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Application of the Milan System of Reporting Salivary Gland Cytopathology: A Retrospective Cytohistological Study in a Tertiary Medical Center

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ABSTRACT

Background. A fine needle aspiration biopsy has been established as a safe, minimally invasive procedure in evaluation of salivary gland lesions. The complex overlapping cytomorphology of these lesions are challenging for pathologists, hence the introduction of an evidence-based system, the Milan System of Reporting Salivary Gland Cytopathology, to improve overall patient care. The study was taken up to re-classify salivary gland lesions from previous FNA biopsies in order to determine sensitivity, specificity, positive and negative predictive values of FNA, and evaluate the risk of malignancy of the various categories of the Milan system.

Methodology. This was a 6-year retrospective descriptive study in a tertiary medical center. All salivary gland FNA cases were reviewed by two pathologists, and re-classified into the six categories of the Milan System. The number of false positive, false negative, true positive and true negative cases were obtained by comparing with the final histopathology diagnosis, and the risk of malignancy per category were calculated.

Results. A total of 76 cases were reviewed and the overall average of the two readers diagnostic accuracy were 85.02% (95% CI: 84.50-85.60%), sensitivity and specificity were 80.77% (95% CI: 79.90-81.60%) and 86.19% (95% CI: 85.70-86.70%), respectively; positive and negative predictive values were 62.16% (95% CI: 60.70-63.60%) and 94.17% (95% CI: 94.00-94.40%), respectively.

Conclusion. The Milan System category with the highest risk of malignancy was Malignant (Category VI - 100%). FNAB is still a reliable tool for clinicians, and use of the Milan System of Reporting Salivary Gland Cytopathology is beneficial in increasing efficacy of communication among clinicians to improve patient care.

Key words: cytopathology, fine needle aspiration biopsy, Milan System, salivary gland

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INTRODUCTION

Salivary gland tumors comprise about 3% to 6.5% of all head and neck tumors.[1,2] To diagnose the nature of these lesions, a fine needle aspiration biopsy (FNAB) is usually performed. This procedure is widely accepted by clinicians, and is considered as an effective and minimally invasive procedure, with a reported sensitivity and specificity of 86 to 100% and 90 to 100%.[3]

The interpretation of the FNAB sample is a challenge to pathologists, as many salivary gland lesions have diverse cytomorphology, with benign and malignant tumors having significant morphologic overlap.[4] The accuracy of FNAB is dependent on multiple factors such as biopsy technique, adequacy and quality of the prepared smears, lesion morphology, and experience of the reading cytopathologist.[1] These aforementioned factors contribute to the complexity of the final FNA reading, which then affects the subsequent treatment and overall prognosis of the patient.[5]

In order to address the challenges of salivary gland FNA samples, the American Society of Cytopathology and the International Academy of Cytology began to work on a

uniform reporting system for salivary gland cytopathology in 2015, with the goal of increasing the overall effectiveness of FNAB.[3] This culminated in the publishing of the book, The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) in 2018. It is an evidence-based system, which contains six categories that have corresponding risk of malignancy (ROM) and suggested clinical management strategies.[3] The six-tier classification system of Milan provides a standardization of terms, which pathologists can use to facilitate better communication with clinicians and improve overall patient care.[3]

This study was undertaken to retrospectively re-classify salivary gland lesions from previous FNA biopsies in order to determine sensitivity, specificity, positive and negative predictive values of FNA, and evaluate the risk of malignancy of the various categories of the Milan system.

METHODOLOGY

Sampling

This was a 6-year retrospective study performed in a tertiary institution. Clearance for the study was obtained from the Institutional Review Board. All cases of fine needle aspiration biopsy of the salivary gland from the year 2014 to 2020, with available surgical follow-up were included in the study. Those cases which lacked either an FNAB or histopathology result within the institution were excluded from the study.

Materials and methods

The demographic data, previous cytology, and histopathology results of patients were obtained by electronic records review. The corresponding slides for cytology cases were retrieved and reviewed by two board certified anatomic pathologists, one with subspeciality in cytology and another in head and neck pathology. Both readers were blinded to official cytology and histopathology results. Cases were randomly arranged for each reader. The Milan System for Reporting Salivary Gland Cytopathology was used in the re-evaluation of the cytological features of each case. Cases were then re-classified into the six categories.

In our institution, salivary gland lesions are aspirated by clinicians, fellows and residents trained in performing aspiration procedures, with or without image guidance. A gauge 22 or 23 needle is commonly used, and aspirates are placed on glass slides which are first air-dried then fixed in 95% ethanol. All smears are then processed in the histopathology section of the laboratory by staining with Papanicolaou stain.

