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AMANDA ALMEIDA LEITE

APLICAÇÃO DO SISTEMA MILÃO PARA RELATAR CITOPATOLOGIA DE GLÂNDULA SALIVAR: UMA EXPERIÊNCIA DE TRÊS ANOS EM UM CENTRO DE CÂNCER

APPLICATION OF THE MILAN SYSTEM FOR REPORTING SALIVARY GLAND CYTOPATHOLOGY: A THREE-YEAR CANCER CENTER EXPERIENCE

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Dissertação apresentada à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Mestra em Estomatopatologia, na Área de Patologia.

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Orientador: Prof. Dr. Luiz Paulo Kowalski

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A Ata da defesa com as respectivas assinaturas dos membros encontra-se no processo de vida acadêmica do aluno.

Na vida, para ser feliz, você deve gostar de caminhar mais do que alcançar o cume da montanha. O topo dura pouco.

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RESUMO

Tumores de glândula salivar (TGS) são neoplasias pertencentes a um grupo de lesões de natureza heterogênea, que exibem características clínico-patológicas complexas. A técnica de Punção Aspirativa por Agulha Fina (PAAF) já provou ser uma ferramenta útil e indispensável no diagnóstico de lesões de glândula salivar. Ela se constitui como um método importante que pode acelerar o processo diagnóstico e diminuir o custo geral do tratamento. Além disso, é uma técnica segura, de fácil execução, geralmente bem tolerada pelo paciente e de baixo custo. Todavia, alguns estudos relatam a dificuldade em se estabelecer diagnósticos específicos. Aliado a isso, a falta de um sistema de classificação citopatológico clinicamente validado para essas lesões representa uma limitação importante que dificulta ainda mais o diagnóstico preciso e a comunicação entre clínicos e patologistas, o que pode influenciar de forma desfavorável na melhor escolha de tratamento para o paciente. Sendo assim, o objetivo do presente estudo foi avaliar retrospectivamente lesões de glândula salivar segundo um sistema de classificação citopatológica recentemente proposto, denominado "Milan System for Reporting Salivary Gland Cytopathology" (MSRSGC), cujas categorias de diagnóstico relacionam os riscos de malignidade às estratégias de conduta clínica para cada grupo. Com essa finalidade, todos os casos de citologia de glândula salivar diagnosticados no período de 2014 a 2017 no AC Camargo Cancer Center, São Paulo, Brasil, foram incluídos no estudo. Dados clínicos como gênero, idade, localização e diagnóstico histopatológico final foram coletados dos arquivos eletrônicos dos pacientes. Os casos que não possuíam os dados clínicos completos ou não tivessem o correspondente cirúrgico foram excluídos do estudo. Todos os casos foram revisados e reclassificados segundo as diretrizes propostas pelo Sistema Milão em uma de suas seis categorias. O risco de neoplasia e o risco de malignidade foram calculados para cada uma das categorias. Ao total, 104 amostras de PAAF de glândula salivar foram avaliadas. A maioria (57,7%) ocorreu no gênero feminino, sendo a proporção mulheres:homens 1.3:1. A média de idade apresentada foi 53,2 anos, e a faixa etária variou de 19 a 93 anos. A glândula parótida foi a principal localização das lesões (89,4%), seguida pela glândula submandibular (10,6%). Não houve casos nas glândulas salivares menores ou sublinguais. O risco de neoplasia para a categoria não diagnóstica, não neoplásica, atipia de significado indeterminado, neoplasia benigna, neoplasia de glândula salivar de potencial maligno incerto, suspeita de malignidade e maligna foi 60%, 44,4%, 90%, 100%, 50%, e 100%, e o risco de malignidade foi 15%, 0%, 40%, 9,5%, 13,3%, 50% e 100%, respectivamente. O uso do Sistema de Milão mostrou-se um método útil para predizer o risco

de neoplasia e malignidade na amostra estudada, como demonstrado em outros estudos publicados. Estudos prospectivos com grandes séries de casos são necessários para avaliar a eficácia dessa classificação a longo prazo.

Palavras-chave: Sistema Milão. Punção aspirativa por agulha fina. Lesões de glândula salivar. Neoplasia.

