Cyto-Histological Correlation Of Salivary Gland Lesions According To The Milan Reporting System

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Abstract

Objective: The objective of this study is to correlate FNAC (Fine Needle Aspiration Cytology) outcomes according to the Milan System for Reporting Salivary Gland Cytology (MSRSGC) with histopathological findings of salivary gland lesions, taking as the gold standard.

Methods: This Descriptive Retrospective study was conducted at a private laboratory in Faisalabad from January 2017 to December 2022. The cytology cases were categorized based on the Milan Salivary Gland Cytology Reporting System (MSRSGC): nondiagnostic, non-neoplastic, benign, or, salivary gland tumor of unknown malignant potential (SUMP), suspicious for malignancy, or malignant. The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of FNAC were calculated. The data was analyzed using SPSS 24 taking a P value < 0.05 as significant.

Results: The most common salivary gland was the parotid gland in 61.9 % of cases. According to the Milan system, the majority of cases were classified as benign category IVa (58.1%), followed by cases in categories II, V, and VI (14.9%, 6.8%, and 12.2%) respectively. The diagnostic accuracy of FNAC was determined to be 95.2% compared to the final histopathological diagnosis. Correspondingly, the associated risk of malignancy for these categories was 0%, 30%, 0%, 30%, 100%, and 100%, respectively.

Conclusion: These findings showed the significant contribution of MSRSGC in accurately diagnosing malignant lesions, aiding clinicians in making well-informed decisions regarding specific treatment strategies.

MeSH Keywords: Fine needle aspiration,histopathology, salivary glands.

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1. Introduction

Salivary gland lesions constitute less than 3% of all head and neck tumours, impacting both major and minor exocrine glands. Various factors, including infection, inflammation, cystic lesions, degenerative processes, obstructions, and both benign and malignant neoplasms, can give rise to salivary gland nodules or metastases.[1,3] Fine needle aspiration cytology (FNAC) plays a pivotal role in the initial assessment of these lesions. However, the intricate and heterogeneous nature of salivary gland tumours, along with cytological similarities between different types and potential complications in FNAC, often pose challenges for accurate diagnosis.[2,5]

Compounding the issue is the absence of a standardized, evidence-based reporting system, leading to cytological reports lacking specific diagnoses. This creates difficulties for treating clinicians in terms of interpretation and planning management.[10,11] To address this gap, the Milan System for Reporting Salivary Cytopathology (MSRSGC) was introduced in 2015 by an international task force comprising cytopathologists, surgical pathologists, and head and neck surgeons. Endorsed by the American Society of Cytopathology and the International Academy of Cytology [10], MSRSGC aims to standardize reporting, enhance communication, and ultimately improve patient care. The system categorizes lesions into six classes: non-diagnostic (category I), non-neoplastic (category II), atypia of undetermined significance (category III), benign neoplasm (category IVa), salivary gland neoplasm; potentially harmful (SUMP) (category IVb), suspected harmful (category V), and harmful (category VI). Each category includes a risk of morbidity (ROM) and provides clinical management recommendations.[11,12]

This study aims to comprehensively review the cytopathological spectrum of salivary gland lesions using the Milan system for reporting, with a particular emphasis on elucidating the role and utility of this

reporting system in the clinical management of salivary gland lesions.

2. Materials & Methods

Our study included cases from January 2017 to December 2022, conducted at a regional laboratory, prospectively. We assessed cytology aspirates from salivary gland lesions in individuals of both genders. Demographic details, including age, gender, lesion location, and duration, were systematically recorded. The cytology cases without subsequent histopathology were excluded from the study. Fine-needle aspiration cytology (FNAC) was performed using a 22-24-gauge needle. To check the cellularity, a Diff Quick stain was applied. If found inadequate, the procedure was repeated, until a satisfactory aspirate was achieved. Thereby, Giemsa and Papanicolaou's stains were applied to the aspirates, with clotted specimens undergoing histological analysis when the material was available. Cytology cases were reviewed and categorized according to the Milan System for Salivary Gland Cytology (MSRSGC), comprising non-diagnostic, non-neoplastic, atypia of undetermined significance (AUS), neoplasm (benign or salivary gland neoplasm of uncertain malignant potential - SUMP), suspicious for malignancy, and malignant. Correlation with subsequent biopsy histopathology, considered the gold standard, was conducted whenever available. The study evaluated sensitivity, specificity, positive predictive value, and negative predictive value. Additionally, a rate of malignancy (ROM) was calculated for each diagnostic category. The Ethics Committee (IEC) approved the study.

