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Original Research Article

Cyto- Histopathology Correlation of Salivary Gland Tumors Pertaining to MILAN System

Thomson Caroline Elizabeth[1], Kadam Monica Mittal[2], Monteiro Rashmi[3], Garg Bhavana[4]

[1]Senior Resident, Tata Memorial Hospital, Mumbai
[2]Assistant Professor, Seth G S Medical College & KEM Hospital, Mumbai
[3]Consultant Pathologist, SRL Diagnostics, Mumbai.
[4]Associate Professor, Pacific Medical College & Hospital, Udaipur, Rajasthan.

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Corresponding Author: Dr. Rashmi Monteiro
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Abstract

Salivary gland neoplasms account for 2%–6.5% of all the head and neck neoplasms. The reporting system called as 'Milan System for Reporting Salivary Gland Cytopathology' (MSRSGC) gives a risk stratification- based classification system with an intrinsic risk of malignancy (ROM) for each diagnostic category, that aims to furnish useful information to the clinicians. This is a 2 years retrospective study that was conducted from January 1, 2018 to December 31, 2019 in the Department of Pathology at a tertiary care institute. Data of 64 patients who underwent an excision of the lesion for histopathological examination following the FNAC were also collected and the Haematoxylin and eosin stained slides were also reviewed.

The male (60.93%) to female (39.06%) ratio was 1.5: 1 showing a male preponderance with the mean age being 44.82 years.Maximum number of cases were seen in the age group of 51 to 60 years (31.25%). Swelling was the most common presenting symptom. Parotid gland (85.93%; $N = 55$) was involved in the majority of cases. The non-diagnostic category i.e. category I included 2 cases (3.12%). Non neoplastic category i.e. category II comprised of 14 cases (21.87%). AUS i.e. category III had 4 cases (6.25%). Benign neoplasm i.e. category IVA was the largest category and comprised of 37 cases (57.81%) and IVB comprised of 2 cases (3.12%). The malignant category i.e. category VI comprised of 5 cases (7.81%). In malignant cases, mucoepidermoid carcinoma - 3 cases (4.68%) was the most commonly diagnosed malignancy on other hand pleomorphic adenoma was the frequent diagnosis in category IV .Histological follow-up was available in 38 cases (59.37%). On follow-up, there were no discordant cases but 1 case from AUS category and 1 case from IV B category turned out to be malignant.

The MSRSGC system helps in appropriate categorisation of salivary gland lesions that leads to minimal misdiagnosis or miscategorisation.

Introduction

Salivary gland neoplasms account for 2%–6.5% of all the head and neck neoplasms. [1] These are uncommon with complex microscopic features. The different causes of a nodule or diffuse enlargement of the salivary gland may be inflammation, cystic lesion, degenerative process or benign/malignant neoplasm.

Over the years, the role fine-needle aspiration (FNA) in the diagnosis of salivary gland lesions has evolved. Although clinical and radiological parameters help to narrow the differential diagnosis the tissue diagnosis still remains the gold standard. [2]

There are many diagnostic challenges that a pathologist faces in reporting salivary gland cytology as there is a wide diversity of tumors arising in the salivary glands along with the lack of a uniform reporting system. [3]

The American Society of Cytopathology and the International Academy of Cytology has therefore proposed an international classification scheme for reporting salivary gland fine needle aspiration in order to develop a standardized terminology for reporting salivary gland cytopathology. This reporting system called as 'Milan System for Reporting Salivary Gland Cytopathology' (MSRSGC) gives a risk stratification- based classification system with an intrinsic risk of

malignancy (ROM) for each diagnostic category, that aims to furnish useful information to the clinicians.

It is based on the experience of experts in the field of cytopathology and on evidence from the literature. [4]

This study has been undertaken to review the cytological features of various salivary gland lesions, to categorize the various entities according to Milan system of reporting salivary gland cytopathology, to correlate with the histological diagnosis and thus determine the accuracy and reliability of cytological diagnosis. [5]

Materials and Methods

This is a 2 years retrospective study that was conducted from January 1, 2018 to December 31, 2019 in the Department of Pathology at a tertiary care institute.

64 cases with the detailed clinical data that includes the age, sex and symptoms were retrieved from the departmental records. The FNAC smears stained with Giemsa and Papanicolaou stain were reviewed. Data of those patients who underwent an excision of the lesion for histopathological examination following the FNAC were also collected and the Haematoxylin and eosin-stained slides were also reviewed.