ABSTRACT

Salivary Gland Tumors (SGT) are neoplasms belonging to a group of heterogeneous nature lesions, which exhibit complex clinical and pathological features. The by Fine Needle Aspiration Cytology (FNAC) technique has proven to be a useful and indispensable tool in the diagnosis of salivary gland lesions. It is an important method that can speed up the diagnostic process and reduce the overall cost of the treatment. Moreover, it is a safe and relatively cheap technique, easy to perform and generally well tolerated by the patient. However, some studies have reported difficulties to establish specific diagnoses. Furthermore, the lack of a cytopathologic classification system clinically validated for these lesions is an important limitation that further complicates the accurate diagnosis and communication among clinicians and pathologists, which can adversely influence the best choice of treatment for the patient. Hence, the aim of this study was to evaluate retrospectively salivary gland lesions according to a recently proposed cytopathological classification system, designated "Milan System for Reporting Salivary Gland Cytopathology" (MSRSGC), which diagnostic categories relate risks of malignancy to clinical management strategies for each group. For this purpose, all cases of salivary gland FNA diagnosed in the period from 2014 to 2017 at the AC Camargo Cancer Center, São Paulo, Brazil, were reassess. Clinical data such as gender, age, location and final histopathological diagnosis was also collected from the patient's electronic files. The cases that did not present complete clinical data or surgical correspondent were excluded from the study. All cases were reviewed and reclassified according to the guidelines proposed by the Milan System in one of its six categories. The risk of neoplasm and the risk of malignancy were calculated for each of the categories. A total of 104 salivary gland FNA sample were evaluated. Most of them (57.7%) occurred in the female gender, representing a female-to-male ratio of 1.3:1. The mean age among de cases was 53.2 years, and the age range was from 19 to 93 years. Pleomorphic adenoma was the most common benign neoplasm, comprising 37.5% of all cases. The parotid gland was the main location of the lesions (89.4%), followed by the submandibular gland (10.6%). There were no cases in the minor or sublingual salivary glands. The risk of neoplasm for the non-diagnostic, non-neoplastic, atypia of indeterminate significance, benign neoplasm, salivary gland neoplasm of uncertain malignant potential, suspicious of malignancy and malignancy categories was 60%, 44.4%, 90%, 100%, 50%, and 100%, and the risk of malignancy was 15%, 0%, 40%, 9.5%, 13.3%, 50% and 100%, respectively. The use of the Milan System proved to be a useful method to predict the risk of neoplasm and malignancy in the sample studied, as demonstrated

in other published studies. Prospective studies with large case series are needed to evaluate the efficacy of this classification in the long term.
Keywords: Milan system. Fine-needle aspiration. Salivary gland lesions. Neoplasm.

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1 INTRODUÇÃO

Tumores de glândula salivar (TGS) são neoplasias de origem glandular pertencentes a um grupo de lesões que apresentam características clínico-patológicas complexas. Além disso, possuem comportamentos biológicos distintos, o que geralmente representa dificuldades na realização do diagnóstico, classificação e tratamento dessas lesões. Relativamente incomuns, representam cerca de 3 a 10% das neoplasias em região de cabeça e pescoço (Ansari, 2007; Oliveira et al., 2009; Fonseca et al., 2012; Jones et al., 2008; Lopes et al., 2016; Wang et al., 2015a).

TGS são clinicamente assintomáticos até atingirem grandes dimensões ou envolverem estruturas adjacentes, como nervos, ductos e músculos (Liu e Zhong, 2016). A maioria deles corresponde a um processo benigno, o que representa 65% dos casos. A menor parte, em torno de 35%, constitui uma neoplasia maligna (Jones et al., 2008).

Dentre os locais mais acometidos, a glândula parótida é o sítio mais comum, sendo afetada em 64 a 80% dos casos. A taxa de malignidade para os tumores de parótida varia de 14 a 27% (Zbären et al., 2004). As glândulas salivares menores, especialmente do palato, e a glândula submandibular são outros sítios comumente atingidos (Oliveira et al., 2009; Fonseca et al., 2012; Lawal et al., 2013). Tumores da glândula sublingual são raros, compreendendo menos de 1% dos casos, mas em torno de 80% deles são malignos (Pinkston e Cole, 1999).

