The Milan System for Reporting Salivary Gland Cytopathology with Histologic follow – up: A 10-year Multi-institutional Study in India

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Abstract

Background: An international group of pathologists proposed evidence-based tiered classification system in 2015 for reporting salivary gland FNAC, designated as "Milan System for Reporting Salivary Gland Cytopathology" (MSRSGC) which culminated with the publication of MSRSGC atlas in February, 2018. It has 6 categories. Category 1 or Non- Diagnostic (ND); Category 2 or Non-neoplastic (NN); Category 3 or Atypia of undetermined significance (AUS); Category 4a or Neoplasm: benign (NB); Category 4b or Neoplasm: Salivary gland neoplasm of uncertain malignant potential (SUMP); Category 5 or suspicious of Malignancy (SFM); and Category 6 or Malignant (M).

Objectives: (1) To evaluate the efficacy and potency of salivary gland FNAC under Milan System. (2) To calculate risk stratification for malignancy, and (3) To compare cytologic diagnoses with histologic diagnoses in available cases.

Methods: The study was carried out from September, 2012 to August, 2022. A total of 1678 cases of FNAC were evaluated under Milan System. Histologic follow up was available in 503 cases.

Results: The distribution of cases into different categories was as follows: ND(51,3.04%), NN (657,39.15%), AUS (52,3.10%), NB (626,37.31%), SUMP (42,2.50%), SFM(36,2.14%), and M(214,12.75%). Overall risk of malignancy (ROM) reported were specificity 95.52%, positive predictive value 97.27%, and negative predictive value 87.37% and diagnostic accuracy 90.85%.

Conclusion: Milan System places salivary gland FNAC into well-defined six categories which limit false – positive and false – negative cases. The MSRSGC classification is useful for assessing risk of malignancy and guides clinicians toward appropriate management.

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Introduction

Among all tumors of the head and neck region, salivary gland lesions (SGL) account for 3-6% of the cases.[1] Fine-needle aspiration cytology (FNAC) of salivary gland lesions is a worldwide accepted technique for initial diagnosis and management planning. FNAC is simple, cost effective, useful and minimal invasive procedure. It reduces the associated risk in contrast to surgical procedure of incisional biopsy or core needle biopsy.

However, FNAC of SGL is a challenging task for cytopathologists because of diversity of different neoplasms and addition of new entities by World Health Organization (WHO) classification of head and neck tumors.[2] Also, morphological overlap and intratumoral heterogeneity complicates the situation. To overcome these problems, the American Society of Cytopathology (ASC) and the International Academy of Cytology (IAC) proposed a tier-based classification in Milan, Italy in 2015.[3] It is known as the Milan system for Reporting Salivary Gland Cytopathology (MSRSGC) and it culminated with the publication of the MSRSGC Atlas in February, 2018.[4] There are six categories in the Milan system (Category 4 has two subclassification i.e. 4a and 4b). These six categories are:

Category 1: Non- diagnostic (ND)
Category 2: Non-Neoplastic (NN)
Category 3: Atypia of undetermined significance (AUS)
Category 4(a): Neoplasm Benign (NB)
Category 4(b): Salivary gland neoplasm of uncertain malignant potential (SUMP)
Category 5: Suspicious of malignancy (SM)
Category 6: Malignant (M)

The Milan system includes diagnostic criteria, explanatory notes, implied risk of malignancy (ROM) and a brief management plan for each diagnostic category.

In the current retrospective study, MSRGC was applied to reclassify the SGL from previous FNAC diagnosis to calculate the ROM in different categories and to correlate cytohistopathological diagnosis of the available surgical specimens.

Methods

FNAC specimens of Salivary Gland Lesions (SGL) and clinical data were retrieved from department of pathology from September, 2012 to August, 2021 in this present retrospective as well as prospective study. The SGLs were reclassified into six categories as per MSRSGC. The follow up histopathological reports wherever available were compared with cytological diagnosis.

