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The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC)

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Abstract
Background: *FNA is a cost-effective and minimally invasive diagnostic tool for sampling salivary gland lesions. However due to intra-tumoral heterogeneity and frequent overlapping of cyto-morphologic features precise subtyping of neoplasms can be challenging. To address this, International panel of experts under the joint effort of the American society of cytopathology and the International academy of cytology developed the MSRSGC.*
Methodology: *356 salivary gland FNA samples were retrospectively analysed and re-categorised into 6 categories of the Milan system. Histopathology diagnoses were retrieved wherever available. Overall ROM were calculated for each category.*
Results: *On re-categorising into the Milan system, 62 cases were assigned to non-diagnostic category (17.4%), 67 to non-neoplastic category (18.8%), 48 as Atypical (13.5%), 101 as benign neoplasms (28.4%), 35 to the salivary gland neoplasm of uncertain malignant potential (9.8%), 16 as suspicious for malignancy (4.5%) and 27 to the malignant category (7.6%).The ROM for above mentioned category were 30%, 7.1%, 14.2%, 3%, 31%, 67% and 95.2% respectively.*
Conclusion: *MSRSGC provides uniform reporting system for salivary gland cytopathology which helps to reduce reporting ambiguities and thus improves overall patient care.*
Keywords: *Fine-needle aspiration; Milan system for reporting salivary gland cytopathology (MSRSGC); Risk of malignancy (ROM).*

Introduction

Salivary gland neoplasm comprise approximately 6.5% of the lesions sampled in the head and neck, out of which approximately 40% are malignant[1]. A multimodal approach is required as a part of initial diagnostic work-up for salivary gland nodules. However, to finalise the malignant potential of a lesion, fine-needle aspiration (FNA) remains the preferred diagnostic test[1-9].

Fine needle aspiration (FNA) of salivary gland is a cost-effective and minimally invasive diagnostic technique in guiding the management of superficial masses[10-13].

Despite the above mentioned advantages, there exist few limitations, including the lack of architecture and cellular complexity of salivary gland neoplasms encountered among the same subtypes and even within an individual tumor[17-19].

In an attempt to address some of these limitations of salivary gland FNA a group of
International pathologists proposed a uniform system known as The Milan system for reporting salivary gland cytopathology (MSRSGC)[14].
Similar to analogous reporting schemes, like the Bethesda System for Reporting Thyroid Cytopathology, this classification system considers the reporting ambiguities inherent to salivary gland pathology, while also risk stratifying lesions, providing a clinical useful guidelines regarding its management[16].The MSRSGC is composed of seven diagnostic categories: non-diagnostic, non-neoplastic, atypia of undetermined significance, benign neoplasm, salivary gland neoplasm of uncertain malignant potential, suspicious for malignancy, and malignant.
As the MSRSGC is still in its infancy, additional studies are needed to evaluate the effectiveness of this classification system[15]. The main objective of this study was to assess the diagnostic accuracy of salivary gland FNAs using the Milan System and evaluate the MSRSGC as a tool for risk assessment.

Materials and Methods

FNA specimens from salivary gland lesions that were registered from January 2016 to September 2018 in the cytology department at Mysore medical college and research institute were retrieved. Oral informed consent was obtained from each patient before routine FNA of salivary gland lesions. FNA procedure were performed by trained cytopathologist.
Major and minor salivary gland swellings, including intraoral lesions, were aspirated via direct percutaneous or trans-oral route with 23-27-gauge needle. Smears were stained with haematoxylin and eosin stains in all cases for immediate on-site evaluation, and few of the direct smears were stained with the Papanicolaou stain following alcohol fixation. All data related to cytological examination, history, clinical examination and investigations were collected.
FNA diagnoses were retrospectively classified according to the Milan system as follows: Non-Diagnostic (ND), Non-Neoplastic (NN), Atypia of Undetermined Significance (AUS), Benign Neoplasm (BN), Salivary gland neoplasm of Uncertain Malignant Potential (SUMP), Suspicious for Malignancy (SM), or Malignant (M).
Histologic diagnoses of surgical specimens were categorized as Non-Neoplastic, Benign Neoplasm and Malignant. Pre and post-operative categorizations were compared to calculate the risk of neoplasm (RON) and risk of malignancy (ROM).Overall accuracy, specificity and sensitivity of the diagnostic categories were calculated.