Apesar da grande variação geográfica na distribuição local, incidência e tipos histológicos dos TGS, a maioria dos estudos indica que o adenoma pleomórfico é o tumor de glândula salivar mais comum. Embora a contraparte maligna mais comum possa variar de um estudo para o outro, o carcinoma mucoepidermóide ou o carcinoma adenóide cístico são geralmente apontados como os mais prevalentes (Al-Khateeb e Ababneh, 2007; Oliveira et al., 2009; Lawal et al., 2013).

No processo diagnóstico destas lesões, os exames de imagem podem representar uma ferramenta importante. Eles auxiliam no estabelecimento de uma localização mais precisa do tumor, além de delimitar a extensão local e as estruturas envolvidas pela lesão, identificando características que podem indicar uma suspeita de lesão maligna, como invasão local e limites mal definidos (Lee et al., 2008).

Embora úteis para o diagnóstico, isolados eles possuem consideráveis limitações (Lewis; Maghami, 2016; Rudack et al., 2007). Ainda que possam evidenciar características

suspeitas de malignidade, um tumor benigno pode facilmente simular esses aspectos radiograficamente (Rudack et al., 2007; Zbären et al., 2004).

Nesse contexto, a punção aspirativa por agulha fina (PAAF) figura como um excelente método de abordagem inicial, por apresentar taxas significativas de sensibilidade e especificidade no diagnóstico de lesões de glândula salivar (Ahn; Kim; Oh, 2013; Ashraf et al., 2010; Tyagi e Dey, 2015).

Além disso, é uma técnica segura, de fácil execução, minimamente invasiva e de baixo custo (Díaz et al., 2014; Mukunyadzi, 2002; Singh Nanda; Mehta; Nanda, 2012; Wang et al., 2015b), sendo útil na distinção de lesões neoplásicas e não neoplásicas e na diferenciação dos principais tipos de neoplasias de glândula salivar (Ameli et al., 2015; Jayaram et al., 1994).

Mesmo que em alguns casos o diagnóstico específico não consiga ser obtido por meio da PAAF, o exame citopatológico consegue ser altamente preditivo de uma lesão de natureza agressiva e pode ser de grande ajuda na distinção de tumores malignos de alto e baixo grau, o que é muito importante no planejamento da estratégia cirúrgica a ser realizada (Colella e Cannavale, 2010; Kim et al., 2013).

Nessa perspectiva, a PAAF constitui-se como uma importante ferramenta de análise inicial dos pacientes, sendo de extrema importância nesse planejamento terapêutico, podendo evitar a realização de cirurgias desnecessárias, diminuindo o custo geral do tratamento e auxiliando também na preservação de estruturas importantes, como o nervo facial (Griffith et al., 2015; Jayaram et al., 1994; Layfield; Gopez; Hirschowitz, 2006; Singh Nanda; Mehta; Nanda, 2012).

No entanto, é importante ressaltar que o sucesso da técnica está diretamente relacionado à qualidade e quantidade adequada de amostra colhida associada à experiência do profissional responsável em sua coleta e avaliação (Ashraf et al., 2010; Kim et al., 2013).

Porém, mesmo com a análise sendo feita por citopatologistas experientes, podem ocorrer respostas inconclusivas a respeito do diagnóstico. Isso não é surpresa frente à conhecida heterogeneidade que essas lesões podem apresentar (Colella e Cannavale, 2010; Rossi et al., 2016).

As questões acima mencionadas são ainda mais intensificadas devido à falta de um sistema de diagnóstico hierárquico pelo qual os achados citológicos sejam classificados e relatados (Griffith et al., 2015; Rossi et al., 2016).

Para abordar esta questão importante, um grupo internacional composto por citopatologistas, patologistas cirúrgicos e cirurgiões de cabeça e pescoço foi formado para

desenvolver um sistema de classificação que está sendo chamado de “Milan System for Reporting Salivary Gland Cytopathology (MSRSGC).”

Esse esforço está sendo patrocinado pela Sociedade Americana de Citopatologia (ASC) e pela Academia Internacional de Citologia (IAC). O objetivo desse sistema é associar as categorias de diagnóstico citopatológico aos riscos de malignidade e correlacioná-los as estratégias de gestão clínica possíveis.

