A CORRELATIVE CYTOLOGICAL AND HISTOPATHOLOGICAL STUDY ON LESIONS OF SALIVARY GLAND

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CERTIFICATE

This is to certify that the dissertation entitled **"A CORRELATIVE CYTOLOGICAL AND HISTOPATHOLOGICAL STUDY ON LESIONS OF SALIVARY GLAND"** presented herewith by **Dr.S.MALLIGA** to the faculty of Pathology. The Tamilnadu Dr.M.G.R.Medical University, Chennai in partial fulfillment of the requirement for the award of M.D degree in Pathology is a bonafide work carried out by her during the period June 2004 –May 2006 under my direct supervision and guidance.

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CONTENTS

INTRODUCTION

Salivary glands are unique amongst the secretory glands, with most heterogenous group of tumors, exhibiting greatest histological diversity.

Bland Sutton aptly said "Tumors of the salivary gland are a pathological puzzle and a source of unsatisfactory speculation".

A swelling involving the salivary gland may be as a result of inflammation, cyst or neoplasm. 30% of parotid masses and 85% of submandibular masses are non-neoplastic. Tumors of salivary glands are uncommon and comprise less than 3% of all tumors of head and neck.

The nature of the lesion cannot be determined on clinical examination and therefore pathological examination is required for definite diagnosis in suspected cases of neoplastic disease.

Nowadays fine needle aspiration cytology has emerged as an effective and sensitive technique in the diagnosis of lesions of major or minor salivary glands. FNA is virtually risk free, simple, rapid, inexpensive technique and provides the clinician a definite preoperative diagnosis and thus can facilitate further management. The usefulness of FNA in salivary gland lesions was first observed by Karolinska group nearly 30 years ago who documented the diagnostic accuracy of FNA in a large series of cases.

Salivary glands are generally not subjected to incisional or core biopsy because of the possible risk of fistula, facial nerve injury and tumor implantation in the cases of neoplasms.

In the present study, the utility of FNA cytology in the diagnosis of salivary gland enlargement was studied by correlating the cytological findings with the histopathological features. Diagnostic accuracy, specificity and sensitivity were evaluated. The diagnostic pitfalls of FNA of salivary lesions were identified and the possible ways to rectify the misdiagnosis were proposed.

In addition, the recent literature regarding epidemiology, clinical features, cytopathology and histomorphology of salivary gland lesions were reviewed.

AIM OF STUDY

- To statistically evaluate the incidence of salivary gland lesions in and around Madurai.
- To assess the usefulness of cytological study in the diagnosis of salivary gland lesions.
- To evaluate the accuracy of FNAC studies in correlation with histopathological study.
- To analyze the false positive and false negative results of FNAC study with relevance to the salivary gland lesions.
- To determine and evaluate the causes for false positivity and negativity and to arrive at possible suggestions to minimize the percentage, in this regard.

REVIEW OF LITERATURE

Salivary glands are exocrine secretory organs specialized for the production of saliva. Saliva is a clear, colorless, tasteless, slightly acidic, viscid fluid, which keeps the mouth moist, lubricates food during chewing, aids digestion, helps to prevent cavities, and kills germs.

ANATOMY

There are both major and minor salivary glands. The major salivary glands are paired and named for their site: Parotid (Para- near; ot-ear), Submandibular (beneath the jaw), and Sublingual (beneath the tongue).

PAROTID GLAND

The parotid gland, or simply, the parotid, is the largest salivary gland. It is shaped like a flattened pyramid and weighs about 14-20 grams. It is enclosed in a sheath of deep cervical fascia and the gland is arbitrarily divided into superficial and deep lobes by the facial nerves.80percent of parotid is superficial to the nerve and 20 percent deep to the nerve entering the parapharyngeal space. Their secretion is serous in nature and drains along stenson's duct, which opens in the vestibule of mouth opposite second upper molar teeth. Accessory lobes are present in less than 50 percent of population.

SUBMANDIBULAR GLAND

The submandibular gland, also known as submaxillary gland, is about one third the size of the parotid and weighs 7-8 grams. They can be divided into larger

superficial and smaller deep lobe. The gland is surrounded by well-defined capsule that is derived from deep cervical fascia, which splits to close it. Its secretion is mixed with predominantly serous substance and opens at the side of the frenulum of the tongue close to the floor of the mouth. There are several lymphnodes immediately adjacent and within the superficial part of the submandibular gland.

SUBLINGUAL AND MINOR SALIVARY GLANDS

Sublingual gland is about one third the size of the submandibular gland, or about 10 percent the size of the parotid and weighs about 3gms.It produces mixed, predominantly mucus secretion and drained by rivinus duct which opens near or into the duct of submandibular gland.

Oral cavity contains approximately 450 minor salivary glands that lie just under the mucosa. Minor salivary glands are nonencapsulated aggregates of mucus or mixed mucus-serous glands, located superficially over the lips, throughout the oral cavity, nasopharynx, sinuses, trachea and bronchi. Overall they contribute to 10 percent of total salivary volume.

EMBRYOLOGY

The parotid derives from ectoderm, and the submandibular and sublingual glands probably derive from endoderm. They are arising as a bud from the oral epithelium between fifth to eighth weeks of embryonic life. The epithelium from the bud grows downward into the underlying connecting tissue and multiplies. The epithelial cells are modified and specialized to form salivary glands. Some of the cells form the secretory cells of the glands and others develop into ducts of the gland. The surrounding mesenchyme forms a capsule and interlobular septa. The

developing gland is colonized by lymphocytes, which eventually give rise to intra and extra parotid lymphnodes.

HISTOLOGY

The glands are organized into lobules. Each lobule consists of a cluster of acini around the terminal duct system. The acini are made up of pyramid shaped epithelial cells that have eccentric nuclei. The cytoplasm is abundant, finely granular and acidophilic in serous glands and clear in mucus glands. Flat myoepithelial cells with elongated nuclei form an outer layer around each acinus, which help to expel the secretion. Intercalated duct lead from the lobules of acini drain into striated ducts, which in turn form a collecting excretory ductal system, tributaries of which collect into large main duct that opens into the mouth. Cuboidal cells line the smaller excretory ducts, whereas those lining larger ducts are tall and columnar. Near the orifice in the oral cavity, the ducts are lined by stratified squamous epithelium

CYTOLOGY

Several types of cells can be seen in salivary gland aspirates, but the aspirate should contain both acinar cells and ductal cells. Acinar cells are normally outnumbering ductal cells. Acinar cells are usually present in cohesive balls, ie, acini. Serous, mucinous, or both types of acinar cells are present, depending on the specific gland aspirated. Ductal cells are present in cohesive, orderly sheets or in tubules. Adipose tissue and loose fibrous tissue and strands of endothelial cells can also see in the aspirate.

FINE NEEDLE ASPIRATION CYTOLOGY

During medieval times, the Arabian physician Abulcasim (1013-1107 AD) described needle puncture of the thyroid to diagnose different types of goiters.

Needle aspiration biopsy was first recorded by Kun in 1847. In the same year formal statement of the cell theory was stated by Schleiden and Schwann.

Before the modern microtomes were invented and routine thin sectioning of tissues were practical, cytologic smears were used to prepare specimens for microscopy. With the arrival of the modern microtome and paraffin embedding, the use of cytology was declined.

Papanicolaou presented his “New Cancer Diagnosis”, later known as the pap smear in the year 1928. After World War II, the Europeans, particularly the Scandinavians, reintroduced aspiration biopsy, now performed with fine needles[98].

There was a brief flowering of interest in cytologic techniques in the later 1920s and early 1930, as reported in the classic papers of Dudgeon and Patrick from England, who use cytologic, scrape preparations of excised tissue[98].

Stewart [121] (1933) commented that ‘parotid tumors are particularly suited to aspiration’ after he had examined 66 samples.

The foundations of current practice were established by the Karolinska group who between 1964-76 published a series of six studies on FNA of salivary glands[35].

Lindberg and Akerman [80] (1976) studied the cytologic reports in 461 patients during the year 1966-1972 and the cytological reports were correlated with final diagnosis. It showed exact agreement in 63% of cases, false reports in 8% and unsatisfactory smears in 11% of patients.

Geisinger and Weidner[56] (1986) commented that marked atypia in reactive, non neoplastic epithelium could result in a false positive diagnosis.

Nettle and Orell[96] (1989) studied FNAC in 187 cases of which 74 were benign tumors, 25 were malignant tumors. The cytologic diagnosis correlated exactly with

the histologic diagnosis in 95% of benign neoplasms and 68% of malignant neoplasms with overall accuracy of 88%.

Kocjan et al [71] (1990) performed FNAB in 52 patients of salivary gland lesions. False positive and false negative rates were 4% due to the morphological variability of these tumors, which could make the sampling and interpretation difficult.

Sherman ME et al [115] (1990) diagnosed a submandibular gland mass as an oncocytic nodule by FNAC, which showed pure populations of oncocytes. Although oncocytic metaplasia is commonly identified in the salivary glands of elderly patients, oncocytes rarely form masses that are targets for needle biopsy and he suggested that FNAC might be useful in salivary gland lesions in elderly patients who are not the candidate for surgery.

Cardillo MR[19] (1992) observed that AG-NOR technique is useful in the diagnosis of salivary gland lesions, with the advantage that the previously stained slides can be used for silver staining. It provides an excellent guide to the diagnosis especially in doubtful cases when corresponding histologic specimens or extra unstained slides are unavailable.

Jayaram et al [67] (1994) in their study of FNAC in 247 cases of salivary gland lesions, found the overall diagnostic accuracy of 91% for neoplastic lesions. The sensitivity rate in detecting malignant tumor was 87.8% and the specificity was 98%. There was 100% sensitivity rate for benign tumors.

Dodd et al [38] (1996) observed that a spectrum of neoplastic and non neoplastic lesions of the salivary glands may contain squamous cells. These include chronic sialadenitis, lymphoepithelial cyst, pleomorphic adenoma, Warthin tumor, mucoepidermoid carcinoma, and squamous cell carcinoma.

Li S et al[79] (2000) described the worrisome histologic alterations following FNAC include squamous metaplasia, infarction, necrosis, sub epithelial stromal hyalinization, granulation tissue with subsequent fibrosis, acute and chronic haemorrhage, inflammation with multinucleated giant cells, cholesterol cleft formation, psuedoxanthomatous reaction and microcystic degeneration.

Mukunyadzi et al [93] (2000) commented that infarction and various tissue effects secondary to FNAC can be minimized by using 25 gauge needles. It is safe and does not alter the histological diagnosis.

Jayaram et al [66] (2001) conducted a FNAC study in 141 salivary gland lesions and he observed that highest numbers of cases were seen in the sixth decade of life. There was no gender preponderance except in Warthin tumors that occurred predominantly in males. The parotid gland was the most frequent salivary gland needled. Pleomorphic adenoma and acinic cell carcinoma were the most common benign and malignant neoplasms diagnosed respectively. The overall diagnostic accuracy of FNA cytological diagnosis in salivary gland lesions was found to be 73.6%.

Lurie et al [85] (2002) studied the effectiveness of FNAC as a preoperative diagnostic tool of parotid tumors in 53 cases. He had 31 true negative and 16 false negative results. The calculated sensitivity, specificity, and accuracy of FNA diagnosis in the study were 66%, 100% 69.2% respectively.

He Y et al [62] (2003) evaluated the effectiveness of FNAC in the diagnosis of parotid gland masses. Among the121 parotid gland masses 62 were males, 59 were females with an average age of 57.88 years. The qualitative diagnostic accuracy was 89.26%. The sensitivity for tumors was 91.25% and the specificity was 100% with a false negative rate of 8.75%.

Das DK et al [30] (2004) conducted a study over a 6-year period (Jan'94-Dec'99). 712 patients aged between 6 months and 91 years (median, 37 years) were subjected to FNA of swellings in their salivary glands regions. Male: female ratio was 1.28:1. Cytologic diagnosis was correlated with histology in 45 cases. Benign nonneoplastic lesions were the most common (73%) followed by neoplasms (20%), and those with atypical cytology (1%). Sensitivity, specificity, and diagnostic accuracy of FNA cytology for all neoplastic lesions of the salivary gland were 60% 95% and 91.1% respectively.

