

# Effectiveness of Milan Classification in Salivary Gland Aspirations

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## ABSTRACT

**Objective:** To determine the effectiveness of Milan system for the evaluation of aspiration cytology to salivary gland lesions classification.

**Study Design:** Cross-sectional observational study.

**Place and Duration of Study:** Department of Pathology, Tertier Centre, University of Health Sciences, Adana City Education and Research Hospital, Adana, Turkey from January 2014 to December 2020.

**Methodology:** Salivary gland aspiration cytology of the last six years was recategorised, according to Milan classification. Risk of malignancy (ROM) and risk of neoplasm (RON) were determined among the subgroups in the cytological materials of 233 patients, who had undergone excisional biopsy.

**Results:** Forty hundred and eighty salivary gland aspiration cytologies were available, in which 250 (52.1%) cases were males and 230 (47.1%) were females. The mean age was  $52.36 \pm 16.05$  years. When aspiration cytology of 233 patients with resection were evaluated, according to Milan classification, ROM in non-diagnostic category was 9.5%, ROM in non-neoplastic category was 19.2%, and ROM in neoplasm-benign category was 8.2%. ROM were found 100% in the suspected malignancy and malignancy categories. There were no patients in the atypia category of undeterminate significance.

**Conclusion:** In aspiration cytology of salivary gland lesions, Milan system provides useful information in classifying patients for clinical follow-up and treatment. However, it can be said that it is difficult to distinguish between the atypia of uncertain significance and neoplasm categories.

**Key Words:** *Salivary glands, Biopsy, Fine-needle, Milan classification.*

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## INTRODUCTION

Fine-needle aspiration biopsy (FNAB) is a well-defined method in the diagnosis, staging and follow-up of salivary gland lesions. It has been widely used in the cytological diagnosis of salivary gland lesions in the last few decades, due to its rapid diagnosis, less invasive method, and low complication rate.<sup>1</sup> Although salivary gland FNAB is affected by a number of factors, such as the technique used, the cytological preparation process, and the experience of the pathologist, it plays an important role in the clinical approach to salivary gland lesions.<sup>2</sup> It provides important information in the differentiation of non-neoplastic-neoplastic lesions and has a high accuracy rate in the differentiation of benign and malignant neoplastic lesions.<sup>3-5</sup>

However, cases reported with cytological interpretation without a specific diagnosis due to intra-tumoral heterogeneity, morphological overlaps in salivary gland lesions and lack of a standardised reporting system may cause confusion in the clinician's treatment preference.<sup>2,6,7</sup> Due to these limitations, the American Society of Cytopathology (ASC) and the International Academy of Cytology (IAC) proposed the Milan classification for aspiration cytology of salivary gland lesions, similar to the thyroid, cervix, pancreaticobiliary, lung and urinary system cytology reporting systems, to establish a standard reporting system.<sup>8,9</sup> For this purpose, the authors recategorised the salivary gland cytology of the last six years in the clinic, according to the Milan system.

The aim was to evaluate the accuracy of the cytology-histology correlation of the results and effectiveness in the management.

## METHODOLOGY

The results of patients aged 10-90 years, who underwent aspiration cytology due to salivary gland lesion in Adana City Education and Research Hospital between 2014 and 2020, were analysed. The approval from Health Sciences University Adana City Education and Research Hospital Ethics Committee was obtained (Decision No. 1201). All cytological materials were reevaluated by

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two experienced pathologists and recategorised, according to the Milan classification. Milan reporting system non-diagnostic (category 1), non-neoplastic (category 2), Atypia of undeterminate significance (category 3), neoplasm-benign (category 4a), Neoplasm-uncertain of malignant potential (category 4b), suspected malignancy (category 5), malignant cytology (category 6), consists of six main headings.<sup>2</sup> Patients, who underwent excision after cytology, were correlated with each other. The risk of neoplasm and malignancy was determined for each category. The cases were grouped according to age, gender, localisation and location.

Patients, who had previously undergone salivary gland surgery and/or received chemotherapy/regional radiotherapy, were excluded from the study.

