The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC): An International Effort Toward Improved Patient Care—When the Roots Might Be Inspired by Leonardo da Vinci

Esther Diana Rossi MD, PhD¹; and William C. Faquin MD, PhD²

The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) represents a standardized, evidence-based reporting system for salivary gland fine-needle aspiration (FNA). The role of FNA is well established for the preoperative evaluation of patients with salivary gland lesions; however, the lack of a uniform system for salivary gland FNA has limited its effectiveness. To address this, an international panel of experienced cytopathologists proposed a uniform reporting system in 2015 under the sponsorship of the American Society of Cytopathology and the International Academy of Cytology. The MSRSGC consists of 6 diagnostic tiers: 1) nondiagnostic, 2) non-neoplastic, 3) atypia of undetermined significance, 4) neoplasm (subdivided into benign and salivary gland neoplasm of uncertain malignant potential), 5) suspicious for malignancy, and 6) malignant. On the basis of evidence from the literature, each category has a suggested risk of malignancy that ranges from 5% for the neoplasm-benign category to >90% for the malignant category. The overall goal of the MSRSGC is to improve the effectiveness of salivary FNA by providing a uniform system with the ultimate result of better communication and improved patient care.

INTRODUCTION

It had long since come to my attention that people of accomplishment rarely sat back and let things happen to them. They went out and happened to things.—Leonardo da Vinci

This quote from Leonardo da Vinci is part of the opening Foreword of the Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) summarizing its evolution.¹ In its early developmental stages, as described in the Foreword by Dr. C. N. Powers, the MSRSGC faced significant challenges imposed by the diversity, complexity, and morphologic overlap of salivary gland neoplasms.¹ Salivary gland fine-needle aspiration (SG FNA) continues to play a key analytic role. The objective of the MSRSGC is to organize the diagnostic information from the FNA into a uniform and pragmatic reporting terminology that allows the pathologist and treating clinician to communicate effectively, with the ultimate goal of improved patient care.²⁻¹³ We designed the current commentary to take the readers through different aspects of the MSRSGC, including the challenges posed by the complexity of salivary gland cytology, the general utility of salivary cytology, the motivation leading to the development of the MSRSGC, and an overview of the 6 main reporting categories. Key aspects of the MSRSGC, as inspired by the Foreword to the MSRSGC Atlas, are introduced by paring them with quotes from the genius of Leonardo da Vinci.
Knowing is not enough; we must apply. Being willing is not enough; we must do.—Leonardo da Vinci

As inspired by da Vinci’s premise, the MSRSGC represents the product of the enthusiasm and hard work of an international team of cytopathologists. What started as a simple idea shared among colleagues developed as a scientific plan during the 2015 US and Canadian Academy of Pathology annual meeting in Boston, Massachusetts. Subsequently, the American Society of Cytopathology and the International Academy of Cytology sponsored a task force to develop a uniform reporting system for SG FNA. Less than 6 months after the initial idea was proposed, the core working group had its first face-to-face meeting during the European Congress of Cytology, which was held September 20 to 23, 2015, in Milan, Italy. An ambitious timeline was set for development of the MSRSGC, and it progressed quickly with the creation of a task force that included an international panel of cytopathologists, subspecialty pathologists, and head and neck surgeons with special interest in the pathology of salivary gland lesions and their clinical management. The result was a tiered reporting system named the Milan System for Reporting Salivary Gland Cytopathology and was inspired by the city where the first discussions were held during the 2015 European Congress of Cytology.

The establishment of the MSRSGC represents an important step toward addressing certain challenges posed by the complexity of SG FNA. The intent of the MSRSGC is not to change any of the well known cytomorphologic criteria, but to provide a uniform format for reporting the results.

