ORIGINAL ARTICLE

Correlation of Milan System of Reporting Salivary Gland Cytology with Histopathology: Two-year Institutional Experience

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Abstract

Background: Fine needle aspiration cytology (FNAC) is a widely acclaimed preoperative primary investigation in the management of salivary gland lesions. But, lack of standardized unambiguous reporting often poses challenge to the clinicians. The six-tiered category-based Milan system of reporting salivary gland cytology (MSRSGC) proposes standardization in the reporting with risk of malignancy (ROM).

Aim: To find out the applicability of Milan system to diagnose the salivary gland cytology by correlating with histological follow-up and to estimate ROM for each of its category.

Methods and materials: Cross-sectional study was conducted in a Tertiary Hospital over a period of 2 years. Fine needle aspiration cytology (FNAC) diagnosis was classified as per MSRSGC categories into (I) nondiagnostic (ND), (II) non-neoplastic (NN), (III) atypia of undetermined significance (AUS), (IVa) benign neoplasm, (IVb) salivary gland neoplasm of uncertain malignant potential (SUMP), (V) suspicious for malignancy, and (VI) malignant. Cytology diagnosis was correlated with histopathology, and ROM was calculated.

Results: Fine needle aspiration cytology (FNAC) diagnosis was made for 50 samples as per MSRSGC. Histopathology follow-up was done for 46 cases (92%). The cytohistopathological correlation was done, and the discrepancy was noted in five cases. Our ROM for non-neoplastic, AUS, benign neoplasm, SUMP, suspicious for malignancy, and malignant categories was 0, 0, 0, 100, 100, and 100%, respectively. The sensitivity, specificity, and accuracy of FNAC were found to be 75, 100, and 98%, respectively.

Conclusion: Implementing Milan system in salivary gland FNAC yields quality, standardized reporting, and also estimation of ROM helps in effective clinical management.

Keywords: Atypia of undetermined significance, Fine needle aspiration cytology, Milan system, Risk of malignancy, Salivary gland neoplasm of uncertain malignant potential.

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Introduction

Tumors of the salivary gland constitute wide range of benign and malignant neoplasms. Though uncommon, they represent about 3–6% of total tumors of the head and neck.[1,2] The incidence of malignant salivary gland tumor varied between 0.4 and 2.6%.[1] Nearly 80% of these total salivary gland tumors occur in the parotid gland, and about 80% of them are benign in nature. The diagnosis of salivary gland lesion on cytology often creates challenge to the pathologist owing to reasons such as heterogenicity in their morphology and also overlapping of the cytological features of this neoplasm hindering the specific diagnosis and subtyping.

Notwithstanding the challenges of FNAC in diagnosing salivary gland lesions, it has revolutionized the field of diagnostic pathology by its minimal invasive nature, easy-to-perform, and rapid diagnosis. All these features gained this modality a wide acceptance among the surgeons. Since the lesions of salivary gland produce a visible lump, it is easily accessible for the cytology procedure which has made FNAC, a popular diagnostic method for preoperative evaluation of salivary gland masses.[3]

The application of FNA in salivary gland lesions consists of dual qualities. Primarily, it confirms the origin of these lesions, since other submandibular/preauricular lesions clinically mimic salivary gland neoplasm. Secondarily, it provides a preliminary diagnosis regarding the disease by discriminating the benign and malignant ones, thus guiding the clinician to proceed with a definite management workout.[4,5]

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Lack of standardized reporting and application of different terminologies become cumbersome for the treating clinician to carry out definite management plan. To deal with this issue, the Milan system working group in 2016 introduced a category-based standardized reporting protocol termed as MSRSGC.[6] Though the diagnostic accuracy of FNAC in the evaluation of salivary gland lesions has been studied earlier, there were mixed response among the researchers regarding its sensitivity and specificity in determining the malignant lesions and interobserver variation in reported results. The study is proposed to appraise the applicability of MSRSGC to categorize

the salivary gland lesions by correlating with histological follow-up and to estimate ROM for each of its category. Thus, the findings of the study would contribute to the existing literature.

Subjects and Methods

The study is a cross-sectional design conducted in the Department of Pathology of Tertiary Teaching Hospital, Chennai, for the duration of 2 years. The study involved 50 cases presented with salivary gland swellings. After obtaining approval from the institute ethics committee, the sample collection was performed.