**Table I: Cytological evaluation of total and excised cases, according to Milan classification.**

	Cytological Diagnosis (480) n (%)	Cytological results of excised cases (233) n (%)
<b>Nondiagnostic</b>	<b>62( 12.9)</b>	<b>21( 9)</b>
Inadequate	33	10
Cyst content	29	11
<b>Nonneoplastic</b>	<b>118(24.6)</b>	<b>26(11.2)</b>
Sialadenitis	56	13
Cystic content	8	3
Lymph node/Reactive lymph node	41	5
Granulomatous inflammation	10	3
Abcess	1	1
Normal salivary gland	2	1
<b>AUS</b>	-	-
<b>Neoplasm-benign</b>	<b>236(49.2)</b>	<b>146(62.7)</b>
Pleomorphic adenoma	100	70
Warthin Tumor	128	70
Lipoma	3	3
Schwannoma	1	1
Myoepithelioma	3	1
Oncocytoma	1	1
<b>SUMP</b>	<b>25(5.2)</b>	<b>12(5.2)</b>
Oncocytic neoplasm	4	1
Myoepithelial neoplasm	4	3
Pleomorphic adenoma with atypical features	7	3
Basaloid neoplasm	7	3
Low Grade Salivary Gland Neoplasm	3	2
<b>SM</b>	<b>14(2.9)</b>	<b>6(2.6)</b>
Lymphoma	4	3
Squamous Cell Carcinoma	4	2
Mesenchymal neoplasm	1	1
Mucoepidermoid Carcinoma	3	-
Acinic Cell Carcinoma	2	-
<b>Malignant</b>	<b>25(5.2)</b>	<b>22(9.4)</b>
Lymphoma	3	3
Squamous Cell Carcinoma	6	6
Metastatic Neoplasm	7	6
Acinic Cell Carcinoma	2	2
Mucoepidermoid Carcinoma	6	4
Adenoid Cystic Carcinoma	1	1

AUS: Atypia of undetermined significance, SUMP: Salivary gland neoplasm of uncertain malignancy potential, SM: Suspicious for malignancy.

Statistical analysis was performed by using statistical package for the social sciences version 19 (SPSS Inc; Chicago, IL, USA). Descriptive data were given as mean and standard deviation (SD) for quantitative variables in frequencies, and percent for qualitative variables.

## RESULTS

In this study, the salivary glands of FNAB of 480 cases were examined in which 250 (52.1%) cases were males and 230 (47.9%) females. The mean age was  $52.22 \pm 16.14$  years. The results of cytological and histopathological evaluations, reclassified according to the Milan system, are summarised in Table I.

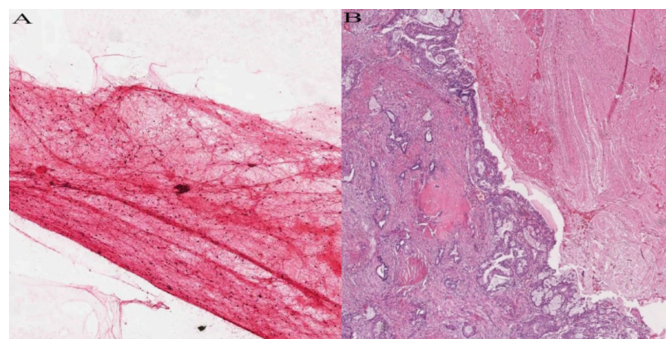
Excision material was available in 233 (48.5%) of the cases. The most common diagnostic category among the cases was neoplasm-benign. It was found to be 236 (49.2%) in all cases and 146 (62.7%) in excised cases. Whartin tumor was diagnosed most in this category (128). The diagnostic category of suspicious for malignancy had the lowest rate, both among all cases and excised cases. The evaluation of neoplasm and malignancy risk according to the Milan classification of surgically excision cases is summarised in Table II.

In the non diagnostic category, 11 cases were reported as non mucinous cyst content. One of these cases had low-grade mucoepidermoid carcinoma histology (Figure 1).

**Table II: Neoplasm and malignancy risk of associated with Milan classification.**

Milan category	Number of cases	Risk of Neoplasm (RON) n(%)	Risk of Malignancy (ROM) n(%)
Non-Diagnostic	21	15( 71.4)	2( 9.5)
Non-Neoplastic	26	6(23)	5(19.2)
AUS	-	-	-
Neoplasm, Benign	146	141(96.6)	12(8.2)
SUMP	12	11(91.7)	5(41.7)
SM	6	6(100)	6(100)
Malignant	22	22(100)	22(100)

AUS: Atypia of undetermined significance, SUMP: Salivary gland neoplasm of uncertain malignancy potential, SM: Suspicious for malignancy.

