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UTILITY OF MILAN SYSTEM FOR SALIVARY GLAND CYTOPATHOLOGY IN A TERTIARY CARE HOSPITAL IN WESTERN INDIA: AN INSTITUTIONAL EXPERIENCE

Pathology

Dr. Saket Sharma* Junior Resident (PGY3), Department of Pathology, Medical College Baroda, India.
*Corresponding Author

Miss Prachi Parikh Third MBBS Student, GMERS College and Hospital Gotri, India.

Dr. Heena Parikh Assistant Professor, Department of Pathology, Medical College Baroda, India.

ABSTRACT

Introduction: Fine-needle aspiration cytology (FNAC) can be challenging to provide a precise diagnosis in salivary gland cytopathology due to diversity of lesions and cytomorphological convergence between the tumors and within the same tumor of salivary gland. The recently proposed Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) provides a risk stratification-based classification system with an intrinsic risk of malignancy (ROM) for each diagnostic category, which aims to furnish useful information to the clinicians. This study was undertaken to evaluate the diagnostic utility and validity of MSRSGC. **Materials and Methods:** A 4-year retrospective study was conducted at a tertiary care hospital in Central Gujarat in Western India. A total of 90 cases of FNAC of salivary gland lesions for the period of January 2018 to March 2021 were reviewed. Patient clinical details, FNAC smears and histological slides where available were retrieved from the departmental records. **Results:** The cases belong to following categories: non-diagnostic (4.4%), non-neoplastic (10%), atypia of undetermined significance (1.1%), benign neoplasm (68.9%), salivary gland neoplasm of uncertain malignant potential (8.9%), suspicious for malignancy (2.2%), and malignant (4.4%). Out of 90 cases, 62 cases (68.8%) had follow-up. The ROM were 7.6% for category IV—A and 50% for category IV-B. The sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratio for differentiating between benign and malignant lesions were recorded as 98.1%, 42.9%, 92.8%, 75.0%, and 1.750, respectively. **Conclusion:** Application of MSRSGC has immense value for standardization of reporting of salivary gland FNAC. The Milan system of reporting is a risk stratification system which can improve the overall effectiveness of reporting and care of patients.

KEYWORDS

Milan System for Reporting Salivary Gland Cytology, Fine-needle aspiration cytology, salivary gland lesions

INTRODUCTION:

Fine-needle aspiration cytology (FNAC) of salivary gland is used world-wide for the diagnosis and management of salivary gland tumors. It provides a minimally invasive, safe, cost-effective, and accurate technique that is extremely useful in identifying a substantial subset of salivary gland nodules as benign and thus reduces unnecessary invasive surgical procedure in patients with benign diseases.[1],[2],[3],[4],[5] In addition, it also helps in further management strategy. Many studies have reported excellent sensitivity and specificity of FNAC to differentiate neoplastic vs. non-neoplastic lesions as well as benign and malignant neoplasms; among different studies, the sensitivity of FNAC ranges from 86% to 100%, and specificity ranges between 90%–100%.[4],[5],[6],[8],[9],[24] FNAC is also an useful tool to differentiate between primary vs. metastatic lesions specially head and neck malignancies and thus helping in deciding the treatment plan.[3],[4],[7],[8],[9]

Despite being a useful sensitive and specific tool for cytopathologists, there are a few challenges for salivary gland FNAC diagnosis, such as diversity and heterogenicity of salivary gland tumors, morphological overlap between different malignant tumors, and even between benign and malignant tumors.[2],[7],[9],[24]

When FNAC is used to subclassify the neoplasm, the accuracy ranges widely from 48% to 94% in different studies.[6],[10] The presence of basaloid cell component, oncocytoid changes, squamous metaplasia, and cystic component are few cytomorphological features that make FNAC a diagnostic challenge. There are many studies proposing use of morphological pattern-based analysis to develop a risk stratification approach for classification of salivary gland neoplasm and providing risk of malignancy (ROM) and to guide for further ancillary test and management plan.[2],[25] However, these studies have a wide variation of ROM in different categories ranging from 6% to 100%, thus lacking a consensus approach.