3. Results

This study evaluated a total of 138 salivary gland FNAC cases, however out of these only 74 cases, whose biopsy was received at our centre were included in our study. These cases included 32 (43.2%) women and 42 (56.8%) men with a mean age of 42 years. The right side was more affected (n=39, 52.7%) than the left side (n=35, 47.3%). According to the Milan system, the majority of cases were classified as benign category IVa (n= 43, 58.1%), followed by non-neoplastic (Cat. II) which is 14.9% (11 cases), No case was seen in Category I (Inadequate), since we used Diff-Quick stain and repeated all inadequate smears, until cellularity was

achieved. Malignant cases in categories V and VI accounted for 14 cases (19%) as shown in Table 1.

Table 1: Frequencies of Milan Categories

Frequencies of Milan Categories	Frequency	%
II (Non-Neoplastic)	11	14.9
III (Atypia of Undetermined Significance)	3	4.1
IV-a (Benign Neoplasm)	43	58.1
IV-b (Salivary gland neoplasm of Uncertain Malignant Potential)	3	4.1
V (Suspicious for Malignancy)	5	6.8
VI (Malignant)	9	12.2
Total	74	100.0

Histopathological findings revealed a variety of lesions with pleomorphic adenoma being the most common (n= 42, 56.8%). The second most common was Mucoepidermoid carcinoma which was 7 cases (9.5%). Other malignant tumours included "Acinic Cell Carcinoma," "Adenoid Cystic Carcinoma," "Carcinoma ex pleomorphic adenoma" and "Metastatic carcinoma" each accounting for 2 cases (2.7%), as shown in Table 3. FNAC and histological pictures of some of these cases are shown in Fig.1 A-E.

Lesions were distributed throughout the salivary glands, with most cases (68.9%) in the parotid gland, while 5 cases (6.8%) from other sites i.e. upper lip (1), palate(2), postauricular (1) and sub-auricular(1) area. (Table 2).

Table 2. Frequency of salivary gland lesion distribution.

	Frequency	Percent%
Parotid gland	51	68.9
Submandibular	17	23.0
Sublingual	1	1.4
Other sites	5	6.8
Total	74	100.0

The city-histopathological correlation according to the Milan categories showed 11 cases in category II (non-neoplastic); one case initially diagnosed as acute sialadenitis via FNAC was subsequently identified as granulation tissue. Another case in the same category revealed a benign epithelial cyst on FNAC, later confirmed as a mucous retention cyst on histopathology, while most of the cases (5) were diagnosed as chronic sialadenitis on both FNAC and histopathology.

Table 3. Cyto-histopathological Correlation with Categories of MILAN System

Milan Category	No. of Cases	Primary FNAC Diagnosis	No. of Cases	No of HPE Cases	HPE Finding
I (Non-Diagnostic)	0				
II (Non-Neoplastic)	11	Acute sialadenitis Chronic Sialadenitis	1 4	11	Granulation tissue Sialadenitis lymphoepithelial cyst
		Benign epithelial cyst Branchial cyst other	1 3 2		Retention cyst Branchial cyst Thyroglossal cyst
III (AUS)	3	Spindle cell lesion	2	02	Schwannoma
		Atypia of Undetermined Significance	1	1	Mucoepidermoid CA
IV-a (Benign Neoplasm)	43	Pleomorphic Adenoma Warthins tumor	40 03	43	Pleomorphic adenoma Warthins tumor
IV-b (SUMP)	3	Salivary Gland Neoplasm	02	02	Pleomorphic Adenoma
		Salivary gland neoplasm	01	01	Acinic cell carcinoma
V (SM)	5	High-grade salivary gland Neoplasm	02	5	High-grade salivary duct CA Adenoid cystic carcinoma Acinic cell carcinoma
		Suspicious for malignancy	03		Carcinoma ex pleomorphic adenoma
VI (Malignancy)	9	Malignant	9	9	Adenoid cystic carcinoma Mucoepidermoid carcinoma Metastatic carcinoma
Total	74		74	74	

