APPLICATION OF THE MILAN SYSTEM IN CYTOLOGICAL DIAGNOSIS AND MALIGNANCY PREDICTION OF PAROTID GLAND TUMORS

Luong Huu Dang[1,2], Tran Vo Quynh Anh[2], Nguyen Kieu Diem[2]

ABSTRACT

Objectives: In Vietnam, the Milan system for Reporting Salivary Gland Cytopathology has been widely adopted in the cytological diagnosis of parotid gland tumors, contributing to the risk assessment of malignancy and neoplasia in these tumors. This study was conducted to evaluate the utility of the Milan system in fine-needle aspiration cytology (FNAC) by comparing cytological results with histopathological findings of parotid gland tumor cases.

Methods: A cross-sectional descriptive study was performed on patients diagnosed with parotid gland tumors at the Department of Otorhinolaryngology, University Medical Center Ho Chi Minh City.

Results: From January 2021 to May 2024, 157 patients with parotid gland tumors were included in the study. Among them, 151 patients had unilateral parotid gland tumors, while 6 patients had bilateral parotid gland tumors. Regarding the diagnostic value for malignancy risk, the Milan system demonstrated high sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy. Specifically, the specificity, negative predictive value, and accuracy were above 90%. For neoplastic risk assessment, the Milan system showed high sensitivity, specificity, positive predictive value, and accuracy (over 90%); however, the negative predictive value was relatively low at 55.56%.

Conclusion: The Milan system proved highly valuable in distinguishing between benign and malignant lesions and identifying cases requiring classification into uncertain diagnostic categories.

Keywords: *Milan system, Fine Needle Aspiration, Parotid salivary tumor*

I. BACKGROUND

Salivary gland tumors are rare, accounting for less than 4% of head and neck tumors. Among these, 70% occur in the parotid gland, and 75% of parotid tumors are benign, primarily affecting individuals aged 40–59 [1]. In Vietnam, data from the Oncology Hospital in Ho Chi Minh City indicate that salivary gland cancer constitutes 0.88% of all cancers in men and 0.71% in women [2].

Fine-needle aspiration cytology (FNA) is widely regarded as an essential diagnostic tool for evaluating salivary gland lesions. Previously, cytological reports for salivary glands were based on reporting frameworks originally developed for other types of cytology, such as the Bethesda System for Thyroid and Cervical cytology. However, these frameworks lacked standardization in terminology and criteria, which often made interpretation and classification of salivary gland lesions inconsistent and challenging. To address these issues, the "Milan system for Reporting Salivary Gland Cytopathology" (MSRSGC) was introduced. This system provides a standardized set of diagnostic categories, practical clinical guidance, and a malignancy risk assessment for each

[1] *Department of Otolaryngology, University Medical Center Ho Chi Minh City, Ho Chi Minh city, Vietnam*
[2] *Department of Otolaryngology, Faculty of Medicine,*
University of Medicine and Pharmacy at Ho Chi Minh city, Ho Chi Minh city, Vietnam
Responsible person: Luong Huu Dang
Email: dang.lh1@umc.edu.vn
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category. The Milan system has demonstrated its value in multiple studies, achieving diagnostic accuracy rates of approximately 97.8% for benign tumors and 97.3% for malignant tumors. These findings highlight its effectiveness in ensuring consistency in cytological reporting and improving both diagnostic accuracy and prognostic predictions. Widespread adoption of the Milan system has the potential to significantly enhance the quality of care for patients with salivary gland tumors [3].

In Vietnam, the Milan system has been increasingly used for the diagnosis of parotid gland tumors (PGTs). However, comprehensive evaluations of its clinical value are still lacking. The University Medical Center in Ho Chi Minh City began implementing the Milan system in 2021, but there have been no formal studies assessing its application and effectiveness in predicting malignancy risk and neoplastic potential in parotid gland tumors.

