DISSERTATION ON

HISTOMORPHOLOGICAL PATTERNS OF SALIVARY GLAND TUMORS

Dissertation submitted to

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MADHURANTAGAM

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CERTIFICATE

Certified that this dissertation entitled **"HISTOMORPHOLOGICAL PATTERNS OF SALIVARY GLAND TUMORS"** is a bona fide work done by **Dr. J. Margaret Theresa**, Post graduate student, Karpaga Vinayaga Institute of Medical Sciences, Madhuranthagam, during the academic year 2015 – 2018.

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DECLARATION BY THE CANDIDATE

I, hereby declare that this dissertation entitled **"HISTOMORPHOLOGICAL PATTERNS OF SALIVARY GLAND TUMORS"** submitted by me for the degree of M.D is the record work carried out by me during the period from August 2015 to September 2018 under the guidance of Dr. A.B. Harke, Professor and Head of the Department of Pathology, Karpaga Vinayaga Institute of Medical Sciences and has not formed the basis of any degree, diploma or fellowship titles in this or any other university or other similar institution of higher learning.

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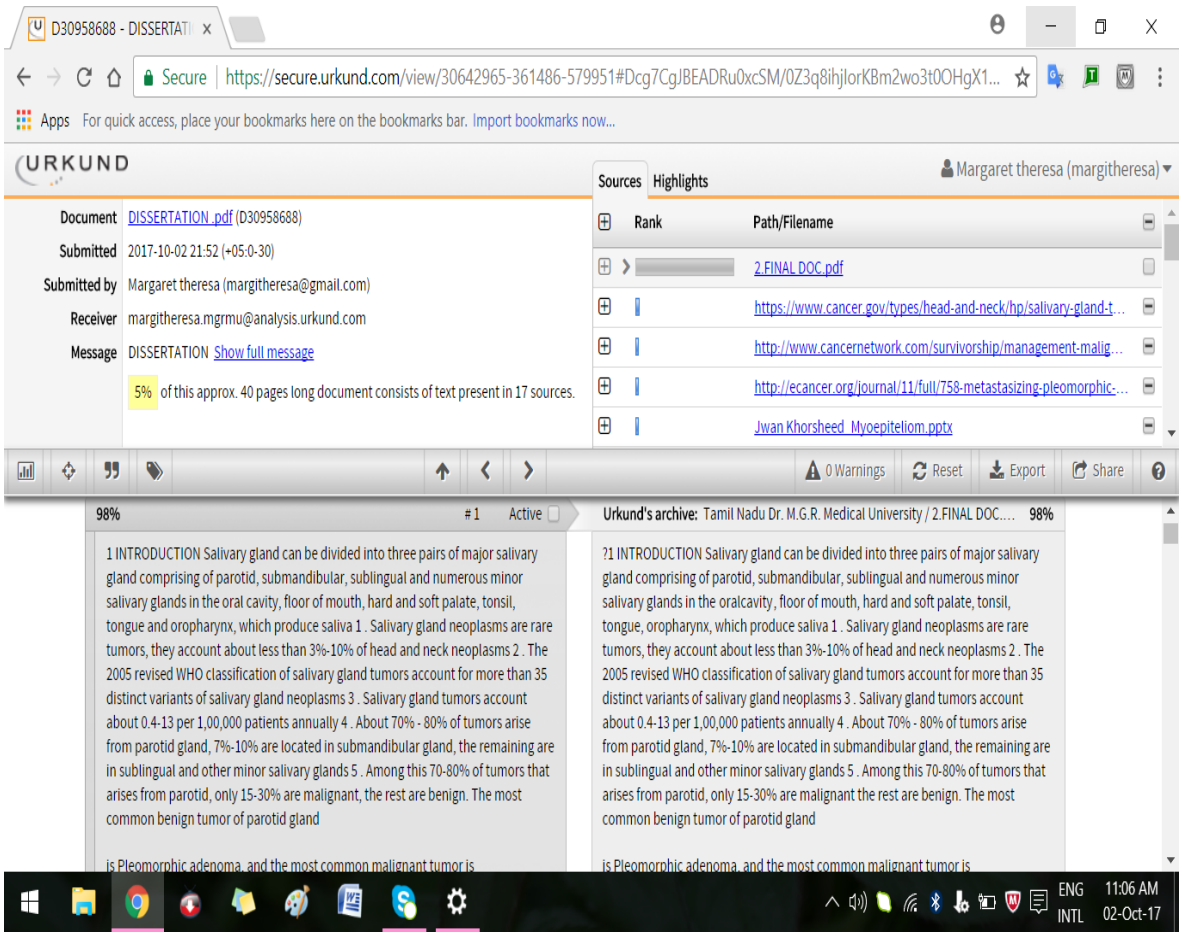
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1 INTRODUCTION Salivary gland can be divided into three pairs of major salivary gland comprising of parotid, submandibular, sublingual and numerous minor salivary glands in the oral cavity, floor of mouth, hard and soft palate, tonsil, tongue and oropharynx, which produce saliva 1 . Salivary gland neoplasms are rare tumors, they account about less than 3%-10% of head and neck neoplasms 2 . The 2005 revised WHO classification of salivary gland tumors account for more than 35 distinct variants of salivary gland neoplasms 3 . Salivary gland tumors account about 0.4-13 per 1,00,000 patients annually 4 . About 70% - 80% of tumors arise from parotid gland, 7%-10% are located in submandibular gland, the remaining are in sublingual and other minor salivary glands 5 . Among this 70-80% of tumors that arises from parotid, only 15-30% are malignant, the rest are benign. The most common benign tumor of parotid gland
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CONTENT

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Salivary gland can be divided into three pairs of major salivary gland comprising of parotid, submandibular, sublingual and numerous minor salivary glands in the oral cavity, floor of mouth, hard and soft palate, tonsil, tongue and oropharynx, which produce saliva[1].

Salivary gland neoplasms are rare tumors, they account about less than 3-10% of head and neck neoplasms[2]. The 2005 revised WHO classification of salivary gland tumors account for more than 35 distinct variants of salivary gland neoplasms[3].

Salivary gland tumors account about 0.4 to 13 per 1,00,000 patients annually[4]. About 70 - 80% of tumors arise from parotid gland, 7-10% are located in submandibular gland, the remaining are in sublingual and other minor salivary glands[5].

Among this 70-80% of tumors that arises from parotid, only 15-30% are malignant, the rest are benign. The most common benign tumor of parotid gland is Pleomorphic adenoma, and the most common malignant tumor is Mucoepidermoid carcinoma. About 50% of tumors that arise from minor salivary glands are malignant. Mucoepidermoid carcinoma, Adenoid cystic carcinoma and Polymorphous low grade adenocarcinoma are more common malignant tumors of minor salivary glands[6].

Benign tumors are commonly seen in younger age group, whereas the malignant tumors are seen in elderly individuals. Clinically benign tumors are indistinguishable from malignant tumors, but some of the malignant tumors exhibit rapid increase in size are unencapsulated and fixed to the underlying tissue; they present with pain, tenderness, facial nerve palsy, and areas of ulceration[7].

Haematoxylin and Eosine (H&E) is considered to be the gold standard in diagnosis of salivary gland tumors, but in recent days the advance in immunohistochemistry (IHC) play an important role in enhancing the accuracy in diagnosis of salivary gland tumors. Immunohistochemistry is useful tool in identifying the nature of cell, cell differentiation, cell proliferation and tumor protein expression[1].

AIMS AND OBJECTIVES

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1. To find out the incidence of various salivary gland tumors in Karpaga Vinayaga Institute of Medical Sciences and Research Centre.

2. To categorize the neoplastic lesions as per the WHO classification.

3. To delineate the histomorphological patterns of salivary gland tumors.

4. To apply immunohistochemistry to enhance the diagnostic accuracy of salivary gland tumors where ever indicated.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

SALIVARY GLAND STRUCTURE

There are three major salivary glands in the oral cavity, they are parotid, submandibular, sublingual and numerous minor salivary glands. Of these most of the salivary glands are located in the oral cavity, some of them in oropharynx, sinonasal tract and in upper respiratory tract[8].

Among these three major salivary glands, parotid is the largest salivary gland which is situated anteroinferior to the external ear. The submandibular glands are located in the floor of the mouth, inferior to the mandible; the sublingual salivary glands are the smallest salivary glands predominantly located inferior to the tongue.

Microscopically salivary glands are covered by capsule and are mainly composed of ducts and acini. Salivary glands are mainly composed of two main type of cells, the serous cells and the mucin secreting cells.

Serous secreting cells are pyramidal in shape with an eosinophilic cytoplasm composed of secretory granules in the apical region, with round basally located nuclei.

Mucous secreting cells are also pyramidal in shape with mucus filled cytoplasm in which the accumulated secretory granules pushes the nucleus to the periphery or at the base of the cytoplasm. In some of the salivary glands both the serous and mucous secreting cells are present[9].

Myoepithelial cells are situated enclosing this serous or mucinous acini. These myoepithelial cells are flattened or spindle shape, highly contractile and

branching, which mainly surround the basement membrane of the acini, these cells are also called as basket cells.

Salivary glands are made up of five different types of ducts, intercalated ducts, striated ducts, excretory intralobular ducts, interlobular ducts and intralobar ducts.

The secretory acini empty the secretory products into the intercalated duct initially which intern connected with striated duct which exhibit tiny basal striations and these striated ducts merge with the large excretory intralobular duct which are surrounded by connective tissue fibers, these ducts are lined by stratified squamous epithelium or cuboidal or columnar epithelium. The main function is to empty the secretory product saliva into the oral cavity[10].

Salivary gland neoplasms

Salivary gland neoplasms are relatively infrequent tumors which account for less than 2% of all tumors[11].

There is a wide range of heterogeneity noted between the benign and malignant tumor of salivary glands, because each tumor exhibit different biological behavior[12]. Its rarity and complexity makes diagnosis challenging. The classification of salivary gland tumors is complex, but it is useful with regards to the diagnostic, prognostic and therapeutic aspect.

The diagnosis of salivary gland tumors is made carefully by assessing the cellular structure, cell differentiation, stromal component architecture of tumor, growth pattern of tumor along with the clinical details.

WHO Histological Classification of Tumors of the Salivary Glands, Eveson et al (2005)	
BENIGN EPITHELIAL TUMORS	**MALIGNANT EPITHELIAL TUMORS**
Pleomorphic adenoma	Acinic cell carcinoma
Myoepithelioma	Mucoepidermoid carcinoma
Basal cell adenoma	Adenoid cystic carcinoma
Warthin's tumor	Polymorphous low-grade adenocarcinoma
Oncocytoma	Epithelial-myoepithelial carcinoma
Canalicular adenoma	Clear cell carcinoma, not otherwise specified
Sebaceous adenoma	Basal cell adenocarcinoma
Lymphadenoma	Sebaceous carcinoma
Ductal papillomas	Sebaceous lymphadenocarcinoma
Inverted ductal papilloma	Cystadenocarcinoma
Intraductal papilloma	Low-grade cribriform cystadenocarcinoma
Sialadenoma papilliferum	Mucinous adenocarcinoma
Cystadenoma	Oncocytic carcinoma
SOFT TISSUE TUMORS	Salivary duct carcinoma
Hemangioma	Adenocarcinoma, not otherwise specified
HEMATOLYMPHOID TUMORS	Myoepithelial carcinoma
Hodgkin's lymphoma	Carcinoma ex pleomorphic adenoma
Diffuse large B-cell lymphoma	Carcinosarcoma
Extranodal marginal zone B-cell lymphoma	Metastasizing pleomorphic adenoma
SECONDARY TUMOR	Squamous cell carcinoma
	Small cell carcinoma
	Large cell carcinoma
	Lymphoepithelial carcinoma
	Sialoblastoma

Pleomorphic adenoma

Pleomorphic adenoma is a benign mixed salivary gland tumor, with epithelial and myoepithelial differentiation. It is the most common benign neoplasm. Majority of the tumor arises from major salivary glands. Among them 80% in parotid, 10% in submandibular glands and only 10% occur in minor salivary glands[13].

The mean age of presentation is 46 years with female predominance; occasionally seen in childrens. Clinically the tumor present as slow growing discrete, multinodular, painless mass which usually occur in lower pole of superficial lobe. At rare instant patient complains of facial nerve paralysis due to extrinsic compression of facial nerve or infections [14].

Grossly the tumor is solitary, encapsulated, round to oval mass, some tumors may lack fibrous capsule. External surface is bosselated or smooth. Cut surface of the tumor is grey to tan in color, firm in consistency. Focal area may be gritty and glistening representing the chondromyxoid differentiation[15] .

Microscopically Pleomorphic adenoma is a mixed tumor, exhibiting both epithelial and myoepithelial differentiation along with variable amount of characteristic stroma. Epithelial cells may be cuboidal, basaloid, squamoid. Myoepithelial cells are spindle, plasmacytoid or clear cell.

The tumor cells show variable amount of growth pattern. Ductal structure which is lined by inner layer of cuboidal cells or columnar cells with vesicular nuclei and a prominent nucleoli, the outer myoepithelial cells may be

spindle enveloping the inner epithelial cells. The duct may be empty or contain eosinophilic secretions. The tumor cells may be arranged in cords and sheets mainly composed of epithelial cells, admixed with myoepithelial cells, lacking the ductal structure.

Occasionally the tumor may show moderate degree of atypia and mitotic figures. The stroma may be myxoid, chondroid and hyalinised which are usually a product of modified myoepithelial cells[16].

In occasional cases the tumor may show squamous metaplasia with keratin pearl formation, sebaceous metaplasia, clear cell change and mucoepidermoid like metaplasia[17].

Immunohistochemistry for Pleomorphic adenoma:

The luminal cells are positive for CK3, CK6, CK10, CK11, CK13. The myoepithelial cells shows positivity for P63, Cytokeratin, S100, Vimentin, Glial fibrillary acidic protein (GFAP), Smooth Muscle Actin (SMA) [18].

The differential diagnosis of Pleomorphic adenoma is Polymorphous low grade adenocarcinoma, Monomorphic adenoma, Adenoid cystic carcinoma, Epithelial myoepithelial carcinoma.

Warthin`s tumor

Warthin`s tumor is otherwise called as Papillary cyst adenoma lymphomatosum, Adenolymphoma, Cyst adenolymphoma[19].

It is the second most common benign salivary gland tumor often involve the parotid. A very low rate of incidence was noted amongst Asian and African population. The tumor is mainly composed of papillary and cystic structure which are lined by bilayered epithelium composed of luminal oncocytic columnar cells surrounded by basal cells .

The tumor clinically present as slow growing tumor mass approximately measuring 2 to 4 cm in diameter, with fluctuation in size. Tumor is most commonly seen in elderly individual with a mean age of 62 years with male predominance. The tumors is strongly associated with heavy smoking, radiation exposure and atom bomb survivors[20] .

Grossly the tumor is encapsulated, spherical to ovoid mass. The external surface of the tumor may be smooth or bosselated, the cut surface may show solid and cystic areas, some of the cystic areas are filled with mucoid and gelatinous fluid.

Microscopically, the tumor exhibit numerous cystic structures lined by bilayered epithelium, which are thrown into numerous papillary infoldings.

The bilayered epithelium are composed of inner luminal oncocytic columnar cells the outer abluminal cells are usually cuboidal basal cells or

flattened cells. The stroma shows dense infiltrations by lymphocytes, plasma cells and few histiocytes. At places lymphocytes form germinal centers[21].

Differential diagnosis of Warthin`s tumor is Papillary cystadenoma which lack the lymphoid stroma, Simple benign lymphoepithelial cyst, Cystic lymphoid hyperplasia, which lack oncocytic epithelium. The squamous metaplastic Warthin`s tumor can be mistaken for Squamous or Mucoepidermoid carcinoma particularly in the infarcted cases of Warthin`s tumor. Squamous metaplasia in Warthin`s tumor lacks keratinization. However keratinization will be prominent feature of Squamous cell carcinoma[22].

Myoepithelioma

Myoepithelioma is a benign salivary gland tumor exclusively composed of tumor cells showing myoepithelial differentiation and they may be spindle, plasmacytoid or epithelioid in nature. The tumor cells are arranged in cords, sheets and islands.

Myoepithelioma most commonly arises from parotid gland, palate, and submandibular gland with a wide range of the age group from 9 to 85 years with a mean age of 55 years. No obvious gender predilection is noted [23].

Myoepithelioma clinically present as a slow growing painless mass. Occasionally Myoepithelial carcinoma can arise from myoepithelioma[24].

Grossly, Myoepithelioma is a encapsulated, well circumscribed tumor mass approximately measuring 1 to 5 cm in diameter. Cut surface of the tumor is tan to white in color.

Microscopically, the tumor is covered by a fibrous capsule in which the cells are arranged in solid sheets, microcystic, reticular growth pattern. The individual cells may be spindle, plasmacytoid, epithelioid or clear cell type. The spindle cell have centrally located nuclei arranged in fascicular growth pattern, which is the most common growth pattern; plasmacytoid cells are round to oval in shape with eccentrically placed nuclei with eosinophilic cytoplasm; they are also called hyaline cells[25].

The epithelial cells are arranged in cords and sheets; they are polygonal in shape with a centrally located nuclei and an eosinophilic cytoplasm.

The clear cells exhibit abundant glycoprotein which are usually positive for Periodic Acid Schiff (PAS). The stroma is usually hyalinized or myxoid.

Immunohistochemistry

Myoepithelial cells shows positivity for Pancytokeratin, P63, S100 and Vimentin[26].

Differential diagnosis for Myoepithelioma and its variants like Spindle cell myoepithelioma should be differentiated from Leiomyoma, Benign fibrous histiocytoma; Plasma cell variants of Myoepithelioma should be differentiated from Plasmacytoma. Myoepithelioma should be differentiated from

Myoepithelial carcinoma based on the invasion, cellular pleomorphism, mitosis, necrosis.

Basal cell adenoma

Basal cell adenoma of salivary glands are rare entity which is mainly composed of basaloid cells. Basal cell adenoma most commonly affect parotid gland, at rare instances it involves minor salivary glands[27].

The tumor most commonly seen with the mean age of 58 years with female predominance. Clinically Basal cell adenoma presents as a superficial, freely mobile, solitary tumor mass.

Grossly it is a well circumscribed tumor mass round to oval in shape; cut surface of the mass being a gray white in color and firm in consistency.

Microscopically the tumor is composed of biphasic basaloid cells, the cells in center are large polygonal in shape with centrally placed nuclei with abundant cytoplasm.

The tumor cells in the periphery are small round cells with basophilic nuclei and scanty cytoplasm exhibiting peripheral palisiding. Basal cell adenoma exhibits numerous microscopic patterns like solid, membranous, tubular and trabecular based on the arrangement of tumor cells; however the most common pattern is solid and mixture of all these patterns[28].

Immunohistochemistry of Basal cell adenoma exhibits luminal and abluminal cell differentiation; luminal cells show positivity for Cytokeratin,

Carcinoembroyonic antigen (CEA), Epithelial membrane antigen (EMA) and the abluminal cells are positive for P63, Calponine, Actin and S100[29].

Differential diagnosis

Basal cell adenoma should be differentiated from Basal cell adenocarcinoma. Basal cell adenocarcinoma shows infiltration of tumor cells into the adjacent tissue. It also shows cellular pleomorphism and high rate of cellular proliferation (>4mitotic figures /10HPF)[30].

Oncocytoma

Oncocytoma is also called as Oncocytic adenoma and Oxyphil adenoma. It is a rare benign tumor of salivary gland composed of oncocytes[31].

Oncocytoma most commonly seen in elderly individuals and have a strong association with radiation exposure[32]. Oncocytoma primarily affects the major salivary gland especially parotid; less commonly involves minor salivary glands. Clinically the tumors are asymptomatic. Grossly the tumors are well circumscribed, lobulated masses, rarely exceed 4 cm in diameter, which is firm in consistency. Occasionally some of the tumors undergo cystic degeneration.

Microscopically the tumors are encapsulated neoplasm, mainly composed of oncocytes. Oncocytes are large polygonal cells with eosinophilic granular cytoplasm and centrally placed vesicular nuclei and are arranged in nested and trabecular pattern with a little fibrovascular stroma. Some of the tumors may show cystic and clear cell changes[33].

Differential diagnosis

Oncocytoma should be differentiated from other salivary gland tumors which undergo oncocytic differentiation like Basal cell adenoma, Pleomorphic adenoma, Mucoepidermoid carcinoma, Adenoid cystic carcinoma and Epithelial myoepithelial carcinoma[34].

Canalicular adenoma

Canalicular adenoma is also known as Monomorphic adenoma and Basal cell adenoma. Canalicular adenoma occurs in the elderly individuals with a mean age of 65 years with female predominance; most commonly affect the minor salivary glands with high predilection to the upper lip[35].

Clinically the tumor is small, less than 3cm in diameter, slow growing, painless mass, firm in consistency and mobile in nature.

Grossly the tumor is variably encapsulated, well circumscribed tumor mass. The cut surface may be tan to yellow and often shows cystic changes filled with gelatinous material.

Characteristic microscopic feature of Canalicular adenoma is a bilayered strands of epithelial cells which runs parallel and at focal places can separate and give rise to beaded pattern. The tumor cells are cuboidal or columnar with basophilic nuclei and eosinophilic cytoplasm. Cellular pleomorphism and mitosis are rare. The stroma is loosely collagenized with prominent vascularity[36].

Immunohistochemistry

Canalicular adenoma shows positivity for S100, Cytokeratin, Vimentin and Glial fibrillary acid protein[37].

Sebaceous adenoma

Sebaceous adenoma, one of the rare benign tumors of salivary gland accounts for 0.1% of salivary gland neoplasms[38]. Some of the salivary gland tumors like Pleomorphic adenoma, Warthin`s tumor, Mucoepidermoid carcinoma, Epithelial myoepithelial carcinoma can also slow sebaceous differentiation at focal places which should be differentiated from this entity.

Sebaceous adenoma most commonly affects the parotid, and is typically seen between the age group of 22 to 90 years with slightly male predilection. Tumor clinically presents with slow growing painless mass.

Grossly the tumor is circumscribed and approximately measures 0.4 to 3cm in diameter. Cut surface of the tumor is solid and cystic which may be gray white to yellow in color.

Microscopically, the tumor is composed of sebaceous cells arranged in nests, which are surrounded by fibrous stroma; focal places tumor may show squamous differentiation.

The tumor is strongly positive for CK, Epithelial membrane antigen (EMA) and negative for Vimentin, S100, Smooth muscle actin (SMA) the myoepithelial markers[39].

Sebaceous lymphadenoma

Sebaceous lymphadenoma was first designated by MC Gavran and Bauer in the year 1960[40].The tumor usually presents as slow growing, nontender mass, exclusively involving the parotid gland, which commonly affects the patient between the age group of 25 to 89 years with no obvious gender predilection.

