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Original Article

Pathology Section

Milan System for Reporting Salivary Gland Cytopathology- An overview with Interobserver Variability and Clinicoradiological Concordance

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ABSTRACT

Introduction: Salivary gland lesions are one of the most heterogenous lesions with overlapping features between low grade malignancy and benign lesions thus making them one of the most difficult areas for diagnosing. Cytology of salivary gland lesions plays an extremely important part in diagnosing the lesions and categorising them into non neoplastic, benign and malignant neoplasms, thereby allowing the patients and clinicians to make an accurate decision regarding whether the lesion is followed, biopsied, excised or a radical operation might be needed.

Aim: To classify salivary gland lesions according to MILAN System for Reporting Salivary Gland Cytopathology (MSRSGC).

Materials and Methods: This observational study was conducted from June 2021 to May 2022 where Fine Neddle Aspiration Cytology (FNAC) of salivary gland lumps was done on patients presenting to the Department of Pathology Rohilkhand Medical College and Hospital, Bareilly. The clinical and radiological features were noted. The cases were diagnosed on conventional cytopathology. Additionally categorisation as per MILAN System was done by two pathologists independently. The results were compared with histopathology, where available. Data was collected, entered and compiled in Microsoft excel followed by analysis using the software Statistical Package for Social Sciences (SPSS) version 23.0. The data was represented in frequency and further analysed using Kappa statistics. Also the validity was calculated in terms of sensitivity, specificity, Positive Predictive Value and Negative Predictive Value (NPV).

Results: Total of 60 cases were included with M:F ratio as 1.6:1. Most common age group was third decade with 17 (28.3%) cases, closely followed by fourth decade with 11 (18.3%) cases. Most common salivary gland to be affected was parotid gland with 30 (50%) cases. Most common MILAN category was II, non neoplastic with 26 (43.3%) cases, followed by IV A, benign neoplasm with 19 (31.67%) cases. The Cohen kappa coefficient was 0.952 which showed a near perfect agreement between the two pathologists. The sensitivity, specificity, PPV and NPV and accuracy was 75%, 92.8%, 75% and 92.8%, 89% respectively. The Risk of Malignancy (ROM) for category I,II,III,IVA,VI was 0%, 0%, 50%, 9%, 100% respectively.

Conclusion: The MILAN System for Reporting Salivary Gland Cytopathology (MSRSGC) offers a structured reporting system. The terminologies are reproducible and convey clear meaning among all the medical professionals including different pathologists and treating physician or surgeon and guide in deciding the accurate treatment based on the ROM for different categories.

Keywords: Heterogenous, Risk of malignancy, Sialadenitis, Sialadenosis

INTRODUCTION

Salivary gland enlargement is one of the frequent presenting complaint of patients seeking medical care in hospitals. After clinical examination, radiological work-up, FNAC is the most practical approach for these patients as it is a quick and easily performed procedure with high sensitivity, specificity and accuracy [1].

Most commonly involved salivary glands are parotid gland and submandibular gland along with many minor salivary glands [2]. They harbor a wide spectrum of pathologies from benign to malignant. Salivary gland lesions are one of the most heterogenous lesions with overlapping features between low grade malignancy and benign lesions thus making them one of the most difficult areas for diagnosing [1].

The sensitivity of the salivary gland lesions is high as FNAC from salivary glands yields ample amount of material more often. But the specificity of the lesions is not as high attributing to the broad spectrum of lesions having subtle or overlapping features [2].

The low grade carcinomas have overlapping features with benign neoplasms thus a careful study of clinical, radiological, cytomorphological features may help to diagnose the lesion more accurately [3]. Cytochemistry of cell block may be used for better diagnosis. Cytology combined with frozen section can improve the sensitivity and specificity further [4].

Thus, the cytology of salivary gland lesions plays an extremely important part in diagnosing the lesions and categorising them into non neoplastic, benign and malignant neoplasms [5,6]. Thus allowing the patients and clinicians to make an accurate decision regarding whether the lesion should be followed, biopsied, excised or a radical operation is needed [2]. A non neoplastic entity may be followed, a benign neoplasm may have a conservative surgery and in a malignant neoplasm radical surgery with lymph nodal resection may be required [2]. If it is a lymphoma or metastatic malignancy in intraparotid lymph nodes the management is entirely different.