This study was conducted to assess the diagnostic utility of the Milan system in fine-needle aspiration cytology for parotid gland tumors. Specifically, it aims to compare Milan system-based cytological findings with histopathological outcomes at the University Medical Center in Ho Chi Minh City.

II. METHODS

The study is a cross-sectional descriptive study conducted from January 2021 to May 2024.

2.1. Pateints selection

Patients diagnosed with parotid gland tumors (PGTs) at the Otorhinolaryngology Department, University Medical Center Ho Chi Minh City. Eligible patients included those who underwent fine-needle aspiration (FNA) with cytological findings classified using the Milan system and had postoperative histopathological results available.

2.2. Sample size calculation

The sample size was determined using the following formula:

$$n = \frac{Z^2 \times P \times (1 - P)}{E^2}$$

Where:

P: Proportion of malignant parotid gland tumors (PGTs), estimated at 18.79% (0.1879).

E: Acceptable margin of error, set at 0.07 (7%).

Z: Z-score corresponding to a 95% confidence level (Z = 1.96).

Using these parameters, the calculated sample size is 120 cases.

2.3. Statistical analysis

Data entry was performed using Excel 2016, and statistical analysis was conducted using Stata/IC 13.0.

III. RESUTLS

From January 2021 to May 2024, we collected data on 157 patients with parotid gland tumors (PGTs). Among these, 151 patients had unilateral PGTs, and 6 patients had bilateral PGTs.

3.1. General characteristics

The mean age of patients was 53.75 ± 14.04 years, with an age range of 18 to 93 years. A higher prevalence was observed in males, with a male-to-female ratio of 1.34:1. Tumors were evenly distributed between the left and right sides.

3.2. Frequency of histopathological lesions by Milan

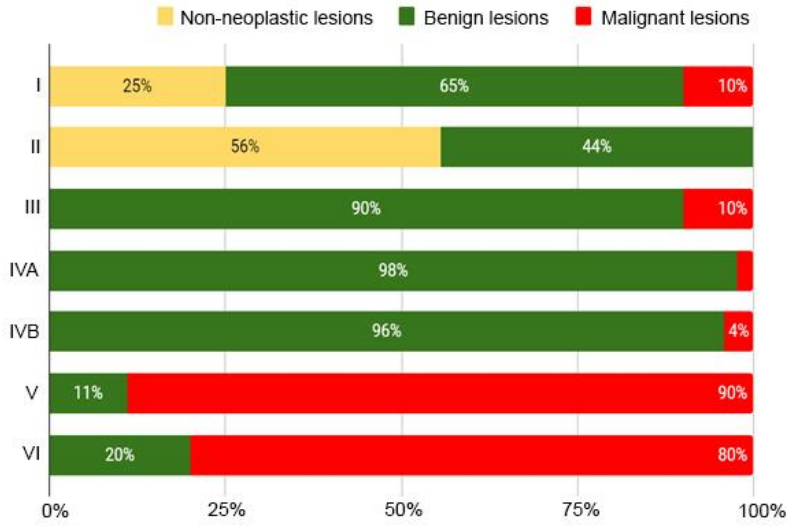

Figure 1: Frequency of histopathological lesions by Milan classification

The distribution of histopathological lesions across the Milan classification groups revealed notable trends (**Figure 1**). Group I exhibited the highest proportion of benign tumors, followed by non-neoplastic lesions, while malignant tumors accounted for approximately 10% of cases. In Group II, non-neoplastic lesions predominated, representing the most frequent finding. Groups III, IVA, and IVB were characterized by a majority of benign lesions, indicating the predominance of non-malignant conditions in these categories. Conversely, Groups V and VI showed a significant shift, with malignant lesions being the most prevalent, emphasizing their association with high-risk and aggressive pathologies.

These patterns highlight the utility of the Milan classification system in stratifying salivary gland lesions based on malignancy risk, thereby aiding clinicians in diagnosis and management decisions.

