e-ISSN: 0975-1556, p-ISSN:2820-2643
Available online on www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2024; 16(3); 673-682

Original Research Article

Milan System of Reporting Salivary Gland Cytopathology: An Institutional Experience with Histological Correlation

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Received: 15-01-2024 / Revised: 20-02-2024 / Accepted: 05-03-2024
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Conflict of interest: Nil

Abstract:

Background: This study was conducted to categorise the spectrum of salivary gland lesions according to the Milan system for reporting salivary gland cytopathology, establish a correlation between pre-operative cytopathology and post-operative histopathology and highlight the diagnostic pitfalls in cases of cyto-histo miscorrelation.

Methods: This was a hospital-based study conducted among 57 patients who underwent FNAC of salivary gland lesions at the Department of Pathology, M.K.C.G Medical College and Hospital, Berhampur, from November 2019 to November 2021, after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Results: 33 patients were followed up for histopathological studies. Upon categorization of all the salivary gland lesion aspirates into 7 categories of MSRSGC, we found the maximum number of cases in category IVA i.e. neoplasm: benign accounting for 38.6% of the cases, followed by category II (non-neoplastic) with 31.58% of the cases. The least number of cases were placed in categories I (non-diagnostic), IVB (SUMP) and V (suspicious for malignancy) with 1.75% of the cases in each of the categories.

Conclusion: The high sensitivity, specificity, positive predictive value, negative predictive value of FNAC when reported according to "The Milan System for reporting salivary gland cytopathology" confirm that preoperative cytology is a quick and reliable diagnostic technique for rapid and early diagnosis and we also conclude that it is a simple and cost effective tool suitable for developing countries like India.

Keywords: Salivary Gland, Milan System for Reporting Salivary Gland Cytopathology (MSRSGC), Risk of malignancy, histopathological follow up.

Introduction

The objectives of "The Milan System for reporting salivary gland cytopathology" are to standardize the terminology for reporting FNAC of salivary glands and improve the communication between clinicians and pathologists. It also provides an estimated risk of malignancy and clinical management recommendations for each category. [1,2-5] This standard reporting system will enhance the overall effectiveness of SG-FNA reporting, with the ultimate result being better communication and improved patient care.

Aims And Objectives

- To categorise the spectrum of salivary gland lesions according to the Milan System for reporting Salivary Gland cytopathology.
- To establish a correlation between pre-operative cytopathology and post-operative histopathology and to highlight the diagnostic pitfalls in cases of cyto-histo miscorrelation.

Materials & Methods

This was a hospital-based study conducted among 57 patients who underwent FNAC of salivary gland lesions at the Department of Pathology, M.K.C.G. Medical College and Hospital, Berhampur, from November 2019 to November 2021, after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Inclusion Criteria

- All patients irrespective of age and sex with clinically detected salivary gland lesions.
- Both major and minor salivary gland swelling; including intraoral lesions.

Exclusion Criteria

- Unwillingness to participate in the study.
- Mesenchymal and hematological lesions

Statistical Methods

The data was entered in MS excel and analysed using SPSS software. Results were presented as tables.

Statistical Formula

- Sensitivity $= \frac{TP}{TP+FN} \times 100$
- Specificity $= \frac{TN}{FP+TN} \times 100$
- Predictive Value for Benign tumors

$$= \frac{TN}{TN+FN} \times 100$$

- Predictive Value for Malignant tumors

$$= \frac{TP}{TP+FP} \times 100$$

Results

Table 1: Demographic Distribution

Age Range	No. of Cases	
0-10	0	
11-20	3(5.26%)	
21-30	9(15.8%)	
31-40	11(19.3%)	
41-50	13(22.8%)	
51-60	11(19.3%)	
61-70	08(14.03%)	
>70	02(3.5%)	
Age Distribution		
SEX	**Male**	**Female**
No. of Cases	32(56.14%)	25(43.86%)
Sex Distribution		

The patient age ranged from 17 years to 85 years and the maximum number of cases were in the age group of 41-50 years (22.8%), with an average age of 44.2 years.

Among the 57 cases studied, 32 (56.14%) were male and 25 (43.86%) were female. The male-to-female ratio was 1.28:1. The most frequently involved salivary gland was the parotid (46 cases, 80.7%) followed by the submandibular gland (11 cases, 19.3%) and no cases involving minor salivary glands were identified.