The present reporting system uses a wide range of terminologies by different pathologists. Sometimes only descriptive reports are used which may be confusing for the clinician. There is no relation to the ROM or the management guidelines [7]. Therefore need of an objective, accurate and unambiguous system of classification of the

lesions arises [8]. The MILAN system offers a structured reporting system with defined categories with their standard definitions and inclusion and exclusion criteria [9]. The terminologies are reproducible and convey clear meaning among all the medical professionals including different pathologists and treating physician or surgeon.

Novelty of this study is that it is a prospective one year study with comparision of clinicoradiologic findings with the cytology findings. It highlights the pitfalls in salivary gland cytopathology and lays emphasis on the cases of category III, IVB and V that pose diagnostic dilemma.

Objectives of the study were

- To classify the salivary gland lesions according to the MSRSGC.
- To analyse interobserver variability.
- To compare the cytology findings with the clinicoradiologic findings
- To compare the results of cytology with histopathology wherever possible.

MATERIALS AND METHODS

The observational study was carried out in the Department of Pathology, Rohilkhand Medical College and Hospital, Bareilly, Uttar Pradesh, India, for one year from June 2021 to May 2022 after getting approval from the Institutional Ethics Committee (IEC No-IEC/07/2021/MAR).

Inclusion criteria: The study included all the routine cases of salivary gland lumps referred from various departments to the Department of Pathology, Rohilkhand Medical College and Hospital for Cytology and Histopathology.

Exclusion criteria: Patients who had infection at the site of FNAC, patients with bleeding disorders or who did not give consent for FNAC were excluded.

Procedure

Clinical and radiological findings were noted. Informed consent was taken followed by FNAC. In non palpable lesions, FNAC was done under Ultrasonography (USG) guidance. The slides were stained routinely and categorised into the six categories of the MILAN system [10] after relating with the clinical and radiological findings by two pathologists independently and thus interobserver variability was studied statistically.

Six categories of Milan System include-

- Category I-Non diagnostic (ND),
- Category II-Non neoplastic (NN),
- Category III-Atypia of Undetermined significance (AUS),
- Category IVA-Neoplasm benign,
- Category IVB-Salivary gland Neoplasm of Uncertain Malignant Potential (SUMP),
- Category V-Suspicious for Malignancy (SM),
- Category VI-Malignant (M).

The cytological findings were correlated with the histopathological findings where available. ROM (Risk of Malignancy) was calculated as proportion of cases that turn out as frankly malignant out of the total cases of that category when the gold standard test is applied [6]. In case of discrepancy opinion of a third pathologist was sought. The cases where biopsy or surgery was carried out later, in such cases final cytological impression was compared with the histopathology.

The relatively low number of histopathology was due to the fact that cases where cytological diagnosis was suggestive of sialadenosis, acute and chronic sialadenitis, simple cyst and were also concordant with clinical and radiological impression were not advised biopsy. Out of 28 cases of category III to VI, 15 cases had histopathological agreement, 13 cases were lost to follow-up.

STATISTICAL ANALYSIS

Data was collected, entered and compiled in Microsoft excel followed by analysis using the software SPSS version 23.0. The data was represented in frequency and further analysed using Kappa statistics. Also the validity was calculated in terms of sensitivity, specificity, PPV and NPV.

RESULTS

Total of 60 cases were received in the Department of Pathology during the study period of one year. The distribution of cases as per age, sex and site is shown in [Table/Fig-1]. Maximum number of cases, 17(28.3%) were found in the third decade. Out of total 37 of the patients were males and 23 were females with the M:F ratio 1.6:1. Most commonly affected salivary gland in this study was parotid gland forming a total of 30 cases out of 60, followed by submandibular gland, 28 cases and minor salivary glands, 2 cases. Clinical diagnosis is tabulated in [Table/Fig-2] and [Table/Fig-3] shows swelling in left posterior part of superficial lobe of parotid. Radiological investigations were done in 42 patients which provided with the lesion size, exact location confirming the salivary gland origin and presence of cystic or solid component inside the lesion as shown in [Table/Fig-4]. Radiological images shown in [Table/Fig-5,6].