Patients of both genders who had underwent FNAC during the study period were included in the study. Aspirates which were inadequate for cytology interpretation and patients who had contraindications for FNA were excluded from the study. After obtaining informed consent, FNAC was performed in all cases by using 22- to 23-gauge needle. Aspirates were smeared on 2–4 clean glass slides; the slides were then wet-fixed with 95% ethanol and air-dried. Fixed slides are then stained by Papanicolaou (PAP), May-Grunwald-Giemsa (MGG) stains, and Hematoxylin and Eosin (H&E) stains. The cytology findings were interpreted, and cases were categorized into following categories based on six-tired MSRSGC classification: Category I: nondiagnostic (ND), Category II: non-neoplastic (NN), Category III: atypia of undetermined significance (AUS), Category IV (A): benign neoplasm, Category IV (B): salivary gland neoplasm of uncertain malignant potential (SUMP), Category V: suspicious for malignancy, and Category VI: malignant.

Histopathological follow-up was done wherever possible. Excisional biopsy of the salivary gland lesions was performed for 46 (92%) cases. After fixation with 10% formalin, the excision biopsies were examined macroscopically, representative sections were processed under routine histotechniques, and the microscopic examinations were performed by using H&E methods. Special stains like PAS and mucicarmine were also done wherever necessary.

Statistical Analysis

After cytohistopathological correlation, statistical analysis was made for determining the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of FNA of salivary gland lesions by calculating true-positive, true-negative, false-positive, and false-negative cases. Risk of malignancy (ROM) for each category of MSRSGC was estimated by calculating the ratio of FNAC cases which turned malignancy on histology follow-up to the total number of FNAC cases with follow-up histology.

Results

In the study, 50 FNA samples were received from 24 males (48%) and 26 females (52%) with a male:female ration of 1:1.08. The age of the patients ranged from 15 to 72 years with a mean age of 46 years. The sampled sites were parotid gland (88%) and submandibular gland (12%). Fine needle aspiration cytology (FNAC) under radiological guidance was obtained for 30% cases. Left-sided lesions (52%) were slightly more when compared with right-sided (48%).

Category-wise distribution of cases according to MSRSGC is shown in Table 1. Histopathological follow-up was available for 46 (92%) FNAC diagnoses. Cytological correlation with histopathology follow-up was demonstrated in Table 2. Majority of the cases (76%) belonged to Category IVa, followed by Category II, $n = 7$ (14%). Categories III, IVb, and V constitute one case (2%) each, respectively, and Category VI contains two (4%) cases. In the study, not a single case was considered unsatisfactory for evaluation.

Cases with discrepancy between cytology and histopathological diagnosis are shown in Table 3. Out of total 46 cases, the discrepant cases were six. Category IV of MSRSGC showed four discordant cases, of which one case of pleomorphic turned out to be monomorphic adenoma, one case of monomorphic adenoma turned out to be pleomorphic adenoma, and two cases diagnosed as possible Warthin's tumors on cytology both turned out to be non-neoplastic entities on follow-up histopathology. A diagnosis of adenoid cystic carcinoma (ACC) was made on a case of SUMP.

Table 1: MSRSGC category-wise case distribution and primary cytological diagnosis made under each category

MSRSGC category	*Primary cytology diagnosis*	*Number of cases*
I (ND)[a]		0 (0%)
II (NN)[b]		7 (14%)
	Chronic sialadenitis	7
III (AUS)[c]		1 (2%)
IVa (neoplastic-benign)		38 (76%)
	Pleomorphic adenoma	31
	Warthin's tumor	05
	Basal cell adenoma	02
IVb (SUMP)[d]		1 (2%)
	ACC	1
V (SM)[e]		1 (2%)
	ACC	1
VI (malignant)		2 (4%)
	Mucoepidermoid carcinoma	2
Total		50 (100%)

ND[a], nondiagnostic; NN[b], non-neoplastic; AUS[c], atypia of undetermined significance; SUMP[d], salivary gland neoplasm of uncertain malignant potential; SM[e], suspicious for malignancy

