CHAPTER

12 Tumors of the Oral Cavity

Tumors of the oral cavity are discussed in this chapter under three separate sections. The first focuses on tumors of oral mucosa. The second and third sections reviews other accessory structures, namely: tumors of salivary glands and odontogenic tumors.

TUMORS OF ORAL MUCOSA

Anatomy

The anterior boundary of oral cavity is the vermilion borders of the lips. The posterior boundary includes: end of hard palate, anterior tonsillar pillar and the junction of anterior two-thirds of the tongue with the posterior third. The oral cavity comprises seven anatomic subsites, including: the lips, buccal mucosa (cheek), upper and lower alveolar margins, floor of mouth, anterior two-thirds of tongue, retromolar area (a triangular area in front of ascending ramus of mandible) and the hard palate (Fig 12-1).

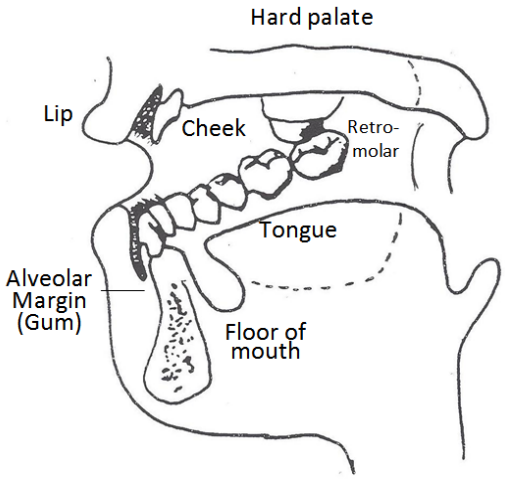

Fig 12-1 *Anatomic landmarks and subsites of the oral cavity.*

Epidemiology

Cancer of the oral cavity accounts for about 4% of all cancers and 30% of head and neck cancer (Myers et al, 2009). The median age of patients is 50 years with a male predominance of 3:1.

Etiology

The following six etiologic factors act synergistically in producing carcinoma of the oral cavity:

1. Tobacco. Cigarette and cigar smoking are confirmed etiologic factors due to their content of carcinogenic agents (benzpyrene and nitrosamine). In India, the habit of betel-nut chewing (mixed with tobacco leaf and lime), as well as, reverse smoking (with lighted end of cigarette in the month) contribute to the very high incidence of oral cancer (about 40% of cancers).

2. Alcohol: Oral cancer is six times more common among drinkers, than nondrinkers. Chronic alcoholism may result in impaired metabolism resulting from liver dysfunction and nutritional deficiencies (especially antioxidants and iron) that may promote carcinogenesis.

3. Solar Radiation: Outdoor workers have an increased risk of cancer of lower lip due to exposure to ultraviolet radiation.

4. Human viruses: Human papilloma virus (especially HPV 16 and 18), as well as, recurrent herpes stomatitis (HSV) increase the risk of developing oral cancer three times.

5. Dental factors: Poor oral and dental hygiene (often associated with alcohol and tobacco abuse) are high-risk etiologic factors. The enzymatic conversion of ethanol by oral microflora can lead to the accumulation of acetaldehyde, a known carcinogen in the oral cavity.

6. Immunologic disorders: Patients with oral lichen planus have an increased risk of developing oral carcinoma.

The above mentioned etiologic factors produce a widespread effect on oral mucosa, as well as, aerodigestive mucosa (field cancerization). This explains the high rate of multiple cancers (11%) and the development of a second primary (14%) usually within 5 years.

Molecular oncogenesis

The concept of multistep carcinogenesis (Fearon and Vogelstein, 1992) is operable in carcinoma of oral cavity. Activation of oncogenes is an early event with increased production of epidermal growth factor receptor (EGFR) and transforming growth factor alpha (TGFα). Other contributing molecular events include: (a) TP53 gene mutation (50% of cases) resulting in genomic instability. (b) TP16 inactivation and cyclin D1 amplification will lead to cell cycle dysregulation and increased cell proliferation, and (c) Increased BCL2/BAX ratio (due to expression of the antiapoptotic gene BCL2 and inhibition of proapoptotic gene BAX) will lead to arrest of apoptosis and increased tumor cell survival.

