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The Milan system for Reporting Salivary Gland Cytopathology (MSRSGC) – An international effort to improve patient care

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Abstract

Fine needle aspiration is a well-established modality for the preoperative evaluation of salivary gland lesions. No standardized classification system was available for cytopathology reporting of salivary gland lesions until recently. The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) is an evidence-based standardized reporting system for salivary gland lesions which was proposed under the sponsorship of the American system of Cytopathology and the International Academy of Cytology in the year 2015. MSRSGC consists of six diagnostic categories, offering the risk of malignancy and clinical management recommendations for each category. The main goal of this system is to improve communication between cytopathologists and clinicians and to enhance reproducibility in the management salivary gland lesions. Here in, we review the essential features, diagnostic criteria and clinical management of each category in MSRSGC along with emphasis on ancillary studies.

Introduction

Salivary gland lesions constitute about 3% to 6% of all lesions involving the head and neck region and it includes a wide spectrum of benign and malignant neoplasm.[1,2] Fine needle aspiration (FNA) is one of the widely accepted procedures used as a primary investigation modality for the diagnosis of salivary gland lesions in conjunction with clinical and radiological findings. The FNA technique is a relatively safe, cost-effective, well-tolerated, minimally invasive procedure. It has a low risk of complications and can be done in outpatient settings and produces fast result [2-6] FNA has high sensitivity in the diagnosis of benign tumors such as pleomorphic adenoma and Warthin tumor and also aids in distinguishing neoplastic and non -

neoplastic lesions which is sometimes difficult to diagnose by radiological investigation because non-neoplastic lesions are usually managed conservatively and neoplastic lesions need surgical management.[2,7] Series of studies concluded that FNA cytology has 86-100% sensitivity and 90-100% specificity in the diagnosis of salivary gland lesions and also the accuracy of FNA in distinguishing benign from malignant tumors ranges from 81-98%.[7-11] The accuracy is also high for effectively discriminating low and high-grade malignant neoplasm so that clinicians can decide the extent of surgery including facial nerve preservation and neck node dissection. Inspite of the popularity of the FNA procedure, certain factors such as FNA technique, inadequate sampling, preparation of cytopathological slides, the experience of reporting cytopathologists, morphological overlapping between various lesions, and morphological heterogenicity of the tumor, and presence of cystic component make it difficult to provide the accurate diagnosis and the affects the overall utility of FNA.[12,13,14]

There was no uniform cytological reporting system for diagnosing salivary gland lesions until recently. To create uniformity in reporting salivary gland cytology, an evidence-based system derived from the literature designated as "The Milan System for Reporting Salivary Gland Cytology "(MSRSGC) has been proposed by an international consortium of experienced health care professionals constitutes a panel of 40 coauthors from 15 countries in the year 2015 at Milan, Italy and the atlas of the same was published in the year 2018.[5,15,16] The primary purpose of MSRSGC is to enhance the better communication between the clinician and cytopathologist and also to provide better guidelines for treatment planning and ultimately improve patient care. This reporting system correlates each diagnostic categories with risk of malignancy (ROM) and clinical management strategies.[17,18] The MSRSGC comprises six diagnostic categories which include the non-neoplastic category and a Neoplasm category that is divided into Benign and Salivary Gland Neoplasm of Uncertain Malignant Potential (SUMP). The six categories in MSRSGC are as follows 1. category I -non-diagnostic, 2. category II- non-neoplastic, 3. category III -atypia of undetermined significance , 4.category Iva- benign neoplasm, 5. Category IVb- salivary gland neoplasm of uncertain malignant potential (SUMP), 6. category V-suspicious for malignancy , and 7. category VI- malignant (table 1).[19,20,21] This review article describes each diagnostic category of the Milan system and its main features. Furthermore, it provides data of ROM in each category from the recent salivary gland series adopting the Milan system for reporting their cases and also emphasis on ancillary studies.