Other major drawback is the terminology of reporting salivary FNAC, which varies markedly. Various reporting formats have been used and although some have tried to diagnose according to histological category, other have tried terminology such as atypical, suspicious, and malignant.[19],[25]

Such diverse classification made it difficult for the treating clinician to interpret the report and decide the further management according to ROM, so to address a standard terminology for reporting salivary gland cytopathology. The American Society of Cytopathology and International Academy of Cytology therefore has proposed a tiered international classification scheme called the "Milan System for Reporting Salivary Gland Cytopathology" (MSRSGC), providing guide for clinical management according to ROM in different categories.[11],[26],[27]

The present study was done to find the effectiveness of FNAC to differentiate benign and malignant lesions when the Milan system of reporting is applied.

MATERIALS AND METHODS:

A 4-year retrospective study was conducted at Department of Pathology in a tertiary care hospital in Central Gujarat in Western India. A total of 90 cases of FNAC of salivary gland lesions for the period of January 2018 to March 2021 were reviewed. Patient clinical details, FNAC smears and histological slides where available were retrieved from the departmental records.

Salivary gland swelling both major and minor were aspirated through a direct percutaneous or intraoral route with 22 or 23 gauze needles with or without ultrasound guidance wherever needed. The smears were aspirated by trained cytopathologists 2–3 times randomly in different areas, and smears were prepared and stained with May-Grunwald-Giemsa stain, H and E stain in all cases and occasionally with Pap stain also.

Based on the cytological details, the salivary gland lesions were reviewed and classified according to MSRSGC categories (as shown in Table 1) by two independent observers into Category I: Non-diagnostic; Category II: Non-Neoplastic; Category III: Atypia of undetermined significance (AUS); Category IV-A: neoplasm: benign; Category IV-B: neoplasm: salivary gland neoplasm of undetermined malignant potential (SUMP); Category V: suspicious of malignancy (SM); and Category VI: malignant in an unbiased manner without referring to the previous diagnosis. Histological correlation was available in 62 cases. Histopathological data wherever available were retrieved, histological diagnosis was considered as gold standard.

The statistical analysis was performed using the GraphPad version 9 statistics software. The number of false positives, false negatives, true positives and true negatives was assessed by comparing cytological diagnosis to that of histological diagnosis. The specificity, sensitivity and diagnostic accuracy of FNAC were then calculated to differentiate benign and malignant lesions of the salivary gland.

TABLE 1: The Milan system for Reporting Salivary Gland Cytopathology: Implied risk of malignancy and recommended clinical management

Diagnostic Categories	Risk of Malignancy	Usual Management
Category I- Non-diagnostic	25%	Clinical and radiologic correlation/repeat FNAC
Category II-Non- Neoplastic	10%	Clinical follow-up and radiological correlation
Category III- Atypia of Undetermined Significance (AUS)	20%	Repeat FNAC or surgery
Category IV- Neoplasm		
IV-A: Benign	<5%	Surgery or clinical follow-up
IV-B: Salivary gland neoplasm of Uncertain malignant potential (SUMP)	35%	Surgery
Category V- Suspicious for Malignancy	60%	Surgery
Category VI- Malignant	90%	Surgery

RESULTS:

The FNAC distribution of 90 cases according to age, sex, and site of involvement is shown in Table 2. Males were slightly more affected than female, 56 vs. 34 the ratio being 1.6: 1. The age of patients ranged 11–82 years, and the mean age was 40.32 years. Largest number of cases were seen in age group 20 to 40 year (48.9%) followed by 41–60 year age group (25.5%). Parotid gland was involved in 72.2% cases followed by submandibular gland in 25.5% cases. There was no significant difference in laterality of salivary gland lesions as almost equal percentage of lesions were seen on both right and left side.

TABLE 2: Distribution of cases according to Sex, Age and Site of Involvement

SEX:	
MALE	56
FEMALE	34
AGE (years):	
<20	09
20-40	44
41-60	23
61-80	13
>80	1
GLAND INVOLVED:	
PAROTID GLAND	65
SUBMANDIBULAR GLAND	23

The FNAC distribution of cases according to MSRSGC is shown in Table 3. Benign neoplasm was the largest category and comprised 62 cases (68.9%) followed by Non-Neoplastic category comprising 9 cases (10%). The Non- diagnostic, AUS, SUMP, Suspicious for Malignancy and Malignant category comprised 4 (4.4%), 1 (1.1%), 8 (8.9%), 2 (2.2%) and 4 (4.4%) cases, respectively. The most common diagnosis on cytology was Pleomorphic adenoma (58 out of 62 cases). In Non-neoplastic category, chronic sialadenitis was most commonly reported on cytology.

