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Assessment of Risk of Malignancy in Salivary Gland Lesions Categorized by the Milan System: A Cytohistopathological Study.

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Abstract

Introduction: Salivary gland lesions encompass a heterogeneous spectrum of non-neoplastic and neoplastic conditions, creating diagnostic challenges on fine-needle aspiration cytology (FNAC). The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) provides a standardized framework for cytological classification and risk stratification. Cytohistopathological correlation is important for evaluating its diagnostic utility. ***Materials and Methods:*** This observational cytohistopathological study included 30 patients with clinically suspected salivary gland lesions who underwent FNAC followed by histopathological examination. Cytological findings were categorized according to the seven-tier Milan System. Histopathology was considered the reference standard. The risk of malignancy (ROM) was calculated for each Milan category, and cytohistopathological concordance was assessed. Diagnostic performance was evaluated using sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy. ***Results:*** Among 30 patients, males constituted 17 (56.7%) cases, and the parotid gland was the most commonly involved site (21, 70.0%). Category IV-A was the most frequent Milan category (11, 36.7%). Cytohistopathological concordance was observed in 26 (86.7%) cases. Histopathology identified 8 (26.7%) malignant lesions. The ROM was 33.3% for Category IV-B and 100.0% for Categories V and VI, while it was 0% for Categories I–IV-A. Considering Categories V and VI as positive for malignancy, the Milan System demonstrated 100.0% sensitivity, 95.5% specificity, 88.9% positive predictive value, 100.0% negative predictive value, and 96.7% diagnostic accuracy. ***Conclusion:*** The Milan System demonstrated good cytohistopathological correlation and high diagnostic performance for identifying malignant salivary gland lesions. The increasing ROM across the higher Milan categories supports its utility as a standardized approach for preoperative risk stratification. Histopathological correlation remains particularly important for indeterminate categories.

Keywords: Salivary gland lesions; Milan System; Fine-needle aspiration cytology; Histopathology; Risk of malignancy.

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INTRODUCTION

Salivary gland lesions comprise a diverse group of neoplastic and non-neoplastic conditions with considerable variation in their clinical presentation, biological behavior, and histopathological characteristics [1]. They may present as localized swellings, pain, facial nerve involvement, or incidental masses, and can range from benign inflammatory processes to aggressive malignant neoplasms [2]. Although most salivary gland tumors are benign, accurate identification of malignant lesions is essential for appropriate treatment planning and prognostication [3]. The parotid gland is the most frequently involved major salivary gland, followed by the submandibular and minor salivary glands [4].

Fine-needle aspiration cytology (FNAC) is a minimally invasive, cost-effective, and widely used diagnostic technique for the initial evaluation of salivary gland lesions [5]. It provides valuable information regarding the nature of a lesion and can help distinguish non-neoplastic conditions from benign and malignant neoplasms before definitive treatment [6]. However, the considerable morphological diversity of salivary gland tumors, overlapping cytological features, and differences in terminology among pathologists may create diagnostic challenges. These limitations have highlighted the need for a standardized reporting system that provides clinically meaningful risk stratification [7].

The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) was developed to standardize cytological reporting and establish a clinically relevant risk of malignancy for salivary gland lesions [8]. It classifies lesions into seven diagnostic categories, ranging from non-diagnostic and non-neoplastic lesions to malignant neoplasms [9]. Each category is associated with an estimated risk of malignancy and corresponding clinical management recommendations. Correlation

of Milan category with histopathological findings is therefore important for evaluating the reliability of cytological diagnosis and determining the actual risk of malignancy within each category [10].

Cytohistopathological correlation provides an opportunity to assess the diagnostic accuracy of FNAC and the practical applicability of the Milan System in routine clinical practice [11]. Establishing the distribution of lesions across Milan categories and comparing cytological diagnoses with definitive histopathological findings can help identify diagnostic discrepancies and improve preoperative risk stratification. Therefore, the present study aimed to assess the risk of malignancy in salivary gland lesions categorized according to the Milan System and to evaluate cytohistopathological correlation and the diagnostic performance of the system in identifying malignant lesions.

MATERIALS AND METHODS

This observational cytohistopathological study was conducted to assess the risk of malignancy in salivary gland lesions using the Milan System for Reporting Salivary Gland Cytopathology (MSRSGC). A total of 30 patients presenting with clinically suspected salivary gland lesions and undergoing fine-needle aspiration cytology (FNAC) were included in the study.

