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Original article

Frequency, Prevalence, Demographic Features, And Histological Subtypes of The Most Common Malignant Salivary Glands Tumours (MECs) in Tripoli Medical Center: A 14 Years Retrospective Study.

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ABSTRACT

Objective: The main purpose of this retrospective study was to survey SGTs, report their frequency and the prevalence, demographic features, and histological subtypes of MEC. **Methods**: These series retrieved from oral biopsy files of Tripoli Medical Centre (TMC) over a 14-year period. **Results**: One hundred ninety-seven tumours were found, 152 benign (77.8%) and 45tumours (22%) lesions, were malignant. Pleomorphic adenoma (PA), adenoid cystic carcinoma (ACC) and MEC were the most encountered benign and malignant tumours (129 cases, 66.8%), (23 cases, 11.6%) and (14 cases, 7.3%) respectively. Of the 45 malignant tumours, MEC (14 of 45), was the second most common neoplasm. Most MECs (7 of 14) were high-grade lesions. One central MEC occurred in the alveolar ridge of the mandible. **Conclusions**: Benign SGTs were much more frequent than malignant SGTs. MEC was the second commonest malignant variety. The parotid gland was the frequently affected site for MECs. High grade MEC constituted large group of different grades of this neoplasm.

Keywords: Malignant Salivary, Glands, Tumours.

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INTRODUCTION

Salivary gland tumours are relatively uncommon lesions representing from 3 to 10% of head and neck tumours with parotid gland and minor salivary glands of the palate being the most frequently affected sites (Jones et al., 2008). Salivary gland tumours are histologically heterogeneous, share overlapping features and occasionally more than one tumour type can be seen in the same lesion (hybrid tumours) Seifert et al. (1996). In addition, malignant salivary gland tumours differ from other malignancies as they exhibit less cellular and nuclear pleomorphism, and tumour margins, whether they are infiltrative or not, play an important role in distinguishing between benign and malignant lesions. Mucoepidermoid carcinoma (MEC) is a malignant glandular epithelial neoplasm represents the most common malignant tumour of salivary glands (Speight and Barrett, 2002; Jones et al., 2008) and is the most common salivary malignancy of childhood (Castro et al., 1972; Jones et al., 2006a). This lesion constitutes about 10% of all

salivary tumours and more than 32% of salivary malignancies (Gnepp et al., 1988; Young et al., 1996; [1.4]; Jones et al., 2008). There is a predilection for females with a male-to-female ratio of 0.8:1 (Jones et al., 2006b; Jones et al., 2008). MEC demonstrates a wide age range from childhood to geriatric life with a mean age of 45 years and 60% of those encountered on the palate being in patients under 40 (Barnes et al., 2005).

MEC is a malignant tumour of both major and minor salivary glands. According to Barnes et al. (2005) this tumour shows a roughly equal distribution between major and minor salivary glands although some studies found the palate is the single most frequent site of presentation. Most MECs of major salivary glands are present as asymptomatic fixed swellings. However, some of those that arise in the superficial lobe of the parotid are relatively movable (Sapp et al., 2004) and those occurring in sublingual glands may evoke pain (Barnes et al., 2005). Although MEC of minor salivary glands usually cause painless swelling, the signs and symptoms are variable depending on the site of presentation. The superficial palatal lesions may present with blue-red colour resembling vascular lesions or mucoceles (Barnes et al., 2005; Regezi et al., 2008). All salivary malignancies share similar clinical manifestations which include rapid growth rate, pain, facial nerve palsy, trismus, childhood occurrence and cervical lymphadenopathy. In addition, involvement of the nasal cavity, nasopharynx, larynx and trachea by any salivary malignancy may evoke facial pain, nasal obstruction, bleeding, hoarseness, voice change, or dyspnoea (Licitra et al., 2003).

A combination of physical examination with other diagnostic radiographic tools including ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI) and pathological studies including fine needle aspiration (FNA) and histopathological examination, are important to diagnose, predict and treat salivary gland tumours (Licitra et al., 2003).