The Milan System categories II, III and IVA were combined into a negative group, while categories IVB, V and VI were combined into a positive group for statistical analysis. This grouping was modeled after the study performed by Hafez et al., which stated that these groupings were chosen as they have similar overall patient management.[1]

Demographic data for each case, including patient's age, sex, and location of lesion were determined by frequency and percentage. Cytological cases were subclassified into true positives, true negatives, false positives (interpreted in cytology as positive, but was either benign or non-neoplastic on final histopathology), and false negatives (interpreted in cytology as negative, but was malignant on histopathology). The sensitivity, specificity, positive predictive value, negative predictive value and risk of malignancy (ROM) were computed first for each reader, and then averaged to obtain the overall values. The final histopathologic diagnosis was considered as the gold standard.

RESULTS

A total of 76 FNAB cases were included in the study. The site of involvement, and distribution of cases by location and age is shown in Table 1. Males (67.11%) were more commonly affected than females (32.89%), and occurred mostly between the ages of 21 to 40 years old (38.16%). The most commonly affected site was the parotid gland (78.95%), followed by the submandibular gland (17.11%).

Of the 76 cases reviewed, the most common cytologic diagnosis was benign neoplasm, Category IVA (46.05%, n=35/76), and were composed of pleomorphic adenoma (82.86%, n = 29/35), Warthin tumor (14.29%, n=5/35), and oncocytoma (2.86%, n=1/35). The second most common cytologic diagnosis was non-diagnostic (17.10%–26.32%, n=13-20/76), and were due to paucicellular smears, hemorrhagic smears, or the lack of lesional cells in a clinically defined mass.

Correlation with histopathology results showed two false positive cases, one which was reported as suspicious for acinic cell carcinoma oncocytic variant, was an oncocytoma on final histopathology; and another case which was reported as suspicious for adenoid cystic carcinoma, turned out to be a pleomorphic adenoma. There was one false negative case, which was read as pleomorphic adenoma on cytology, but turned out to be a low grade mucoepidermoid carcinoma. Two cases had mis-subtyping and were both called Warthin tumor on cytology but turned out to be an oncocytoma on final histopathology. Among the non-diagnostic cases, one was chronic sialadenitis on final histopathology, one was atypical lymphoid proliferation, three were lymphoepithelial cysts, one lipoma, one chordoma, one infarcted pleomorphic adenoma, three Warthin tumors, and two malignant cases (lymphoepithelial-like carcinoma, and carcinoma with adenosquamous and oncocytic features). Table 2 summarizes all discordant cyto-histological cases.

Table 1. Distribution of cases by age, sex, and site of involvement

Parameter	Number of cases (Total N = 76)
Sex	
Male	51 (67.11%)
Female	25 (32.89%)
Age (years)	
<20	2 (2.63%)
21 to 40	29 (38.16%)
41 to 60	26 (34.21%)
61 to 80	19 (25.00%)
Gland involvement	
Parotid gland	60 (78.95%)
Submandibular gland	13 (17.11%)
Unspecified	3 (3.95%)

Table 2. Cyto-histologic correlation of discordant cases

Milan System diagnostic category	Cytologic diagnosis	Histopathologic diagnosis (N)
I. Non-diagnostic	Non-diagnostic smears	Atypical lymphoid proliferation (1)
		Benign lymphoepithelial cyst (3)
		Chronic sialadenitis (1)
		Lipoma (1)
		Warthin tumor (1)
	Hemorrhagic smears	Warthin tumor (2)
		Chondroma (1)
		Infarcted pleomorphic adenoma (1)
		Lymphoepithelioma-like carcinoma (1)
		Carcinoma with adenosquamous and oncocytic features (1)
II. Non-neoplastic	Sialadenitis	Warthin tumor (2)
	Reactive lymphadenitis	Pleomorphic adenoma (1)
III. AUS	Oncocytic neoplasm, paucicellular smears	Granulomatous lymphadenitis with caseation necrosis consistent with tuberculous lymphadenitis; Unremarkable submandibular gland (1)
	Sparse atypical cells	High grade mucoepidermoid carcinoma (1)
IVA. Neoplasm, benign	Pleomorphic adenoma	Low grade mucoepidermoid carcinoma (1)
IVB. SUMP	-	-
V. Suspicious for malignancy	Suspicious for malignancy, consider acinic cell carcinoma, oncocytic variant	Oncocytoma (1)
	Suspicious for adenoid cystic carcinoma	Pleomorphic adenoma (1)
VI. Malignant	-	-

Table 3. Recategorization of cases according to the Milan System with computed risk of malignancy

Milan System diagnostic category	No. of cases	Reader 1 (ROM)		No. of cases	Reader 2 (ROM)	
I. Non-diagnostic	13	3/13	(23.08%)	20	2/20	(10.00%)
II. Non-neoplastic	8	0/8	(0%)	4	0/4	(0%)
III. AUS	3	1/3	(33.33%)	1	1/1	(100%)
IVA. Neoplasm, benign	35	0/35	(0%)	35	1/35	(2.86%)
IVB. SUMP	10	2/10	(20.00%)	6	1/6	(16.67%)
V. Suspicious for malignancy	4	4/4	(100%)	4	2/4	(50.00%)
VI. Malignant	3	3/3	(100%)	6	6/6	(100%)

The recategorization of cytological cases along with the ROM per category is shown in Table 3. Concordance and discordance between cytologic and histopathologic diagnosis was calculated for all cases, excluding the non-diagnostic category. Concordance was found at 95.24% (n=60/63) and 96.43% (n=54/56) for reader 1 and 2, respectively, and discordance was found at 4.76% (n=3/63), and 3.57% (n=2/56), for each reader, respectively.