Sendo assim, o objetivo desta análise foi avaliar retrospectivamente as lesões de glândula salivar do nosso serviço e reclassificá-las segundo o MSRSGC, com o intuito de legitimar um esquema de classificação em citopatologia de glândula salivar que seja prático e uniforme para a nossa rotina, otimizando as vantagens já conhecidas da PAAF, bem como melhorando a comunicação entre patologistas e clínicos.

2 ARTIGO: Application of the Milan System for reporting salivary gland cytopathology: a three-year Cancer Center experience.

Artigo submetido ao periódico Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology (Anexo 2).

Amanda Almeida Leite[1], DDS, MSc, Pablo Agustin Vargas[1], DDS, PhD, Alan Roger dos Santos Silva[1], DDS, PhD, Marisol Miranda Galvis[1], DDS, MSc, Raisa Sales de Sá[1], DDS, MSc, Clóvis Antonio Lopes Pinto[2], MD, PhD, Mauro Saieg[2,3], MD, PhD, Luiz Paulo Kowalski[4], MD, PhD.

[1]Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas, Brazil

[2]Department of Pathology, A.C.Camargo Cancer Center, São Paulo, Brazil

[3]Department of Pathology, Santa Casa Medical School, São Paulo, Brazil.

[4]Department of Head and Neck Surgery and Otorhinolaryngology, A.C. Camargo Cancer Center, São Paulo, Brazil

Corresponding Author:

Mauro Saieg

Department of Pathology, A.C. Camargo Cancer Center, São Paulo,Brazil.

Rua Prof. Antonio Prudente, 211; Liberdade, São Paulo, São Paulo – Brazil

Email: maurosaieg@yahoo.com

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Abstract

Objective. To retrospectively evaluate salivary gland lesions from a cancer center according to a recently proposed cytopathological classification system, designated Milan System for Reporting Salivary Gland Cytopathology (MSRSGC). **Study Design.** All cases of salivary gland fine needle aspiration cytology (FNAC) with surgical follow-up sequentially diagnosed in the period from 2014 to 2017 at the AC Camargo Cancer Center, Brazil, were reviewed and reclassified, according to the guidelines proposed by the Milan System. The risks of neoplasm and malignancy were calculated for each category. **Results.** 104 salivary gland FNAC was evaluated. The specimens were classified as non-diagnostic (ND) (19.2%), non-neoplastic (NN) (8.7%), atypia of undetermined significance (AUS) (9.6%), benign neoplasm (BN) (40.4%), salivary gland neoplasm of uncertain malignant potential (SUMP) (14.4%), suspicious for malignancy (SFM) (1.9%) and malignant (M) (5.8%). The risk of neoplasm and malignancy for each category was classified as ND (60%-15%), NN (44,4%-0%), AUS (90%-40%), BN (100%-9.5%), SUMP (100%-13.3%), SFM (50%-50%) and M (100%-100%). **Conclusions.** The use of the MSRSGC proved to be a useful method to predict the risk of neoplasm and malignancy in the current sample. Prospective studies with large malignant case series are needed to evaluate the efficacy of this classification in the long term.

Introduction

Salivary Gland Tumors (SGT) are neoplasms belonging to a group of lesions that present complex clinical-pathological features, with a high diversity of morphological and cellular aspects[1-6]. Fine-needle aspiration cytology (FNAC) appears to be an excellent method of initial approach to these lesions, with high sensitivity and specificity[7-10]. Moreover, it is a safe, easy-to-perform, minimally invasive and inexpensive technique[7,11-14]. However, diverse nomenclatures and reports may lead to erroneous interpretations and systematic diagnostic criteria is warranted to define global improvement in the overall performance of FNAC[15,16].

Accordingly, the newly proposed "Milan System for Reporting Salivary Gland Cytopathology (MSRSGC)" is a multidisciplinary effort to standardize salivary gland cytology reports[17,18]. It has also the purpose of correlating each diagnostic category to a recommended clinical management and assumed risk of malignancy (ROM), improving the communication between pathologists and clinicians and guiding the best therapeutic decisions available[18].

The objective of the current study was to retrospectively apply the MSRSGC in a set of cases with surgical correlation, checking its applicability in a tertiary Cancer Center environment.

There are few studies that have evaluated the applicability of the Milan System in its diagnostic routine[18-26]. Therefore, the aim of this study was to reassess the salivary gland lesions of our service using the MSRSGC. To the best of our knowledge this is the first Brazilian paper assessing Milan System in salivary gland FNAC.