FNA is a simple, cost effective technique that has been widely used to diagnose salivary gland lesions in an attempt to avoid facial nerve injury and the possible tumour dissemination of open biopsy. Histologically, the tumour consists mainly of a mixture of mucous (large cells with pale cytoplasm and peripherally displaced nuclei), epidermoid (squamous) and intermediate cells (basaloid or cuboidal) along with clear, columnar and oncocytic cells. The cells form solid islands and cysts that are separated by mature fibrous stroma. The proportion of different cell types and the predominance of cystic or solid areas varies in and between tumours. Hence, MECs are histologically classified into low-, intermediate- and high-grade. Although MECs are often well circumscribed, lobular infiltration of adjacent tissue is evident. Occasionally, the non-typical cells may predominate, therefore, variants of MEC have been described such as clear cell variant, oncocytic variant, sclerosing variant , goblet cell aggressive variant and pigmented MEC.

Dedifferentiation in MEC means transformation of a salivary gland cancer to a high-grade carcinoma with loss of typical features. It has been identified in different salivary malignancies and in MEC has been reported by Nagao et al (2003), who found the dedifferentiation occupied the majority of the lesion with clear demarcation from the other low-grade MEC components.

MEC exhibits a diverse morphologic appearance and clinical behavior, for which a particular grading scheme is warranted. This lesion was initially named as a mucoepidermoid tumour by Stewart et al (1945) and divided into two types benign and other lesions that are capable of metastazing. Foote and Frazell (1953) found that some of those classified as benign had metastasized therefore, they proposed to divide MECs into low and high grade tumours. Subsequently Jakobsson et al (1968) analyzed the histologic and clinical features of 63 MEC cases in a follow-up period ranging from 5 to 25 years. They found a difference between the prognosis in the two groups with better prognosis for low-grade tumours. However, they found their grading did not correlate well with prognosis as two cases that were classified as low grade died from their tumour; hence they emphasized

the importance of considering low-grade MECs as carcinomas rather than benign tumours. In a study of 60 MEC cases by Healey et al. (1970), there was close correlation between grading and prognostic outcome. They considered cystic areas, cytological atypia, degree of cellular anaplasia, mitotic activity and the extent of invasion as the key features to divide lesions into grade I, II and III, this corresponded to well, moderately and poorly differentiated MEC respectively. Several grading schemes have recently been proposed to make grading of MEC objective rather than subjective, but none has been universally accepted (Barnes et al., 2005). The most important schemes are from the Armed Forces Institute of Pathology (AFIP) by Goode et al. (1998) and Brandwein et al. (2001). AFIP found that death correlated with high grade histopathological features in minor glands and parotid tumours but not the submandibular gland tumours. Brandwein et al. (2001) demonstrated that the AFIP had a tendency to downgrade tumours and modified the AFIP scheme by adding three more features related to invasion. They found that despite the usefulness of grade, stage and free surgical margins are better prognostic factors.

In a recent study by Loh et al. (2009) of minor salivary gland tumours, although the grading criteria were not mentioned, they suggested that the grade of a lesion is a significant prognostic tool as high grade tumours were associated with poorer disease specific survival and a shorter disease free interval than low-grade tumours. Grade is important as a predictor of tumour outcome but it should be considered with other clinical features especially stage as a high grade small malignancy may have a better prognosis than a low grade large malignancy (Speight and Barrett, 2002).

The differential diagnosis of MEC includes necrotizing sialometaplasia, inverted ductal papilloma, cystadenoma, tumours containing clear cells such as clear cell carcinoma (not otherwise specified), acinic cell carcinoma, oncocytoma, myoepithelial carcinoma, pleomorphic adenoma, metastatic renal cell carcinoma and other metastasis, adenosquamous carcinoma, squamous cell carcinoma (Jakobsson et al., 1968; Brandwein et al., 2001; Barnes et al., 2005).