Table 2: Distribution of Cases as per MSRSGC

Category	No. of Cases	Percentage (%)
I. Non-diagnostic	01	1.78
II. Non-neoplastic	18	32.14
III. Atypia of undetermined significance(AUS)	03	5.35
IVA. Neoplasm:benign	22	39.28
IVB. Neoplasm:SUMP	01	1.78
V. Suspicious for malignancy	01	1.78
VI. Malignancy	10	17.86

Follow-up histopathology was available for 33 cases out of the 57 patients. The cytohistopathological correlation revealed discordance in 8/33 cases (21.2%).

One case had paucicellular yield even after repeated aspirations and hence was categorized as nondiagnostic i.e. category I (1.75%), the non-neoplastic category (category II) was reported in 18 cases (31.58%) and chronic sialadenitis was the most common cytological diagnosis (8/18) in this category. Discordance was seen in 4/18 cases. Three cases of chronic sialadenitis on cytology turned out to be pleomorphic adenoma, adenoid cystic carcinoma and cellular pleomorphic adenoma and a case of retention cyst came out to be a low grade mucoepidermoid carcinoma.

The AUS category (category III) was noted in 5.35% of cases (3/57) and the cases had a descriptive cytology report stating the presence of cells with a variable degree of atypia. One of the two such cases had histopathological follow-up which was reported as intermediate grade mucoepidermoid carcinoma on histopathology. Another case in this category was a cystic lesion with abundant mucin and few atypical cells (mucocele vs. LGMEC) that turned out to be low grade mucoepidermoid carcinoma after resection. The benign neoplasm category (category IVA) comprises the maximum number of cases i.e. 22/57 cases (38.6%) and the most common cytological diagnosis was Pleomorphic adenoma (19/22). 14 out of 22 cases underwent surgical resection, of them discordance was seen in two cases which were reported as pleomorphic adenoma and myoepithelioma on cytology, but turned out to be adenoid cystic carcinoma and cellular pleomorphic adenoma respectively on histopathology. Category IVB (SUMP) and category V (Suspicious for malignancy) accounted for only 1.75% (01/57) each and both of them were adenoid cystic carcinoma on histopathology. 11 out of 57 (19.3%) cases were classified as malignant, i.e. category VI, of which histopathological follow-up was available in 9 cases and all except one were malignant tumours. The most commonly interpreted malignant tumour was mucoepidermoid carcinoma.

Table 3: Risk of Malignancy (ROM) in Each Diagnostic Category

Category	No. of Malignant Cases	ROM (%)
I. Non-diagnostic	0	0
II. Non-neoplastic	01	16.67
III. Atypia of undetermined significance (AUS)	02	100
IVA. Neoplasm: benign	01	7.14
IVB. Neoplasm: (SUMP)	01	100
V. Suspicious for malignancy	01	100
VI. Malignancy	07	88.9

The risk of malignancy was 100% in categories III, IVB and V, 16.67% in category II and 7.14% in category IVA which is slightly higher than the published MSRSGC rates. In categories I and VI, the ROM was 0% and 88.9% respectively.

Table 4: Categorization as per MSRSGC and Cyto-Histo Correlation

Category	No. of Cases	FNA Diagnosis	No. of HPE Cases	HP Diagnosis	Correlation
I. Non-Diagnostic	01	Paucicellular	---	---	---
II. Non-Neoplastic	18	Sialadenosis(4)	02	Sialadenosis(2)	C
		Chronic Sialadenitis (9)	03	PA(1)	DC
				Sialadenosis(1)	DC
				Cellular PA(1)	DC
		Retention Cyst(4)	01	LG MEC(1)	DC
		Parotid Abscess(1)	---	---	---
III. AUS	03	Few Atypical Cells(2)	01	IG MEC(1)	DC
		Cystic Lesion with Few Atypical Cells (Mucocele Vs MEC)	01	LG MEC(1)	C
IVA. Neoplasm: Benign	22	Pleomorphic Adenoma(19)	12	Pleomorphic Adenoma(11)	C
				Adeoid Cystic Ca.(1)	DC
		Myoepithelioma(1)	01	Cellular PA(1)	DC
		Warthin Tumor(2)	01	Warthin Tumor(1)	C
IVB. Neoplasm:	01	Basaloid Neoplasm(1)	01	Adenoid Cystic Ca.(1)	C