As a routine practice all FNAs were performed after taking informed consent from the patients. The lesions were aspirated using a 22–23-gauge needle and smears were prepared in each case- 50% were air-dried for Giemsa stain and 50% were alcohol-fixed for Papanicolaou (Pap) stain, respectively.

The cases were evaluated based on the cytological features and categorized as per the Milan system of reporting Salivary Gland cytopathology (MSRSGC). These were correlated with the histopathological diagnosis as histopathology is considered as the gold standard.

The sensitivity, specificity, positive and negative predictive values and diagnostic accuracy of FNA to detect malignant lesions were calculated. ROM was determined by dividing the number of malignant cases by a total number of histopathological follow-up available in the particular category.

Results

A total of 64 patients visited for FNAC of salivary gland lesion at the cytology section of the Department of Pathology in the institute over a period of 2 years.

The male (60.93%) to female (39.06%) ratio was 1.5: 1 showing a male preponderance. The patient's age ranged from 16 to 88 years with the mean age being 44.82 years. The maximum number of cases were seen in the age group of 51 to 60 years (31.25%) followed by 41 to 50 years (23.43%).

All patients presented with a swelling (100%) and pain was the second most common presenting symptom (25.6%). Parotid gland (85.93%; $N = 55$) was involved in the majority of cases while the submandibular gland was affected in (12.5%; $N = 8$) of cases. The minor salivary gland was affected only in 1.56%; $N = 1$ of cases.

All the cytology cases were reviewed and categorized according to the MSRSGC. The non diagnostic category i.e., category I included 2 cases (3.12%). Non neoplastic category i.e., category II comprised of 14 cases (21.87%). AUS i.e., category III had 4 cases (6.25%). Benign neoplasm i.e., category IVA was the largest category and comprised of 37 cases (57.81%) and IVB comprised of 2 cases (3.12%). The malignant category i.e. category VI comprised of 5 cases (7.81%)

In malignant cases, mucoepidermoid carcinoma - 3 cases (4.68%) was the most commonly diagnosed malignancy. Among the non-neoplastic category, chronic sialadenitis was the most common diagnosis comprising 10 (15.6%) cases. Overall, the most common diagnosis was found to be under category IVA, pleomorphic adenoma (PA) comprising of 32 (50%) cases.

Histological follow-up was available in 38 cases (59.37%). On follow-up, there were no discordant cases but 1 case from AUS category and 1 case from IV B category turned out to be malignant.

ROM was calculated for all categories. (Table 1)

In the present study, sensitivity was 71.43 %, specificity was 100 %, positive predictive value (PPV) was 100 %, negative predictive value (NPV) was 93.94%, and cytological diagnostic accuracy of 94.74 % was obtained.

Table 1: Cytohistopathological correlation & risk of malignancy (ROM)

MSRSGC category	No. of cases with histopathology follow up	Histopathology diagnosis	ROM (%)
II	2/14 cases	2 cases- Chronic sialadenitis	0%
III	4/4 cases	3 cases- Mucous retention cyst 1 case- Mucoepidermoid carcinoma	25%
IVA	25/37 cases	20 cases- Pleomorphic adenoma	

		5 cases- Warthins tumor	0%
IVB	2/2 cases	1 case- Low grade mucoepidermoid carcinoma 1 case- Basal cell adenoma	50%
VI	5/5 cases	3 cases- Mucoepidermoid carcinoma 2 cases-Adenoid cystic carcinoma	100%

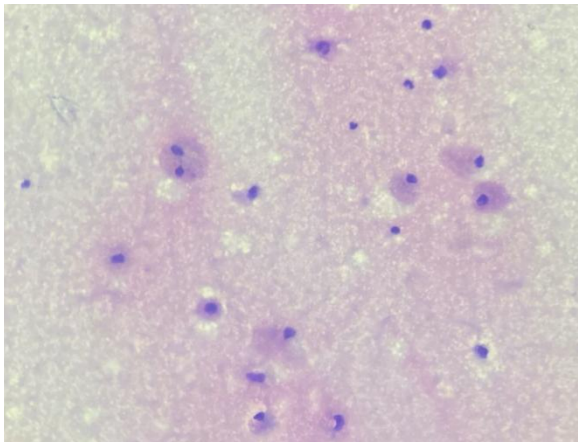

Figure 1: Category I (Non-Diagnostic) - Paucicellular smear showing macrophages and few inflammatory cells with no epithelial cells.