Variables	No. of cases	Percentage
Age distribution (years)		
11-20	3	5
21-30	17	28.3
31-40	11	18.3
41-50	9	15
51-60	10	16.7
61-70	7	11.7
71-80	3	5
Gender		
Male	37	61.7
Female	23	38.3
Sites		
Parotid	30	50
Submandibular	28	46.67
Minor salivary glands	2	3.33

[Table/Fig-1]: Distribution of cases according to age, gender and site.

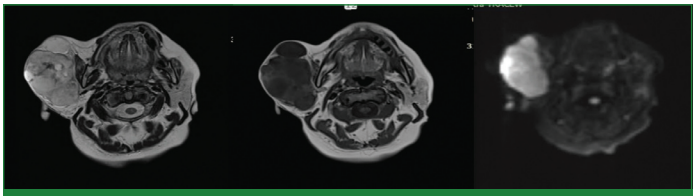
S. No.	Clinical diagnosis	No. of cases
1	Sialadenosis	06
2	Sialadenitis	15
3	Non specific swelling	10
4	Tumour	29

[Table/Fig-2]: Clinical Findings.

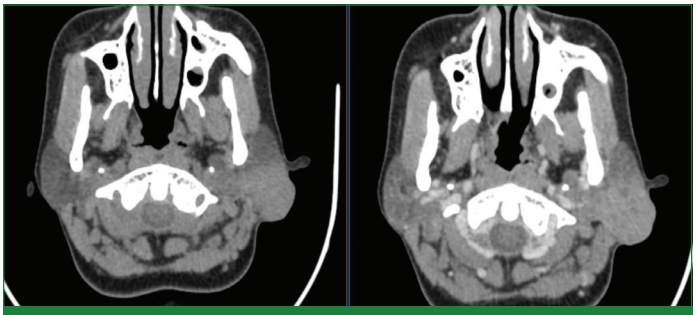
[Table/Fig-3]: A 58-year-old female with a swelling in left posterior part of superficial lobe of Parotid.

S. No.	USG/CT/MRI	No. of cases
1	Diffuse lesion suggesting Sialadenitis/ sialadenosis	16
2	Focal pathology suggesting mass lesion	26
2a	Simple cyst	4
2b	Solid cystic mass	8
2c	Solid mass	14
	Total	42

[Table/Fig-4]: Radiological findings.
USG: Ultrasonography; CT: Computed tomography; MRI: Magnetic resonance imaging



[Table/Fig-5]: MRI-T1W, T2W and DW show a large lobulated solid appearing mass lesion involving the superficial lobe of right parotid gland.



[Table/Fig-6]: NCCT and CECT images reveal mildly enhancing solid appearing mass lesion involving superficial lobe of left parotid gland.
NCCT: Non contrast computerised tomography; CECT: Contrast-enhanced computed tomography

The diagnosis on conventional cytology as shown in [Table/Fig-7] was non diagnostic seen in 2 cases, sialadenosis-7 cases, acute suppurative lesion 5 cases, acute sialadenitis 5 cases, acute on chronic sialadenitis 4 cases, chronic sialadenitis 3 cases, retention cyst 2 cases, pleomorphic adenoma 15 cases, warthin tumour 1 cases, spindle cell lesion 1 case, malignant neoplasm 4 cases, cystic lesion 4 cases, salivary gland neoplasm 3 cases, adenocarcinoma 1 case, mucoepidermoid carcinoma 1 case, suspicious for malignancy 1 case and one case in which we gave a differential diagnosis of 1. Pleomorphic Adenoma 2. Myoepithelioma 1 case. Histopathology could not be obtained in this case but since both the differentials were of benign tumours it was categorised as category IV A-Benign tumour on MILAN category.