Anjali et al[8] (2005) conducted a study in 185 patients with salivary gland enlargement. Histopathological correlation was done in 40% of benign and 80% of malignant neoplasms. Sensitivity of cytodiagnosis of benign and malignant neoplasms was 96.8% and 100% respectively. The specificity for cytodiagnosis of malignant neoplasms were 96.9%.

Maheswari et al [88] (2005) performed FNAC in 135 cases. The parotid glands were involved in majority of lesions (73.4%), followed by submandibular glands (20.2%) and minor salivary glands (6.30%). The cytological diagnosis was correlated with histopathology in 76 cases. The diagnostic accuracy for benign, malignant, and tumor like lesions were 94.7%, 71.4% and 95.48% respectively with an overall accuracy rate of 90.7%.

PLEOMORPHIC ADENOMA

The coexistence of apparently epithelial and mesenchymal elements gives rise to the synonym "mixed tumor"[36].

Mixed tumors represent 45% to 74% of all benign and malignant salivary gland tumors, about 50% of all parotid neoplasms and about 75% of the benign

tumors from all salivary gland sites[41]. Most common type seen in children and adolescents with a female predominance[55].

Frazell et al[101] (1951) found that the youngest patient was 7 years old and the oldest was 82 years of age in his study.

Histologically similar tumors occur in the lacrimal gland, skin (mixed tumor of skin or chondroid syringoma), breast and soft tissues[103].

HISTOPATHOLOGY

The histologic appearance consists of narrow tubular structures enveloped by myoepithelial mantles submerging in a chondromyxoid stroma. The myoepithelial mantle radiates centrifugally into sheets, clusters, and isolated cells, appearing to "melt" into the sea of stroma they produce[36].

Seifert et al (1986) sub classified Mixed tumors into four types according to the relative proportion of stroma and cellular components[36].

Type I : Extra cellular stroma comprises 30 -50% of the tumor(30% of the cases).

Type II : Extra cellular stroma comprises 80 % of the tumor (55 % of the cases).

Type III : Extra cellular stroma comprises 20-30 % of the tumor (9% of the cases).

Type IV : Extra cellular stroma attains similar proportion to that of type III but there is focal monomorphic differentiation in the epithelial component.

Erlandson et al [47] (1984) described the histogenesis and stated that pure epithelial tumor arises from the cells of the intercalated ducts that have the capacity to differentiate into both epithelial and mesenchymal components.

In immunohistochemistry the glandular lumina can be highlighted by EMA or CEA. The myoepithelial component is commonly positive for S-100 protein[36].

CYTOLOGY

The most common problem encountered in FNAB of salivary gland tumors was that of atypical features in pleomorphic adenoma, raising a suspicion of low-grade malignancy[99].

Buchner et al[18] (1981) stated that hyaline cells are modified myoepithelial cells and owe the dense hyaline appearance of their cytoplasm due to masses of intermediate prekeratin filaments.

Erlandson et al [47] (1984) declared that both epithelial cells, which are closely intermingled with loose clusters of mesenchymal cells, must be present for the diagnosis.

Stanley et al [120] (1990) observed that the epithelial component may show mucinous, squamous, oncocytic or sebaceous metaplasia and Palmer et al[100] commented that oncocytic metaplasia can be so extensive as to stimulate an oncocytoma or Warthin tumor.

Chan et al [22] (1992) found that hyaline cells have a plasmacytoid configuration with eccentric nuclei, the chromatin is relatively fine and evenly dispersed unlike the chromatin in plasma cells and the cytoplasm is dense and glassy unlike the granular cytoplasm of oncocytes or acinar cells.

Layfield et al [76] (1992) observed that squamous metaplasia may occur, in some cases yielding well – differentiated squamous cells and even pearls. Atypical squamous metaplasia (e.g.) associated with tumor infarction, may be misinterpreted as evidence of mucoepidermoid carcinoma. Mucus or goblet metaplasia can further mimic mucoepidermoid carcinoma.

Murthy et al [94] (1993) described the epithelial cells as round to oval to columnar cells with moderate pale staining cytoplasm. The cells usually have central or eccentric uniform, round nuclei with bland chromatin and tiny nucleoli. Intranuclear cytoplasmic invaginations can be seen.

Lee et al [77] (1996) evaluated the distinguishing morphologic features of pleomorphic adenoma and adenoid cystic carcinoma. He observed plasmacytoid individual tumor cells with abundant cytoplasm. It was a reliable finding in pleomorphic adenoma, and hence be differentiated from adenoid cystic carcinoma, which showed little cytoplasm.

Viguer et al [128] (1997) assessed the value of FNAC in the diagnosis of pleomorphic adenoma and the cytologic variations responsible for diagnostic errors. They studied 212 cases cytologically diagnosed as pleomorphic adenoma. The sensitivity and specificity were 92.6% and 98.4%. The cytologic variations such as celluar atypia, cystic transformation, and presence of cylindromatous pattern were responsible for the majority of the errors.

Mathur et al [91] (2002) reported 4 cases initially diagnosed on FNAC as spindle cell tumors, possibly benign peripheral nerve sheath tumor in the salivary gland lesions. Later histopathologically it was proved to be schwannoma in two cases and pleomorphic adenoma in other two cases. He concluded that benign peripheral nerve sheath tumor should be considered in the differential diagnosis of pleomorphic adenoma.

METASTASIZING MIXED TUMOR

Pitman et al[106] (1992) reported two cases of benign salivary gland pleomorphic adenoma metastatic to bone (benign metastasizing pleomorphic adenoma) which showed benign epithelial, myoepithelial, and stromal components

in FNAC. He also suggested that radiotherapy and vascular infiltration, either natural or iatrogenic during surgery as the possible factors that may contribute for subsequent metastases.

The site of metastases included bone, lung, regional lymph nodes, skin, kidney, retroperitoneum, oral region, pharynx, skull and brain. Metastases may occur synchronously with local recurrence, but may manifest many years after recurrence[58].

WARTHIN TUMOR.

First described by Albrecht[3] and Arzt in 1910 as papillary cyst adenoma though it is often known after Warthin (1929) who described further cases under the name of papillary cyst adenoma lymphomatosum[101] .

The second most common benign parotid neoplasm and it makes up to 6-10% of cases of parotid tumors. Bilateral or multicentric Warthin tumors are seen in 10% of cases[7].

The most popular pathogenetic concept is that Warthin tumor is a neoplasm that develops from heterotopic salivary duct present within preexisting intraparotid or paraparotid lymphoid tissue[3].

Allegra[5] (1971) suggested that Warthin tumor is a hypersensitivity reaction, rather than a true neoplasm triggered by metaplasia of the parotid ductal epithelium.

Kotwall[73] (1992) found that smokers have an increased risk of developing Warthin tumor.

Yoo et al [129] (1994) commented that an increasing incidence among women has been noted, possibly related to an increased prevalence of smoking among women.

HISTOPATHOLOGY

Warthin tumor is characterized by cystic spaces lined by a papillary proliferation of bilayered oncocytic epithelium whose supporting stroma is largely lymphoid tissue[7].

David et al [32] (1978) found that the lumen of the cysts contain thick proteinaceous secretions, cellular debris, cholesterol crystals, and sometimes laminated bodies that resemble corpora amylacea.

CYTOLOGY

Eneroth et al [43] (1967) described aspirates containing sheets of flat polyhedral oncocytes and scattered among amorphous debris mixed with lymphocytes. He found that oncocytes are highly characteristic feature of Warthin tumor but may be sparse.

Bottles et al [16] (1985) observed that Warthin tumor often has mast cells, which are best appreciated in Diff – Quick as small, round cells with, central nuclei and metachromatic cytoplasmic granule.

Eveson et al [50] (1986) reported that some of the apical cells show ciliated cells (which has been reported earlier in 1929 by Warthin) It must be rare, as most other investigators have failed to find such cells.

Smallman[116] (1989) found mucous or goblet cells or focal squamous metaplasia in Warthin tumor.

Chan et al [22] (1992) observed that in some oncocytes, the nuclei can be atypical (e.g., pleomorphism , binucleation, prominent nucleoli) .Nuclear pyknosis and nuclear ghosts (karyolysis) may also occur.

Mac leod et al [87] (1993) stated that Warthin tumor is a cystic neoplasm that may have glandular cells, squamous (metaplastic) cells, and mucus, as well as squamous like degenerated oncocytes and can mimic mucoepidermoid carcinoma in cytology.

Raymond et al [108] (2002) conducted a study during 1992-2000 to find out the accuracy of FNAC diagnosis from the suspected cases of Warthin tumor. A total of 41 cases were included in the study. The sensitivity and positive predictive value were 89.2% and 89.2% respectively. Three acinic cell carcinomas and one pleomorphic adenoma were misdiagnosed as Warthin tumor in FNAB.

Chae et al [21] (2004) reported a case of unilateral multicentric Warthin tumor arising from the peri and intra parotid glands with atypical squamous metaplasia cytologicallly mimicking metastatic cystic squamous carcinoma.

ONCOCYTOMA

The term oncocyte is derived from the greek word " onkousthai" meaning to swell. Hamperl applied this name to large cells with granular eosinophilic cytoplasm in the year 1931[101].

In line with the natural history of oncocytic metaplasia, oncocytoma most commonly occurs in the parotid gland of older adults. Radiation exposure to the head and neck region has been implicated in the pathogenesis of some cases[100].

HISTOPATHOLOGY

Oncocytomas have an organoid pattern of clusters of cells, separated by thin fibrovascular strands and often surround small lumens, but some tumors are arranged in short serpentine cords[7].

Ultra structurally, abundant cytoplasmic mitochondria are conspicuous and may occupy 60 percent or more of the cytoplasmic compartment[20].

CYTOLOGY

Eneroth et al [45] (1965) found that oncocytes usually have more abundant cytoplasm than Warthin tumor, and sometimes the cytoplasm contains coarser granules.

Feiner et at [51] (1986) observed psammoma bodies with in the lumen of glandular spaces in oncocytoma.

Dejmek et al [34] (1990) observed degenerated oncocytes (pyknotic nuclei, orange cytoplasm, pseudokeratosis), which can mimic squamous cell carcinoma.

Palmer et al[100] (1990) found that the tumor often consists of cells with granular, light and dark, eosinophilic cytoplasm.

Goode et al[59] (1988) found that minor degree of cellular atypia with nuclear hyperchromatism and pleomorphism may be allowable.

Brandwin et al[17] (1991) commented that the best method for demonstrating the mitochondria is phosphotungstic acid haematoxylin after 48 hours of incubation and they stain as dark blue cytoplasmic granules.

Cohen et al[28] (1992) found that the oncocytes may also form three – dimensional groups or microacinar structures, unlike Warthin tumor.

Verma and Kapila [127] (2003) noted that in oncocytoma, the aspirates were cellular, and oncocytic epithelial cells were found in sheets, papillary fragments as well as singly. Epithelial aytpia was minimal and lymphoid component was absent.

MONOMORPHIC ADENOMA

Monomorphic adenoma is a confusing term because it has been used to describe a specific entity, basal cell adenoma, as well as a diverse group of neoplasms that includes virtually any benign salivary gland tumor, except pleomorphic adenoma. Yet, many of these adenomas are probably variants of pleomorphic adenoma, with little or no stromal production[65].

BASAL CELL ADENOMA

Basal cell adenoma is a benign neoplasm dominated by basaloid epithelial cells and a uniform monomorphous architecture, and lacks the chondromyxoid stroma characteristic of mixed tumor[102].

Foote and Frazell referred these tumors as adenomatoid variant of a benign mixed tumor[7].

More than 75% occur in the parotid gland, and 6 % develop in the upper lip, the most common location being intra oral[103].

Microscopically the tumor cells are clearly separated from the non mucoid stroma by a well defined basement membrane. Peripheral cell palisading is the characteristic finding. Basal cell adenoma can be sub typed into solid, trabecular, tubular, and membranous categories on the basis of predominant pattern[7].