Table 2: Correlation of FNAC findings with histology follow-up findings

Cytology				*Histopathology follow-up*		
MSRSGC category	*No. of cases*	*Primary diagnosis*	*No. of cases*	*Available*	*Final diagnosis*	*No. of cases*
II (NN)[a]	7 (14%)	Chronic sialadenitis	07	03 (42.86%)	Chronic sialadenitis	2
					Warthin's tumor	1
III (AUS)[b]	01 (2%)		01	01 (100%)	Chronic sialadenitis	1
IVa (benign)	38 (76%)	Pleomorphic adenoma	31	31 (100%)	Pleomorphic adenoma	30
			05	05 (100%)	Basal cell adenoma	01
		Warthin's tumor			Warthin's tumor	03
			02	02 (100%)	Lymphoepithelial cyst	01
					Chronic sialadenitis	01
		Basal cell adenoma			Basal cell adenoma	01
					Pleomorphic adenoma	01
IVb (SUMP)[c]	01 (2%)	ACC		1	ACC	1
V (SM)[d]	01 (2%)	ACC	1	1 (100%)	ACC	1
VI (malignant)	02 (4%)	Mucoepidermoid carcinoma	2	2 (100%)	Mucoepidermoid carcinoma	N2
Total	50 (100%)		50	46		46

NN[a], non-neoplastic; AUS[b], atypia of undetermined significance; SUMP[C], salivary gland neoplasm of uncertain malignant potential; SM[d], suspicious for malignancy

Table 3: Comparison of estimated ROM for each category against proposed ROM as per MSRSGC ($n = 46$)

Category as per MSRSGC[a]	*No. of cases*	*Estimated ROM*[b] *in (%)*	*ROM*[b] *as per MSRSGC*[a] *in (%)*
I (ND)[c]	0	—	25
II (NN)[d]	03 (6.52%)	0	10
III (AUS)[e]	01 (2.17%)	0	20
IVa (neoplastic-benign)	38 (78.26%)	0	<5
IVb (SUMP)[f]	01 (2.17%)	100	35
V (SM)[g]	01 (2.17%)	100	60
VI (malignant)	02 (4.35%)	100	90

MSRSGC[a], Milan system of reporting salivary gland cytology; ROM[b], risk of malignancy; ND[c], nondiagnostic; NN[d], non-neoplastic; AUS[e], atypia of undetermined significance; SUMP[f], salivary gland neoplasm of uncertain malignant potential; SM[g], suspicious for malignancy

One case in the AUS Category III showed non-neoplastic (chronic sialadenitis) on histological follow-up. There was no false-positive or false-negative malignancy encountered.

The statistical analysis showed that the sensitivity, specificity, PPV, NPV, and accuracy of FNAC in diagnosing malignant salivary lesions were 75, 100, 100, 97, and 98%, respectively. The ROM was calculated for each of the categories and compared with the proposed ROM as per MSRSGC (Table 3).

Discussion

Swelling of the salivary gland lesions produces visible lump; consequently, it raises concern among patients. Diagnosis of salivary gland lesions is often challenging among clinicians and pathologists. Various diagnostic modalities are available for the screening and diagnosis of these lesions. Fine needle aspiration cytology (FNAC) is considered as safe, rapid, and cost-effective technique for the preoperative diagnosis of salivary gland lesions. Clinicians often refer the cytology interpretations as diffuse, ambiguous, and clinically not useful, due to lack of standard reporting format. This can be addressed by implanting MSRSGC, which focuses on standardized approach for reporting salivary gland lesions and also facilitates better interaction between clinicians and pathologists.

The study showed a small degree of female dominance, which is in concordance with other similar studies.[7–9] The study done by various researchers demonstrated that the mean age-group is 6th decade, and this is not in accord with the current study finding which showed mean age-group is 46.[8–11] In this study, majority of the lesions were from parotid, and this finding was well supported by other studies.[7–11]

Milan system of reporting salivary gland cytology (MSRSGC) proposes that the rate of nondiagnostic (ND/UNS) aspirate should be kept less than 10%.[6] Previous studies had shown that the rate of ND/UNS ranged from 1.1 to 8%.[7,12–16] In the current study, no case has been recorded in Category I, and this might be because of the application of rapid onsite evaluation technique, which produced the improved results by reducing the chances of sampling errors. In Category II, a case of reported as chronic sialadenitis on cytology turned out to be Warthin's tumor on histology follow-up. The cytology picture in this case showed clusters of acinar cells along with collections of lymphocytes which mislead to the diagnosis of non-neoplastic entity. Koybaşioglu et al. also showed similar findings in his study.[17] Our ROM in the Category II was 0%, which is in agreement with the proposed ROM by MSRSGC. Studies done by Karuna et al. and Gaikwad et al. also showed ROM of 0%.[13,18] But, the study done by Viswanathan et al. and Kala et al. showed

ROM of 7.1 and 5%, respectively, which is higher than those of the present study.[9,14]