Material and methods

We retrospectively collected all cases of salivary gland FNAC with surgical follow-up performed in a three-year period (from January 2014 to January 2017) at the AC Camargo Cancer Center. Clinical data such as gender, age, location and final histologic diagnosis was also collected from the patient's electronic files. All FNAC were performed under ultrasound (US) guidance in the radiology department, using a Toshiba Aplio500 Ultrasound system (Toshiba Corporation, Tokyo, Japan) with a linear 6- to -12 MHz transducer. Rapid on-site evaluation (ROSE) was performed for seventy-eight cases, with production of conventional smears stained by Hematoxylin-eosin (HE) and/or Romanowsky stain (according to the pathologists' experience). Additional smears were also fixed in ethanol for further Papanicolaou staining in a part of the cases. Whenever appropriate, a cell block was also produced, fixing the aspirated material in 10% formaldehyde, with further

processing with HistoGel. For procedures without ROSE, twenty-six cases were processed only in liquid-based preparations (Thin Prep, Hologic, MA, USA).

Review of the cases was performed by an experienced cytopathologist blinded to the original diagnosis, according to the recently proposed criteria by the MSRSGC (Table I).

Table I. Categories of the Milan System for Reporting Salivary Gland Cytopathology[21]

Category	Definition	Management
Non-Diagnostic	Insufficient quantitative or qualitative cellular material to make a cytologic diagnosis	Clinical and radiologic correlation/repeat FNA.
Non-Neoplastic	There is no evidence of a neoplastic process. Include inflammatory, metaplastic and reactive lesions.	Clinical follow-up.
Atypia od Undetermined Significance	Cannot entirely excluded a neoplasm. A majority will be reactive atypia or poorly sampled neoplasm.	Repeat FNA or surgery.
Benign Neoplasm	Reserved for classic benign neoplasms. Include conventional cases of PA, WT, lipoma, others.	Conservative surgery or clinical follow-up.
Salivary Gland Neoplasm of Uncertain Malignant Potential	Diagnostic of a neoplasm; however, a diagnosis of a specific entity cannot be made.	Conservative surgery.
Suspicious for Malignancy	Highly suggestive of malignancy but not definitive. Often high-grade carcinomas with limited sampling or other limitation.	Surgery: Correlate LG vs HG.
Malignant	Aspirates which are diagnostic of malignancy.	Surgery: Correlate LG vs HG.

PA indicates pleomorphic adenoma; WT, Warthin's tumor; LG, low grade; HG, high grade.

Cases were therefore classified in each category of the system (non-diagnostic, non-neoplastic, AUS, benign neoplasm, SUMP, suspicious, and malignant), and risk of neoplasm (RON) and risk of malignancy (ROM) was calculated for each of the categories.

To assess the concordance between the diagnoses of FNAC and the histopathological diagnoses, these were interpreted as 1) non-neoplastic, 2) benign or 3) malignant neoplasm. If the FNAC diagnosis in the MSRSGC category could include the category of histological diagnosis, the two results were considered concordant. The cases within the non-diagnostic category did not have sufficient material for correct evaluation and correlation. If the FNAC diagnosis was AUS, essentially any pathological diagnosis was considered concordant, and for the FNAC result of SUMP, any neoplastic or malignant

histologic diagnosis was concordant. The approval of the research ethics council was requested and obtained for this study under registration number 2351/17.

Results

A total of 104 salivary gland FNAC samples were evaluated. Patients were predominantly female (57.7%, female-to-male ratio of 1.3:1), with a median age of 53 years old, ranging from 19 to 93 years old. The parotid gland represented the main location of the lesions (n=93, 89.4%), followed by the submandibular gland (n=11, 10.6%).

Based on the MSRSGC, twenty cases (19.2%) were classified in category 1) non-diagnostic (ND) (Table II).

Table II. Distribution of cases in the categories of Milan System

Category	Cases (n=104)	Rate
Non-diagnostic	20	19.2%
Non-neoplastic	9	8.7%
AUS	10	9.6%
Benign Neoplasm	42	40.4%
SUMP	15	14.4%
SFM	2	1.9%
Malignant	6	5.8%

AUS indicated atypia of undetermined significance; SUMP, salivary gland neoplasm of uncertain malignant potential; SFM, suspicious for malignancy.