P value: 0.000, Pearson Chi-square: 194.673

Note: FNAC - Fine Needle Aspiration Cytology; HPE - Histopathological Examination; AUS - Atypia of Undetermined Significance; SUMP - Salivary Gland Tumor of Uncertain Malignant Potential; SM - Suspicious for Malignancy.
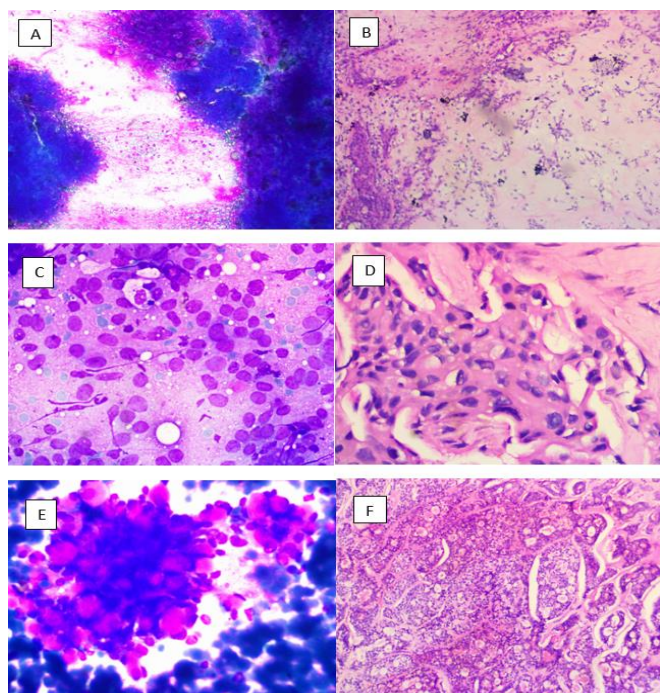

Figure-1: A) FNAC of Pleomorphic adenoma; Diff Quick stain 10x, B) Biopsy of Pleomorphic adenoma; H& E stain10x, C) FNAC of Mucoepidermoid carcinoma; Giemsa stain 20x, D) Biopsy of Mucoepidermoid Carcinoma, H& E stain 20x, E) FNAC of Adenoid cystic carcinoma, Giemsa stain 40X, F) Biopsy of Adenoid cystic carcinoma; H& E stain 10X.

Within the three cases falling into category III (AUS - Atypia of Undetermined Significance), two cases were later confirmed as a Schwannoma, while 3rd case proved to be "Mucoepidermoid carcinoma, low grade" on subsequent histopathology. Histopathological examination of the biggest category IV a (Benign) had 43 cases, which were confirmed on subsequent histopathology to be 40 cases of pleomorphic adenomas, 2 cases of Warthin's tumour and 1 case of Neurofibroma. Five (5) cases classified as category V (suspicious for malignancy), were all confirmed to be malignancy of one type or other. The last category VI (malignant) included 9 cases, which were also proved to be malignant on histopathology with 5 cases of "Mucoepidermoid carcinoma, 2 cases of metastatic carcinoma, 1 case of "Salivary duct carcinoma" and 1 case of "Carcinoma ex pleomorphic adenoma", as shown in Table 3. The P value of FNAC to differentiate and diagnose salivary gland tumours was 0.000 which is highly significant.

Overall, fine needle aspiration cytology (FNAC) demonstrated a sensitivity of 95.2% and a specificity of 71.7%. The positive predictive value is 77.6%, and the negative predictive value is 93.5%. The diagnostic accuracy of FNAC was determined to be 83.6% compared to the final histopathological diagnosis.

The distribution of cases based on Milan categories was as follows: 14.9%, 4.1%, 58.1%, 4.1%, 6.8%, and 12.2% for Milan categories II, III, IVa, IVb, V, and VI, respectively. Correspondingly, the associated risk of malignancy for these categories was 0%, 30%, 0%, 30%, 100%, and 100%, respectively.