Before starting the task of constructing a reporting system, the Milan system task force developed online surveys that included specific questions related to the taxonomies, practices, and diagnostic entities of salivary gland cytology.5 Questions were generated in accordance with the current literature and the experience of authors in the core group. Questions were directed at the most significant and critical aspects of daily salivary gland cytopathology practice. The results of these surveys formed the framework for the MSRSGC.5

The MSRSGC was influenced by the highly successful structures that resulted in The Bethesda System for Reporting Cervical Cytology during the 1990s and the subsequent The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) in 2010.14,15 Similar to its predecessors, the MSRSGC represents a multidisciplinary collaborative effort to formulate an evidence-based reporting system in which each diagnostic category is associated with a suggested risk of malignancy (ROM) and is linked to a clinical management algorithm. In addition, the MSRSGC atlas includes definitions, morphologic criteria, diagnostic category explanations, and sample reports. The MSRSGC also dedicates specific chapters to the application of ancillary studies, clinical management, and current histologic considerations.1

The MSRSGC was unveiled to the cytopathology community during a symposium at the 2017 American Society of Cytopathology companion meeting titled Time to Standardize the Cytology Reporting for Salivary Glands: Introduction of the Milan System, and was followed by presentations at the 2018 meeting of the US and Canadian Academy of Pathology by Drs. Faquin, Rossi, and Vielh. From that meeting to its publication in January 2018, the MSRSGC has been presented and discussed in many international meetings, conferences, and workshops, enthusiastically leading to multiple research studies and publications.

Nothing can be loved or hated unless it is first understood.—Leonardo da Vinci

THE JOURNEY INTO THE HISTORY OF THE MSRSGC

Science is the captain, and practice the soldiers.—Leonardo da Vinci

The captain (FNA), through his brave and loyal soldiers (the cytopathology community), has been refining and strengthening salivary gland cytology for decades. FNA plays a significant role as an initial diagnostic and minimally invasive procedure for the evaluation and triage of patients with salivary gland lesions.2‒12 The popularity of SG FNA is because of the ease with which the procedure can be performed and the effectiveness with which it can specifically diagnose a majority of the most common neoplastic and non-neoplastic salivary gland lesions. In addition, FNA can differentiate between many of the low-grade and high-grade malignancies.2‒10 The cytologic features of the most common salivary gland entities have been well defined by various authors; and, in most SG FNA series, there is a reported sensitivity of 86% to 100%, with overall high accuracy.10‒20

In a minority of benign neoplasms (namely, pleomorphic adenoma [PA] and Warthin tumor), FNA can
provide a specific FNA diagnosis, which allows for the option of: 1) surgical intervention in a subset of patients or 2) management of the patient by clinical follow-up and imaging, depending on health status and patient wishes. Nonetheless, the specificity for subtyping a particular salivary gland neoplasm has a wide range (48%-94%) related to the broad spectrum of tumor types encountered in the salivary glands. In addition, some of the challenges of SG FNA are related both to preanalytic factors and to the inherent nature of the lesions themselves. Addressing these challenges is important given the potential impact of SG FNA on determining the extent of surgery, including decisions about preservation of the facial nerve in the case of malignant parotid tumors and indications for neck dissection.

One way that various cytology reporting systems have responded to these challenges is by incorporating a risk-stratification approach in which a specific ROM is provided for each diagnostic category. This strategy is a key principle that is incorporated into the structure of the MSRSGC. In this way, treating clinicians are provided with a well characterized, probabilistic result on which to base patient therapy. The unified objectives that the coauthors of the Milan system atlas wanted to achieve included: 1) creation of a uniform and internationally accepted reporting system, 2) improved communication between pathologists and treating clinicians, 3) facilitation of cytohistologic correlation, 4) enhanced sharing of data between institutions, and 5) promotion of research related to SG FNA diagnosis.

Every action needs to be prompted by a motive.—Leonardo da Vinci

Reporting systems exist for cervical, thyroid, bladder, pancreas, lung, and breast cytology, in which they represent valid aids in the diagnosis and management of lesions at these anatomic sites. These cytology systems add to the clarity and uniformity of cytologic reporting as well as providing a useful interface with clinical management. However, there are unique challenges to creating a reporting system for salivary glands given the rarity and complex diversity of salivary gland lesions. The diagnosis of a salivary gland lesion is associated with a range of sensitivities and specificities, which depend on various factors. The rate of correctly diagnosing a benign or malignant entity by SG FNA ranges from 81% to 98%, and a specific diagnosis can be made in 60% to 75% of cases. Factors that can affect the diagnostic accuracy and specificity of an SG FNA include the technical experience of the individual performing the FNA, the quality of the cytologic preparations, the diagnostic experience of the cytopathologist, the cytomorphic complexity and overlap of various salivary gland lesions, and the cystic nature of some salivary gland aspirates. A recent analysis by the College of Pathologists (CAP) highlighted the diagnostic challenges of basaloïd tumors, in which the differential diagnosis can range from PA and basal cell adenoma to adenoid cystic carcinoma (AdCC) and basal cell adenocarcinoma. The CAP study indicated that a malignant classification of AdCC was made by only 63% of respondents, and a specific classification of AdCC was made by only 38%.

