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Application Of Milan System for Salivary Gland Cytopathology-A Prospective Study

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Abstract:
Introduction-Fine needle aspiration cytology (FNAC) of the salivary gland is a minimally invasive, safe, cost-effective diagnostic tool with apt sensitivity and specificity which varies from 86% to 100% and 90% to 100% respectively. To overcome this a uniform reporting system, the Milan system, was proposed by the American Society of Cytopathology (ASC) and the International Academy of Cytology (IAC), in 2015 in Milan, Italy. Prospective study to classify salivary gland lesions according to Milan System, assess the accuracy, risk of malignancy, and prognosis. **Materials and Methods-** All types of salivary gland lesions coming to the pathology department and their FNA smears, histopathology follow up along with clinical details were taken. These cases are classified according to the Milan system. False positive, false negative, true positive, and true negative cases were calculated by comparing with the final histopathological diagnosis and then the accuracy and risk of malignancy of each diagnostic category were calculated. **Results-** The sensitivity, specificity, negative predictive value, and positive predictive value were 65.2 %, 93.5 %, 46.62 %, and 96.87 % respectively. The overall diagnostic accuracy to differentiate the benign and malignant cases was 87%. Also, the risk of malignancy in each category was 33.3% (cat-I), 11.7%(cat-II), 100%(cat-III), 6.9(cat-IVa)%, 100%(cat-IVb), 100%(cat-V) and 100% (cat-VI)respectively. The highest risk of malignancy in the present study was noted in categories III and V**. Conclusion**-Milan system for reporting of salivary gland cytopathology provides good communication between pathologists and clinicians. This also results in lesser false positive and false negative results. The ROM in the present study was according to MSRSGC except for category III, atypia of undetermined significance which was 100%.

Keywords: Salivary Gland, Milan System for Reporting Salivary Gland Cytopathology (MRSSGC), Risk of Malignancy, FNAC, Cytology, Histopathology.

1. Introduction:

Salivary gland neoplasms comprise approximately 6.5% of the lesions sampled in the head and neck, and among these, approximately 40% are malignant[4]. Fine needle aspiration cytology (FNAC) of salivary gland is a minimally invasive, safe, cost-effective diagnostic tool with apt sensitivity and specificity which varies from 86% to 100% and 90% to 100% respectively according to various studies[1-3].

FNA intends to delineate neoplastic from nonneoplastic and benign from malignant in order to provide valuable information to the clinicians in deciding further treatment modality, thus avoiding unnecessary surgeries for nonneoplastic lesions [5,6]. The initial diagnostic workup of a salivary gland nodule uses a multimodal approach. Initial imaging using ultrasound guidance (USG) and/or magnetic resonance imaging enables localization of the lesion within the salivary gland and provides information regarding the imaging characteristics, including the contours of the lesion. In addition, imaging assists with surgical planning for larger tumors within the salivary gland. However, to clarify the malignant potential of a lesion, fine-needle aspiration (FNA) remains the preferred diagnostic test[7-14]. FNA plays a key role in guiding clinical management and provides useful information such as distinguishing between a neoplastic and a non-neoplastic lesion, ascertaining whether a lesion is benign or malignant, and, last, providing prognostic information and a sample for ancillary testing such as molecular studies.

A few limitations exist, including the lack of architecture with which to assess invasion, the heterogeneity and significant cytomorphologic overlap between salivary gland lesions, and the ever-expanding portfolio of head and neck tumors with continued molecular classification of these tumors. For these reasons, salivary gland cytology continues to remain a challenging area in cytopathology and along with this The final diagnosis is also affected by site of aspiration of tumors (as in solid cystic tumors), the quality of smearing and staining, experience of the cytopathologist and absence of any category based reporting. To overcome this an uniform reporting system, Milan system, was proposed by American Society of Cytopathology (ASC) and the International Academy of Cytology (IAC), in 2015 at Milan, Italy.

2. Materials And Methods

This is a prospective study conducted on all 100 cases of salivary gland lesions coming to department of pathology for FNAC. Patients of all ages, all genders were included in the study. Histopathological correlation was done wherever available. Smears of all the cases were air dried Giemsa stained and classified according to MSRSGC into six categories including nondiagnostic, non-neoplastic, atypia of undetermined significance, neoplasm (benign or salivary gland neoplasm of uncertain malignant potential), suspicious for malignancy, and malignant.