Grossly it is a encapsulated neoplasm with the size ranging between 1.3 to 6 cm in diameter; the tumor shows solid and cystic areas which is tan to yellow in color, the cystic spaces are usually filled with sebum.

Microscopically the tumor is a well circumscribed neoplasm composed of uniformly distributed sebaceous cells with cystic and duct like structures, in a lymphoid background. The cystic spaces are usually lined by cuboidal, columnar, squamous and sebaceous epithelium. Some cases may show oncocytic change.

Occasional tumor may show foreign body giant cell reaction around the extravasated sebum; the lymphoid stroma may also show germinal centres[41].

Differential diagnosis of sebaceous lymphadenoma are Low–grade mucoepidermoid carcinoma and Warthin`s tumor.

Ductal papilloma

Ductal papilloma arises from excretory ductal unit characterized by papillary configuration. These tumors most commonly affect the minor salivary

gland and salivary ductal system. Ductal papilloma can be classified into three distinct tumor types namely intraductal papilloma, inverted ductal papilloma and sialadenoma papilliferum.

Intraductal papilloma:

Intraductal papilloma is characterized by proliferation of bland looking cuboidal to columnar cells in papillary configuration[43]. The tumor most commonly affect the parotid but rarely can also involve the submandibular or sublingual glands.

Intraductal papilloma clinically presents as a submucosal painless mass. Most commonly affects the elderly individuals between the age group of 6th and 7th decade [44].

Grossly the tumor is unilocular cystic mass approximately measuring 0.5 to 2 cm in diameter.

Microscopically the tumor shows cystically dilated structures with papillary infolding which are lined by single or double layer of cuboidal or columnar cells with a central fibrovascular core. There is no cellular atypia, however occasionally tumor shows few mitotic figures.

The tumor is immunoreactive for Pancytokeratin, Epithelial membrane antigen and negative for SMA[45].

Sialadenoma papilliferum

Sialadenoma papilliferum exhibits a biphasic growth pattern; the tumor exhibits both exophytic squamous pattern and endophytic glandular pattern. Sialadenoma papilliferum has similar features of Syringocystadenoma papilliferum of the skin[42].

Sialadenoma papilliferum is a rare neoplasm most commonly involving the minor salivary gland, mainly the palate. Clinically the tumor presents as a painless mass in the surface mucosa. The mean age of presentation is 59 years with slightly male predominance[44].

Grossly the tumor is well defined papillary exophytic mass approximately measuring 0.3- 2 cm in diameter[44]

Microscopically two growth pattern are noted, the exophytic and endophytic growth pattern in the oral mucosa. The exophytic component exhibits papillary projections which are lined by stratified squamous epithelium with a central fibrovascular core. This stratified squamous epithelium may show hyperkeratosis, parakeratosis and focal hypergranulosis.

The endophytic pattern is composed of double layers of outer cuboidal and inner columnar cells admixed with few scattered mucous cells. The supporting fibrovascular core often contain few plasma cells and lymphocytic infiltrate[44].

Immunohistochemistry

Sialadenoma papilliferum is immunoreactive for Cytokeratin, CEA, EMA for luminal cells and basal cells show positivity for Vimentin, Cytokeratin and Smooth Muscle Actin[46].

Inverted ductal papilloma

It is a rare type of the ductal papilloma, most frequently arises from minor salivary gland with high predilection towards lip and buccal mucosa, rarely the tumor may arises from palate and floor of mouth[44].

Inverted ductal papilloma have got a male predilection and affects the age group ranging from 28 to 77 years. Clinically inverted ductal papilloma presents as a submucosal painless nodular swelling with a central punctum.

Grossly the tumor is well circumscribed approximately measuring 0.5 to 1.5 cm in diameter, occasional area showing cystic changes[44].

Microscopically the dilated ductal structure shows papillary infolding with fibrovascular core, which is lined by non-keratinized stratified squamous epithelium. No cellular atypia and mitotic figures are seen.

Immunohistochemistry

The tumor is positive for Pancytokeratin, Epithelial Membrane Antigen, CEA and negative for S100, SMA, Vimentin[47].

Cystadenoma

It is a rare benign epithelial tumor characterized by proliferation of benign ductal epithelial cells resulting in multicystic growth pattern[48]. Previously this entity was considered to be reactive cystic hyperplasia; however in recent days it is considered to be a proliferative neoplasm. Cystadenoma affects both major and the minor salivary glands of the oral cavity. The mean age of presentation is 57 years with a female predominance[49].

Cystadenoma clinically presents as a slow growing, painless, cystic mass usually measuring 1cm in diameter which clinically resemble mucocele.

Grossly it is a well circumscribed tumor mass with or without fibrous capsule, cut surface shows multiple cystic cavity or single large cyst.

Microscopically the tumor shows numerous cystic spaces and these cystic spaces are separated by dense fibrous stroma. These cystic spaces are lined by cuboidal or columnar epithelium which may be thrown into papillary infoldings in some cases where they are called as Papillary cystadenoma. Occasionally apocrine, squamous, mucinous and oncocytic differentiation are also noted at focal places[50]. The cystic spaces are filled with eosinophilic proteinaceous material. Also seen are psammoma bodies and tyrosine rich crystals within the secretions. The variants of cystadenoma are Mucinous cystadenoma and Oncocytic cystadenoma.

Differential diagnosis of Cystadenoma is salivary duct cyst, Polycystic disease, Low grade mucoepidermoid carcinoma, Papillary variant of acinic cell carcinoma and Cystadenocarcinoma[51].

Mucoepidermoid carcinoma

Mucoepidermoid carcinoma is a malignant epithelial neoplasm composed of proliferation of mucous secreting cells, intermediate cells and epidermoid cells.

Mucoepidermoid carcinoma is the most common malignant salivary gland neoplasm that occurs in adult and in children with the mean age of patient presentation being 45 years and a slight higher predilection in female population[42]. One of the important etiological factor is history of exposure to radiation and most of the atom bomb survivors of Hiroshima and Nagasaki were affected with Mucoepidermoid carcinoma[52].Tumor is also frequently noted in patients who received radiotherapy for tumors like Leukemia, Retinoblastoma and some Brain tumors[53].

Clinically tumor presents as a painless, slow growing tumor mass, which is firm in consistency; were as the high grade tumors have rapidly growing tendency which is associated with complains of dysphagia, pain associated with facial nerve palsy[43].

Grossly the tumor is partially encapsulated, well circumscribed tumor, firm to hard in consistency, occasionally shows cystic spaces filled with brownish or mucoid material. High grade tumors may show areas of haemorrhage and necrosis[43].

The tumor is composed of three population of cells, the squamous cells, intermediate cells and mucous cells which are arranged in nests admixed with

haphazardly dispersed mucin filled cystic spaces. The stroma is sclerotic with inflammatory cell infiltrate. Occasional cases show extravasation of mucin[49].

Mucoepidermoid carcinoma can be divided into low grade, intermediate grade, high grade.

Low grade mucoepidermoid carcinoma is mainly composed of numerous mucous filled cystic spaces line by mucous cells admixed with solid sheets of intermediate cell.

Some of the cystic cavity may show papillary infoldings, cellular pleomorphism and mitotic figures are rare in low grade tumors. Occasional tumor may show squamous and clear cell differentiation[54].

Intermediate mucoepidermoid carcinoma is predominantly composed of intermediate cells and epidermoid cells, which are usually arranged in sheets and nests. The tumor nests are admixed with few scattered cystic spaces which are lined by columnar cells and mucous secreting cells. There is moderate amount of nuclear pleomorphism and focal areas in tumors may show invasion.

High grade mucoepidermoid carcinoma predominantly is composed of epidermoid cells with few scattered intermediate cells arranged in sheets, nests, showing highly pleomorphic cells, with increased mitotic activity. High grade tumors exhibit marked infiltration with areas showing necrosis. Perineural and lymphovascular invasion is present[55].

It has been reported that in rare conditions Mucoepidermoid carcinoma can arise from Warthin`s tumor and Pleomorphic adenoma[56].

Tumor cells show positivity for Pancytokeratin, variable staining for S100, EMA, CEA. P63 may be positive for epidermoid cells, intermediate cells and clear cells[57].

Differential diagnosis of Mucoepidermoid carcinoma is Cystadenocarcinoma and Necrotizing Sialometaplasia[58].

Adenoid cystic carcinoma

Adenoid cystic carcinoma is otherwise called Cylindroma, Adenoepithelioma. It is a invasive malignant neoplasm of salivary glands composed mainly of epithelial and myoepithelial cells in various morphological growth pattern like cribriform, solid, tubular[42].

Clinically the tumor occurs at the peak age group between 5^{th} and 7^{th} decade with female predominance[59]. The tumors most commonly affects the major salivary gland like parotid, submandibular gland and rarely sublingual gland. Adenoid cystic carcinoma is also reported in other sites like lacrimal glands[60], esophagus, trachea, bronchus[61], uterine cervix, prostate and ovary.

The tumors are slow growing, infiltrating masses, which are usually painful and can induce cranial nerve lesions and facial nerve palsy[62]. At rare instant the tumor may show metastasis as a presenting manifestation[63].

Macroscopically the tumors are well circumscribed but rarely encapsulated, solid tumor mass, the cut surface of the tumor is grey to tan in color.

Microscopically the tumor cells are arranged in different morphological growth patterns like cribriform, tubular, solid, and mixed pattern. The most common pattern is cribriform pattern which is composed of numerous pseudocystic spaces which are filled with hyalinized eosinophilic material. In tubular pattern bilayered epithelium is made up of, the inner ductal epithelial cells and the outer myoepithelial cells. Occasional cases show squamous, oncocytic and sebaceous metaplasia[64].

The least common variant is the sloid variant composed of islands of basaloid cells admixed with few ductal epithelial cells. The stroma is fibrous. Comedo necrosis and perineural invasion is common in Adenoid cystic carcinoma. Immunohistochemically, the epithelial cells are strongly positive for Cytokeratin, CEA, EMA. The myoepithelial cells are positive for P63, Calponine, Actin, S100 protein[65].

Differential diagnosis of Adenoid cystic carcinoma is Polymorphous low grade adenocarcinoma, Basaloid squamous cell carcinoma, Epithelial-myoepithelial carcinoma[66]

Acinic cell carcinoma

It is the malignant epithelial tumor of salivary gland, at focal places showing seroacinar cell differentiation[42]. Acinic cell carcinoma accounts about

3 to 6% of salivary gland neoplasm. Most commonly affect major salivary gland, the parotid accounting about 80% to 90%. The tumor is predominantly seen in female population with a wide range of age distribution between 30 to 90 years.

Clinically patients present with mobile mass, usually painless, slow growing; occasionally tumors show nodularity[67]. Some of the cases may show facial nerve involvement[68].

Grossly the tumor is circumscribed, round to oval, lobulated, firm mass approximately measuring < 3cm in diameter. The cut surface of the tumor is gray white to yellow in color with focal areas showing cystic degeneration[69].

Microscopically Acinic cell carcinoma exhibit a wide range of cellular heterogeneity and morphological diversity which result in numerous histological variants of tumors. They also show wide range of varying architectural growth patterns and cell types with features of seroacinar differentiation[69].

Among this the most common type of cells that we see are acinar cells. The acinar cells are round to polygonal in shape, which are uniformly arranged with a round, basophilic nuclei, typically located at the periphery and abundant pale to basophilic cytoplasm. Acinar cells are composed of zymogen granules, which shows positivity for PAS[69].

Intercalated duct cells are cuboidal in shape with centrally located nuclei and eosinophilic cytoplasm which line the duct like structure. The non specific

glandular cells are polygonal in shape with a large, vesicular nuclei and amphophilic cytoplasm.

Acinic cells exhibit a variety of growth patterns - microcystic, solid, follicular and papillary pattern. The microcystic pattern is the most common pattern which is also called as lattice like pattern because of the presence of numerous cystic spaces within the tumor. In this type the acinar cells are admixed with vacuolated cells and intercalated ductal cells[69].

Occasionally the tumors shows intracystic papillary proliferation, and hobnailing pattern. One of the rare variant is the follicular variant composed of multiple cystic spaces lined predominantly by intercalated ductal cells. The cystic spaces contain homogenous proteinaceous material[70].

The stroma is made up of delicate fibrovascular tissue. Occasionally tumors show psammoma bodies and lymphocytic infiltrate with germinal centre formation.

Acinic cell carcinoma are immunoreactive for Cytokeratin, Carcinoembryonic antigen and COX-2 [71].

Differential diagnosis of Acinic cell carcinoma is Papillary cystadenocarcinoma of salivary gland, Mucoepidermoid carcinoma and Metastatic granular renal cell carcinoma.

Polymorphous low grade adenocarcinoma

Polymorphous low grade adenocarcinoma (PLGAC) is the second most common malignant neoplasm of minor salivary gland[72].

The tumor is characterized by diverse morphological features, uniform cellular features with an infiltrating growth pattern and a low metastatic tendency.

The tumors usually occur with the mean age of 59 years with female predominance. These tumors also show ethnic predilection towards black population[43].

Polymorphous low grade adenocarcinoma is a slow growing, painless mass, most commonly involve the palate, cheek and upper lip. Some of the tumors show ulceration of the surface[73]. Occasional cases of Polymorphous low grade adenocarcinoma may be associated with Carcinoma ex-pleomorphic adenoma[74].

Grossly the tumor is well circumscribed, approximately measuring 0.4 to 6cm in diameter which is tan to gray in color with an infiltrating margin.

Microscopically the tumor cells exhibit variable growth patterns like solid, tubular, fascicular, cribriform and papillary growth pattern. The tumor cells are uniform which are small to medium in size with a round to oval nuclei, dispersed fine chromatin, inconspicuous nucleoli and abundant eosinophilic cytoplasm.

The stroma is hyalinized or mucoid. Some of the tumors show psammoma bodies and tyrosine rich crystalloids[75].

The tumor cells are immunoreactive for Cytokeratin, Epithelial membrane antigen, S100and Vimentin[76].The proliferative activity of the tumor cells can be identified using Ki67, which is usually low for Polymorphous low grade adenocarcinoma.

Differential diagnosis:

Differential diagnosis of Polymorphous low grade adenocarcinoma is Pleomorphic adenoma and Adenoid cystic carcinoma[77].

Epithelial – Myoepithelial carcinoma

Epithelial-myoepithelial carcinoma can also be called as Glycogen rich adenocarcinoma, Clear cell adenoma or Tubular carcinoma[78].

It is a rare malignant neoplasm usually forms duct like structure lined by double layered epithelium; the inner ductal epithelium and the outer myoepithelium. The tumor most commonly seen with the mean age of 60 years with female predominance [79].

The tumor most commonly affect the parotid in 75% of cases, and submandibular gland in 10-12% of cases. Clinically the tumors present as a slow growing, painless mass rarely present with facial nerve palsy[80].

Grossly the tumor is well defined, nodular, multilobular swelling measuring 2 to 8 cm in diameter, which is firm in consistency. The cut surface of the tumor is gray white to yellow in color with cystic areas [81].

Microscopically the tumor is composed of epithelial and myoepithelial cells which form double layered ductal structures, which contains proteinaceous material.

The luminal cells are cuboidal to columnar with centrally located round to oval nuclei and eosinophilic cytoplasm.

The abluminal cells are large, polygonal, spindle in shape with vesicular, eccentrically placed nuclei with clear cytoplasm, which are located at the periphery surrounding the luminal cells. Some of the tumor cells are arranged in sheets and nesting pattern. Often the stroma is fibrous surrounding the tumor cells. The stroma may also be Myxoid and hyalinized.

Some of the tumor cells show sebaceous differentiation and oncocytic differentiation[82]. Cellular atypia is minimal, mitotic figures are usually rare 2-3/10HPF. Minority of the tumor cells may show infiltrative growth pattern and perineural invasion[83].

Immunohistochemistry

Epithelial- myoepithelial carcinoma composed of ductal cells and myoepithelial cells. The ductal cells are strongly positive for Cytokeratin and

CAM5.2.The Myoepithelial cells are positive for P63, S100, Vimentin, Calponine, Glial Fibrillary Acidic Protein.

Differential diagnosis of Epithelial-myoepithelial carcinoma is Pleomorphic adenoma, Myoepithelial carcinoma, Adenoid cystic carcinoma, Polymorphous low grade adenocarcinoma.

Clear cell carcinoma (NOS)

Clear cell carcinoma is otherwise called as Adenocarcinoma of clear cell. The tumor is mainly composed of monomorphic population of epithelial cells which exhibit clear cytoplasm.

Clear cell carcinoma is diagnosed when other tumors like Myoepithelial carcinoma, Clear cell oncocytoma and Mucoepidermoid carcinoma exhibiting clear cell feature are excluded[84].

Clear cell carcinoma is a uncommon salivary gland neoplasm, most commonly involve the minor salivary glands of oral cavity. It most commonly occurs between 4^{th} and 7^{th} decade, there is no sex predilection. The tumor clinically presents as a slow growing, painless mass with focal areas showing ulceration[85].

Grossly the tumor is unencapsulated and poorly circumscribed approximately measuring 3 cm in diameter; the cut surface of the tumor is grey white in color and firm in consistency.

Microscopically, the tumor cells are arranged in solid sheets, trabecular and nests; the individual cells are round to polygonal in shape with eccentrically located round nuclei showing granular cytoplasm, inconspicuous nucleoli with abundant clear cytoplasm which is usually positive for PAS. Mitosis is uncommon. A small subset of tumor population may show eosinophilic cytoplasm[86].

Clear cell carcinoma shows variable immunoreactivity for Low molecular weight Cytokeratin and negativity for S100, Calponine and Actin .

Basal cell adenocarcinoma

Basal cell adenocarcinoma synonymously called as Hybrid basal cell adenocarcinoma[87].Basal cell adenocarcinoma has got a similar morphological findings of basal cell adenoma; but it is highly invasive tumor with potent metastatic potential[88].

Majority of the Basal cell adenocarcinomas arise denovo but some cases arise from preexisting Basal cell adenoma[89]. Basal cell adenocarcinoma is a rare salivary gland tumor most commonly affects the major salivary glands, the parotid and submandibular gland[90]. There is no gender predilection; peak incidence ranges between 6^{th} and 7^{th} decade.

Tumor clinically presents as long standing painless mass. Occasional cases may present as painful mass.

Basal cell adenocarcinoma ranges between the size of 2 to 3.5 cm in diameter; it is usually a unencapsulated tumor mass with focal areas showing invasion to the adjacent tissue .

Microscopically, the tumor cells are arranged in solid sheets, trabecular, tubular, membranous patterns with peripheral palisading of the tumor nests. Basal cell carcinoma exhibits two distinct population of cells, the dark basaloid cells and large pale cells.

The basaloid cells are usually arranged in solid and membranous pattern. The large pale cells are usually arranged in ductal structure. The tumor cells exhibit mild nuclear pleomorphism which is virtually indistinguishable from basal cell adenoma. The tumor shows extensive areas of necrosis. Mitosis is usually 4/10 HPF. The tumor commonly shows extensive vascular invasion.

Immunohistochemistry

Basal cell adenocarcinoma is composed of both ductal and myoepithelial cells. The ductal cells are positive for Cytokeratin, focal positivity is noted in Epithelial Membrane Antigen, CEA. The myoepithelial cells are positive for SMA, S100, Vimentin. KI-67 index is higher in Basal cell adenocarcinoma than in Basal cell adenoma[91].

Differential diagnosis

Basal cell adenocarcinoma should be differentiated from basal cell adenoma, Adenoid cystic carcinoma, Small cell carcinoma, Large cell Neuroendocrine carcinoma[90].

Sebaceous carcinoma

Sebaceous carcinoma is synonymous with Sebaceous adenocarcinoma. Sebaceous carcinoma is a malignant epithelial tumor composed of sebaceous cells with varying degree of nuclear pleomorphism and invasion[92].

Sebaceous carcinoma is a rare tumor of salivary gland most commonly affecting the major salivary glands usually the parotid, sublingual and submandibular gland[93].

Sebaceous carcinoma usually presents with bimodal age distribution, the peak incidence is seen in third and seventh decade.

Tumor typically present as slow growing tumor mass associated with pain and often shows facial nerve involvement[94].

Grossly the tumor ranges from 0.5 to 8.5 cm in diameter, which is usually well circumscribed; cut surface of the tumor is gray white in color.

Microscopically the tumor cells are arranged in sheets and nests with variable degree of nuclear pleomorphism. The tumor may also exhibit numerous duct like structures admixed with cystic spaces. The tumor cells may also exhibit squamous and basaloid differentiation.

Sebaceous lymphadenocarcinoma

Sebaceous lymphadenocarcinoma is a rare malignant salivary gland neoplasm which is the counter part of benign tumor Sebaceous lymphadenoma.

The tumor presents between the age group of 50 to 70 years with male predominance.

Clinically the tumor presents as a painless tumor mass.

Grossly the tumor is well circumscribed which is yellow to gray in color with focal areas showing tumor infiltration[94].

Microscopically, the tumor shows characteristic feature of sebaceous adenoma intermingled with carcinomatous component showing cellular pleomorphism with increased mitotic activity[94].The tumor may arise from lymphadenoma as well. The tumor may also show xanthogranulomatous inflammation.

Cystadenocarcinoma

Cystadenocarcinoma is the malignant counterpart of benign tumor cystadenoma. It is a rare low grade invasive salivary gland neoplasm characterized by numerous cystic spaces with papillary projections, so it is also called as papillary cyst adenocarcinoma[95]. The tumor is also called as malignant papillary cystadenoma, and Low grade papillary adenocarcinoma[96]. About 65% of tumors affect the major salivary glands most commonly the Parotid.

The remaining 35% of tumors affect the minor salivary gland. About 70% of tumors are seen with the mean age of over 50 years, there is no sex predilection[97].

Clinically the tumor presents as a slow growing tumor mass; occasional cases may show tumor infiltrate into nasal cavity or in maxillary sinuses.

Grossly the tumors are partially circumscribed with the average size of 2.2 to 2.4 cm in diameter. Cut surface of the tumors reveal multiple cystic spaces filled with brownish to mucoid material.

Microscopically cystadenocarcinoma resembles the benign tumor cystadenoma, however cystadenocarcinoma shows infiltration into the surrounding tissue.

Cystadenocarcinoma shows multiple cystic spaces lined by the cuboidal Or columnar cells with mild to moderate nuclear pleomorphism with very few mitotic figures[97].

About 75% of tumor shows papillary growth pattern called as papillary cystadenocarcinoma. Some of the tumors may show marked nuclear pleomorphism with prominent nucleoli[98].

Cystadenocarcinoma is usually immunoreactive for Pancytokeratin, EMA and Carcinoembryonic Antigen[99].

Differential diagnosis:

Papillary Cystadenocarcinoma should be differentiated from, Cystadenoma, Low-grade Mucoepidermoid carcinoma, Polymorphous low grade carcinoma, Papillary variant of Acinic cell carcinoma, Salivary duct carcinoma, Metastatic papillary thyroid carcinoma.