Both major and minor salivary gland swellings were aspirated via a direct percutaneous or transoral route. Fine needle aspiration (FNA) was done by trained cytopathologists using 22–25-gauge needles depending on the size and location of the swelling. Air-dried smears were stained with May-Grunewald-Giemsa (MGG) and alcohol fixed smears were stained with Papanicolaous (Pap) stain and/or Haematoxylin and Eosin (H&E) stain.

Histopathological diagnosis was made as per latest WHO classification. Cytological (FNAC) findings as well as histological (biopsy) findings were evaluated by two separate consultant pathologists. To calculate ROM, the following formula was used:

$$\text{ROM (Risk of Malignancy)} = \frac{\text{No. of malignant cases in each category after histological examination}}{\text{No. of cases in each category in cytology}}$$

Results

The FNAC distribution of 1678 cases according to age, sex and gland involvement is shown in Table I. Males were slightly more affected (858 vs. 820) with a ratio of 1.05:1.

Maximum number of cases were seen in the 4th decade (33.37%) followed by 5th decade (21.93%). Parotid gland was most commonly affected (71.99%) followed by submandibular gland (Table I).

Distribution of salivary gland cytopathology cases (FNAC) according to Milan system (MSRSGC) is shown in Table II. The FNAC cases were classified into six tiers as per Milan system. Category 2 or Non-neoplastic (NN) group emerged as largest category (39.15%) followed by Category 4a or neoplasm: Benign (37.31%). The other groups like M, AUS, ND, SUMP and SM constituted 12.75%, 3.10%, 3.04%, 2.50% and 2.14% of the total FNAC cases.

Histological follow-up was available in 503 cases and cytohistological correlation of these 503 cases is shown in Table III. Concordance was seen in 426 cases and discordance was noted in 77 cases. In the seven discordant cases of non-diagnostic group; 6 were benign (chronic sialadenitis 4 cases, sialadenosis 2 cases) and 1 case was malignant (low grade mucoepidermoid carcinoma) after histologic follow-up. Details of other discordant cases after histologic follow-up are shown in Table III.

Risk of malignancy (ROM) and overall risk of malignancy (OROM) of each category are shown in Table IV. ROM was highest in SM group (100%) followed by Malignant group (93.48%), AUS (62.5%), SUMP (58.82%), Non-diagnostic (14.28%), non-neoplastic (5.71%) and benign (3.81%). On the OROM was not common in malignant group (80.37%), followed by SM (44.44%), SUMP (23.81%), AUS (9.61%), non-diagnostic (1.96%) and benign neoplasm (1.44%).

Table I: Distribution of FNAC Cases according to age, sex and gland involvement (n=1678)

Parameter	No. of Cases (%)	Male (%)	Female (%)
i) Age in years			
<10	61 (3.63%)	38 (2.26)	23 (1.37%)
11-20	102(6.08%)	44 (2.62%)	58 (3.46%)
21-30	172(10.25%)	96 (5.72%)	76 (4.53%)
31-40	560 (33.37%	307 (18.29%)	253 (15.08%)
41-50	368(21.93%)	198 (11.80%)	170 (10.13%)
51-60	256 (15.26%)	102 (06.08%)	144 (08.58%)
61-70	93(05.54%)	37 (02.20%)	56 (03.34%)
71-80	45 (02.68%)	26 (01.55%)	19 (01.13%)
>81	21 (01.25%)	10 (0.59%)	11 (0.65%)
Total	1678 (100%)	858 (51.13%)	820 (48.87%)
ii) Types of involved Salivary Gland			
Parotid	1208(71.99%)	626 (37.31%)	582 (34.68%)
Submandibular	369 (21.99%)	189 (11.26%)	180 (10.73%)
Sublingual	05 (0.30%)	03 (0.18%)	02 (0.12%)
Minor Salivary Gland	96 (5.72%)	40 (2.38%)	56 (3.34%)

Table II: Distribution of salivary gland cytopathology cases according to Milan System (n=1678)