Seifert et al[113] (1992) stated that trabecular adenoma is a rare, benign neoplasm, a subtype of basal cell adenoma, which can produce hyaline globules (spheres and cylinders) similar to those seen in adenoid cystic carcinoma.

Lopez et al [83] (1993) described that exuberant hyalinization results in a picture similar to that of dermal eccrine cylindroma, the membranous type of basal cell adenoma, also known as dermal analog tumor.

CYTOLOGY

Hood et al [64](1983) found that the cells have uniform, dark, round nuclei, scant cytoplasm, and high nuclear / cytoplasmic (N/C) ratios, The chromatin is granular, nucleoli are small and inconspicuous. Basosquamous whorling (akin to pearls) has been noted in some cases.

Cohen et al[28] (1992) observed that the aspirate of basal cell adenoma is cellular and may be similar to pleomorphic adenoma. However it consists almost entirely of monomorphic epithelial cells, in cohesive groups, cords, or irregularly branching clusters, with variable numbers of single cells.

Vera Alvarez et al[126] (2004) found that basal cell adenoma in FNAC is characterized by aggregates of uniform epithelial cells and cell groups bordered on thick basement membrane like material.

CANALICULAR ADENOMA

Canalicular adenoma represents about 4-6% of minor salivary gland tumors especially involves mucosa of the upper lip or buccal mucosa adjacent to the lip[102].

Histologically canalicular adenoma is characterized by somewhat parallel rows of short to columnar cells forming elongated duct like structures that are reminiscent of canals. This unique growth pattern is responsible for the term canalicular adenoma[55].

Hruben et al[65] (1988) found that canalicular adenoma is composed of small, uniform cells, forming densely packed, cohesive tubule, trabeculae, or papillae, with scattered single cells. Intranuclear cytoplasmic invaginations may be seen, but neither mitotic figures nor necrosis is present.

Orell et al[99] (1988) stated that the nuclei appear bland, round, and uniform, with finely granular chromatin and inconspicuous nucleoli in cytology.

Abad et al[1] (1992) observed cytologically, this tumor can resemble adenoid cystic carcinoma, including the presence of hyaline globules and small basaloid cells.

SEBACEOUS ADENOMA, LYMPHADENOMA

Sebaceous glands are found in about 10 percent of normal parotid glands and 6 percent of sub mandibular glands but less than 0.2 percent of salivary gland tumors reveal sebaceous elements[55]. Sebaceous adenoma is a variant of monomorphic adenoma composed of vacuolated cells similar or identical to sebaceous cells occurring in the skin[102].

Auclair et al[11] (1991) stated that sebaceous lymphadenoma contains sebaceous cell nests, in a background of lymphoid tissue with well-developed germinal centers.

MYOEPITHELIOMA

Myoepithelioma is a benign tumor composed exclusively of neoplastic myoepithelial cells and their derivatives. It requires total absence of any ductal components for this designation[55]. Myoepithelioma tends to be more aggressive than pleomorphic adenoma and may convert into malignant myoepithelioma[124].

Myoepithelioma most frequently affects the parotid gland and palate, less commonly it can occur in the skin, breast or soft tissue [68].

Schultenover et al [112] (1984) observed that hyaline myoephitelial cells have a plasmacytoid appearance. They have an eccentric nucleus and abundant, homogeneous, dense or glassy, nongranular cytoplasm. The nuclei can be somewhat pleomorphic or hyperchromatic, but mitosis in the benign tumor are rare or nonexistent.

Franquemont & Millis [53](1993) described that the tumors composed primarily of plasmacytoid hyaline cells as non- myoepithelial monomorphic adenoma due to lack of immunohistochemical and ultrastructural evidence of myoid differentiation.

Dodd et al [37](1994) noted that spindle myoepithelial cells naturally are in a spindle or stellate shape. The cells have oval to elongated nuclei with fine, even chromatin. Nucleoli are inconspicuous. The cytoplasm is thin and wispy.

CYSTADENOMA

Cystadenoma represents about 4% of benign salivary gland tumor and 8 % of minor salivary gland tumors[55].

Cystadenoma is a benign salivary gland tumor, characterized by cystic proliferation of ductal epithelium. Since intraluminal papillary proliferation of the lining epithelium is a constant feature, cystadenoma is sometimes called as papillary cystadenoma[11].

Mucus and oncocytic metaplasia are some times present focally and even predominant occasionally[11].

INVERTED DUCTAL PAPILLOMA:

It is a rare benign tumor usually occurs in the lip and adjacent buccal mucosa. Patients are generally adults older than 30 years and there is no sex predilection. It is an intraductal papillary proliferation at the junction of salivary gland duct and oral mucosal surface epithelium. Papillary proliferation is primarily composed of stratified squamous epithelium covered by a layer of columnar ductal cells[55].

INTRADUCTAL PAPILLOMA

Intra ductal papilloma is a tumor involves excretory ducts of intra oral minor salivary glands. An extensive papillary tissue proliferation partially or completely fills a unilocular cystic structure. Histopathology shows intricately branching fronds of a single or double layer of uniform cuboidal to tall columnar ductal epithelium which is supported by thin cores of fibro vascular tissue[55].

Soofer and Tabbara[117] (1999) described the cytologic features of intra ductal papilloma. Three dimensional epithelial clusters, some with a papillary configuration and histiocytes were the main cellular components. The majority of the cells showed oncocytic differentiation, however benign appearing ductal cells in honeycomb sheets were also present.

SIALADENOMA PAPILLIFERUM

Sialadenoma papilliferum is a rare neoplasm occurs most often in hard or soft palate of adults[55]. Abrams and Finck (1969) reported a unique benign salivary gland tumor and they termed it as sialadenoma papilliferum because of its gross and microscopic resemblance to syringo cystadenoma papilliferum of the skin[36].

This tumor shows an exophytic or endophytic papillary proliferation of mucosal surface epithelium and salivary duct epithelium. Papillary stalks of stratified squamous epithelium with fibrovascular cores are in continuity with a cystic and ductal glandular epithelial proliferation immediately subjacent to the papillary mucosa[55].

MUCOEPIDERMOID CARCINOMA

Earlier in 1929 Mason & Berger described the neoplasm as 'epithelioma a double metaplasie'. Later De et al (1939) called it as a mixed epidermoid and mucus secreting carcinoma. The tumor was first described as a distinct entity by Stewart et al in 1945 who reported 45 cases[101].

It is the most common malignant salivary gland tumor and represents 41% of all malignant tumors of major and minor salivary glands in adults and childhood. The parotid (45%) and palate (21%) are the common sites of occurrence[41].

HISTOPATHOLOGY

Nicolatou et al[97] (1979) stated that the histological examination exhibits epidermoid cells growing in solid pattern, mucus producing cells and intermediate so called basal cells.

Liniger et al[81] (1981) stated that squamous cell carcinoma, which occurs in the salivary gland either as primary tumor (rare) or as a metastasis, is the main differential diagnosis of high –grade mucoepidermoid carcinoma.

The two-tier grading system is introduced by Evans[48] (1984) and it assesses only the histologic features. Low grade tumors have more than 10 percent intracystic spaces (areas occupied by stroma and extravasated mucin being not counted), while high-grade ones have less than 10 percent intracystic spaces.

Mucoepidermoid carcinoma can be classified into low, intermediate, and high grade types on the basis of morphology and cytologic features[102].

Low-grade tumors are often prominently cystic occasionally with papillary intraluminal growth; they have few mitotic figures and lack neural invasion, necrosis and cellular anaplasia. Intermediate grade tumors are usually more solid and have

cellular anaplasia and sometimes, neural invasion. In high-grade tumors, solid growth, anaplasia, and a high mitotic rate are typical and in some cases necrosis and neural invasion are evident.

The tumor cells are positive for keratin, EMA, CEA and actin. S-100 protein shows variable positivity[36].

CYTOLOGY

Zajicek et al[130] (1976) found that intermediate cells are relatively small cells, with high N/C ratios, and resemble normal ductal cells. Smears from low-grade tumors are dominated by mucoid material and well-differentiated, mucus-producing cells, whereas smears of high-grade mucoepidermoid carcinoma are dominated by clearly malignant-appearing cells, including glandular and squamous cells.

Kline et al [69] (1981) stated that both glandular and squamous components should be present to make a firm diagnosis of mucoepidermoid carcinoma and sometimes the immature squamous cells may have mucin vacuoles.

Clear cell make up (Miura et al 1986), oncocytic change (Sidhu et al 1975), and sebaceous differentiation (Hayes et al 1993) can also occur in mucoepidermoid carcinoma[7].

Cohen et al [27](1990) noted that mucoepidermoid carcinoma could be difficult to diagnose specifically with FNA biopsy. Different diagnostic problems occur with both high and low-grade tumors. Intermediate cells are most easily recognized when they are in cohesive clusters but they are often single and inconspicuous. Intermediate cells may be unique to mucoepidermoid carcinoma.

Cohen MB et al [27](1990) analyzed the FNAB in 96 specimens including 34 cases of mucoepidermoid carcinoma in order to identify the most useful criteria for

diagnosing mucoepidermoid carcinoma. The cytologic features selected as most predictive were intermediate cells, squamous cells and overlapping epithelial groups. Using these three features the sensitivity and specificity of accurately diagnosing mucoepidermoid carcinoma were 97% and 100% respectively.

Mac Leod et al [87](1993) found that the characteristic combination of squamous and mucinous cells in a cluster may not be seen in every case. The glandular cells are relatively bland, tall columnar, and contain mucin. They may resemble muciphages. Sparse cellularity and bland cells can result in a false-negative diagnosis.

Schneller et al [111](2001) commented that cytologic differential diagnosis of low grade mucoepidermoid carcinoma is with mucinous cystadenocarcinoma. He found bland nuclei in both mucinous cystadenocarcinoma and low-grade mucoepidermoid carcinoma.

ACINIC CELL CARCINOMA

10 % primary salivary gland carcinomas are acinic cell carcinomas. Most of these tumors arise in parotid gland and occasionally arise in submandibular gland or intra oral minor salivary glands. There is a slight female preponderance[102].

HISTOPATHOLOGY

Although serous acinar cell differentiation characterizes this group of tumors, they have a broad spectrum of architectural and cytologic features. Solid, microcystic, papillary- cystic and follicular growth patterns may contain acinar, intercalated ductal, vacuolated, clear, and nonspecific glandular cells[55].

Lewis et al [78](1991) found that the tumor is composed of serous acinic cells, usually well differentiated, without ducts in microscopy (although intercalated ductal cells can be demonstrated ultra structurally).

CYTOLOGY

Eneroth et al [46] (1966) observed that in acinar cells the cytoplasm is abundant and varies from foamy to coarsely granular. The zymogen granules are variably sized and are basophilic in papanicolaou, and reddish in Diff –Quick.

Eneroth et al[44] (1971) described that rarely this tumors are grossly cystic. The FNA biopsy specimen is more cellular than most nonneoplastic lesions and the cytologic diagnosis is based on finding acinic cells only, with a total absence of recognizable ducts.

Qizilbash et al[107] (1985) noted that the zymogen granules of acinic cells are diastase resistant, periodic acid-Schiff (DPAS) positive, in contrast with mitochondria of oncocytes and numerous naked nuclei may be seen in the background.

Nagel H et al [95](1997) noted that cytomorphologically acinic cell carcinoma is characterized by acinar differentiated tumor cells. In addition to these diagnostic clue cells, other types of neoplastic cells including vacuolated cells, cells resembling oncocytes and non-specific glandular cells are encountered. A pronounced lymphocytic reaction is a hallmark in 10 percent of tumors.

Ali SZ[4] (2002) disclosed the cytologic characters of papillary-cystic variant of acinic cell carcinoma after a retrospective morphologic review of the smears. Mostly tightly cohesive fragments of neoplastic epithelium are seen as monolayered sheets or with a prominent papillary architecture, high nuclear: cytoplasmic ratio

ductal- type epithelium, cystic material and degenerated cellular debris, histiocytes, cells with squamoid and metaplastic oncocytic changes, vacuolated and pigmented histiocyte-like tumor cells.

