Update on Salivary Gland Fine-Needle Aspiration and the Milan System for Reporting Salivary Gland Cytopathology

Marc Pusztaszeri, MD; Esther Diana Rossi, MD, PhD; William C. Faquin, MD, PhD

• ***Context.***—**Fine-needle aspiration (FNA) is a well-established procedure for the diagnosis and management of salivary gland lesions, despite challenges imposed by salivary gland tumor diversity, complexity, and cytomorphologic overlap. Until recently, the reporting of salivary gland FNA specimens was inconsistent among different institutions throughout the world, leading to diagnostic confusion among pathologists and clinicians. In 2015, an international group of pathologists initiated the development of an evidence-based tiered classification system for reporting salivary gland FNA specimens, the Milan System for Reporting Salivary Gland Cytopathology (MSRSGC). The MSRSGC consists of 6 diagnostic categories, which incorporate the morphologic heterogeneity and overlap among various nonneoplastic, benign, and malignant lesions of the salivary glands. In addition, each MSRSGC diagnostic category is associated with a risk of malignancy and management recommendations.**

Objective.—**To review the current status of salivary gland FNA, core needle biopsies, ancillary studies, and the beneficial role of the MSRSGC in providing a framework for reporting salivary gland lesions and guiding clinical management.**

Data Sources.—**Literature review and personal institutional experience.**

Conclusions.—**The main goal of the MSRSGC is to improve communication between cytopathologists and treating clinicians, while also facilitating cytologic-histologic correlation, quality improvement, and research. Since its implementation, the MSRSGC has gained international acceptance as a tool to improve reporting standards and consistency in this complex diagnostic area, and it has been endorsed by the 2021 American Society of Clinical Oncology management guidelines for salivary gland cancer. The large amount of data from published studies using MSRSGC served as a basis for the recent update of the MSRSGC.**

(*Arch Pathol Lab Med*. 2024;148:1092–1104; doi: 10.5858/arpa.2022-0529-RA)

The majority of salivary gland lesions arise in the major glands, especially the parotid, and are most often benign tumors such as pleomorphic adenoma (PA) and Warthin tumor (WT).[1,2] Salivary gland malignancies are rare neoplasms accounting for less than 1% to 5% of all head and neck cancers.[2–4] The risk of malignancy (ROM) for a salivary gland mass varies depending upon its anatomic location, from 20% to 25% in the parotid gland, from 40% to 50% in the submandibular gland, and from 50% to 81% in the sublingual and minor salivary glands of the upper aerodigestive tract.[1,5] Differentiating neoplastic from nonneoplastic (NN) lesions and malignant from benign neoplasms of the salivary gland is crucial to guide the clinical management and to avoid unnecessary surgery for reactive/inflammatory conditions, or to tailor the management for advanced or metastatic cancer or lymphoma.[3–7] While most salivary gland tumors (SGTs) will require surgical excision, the extent of surgery, including preservation of the facial nerve in the case of parotid tumors and indications for neck dissection, and the timing of the surgery depend on the specific diagnosis or at least the nature (primary versus secondary) and grade (low-grade versus high-grade) of the neoplasm.[1–5] A subset of benign SGTs (especially WT) may be managed nonsurgically by clinical and imaging follow-up, depending upon patient age, symptoms, preferences, and comorbidities.[5] For metastatic disease, treatment varies according to the primary anatomic site and extent of tumor and may include surgery, local radiation, systemic therapy, and/or targeted therapy.[3,4,6]

Fine-needle aspiration (FNA) is now widely accepted as an efficient and reliable first-line diagnostic test for the management of salivary gland lesions, since it is rapid and easy to perform (often in an outpatient setting), minimally invasive, safe, and inexpensive.[3–7] Along with clinical history, physical exam, and imaging studies such as ultrasound (US), contrast-enhanced computed tomography (CT), or magnetic resonance imaging (MRI) with contrast, FNA contributes to the development of a management plan that can range from observation to limited or extensive

Accepted for publication February 15, 2023.
Published online May 23, 2024.

From the Department of Pathology, Jewish General Hospital and McGill University, Montréal, Canada (Pusztaszeri); Division of Anatomic Pathology and Histology, Agostino Gemelli School of Medicine, Università Cattolica del Sacro Cuore, Rome, Italy (Rossi); and the Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts (Faquin).

The authors have no relevant financial interest in the products or companies described in this article.

Presented in part at the Ninth Princeton Integrated Pathology Symposium, on May 7, 2022; virtual.

Corresponding author: Marc Pusztaszeri, MD, Department of Pathology, McGill University, Chemin de la Côte des Neiges, Montréal, Quebec H3T1E2 Canada (email: marc.pusztaszeri@mcgill.ca).