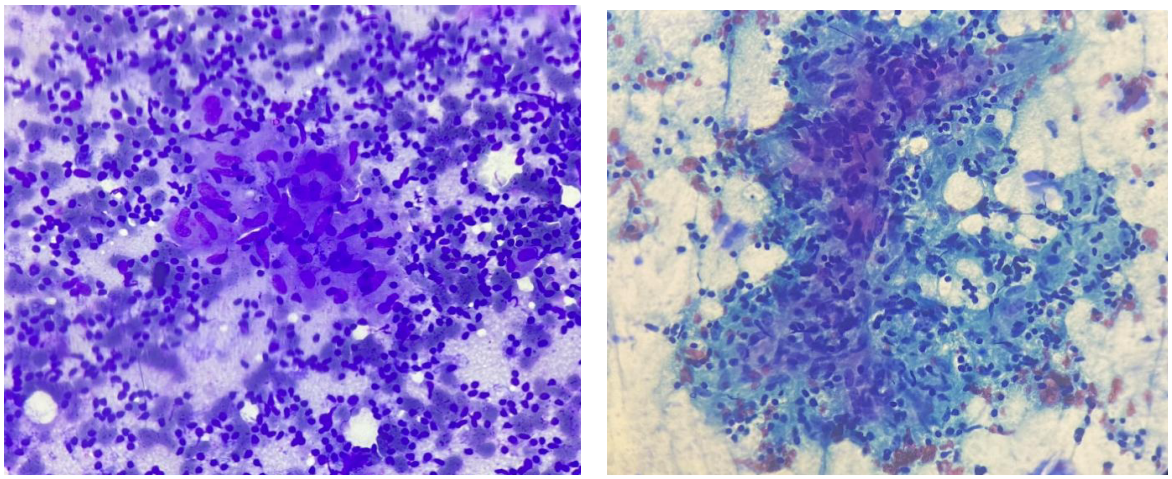

Figure 2: Category II (Non neoplastic category)- Cellular smears showing epithelioid cells forming granuloma with chronic inflammation and RBCs in the background.

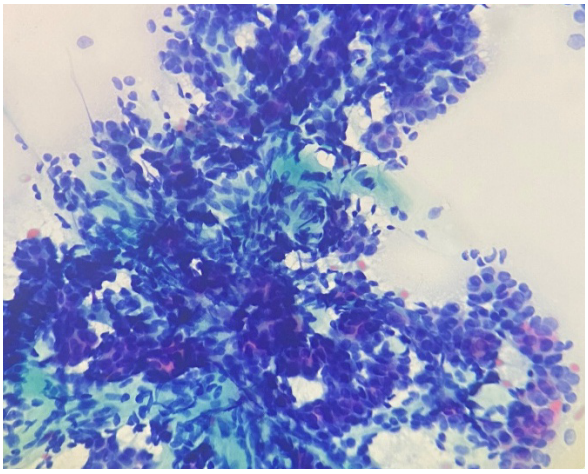

Figure 3: low power view of Pleomorphic Adenoma smear showing loosely cohesive epithelial cells embedded in myxoid stroma

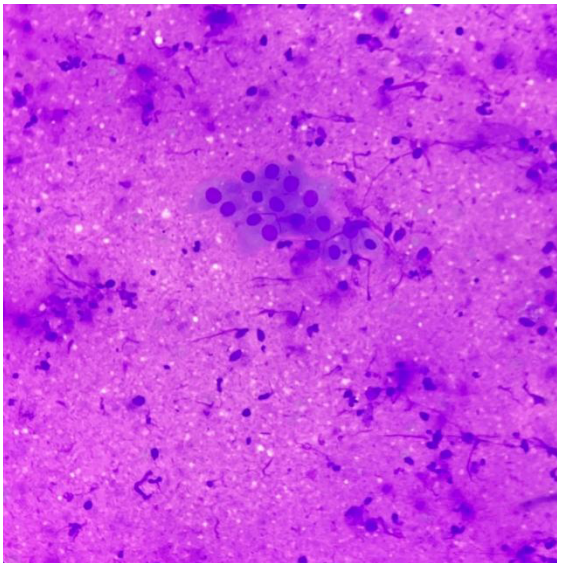

Figure 4: FNAC smear of Warthins tumor showing cohesive clusters of oncocytic cells and scattered lymphocytes with proteinaceous material in background