Prognosis of MEC is largely affected by histologic grade, adequacy of surgical excision and clinical stage (Brandwein et al., 2001; Speight and Barrett, 2002; Triantafillidou et al., 2006). Other studies have shown correlation between factors such as age (more than 56) (Lopes et al., 2006; Ozawa et al., 2008), sex (male), site (palate) (Lopes et al., 2006) and poor survival rates. Overall most patients have a favourable outcome, as 5 year survival rates range from 92 to 100% , 75 to 83% and 24 to 40% for low, intermediate and high-grade respectively (Spiro et al., 1978; Lopes et al., 2006). Surgical excision is the treatment of choice with adjuvant radiotherapy in high-grade tumours and in tumours that cannot be adequately removed surgically (Brandwein et al., 2001; Ozawa et al., 2008). For high-grade tumours elective neck dissection, and cervical node dissection in case of lymph node involvement, have been advocated. Central (intra-bony) MECs which are often low-grade, are treated by en bloc resection (Sapp et al., 2004; Regezi et al., 2008).

MATERIALS AND METHODS

The files of the pathology laboratory of Tripoli Medical Centre, Libya, were reviewed and all cases of MEC in a 14-years period from January 2002 to November 2015 were retrieved. This laboratory serves the communities of east of Libya with most biopsies received from other hospitals, private oral and maxillofacial surgeons as well as cases submitted for consultation from other oral or general pathologists.

Data of demographic features, anatomic location, duration of the lesions at the time of presentation, type of surgical procedure, histopathology, clinical features, outcome and the referring practitioners were obtained from patients' records. The histology of hematoxylin-eosin–stained slides of 14 MECs were reviewed and classified according to the World Health Organization (WHO) Histological Typing of Salivary Gland Tumors (Seifert et al., 1991), the Armed Forces Institute of Pathology (AFIP) (Goode et al.,1998), and

the WHO Classification of Head and Neck Tumours "(Barnes et al., 2005).

RESULTS

One hundred ninety seven tumours were found,152 benign (77.8%) and 45 tumours (22%) lesions, were malignant. Pleomorphic adenoma (PA), adenoid cystic carcinoma (ACC) and MEC were the most encountered benign and malignant tumours (129 cases,66.8%), (23 cases,) and (14 cases, 7.3%) respectively. The tumours were more frequent in patients between 30 and 70 years of age (85%), with 1/1 male/female ratio. Parotid gland was the most common site with 6 cases (50%). Other affected areas included submandibular gland (3 cases), thyroid gland (2 cases), tongue, alveolar ridge and nasal cavity one case each. Of 14 cases of MECs 6 cases were sent from outside the hospital for second opinion. The remaining 8 cases were staged following TNM classification of carcinomas of salivary glands. T3 was the more frequent stage (50%) and 5 patients out of 8 (62.5%) were staged as N1. The scheme from the Armed Forces Institute of Pathology (AFIP) by Goode et al. (1998) was used as a grading scheme. Most tumours (50%) were classified as high grade of malignancy. Microscopic examination of the slides of high grade tumours received showed groups of malignant cells with nuclear pleomorphism and hyperchromatism, high mitotic activity (mitosis 4 or more per 10 high-power fields (HPF), cellular crowding and discohesion (figure 1a). Cells with obvious squamoid differentiation were seen along with very occasional vacuolated cells with a suggestion of intracytoplasmic mucin (figure 1b) .There were foci of vascular invasion (figure 1c) and the surgical margins were infiltrated by neoplastic cells. Areas of necrosis were marked in some high grade tumours (figure 1d). Intermediate grade tumours composed mainly of nests of lobules of squamous cells (epidermoid) with pale eosinophilic cytoplasm, few cellular and nuclear pleomorphism and distinct cell borders with intercellular bridges, no keratin pearls and rare mitosis (figure 2 a & b). There were occasional lumens containing mucin around these nests of epidermoid cells (figures 2 c & d). Low grade tumours were composed mainly of cystic structures lined by mucous secreting columnar epithelium with an intermingling of intermediate and squamous cells (figure 3 a, b& c). No cytological atypia nor mitotic activity were seen. In all cases of incesional or exesional biopsies the surgical margins were infiltrated by neoplastic cells. In addition fibrous stroma were infiltrated by chronic inflammatory cells and in some cases extensive lymphocytic proliferation with germinal centres were found. No perineural invasions were seen.