3.3. Histopathological profiles of Milan groups I, II, and III

Table 1: **Types of tumors by histopathological findings in Milan groups I, II, and III**

	Lesions	Milan I (n,%)	Milan II (n,%)	Milan III (n,%)
Non-Neoplastic Lesions	Kimura Disease		1 (11.11%)	
	Lymphoepithelial Cyst	1 (5%)	1 (11.11%)	
	Salivary Gland Cyst	2 (10%)		
	Chronic Sialadenitis	2 (10%)	3 (33.33%)	
Benign Tumors	Pleomorphic Adenoma	2 (10%)		2 (20%)
	Warthin Tumor	7 (35%)	3 (33.33%)	7 (70%)
	Basal Cell Adenoma	2 (10%)		
	Solitary Fibrous Tumor	1 (5%)		
	Hemangioma	1 (5%)		
	Lymphoepithelial Adenoma		1 (11.11%)	
Malignant Tumors	Mucoepidermoid Carcinoma	1 (5%)		1 (10%)
	Sarcomatoid Carcinoma	1 (5%)		
	Total	20	9	10

The histopathological findings within Milan Groups I, II, and III reflect distinct patterns of lesion prevalence and classification (**Table 1**). In Milan Group I, Warthin tumors were the most common, with two malignant cases also reported. In Milan Group II, chronic sialadenitis predominated, alongside benign tumors such as Warthin tumors and lymphoepithelial adenomas. No malignancies were recorded. In Milan Group III, Warthin tumors were the most frequent, with one case of mucoepidermoid carcinoma (10%). No non-neoplastic lesions were noted.

3.4. Histopathological profiles of Milan groups IVA and IVB

Table 2: Types of tumors by histopathological findings in Milan groups IVA and IVB

	Lesions	Milan IVA (n,%)	Milan IVB (n,%)
Benign Tumors	Pleomorphic Adenoma	34 (39.53%)	12 (50%)
	Warthin Tumor	42 (48.84%)	5 (20.83%)
	Basal Cell Adenoma	2 (2.22%)	5 (20.83%)
	Oncocytoma	3 (3.39%)	1 (4.17%)
	Schwannoma	1 (1.16%)	
	Mixed Parotid Tumor	1 (1.16%)	
	Myoepithelioma	1 (1.16%)	
Malignant Tumors	Mucoepidermoid Carcinoma	1 (1.16%)	1 (4.17%)
	Adenoid Cystic Carcinoma	1 (1.16%)	
	Total	86	24

The histopathological findings within Milan Groups IVA and IVB demonstrate distinct patterns in tumor prevalence and classification (**Table 2**). In Milan Group IVA, Warthin tumors were the most frequent, followed by pleomorphic adenomas. Two malignant cases-mucoepidermoid carcinoma and adenoid cystic carcinoma-were also included in this group. In Milan Group IVB, pleomorphic adenomas were the most common, followed by Warthin tumors and basal cell adenomas, each accounting for 20.83% of cases. One malignant case, mucoepidermoid carcinoma, was documented in this group.

3.5. Histopathological profiles of Milan groups IV and VI

Table 3: **Types of tumors by histopathological findings in Milan groups IV and V.**

	Lesions	Milan V (n,%)	Milan VI (n,%)
Benign Tumors	Basal Cell Adenoma		1 (20%)
	Pleomorphic Adenoma	1 (11.11%)	
Malignant Tumors	Epithelial-Myoepithelial Carcinoma		1 (20%)
	Adenoid Cystic Carcinoma	2 (22.22%)	
	Mucoepidermoid Carcinoma	1 (11.11%)	1 (20%)
	Adenocarcinoma, Not Otherwise Specified (NOS)	1 (11.11%)	1 (20%)
	Squamous Cell Carcinoma	2 (22.22%)	1 (20%)
	Lymphoma	1 (11.11%)	
	Salivary Duct Carcinoma	1 (11.11%)	
	Total	9	5

The histopathological findings within Milan Groups V and VI reflect a predominance of malignant tumors, with distinct subtype distributions (**Table 3**). In Milan Group V, malignant tumors accounted for the majority of cases. Six distinct histopathological subtypes were identified, with squamous cell carcinoma and adenoid cystic carcinoma being the most frequent. In Milan Group VI, malignant tumors also dominated, with four distinct histopathological subtypes observed.