SUMP					
V: Suspicious For Malignancy	01	Suspicious for Adenoid Cystic Carcinoma	01	Adenoid Cystic Ca.(1)	C
VI: Malignant	11	Adenoid Cystic Carcino-ma(2)	02	Adenoid Cystic Carcino-ma(1)	C
				Basal Cell Adenoma(1)	DC
		MEC(4)	03	LGMEC(2) IGMEC(1)	C
		Carcinoma Ex Pleo-morphic Adenoma(1)	01	Carcinoma Ex Pleomorphic Adenoma(1)	C
		Squamous Cell Carcino-ma(1)	0	----	
		Acinic Cell Carcinoma(2)	02	Acinic Cell Carcinoma(2)	C
		Adenocarcinoma(1)	01	Adenocarcinoma (1)	C
C- concordant DC - Discordant					

There was one false positive case in the malignant category i.e., the case of basal cell adenoma was over diagnosed as Adenoid cystic carcinoma. Among the 20 benign aspirates categorized as non-neoplastic and benign neoplasms with histologic follow-up, two cases were false-negative which included low grade mucoepidermoid carcinoma and adenoid cystic carcinoma. For the indeterminate categories, there were 2 cases in AUS and 1 case in SUMP, all of these cases turned out to be malignant.

Table 5: Performance of MSRSGC for Detecting Malignancy

	With Inclusion of AUS and SUMP %	**Without Inclusion of AUS and SUMP %**
Sensitivity	85.7	81.8
Specificity	94.73	94.73
Positive predictive rate	92.33	90
Negative predictive rate	90	90

To distinguish between benign and malignant, with or without inclusion of AUS and SUMP, the sensitivity, specificity, positive predictive rate and negative predictive rate are 85.7%, 94.73%, 92.33%, 90%, and 81.8%, 94.73%, 90%, 90% respectively.

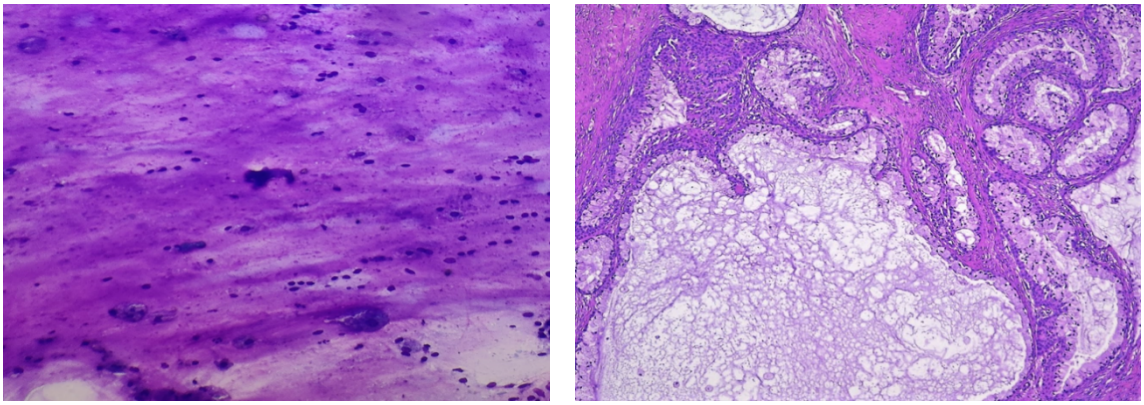

Figure 1 (a & b): Smear shows abundant thick Mucin, hence reported as Mucus Retention Cyst on Cytology (A, Diff Quik, 100x), which came out to be Low Grade Mucoepidermoid Carcinoma with extensive cystic areas, (B, H&E 100x)

