*NEOPLASTIC DISEASE OF SALIVARY GLAND*

**Introduction**

A wide variety of neoplasms originate in salivary glands. These tumors are said to have the most complex and diverse histopathology of any organ in the body. Salivary gland neoplasms are also relatively uncommon. The annual incidence in the United States is about 2.2 to 2.5 cases per 100,000 people i.e. they constitute only about 2% of all head and neck neoplasms. Out of which, 80% of these tumors occurs in the parotid glands, 15% in submandibular glands and the remaining 5% in sublingual and minor salivary glands.

The benign neoplasms make up about 80% of parotid tumors, 50% of submandibular tumors and less than 40% of sublingual and minor salivary gland tumors. Comprehensive review of various salivary gland tumours exist in literature.

**BENIGN NEOPLASMS**

***PLEOMORPHIC ADENOMA***

* Name derived Greek term *pleos =* many; *morphus=* form.
* Benign mixed tumor of salivary glands because of heterogeneous nature of its histologic appearance
* Term suggested by Willis
* Accounts for 2/3 of all salivary tumors.
* It affects parotid - 90% are superficial to facial nerve.

Grossly this tumor has well defined capsule macroscopically



***Histogenesis***

1971, Eversole proposed two theories:

* Pluripotential unicellular theory
* Semipluripotential bicellular theory.

Darkick proposed;

Multicellular theory.

***Pluripotential unicellular theory:***

Excretory duct reserve cell is capable of generating squamous or epidermoid elements or intercalated-like cells

Basal cells of excretory duct responsible for development of all remaining salivary elements.

***Semipluripotential bicellular theory:***

In this theory , the development of intercalated, straited and acinar units is mainly due to the basal cells of excretory duct form intercalated duct units, and luminal progenitor cells of basal excretory duct cells.

***Multiple cellular theory;***

* + Any one of the multiple cell types in the normal salivary gland may have the potential to give rise to any of the various types of tumor occurring in these tissues.

Hubner and his associates have postulated that the myoepithelial cell is responsible for the morphologic diversity of the tumor, including the production of the fibrous, mucinous, chondroid and osseous areas. Regezi and Batsaskis postulated that the interacalated duct reserve cell can differentiate into duct and myoepithelial cells and the latter, in turn can undergo mesenchymal metaplasia

***Gross pathology***

Gross appearance of Pleomorphic adenoma is a smooth or lobulated. It is well-encapsulated tumor with clear demarcation from the surrounding normal salivary gland. These tumors are typically solid and may have areas of gelatinous myxoid stroma. Except in large and long-standing lesions, we may rarely see Cystic degeneration or tumor infarction and necrosis .

* Smooth
* Well-demarcated
* Solid
* Cystic changes
* Myxoid stroma
* Intra-oral accessory glands not >1 to 2 cm in size
* Difficulties in mastication, speech,

***Microscopic features***

Microscopically, pleomorphic adenoma is composed of varying proportions of gland-like epithelium and mesenchymal stroma. The epithelial cells may display several different patterns of growth ranging from small nests, solid sheets to ductal structures or anastomosing trabeculae. The stroma may be myxoid, chondroid, fibroid or osteoid. On microscopic examination, the characteristic feature of pleomorphic adenoma isincomplete encapsulation and transcapsular growth of tumor pseudopods

Tumors are grossly encapsulated.

* There may be “finger-like” projections, “pseudopodia”
* Associated with increased rate of recurrence
* Admixed epithelial & mesenchymal components - “mixed tumor”
* Epithelia component is remarkably diverse, and may show combination of ductal, squamous, clear, spindled, oncocytic and mucous cells and hence called “pleomorphic”
* Mesenchymal components may be, hyalinized, myxomatous, chondromatous or even osseous

***Diagnostic dilemmas***

* Distinctive histopathology pleomorphic nature.
* Chondroid syringoma which is a mixed tumor of the skin, is a firm nodule and has predilection for head and neck area. If occurs over salivary glands mimic salivary tumor.
* Cribriform areas on histology mimic tumor as adenoid cystic carcinoma but with adequate tissue specimen. Pleomorphic areas are distinctive
* Development of carcinoma in pleomorphic adenoma is another diagnostic concern but focal areas of malignant degeneration are usually evident.