According to the histopathological analysis, twelve cases (60%) were diagnosed as neoplasms; nine cases were benign neoplasms (n=9, 45%) and three cases (15%) showed poorly sampled malignancies, one of them was a low grade mucoepidermoid carcinoma. Category 2) non-neoplastic (NN) grouped nine lesions (8.7%). Four cases (44.4%) represented benign neoplasms, two Warthin's tumors, one pleomorphic adenoma and, one schwannoma.

The category 3) atypia of undetermined significance (AUS) was employed in ten cases, which represents 9.6% of the total sample. Among these cases, nine neoplasms (90%) were diagnosed in the surgical specimen, in which four of them had a malignant nature. One case represented a reactive atypia that was histologically confirmed as a mucous retention cyst.

The category 4) is subdivided into 4a) benign neoplasm and 4b) salivary gland neoplasm of uncertain malignant potential (SUMP). Regarding category 4a), all cases diagnosed cytologically as neoplasms (n=42, 40.4%) were histologically confirmed. In the

group of neoplasms with uncertain malignant potential, fifteen cases (14.4%) were grouped. All represented a neoplastic process, being most of benign nature (n=13, 86.7%).

The category 5) suspected for malignancy (SFM) had two cases (1.9%), being one a reactive atypia and the other one a carcinoma ex pleomorphic adenoma, both confirmed histologically. All the cases (n=6, 5.8%) designated in category 6) malignancy represented a malignant process.

The risk of neoplasm and malignancy calculated for each category was non-diagnostic (60% -15%), non-neoplastic (44.4% -0%), AUS (90% -40%), benign neoplasm (100% -9.5%), SUMP (100% -13.3%), suspicious for malignancy (50% -50%) and malignant (100% -100%), respectively (Table III).

Table III. Neoplasm and malignancy risk associated with Milan System categories

Diagnostic category	Neoplasm Risk	Malignancy Risk	MSRSGC-suggested ROM
Non-diagnostic	60%	15%	25%
Non-neoplastic	44.4%	0%	10%
AUS	90%	40%	20%
Benign Neoplasm	100%	9.5%	<5%
SUMP	100%	13.3%	35%
SFM	50%	50%	60%
Malignant	100%	100%	90%

AUS indicates atypia of undetermined significance; SUMP, salivary gland neoplasm of uncertain malignant potential; SFM, suspicious for malignancy; ROM, risk of malignancy.

In the histopathological analysis, fifteen cases (14.4%) were diagnosed as non-neoplastic lesions, sixty-nine (63.3%) as benign neoplasms and twenty (19.2%) as malignant neoplasms. The most common benign neoplasm was pleomorphic adenoma (n=39, 37.5%), followed by Warthin's tumor (n=20, 19.2%). Mucoepidermoid carcinoma (n=5, 5.6%) was the most common malignant neoplasm, comprising 25% of all malignant cases (Table IV).

Table IV. Milan System categorical diagnoses correlated with final surgical diagnoses

MSRSGC	PA	WT	BCA	MA	BC	SW	OCC	VMF	BLP	CS	AI	MEC	ACC	CaexPA	SCC	ML	SDC	SB	SS	ASC	BSCC
ND	1	7	1		2			1	3	1	1	1			2						
NN	1	2				1			3	2											
AUS	2	2			1		1					2	1					1			
BN	26	12												1		1	1				1
SUMP	9		1	2			1						1						1		
SFM										1				1							
M												2			3					1	

ND indicates non-diagnostic; NN, non-neoplastic; AUS, atypia of undetermined significance; BN, benign neoplasm; SUMP, salivary gland neoplasm of uncertain malignant potential; SFM, suspicious for malignancy; M, malignant; PA, pleomorphic adenoma; WT, Warthin's tumor; BCA, basal cell adenoma; MA, monomorphic adenoma; BC, benign cyst; SW, schwannoma; OCC, oncocytoma; VMF, vascular malformation; BLP, benign lymphoid proliferation; CS, chronic sialadenitis; AI, acute inflammation; MEC, mucoepidermoid carcinoma; ACC, acinar cell carcinoma; CaexPA, carcinoma ex pleomorphic adenoma; SCC, squamous cell carcinoma; ML, malignant lymphoma; SDC, salivar duct carcinoma; BC; SB, sebaceous carcinoma; SS, synovial sarcoma; ASC, adenosquamous carcinoma; BSCC, basaloid squamous cell carcinoma.

