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# A study on cytological evaluation of salivary gland lesions by Milan system with Histopathological correlation

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***Abstract***
***BACKGROUND:*** *Lesions of the salivary glands constitute for 2–6% of head and neck lesions. For the preoperative diagnosis of salivary gland lesions, FNAC is a quick, accessible, and essential investigative tool. There are certain difficulties in its widespread usage as a diagnostic tool for salivary gland lesions, because of the overlap of cytological characteristics and heterogeneity of the spectrum of lesions. To overcome this, in 2015, a standardized reporting system – " MILAN SYSTEM FOR REPORTING SALIVARY GLAND CYTOPATHOLOGY (MSRSGC) " was introduced for proper diagnosis, management, and determining the risk of malignancy in different categories.* ***AIMS AND OBJECTIVES :*** *1) To stratify the salivary gland lesions according to Milan system of reporting and correlate with histopathological diagnosis, 2) To estimate the risk of malignancy in each category.* ***STUDY SETTING AND DESIGN :*** *Present study is a retrospective study carried out over a period of 3.5 years from Jan 2018 to July 2021, conducted in the Department of Pathology, Sri Venkateswara Medical college, Tirupathi.* ***MATERIALS AND METHODS :*** *Salivary gland swellings were palpated, aspirated, and clinically assessed while being compared to information on the request forms and ultrasound results. Salivary gland swellings of all ages were included in this study. Unco-operative patients and morbidly ill cases were excluded from the study. The aspirate of about 214 salivary gland lesions were analysed for cytological evaluation and were categorized according to Milan system; The results of FNAC are further correlated with histopathological findings and the risk of malignancy was evaluated for all the diagnostic categories.* ***RESULTS :*** *out of 214 cases, histopathological correlation is available in 72 cases, concordance seen in 47 cases (65.27%), and discordance seen in 25 cases(34.72%) mostly seen in indeterminate categories like AUS, SUMP and SFM. The ROM were 0%, 0%, 25%, 4.7%, 25%, 66.66% and 100% in each Milan's categories I, II, III, IVa, IVb, V, and VI, respectively. ROM of the present study correlated with the predetermined ROM for the all the above categories except in category III (AUS).* ***CONCLUSION :*** *Milan system was effective in categorising salivary gland pathologies. Helps with risk assessment and guides the clinician for appropriate management. Limits the possibilities of false negative and false positive cases.*
***KEY WORDS:*** *Milan System of Reporting Salivary Gland Cytopathology (MSRSGC), Histopathological correlation, Risk Of Malignancy (ROM), Category AUS.*

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## I. Introduction :

Salivary gland cancers are rare, accounting for only 0.2% of all cancers and 6.1% of head and neck tumours[1]. The salivary gland lesions (SGLs) include a wide range of lesions, from non-neoplastic to benign and malignant lesions. Particularly in biphasic tumours, the malignant salivary gland lesions exhibit diverse morphology and architecture[3]. For the detection and treatment of salivary gland tumours, fine-needle aspiration cytology (FNAC) of the salivary gland is employed globally[1]. An accurate diagnosis of non-neoplastic lesions can help avoid unnecessary surgeries[5]. Numerous research have revealed that FNAC has great specificity and sensitivity for identifying benign and malignant neoplasms as well as neoplastic vs. non-neoplastic lesions. According to multiple studies, FNAC's sensitivity ranges from 86% to 100%[1]. However, a precise diagnosis may only be made in 60–75% of cases due to insufficient sample, a lack of architectural pattern, and cytomorphologic overlap between different lesions of the salivary glands[4]. In the past, pathologists utilised various confusing, inconsistent reporting standards and nomenclature; as a result, appropriate results did not

develop and confusion among pathologists, surgeons, and radiologists developed[4]. It also prevents the difficulties that clinicians frequently encounter while interpreting FNAC reports[5]. The Milan system (Six tier) was proposed by the International Academy of Cytology (IAC) and the American Society of Cytopathology (ASC) in Italy in 2015 in order to establish a standardised nomenclature for reporting salivary gland cytopathology. It was eventually published in 2018[4]. Those 6 categories were as follows: category I – Non-diagnostic (ND); category II – Non-Neoplastic (NN);category III – Atypia of undetermined significance (AUS); category IV – Neoplasm (N), subdivided into Benign (IVa; B) and salivary gland neoplasm of uncertain malignant potential (IVb; SUMP); category V– Suspicious for malignancy (SFM); and category VI – Malignant (M), respectively[4]. The MSRSGC contains the best operational guidelines for salivary gland FNA, including indications, the standard FNA technique, uniform reporting of results, and the use of ancillary tests like immunochemistry (IHC) and molecular testing, as necessary[3]. Each category has a standard management strategy and an implied ROM[4].