ADENOID CYSTIC CARCINOMA

First described in 1859 by Billroth who referred the tumor as a cylindroma (that describe the cylinder like top hat characteristic of the lesion)[101].

The word adenoid was derived from the greek words " adeno" means gland and "eidos" means "form". Foot and Frazell popularized the term adenoid cystic carcinoma in 1953[101].

Adenoid cystic carcinoma constitutes about 7.5% of carcinomas and 4% of all benign and malignant salivary gland tumors[55].

HISTOPATHOLOGY

There are two types of neoplastic cells in adenoid cystic carcinoma. The majority of cells are small basaloid myoepithelial type cells and foci of intercalated duct type cells and forming cribriform, tubular, and solid pattern[23].

Tandler[122] (1971) described that the neoplastic cells are surrounded by hyalinized stroma and are arranged around microscopic, pseudoglandular or microcystic spaces, which explains the designation, adenoid cystic. The spaces contain basement membrane – like material secreted by the myoepithelial cells that appears practically clear in haematoxylin and eosin or papanicolaou stain but it is intensely metachromatic (bright magenta) in Diff – Quick.

CYTOLOGY

Anderson et al[6] (1985) observed that the cytologic findings may be deceptively benign appearing, despite the malignant nature of the tumor, even in metastases.

Azumi et al[13] (1987) found that the tumor is composed of small cells, including undifferentiated cells, basaloid (ductal) epithelial cells, and myoepithelial cells.

Layfield et al[75] (1991) found that the hyaline globules of adenoid cystic carcinoma are intensely metachromatic, while the staining of those in trabecular adenoma is variable.

Chan et al[22] (1992) commented that occasionally, single cells are plentiful (but are not plasmacytoid, in contrast with hyaline cells)

Orell et al [98] found that the hyaline globules in monomorphic adenoma are smaller and of relatively uniform size which differentiate from adenoid cystic carcinoma.

POLYMORPHOUS LOW-GRADE ADENOCARCINOMA (PLGA)

Polymorphous low grade adenocarcinoma was first reported by Freedman and Lumerman in 1983 as lobular carcinoma and the following month by Batsakis et al as terminal duct carcinoma. During the following year, the term polymorphous low-grade adenocarcinoma was suggested as a clinically and morphologically descriptive term[55].

More than 70% of PLGA occur from 5th to 8th decades. The average age of patient is 59 years. There is 2:1 female predilection. The commonest site of

occurrence is the palate (60-70%) followed by buccal mucosa, upper lip and the tumor occurs exclusively in minor salivary glands[41].

Microscopically PLGA is characterized by cytological uniformity and morphological diversity. It has cells with regular bland nuclei arranged in a variety of patterns, including ducts, cribriform, papillary, and solid structures and diffuse infiltration with Indian filing[36].

CYTOLOGY

Cleveland et al [26](1994) observed that the FNA biopsy contains sheets, large tight clusters, or small acinic groups of cells with central lumens. Slight nuclear pleomorphism or membrane irregularity may be present.

Frierson et al [54](1987) noted that the cells are uniform, cuboidal to elongated myoepithelial or luminal duct cells, with uniform, round to oval nuclei granular chromatin, inconspicuous or absent nucleoli, and scant to moderate, granular cytoplasm.

MALIGNANT MIXED TUMOR

Malignant mixed tumor refers to two different entities, carcinoma ex pleomorphic adenoma (which is more common) and carcinosarcoma.

CARCINOMA EX-PLEOMORPHIC ADENOMA

Carcinoma ex-pleomorphic adenoma represents malignant transformation of a pre-existing pleomorphic adenoma, usually in the setting of an untreated, long-standing benign pleomorphic adenoma or in a tumor with multiple local recurrences[7].

The reported incidence of malignant transformation ranges from 1.9% to 23.3%[55].

Li volsi et al [82](1977) found that the diagnosis requires microscopic evidence of benign mixed tumor in association with carcinoma or carcinoma arising from a site of previous excision of a mixed tumor

Ellis et al[41] (1996) observed that the malignant element is most commonly undifferentiated carcinoma or poorly differentiated adenocarcinoma. PLGA, salivary duct carcinoma, squamous cell carcinoma, mucoepidermoid carcinoma, malignant myoepithelioma, adenoid cystic carcinoma, clear cell carcinoma, and papillary carcinoma have also been reported.

CARCINOSARCOMA

It is referred as true malignant mixed tumor, a rare neoplasm that comprises both epithelial and mesenchymal elements[102]. Although some have an antecedent history of pleomorphic adenoma, the majority of tumors arise de novo[7].

It represents less than 1% of salivary gland neoplasms in AFIP's files. About 65% have occurred in the parotid gland and another 22 percent have developed in the submandibular gland[102].

Microscopiclly the sarcomatous component is most often chondrosarcoma but osteosarcoma, fibrosarcoma, myxosarcoma, malignant fibrous histiocytoma and liposarcoma have been identified[55].

Ductal carcinoma is the most frequent carcinomatous element but squamous carcinoma and undifferentiated carcinoma have also been identified. The sarcomatous component usually dominates over the carcinomatous element[55].

EPITHELIAL / MYOEPITHELIAL CARCINOMA

This tumor had been previously described as glycogen rich clear cell adenoma (Feyrter1963) and first recognized by Donath et al (1972) as a malignant tumor. It comprises about 1 % of salivary gland neoplasms and about 75% of the neoplasm occurs in parotid gland[102].

The tumor composed of duct like structures lined by a single layer of ductal cells, which are surrounded by a single, or multiple layers of large clear myoepithelial cells[36].

CYTOLOGY

Kocjan et al[70] (1993) found that the FNA biopsy specimen shows two-cell population the epithelial and myoepithelial cells.

Arora et al[10] (1990) observed that the cells are arranged in cohesive, ball-like clusters and sheets, with a few isolated cells. Naked, oval, myoepithelial nuclei, similar in appearance to naked bipolar nuclei associated with benign breast aspirates, may be numerous.

SALIVARY DUCT CARCINOMA

Salivary duct carcinoma is a highly aggressive malignant tumor consisting of solid, papillary cystic, and cribriform patterns of growth and resembles in situ as well as invasive ductal carcinoma of the breast[84].

It constitutes 0.5 to 3.9 % of salivary glands carcinomas and 90% have developed in the parotid gland. The peak incidence is in the 6th to 7th decade of life. More prevalent in man than woman by the ratio of 2.5: 1[102].

Elsheikh et al[42] (1994) found that it is morphologically similar to ductal carcinoma of the breast, with a cribriform pattern that often exhibits central comedo necrosis

Microscopically variably sized, circular nodules of tumor that resemble intra ductal carcinoma of the breast are characteristic. Most tumor nodules are cystic and central comedo necrosis is a frequent finding with in the cystic nodules[102].

CYTOLOGY

The FNA biopsy is highly cellular and shows broad, flat, branching sheets or occasionally papillae of large, polygonal epithelial cells. The nuclei are round to oval with fine chromatin and prominent nucleoli[42].

Dee et al [33](1993) stated that the tumor is composed of malignant appearing large pleomorphic cells with abundant cytoplasm and prominent nucleoli.

Van Krieken et al[125] (1993) found positive staining for prostate specific antigen in salivary duct carcinoma.

BASAL CELL ADENOCARCINOMA

Basal cell adenocarcinomas are the uncommon malignant counterpart of basal cell adenoma[41].

Most basal cell adenocarcinomas arise de novo, but Luna et al have reported a series of eight carcinomas arose in basal cell adenoma[84].

Microscopically these carcinomas resemble cytologically and morphologically basal cell adenoma. Peripheral palisading of nuclei is less frequent and less prominent than in basal cell adenoma[55].

Seifert et al[113] (1992) commented that basal cell adenocarcinoma, should be distinguished from basal cell carcinoma of the skin.

CYTOLOGY

Pisharodi[105] (1995) found the FNAB specimen of basal cell adenocarcinoma contained cohesive, focally papillary and filiform groups of neoplastic cells which were highly reminiscent of basal cell adenoma (on low powder examination), but high power revealed significant cytologic atypia and mitotic activity.

UNDIFFERENTIATED CARCINOMA

World Health Organisation has defined undifferentiated carcinoma of salivary gland origin as "A malignant tumor of epithelial structure that is too poorly differentiated (by light microscopy) to be placed in any other groups of carcinoma"[103].

Undifferentiated carcinoma can be categorized into small cell type, large cell type and undifferentiated carcinoma with lymphoid stroma (lymphoepithelial carcinoma)[36].

Tumors composed of cells smaller than 30 micron are classified as small cell carcinoma and those with large cells as large cell carcinoma[36].

SMALL CELL CARCINOMA

This tumor is recognised since 1972 and Koss et al coined the name oat cell carcinoma[72].

The tumor cells are about twice as large as lymphocytes and uniform in size and shape. Nuclear molding, duct- like structures, psuedoglandular spaces and

rarely psuedorosettes can be evident. Para nuclear blue cytoplasmic inclusions similar to those seen in merkel cell carcinoma have been noted[55].

Currens et al[29] (1982) stated that the cytologic appearance is similar in many ways to that of small cell carcinoma of the lung, and a lung primary must be excluded before accepting this diagnosis.

Mair et al[90] (1989) found that the FNA biopsy yields abundant material, showing poorly cohesive small blue cells with high N/C ratio and nuclei about two to four times the size of a lymphocyte, with some nuclear molding and no glandular or squamous differentiation.

Chan et al [22](1992) stated that the smears show cells with vesicular nuclei, prominent nucleoli, a moderate amount of undifferentiated cytoplasm, and are commonly mixed with lymphocytes and plasma cells.

LARGE CELL CARCINOMA

Large cell undifferentiated carcinoma represents only about 1% of epithelial salivary gland neoplasms[119].

Microscopically, no distinct features of specific differentiation, such as acinar, ductal, epidermoid, or myoepithelial, are identifiable, although ultrastructural examination have described adenomatous, epidermoid, and neuroendocrine features among undifferentiated tumor cells[102].

The tumor cells are arranged in sheets, nests, and trabeculae within a fibrous stroma. The pleomorphic tumor cells may be predominately round or polygonal (spheroidal cell type) or fusiform (spindle cell type). The former cell type may result in confusion with a lymphoma and later with a sarcoma[103].

Moore JB et al [92](1998) described the cytologic findings in two cases of large cell undifferentiated carcinoma, which showed isolated loosely cohesive large cells with abundant cytoplasm and variability pleomorphic nuclei with prominent nucleoli. The pattern of positive Keratin, negative S-100 and HMB-45 and lack of conspicuous mucin production were helpful in establishing the correct diagnosis.

LYMPHOEPITHELIAL CARCINOMA

Malignant lymphoepithelial lesion and undifferentiated carcinoma with lymphoid stroma are synonymous with lymphoepithelial carcinoma[49].

These constitutes about 1% of salivary gland neoplasms[55]. The age of patients ranged from 10-86 years. An association of Epstein Barr virus infection and lymphoepithelial carcinoma has been documented[102].

Malignant epithelial cells are similar to those described for large cell undifferentiated carcinoma. Irregular islands of eosinophilic epithelioid cells are seen and permeated by lymphoid stroma, which may contain germinal centers[102].

ONCOCYTIC CARCINOMA

Oncocytic carcinoma is a highly aggressive neoplasm, represents less than 1% of all salivary gland tumors. The average age of patient is 63 years. Commonly affects parotid gland[102].

Microscopically the tumor cells have centrally located moderately pleomorphic nuclei with an abundant finely granular eosinophilic cytoplasm and tumor cells infiltrate salivary parenchyma and surrounding tissues. Ultra structure or special stains confirm excessive mitochondria[102].

Coagulative tumor necrosis appears to be specific for oncocytic carcinoma versus oncocytoma, and may confer an ominous prognosis[17].

PRIMARY SQUAMOUS CELL CARCINOMA

Diagnosis of primary salivary gland squamous cell carcinoma requires exclusion of primary disease in some other site, particularly the head and neck[102].