There is abundant evidence that the initiation and progression of periodontal disease depend on complex interactions between periodontopathogenic bacteria and the host immune system. Major tissue destruction in periodontitis lesion results from the recruitment of host cells via activation of monocytes, macrophages, lymphocytes, fibroblasts and other cell types (4).

In addition, periodontal disease is elicited by the complex of bacterial species interaction with host tissues and cells. This interaction causes the release of broad array of proteolytic enzymes as matrix metalloproteinases, inflammatory cytokines, chemokines, and several mediators that will result in destruction of periodontal structures (5).

Socranskyet(6) al, 2005 has described the improved methods for examining the association of oral microbial communities with change from health to diseases. These investigators catalogued and stratified the microbiota into groups or complexes representing bacterial consortia that appear to occur together and that are associated with the biofilm in gingival health, gingivitis and periodontitis. The different microbial complexes have been associated with the sequence of colonization on the tooth surface as well as with severity (6).

The Red complex which appears later in biofilm development, comprises species that are considered periodontal pathogens, namely (Porphyromonasgingivalis, Tannerella forsythia and

Treponemadenticola). It has been suggested that the red complex, presents a portion of the climax community in the biofilm at the sites expressing progressing periodontitis (7).

Among these periodotopathogens, Porphyromonasgingivalis belongs to the genera Porphyromonas from the family Bacteroidaceae. These bacteria are Gram-negative strict anaerobic coco-bacilli (8). Several lines of evidence support its etiological role as a true periodontal pathogen, more likely associated with chronic periodontitis (3). Moreover, its importance as a periodontal pathogen is also highlighted by the research efforts aimed at developing a vaccine immunizing against this bacterial species and thus preventing periodontitis (9).

Conventional periodontal therapy includes both surgical and non-surgical approaches that involve instrumentation of the inflamed dentogingival complex (10). Non-surgical therapyby mechanical instrumentation is primary recommended approach to control periodontal infection (11). Because conventional therapies result in wounding of the already inflamed periodontal tissues, the consequence of such therapeutic procedures depends largely on the cellular and molecular events associated with wound healing (12). Although surgical and non-surgical approaches, such as scaling and root planning are still regarded as important and useful modalities, it is essential to improve further possibilities (13).

In the last decade, applying lasers as an adjunctive or alternative to current mechanical treatment had a great run in the treatment of gingival inflammation (14,15). Among laser application, low –level laser therapy (LLLT) is recommended for its pain-reducing, wound- healing promoter and anti-inflammatory effects(16). It is suggested that LLLT alters cellular behavior by affecting the mitochondrial respiratory chain or membrane calcium channels , and that it can facilitate collagen synthesis, angiogenesis, and growth factor release, which eventually accelerate wound healing (17, 18, 19).

Additionally, LLLT can positively impact biologic tissues via improved microcirculation, nerve conduction, and cell proliferation, other positive effects may include stimulation of the host immune system, increased enzyme activity and DNA synthesis, and enhancement of cell membrane structure (20).