Similar diagnostic challenges also were observed in the CAP evaluation of oncocytic salivary gland tumors. The recently developed MSRSGC helps to address some of these issues by providing a uniform reporting framework. During the development of the MSRSGC, Griffith et al proposed a morphologic classification that uses cytologic patterns to triage SG FNAs into risk groups. Their pattern-based approach emphasized the morphologic features of basaloïd and oncocytic neoplasms, which were further subdivided based on different background characteristics. Some aspects of this proposal were incorporated into the salivary gland neoplasm of uncertain malignant potential (neoplasm-SUMP) category of the MSRSGC.

The noblest pleasure is the joy of understanding.—Leonardo da Vinci

To endorse the MSRSGC as an international effort and to foster collaboration, the Milan system task force included participation by 47 experts in the fields of salivary gland cytology, pathology, and head and neck surgery from 15 countries as coauthors of the atlas. Two online surveys related to the practice of salivary gland cytology were conducted, and the results of these surveys assisted in formulating the initial framework for the MSRSGC. The print atlas is organized into 10 chapters, including 6 separate chapters covering the general diagnostic categories: nondiagnostic, non-neoplastic, atypia of undetermined significance (AUS), neoplasm-benign, neoplasm-SUMP, suspicious for malignancy (SM), and malignant. The frequency with which each diagnostic category is used will vary, depending on individual institutions and patient populations. For example, it has been demonstrated...
that the frequency of the malignant diagnostic category ranges from 5% to 22%, depending on the study, although the neoplasm-benign and non-neoplastic categories are consistently among the most frequently used (Fig. 1). In contrast, it is recommended in the atlas that the nondiagnostic and AUS categories be limited to less than 10% of the institution’s overall SG FNAs.1

For each diagnostic category, the corresponding atlas chapter includes definitions, morphologic criteria, explanations with pitfalls and differential diagnostic considerations, and reporting examples. Most important, each diagnostic category of the MSRSGC is associated with an evidence-based ROM and clinical management strategies (Table 1). Management options can include clinical follow-up, repeat SG FNA, radiologic imaging, and surgery. Three additional chapters of the atlas are dedicated to the application of ancillary studies to SG FNA, clinical management issues, and up-to-date histologic considerations.

The following is an overview of each diagnostic category. Although the diagnostic categories are numbered

<table>
<thead>
<tr>
<th>Diagnostic Categories</th>
<th>ROM, %</th>
<th>Clinical and Radiologic Follow-Up</th>
<th>Repeat FNA</th>
<th>Application of Ancillary Studies</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiagnostic</td>
<td>25.0</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Non-neoplastic</td>
<td>10.0</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUS</td>
<td>20.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplasm-benign</td>
<td>&lt;5.0</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplasm-SUMP</td>
<td>35.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>60.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>&gt;90.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Abbreviations: AUS, atypia of undetermined significance; FNA, fine-needle aspiration; ROM, risk of malignancy; SUMP, uncertain malignant potential.
from I to VI, the authors strongly encourage including the full diagnostic category name in the official SG FNA report. The ROM associated with each diagnostic category is based on calculations from the available literature (Table 1). Actual values for ROM are likely to vary, depending on the characteristics of the patient population at any given institution as well as the anatomic site, radiologic features, and other characteristics of the individual tumor.