***Management***

The treatment of pleomorphic adenomas is complete surgical excision with a surrounding margin of normal tissue, i.e., superficial parotidectomy with facial nerve preservation. For submandibular gland, excision and a wide local excision for a minor salivary gland tumor. In the past, it is seen that simple enucleation of these tumors leads to high local recurrence rates and should be avoided. Another reason for recurrence could berupture of the capsule and tumor spillage in the wound , to prevent this , meticulous dissection is paramount.

**Warthin’s Tumor**

* Papillary Cystadenoma Lymphomatosum or Adenolymphoma
* 5-14% of parotid neoplasms, 2nd most common benign tumor
* Pathogenesis is uncertain.
* Believed to arise from heterotrophic salivary gland tissue found within the parotid lymph nodes. OR
* Proliferation of salivary gland ductal epithelium that is associated with secondary formation of lymohoid tissue
* Risk factor = smokers have 8 fold greater risk.
* EBV (Epstein Barr Virus)

***Clinical Features***

* Appears as painless, slow growing, nodular mass.
* Firm or fluctuant.
* Tail of parotid is a common site.
* Unique characteristic = occurs bilaterally (5-14%)
* Rare in sub-mandibular/lingual glands.
* Older, Caucasian, males… 6th – 7th decade.

***Gross Pathology***

* Encapsulated
* Smooth/lobulated surface
* Cystic spaces of variable size, with turbid fluid, caseous debris, & tenaceous mucoid material with shaggy epithelium
* Solid areas with white nodules representing lymphoid follicles…

***Histology***

* Epithelium: mixed ductal with lymphoid stroma.
* Double cell layer.
* Luminal cells= tall columnar, centrally placed, palisaded.
* Basal cells= cuboidal, with more vesicular nuclei.
* Lining epithelium demonstrates papillary projections into cystic spaces surrounded by lymphoid stroma.
* Stroma: mature lymphoid follicles with germinal centers
* Focal areas of metaplasia may be seen.

The characteristic microscopic features are epithelial cells forming papillary projections into cystic spaces with lymphoid stroma. The epithelium is a double cell layer with tall columnar cells lining the cystic spaces and cuboidal cells along the basement membrane. The nuclei of the columnar cells are oriented toward the cystic space while the nuclei of cuboidal cells are oriented toward the basement membrane.

***Management***

* Surgical excision
* Malignant transformation potential is rare but Seifert showed a study results of squamous metaplasia of 7.5%.
* Synodeman, & Johnson demonstrated 12% recurrence rates.
* Superficial parotidectomy is Rx of choice.

Treatment of Warthin’s tumors is surgical resection. The ideal management is superficial parotidectomy with facial nerve preservation. Enucleation of the tumor can also be done in some cases

***Oncocytoma***

* Composed of large epithelial cells known as ONCOCYTES
* Constitutes 1-2% of all salivary tumors.

***Clinical Features***

* Tumor of elderly - 8th decade
* Female predilection.
* Major salivary glands = parotid⎝80-90%
* Firm, slow growing, painless mass. Rarely >4cm.

***Gross***

* Encapsulated
* Homogeneous, smooth
* Orange/rust color

Grossly, it is a homogenous tumor with smooth surface which may be divided into lobules by fibrous tissue septae.

***Histology***

* Well circumscribed, with Large sheets of polyhedral cells.
* Granular, eosinophilic cytoplasm.
* Granular appearance is due to abundance of mitochondria.
* Cords of uniform cells and thin fibrous stroma
* Distinct cell membrane
* Central, round, vesicular nucleus.

Microscopically, the oncocytes may be arranged in the form of sheets, nests or cords in a uniform pattern. These cells are large with distinct borders with an acidophilic granular cytoplasm. The granularity of the cytoplasm is due to the presence of large numbers of mitochondria that may constitute up to 60% of the cell volume. Special staining procedures such as the Bensley’s aniline-acid fuchsin or phosphotungstic acid hematoxylin stain, or Luxol-fast-blue reaction are helpful in making the diagnosis of oncocytoma. Electron microscopy can also be done.

***Management***

* Best treated by surgical excision.
* Partial parotidectomy (lobectomy) and for submandibular gland ⎝ total gland removal.
* Minor salivary gland oncocytomas may be excised with small margin of normal tissue.
* Good prognosis and low recurrence rate.
* There are examples of malignant oncocytoma, which though are very rare and have poor prognosis.