## II. Materials And Methods :

Clinical data of the cases and FNAC specimen from salivary gland lesions were retrieved from the department of pathology from Jan 2018, July 2021 (3.5yrs). A total of 214 FNACs were performed, and the MSRSGC categories were used to reclassify the salivary gland lesions. This study included swellings of the salivary glands in people of all ages. Unco-operative patients and morbidly ill cases were excluded from the study.

FNAC was performed using standard technique under aseptic precautions with the patients lying/sitting in a comfortable position and pillow under the head if needed. Three passes per case was performed using 10 ml syringe with 21-23G, ½, 1, and 1½ inch (according to the size of swelling) needle. In cases with bloody material and cystic swelling, further needling was performed. At least three smears were prepared on pre-cleaned slides using the standard one-step conventional methods and stained with H & E. Smears were examined under microscope after mounted with DPX (dextrene polystyrene xylene) . Histopathological data wherever available were retrieved. Received surgical tissue was processed as standard of protocol. Considering histopathology as a gold standard, ROM of each category (resected cases only) were calculated. ROM was determined by dividing the number of malignant cases, by a total number of histopathological follow-up available in the particular category. Results thus obtained were subjected to statistical analysis.

## III. Results :

A total of 214 patients were included in this study. The fine needle aspirate result was categorized according to The Milan system. Among them, 110 (51%) were males and 104 (49%) were females with M : F ratio of 1.05:1. Largest number of cases were seen in age group of 41-60 years (42.52%) followed by 21 – 40 years (33.6%).