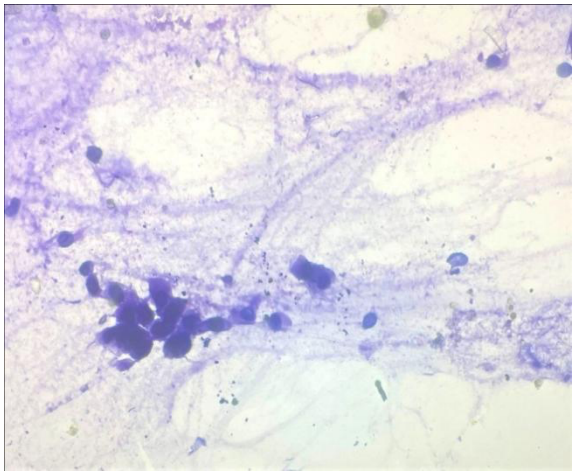

Figure 2A: Paucicellular cytosmear with mucinous background and few atypical looking cells, hence assigned the Category III:AUS (Diff Quik, 400x

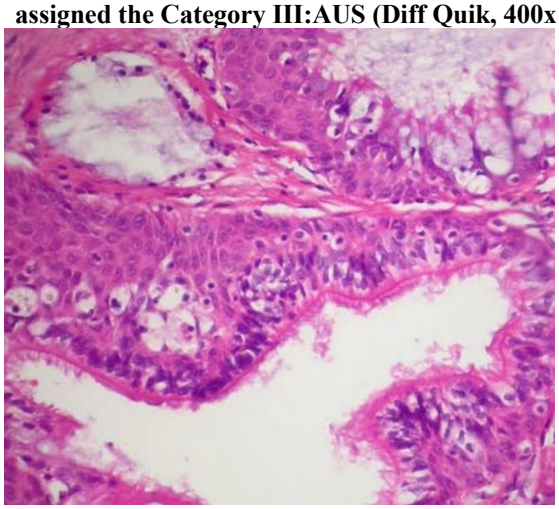

Figure 2B: After resection, this came out to be Low Grade Mucoepidermoid Carcinoma. (H&E, 400x)

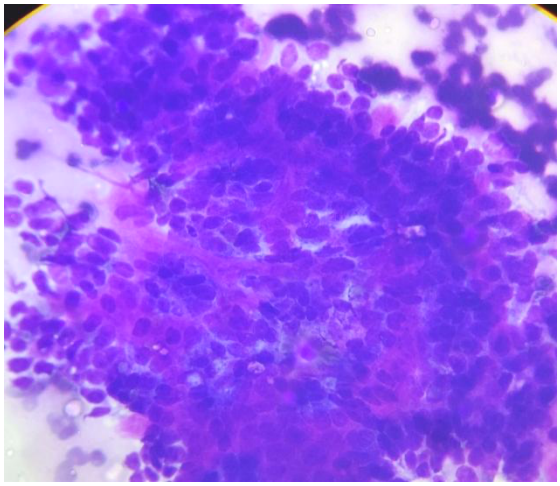

Figure 3A: Clusters of basaloid cells with scant matrix material were seen on the cytosmear and was reported as "Basaloid Neoplasm" – Category IVB: SUMP. (Diff Quik, 400x)

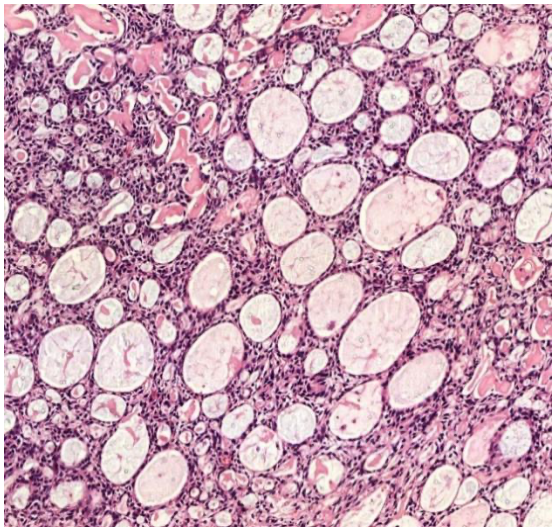

Figure 3B: Characteristic 'swiss cheese' cribriform pattern of Adenoid Cystic Carcinoma was seen on histology (H&E, 100x)

