

# Nonsquamous Cell Malignant Tumours of the Oral Cavity: An Overview

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## A b s t r a c t

Many malignant tumours other than squamous cell carcinoma may present in the oral cavity. Melanomas of the oral cavity are usually pigmented, aggressive tumours associated with a poor prognosis. Neoplasms of the minor salivary glands have a greater tendency to be malignant than those of the major glands, and some exhibit a predilection for occurring in the mouth. Many types of connective tissue malignant tumours (sarcomas) may arise in the mouth, including soft-tissue cancers and lesions of hematologic cells such as lymphoma, whereas osteosarcoma is the most common malignancy of the hard tissues found in the mouth. Cancers from distant organs such as breast, lung and prostate may metastasize to the oral cavity. This paper presents a brief overview of nonsquamous cell oral cancers, with emphasis on those most likely to be encountered by the practising dentist.

**MeSH Key Words:** diagnosis, differential; mouth neoplasms/epidemiology; mouth neoplasms/pathology

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This article has been peer reviewed.

Although squamous cell carcinoma accounts for approximately 90%<sup>1</sup> to 94%<sup>2</sup> of malignant tumours of the oral cavity, many other types of malignant lesions, including melanoma, carcinomas of the salivary glands, sarcomas of soft and hard connective tissues, and metastatic cancers, are also encountered. The clinical presentation of these lesions, their treatment and the prognosis is highly variable, depending on the type of tumour, its histologic variant and grade, and the extent of spread at the time of biopsy. **Table 1** lists the more common of these oral cancers. Any of these nonsquamous cell cancers may be encountered by the practising dentist. Selected entities are briefly reviewed in this article.

### Melanoma

Melanoma is a malignant tumour of the melanocytes, the cells that produce brown pigmentation in the epithelia. Consequently, most (though not all) melanomas appear as irregular brown to black pigmentation of the affected area. Although lesions may be flat and painless during the early stages, there is often associated nodularity, induration and ulceration at the time of biopsy. The palate and maxillary gingiva of middle-aged and older adults, men more often than women, are the most common sites for oral

melanoma.<sup>3</sup> Rapid growth, bone invasion and metastasis to adjacent lymph nodes or distant organs are characteristic of this aggressive cancer. Microscopically, the tumours consist of theques and sheets of malignant cells, usually containing melanin pigmentation, invading both the epithelium and (eventually) the underlying connective tissues. Diagnosis of nonpigmented melanomas can be confirmed immunohistochemically. Treatment is radical surgery, including block removal of portions of the jaws when bone is involved. Regional lymph node dissection may be necessary. The prognosis is poor,<sup>1</sup> with 10-year survival less than 30%.<sup>2</sup>

### Salivary Gland Carcinomas

The oral cavity contains hundreds of minor salivary glands below the oral epithelium as well as 3 pairs of major salivary glands. Although malignant tumours may be seen anywhere that salivary glands occur, they have a predilection for the slope of the hard palate and the soft palate and occur only rarely in the lower lip. Proportionately more malignant tumours occur in the minor salivary glands than in the major glands.

There are many types of salivary gland cancers<sup>4</sup> (**Table 2**), but most are too rare to warrant review. The most common malignant tumours of the intraoral salivary glands