**Figure 1:** Distribution of salivary gland lesions according to sex

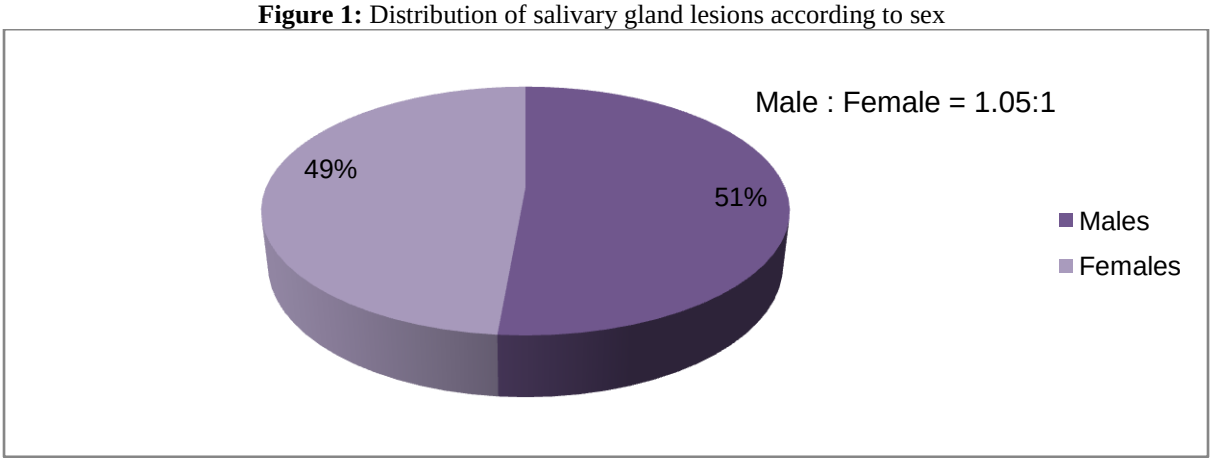


**Figure 2 :** Distribution of salivary gland lesions according to age group

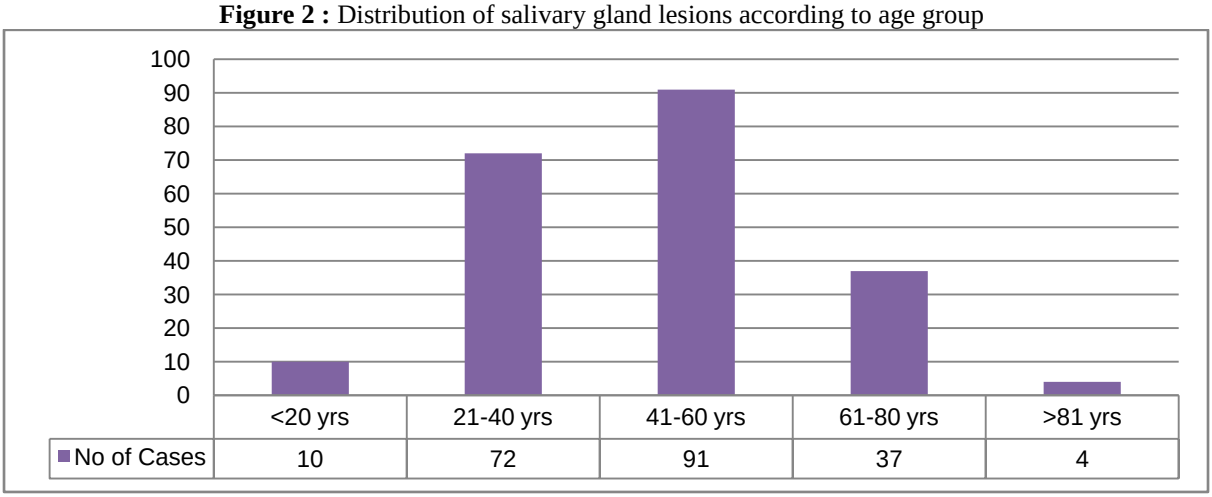



**Table 1** : Distribution of cases according to site involvement

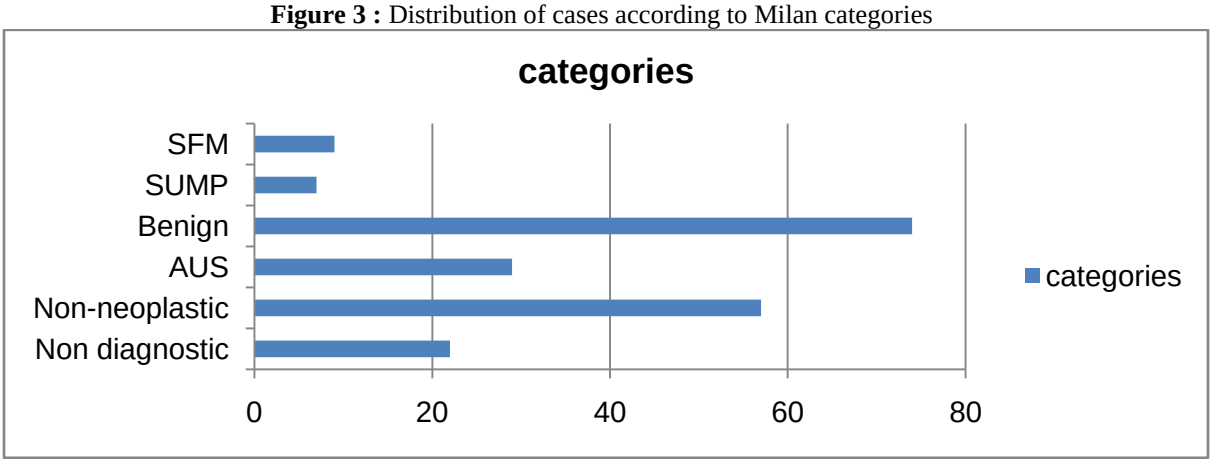
| GLAND INVOLVED | NO. OF CASES | % OF CASES |
|---|---|---|
| **Parotid** | 139 | 65 % |
| **Sub mandibular** | 68 | 32 % |
| **Minor salivary gland** | 7 | 3 % |