Cytologic-histologic concordance was observed in seventy-five of the eighty-four evaluated cases (89.2%) (Table V).

Table V. Cytohistologic correlation

MSRSGC	Final histopathological diagnosis			Total
	Non-neoplastic	Benign neoplasm	Malignant neoplasm	
ND	8	9	3	20
NN	5	4	0	9
AUS	1	5	4	10
BN	0	38	4	42
SUMP	0	13	2	15
SFM	1	0	1	2
M	0	0	6	6
				104

ND indicates non-diagnostic; NN, non-neoplastic; AUS, atypia of undetermined significance; BN, benign neoplasm; SUMP, salivary gland neoplasm of uncertain malignant potential; SFM, suspicious for malignancy; M, malignant.

Discussion

FNAC has proven to be an excellent initial diagnostic method for salivary gland lesions, because it has high sensitivity and specificity rates[7,8], as well as important advantages such as ease of technique, low cost and good patient acceptability[7,11].

To improve the results of cytological analyzes, by grouping diagnoses and correlating them with specific clinical management strategies, the MSRSGC[17,26] was proposed, a standard classification system in cytology of salivary gland, evidence-based approach to risk stratification.

In 19.2% of the sample (n=20), the aspirates were classified as non-diagnostic, like other studies[23,24]. According to Thiryayi et al[23] this can occur due to failures in the execution of the technique or due to the presence of necrosis, hemorrhage or cystic areas. The availability of clinical and radiological information also directly influences this category. If the presence of a salivary gland mass is not clear to the cytopathologist, the sample may be classified in the non-diagnostic category (presence of clinically and/or radiologically defined mass) instead of the non-neoplastic category (without presence of a distinct mass)[23,24]. In sequence, twelve cases represented a neoplasia. Of these, ten cases had a cystic component, including a non-diagnostic case in the cytology of low grade mucoepidermoid carcinoma, which justifies our findings. Two cases represented invasive and undifferentiated squamous cell carcinomas with pronounced necrotic content. According to the guidelines proposed by

the MSRSGC[17,26], the recommended management for non-diagnostic cases should be clinical and radiographic correlation and repeat FNAC.

Regarding to aspirates representing the non-neoplastic category (n=9, 8.7%), four of them showed a benign neoplastic process in histopathological analysis (two Warthin's tumors, one pleomorphic adenoma and one schwannoma). Most lesions represented sialadenitis, reactive lymphoid infiltrates and intra-parotid lymph nodes, like other studies[20,23,24]. There was no malignant case in this category, unlike the study by Rohilla et al.[18], where four cases were malignant in histopathology, being classified in the non-neoplastic category probably due to the low cellular representation in the sample. These cases included two low grade mucoepidermoid carcinomas, one carcinoma ex pleomorphic adenoma and one secretory carcinoma.

One of the objectives of the Milan System is to keep the number of FNAC samples labeled as atypical <10% [25]. In this study, the atypia of undetermined significance represented ten cases (9.6%) of the sample, within the expected, and it presented a 40% risk of malignancy. Similar studies have shown varying risk of malignancy. Viswanathan et al.[25] and Hollyfield et al.[21] showed rates of malignancy for the AUS category of 38.9% and 33%, respectively, similar to our study. However, in the study performed by Rohilla et al.[18], the malignancy rate was 100% in this category. Nevertheless, it is worth mentioning that the number of cases interpreted as atypical was very limited (only 2), which may justify this result.

Like other studies[20,21,23], benign salivary aspirates represented the most significant number of cases in this study (n=42, 40.4%). In the histological follow-up, the majority of cases were represented by pleomorphic adenomas and Warthin's tumors, as previously reported[21,24]. However, the malignancy rate for this category was 9.5%, different from the findings of other authors[21,24], who observed lower rates (4 and 5%, respectively). This may be justified by the categorization in these cases of low grade malignancies that may be difficult to be cytologically distinguished from conventional benign neoplasms. In addition, in the presence of cystic lesions, the cellularity of the aspirate is generally low, therefore malignant cells can be lost, generating false-negative results[20].