Category I - Non-diagnostic

In cytopathology, adequate cellularity from a targeted lesion is very important to provide an accurate diagnosis. This category focus on samples with limited cellularity and preservation artifacts. A non-diagnostic category is described as the aspirate which gives insufficient diagnostic material to provide an informative interpretation.[19]

Diagnostic criteria for non- diagnostic category include scant or absent cells that are less than 60 lesional cells, slides with artifacts such as air-drying, obscuring blood, and poor staining, non-neoplastic salivary gland elements in the setting of a clinically or radiologically defined

mass, non-mucinous cyst content without an epithelial component that is subcategorized as non-diagnostic, cystic fluid only. Salivary gland aspirates containing necrotic debris with no viable cells should be diagnosed as non-diagnostic and comment can be added that it may represent infarcted neoplasm. [2,19,22]

Some exceptions are also given in this category that includes an aspirate with cytologic atypia, mucinous cyst fluid content, or the presence of abundant inflammatory cells without an epithelial component and the presence of a matrix component which may suggest neoplasm. If the nature of the cyst fluid is not clear, an explanatory comment should be provided.[19]

All cystic salivary gland lesions are better to be performed and interpreted in the availability of clinical and ultrasound features. Cystic fluid can be analysed by biochemical methods that can be incorporated into the diagnostic report whenever possible. The ROM for non-diagnostic category is 25%.[19]

The common clinical management for this category is repeat FNA with the help of ultrasound guidance and rapid on-set evaluation (ROSE) is recommended to prevent a second Non-Diagnostic report.[12,22,23] Computed tomography(CT) or magnetic resonance imaging(MRI) may be useful for this group of patients as additional imaging modalities. Open biopsy, core needle biopsy, or surgical resection may be recommended whenever there is suspicious of neoplasm.[19,22]

Category II- Non-Neoplastic

The non-neoplastic salivary gland lesions are relatively common.[24,25] These lesions can clinically mimic a neoplasm due to the presence of a distinct mass.[23] The non-neoplastic designation is used for specimens that show benign non-neoplastic changes associated with acute or chronic reactive and metaplastic responses to inflammation, structural alterations, and infection. Lesions such as acute, chronic and granulomatous sialadenitis, reactive lymphnode hyperplasia, and lymphoepithelial sialadenitis (LESA) are included in this category. Sialolithiasis, sialadenosis, and oncocytosis are also included. The designation is intended to be used in conjunction with available clinical and radiological information.[19]

The ROM for the non-neoplastic category is approximately 10% with studies showing a range from 0 to 20%.[5,26,27] The major pitfall of this category is the possibility of false negative report due to inadequate sampling.

The clinical management of non-neoplastic lesion is mainly non-surgical. The patient should be followed clinically by a repeat physical examination. Repeat FNA is suggested if there is change in physical or radiological examination. To reduce the chances of inadequate sampling and false negative diagnosis, ultrasound-guided FNA can be used. Flow cytometry studies are useful to confirm the diagnosis of reactive lymphnodes and to exclude a low-grade lymphoproliferative lesion.[19,22]

Category III -Atypia of Undetermined Significance (AUS)

Salivary gland FNA aspirates that are indefinite for a neoplastic condition are classified as atypia of Undetermined Significance in the Milan system of reporting. The prime aim of this category is to reduce the false negatives in non-neoplastic category as well as to reduce the number of false positive diagnoses in the neoplasm category. AUS category is heterogenous in nature and exhibits morphological overlap between neoplastic and non-neoplastic processes.[19,23]

The designation applies to the FNA samples that lack either qualitative or quantitative cytomorphologic features to be diagnosed with confidence as non-neoplastic or neoplastic, and also includes atypical cytomorphologic feature that excludes the possibility of classifying it as non-diagnostic.[19]

The cytologic criteria include 1. Reactive and reparative atypia indefinite for a neoplasm 2.Squamous, oncocytic, or other metaplastic changes are indefinite for a neoplasm 3. Sparse cellular specimens are suggestive of, but not diagnostic of a neoplasm 4. Mucinous cystic lesions with abundant mucin and/or very scant epithelial component 5. Salivary gland aspirates that are indefinite for a lymphoproliferative disorder 6.Specimens with preparation artifacts hampering the distinction between a non-neoplastic and neoplastic process.[22,23]

