosis. The most sensitive test is to use reverse transcription polymerase chain reaction (RT-PCR) to demonstrate a transcriptionally active virus, but DNA *in situ* hybridisation (ISH) can also be used to identify the presence of HPV DNA.[26] In practice, however, these molecular techniques can be expensive and not widely available in routine pathology laboratories. HPV infection results in production of the E7 viral protein, which binds to the Rb protein, and inhibits negative feedback of the tumour suppressor protein p16, which then accumulates within the cell. The demonstration of p16 protein using immunohistochemistry is therefore a useful surrogate marker for HPV infection[25,27] and has been endorsed by the WHO for use in routine clinical practice as a diagnostic test for oropharyngeal carcinomas that show the typical morphological features described below.[28] Squamous cell carcinomas of the oral cavity are rarely associated with HPV or express p16 by immunohistochemistry.

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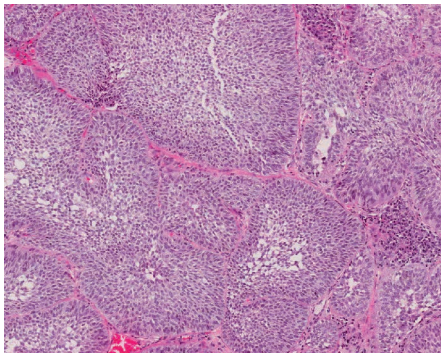

Fig. 7 HPV associated oropharyngeal carcinoma. The lesion is composed of sheets and islands of epithelial cells with a basaloid or occasionally spindled morphology

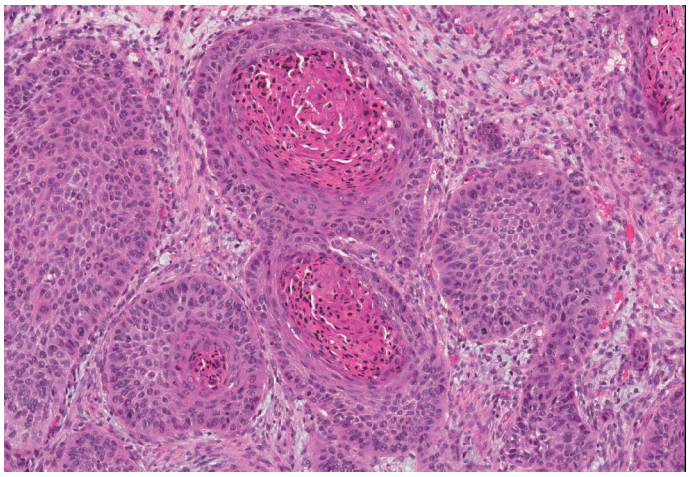

Fig. 8 Occasionally, small areas of keratinisation can be seen in HPV-associated lesions

Histologically, oropharyngeal squamous cell carcinomas are typically non-keratinised and have a 'basaloid' morphology (Fig. 7).[28,29] Originally, this was thought to indicate that the tumours were poorly differentiated, but it is now appreciated that this characteristic morphology resembles the non-keratinising tonsillar crypt epithelium from which the tumours arise, and suggests that the oropharyngeal carcinomas are in fact well differentiated[30] and may have a better prognosis than conventional squamous cell carcinomas. For this reason, the grading scheme described above for conventional squamous cell carcinoma of the oral cavity cannot be used for these lesions and HPV-associated carcinomas are not graded.[28] Also, the term 'basaloid' should not be used for oropharyngeal carcinomas, since it may cause confusion with the basaloid variant of squamous cell carcinoma, which is a poorly differentiated lesion, with a poor prognosis (Table 2). The latest WHO classification uses the term 'HPV-associated squamous cell carcinomas' for these oropharyngeal cancers.[28]