The risk of malignancy and diagnostic accuracy was assessed. Number of false positive, false negative, true positive and true negative were identified. Sensitivity, specificity, positive predictive value and negative predictive value were calculated. SPSS software version 14 was used for all statistical analysis.

3. Results:

The study included 100 cases of which males were more than females. (M: F = 3:2). The distribution of cases according to sex, age and site of aspiration are elaborated in table 2.

The most commonly affected age group was from 21 to 40 years with 55% of cases. Most of the study subjects were presented with parotid swellings (61%) followed by submandibular (27%).

The correlation between cytological and histological cases were shown in table 3. Histological correlation was available in 76 cases of which 8 cases were discordant. Non –neoplastic category out of 21 cases, 17 cases had histopathological follow-up of which one were low grade mucoepidermoid as well as acinic cell carcinoma which were diagnosed as retention cyst and sialadenosis respectively on cytology. One case of pleomorphic adenoma and basal cell adenoma which was diagnosed on cytology was diagnosed to be adenoid cystic carcinomas on histology. One of case diagnosed as suspicious for malignancy on cytology was diagnosed as oncocytoma. The highest risk of malignancy of 100% was noted in category III, V and Salivary gland neoplasm of uncertain malignant potential (SUMP). Rest all malignant cases were diagnosed as malignant on histology in categoryVI (Table 4).

Table 2: Distribution of cases according to age, sex and site of lesion

Variables	**Frequency**	**Percentage**
Gender		
Male	**58**	**58%**
Female	**42**	**42%**
Age group		
0-20	10	10%
21-40	55	55%
41-60	21	21%
60-70	13	13%
>70	01	01%
Salivary gland involved		
Parotid	61	61%
Submandibular	27	27%
Other minor glands	12	12%

Table 3: Correlation between cytological and histopathological cases

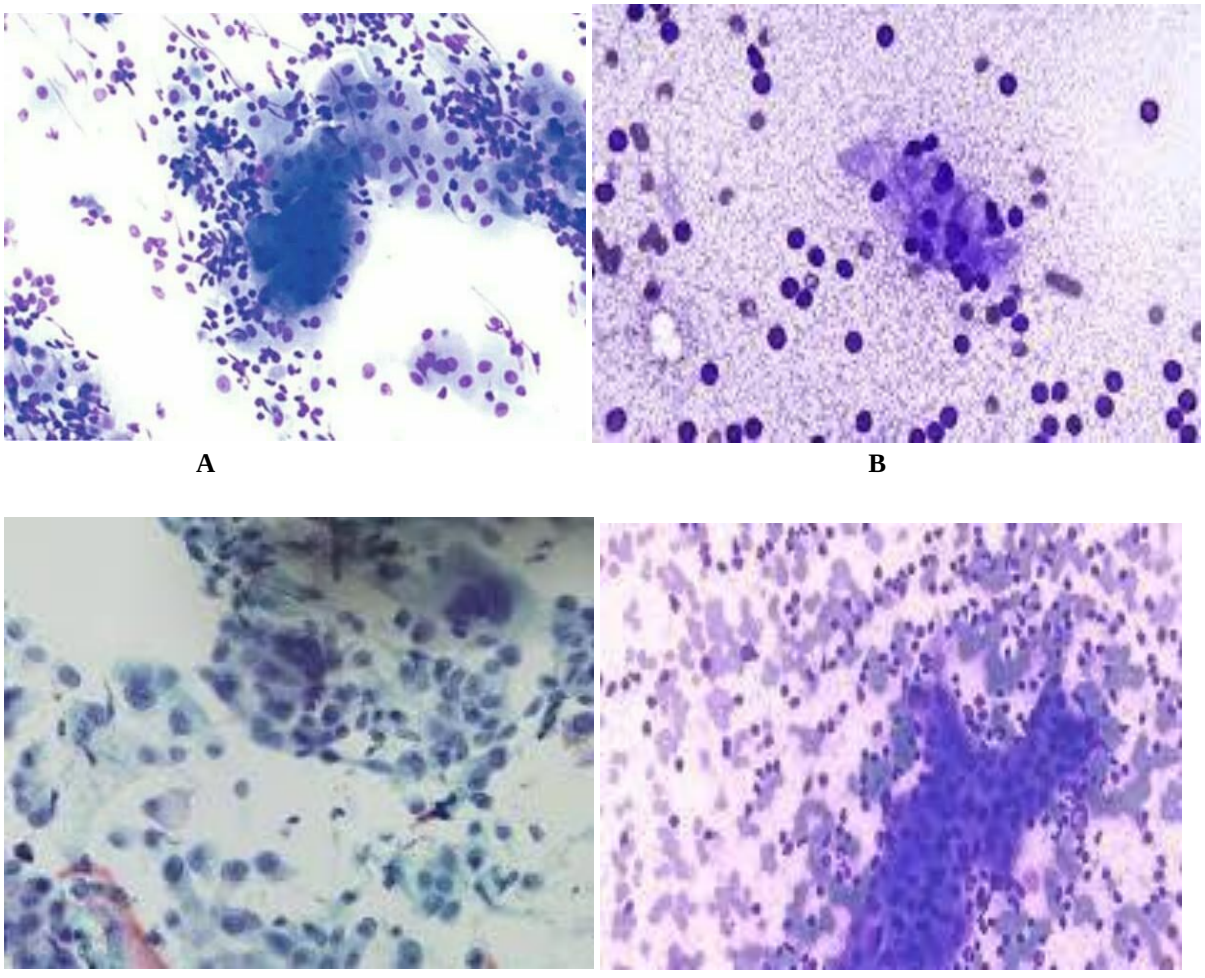
Cytological diagnosis	No.of cases	No. of cases with histological correlation
Non diagnostic	05	03
Sialadenosis	10	08
Chronic Sialadenitis	06	06
Retention cyst	04	02
Pleomorphic adenoma	43	35
Basal cell adenoma	05	04
Oncocytoma	01	01
Warthins tumor	04	03
Lymphoepithelial cyst mucocele	02	01
Neoplasm of uncertain malignant potential	02	01
Suspicious of malignancy	03	02
Mucoepidermoid carcinoma	07	05
Acinic cell carcinoma	02	01
Ca ex pleomorphic adenoma	01	NIL
Epithelial myoepithelial carcinoma	01	NIL
Squamous cell carcinoma	01	01
Metastatic carcinoma	01	01
Lymphoma	02	02