Surgical excision with a margin of normal remains the standard treatment. There is an exceptionally low rate of recurrence of these tumors if complete removal is done. Enucleation or curettage is not appropriate.

**Myoepithelioma**

Myoepithelioma accounts for less than 1% of all salivary gland neoplasms which makes it very rare. They are mainly seen in the minor salivary glands, parotid glands, palate, and occasionally in the submandibular glands. Like pleomorphic adenomas, these are also seen in the 5th decade of life with female predilection. The clinical presentation is similar to that of other benign salivary neoplasms. These tumors are an asymptomatic, slow-growing mass and are well-circumscribed. Grossly they are similar to a pleomorphic adenoma but without the myxoid stroma.

MICROSCOPIC FEATURES

Three patterns have been described, they are spindle cell pattern, plasmacytoid pattern and the combination of spindle cell and plasmacytoid pattern. The most common is the spindle cell pattern and is typical for parotid myoepitheliomas. The plasmacytoid pattern is less common but the most frequently encountered pattern in palate tumors. The third pattern is uncommon. Myoepitheliomas tend to exhibit benign behavior.

Treatment is complete surgical excision.

**Malignant Neoplasms**

* Malignant tumors are outnumbered by benign tumors by about three to one.
* But may not be applicable to site specific descriptions. eg: parotid = benign (75%) sublingual = malignant (75%)
* Four Ca in order of frequency
* 1. mucoepidermoid ca, 2. adenocarcinoma (NOS)
* 3. acinic cell carcinoma 4. adenoid cystic ca.
* Malignant nature not apparent clinically.
* These also produce asymptomatic swellings
* Prognostic guidelines for Salivary malignancies
* Strongly influenced by stage of tumor. Higher the stage the worse the prognosis.
* High grade ca are more aggressive than low grade carcinoma
* Tumor location often influences clinical outcomes.
* Ca of submand glands have worse prognosis than parotid tumors.
* Extended follow up is required to assess recurrence. The follow up may be up to 20 yrs.

**Adenoid Cystic Carcinoma**

* Term coined by Foote & Frazell in 1953. Originally called as cylindroma
* 2nd most salivary malignancy, 5-10% of major & 35% of minor
* 40-60% of sublingual gland.
* M=F, mean age of occurrence 45yrs.
* Painless mass with 20% cases of paresthesia, & 30% CN VII palsy.
* Tumor has highest propensity for neural invasion.hallmark of this tumor.

***Gross pathology***

* + - Well-circumscribed
* Solid, rarely with cystic spaces
* infiltrative

***Clinical behavior is a paradox:***

* Tumor growth is slow, clinical course is relentless & progressive,
* Operative intervention is usually feasible, but multiple local recurrences is the rule
* Metastatic spread to lymph nodes is uncommon, but distant spread is frequent.
* 5yr survival rates are optimistically high, but 10-20yrs survival rates are dismally low.

***Histology—cribriform pattern***

* Most common
* “swiss cheese” appearance,
* Histology- tubular or trabecular pattern.
* More glandular architecture,
* Layered cells forming duct-like structures
* Basophilic mucinous substance
* Histology- solid pattern.
* Solid nests of cells without cystic or tubular spaces,
* Little or no luminal spaces.

***Management***

* Lymphatic spread rare but only 17%.
  + - Recurrence may show up to 20yrs.
    - It’s a relentless tumor prone for recurrence, and also for distant metastasis. (lung is most common)
* Wide surgical excision is Rx of choice.
* Tubular variety has good prognosis whereas solid has worse prognosis.
* Eneroth et al 10 yr survival rate = zero for solid type and for cribriform 62%,
* Neural invasion may be antegrade or retrograde.

***Acinic Cell Carcinoma***

* It was classified as benign adenoma until 1953.
* Many authors now believe this tumor as malignant but with low potential,
* Vast majority occur in parotid- 2nd most common site in oral cavity.
* 2-5% of all salivary tumors.
* In 3% of cases shows bilateral involvement
* 30-60yrs of age with M:F ratio = 1:2.

***Gross pathology:***

* Uncapsulated,
* Well-demarcated
* Most often homogeneous
* Cut surface = britlle, gray-white color,
* May be solid or cystic.