Low grade cribriform cystadenocarcinoma

Low grade cribriform cystadenocarcinoma is a variant of Cystadenocarcinoma which was categorized in 2005 WHO classification. It is a rare malignant salivary gland neoplasm[100]. Most commonly affects the parotid gland, occasionally involve the submandibular and minor salivary gland. Most of the patients are in 6th and 7th decade with female predominance[100].

Low grade cribriform cystadenocarcinoma is a well circumscribed neoplasm without a capsule. The tumor is mainly composed of multiple cystically dilated duct like spaces. The spaces are lined by cells which are usually multilayered and form micropapillary projections, tufting and cribriform pattern[101].

These proliferating ductal cells are usually cuboidal and polygonal cells with dispersed chromatin and a small nucleoli.

Cellular pleomorphism is usually absent with very minimal mitotic figures and absence of necrosis. Some of the tumors may show microinvasion. No perineural or vascular invasion noted[102].

Mucinous Adenocarcinoma

Mucinous adenocarcinoma is otherwise called colloid carcinoma. It is a malignant epithelial tumor characterized by clusters of malignant epithelial cells floating in a pool of mucin.

Mucinous carcinoma present between the age group of 42 to 86 years with no obvious sex predilection. Tumors most commonly affect the minor salivary glands particularly the palate and can also affect submandibular and sublingual glands[103] The tumor clinically presents as a slow growing tumor mass, occasional cases may show ulceration.

Grossly the tumor measures 2 to 7 cm in diameter. External surface of the tumor is bosselated; cut surface of the tumor is grey white in color with multiple cystic spaces filled with gelatinous mucinous material.

Microscopically the tumor cells are arranged in solid nest and duct like structure in variable size. These clusters of tumor cells float in the pool of mucin which is separated by fibrous septa. The epithelial cells may be cuboidal or columnar with centrally placed hyperchromatic nuclei in a clear cytoplasm, infrequent mitosis are also noted.

Immunohistochemistry:

Mucinous adenocarcinoma is strongly positive for Pancytokeratin. Tumor usually negative for Smooth Muscle Actin, Estrogen and Progesterone[104].

Oncocytic carcinoma

Oncocytic carcinoma it is a rare malignant neoplasm characterized by proliferation of oncocytes with an infiltrative nature. These tumors are also

called as Oncocytic adenocarcinoma, Malignant oncocytoma, Malignant oxyphilic adenoma .

These tumors usually arises denovo and also arises from the persisting oncocytoma.The tumor most commonly is seen in elderly individuals, with a mean age of about 60 years with a male predominance[43].

Parotid is the most commonly affected organ in 80% of cases and also seen in submandibular gland, intraoral and upper respiratory tract.

Patient complaints as a slow growing painless mass. But some rare cases present with complaints of painful mass with facial nerve palsy.

Grossly Oncocytic carcinoma is a variably capsulated tumor mass, may be single or multifocal. Cut surface is grey brown to tan, firm in consistency with focal areas may show necrosis.

Microscopically the tumor cells are arranged in sheets, nests and occasionally show ductal differentiation. The individual tumor cells are round to polygonal in shape with a centrally placed vesicular nuclei in a granular eosinophilic cytoplasm. The tumor also shows frequent mitotic figures with focal areas showing necrosis. There is also evidence of perivascular and neuronal infiltration.

Ki67 index is useful in differentiating oncocytoma from oncocytic carcinoma which have a high proliferative index[105].

Salivary duct carcinoma

Salivary duct carcinoma is a aggressive adenocarcinoma which have a similar features of ductal carcinoma of breast [106].Salivary duct carcinoma accounts approximately about 2% of all salivary gland neoplasms[106].The peak incidence is seen between the age group of 6^{th} to 7^{th} decade with male predominance.

The tumor most commonly affects the parotid gland but is also noted in submandibular and minor salivary gland. Salivary duct carcinoma arises denovo or develops as a malignant component of Carcinoma ex pleomorphic adenoma[107].

The tumor clinically presents as a rapid growing painful mass, associated with facial nerve palsy.

Grossly the tumor is unencapsulated, solid mass, approximately measuring 6cm in diameter. Cut surface of the tumor is solid with focal areas showing necrosis and cystic changes[43].

Microscopically there is a mixture of two different components, the intraductal and invasion component. In intraductal component there are large, multiple dilated ductal structures showing papillary, cribriform or solid architecture with central area often showing comedo necrosis. Focal areas of tumor also show psammoma bodies and squamous differentiation with keratinization.

In invasive component, the tumor cells are arranged in cords and irregular glands with a desmoplastic stroma. The individual cells are large with highly pleomorphic large nuclei with coarse chromatic and a prominent nucleoli in an abundant eosinophilic cytoplasm.

There is increased mitotic activity along with apocrine metaplasia. The tumor also shows lymphovascular invasion.

The tumor cells show strongly immunoreactivity for Her2neu, Cytokeratin, EMA and CEA[108.]

Differential diagnosis of salivary duct carcinoma is Adenocarcinoma (NOS), Metastatic adenocarcinoma and Squamous cell carcinoma[43].

Adenocarcinoma (NOS)

Adenocarcinoma is a malignant salivary gland tumor which shows ductal differentiation but lacking glandular diagnostic features of other defined tumors categoriesed[42].

The tumor is most commonly seen in elderly individuals between sixth and seventh decade with female predominance. Parotid is most commonly affected major salivary gland. Patient clinically presents with a painless solitary mass and some of the tumors are fixed to the underlying soft tissue[109].

Grossly the tumors show infiltrating borders and focally circumscribed tumor mass. Cut surface of the tumor is gray white in color, firm in consistency with areas of necrosis and haemorrhage.

Microscopically the tumors are characterized by variable glandular or ductal structures with variable growth pattern; Some of the architectural patterns are solid, papillary, sheets, trabecular, cords and cribriform pattern, lacking the characteristic histological features of recognized salivary gland neoplasms.

Small foci of tumors may show features of Adenoid cystic carcinoma, Epithelial- myoepithelial carcinoma and Cystadenocarcinoma.

The tumors show invasion into the adjacent salivary gland parenchyma, with areas of necrosis, perineural and vascular invasion. Adenocarcinoma (NOS) can be graded into low grade, intermediate grade, high grade based on the gland formation, cellular atypia, mitotic index and necrosis.

Low grade tumors are distinguished from high grade based on the increased nuclear pleomorphism, high mitotic figures, extensive areas of necrosis and perineural and lymphovascular invasion[110].

Immunohistochemistry:

The tumor cells are usually positive for Pancytokeratin, Negative for S100, SMA and Calponine[69].

Differential diagnosis:

Adenocarcinoma (NOS) is based on exclusion of other gland forming carcinomas of salivary gland. The differential diagnosis are Polymorphous low grade adenocarcinoma, Epithelial-myoepithelial carcinoma, Salivary duct carcinoma, Cystadenocarcinoma and Metastatic adenocarcinoma[69].

Myoepithelial carcinoma

Myoepithelial carcinoma is a rare malignant neoplasm of salivary gland, which is the malignant counterpart of Myoepithelioma and it accounts about < 0.4% of salivary gland tumors[111].

Myoepithelial carcinoma is composed of tumor cells showing myoepithelial differentiation with cellular pleomorphism, infiltrative growth pattern and metastatic potential[112].

The mean age of presentation is 55 years, there is no gender predilection. Tumor predominantly involves parotid gland in 75% of cases and also involves minor salivary gland preferentially in palate, 25%[112].

Myoepithelial carcinoma usually arises from the preexisting benign lesion like Myoepithelioma, Pleomorphic adenoma but can also arises denovo.

Grossly it is a unencapsulated solid, nodular tumor mass. Cut surface of the tumor is grey white to tan in color. Focal area showing cystic degeneration filled with gelatinous material[113].

Microscopically, the tumor cells are arranged in various morphological patterns like reticular, trabecular, sheet-like and lace–like growth patterns, similar to Myoepithelioma. Myoepithelial carcinoma also shows numerous cell types consisting of spindle, epithelioid, plasmacytoid and clear cell type. The stroma is hyalinized or Myxoid .The tumor often undergoes myxoid degeneration.

Immunohistochemistry

Myoepithelial carcinomas are usually immunoreactive for P63, CK14, S100. Differential diagnosis of Myoepithelial carcinoma is Myoepithelioma. It can be differentiated based on the pleomorphism of the cells, increased mitotic activity and perineural invasion.

Carcinoma ex pleomorphic adenoma

Carcinoma ex pleomorphic adenoma is a malignant epithelial tumor usually arising from a benign mixed tumor or recurrent pleomorphic adenoma. The incidence of carcinoma ex pleomorphic adenoma ranges from 0.9 to 14% of salivary gland neoplasm[81].

Parotid gland is most commonly affected in 82 % of cases, but tumor may also occur in other regions like submandibular and sublingual glands[114].

Most commonly affected age group is between 6th to 7th decade. Patient clinically presents as rapidly growing painless tumor mass; but in rare cases the tumor is painful, fixed, ulcerated and associated with facial nerve palsy. Recurrence and metastasis is commonly noted[114].

Grossly the tumor is poorly circumscribed with intensive infiltration to the surrounding tissue; approximately the size ranges from 1.5 to 25cm in greatest diameter; cut surface of the tumor may show areas of necrosis, hemorrhage and cystic regeneration[115].

Microscopic finding of carcinoma ex pleomorphic adenoma requires presence of both benign mixed tumor and malignant carcinomatous component. The tumor usually shows infiltrative growth pattern with high nuclear pleomorphism, increased mitotic figures and extensive areas of tumor necrosis.

The malignant component is dominated most frequently by Poorly differentiated adenocarcinoma (NOS) or salivary duct carcinoma. But occasionally Polymorphous low grade adenocarcinoma, Mucoepidermoid carcinoma, Adenoid cystic carcinoma or Myoepithelial carcinoma may be noted as a malignant component[116].

Differential diagnosis of Carcinoma ex pleomorphic adenoma is Salivary duct carcinoma and Carcinosarcoma.

Carcinosarcoma

Carcinosarcoma is a malignant mixed tumor composed of both carcinomatous and sarcomatous component[42]. The tumor is also called as malignant mixed tumor which accounts for <0.2% of malignant tumors of salivary gland.

The tumor most commonly involve parotid, submandibular and palate. The mean age of presentation is 58years.The tumor most commonly arises denovo but in some cases the tumor may arise from recurrent pleomorphic adenoma[117].

Carcinosarcoma clinically presents as a painful mass, usually fixed to the underlying tissue with areas of ulceration. Some of the tumors may show facial nerve palsy and regional lymphnode involvement.

Microscopically Carcinosarcoma is a biphasic tumor composed of both carcinomatous and sarcomatous components. Most of the tumors exhibit prominent sarcomatous element mainly the chondrosarcoma, osteosarcoma, fibrosarcoma. The most common carcinomatous component are undifferentiated carcinoma and Poorly differentiated adenocarcinoma.

Occasionally tumors shows carcinomatous element such as Salivary duct carcinoma and Adenoid cystic carcinoma[118].

Metastasizing pleomorphic adenoma

Metastasizing pleomorphic adenoma is a rare salivary gland tumor which is also called as Malignant mixed tumor. The tumors are histologically benign looking Pleomorphic adenoma which manifest with local or distant metastasis [42].

The mean age of presentation of tumors are 33 years with no obvious sex predilection. Most of the tumors are seen in parotid but some tumors are also distributed in submandibular gland and palate[119].

The tumors usually arise from the background of longstanding Pleomorphic adenoma or multiple recurrent pleomorphic adenoma. The mean

age of development of metastasizing pleomorphic adenoma from a recurrent or longstanding pleomorphic adenoma is 16 years[120]

Microscopically the tumors are similar to benign pleomorphic adenoma with local or distant metastatic potential. Some of the tumors shows nuclear pleomorphism and mitotic figures. Although there is no evidence of frank malignancy.

Immunohistochemistry:

Immunohistochemistry which is similar to conventional pleomorphic adenoma; the luminal cells are positive for CK3, CK6, CK10 and CK13. The myoepithelial cells are positive for P63, Cytokeratin, S100, Vimentin and SMA.

Squamous cell carcinoma

Squamous cell carcinoma is a primary malignant epithelial tumor, which is mostly confined to major salivary gland parotid.

The tumors are mainly composed of epidermoid cells which produces keratin. In addition, it is essential to exclude the tumors that can metastases from overlying skin, external auditory meatus and upper digestive tract.

Primary Squamous cell carcinoma of the major salivary glands are rare. The tumors which accounts less than 1% of salivary gland tumors.

The tumors most commonly seen with the mean age group of 60 to 65 years with male predominance. Some of the tumors are strongly associated with previous radiation exposure for long period of time[121].

Patient clinically presents as a painless, rapidly enlarging tumor mass. Some tumors are painful, fixed to the underlying tissue associated with facial nerve palsy.

Grossly the tumor is large, firm mass with evidence of infiltration to the adjacent tissue. The cut surface of the tumor is gray white with areas of necrosis.

Microscopically the tumor is similar to that of Squamous cell carcinoma of the head and neck, which can be classified into well differentiated, moderately differentiated and poorly differentiated tumors[43]. Some tumors may show ductal dysplasia and squamous metaplasia. The tumors usually show perineural and local invasion.

Differential diagnosis

The tumor should be differentiated from Metastatic Squamous cell carcinoma, Mucoepidermoid carcinoma, Salivary duct carcinoma**.**

Small cell carcinoma

Small cell carcinomas are extremely rare malignant epithelial tumors showing small cells with scanty cytoplasm, fine nuclear chromatin and inconspicuous nucleoli.

Most of the small cell carcinomas exhibit neuroendocrine differentiation. The tumors are more commonly seen in male population in 5th and 7th decade[122]. The tumors most commonly affect the parotid and rarely involve the submandibular and minor salivary gland.

Clinically, the tumors present as painless rapidly growing masses, with cervical lymphadenopathy and facial nerve palsy[123].

Grossly the tumors are firm, grey white in color, poorly circumscribed tumor masses often infiltrative into the adjacent tissue. The tumors are commonly accompanied with necrosis and haemorrhage.

Microscopically small cell carcinomas are characterized by sheets, cords, nests of anaplastic small sized tumor cells in a variable amount of fibrous stroma.

Regardless of cellular size, nuclear chromatin is finely granular with inconspicuous nucleoli. Cell borders are ill defined with nuclear molding. Numerous mitotic figures are present with extensive areas showing necrosis, vascular and perineural invasion.

Immunohistochemistry

Most of the small cell carcinomas are positive for Neuron Specific Enolase (NSE), Chromogranin, Synaptophysin, Neurofilament and about three fourth of the tumors are immunoreactive for Cytokeratin 20.

Large cell carcinoma

Large cell carcinomas are high grade malignant salivary gland tumors composed of large Pleomorphic cells with abundant cytoplasm[42].

Absence of component of any other specific tumor type should be confirmed before making the diagnosis of salivary gland large cell carcinoma. Rarely these tumors exhibit neuroendocrine differentiation called Large cell neuroendocrine carcinoma[124] .

The tumors are most commonly seen in elderly individuals with mean age of 60 years. No obvious sex predilection is noted. The tumors most commonly involve the parotid; the tumor clinically presents as a rapidly growing fixed mass which is firm in consistency. Commonly associated with facial nerve palsy and cervical lymphnode involvement.

Grossly the tumor is poorly circumscribed, solid tumor which is tan to white in color. Focal areas may show necrosis and haemorrhage.

Microscopically the tumor cells are arranged in sheets and trabecular pattern which are composed of large Pleomorphic cells with abundant eosinophilic cytoplasm. The nuclei are polygonal in shape with prominent nucleoli and coarse chromatin. The cells are bizarre with well defined cell borders. The stroma is fibrous[69]. Mitotic figures are frequent with prominent perineural and vascular invasion.

Immunohistochemistry

Large cell carcinoma are positive for Cytokeratin and EMA Large cell neuroendocrine carcinoma are positive for Chromogranin, Synaptophysin, Neuron – Specific Enclose (NSE)

Differential diagnosis

Large cell carcinoma should be differentiated from Metastatic malignant melanoma, Anaplastic large cell lymphoma, Metastatic undifferentiated carcinoma[125].

Lymphoepithelial carcinoma

Lymphoepithelial carcinoma is also called as undifferentiated carcinoma having lymphoid stroma[126].Lymphoepithelial carcinoma shows histological features identical to that of nasopharyngeal origin.

Most of the lymphoepithelial carcinomas arise denovo or from preexisting lymphoepithelial sialadenitis. Lymphoepithelial carcinomas are rare malignant salivary gland tumors although higher incidence have been reported in Mangolians[127] and South Chinese population. It is most commonly seen with the mean age of 40 years and has slight female predominance.

The tumor most commonly involves the parotid in 90% of cases, followed by submandibular, sublingual and minor salivary gland. The tumor clinically presents as a rapidly growing firm mass with facial nerve palsy. About 40% of patients also show cervical lymphadenopathy[128].

Grossly the tumors are solid to firm, ranging from 1 cm to 10 cm in diameter. The cut surface of the tumor is well circumscribed, partially encapsulated and typically shows extensive infiltration into the adjacent tissue.

Microscopically the lymphoepithelial carcinoma is characterized by cluster formation of large anaplastic cells enclosing within a prominent sheet of lymphoid cells. Most of the tumor cells often show infiltration into the adjacent salivary gland in lymphoid stroma.

The tumor cells are usually arranged in solid sheets and in trabecular pattern. The tumor cells are large polygonal in shape with vesicular nuclei and a prominent eosinophilic nucleoli with an abundant amphophilic cytoplasm. There is increased mitotic activity and perineural invasion is common.

The tumor cells are positive for Pancytokeratin, EMA and negative for lymphoid markers[129]. P63 shows diffuse positivity and Ki67 labeling index is high.

Differential diagnosis

Metastatic lymphoepithelial carcinoma, Large cell carcinoma, Malignant lymphoma and Lymphadenoma.

Sialoblastoma

Sialoblastoma is a rare aggressive malignant salivary gland tumor usually present at birth[42] .Sialoblastoma is also called as congenital basal cell adenoma, basaloid adenoma and embryoma.

Sialoblastoma most commonly affects the parotid gland and submandibular gland. Most of the tumors are seen within the first decade of life, occasional cases seen in second and third decade of life [130].

Clinically the tumor presents as a painless, firm mass with focal areas showing ulceration and facial nerve palsy. Occasional cases may show coexistence with congenital nevi.

Macroscopically the tumor is partially encapsulated, firm mass ranging from 1.5 to 15 cm in diameter, focal areas in the tumor may show infiltration. Cut surface of the tumor is tan to yellow in color with areas of haemorrhage and necrosis.

Microscopically the tumor is mainly composed of basaloid cells. The individual cells are round to oval nuclei with inconspicuous nucleoli and a scanty eosinophilic cytoplasm.

The cells exhibit variable pleomorphism. The tumor cells are usually arranged in solid sheets, nest and the outer layer shows nuclear palisading. Some of the myoepithelial cells in the tumors may show sebaceous and squamous differentiation[131].The stroma is variable and consists of myxoid tissue, fibrous, cellular fibroblastic areas.

Immunohistochemistry

The tumor cells are usually positive for Pancytokeratin like CK5, CK6, CK7, CK14 and negative for CK20[132]. Myoepithelial cells are positive for SMA, S100 and Calponine.

Differential diagnosis

Sialoblastoma should be distinguished from Basaloid neoplasms like Basal cell adenoma, Basal cell adenocarcinoma and Adenoid cystic carcinoma.

Immunohistochemistry

Most of the salivary gland neoplasms arise from or differentiate towards the same cell lineage like epithelial (ductal and acinar), myoepithelial and basal cell. Similarly each cell can also undergo different metaplastic change which results in overlap at all levels[133].

Salivary gland tumors often show a variety of growth patterns and significant morphological variability which results in the diagnostic difficulties of salivary gland tumors[134]. Although Haematoxylin & Eosin (H&E) staining is the gold standard for diagnosis of salivary gland tumors, immunohistochemistry enhances the accuracy and serves as a helpful tool in cases to investigate the subjects that cannot be assessed by histological examination like nature of cell, differentiation status, cell proliferation and tumor protein expression.

Cell differentiation:

Salivary glands are composed of four types of cells, ductal, acinar, myoepithelial and basal cells. The ductal and acinar cells are called luminal cells; myoepithelial and basal cells are called abluminal cells. All these four cells are usually positive for Pancytokeratin. In addition ductal and acinar cells show positivity for EMA and CEA. The acinar cells also show α- amylase positivity. The myoepithelial cells are positive for CK14, P63, Muscle Specific Actin (MSA), Calponine, Podoplanin[135], Vimentin. S100 protein staining is variable for all four cells in the salivary gland.

Summary of the useful Immunohistochemical markers of salivary gland tumors in general surgical pathology practice[136]

Markers	Positivity in cells of normal salivary gland	Uses and significance for salivary gland tumors
Pan-cytokeratin (CK) [AE1/AE3]	Both luminal and abluminal cells	Epithelial marker; differential diagnosis between myoepithelioma/ myoepithelial carcinoma or "undifferentiated carcinoma" and non-epithelial tumors
Epithelial membrane antigen (EMA)	Luminal cells	Ductal (luminal) cell marker; apical staining pattern; bubbly positive in sebaceous cells
Carcinoembryonic antigen (CEA)	Luminal cells	Ductal (luminal) cell marker
α-Smooth muscle actin (SMA)	Myoepithelial cells	Myoepithelial marker (high specificity, very useful)
Calponine	Myoepithelial cells	Myoepithelial marker (high specificity, very useful)
Muscle-specific actin (MSA)	Myoepithelial cells	Myoepithelial marker (high specificity)
p63	Myoepithelial and basal cells	Myoepithelial marker (note: also positive for basal and squamous epithelial cells)
CK14	Myoepithelial and basal cells	Myoepithelial marker (note: also positive for basal and squamous epithelial cells)

Glial fibrillary acidic protein (GFAP)	Myoepithelial cells (variable)	Myoepithelial marker (low sensitivity); highly positive in pleomorphic adenoma and myoepithelioma
S-100 protein	Variable	Myoepithelial marker (good for screening, low specificity)
Vimentin	Myoepithelial cells	Myoepithelial marker (good for screening, low specificity
Ki-67 [MIB-1]	Few cells	Cell proliferation marker; differential diagnosis between benign and malignant tumors; prognostic factor
P53	Negative	Differential diagnosis between benign and malignant tumors; prognostic factor
HER2/neu	Negative to weakly positive in ductal cells	Highly over expressed in salivary duct carcinoma; diagnosis of non-invasive carcinoma ex pleomorphic adenoma; expected use for molecular targeted therapy
α-Amylase	Acinar cells	Positive in Acinic cell carcinoma (low sensitivity)
Androgen receptor (AR)	Negative	Often positive in salivary duct carcinoma; diagnosis of non-invasive carcinoma ex pleomorphic adenoma;

Renal cell carcinoma/CD10	Negative	Diagnosis for metastatic renal cell carcinoma
Melan A	Negative	Diagnosis for metastatic malignant melanoma
Lymphoid cell marker	Negative	Diagnosis for malignant lymphoma
EBER in situ hybridization	Negative	Positive in lymphoepithelial carcinoma

The role of IHC with regard to cell differentiation

Approximately 70% of salivary gland tumors exhibit myoepithelial differentiation, the tumors that do not differentiate into myoepithelium are considered to be acinar cell differentiation called the Acinar cell carcinoma. The tumors are further classified based on the presence or absence of luminal cell differentiation. The luminal cells always show positivity for EMA and CEA[136].