Microscopically, these tumors are typical keratinizing squamous cell carcinomas that are usually well to moderately differentiated[102].

Layfield et al [75](1991) observed that the presence of heavy keratinization and prominent pearl formation favours primary squamous cell carcinoma than high grade mucoepidermoid carcinoma.

CLEAR CELL ADENO CARCINOMA

Some monomorphous clear cell neoplasms lack features that are characteristic of other types of carcinomas and are classified separately as clear cell adenocarcinoma[102]. Uncommon salivary gland neoplasm comprised about I % of salivary gland neoplasms reviewed at the AFIP[55].

Microscopically monomorphous population of polygonal to round cells are seen with clear cytoplasm arranged in sheets, nests or cords. The cytoplasmic glycogen is demonstrated with periodic acid schiff staining[102].

CYSTADENO CARCINOMA

Cystadeno carcinoma is a malignant counter part of benign cyst adenoma and more than 60 percent occurs in the major glands[102].

Microscopically, the tumor is composed of numerous cyst like spaces and duct like structures lined by bland cuboidal epithelium. They infiltrate salivary gland parenchyma and surrounding connective tissue[102].

ADENO CARCINOMA (NOT OTHER WISE SPECIFIED)

The salivary gland adeno carcinoma termed not other wise specified fails to exhibit prominence of any of the histomorphological features that characterize the other, more specific carcinoma types[102]. They have been reported as miscellaneous, unclassified, or simply, adenocarcinoma[55].

The tumors are characterized by glandular or ductal structures with variable organization[102].

Grading[55] is based on cytomorphologic features and correlates with biologic behaviour. Low grade tumors have well formed ducts and tubular structures, minimal nuclear variability, and rare mitoses. Inter-mediate grade tumors have a moderate nuclear variability and a higher mitotic rate, whereas high grade tumors have hyperchromatic, pleomorphic nuclei, and numerous mitoses.

MUCUS-PRODUCING ADENOCARCINOMA

This tumor is characterized by clusters of tumor cells floating in pools of extracellular mucin[36].

Das et al [31] (1993) stated that the tumor exhibits overlapping groups of cells with abundant cytoplasm and occasionally contains small globules of intensely metachromatic mucus like material as seen in adenoid cystic carcinoma.

MALIGNANT MYOEPITHELIOMA / MYOEPITHELIAL CARCINOMA

This tumor can be defined as a malignant epithelial neoplasm in which the prominent differentiation of the tumor cell is myoepithelial cells[102].

Savara et al [109] (1999) mentioned that malignant myoepithelioma is distinguished from benign myoepithelioma by its infiltrative growth, increased mitotic activity, and cytologic atypia.

MALIGNANT LYMPHOMA

Primary lymphomas of the salivary glands are rare, accounting for only 2.4%-4.5% of salivary gland tumors. Salivary gland lymphomas can arise from salivary gland proper or from intra or para glandular lymph node[36].

According to the study by Gleeson et al [57] (1986), approximately 35% of cases are large cell lymphomas, 35% follicular lymphomas and 30% small cell lymphomas.

Seifert et al [113] (1992) commented that the lymphoma of the salivary glands is a component of the mucosa-assoicated lymphoid tissue (MALT).

MESENCHYMAL TUMORS

Kline et al[69] (1981) noted lipoma in the salivary glands, and FNA biopsy yields adipose tissue, perhaps with admixed acinic-ductal fragments.

Lay field et al[74] (1991) have drawn attention to lipomatous lesion of the parotid gland as a potential source of non diagnostic FNA reports as the material may be misinterpreted as subcutaneous fat.

Guttman[60] (1994) observed lymphangiomas in the salivary gland region.

Henke et al [63] (2001) reported a case of parotid lymphangioma which in FNAC showed 13cc of yellow coloured fluid with red blood cells, lymphocytes and rare fragments of benign appearing salivary gland epithelium.

Mathur et al[91] (2002) found that schwannoma in FNAC is characterized by spindle cells embedded in acellular ground substance, and mimics the stroma of pleomorphic adenoma.

SIALADENOSIS

Sialadenosis is a non inflammatory, non neoplastic diffuse salivary gland swelling and is usually bilateral[35].

Droese [39] (1981) found that the normal acini of the parotid measures about 50 micron in diameter, while in sialadenosis the acini enlarges up to 60 to 75 micron and can measure even up to 100 micron. The FNA biopsy usually obtains at least a few very large acini.

Layfield et al [75] (1991) observed that salivary gland enlargement occurs as a result of hypertrophy of the acinic cells and acini with fatty infiltration of the gland unassociated with inflammation and neoplasia. He also found that the acinic cell cytoplasm is swollen and may be deregulated.

SIALADENITIS

Sialadenitis commonly occurs in children and chronic sialadenitis affects the submandibular gland[39]. After radiation therapy, patients may develop salivary gland enlargement, particularly of the submandibular gland[75].

Droese[39] (1981) described the cytologic findings in sialadenitis. The smear contains a mixed population of neutrophils, foamy cells, and endothelial cells.

Droese [39] (1981) found that the FNA biopsy specimen is poorly cellular, containing groups of ductal epithelial cells, with irregular arrangement of nuclei,

some of which are pyknotic. Slight nuclear pleomorphism and vacuolization may be present in cases of radiation sialadenitis.

M. Frable et al[52] (1982) found that a neoplasm can obstruct a duct causing secondary chronic sialadenitis, which can result in false negative report.

Cohen et al[28] (1992) described that the ducts become dilated and filled with protein plugs and cyst formation occurs in some cases of sialadenitis.

Seifert et al[113] (1992) named a tumorus mass that may be hard and fixed in a patient with no prior history of pain and inflammation and affecting the submandibular gland as Kuttner' tumor or chronic scelrosing sialadenitis.

GRANULOMATOUS SIALADENITIS

Granulomatous diseases are more commonly found in lymph nodes than salivary glands. Among the salivary glands, parotids are particularly involved in about 6%of cases of sarcoidosis[116].

Mair et al[89] (1989) observed that microscopically, the granulomas are typical in appearance, ie, nodular collections of epithelioid histiocytes in which giant cells may also be found. The differential diagnosis should include granulomatous infections, such as tertiary syphilis and leprosy, as well as foreign body reactions.

Aggarwall et al[2] (1989) mentioned that granulomatous sialadenitis is usually due to sarcoidosis and sometimes it may be due to tuberculosis, cat scratch, toxoplasmosis, and fungal disease.

Aggarwall et al[2] (1989) described the cytological features of granulomatous sialadenitis. Epithelioid histiocytes are characterized by fibrillar cytoplasm and elongated, bland nuclei, with folded nuclear membranes and tiny nucleoli.

Variable numbers of lymphocytes, acinic and ductal cells, which may be distorted and degenerated can also be seen.

Perez Guillermo et al[104] (1992) described asteroid bodies, schaumann bodies and calcium crystals that are highly suggestive of sarcoidosis but are rarely found.

NECROTIZING SIALOMETAPLASIA

Spark et al[118] (1978) explained that necrotizing sialometaplasia is an uncommon benign disease that can mimic malignancy both clinically and microscopically. There is extensive squamous metaplasia of the ducts and acini accompanied by severe inflammation and granulation tissue.

Smallman[116] (1989) noted that necrotizing sialometaplasia occurs almost exclusively in minor salivary glands particularly of the palate and forms a well demarcated deep-seated ulcer or occasionally a swelling.

Schelkun et al[110] (1991) found that it is due to ischemic necrosis and usually occurs in a traumatized site or following radiation therapy.

ADENOMATOID HYPERPLASIA

Adenomatoid hyperplasia is a rare lesion of the mucous salivary glands and clinically appears as asymptomatic tumor like nodules and usually affect the palate. Histologically the lesion is characterised by non neoplastic proliferation of mucous glandular epithelium[9].

Aufdemorte et al[12] (1985) found that it mimics low grade mucoepidermoid carcinoma both clinically and cytologically.

BENIGN LYMPHOEPITHELIAL LESION

Benign lymphoepithelial lesion is referred as Mikulicz disease and myoepithelial sialadenitis, and is characterised by lymphoid infiltration of the salivary parenchyma, associated with atrophy of acini and ductal proliferation with formation of epimyoepithelial islands[102].

Droese[39] (1981) found that degenerative changes are characteristic but such clusters cannot be distinguished from ordinary regenerative ductal epithelium in chronic sialadenitis. The presence of hyalinized plaques indicates epimyoepithelial islands.

Batsakis[15] (1982) described two types of autoimmune sialadenitis mikulicz disease-localized and sjogren's syndrome – systemic where BLL is common.

Smallman[116] (1989) found that the patients are at increased risk of developing malignant lymphoma and carcinoma.

Mac Loed et al[86] (1991) observed that cytologically the epimyoepithelial islands resemble small three-dimensional clusters of reactive ductal cells infiltrated by lymphocytes.

Shaha et al[114] (1993) described the lesions show follicular hyperplasia, cystic dilatation of the ducts and ducts lined by psuedo stratified squamous epithelium and lymphocytic infiltrates.

BENIGN LYMPHOEPITHELIAL CYST

Elliot et al[40] (1990) observed that HIV-associated parotid cysts are characteristically multiple and bilateral. They are lined by epithelium surrounded by dense lymphocytic infiltration, with or without germinal center formation. Aspirated material contains a mixed population of small lymphocytes, follicular center cells,

immunoblasts, foamy histiocytes, tingible body macrophages, lymphohistiocytic aggregates, and plasma cells. A variety of multinucleated giant cells including foreign body, Touton and Warthin-Finkeldey types have also been described.

Shaha et al[114] (1993) noted the cytologic findings reflect the components of the cyst and inflammatory cells including macrophages may be the only cells in some aspirates.

Cleary et al[25] (1990) described the pathogenesis of benign lymphoepithelial cysts may be due to duct obstruction related to lymphoid hyperplasia or duct destruction related to cell-mediated immunity.

PAROTID GLAND IN HIV INFECTION:

Elliott et al[40] (1990) commented that parotid cysts or lymphadenopathy may be the presenting complaint in patients with HIV infection. Therefore, HIV infection should be excluded in patients presenting with enlarged or cystic parotid glands.

Tao et al[123] (1991) found that the aspiration of a cystic parotid lesion with abundant lymphoid stroma may suggest Warthin tumor, but oncocytes are not expected in HIV-associated cysts.

Chhieng et al[24] (1999) conducted a FNAB study in HIV infected cases with salivary gland lesions, and the majority of salivary gland lesions were cystic benign lymphoepithelial lesions, which can be managed conservatively. He stated that FNAC is a simple and cost effective procedure for the diagnosis of HIV related salivary gland lesions.

MATERIAL AND METHODS

Specimens from patients presented with symptoms and signs of salivary gland enlargement (unilateral or bilateral) of Rajaji Hospital, Madurai Medical College, Madurai during the period from June 2004 to May 2006 were included in the study.

Patients thorough clinical history including the site of swelling, duration, consistency, nature of facial nerve involvement, and status of adjacent lymphnodes were obtained (Annexure I).

The cytology smears were wet fixed in isopropyl alcohol for H & E[61] and PAP[61] stains, and air-dried for Giemsa stains[14].

As this study includes the histopathological correlation of salivary gland lesions, the received specimens were fixed in 10% buffered neutral formalin and processed either in toto or as small sections of 2-3 mm thickness in the usual way. Sections of 5-micron thickness were cut and stained with H&E. In doubtful cases the sections were submitted for special stains such as Alcian blue and PAS (Annexure III). Immunohistochemistry was done for some cases.

Photographs of the specimen and photomicrographs of the smears and sections were represented at relevant areas in discussion.

The salivary gland tumors are classified as per revised WHO classification and is shown in Annexure II.