The SUMP category generally applies to neoplasms of salivary glands without clear cytological distinction between benignity and malignancy[22]. In this study, fifteen cases (14.4%) were classified as neoplasms of uncertain malignant potential, evidencing a risk of neoplasm of 100%, as expected, and a malignancy risk of 13.3%, a little lower than founded in previous published studies[20,21, 25]. This can be explained by the considerable number of

neoplasms with basaloid features seen in this sample, which histologically represented pleomorphic adenomas and were included in this category, reducing their general risk of malignancy. Cases with these features may represent any entity, benign or malignant, and a clear distinction and interpretation of these lesions is difficult[22,23].

The category suspicious for malignancy also includes lesions which do not allow to definitively characterize a lesion as benign or malignant[25], but with strong signs of malignancy. In this series, only two cases (1.9%) were thus characterized. The first presented an inflammatory reactive infiltrate that was diagnosed as a proliferative lymphoid process in cytology, and the second represented a carcinoma ex pleomorphic adenoma, which had an atypical cellular component immersed in a myxoid background. In the recent published study of Viswanathan et al.[25], "lymphoid-rich" scenarios accounted for 44.8% of the atypical diagnosis, and were also included in the "undeterminate" categories (AUS, SUMP, SFM). In these cases, the main challenge is to distinguish a possible lymphoma from a reactive lymphoid process, and auxiliary tests such as flow cytometry (FC), immunohistochemistry and molecular tests may be useful in this differentiation[23,25].

The malignant category (n=6) represented 5.8% of the current sample. All cases were confirmed histologically, and the risk of neoplasia and malignancy were both 100%, consistent with findings from other authors[20,21]. The main malignant neoplasm seen was squamous cell carcinoma, as also observed in other studies[14,25].

In conclusion, the use of the Milan System proved to be a useful tool to predict the risk of neoplasm and malignancy in the major salivary glands, as confirmed by other recent published scientific paper. Further prospective studies with large malignant case series are needed to evaluate the accuracy of this classification in the long term.

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3 CONCLUSÃO

Os resultados encontrados nesta análise são consistentes com outros estudos publicados, o que mostra que a ferramenta é válida.

O uso do Sistema Milão demonstrou ser um método útil para predizer o risco de neoplasia e malignidade na amostra estudada.

Estudos prospectivos com grandes séries de casos são necessários para avaliar a eficácia dessa classificação a longo prazo, especialmente no que diz respeito as categorias “duvidosas” (atípica, potencial maligno incerto e suspeita para malignidade).

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ANEXO 1- Certificado do Comitê de Ética em Pesquisa

A.C.Camargo Cancer Center
Centro Integrado de Diagnóstico, Tratamento, Ensino e Pesquisa

COMITÊ DE ÉTICA
EM PESQUISA - CEP

APROVAÇÃO

Os membros do Comitê de Ética em Pesquisa em Seres Humanos da Fundação Antonio Prudente – A.C. Camargo Cancer Center, em sua última reunião de **18/04/2017, aprovaram** a realização do projeto nº **2351/17** intitulado: **"Punção Aspirativa por Agulha Fina: Estudo de uma classificação citopatológica para lesões de glândula salivar."**

Pesquisador responsável: Luiz Paulo Kowalski.
Aluna: Amanda Almeida Leite (Mestrado).

Informações a respeito do andamento do referido projeto deverão ser encaminhadas ao CEP dentro de 06 meses em relatório (modelo CEP).

São Paulo, 25 de abril de 2017.

Atenciosamente,

Dra. Sandra Caires Serrano
2ª. Vice-Coordenadora do Comitê de Ética em Pesquisa

ANEXO 2 – Certificado de submissão do artigo

Elsevier Editorial System(tm) for Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology
Manuscript Draft

Manuscript Number:

Title: Retrospective application of the Milan System for reporting salivary gland cytopathology: a three-year Cancer Center experience.

Article Type: Original Research Article

Keywords: Salivary Gland; Fine Needle Aspiration; Milan System; Tumor.

Corresponding Author: Dr. Mauro Saieg,

Corresponding Author's Institution: Santa Casa Medical School

First Author: Amanda A Leite, MSc