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Original research article

Simultaneous use of Milan System and Pattern Based Risk Stratification Approach for Salivary Gland Cytology

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Abstract

Background: The well-established method of fine-needle aspiration cytology (FNAC) presents certain difficulties in its widespread application due to the heterogeneity and morphological overlap of the spectrum of salivary gland disorders. The recent "Milan system for reporting salivary gland cytopathology" (MSRSGC), offers guidelines for diagnosis and treatment based on various categories of malignancy risk (ROM). The goal of this study is to stratify the lesions by assigning the risk of malignancy based on pattern, interpret salivary gland lesions based on MSRSGC, and record interobserver variability.

Methods: FNAC was performed routinely on all palpable salivary gland lesions confirmed by prior USG. FNAC was done under aseptic conditions using 22–24 gauge needles, via percutaneous route either by non-guided or guided aspiration. A minimum of 2 passes were made by trained residents in the department of Pathology. The cytosmears are fixed in 95% ethyl alcohol or air dried and are routinely stained by Hematoxylin and Eosin and PAP stain where ever needed. Each case was evaluated for adequacy and categorized into one of the six categories according to MSRSGC by two different faculty members and tabulated. These cases were assigned to categories based on established criteria in the literature.

Results: Most commonly categorized category is Category-IVa. Benign neoplasm (68/136) in this Pleomorphic adenoma (56/68) is the commonest diagnosis. In Non-Neoplastic; chronic sialadenitis (24/40) was the most common diagnosis. We have received 49 cases for histopathological examination. In cyto-histopathological correlation, concordance was seen with 39/49 cases. 10/49 cases were found to be discordant out of them 4/10 were benign and 6/10 were malignant.

Conclusion: the use of the Milan System of Reporting Salivary Gland Cytopathology in regular cytology reporting to improve the communication between pathologists and also with the clinician for better patient care. The use of pattern-based categorization could help in

complimenting MSRSGC, as it adds to the risk stratification. as it has a higher positive predictive value.
Keywords: Milan system for reporting salivary gland cytopathology" (MSRSGC), risk of Malignancy (ROM)

Introduction

Fine Needle Aspiration (FNA) is an easy, cost-effective triage tool for Salivary gland lesions. It enables the clinician to select patients for surgical intervention and also to determine the extent of surgery thereby reducing the number of patients undergoing surgery. The diagnostic accuracy of FNA is estimated as a Sensitivity of 96%, Specificity of 98%, in the distinction of non-neoplastic from neoplastic, and a Sensitivity of 80%, Specificity of 97%, in the assessment of Benign versus Malignant. [1] The lower sensitivity of 80% in differentiating benign and malignant is accounted for a wide range of issues like the diversity of salivary gland neoplasms, intramural heterogeneity, and morphological overlap. Till now there is no standard risk stratification-based reporting system. As FNAC of Salivary glands has the potential to restrict the need for surgery of Non-Neoplastic Salivary gland lesions, thereby reducing the risk of intraoperative Facial nerve damage and tumor implantation. The American Society of Cytopathology and International Academy of Cytology proposed an International standardized classification for salivary gland cytology "Milan System for Reporting Salivary Gland Cytopathology" (MSRSGC) in 2015. This system uses fairly traditional cytologic categories such as Non-Diagnostic, Non-Neoplastic, Atypia of Undetermined Significance (AUS), Neoplastic (subdivided into benign and undetermined malignant potential), Suspicious for malignancy, and Malignant. [2] The 4th category i.e., Neoplasm has subdivided into benign and uncertain malignant potential shows the importance of determining the presence of neoplasia and the significant overlap between benign and malignant neoplasm that exist in the settings of salivary glands. This system MSRSGC has risk stratification that might guide clinical management. [3] A note on pattern-based risk stratification could supplement the MSRSGC that patterns like basaloid and oncocytoid need further evaluation as they contribute to a higher risk of malignancy in certain backgrounds. The purpose of this study is to interpret the Salivary gland lesions based on MSRGC and record the inter-observer variability as well as stratify the lesions assigning the risk of Malignancy based on the pattern.