4. Discussion

FNAC (Fine Needle Aspiration Cytology) has been extensively employed as an initial assessment and triage tool for patients presenting with salivary gland lesions.[2-4] The MSRSGC (Milan System for Reporting Salivary Gland Cytopathology) represents a sophisticated framework for categorizing salivary gland lesions based on risk levels, aiming to enhance communication between clinicians and cytopathologists, ultimately elevating the standard of patient care. An additional benefit of this system lies in its capacity to assess the risk of malignancy and support reproducibility.[11,12] In the context of this study, 74 cases were categorized using the Milan system, and these classifications were subsequently correlated with histopathological findings. In our study, there were 42 males (56.8%) and 32 females (43.2%), aligning closely with the demographics reported in several other published studies.[1-9,11] The mean age in our study was 42.11 years, ranging from 2 to 78 years. This is in concordance with the study done by Naz S et al, the mean age of patients was 42 (±21) years while on the contrary male to female ratio was 1:1.[16] These findings are also consistent with research conducted by Datta B et al, where 57 salivary gland lesions were examined, revealing that 54.38% were males and 45.6% were females, with a median age of 34 years (range 6-70 years). Similar results were observed by Tabassum M et al.[1,5,16] AlGhamdi G Z et al, who assessed 37 salivary gland lesions, reported slight female predominance, 20 female and 17 male patients and the mean age group of patients was in the range of 30-40 years (30%).[2]

In our study, the parotid gland emerged as the most commonly affected site, accounting for 69.9%, with the submandibular gland following at 23%. These observations align with findings from other literature, as highlighted by Anuj Poudel et al, who reported a predominant involvement of the parotid gland at a frequency of 66.7% in their studies.[1,3,9]

In our study, 11 cases were classified under MSRSGC category II (non-neoplastic), constituting 14.9% of the total cases. One study by Isgor IS et al reported a non-neoplastic category prevalence of 3.5% while the distribution of non-neoplastic cases was higher in studies conducted by Pahwa S (26.3%), S. Bhat A. (13.8%), Mishra S et al (55.4%), Rohilla et al (55.8%), and Datta B et al (24.6%).[1,10,11,12,14] The reason for this diversity may be related to selections of cases or demographic differences.

Category III AUS (Atypia of Undetermined Significance) is designated for lesions displaying morphologic characteristics that overlap between non-neoplastic and neoplastic cases. According to MSRSGC, the preference is to keep the number of cases classified as AUS below 10%.[1] In our study, the AUS category comprised 4.1% of the cases, a figure comparable to other research findings, such as Datta B et al (7%), S. Bhat A (2.3%), Pahwa S (4.7%), and Isgor IS et al (10.5%).[1,12,14,15] It is important to note that one case in our study initially presented only mucinous contents without epithelial cells, later revealed to be Mucoepidermoid carcinoma upon histopathological examination. Two other cases, identified as a spindle cell lesion through cytology, were confirmed as Schwannoma through histopathology. In the study conducted by Isgor IS et all, three out of nine total cases (33.3%) in the AUS category were pleomorphic adenomas and the rest were lymphomas.[15]

In our study, the benign category IVa had the highest percentage, accounting for 58.1%. This is consistent with similar findings reported in published literature, such as the study conducted by Anuj Poudel and Neera JA et al, where pleomorphic adenoma (PA) was the most prevalent salivary gland neoplasm, with a frequency of 51.84%.[3, 4, 5, 6, 16, 17] 40 cases diagnosed in our study as category IVa were subsequently confirmed as pleomorphic adenoma upon histopathological follow-up, while 2 cases were diagnosed as Warthins tumour and 1 case as Nuerofibroma. Category IVb, designated as SUMP (Salivary Gland Neoplasm of Uncertain Malignant Potential), is reserved for salivary gland FNAs exhibiting morphologic features suggestive of a neoplastic process, but with a differential diagnosis encompassing both benign and malignant entities.[1] In our study, the percentage of cases falling into the IVb category was 4.1%, aligning with results from other studies, such as Pahwa et al (3.5%), S. Bhat A. (9.2%), and Mishra S et al (1.7%).[11,12,14] It's noteworthy that 2 cases were initially reported as a salivary gland neoplasm with a differential diagnosis of Pleomorphic

adenoma versus Adenoid cystic carcinoma, but the histopathological follow-up confirmed it as pleomorphic adenoma. There were myxoid matrix, hyaline globules, and tumour cells with clear cytoplasm. Another case, initially categorized as SUMP based on MSRSGC due to the presence of foam cells, and salivary gland acini, was later confirmed as Acinic cell carcinoma upon histopathological follow-up.