The myoepithelial cells usually do not demonstrate glandular formation, but occasionally some of the cells which are located around the ductal cells exhibit glandular formations. The myoepithelial cells exhibit various cell morphology like epithelioid, spindle, plasmacytoid and clear cell types. Hence immunohistochemistry analysis is necessary for more accurate diagnosis of tumors that show myoepithelial differentiation[136].

Although several markers are available P63 and Cytokeratin is a reliable marker in identifying the myoepithelial cells; they are not only positive in

neoplastic myoepithelial cells but also positive in basal cell, squamous cells and epidermoid cells of Mucoepidermoid carcinoma. It is also essential to know the staining patterns of different types of myoepithelial cell to a particular marker.

Spindle cell myoepithelium shows diffuse positivity by α-SMA, MSA and Calponine whereas they show only focal positivity in epithelioid and clear cell type of myoepithelial cells. Plasmacytoid myoepithelial cells are Calponine positive but negative for α-SMA[137].

Role of IHC in Salivary gland tumor exhibiting cribriform pattern

The tumors that exhibit cribriform pattern are Adenoid cystic carcinoma and Salivary duct carcinoma. In addition Basal cell adenoma, Pleomorphic adenoma, Epithelial myoepithelial carcinoma, Polymorphous low grade adenocarcinoma, Basal cell adenocarcinoma needs to be differentiated.

a-SMA / Calponine is used to differentiate Adenoid cystic carcinoma from Basal cell adenoma . S100 is a useful marker in identifying Polymorphous low grade adenocarcinoma (PLGAC) from Salivary duct carcinoma (SDC). GFAP is useful in differentiating Pleomorphic adenoma from Polymorphous low grade adenocarcinoma, Basal cell adenoma, Epithelial and myoepithelial carcinoma[136].

Benign and malignant counterpart of salivary gland tumors

Ki67 labeling index is useful in differentiating benign tumors from malignant tumors. Ki67 index is high (>10%) in malignant tumors, which is (<10%) in benign tumors. They are used in differentiating myoepithelioma from myoepithelial carcinoma, Basal cell adenoma from Basal cell adenocarcinoma [138].

Tumors exhibiting clear cell changes

Tumors like Epithelial-Myoepithelial carcinoma, Mucoepidermoid carcinoma, Myoepithelioma, Myoepithelial carcinoma, Acinic cell carcinoma, Oncocytoma, Sebaceous adenoma, Clear cell carcinoma, Metastatic renal cell carcinoma, Malignant melanoma exhibit clear cell differentiation[139].

Initially it is recommended to use myoepithelial markers like Calponine and α-SMA which shows positivity for tumors that arises from myoepithelium like Myoepithelioma, Myoepithelial carcinoma and Epithelial- Myoepithelial carcinoma; EMA can be used to distinguish Epithelial-Myoepithelial carcinoma from Myoepithelioma and Myoepithelial carcinoma which show positivity in the apical portion at the glandular luminal surface.

Metastatic renal cell carcinoma (RCC) and Malignant melanoma can be identified by using RCC, CD10 and Melan-A[140]. However it is difficult to differentiate these tumors only through Immunohistochemistry.

Diagnosis of Specific Tumor Type

Adenoid cystic carcinoma

C-kit show diffuse expression in Adenoid cystic carcinoma, but in recent days its specificity is questionable. Strong MYb immunostaining is a specific and useful diagnostic marker for Adenoid cystic carcinoma. However some Non Adenoid cystic carcinoma also show focal positivity in MYb.

Salivary duct carcinoma:

20% of tumor show diffuse and strong membrane staining for HER2/new. AR and HER2/neu are expected use for molecular targeted therapy[136].

METHODOLOGY

METHODOLOGY

This retrospective and prospective study on salivary gland tumors was carried out in the department of pathology at Karpaga Vinayaga Institute of Medical Sciences, Madhuranthagam from August 2012 to July 2017 for a period of five years. The study was conducted on biopsy and excised specimens of salivary gland tumors received in department of pathology, KIMS. The information regarding the retrospective cases was retrieved from laboratory archives. Institutional Ethics Committee approval was obtained.

All clinical data like age, gender, location of tumors, duration of symptoms was obtained. Routine investigations and radiological examination like X–ray, ultrasound, CT Scan reports were reviewed and documented.

INCLUSION CRITERIA

Patients with Benign and Malignant Salivary gland tumors.

EXCUSION CRITERIA

Patients with inflammatory conditions of salivary gland. Specimens with incomplete records and discordant diagnosis.

SPECIMEN COLLECTION

Gross examination of Biopsy and Excised specimen was carried out in detail. All the biopsy specimens were well fixed in 10% formalin and then processed into paraffin embedded sections and stained with Haematoxylin-Eosin. All the slides were examined under the light microscope by pathologist

for identification of the histomorphological pattern of salivary gland tumors. Special stains like PAS was applied to the sections where ever indicated.

Immunohistochemical markers were also applied, where ever possible, to the tissue sections to enhance the accuracy of diagnosis.

STATISTICAL METHODS

All data were entered in Microsoft excel and managed using SPSS software.

RESULTS

RESULTS

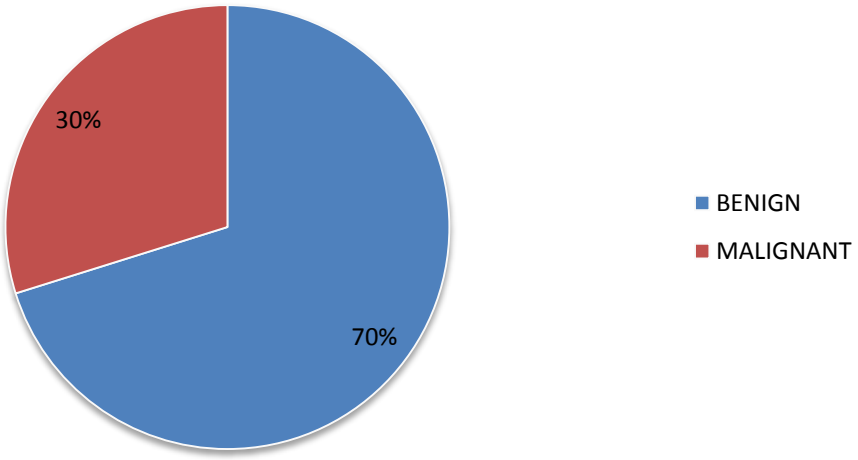
Over a period of five years, from September 2012 to August 2017, we encountered 57 cases of Salivary gland tumors in the present study.

Incidence :

Table 1: Incidence of Salivary gland Tumors

Tumors	No. of. cases	Percentage
Benign	40	70.1%
Malignant	17	29.8%
Total	57	100%

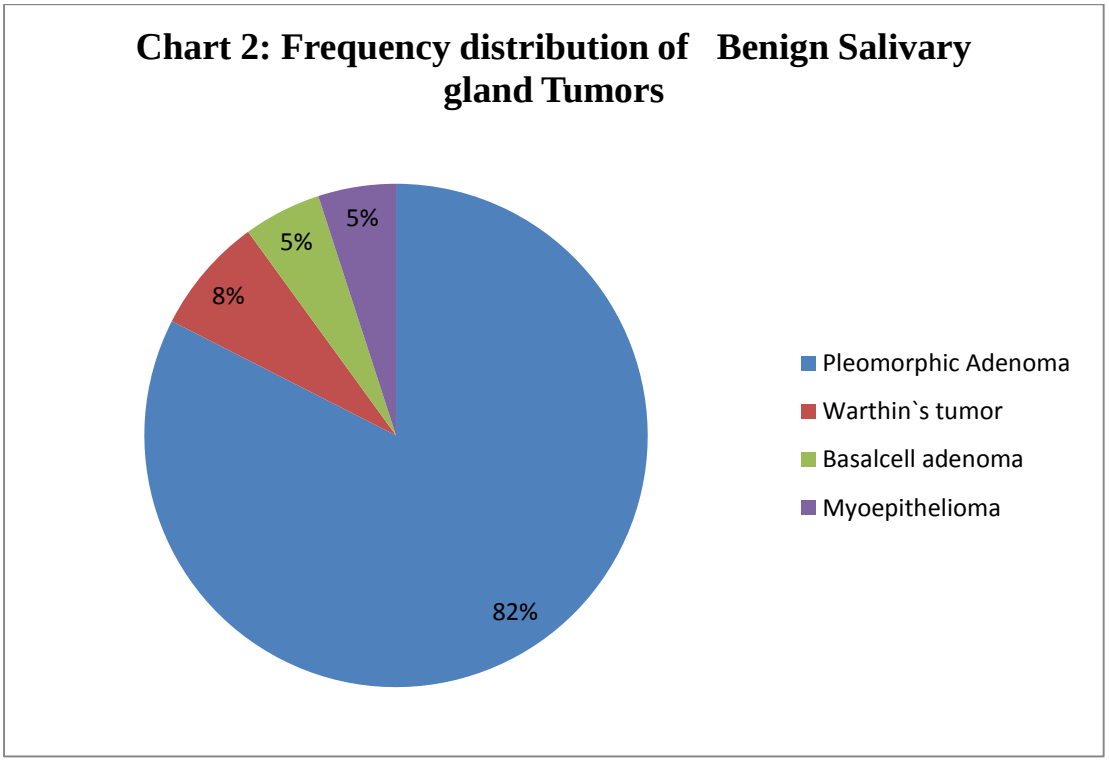
Chart 1: Incidence of Salivary gland Tumors



Out of 57 cases of salivary gland tumors, 40 cases were benign (70.1%) and remaining 17 cases were malignant tumors (29.8%). [Table 1 and Chart 1]

Table 2: Frequency distribution of Benign Salivary gland Tumors

Benign Tumors	No .of .cases	Percentage
Pleomorphic Adenoma	33	82.5%
Warthin`s tumour	3	7.5%
Basal cell adenoma	2	5%
Myoepithelioma	2	5%
Total	40	100%



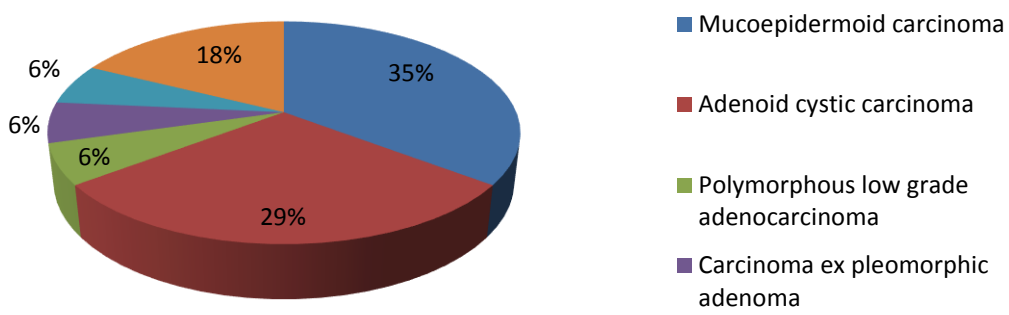
Out of 40 benign tumors 33 were Pleomorphic adenoma (82.5%), 3 were Warthin`s tumor (7.5%), 2 Basal cell adenoma (5%), and 2 Myoepithelioma (5%). [Table 2 and Chart 2].

Pleomorphic adenoma was the most commonly observed benign tumor in the present study.

Table 3: Frequency distribution of Malignant Salivary gland Tumor

Malignant Tumors	No. of cases	Percentage
Mucoepidermoid carcinoma	6	35.2%
Adenoid cystic carcinoma	5	29.4%
Polymorphous low grade adenocarcinoma	1	5.8%
Carcinoma ex pleomorphic adenoma	1	5.8%
Basal cell adenocarcinoma	1	5.8%
Salivary duct carcinoma	3	17.6%
Total	17	100%

Chart 3: Frequency distribution of Malignant Salivary gland Tumor

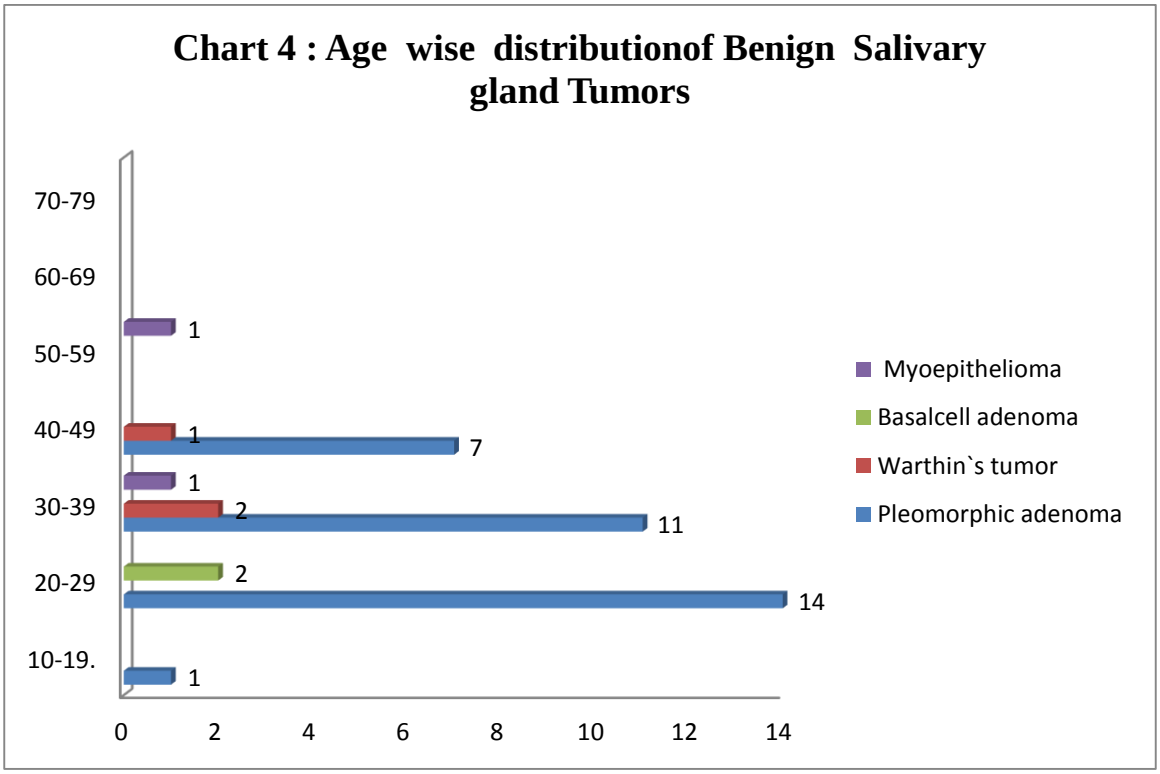


Out of 17 malignant tumors encountered in the present study, six were Mucoepidermoid carcinoma (35.2%), five Adenoid cystic carcinoma (29.4%), one Polymorphous low grade adenocarcinoma (5.8%), one Carcinoma ex-pleomorphic adenoma (5.8%), one Basal cell adenocarcinoma (5.8%) and three were Salivary duct carcinoma (17.6%) [Table 3 and Chart 3]. Mucoepidermoid carcinoma was the most commonly observed malignant tumor in the present study.

Age Incidence:

Table 4: Age wise distribution of Benign Salivary gland Tumor

Name of the benign Neoplasm	Age					
	10-19	20-29	30-39	40-49	50-59	Total
Pleomorphic adenoma	1	14	11	7	-	33
Warthin`s tumor	-	-	2	1	-	3
Basal cell adenoma	-	2	-	-	-	2
Myoepithelioma	-	-	1	-	1	2
Total	1	16	14	8	1	40



The benign tumors were observed widely in the age group between 20 and 40 years, with the mean age of 31 years. Most commonly observed benign salivary gland tumor was Pleomorphic adenoma.

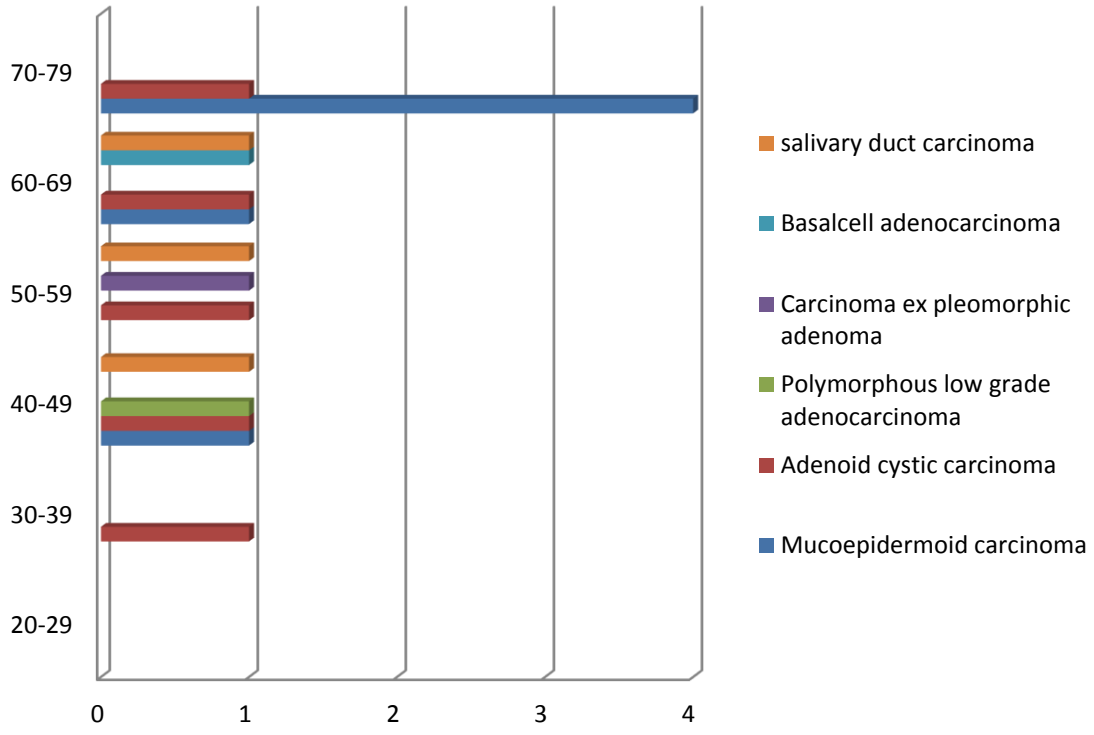
Out of 40 benign tumors encountered in the present study 33 were Pleomorphic adenomas making it 82.5%. Majority of the Pleomorphic adenomas fell between 3^{ed} and 4th decade of life.

Three out of 40 benign tumors were Warthin`s tumor making it 7.5% of benign tumors. It was observed during the 4th decade of life. Basal cell adenoma and Myoepithelioma made the least commonly observed benign tumors in the present study, making it 5% each. [Table 4 and Chart 4].

Table 5: Age wise distribution of Malignant Salivary gland Tumor

Name of the malignant neoplasm	Age						
	30-39	40-49	50-59	60-69	70-79	80-89	Total
Mucoepidermoid carcinoma	-	1	-	1	4	-	6
Adenoid cystic carcinoma	1	1	1	1	1	-	5
Polymorphous low grade adenocarcinoma	-	-	-	1	-	-	1
Carcinoma ex pleomorphic adenoma	-	-	1	-	-	-	1
Basal cell adenocarcinoma	-	-	-	1	-	-	1
Salivary duct carcinoma	-	1	1	1	-	-	3
Total	1	3	3	5	5	-	17

Chart 5: Age wise distribution of Malignant Salivary gland Tumor



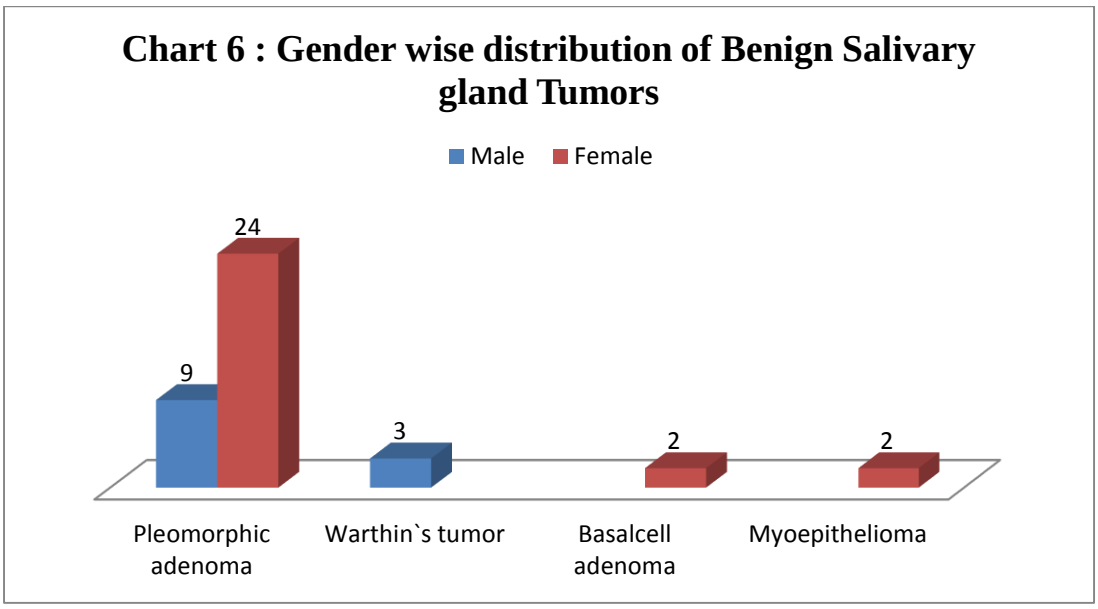
Malignant salivary gland tumors were more commonly observed between 5th and 8t^{h} decade with the mean age of 59 years. The most commonly observed malignant salivary gland tumor was Mucoepidermoid carcinoma.

We encountered 6 cases of Mucoepidermoid carcinoma out of 17 cases of malignant tumors in the present study, making it 35.2% of all malignant tumors. It was followed by Adenoid cystic carcinoma, 5 out of 17 malignant it 29.4% of all malignant tumors.