Precursor lesions

1. Leukoplakia: Appears as a white patch in mucosa not removed by scrapping. Histologically, dysplasia and hyperkeratosis are evident (P 12-1). The risk of malignant transformation is about 15%.

2. Erythroplasia: Appears as a red patch (P 12-2) and is usually associated with carcinoma in situ (CIS). This is a high-risk lesion with a tendency to progress to invasive squamous carcinoma in about 50% of cases.

3. Lichen planus: This idiopathic lesion is possibly autoimmune disease. It presents as mucosal ulcers with lace-like network of white lines (P 12-3). The histology is characterized by saw-toothed pattern of epithelium with loss of basal layer and associated inflammatory reaction. It is a low-risk lesion, with tendency to progress to malignancy in only 2.5% of cases.

In all precancerous lesions, a careful study of epithelium-stroma interface is essential to rule out microinvasive carcinoma (P 12-4).

Classification

The oral mucosa may be affected by a variety of tumors (Table 12-1), but, squamous cell carcinoma markedly predominates contributing about 90% of cases. Grossly, it appears as an ulcer, mass, or diffusely infiltrating lesion (P 12-5 and P 12-6). Besides the usual conventional type (P 12-7), four variants are recognized, namely: the verrucous variant (P 12-8), papillary, basaloid and spindle cell or sarcomatoid variants. Squamous carcinoma is graded by a three tier system (G1, G2 and G3). The site distribution of carcinomas is presented in (Table 12-2).

Table 12-1 Histologic Classification of Tumors of Oral Cavity

Type (frequency %)
Benign tumors (-)
Squamous papilloma
Angioma (pyogenic granuloma)
Fibroma
Granular cell tumor
Squamous cell carcinoma (90%)
Conventional
Verrucous variant
Papillary variant
Basaloid variant
Spindle cell variant
Nonsquamous malignancies (10%)
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Kaposi sarcoma
Extranodal non-Hodgkin lymphoma
Malignant melanoma

Table 12-2 Site Distribution of Mucosal Carcinomas of Oral Cavity

Site	Frequency %
Tongue	37
Lip	30
Floor of mouth	12
Lower gingiva	12
Buccal (cheek)	5
Upper gingiva	4
Hard palate	0.5

(Feig and ching, 2012)

Differential Diagnosis

Two lesions in the oral cavity may be associated with atypical squamous epithelial changes which may be misdiagnosed as squamous carcinoma:

1. Granular cell tumor produces growth factors which cause marked pseudoepitheliomatous hyperplasia of overlying epithelium indistinguishable form invasive squamous carcinoma (P 12-9). Identification of the underlying granular cell tumor will help to avoid the misdiagnosis.

2. Necrotizing sialometaplasia: A common location is the hard palate and is due to traumatic necrosis in a submucous minor salivary gland. The marked squamous metaplasia of salivary ducts may be confused with squamous or mucoepidermoid carcinoma (P 12-10). However, such lesion is restricted to ducts, with preservation of lobular pattern, no invasion and associated necrosis and inflammation are evident.

Nonsquamous Malignancies

About 10% of oral malignant tumor are non-squamous types. Common examples include:

1. Salivary gland carcinomas, especially muco-epidermoid and adenoid cystic carcinomas.
2. Non-Hodgkin lymphoma especially primary plasmacytoma and Burkitt lymphoma.
3. AIDS-related Kaposi sarcoma.
4. Malignant melanoma (primary extracutaneous).

Spread

1. Local spread: to involve soft tissue of floor of month or related bones such as alveolar margin, mandible or maxilla.

2. Lymphatic spread: Cervical lymph node metastases are evident in about 30% of patients, but, both the frequency and level of metastases vary according to the site of primary tumor (Table 12-3).