TABLE 3: Distribution of cases as per Milan Grading system and their histological follow-up

MILAN Category	Category I (Non-Diagnostic)	Category II (Non-Neoplastic)	Category III (AUS)	Category IV-A (Benign)	Category IV-B (SUMP)	Category V (Suspicious for Malignancy)	Category VI (Malignancy)	Total
No. of Cases	4 (4.4%)	9 (10%)	1 (1.1%)	62 (68.9%)	8 (8.9%)	2 (2.2%)	4 (4.4%)	90
No. of cases with histological follow up	2 (3.2%)	1 (1.6%)	0	52 (83.9%)	2 (3.2%)	2 (3.2%)	3 (4.8%)	62 (68.8%)
Discordant cases	2 (Malignant)			4 (7.6%) (Malignant)	1 (Non-neoplastic)			

Histological follow up was available in 62 cases (68.8%). Overall, the most common diagnosis on histological follow up was found to be Pleomorphic adenoma (PA) comprising 48 (77%) of all cases. In malignant cases, Mucoepidermoid Carcinoma was the most commonly diagnosed malignancy comprising 10 (16.1%) of all cases on histological follow up. On follow-up, the number of discordant cases was also noted as shown in Table 2.

In category I (Non-Diagnostic) out of 4, follow-up was available in only 2 cases and both of them turned out to be Mucoepidermoid Carcinoma on histological follow-up.

In category II (Non- Neoplastic), histological follow-up of only 1 case was available out of total 9 cases which was diagnosed as Chronic sialadenitis on histopathology. Clinical follow-up of rest of 8 cases was done and all of them showed complete remission after conservative medical management.

Only one case of Category III (AUS) was reported and histological follow up was not available.

Category IV-A had histological follow-up of 52 cases out of 62 cases. Out of 58 cases diagnosed as PA on FNAC, 48 showed concordance on histological follow-up, and 4 cases were reclassified into Malignant category; all of them being Mucoepidermoid Carcinoma.. Overall, Risk of malignancy reported was 7.6% (04 out of 52) in this category.

Category IV-B cases were those, where a specific neoplastic entity cannot be made, and out of 8 cases histological follow up was available only in 2 cases. One case was reclassified as Mucoepidermoid carcinoma and the other case turned out to be an inflammatory etiology. Risk of malignancy reported was 50% (01 out of 02) in this category.

Category V had histological follow-up of both 2 cases; they showed concordance with diagnosis of malignancy and were reported as Mucoepidermoid Carcinoma.

Category VI is for the smears that are diagnostic for malignant lesion, and histological follow-up of 3 out of 4 cases was available. All 3 cases showed concordance with the diagnosis of malignancy; one case each of Mucoepidermoid carcinoma, Acinic Cell Carcinoma and Salivary Duct Carcinoma was reported.

Utilizing MSRSGC for differentiating between neoplastic and non-neoplastic lesions by FNAC, overall sensitivity was 96.7%, specificity was 50%, positive predictive value was 98.3%, and negative predictive value was 33.3% with a Likelihood Ratio of 1.933 when compared with histological follow-up. Low specificity values were attributed to lack of histological follow up in majority of non-neoplastic cases.

Utilizing MSRSGC for differentiating between Benign and Malignant neoplastic lesions by FNAC, overall sensitivity was 98.1%, specificity was 42.9%, positive predictive value was 92.8%, and negative predictive value was 75.0% with a Likelihood Ratio of 1.750 when compared with histological follow-up. Low specificity values were attributed to difficulty in differentiating between a benign neoplasm and low-grade malignant neoplasm.

DISCUSSION:

FNAC is a safe, accurate, and cost-effective method for evaluation of salivary gland swelling and can help in management of the patient by providing nature of the lesion.[7] In our study, salivary gland lesions were found to be more common in males as compared to females, with a male: female ratio of 1.6:1. Most commonly involved salivary gland was parotid gland followed by submandibular gland. These findings were similar to studies done by Rohilla and Kala et al.[11],[17]

MSRSGC is a newer system for reporting salivary gland lesions according to risk stratification with an objective to provide a better communication between clinicians and cytopathologists so as to improve overall patient management. It is an evidence based six tiered system, which provides ROM and clinical management strategies for each category.[3],[5],[25],[It classified FNAC into six categories; Non-diagnostic, Non-neoplastic, Atypia of Undetermined Significance, Neoplastic- Benign, Neoplastic- Salivary gland neoplasm of undetermined malignant potential, Suspicious of malignancy, and malignant with ROM of 25%, 10%, 20%, 5%, 35%, 60%, and 90% for each category. In our study also the salivary gland lesions were classified into the above-mentioned categories and histological follow-up was done wherever available.