Microscopically seven variety of patterns are described;

* 1. acinar-lobular, 2. microcystic, 3. follicular, 4. papillary cystic,
* 5. medullary, 6. ductoangular, and 7. primitive tubular.
* 30% of histologic component⎝ lymphoid, and hence like Warthin’s tumor appears to arise from lymphnodes in the glands.
* Calcifications may be seen.
* Composed entirely of serous elements.

***Histology***

* Solid sheets
* Numerous small cysts
* Polyhedral cells
* Small, dark, eccentric nuclei
* Basophilic granular cytoplasm

***Management***

* Complete local excision.
* +/- postoperative RT (doubtful benefits following RT)

***Mucoepidermoid Carcinoma***

***Clinical Features:***

* 10% of all major salivary tumors & 10-15% of minor salivary tumors.
* Occurs at all ages but rare in first decade.
* Most common malignancy of children,
* Asymptomatic swelling.
* High grade tumors⎝CN VII palsy & pain.
* Affects minor glands in palate.
* May be fluctuant, bluish to red color.

***Gross pathology***

* Well-circumscribed to partially encapsulated to unencapsulated
* Solid tumor with cystic spaces

On gross examination, some mucoepidermoid carcinomas appear well-circumscribed and may be partially encapsulated or unencapsulated while others are poorly defined and infiltrative. The cut surface of the tumor may contain solid areas or cystic areas or both. The cystic spaces comprehend viscous or mucoid material.

***Histology***

* + - * Mucous-producing cells and epidermoid cells.
  + Mucous cells - foamy cytoplasm.
* Epidermoid cells - squamoid features, polygonal cells, with intercellular bridges.
* Sometimes third type cells- intermediate cells.
  + Progenetor of mucous & epidermoid cells.
* Also described to have varied six celluar patern
  + 1. maternal cell, 2. intermediate cells, 3. epidermoid cell, 4. clear cell, 5. columnar cell & 6. mucous cell.
* Generally lacks the capsule
* Auclair, Goode & Ellis; in 1992 & 1998; gave ***histologic predictors for prognosis;***
* Cystic component (20% or less=good prognosis)
* Tumor necrosis
* Neural invasion,
* Cellular anaplasia and,
* Mitotic activity.
* Histologically tumors are categorized on basis of;
* Amount of cyst formation.
* Degree of cytologic atypia
* Relative numbers of mucous, epidermoid, and intermediate cells.
* Histology - Low-grade
* Mucus cell > epidermoid cells
* Prominent cysts
* Mature cellular elements
* Histology— Intermediate- grade
* Mucus = epidermoid
* Fewer and smaller cysts
* Increasing pleomorphism and mitotic figures
* Histology— High-grade
* Epidermoid > mucus
* Solid tumor cell proliferation
* Mistaken for SCCA

***Management***

* Influenced by site, stage, grade
* Stage I & II
  + Wide local excision.
  + Parotid = subtotal parotidectomy with CN VII preservation.
  + Submand = total gland removal.
  + Minor glands = wide excision.
  + Margins = low grade min, high grade wide approx. 3mm+
* Stage III & IV
* Radical excision, total parotidectomy, submand gland removal, and bone resection if involved etc.
* +/- neck dissection for suspected metastasis or high grade tumors.

+/- postoperative radiation therapy for more aggressive tumors

**SALIVARY GLAND NEOPLASMS OF PARAPHARYNGAEL SPACE.**

The most common tumors arising in the parapharyngeal space are of salivary gland origin. This accounts for 40-50% of PPS lesions and are located in the prestyloid PPS. These tumors may originate either in deep lobe of parotid gland, ectopic salivary gland nests, or minor salivary glands of the lateral pharyngeal wall. The incidence of tumor that occurs within the deep lobe of the parotid gland is identical to that of the superficial lobe, but, only a small percentage of deep lobe parotid tumors involve parapharyngeal space. The most common prestyloid PPS lesion is “pleomorphic adenoma”. this accounts about 80-90% of salivary neoplasms in the PPS. Other benign salivary lesions, including Warthin’s tumor and oncocytomas, occur in the prestyloid PPS, as do malignant salivary lesions. Carcinoma ex. Pleomorphic adenoma i.e carcinoma on top of pleomorphic adenoma, and adenoid cystic carcinoma are the most frequently reported salivary malignancies of the PPS. Approximately 20% of all salivary lesions in the PPS are malignant. The figure below showing MRI imaging of the deep lobe of the parotid tumor.

