Original article

A CLINICOPATHOLOGIC EVALUATION AND ANALYSIS OF 56 CASES OF MUCOEPIDERMOID CARCINOMA USING GRADING SYSTEMS

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ABSTRACT

OBJECTIVE: Mucoepidermoid carcinoma (MEC) is the most common malignant epithelial salivary gland tumour and histologically it presents with varying proportions of epidermoid, mucous, and intermediate cells. This study aims to describe the clinicohistological features of MEC managed at Lagos University Teaching Hospital (LUTH) and compare two quantitative histologic grading systems for MEC.

METHODS: The study examined previously diagnosed cases of MEC between 1980 and 2018 in LUTH. Data on age, sex and site were retrieved from the archives. Cases were categorized according to Armed Forces Institute of Pathology (AFIP) and modified Brandwein (MB) criteria. Data analysis was done using SPSS Windows version 21.0.

RESULTS: Of the 56 cases of MEC studied 30 (53.4%) were males and 26 (46.6%) were females (1.15:1). The minor glands were the most frequently involved site with 43 (76.8%) cases. There was a significant difference between the mean age of patients with minor salivary glands (45.3±19.6) MEC and major glands (27.9±21.4) MEC, (P=0.007). High grade tumours were the most common histological type in both the AFIP 31 (55.4%) and MB 35 (62.5%) systems. For the MB criteria, there was a significant association (P=0.021) between the occurrences of high grade MEC in the minor salivary glands.

CONCLUSION: In this study, MEC had an almost equal sex predilection and was more common in minor salivary glands. The MB grading system uncovers more MECs as high-grade tumours than the AFIP system. Appropriate grading of MEC is an indispensable part of good case management.

Keywords: Mucoepidermoid carcinoma, Classification, AFIP grading system, Modified Brandwein grading system

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INTRODUCTION

Mucoepidermoid carcinoma (MEC) is a malignant epithelial glandular tumour with varying proportions of epidermoid, mucous and intermediate cells. Occasionally, clear, columnar, and/or oncocytic cells are also seen within the tumour[1,2]. Although it has been reported as the most common primary malignant tumour of the salivary glands globally[1,3], studies in the Nigerian populace however have reported

it to be the second most common salivary gland malignancy after adenoid cystic carcinoma[4,5].

Mucoepidermoid carcinoma shows a wide, nearly uniform age distribution, which decreases in the pediatric and geriatric age groups, and a 3:2 female predilection[2]. This tumour has a site predilection for the major salivary glands; and about 48% of cases are diagnosed in the parotid gland, 11% in the submandibular gland, and only 1% in the sublingual gland[6,7]. Approximately 35% of MECs occur within the minor salivary glands with the palate and the buccal mucosa being the most frequent sites[6,7, 8]. Other sites in order of frequency are; the maxillary antrum, tongue, gingiva, floor of mouth, and nasal cavity[6,9]. Occasionally, the tumour may occur in the mandible and such cases are referred to as central mucoepidermoid carcinoma[7].

In the past, mucoepidermoid carcinoma was classified based on the relative proportion of the two main cell types into a two-tier system of low grade and high grade tumours[10]. Over time, different grading systems have emerged as the initial simplistic method was not easy to replicate. Goode and his colleagues in 1998[7] proposed a classification scheme based on quantitative scoring to give a three-tier scheme for MEC namely; low, intermediate and high grade (Table 1) (Figures 1 and 2). This is popularly known as the AFIP classification and it has wide acceptance than the former simplistic system as it was more uniform, reproducible and correlated well with clinical outcome. Each of the histopathological parameters is assigned a point value, and the sum of the points for these variables determined the tumour grade. However, in an attempt to provide a precise picture of the invading front of the tumour the AFIP classification was revised by Brandwein et al [11] (Table I).

The aim of this study is to present the clinico-pathologic features of mucoepidermoid carcinomas diagnosed at the Lagos University Teaching Hospital and to compare two quantitative histologic grading systems for MEC; the Armed Forces Institute of Pathology (AFIP) and modified Brandwein (MB).

MATERIALS AND METHODS

A retrospective clinico-pathological study was undertaken on mucoepidermoid carcinomas histologically diagnosed over a 38-year period (1980-2018) at the Department of Oral and Maxillofacial Pathology/Biology, Lagos University Teaching Hospital, Idi-Araba, Lagos, Nigeria. Demographic records which include; age of patient, sex of patient, and site of tumour were recorded for statistical analysis.