Cytological diagnosis	No. of cases	Percentage
Non diagnostic	2	3.33
Sialadenosis	7	11.67
Acute suppurative lesion	5	8.33
Acute sialadenitis	5	8.33
Acute on Chronic sialadenitis	4	6.67
Chronic sialadenitis	3	5.0
Retention cyst	2	3.33
Pleomorphic adenoma	15	25.0
Warthins tumour	1	1.67
Spindle cell lesion	1	1.67
Malignant neoplasm	4	6.67
Cystic lesion	4	6.67
Adenocarcinoma	1	1.67
Mucoepidermoid carcinoma	1	1.67
Suspicious for malignancy	1	1.67
D/D 1.PA 2. Myoepithelioma	1	1.67
Salivary gland neoplasm	3	5.0
Total	60	100

[Table/Fig-7]: Diagnosis on conventional cytology.
PA: Pleomorphic adenoma

[Table/Fig-8] shows clinical impression and cytological diagnosis. Clinically 6 cases were diagnosed as sialadenosis. On cytology along with these, one more case with non specific swelling was diagnosed as sialadenosis. 15 cases of sialadenitis were confirmed on cytology. Along with these 2 more cases were diagnosed as sialadenitis on cytology. Cases clinically as mass lesion were 27 with 25 as tumour and two as cyst on cytology. The cases with non specific swelling showed most heterogeneity with cases of inadequate, sialadenosis, sialadenitis, and cyst and suspicious of malignancy on cytology, thus giving a concordance of 91.67%.

Clinical diagnosis	n	Cytological diagnosis	n
Sialadenosis	6	Sialadenosis	6
Sialadenitis	15	Sialadenitis	15
Non specific swelling	10	Sialadenosis	1
		Sialadenitis	2
		Case suspicious of Malignancy	1
		Inadequate	2
		Cystic lesion	4
Tumour/mass lesion	29	Tumour	27
		Cyst	2
Total	60	Total	60

[Table/Fig-8]: Concordance between Clinical diagnosis and Cytology.

[Table/Fig-9] shows radiological and cytological comparison. No major discordance was seen. Only two cases which were suggested as diffuse swelling were inadequate on cytology giving a concordance of 95%.

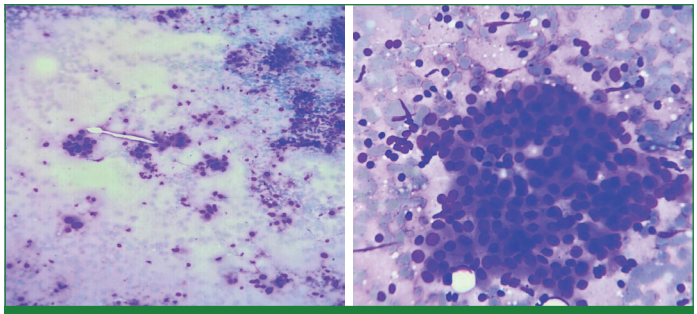
Diagnosis	Radiology	Cytology
Diffuse lesion s/o sialadenitis/sialadenosis	16	14 Concordant 2 Inadequate
Focal lesion including cyst and mass lesion	26	26 cases of cyst/tumour
Total	42	42

[Table/Fig-9]: Concordance between Radiological diagnosis and Cytology diagnosis.

[Table/Fig-10] shows all the cases were categorised by two pathologists independently as per the MILAN categorisation. 58 cases showed similar categorisation. There were 6 cases in category I, 26 cases in category II, 19 cases in category IV A, 1 case in category IV B, and 6 cases in category VI. [Table/Fig-11] shows non neoplastic salivary gland tissue in a patient who presented with fever and bilateral parotid region swelling thus suggestive of (s/o) sialadenosis. [Table/Fig-12] shows oncocytes

		2nd Assessor						
1st Assessor	MILAN category	I	II	III	IVA	IVB	V	VI
	I	6 (10%)	0	0	0	0	0	0
	II	0	26 (43.33%)	0	0	0	0	0
	III	0	0	0	0	0	0	0
	IV A	0	0	0	19 (31.67%)	0	0	0
	IV B	0	0	1 (1.67%)	0	1 (1.67%)	0	0
	V	0	0	1 (1.67%)	0	0	0	0
	VI	0	0	0	0	0	0	6 (10%)