Table 4: Categorisation of cases according to Milan system for reporting of salivary gland cytopathology along with risk of malignancy**.**

Category	No. of cases	Risk of malignancy
Non diagnostic I	05	1/3(33.3%)
Non neoplastic II	21	2/17(11.7%)
AUS III	01	1/1(100%)
Neoplasm IV **Benign** **SUMP**	 53 02	 3/43 (6.9%) 1/1 (100%)
Suspicious of malignancy V	03	1/1(100%)
Malignant VI	15	10/10(100%)
Total	100	1/3(33.3%)

AUS- Atypia of Undetermined significance, SUMP- Salivary gland neoplasm of uncertain malignant potential.

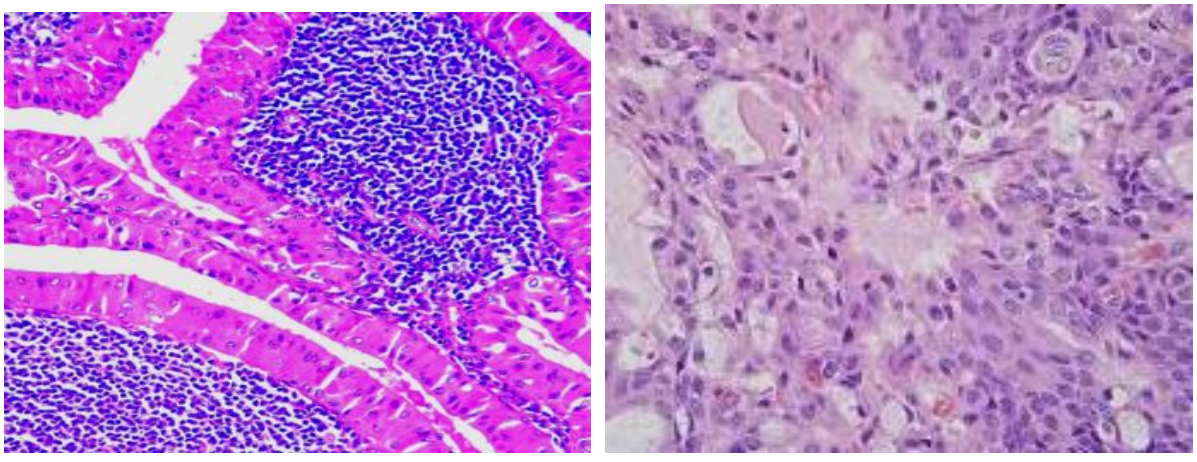
The sensitivity, specificity, negative predictive value and positive predictive value of FNAC using Milan system were 65.22%, 93.5 %, 46.62 % and 96.87 % respectively. The overall diagnostic accuracy to differentiate the benign and malignant cases was 87%.