The **nondiagnostic** category includes SG FNAs with significant limitations, often caused by scant cellularity or preservation artifacts. Adequate cellularity from a target lesion is essential for an accurate FNA interpretation. Specific adequacy criteria for SG FNA have not previously been defined, but guidelines are presented in the MSRSGC Atlas. Both qualitative and quantitative aspects of the sample can influence the ability to interpret the FNA. Analogous to TBSRTC, the authors of the MSRSGC suggest a minimum of 60 lesional cells as an adequacy criterion. Similar to other cytologic reporting systems, an attempt should be made to limit the rate of nondiagnostic FNAs to 10% or lower. The ROM for the nondiagnostic category is 25%. This somewhat high ROM most likely reflects sampling limitations at the pre-analytic level. In addition, future studies may better define the ROM for this category, possibly at a lower level.

Examples of SG FNAs classified as nondiagnostic include nonmucinous cyst contents, *normal* salivary gland elements in the setting of a clinically and radiologically defined mass, and samples with very scant or absent cellularity and lacking atypia (Fig. 2A,B). Exceptions to these nondiagnostic cytologic criteria include mucinous cyst contents, aspirates with atypia, and specimens that contain abundant acellular matrix material or abundant inflammatory cells without an epithelial component. For repeat aspirates from a previous nondiagnostic SG FNA, radiographically guided FNA is highly recommended to reduce sampling errors.

**Non-neoplastic** lesions of the salivary gland are common; and, clinically, they can be misinterpreted as neoplasms because of the presence of a distinct mass. Nonetheless, a pitfall of salivary gland aspirates diagnosed as non-neoplastic is the possibility of a false-negative diagnosis because of inadequate sampling. In the MSRSGC, the non-neoplastic category includes benign conditions like reactive, metaplastic, and inflammatory processes (Fig. 2C,D), including acute, chronic, and granulomatous sialadenitis. Another common non-neoplastic entity is the reactive lymph node, which necessitates flow cytometry or some other method of immunophenotyping to avoid a false-negative diagnosis. The suggested ROM for the non-neoplastic category is expected to be lower than 10% if strict criteria of inclusion are applied. The ROM for aspirates of non-neoplastic salivary gland tumors ranges from 0% to 20%, which seems to be an overestimate, because only a subset of patients with non-neoplastic aspirates undergo surgery.8–13,17

Akin to TBSRTC, the MSRSGC introduced a diagnostic category designated *atypia of undetermined significance* (AUS) (Fig. 2E,F). A limited subset of SG FNAs (≤10%) should be diagnosed as AUS. A goal of this diagnostic category is to reduce the number of false-negative results in the non-neoplastic category and the number of false-positive results in the neoplasm category. The AUS category is heterogeneous, exhibiting morphologic overlap between non-neoplastic and neoplastic processes, with a ROM of approximately 20%. FNAs classified as AUS often will have preanalytic issues (eg, preparation artifact or sampling limitations). A majority of SG FNA samples classified as AUS will represent reactive atypia or, in some cases, poorly sampled neoplasms. Different scenarios in the AUS category include: 1) reactive and reparative atypia; 2) low cellularity samples that are suggestive, but not diagnostic, of a neoplasm; 3) cystic lesions with abundant mucin and/or a scant epithelial component, and 4) parotid gland aspirates indefinite for a lymphoproliferative disorder.

Salivary gland neoplasms are uncommon, more frequently involving the parotid gland, and comprise 6% of all head and neck tumors and 0.35% of all malignancies. The neoplasm category of MSRSGC is used for aspirates that are diagnostic of a neoplasm. It is divided into 2 diagnostic subcategories 1) *benign* and 2) *salivary gland neoplasm of uncertain malignant potential* (SUMP). The neoplasm-benign subcategory is used for those aspirates in which a definitive diagnosis of a specific benign neoplasm can be made based on the presence of conventional cytomorphologic features. The most common entities included in the benign neoplasm category are PA and Warthin tumor as well as lipoma, schwannoma, lymphangioma, and hemangioma (Fig. 2G,H). The ROM for the neoplasm-benign category is expected to be low (<5%), and the majority of these lesions can be managed through excisional biopsy.
Figure 2. (Continued)
by conservative surgical resection or, in selected cases, patients may be followed clinically to avoid potential surgical complications or because of certain medical contraindications. To maintain the low ROM associated with this category, stringent cytomorphologic criteria need to be used.