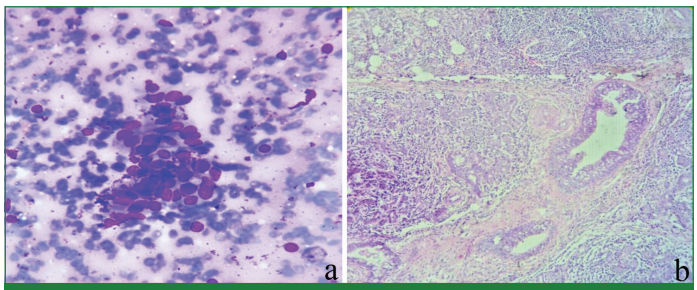
[Table/Fig-10]: Cases as per MILAN categorisation



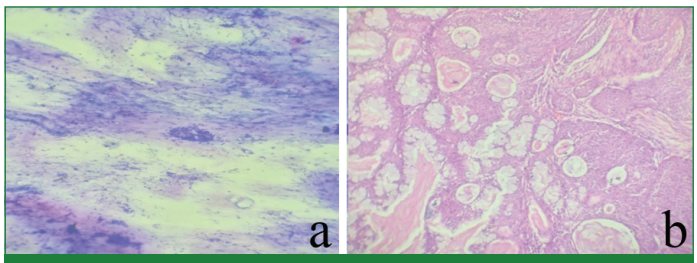
[Table/Fig-11]: Sialadenosis, MILAN category II on cytopathology. (40X, Leishman Giemsa). **[Table/Fig-12]:** Warthin tumour MILAN category IV A on cytopathology (400X, Leishman Giemsa). (Images from left to right)

and lymphocytes in a dirty background s/o Warthin Tumour.

Only two cases showed variation in categorisation. One of the case as shown in [Table/Fig-13a] showed few crowded clusters of cells showing mild hyperchromasia and pleomorphism. Thus, it was categorised as category III (Atypia of undetermined significance) while the other pathologist categorised it as category V (Suspicious for malignancy). Histopathology [Table/Fig-13b] revealed hyperplasia and reactive atypia along with fibrosis, thus the case was diagnosed as chronic sialadenitis with ductular hyperplasia and reactive atypia. The other case as depicted in [Table/Fig-14a] had low cellularity of monomorphic bland small cells with mucoid background. Thus it was diagnosed as salivary gland neoplasm on cytology. MILAN categorisation was category III (AUS) and IVB (SUMP) by the two pathologists respectively. Later in histopathology [Table/Fig-14b] it was diagnosed as low grade mucoepidermoid carcinoma. The interobserver variability was calculated. The Cohen Kappa score was calculated as 0.952 which is a near perfect agreement.



[Table/Fig-13a]: Case reported as suspicious of malignancy on cytopathology (400X, Leishman Giemsa). MILAN categorisation III and V by two assessors. **[Table/Fig-13b]:** Later reported as chronic sialadenitis with ductular hyperplasia and reactive atypia on histopathology (100X, H&E).



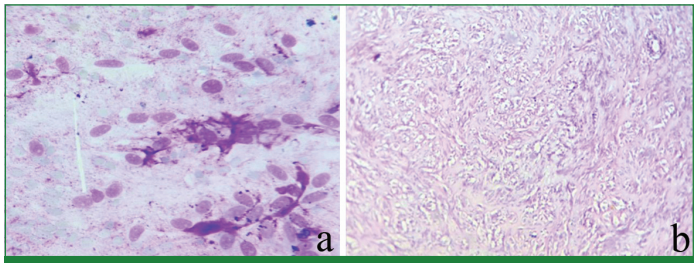
[Table/Fig-14a]: Case reported as salivary gland neoplasm on cytopathology. MILAN category III and IVB by two assessors. **[Table/Fig-14b]:** On histopathology it was diagnosed as mucoepidermoid carcinoma (100X, H&E).

The cases where histopathological comparison was available are tabulated in [Table/Fig-15]. The cytological diagnosis as well as the MILAN category by both the observers is noted. Out of 18 cases of histopathology, 14 were benign and 4 were malignant. Out of the benign cases, 9 cases were of pleomorphic adenoma, 3 were of chronic sialadenitis, two were of Warthin tumour. Out of the four malignant cases, two were mucoepidermoid carcinoma, and two were poorly differentiated carcinoma. Cytohistopathological concordance was present in 16 cases. In one case, cytology report was suspicious of malignancy while on histopathology, it was chronic sialadenitis with ductular hyperplasia and reactive atypia. One other case was diagnosed as pleomorphic adenoma which later was diagnosed as poorly differentiated carcinoma.