For reader 1, the sensitivity, specificity, positive predictive value, and negative predictive values were 69.20% (95% Confidence Interval [CI]: 38.60–90.90%), 87.30% (95% CI: 76.50–94.40%), 52.90% (95% CI: 27.80–77.00%), and 93.20% (95% CI: 83.50–98.10%) respectively. For reader 2, the sensitivity, specificity, positive predictive value and negative predictive value were 69.20% (95% CI: 38.60–90.90%), 88.90% (95% CI: 78.40–95.40%), 56.20% (95% CI: 29.90–80.20%), and 93.30 (95% CI = 83.80–98.20%), respectively. The diagnostic accuracy was 84.21% (95% CI: 84.00–85.8%) and 85.83% (95% CI: 84.00–85.8%) for each reader, respectively.

Upon exclusion of the non-diagnostic category from analysis, the re-computed values are as follows: For reader 1, the sensitivity, specificity, positive predictive value and negative predictive value were 76.92% (95% CI: 46.19–94.96%), 84.00% (95% CI: 70.89–92.83%), 55.56% (95% CI: 38.27–71.60%), and 93.33% (95% CI: 73.84–97.44%). While for reader 2, the sensitivity, specificity, positive predictive value and negative predictive value were 84.62% (95% CI: 54.55–98.08%), 88.37% (95% CI: 74.92–96.11%), 68.75% (95% CI: 48.31–83.81%), and 95.00% (95% CI: 84.09–98.56%). The diagnostic accuracy was 82.54% (95% CI: 70.90–90.95%) and 87.50% (95% CI: 75.93–94.82%) for each reader, respectively.

For the overall findings, the average of the two readers were taken and the values are as follows: sensitivity and specificity were 80.77% (95% CI: 79.90-81.60%) and 86.19% (95% CI: 85.70-86.70%), respectively; while positive and negative predictive values were 62.16% (95% CI: 60.70-63.60%) and 94.17% (95% CI: 94.00-94.40%), respectively. The summary of all these values is seen in Table 4.

DISCUSSION

The MSRSGC is a relatively new classification system, which is evidence based and provides risk stratification by reporting ROM per category, with suggested clinical management.[3] The reported ROM per category can be found in Table 1. The ROM computed in the present study appears to be at par with the reported ROM in MSRSGC and other similar studies (Table 5).

When the non-diagnostic category was included in the analysis, the sensitivity of each reader (69.20%) was found to be lower than that reported in MSRSGC (86-100%), and in a meta-analysis of 92 studies (96.9%); while the specificity for each reader was at par (87.30 and 88.90%)

Table 4. Summary of computed statistics in comparison to other similar studies

Parameter	Present Study (Reader 1)		Present Study (Reader 2)		Present Study Average (Excluded ND cases)	Santiago et al[7]	Amita et al[8]	Hafez et al[1]	Farahani et al[6]	MSRSGC[3]
	Included ND Cases	Excluded ND Cases	Included ND Cases	Excluded ND Cases						
Sensitivity	69.20%	76.92%	69.20%	84.62%	80.77%	46%	89.4%	84.6%	96.9%	86-100%
Specificity	87.30%	84.00%	88.90%	88.37%	86.19%	100%	100%	88.2%	95.3%	90-100%
PPV	52.90%	55.56%	56.20%	68.75%	62.16%	90%	100%	78.6%	-	-
NPV	93.20%	93.33%	93.30%	95.00%	94.17%	91%	95.74%	91.8%	-	-

ND – Non-diagnostic; PPV – Positive Predictive value; NPV – Negative predictive value