Material and Methods

This prospective study was performed in the Department of Pathology, Kakatiya Medical College and MGM Hospital, Warangal over a period of 1-year, from June 2018 to June 2019. FNAC was performed routinely on all palpable salivary gland lesions confirmed by prior USG. A total of n=136 cases were included in the study. Clinical details including age, sex, site size, and radiologic details were tabulated. Informed consent was taken before the procedure. FNAC was done under aseptic conditions using (22-24) gauge needles, via percutaneous route either by non-guided or guided aspiration. A minimum of 2 passes were made by trained residents in the department of Pathology. The cytosmears are fixed in 95% ethyl alcohol or air dried and are routinely stained by Hematoxylin and Eosin and PAP stain where ever needed. Each case was evaluated for adequacy and categorized into one of the six categories according to MSRSGC by two different faculty members and tabulated. These cases were assigned to categories based on established criteria in the literature. [4-6]

Histopathology was considered a gold standard and was correlated with our cytology wherever possible. Following cyto-histological evaluation, these cytology cases were further divided into True Positives (malignancy suspicious both on cytology and histopathology), False Positives (diagnosed incorrectly as malignancy or suspicious for malignancy on cytology) True Negatives (absence of malignancy on both cytology and histopathology) False negatives (failure to diagnose malignancy on cytology). Sensitivity, Specificity, Positive predictive value, and Negative predictive values were calculated. The Risk Of Malignancy (ROM) was evaluated and assigned to all cases received for histopathology. ROM is defined as the ratio of cytology cases with malignant histopathology to the total number of cytology cases with or without follow-up histopathology for that category. Inter-observer concordance was determined and correlated with histopathology. Pattern-based risk stratification was done for smears with basaloid and oncocytoid patterns. This was related to the pattern-based classification proposed by Griffith et al., [4]

Results

This is a prospective study conducted from June 2018 to June 2019. A total of n=136 cases were received in cytology out of which 69/136 were males and 67/136 were females. There was a slight male preponderance. Male to Female ratio was 1:1 approximately. A higher incidence of cases was found to be between 30-39 years comprising 30/136 cases. In males, the higher incidence was seen in the 3rd, 4th, and 5th decades comprising 36/136 cases. In females, a higher incidence was seen in the 2nd, and 3rd decades comprising 35/136. The age and sex-wise distribution of cases were tabulated in Table 1.

Table 1: Age and Sex wise distribution of cases

Age In Years	*Male*	*Female*	*Total*
<10	02	00	02
11-19	07	07	14
20-29	04	17	21
30-39	12	18	30
40-49	12	10	22
50-59	12	07	19
60-69	11	07	18
>70	09	01	10
Total	69	67	136

Among the salivary glands involved Parotid was the most commonly affected site followed by the sub-mandibular gland, sublingual gland, and minor salivary glands. The case distribution was tabulated in Figure 1. Consistency in the majority of cases was firm (119/136). The rest of the cases were cystic (11/136) and hard (6/136). Signs of inflammation were seen in (34/136) cases. Size was ranging from 0.5 X 0.5 cms to 7 X 7 cms. In most cases aspirate was blood mixed granular aspirate, few cases showed mucoid, serous, murky, and grey-white aspirates.