Among these LLLT, diode laser has become an important tool in the dental armamentarium due to its exceptional ease of use and affordability. It also has key advantages with regard to periodontal treatment. The diode laser is well absorbed by melanin, hemoglobin, and other chromophores that are present in periodontal tissues (21). The effects of LLLT on periodontitis had been investigated; however, the results were conflicting. There are few in vivo studies that evaluated LLLT as an adjunct to conventional periodontal treatment. Qadri(22) et al, 2005 showed reduced periodontal gingival inflammation with two different low-level lasers used as an adjunct to periodontal treatment. On the other hand, Lai23 et al, 2009 reported that low-power helium-neon laser as an adjunct to non- surgical periodontal treatment did not show any additional clinical benefit. More recently, many authors reported the efficacy of LLLT and diode laser as an adjunct to non-surgical periodontal treatment in patients with chronic periodontitis (24, 25, 26).

The laser energy is transmitted through a thin fiber that can easily penetrate into deep periodontal pockets to deliver its therapeutic effects (27). Therefore, the bactericidal and detoxifying effect of laser treatment is advantageous in periodontal therapy (28).

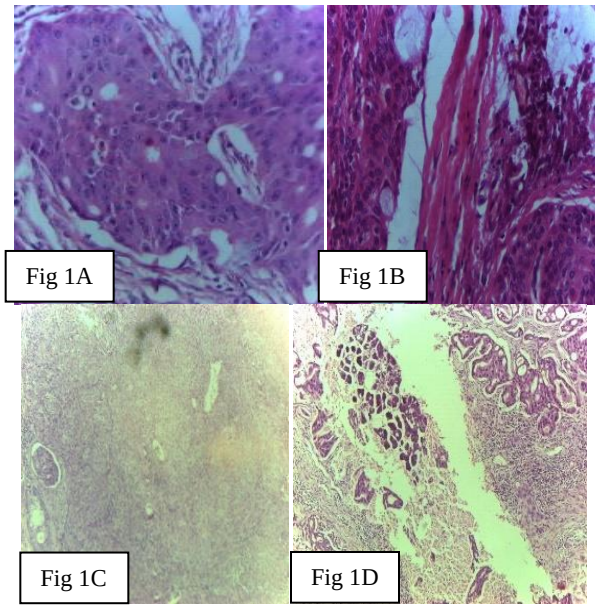

Figure1 A & B photomicrographs showing cellular and nuclear pleomorphism, mitosis and hyperchromatism of high grade MEC. C showing vascular invasion. D showing necrosis and colonies of chronic inflammatory cells. The original magnifications were x400 for A & B and x100 for C & D.

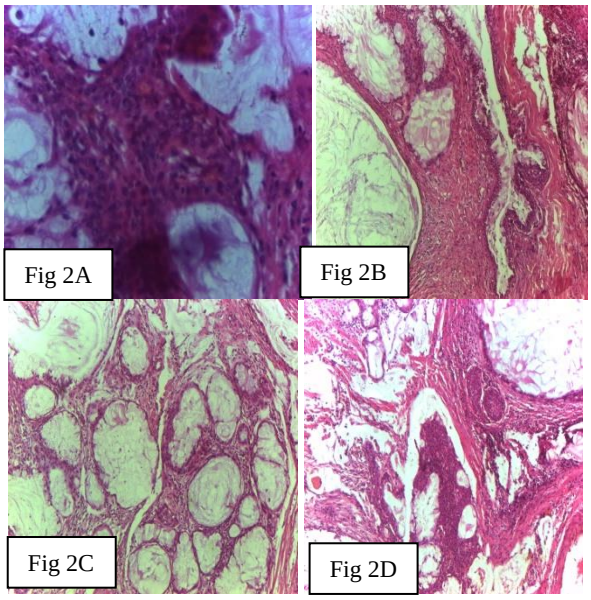

Figure 2 A photomicrograph showing cystic spaces, cellular and nuclear pleomorphism and hyperchromatism. B, C &D showing nests of lobules of squamous cells (epidermoid) with pale eosinophilic cytoplasm, few cellular and nuclear pleomorphism, rare mitosis and lumens containing mucin around these nests of epidermoid cells. The original magnifications were x400 for A and x200 for B, C & D.