3. Hematogenous spread: Distant metastases eventually occurs in about 15% of patients. Common metastatic sites include the lung, bone and liver in descending order.

Staging and Prognosis

The general rules of TNM staging for head and neck is applicable to different tumor sites of oral cavity. Prognosis is largely dependent upon the stage of carcinoma (Table 12-4 and 12-5).

Table 12-3 Frequency and Levels of Lymph Node Metastasis in Oral Carcinomas

Primary site	L.Node +ve %	Level
Tongue	45	II, III, IV
Floor of mouth	40	I
Alveolar margin	30	I, II
Palate	15	I
Lip	10	I

Table 12-4 TNM Staging and Survival of Carcinoma of Lip

Stage		5-year survival %
0	Carcinoma in situ	–
I	Tumor confined to lip <2 cm (T1) No nodal or distant metastases (N0, M0)	59
II	Tumor confined to lip 2-4 cm (T2)	62
III	Tumor confined to lip >4 cm (T3) or associated node metastasis (N1), single node <3 cm	55
IVA	Invasion of alveolar margin, or ipsilateral node metastases 3-6 cm (N2) or invasion of skin of face	39*
IVB	Invasion of floor of month or tongue, node metastases >6 cm	
IVC	Any T or N with distant metastasis (M1)	

(Edge, 2010) * All stage IV

Table 12-5 TNM Staging and Survival of Carcinoma of Tongue

Stage		3-year survival %
0	Carcinoma in situ	–
I	Tumor confined to tongue <2 cm (T1)	80
II	Tumor confined to tongue 2-4 cm (T2)	70
III	Tumor confined to tongue >4 cm (T3) or associated node metastasis (N1) single node	50
IVA	<3 cm, Deep muscle invasion or invasion of bone of mandible	40*
IVB	Invasion of pterygoid space, masticator space or carotid artery	
IVC	Any T or N with distant metastases (M1)	

(Edge, 2010) * All stage IV

TUMORS OF SALIVARY GLANDS

Surgical Anatomy

The salivary glands are classified into major and minor salivary glands. The major glands are the parotid, submandibular and sublingual glands; all drain into the oral cavity by distinct duct system. The minor salivary glands are numerous and widely dispersed throughout the mucosal lining of the upper aerodigestive tract.

The parotid gland, the largest of the three major salivary glands, is divided by the facial nerve into superficial and deep parts (not lobes). Tumors of the deep part may pass through the stylomandibular tunnel to present as a mass in oropharynx (Fig 12-2).

Histology

Salivary acini (lined by both serous and mucinous cells) drain by a series of ducts (intercalated and striated ducts) which empty into an excretory duct (Fig 12-3). Contractile myoepithelial cells (calponin and S-100 positive) surround the acini and intercalated ducts and help in draining saliva through the ductal system. Serous acini predominate in the parotid gland, whereas, mucinous acini are more abundant in other major and minor salivary glands.

Histogenesis

In the past, it was believed that cancer arises from mature cells and in case of salivary tumors, pleomorphic adenoma and adenoid cystic carcinoma arise from intercalated cells, whereas, mucoepidermoid carcinoma arises from excretory ducts. A major obstacle to this concept is that adult cells are terminally differentiated cells incapable of proliferation and ultimately die by apoptosis.

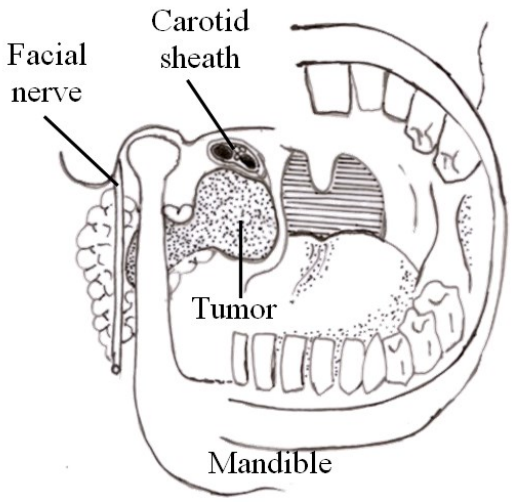

Fig 12-2 *The parotid gland is divided by the facial nerve into superficial and deep parts. Tumors arising from the latter may pass through the stylomandibular tunnel to present in oropharynx.*