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*Axial T1W (a) and T2W (b) MR scans show a slightly dumbbell-shaped left deep lobe parotid begin mixed tumor. The mass lies anterior to the internal carotid artery (arrow-head). Note that there is no fat plane between the posterolateral margin of the tumor and the parotid gland*

**MALIGNANT MIXED TUMORS**

* Represent malignant counterparts of benign tumors.
* 2-6% of all salivary tumors
* Three categories;
  + - Carcinoma Ex Pleomorphic adenoma,
    - Carcinosarcoma and
    - Metastasizing mixed tumor.
* Most common is Ca Ex Pleomorphic adenoma characterized by malignant transformation of epithelial components of previously benign pleomorphic adenoma
* Carcinosarcoma is a rare mixed tumor⎝has both carcinomatous & sarcomatous elements.

Following types of malignant mixed tumors are discussed

*Carcinoma ex-pleomorphic*

*Carcinosarcomas*

*Squamous Cell Carcinoma*

*Clear Cell Carcinoma*

*Polymorphous Low-grade Adenocarcinoma*

*Epithelial-myoepithelial Carcinoma*

*Undifferentiated Carcinoma*

***a) Carcinoma ex-pleomorphic*** adenoma is the most common of three salivary neoplasms that are broadly referred to as malignant mixed tumors. It occurs when a carcinoma develops from the epithelial component of a preexisting pleomorphic adenoma. The other two tumors in this category, carcinosarcoma and metastasizing mixed tumor, are much less common. In a carcinosarcoma, the metastatic lesions contain both the stromal and epithelial elements. This is different from the carcinoma ex-pleomorphic adenoma in which only the epithelial elements are present in metastasis. The metastasizing mixed tumor refers to an otherwise benign acting pleomorphic adenoma that developes metastatic deposits of tumor.

 Carcinoma ex-pleomorphic adenoma accounts for about 3.6% of all salivary neoplasms. It presents in the 6th to 8th decade of life with patients averaging 10 years older than those with pleomorphic adenomas. It occurs most often in the parotid, followed by the submandibular gland and palate. Presentation is usually a painless mass but some patients will report recent quick enlargement of a long-persistent nodule. Pain, adherence to the skin and facial lethargy are commonly present. The risk of malignant degeneration in a pleomorphic adenoma increases from about 1.5% in the first five years to 9.5% for adenomas present exceding 15 years. On gross examination pathology of carcinoma ex-pleomorphic adenoma often shows a poorly circumscribed, infiltrative, hard mass. On microscopic examination malignant appearing cells are present adjacent to a typical looking pleomorphic adenoma. The malignant part of the tumor can taken in the form of any epithelial malignancy except acinic cell. Most commonly this will be in the form of an undifferentiated carcinoma (accounting to 30%) or adenocarcinoma (acoounting to 25%). This tumor tends to be more aggressive as compared to other salivary malignancies and about 25% of patients will have lymph node metastasis on examination. Treatment comprises of radical surgical resection, often in conjunction with neck dissection, and postoperative radiation therapy. Prognosis is related to the local extent of disease and the histologic variation of the carcinoma component.

***b) Carcinosarcomas***, or true malignant mixed tumors, are very rarely occuring tumors accounting to only .05% of salivary gland neoplasms. Average age at presentation is about 60 years and men and women affected are equal in ratio . The parotid gland is the most common site of occurrence. On microscopic examination , these tumors have both sarcomatous and carcinomatous components. In the major population, the sarcoma is the dominating component and chondrosarcoma is the most commonly occuring type of cell. The carcinoma element is usually an undifferentiated or high-grade ductal adenocarcinoma. This is also an aggressive tumor and it is not uncommon for patients to have distant metastasis on clinical examination. Nowadays the suggested treatment protocol comprises of radical surgery, neck dissection for palpable nodes and postoperative XRT. Inspite of these the efficienty of the protocols is yet to be proven, chemotherapy is likely to have a role in the treatment of this disease given the high rate of distant metastasis.