Category V, suspicious for malignancy (SM) is reserved for salivary gland FNACs where overall cytologic features suggest malignancy, but the specific criteria for a definitive malignant diagnosis are not fully met. In our study, the percentage of cases falling into the SM category was 6.8%, consistent with findings from various studies,[11,12,14] although a slightly higher percentage of cases 11.7% reported by Isgor IS et al.[15] There were 5 cases in category V, all of these cases proved to be malignant on subsequent histopathology. Out of these 2 cases were proved to be Adenoid cystic carcinoma, 1 case each of Mucoepidermoid carcinoma, Acinic cell carcinoma and Carcinoma ex pleomorphic adenoma.

The overall percentage of cases categorized as MSRSGC Category VI malignant in our study was 12.2%, a little higher than other studies,[12,14,15] but comparable to 12.6% reported by Mishra S et al.[11] One case was frankly malignant, diagnosed as high-grade salivary gland neoplasm, later confirmed as High-grade salivary duct carcinoma. The most common cases in this category were Mucoepidermoid carcinoma, which in literature is also reported as the most common malignancy of salivary glands.[11,12,15]

Our study's reported risk of malignancy for each category was 0%, 30%, 0%, 30%, 100%, and 100%, respectively, aligning with MSRSGC and recent studies.[10,12,13] The overall diagnostic accuracy of cytologic reporting for salivary gland lesions using Milan nomenclature in our institution was 83.6%, comparable to other studies with accuracy ranging from 80.1% to 96.9%. Sensitivity, specificity, positive predictive value, and negative predictive value for malignant diagnoses in our study were 95.2%, 71.7%, 77.6%, and 93.5%, respectively.[13,16,17] These figures were in line with comparable studies. The slightly lower sensitivity in our study might be attributed to the lower incidence of malignant cases in our patient population. Nonetheless, our findings underscore the positive impact of MSRSGC in accurately identifying malignant lesions, aiding clinicians in making informed management decisions.

It is essential to acknowledge several limitations in this series, inherent to retrospective analysis, including a low sample size and fewer histopathological follow-ups.

5. Conclusion

This study showed 83.6% diagnostic accuracy using the Milan System for Reporting Salivary Gland Cytopathology. This system facilitated in accurately identifying malignant lesions, guiding clinicians in management decisions. Salivary gland fine-needle aspiration maintains high diagnostic precision, especially in challenging cases, offering valuable risk stratification for improved patient management.

INSTITUTIONAL REVIEW BOARD

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CONFLICTS OF INTEREST- None

References

1. Datta B, Daimary M, Bordoloi K, Thakuria C, Cytopathological Spectrum of Salivary Gland Lesions According to Milan Reporting System: A Retrospective Study, VOL 8 NO 3 (2023),DOI 10.31557/APJCC.2023.8.3.465-470.
2. AlGhamdi G Z, Alzahrani A K, Saati H, Correlation Between Fine Needle Aspiration Cytology (FNAC) and Permanent Histopathology Results in Salivary Gland Masses. Cureus. March 18, 2021.13(3): e13976. doi:10.7759/cureus.13976.
3. Anuj Poudel, Bigya Shrestha & Sudeep Regmi .Evaluation of Salivary Gland Lesions by Fine Needle Aspiration Cytology at a Tertiary Care Hospital, Western Nepal, Pathology and Laboratory Medicine International,2020;12: 9-17, DOI: 10.2147/PLMI.S266866.
4. Neera JA P, Kalavathi CL, Reedy CB. A Study Of Spectrum Of Neoplastic and Non-Neoplastic Lesions Of Salivary Gland And Their Cytological Correlation With Histopathology. Asian J Pharm Clin Res [Internet]. 2023 May 7 [cited 2024 Jul. 18];16(5):84-8. Available from:

https://journals.innovareacademics.in/index.php/ajpcr/article/view/47896

5. Tabassum M, Deka MK, Khakhlari NM. Correlation of fine needle aspiration cytology and histopathology in the diagnosis of salivary gland lesions in a tertiary care hospital in the Southern part of Assam: a 2 year observational study. Int J Res Med Sci [Internet]. 2019 Dec. 25 ;8(1):226-9. https://doi.org/10.18203/2320-6012.ijrms20195912. https://www.msjonline.org/index.php/ijrms/article/view/7456

6. Dharwadkar A, Paul B, Buch A, Agarwal N, Naik M, Gore C. Cytological Study of Salivary Gland Lesions along with Histopathological Correlation in a Tertiary Care Centre. International Journal of Scientific Research in Dental and Medical Sciences, 2022; 4(3): 101-109. doi: 10.30485/ijsrdms.2022.349695.1328.