We also encountered three cases of Salivary duct carcinoma (17.6%). The least commonly observed malignant tumors in the present study were Basal cell adenocarcinoma, Polymorphous low grade adenocarcinoma and Carcinoma ex-Pleomorphic adenoma. [Table 5 and Chart 5]

Table 6: Gender wise distribution of Benign Salivary gland tumors

Neoplasm	Male	Female	Total
Pleomorphic adenoma	9	24	33
Warthin`s tumor	3	-	3
Basalcell adenoma	-	2	2
Myoepithelioma	-	2	2
Total	12	28	40

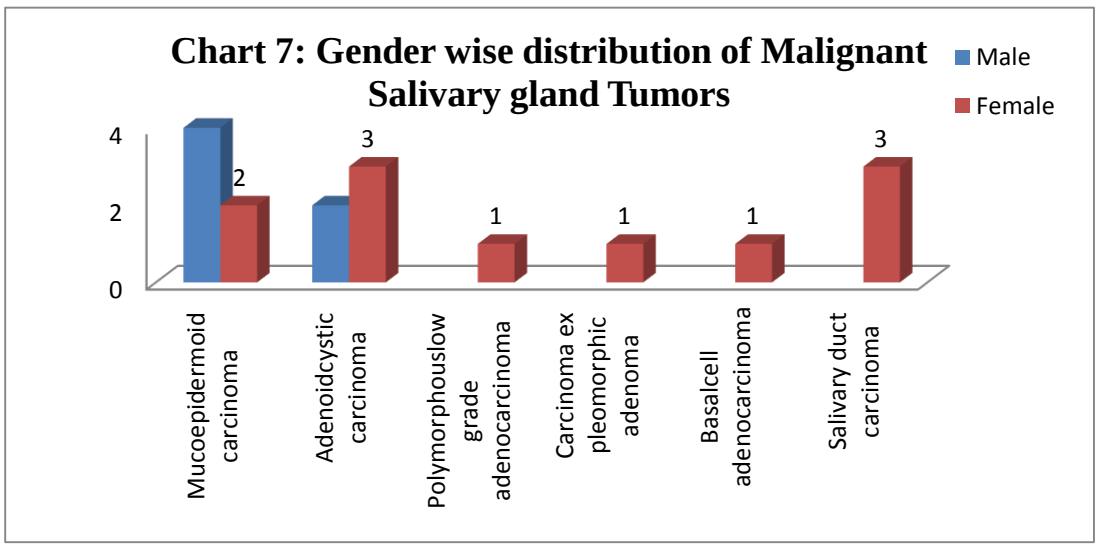


Most of the benign tumors were predominantly observed in female population.

Out of 40 benign tumors encountered in the present study 28 were observed in female population making it (70%) and 12 were observed in male population making it (30%). [Table 6 and Chart 6].

Table 7: Gender wise distribution Malignant Salivary gland Tumors

Malignant	Male	Female	Total
Mucoepidermoid carcinoma	4	2	6
Adenoid cystic carcinoma	2	3	5
Polymorphous low grade adenocarcinoma	-	1	1
Carcinoma ex pleomorphic adenoma	-	1	1
Basal cell adenocarcinoma	-	1	1
Salivary duct carcinoma	-	3	3
Total	6	11	17

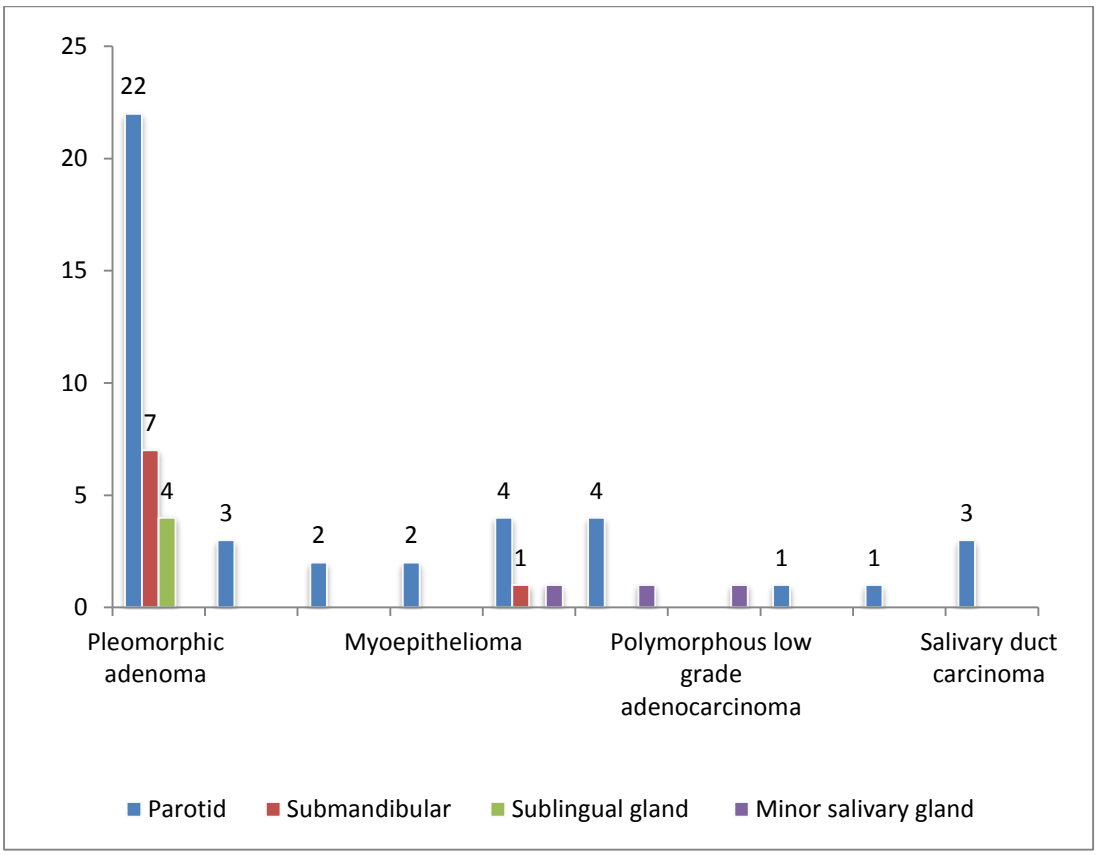


In the present study, most of the malignant salivary gland tumors were observed in female population. Out of 17 malignant salivary gland tumors 11 were observed in female population making it 64% and 6 were observed in male population making it 35.2%.[Table 7 and Chart 7].

Table 8: Site wise distribution of Salivary gland Tumors

Neoplasm	Parotid	Submandibular	Sublingual	Minor SG	Total
Pleomorphic adenoma	22	7	4	-	33
Warthin`s tumor	3	-	-	-	3
Basal cell adenoma	2	-	-	-	2
Myoepithelioma	2	-	-	-	2
Mucoepidermoid carcinoma	4	1	-	1	6
Adenoid cystic carcinoma	4	-	-	1	5
Polymorphous low grade adenocarcinoma	-	-	-	1	1
Carcinoma ex pleomorphic adenoma	1	-	-	-	1
Basal cell adenocarcinoma	1	-	-	-	1
Salivary duct carcinoma	3	-	-	-	3
Total	42	8	4	3	57

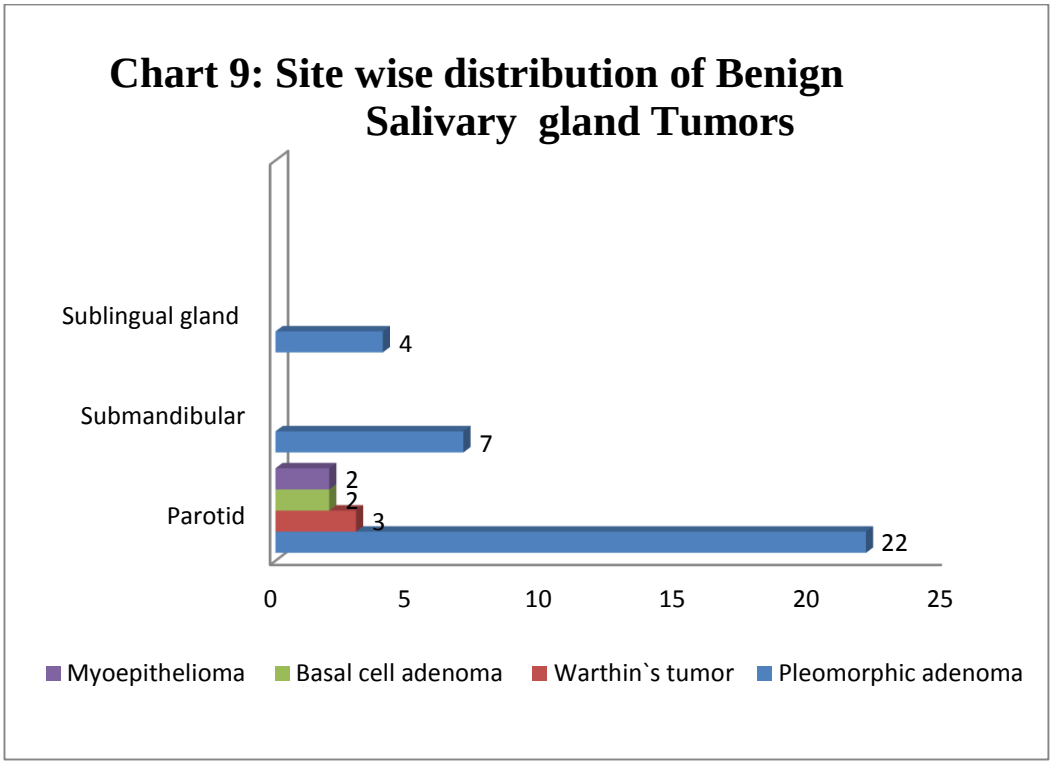
Chart 8: Site wise distribution of salivary gland tumor



Most commonly affected Salivary gland in the present study was parotid. Out of 57 neoplastic lesion 42 were observed in parotid, 8 were observed in submandibular gland, 4 were observed in Sublingual gland and 3 were observed in minor salivary gland. [Table 8 and Chart 8].

Table 9: Site wise distribution of Benign Salivary gland Tumors

Neoplasms	Parotid	Submandibular	Sublingual	Minor SG	Total
Pleomorphic adenoma	22	7	4		33
Warthin`s tumour	3	-	-	-	3
Basal cell adenoma	2	-	-	-	2
Myoepithelioma	2	-	-	-	2
Total	29	7	4		40

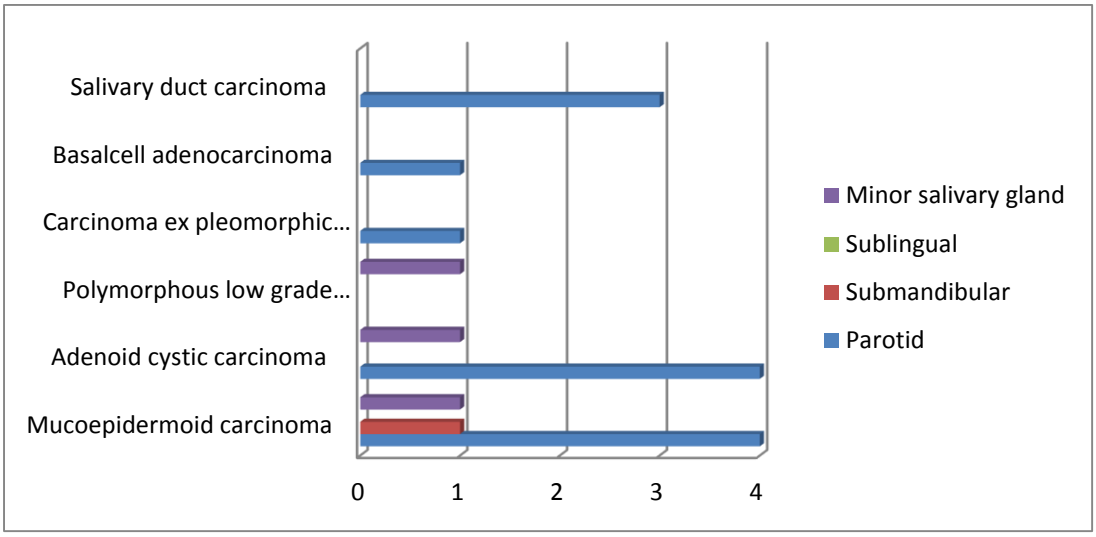


The most commonly involved salivary gland by the benign tumors was parotid gland. Out of 40 benign tumors 29 were observed in parotid gland. The submandibular salivary gland showed involvement by 7 benign tumors. The least commonly involved salivary gland was minor salivary gland. [Table 9, Chart 9].

Table 10: Site wise distribution of Malignant Salivary gland Tumors

Malignant	Parotid	Submandibular	Sublingual	Minor SG	Total
Mucoepidermoid carcinoma	4	1	-	1	6
Adenoid cystic carcinoma	4	-	-	1	5
Polymorphous low grade adenocarcinoma	-	-	-	1	1
Carcinoma ex pleomorphic adenoma	1	-	-	-	1
Basal cell adenocarcinoma	1	-	-	-	1
Salivary duct carcinoma	3	-	-	-	3
Total	13	1	-	3	17

Chart 10: Site wise distribution of Malignant Salivary gland Tumors :



The most commonly involved salivary gland by the malignant tumors was parotid gland. Out of 17 malignant tumors 13 were observed in parotid gland. The minor salivary gland showed involvement by 3 malignant tumors. The least commonly involved salivary gland was sublingual glands. [Table 10, Chart 10].

Table 11: P63 Expression in salivary gland tumors:

Tumors	No. of cases	No. of. Positive cases	IHC SCORE			Cellular location
			Weak	Moderate	Strong	
Pleomorphic adenoma	33	33	-	3	30	Myoepithelial cells
Mucoepidermoid Carcinoma	6	6	-	2	4	Intermediate, Squamous, Clear cells
Adenoid Cystic Carcinoma	5	5	1	4	-	Abluminal cells
Carcinoma ex Pleomorphic Adenoma	1	1	-	-	1	Malignant Squamous epithelium

Interpretation of P63 immunostaining:

Immunostaining was scored as below;

Negative : less than 10% of tumor nuclear stained.

Weakly positive: 10-25% of tumor nuclear stained.

Moderately positive: 26-75% of tumor nuclear stained.

Strongly positive : 76-100% of tumor nuclear stained.

The grading was performed semiquantitatively by double blinded pathologists.

The normal salivary tissue adjacent to the tumor shows P63 expression in the nuclei of basal cells and myoepithelial cells.

In the present study all 33 (100%) cases of Pleomorphic adenoma were P63 positive of which 30 showed strong diffuse nuclear reactivity in myoepithelial cells and three showed weak reactivity.(Fig: 14)

Out of six cases of Mucoepidermoid carcinoma in the present study, four showed strong nuclear reactivity in intermediate, squamous and clear cells, while two showed weak positivity.(Fig:15)

Out of five cases of Adenoid cystic carcinoma four cases showed moderate positivity in the nuclei of tumor cells, while one case showed weak positivity.(Fig:17)

A solitary case of Carcinoma ex Pleomorphic adenoma in the present study showed strong nuclear positivity in the malignant squamous cells. (Fig: 21)

Table 12: CK-14 Expression in salivary gland tumors

Tumors	No.of cases	No.of. Positive cases	IHC SCORE			Cellular location
			Weak	Moderate	Strong	
Mucoepidermoid Carcinoma	6	6	-	-	6	Intermediate Squamous, Clear cells
Adenoid Cystic Carcinoma	5	5	-	5	-	Abluminal Cells
Carcinoma ex Pleomorphic Adenoma	1	1	-	-	1	Malignant Squamous epithelium
Salivary Duct Carcinoma	3	3	3	-	-	Squamous cells

In normal salivary gland all four types of cells are Pan-Cytokeratin (CK) positive. In the present study all six cases of Mucoepidermoid carcinoma showed strong cytoplasmic CK-14 positivity in intermediate, squamous and clear tumor cells. (Fig : 16)

All five cases of Adenoid cystic carcinoma showed moderate cytoplasmic positivity in tumor cells. (Fig: 18). All three cases of Salivary duct

carcinomas in the present study showed weak cytoplasmic positivity for CK-14. (Fig : 20).

Solitary case of Carcinoma ex Pleomorphic Adenoma in the present study showed strong cytoplasmic positivity in the tumor cells. (Fig : 22)

HER 2/ neu expression:

Normal salivary gland parenchymal cells are negative to weakly positive in ductal cells for HER2/neu. However it is highly over expressed in Salivary duct carcinoma[136].In the present study all three salivary duct carcinomas expressed diffuse and strong membrane positivity in carcinoma cells. (Fig : 19)

IMAGE GALLERY

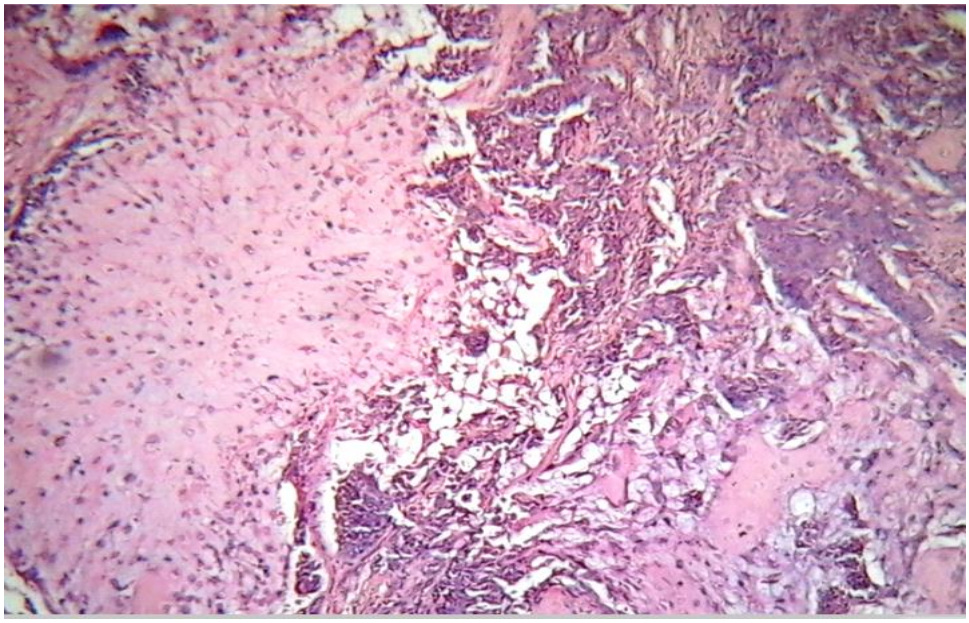


Figure 1: Pleomorphic Adenoma showing epithelial and myoepithelial cell proliferation in a chondromyxoid stroma [HE,X100]

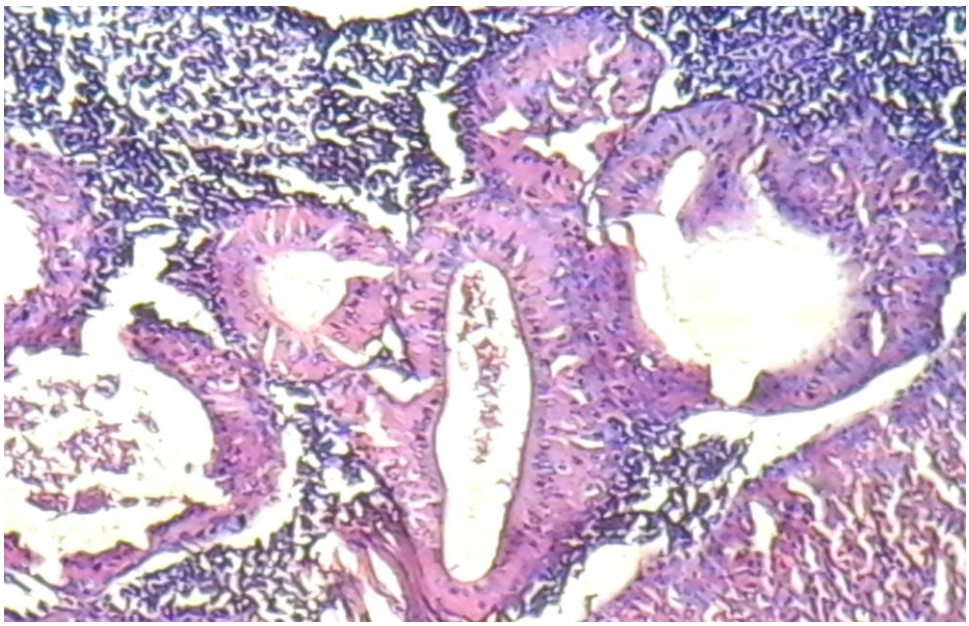


Figure 2: Warthin`s Tumor showing cystic and papillary projections lined by the double layered oncocytic epithelium in a lymphoid stroma [HE, X400]

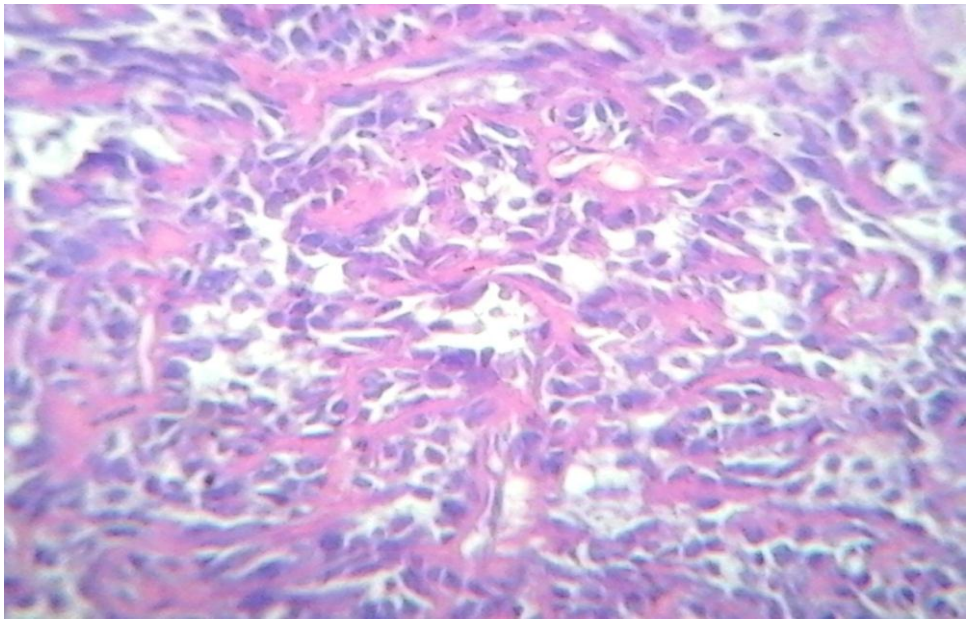


Figure 3: Myoepithelioma showing spindle shape myoepithelial cells [HE, X400]