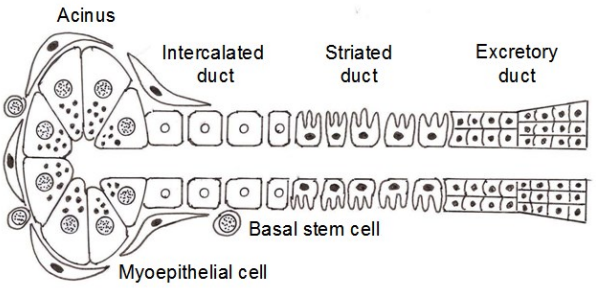

Fig 12-3 *The basic histologic structure of a salivary gland unit. Heterotopic sebaceous glands may also be present. Multipotent basal stem cell is the source of normal cell renewal, as well as, histogenosis of epithelial tumors.*

The recent cancer stem cell theory postulates that tumors arise from the multipotent stem cells and the resulting tumor type is largely determined by the lineage differentiation of stem cells. In this model, pleomorphic adenoma and adenoid carcinoma represent stem cell differentiation towards myoepithelium and intercalated ducts, whereas, in Mucoepidermoid carcinoma it is towards excretory duct differentiation.

Pathology

Cancer of the salivary glands contributes about 0.6% of all cancer and 5% of head and neck cancer. A classification of epithelial salivary tumors is presented in (Table 12-6) adapted from Myers et al (2009). Included in the list are the uncommon malignant tumors reported in the revised WHO classification (Barnes et al, 2005).

Table 12-6 Classification of Primary Epithelial Salivary Tumors

Class (%)	Subclass and type (%)
Benign (54%)	**Common (97)**
	Pleomorphic adenoma (75)
	Warthin's tumor (22)
	Uncommon (3)
	(Monomorphic adenomas)
	Oncocytoma, tubular adenoma
	Basal adenoma, canalicular adenoma
	Papillary cystadenoma, sebaceous adenoma
	Benign myoepithelioma
Malignant (46%)	**Common (97)**
	Mucoepidermoid (33)
	Adenoid cystic (22)
	Adenocarcinoma, NOS (18)
	Malignant mixed tumor (13)
	Acinic cell Carcinoma (7)
	Squamous cell Carcinoma (4)
	Uncommon (3)
	Polymorphous low grade ca.
	Myoepithelial ca.
	Basal cell Carcinoma,
	Epithelial myoepithelial ca.
	Clear cell carcinoma,
	Sebaceous Carcinoma,
	Oncocytic Carcinoma

(Barnes et al, 2005)

Benign tumors

1. Pleomorphic adenoma (benign mixed tumor) is the most common salivary tumor with overwhelming predominance in the parotid gland (P 12-11). It is characterized by its multiple histologic components, namely: epithelial, myoepithelial and myxoid or chondroid stroma (P 12-12). The matrix stromal changes are products of myoepithelial cells. Adenomas may also show squamous or osseous metaplasia (P 12-13). Pleomorphic adenomas have a pseudocapsule through which finger-like projections of tumor penetrate into the surrounding glandular parenchyma, hence, simple enucleation of the tumor will leave behind neoplastic foci that result in local recurrence (P 12-14). Postoperative radiotherapy may minimize this complication, but, adequate excision will avoid it.

2. Warthin's tumor (papillary cystadenoma lymphomatosum). The tumor shows solid and cystic areas (P 12-15) and is bilateral in 10% of cases. The diagnostic histologic features include: a papillary intracystic pattern, lined by a double layer of columnar epithelium with eosinophilic cytoplasm and stroma rich in lymphoytes (P 12-16).