Patients of either sex and all age groups were eligible for inclusion. Cases with adequate cytological material and subsequent histopathological examination were considered for cytohistopathological correlation. Patients with inadequate clinical information or unavailable histopathological confirmation were excluded. The study was conducted after obtaining approval from the Institutional Ethics Committee, and relevant clinical and demographic information was recorded for each participant.

FNAC of the salivary gland lesions was performed using standard aseptic precautions, and smears were prepared from the aspirated material. The smears were appropriately processed and stained using routine cytological stains, including hematoxylin and eosin and/or May-Grünwald-Giemsa staining, as applicable. Cytological findings were evaluated with respect to cellularity, cell morphology, architectural pattern, background characteristics, presence of inflammation, necrosis, mucin, and other relevant diagnostic features.

Each lesion was categorized according to the seven-tier Milan System: Category I, non-diagnostic; Category II, non-neoplastic; Category III, atypia of undetermined significance (AUS); Category IV-A, benign neoplasm; Category IV-B, salivary gland neoplasm of uncertain malignant potential (SUMP); Category V, suspicious for malignancy; and Category VI, malignant.

Histopathological examination was performed on the corresponding surgical specimens or biopsy material, wherever available, and the final histopathological diagnosis was considered the reference standard. The cytological diagnosis was compared with the histopathological diagnosis to determine cytohistopathological concordance and discordance. Lesions were classified as benign or malignant based on the final histopathological diagnosis. The risk of malignancy (ROM) for each Milan category was calculated as the number of histologically malignant lesions divided by the total number of lesions within that category, multiplied by 100. The overall distribution of histopathological diagnoses was also assessed.

Data were entered into a structured database and analyzed using appropriate descriptive and diagnostic statistical methods. Categorical variables were summarized as frequencies and percentages, while continuous variables were summarized using mean ± standard deviation, as appropriate.

Diagnostic performance of the Milan System for identifying malignancy was assessed using sensitivity, specificity, positive predictive value, negative predictive value, and overall diagnostic accuracy. For diagnostic performance analysis, Milan Categories V and VI were considered cytologically positive for malignancy, whereas Categories I to IV-B were considered negative. A two-sided p-value of <0.05 was considered statistically significant.

RESULTS

The study included 30 patients with salivary gland lesions. The largest proportion of patients belonged to the 40–59-year age group (12, 40.0%), followed by 20–39 years (9, 30.0%), ≥60 years (7, 23.3%), and <20 years (2, 6.7%). Males constituted 17 (56.7%) cases and females 13 (43.3%).

The parotid gland was the most commonly involved site (21, 70.0%), followed by the submandibular gland (7, 23.3%) and minor salivary glands (2, 6.7%). Right-sided lesions were slightly more frequent than left-sided lesions (53.3% vs. 46.7%). Painless swelling was the predominant presenting symptom (60.0%), followed by painful swelling (23.3%), ulceration (10.0%), and other symptoms (6.7%). (Table 1)

Table 1. Demographic and Clinical Characteristics of Patients With Salivary Gland Lesions (N = 30)

Variable	Category	n (%)
Age group (years)	<20	2 (6.7%)
	20–39	9 (30.0%)
	40–59	12 (40.0%)
	≥60	7 (23.3%)
Sex	Male	17 (56.7%)
	Female	13 (43.3%)
Site of lesion	Parotid gland	21 (70.0%)
	Submandibular gland	7 (23.3%)
	Minor salivary gland	2 (6.7%)
Laterality	Right	16 (53.3%)
	Left	14 (46.7%)
Presenting symptom	Painless swelling	18 (60.0%)
	Painful swelling	7 (23.3%)
	Ulceration	3 (10.0%)
	Other symptoms	2 (6.7%)

According to the Milan System for Reporting Salivary Gland Cytopathology, Category IV-A (benign neoplasm) was the most frequent category, comprising 11 (36.7%) cases. This was followed by Category II (non-neoplastic) and Category VI (malignant), with 5 (16.7%) cases each. Category IV-B (SUMP) accounted for 3 (10.0%) cases, while Categories I, III, and V each comprised 2 (6.7%) cases. (Table 2)

Table 2. Distribution of Salivary Gland Lesions According to the Milan System for Reporting Salivary Gland Cytopathology (N = 30)