Paraffin blocks of cases were retrieved and sectioned for preparation of haematoxylin and eosin (H&E) slides, this was used to confirm diagnosis as well as categorize the cases. All cases with complete demographic data which were confirmed to be MEC were included in the study. Grading of cases was done using both the AFIP and modified Brandwein criteria (Table 1). Slides of cases were circulated independently amongst all authors for each to categorize using both grading systems. Reconciled observations were then recorded for each case investigated. Grading obtained using both systems was then compared. For the purpose of this study, authors were blinded to all prior histo-pathological grading done for the selected cases.

Table 1: Armed Forces Institute of Pathology and Modified Brandwein systems for grading of salivary gland mucoepidermoid carcinoma

AFIP		Modified Brandwein	
Parameters	**Points**	**Parameters**	**Points**
Cystic component <20%	+2	Cystic component <25 %	+2
Perineural invasion	+2	Perineural invasion	+3
Necrosis	+3	Necrosis	+3
Mitoses (≥4/10 HPFs)	+3	Mitoses (≥4/10 HPFs)	+3
Anaplasia	+4	Anaplasia	+2
		Aggressive pattern of invasion	+2
		Lympho-vascular invasion	+3
		Bony invasion	+3
Total points available = 14		**Total points available = 21**	
Low grade: 0-4; Intermediate grade: 5-6; High grade: 7-14		Low grade: 0; Intermediate grade: 2–3; High grade: ≥4	

Data obtained was analyzed using the SPSS Windows version 21.0. Descriptive statistics was used in presenting categorical variables as frequencies and percentages. Means and standard deviation were computed. Chi-square test was used to compare multiple variables and level of significance was set at $P \leq 0.05$.

Approval for this study was sought for and granted by the Ethics Committee of the Lagos University Teaching Hospital, Idi-Araba.

RESULTS

General

Fifty-six cases of mucoepidermoid carcinomas were studied, there were 30 (53.4%) males and 26 (46.6%) females (M:F=1.15:1). Age range between 4-86years, with mean of 41.2 (±20.9) years, and most cases were diagnosed in the 4th and 7th decades. The minor salivary glands 43(76.8%) was the most affected and the palate accounted for about a third (33.9%) of the cases (Table 2).

Table 2: Demographic and clinical characteristics of 56 cases of Mucoepidermoid carcinoma

Characteristic	Number of patients (n=56)	Percentage (%)
Mean age (±SD)	41.2 (±20.9)	
Males	40.9 (±21.3)	
Females	41.6 (±20.7)	
Median (age range) in years	38.5 (4.0-86.0)	
Age group		
1-40 years	29	51.8
Above 40 years	27	48.2
0-9	2	3.6
10-19	8	14.3
20-29	7	12.5
30-39	11	19.6
40-49	7	12.5
50-59	5	8.9
60-69	11	19.6
70-79	4	7.1
80-89	1	1.8
Sex		
Males	30	53.4
Females	26	46.6
Gland type		
Minor salivary gland	43	76.8
Major salivary gland	13	23.2
Anatomic site		
Oral cavity	43	76.8
Parotid gland	10	17.9
Submandibular/submental gland	3	5.3
Individual oral cavity site		
Palate	19	33.9
Jaws	15	26.8
Lip	3	5.4
Floor of mouth	2	3.6
Retro-molar	2	3.6
Tongue	2	3.6
Maxilla	9	16.1
Mandible	4	7.1
Maxillary antrum	2	3.6

There was a significant difference between the mean age of patients with minor glands MEC (45.3±19.6) years in comparison to major glands MEC (27.9±21.5) years, (P=0.007). Analysis of the histologic grade shows high grade MEC (Figure 1a-c) as the most common histologic type for both the AFIP 31 (55.4%) and modified Brandwein 35 (62.5%) classifications. This was followed by the low grade MEC (Figure 2a-c) 16 (28.6%) for AFIP classification and intermediate grade 13 (23.2%) for MB.