**Table 1 Oral cancers other than squamous cell carcinoma**

Cells or tissue of origin	Cancer name	Usual age group	Prognosis
Melanocytes	Melanoma	Adults	Very poor
Salivary glands	Many types	Adults	Good to poor
Fibroblasts	Fibrosarcoma Malignant fibrous histiocytoma	Young adults Older adults	Intermediate to poor Intermediate to poor
Myofibroblasts	Myofibrosarcoma	Adults	Intermediate to poor
Fat cells	Liposarcoma	Adults	Intermediate to poor
Skeletal muscle	Rhabdomyosarcoma	Children and adolescents	Intermediate
Smooth muscle	Leiomyosarcoma	Adults	Poor
Peripheral nerves	Neurosarcoma Malignant granular cell tumour	Young adults Adults	Very poor to poor Poor
Synovial cells	Synovial sarcoma	Adolescents and young adults	Poor
Endothelial cells	Angiosarcoma AIDS-related Kaposi's sarcoma Classic Kaposi's sarcoma	Elderly people Young adults Elderly men	Very poor Poor Good
Lymphocytes	Lymphoma	Adults and children	Good, intermediate or poor
Plasma cells	Plasmacytoma Multiple myeloma	Adults Older adults	Good to intermediate Poor to very poor
Bone cells	Osteosarcoma Parosteal osteosarcoma	Children and young adults Children and adults	Intermediate to poor Good
Cartilage cells	Chondrosarcoma	Adults	Intermediate
Odontogenic cells	Various carcinomas and sarcomas	Adults	Poor
Metastatic tumours	Breast, lung, prostate, kidney, thyroid Leukemic infiltrate	Adults Children and adults	Very poor Variable

**Table 2 Carcinomas of the salivary glands**

Tumour	Relative intraoral frequency	Prognosis
Mucoepidermoid carcinoma	Common	Good
Adenoid cystic carcinoma	Common	Intermediate to poor
Polymorphous low-grade adenocarcinoma	Common	Good
Acinic cell carcinoma	Rare	Good to intermediate
Carcinoma ex pleomorphic adenoma	Rare	Poor
Adenocarcinoma	Uncommon	Poor
Epithelial myoepithelial carcinoma	Rare	Intermediate
Clear cell carcinoma	Rare	Intermediate
Salivary duct carcinoma	Rare	Poor
Basal cell adenocarcinoma	Rare	Intermediate
Undifferentiated carcinoma	Rare	Poor
Others	Very rare	Variable

are mucoepidermoid carcinoma, adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma.

### ***Mucoepidermoid Carcinoma***

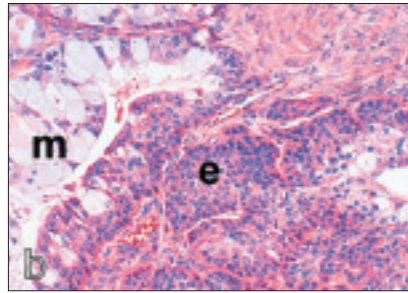
Mucoepidermoid carcinoma is most often a low-grade lesion composed of well-differentiated mucous cells and epidermoid cells, often forming cystic spaces but invading adjacent tissues without encapsulation. It occurs over a wide age range in both males and females, including children. A typical low-grade lesion presents as a fluctuant, bluish, poorly defined, painless and slow-growing subepithelial mass, sometimes mimicking a mucocele or mucous retention cyst (Figs. 1a and 1b). Treatment is by surgical excision, and the prognosis for low-grade lesions is excellent, with a cure rate of over 90%.<sup>2</sup> Intermediate-grade lesions are more aggressive, whereas high-grade lesions, although rare, carry a grave prognosis.<sup>5</sup>

### ***Adenoid Cystic Carcinoma***

Perineural invasion is a hallmark of adenoid cystic carcinoma, which is composed of masses of basaloid neoplastic myoepithelial cells containing occasional ductal structures and typically forming a cribriform growth pattern. It usually presents as a slowly growing, firm, poorly defined, subepithelial mass, sometimes associated



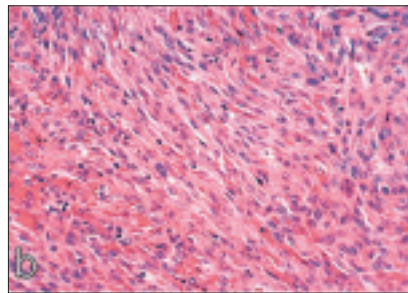
**Figure 1a:** Mucoepidermoid carcinoma in a 61-year-old man who presented with a painless, slowly growing, slightly bluish mass of the soft palate.