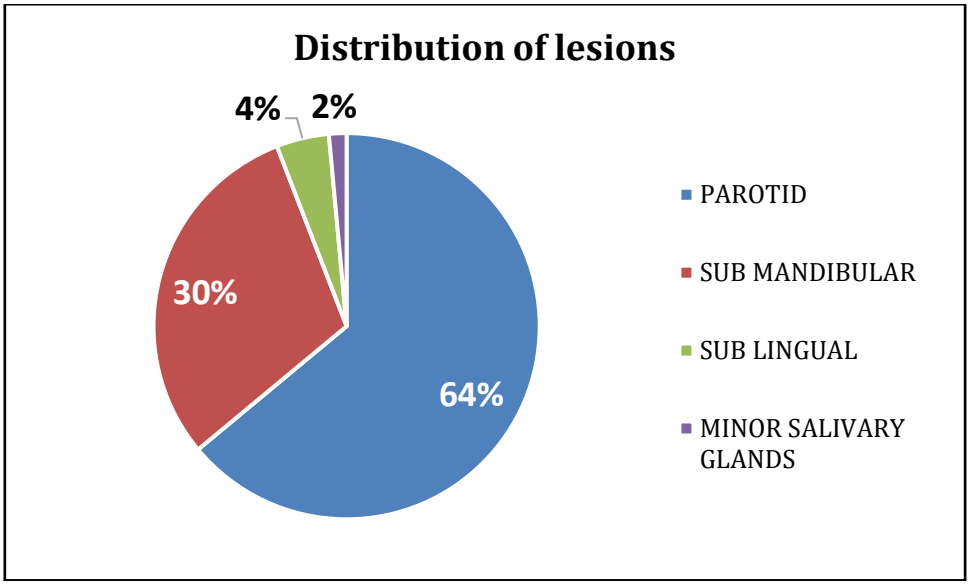


Figure 1: Distribution of the lesions across different salivary glands

FNAC results were categorized into 6 groups of Milan System of Reporting Salivary Gland Cytopathology (MSRSGC) and results were tabulated in Table 2

Table 2: Distribution of cases based on Milan System of Reporting Salivary Gland Cytopathology

Category	*Name of Category*	*Number of Cases*
	Non-Diagnostic	04
	Non-Neoplastic Acute Sialadenitis (16) Chronic Sialadenitis (24)	40
	Atypia of Undetermined Significance (AUS)	16
	Neoplastic Benign Pleomorphic adenoma (56) Warthins tumor (03) Basal cell adenoma (02) Monomorphic adenoma (02) Benign Salivary gland Neoplasm (04) Unknown Malignant Potential (SUMP)	71 68 03
	Suspicious For Malignancy (SFM)	02
	Malignant	03
TOTAL		136

The most commonly categorized category is Category-IV a. Benign neoplasm (68/136) in this Pleomorphic adenoma (56/68) is the commonest diagnosis. In Non-Neoplastic; chronic sialadenitis (24/40) was the most common diagnosis. We have received 49 cases for histopathological examination. In cyto-histopathological correlation, concordance was seen with 39/49 cases. 10/49 cases were found to be discordant out of them 4/10 were benign and 6/10 were malignant. The results are tabulated in Table 3.

Table 3: Cyto-histologic concordance and discordance

Cytologic Diagnosis	Number of cases (Cytology)	Concordance with Histology	Discordance in Histology	
			Benign	Malignancy
Non-Diagnostic	01	-	Pleomorphic Adenoma (01)	-
Non-Neoplastic	06	06 Sialadenitis (06)	-	-
AUS	06	03 Mucus retention cyst (03)	Basal Cell Adenoma (02)	Mucoepidermoid (01)
Neoplastic	32	27	-	-
Benign	30	27 Basaloid neoplasm with fibrillary stroma (Pleomorphic adenoma) (25) Basaloid neoplasm with non-fibrillary stroma (Basal cell adenoma) (01) Warthins tumor (01)		Basaloid neoplasm with non-fibrillary stroma (Polymorphous Low-Grade Adenocarcinoma) (03)
SUMP	02		Pleomorphic Adenoma (01)	Oncocytoid neoplasm with the mucinous background (Adenoid Cystic carcinoma) (01)
Suspicious For Malignancy	01	-	-	Pleomorphic basaloid neoplasm (Adenoid Cystic Carcinoma) (01)
Malignancy	02	02 Muco epidermoid carcinoma (01) Adenoid cystic carcinoma (01)		
Total	49	39	04	06