3. Monomorphic adenomas: These uncommon monophasic tumors are composed of only one cell type (epithelial or myoepithelium) and lacks distinct stroma. Seven subtypes are recognized (Table 12-6) and their histology displayed in (P 12-17 to P 12-21).

Malignant tumors

The six commonly encountered malignant tumors are listed in (Table 12-6). The relative frequency of malignant tumors, as well as, histologic types, vary among salivary glands. Thus, the relative frequency of malignancy is inversely proportional to the size of salivary glands, being 20% in parotid gland, 50% in submandibular gland and 80% in minor salivary glands. In regard to histologic type, mucoepidermoid carcinoma predominates in parotid gland (32%), whereas, adenoid cystic carcinoma predominates in submandibular (41%) and minor salivary glands (55%).

1. Mucoepidermoid carcinoma is the most common malignant salivary tumor. It has a triphasic structure of squamous, intermediate and mucin-secreting cell components (P 12-22). Grading of the tumor is based upon: anaplasia, necrosis, mitosis and perineural invasion (Barnes et al, 2005). High-grade tumors have a predominance of undifferentiated squamous and intermediate cells (P 12-23), whereas, mucocytes predominate in low-grade carcinoma.

2. Adenoid cystic carcinoma: this carcinoma is unique

because of its slow growth, marked tendency of perineural invasion for a long distance with skip areas and high rate of pulmonary metastases (40%). The diagnostic feature is a triad of tumor patterns, namely: cylindromatous, tubular and solid (in descending order) often present in combination in different tumor areas (P 12-24 and P 12-25). In the cylindromatous pattern, the lumina are filled with mucin or basement membrane material (collagen IV and laminin positive). Postoperative radiotherapy is necessary for this tumor to control residual perineural invasion.

3. Adenocarcinoma, not otherwise specified (NOS): this is a diagnosis by exclusion, when a carcinoma lacks the characteristic histologic features of muco-epidermoid or adenoid cystic carcinoma. Histologically, it simulates invasive duct carcinoma of breast (P 12-34).

4. Malignant mixed tumor: Two variants are recognized (a) carcinoma ex-pleomorphic adenoma, which arises on top of previous pleomorphic adenoma. It is characterized by a malignant epithelial component associated with a benign myxoid or chondroid stroma (P 12-27). (b) Carcinosarcoma is a de-novo malignant mixed tumor in which both epithelial and stromal elements are malignant (P 12-28).

5. Acinic cell carcinoma is characterized by serous acinar cells with granular basophilic cytoplasm (PAS positive zymogen granules) not associated with ductal structures (P 12-26). It may show microcystic pattern.

6. Squamous cell carcinoma is composed entirely of malignant squamous cells and is considered the most aggressive salivary tumor.

The seven uncommon salivary carcinomas are listed in (Table 12-6) and their histology displayed in (P 12-29 to P 12-33).

Nonepithelial Tumors

Angiomas are the most common nonepithelial tumor in major salivary glands. Common primary malignant tumors are lymphomas (MALT related or large cell type arising in parotid lymph nodes) and soft tissue sarcomas. Metastases encountered are either from carcinomas or melanoma.

Differential Diagnosis *(tumor-like lesions)*

1. Necrotizing sialometaplasia must not be diagnosed as squamous carcinoma (the lesion is restricted to ducts).

2. Lymphoepithelial lesion (Mikulicz disease) must not be misdiagnosed as lymphoma. It is an example of reactive mucosa-associated lymphoid tissue (MALT) and salivary glandular epithelium is preserved in the lesion. (P 12-35).

3. Sarcoidosis, the parotid is a selected site of this noncaseous granuloma.

4. Sialosis: the enlarged salivary gland is due to increase in fat cells.

5. Oncocytosis represent focal oncocytic metaplasia of acinar epithelium, must not be confused with oncocytic tumors.

Staging and Prognosis

The TNM staging system for head and neck cancers (chapter 9) is applicable to salivary carcinomas. Prognosis is largely dependent on the stage of tumor (Table 12-7). However, histologic type and grade of carcinomas also affect prognosis (Table 12-8).