			MILAN SYSTEM		
S. No.	Cytology	No. of cases	1st pathologist	2nd pathologist	Histopathology
1	Chronic sialadenitis	1	II	II	Chronic sialadenitis with sialolithiasis
2	Chronic sialadenitis	1	II	II	Chronic sialadenitis
3	Suspicious for malignancy	1	III	V	Chronic sialadenitis with ductular hyperplasia and reactive atypia
4	Salivary gland neoplasm	1	III	IVB	Mucoepidermoid carcinoma
5	Mucoepidermoid carcinoma	1	VI	VI	Mucoepidermoid carcinoma
6	Pleomorphic adenoma	1	IVA	IVA	Poorly differentiated carcinoma
7	Spindle cell lesion	1	IVA	IVA	Pleomorphic adenoma
8	Pleomorphic adenoma	8	IVA	IVA	Pleomorphic adenoma
9	Cystic lesion	1	I	I	Warthins tumour
10	Warthin's tumour	1	IVA	IVA	Warthins tumour
11	Malignant cells present	1	VI	VI	Poorly differentiated carcinoma
	Total	18			

[Table/Fig-15]: Cases with histopathology concordance.

With this data the sensitivity of cytology as diagnostic tool was calculated as 75%, specificity as 92.8%, PPV as 75% and NPV as 92.8% and accuracy as 89%. [Table/Fig-16a] shows spindle shaped cells with scanty cytoplasm. Chondromyxoid stroma was not seen. Atypia or necrosis was not seen, thus case was diagnosed as benign neoplasm, category IVA. On histopathology, it was categorised as pleomorphic adenoma [Table/Fig-16b].



[Table/Fig-16a]: Case reported as spindle cell lesion on cytopathology (400X, Leishman Giemsa). **[Table/Fig-16b]:** On histopathology it was reported as Pleomorphic Adenoma(100X, H&E).

[Table/Fig-17] shows the ROM in our study. [Table/Fig-18] compares the ROM of this study with other studies. In category I, one case diagnosed as cystic lesion on cytopathology, came out to be Warthin tumour. In category II, two cases diagnosed as chronic sialadenitis turned out to be the same on histopathology, thus the ROM for category I, and II was nil. In category III, amongst two cases, one case turned out to be chronic sialadenitis with ductular hyperplasia and reactive atypia, while the other case turned out to be Mucoepidermoid carcinoma, this is the category where discrepancy between the two reporting pathologists were noted, the two pathologists had reported the case as category III and IVB respectively, thus the ROM for this category came out to be 50%. In category IVA, out of 11 cases, 9 cases of pleomorphic adenoma,

one case as salivary gland neoplasm and one case as Warthin tumour. One of these 11 cases turned out to be poorly differentiated carcinoma on histopathology, thus the ROM for this category was calculated as 9%. Category VI had 2 cases, both turned out to be malignant on histopathology, one was poorly differentiated carcinoma and one was mucoepidermoid carcinoma, the ROM thus was 100% in this category.

S. No.	Category	No. of cases	Benign or malignant	ROM %
1	Category I	1 case	1-Benign	0
2	Category II	2 cases	2-Benign	0
3	Category III	2 cases	1-Benign, 1-Malignant	50%
4	Category IV A	11 cases	10-Benign, 1-Malignant	9%
5	Category IV B	0	-	-
6	Category V	0	-	-
7	Caegory VI	2 cases	2-Malignant	100%
	Total	18 cases		

[Table/Fig-17]: Risk of malignancy.

Studies	MILAN categories ROM%						
	I	II	III	IVA	IVB	V	VI
Present study, 2023	0	0	50	09	-	-	100
Singh G et al., 2021 [11]	0	0	-	11.1	100	100	100
Vishwanathan K et al., 2018 [19]	6.7	7.1	38.9	05	34.2	92.9	92.3
Katta R and Chaganti DP, 2019 [16]	-	11.1	100	6.9	-	-	87.5

[Table/Fig-18]: ROM in other studies.