The effectiveness of fine needle aspiration cytology of salivary lesions as an initial diagnostic tool can be expressed using the following parameters. The formula for assessing the sensitivity, specificity and diagnostic accuracy is as follows:

Screening Test Result	Diagnosis		Total
	Diseased	Not diseased	
Positive	True positive (a)	False positive (b)	a + b
Negative	False negative (c)	True negative (d)	c + d
Total	a + c	b + d	a + b + c + d

The following formulae are used,

* Sensitivity = $\frac{a}{(a+c)}$ x 100

* Specificity = $\frac{d}{(b+d)}$ x 100

* Accuracy = $\frac{a+d}{(a+b+c+d)}$ x 100

* Percentage of false negatives = $\frac{c}{a+c}$ x 100

* Percentage of false positives = $\frac{b}{b+d}$ x 100

OBSERVATION AND RESULTS

In the two-year study period from June 2004 to May 2006, 10442 general biopsy materials were received from Government Rajaji Hospital, Madurai. Among these, 103 cases were from salivary gland lesions. The average incidence of salivary gland lesions in this hospital was 0.98%.

Among the 103 cases, 82 (79.6%) were salivary tumors and 21 (20.4%) were tumor like lesions. (Diagram 1). Out of these 82 salivary gland tumors, 53 cases were benign tumors. Pleomorphic adenoma was diagnosed in 44 cases, basal cell adenoma (Fig 24) in 3 cases, Warthin tumor in 4 cases and oncocytoma in one case. The incidence of benign tumor was 51.45%.

29 were diagnosed as malignant tumors. Mucoepidermoid carcinoma was diagnosed in 14 cases, adenoid cystic carcinoma (Fig 22) in 5 cases, acinic cell carcinoma in 5 cases, carcinoma in Pleomorphic adenoma in 4 cases and PLGA (Fig 23) in one case. The incidence of malignant tumors of salivary gland was 28.15% (Diagram 2).

AGE INCIDENCE:

Among the patients with salivary gland enlargement 8 cases were seen in 11-20 years of age, 22 cases in 21-30 years, 21 cases in 31-40 years, 28 cases in 41-50 years, 13 cases in 51-60 years, 10 cases in 61-70 years and 1 case in above 70 years.

The peak incidence of salivary gland neoplasm was noted in the age group of 41-50 years (27.18%), followed by 21-30 years (21.25%) and lowest incidence in above 70 years of age. (Diagram 3)

Mean age incidence for benign tumors was 41 years and for malignant tumors was 46.5 years. In our study, the youngest patient was 13 years old and oldest was 75 years old.

SEX INCIDENCE:

Among the 103 cases with salivary lesions, 59 patients were female (57.28%) and 44 patients were male (42.72%). There is a female preponderance with a Male: Female ratio of 1:1.34. The age of female patients are ranging from 14-70 years and male patients from 13-75 years. Neoplastic lesions were predominantly seen in female and non neoplastic lesions were predominantly seen in male population. (Diagram 4).

ANATOMICAL DISTRIBUTION:

Among the 103 cases of salivary lesions, 60 cases were found in parotid with an incidence of 58.25%. Sub mandibular lesions were observed in 30 cases (29.12%). The other minor salivary glands involvement was observed in 13 cases (12.6%). (Diagram 5).

In parotid, among the 60 cases, pleomorphic adenoma was the common lesion, with the incidence of 48.3% followed by mucoepidermoid carcinoma, which showed the incidence of 16.7%. In sub mandibular gland, among the non neoplastic lesions, chronic sialadenitis was the most common lesion (incidence 46.6%). In minor salivary glands, malignant tumors predominate the lesions with the incidence of 53.8%.

FINE NEEDLE ASPIRATION CYTOLOGY OF SALIVARY LESIONS

During the study period, FNAC was performed in 97 cases, 75 patients with parotid swelling, 20 with submandibular swelling and 2 cases from minor salivary lesions. Among them, 48 cases had post surgical histopathological correlation.

CYTOLOGIC DIAGNOSIS:

Out of the 48 smears, benign salivary gland tumor was reported in 26 cases. Among them pleomorphic adenoma (Fig 1,2) was the commonest tumor found in 24 cases. One case of Warthin tumor (Fig 6) and one case of oncocytoma (Fig 8) were reported.

Mucoepidermoid carcinoma (Fig 12,13,14) was the common malignant tumor diagnosed in 7cases. Two cases were found to be acinic cell carcinoma (Fig 18,19). 9 cases were reported as non-neoplastic lesions. (Table No.1)

HISTOPATHOLOGICAL DIAGNOSIS:

With histopathological study, the most common benign tumor encountered was pleomorphic adenoma (Fig 4) with the incidence of 43.75%. Warthin tumor (Fig 7) and oncocytoma (Fig 9) were the other two cases.

Among the malignant tumors, mucoepidermoid carcinoma (22.91%) was the commonest lesion (Fig 16). Acinic cell carcinoma (Fig 21) and carcinoma in Pleomorphic adenoma were the other cases diagnosed.

In the 9 non-neoplastic lesions, 5 cases were found to be chronic non specific sialadenitis. One case of actinomycosis (Fig 25), one case of tuberculous sialadenitis (Fig 26) and one case of benign lymphoepithelial cyst were encountered in the rest of the cases. (Table 2)

CORRELATION BETWEEN CYTOLOGICAL AND HISTOPATHOLOGICAL DIAGNOSIS

In the present study, 24 cases were cytologically diagnosed as pleomorphic adenoma. Among them 19 cases were subsequently confirmed. Among the rest of

5 cases, one case was reported as tuberculous sialadenitis .The other 3 cases were false negatively diagnosed as benign lesions, but histopathology revealed carcinoma in pleomorphic adenoma and one case was found to be Neurofibroma.

7 cases, which were given as mucoepidermoid carcinoma in cytology, and later confirmed by histopathology. 2 cases were reported in cytology as Acinic cell carcinoma and confirmed by histopathology.

Of the 9 cases, which were reported as non neoplastic lesions in cytology, five cases were found to be chronic, non - specific sialadenitis, one case of tuberculous sialadenitis, one case of actinomycosis of parotid gland and one case as a benign lymphoepithelial cyst in histopathology. One case was reported as a cystic lesion in cytology later found to be a low grade mucoepidermoid carcinoma.

Among the four unsatisfactory smears, 3 cases were found to be mucoepidermoid carcinoma and one case of pleomorphic adenoma in histopathology. (Table3).

SENSITIVITY AND SPECIFICITY:

PLEOMORPHIC ADENOMA:

In the present study, a cytological diagnosis of pleomorphic adenoma was made in 24 cases, among them 19 cases were proved in histopathology. One case was reported as tuberculous sialadenitis (false positive) in histopathology. The other 3 cases were false negatively diagnosed as benign lesions, but in histopathology it revealed carcinoma in pleomorphic adenoma and one case was found to be neurofibroma. The sensitivity of FNAC in diagnosing pleomorphic adenoma in our series is 86.36% while the specificity is 90.9%. The diagnostic accuracy is 88.63%.

MUCOEPIDERMOID CARCINOMA:

Final confirmatory histopathological diagnosis of mucoepidermoid carcinoma was made in 7 (True Positive-7) out of 7 cases with initial cytological diagnosis of mucoepidermoid carcinoma. One case was false negatively reported as cystic lesion in cytology, but histopathology showed features of mucoepidermoid carcinoma.

After evaluating the above findings, the sensitivity, specificity and accuracy in detecting mucoepidermoid carcinoma were found to be 87.5%, 100% and 97.72% respectively.

WARTHIN TUMOR

Out of 48 cases of FNAC studied, only one case was detected as Warthin tumor. This was later confirmed in histopathology with a diagnostic accuracy of 100%.

ONCOCYTOMA

One case of oncocytoma was reported in cytology. Histopathology also revealed the same and the diagnostic accuracy was found to be 100%.

ACINIC CELL CARCINOMA

Acinic cell carcinoma was diagnosed in 2 cases out of the 48 smears. It was confirmed in histopathological examination and showed a diagnostic accuracy of 100%.

NON NEOPLASTIC LESIONS

Among the 9 cases, which were diagnosed in cytology as non neoplastic lesions, 5 cases were found to be chronic non specific sialadenitis and one case of tuberculous sialadenitis. Actinomycosis and benign lymphoepithelial cyst were the other 2 cases. One case was false negatively diagnosed cystic lesion but histopathology revealed mucoepidermoid carcinoma. In diagnosing non neoplastic lesions the sensitivity was 88.8%, while the specificity of 97.14% and the diagnostic accuracy of 95.45%.

DISCUSSION

Recently FNAC is becoming a widely recognized practical and useful technique in the diagnosis of salivary gland lesions.

The technique is simple and rapid, and no expensive instruments are needed. The cytological diagnosis is rapid and eliminates the need for surgical procedures. Moreover it is safe and well tolerated by most of the patients.

The salivary gland lesions in the present study show the incidence rate of 0.98%, which is fairly correlating with similar studies conducted in other centers.

AGE INCIDENCE

Most cases in our study were in 5th decade. He Y et al[62] and Jayaram et al[66] in their studies had higher incidence of cases in 6th decade.

Mean age incidence for benign and malignant tumors was 41 years and 46.5 years respectively. It correlates with the study of AFIP registry[41], which showed 46.1 years for benign tumors and 47.1 years for malignant tumors.

SEX INCIDENCE:

In the present study there is a female preponderance with a Male: Female ratio of 1:1.34. Das DK et al[30] and Anjali et al[8] showed a higher incidence cases in male population. Table 4 shows the comparison of sex incidence with other series.

ANATOMICAL DISTRIBUTION:

In the present study, most of the salivary gland tumors are found in parotid region (64.63%) followed by submandibular (19.51%) and 15.85% in minor salivary glands.

When compared with other centers the minor salivary gland showed higher incidence of tumors in our study. Table no.5 shows the distribution of salivary gland neoplasms with comparison.

FNAC DIAGNOSIS AND ASSESSMENT OF HISTOPATHOLOGICAL FOLLOW-UP AND CORRELATION

Fine needle aspiration was carried out using 5cc/10cc disposable syringe with 22 gauge needle. All possible efforts were taken in the technique of sampling and smear preparation so as to obtain better cytological / histopathological correlation.

PLEOMORPHIC ADENOMA

Pleomorphic adenoma was the commonest benign tumor in our study. The criteria used to define pleomorphic adenoma were, Chondromyxoid background, and varying combinations of epithelial and mesenchymal cells. (Figure 1,2).

Pleomorphic adenomas were grossly presented as well circumscribed tumors with smooth surface. The cut surface showed tan to white colour with myxo chondroid zones. (Figure 3).

Histopathologically Pleomorphic adenoma showed biphasic appearance with intimate admixture of epithelium and chondromyxoid stroma. (Figure 4). Immunohistochemistry showed S-100 protein positivity in the abluminal myoepithelial cells. (Fig 5)

The sensitivity of FNAC in diagnosing pleomorphic adenoma in our series is 86.36% while the specificity is 90.9%. Viguer et al[128] also had the sensitivity and specificity of 92.6% and 98.4% respectively. The reason for low sensitivity in our study was due to 3 false negative cases. 3 cases of carcinoma in pleomorphic adenoma were reported as pleomorphic adenoma in cytology. The specificity in our study when compared to Viguer et al[128] was low.

Sampling and interpretation errors are the reason. This can be avoided by taking adequate samples and aspirations from multiple sites. The cytologic variations in FNAC of pleomorphic adenoma must be considered in order to avoid important errors in diagnosing salivary gland lesions.

WARTHIN TUMOR:

1 case has cytohistopathological correlation and was later histopathologically confirmed with the diagnostic accuracy of 100%. FNAC showed bland oncocytic cells in cohesive monolayered sheets and many lymphocytes. (Figure 6). Histopathologically Warthin tumor showed cystic spaces lined by papillary proliferation of bilayered oncocytic epithelium with a supporting lymphoid tissue rich stroma. (Figure 7).

ONCOCYTOMA:

1 case was diagnosed in cytology, and later confirmed by histopathology in a female patient. Cytology revealed sheets and groups of cells with abundant granular eosinophilic cytoplasm, central or eccentric vesicular nuclei with distinct cell boundaries. (Figure 8) Oncocytoma showed an organoid pattern of clusters of cells with abundant eosinophilic cytoplasm separated by thin fibro vascular strands in histopathology. (Figure 9).The diagnostic accuracy in diagnosing oncocytoma was 100% in the present study.