Category I cases which are nondiagnostic and had insufficient diagnostic material without any sufficient information. This category included four cases (4.4%). In all these lesions, mainly fluid was aspirated, cellularity was low and smears showed only occasional cystic macrophages and inflammatory cells as shown in Figure 1. Two cases were available for follow-up and histology. Both of these cases were reclassified into malignant category as Mucoepidermoid carcinomas. In such cases, various authors have suggested multiple passes from different planes and FNAC under ultrasound guidance when required, to overcome the drawback of diagnostic difficulty caused due to less cellularity on smear.[5],[6],[12],[14],[24]

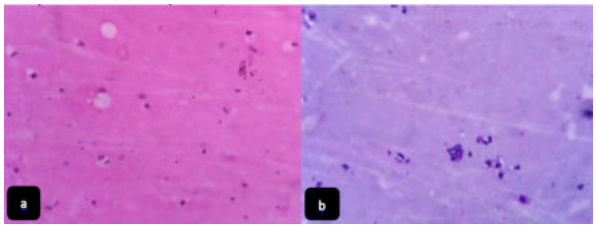

Figure 1: Category I (Non Diagnostic)

(a and b) Fine Needle Aspiration smears showing hypocellular aspirate with scant non-lesional cells mainly macrophages (Hematoxylin and eosin x400; May Grunwald Giemsa x400)

An absolute number of cells needed for salivary gland FNA adequacy has not been validated and established in the literature. However cytologic criteria used to render a sample non-diagnostic includes rare or absent cells; <60 lesional cells, poorly prepared slides with artifacts, non-mucinous cyst fluid without an epithelial component and non-neoplastic/normal salivary gland elements in the setting of a clinically or radiologically defined mass.[27]

The Non-neoplastic category (category II) includes benign, reactive, inflammatory and metaplastic processes without the presence of any atypical features.[27] Our study included a total 9 (10%) cases. The most common diagnosis in this category was chronic sialadenitis (shown in Figure 2). These cases revealed benign clusters of ductal cells with scant acinar cells in a background of lymphocytes. Similar results were obtained in the study done by Kala et al. and Karuna et al.[11],[15] Histological follow-up was available in only one case which confirmed it as Chronic sialadenitis. Many of these lesions can be managed conservatively by antibiotics and therefore resection was not done in majority of these cases. Cystic lesions form an important area of diagnostic pitfall as these can include a wide range of lesions, namely benign cysts comprising of simple retention cyst, mucocele, lymphoepithelial cyst along with benign tumors such as Warthins tumor, cystic PA and malignant cystic lesions such as MEC and acinic cell carcinoma.[16],[17]

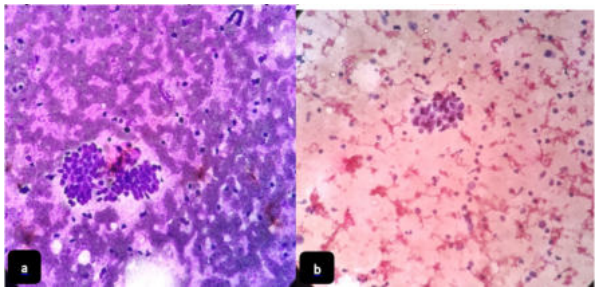

Figure 2: Category II (Non-Neoplastic)

(a and b) Fine Needle Aspiration smears are cellular and show clusters of cytologically bland ductal cells with chronic inflammatory cells in background. This case was reported as Category II- Chronic Sialadenitis (May Grunwald Giemsa x400; Hematoxylin and eosin x400)

The Category III - AUS includes cases with limited atypical features where a malignancy cannot be completely ruled out. In our study, there was only one such case for which histological follow-up was not available. This case showed focal areas of high cellularity and few reactive changes, and hence, it was placed in this category. The goal of introducing this category is to reduce the number of false negatives in NN category. This category should however comprise of<10% of all salivary gland FNAC samples according to the Milan system.[18] In our study, this category comprised 1.1% of total salivary gland lesions.