Table 5. Comparison of ROM across several studies

Author	Category I	Category II	Category III	Category IVA	Category IVB	Category V	Category VI
MSRSGC[3]	25% (0 to 67%)	10% (0 to 20%)	20% (10 to 35%)	<5% (0 to 13%)	35% (0 to 100%)	60% (0 to 100%)	90% (57 to 100%)
Present Study							
Reader 1	23.08%	0%	33%	0%	20%	100%	100%
Reader 2	10%	0%	100%	2.86%	16.67%	50%	100%
Hafez 2019[1]	33.30%	11.8%	37.50%	2.10%	44.40%	60%	100%
Amita 2018[8]	-	6.25%	100%	0%	25%	100%	100%
Viswanthan 2018[9]	6.70%	7.10%	5%	38.90%	34.20%	92.60%	92.30%

with those reported in MSRSGC (90-100%) and the meta-analysis (95.3%).[3,6] Upon re-computation of these statistics to exclude those non-diagnostic cases, the sensitivity per reader increased (76.92% and 84.62%, respectively). In comparison, our values are similar those reported in a local study performed by Santiago et al., in 2016, which focused on parotid gland FNAB.[7] With a similar sample size of 76 cases, their findings were a sensitivity of 46% and specificity of 100%. In their study, the low sensitivity was due to a high false negative rate of 53.85% (n = 7/13).[7] This was attributed to the misdiagnosis of malignant salivary gland tumors as benign.[7] However it can be noted that for our study, the non-diagnostic cases contributed to the low sensitivity, which took up to 26.32% (n = 20/76) of the cases reviewed, as re-computation showed an increase in the sensitivity for each reader (Table 4). In our study the false negative rate is 30.77% (n = 4/13), much lower than the one presented in Santiago et. al.[7] In the present study, one case was read as pleomorphic adenoma by one reader, and the final outcome was a low-grade mucoepidermoid carcinoma. The other three cases were non-diagnostic; two cases with a final histopathology report of malignancy (Lymphoepithelioma-like carcinoma, Carcinoma with adenosquamous and oncocytic features); and one case with atypical lymphoid proliferation.

Among the non-diagnostic cases in our study, up to 20 (17.11–26.32%) were predominantly due to pauci-cellularity, or hemorrhagic smears. The non-diagnostic rate in other studies range from 5 to 10%, though some studies have a reported non-diagnostic rate of 4.3% up to 12%.[5,8,9] Some factors which may have contributed to the high number of non-diagnostic cases in our study may be poorly prepared slides, three of which contained obscuring blood, while others were due to the overt lack of lesional cells, and the fading of stains from storage, which rendered the slides more difficult to interpret. This is supported by the findings in similar studies which state that aspiration technique, presence of artifacts or obscuring elements, inherent lesion characteristics, and experience of the performer are among several factors that can contribute to the final diagnosis.[5,8,9]

Some studies suggest the use of rapid on-site evaluation (ROSE) to decrease the number of false negative cases.[5,10,11] It has been found that ROSE can be used to determine the adequacy of a sample and findings of atypia or malignancy during the procedure can be useful to facilitate early clinical decision making.[10,11] One of the disadvantages of ROSE may be the need for a proficient cytopathologist, or an expert on salivary gland tumors during the procedure.[5] However the current MSRSGC does not mention ROSE, instead they suggest to use the adequacy guidelines similar to that found in the Bethesda system for Reporting Thyroid Gland Cytopathology, or to count at least 60 lesional cells.[3] It is recommended to keep the non-diagnostic rate at 10% or below, in order to avoid high false negative rates.[3]

For the non-neoplastic cases in the study, the ROM for both readers were 0%, much lower compared to those reported in other studies (Table 5). Nearly all cases (62.5%, n = 5/8) classified under this category turned out to be chronic sialadenitis, with three cases being benign neoplasms (Warthin tumor and Pleomorphic adenoma) on final histopathology. Review of the cases revealed hypocellular smears containing mostly benign acinar cells with a predominantly chronic inflammatory infiltrate in the background (Figure 1). A Warthin tumor may be misdiagnosed as chronic sialadenitis, since both lesions contain a lymphoid background. This finding was similarly reported in a study by Amita et al.[8]

A total of three cases were classified under the AUS category, which turned out to be granulomatous lymphadenitis with caseation necrosis, chronic sialadenitis, and high grade mucoepidermoid carcinoma. The ROM for this category varies widely across studies from as low as 5% up to 100%, and also showed variation between the two readers (Table 5).[8,9] The variation in the ROM for this category reflects its heterogeneity. It includes lesions which may show reactive atypia or may represent poorly sampled neoplasms (Figure 2).[3] The MSRSGC has recommended that AUS be used in less than 10% of cases, and recommends a repeat FNAB for some lesions or surgery for more worrisome lesions.[3] It is suggested that careful assessment of smears, and paying attention to