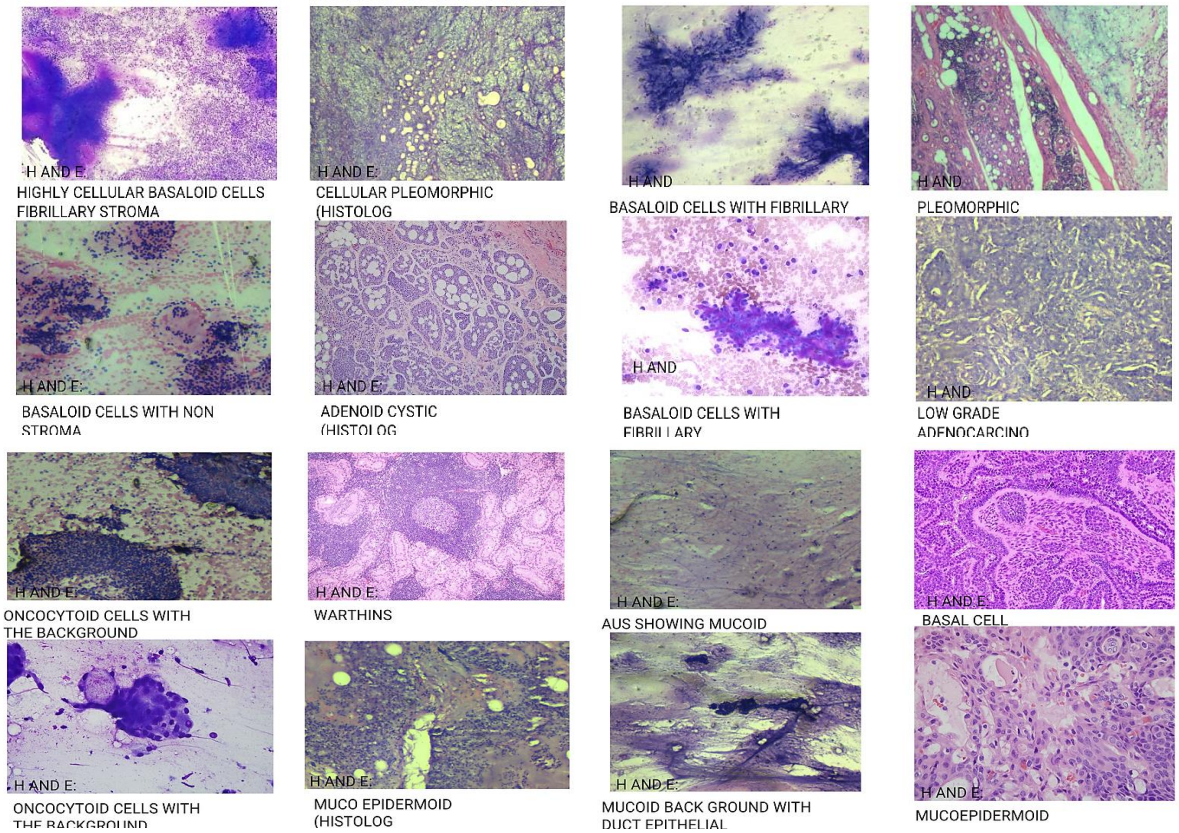
The non-diagnostic case was reported as pleomorphic adenoma on histopathology. There was no discordance in the Non-neoplastic, Suspicious for Malignancy, and Malignant categories. In Benign Neoplasms, 3/30 cases were diagnosed to be polymorphous low-grade adenocarcinoma. In SUMP (02) cases one turned out to be pleomorphic adenoma and the other turned out to be adenoid cystic carcinoma. Cases diagnosed as AUS (06) on cytology 3/6 were diagnosed as mucus retention cyst, 2/6 were diagnosed as basal cell adenoma and 1/6 was

diagnosed as mucoepidermoid carcinoma. Sensitivity, Specificity, Positive predictive value, and Negative predictive value in diagnosing salivary gland lesions using MSRSGC are 62.5%, 97.5%, 83.3%, and 93%. The percentage of the total number of cases and the category-wise risk of malignancy is tabulated in Table 4