**Figure 1b:** Microscopic examination showed well-differentiated mucous cells (m) and epidermoid cells (e), with cyst formation, characteristic of low-grade mucoepidermoid carcinoma. (Hematoxylin and eosin, x200.)



**Figure 2a:** Kaposi's sarcoma in a 28-year-old HIV-positive man who presented with multifocal flat to nodular purple lesions of the facial skin and oral mucous membranes. Facial (black arrow), palatal and tongue (white arrow) lesions are illustrated.



**Figure 2b:** Microscopically, the tumours were composed of sheets of spindle-shaped endothelial cells associated with hemorrhage. (Hematoxylin and eosin, x200.)

with pain or paresthesia related to the perineural invasion.<sup>6</sup> Palatal lesions may exhibit bone invasion and destruction. Middle-aged and older individuals are affected most often. Treatment is by surgical excision with or without therapeutic radiation, but recurrence is common, and distant metastases may occur late in the disease process. Short-term (5-year) prognosis is good (70%), but long-term survival (to 20 years) is poor (20% to 30%), a reflection of the tumour's persistence and recurrence.<sup>2</sup>

### **Polymorphous Low-Grade Adenocarcinoma**

Polymorphous low-grade adenocarcinoma is a low-grade malignant tumour seen most often at the junction of the hard and soft palate in older men and women. Clinically, it presents as a slow-growing, painless mass that may erode adjacent bone. Microscopically, it is composed of both ductal and myoepithelial elements exhibiting a variety of growth patterns and invading adjacent tissues.<sup>7</sup> Wide surgical excision is the treatment of choice. Local recurrence is reported in up to 17% of cases,<sup>1</sup> metastasis to regional lymph nodes is uncommon (less than 10% of cases), and death from the tumour is rare.

### **Others**

Other malignant tumours of the salivary gland are listed in Table 2, along with their prognoses. These are usually seen in the parotid or submandibular glands and uncommonly or rarely affect the oral cavity.<sup>4</sup>

### **Soft-Tissue Sarcomas**

Malignant tumours arising from the connective tissues, including any of the connective tissues of the maxillofacial complex, are called sarcomas. Oral sarcomas include fibrosarcoma, liposarcoma, rhabdomyosarcoma, leiomyosarcoma, angiosarcoma, neurosarcoma<sup>8</sup> and malignant tumours of the hematologic tissues such as lymphoma,<sup>9</sup> myeloma and leukemia.<sup>2</sup> Most of these are rarely encountered in the oral cavity, but some are more frequent. Most types of sarcomas appear clinically as subepithelial nodules of variable growth rate, forming infiltrating masses that may be associated with ulceration. Microscopic examination is necessary for diagnosis since the clinical characteristics are too vague

for precise recognition. Microscopy of soft-tissue sarcomas is sometimes difficult, and adjunctive immunohistochemical studies may be required for better definition. Treatment ranges from local surgical excision to a combination of surgery, radiation and chemotherapy. The prognosis depends on the type, histologic variant and grade, and stage of the tumour.<sup>8</sup> The more common soft-tissue sarcomas are reviewed here.

### **Malignant Fibrous Histiocytoma**

Cells producing malignant fibrous histiocytomas exhibit both fibroblastic and histiocytic characteristics on microscopic examination. There are a variety of growth patterns, the most characteristic being the presence of swirled fascicles of spindle-shaped cells with associated vascularity and polygonal cells or giant cells.<sup>8</sup> Most such tumours occur in older individuals as firm, pink, occasionally ulcerated subepithelial masses that may be painful. Treatment is by radical surgical excision. Recurrence and metastasis occur in about 40% of cases,<sup>2</sup> and death may ensue.