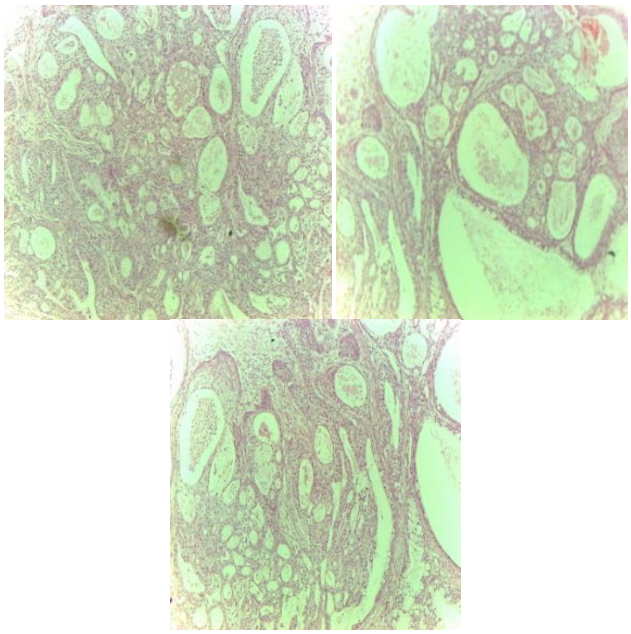

Figure 3 A, B & C photomicrographs showing Low grade tumours composed mainly of cystic structures lined by mucous secreting columnar epithelium with an intermingling of intermediate and squamous cells (figure 3 a, b& c). No cytological atypia nor mitotic activity were seen. The original magnifications were x100 for A, B & C.

year	age	sex	site	Duration & clinical feature	type of biopsy	grade of MEC	stage
2002	60	m	Nasal cavity	mass	incisional	High grade MEC	Second opinion
2002	24	f	tongue		incisional	High grade MEC	T1 N0
2002	63	m	thyroid		incisional	intermediate grade	T2 N1
2002	30	f	thyroid		incisional	Low grade MEC	T1 N1
2004	60	m	parotid		parotidectomy	high grade MEC	T3 N1
2006	30	m	left parotid	sewlling since 2 years	parotidectomy	Low grade MEC	Second opinion
2006	26	f	left submandibular	swelling since 2 years	sialoadenectomy	Intermediate grade	Second opinion
2006	48	f	parotid	painless mass	FNA	Low grade MEC	Second opinion
2007	40	m	left parotid	swelling since 2 months	parotidectomy	high grade MEC	T3 N0
2007	74	m	right submandibular	painless swellin	sialoadenectomy	High grade MEC	Second

				g for 3 months			opinio n
200 9	34	f	parotid	swellin g	parotidectomy	Intermedia te MEC	T3 N1
201 0	70	f	submandibul ar	Painful tendres s mass since 1 month	FNA	High grade MEC	Secon d opinio n
201 4	70	m	alveolar ridge	white patch	incisional	high grade MEC	T1 N0
201 4	60	f	left parotid	swellin g since 3 years	FNA	intermedia te MEC	T3 N1