Minor glands

For mucoepidermoid carcinoma of the minor salivary glands, patients' age varied broadly from 11 to 86 years old with a mean age of 45.3 (±19.6) years and a modal age group of between 60-69 years. Males were slightly more affected than females with a ratio 1.15:1 (Table 3). The most common site of minor salivary gland involvement was the palate 19 (44.2%). In the minor salivary glands, high grade MEC was the most common histologic type for both the AFIP 24 (55.8%) and MB 31 (72.1%) classifications. This was followed by the low grade 13 (30.2%) for AFIP classification and intermediate grade 7 (16.3%) for modified Brandwein classification. (Table 4).

Table 3: Demographic characteristics of mucoepidermoid carcinoma in major and minor salivary glands

Demographic characteristics	Major glands (n=13) n (%)	Minor glands (n =43) n (%)	P-value
Age (years)			
Median (range)	23.0 (4-72)	43.0 (11-86)	0.007[a]
Mean (±SD)	27.9 (±21.5)	45.3 (±19.6)	
Gender			
Male	7 (12.5)	23 (41.1)	0.615[b]
Female	6 (10.7)	20 (35.7)	
Age group (years)			
0-40	10 (17.9)	19 (33.9)	0.038[b]
>40	3 (5.4)	24 (42.9)	
Age group			
0-9	2 (3.6)	0 (0.0)	
10-19	4 (7.1)	4 (7.1)	
20-29	2 (3.6)	5 (8.9)	
30-39	2 (3.6)	9 (16.1)	
40-49	1 (1.8)	6 (10.7)	
50-59	0 (0.0)	5 (8.9)	0.122[c]
60-69	1 (1.8)	10 (17.9)	
70-79	1 (1.8)	3 (5.4)	
80-89	0 (0.0)	1 (1.8)	

SD: Standard deviation; n: number of cases; [a] t-test; [b] Chi square test; or [c] Fisher exact test. P≤0.05 accepted as significant.

Major glands

In the major salivary glands, the age range of patients with mucoepidermoid carcinoma varied broadly from 4 to72 years with a mean age of 27.9 (±21.5) years and median age of 23 years. The modal age group reported was between 10-19 years of age (Table 3). There was an almost equal gender distribution of M:F, 1.17:1 and the parotid gland was the most commonly affected anatomic site 10(76.9%). For the major salivary glands, the most common histologic type was high grade MEC (53.8%), followed by intermediate grade (23.1%) in the AFIP classification, while the most common histologic type was the intermediate grade MEC (46.2%), followed by high grade (30.7%), using the modified Brandwein (MB) classification. (Table 4)

The mean age of patients with high grade tumours (43.7±21.5) years was higher than those with intermediate grade (39.5±19.7) years and low grade (28.4±20.1) years (P=0.133). Patients aged 40 years and above was found to have a higher proportion of high-grade tumours (AFIP: 70.4%) and (MB: 66.7%) than those below the age of 40 years (AFIP: 41.4%) and (MB: 58.6%) (Table 4).

High grade mucoepidermoid carcinoma was also found to occur more commonly in the minor salivary gland 31 (72.1%) than in the major gland 4 (30.7%), and this was found to be statistically significant. (P= (0.025). The relationship of histologic grade with other clinicopathological parameters is summarized in Table 4.

Table 4: Distribution of demographic and clinical features of Mucoepidermoid carcinoma according to histologic grade

Parameter	Histologic grade (AFIP)			Histologic grade (Modified Brandwein)			
	LG	IG	HG	LG	IG	HG	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Gland type							
Major glands	3 (23.1)	3 (23.1)	7 (53.8)	3 (23.1)	6 (46.2)	4 (30.7)	13 (100.0)
Minor glands	13 (30.2)	6 (14.0)	24 (55.8)	5 (11.6)	7 (16.3)	31 (72.1)	43 (100.0)
Total	16 (28.6)	9 (16.0)	31 (55.4)	8 (14.3)	13 (23.2)	35 (62.5)	56 (100.0)
P-value		**0.756** [b]			**0.021** [b]		
Gender							
Male	6 (20.0)	6 (20.0)	18 (60.0)	3 (10.0)	8 (26.7)	19 (63.3)	30 (100.0)
Female	10 (38.5)	3 (11.5)	13 (50.0)	5 (19.2)	5 (19.2)	16 (61.6)	26 (100.0)
Total	16 (28.6)	9 (16.0)	31 (55.4)	8 (14.3)	13 (23.2)	35 (62.5)	56 (100.0)
P-value		**0.290** [a]			**0.586**[a]		
Age (years)							
1-40 (%)	12 (41.4)	5 (17.2)	12 (41.4)	5 (17.2)	7 (24.2)	17 (58.6)	29 (100.0)
>40	4 (14.8)	4 (14.8)	19 (70.4)	3 (11.1)	6 (22.2)	18 (66.7)	27 (100.0)
Total	16 (28.6)	9 (16.0)	31 (55.4)	8 (14.3)	13 (23.2)	35 (62.5)	56 (100.0)
P-value		**0.057** [b]			**0.860** [b]		