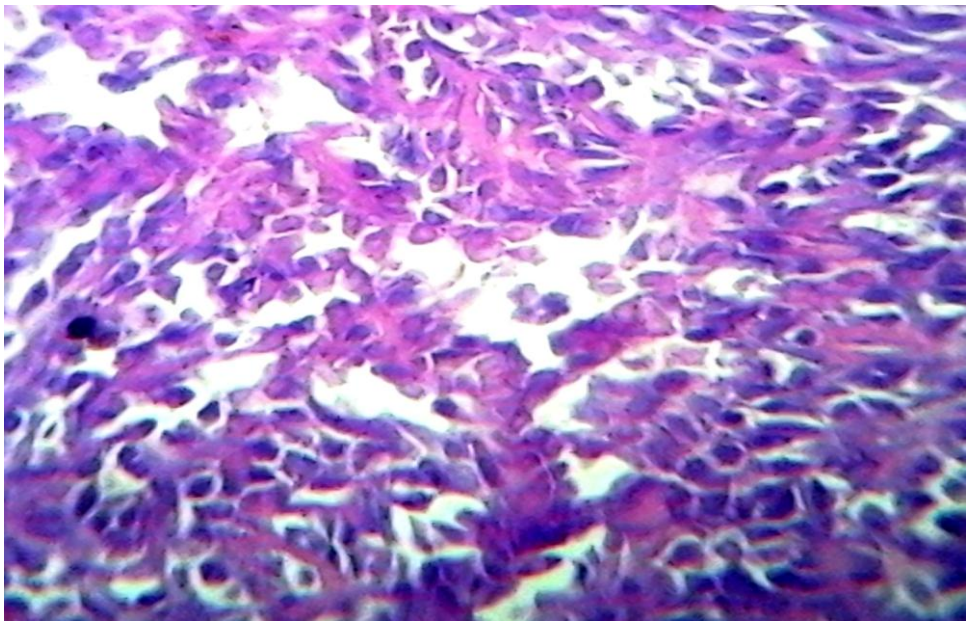


Figure 4: Myoepithelioma showing plasmacytoid myoepithelial cells [HE, X400]

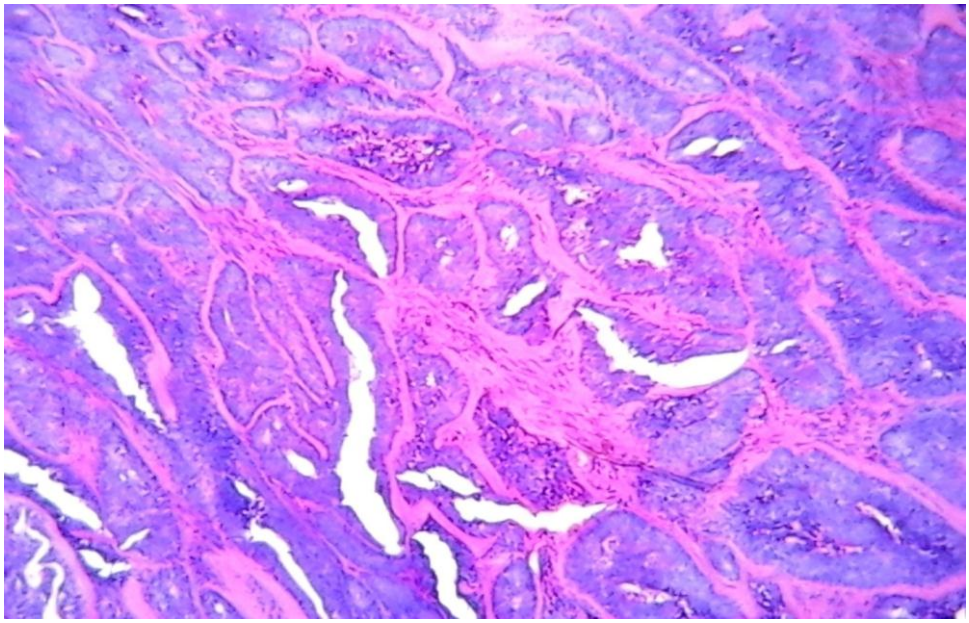


Figure 5: Basal cell Adenoma showing tubules lined by basaloid cells with peripheral palisading. [HE,X 100]

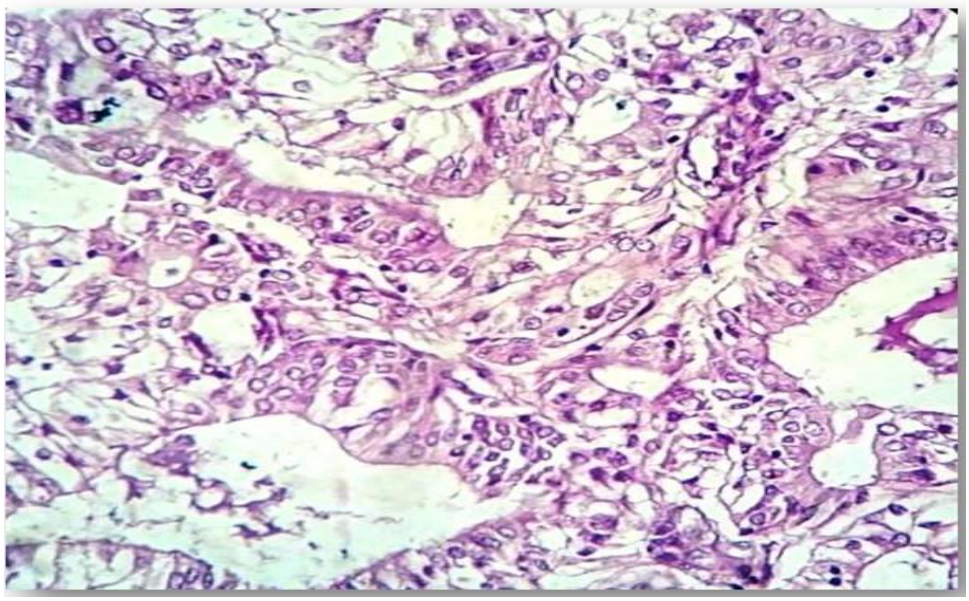


Figure 6: Low grade Mucoepidermoid carcinoma showing glandular structures lined by mucous secreting cells. [HE, X 400]

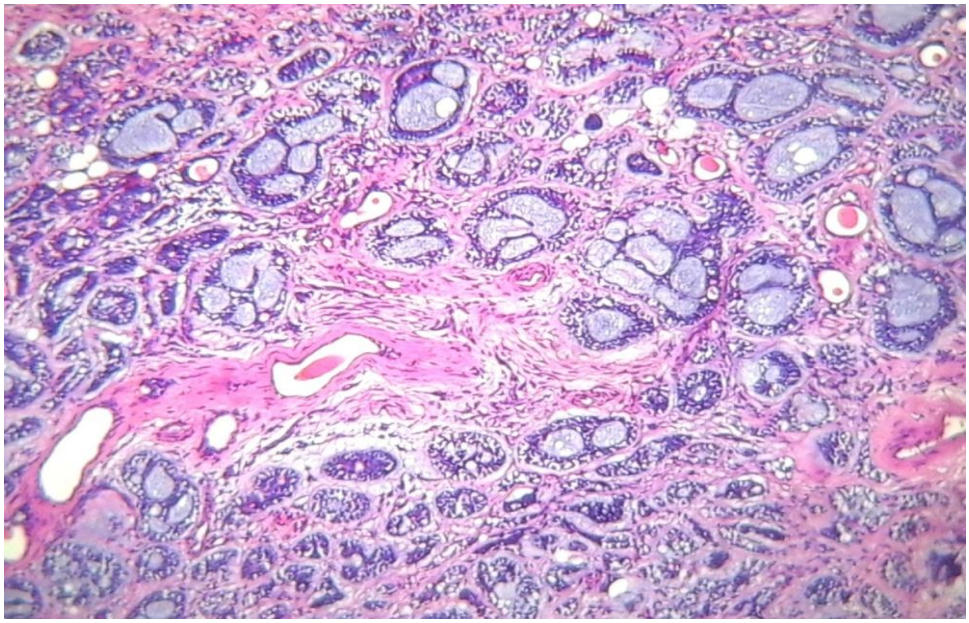


Figure 7: Adenoid cystic carcinoma showing proliferation of tumor cells in cribriform growth pattern enclosing basophilic material [HE, X100]

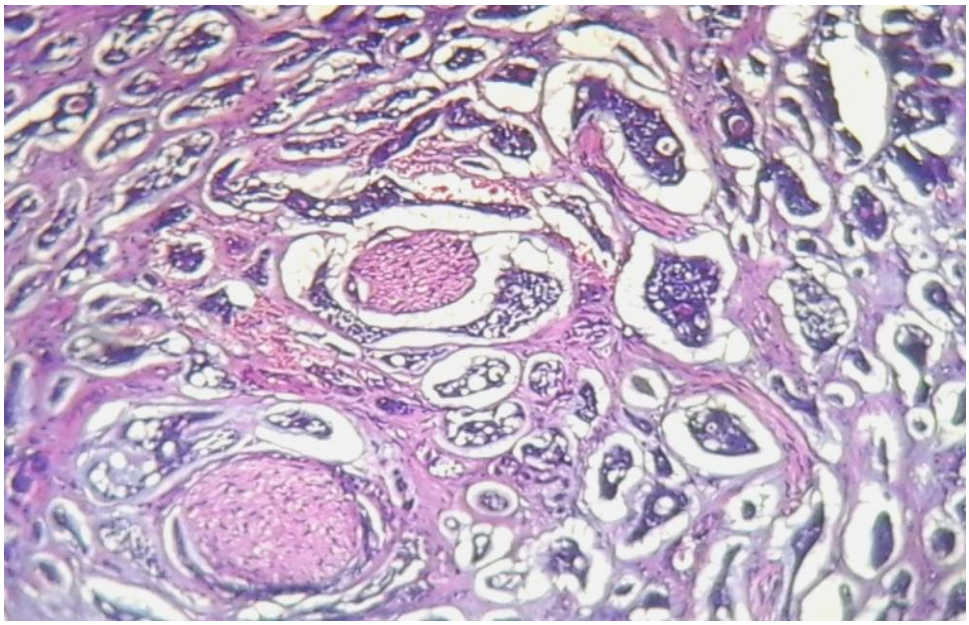


Figure 8: Adenoid cystic carcinoma showing perineural invasion [HE, X100]

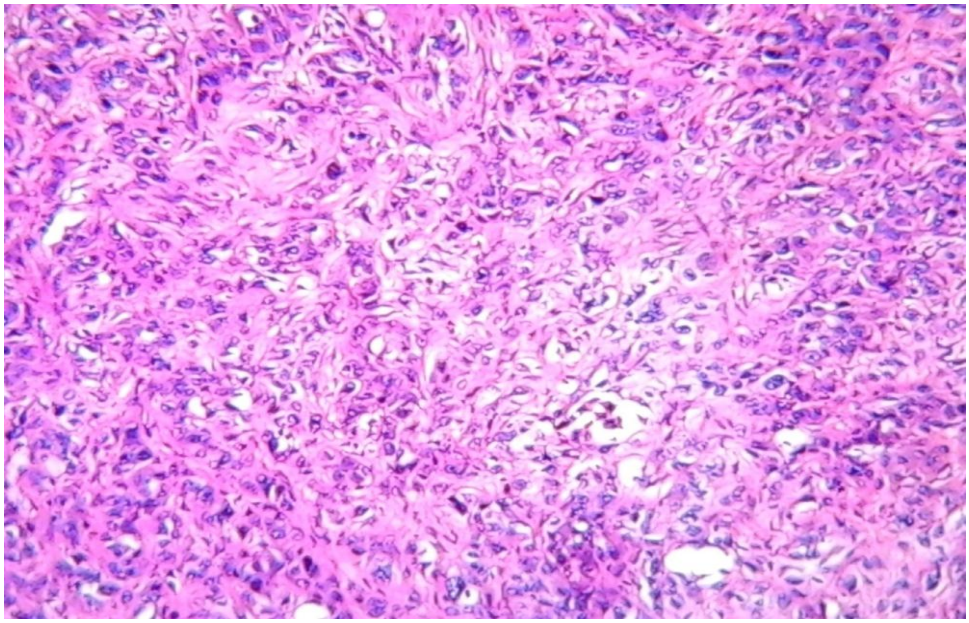


Figure 9: Carcinoma ex pleomorphic adenoma showing both benign and malignant components [HE, X400]

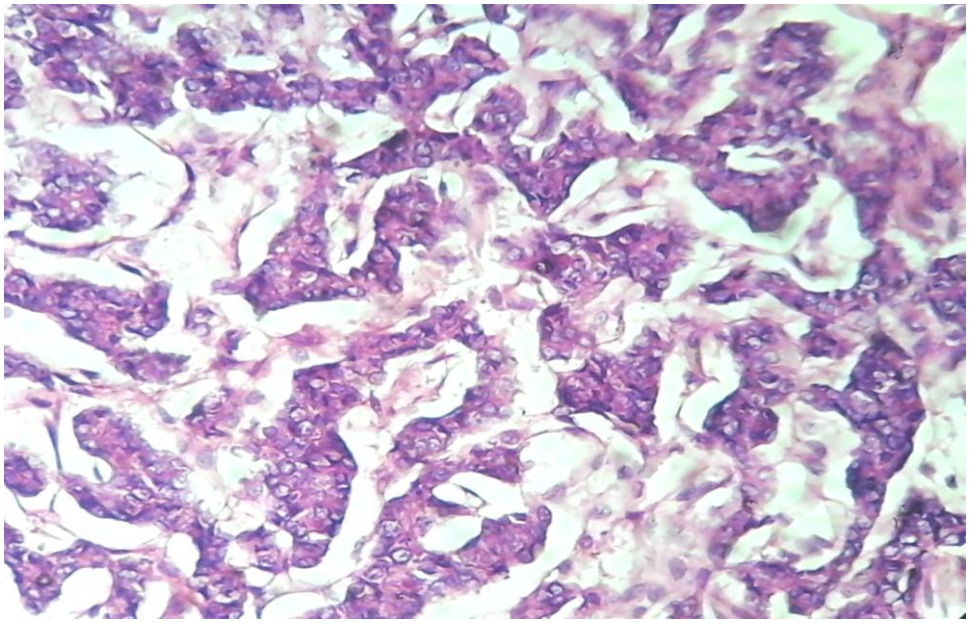


Figure 10: Polymorphous low grade Adenocarcinoma showing tumor cells arranged in cord like pattern [HE, X400]

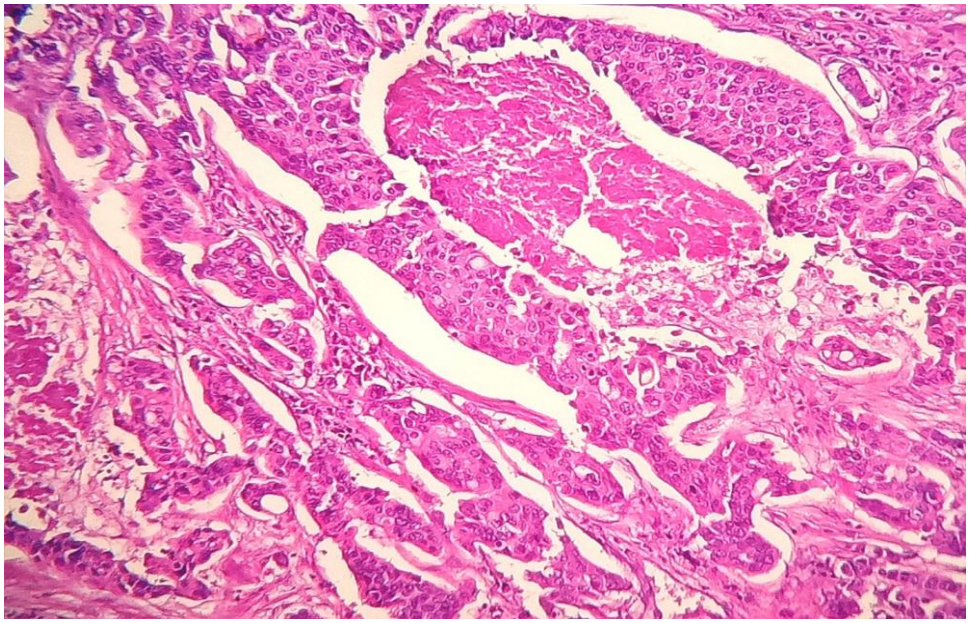


Figure 11: Salivary duct carcinoma showing highly Pleomorphic tumor cells lining the ductal structures with comedo necrosis [HE, X400]

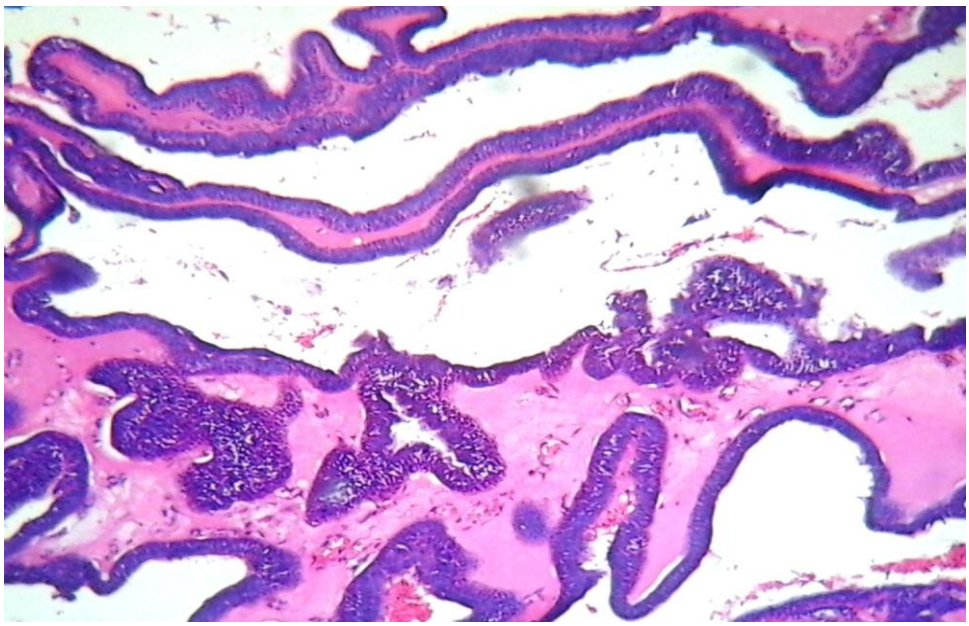


Figure 12: Basal cell Adenocarcinoma showing tubular structures arranged in trabecular pattern [HE,X100]

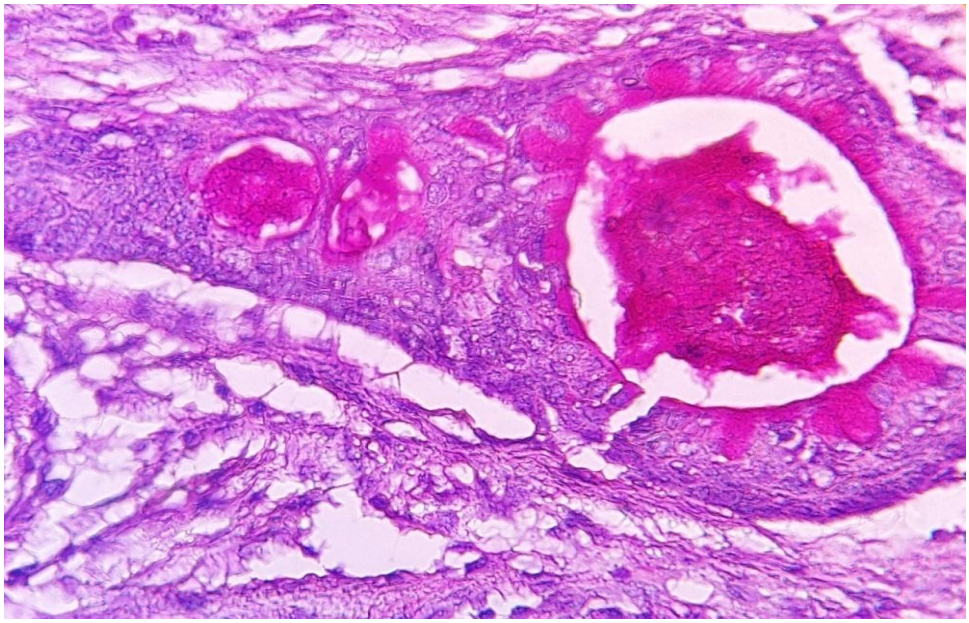


Figure 13: Mucoepidermoid carcinoma –PAS Stain: Positive for mucin.