Table 12-7 TNM Staging and Survival of Parotid Carcinoma

Stage		5-year survival (%)
0	Carcinoma in situ	
I	Organ Confined, tumor <2 cm	91
II	Organ Confined, tumor 2-4 cm	
III	Tumor > 4 cm and / or extraparotid spread, or single ipsilateral node <3 cm (N1)	56
IV A	Invasion of skin, ear canal, facial nerve and / or large (>3 cm) or bilateral node metastases	
IV B	Invasion of skull base, pterygoid plate or carotid artery	
IV C	Any T or N, distant metastases	25

(Edge et al, 2010 and SEER survival data classified into 3 groups only: localized, regional and metastatic)

Table 12-8 Survival of Salivary Gland Carcinoma in Relation to Histologic type

Histologic type	5-year survival %
Polymorphous low grade	90
Mucoepidermoid, low grade	90
Acinic cell	90
Adenoid cystic	70 *
Malignant mixed	60
Squamous carcinoma	50
Mucoepidermoid, high grade	25

(Feig and Ching, 2012)
*10-year survival drops to only 30%

ODONTOGENIC TUMORS

Histogenesis

In order to understand odontogenic tumors it is necessary to review the development and basic structure of teeth. A tooth originates by invagination of ectoderm (dental lamina) which differentiate into ameloblasts and stellate reticulum, the former is responsible for enamel formation. Dentin-forming cells (the odontoblasts) are of neural crest origin, whereas, cementum-forming cells (the cementoblasts) are of mesenchymal origin (Fig 12-4). Remnants of odontogenic progenitor cells entrapped within the jaws are the source of development of odontogenic cysts or tumors.

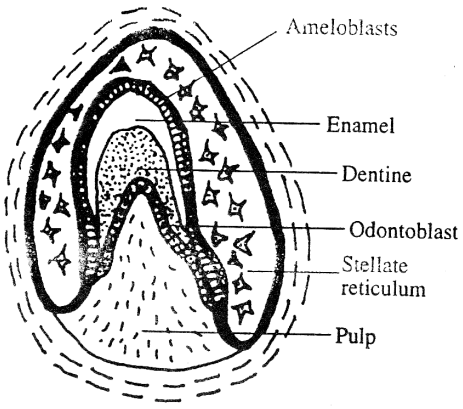

Fig 12-4 *Histologic structure of a developing tooth. Three cell types: ameloblasts, odontoblasts and cementoblasts are responsible for the formation of matrix material, namely: enamel, dentine and cementum respectively.*

Classification

Two classifications are available for odontogenic tumors, one is histogenetic (morphologic) and the other biologic (or behavioral).

1. The histogenetic classification (Table 12-9) is based on the relative contribution of mesenchyme and tooth matrix to the histologic structure of the tumor. Accordingly, tumors are classified into three main groups, namely: mesenchymal predominance, epithelial predominance and dual or mixed structure. The histology of tumors with mesenchymal predominanceis shown in (P 12-36 and P 12-27), tumors with epithelial predominance are presented in (P 12-38 to P 12-44). Finally, tumors of mixed cell structure are shown in (P 12-45 to P 12-48).

2. The behavioral classification stratify the tumors according to their clinical biologic behavior (Table 12 -10). Accordingly, odontogenic tumors may be classified into three main groups, namely: benign, recurring but non metastasizing, and malignant.

Each of the above mentioned classifications has its own value, thus, the histogenetic classification has a diagnostic value, whereas, the behavioral classification is useful to guide therapy and predict prognosis.