7. Negi S, Mardi K, Sood S, Gupta N, Mohindroo NK, Kumar M, et al. Cyto-histological correlation of salivary gland lesions- a prospective study in a tertiary care institute. Int J Res Med Sci. 2022;10:425-30. https://doi.org/10.18203/2320-6012.ijrms20220286

8. Omhare A, Singh SK, Nigam JS, Sharma A. (2013). Cytohistopathological Study of Salivary Gland Lesions in Bundelkhand Region, Uttar Pradesh, India. Pathology Research International, 2014(1), 804265. https://doi.org/10.1155/2014/804265

9. Rohilla M, Singh P, Rajwanshi A, Gupta N, Srinivasan R, Dey P, Vashishta RK. Three-year cytohistological correlation of salivary gland FNA cytology at a tertiary center with the application of the Milan system for risk stratification. Cancer Cytopathol. 2017 Oct;125(10):767-775. doi: 10.1002/cncy.21900. Epub 2017 Aug 7. PMID: 28786207.

10. Mishra S, Ray S, Sengupta M, Sengupta A. A cytohistological correlation in salivary gland swelling with special reference to the proposed Milan system. Indian J Pathol Microbiology. 2019;62:379-83. https://doi.org/10.4103/ijpm.ijpm_662_17

11. S. Bhat A, Alisha M. A two-year study on fine needle aspiration cytology of salivary gland lesions with cytohistologic correlation and application of the Milan system. Biomedicine. 2023 Aug. 30;43(4):1291-5. https://biomedicineonline.org/index.php/home/article/view/2903. https://doi.org/10.51248/.v43i4.2903

12. Karuna V, Gupta P, Rathi M, Grover K, Nigam JS, Verma, N. Effectuation to cognize malignancy risk and accuracy of fine needle aspiration cytology in salivary gland using "Milan System for reporting salivary gland cytopathology. ": A 2-year retrospective study in academic institution. Indian J Pathology Microbiology. 2019;62:11-16. https://doi.org/10.4103/ijpm.ijpm_380_18

13. Pahwa S, Panjwani P, Gnanapriya V. Reclassification of Salivary Gland Aspirates Based on "The Milan System for Reporting Salivary Gland Cytology": A Five-Year Retrospective Study. J Cytol. 2022 Jul-Sep;39(3):98-104. doi: 10.4103/joc.joc_106_21. Epub 2022 Aug 2. PMID: 36277807; PMCID: PMC9585809.

14. Isgor IS, Ercetin SY, Enver N, Cinel L. Histopathological Review of Diagnostic Categories of the Milan System for Reporting Salivary Gland Cytopathology - An Institutional Experience of 6 Years. J Cytol. 2021 Oct-Dec;38(4):203-209.

doi: 10.4103/JOC.JOC_193_20. Epub 2021 Nov 12. PMID: 35002113; PMCID: PMC8670457

15. Naz S, Hashmi AA, Khurshid A, Faridi N, Edhi MM, Kamal A, Khan M. Diagnostic role of fine needle aspiration cytology (FNAC) in the evaluation of salivary gland swelling: an institutional experience. BMC Res Notes. 2015 Mar 27;8:101. doi: 10.1186/s13104-015-1048-5. PMID: 25879702; PMCID: PMC4381422.

16. Ali, N., Nawaz, A., Rajput, S., Ikram, M. (2010). Parotidectomy: A review of 112 patients treated at a teaching hospital in Pakistan. Asian Pacific Journal of Cancer Prevention ; 11(4): 1111-3. https://ecommons.aku.edu/pakistan_fhs_mc_surg_otolaryngol_head_neck/30.