The proportion of FNA samples diagnosed as AUS should be limited and should be less than 10%, hence cytopathologists should attempt to classify this lesion in other specific categories. The ROM for this category is not yet well defined and is approximately 20%.[19,28-30]

The suggested clinical management always starts with repeat FNA. Core-needle biopsy, open biopsy, or surgical excision may be considered when clinically suspicious of malignancy. For cystic lesions, ultrasound-guided aspiration of any residual mass may help to achieve a more specific diagnosis. [19]

Neoplasm

Parotid gland is the major salivary gland most commonly involved in neoplasms and about 80% of the neoplasms involving the parotid gland are benign.[19,31-33] Pleomorphic adenoma is the most common benign tumor in adults constituting about 50% followed by Warthin tumor. The neoplasm category is subclassified into two distinct groups in MSRSGC; 1) Benign and 2) Salivary gland neoplasm of uncertain malignant potential (SUMP).[19,22]

Category IVA–Benign neoplasm

This diagnosis is made only when the aspirate shows cytomorphologic features characteristic of specific benign epithelial or mesenchymal neoplasm of the salivary gland. This category includes the neoplasm such as pleomorphic adenoma, Warthin tumor, oncocytoma, lipoma, schwannoma, lymphangioma, and hemangioma.[22,23]

The benign neoplastic category carries ROM of less than 5%.[2] The clinical management for this benign category is complete excision of the tumor. Preoperative cross-sectional imaging is mandatory to know the extent of the tumor before excision. A subset of

patients who are not surgical candidates or who do not accept the risk of potential nerve injury might be clinically followed without surgical management.[19]

Category IV B- Salivary Gland Neoplasm of Uncertain Malignant Potential (SUMP)

This designation is reserved for FNA aspirates in which cytologic findings cannot distinguish between a benign and malignant neoplasm, but cytomorphologic features are diagnostic of a neoplastic process.[19,33] The main aim of introducing this category is when malignant neoplasm cannot be entirely excluded from the aspirate.

This category includes entities such as cellular benign neoplasms, neoplasms with monomorphic lesional cells, neoplasms with atypical features, basaloid neoplasms, oncocytic neoplasms, neoplasms with clear cell features, and low-grade carcinomas. The ROM for SUMP is assessed to be 35%.[22]

The clinical management is surgical resection of the tumor because of the increased risk of low-grade malignancy in this category. Preoperative imaging by MRI or CT should be performed on these patients to evaluate the extent of the tumor as well as to assess the neck. Intraoperative frozen section is very much helpful for better histological classification and helps to decide concomitant neck dissection for low-grade and high-grade malignancies.[19]

Category V- Suspicious for Malignancy (SM)

SM category is a part of indeterminate diagnostic categories in the Milan System along with AUS and SUMP.[12] The main aim of separating this category from the malignant category is to preserve the high positive predictive value (PPV) of an FNA classified as malignant.

The defining criteria for SM is the aspirates are highly suggestive of malignancy but not all the criteria for a specific diagnosis of malignancy are present that is the cytomorphological features are not definitive.[19,22]

This category includes scenarios such as 1. markedly atypical cells with artifacts 2. sparsely cellular aspirate with the presence of limited cytologic features of a specific malignant lesion 3. markedly atypical and/or suspicious cytologic features in a subset of cells admixed with features of a benign salivary gland lesion. 4. Scanty cellular aspirates with atypical features suggestive of a neuroendocrine neoplasm. Atypical features can include increased nuclear to cytoplasmic ratio, nuclear pleomorphism, prominent nucleoli, nuclear molding, atypical mitosis, and coarse clumped chromatin.[19]

SM category carries ROM of 60% and some studies reported the risk as high as 83%.[34] This category lesions require preoperative cross-sectional imaging to assess the extent of the tumor. Clinical and radiological correlation is very essential before concluding the diagnosis as SM. Repeat FNA, core biopsy, and surgical excision would be helpful. Intraoperative frozen section can be considered in appropriate cases to decide the extent of surgery. Ancillary techniques from the FNA aspirate may be beneficial for specific diagnosis.[19,22,35]