Results

A total of 356 FNA specimens were identified between January 2016 and September 2018 which included 189 females and 167 males (female:male ratio of 1.1:1) with an average age of 52 years (range 12-90 years). The most frequent site of involvement was the parotid gland (232/356, 65.1%), followed by the submandibular gland (118/356, 33.1%), and last the minor salivary glands (6/356, 1.7%).
The pre-operative cytology classifications and histologic follow-up are summarized in (Table 1).
For the FNA cases with surgical follow-up, the risks of neoplasm and malignancy were calculated for each of the Milan System diagnostic categories (Table 1). The most common benign and malignant diagnoses in each category are listed in (Table 2).
Discordance between FNA and histologic diagnoses was observed in 5 cases. In the non-neoplastic FNA group, 1/14 (7.1%) case was ultimately diagnosed as lipoma and 1/14 (7.1%) were diagnosed as lymphoma. Among cases called benign neoplasm on FNA, 2/67 (3.0%) were reported to be malignant on resection which included cases of adenoid cystic carcinoma and mucoepidermoid carcinoma.

Finally, of cases called malignant on FNA, 1/21 (4.8%) was Warthin tumor on histologic follow-up.

Malignancies represented by the AUS category included lymphoma (2), mucoepidermoid carcinoma (2), squamous cell carcinoma (1) and adenoid cystic carcinoma (1). Non-neoplastic entities included lymphoepithelial cyst (4), benign salivary gland tissue (6), sialadenitis (2) and reactive lymphoid tissue (2). The overall sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were 82.4%, 96.2%, 89.4%, and 100%, respectively.

Table 1: Histopathology follow-up and risk estimation of salivary gland lesions on FNA cytology using the Milan system

		ND	NN	AUS	BN	SUMP	SM	M
Cytology Diagnosis	Total n= 356	62(17.4%)	67(18.8 %)	48(13.5%)	101(28.4%)	35(9.8%)	16(4.5%)	27(7.6%)
	Non-neoplastic n= 37 (18.9%)	2(20.0%)	12(85.7 %)	14(33.3%)	8(11.9%)	0(0%)	1(8.3%)	0(0%)
Surgical follow-up n=195(54.8%)	Benign neoplasm n=109 (56%)	5(50.0%)	1(7.1%)	22(52.4%)	57(85.0%)	20(69%)	3(25.0%)	1(4.8%)
	Malignant n=49 (25.1%)	3(30.0%)	1(7.1%)	6(14.3%)	2(3.0%)	9(31.0%)	8(66.7%)	20(95.0%)
Risk of neoplasm		80.0%	14.3%	66.7%	88.1%	100%	91.2%	100%
Risk of malignancy		30.0%	7.1%	14.2%	3.0%	31.0%	66.7%	95.2%

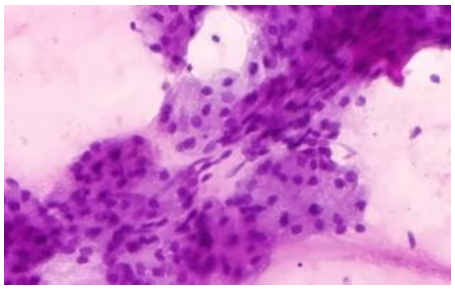
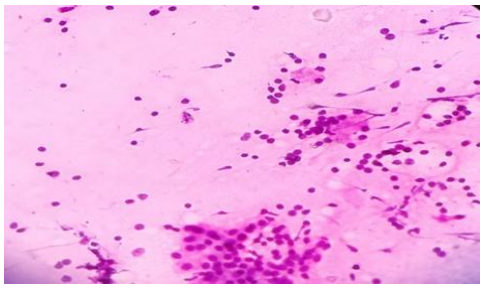
Abbreviations: ND—Non-diagnostic; NN—Non-neoplastic; AUS—Atypia of undetermined significance; BN— benign neoplasm; SUMP— salivary gland neoplasm of uncertain malignant potential; SM—suspicious for malignancy; M—Malignant.