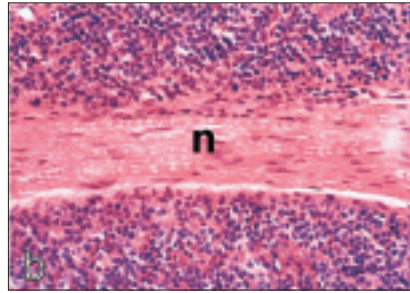
### **AIDS-related Kaposi's Sarcoma**

The AIDS epidemic has brought a new type of Kaposi's sarcoma, which occurs only in HIV-infected

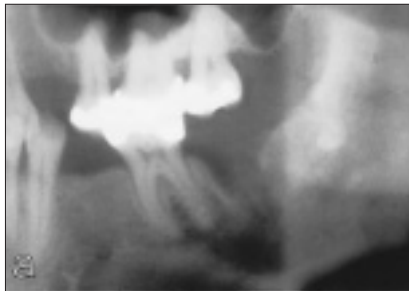




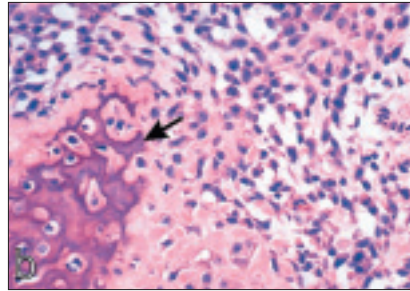
**Figure 3a:** Lymphoma in a 79-year-old woman who presented with a rubbery, painless mass that was moulded to accommodate the buccal surface of her upper denture.



**Figure 3b:** A biopsy showed the presence of sheets of atypical lymphocytes infiltrating and displacing the normal tissues. Here, the tumour is strangling a peripheral nerve (n) seen across the centre of the photomicrograph. (Hematoxylin and eosin,  $\times 200$ .)



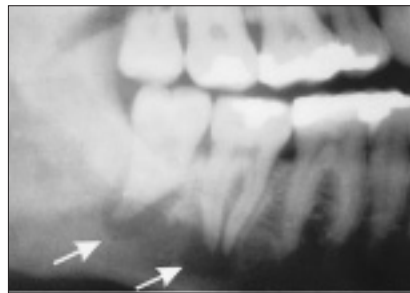
**Figure 4a:** Osteosarcoma in a 36-year-old woman who complained of discomfort and pain of the left posterior mandible. A mobile second molar was extracted, but the symptoms did not resolve. The radiograph illustrates a poorly defined radiolucency with vague internal radiopacities.



**Figure 4b:** A biopsy of the lesion showed a malignant bone-producing tumour (arrow) characteristic of osteosarcoma. (Hematoxylin and eosin,  $\times 300$ .)



**Figure 4c:** Parosteal osteosarcoma in a 34-year-old woman in whom a painless, bony, hard, progressively enlarging nodule of the maxillary alveolus developed. A radiograph showed an exophytic radiopaque mass extending from the cortical bone and not involving the trabecular bone. Microscopic examination revealed a well-differentiated osteosarcoma.



**Figure 5:** Metastatic disease in a 32-year-old woman who complained of paresthesia of the right lower lip and chin. A radiograph revealed multifocal radiolucencies mimicking periapical disease (arrows), but the teeth were vital. A biopsy showed metastatic breast carcinoma.

persistently and may become so large that they interfere with oral function. The cancer invades the jaw bones, causing loosening or exfoliation of teeth. Widespread dissemination to other organs and lymph nodes is common. Microscopically, the tumours are composed of sheets of spindle cells associated with hemorrhage and hemosiderin. Diagnosis may be assisted by vascular markers, which are identified immunohistochemically. Treatment is usually palliative, involving radiation and chemotherapy to control but not cure the growth. Affected patients usually die of other causes, such as disseminated infections, before succumbing to the Kaposi's sarcoma.