Atypia of undetermined significance (AUS) rate in the study was 2% (n = 1), which is well within the accepted rate (<10%) recommended by MSRSGC. This case on follow-up histopathology turned out to be non-neoplastic lesion (chronic sialadenitis). The discrepancy in cytology might be due to the low cellularity, artifactual changes, and reactive atypia. Gaikwad et al. also demonstrated in his study that a case of AUS was diagnosed as sialadenitis on histology follow-up.[18] Viswanathan et al. in his study showed two cases (11.1%) of AUS on histology follow-up and chronic sialadenitis, and the most common benign condition under AUS category was chronic sialadenitis.[9] ROM for the Category III (AUS) in the current study was 0%, and this finding was well supported by a similar study done by Gaikwad et al., Vallonthaiel et al., and Park et al., which also showed 0% ROM in the AUS category.[18–20] The finding was contradictory to the study done by Katta et al., Karuna et al., and Layfield et al. which demonstrated ROM of 100, 50, and 19%, respectively.[13,15,21]

Benign category (IVa) contributed for majority of the cases, 76% (38 cases) of which pleomorphic adenoma (31 cases) being the commonest type of neoplasm accounting to 81.58% of Category IVa and 62% of overall cases. Studies done by Park et al. and Mullen et al. also demonstrated that more than half of the number of cases belonged to Category IVa, and this finding is in consensus with our study, but contrary to the study done by Maleki et al. which showed only 18.7% of cases in benign neoplastic category.[20,22,23] The calculated ROM in this category was 0%, and it was in consensus with the proposed ROM (<5%) as per MSRSGC. Mullen et al. and Gaikwad et al. also showed in their study that the estimated ROM in the benign neoplastic category (IVa) was 0%, and this finding is in agreement with our study. But, the study done by Pujani et al. and Viswanathan et al. demonstrated that the calculated ROM in Category IVa was 2.5 and 5%, respectively.[9,16]

The sensitivity, specificity, and accuracy of the FNAC in differentiating the benign and malignant lesions ranged 70.4–96.84%, 80.95–100%, and 80.8–96.9%, respectively. The current study demonstrated slightly higher accuracy rate than that of these studies.[11,13,14,16,18]

Fine needle aspiration (FNA) findings in the single case of SUMP showed cellular aspirate with cohesive sheets of basaloid cells against a scant nonfibrillary matrix. These cells were uniformed with high N:C ratio noticed in few clusters. There were no cytological evidence of necrosis and mitosis. Hence, a diagnosis of SUMP with a subcategorization of cellular basaloid neoplasm was made on cytology. The histological follow-up of this study showed features of malignant neoplasm diagnosed as ACC with the ROM of 100%. Though recommended ROM as per MSRSGC for SUMP category is 35%, various studies had demonstrated a wide range of ROM from 26 to 100%.[3,9] The high ROM in the present study is due to the limited number of cases in that category. Study done by Gaikwad et al. also showed 100% ROM under IVb category, and this finding is in accord with the present study.[18]

Histological follow-up on all two cases of Category VI confirmed the cytological diagnosis of MEC. The estimated ROM in this category is also 100%, which is not in consensus with the recommended ROM of 90% as per MSRSGC. However, majority of studies demonstrated 100% ROM in consensus with our study.[8,16,18–20]

Category V of MSRSGC is suspicious of malignancy; in the study, a single case was placed under this category. On cytology, the smear was cellular and showed abundant matrix; hence, a differential diagnosis of ACC was made. This case on histopathological follow-up also confirmed the diagnosis of ACC with a calculated ROM of 100% which is higher than the proposed ROM of 60% as per MSRSGC. Karuna et al., Pujani et al., and Gaikwad et al. had demonstrated 100% ROM in Category V in their studies, which is similar to our findings.[16,18,21,22]

Limitation of the Study

The analysis in the current study was based on the limited number of samples. There was only single case each under the indeterminate category (Categories III, IVa, and V), which led to the high ROM in these categories. Taking this study as a reference point, further studies with larger sample size can be planned, so that the comparison can be made with confidence.

Conclusion

The present study provides additional supportive evidence that FNAC is a cost-effective efficient preoperative diagnostic tool for the evaluation of salivary gland lesions. The six-tired category-based Milan system emerges to be a valuable tool in the reporting of salivary gland cytology. Application of MSRSGC improves the quality of the cytology reporting by providing a comprehensive, unambiguous, and accurate classification of lesions. It also strengthens interactions between pathologists and clinicians, which in turn foster better patient care.

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