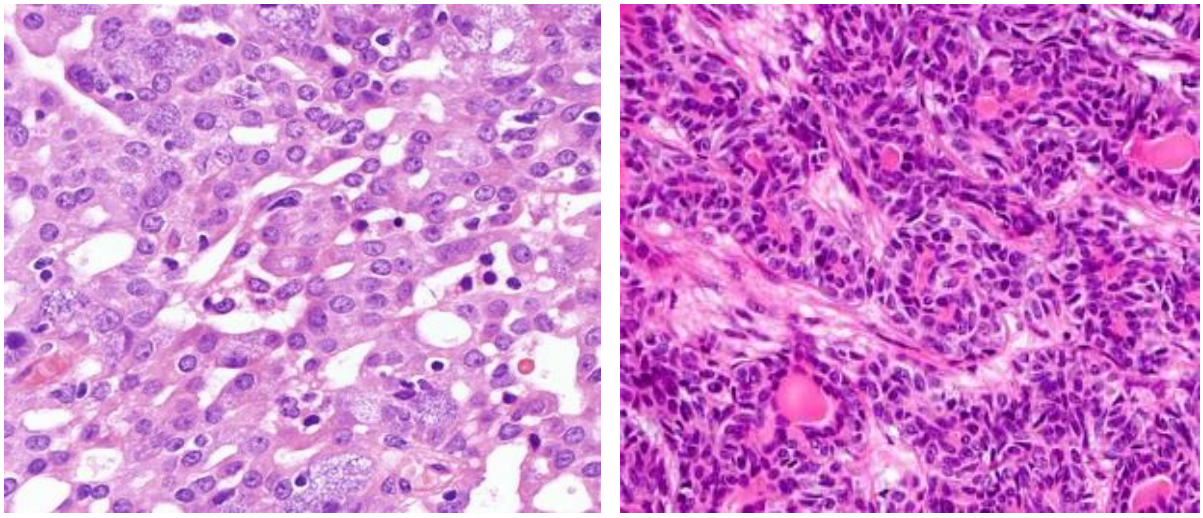
A **B**

C **D**

Fig 1: Fine needle aspiration cytology (A) Warthins tumor (B) Acinic cell carcinoma (C) Mucoepidermoid carcinoma (D) Chronic sialadenitis.



A **B**



C D

Fig 2: Histopathology (A) Warthin tumor (B) Mucoepidermoid carcinoma (C) Acinic cell carcinoma (D) Basal cell adenoma

4. Discussion

FNAC is a first line initial diagnostic tool among the clinicians due to ease of performance and rapid diagnosis. The technique is minimally invasive, rapid, and cost-effective, and can be used efficiently in the outpatient setting[1,27].The clinical value of FNAC is not limited to neoplastic conditions. It is also valuable in the diagnosis of inflammatory, infectious and degenerative conditions. This method is applicable to superficial lesions mainly. Proper definitive FNAC results depends on samples must be representative of the lesion investigated, adequate in terms of cells and other tissue components and correctly smeared and processed. But this technique also has some limitations, firstly results and accuracy are highly depend on the quality of samples and smears. Many pathological processes are heterogeneous, and the tiny samples obtained with a fine needle may not be representative. Some lesions are recognised mainly on the microarchitectural patterns, which may not be sufficiently represented in cytological preperations. Inadequate aspirate are a challenge on FNAC. This can be due to small size of lesion, deep location or dense fibrosis/sclerosis in the lesion. Also, the overlapping morphological features and cytomorphological heterogenicity within the same lesions makes it difficult to identity and subcategorize a particular salivary gland lesion correctly. Presentation, clinical history and communication between clinicians and pathologists is also important for correct diagnosis of the lesions. Thus to improve overall care and uniformity in diagnosis of salivary gland lesions a category based system, Milan system, was introduced. Griffith et al. had proposed an adequacy criterion of presence of epithelial cells in more than four high power fields[16]. Milan system has recommended a minimum of 60 lesional cells in the diagnosis of salivary lesion as for now[15].