The neoplasm subcategory of SUMP is adopted for SG FNAs in which the morphologic features are compatible with a neoplastic process, but a specific diagnosis cannot be made. More important, a malignant neoplasm (usually low-grade) cannot be entirely excluded. FNAs diagnosed as SUMP are associated with a differential diagnosis, which includes both benign and malignant entities (Fig. 2I,J). To assist in formulating a differential diagnosis, the SUMP category can be further divided based on the presence of basaloid, oncocytic, or clear cell features. The presence of a cystic or matrix component or of significant atypia can further influence the differential diagnosis. Clinical management in most cases of SUMP will be conservative surgical resection.

The suspicious for malignancy (SM) category is similar to the corresponding conventional diagnostic category used in other nongynecologic reporting systems (Fig. 2K,L). Along with AUS and SUMP, the SM category represents an indeterminate diagnostic category in the MSRSGC. The cytomorphologic features of SM are characterized by a sample that is highly suggestive of a malignant neoplasm, but the cytomorphologic features are not definitive. Scenarios in which a diagnosis of SM might be made include a limited sample containing few markedly atypical cells or a specimen suggestive of lymphoma but without material for immunophenotyping. Many specimens diagnosed as SM potentially could benefit from the application of ancillary studies.

The diagnostic category malignant includes a broad range of different primary malignant neoplasms from both the major and minor salivary glands (Fig. 2M,N). A majority of neoplasms in this category will be carcinomas, and they also include secondary metastatic carcinomas to the salivary gland lymph nodes. Other less common entities included in the malignant category are lymphomas and sarcomas. Once an FNA is diagnosed as malignant, an attempt to make a specific classification based on the 2017 edition of the World Health Organization Classification of Head and Neck Tumors should be made.24 Even more important is that the tumor should be graded, when possible, as low-grade versus high-grade given the impact of tumor grade on clinical management.

The past decade has witnessed the identification of significant numbers of immunohistochemical markers and molecular features, mostly gene rearrangements, for many of the more common salivary gland tumors10,13,25–28 (Table 2).1,3,4,23,29,30 When material is available (usually in the form of a cell block), ancillary studies can be used in selected cases to improve the specificity of SG FNA. Although molecular techniques like fluorescence in situ hybridization and next-generation sequencing are potentially powerful tools, they also can be expensive and should be used judiciously by considering on a case-by-case basis the potential impact of results on clinical management decisions.

With regard to clinical management, and informed by an international team of 3 head and neck surgeons, each diagnostic category of the MSRSGC is linked with a set of clinical management options. The MSRSGC diagnosis is used in conjunction with clinical and radiologic findings to assist in formulating a management plan. By linking each diagnostic category with an ROM, the information provided is more useful and can lead to better patient care.
Commentary

**The greatest deception men suffer is from their own options. — Leonardo da Vinci**

There are challenges to determining the ROMs for some diagnostic categories of the MSRSGC as a new reporting system for SG FNA. Studies published before formal publication of the MSRSGC were limited by knowledge of the diagnostic category stratification and detailed criteria. Wang et al, in a multi-institutional study from 5 tertiary medical centers comprised of 154 cytohistologic salivary lesions with a diagnosis of atypical features, established that the ROM in the subset of atypical cases with histologic follow-up varied from 0% to 73%.10 The highly variable ROMs of the atypical and neoplasm of uncertain malignant potential categories among different institutions likely reflected the variable practices at each individual institution as well as retrospective ability to correlate cases with current MSRSGC criteria. Table 3 lists the ROMs for the different diagnostic categories as reported in recent studies comparing their results with the MSRSGC. The ROM can vary slightly, depending on various factors, some of which may be related to individual institutional diagnostic trends and histologic correlations, as demonstrated in Table 3.

A study by Liu et al confirmed that the neoplasm-SUMP category represents a diagnostic challenge. Their series included a limited number of cases with uncertain malignant potential.