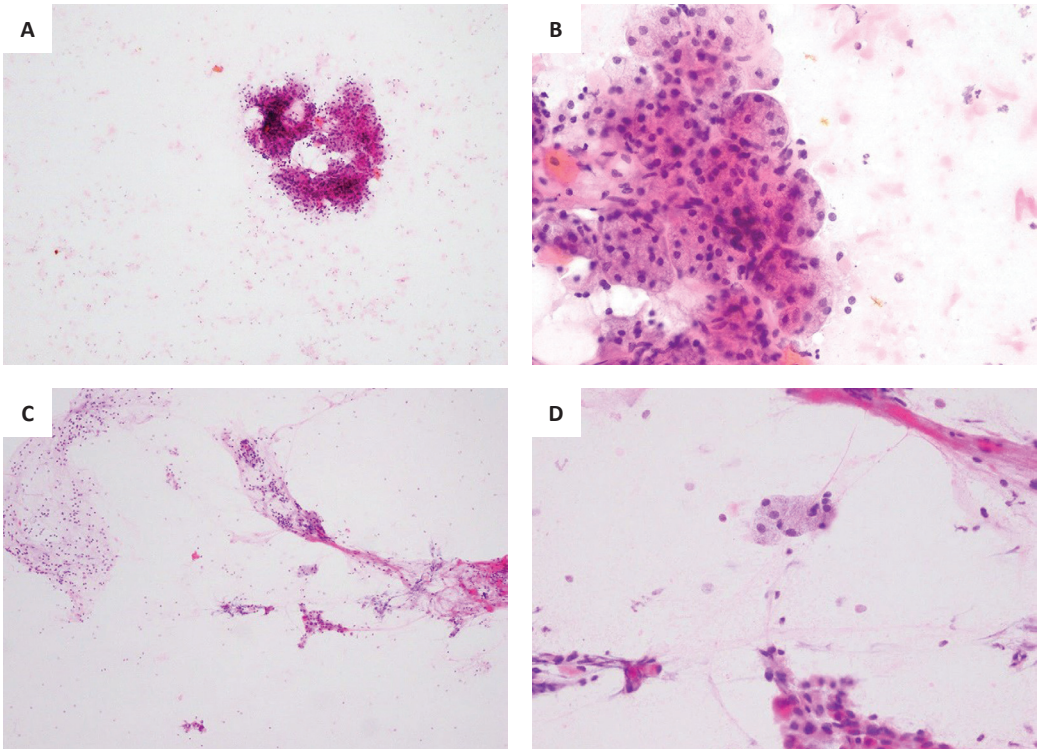

Figure 1. ***Non-neoplastic smears.*** Upper row: **(A and B)** This smear contained few groups of normal appearing acinar cells [**(A)** Papanicolaou, 100x and **(B)** 400x]. Lower row: **(C and D)** Smear containing rare acinar cells and background inflammatory cells [**(C)** Papanicolaou, 100x and **(D)** 400x].

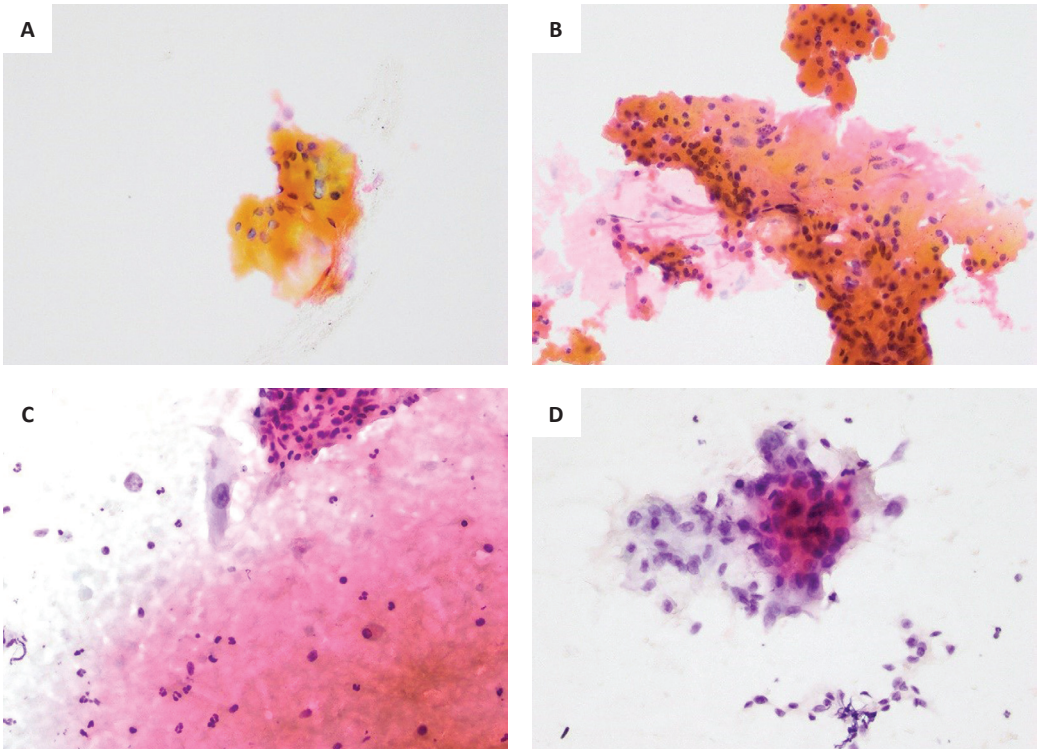

Figure 2. ***Atypia of undetermined significance.*** Upper row: **(A and B)** Cells shown were described to have oncocytoid features with mild nuclear atypia (Papanicolaou, 400x.) Lower row: Rare large atypical cells seen singly **(C)** or in groups **(D)** are shown, with enlarged nuclei and irregular nuclear borders (Papanicolaou, 400x).