3.6. Malignancy risk

Table 4: Risk of malignancy (ROM) by Milan groups

Milan Groups	Benign Cases (n)	Malignant Cases (n)	ROM (%)
I	18	2	10%
II	9	0	0%
III	9	1	10%
IVA	84	2	2.32%
IVB	23	1	4.17%
V	1	8	89.99%
VI	1	4	80%
Total	145	18	11.04%

As presented in **Table 4**, the risk of malignancy (ROM) varies across Milan groups. In diagnostic groups suggestive of benignity, the ROM was low, with 0% in Group II and 2.32% in Group IVA. Conversely, groups associated with malignancy exhibited the highest ROM, with 89.99% in Group V and 80.00% in Group VI. For diagnostic groups with indeterminate findings, ROM was 10% in Group I and 4.1% in Group IVB.

Table 5: Malignancy grades by Milan groups

Milan Groups	Malignancy Grades		
	Low (n,%)	Intermediate (n,%)	High (n,%)
I	1 (50.50%)	0 (0%)	1 (50.50%)
II	0 (0%)	0 (0%)	0 (0%)
III	1 (100%)	0 (0%)	0 (0 %)
IVA	2 (100%)	0 (0%)	0 (0%)
IVB	0 (0%)	1 (100%)	0 (0 %)
V	4 (50%)	1 (12.50%)	3 (37.50%)
VI	1 (25%)	0 (0%)	3 (75%)
Total	9 (50%)	2 (11.11%)	7 (38.89%)

As shown in **Table 5**, the distribution of malignancy grades differs between Milan groups. Group V predominantly comprised low-grade malignancies, with high-grade malignancies occurring less frequently. In contrast, Group VI was characterized by a higher prevalence of high-grade malignancies, while low-grade malignancies were less common.

3.7. Diagnostic value of FNA for malignancy risk based on the Milan system

Table 6: Correlation table for malignancy risk using the Milan system

Milan Groups	Malignant (n)	Benign (n)
Groups V and VI	12	2
Groups II and IVA	2	93

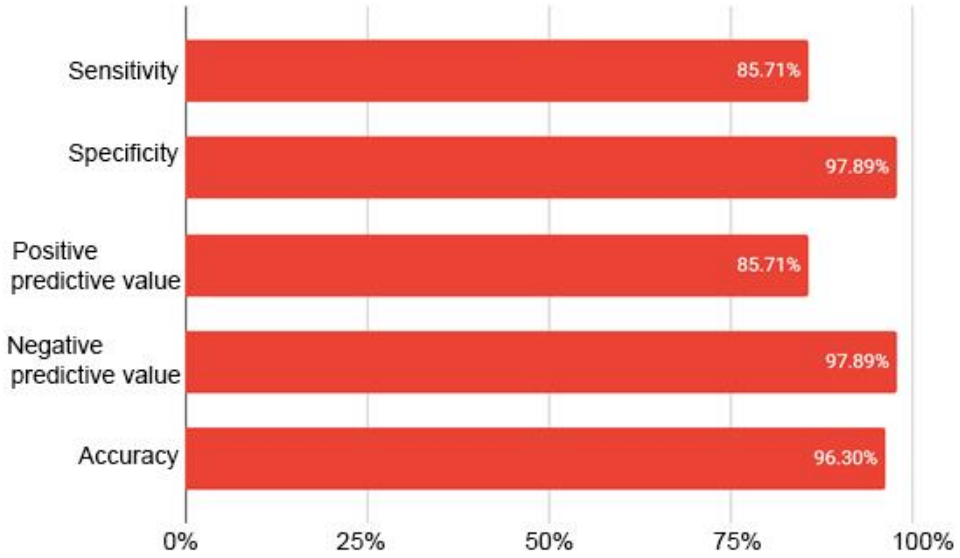

Figure 2: Diagnostic value of the Milan system for malignancy risk

As shown in **Table 6**, the Milan system effectively differentiates between malignant and benign lesions. The system demonstrated high diagnostic performance for predicting malignancy, as illustrated in **Figure 2**. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy were all high. Notably, specificity, NPV, and accuracy exceeded 90%, underscoring the reliability of the system in differentiating benign from malignant lesions.