The benign category IV-A (shown in Figure 3) had 62 cases (68.9%), and histological follow-up was available in 52 cases. Pleomorphic adenoma constituted the highest percentage of all salivary gland neoplasm. FNAC is an effective tool to distinguish benign and malignant neoplasm with high sensitivity of 98.1%. However, some time it is very difficult to differentiate between a benign neoplasm and low-grade malignant neoplasm which has led to a low specificity value in our study. In our study, 4 cases were reclassified as Low grade Mucoepidermoid carcinoma on histology, which were diagnosed as Category IV-A Pleomorphic adenoma on FNAC; the presence of abundant mucoid background with lack of malignant epithelial component might had led to false diagnosis of on cytology. Overall, Risk of malignancy reported was 7.6% (04 out of 52) in this category.

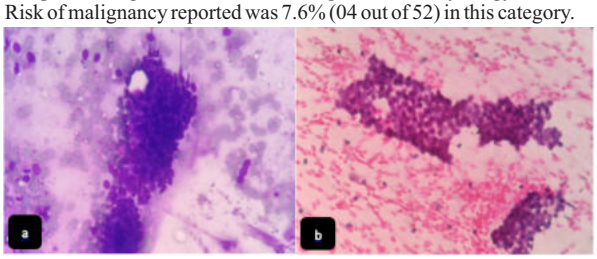

Figure 3: Category IV-A (Neoplasm- Benign)

(a and b) Fine Needle Aspiration smears are cellular with sheets of benign ductal epithelial cells embedded in a fibrillary matrix. Myoepithelial cells were also noted in these smears. The smears were reported as Category IV-A, Pleomorphic Adenoma and was confirmed to be the same on histopathology (May Grunwald Giemsa x400; Hematoxylin and eosin x400)

The diagnosis of SUMP is reserved for FNAC specimen, where cytological features are diagnostic of a neoplastic process, but the cytological findings cannot effectively distinguish between a benign and malignant neoplasm (shown in Figure 4).[27] Out of 8 cases (8.9%) diagnosed as SUMP, one case was reclassified as Non-neoplastic and one case was reclassified as Mucoepidermoid carcinoma on histological follow-up. Overall, Risk of malignancy reported was 7.6% (04 out of 52) in this category.

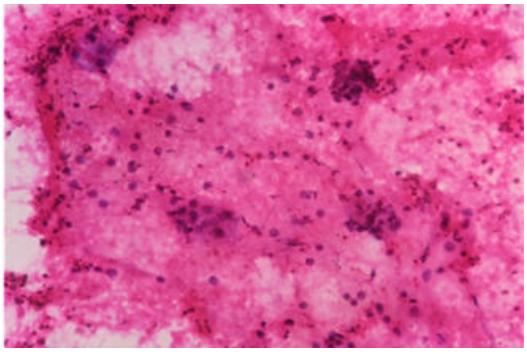

Figure 4: Category IV-B (Neoplasm- Salivary gland Neoplasm of Uncertain Malignant Potential)

Fine Needle Aspiration smears are cellular and show loosely cohesive groups of cells with indistinct cytoplasm. Nuclei are small to medium sized with even chromatin. No nuclear pleomorphism is seen. The cells are imparting a bit oncocytoid characteristic as well. This case was reported as Category IV-B SUMP (Hematoxylin and eosin x400)

Suspicious for malignancy SM category is reserved for FNAC specimens, where overall cytomorphological features are suggestive of malignancy, but not all the criteria for a specific diagnosis of malignancy are present (shown in Figure 5).[27] The categories AUS, SUMP, and SM represent the intermediate diagnostic categories in Milan system.[26] The SM category was used by cytopathologists since long-time and is well-known to clinicians also.[4],[7],[10],[24] In our study, 2 FNAC cases classified as SM had high-grade features precluding them a definite diagnosis of malignant lesion. Both of these cases were confirmed to be malignant on histological follow-up and were reclassified as Mucoepidermoid carcinoma.