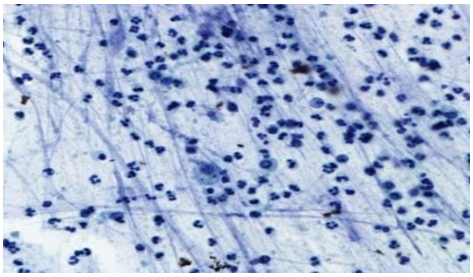
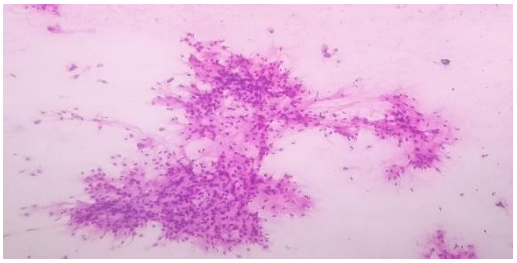
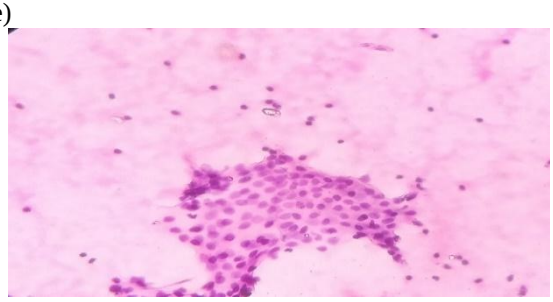
Table 2 Most Common Benign and Malignant Salivary Gland Diagnoses in Each Category of the Milan System for Reporting Salivary Gland Cytopathology

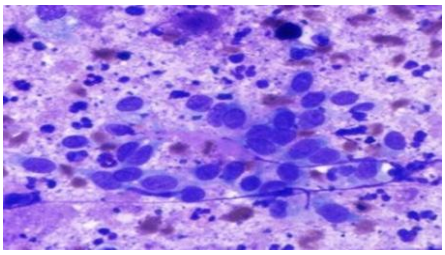
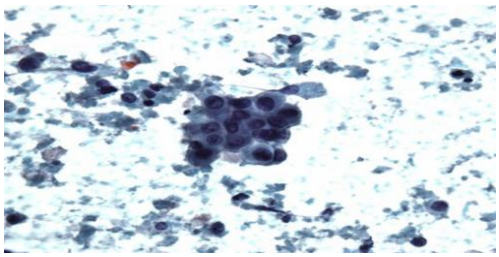
Category	Most common benign diagnosis	Most common malignant diagnosis
1.Non diagnostic	PA (2cases) and lipoma (2cases)	ACC (2cases)
2.Non neoplastic	Intra parotid lymphnode (5cases)	Lymphoma (1case)
3.Atypia of undetermined significance	Warthintumor (15 cases)	MEC (2 cases)
4a.Benign neoplasm	PA (32 cases)	MEC (1 case) ACC (1case)
4b.Salivary gland neoplasm of uncertain malignant potential	PA (12 cases) MEC (5 cases)	MEC (5cases)
5.Suspicious for malignancy	PA (2cases)	MEC (4 cases)
6.Malignant	Warthintumor (1 case)	SCC (primary and metastatic; 9 cases)

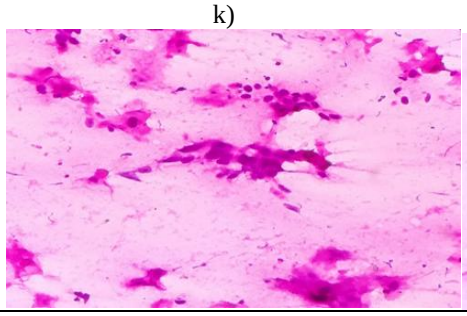
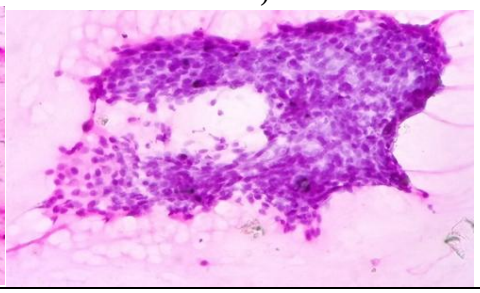
Abbreviations: ACC —Adenoid cystic carcinoma; MEC—Mucoepidermoid carcinoma, PA—Pleomorphic adenoma, SCC—Squamous cell carcinoma.'