3.8. Diagnostic value of FNA for neoplastic risk based on the Milan system

Table 7: Neoplastic risk by Milan groups

Milan Groups	Benign and Malignant Neoplastic Cases (n)	Non-Neoplastic Cases (n)	RON (%)
I	15	5	75%
II	4	5	44,44%
III	10	0	100%
IVA	86	0	100%
IVB	24	0	100%
V	9	0	100%
VI	5	0	100%
Total	153	10	

Milan Groups III, IVA, IVB, V, and VI showed the highest Risk of Neoplasia (RON) at 100%, followed by Group I at 75%, and Group II with the lowest RON at 44% (**Table 7**).

Table 8: Correlation table for neoplastic risk using the Milan system

Milan Groups	Benign and Malignant Neoplastic Cases (n)	Non-Neoplastic Cases (n)
Groups IVA, IVB, V, and VI	124	0
Group II	4	5

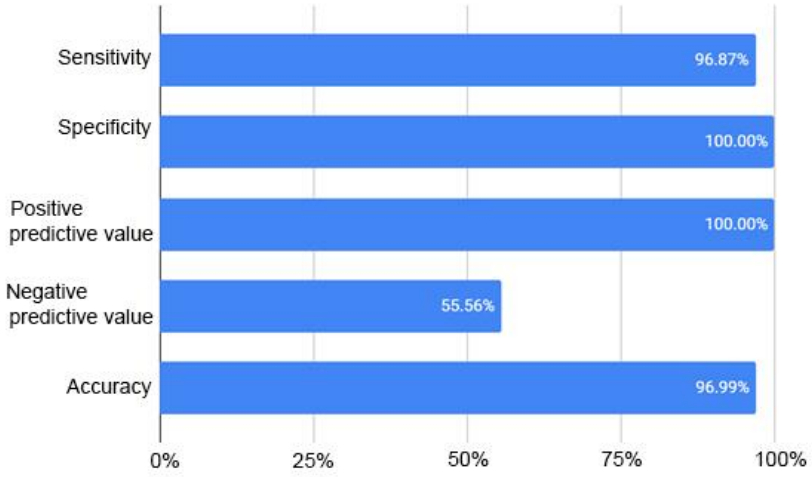

Figure 3: Diagnostic value of the Milan system for neoplastic risk

As shown in **Table 6**, the Milan system effectively differentiates between benign, malignant, and non-neoplastic lesions, demonstrating high diagnostic performance for predicting neoplastic risk, as illustrated in **Figure 3**. The Milan system demonstrated high sensitivity, specificity, positive predictive value (PPV), and overall accuracy for predicting neoplastic risk, all exceeding 90%. However, the negative predictive value (NPV) was relatively low at 55.56%, indicating some limitations in ruling out neoplastic lesions.

IV. DICUSSIONS

4.1. Prognostic value for malignancy risk using the Milan system

In our study, the Milan system demonstrated a high overall diagnostic accuracy of 96.3% for the cytological evaluation of parotid gland tumors (PGTs). This result aligns closely with findings from other studies, which report accuracy rates ranging from 93.6% to 99.3%, highlighting the system's reliability and effectiveness in clinical practice (**Table 9**).