### **Non-Hodgkin's Lymphoma**

Non-Hodgkin's lymphomas occurring in the mouth usually present as red or purple extranodal rubbery masses, most commonly occurring on the palatal mucosa, buccal vestibule or gingiva in middle-aged and older patients. Lymphoma may also present within the jaw bones, producing a ragged radiolucency with vague pain or paresthesia and eventual cortical expansion or perforation (or both). There may be associated enlargement of the cervical lymph nodes, and the patient may have symptoms such as fatigue, weight loss and night sweats. Biopsy is necessary to establish a diagnosis of non-Hodgkin's lymphoma and to further characterize the specific type, usually by identification of immunohistochemical markers or gene rearrangement studies (or both). Determining the specific type of non-Hodgkin's lymphoma is extremely important because lymphomas exhibit a wide range of aggressiveness and response to treatment.<sup>9</sup> In 85% of cases, oral

lymphomas are composed of masses of B cells (small, large or both)<sup>2</sup> in a diffuse or follicular pattern associated with intermediate-grade malignant behaviour (Figs. 3a and 3b). Treatment for intermediate-grade and high-grade lesions consists of radiation with or without multiagent chemotherapy, whereas low-grade lesions may not be treated at all. The prognosis depends on the specific type of lymphoma and the

lymphomas are composed of masses of B cells (small, large or both)<sup>2</sup> in a diffuse or follicular pattern associated with intermediate-grade malignant behaviour (Figs. 3a and 3b). Treatment for intermediate-grade and high-grade lesions consists of radiation with or without multiagent chemotherapy, whereas low-grade lesions may not be treated at all. The prognosis depends on the specific type of lymphoma and the

**Table 3** Examples of very rare oral cancers

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Alveolar soft parts sarcoma
Ewing's sarcoma
Hodgkin's disease (Hodgkin's lymphoma)
Acute disseminated Langerhans cell histiocytosis (Letterer-Siwe disease)
Mycosis fungoides
T cell lymphomas
Merkle cell carcinoma
Primitive neuroendocrine tumour
Neuroblastoma
Malignant triton tumour
Malignant teratoma
Inflammatory pseudotumour/sarcoma

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extent of spread, with median survival of 8 to 10 years or more for low-grade tumours but 60% mortality within 5 years for high-grade lesions.<sup>2</sup> Burkitt's lymphoma, a high-grade tumour seen more commonly in Africa than in North America, has a predilection for the head and neck in children.<sup>1</sup>

### **Neurofibrosarcoma**

Neurofibrosarcomas, also known as malignant peripheral nerve sheath tumours, malignant schwannomas and neurosarcomas, account for about 10% of soft-tissue sarcomas, and approximately half of these lesions occur in the setting of neurofibromatosis type 1 (NF1). Neurofibrosarcomas occur only rarely in the head and neck region and are most common in young adults (mean age 40 to 46 years). The mean age of occurrence in patients with neurofibromatosis is 29 to 36 years, although such lesions have been described in younger patients.<sup>11</sup> Malignant transformation usually occurs in association with a large, diffuse neurofibroma in cases of NF1. In the oral regions, the mandible, lips and buccal mucosa are most commonly involved. The tumours present as rapidly enlarging masses, sometimes with associated pain. Radiographs may show widening of the inferior alveolar canal, with or without destruction of surrounding bone and involvement of the inferior alveolar nerve. Microscopically the tumour shows fascicles of atypical spindle-shaped cells, which may resemble those of fibrosarcoma but which are usually more irregular, with wavy or comma-shaped nuclei. Some less cellular myxoid areas may also be seen. Positive immunostaining for S100 protein is often helpful, but a definitive diagnosis of neural origin is often difficult.<sup>2</sup> The prognosis for patients with neurofibrosarcoma arising *de novo* is about 50% for 5-year survival, whereas it is 15% for neurofibrosarcoma arising in cases of neurofibromatosis.<sup>2</sup>

### **Hard-Tissue Sarcomas**

Osteosarcoma and chondrosarcoma of the jaws are the 2 types of hard-tissue malignant tumours that occur in the

mouth. Malignant odontogenic tumours involving hard-tissue production (dentin, enamel) are extremely rare.