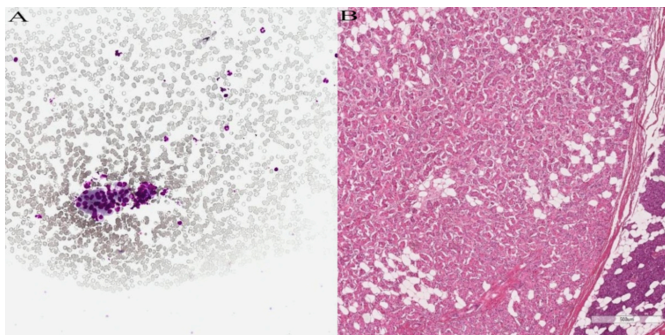


**Figure 1: (A) Cystic content containing inflammatory cells in the smear diagnosed as nondiagnostic. (Hematoxylin & Eosin stain 40x). (B) Histological sections of the sample in Figure 1A. Mucoepidermoid carcinoma with cystic area (upper right). Within the desmoplastic stroma and around the cystic area, an invasive tumor consisting of epidermoid, intermediate and mucocytes is seen at varying rates. (Hematoxylin & Eosin stain 40x).**

Ten cases were reported as insufficient material and one of these cases was diagnosed as adenoid cystic carcinoma.

There was discordance in the histological examination of six cases in the non-neoplastic category. There was histological discordance in 9 cases reported as Warthin tumor (Figure 2) and in 10 cases reported as pleomorphic adenoma in the neoplasm-benign category. Cases with cytology-histology discordance are summarised in Table III.

No cases were reported in the AUS. There were 12 case excisions in the SUMP category. Five cases were reported as malignant.



**Figure 2: (A)** A small number of polymorphonuclear leukocytes and lymphocytes are observed in the erythrocytic background. Cell group with oncocytic appearance in the central area. It was diagnosed with a Warthin tumor. (May Grunwald Giemsa stain 40x). **(B)** Histological sections of the case in Figure 2A. In the normal salivary gland, thin fibrous capsules with separated eosinophilic cytoplasm, oncocytic cells arranged in a follicular pattern, and lipocytes in between are observed. Histologically, oncocytoma was diagnosed. (Hematoxylin & Eosin stain 40x).

**Table III: Cases with Cytology-histopathology discordance.**

Nondiagnostic	FNAB (n)	Histopathological diagnosis (n)
Cyst content	11	Warthin Tumor (7) Lymphoepithelial cyst (2) Pilomatrixoma (1) Low grade Mucoepidermoid carcinoma(1)
Inadequate	6	Basal cell adenoma (1)
		Warthin Tumor (2)
		Lymphoepithelial cyst (1)
		Lipoma(1)
		Adenoid cystic carcinoma (1)
Nonneoplastic		
Sialadenitis	1	Lipoma
Abscess	1	Squamous cell carcinoma metastasis
Granulomatous inflammation	1	Malignant melanoma metastasis
Reactive lymph node	3	Fibrohistiocytic neoplasm (1) Epithelial/myoepithelial carcinoma (1) Lymphoma (1)
Neoplasm-Benign		
Warthin tumor	9	Abscess (1) Pleomorphic Adenoma (1) Oncocytoma (1) Inflammatory myofibroblastic tumor (1) Lymphoepithelial cyst (2) Chronic Sialadenitis (1) Squamous cell carcinoma metastasis (1) Pleomorphic Adenoma ex Carcinoma (1)
Pleomorphic adenoma	10	Pleomorphic Adenoma ex Carcinoma (4) Squamous cell carcinoma metastasis (2) Malignant melanoma metastasis (2) Adenoid cystic carcinoma (1) Basal cell adenoma (1)

## DISCUSSION

FNAB is a method that is widely used by clinicians in the first approach to salivary gland lesions.<sup>10</sup> After the recommendation

of ASC and IAC in 2015 and the work of Rossi *et al.*, the effectiveness of the Milan classification system and the risk of malignancy (ROM) were evaluated in various studies.<sup>7</sup> In various studies, the neoplasm-benign category was found as the most common category. The rates in these studies were found to be 36.9%, 33%, and 31.4%.<sup>11-13</sup> In this study, neoplasm-benign category was the most common with frequency of 49.2%. This high rate in the series may be due to regional or interracial differences.