Table 9: **Comparison of prognostic accuracy for malignancy risk using the Milan system**

	Our study (n = 163)	**Phan Nguyễn Hoàng Đăng *et al.* [4] (n = 628)**	**Higuchi *et al.* [3] (n = 1608)**	**Lee *et al.* [5] (n = 421)**	**Savant *et al.* [6] (n = 199)**	**Viswa-nathan *et al.* [7] (n = 373)**
Sensitivity	85.71%	97.20%	91.40%	76.50%	96.10%	79%
Specificity	97.89%	99.70%	99.10%	99.10%	100%	96%
Positive Predictive Value (PPV)	85.71%	98.50%	96.70%	92.90%	100%	92%
Negative Predictive Value (NPV)	97.89%	99.40%	97.50%	96.60%	96.20%	94%
Accuracy	96.30%	99.20%	97.30%	96.20%	99.30%	

Our study recorded a specificity of 97.89% for the Milan system, comparable to previous studies by Phan Nguyễn Hoàng Đăng *et al.* [4] (99.7%), Lee *et al.* [5] (99.1%), and Savant *et al.* [6] (100%). The positive predictive value (PPV) in our study was slightly lower than that of other studies, whereas the negative predictive value (NPV) were within the reported ranges. Our study demonstrated a sensitivity of 85.7%, which falls within the reported range of other studies (76.5%–97.2%) and is notably higher than that reported by Lee *et al.* [5] (76.5%). In the study by Lee et al., prior diagnoses were retrospectively reclassified using the Milan system, with a specific focus on minimizing false negatives in Group IVA. While this approach aligned with the overarching goals of the Milan system, it did not fully adhere to its diagnostic criteria. Consequently, although the number of false negatives in Group IVA was significantly reduced, an increased incidence of false negatives in Group II resulted in a lower overall sensitivity. This highlights the importance of adhering strictly to the Milan system's diagnostic criteria to avoid trade-offs, such as reducing false negatives in one group while inadvertently increasing them in another, which can affect overall sensitivity. These studies thoroughly re-evaluated cytological specimens and applied the Milan system's diagnostic criteria. This highlights that when the Milan system is strictly implemented, the sensitivity of cytological diagnosis for parotid gland tumors can achieve very high levels. The Milan system proved highly effective in distinguishing benign from malignant lesions and identifying cases requiring classification into indeterminate groups. However, further refinement of guidelines is needed to reduce the number of benign cases misclassified into indeterminate categories, particularly Groups III and IVB.

4.2. Prognostic value for RON using the Milan system

Table 10: **Comparison of RON Using the Milan system**

Milan Groups	Our study (n = 163)	Higuchi *et al.* [3] (n = 1608)	Tochtermann *et al.* [8] (n = 753)
Group I	75%	72.90%	93.30%
Group II	44.44%	15.20%	24.30%
Group III	100%	77.90%	70%
Group IVA	100%	99%	99.20%
Group IVB	100%	94.80%	98.70%
Group V	100%	100%	92%
Group VI	100%	100%	100%

Our study identified the highest absolute RON (100%) in Groups III, IVA, IVB, V, and VI, followed by Group I with a RON of 75%, and the lowest RON in Group II at 44%. When compared with other studies, we observed that RON in Groups IVA, IVB, V, and VI was consistently high and closely aligned with findings reported by other authors (**Table 10**). In Group I, our RON (75%) fell within the range of 72.9%–100% reported in the literature. However, RON for Groups II and III in our study was notably higher than that reported by other authors, suggesting possible differences in sample characteristics or classification criteria. These findings demonstrate that the Milan system

reliably predicts neoplastic risk across most groups, though variations in RON for certain groups highlight the need for further investigation into classification consistency and sample characteristics.

V. CONCLUSION

The Milan system has proven highly effective in distinguishing between benign and malignant lesions while identifying cases that require classification into indeterminate groups. However, more specific guidelines are needed to minimize the misclassification of benign cases into indeterminate categories.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICAL DECLARATIONS

This study was approved by the Biomedical Research Ethics Committee of the University of Medicine and Pharmacy at Ho Chi Minh City, under Decision No. 746/HĐĐĐ-ĐHYD, dated August 17, 2023.

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