Discussion

Fine needle aspiration cytology has been widely accepted as a first-line initial diagnostic tool among clinicians due to its ease of performance and rapid diagnosis. [6] However, cytomorphological interpretation can be challenging when dealing with tumors showing diverse morphology, metaplasia and cystic changes. MSRSGC is a newer system for reporting salivary gland lesions with the objective of providing a better communication between clinicians and cytopathologists so as to improve overall patient management. It is an evidence-based six-tiered system, that provides ROM and clinical management strategies for each category. It classified FNAC into six categories: non-diagnostic, non-neoplastic, atypia of uncertain significance, neoplastic-benign, neoplastic- salivary gland neoplasm of uncertain malignant potential (SUMP), Suspicious of malignancy, and malignant with ROMs of 25%, 10%, 20%, 5%, 35%, 60%, and 90% for each category. [7] In our study, the salivary gland lesions were also classified into the above-mentioned categories and histological follow-up was done wherever available. In order to support the available published data of the MSRSGC and to report our institutional experience, we tried to assess the accuracy of salivary gland FNAC over a period of three years, re-classified the cytological materials based on the criteria of the MSRSGC, and calculated ROM for each category.

In the present study, there was a slight male preponderance (M:F = 1.28:1), the mean age group was 44.2 years, most of the cases belonged to the 4th and 5th decade which was comparable to most of the studies carried out in India like Rohilla et al., Kala et al., and Gaikwad et al. [8,9,10] This finding was in contrast to studies done worldwide, where the mean age group was on the higher side, i.e. in the 6th decade [11,12,13-15] which may be due to their better health care facilities. In our study, the parotid was the most common salivary gland involved (80.7%) followed by the submandibular gland (19.3%), which is similar to most of the studies like Sharma et al., Singh et al., and Kala et al. [16,17]

MSRSGC recommends a minimum of 60 lesional cells as an adequacy criterion. [18,19] In the present study, the non-diagnostic category (category I) has been assigned to a salivary gland aspirate with very low cellularity (1.78%), not meeting the adequacy criterion suggested by MSRSGC. There was no histopathologic follow-up available for this case. This can be due to the small size of the lesion, its deep location or dense fibrosis or sclerosis in the lesion. Maleki et al. studied submandibular gland lesions with 21.4% of the cases in the non-diagnostic category. The reason behind this were the cases of chronic sclerosing sialadenitis (Kuttner tumour) which is more common in the submandibular gland and the aspirates from these lesions are often paucicellular and difficult to yield. [20] Vaithy K. et al. have 2.6% cases in this category which on histopathologic follow-up were reported as chronic sialadenitis and myoepithelioma. [21] The diagnosis of chronic sialadenitis was missed on cytology because of fibrosis and loss of acini and myoepithelioma due to the acellular aspirate from the cystic areas of the lesion during FNAC. To overcome inadequate aspiration, several studies have suggested that the ROSE (Rapid On-Site Evaluation) technique can be useful in reducing the number of passes used to get an adequate sample. It has been seen that the ROSE technique can also reduce turnaround time and cost. [22,23,24] But the most important disadvantage of this technique is the need for an efficient on-site expert. [25]

Another important diagnostic pitfall is the cystic salivary gland lesions that range from non-neoplastic lesions like simple retention cysts to benign tumours such as warthin tumours and malignant tumours like mucoepidermoid carcinoma. Studies have suggested that diagnostic yield can be increased by reaspiration and radiological guidance [26,27] In the present study, two of the cystic lesions of mucoepidermoid carcinoma were wrongly placed in MSRSGC categories II and III based on their cytology diagnosis. One of these cases was categorized as AUS (category III) according to the Milan system due to the presence of a few atypical cells. The abundant mucinous fluid aspirate from the other cystic lesion, even after repeated aspirations, made us place this in the non-neoplastic category (category II).

A total of 18/57 cases (31.58%) were classified as Non-neoplastic (category II), and chronic sialadenitis (44.4%) was the most common cytological diagnosis in this category. The cases revealed benign clusters of ductal cells with scant acinar cells against a background of lymphocytes. Similar results were obtained in the studies done by Singh et al., Kala et al. and Karuna et al. [28] In the present study, 6 cases of category II had histopathological follow-up, of which 3 cases that had been reported as chronic sialadenitis on cytology turned out to be pleomorphic adenoma, cellular pleomorphic adenoma and sialadenosis. One case of retention cyst came out to be a low grade mucoepidermoid carcinoma. The calculated ROM for this category was 16.67% which is slightly higher than the ROM of 10% proposed by the MSRSGC**,** 5% by Kala et al., 7.1% by Vishwanathan et al., 11.1% by Katta et al., and 11.8% by Hafez et al. [29] Rohilla et al. reported a relatively higher ROM of 17.4%.