Sl No.	Category	Cytological Diagnosis	Number of Cases (%)
I	Non-Diagnostic (ND)	Only necrotic debris (06), only fluid (05), haemorrhage only (6), artefact (03), very low cellular yield (21)	51 (3.04)
II	Non-Neoplastic (NN)	Acute sialadenitis (119), Sialadenosis (205), Chronic Sialadenitis (252), Benign Cyst (14), Granulomatous inflammation consistent with tuberculosis (03), Retention cyst (21), Vasoformative lesion (05), Giant cell lesion (11), Lymphoepithelial sialadenitis (18), Granulomatous inflammation (09)	657 (39.15)
III	Atypia of undetermined significance (AUS)		52 (3.10)
IV	IVa. Neoplasm : Benign (NB)	PSA (533), Warthin's tumor (67), Monomorphic adenoma (15), Myoeoithelioma (04), Oncocytoma (04), Schwannoma (03)	626 (37.31)
	IVb. Neoplasm Salivary Gland Neoplasm of uncertain malignant potential (SUMP)	---	42 (2.50)
V	Suspicious for malignancy (SFM)		36 (2.14)
VI	Malignant (M)	Mucoepidermoid carcinoma (11.4), Adenocarcinoma NOS (27), Poorly differential carcinoma (21), Acinic cell carcinoma (12), PLGA (11), Non-Hodgkin Lymphoma (14), Salivary duct adenocarcinoma (05), Infiltration by leukemia (03), Metastasis (07)	214 (12.75)

PSA : Pleomorphic Salivary adenoma; PLGA : Polymorphus low grade adenocarcinoma

Table III: Cytohistological correlation between Milan System and histologic diagnosis (n=503)

Sl No.	Cytologic Diagnosis (Milan System)	No. of cytology cases with histology follow-up	Histology		
			Concordance	Discordance	
				Benign (n,%)	Malignant (n,%)
1	Non Diagnostic	7		(a) Chronic sialadenitis (04,57.1%) (b)Sialadenosis (02,28.57%)	(a) Low Grade MEC (1, 14.28%)
2	Non Neoplastic	35	29 (82.9%)	(a) Pleomorphicadenoma (3,8.57%) (b) Monomorphic adenoma (1, 2.9%)	(a) Low Grade MEC (1, 2.86%) (b) High Grade MEC (1, 2.86%)
3	AUS (Atypia of Undetermined Significance)	8		(a) PSA with cellular atypia (03, 37.5%)	(a) Low Grade MEC (4, 50%) (b) PLGA (1, 12.5%)
4	Neoplastic				
	(i) Benign	236	227 (96.2%)	--	(a) Low Grade MEC (06, 2.5%) (b) Carcinoma ex PSA (02, 0.8%) (c)Basal cell adenocarcinoma (01, 0.4%)
	(ii) SUMP (Salivary Gland neoplasm of uncertain malignant potential)	17		(a) Pleomorphic adenoma (04, 23.5%) (b) Monomorphic adenoma (2,11.8%) (c) Myoepithelioma (1, 5.9%)	(a) Low Grade MEC (06, 35.3%) (b) Basal cell adenocarcinoma (02, 11.8%) (c) PLGA (02, 11.8%)
5	Suspicious for Malignancy	16			(a) Low Grade MEC (05, 31.2%) (b) High Grade MEC (02, 12.5%) (c) Lymphoma (02, 12.5%) (d) Poorly differentiated adenocarcinoma (7, 43.7%)
6	Malignancy	184	172 (93.5%)	(a) Monomorphic adenoma (03,1.6%) (b) PSA with cellular atypia (9, 4.9%)	

PSA-pleomorphic Salivary adenoma, MEC-Mucoepidermoid carcinoma, PLGA-Polymorphous low grade adenocarcinoma, NOS-Not otherwise specified

Table IV: Risk Classification for Salivary Gland Lesions (n=1678)