DISCUSSION

The aim of this study was to report the prevalence of SGTs and the clinic pathological data of MEC in oral biopsy files of TMC during the last 14 years. A total of 197 SGTs, including 152 benign (77%) and 45 malignant (22.8%) lesions, were found. The most common tumours were PA (129 cases,65%), ACC (23 cases, 11.6%) and MEC (14 cases, 7%) representing together 78%of registered cases. These data were consistent with other data achieved an by Wei-Yung Yih et al. (2005) and Jones et al. (2008) in epidemiological studies of SGTs. Concerning MEC of our series the highest incidence was found in patients between 30 and 70 years of age (85%) similar results to a study by Buchner et al. (2007). Although MEC has been described as the most common salivary malignancy of childhood (Castro et al., 1972; Franklin et al., 2006a), no case in children was found in our cohort. Of all SGTs the youngest patient was 11 years old with PA and the eldest 88 years old with ACC. Of MEC the youngest age was 24 years old and the eldest 74 years old. In the vast majority of various histological types of these MEC cases male/female ratio was 1:1.That is slightly different from other studies by Jones et al. (2006b) and Jones et al. (2008) with a predilection for females. Regarding the site of distribution of MEC, parotid gland was the most common site with 6 cases (50%), followed by submandibular gland with 3 cases. According to Barnes et al. (2005) this tumour shows a roughly equal distribution between major and minor salivary glands and in other studies found the palate is the single most frequent site of presentation (Eveson et al.1985, Triantafillidou et al. 2006, Buchner et al. 2007 and Pires et al. 2007). Our series of MEC followed different pattern of occurrences to these studies as no case of palate was found except one case of nasal cavity which could be MEC of palate extended to this ultimate area of contact. Central (intra-bony) MEC although is very rare, one case was registered in our series and was in the mandible. Presence of this type of MEC in the lower jaw support the other studies that showed a predominance to the mandible (Sapp et al., 2004; Yi et al., 2008; Raut and Khedkar, 2009). The patient complained of non raised white patch of the lower alveolar ridge. Sections examined from the submitted tissue revealed hyperplastic part of nonkeratinized squamous epithelium, the underlying tissue showed an infiltrative malignant tumor composed of ill formed glands ,sheets and nests of pleomorphic epithelial cells with hyperchromatic nuclei , evidence of intracytoplasmic mucin , along with foci of necrosis .This type of MEC may arise from ectopic salivary tissue in the bone or from neoplastic changes in mucous cells of odontogenic cysts (Regezi et al., 2008; Raut and Khedkar, 2009). MEC contains mainly a mixture of mucous, intermediate and epidermoid cells. According to the dominance of these cells and of solid or cystic areas, MEC is traditionally subdivided into low, intermediate and high-grades. Low-grade tumours behave less aggressively and are associated with better prognosis than high-grade tumours, therefore MEC is characterized by a marked variation in prognosis (Brandwein et al., 2001) and a grading scheme is required (Goode et al., 1998). As far as grading of MEC was concerned, a scheme from the Armed Forces Institute of Pathology (AFIP) by Goode et al. (1998) was used in the grading of our cases. The histological review showed that most MECs were high, intermediate and low-grades respectively.

Barnes et al. (2005) in a definition of MEC mentioned the presence of columnar, clear cell and oncocytes along the characteristic cells of MEC. Our samples showed only columnar mucous cells and clear cells. Prognosis of MEC is largely affected by histologic grade, adequacy of surgical excision and clinical stage (Brandwein et al., 2001; Speight and Barrett, 2002; Triantafillidou et al., 2006). Other studies have shown correlation between factors such as age (more than 56) (Lopes et al., 2006; Ozawa et al., 2008), sex (male), site (palate) (Lopes et al., 2006) and poor survival rates. Overall, of various histological types of 14 cases of MECs 6 cases were sent from outside the hospital for second opinion. The remaining 8 cases were staged following TNM classification of carcinomas of salivary glands Barnes et al. (2005). 3 cases were T1, 3 cases were T2 and 2 cases were T3. Considering lymph node metaststasis 3 low grade MEC cases were N1, one case of intermediate grade was N1 and a case of high grade was N1. Our data exaggerate the importance of the clinical stage as 3 cases of low grade tumours showed lymph node metastasis and one case of each high and intermediate grades showed involvement of the adjacent lymph nodes. No correlation between other factors such as age, sex and site and survival rates were achieved as follow up intervals with the patient were lost and no data could be attained.

To sum up, MEC was the second most encountered malignancy of SG. and parotid gland was the commonest place of occurrence. Although MEC is a malignancy of childhood, no case of MEC in children was found with wide age range. High grade MEC constituted large group of the different grades of this neoplasm. Staging of MECs according to TNM classification of carcinomas of salivary glands is more important than histological grading.

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Conflict of Interest

Not declared.

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