The characteristic histological appearance is of a non-keratinising squamous cell carcinoma composed of sheets or islands of basaloid or spindled epithelial cells with hyperchromatic nuclei and prominent mitoses (Fig. 7). Focal areas of necrosis are common. Although termed non-keratinising, obvious squamous cells and occasional keratin pearls may be evident, but these comprise less than 10% of the tumour.[28–32] (Fig. 8). The tumour is often surrounded by dense infiltrates of lymphoid cells giving an appearance similar to lymphoepithelial carcinomas of the nasopharynx.[30,31,33] Immunohistochemistry is positive for p16 in virtually all of these lesions (99%) (Fig. 9) and 100% are positive for HPV by RT–PCR.[33] As mentioned above, p16 positivity is an acceptable surrogate marker for the presence of HPV,[28] and should show strong diffuse nuclear and cytoplasmic staining in more than 70% of the tumour cells.[25,27] Occasionally, an carcinoma in the oropharynx may show features similar to conventional squamous cell carcinoma and show prominent keratinisation with formation of keratin pearls. Most of these probably represent a conventional squamous carcinoma of the oral cavity-type, which has arisen at this site, and may be associated with tobacco and/or alcohol use. Less than 10% of this type can be shown to contain HPV and only about 25% express p16 protein.[34]

Prognostic factors in HPV-associated carcinoma

HPV-associated squamous cell carcinomas of the oropharynx have been shown to have a significantly better prognosis than conventional non-HPV infected squamous cell carcinomas.[35,36] In one study, 95% of patients with HPV-positive carcinomas survived two years compared to only 62% for site-matched HPV-negative lesions.[37] The reasons for this improved survival are not clear, but it may be associated with an overall better response to combined treatment with chemotherapy and radiotherapy.[35] HPV-positive carcinomas may also show less genomic damage and may not be associated with field change, both of which are significant causes of recurrence in conventional carcinomas.[35]

Although, overall, HPV positive carcinomas appear to have a better prognosis than conventional oral carcinomas, predicting the prognosis of oropharyngeal carcinomas for individual patients is difficult. The prognostic indicators described above for oral squamous cell carcinoma, such as grade and depth of invasion, do not apply to HPV-related lesions, and the prognostic significance of intravascular or perineural invasion have not been determined. With regard to staging, the new eighth edition of the UICC TNM classification stages HPV positive oropharyngeal cancer differently to oral cancer, so the scheme in Table 4 does not apply.[14,15] For oropharyngeal cancers that are p16 positive (HPV-associated), a metastasis in an ipsilateral node is classified as N1 even up to 6 cm in diameter. For oral cancer, Stage I and II carcinomas correspond directly to size, without any evidence of metastases (T1, N0, M0 and T2, N0, M0, respectively). In the oropharynx, however, p16 positive carcinomas are staged as Stage I even if they are larger and have up to four positive nodes (T1 or T2, N0 or N1, M0), and Stage II lesions can be larger than 4 cm (T3) and may have metastases in multiple (5 or more) nodes at any site (N2).

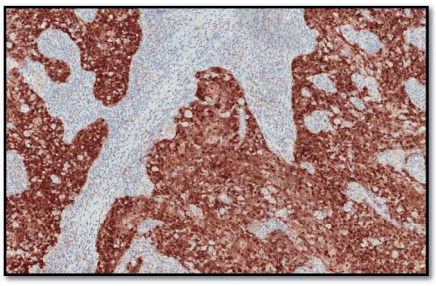

Fig. 9 This oropharyngeal lesion is strongly positive, by immunohistochemistry, for p16, indicating that the lesion is associated with HPV infection

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Only tumours with extensive invasion (T4), with large metastases (greater than 6 cm) or with distant metastases (M1) are staged as III or IV. This new staging reflects the assumed better prognosis of HPV-positive carcinomas, and means that more extensive disease is classified as earlier stage for management purposes. However, more research is needed to determine the clinical significance of this new staging scheme and to correlate the classification with clinical outcomes.

Summary and conclusions

'Oral cancer' is not a single disease and should be divided into oral (mouth) cancer and oropharyngeal cancer. These have distinct pathological features that may determine their clinical presentation. Traditional tumour grade and stage are useful for prediction of prognosis but pathologists may use a range of other histological features to try to support management for individual patients. For the general dentist, the primary role is early detection and referral. Oral cancer can usually be detected on clinical examination of the oral cavity and dentists can therefore play a key role in early detection and diagnosis. Oropharyngeal cancer, however, arises in the base of the tongue and tonsils and may not be easily visible during routine examinations. Dentists must therefore be alert to unusual signs or symptoms and to the presence of enlarged cervical lymph nodes, which is often the first sign of a cancer arising in the oropharynx.

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