DISCUSSION

Salivary gland neoplasms form 6% of head and neck neoplasms [11]. The cases in this study were diagnosed on cytopathology. The MILAN categorisation was done by two pathologists in all the cases. The results were compared with histopathology where available.

In the present study, most common age group was third followed by fourth decade. The results are consistent with other studies as shown by Gautam D and Thapa R [12]. The male: female ratio 1.6:1 which is also consistent with Gautam D and Thapa R, Rohilla M et al., and Kala C et al., [12-14].

The most common salivary gland to be affected was parotid gland having 50% of the cases followed by the submandibular gland having 46.6% of the cases. This is consistent with many more studies who have shown parotid gland pathologies to exceed all other salivary gland pathologies like Chopra S et al., Gautam D and Thapa R and Katta R et al., [12,15,16].

The MILAN categorisation done by two pathologists separately shows near complete concordance. Only two out of sixty cases show different categorisation. The Cohen Kappa coefficient was 0.952 which is near perfect agreement. Other studies like Chopra S et al., who shows kappa score as 0.965 and Garg N et al., who also show near perfect agreement [15,17]. This highlights the fact that this new system of reporting salivary gland cytology is an excellent and objective method for cytology reporting which removes the personal biases while reporting and converts the diagnostic points into well-defined criteria.

The strong agreement between two pathologists were seen in categories I,II,IV A, and VI while the categories III, IV B and V showed some discrepancy by the two pathologists. Similar results are shown in other studies like Layfield J et al., [18].

The most prevalent category in our study was category II ie non neoplastic comprising of 26 (43.3%) cases followed by IV A, benign neoplasm comprising of 19 (31.2%) cases, category VI comprising of 6 cases (10%) and category I comprising of 6 cases (10%). This is slightly different with other studies like the study of Vishwanathan K et al., [19] and Chopra S et al., [15] who have shown category I as second most common category and category IV A as the first most common category [15,19]. The percentage of malignant cases was similar in the present study and these studies at 10%.

Out of 60 cases, in 18 cases histopathological agreement was available. The cytohistological agreement was seen in 16 of 18 cases which shows an accuracy of 89%. Similar results are shown by other researchers like Garg N et al., who have shown 12 of 55 cases showing discrepancy on histopathology. The present study shows sensitivity of 75%, specificity of 92.8%, PPV of 75% and NPV of 92.8% which is consistent with other studies like Vishwanathan K et al., who have respectively shown a result of 79%, 98%, 94% and 92% and Katta R and Chaganti DP who have shown results of 73.34%, 95.56%, 84.6% and 91.49% and Jha S et al., have shown results of 64.2, 97.01, 90, 90 respectively [16,17,19,20].

The ROM in the present study for various categories is category I-0%, II-0%, III-50%, IV A-9%, VI-100%. These findings are similar to the ROM calculated by other researchers like Singh G et al., [11] conducted in the year 2021 who have shown ROM for categories II-0%, IVA-11.1%, VI-100% [11]. And Vishwanathan K et al., [19] conducted in year 2018 who have shown ROM for II-7.1%, III-38.9%, IVA-5% and VI-92.3% [19]. Other researchers have also shown comparable results like Katta R et al., conducted in year 2019 who have shown the ROM for categories II,IVA, and VI as 11.1,6.9 and 87.5. the ROM for category III as shown by Katta R and Chaganti DP is 100 where the present study shows an ROM as 50, highlighting the heterogenous nature of this category [16]. Other researchers have shown comparable results making cytopathology reporting with MILAN system as an unavoidable diagnostic modality [21-25].

Limitation(s)

1. The cases which posed diagnostic dilemma were limited.
2. Immunohistochemical and molecular studies were not attempted.

CONCLUSION(S)

The present study concludes that the MILAN System for Reporting Salivary Gland Cytopathology is better than the conventional reporting system, as it is a structured and objective reporting system with defined definitions and ROM for each category, but category III, IVB and V create diagnostic dilemma. In our experience category III, IVB and V cases should undergo further diagnostic work-up including biopsy for definite categorization even if the clinical and radiological findings are non sinister.

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