LG= low grade; IG= Intermediate grade; HG = High grade; n= number of cases; [a] Chi-square test; [b] Fischer exact test

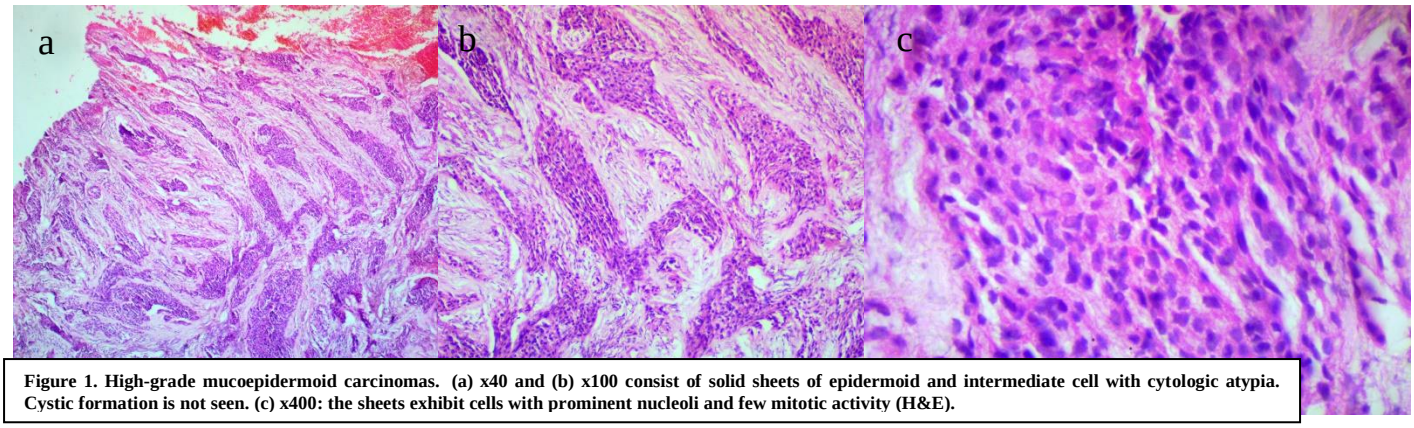

Figure 1. High-grade mucoepidermoid carcinomas. (a) x40 and (b) x100 consist of solid sheets of epidermoid and intermediate cell with cytologic atypia. Cystic formation is not seen. (c) x400: the sheets exhibit cells with prominent nucleoli and few mitotic activity (H&E).