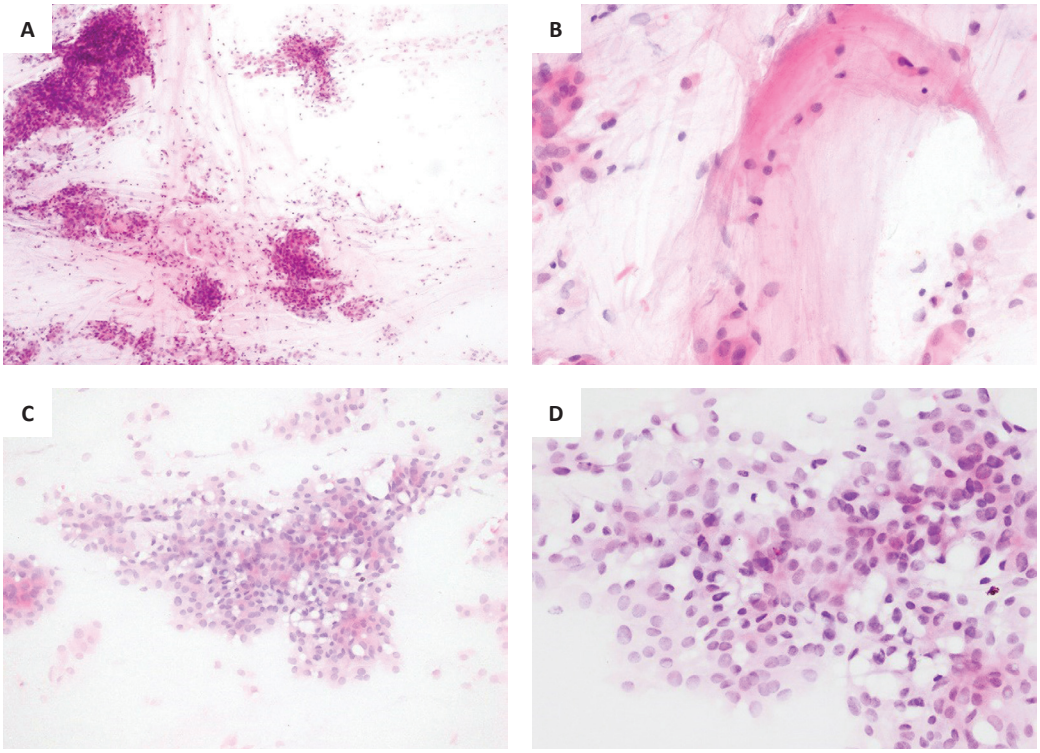

Figure 3. ***Non-neoplastic smears.*** Smears of **(A)** and **(B)** show groups of bland appearing, plasmacytoid cells within an eosinophilic fibrillary-like stromal background [**(A)** Papanicolaou, 100x and **(B)** 400x]. **(C)** The cells are fairly uniform, without ball-like clustering (Papanicolaou, 100x). **(D)** There is mild to no nuclear atypia with fine chromatin, and vacuole-like spaces are seen in the cytoplasm (Papanicolaou, 400x).

detail may aid in reducing the use of this category, thus lowering the variation in ROM.[1] Some features to take note of, besides cellular atypia, would be the presence or absence of mucin in the background, heterogeneity of the cell population and the degree of atypia in lymphoid populations.[1,3] One study further investigated the ROM of AUS category, by subclassifying AUS further into 6 groups which were: reactive and reparative atypia; squamous, oncocytic, or metaplastic changes; low cellularity; specimens with preparation artifacts, mucinous cystic lesions; and lymph node or lymphoid lesions.[12] This study found that further subtyping of the AUS category showed differences in ROM, and highest ROM (100%) was noted in the specimens with preparation artifacts hampering the distinction between non-neoplastic and neoplastic lesions.[12] They therefore suggest that subtyping AUS cases may be beneficial to guide clinical management.[12]