Category VI- Malignant

This category includes primary neoplasms involving both the major and minor salivary gland, sarcomas, and lymphomas, as well as metastatic malignancy to salivary gland lymphnodes. Malignant category is designated for FNA aspirates containing either cytomorphologic features alone or in combination with ancillary studies, is diagnostic of malignancy. Always, an attempt should be made to categorize the neoplasm as low-grade or high-grade malignancy to improve clinical management. If the aspirate is diagnosed as malignant, an attempt should do to make a specific diagnosis based on the 2017 world health organization classification of Head and Neck tumors.[36]

The malignancies involving the salivary gland include low-grade carcinomas such as acinic cell carcinoma, epithelial-myoepithelial carcinoma, secretory carcinoma, and high-grade carcinomas such as salivary duct carcinoma, small cell neuroendocrine carcinoma, and cancer with indeterminate grade carcinomas such as mucoepidermoid carcinoma, adenoid cystic carcinoma, myoepithelial carcinoma, carcinoma ex pleomorphic adenoma, hematolymphoid tumors, and malignant mesenchymal tumors and metastatic tumors.[19]

The estimated ROM for the malignancy category is over 90%. After obtaining the malignant FNA aspirate, CT of the neck and chest should consider for staging and planning surgery. For low- grade malignancies involving the parotid gland without neck involvement, complete excision of the tumor with nerve-sparing parotidectomy is indicated. Those cases are diagnosed as intermediate and high-grade malignancies are often followed by total parotidectomy, facial nerve dissection, and selective neck dissection regardless of neck status.[22]

For low-grade malignancies involving the submandibular gland without neck involvement, suprafascial resection is indicated. For cases diagnosed as intermediate and high-grade malignancies, suprafascial resection with selective neck dissection should usually be performed regardless of neck status.[22]

For metastatic lesions involving the salivary gland, the diagnosis should be made based on cytomorphological features in combination with ancillary techniques and also with a proper clinical history of the patient. If the origin of the metastatic lesion is confirmed, management should follow standard care based on the primary tumor.[2,22]

Ancillary studies for salivary gland cytology

The lesions which are commonly encountered can be diagnosed based only on cytomorphological features, but some entities remain the diagnostic challenge. Hence ancillary studies may help in those cases for specific diagnosis that leads to better patient care. Whenever FNA material is available, the ancillary test should be performed in selected cases to improve the specificity of salivary gland FNA. Advancement in immunohistochemical markers, flow cytometry, and molecular techniques such as polymerase chain reaction, fluorescence in situ hybridization, and next-generation sequencing helps to make a specific diagnosis. Concerning the cost of the ancillary tests, this should be used judiciously in specific cases whenever needed.

Most common immunohistochemistry (IHC) markers for various salivary gland tumors tumors are given in table 2. IHC markers to identify probable site of origin in metastatic salivary gland tumors are given in table 3.

Salivary gland tumors with specific molecular features

In pleomorphic adenoma, 50% -60% show t(3;8)(p21;q12) involving PLAG1 and one of several other fusion partners, commonly CTNNB1. Pleomorphic adenoma and carcinoma ex pleomorphic adenoma exclusively have the PLAG1 and HMGA2 gene rearrangement and not found in other salivary gland lesions. In mucoepidermoid carcinoma, 60%-70% show t(11;19) (q14-21;p12-13), involving the CRTC1 gene at chromosome 19 and the MAML2 gene at chromosome 1. This translocation in mucoepidermoid carcinoma associated with fewer recurrences and metastasis and also considered as a reliable prognostic marker. Adenoid cystic carcinoma show t(6;9) (q21-24; p13-23), involving MYB and NFIB genes and seen in up to 86% of this tumor. A specific translocation t(12;15) (p13;q25), involving ETV6 and NTRK3 can be found in nearly 100% in secretory carcinoma. Hyalinizing clear cell carcinoma is a rare tumor characterized by t(12;22) (q13;q12) , involving EWSR-1 and ATF1 genes can be found in 85% of cases. [37,38]

Conclusion

Salivary gland cytology is one of the important diagnostic tool in the primary evaluation of the salivary gland mass which helps for guiding clinical management. The MSRSGC is an evidence-based, standardized international reporting system that helps to stratify the lesions, to lower the non-diagnostic rate, and also provides better communication between pathologists and clinicians. Implementation of MSRSGC in FNA cytology helps to allow for a better understanding of the risk of malignancy associated with different categories of salivary gland lesions. In addition to that judicious use of ancillary techniques will improve the sensitivity of salivary gland FNA. The MSRSGC system helps the clinician to decide on appropriate management and overall it improves patient care.