In the category of AUS (category III) 5.26% of cases were included, whose aspirates were hypocellular with limited atypia, so it could not be ascertained whether they were non-neoplastic or a neoplastic process. Two cases were followed up for biopsy and both were reported as mucoepidermoid carcinoma, thus, the ROM for this category was 100% which is much higher than that recommended by the MSRSGC (20%)**,** but in concordance with the studies by Katta et al. and Rohilla et al. The extremes of findings are likely because of the low number of cases and inadequate histopathologic follow-up. Low-grade mucoepidermoid carcinoma always poses a diagnostic difficulty due to its low cellularity, lack of cytologic atypia and abundant mucinous background along with inflammatory cells, thus causing significant morphological overlap with other cystic lesions and leading to a false negative diagnosis. The inclusion of such cases in the AUS category will definitely decrease the number of false-negative cases. [30]

The benign neoplasm category (category IVA) had 22 (38.6%) cases in our study, and histological follow up was available in 14 cases. PA followed by Warthin tumor, was the most common diagnosis in this category. This was similar to the studies by Kala et al., Singh et al., and Karuna et al. PA usually reveals metachromatic fibrillary chondromyxoid stroma with frayed margins in the background with clusters of round to plasmacytoid epithelial cells, thus rendering an easy diagnosis. Warthin tumor, however, shows abundant lymphoid cells accompanied by oncocytic cells in a thin, dirty to mucoid background. This category has been found to have a higher diagnostic accuracy according to various reported studies. However, in a few cases, differentiating between benign and low-grade malignant neoplasms may be difficult. This is due to the overlapping morphological features and heterogeneity of these tumors. In our study, two cases from this category were discordant on histological follow-up. One case turned out to be adenoid cystic carcinoma (false negative), which revealed myxoid material with ductal cells. Typical hyaline globules were, however, not seen, hence the diagnosis of pleomorphic adenoma on cytology. Similarly, Rohilla et al. found two cases of MEC and one case of oncocytic carcinoma as false negatives in category IVA. Another case was misinterpreted as myoepithelioma in our work, which had abundant plasmacytoid and spindle shaped cells and a lack of extra fibrillary matrix. This led to a false diagnosis of PA. The ROM of this category is expected to be low, less than 5 percent as reported by Rossi et al. (1), and these cases are managed by conservative surgical resection or follow-up in few cases. But in our study, the ROM was found to be 7.14% and was concordant with various studies that reported the ROM to be 0%–13%. [31]

In spite of the adequacy of cytological smears, a definitive diagnosis is not possible in some cases, even in experienced hands. So these indeterminate cytological interpretations fall into the MSRSGC categories of “AUS” (category III), “SUMP” (category IVB), and “suspicious for malignancy” (category V). The category SUMP includes smears that are certainly classified as neoplasms based on their cytomorphologic features, but a clear differentiation between benign and malignant cannot be made. Surgical resection is used to identify the invasive nature of neoplasms and verify malignancy. In the present work, only one case (1.75%) each was included in categories IVB (SUMP) and V (suspicious for malignancy) which is less than that of studies by Karuna et al., Katta et al. and Pukhrambam et al. [32] The case of the SUMP category in this study yielded a cellular

aspirate with sheets and clusters of basaloid cells and scant matrix, the cells were larger in size but had bland nuclear features. After careful examination of all the cytosmears, a few clusters showed nuclei with a high N:C ratio, hyperchromasia and anisonucleosis. Hence, the cytologic diagnosis of 'basaloid neoplasm' was rendered for this particular case and the post-operative histopathologic diagnosis was adenoid cystic carcinoma. Another case with basaoid cells and hyaline matrix, some foci with hyaline globules, had unclear cellular features due to the overlapping blood elements. Therefore, it was classified under category V reported as 'suspicious of adenoid cystic carcinoma' and confirmed after histological evaluation. The ROM was 100% for both categories IVB and V, which is similar to that calculated by Gaikwad et al. and Manju Kumari et al. [33] Our results were greater than those proposed by MSRSGC (35% and 60% respectively). This can be explained by the fact that each category had only one case that, on histopathologic follow-up came out to be malignant.