Table 4: Category-wise- the risk of malignancy

MSRSGC Category	*Percentage of cases*	*Risk of malignancy (ROM)*
	2.9%	00%
II	29.4%	00%
III	11%	16%
IV a	50%	10%
IV b	2.2%	50%
V	1.4%	100%
VI	2.2%	100%

There was 97% concordance between both the cytopathologists, the 3% cases i.e., 4/136 cases had discordance 2/4 cases were categorized as SUMP by one pathologist and SFM by the other pathologist, on HPE it was malignant.1/4 cases was given as AUS by one pathologist and SUMP by the other, on HPE this was diagnosed to be Basal cell adenoma.1/4 cases were given benign neoplasm by one pathologist and as SUMP by the other pathologist, on HPE it was diagnosed as pleomorphic adenoma.



Discussion

FNAC of salivary gland lesions is a rapid non-invasive, cost-effective, outpatient technique more than pre-operative FNA aids the clinician to avoid unnecessary surgery. FNAC helps to know the origin of lesion, type of pathology, benign or malignant. Despite these advantages it

also had lacunae. The limitations are the lack of well-established criteria for grouping lesions. 2. Variability in cytologic practices in different institutions, like the number of passes, reporting patterns, and staining techniques. [3] Heterogeneity of Salivary gland, morphological variations in patterns. Well-established internationally accepted criteria and risk of malignancy for each category. For standardizing the reporting of salivary gland cytology, a universally acceptable system was mandatory. Much previous literature on lesions of salivary glands was divided into many formats. A 5-group approach system was proposed by Maleki Z et al., [7] which included Myxoid-hyaline, Basaloid, Oncocytoid, Lymphoid, and Squamoid. Tessy PJ et al., [8] classified lesions into Inflammatory, Benign, Malignant, and others. Milan system of reporting salivary gland cytopathology was proposed by IAC and ASC in 2015 which included [7] categories namely Non-Diagnostic, Non-Neoplastic, Atypia of Undetermined Significance (AUS), Neoplastic (subdivided into benign and undetermined malignant potential), Suspicious for malignancy, and Malignant. Specimen adequacy [quantitative and qualitative] has not been clearly defined. Several factors such as aspiration technique, the gauge of the needle used, the experience of the performer, target lesion, characteristics, obscuring elements, and smearing and staining artifacts play an important role in the diagnosis. Griffith et al., [4] have proposed adequacy criteria for more than 4 high-power fields of epithelial cells. The Milan system has recommended using the adequacy criteria of TBSRTC a minimum of 60 lesional cells in the diagnosis of the salivary lesion as well for the time being.