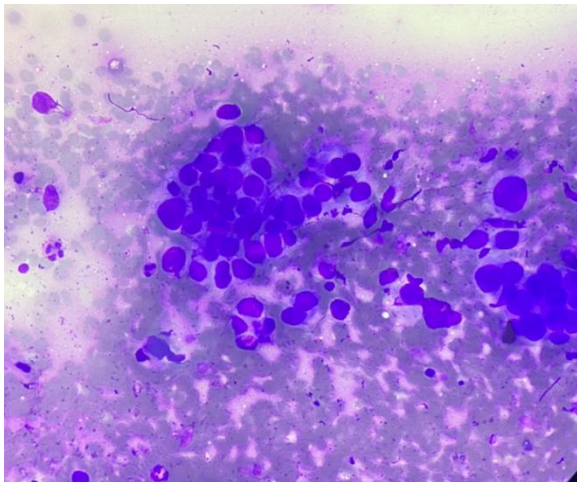

Figure 5: FNAC smear of Mucoepidermoid carcinoma showing clusters of tumor cells (squamoid) with moderate nuclear pleomorphism. The background shows mucin admixed with RBcs.

Discussion

MSRSGC is formulated to provide an accurate diagnostic category to the salivary gland lesions through fine needle aspiration cytology, which will provide appropriate information to the clinician for its further treatment. Our study had a total of 64 cases over a period of 2 years. Gaikwad VP et al [6] had studied a total of 79 cases over a period of 2 years, Chirmade J et al [7] studied 120 cases in 5 years and Rohilla M et al[8] studied 631 cases over a period of 3 years.

In our study the male (60.93%) to female (39.06%) ratio was 1.5: 1 showing a male preponderance. The male: female ratio in the study done by Singh S et al [9] was 2.6:1, Chirmade J et al7 was 2:1 and Rohilla M et al [8] was 1.7:1 showing a male preponderance similar to our results while in the study done by Gaikwad VP et al6 the male to female ratio was 1:1.26 showing a female preponderance.

In the present study, the patient's age ranged from 16 to 88 years with the mean age being 44.82 years and the results were similar to the study done by Rohilla M et al [8] in which the age of the patients ranged from 1 to 95 years with the mean age of 43.7 years, Gaikwad VP et al [6] that had age range from 7 to 85 years with the mean age being 46 years and Chirmade J et al [7] that had patient's age ranged from 5 to 85 years with a mean age of 42 years. The maximum number of cases were seen in the age group of 51 to 60 years (31.25%) followed by 41 to 50 years (23.43%) in the current study while Chirmade J et al had maximum number of cases in the age group of 21 to 30 years (21.6%) followed by 41 to 50 years (20%).

In the present study all patients presented with a swelling (100%) and pain was the second most

common presenting symptom (25.6%), while similar results were observed in the study done by Chirmade J et al, Rajdeo R et al [10] and Wahiduzzaman M et al [11]. Parotid gland (85.93%; *N* = 55) was the most common salivary gland that was affected in our study and this finding was similar to the studies done by Chirmade J et al[7], Gaikwad VP et al6 and Singh S et al

According to the MSRSGC categorisation the non-diagnostic category i.e. category I included 2 cases (3.12%) in our study. In both the cases only non-mucinous fluid was aspirated and the smears were paucicellular showing macrophages and few inflammatory cells with no epithelial cells. Repeat aspiration was advised but the patient did not come back and no follow up was available for these cases. Many authors have suggested multiple passes from different areas and FNAC under ultrasound guidance, so as to overcome diagnostic difficulty faced due to less cellularity on smear. [12,13] 10% is the maximum rate of diagnosing non diagnostic category according to MSRSGC and our institute is within the range.

Non neoplastic category i.e. category II comprised of 14 cases (21.87%) in our study. Majority of them (10 cases) were diagnosed as chronic sialadenitis and the smear studied showed benign clusters of ductal cells with scanty acinar cells in a background of lymphocytes, 3 cases were diagnosed as acute sialadenitis and 1 case was diagnosed as sialadenosis on cytology. Among them only 2 cases had histopathology follow up and were confirmed as chronic sialadenitis. Other patients were on medical management and their swelling subsided after the treatment. MSRSGC has set the ROM as 10% for non-neoplastic cases. The ROM for category II in our study was 0% and was concordant with the studies done by Chirmade J et al and Gaikwad VP et al. While the ROM of category II was 14.28% in a study done be Singh S et al [9].