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**TABLE 2.** Comparison of the Risk of Malignancy (ROM) From the Milan System for Reporting Salivary Gland Cytopathology With the ROM From Recent Retrospective Studies

<table>
<thead>
<tr>
<th>Category</th>
<th>Rohilla 20172</th>
<th>Thiryavi 201823</th>
<th>Liu 20184</th>
<th>Hollyfield 201823</th>
<th>Viswanathan 201830</th>
<th>MSRSGC: Faquin and Rossi 20184</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiagnostic</td>
<td>—</td>
<td>8.5</td>
<td>—</td>
<td>6.7</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td>Non-neoplastic</td>
<td>17.4</td>
<td>1.6</td>
<td>—</td>
<td>7.1</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>AUS</td>
<td>100.0</td>
<td>0.0</td>
<td>—</td>
<td>33.0</td>
<td>38.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Neoplasm benign</td>
<td>7.3</td>
<td>1.9</td>
<td>27.6</td>
<td>5</td>
<td>&lt;5.0</td>
<td></td>
</tr>
<tr>
<td>Neoplasm-SUMP</td>
<td>50.0</td>
<td>26.7</td>
<td>24.11</td>
<td>33.0</td>
<td>34.2</td>
<td>35.0</td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>—</td>
<td>100.0</td>
<td>—</td>
<td>92.9</td>
<td>60.0</td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>96.0</td>
<td>100.0</td>
<td>100</td>
<td>92.3</td>
<td>&gt;90.0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AUS, atypia of undetermined significance; MSRSGC, Milan System for Reporting Salivary Gland Cytopathology; SUMP, uncertain malignant potential.

*This differed from the ROM for oncocytic neoplasms (20%).

**TABLE 3.** Immunochemical and Molecular Profiles of Salivary Gland Tumors

<table>
<thead>
<tr>
<th>Salivary Gland Tumor</th>
<th>Immunochemical Stain</th>
<th>Molecular Alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA</td>
<td>Myoepithelial and ductal markers positive, PLAG1 positive, HMGA2 positive</td>
<td>PLAG1 rearrangement: t(3;8) (P21;q12) and t(5;8) (p13;q12); HMGA2 rearrangement: t(3;12) (p14.2;q14-5)</td>
</tr>
<tr>
<td>MEC</td>
<td>P63 positive</td>
<td>CRTCL-MAMLL2: t(11;19) (p21-22; q13); CRTCL2-MAMLL2: t(11;15) (p21; q26)</td>
</tr>
<tr>
<td>AdCC</td>
<td>Myoepithelial and ductal markers positive; MYB, and CD117 positive</td>
<td>MYB-NFI: t(6;9) (p22;q23-24)</td>
</tr>
<tr>
<td>Secretory carcinoma</td>
<td>Mammaglobin, GCDFP15, S100 positive</td>
<td>ET6 rearrangement: t(12;15) (p13;q25)</td>
</tr>
<tr>
<td>HCCC</td>
<td>P63, HMW keratin positive</td>
<td>EWSR1-ATF: t(12;22) (q13;q12)</td>
</tr>
<tr>
<td>Cribriform Ca of the minor salivary gland</td>
<td>P63 positive</td>
<td>PRKD1 rearrangement/mutation</td>
</tr>
</tbody>
</table>