In this study, we found n=136 cases for cytology there was a slight pale preponderance Male: Female 69:67 (1: 1). In our study most commonly affected Salivary gland is Parotid followed by Sub Mandibular, Sub Lingual, and Minor Salivary Glands. Similar findings were seen in studies by Sonal et al., [9] and Jain et al., [10] Higher incidence of cases was in the 3rd decade. Females of the younger age group were more affected. Males of middle age had a higher incidence. Size was ranging between 0.5 X 0.5 cms and 7 X 7cms. With a mean average of 2 X 2cms. Maximum cases were seen in category IVa which is a benign neoplasm, followed by non-neoplastic. This correlates with studies of Subrata et al., [11] and Yogambal et al., [12] 49 cases were sent for histopathological evaluation out of them 39 were concordant with that of cytology. The cyto-histology correlation was 79.5%, which is better than Mihashi H et al., [12] i.e., 30%. This study has an 80% of cyto-histological correlation in the case of malignant tumors. Jain et al., [10] observed a cyto-histology correlation of 64.2 %. The Sensitivity, Specificity of FNAC for the diagnosis of salivary gland lesions ranges from 62% to 97.6%. and 94.3%, 100% respectively. This study has a Sensitivity, Specificity, Positive predictive value, and Negative predictive value in diagnosing salivary gland lesions using MSRSGC is 62.5%, 97.5%, 83.3%, and 93% respectively. Lower sensitivity is due to 3 false negative cases. Wang et al., [14] evaluated all salivary gland FNAC with an atypical diagnosis with their HPE from 5 tertiary care medical centers in the USA, Europe, and China. A total of 504/12606 salivary gland FNAC were reported as atypical out of which 154 cases had HPE follow-up (61%-malignant tumors, 21.4%-benign tumors, and 16.2% benign lesions) ROM of the atypical subset of cases showed wide variation from 73.08% to 0%. Thereby reflecting variable practices across institutions. According to this study, the ROM for non-diagnostic and non-neoplastic was 0%. For the AUS category, it is 16% and for the benign neoplastic category, it is 10%. SUMP-50%, SFM, and malignant category showed a 100% risk of malignancy. Indeterminant categories like AUS, SUMP, and SFM had a risk of malignancy of 33.3%.
Viswanathan et al., [15] applied MSRSGC retrospectively on salivary gland lesions to access ROM over 5 years. They observed a near-perfect agreement between 2 cytopathologists regarding the categorization of salivary gland lesions (626/627- 99.8%) as per MSRSGC. In this study 132/136- 97% of cases were in concordance. In the current study, 4/136 cases had

discordance 2/4 cases were categorized as SUMP by one pathologist and SFM by the other pathologist this was purely accounted to the cellularity and number of cells with atypia, on HPE it was malignant. 1/4 cases were given as AUS by one pathologist and SUMP by the other, because of the mucoid areas and moderate cellularity it was classified under AUS, on HPE this was diagnosed to be Basal cell adenoma. It was misdiagnosed as the aspiration might have been done from the adjacent dilated duct due to compression by the tumor 1/4 case was given benign neoplasm by one pathologist and as SUMP by the other pathologist, on HPE it was diagnosed as cellular pleomorphic adenoma. This is attributed to the cellularity and the atypia usually seen in cases of pleomorphic adenoma. In this study we have observed various patterns which could relate to the risk stratification, i.e., tumors with basaloid patterns are further subdivided based on the stroma. The neoplasms lacking identifiable and uniform fibrillary stroma have a higher risk of malignancy when compared to tumors with abundant fibrillary stroma. Oncocytoid tumors with the presence of mucus in the background or tumor cells with granular vacuolated cytoplasm are associated with higher ROM, than the tumors lacking mucus in the background. Similar results were noted in studies by Giffith et al., [5] The misinterpretation of mucoepidermoid carcinoma as a cystic lesion was the most common reason for false negative results. Implementation of MSRGSC will be challenging on account of inter-institutional variability account of sampling techniques and cytology practice protocols. Global-wide institutional usage of MSRSGC can help in overcoming this problem. Further pattern-based sub-categorization can complement the current Milan system of reporting salivary gland cytopathology. The limitations of this study are that it is a single-center study and there could be variations in cytology practices in different centers.

Conclusion

This study emphasizes the use of the Milan System of Reporting Salivary Gland Cytopathology in regular cytology reporting to improve the communication between pathologists and also with the clinician for better patient care. The use of pattern-based categorization could help in complimenting MSRSGC, as it adds to the risk stratification. as it has a higher positive predictive value. Cases with Mucoid and vague fibrillary backgrounds have to be evaluated with utmost care as they pose a higher risk of malignancy.

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