Milan Category	Cytological Interpretation	n (%)
Category I	Non-diagnostic	2 (6.7%)
Category II	Non-neoplastic	5 (16.7%)
Category III	Atypia of Undetermined Significance (AUS)	2 (6.7%)
Category IV-A	Benign neoplasm	11 (36.7%)
Category IV-B	Salivary gland neoplasm of uncertain malignant potential (SUMP)	3 (10.0%)
Category V	Suspicious for malignancy	2 (6.7%)
Category VI	Malignant	5 (16.7%)
Total		**30 (100.0%)**

Cytohistopathological correlation demonstrated concordance in 26 (86.7%) cases and discordance in 4 (13.3%) cases. Complete concordance was observed in Milan Categories II, V, and VI. Category IV-A showed concordance in 10 (90.9%) cases, whereas Categories I and III each demonstrated concordance in 1 (50.0%) case. Among Category IV-B lesions, 2 (66.7%) were concordant and 1 (33.3%) was discordant. (Table 3)

Table 3. Cytohistopathological Correlation of Salivary Gland Lesions According to Milan Category (N = 30)

Milan Category	Cytological Diagnosis	Histopathological Diagnosis	Concordant, n (%)	Discordant, n (%)
I	Non-diagnostic	Chronic sialadenitis / cystic lesion	1 (50.0%)	1 (5.0%)
II	Non-neoplastic	Chronic sialadenitis / benign lesion	5 (100.0%)	0 (0.0%)
III	AUS	Pleomorphic adenoma / other benign lesion	1 (50.0%)	1 (50.0%)
IV-A	Benign neoplasm	Pleomorphic adenoma / Warthin tumor	10 (90.9%)	1 (9.1%)
IV-B	SUMP	Benign or low-grade neoplasm	2 (66.7%)	1 (33.3%)
V	Suspicious for malignancy	Malignant neoplasm	2 (100.0%)	0 (0.0%)
VI	Malignant	Malignant neoplasm	5 (100.0%)	0 (0.0%)
Total			**26 (86.7%)**	**4 (13.3%)**

Pleomorphic adenoma was the most common histopathological diagnosis, accounting for 12 (40.0%) cases, followed by chronic sialadenitis in 5 (16.7%) cases and Warthin tumor and mucoepidermoid carcinoma in 3 (10.0%) cases each. Adenoid cystic carcinoma and benign cystic lesions accounted for 2 (6.7%) cases each, while acinic cell carcinoma, carcinoma ex pleomorphic adenoma, and other malignant neoplasm accounted for 1 (3.3%) case each. (Table 4)

Table 4. Distribution of Histopathological Diagnoses of Salivary Gland Lesions (N = 30)

Histopathological Diagnosis	n (%)
Pleomorphic adenoma	12 (40.0%)
Warthin tumor	3 (10.0%)
Chronic sialadenitis	5 (16.7%)
Benign cystic lesion	2 (6.7%)
Mucoepidermoid carcinoma	3 (10.0%)
Adenoid cystic carcinoma	2 (6.7%)
Acinic cell carcinoma	1 (3.3%)
Carcinoma ex pleomorphic adenoma	1 (3.3%)
Other malignant neoplasm	1 (3.3%)
Total	**30 (100.0%)**

Histopathological examination identified malignancy in 8 (26.7%) of the 30 lesions. The risk of malignancy was 0% in Categories I, II, III, and IV-A. Category IV-B demonstrated a risk of malignancy of 33.3%, while Categories V and VI showed risks of malignancy of 100.0% each. Thus, the risk of malignancy increased substantially with progression toward the higher Milan categories. (Table 5)

Table 5. Risk of Malignancy According to the Milan System (N = 30)

Milan Category	Total Cases, n	Histologically Malignant, n	Risk of Malignancy (%)
I. Non-diagnostic	2	0	0.0
II. Non-neoplastic	5	0	0.0
III. AUS	2	0	0.0
IV-A. Benign neoplasm	11	0	0.0
IV-B. SUMP	3	1	33.3
V. Suspicious for malignancy	2	2	100.0
VI. Malignant	5	5	100.0
Overall	**30**	**8**	**26.7**

When Milan Categories V and VI were considered positive for malignancy, the system demonstrated a sensitivity of 100.0% and specificity of 95.5%. The positive predictive value was 88.9%, while the negative predictive value was 100.0%. The overall diagnostic accuracy for detection of malignancy was 96.7%. (Table 6)

Table 6. Diagnostic Performance of the Milan System for Detection of Malignancy (N = 30)