Table 3 Cytological diagnostic categories of MSRSGC with illustrative examples

1.Non-diagnostic	**2. Non- neoplastic**
Inadequate quality and or quality e.g.- normal salivary gland elements (a), non-mucinous cyst contents a) 	Inflammatory, metaplastic, reactive components e.g.-chronic sialadenitis (b), reactive intra parotid lymphnode b) 

3.Atypia of undetermined significance	4a. Benign neoplasm
Poorly sampled neoplasm or reactive atypia e.g. mucinous cyst contents (c), atypical cell cluster,oncocytes c) 	Classic benign cases e.g. pleomorphic adenoma (d) , Warthintumor (e), lipoma d)  e) 

4b. Salivary gland neoplasm of uncertain malignant potential	5. Suspicious for malignancy
Diagnostic of neoplasm but with no specific entity, malignancy cannot be ruled out. e.g.atypia (i), low grade carcinoma, basal cell neoplasm i) 	High grade features with limited sampling (j) j) 

6.Malignant
Specific type and grade of malignancy (low grade and high grade), including metastases. Mucoepidermoid carcinoma (k), Adenoid cystic carcinoma (l), Acinic cell carcinoma k)  l) 

Discussion

Despite widespread acceptance of FNA as first line diagnostic approach in patients with salivary gland lesion, it remains one of the most challenging areas within cytopathology[6,8,9,20-25]. Hence there is a need for application of standardised system for reporting salivary gland FNA, which would help to optimise the clinical utility of this test.

Similar to Bethesda system for reporting thyroid cytopathology, the MSRSGC represents a tiered classification system that provides diagnostic information, risk assessment, and management guidelines[17]. In this retrospective study, we found MSRSGC are fairly easy to adopt in daily practise.

In our study, we found 17.4% (62/356) of aspirates were non-diagnostic. Reason for not obtaining representative aspirate could be due to various reasons like improper positioning of the needle, haemorrhage and cystic areas within the tumor. Ultrasound guided FNA plays a major role in increasing diagnostic accuracy and reduce the chance of sampling errors in cases of repeat FNA for non-representative samples.

Overall on surgical follow-up majority of cases were benign 74.9% while 25.1%were malignant. Risk of malignancy for benign category was found to be compatible with <5% rate as suggested by MSRSGC[27]. Histological malignant cases under this category included adenoid cystic carcinoma (1) and carcinoma ex pleomorphic adenoma (1). According to recent literature review, cases such as carcinoma ex pleomorphic adenoma, mucoepidermoid carcinoma, and adenoid cystic carcinoma could be miscategorised under benign category. Adenoid cystic carcinoma could mimic pleomorphic adenoma on FNA due to shared cellular and matrix components, and when mucoid material in case of pleomorphic adenoma take the shape of hyaline globule it can be confused for adenoid cystic carcinoma[30]. Malignant component in case of Carcinoma ex pleomorphic adenoma can be missed due to inadequate sampling giving it a false impression of benign lesion on FNA.

95.2% risk of malignancy for malignant category in our study was found concordant with above 90% ROM as suggested by MSRSGC. One case of Warthin tumor had been falsely diagnosed under malignant category on FNA, for which the probable reason could be squamous metaplasia and dirty background in a Warthintumor, giving it a false impression for squamous cell carcinoma or mucoepidermoid carcinoma.

Under the indeterminate categories, SM category carried 66.7% ROM which varies widely from institution to institution ranging from 58.6% to 100% based on variability of pathologist's experience and their practices[2925, 30-32].The SUMP category had 100% and 31% risk of neoplasm and risk of malignancy respectively. This ROM is found compatible with 35% target rate given by MSRSGC. 13.5% cases were included under AUS category which was found to be slightly higher compared to <10% recommendation given by MSRSGC. The AUS category carried a 66.7% risk of neoplasm and 14.2% risk of malignancy, in line with 20% ROM given by MSRSGC[27].

Milan system also provides management guidelines, under which non-neoplastic category were monitored without surgical follow-up whereas atypical to malignant category had surgical follow-up.

The major limitation of our study is its retrospective nature, which might lead to bias in assigning cases according to the Milan system, particularly when histologic follow-up was already known. However due to limited acceptance of the Milan system in most of the institutions, retrospective study remains to be the main mode of assessing this study.

Conclusion

The recently proposed MSRSGC represents a standardised method for reporting salivary gland FNA. It is a uniform system accepted internationally for reporting salivary gland FNA. It helps to bring in better communication between cytopathologists and treating clinicians also between institutions, thus result in overall improved patient care. However, larger studies with clinical follow-up are required to determine the overall accuracy of MSRSGC.

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