NEUROFIBROMA:

One case was diagnosed as neurofibroma (Fig 11) in parotid gland, earlier in cytology it was reported as pleomorphic adenoma. Cytology revealed spindle cells with moderate degree of cellular pleomorphism and fibrillar background (Fig 10), and misdiagnosed as pleomorphic adenoma. Benign peripheral nerve sheath tumor should be considered in the differential diagnosis of pleomorphic adenoma as observed by Mathur et al[91].

MUCOEPIDERMOID CARCINOMA:

In cytology, the smears showed cohesive clumps and sheets of cells and small streams of cells within mucus with dirty background. Variation in cell type- intermediate, squamous, mucin secreting cell with abundant cytoplasm were also observed. (Fig12,13). Cytoplasm showed metachromatic mucin vacuoles in Giemsa stain (Fig 14).

Mucoepidermoid carcinoma grossly presented as grey to tan yellow solid mass, with cystic degeneration (Fig 15).

Histopathology showed varying combinations of mucus, epidermoid and intermediate cells in both solid and cystic configuration. In high grade tumors solid growth with areas of necrosis and neural invasion are evident. Low grade mucoepidermoid carcinomas are prominently cystic in nature. (Fig 16). Immunohistochemistry showed EMA positivity. (Fig 17).

The sensitivity, specificity and accuracy rates in detecting mucoepidermoid carcinoma were found to be 87.5%, 100% and 97.72% respectively. The diagnostic accuracy in the present study is in accordance with the study of Maheswari et al[88] who reported an accuracy rate of 85.7%. Cohen et al[27] had the sensitivity and specificity of 97% and 100%respectively.

The low sensitivity in our study was due to false negative reporting of one case of mucoepidermoid carcinoma as a cystic lesion. Low grade Mucoepidermoid carcinoma is usually cystic and the aspirate yields mucoid fluid and sparse cellularity with no obvious malignant nuclear features. These aspirates often lead to false- negative interpretations. The cytologic diagnosis of cystic aspirates should be interpreted with caution.

ACINIC CELL CARCINOMA

2 cases had been reported in cytology as acinic cell carcinoma with a cytohistopathological correlation. Both were female patients with a history of recurrence. The cytology showed highly cellular smears. The cells were in cohesive clusters with mildly pleomorphic nuclei and abundant granular cytoplasm and were resembled acinar cells (Fig 18). In MGG stained smears the cytoplasm was vacuolated foamy and gray. (Fig 19).

Grossly acinic cell carcinoma was found as solid, multi nodular grey to yellow mass. (Fig 20). Histopathology showed solid sheets of differentiated acinar cells traversed by thin fibrovascular strands. Clear cells were predominating the lesion in some cases. (Fig 21). The diagnostic accuracy in diagnosing acinic cell carcinoma was found to be 100%.

NON NEOPLASTIC LESIONS

Submandibular gland showed the most of the non neoplastic lesions. The cytological smears showed mostly ductal epithelial cells and fewer atrophic acinar cells in the background of inflammatory cells and were reported as inflammatory non neoplastic lesions.

Of the 9 cases, five cases were chronic, non specific sialadenitis, one case was tuberculous sialadenitis. Tuberculous sialadenitis in cytology revealed epithelial cells and collections of epithelioid cells in a necrotic background. Histopathology also showed epithelioid cell granulomas with Langhans' giant cells. (Fig 26).

One case of actinomycosis of parotid gland was diagnosed which showed inflammatory cells in the cytology. Gram positive actinomycotic bacterial filaments with peripheral Hoeppli- Splendore reaction were observed in histopathological sections (Fig 25).

One case was diagnosed as benign lymphoepithelial cyst. Histopathology showed salivary acini and a cyst lined by stratified squamous lining with lymphoid tissue.

In cytology one case was false positively reported as pleomorphic adenoma but histopathology revealed tuberculous sialadenitis. Necrotic background and epithelioid cells were misinterpreted in cytology as Pleomorphic adenoma.

In diagnosing non neoplastic lesions, the sensitivity was 88.8% and the specificity was 97.14%. The diagnostic accuracy was 95.45% which is in accordance with the study of Maheswari et al[88] who had the diagnostic accuracy of 95%.

The overall diagnostic accuracy in diagnosing salivary gland lesion was found to be 86.36%, which correlates with the studies, conducted by Jeyaram et al[66], Nettle & Orell[96] and Maheswari et al[88]. The comparative study is shown in table no.6.

SUMMARY

The study, FNAC of salivary gland lesion with subsequent correlation of histopathology revealed the following findings.

1. Of the 10442 general biopsy materials received from Government Rajaji Hospital, Madurai during the study period (June 2004-May 2006) salivary gland masses were encountered in 103 cases with an incidence of 0.98 %.
2. The most common lesion in the present study was pleomorphic adenoma, which accounted for 50% of the cytology smears and 41.6% of histopathology specimens.
3. The malignant tumors had the incidence of 18.75% in cytology and 33.3% in histopathology.
4. Mean age at diagnosis for benign tumors was 41 years and for malignancy 46.5 years.
5. The peak incidence for the salivary lesions was noted in the age group of 5^{th} decade and was rare after the 7^{th} decade.
6. There was a female preponderance with a male: female ratio of 1:1.34.
7. The sensitivity, specificity, diagnostic accuracy in diagnosing benign neoplasms in the present study were found to be 88%, 94.3% and 90.9% respectively.
8. The low sensitivity was due to false negative reporting of 3 malignant tumors as benign lesions in cytology.

9. In diagnosing malignant lesions, the sensitivity was 87.5%, the specificity was 100% and the diagnostic accuracy was 97.72%.
10. One case of Mucoepidermoid carcinoma was false negatively diagnosed as cystic lesion in cytology. So, the cystic aspirates should be interpreted with caution.
11. In diagnosing non neoplastic lesions, the sensitivity was 88.8% and the specificity was 97.14%. The diagnostic accuracy was 95.45%.
12. The overall diagnostic accuracy of fine needle aspiration cytology in diagnosing salivary lesions was found to be 86.36%

CONCLUSION

FNA is a simple, rapid and sensitive technique for the diagnosis of salivary gland lesions. It is a difficult area for the cytopathologist, due to great variety of benign and malignant neoplasms occurring in this site.

In the present study, the sensitivity, specificity, and diagnostic accuracy in diagnosing benign neoplasms were found to be 88%, 94.3% and 90.9% respectively. In diagnosing malignant lesions, the sensitivity was 87.5%, the specificity was 100% and the diagnostic accuracy was 97.72%.

In our experience, we feel, however, that sufficiently high accuracy can be achieved by FNA study and this can be an useful guide in making decisions for further management in patients with salivary gland lesions.

In an era where advances in technology have added enormously to the burden of healthcare costs and facilities like ultrasound, sialography, CT sialography and immune markers are available to aid the diagnosis of salivary gland tumors. The continued and accelerated use of the FNA cytology has reduced the costs and has released significant resources for alternate uses, a matter, that the pathologist can feel justifiably proud of.

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ANNEXURE -I

PROFORMA

Name : Age : Sex :

IP/OP No. : Unit : Ward :

Cytology No. : Histopathology No. :

CLINICAL SYMPTOMS

Site of Swelling	:	Parotid / Submandibular / Sublingual / Others
Duration of Swelling	:	
Pain	:	Present / Absent
Rate of growth	:	Slow / Rapid
H/O of previous surgery	:	Present / Absent
H/O Recurrence	:	Present / Absent
Facial nerve involvement	:	Present / Absent

GENERAL EXAMINATION:

X-Ray, Ultra Sound / C.T : If done findings

LOCAL EXAMINATION :

Site	:	Parotid / Submandibular / Sublingual / Others
Size	:	
Consistency	:	Soft / Firm / Hard / Cystic
Fixity	:	Mobile / Immobile
Ulceration of skin	:	Present / Absent
Sinus Tract	:	Present / Absent
Facial Palsy	:	Present / Absent
Lymphadenopathy	:	Present / Absent
		Site / Number / Size / Consistency / Matted/ Discrete

CYTOLOGY:

Cellularity	:	Scanty / Adequate / Cellular
Epithelial Cells	:	Uniform / Pleomorphic
Myoepithelial cells	:	Spindle / Plasmacytoid
Variation in epithelial cell type	:	Intermediate / Squamous / Mucous
Oncocytes	:	Monolayered / Multilayered
Inflammatory cells	:	Neutrophils / Lymphocytes
Hyaline Globules	:	Present / Absent
Back ground stroma	:	Dirty / clean / chondromyxoid / mucoid / haemorrhagic

DIAGNOSIS

HISTOPATHOLOGY

GROSS:

MICROSCOPIC FINDINGS:

MARKER STUDY:- (If any)

DIAGNOSIS:

ANNEXURE - II

CLASSIFICATION OF SALIVARY GLAND TUMORS

Revised WHO histological classification of salivary gland tumors and tumor like lesions

1. Adenomas

1.1 Pleomorphic adenoma

1.2 Myoepithelioma

1.3 Basal cell adenoma

1.4 Warthin tumor

1.5 Oncocytoma

1.6 Canalicular adenoma

1.7 Sebaceous adenoma

1.8 Ductal papilloma

1.8.1 Inverted ductal papilloma

1.8.2 Intra ductal papilloma

1.8.3 Sialadenoma papilliferum

1.9 Cyst adenoma

1.9.1 Papillary cystadenoma

1.9.2 Mucinous cystadenoma

2. Carcinomas

2.1 Acinic cell carcinoma

2.2 Mucoepidermoid carcinoma

2.3 Adenoid cystic carcinoma

2.4 Polymorphous low grade adenocarcinoma

2.5 Epithelial and myoepithelial carcinoma

2.6 Basal cell adenocarcinoma

2.7 Sebaceous carcinoma

2.8 Papillary adenocarcinoma

2.9 Mucinous cystadenocarcinoma

2.10 Oncocytic carcinoma

2.11 Salivary duct carcinoma

2.12 Adeno carcinoma (not otherwise specified)

2.13 Malignant myoepithelioma

2.14 Carcinoma in Pleomorphic adenoma

2.15 Squamous cell carcinoma

2.16 Undifferentiated carcinoma

2.17 Other carcinomas

3.Nonepithelial tumors (Angioma, Lipoma, Neural tumors)

4.Malignant Lymphomas

5.Secondary tumors

6.Unclassified tumors

7.Tumor like lesions

7.1 Sialadenosis

7.2 Oncocytosis

7.3 Necrotising sialometaplasia

7.4 Benign lymphoepithelial lesion

7.5 Salivary gland cysts

7.6 Chronic sclerosing sialadenitis of submandibular glands (Kuttner tumor)

7.7 Cystic lymphoid hyperplasia in AIDS

ANNEXURE – III

MAY – GRUNWALD – GIEMSA TECHNIQUE[14]

Stock Stain	-	Giemsa powder 0.38 gm
		Glycerin 25 ml
		Methyl alcohol 25 ml
Working solution		To 1 ml of stock stain add 10 ml of distilled water

STAIN PROCEDURE:

Immerse air dried aspiration smears in May – Grunwald working stain for 15 mintues. Rinse gently in tap water Immerse smears in Giemsa stain for 15 minutes. Rinse gently in tap water. Allow to air dry. Dip in xylene and mount in D.P.X.

PERIODIC ACID SCHIFF TECHNIQUE[61]

1. Bring sections to water.
2. Oxidize for 5-10 minutes in 1% aqueous periodic acid.
3. Wash in running water for 5 minutes and rinse in distilled water.
4. Treat with schiff reagent for 10-30 mintues.
5. Transfer directly to first sulphite rinse for 1 minute and to the second sulphite rinse for 2 minutes. Transfer to the third sulphite rinse for 2 minutes.
6. Wash for 10 minutes in running water.
7. Counter stain with haematoxylin.
8. Dehydrate clean and mount in D.P.X.