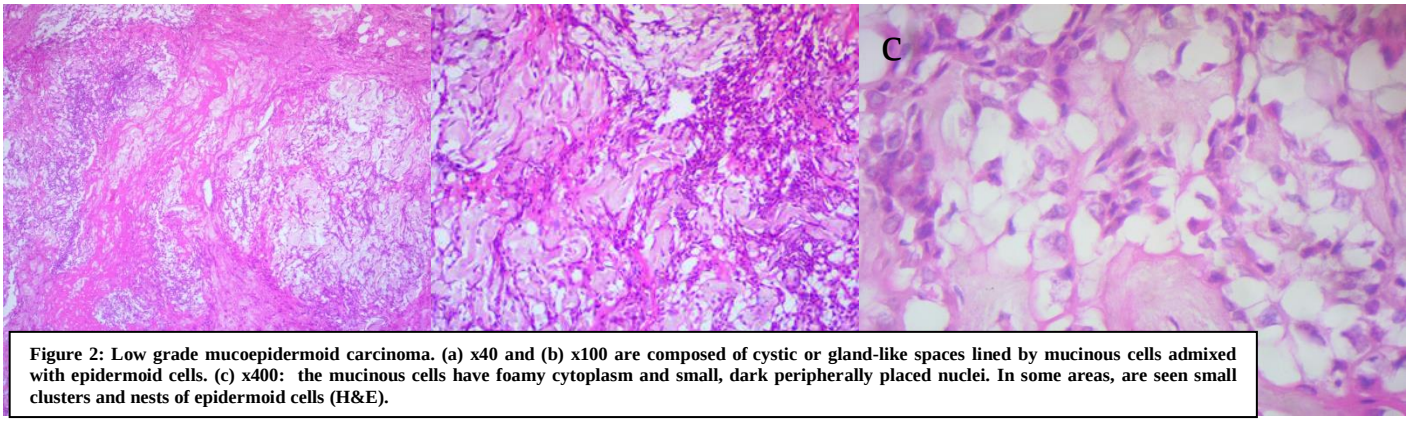

Figure 2: Low grade mucoepidermoid carcinoma. (a) x40 and (b) x100 are composed of cystic or gland-like spaces lined by mucinous cells admixed with epidermoid cells. (c) x400: the mucinous cells have foamy cytoplasm and small, dark peripherally placed nuclei. In some areas, are seen small clusters and nests of epidermoid cells (H&E).

Table 5: Comparative demographic, anatomic distribution and analysis of AFIP grading and modified Brandwein grading system of Mucoepidermoid carcinoma in published studies

Author/Year	Sample size	Age (years)	Sex (M:F)	Site	AFIP Grading system	Modified Brandwein system (MB)	Upgrade (UPG)
Present study 2020	56	4-86 Mean: 41.2 Median: 38.5	1.15:1	MASG: 13 (23.2%) MISG: 43 (76.8%)	LG: 16 (28.6%) IG: 9 (16.0%) HG: 31 (55.4%)	LG: 8 (14.3%) IG: 13 (23.2%) HG: 35 (62.5%)	(8) MB UPG 4 each from LG to IG and HG
Cipriani et al. 2019 [30] (Cipriani et al. 2019)	53	9-85 Mean 52.7	1:1.8	MASG: 21 (39.6%) MISG: 32 (60.4%)	LG: 36 (80%) IG: 2 (4%) HG: 7 (16%)	LG: 14 (31%) IG: 18 (40%) HG: 13 (29%)	(22) MB UPG 16 from LG to IG and 6 from LG to HG
Bai et al. 2013 [31] (Bai et al. 2013)	76	7-81 Mean 51	1:3	MASG: 46 (60.5%) MISG: 30 (39.5%)	LG: 31 (40.8%) IG: 10 (13.2%) HG: 35 (46.0%)	LG: 6 (7.9%) IG: 25 (32.9%) HG: 45 (59.2%)	MB UPG 20/25 from LG to IG, and 5/25 from LG to HG. Five of 10 from IG were upgraded to HG.
Katabi et al. 2014 (Katabi et al. 2014)	52	9-79 Median 50	1:2.05	MASG ONLY: Parotid: 50 (96%) SMG: 2 (4%)	LG: 47 (90.3%) IG: 2 (3.8%) HG: 3 (5.8%)	LG: 28 (53.8%) IG: 17 (32.7%) HG: 7 (13.5%)	(19) MB UPG 15 from LG to IG and 4 from LG to HG
Qannam et al. 2016 (Qannam and Bello 2016)	20	11-80 Median 35	1.4:1	MISG ONLY: Palate 14 (74%), retromolar 2 (11%), Cheek, lip & Maxi. sinus 1 (5%) each	LG: 11 (55%) IG: 6 (30%) HG: 3 (15%)	LG: 4 (20%) IG: 4 (20%) HG: 12 (60%)	MB UPG 7 from LG to HG and 2 from IG to HG

MASG: Major salivary gland; MISG: Minor salivary gland; LG= low grade; IG= Intermediate grade; HG = High grade; AFIP: Armed forces institute of pathology; Modified Brandwein system (MB); Upgrade (UPG); n= number of cases; [a] Chi-square test; [b] Fischer exact test

DISCUSSION

Different grading systems have emerged to replace the initial simplistic method of classification of mucoepidermoid carcinoma into low grade and high grade tumours, based on the relative proportion of the two main cell types [10]. Accordingly, this clinicopathologic study analyzed fifty-six (56) cases of mucoepidermoid carcinoma of the Oral and Maxillofacial region managed at a single institution over a 38-year period (1980-2018) and compared two quantitative grading systems for MEC; the AFIP and modified Brandwein classification systems.