Most commonly involved gland was parotid (65%) followed by submandibular (68%) and minor salivary gland (3%). Of the total 214 cases, there were 22 cases (10.28%) of ND (I), 57 cases (26.6%) of NN (II), 29 cases (13.55%) of AUS (III), 74 cases (34.57%) of B (IVa), 7 cases (3.27%) of SUMP (IVb), 9 cases (4.20%) of SFM, and 16 cases (7.47%) of M. Surgical specimens were received in 72/214 (33.64%) cases. Cytohistopathological correlation exhibit concordance in 47/72 (65.21%) cases, whereas discordant in 25/72 (34.72%) cases mostly seen in indeterminate categories like AUS, SUMP and SFM. Overall, ROM was 13.88% (10/72) in resected lesions. The ROM were 0%, 0%, 25%, 4.7%, 25%, 66.66% and 100% in each Milan's categories I, II, III, IVa, IVb, V, and VI, respectively. In the present study, pleomorphic adenoma is the most common benign tumor – 46 cases (63.8%). MEC is the most common malignant tumor, accounting for 5 cases (6.9%) of all tumors followed by Adenoid cystic carcinoma – 2 cases(2.7%).

**Table 2:** Distribution of cases according to Milan categories with histopathological follow up

| **category** | **1(ND)** | **2(NN)** | **3(AUS)** | **4a(NB)** | **4b(N SUMP)** | **5(SFM)** | **6(M)** | **Total** |
|---|---|---|---|---|---|---|---|---|
| **No. of cases** | 22 | 57 | 29 | 74 | 7 | 9 | 16 | 214 |
| **No. of cases with histopathological follow up** | 3 | 9 | 8 | 42 | 4 | 3 | 3 | 72 |
| **Non- neoplastic** | 2 | 7 | 2 | 3 | 3 | 0 | 0 | 14 |
| **Benign** | 1 | 2 | 4 | 37 | 0 | 1 | 0 | 48 |
| **Malignant** | 0 | 0 | 2 | 2 | 1 | 2 | 3 | 10 |
| **ROM** | 0 % | 0% | **25%** | 4.7% | 25% | 66.66% | 100% | |

**Figure 3 :** Distribution of cases according to Milan categories




## IV. Discussion :

FNA is a widely accepted tool for the diagnosis of salivary gland lesions[1]. FNAC is safe, accurate, and cost effective method for evaluation of salivary gland swelling and can help in the management of the patient by providing nature of the lesion[2].

MSRSGC is a newer system for reporting salivary gland lesions according to risk stratification with an objective to provide a better communication between clinicians and cytopathologists so as to improve overall patient management. It is an evidence based six tiered system, which provides ROM and clinical management strategies for each category[2]. It classified FNAC diagnosis into six categories: ND, NN, AUS, NB, SUMP, SM and malignant with ROM of 25%,10%, 20%, 5%, 35%, 60% and 90% for each category respectively[2,5,7]. Present study also categorized salivary gland cytodiagnosis into six categories according to MSRSGC, and overall ROM was calculated.

Category 1 (ND) includes the cases where material aspirated from the salivary gland lesions are insufficient for providing any information for diagnosis. In present study 22 cases were reported as Non-diagnostic on cytology. 3/22 cases were available for histological follow up out of which 2 cases were diagnosed as chronic sialadenitis and 1 case as benign pleomorphic adenoma. So the ROM for this category was 0%. Similar results seen in a study by Kala et al, 2 cases that were diagnosed as ND on cytology, were confirmed as chronic sialadenitis after histopathology. Loss of acini and marked fibrosis could be the possible reasons for the misdiagnosis. Another case of Adenoid cystic carcinoma was diagnosed as ND, as aspiration from the cystic areas yielded acellular smears[2].

9 out of 57 cases were available for histological follow up in category 2(NN). 7 cases were confirmed to be non neoplastic. 2 cases were reclassified as benign neoplasms. A case of pleomorphic adenoma was diagnosed as non neoplastic as it showed cystic change, so aspiration from the cystic area showed cellular debris and histiocytes. So the ROM for this category was 0%.