The category of benign neoplasms composed the bulk of the present study (46.05%, n = 35/76), and the most common entities were pleomorphic adenoma and warthin tumor. This is similar to other studies which also reported pleomorphic adenoma as the most commonly aspirated benign lesion.[5–7,13] The ROM obtained in the present study for this category is also at par with similar studies (Table 5). In the present study, one case of low grade mucoepidermoid carcinoma was called a pleomorphic adenoma in cytology (Figure 3). It is stated that there is much difficulty in distinguishing benign from low grade lesions, due to their overlapping cytomorphologic features.[13] Review of the smears showed increased cellularity, though individual cells had an overall bland appearance, with minimal atypia and poor staining. Careful examination of the smears showed some cells with rare cytoplasmic inclusions. These factors in addition to possible misinterpretation of background stroma, may lead to an erroneous diagnosis.[5,13] In addition, it is recommended to have a smear stained with Giemsa or Diff Quick, as these stains better highlight the appearance of background stroma.[3]

In the present study, up to ten cases were classified under SUMP category. The ROM for this category was also comparable to other similar studies (Table 5). Two cases of SUMP turned out to be adenoid cystic carcinoma, another two were basal cell adenoma, and the remaining cases were cellular pleomorphic adenoma. This category is used when a diagnosis for a definitive entity cannot be made, and malignancy cannot be excluded.[3] The high cellularity of smears, predominantly basaloid population of cells, and matrix poor background are among the following factors which contribute to this diagnosis and is similarly found in other studies (Figure 4).[1,8,13]

In the present study, four cases were classified under suspicious malignancy, which comprised 5.26% of all reviewed cases. Two of the four cases were falsely positive, and final histopathology showed an oncocytoma, and another was pleomorphic adenoma (Table 2). The increased cellularity, along with presence of cellular atypia, obscuring blood and quality of stains were among some factors attributed to the misdiagnosis (Figure 5). This finding is similar to one reported study wherein smears were suspicious for a mucoepidermoid

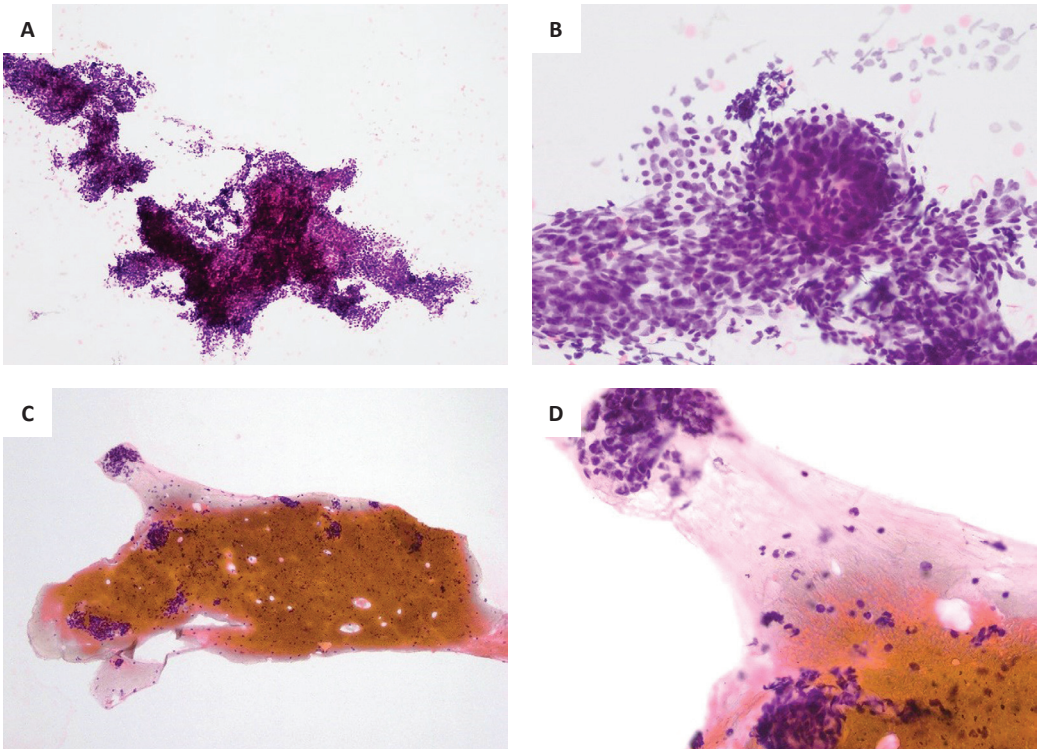

Figure 4. ***Salivary gland neoplasm of uncertain malignant potential.*** Upper row: **(A)** and **(B)** showing a cellular smear composed of sheets of basaloid appearing cells with mild nuclear atypia. There is lack of any distinct matrix in the background [**(A)** Papanicolaou, 100x and **(B)** 400x)]. Lower row: The thick preparation of **(C)** and **(D)** slightly obscure nuclear features of this sample, though the basaloid character of the cells can still be appreciated [**(C)** Papanicolaou, 100x and **(D)** 400x)].