### **Osteosarcoma**

Malignancy of bone-forming cells may occur in the maxilla or the mandible. Jaw osteosarcoma usually affects adolescents and young to middle-aged adults of both sexes; either jaw may be affected, but there is a predilection for the mandible.<sup>12</sup> Osteosarcoma presents as a moderate- to fast-growing, asymmetric, often painful enlargement of the bone with invasion of the antrum in maxillary lesions. Teeth may become loose or displaced. Radiographically, there may be widening of the periodontal ligament in the early stages, associated with irregular mixed radiolucency or radiopacity. In some cases there is a sunburst periosteal reaction as the tumour mass expands through cortical bone. Microscopically, there are masses of polygonal or spindle-shaped cells associated with highly variable amounts of osteoid, some of which is calcified (Figs. 4a and 4b). The tumour is invasive and may hematogenously metastasize to distant sites such as lung and brain. Treatment is by radical surgical resection. Adjuvant chemotherapy may also be effective in reducing the risk of death. The prognosis for affected patients is poor, with 5-year survival rates ranging from 30% to 50%.<sup>2</sup>

Osteosarcoma sometimes arises from the cortex rather than from cells deep within the bone. These juxtacortical osteosarcomas (Fig. 4c), most commonly of the parosteal type, present as exophytic, hard, slow-growing masses. They are typically better differentiated than intrabony tumours, and the prognosis is good with local surgical excision.<sup>2</sup>

### **Chondrosarcoma**

Chondrosarcomas are rare, slow-growing cartilage-forming tumours that usually occur in the maxilla of middle-aged and older individuals, but which are sometimes observed in young patients. Radical surgical excision is the treatment of choice. Short-term (5-year) prognosis is good, but recurrence is common, and the long-term prognosis is variable and depends on a variety of factors.<sup>1,2</sup>

### **Metastatic Tumours**

Tumours from other organs and body parts may metastasize to the jaw bones and oral soft tissues by either the lymphatic or blood vascular systems. Metastatic tumours may present in adults as one or more soft-tissue nodules, which are painless but which have persistent growth. They may eventually induce painful ulceration of the soft tissues. More commonly, metastases present within the jaws, especially the posterior mandible (Fig. 5). They are often discovered when teeth become loose or painful; in such cases, radiography will show one or more irregular, moth-eaten radiolucencies. Unilateral numbness of the chin is a

frequent symptom of mandibular metastatic lesions. Some tumours, such as prostatic carcinoma and some breast carcinomas, may induce bone formation, producing a mixed opaque and lucent radiographic appearance. Carcinomas metastasize to the jaws far more frequently than sarcomas do. The most common metastatic tumours found in the oral tissues are carcinoma of lung and adenocarcinoma of breast, prostate, kidney and thyroid.<sup>1</sup> Metastasis to the maxillofacial region is a grave prognostic sign, suggesting disseminated metastasis. Most patients die within 1 year.<sup>2</sup>

### Other Cancers

Cancers arising from the odontogenic apparatus are very rare.<sup>13</sup> The most common is ameloblastic carcinoma, which occurs in older individuals, causing destruction of the jaw, usually the posterior mandible. The prognosis is poor. The discussion of other odontogenic carcinomas and sarcomas<sup>13</sup> is beyond the scope of this paper.

Other malignant tumours (Table 3) rarely affect the oral regions.

### Conclusions

Dental personnel cannot be expected to know the details of all types of cancers that may affect the maxillofacial region. They should, however, be aware that such lesions exist and should have some knowledge of those that are most likely to be encountered. ♦

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*Acknowledgement: The authors wish to thank Dr. G.P. Wysocki for contributing the photomicrographs.*

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*The authors have no declared financial interests.*

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