The AUS category includes the cases, where a neoplastic lesion cannot be completely ruled out, and we had 29 cases in this category. Histological follow-up was available for 8 cases, 2 cases were diagnosed as non-neoplastic, 4 as benign and 2 cases were reclassified as Adenoid Cystic Carcinoma (AdCC). The presence of occasional basaloid cell with atypia might be the reason of categorization into AUS on cytology. So the ROM for this category was 25% which is more than the predetermined ROM in Milan's system (20%) . Many literatures showed wide range of differences in the ROM ranging from 0.0% to 100%. Comments on actual or various malignancy rates of this category are challenging. The reason behind this point might be overuse and minorities of cases undergo excision.

Category 4a (Neoplastic: Benign) had 74 cases, out of which histological follow up was available in 42 cases. Pleomorphic adenoma (PA) were the majority cases, followed by Basal cell adenoma and warthin's tumor. 3 non-neoplastic lesions and 2 MEC cases were misinterpreted as benign lesions on cytology, few other studies did show similar results. In another study, 3 cases of MEC were diagnosed as PA on cytology. Smears showed paucicellularity and bland epithelial cells which could be intermediate cells[2]. Studies done by Kotwal et al [11] and Noor et al [12] observed similar finding in their cases. Adenoid cystic carcinoma is considered most common false -positive diagnosis for PA.

Category 4b (SUMP) includes those cases where cytological features are suggestive of a neoplastic lesion, but these features cannot distinguish efficiently between a benign and malignant neoplasm. We had 7 cases diagnosed as SUMP, 4 were available for histopathological follow-up,3 cases were recategorised as non-neoplastic and 1 case as AdCC on histological follow-up. On FNAC, the smears showed tumor with magenta coloured matrix but cells were not arranged around hyaline globules, which is a typical feature of AdCC.

Suspicious for malignancy( SFM) category is reserved for cases, where overall cytomorphological features suggest malignancy, but does not show all the criteria for a specific diagnosis of malignancy[7]. AUS, SUMP, and SM represent the intermediate categories in Milan system[7].In our study, 9 cases were reported as suspicious for malignancy, 3 cases were available for histopathological follow-up, out of which 1 case diagnosed as benign and 2 cases as AdCC, and low grade Mucoepidermoid carcinoma.

Category 6 (Malignant) includes cases where cytological features are diagnostic of malignancy. 3 cases diagnosed as malignancies on cytology in the current study were confirmed on histopathology as Myoepithelial carcinoma, AdCC and Low grade MEC.

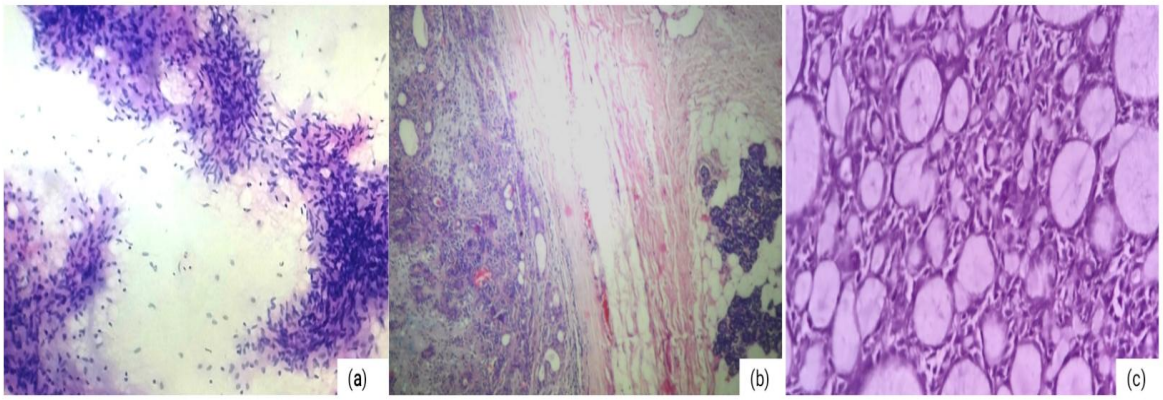



Figure (a) -Cytosmear in H & E (400X) Poorly cohesive clusters and individually dispersed epithelial cells, background shows fibromyxoid stroma ;Figure (b) : Histopathology in H & E (400X) Epithelial cells arranged in glandular pattern, areas of fibromyxoid stroma with adjacent normal salivary gland tissue, Inner ductal and outer myoepithelial cells; Figure (c) -Histopathology in H & E (100X) : pseudocysts lined by monolayer of bland appearing epithelial cells in cribriform pattern