RESULT :

PAS positive substances are bright red in colour.

ALCIAN BLUE TECHNIQUE[14]

STAINING SOLUTION :

Alcian blue	-	1gm
Glacial acetic acid	-	3 ml
Distilled water	-	97 ml

Mix and filter. Add a crystal of thymol to prevent mold. pH should be adjusted to 2.6.

PROCEDURE:

Bring sections to water.

Place in 3% acetic acid for 2 minutes.

Place in alcian blue solution for 30 minutes.

Wash in running water, counterstain with Harri's haematoxylin

Dehydrate in graded alcohol, clear in xylene and mount.

RESULT:

Mucinous substances are bright turquoise blue in colour.

ANNEXURE-IV

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ANNEXURE – V

MASTER CHART

S.No	AGE	SEX	OP/ IP No	SITE	DURATION	HPE. NO	DIAGNOSIS	CY.NO	DIAGNOSIS
1	26	M	206604	1	3months	2164/04	Chronic sialadenitis	_	_
2	17	F	271083	2	6months	2177/04	Chronic sialadenitis	_	_
3	54	M	275308	2	3months	2281/04	Chronic sialadenitis	_	_
4	42	M	272261	1	1year	2369/04	Pleomorphic adenoma	_	_
5	75	M	272493	1	2years	2503/04	Pleomorphic adenoma	705/04	Pleomorphic adenoma
6	23	F	245539	1	6months	2767/04	Mucoepidermoid carcinoma	83/04	Scanty
7	32	M	282082	2	6months	2868/04	Chronic sialadenitis	880/04	Sialadenitis
8	50	M	281708	1	8months	2935/04	Warthin tumor	845/04	Warthin tumor
9	37	F	287297	2	1year	3042/04	Pleomorphic adenoma	_	_
10	50	F	284459	3	3months	3163/04	Adenoid cystic carcinoma	_	_
11	70	F	285095	1	25years	3177/04	Pleomorphic adenoma	942/04	Pleomorphic adenoma
12	21	M	285874	1	2years	3228/04	Carcinoma in pleomorphic adenoma	_	_
13	50	M	292885	2	6months	3651/04	Adenoid cystic carcinoma	_	_
14	50	M	292849	3	2years	3656/04	Pleomorphic adenoma	_	

S.No	AGE	SEX	OP/ IP No	SITE	DURATION	HPE. NO	DIAGNOSIS	CY.NO	DIAGNOSIS
15	40	F	294987	1	5years	3767/04	Pleomorphic adenoma	_	_
16	65	M	11463	3	6months	3862/04	Adenoid cystic carcinoma	_	_
17	26	F	294254	1	8months	3941/04	Pleomorphic adenoma	_	_
18	57	M	300733	3	1year	3972/04	Pleomorphic adenoma	_	_
19	15	F	301889	1	6months	4108/04	Pleomorphic adenoma	1321/04	Pleomorphic adenoma
20	51	M	253985	2	3months	4196/04	Sialadenitis	_	_
21	44	M	302841	2	2months	4289/04	sialadenitis	_	_
22	50	F	298963	1	1year	4388/04	Pleomorphic adenoma	1248/04	Pleomorphic adenoma
23	36	M	305369	1	1year	4475/04	Pleomorphic adenoma	_	_
24	30	M	304888	1	5year.s	4498/04	Pleomorphic adenoma	1376/04	Pleomorphic adenoma
25	37	F	315076	1	3years	4947/04	Carcinoma in pleomorphic adenoma	1687/04	Pleomorphic adenoma
26	42	M	319608	3	6months	5086/04	Pleomorphic adenoma	_	_
27	60	F	322878	3	3months	5087/04	Adenoid cystic carcinoma	_	_
28	25	F	317000	3	2years	5088/04	Mucoepidermoid carcinoma	_	_
29	36	F	322882	1	1year	13/05	Pleomorphic adenoma	_	_
30	30	F	319446	2	6months	28/05	sialadenitis	_	_

S.No	AGE	SEX	OP/ IP No	SITE	DURATION	HPE. NO	DIAGNOSIS	CY.NO	DIAGNOSIS
31	33	F	324993	2	1year	45/05	Pleomorphic adenoma	_	_
32	40	F	323012	1	6months	83/05	Acinic cell carcinoma	_	_
33	28	M	325759	1	2years	267/05	Pleomorphic adenoma	_	_
34	43	F	329786	2	2years	705/05	Mucoepidermoid carcinoma	243/05	Mucoepidermoid carcinoma
35	55	F	339625	1	8years	992/05	Carcinoma in pleomorphic adenoma	315/04	Pleomorphic adenoma
36	21	F	346162	3	6months	1387/05	Pleomorphic adenoma	_	_
37	40	F	3691	1	2years	1396/05	Pleomorphic adenoma	_	_
38	57	F	337577	2	6years	1473/05	Mucoepidermoid carcinoma	204/05	Mucoepidermoid carcinoma
39	57	F	343828	1	1year	1599/05	Pleomorphic adenoma	536/05	scanty
40	45	F	350525	1	20days	1724/05	Actinomycosis	456/05	inflammatory
41	25	F	352059	2	4years	1861/05	Adenoid cystic carcinoma	_	_
42	30	F	354127	2	1year	2062/05	Mucoepidermoid carcinoma	700/05	scanty
43	27	M	201181	1	1 year	2105/05	Pleomorphic adenoma	_	_
44	45	F	360482	2	3years	2183/05	Pleomorphic adenoma	790/05	Pleomorphic adenoma
45	42	F	6432	1	3years	2259/05	Oncocytoma	2259/05	oncocytoma
46	63	M	352824	1	2years	2298/05	Neurofibroma	690/05	Pleomorphic adenoma

S.No	AGE	SEX	OP/ IP No	SITE	DURATION	HPE. NO	DIAGNOSIS	CY.NO	DIAGNOSIS
47	40	F	9775	3	6months	2497/05	Acinic cell carcinoma	_	_
48	60	M	9368	1	4years	2548/05	Mucoepidermoid carcinoma	_	_
49	21	M	365928	2	3months	2562/05	Sialadenitis	_	_
50	42	F	360268	1	2years	2584/05	Mucoepidermoid carcinoma	661/05	Mucoepidermoid carcinoma
51	42	F	365307	1	7months	2588/05	Pleomorphic adenoma	553/05	Pleomorphic adenoma
52	18	M	361981	1	2months	2711/05	Sialadenitis	870/05	Inflammatory
53	46	F	358512	1	2months	2755/05	Pleomorphic adenoma	869/05	Pleomorphic adenoma
54	40	F	8886	1	2years	2818/05	Pleomorphic adenoma	_	_
55	28	F	372854	1	1year	2987/05	Mucoepidermoid carcinoma	1037/05	Cystic lesion
56	67	M	371592	1	15years	2988/05	Pleomorphic adenoma	1127/05	Pleomorphic adenoma
57	40	F	381760	2	1year	3061/05	Monomorphic adenoma	_	_
58	48	F	373456	1	2months	3139/05	Lympho epithelial cyst	1054/05	inflammatory
59	41	F	13492	1	3years	3361/05	Pleomorphic adenoma	_	_
60	36	M	718805	1	3months	3656/05	Pleomorphic adenoma	1103/04	Pleomorphic adenoma
61	37	M	383871	2	6months	3675/05	Sialadenitis	1351/05	inflammatory
62	43	M	11435	1	2years	3681/05	Pleomorphic adenoma	_	_
63	14	F	392933	1	4years	3981/05	Pleomorphic adenoma	1528/05	Pleomorphic adenoma

64	55	F	391297	2	8months	4057/05	Pleomorphic adenoma	1558/05	Pleomorphic adenoma

S.No	AGE	SEX	OP/ IP No	SITE	DURATION	HPE. NO	DIAGNOSIS	CY.NO	DIAGNOSIS
65	30	F	16284	2	3months	4127/05	Sialadenitis	_	_
66	53	M	395675	1	7months	4188/05	Mucoepidermoid carcinoma	1475/05	Mucoepidermoid carcinoma
67	42	F	392153	2	15years	4278/05	Pleomorphic adenoma	1436/05	Pleomorphic adenoma
68	35	M	18591	1	2years	4428/05	Sialadenitis	_	_
69	24	F	395040	1	3months	4438/05	Pleomorphic adenoma	1542/05	Pleomorphic adenoma
70	60	F	400946	2	20years	4552/05	Pleomorphic adenoma	1675/05	Pleomorphic adenoma
71	40	F	403854	1	1year	4877/05	Acinic cell carcinoma	1775/05	Acinic cell carcinoma
72	38	F	409661	3	3months	5056/05	Pleomorphic adenoma	_	_
73	40	M	407169	1	6years	5076/05	Pleomorphic adenoma	1822/05	Pleomorphic adenoma
74	50	M	399515	1	6months	13/06	Mucoepidermoid carcinoma	1643/05	Mucoepidermoid carcinoma
75	65	F	411607	3	2years	93/06	Pleomorphic adenoma	_	_
76	30	F	411631	1	3months	98/06	TB Sialadenitis	1777/05	Pleomorphic adenoma
77	28	F	401834	2&3	1year	100/06	Acinic cell carcinoma	1698/05	Acinic cell carcinoma
78	70	M	418411	1	2years	314/06	Mucoepidermoid carcinoma	16/06	Mucoepidermoid

									carcinoma
79	50	F	417254	1	1.5years	447/06	TB Sialadenitis	92/06	TB Sialadenitis
80	48	F	24693	1	3years	487/06	Basal cell adenoma	_	_

S.No	AGE	SEX	OP/ IP No	SITE	DURATION	HPE. NO	DIAGNOSIS	CY.NO	DIAGNOSIS
81	19	F	418881	1	2months	586/06	Mucoepidermoid carcinoma	_	_
82	43	M	22637	1	6years	603/06	Pleomorphic adenoma	_	_
83	27	F	25055	2	8months	609/06	Chronic sialadenitis &mucus retention cyst	_	_
84	33	M	418111	1	2months	710/06	Pleomorphic adenoma	126/06	Pleomorphic adenoma
85	45	F	418493	3	9months	736/06	PLGA	_	_
86	48	M	421572	1	6years	786/06	Mucoepidermoid carcinoma	203/0	scanty
87	62	M	427860	1	1year	951/06	Warthin tumor	_	_
88	13	M	429997	2	3months	986/06	Pleomorphic adenoma	_	_
89	18	F	427289	2	1year	1012/06	Pleomorphic adenoma	_	_
90	45	M	428710	1	3months	1091/06	Warthin tumor	_	_
91	31	M	471960	1	6months	1131/06	Pleomorphic adenoma	351/06	Pleomorphic adenoma
92	69	M	427214	1	4months	1157/06	Mucoepidermoid carcinoma	296/06	Mucoepidermoid carcinoma
93	65	F	434252	1	2years	1206/06	Basal cell adenoma	_	_
94	36	M	437500	1	3years	1397/06	Warthin tumor	_	_
95	58	M	436098	2	3months	1432/06	Chronic sialadenitis	313/06	Inflammatory
96	70	F	428965	1	6months	1433/06	Acinic cell carcinoma	_	_
97	46	M	478824	1	2years	1492/06	Pleomorphic adenoma	260/06	Pleomorphic adenoma

S.No	AGE	SEX	OP/ IP No	SITE	DURATION	HPE. NO	DIAGNOSIS	CY.NO	DIAGNOSIS
98	17	M	439780	2	6months	1531/06	Chronic sialadenitis	446/06	Inflammatory
99	25	F	30045	2	1year	1629/06	Chronic sialadenitis	_	_
100	30	M	441449	2	4months	1753/06	Chronic sialadenitis	_	_
101	48	F	29309	2	3years	1799/06	Pleomorphic adenoma	_	_
102	30	F	444006	1	2years	1897/06	Pleomorphic adenoma	_	_
103	52	F	442033	3	1year	1993/06	Carcinoma in pleomorphic adenoma	570/06	Pleomorphic adenoma

SITE CODES

1. Parotid
2. Submandibular gland
3. Other minor salivary glands