Category VI (malignant) consists of cases with diagnostic features of malignancy. The aim of introducing this category is to subclassify tumors, especially low-grade and high grade, because the approaches to management of these cases are different. In our study, it comprised a total of 11 (19.3%) cases with histological follow-up available in nine of them. Mucoepidermoid carcinoma with 4 (36.36%) cases, was found to be the most common diagnosis. This finding was in concordance with studies by Rohilla et al., Katta et al. and Manju Kumari et al**.** 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 the cystic component vary according to the differentiation of the tumor.

Cytological smears of adenoid cystic carcinoma may show variable cellularity of small basaloid cells depending on the histological subtypes of this tumor. However, a case of basal cell adenoma was overdiagnosed as adenoid cystic carcinoma (false positive) due to increased cellularity and the presence of hyaline globules in some places. The calculated risk of malignancy for this category was 88.9% which was slightly lower than the ROM of 90% as per MSRSGC and various other studies with ROM ranging from 87% to 100%.

Table 4: Comparison of Risk of Malignancy (ROM %) among Various Studies Conducted Between 2017-2021

Authors	I (%)	II (%)	III (%)	IVA (%)	IVB (%)	V (%)	VI (%)
MSRSGC	25	10	20	<5	35	60	90
Hafez et al.	33.3	11.8	37.5	2.1	44.4	60	100
Vishwanathan et al.	6.7	7.1	38.9	5	34.2	92.9	92.3
Karuna et al.	0	0	50	2.44	33.33	100	93.33
Kala et al.	25	5	20	4.4	33.3	85.7	97.5
Katta et al.	33.33	11.1	100	6.9	50	66.6	87.5
Rohilla et al.	0	17.4	100	7.3	50	-	96
Gaikwad et al.	-	0	50	0	100	100	100
Vaithy K et al.	0	3.84	0	0	0	0	78.2
Manju Kumari et al.	20	14.3	100	4.2	100	83.33	100
Amita et al.	-	6.25	100	0	25	100	100
Present study	-	16.67	100	7.14	100	100	88.9

The ROM acts as a guide for treating physicians on the possible malignant outcome so that further management strategies can be planned out. According to different previous studies, the sensitivity of FNA varies from 54% to 98% with high specificity values of 88% to 99% for distinguishing benign lesions from malignant lesions. Similarly, in the present study, the sensitivity was 85.7%, and the specificity was 94.73%, positive predictive rate and negative predictive rate were 92.3% and 90% respectively. FNA accurately discerns the neoplastic nature of the lesion in most cases. However, the exact categorization may be difficult because of the overlapping morphological features and significant cytomorphological heterogeneity within the same cell of origin.

Authors	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Karuna et al.	85	98.14	94.44	94.64
Kala et al.	83.3	98.3	95.7	92.8
Katta et al.	73.34	95.56	84.62	91.49
Manju Kumari et al.	78.57	98.84	97.06	90.43
Gaikwad et al	75	100	100	92.8

Rohilla et al	79.4	98.3	96.4	89.2
Vaithy K et al.	84.2	98.21	94.64	91.70
Present study	85.7	94.73	92.33	90

Conclusion

Though, fine needle aspiration cytology has been observed to be a simple, quick and inexpensive procedure with a high degree of accuracy in the hands of experienced cytopathologists, it has many limitations, especially when dealing with some cystic lesions and some lesions with extensive fibrosis or necrosis. In some cases, the exact diagnosis cannot be ascertained. As a result, the cytopathologists tend to give a descriptive report which is often difficult for the clinicians to understand, and there is a lack of clarity in the management guidance. The Milan system for reporting salivary gland cytopathology helps in standardisation of terminologies for reporting FNAC of salivary glands and improves communication between clinicians and pathologists. It also provides the estimated risk of malignancy and clinical management recommendations for each category. The classification of the cytological diagnoses according to Milan system has reduced the number of false negative and false positive cases, thus making fine needle aspiration cytology a more sensitive and specific technique for evaluation of salivary gland cytopathology. The high sensitivity, specificity, positive predictive value, and negative predictive value of FNAC when reported according to "The Milan System for reporting salivary gland cytopathology" confirm that preoperative cytology is a quick and reliable diagnostic technique for rapid and early diagnosis and we also conclude that it is a simple and cost-effective tool suitable for developing countries like India.

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