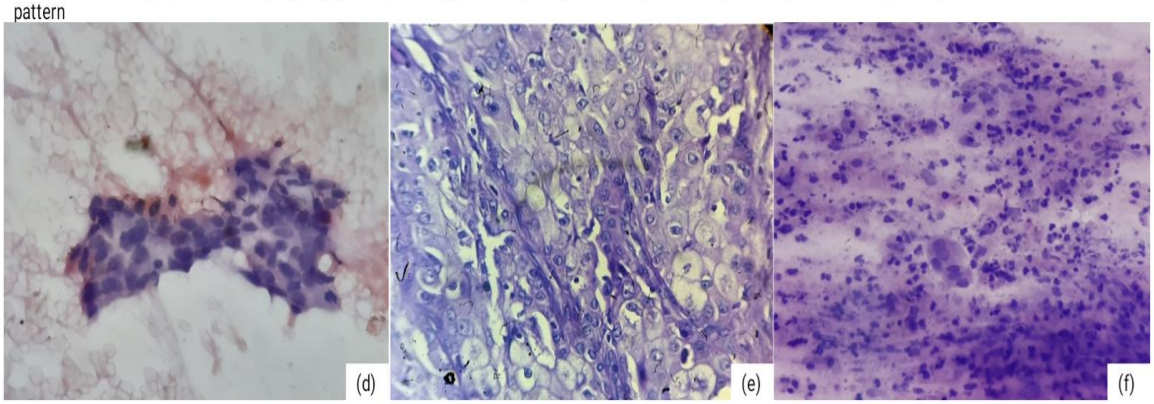



Figure (d) -Cytosmear in H & E (100x) : poorly cohesive squamous metaplastic cells represent intermediate cells; Figure (e) -Histopathology in H & E (400X) : Cysts lined by mucin producing cells, areas of cells with squamous differentiaition ; Figure (f): cytosmear in H& E (100x) – smears shows few atypical cells with increased N:C ratio in a background of inflammation and mucinous material

**Table 3 :** comparison of ROM of present study with other studies

| Diagnostic category | % ROM MSRSGC | % ROM Present study | Karuna V et al[6] | Kala C et al[2] | Bharti JN et al[3] | Gupta I et al[1] |
|---|---|---|---|---|---|---|
| Cat 1 | 25% | 0% | 20% | 25% | 0 % | 16.6% |
| Cat 2 | 10% | 0% | 11.43% | 5% | 0 % | 6.6% |
| Cat 3 | 20% | 25% | 53.85% | 20% | 100% | 33.3% |
| Cat 4a | <5% | 4.7% | 5.13% | 4.4% | 5.5% | 3.33% |
| Cat 4b | 35% | 25% | 43.75% | 33.3% | 33.3% | 100% |
| Cat 5 | 60% | 66.6% | 83.33% | 85.7% | 0% | 50% |
| Cat 6 | 90% | 100% | 100% | 97.5% | 80% | 80% |

The overall risk of malignancy for Non-diagnostic, Non-neoplastic, Atypia of undetermined significance, Benign, SUMP, Suspicious for malignancy and Malignancy in our series were 0%, 0%, 25%, 4.7%, 25%, 66.66%, and 100%, respectively. The reported frequency in other studies varied from 0–25%, 10–

18%, 2–7%, 18–50%, 50–75%, and 91–100% for each of non diagnostic, non neoplastic, benign, SUMP, suspicious for malignancy, and malignancy respectively [2,8,9].

## V. Conclusion :

Salivary gland diseases were effectively categorised using the Milan system. aids in risk assessment and directs the clinician toward the best course of action. decreases the possibilities of false negative and false positive cases.

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