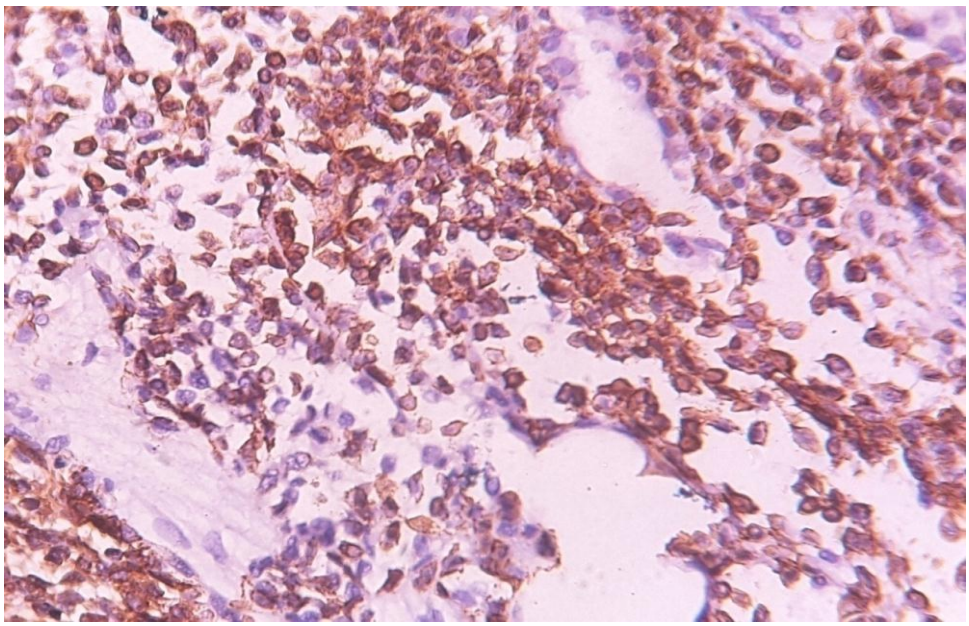


Figure 14: P63 expression in Pleomorphic Adenoma - Nuclear positivity

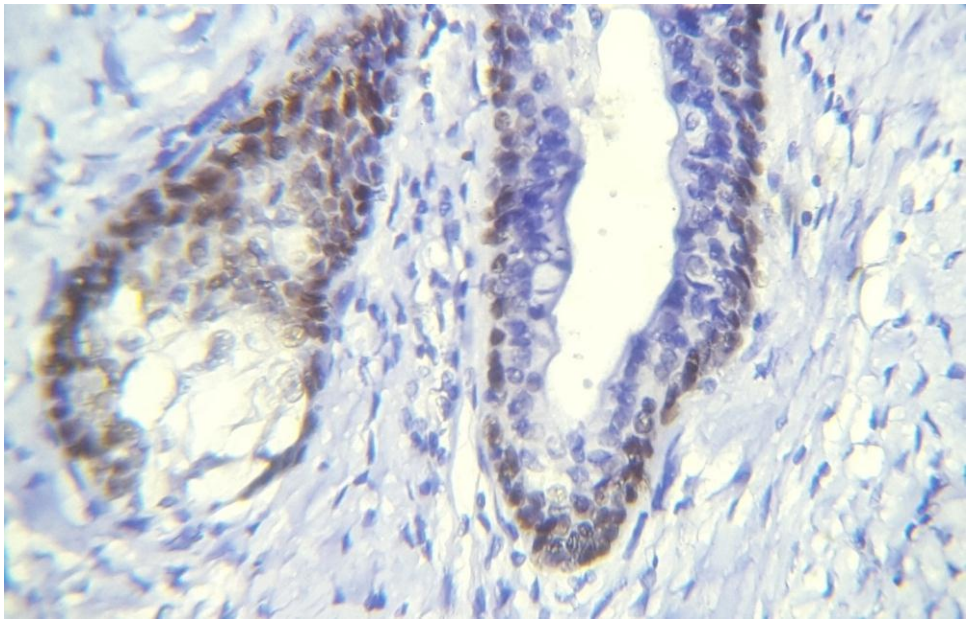


Figure 15: P63 expression in Mucoepidermoid carcinoma– Nuclear positivity.

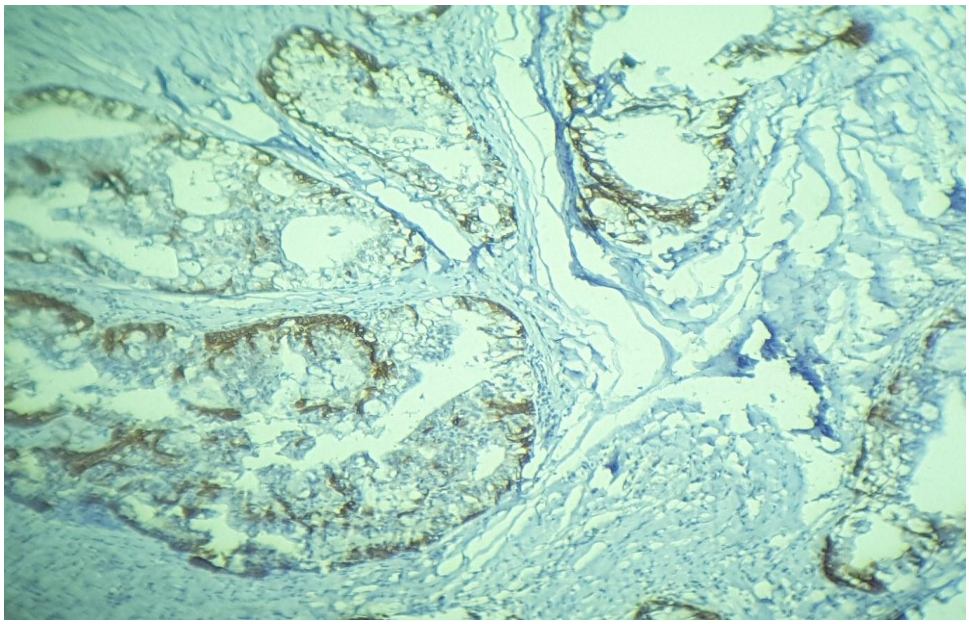


Figure 16: CK-14 expression in Mucoepidermoid carcinoma– Cytoplasmic positivity

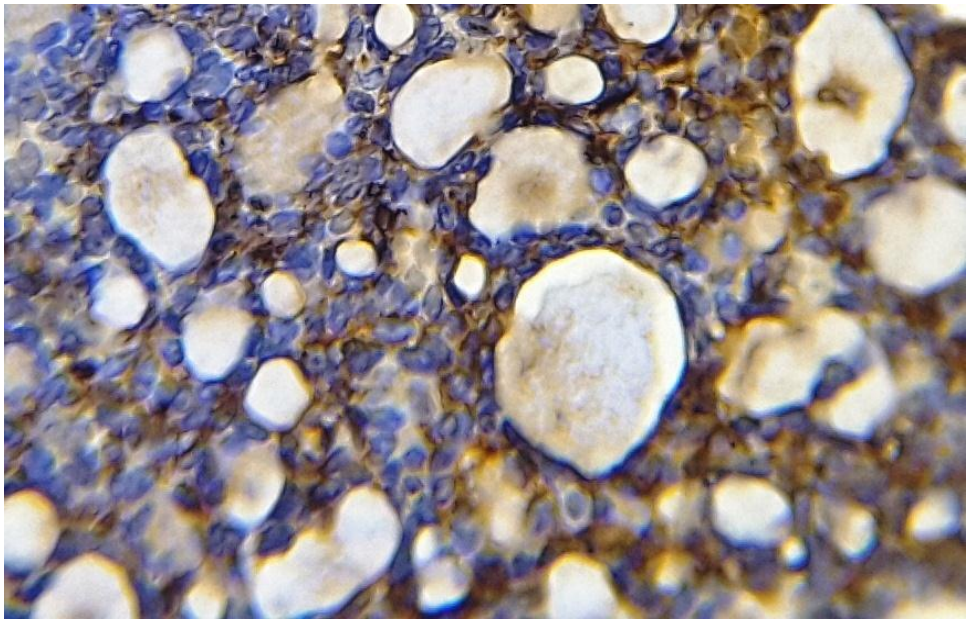


Figure 17 : P63 expression in Adenoid cystic carcinoma – Nuclear positivity.

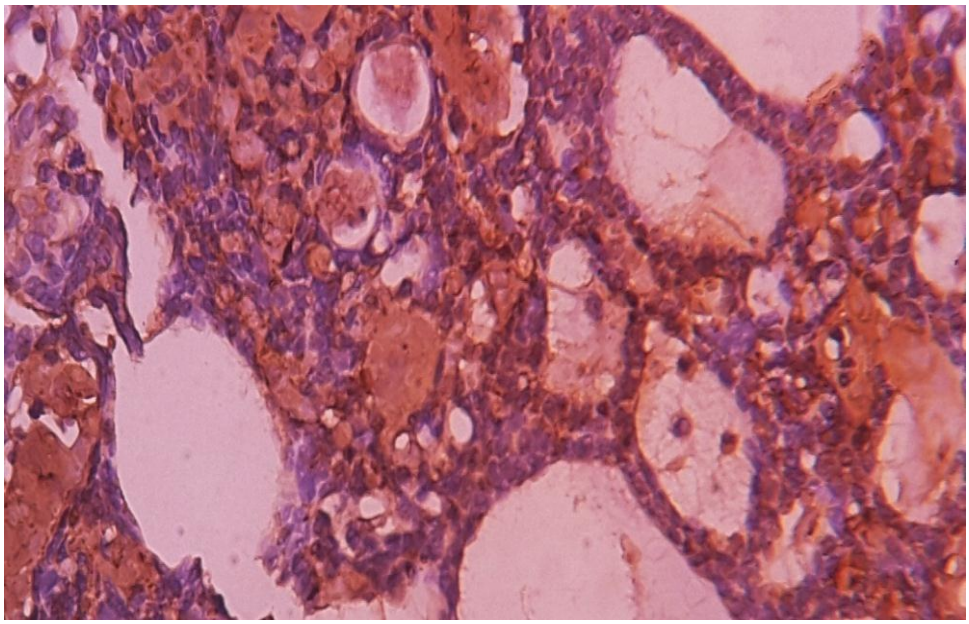


Figure 18 : CK-14 expression in Adenoid cystic carcinoma – Cytoplasmic positivity

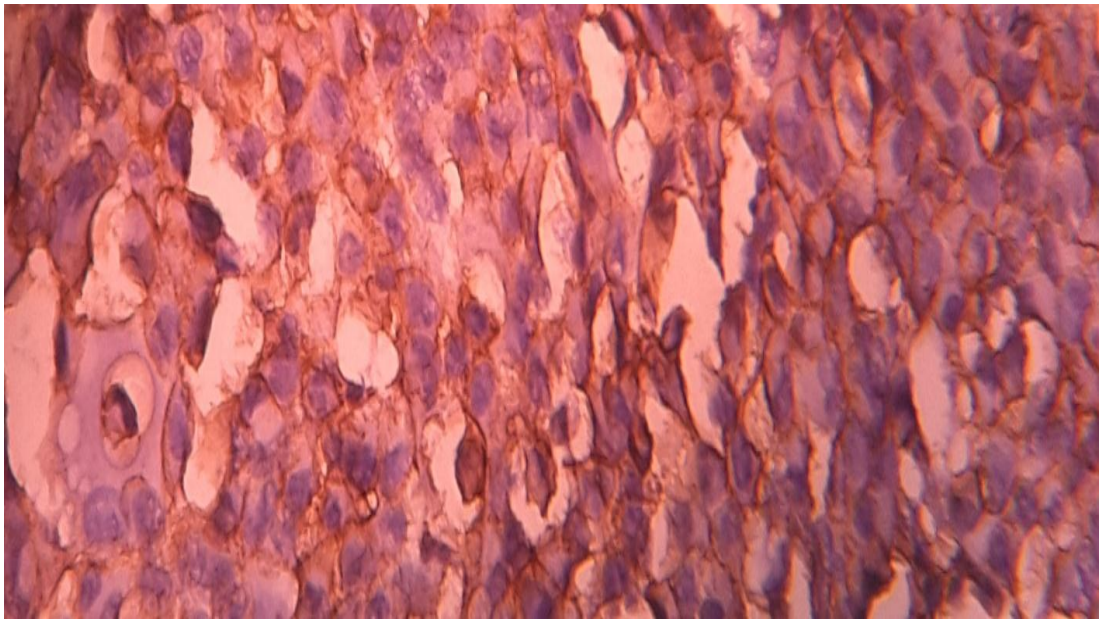


Figure 19: Her 2 neu expression in salivary duct carcinoma – Membrane positivity.

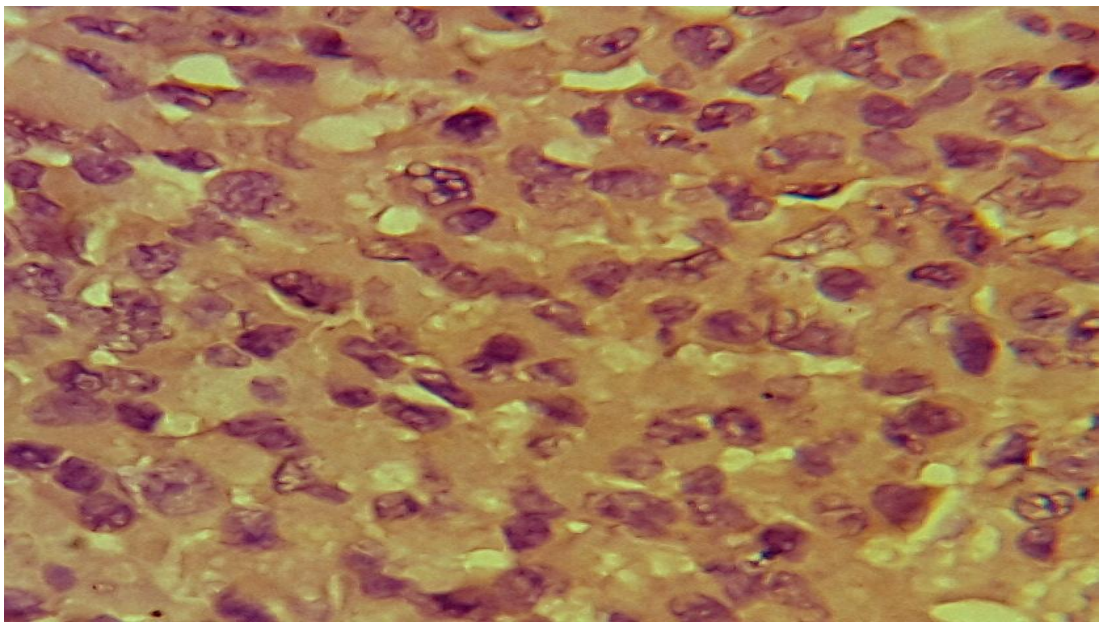


Figure 20 : CK-14 expression in salivary duct carcinoma- Weak cytoplasmic positivity

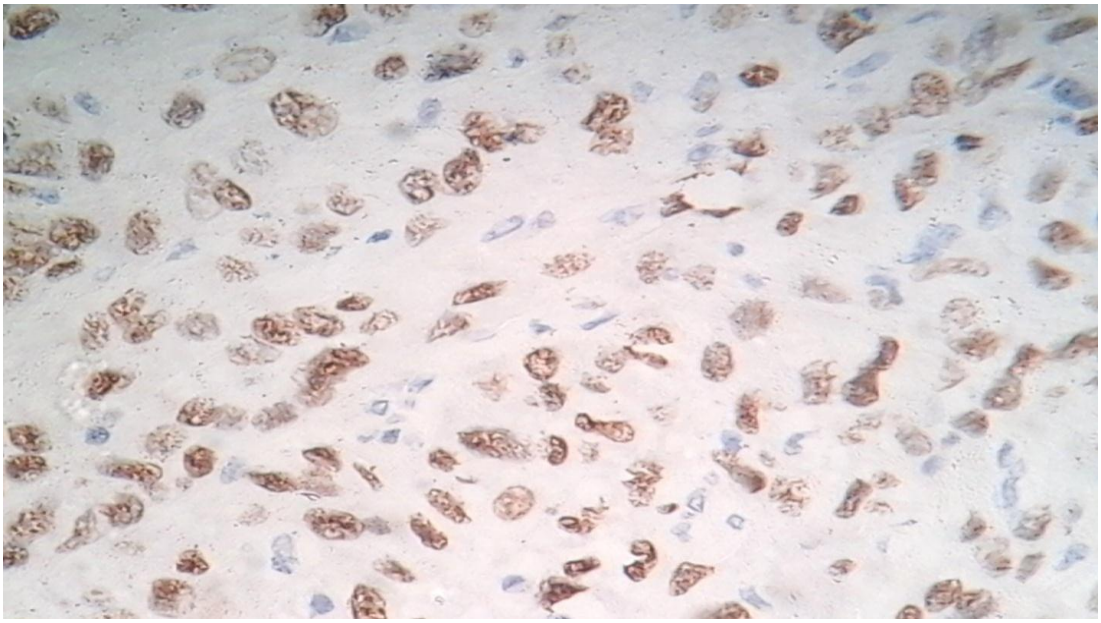


Figure 21 : P63 expression in carcinoma ex pleomorphic adenoma – Nuclear Positivity

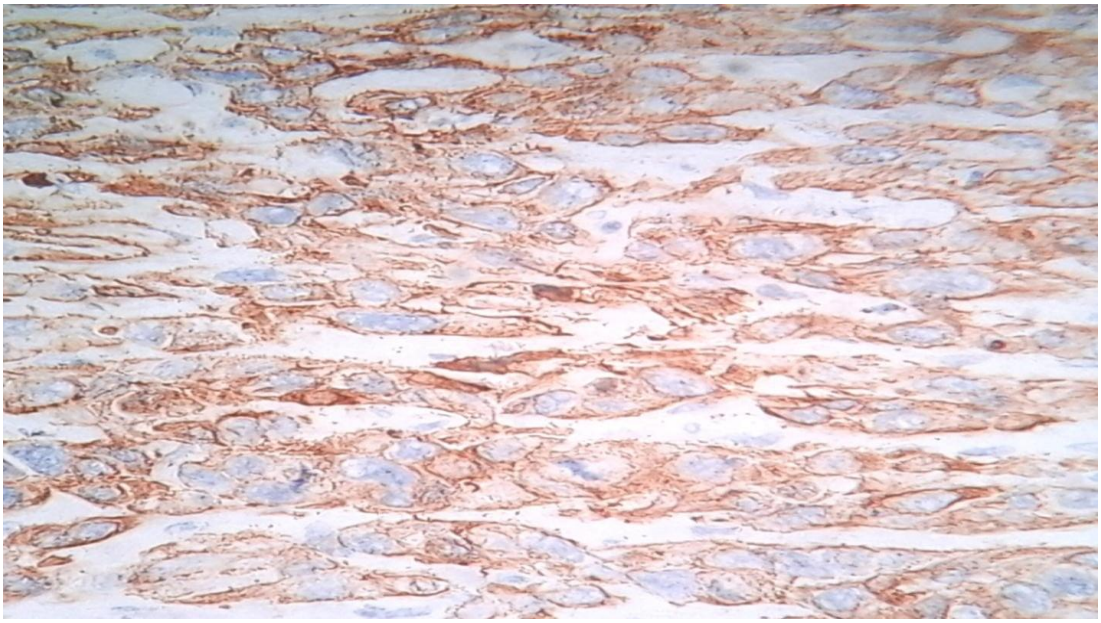


Figure 22 : Cytokeratin expression in carcinoma ex pleomorphic adenoma – Cytoplasmic positivity

DISCUSSION

DISCUSSION

Salivary gland tumors exhibit a diverse group of benign and malignant tumors which show multifaceted clinical pictures, variable morphological architecture with unpredictable prognostic status.

The present study was carried on 57 consecutive cases of various types of salivary gland neoplasms.

The main aspects considered in present study are the histomorphological findings made out by light microscopic examination and also by using special stains where ever required, the incidence rate of the salivary gland tumors in different age groups and to observe Immunohistochemical reactions exhibited by the tumor cells of different salivary gland neoplasms.

Incidence:

Out of 57 cases encountered in the present study 40 were benign (70.1%) and remaining 17 cases were malignant (29.8%).

Table 11 : Incidence of Salivary gland Tumors in various studies

S. N	Study	Place	Year	Total case	Benign	Malignant
1	Janu Devi et al [141]	Assam	2	84	57(67.8%)	27(32.2%)
2	Juan Araya et al[142]	Valparaiso chile	11	279	196(70.2%)	83(29.7%)
3	Rajesh singh et al[143]	Manipur	10	104	56(53.8%)	22(21.1%)
4	M.S.Gill et al[144]	Karachi	8	379	277(73.0%)	102(26.9%)
5	AlpanaBanerjee et al[145]	Tripura	7	46	37(80.4%)	9(19.5%)
6	Nepal et al[146]	Nepal	5	51	41(80.3%)	10(19.6%)
7	Present study	kanchipuram	5	57	40(70.1%)	17(29.8%)

The result observed in the present study is in correlation with Janu devi.et al[141], Juan Araya.et al[142], Rajesh Sing.et al[143], M.S.Gill.et al[144], Alpana Banerjee.et al[145] and Nepal.et al[146], irrespective of total number of cases. The benign lesions were more common followed by malignant lesions.

The benign neoplasms outnumber the malignant ones. Out of 57 total salivary gland neoplasms 40 were benign (70.1%) and 17 were malignant (29.8%). This observation is also in correlation with those quoted by Janu devi.et al[141], Juan Araya.et al[142], Rajesh Sing.et al[143], M.S.Gill.et al[144], Alpana Banerjee.et al[145] and Nepal.et al[146].

M.S.Gill et al[144] who studied 379 neoplasms of salivary gland found 277 (73.0%) benign neoplasms and 102 (26.9%) malignant neoplasms.

Similarly Juan Araya et al[142] who studied 279 of salivary gland neoplasm found 196 benign neoplasms making it 70.2% and 83 malignant neoplasms making it 29.7%.

Table 12: Distribution of Benign Salivary gland Tumors

Benign tumors	Shahidaniazi.et.al[147]	ShilpaH Gandhi.et.al[148]	Shafkat Ahrnad et.al[149]	Present study
Pleomorphic adenoma (PA)	146(90.1%)	33(78.5%)	73(85.8%)	33(82.5%)
Warthin tumour	8(4.9%)	8(19.4%)	-	3(7.5%)
Basal Cell adenoma	1	1	-	2
Myoepithelioma	1	-	1	2
Oncocytoma	1	-	-	-
Sebaceous Lymphadenoma	1	-	-	-
Lipoma	3	-	5	-
Hemangioma	1	-	2	-
lymphangioma	-	-	2	-
Neurofibroma	-	-	1	-
cystadenoma	-	-	1	-
Total Benign Tumours	162	42	85	40

Out of 40 benign neoplasms in the present study, 33 were Pleomorphic adenoma making it 82.5% of total benign tumors.

Thus Pleomorphic adenoma was the most commonly observed benign tumor in the present study. Similar observations were quoted by Shahidaniazi.et.al[147], Shilpa.H.Gandhi.et.al[148], Shafkat Ahrnad et.al[149].

Out of 162 benign tumors reported by Shahidaniazi.et.al[147], 146 were Pleomorphic adenoma making it 90.1%, out of 42 benign tumors by Shilpa .H. Gandhi.et.al[148] 33 were Pleomorphic adenoma making it 78.5% and out of 85 benign tumor reported by Shafkat Ahrnad et.al[149] 73 were Pleomorphic adenoma making it 85.8%. Our observations in the present study are comparable with all above three studies.

Table 13: Distribution of Malignant Salivary gland Tumors

Malignant tumors	Khandekar. et al[150]	Shashikala et al[151]	Present study
Mucoepidermoid carcinoma (MEC)	11(50.0%)	5(71.4%)	6(35.2%)
Adenoid Cystic Carcinoma	8(36.3%)	-	5(29.4%)
Acinic Cell Carcinoma	-	1	-
Polymorphous Low Grade Adenocarcinoma	-	-	1
Salivary duct carcinoma	-	-	3
Basalcell adenocarcinoma	-	-	1
Carcinoma ex pleomorphic adenoma	-	1	1
Squamous cell carcinoma	2	-	-
Adenocarcinoma	1	-	-
Total malignant tumor	22	7	17

Out of 17 malignant neoplasms in the present study, six were Mucoepidermoid carcinoma making it 35.2% of total malignant tumors.

Thus Mucoepidermoid carcinoma was the most commonly observed malignant tumor in the present study. Similar observations were quoted by Khandekar. et al[150], Shashikala. et al[151].