Abbreviations: AdCC, adenoid cystic carcinoma; Ca, carcinoma; CD117, mast/stem cell growth factor receptor (cluster of differentiation 117); CRTCL1-MAMLL2, CREB-regulated transcription coactivator 1–mastermind-like 2 fusion; ET6, ETS variant 6; EWSR1-ATF, Ewing sarcoma breakpoint region 1–cyclic adenosine monophosphate-dependent transcription factor; GCDFP15, gross cystic disease fluid protein 15; HCCC, hyalinizing clear cell carcinoma; HMGA2, high-mobility group AT-hook 2; HMW, high molecular weight; MEC, mucoepidermoid carcinoma; MYB, Myb proto-oncogene protein; MYB-NFI, Myb proto-oncogene protein–nuclear factor IB fusion; P63, tumor protein P63; PA, pleomorphic adenoma; PLAG1, pleomorphic adenoma gene 1; PRKD1, protein kinase D1; PTC, papillary thyroid carcinoma; S100, a low-molecular-weight protein used for staining.
surgical follow-up (54 patients) and contained a subset of neoplasms with a predominant oncocytic cell component, including 18 of 25 neoplasms that correlated with nodular oncocytosis, Warthin tumor, or oncocytoma. Liu and colleagues estimated a ROM of 24.1% for the neoplasm-SUMP category. In separate study, Rohilla et al retrospectively analyzed a series of 631 SG FNAs using the Milan system categories, and they reported ROMs that had both similarities and some deviations from the average values in the MSRSGC. For example, their ROM for the neoplasm-SUMP category was 50%. In a subsequent study, Thiryavi et al analyzed a retrospective series of 287 SG FNAs that were assigned to a diagnostic category from the MSRSGC. One hundred thirty-eight of their cases were correlated with subsequent histology, clinical, and radiologic follow-up. Their reported ROMs were as follows: nondiagnostic (8.5%), non-neoplastic (1.6%), AUS (9%), neoplasm-benign (1.9%), neoplasm-SUMP (26.7%), suspicious for malignancy (100%), and malignant (100%) (Table 2). Hollyfield et al assessed SG FNA results and ROM rates at the University of North Carolina along with the interobserver reliability of the AUS and SUMP categories. Those authors observed fair agreement and slight agreement for the AUS and SUMP categories, respectively. Viswanathan et al analyzed a total of 627 SG FNA specimens, with histologic follow-up available for 373 cases. The original diagnoses were recategorized using the MSRSGC, and the authors concluded that the MSRSGC is a valuable tool that can help to standardize reporting and stratify cases preoperatively, including better defining the indeterminate FNA diagnoses and refining risk-classification criteria (Table 3).

When considering the average suggested ROM for the MSRSGC, or for any cytologic reporting system, it is important to consider that the published ROM commonly represents an overestimation, because it is based on cases with surgical follow-up and may have been impacted by factors such as patient demographics, institutional referral patterns, and publication bias. In this way, it is reasonable to assume that the true ROM may vary, depending on how the ROM was calculated. Furthermore, for a particular case of a salivary gland mass, the true ROM is influenced by the size and anatomic location of the mass. It is anticipated that the ROMs in the MSRSGC will be refined as more evidence-based data are gathered from prospective series using specific criteria defined by the MSRSGC.

Before the 2018 publication of the MSRSGC atlas, a web-based interobserver study (the Milan System Interobserver Reproducibility Study [MIRST]) was performed to identify cytomorphologic features and cytologic reporting categories that represent potential sources of poor interobserver agreement. Participants were recruited through national and international cytopathology societies. Study participants evaluated 75 web images chosen from the MSRSGC image set, before the release of the MSRSGC atlas. The images were selected from the respective diagnostic categories of the atlas and included typical and borderline cytomorphology. Preliminary data indicate, as expected, that the best interobserver agreements correspond to the neoplasm-benign, non-neoplastic, nondiagnostic, and malignant categories. Given the complexity of salivary gland cytology in general as well as the novelty of a new and unfamiliar reporting system, there will be a need for educational efforts aimed at cytologists and treating clinicians. Future reproducibility studies can be used to assess implementation of the MSRSGC and refine certain aspects of it.

**Learn how to see. Realize that everything connects to everything else. —Leonardo da Vinci**

In conclusion, as in this quote by Leonardo da Vinci, the MSRSGC connects principles of conventional diagnostic cytology with a standardized international reporting system rooted in the same nomenclature used for reporting cytology results from other anatomic sites. As the co-editors of the MSRSGC, along with contributors from 15 countries, we enthusiastically look forward to the implementation of the MSRSGC. We hope that practicing cytologists will view the MSRSGC as an important opportunity to adopt a uniform, international reporting system for SG FNA. Informational videos about the MSRSGC are available online in more than 7 languages. We encourage the cytoLOGY community to follow the MSRSGC on Twitter (available at: https://twitter.com/MilanSystem) and Facebook (available at: https://www.facebook.com/MilanSystem) and at its website (available at: MilanSystem.org) to receive the latest updates, review case examples, and participate in discussions related to SG FNA.
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REFERENCES