Table 1: The Milan system of reporting salivary gland cytopathology- Risk of malignancy with clinical management[(23)]

Diagnostic Category	Risk of malignancy (ROM)	Clinical management
Nondiagnostic	25	Repeat FNA, clinical and radiological follow-up
Non-neoplastic	10	Clinical and radiological follow-up
Atypia of undetermined significance(AUS)	20	Repeat FNA or surgery
Neoplasm- Benign	<5	Surgery or clinical and radiological follow-up
Neoplasm-salivary gland	35	Surgery

neoplasm of uncertain malignant potential (SUMP)		
Suspicious for malignancy	60	Surgery
Malignant	>90	Surgery

Table 2: Most common immunohistochemical (IHC) markers for various salivary gland tumors[19]

Diagnosis	**Positive IHC markers**
Pleomorphic adenoma	P63, P40, SMA, Calponin, S100, PLAG1
Warthin tumor/oncocytoma	P63
Basal cell adenoma/basal cell carcinoma	P63, P40, SMA, Calponin, LEF1
Adenoid cystic carcinoma	SMA, Calponin, S100, CD117
Acinic cell carcinoma	SOX10, DOG1
Mucoepidermoid carcinoma	P63, P40
Secretory carcinoma	S100, MGB, SOX10, GATA3
Myoepithelioma/ Myoepithelial carcinoma	P63, P40, SMA, Calponin, S100
Epithelial myoeithelial carcinoma	P63, P40, SMA, Calponin, S100
Salivary duct carcinoma	GATA3, AR

SMA- smooth muscle actin, PLAG1-pleomorphic adenoma gene 1, LEF-1-lymphoid enhancer binding factor, DOG1-discovered on GIST 1, GATA3- GATA binding protein 3, AR- androgen receptor, MGB- mammoglobin, SOX10- SRY-Box transcription factor 10

Table 3: Common IHC markers for metastatic salivary gland tumors to identify the probable site of origin[19]

IHC marker	**Probable site of origin**
CDX-2 AND SATB-2	Enteric
TTF-1,Thyroglobulin	Thyroid
Napsin A, TTF-1	Lung
ER, PR, GATA3,GCDFP15 and MGB	Breast
PAX-8,CD10,RCC	Kidney
Hep par-1, glypican 3	Hepatocellular
P63, P40 and cytokeratin5/6	Squamous or urothelial

TTF-1- thyroid transcription factor, ER- estrogen receptor, PR-progesterone receptor, RCC-renal cell carcinoma, GATA3- GATA binding protein, GCDFP15- gross cystic disease fluid protein 15, MGB- mammoglobin, SATB-2- special AT rich sequence binding protein

Table 4: Comparison of the risk of malignancy (ROM) from the MSRSGC with the ROM from recent (2022) studies

Category	Wang G et al [39]	Malki Z et al [34]	Reeds STH et al[17]	Ahuja S et al [40]	Cornier CM et al [41]	Higuchi K et al [42]
Nondiagnostic	11.4	5.9	14.4	30	0	13.4
Non-neoplastic	10.9	9.1	4.4	8.3	0	9.1
AUS	30.5	35.7	37.0	25	50	24.9
Neoplasm-Benign	2.8	3.3	3.9	3.9	0	1.8
Neoplasm-SUMP	37.7	31.8	40.7	33.3	40	37
SM	83.8	100	76.5	71.4	100	89.7
Malignant	97.7	100	91.3	93.3	100	99.3

AUS- atypia of undetermined significance, SUMP- salivary gland neoplasm of uncertain malignant potential, SM- suspicious for malignancy

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