Another reason for false negative cases is cystic lesions. A cyst lesion can be nonneoplastic, benign or malignant for example retention cyst, warthins tumor or mucoepidermoid carcinoma. The aspiration of only fluid in these cases can lead to a diagnostic pitfall. The fluid aspirated is paucicellular and the diagnosis in such cases is very difficult and challenging. Cystic lesion should be palpated after aspiration of the fluid to look for any solid areas and a second attempt should be done from these solid areas. Also, guided FNAC can be useful in such cases to aspirates the representative area. In the present study two of the cystic lesion which were found to be low grade mucoepidermoid carcinoma on histopathology were diagnosed as retention cyst incorrectly on cytology. One of these cases was recategorized into AUS category according to Milan system due to presence of few atypical cells with very low cellularity.

The present study had male to female ratio of 3:2 which is comparable to other studies[17,19]. Parotid gland was most commonly involved followed by submandibular gland and minor salivary glands. Similar findings were noted by Kala and Sonal et al[17,18,19].

The sensitivity and specificity of the present study is 65.22 % and 93.5 % along with diagnostic accuracy of 87% to differentiate benign lesions from malignant lesions. This is comparable to other studies done by Manju Kumari et al., Zubair et al., Santosh et al. and Katta et al[19,20,21,22].

Amongst the non neoplastic, benign and malignant lesions sialadenosis (47.61%; 10/21), pleomorphic adenoma (81.13%; 43/53) and mucoepidermoid carcinoma (46.66%; 5/15) are the most common lesions in the present study. The percentage of chronic sialadenitis were in concordance to previous studies. But the percentage of mucoepidermoid carcinomas were higher than other studies[12,13].

The present study had maximum cases in category IV (55%) followed by category II (21%) and category VI (15%) which is similar to studies conducted by Manju et al. , Sheetal et al. and Yogambal et al[19,24-26].

Pleomorphic adenoma have a characterstic chondromyxoid background but it can also be confused with hyaline globules or basement membrane like material which adds difficulty in its diagnosis like in our study two cases of each basal cell adenoma and adenoid cystic carcinoma were misdiagnosed as pleomorphic adenoma. Same as two cases of each pleomorphic adenoma and adenoid cystic carcinoma were misdiagnosed as basal cell adenoma.

The category AUS is for lesions that contained limited atypia and a neoplastic process cannot be excluded. The cases diagnosed as AUS is expected <10% of all salivary gland FNAs. In the present study this group had only one case (1.1%).

On histopathology this category had ROM of 100% which is higher due to presence of only one case in this category that too was malignant on histopathology. This could have affected the ROM in the present study as it is reported to be 0% to 73% in other studies but same as study conducted by Manju et al. and Kala C et al[19,17].

An update of Milan Classification System for Salivary Gland Tumors was presented by Esther et al. to provide an emphasis on diagnostic pitfalls, differential diagnosis to provides a uniform and practical reporting system with the risks of malignancy[27].

The present study depicted that the risk of malignancy, diagnostic accuracy, sensitivity and specificity of FNAC to differentiate benign versus malignant lesions of salivary glands at our institute were comparable to other studies as shown in table 5 and 6.

Table 5: Statistical comparison of the present study with other studies.

	Present study (%)	**Manju et al (%)**	**Karuna et al (%)**	**Rohilla et al (%)**
Diagnostic accuracy	87.00	92.19	94.59	91.40
Sensitivity	65.22	78.57	85.00	79.40
Specificity	93.5	98.84	98.14	98.30
PPV	96.87	97.06	94.44	
NPV	46.62	90.43	94.64	

PPV – Positive predictive value, NPV – Negative predictive value

Table 6: Comparison of risk of malignancy of various categories of Milan system of present study with others.

Category	Present Study	Manju et al	Karuna et al	Rohilla et al	Liu et al.
Nondiagnostic (%)	33.3	20	0.0	-	-
Non neoplastic (%)	11.7	14.3	0.0	17.4	-
AUS	100	100	50	100	-
Neoplasm **Benign** **SUMP**	 6.9 100	 4.2 100	 02.44 33.33	 07.3 50	 - 24.1
Suspicious for malignancy (%)	100	83.33	100	-	-
Malignant (%)	100	100	93.33	96	-

5. Conclusion:

The Milan system of reporting salivary gland cytopathology provides risk stratification with risk of malignancy, which is helpful in deciding patient counselling and management. It reduces false positive and false negative cases on FNAC.

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