***c) Squamous Cell Carcinoma***

The occurrence of primary squamous cell carcinoma of the salivary gland is very rare, accounting for about 1.6% of salivary gland neoplasms. With the purpose of making this diagnosis, high-grade mucoepidermoid carcinoma, we should first exclude the metastatic squamous cell to the gland or intraglandular nodes and direct extension of a squamous cell carcinoma .The ratio of occurrence is 2:1 from male to female and the age of the patients are usually over 60 years. On clinical examination these tumors are seen as a firm enlarging masses that are not uncommonly fixed to surrounding tissue along with pain or facial weakness. The gross and microscopic examination the tumor’s appearance there is great resemblance to squamous cell carcinoma of other primary sites and differs from well-differentiated with keratinization to poorly-differentiated without keratinization. Salivary gland squamous cell carcinoma presents an aggressive behavior with rapid growth and initial spread to regional lymph nodes. The treatment protocol comprises of surgical resection, neck dissection and postoperative radiation .

***d) Clear Cell Carcinoma***

Clear cell carcinoma is also referred to as glycogen rich carcinoma. These tumors are rare that occur most frequently in the minor salivary glands of the palate and the parotid. They male to female ratio is almost equal and typically present in the 6th to 8th decades of life. On microscopic examination these tumors display a uniform pattern of round or polygonal cells with peripherally displaced dark nuclei and clear cytoplasm. Tumor cells can variably grow in nests or cords separated by fibrous stroma or solid sheets of cells.Characteristically there is a local infiltrative growth. On classification clear cell carcinoma are low-grade tumors and are treated with complete local excision.

***e) Polymorphous Low-grade Adenocarcinoma***

Polymorphous low-grade adenocarcinoma (PLGA) is the second most commonly occuring malignancy in the minor salivary glands and most frequently occurs in the palate, lip and buccal mucosa. On clinical examination This tumor typically presents in the 7th decade of life and is more common in women (accounting to 67%) as compared to men. It presents as a painless submucosal swelling that slowly enlarges and may cause ulceration and bleeding. On microscopic examination the appearance of these tumors is reason they are being referered to as polymorphous low grade adenocarcinoma. It occurs in a variety of growth patterns (solid, tubular, trabecular, glandular, cribriform, cystic) and can be seen within the same lesion or among different lesions. PLGA presents with a tendency for perinerual and perivascular invasion, however it follows an industrious course which is a very typical feature of this tumor. The treatment protocol comprises of a conservative yet complete local excision. Postoperative radiation and neck dissection are not necessary most of the times. Distant metastasis has not been reported.

***f) Epithelial-myoepithelial Carcinoma***

Epithelial-myoepithelial carcinoma comprises of less than 1% of salivary gland neoplasms. It occurs in the 6th and 7th decades of life, in occurs more in women as compared to men, and majorly in the parotid gland. Some of the researches have suggested that patients with these tumors have an increased risk potency for a second primary malignancy—either in the salivary glands or in a separate site (for example breast and thyroid). On gross examination, these are well-circumscribed, multinodular firm masses with irregular cystic spaces. On microscopic examination appearance can be highly variable but displays a very typical biphasic character. “Subunits” of tumor growth include a surrounding thickened basement membrane, outer clear myoepithelial cells, and inner cuboidal epithelial cells lining small duct-like structures. The treatment protocol comprises of complete surgical resection. Because this tumor is so rare, little is known about whether adjuvant radiotherapy or chemotherapy is beneficial.

***g) Undifferentiated Carcinoma***

The undifferentiated carcinomas are uncommon in nature but have an aggressive nature and have a poor prognosis as other salivary gland tumors are compared. Lymphoepithelial carcinoma of the salivary glands have the most common occurence in North American and Greenland Eskimos and Asians. Among Eskimos, the parotid gland is most often affected, there is a female and a familial pattern of the disease. In Asian population , the submandibular gland is the most common site affected and men are affected more often than women. Undifferentiated large-cell carcinoma has a bimodal age distribution with the first peak in the 6th and 7th decades of life and a second peak in the 9th decade. Men are affected more frequently than women and the parotid is the most commonly affected site. Undifferentiated small-cell carcinoma common site of occurrence is in the parotid, in patients 50-70 years old, and with a 1.6:1 male-to-female ratio.

All of these malignancies have a capability for local recurrence, regional and distant metastasis. The treatment protocols comprises of complete surgical excision, with neck dissection for palpable disease and consideration given to postoperative radiation therapy and in some cases chemotherapy.