In this study, the mean age of patients with MEC was 41.2 (±20.9) years with a bimodal peak age incidence in the fourth and seventh decades. A peak age of occurrence between the third and sixth decade has been reported to be the commonest age group in most series[12]. This study also observed a slight male predominance which is similar some studies in the literature[13, 14,15]; however other studies have reported MEC to be slightly more common in females[12,16] AOPRC group[5] reported an equal gender distribution of MECs in Nigerians.

In this analysis, MECs affected minor salivary gland more than the major glands and the palate was the commonest minor salivary gland site affected. This is similar to studies in scientific literature which reported MECs to be commoner in minor salivary gland with prevalence between 46% and 52% of malignant tumours[16-20]. The palate has also been reported to be the commonest minor salivary gland site affected with prevalence between 42% and 75%[16,17,21]. This high prevalence of MECs on the palate might not be unexpected because the palate is the region with the highest gland density[22]. Furthermore, this predilection for the palate may also be connected to the proximity of the palate to the maxillary antrum which contains many mucous glands. Other studies have reported major salivary gland tumours to be more affected, with the parotid gland being the most commonly affected anatomic subtype[15,23]. In this study a relatively high number of intraosseous MECs was found within the mandible (16.1%) and the maxilla (7.1%). The reason for this relatively high number of intraosseous MEC needs to be further investigated.

In this study, when the modified Brandwein criteria were employed, 62.5% of the cases were high grade tumours. This is in contrast to many studies, which observed a lower number of cases of high-grade tumours in their series[24-27]. The study by Guevara et al.[23] showed an equal distribution between low and high grades using the AFIP grading system. While Spiro et al.[8] utilized the relative proportion of the two main cells reported higher grade MEC than low grade MECs.

The greater percentage of cases with high-grades may be due to the health seeking culture in the studied population, in which the patients tend to consult a professional mostly when the disease is at an advanced stage[28] and there has been reports of positive correlation between histological grade and stage of mucoepidermoid carcinoma[3]. Most MECs are of low or intermediate grade[24, 29], more so, the MECs of minor gland tend to be of low and intermediate grades compared to major glands[30].

Finally, in comparing the agreement in grading categorization between the AFIP and the modified Brandwein methods, the histologic grading of our cases showed 62.5% of cases to be high grade MECs using the modified Brandwein system compared to 55.4% when the AFIP method was used to grade. This showed that just 4 cases of MECs were upgraded to high grade from AFIP using the Brandwein. The different studies that compared the grading system of Brandwein with other grading systems is shown in Table 5. Qannam and Bello 2016[29] using both systems found a higher proportion of high grade MECs after using the Brandwein method. Katabi et al. 2014[25] also observed a lack of consensus in the diagnosis of high grades MEC of major glands between AFIP and Brandwein methods. Low grade tumours in our cohort was down graded in the Brandwein compared to the AFIP, whereby 16 cases of low grade tumours in AFIP were downgraded and 8 cases in the Brandwein system.

However, agreement between grading systems is far more likely to be seen when tumours are graded as high or low grades, but not

intermediate grade. This is testament to the imperfection that is associated with classifying MEC as an intermediate grade tumour. The implication and benefit of correctly establishing a tumour as high grade is such that these patients will be subjected to more aggressive treatment which may improve survival, as adjunct radiation therapy has been shown to confer a survival benefit[13]. Moreover, patients with multiple poor prognostic features such tumour size greater than 4 cm, that show extra glandular extension and nodal disease are high grade tumours; exhibiting poorer survivals and may be candidates for more aggressive treatment protocols.

This study is limited in its inability to correlate the grading systems with survival rates in the cases studied. This can be attributed to loss to follow-up of patients, as patients often do not comply with long term follow-up plans after surgery.

CONCLUSION

This study of mucoepidermoid carcinoma had an almost equal sex predilection, it was more common in the minor salivary gland, and using both the AFIP and the MB criteria, the most frequent type was the high grade tumour. The MB grading uncovers more MECs as high-grade tumours than the AFIP system and there was a 50% upgrade to either IG or HG from LG when the MB was used. Although, the AFIP method appears to be less ambiguous, it has the potential risk of placing biologically more aggressive tumours into the low-grade category. As this study was not designed to compare the predictive performance of the two grading systems employed, we recommend future study in this direction as appropriate grading of mucoepidermoid carcinoma is crucial for good case management.

No conflict of interest declared.

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