	Non diagnostic, category 1	Nonneoplastic, category 2	AUS, category 3	Benign Neoplasm, Category 4 a	SUMP, category 4 b	SFM, Category 5	Malignant Neoplasm, Category 6	Total
Total number of FNAs	51	657	52	626	42	36	214	1678
FNAs with follow-up	7	35	8	236	17	16	184	503
Benign cases	4	4	3	227	7	0	12	257
Malignant cases	1	2	5	9	10	16	172	215
Inconclusive cases	2	3	0	1	2	1	0	9
ROM	14.28%	5.71%	62.50%	3.81%	58.82%	100%	93.48%	
OROM	1.96%	0.30%	9.61%	1.44%	23.81%	44.44%	80.37%	

ROM -Risk of malignancy, OROM - Overall risk of malignancy

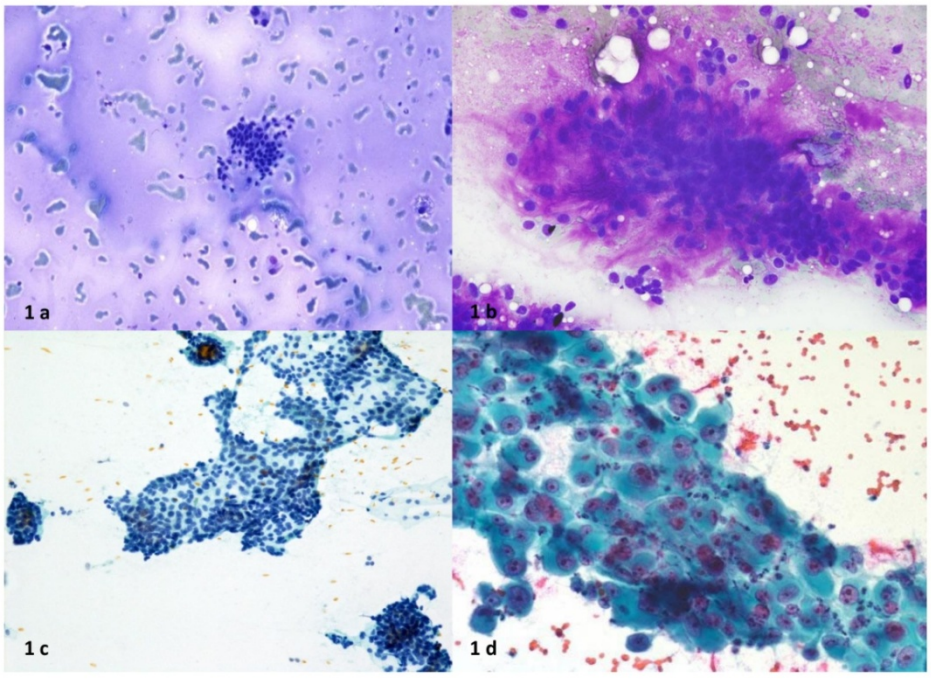

Figure 1. 1a: Non-Neoplastic (Colloid goitre) [MGG, 100x]; 1b: Neoplasm: Benign (pleomorphic salivary adenoma) [MGG,100x]; 1c: Suspicious for malignancy(SFM).Cellular salivary gland neoplasm with basaloid features proven to be adenoid cystic carcinoma on resection [Papanicolaou stain, 200x); 1d:Malignant.Mucoepidermoid carcinoma(MEC), high grade.