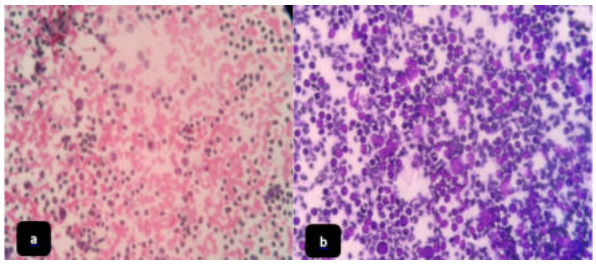

Figure 5: Category V (Suspicious for Malignancy)

(a and b) Fine Needle Aspiration smears are cellular and show epithelial cells with epidermoid features and are highly suggestive of Mucoepidermoid carcinoma and it was confirmed to be the same on histopathology (Hematoxylin and eosin x400; May Grunwald Giemsa x400)

Category 6 consists of cases with diagnostic features of malignancy (shown in Figure 6). The aim of introducing this category is to sub classify tumors, especially into low grade and high grade because the approach to management of these cases are different. In our study, it comprised a total of 4 (4.4%) cases with histological follow-up available in three cases. One case each of Mucoepidermoid carcinoma, Acinic Cell Carcinoma and Salivary duct carcinoma was diagnosed on histological follow-up. FNAC of MEC predominantly shows three types of cells including squamoid, intermediate, and mucus secreting cells with a dirty to mucoid background. The number of these cells and cystic component vary according to the differentiation of the tumor.

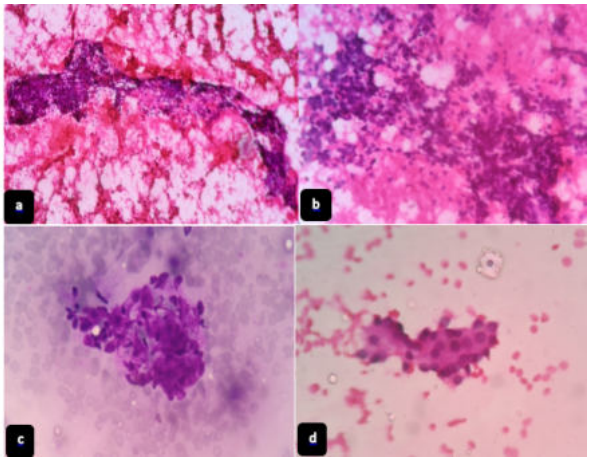

Figure 6: Category VI (Malignant)

(a, b and c) Fine Needle Aspiration smears are cellular with three-dimensional groups of epithelial cells with moderate amounts of cytoplasm and hyperchromatic pleomorphic nuclei with prominent nucleoli. The smears were reported as Category VI, High Grade Salivary Duct Carcinoma and was confirmed to be the same on histopathology. (Hematoxylin and eosin x100; Hematoxylin and eosin x400; May Grunwald Giemsa x400)

d) This aspirate shows bland epidermoid cells with moderate amounts of dense cytoplasm and well-defined cell borders. Mucus cells containing abundant mucinous cytoplasm were also noted in this smear. The smear was reported as Category VI, Low Grade Mucoepidermoid Carcinoma and was confirmed to be the same on histopathology. It is to be noted that this scenario can sometimes be confused with Pleomorphic adenoma. (Hematoxylin and eosin x400)

MSRSGC is a recent six category scheme to classify salivary gland smears; despite being heterogenicity and morphological overlap between different salivary gland lesions, it will definitely cater the need of cytopathologists and treating clinician because beside the benefit of risk stratification and providing ROM, this system proposed a tiered scheme which places salivary gland FNAC into well-defined categories that limit the possibilities of false negative and false positive cases.[11],[12],[13],[14],[16],[19],[20],[21],[22],[23] By incorporating MSRSGC for diagnosing salivary gland lesions, a sensitivity, specificity, positive predictive value and likelihood ratio of 98.1%, 42.9%, 92.8% and 1.750 respectively, were obtained in our study.

CONCLUSION:

The MSRSGC is a newly introduced six category scheme which helps to stratify salivary gland lesions, escalate standardized and uniform communication and lower the nondiagnostic reporting rates. The system conveys specific risk of malignancy and is very effective in differentiating between neoplastic and non-neoplastic as well as benign and malignant lesions of salivary gland., thereby helping the clinician to plan the therapeutic approach in patients and hence improves overall care. Despite being heterogenicity and morphological overlap between different salivary gland lesions, it will definitely cater the need of cytopathologists and treating clinician because beside the benefit of risk stratification this system proposed a tiered scheme which places salivary gland FNAC into well-defined categories that limit the possibilities of false negative and false positive cases. As per our study though care should be taken while differentiating between benign neoplasm and low-grade malignant neoplasm which can be a major pitfall in salivary gland FNAC.

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None

CONFLICTS OF INTEREST:

There are no conflicts of interest.

ABBREVIATIONS: MSRSGC: Milan System for Reporting Salivary Gland Cytopathology, ROM: risk of malignancy

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