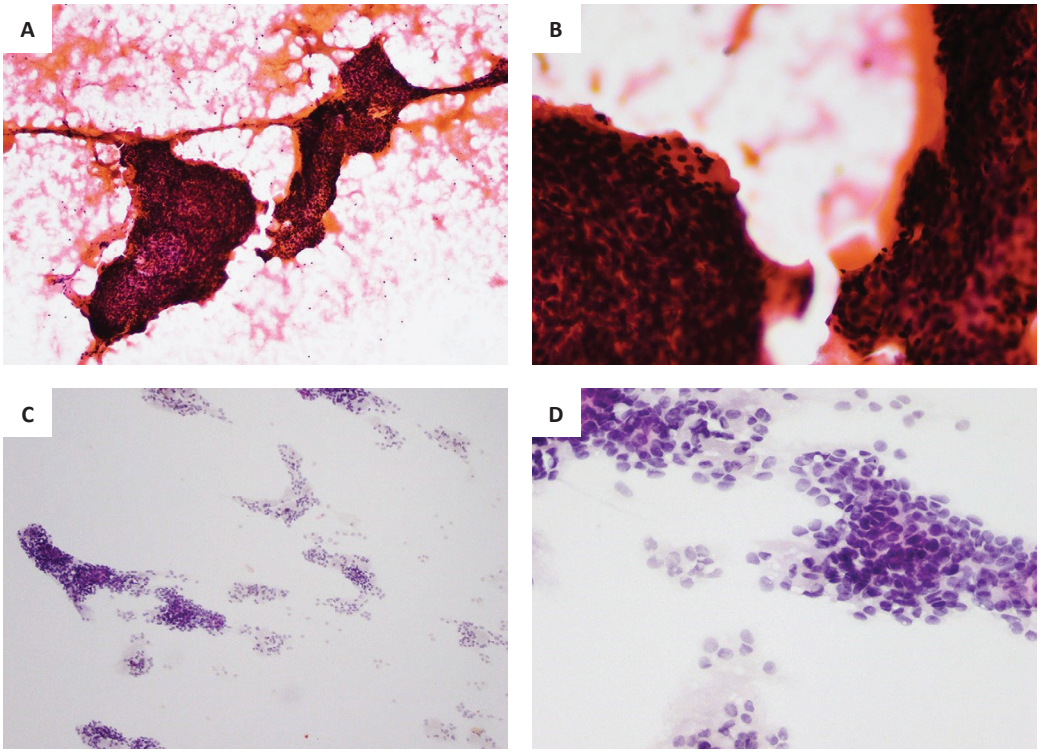

Figure 5. ***Suspicious for malignancy.*** Upper row: Smears of **(A)** and **(B)** show large groups of cells obscured by blood. Overall cellularity is increased and show atypical features with overlapping enlarged, hyperchromatic nuclei with variable eosinophilic cytoplasm [**(A)** Papanicolaou, 100x and **(B)** 400x]. Lower row: Smears of **(C)** and **(D)** show basaloid cells with atypical nuclear features of hyperchromatic nuclei, irregular nuclear membranes, and scant cytoplasm [**(C)** Papanicolaou, 100x and **(D)** 400x].

carcinoma, but turned out to be a pleomorphic adenoma on histopathology.[13] As for the malignant category, all cases had cytohistologic correlation, and the ROM was at par with that reported in the MSRSGC (Table 5).

CONCLUSION

The current study finds that the sensitivity is lower than that reported by MSRSGC.[3,6] This may be due to the discordant cases which were predominantly non diagnostic, with poor cellularity or poor quality of smears. This highlights the importance of pre-analytical factors in rendering the final diagnosis. ROSE may be recommended to decrease the number of non-diagnostic samples and facilitate clinical management. Lesion morphology is still a challenge, however the overall ROM of the present study is found to be comparable to that reported in MSRSGC and other similar studies, which is shown in Table 5.[1,3,8,9] The slight variation in ROM, especially for AUS category, may be attributed to the heterogeneity of included samples and experience of the reading pathologists. Using a tiered classification system like the MSRSGC can facilitate standardization of reporting and improve clinical decision making. The overall findings of the study suggest that FNAB is still a reliable tool for clinicians in the diagnosis of salivary gland tumors, and that application of MSRSGC in the local setting can be beneficial in reducing misdiagnosis and facilitate better patient care.

Some limitations of the current study include the limited sample size, retrospective design, and the faded quality of stored smears. It is recognized that the entities described in this study may not represent those seen in other institutions. Furthermore, the lack of Giemsa-stained smear preparations may have contributed to the misdiagnosis of some cases. It is thus recommended to consider including this stain as part of the routine processing procedure for future salivary gland samples. The interobserver variability and concordance rates between or among observers was not determined in this study. The determination of an over-all recategorization of cases for final cytologic diagnosis among readers was not performed in this study. Further investigation of the Milan System to determine concordance among pathologists, or investigation using a prospective study design may also be undertaken.

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STATEMENT OF AUTHORSHIP

All authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

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