Excision was made in 48.5% (233) of the cases. When the histologically examined cases were classified as benign neoplasm, malignant neoplasm and non-neoplastic, 63.9% of the cases were diagnosed as benign neoplasm, 22.3% as malignant neoplasm and 13.8% as nonneoplastic lesion. In a meta-analysis study, in which 4,506 cases were examined histologically, 62.0% of cases were diagnosed as benign neoplasm, 26.0% for malignant neoplasm, and 12.0% for nonneoplastic.<sup>14</sup> Due to the similarity of these ratios, it can be concluded that this series has a similar distribution with the studies in the literature. When the cases with surgical excision were evaluated, the non-diagnostic category comprised 9% of the cases and ROM was determined as 9.5%. Most of the cases in this category were lesions of cystic nature. Only three cases were of solid lesions. These findings show that careful evaluation of the cyst content, especially in cystic lesions, and non-diagnostic diagnosis in cases with insufficient cellular elements, is the correct approach. As a result, it is important for the pathologists to know the ultrasonographic features of the lesion. Although the expected ROM in this category is 25%, many different studies have found different rates, as in this study.<sup>13-16</sup> More importantly, rapid onsite evaluation can reduce rate of non-diagnostic category and provide more advantages for patients, and reduce the workload for health-care professionals. The expected ROM in the non-neoplastic category is 10%. In a meta-analysis study, ROM in this category was found to be in the range of 0-37%, with an average of 10.2%.<sup>14</sup> While ROM in this category was 17% in one study in the USA, and it was 17.4% in another study.<sup>12,19</sup> In this series, ROM was 19.2%. Possible inappropriate sampling in these cases could explain this high rate.

No case was reported in the AUS. This may indicate that atypical cellular elements observed in smears are mostly evaluated in the neoplasm category.

It is recommended that ROM should be below 5% in the benign neoplasm category.<sup>15</sup> In the meta-analysis study of Wei *et al.*, the mean ROM in this category was found to be 3.4% (0-13%).<sup>14</sup> In various studies, ROM in this category was found to be 1.9%, 4%, 5%, 5%, 6.9%, 2.1%, 7.3%, respectively.<sup>11-13,16-19</sup> In this study, the authors found ROM in this category to be 8.2%. Tumor heterogeneity, especially in pleomorphic adenoma ex-carcinoma cases, may explain the high malignancy risk as found in this category. However, the fact that no cases were reported in the AUS suggests that the cytology in this group may have been included in the neoplasm category as mentioned before, and therefore may be one of the reasons for the high



malignancy rate found in the benign neoplasm category.

The expected ROM in the SUMP category was 35%.<sup>15</sup> In other studies in the literature, this rate was found to be 26.7%, 33%, 34.2%, 40%, 50%, 44.4% and 50%, respectively.<sup>11-13,16-19</sup> In this series, ROM was 41.7%. The results show that are important in terms of being a warning to the clinician in cases reported as basaloid neoplasm and low-grade salivary gland neoplasm in the SUMP category, highlighting the addition of an explanatory note for the differential diagnosis of these lesions.

The expected ROM in SM category was 60%.<sup>15</sup> In other studies in the literature, this rate was found to be 100%, 67%, 92.9%, 60%, 66.6%, and 60%, respectively.<sup>11-13,16-18</sup>

The ROM was found to be 100% in this study. This value was higher than many similar studies. It can be said that this high rate shows that we tend to evaluate some cases in the malignant category as a subcategory SM. Expected rate ROM in malignant category was 90%.<sup>15</sup> In this study, all cases in the malignant category were histologically malignant (100%). In similar studies, this rate was 100%, 100%, 92.3%, 93%, 87.5%, and 100%, respectively.<sup>11-13,16-18</sup>

The main limitations of this study are the higher frequency of lymphomas and metastatic carcinomas in SM and malignant categories than primary salivary gland malignancies. Since the head and neck region is rich in lymph nodes, it should be kept in mind that metastasis to lymph nodes in and around the salivary glands may be more common.

## CONCLUSION

Milan classification seems to be a useful categorisation system in terms of creating a common language between the pathologists and the clinicians in the approach to salivary gland lesions in this study and making a clear-risk classification for the patients. The fact that ROM was low in the non-diagnostic category and high in the non-neoplastic, benign neoplasm, and SUMP categories in this study, reveals that appropriate sampling, rapid on-site evaluation, and cytopathological experience are important. The fact that few cases were reported in many studies in the AUS and SUMP categories, as in this study, may indicate a confusion in pathologists, especially for these two groups. For this reason, determining the strict cytomorphological criteria and using immuno-histochemical and molecular methods together by obtaining cell block, can help in determining the categories in the classification, especially in the differentiation of lesions with morphological overlap.

## ETHICAL APPROVAL:

The approval from Health Sciences University, Adana City Education and Research Hospital Ethics Committee was obtained (Decision No. 1201).

## PATIENTS' CONTENT:

Patients' consent was not obtained as the study was designed on retrospective pathology archive preparations.

## CONFLICT OF INTEREST:

The authors declared no conflict of interest.

## AUTHORS' CONTRIBUTION:

ZAT, OK: Conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that question related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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