Discussion

FNAC is a noninvasive diagnostic procedure which is safe and cost effective.[4] Similar to the Bethesda system for reporting thyroid cytopathology, the Milan System also has a 6-tiered classification. A recent survey reveals that almost 72% of the participants with cytopathology expertise now favor the tiered classification system for salivary gland lesions like Milan System.[5] Not only in the conventional smear method, the Milan system can also be applied to the LBC (Liquid based cytopathology).[6]

Previously some authors also tried to formulate a tiered system for SGL. A five-group approach system was proposed by Miller's system which includes: (1) myxoid-hyaline, (2) basaloid, (3) oncocytoid, (4) lymphoid, and (5) squamoid lesions.[1]

Some authors advocated for three tiered system like non-neoplastic lesions, benign and malignant lesions.[1] Tessy et al. proposed the classification as inflammatory, benign, malignant tumors and others (four tiered system).[7]

In our study, male female ratio is almost equal (1·05:1), which is similar to study by Kala, er.al. [8]. But in other studies, male patients outnumbered female patients. Karuna et.al reported a ratio of 2·2:1 while Rohilla M et. al reported a ratio of 1·7:1.[1,2]

Parotid gland was most commonly involved (71.99%) followed by submandibular gland (21.99%), sublingual gland (0.30%) and minor salivary gland (5.72%). Like most previous studies, parotid gland was commonest salivary gland in this study.[9-14] But unlike other studies, we found sublingual salivary gland involvement also, though very negligible involvement (0.30%).[1,2,8] This may be due to the fact that, present study comprised of a larger number of cases unlike most other studies.

In this study, the percentage of non-diagnostic is 3.04%, non-neoplastic is 39.15%, atypia of undetermined significance (AUS) is 3.10%. Neoplasm-benign is 37.31%, SUMP is 2.50%, SM is 2.14% and malignant is 12.75% which corroborated most other studies.

As previously mentioned, AUS, SUMP and SFM were grouped in a separate class of 'intermediate' group because they cannot be categorized as benign or malignant. The AUS category cases are those, where a neoplastic lesion cannot be completely ruled out. The diagnosis of SUMP was rendered when cytological features are diagnostic of a neoplastic process but cannot confirm it as benign or malignant. The diagnosis of SFM is reserved for those FNAC cases where overall features are suggestive of malignancy but all criteria of malignancy are not present.

As proven from thyroid cytology, this 'indeterminate' group in SGL also poses similar challenges in management. Hence, we analyzed this indeterminate group to gain better understanding and its significance.[5] In this indeterminate group, the most common malignant tumor on histologic follow up was mucoepidermoid carcinoma. But Viswanathan et. al reported lymphoma as commonest malignant tumor.[5]

On histologic follow-up (503 cases), present study calculated the overall ROM for all 6 categories similar to MSRSGC. But in some studies, there were significant deviations which were noted in AUS and SUMP category.[15,16,17] The AUS category should be <10% of all SGL and in our study, it was only 3.10%. The recommended management of AUS is repeat FNAC and Surgery.[10] Rossi et. al suggested expected ROMs for each category as follows: 25% for ND, 10% for NN, 20% AUS, 5% for NB, 35% for SUMP,

60% for SFM and 90% for M.[4] In our study ROM for AUS category was 62.5% and it was higher than the range of 10% to 35% provided in the MSRSGC atlas. But there may be wide variations as reported by different institutions. Even, Rohilla et. al. Reported a ROM of 100% for AUS category,[4] while Wang et. al reported a ROM for AUS 0-68% in 5 different institutions.[9]

When the indeterminate group (AUS, SUMP, SFM) was excluded, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy were 94.06%, 95.52%, 97.27%, 87.37% and 90.85% respectively in the present study. Overall sensitivity, specificity and diagnostic accuracy for different salivary gland lesions (SGLs) varies from 86-100%, 90-100%, and 48-94% respectively, reported in different studies.[18,19,20] Our statistical analysis corroborated studies of Karuna et. al Rohilla et. al and Chen YA et. al.

Conclusion

The Milan system will facilitate more consistent and uniform reporting of salivary gland lesions by FNAC. The establishment of the indeterminate group increases the doctor's awareness of lesions which prove to be diagnostically challenging on FNAC smears. This indeterminate group also directs clinicians and cytopathologists for clinical and radiologic correlation. Histologic follow up and use of other ancillary tests are required to refine this category further and to provide optimum care and outcomes to treating patients.

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