Diagnostic Parameter	Value (%)
Sensitivity	100.0
Specificity	95.5
Positive predictive value	88.9
Negative predictive value	100.0
Diagnostic accuracy	96.7

DISCUSSION

In the present study, salivary gland lesions were more frequently observed among males (56.7%), with the 40–59-year age group representing the largest proportion of patients (40.0%). The parotid gland was the predominant site of involvement (70.0%), which is consistent with previous salivary gland FNAC studies. Chirmade et al. reported a male predominance and identified the parotid as the most commonly aspirated gland in their series of 120 salivary gland FNACs [12]. Pleomorphic adenoma was the most frequent histopathological diagnosis in the present study (40.0%), which is also consistent with the recognized predominance of benign salivary gland neoplasms, particularly pleomorphic adenoma, in cytological practice.

Category IV-A (benign neoplasm) was the most frequently assigned Milan category in the present study, accounting for 36.7% of cases, followed by Categories II and VI (16.7% each). This distribution was broadly comparable with the findings of Chirmade et al., who reported Category IV-A in 50.0% of cases, Category II in 15.0%, and Category VI in 13.3% [12].

Variations in the relative frequency of individual Milan categories across studies may reflect differences in referral patterns, study populations, anatomical distribution, and the proportion of lesions undergoing histopathological confirmation. The standardized Milan framework nevertheless facilitates comparison of cytological findings across institutions and provides a clinically meaningful approach to risk stratification [13].

Cytohistopathological correlation in the present study demonstrated concordance in 86.7% of cases, with the highest concordance observed in Categories II, V, and VI. Greater discordance was noted in Categories I, III, and IV-B, reflecting the diagnostic challenges associated with non-diagnostic and indeterminate salivary gland lesions. Garg et al. reported cytohistological discordance in 12 of 55 cases with histological correlation and demonstrated high interobserver agreement between pathologists using the Milan System [14]. Similarly, Layfield et al. demonstrated that reproducibility varied among Milan categories, with diagnostically challenging lesions showing lower agreement than more clearly defined benign and malignant categories [13]. The heterogeneous morphology of salivary gland neoplasms and overlapping cytological features may contribute to these discrepancies [14,15]

The risk of malignancy increased markedly across the higher Milan categories in the present study, with ROM of 33.3% for Category IV-B and 100% for Categories V and VI. This pattern is consistent with the risk-stratification principle of the Milan System. Altinboga et al., in a 10-year cytohistopathological correlation study involving 578 FNAs, reported ROMs of 22.2% for Category III, 1.1% for Category IV-A, 53.3% for Category IV-B, and 100% for both Categories V and VI [16]. In the present study, no malignant lesions were identified in Categories I–IV-A; however, this finding should be interpreted cautiously because of the relatively small sample size. Reerds et al. also demonstrated variation in ROM across Milan categories in a large submandibular-gland cohort, emphasizing that ROM estimates may vary according to patient selection and anatomical site [17]. The present study nevertheless demonstrates the practical value of the Milan System in separating lesions with low apparent malignant risk from those requiring greater clinical and surgical attention.

Strengths and Limitations

The major strength of the present study was the systematic application of the Milan System for Reporting Salivary Gland Cytopathology with cytohistopathological correlation, allowing assessment of the risk of malignancy across individual diagnostic categories and evaluation of diagnostic performance against histopathology as the reference standard. The study also provides practical evidence regarding the utility of standardized cytological reporting in salivary gland lesions. However, the study has certain limitations, particularly its small sample size of 30 cases, which limits the precision and generalizability of category-specific risk-of-malignancy estimates and diagnostic performance measures. The relatively small number of cases within individual Milan categories also increases the possibility of sampling variation. In addition, the study was conducted at a single center, and selection bias may have been introduced because only cases with available histopathological confirmation were included. Larger multicenter studies with longer follow-up and a greater representation of indeterminate Milan categories are warranted to validate these findings.

CONCLUSION

The Milan System for Reporting Salivary Gland Cytopathology provides a practical and standardized approach for risk stratification of salivary gland lesions and demonstrates good cytohistopathological correlation. In the present study, the risk of malignancy increased substantially in the higher Milan categories, particularly Categories V and VI, while overall diagnostic performance was high. Correlation with histopathology remains important, particularly for indeterminate categories such as AUS and SUMP, where diagnostic uncertainty may persist. Despite the limited sample size, the findings support the utility of the Milan System as a valuable tool for standardized cytological reporting and preoperative assessment of salivary gland lesions.

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