Out of 22 malignant tumor reportred by Khandekar. et al[150] 11 were Mucoepidermoid carcinoma making it 50.0% and out of 7 malignant tumor reported by Shashikala. et al[151] 5 were Mucoepidermoid carcinoma making it 71.4%. Our observations in the present study are comparable with all above studies.

Age incidence:

Table 14 : Age incidence of Salivary gland Tumors

Study	Benign	Malignant
Dave P.N et al[152]	3ed decade	5th decade
Shree devi S. Bobati et al[153]	4th decade	6th decade
Shrestha .S et al[154]	4th decade	5th decade
Dhanamjeya Rae Teeda et al[155]	4th decade	6th decade
Shazia Bashir et al[156]	4th decade	5th decade
Present study	3nd and 4th decade	5th and 8th decade

All the salivary gland tumors were observed between a wide range age group starting from 3rd decade of life to 8th decade. This finding is similar to Dave P.N.et al[152], Shree devi S.Bobati.et al[153],Shrestha.S.et al[154], Dhanamjeya Rae Teeda .et al[155],Shazia Bashir.et al[156].

The youngest patient in the present study was 17 years female and the oldest was 76 years. The youngest had Pleomorphic adenoma while the oldest had Mucoepidermoid carcinoma. The maximum number of salivary gland tumors were encountered during 3rd decade of life and were benign in nature which is comparable to the finding noted by Dave.P.N et al[152]. Malignant salivary gland tumors were more commonly observed between 5th and 8th decade with the mean age of 59 years in the present study. Dave P.N.et al[152], Shree devi S.Bobati.et al[153], Shrestha.S.et al[154], Dhanamjeya Rae Teeda.et al[155], Shazia Bashir.et al[156], also encountered the similar results.

Gender wise distribution of salivary gland tumors

Table 15 : Gender wise distribution of Salivary gland Tumors

Tumors	Samina zaman et al[157]		Present study	
	Male	Female	Male	Female
Pleomorphic adenoma	16	27	9	24
Warthin`s tumor	1	1	3	-
Basalcell adenoma	1	1	-	2
Myoepithelioma	1	2	-	2
Oxyphilic adenoma	-	1	-	-
Mucoepidermoid carcinoma	4	1	4	2
Adenoid cystic carcinoma	1	1	2	3
Acinic cell carcinoma	-	3	-	-
Polymorphous low grade adenocarcinoma	-	1	-	1
Carcinoma ex pleomorphic adenoma	1	-	-	1
Basalcell adenocarcinoma	-	-	-	1
Epithelial-myoepithelial carcinoma	1	-	-	-
Salivary duct carcinoma	-	-	-	3
Total	26	38	18	39

In the present study majority of benign and malignant salivary gland tumors were observed predominantly in female population with the female : male ratio 2:1, which is comparable to the findings quoted by Samina zaman. et al[157].Out of 33 Pleomorphic adenomas in the present study, 24 were found in females and 9 in males making it 3:1.

Table 16 : Site wise distribution of Salivary gland Tumors

Study	Parotid	Submandibular gland	Sublingual gland	Minor salivary gland	Total
Krishnaraj Subhashraj et al[158]	414	116		150	680
Lakshmibai B Mallappa et al[159]	17	8	3		28
Maj T Chatter jee et al[160]	243	30		14	287
Kirti N. Jaiswal et al[161]	68	13		15	96
Subhashini Bandar et al[162]	33	8		7	48
Present study	42	8	4	3	57

The most commonly affected salivary gland by neoplastic lesion was parotid in the present study followed by submandibular salivary gland and minor salivary glands.

Out of 57 salivary gland tumors encountered in the present study 42 cases were observed involving parotid gland (73.6%) and 8 cases were involving submandibular gland (14.3%). The sublingual and minor salivary gland were least affected. These findings are comparable with other studies quoted by Krishnaraj Subhashraj et al[158], Lakshmibai B Mallappa et al[159], Maj T Chatter jee et al[160], Kirti N. Jaiswal et a1[161], Subhashini Bandar et al[162].

Out of 40 benign tumors 29 were observed in parotid gland (72.5%), 7 in submandibular gland (17.5%%)and 4 in sublingual gland (10%). Similarly out of 17 cases of malignant tumors 13 were observed in parotid (76.4%), three cases were observed in Minor salivary gland (17.6%), one was observed in submandibular gland (6.2%).

Immunohistochemical analysis of salivary gland tumors

In the present study we examined the expression of P63, CK-14 and HER2/neu in various salivary gland tumors to assess their possible role in the diagnosis and differential diagnosis of these tumors.

P63

P63 is a member of the P53 family of transcription factors. Myoepithelial cell differentiation occurs to variable degrees in Pleomorphic adenomas, Adenoid cystic carcinomas, Polymorphous low grade adenocarcinomas and Epithelial- Myoepithelial carcinoma. Intermediate cells of Mucoepidermoid carcinoma also demonstrate characteristics of modified myoepithelial cells[163].

In the present study all the 33 cases (100%) of Pleomorphic adenoma were P63 positive of which 30 showed strong diffuse nuclear reactivity in myoepithelial cells and three showed weak reactivity.

Out of six cases of Mucoepidermoid carcinoma in the present study, four showed strong nuclear reactivity in intermediate, squamous and clear cells,

while two showed weak positivity. These result support those of Ralph and Douglas[163] who reported strong positive nuclear staining for P63 in 100% of examined MEC. Seethala et al[164] and Bilal et al[165] also reported same results in their studies.

Out of five cases of Adenonoid cystic carcinoma four cases showed moderate positivity in the nuclei of tumor cells, while one case showed weak positivity, these results are comparable to the study of Seethala et al [164] and Bilal et al[165].

A solitary case of Carcinoma ex Pleomorphic adenoma in the present study showed strong nuclear positivity for P63 in the malignant squamous cells.

Cytokeratin (CK-14)

In the present study all six cases of Mucoepidermoid carcinoma showed strong cytoplasmic CK-14 positivity in intermediate, squamous and clear tumor cells.

All five cases of Adenoid cystic carcinoma showed moderate cytoplasmic positivity in tumor cells.

Solitary case of Carcinoma ex Pleomorphic Adenoma in the present study showed strong cytoplasmic positivity in the tumor cells.

All three cases of Salivary duct carcinomas in the present study showed weak cytoplasmic positivity for CK-14

Our results on CK14 positivity in various salivary gland tumors tally with those observations quoted by Toshitaka Nagao et.al[136].

HER2/neu expression:

Salivary duct carcinoma is a high grade malignancy and displays similar histological appearances to ductal breast carcinoma.

The estrogen receptor and progesterone receptor are not detected in most salivary duct carcinomas. This finding is some time useful for distinguishing this tumor from breast cancer metastasis. However more than 20% of salivary duct carcinomas show diffuse and strong membranous staining for HER2/neu that correlates with aggressiveness of the tumor[136].

In present study all three salivary duct carcinomas encountered, showed strong immunoreactivity for HER2/neu. Our findings are in corroboration with the observations made my Toshitaka Nago et al[136] .

In conclusion, we tried in the present study to clarify the possible role of P63, CK-14 and HER2/neu in the diagnosis and differential diagnosis between various types of salivary gland tumors.

We found that P63, which is a nuclear marker is positive in tumors like Pleomorphic adenoma, Mucoepidermoid carcinoma, Adenoid cystic carcinoma and Carcinoma ex-pleomorphic adenoma.

CK-14 , which is a cytoplasmic marker is positive in Mucoepidermoid carcinoma, Adenoid cystic carcinoma, Carcinoma ex pleomorphic adenoma and Salivary duct carcinoma.

HER2/neu shows diffuse and strong membranous staining in salivary duct carcinoma.

Limitations of this study included a limited number of available cases of each tumor type and missing of some tumor types such as Acinic cell carcinomas due to its relatively infrequent occurrence. Hence we recommend further studies for studying the immnunohistochemical expression of p63 and CK-14 in other types of salivary gland tumors not encountered in the present study.

SUMMARY

AND

CONCLUSION

SUMMARY AND CONCLUSION

- In the present study we analyzed the incidence, distribution and histomorphological patterns of Salivary gland Tumors over a period of five years from September 2012 to August 2017 in the department of pathology at Karpaga Vinayaga Institute of Medical Sciences and Research Institute Centre.
- Out of 57 salivary gland tumors studied in the present study 40 were benign making it 70.1% and 17 were malignant making it to 29.8% of the total Salivary gland Tumors.
- Pleomorphic Adenoma was the most commonly observed benign tumor. Out of 40 benign tumors 33 were Pleomorphic adenomas making it 82.5% of all the benign tumors.
- Mucoepidermoid carcinoma was the most commonly observed malignant tumor. Out of 17 malignant tumors 6 were Mucoepidermoid carcinomas making it 35.2% of all the malignant tumors.
- Most of the benign tumors were found between the age group of 20 to 40 years with the mean age of 31 years and most of the malignant tumors were found between the age group of 40 to 70 years with the mean age of 59 years.
- Female gender was the most commonly affected gender by both benign and malignant salivary gland tumors. Out of 57 cases of salivary gland tumors 39 were females and 18 were males making it a ratio of 2:1.

- Parotid was the most commonly affected salivary gland irrespective of the nature of the neoplasm. Out of 57 salivary gland neoplasms 42 were observed in parotid gland (73.6%), 8 were observed in submandibular salivary gland (14%), 4 neoplasms were observed in sublingual gland (7%) and 3 were observed in minor salivary gland (5.2%) .
- In the present study we tried to clarify the possible role of P63, CK-14 and HER2/neu in the diagnosis and differential diagnosis between various types of salivary gland tumors.
- We found that P63, which is a nuclear marker, is always positive in diagnosing Pleomorphic adenoma, Mucoepidermoid carcinoma, Adenoid cystic carcinoma and Carcinoma ex-pleomorphic adenoma.
- CK-14, which is the cytoplasmic myoepithelial marker, is always positive in Mucoepidermoid carcinoma, Adenoid cystic carcinoma, Carcinoma ex pleomorphic adenoma and Salivary duct carcinoma.
- HER2/neu shows diffuse and strong membranous staining in salivary duct carcinoma.
- Limitations of this study included a limited number of available cases of each tumor type and missing of some tumor types such as Acinic cell carcinomas due to its relatively infrequent occurrence. Hence we recommend further studies for all the immnunohistochemical markers in all the types of salivary gland carcinomas.

INSTITUTIONAL ETHICAL COMMITTEE

KARPAGA VINAYAGA INSTITUTE OF MEDICAL SCIENCES & RESEARCH CENTRE

MADURANTHAGAM - 603 308.

EC Ref. No: 19/2016

CERTIFICATE FOR APPROVAL

The Institutional Ethical Committee of Karpaga Vinayaga Institute of Medical Sciences & Research Centre, Maduranthagam reviewed and discussed the application for approval **"Histomorphological patterns of salivary gland tumors"** by **Dr. J. Margaret Theresa**, post graduate, Guided by **Dr. A.B.Harke**, **Professor, Department of Pathology,** Karpaga Vinayaga Institute of Medical Sciences & Research Centre, Maduranthagam.

The proposal is **APPROVED**

The Institutional Ethics Committee expects to be informed about the progress of the study and any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

23/01/16

Chairperson, Ethics Committee

Date: 23.01.2016

CHAIRMAN
KIMS
Member Secretary Institutional Ethical Committee

ANNEXURES

ANNEXURE A

DATA COLLECTION FORM

NAME : DATE:

AGE:

I.P.NO:

WEIGHT:

PARITY :

CHIEF COMPLAINTS :

PAST MEDICAL HISTORY:

GROSS FINDINGS:

HISTOPATHOLOGICAL FINDING :

ANNEXURE B

STAINING TECHNIQUE

Hematoxylin and eosin (H&E)

Procedure

1. Bring sections to water
2. Stain with harris hematoxylin for 2- 3 minutes
3. Wash with running tap water
4. Differentiate in 1% acid alcohol
5. Wash and blue with running tap water
6. Counter stain with aqueous eosin for 2 minutes
7. Dehydrate with absolute alcohol (2-3changes)
8. Clear with 2-3changes of xylene
9. Mount using Dibutyl phthalate polystyrene xylene (Dpx)

Result

Nucleic acid – blue

Cytoplasm – pink

ANNEXURE C : PERIODIC ACID SCHFF`S STAINING(PAS)

1. Cut paraffin sections 4 to 5 microns thick
2. Deparaffinise using xylene for 5 minutes
3. Take to alcohol two chages each 5 minutes
4. Bring sections to water
5. Periodic acid for 5 to 10 minutes
6. Wash thoroughly in water for 1minute.
7. Place the sections in Schiff`s reagent for 15 minutes.
8. Wash the sections in running water for 10 minute.
9. Counter stain in Harris haematoxyline for half minute
10. Wash sections well to blue the haematoxyline.
11. Dehydrate with 95% and absolute alcohol, clear with Xylene and mount the sections

ANNEXURE D

FLOW CHART FOR IMMUNOHISTOCHEMISTRY

1.Cut 3mm sections on charged slides and incubated at 60-70 C for 1hour

2.Deparafinized by 2 changes of xylene 5minutes each.

3.Hydrate through descending grade of alcohol as follows:

Absolute alcohol –two changes , 5 minutes each

90% alcohol -5 minutes

70% alcohol – 5minutes

Wash in distilled water , two changes, 2minutes each

4.Antigen retrival for 15-20 minutes in MERS. Ph of retrival buffer may be either 6,8 or 9.5acorrding to the marker.

5.Wash in distilled water, two changes, 2minutes each.

6.Wash in Triss buffer solution for 2minutes.

7.Do endogenous peroxidase blocking by adding H2O2 on the section, keep for 5minutes.

8.Wash in the wash buffer for 2 minutes , twice.

9. Add primary antibody and keep for 30 minutes in a moist chamber . then wash in wash buffer2 times, 2minutes each.

10. Add polyexcel Target binder reagent and keep for 15 minutes. Wash in two changes.

11. Add polyexcel HRP and incubate for 15 minutes. Wash with buffer , 2 minutes two changes.

12.Add working DAB chromogen (1ml DAB Buffer +1 drop of DAB chromogen, mix well) and keep for 2-5, then wash in distilled water .

13. counter stain with haematoxlinn for 30seconds , wash with water.

14.Dehydrate , clear and mount the slide .

ANNEXURE – E

LIST OF ABBREVIATIONS

H&E	-	Haematoxylin and Eosine
IHC	-	Immunohistochemistry
MEC	-	Mucoepidermoid carcinoma
EMC	-	Epithelial –myoepithelial carcinoma
PLGAC	-	Polymorphous low-grade adenocarcinoma
SDC	-	Salivary duct carcinoma
AdCC	-	Adenoid cystic carcinoma
LCC	-	Low-grade cribriform Cystadenocarcinoma
CEA	-	Carcinoembryonic antigen
EMA	-	Epithelial membrane antigen
SMA	-	Smooth muscle actin
GFAP	-	Glial fibrillary acidic protein
CK	-	Cytokeratin
MSA	-	Muscle specific antigen
AR	-	Androgen receptor

ANNEXURE – F

LIST OF TABLES

ANNEXURE – G

LIST OF CHART

CHART NO`S	DESCRIPTION OF CHART
1	Incidence of Salivary gland Tumors
2	Frequency distribution of Benign Salivary gland Tumors
3	Frequency distribution of Malignant Salivary gland Tumors
4	Age wise distribution of Benign Salivary gland Tumors
5	Age wise distribution of Malignant Salivary gland Tumors
6	Gender wise distribution of Benign Salivary gland tumors
7	Gender wise distribution Malignant Salivary gland Tumors
8	Site wise distribution of Salivary gland Tumors
9	Site wise distribution of Benign Salivary gland Tumors
10	Site wise distribution of Malignant Salivary gland Tumors

ANNEXURE – H

LIST OF FIGURES

ANNEXURE – I

MASTER CHART

S.NO	AGE	SEX	IP.NO	HP.NO	BENIGN/ MALIGNANT	NEOPLASM TYPE	ORGAN AFFECTED	P63 EXPRESSION	CK14 EXPRESSION	HER 2/ neu EXPRESSION
1	42	F	140512001	318/12	Benign	Pleomorphic adenoma	Parotid	Strongly Positive	-	-
2	23	F	2408120076	574/12	Benign	Pleomorphic adenoma	Parotid	Strongly Positive	-	-
3	75	M	1911120001	728/12	Malignant	Mucoepidermoid carcinoma	Submandibular	Weakly Positive	Strongly Positive	-
4	30	F	281212002	015/13	Benign	Pleomorphic adenoma	Parotid	Strongly Positive	-	-
5	36	M	180213002	148/13	Benign	Warthin's tumour	Parotid	-	-	-
6	76	M	180213003	165/13	Malignant	Mucoepidermoid carcinoma	Parotid	Moderately Positive	Strongly Positive	-
7	29	F	907130001	567/13	Benign	Pleomorphic adenoma	Submandibular gland	Moderately Positive	-	-
8	43	M	1702140087	150/14	Benign	Warthin's tumour	Parotid	-	-	-
9	20	M	406140013	510/14	Benign	Pleomorphic adenoma	Sublingual gland	Moderately Positive	-	-
10	40	M	1306140008	536/14	Malignant	Adenoidcystic carcinoma	Parotid	Weakly Positive	Moderately Positive	-
11	20	F	3007140024	700/14	Benign	Pleomorphic adenoma	Parotid	Strongly positive	-	-
12	74	M	2804140018	766/14	Malignant	Mucoepidermoid carcinoma	Minor salivary gland	Moderately Positive	Strongly Positive	-

13	36	F	109140276	809/14	Benign	Pleomorphic adenoma	Parotid	Strongly Positive	-	-
14	51	F	809140022	839/14	Benign	Myoepithelioma	Parotid	-	-	-
15	23	M	812140032	1120/14	Benign	Pleomorphic adenoma	Submandibular gland	Strongly Positive	-	-
16	31	M	3112140015	018/15	Benign	Pleomorphic adenoma	Parotid	Strongly Positive	-	-
17	34	F	907140035	048/15	Benign	Myoepithelioma	Parotid	-	-	-
18	40	F	401160042	074/15	Malignant	Mucoepidermoid carcinoma	Parotid	Strongly Positive	Strongly Positive	-
19	20	F	1002150205	137/15	Benign	Basal cell adenoma	Parotid	-	-	-
20	43	M	402150012	151/15	Benign	Pleomorphic adenoma	Submandibular gland	Strongly Positive	-	-
21	29	F	603150031	228/15	Benign	Pleomorphic adenoma	Parotid	Strongly Positive	-	-
22	60	F	60515007	495/15	Malignant	Basal cell adenocarcinoma	Parotid	-	-	-
23	38	F	2404150210	561/15	Benign	Pleomorphic adenoma	Submandibular gland	Strongly Positive	-	-
24	58	F	26051550041	661/15	Malignant	Carcinoma expleomorphic adnoma	Parotid	Strongly Positive	Strongly Positive	-
25	25	F	2106150015	750/15	Benign	Pleomorphic adenoma	Parotid	Strongly Positive	-	-
26	28	M	2406150057	776/15	Benign	Pleomorphic adenoma	Parotid	Strongly Positive	-	-
27	58	F	409150152	1220/15	Malignant	Adenoidcystic carcinoma	Minor salivary gland	Moderately Positive	Moderately Positive	-

28	49	F	1612150035	1797/15	Benign	Pleomorphic adenoma	Parotid	Strongly Positive	-	-
29	42	F	3112150074	1829/15	Malignant	Salivary duct carcinoma	Parotid	-	Weakly Positive	Strongly Positive
30	31	M	1202160040	490/16	Benign	Pleomorphic adenoma	Sublingual gland	Strongly Positive	-	-
31	35	M	1003160046	761/16	Benign	Warthin’s tumour	Parotid	-	-	-
32	22	F	3003160189	975/16	Benign	Pleomorphic adenoma	Parotid	Strongly Positive	-	-
33	48	F	3103160023	1031/16	Benign	Pleomorphic adenoma	Parotid	Strongly Positive	-	-
34	64	M	1104160057	1127/16	Malignant	Mucoepidermoid carcinoma	Parotid	Strongly Positive	Strongly Positive	-
35	23	F	1207160111	2243/16	Benign	Pleomorphic adenoma	Submandibular gland	Strongly Positive	-	-
36	26	M	2107160034	2374/16	Benign	Pleomorphic adenoma	Parotid	Strongly Positive	-	-
37	65	F	508160150	2543/16	Malignant	Polymorphous low grade adenocarcinoma	Minor salivary gland	-	-	-
38	42	F	20160803049	2602/16	Benign	Pleomorphic adenoma	Parotid	Strongly Positive	-	-
39	24	M	908160195	2641/16	Benign	Pleomorphic adenoma	Parotid	Moderately Positive	-	-
40	42	M	2608160033	2866/16	Benign	Pleomorphic adenoma	Parotid	Strongly Positive	-	-
41	40	F	20160970064	3013/16	Benign	Peomorphic adenoma	Submandibulargland	Strongly Positive	-	-
42	70	M	20160826082	3017/16	Malignant	Adenoidcystic carcinoma	Parotid	Moderately Positive	Moderately Positive	-

43	24	F	2809160181	3211/16	Benign	Pleomorphic adenoma	Parotid	Strongly Positive	-	-
44	38	F	20160926037	3223/16	Malignant	Adenoidcystic carcinoma	Parotid	Moderately Positive	Moderately Positive	-
45	30	F	1801170079	156/17	Benign	Pleomorphic adenoma	Parotid	Strongly Positive	-	-
46	39	F	20170221045	503/17	Benign	Pleomorphic adenoma	Sublingual gland	Strongly Positive	-	-
47	23	F	2303170144	798/17	Benign	Basal cell adenoma	Parotid	-	-	-
48	70	F	2612160187	442/17	Malignant	Mucoepidermoid carcinoma	Parotid	Strongly Positive	Strongly Positive	-
49	38	F	20170413054	992/17	Benign	Pleomorphic adenoma	Submandibular	Strongly Positive	-	-
50	60	F	20170419014	1009/17	Malignant	Adenoidcystic carcinoma	Parotid	Moderately Positive	Moderately Positive	-
51	31	F	2704170073	1077/17	Benign	pleomorphic adenoma	Parotid	Strongly Positive	-	-
52	35	F	1802170156	1139/17	Benign	Pleomorphic adenoma	Parotid	Strongly Positive	-	-
53	50	F	20170508073	1192/17	Malignant	Salivary duct carcinoma	Parotid	-	Weakly Positive	Strongly Positive
54	17	F	20170515045	1232/17	Benign	Pleomorphic adenoma	Parotid	Moderately Positive	-	-
55	23	F	706170076	1455/17	Benign	Pleomorphic adenoma	Sublingual gland	Strongly Positive	-	-
56	35	F	20170630043	1648/17	Benign	Pleomorphic adenoma	Parotid	Strongly Positive	-	-
57	65	F	20170803062	1982/17	Malignant	Salivary duct carcinoma	Parotid	-	Weakly Positive	Strongly Positive

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