AUS i.e. category III had 4 cases (6.25%) in our study. The aspirate of all 4 cases were paucicellular but with the presence of mucinous aspirate with few epithelial cells and hence, these cases were categorised into the III category. All 4 cases had histopathology follow up: 3 cases were diagnosed as mucous retention cyst and 1 case was diagnosed as mucoepidermoid carcinoma. This category was introduced in MSRSGC to reduce the number of false negatives in the non-neoplastic category. This category should comprise of <10% of all salivary gland FNAC samples according to the Milan system. [14] In our study, this category comprised 6.25% cases and ROM was calculated as 25% which was higher than the range recommended by MSRSGC (20%) but was similar to study done by Singh S et al [9] (33.3%). Other studies had a higher ROM in AUS category, Gaikwad VP et al6 and Chirmade J et al7 had ROM as 50% and Rohilla M et al8 had ROM of 100%.

Table 2: Correlation between histopathological diagnosis and (cytopathology) MSRSGC categorization of 38 cases

	Histopathological diagnosis		
MSRSGC cases	Malignant	Benign	**Total**
Malignant (5)	5	0	5
Benign (33)	2	31	33
Total	7	31	**38**

Benign neoplasm i.e. category IVA was the largest category in present study and comprised of 37 cases (57.81%). Pleomorphic adenoma was the most common diagnosis followed by Warthins tumor. This was also noted in Kala et al [15], Chirmade J et al [7] and Singh S et al. On cytology smears, pleomorphic adenoma exhibited round to plasmacytoid epithelial cells along with fibrillary chondromyxoid stroma. Warthins tumor showed oncocytic cells with plenty of lymphocytes in a dirty mucoid background. 25 out of 37 cases had histopathology follow up and among them 20 cases were pleomorphic adenoma and 5 cases were warthins tumor. The ROM for this category was 0% which is well within the limit (< 5%) as described by MSRSGC. In our study no false negative cases were noted in this category, probably due to the presence of the characteristic features on cytology smears. This was similar to the findings in studies done by Gaikwad VP et al6 and Chirmade J et al. In a study done by Singh S et al two cases of this category were classified as adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma on histological follow-up and the ROM was 5.71%.

Category IVB neoplasm of uncertain malignant potential, (SUMP) comprised of 2 cases (3.12%). One case showed smears with high cellularity of ductal and myoepithelial cells along with scanty matrix, with focal atypia and therefore it was categorised as SUMP. On histopathological follow up it was diagnosed as low grade mucoepidermoid carcinoma. The cytology smears of the second case showed high cellularity with basaloid cells and basement membrane material. It was diagnosed as cellular basaloid neoplasm suggestive of basal cell adenoma on cytology and was confirmed as basal cell adenoma on histopathology. The ROM of this

category in our study was 50%. This category comprises of aspirates with features of a neoplasm but no specific entity can be given nor malignancy can be ruled out. The ROM of SUMP in different studies vary, Gaikwad VP et al6 had 100% , Singh S et al had 67% while Chirmade J et al7 had 28.57%. MSRSGC recommends ROM for SUMP as 35%, but values vary from 0-100% in various studies probably due to the low number of cases under SUMP category. [4,6]

The malignant category i.e., category VI included 5 cases (7.81%) in our study. All cases had followed up and according to histopathology was diagnosed as mucoepidermoid carcinoma- 3 cases and adenoid cystic carcinoma- 2 cases. The ROM for this category in our study was 100% which was higher than ROM of 90% as stated by MSRSGC. The results were comparable to studies done by Gaikwad VP et al6, Singh S et al [9] and Chirmade J et al.

The statistical parameters calculated were similar to the studies done by others (Table 3)

Table 3: Comparison of statistical parameters of various studies

Study	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
Present study	71.43%	100%	100%	93.94%	94.74%
Gaikwad VP et al[6]	75%	100%	100%	92.8%	94.1%
Chirmade J et al[7]	92.30%	100%	100%	98.27%	98.57%
Singh S et al[9]	80%	89.80%	-	-	87.50%
Rohilla M et al[5]	79.4%	98.3%	96.4%	89.2%	91.4%

Conclusion

The MSRSGC system helps in appropriate categorisation of salivary gland lesions that leads to minimal misdiagnosis or mis categorisation. The AUS and SUMP category has proved to be useful as it conveys the dilemma the pathologist has to the clinician. MSRSGC also provides a standard and uniform system which alerts the clinician about the ROM of each category. In cases with overlapping features, the ROM will be beneficial for the clinician to plan an effective management for the patients.

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