Table 12-9 Histogenetic Classification of Odontogenic Tumors

Mesenchymal predominance
Odontogenic fibroma
Odontogenic myxoma
Cementoblastoma
Ameloblastic sarcoma
Epithelial predominance
Ameloblastoma
Adenomatoid odontogenic tumor
Calcifying epithelial odontogenic tumor
Dentigenic ghost cell tumor
Ameloblastic carcinoma
Mixed (epithelium-mesenchyme)
Ameloblastic fibroma
Ameloblastic fibroodontoma
Odonto-ameloblastoma
Odontomas (complex and compound)

(Silverberg, 2006)

Table 12-10 Behavioral Classification of Odontogenic Tumors

Benign
Odontogenic fibroma
Cementoblastoma
Adenomatoid odontogenic tumor
Calcifying epithelial odontogenic tumor
Dentigenic ghost cell tumor
Ameloblastic fibroma
Ameloblastic fibroodontoma
Odonto-ameloblastoma
Odontoma (complex and compound)
Recurring non-metastasizing
Ameloblastoma
Odontogenic myxoma
Malignant
Ameloblastic carcinoma
Ameloblastic sarcoma

(Barnes et al, 2005)

MANDIBULAR TUMORS

The histologic profile of mandibular tumors is an extensive one, considering the numerous cells of origin in such a location. All these tumors present as a mass lesion on radiography, and histopathology is essential to reach a definitive diagnosis. Mandibular tumors are classified into six distinct groups (Table 12 -11).

1. Tumor-like lesions: Cystic lesions of the mandible may be odontogenic or nonodontogenic. Odontogenic cysts include the dentigerous cyst which is related to unerupted tooth, the inflammatory or radicular cyst which is related to the root of an inflamed tooth and, finally, keratocyst which is unrelated to any tooth abnormality. All previously-mentioned cysts are lined by squamous epithelium. Non-odontogenic cysts include simple bone cyst and aneurysmal bone cyst.

Solid tumor-like lesions of the mandible include giant cell granuloma and fibrous dysplasia. The former (better called giant cell lesion) is an obscure reactive condition, completely unrelated to giant cell tumor of bone (P 12-49 and P 12-50). Fibrous dysplasia is commonly monostotic, affecting adolescents, and the histology of the lesion shows immature dysplastic bone, lacking osteoblastic rimming and separated by fibrous tissue.

2. Mesenchymal tumors: The three nonosteogenic soft tissue neoplasm which affect bone are: hemangioma, desmoplastic fibroma and fibrosarcoma.

3. Odontogenic tumors: Their detailed classification is presented in (Table 12-10). Ameloblastoma is the most common odeontogenic tumor, affecting adults and 70% of cases occur at mandibular ramus and molar region. It is a locally aggressive tumor with a tendency of local recurrence if incompletely resected.

4. Bone tumors: Ossifying fibroma (adult and juvenile variants) is a locally aggressive fibro-osseous tumor, almost restricted to jaw bones. Histologically, the osteoid component shows osteoblastic rimming (P 12-51 and P 12-52). About 5% of all osteosarcomas occur in the jaws, especially the mandible (P 12-53). It effects adults (mean age 34 years) and is commonly a low grade fibroblastic type osteosarcoma. Non-Hodgkin lymphomas include Burkitt lymphoma in children (P 12-54).

Table 12-11 Classification of Mandibular Tumors

Tumor-like lesions
Odontogenic cysts, simple bone cyst, aneurysmal bone cyst, central giant cell granuloma and fibrous dysplasia
Mesenchymal tumors
Benign: Hemangioma
Recurring: Desmoplastic fibroma
Malignant: Fibrosarcoma
Odontogenic tumors
(Table 12-10)
Bone tumors
Benign: osteoma
Recurring: ossifying fibroma, osteoblastoma
Malignant: osteosarcoma, chondrosarcoma, Ewing sarcoma and lymphoma (NHL)
Ectopic tumors
Pigmented neuroectodermal tumor, mucoepidermoid tumor, meningioma
Secondary tumors
Local invasion from oral cavity or oropharynx
Metastatic spread from cancers of breast, kidney, lung, thyroid and prostate

5. *Ectopic tumors* of the mandible are usually either of salivary of neuroectodermal in origin.

6. Secondary tumors of the mandible may occur as a result of local invasion from nearby primaries or metastatic from distant primaries.

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