surgical resection and possible adjuvant therapy.[3–7] Almost any nodule or swelling of the salivary glands is amenable to evaluation by FNA, especially under US guidance. Salivary gland FNA test performance shows a range of sensitivities and specificities depending upon a wide variety of preanalytical, analytical, and postanalytical factors including the use of US guidance, experience level of the operator performing the FNA and the pathologist, quality of the cytologic preparations, morphologic heterogeneity of the lesion, presence of a cystic or necrotic component, use of rapid on-site evaluation (ROSE) and/or ancillary studies, and the reporting scheme (especially the reporting of indeterminate results).[5,8,9] The reported overall sensitivity and specificity of salivary gland FNA in distinguishing malignant from benign lesions in most series ranges from 86% to 100% and from 90% to 100%, respectively.[1,5,8,9] The proportion of inadequate or nondiagnostic (ND) FNA samples can be significant and varies widely depending on the institution (0%–50% with a mean value of 16.9%).[1,5,10] False-negative (FN) and false-positive (FP) diagnoses are uncommon.[1,5,8–11] A review of 6249 salivary gland FNAs from 1999 to 2003 identified malignant cases with the highest FN rates as lymphoma (57%), acinic cell carcinoma (AciCC, 49%), low-grade mucoepidermoid carcinoma (MEC, 43%), and adenoid cystic carcinoma (AdCC, 33%), while benign cases with the highest FP rates were mostly ''monomorphic'' adenoma (53%), intraparotid lymph nodes (36%), and oncocytoma (18%).[11] The reported ranges of sensitivity and specificity to differentiate neoplastic from NN salivary gland lesions are 79% to 100% and 71% to 100%, respectively, while the accuracy of FNA in distinguishing benign from malignant salivary gland lesions ranges from 81% to 100%.[1,5,8–10]

This is related to the fact that PA and WT are the most common SGTs, and the majority can be reliably diagnosed by FNA based on key, consistent cytomorphologic features. In most cases, FNA can also differentiate between low-grade and high-grade carcinomas.[12] However, the accuracy of salivary gland FNA when used to specifically subtype a neoplasm shows a wide range, varying from 48% to 94%.[1,5,8] This limitation is mainly due to the inherent morphologic heterogeneity of salivary gland lesions and the significant cytomorphologic overlap between some benign neoplasms and low-grade carcinomas as well as between the different types of high-grade carcinomas.[1,5,8] In contrast to core needle biopsies (CNBs) (see below), FNA of salivary gland lesions also lends itself to ROSE, which can significantly improve triage of the material for definitive diagnosis/therapy and ancillary studies (Figure 1), especially when used in conjunction with clinical assessment and imaging studies.[13] Provided there is enough material for testing, ancillary studies can significantly improve the diagnostic accuracy of FNA (see below). Infarction or hemorrhage of SGTs post-FNA occasionally occurs, especially in oncocytomas and WT. Necrosis and subsequent reactive or metaplastic changes and repair, particularly squamous metaplasia, can sometimes cause difficulties for histologic diagnosis.[14]

THE ROLE OF CNB FOR SALIVARY GLAND LESIONS

US-guided CNB of salivary glands is also a diagnostic tool that performs well in terms of accuracy, technical performance, and safety profile, with the advantage of obtaining a specimen with preserved tissue architecture.[3,15,16] At many large medical institutions, including ours, FNA is the preferred method for evaluating tumors of the major salivary glands, and CNB is reserved for biopsies of minor SGTs of the upper aerodigestive tract. The 2021 American Society of Clinical Oncology (ASCO) guideline for the management of patients with salivary gland malignancies strongly recommends that providers perform a tissue biopsy, either FNA or CNB, to support distinction of salivary gland cancers from nonmalignant salivary lesions.[3] Furthermore, it recommends that providers may perform CNB if FNA is inadequate or ND or if the subsite, such as deep minor salivary glands, precludes FNA.[3] The use of US-guided CNB has been shown to have an estimated sensitivity of 94% and specificity of 98%, with only 1.2% of biopsies having an inadequate sample.[3,16] Like FNA samples, CNBs do not allow for assessment of the interface between the tumor and surrounding tissues, and thus are limited in being able to distinguish between some benign SGTs and their low-grade malignant counterparts (eg, myoepithelioma versus myoepithelial carcinoma or basal cell adenoma versus adenocarcinoma). However, the surgical management of these SGTs is often similar (ie, conservative excision with clear margins). Ancillary studies (see below) can be judiciously applied on some of these FNA and CNB cases to specifically classify various low-grade SGTs when needed.

THE COMPLEMENTARY ROLE OF INTRAOPERATIVE EVALUATION (OF A FROZEN SECTION) FOR SALIVARY GLAND LESIONS

The inherent major limitation of FNA and CNB to assess for invasion, which is sometimes the only feature that distinguishes benign SGTs from their malignant counterparts, may be overcome to some extent by the use of an intraoperative frozen section (FS) allowing for the evaluation of the tumor interface. Intraoperative FS examination is a useful adjunct to preoperative examinations in identifying malignant SGTs, particularly when this influences surgical decision making (eg, facial nerve sacrifice and/or lymph node dissection).[3,4,17] The reported accuracy of FS evaluation is 99% in identifying neoplastic lesions and 96% in identifying NN lesions, with a 98.5% sensitivity and a 99% specificity in detecting malignant parotid tumors.[17] However, akin to FNA and CNB, FS evaluation is less accurate when attempting to report the exact tumor type: 90% in benign lesions as opposed to 59% in malignant lesions.[17] FSs can clarify diagnoses when other modes of preoperative diagnosis (FNA and/or CNB) are inconclusive. FSs can also be used as a complementary tool to confirm or refine a presurgical diagnosis, with an improved accuracy when used in combination with FNA and CNB.[17] If there is discordance of FNA findings with the clinical and radiographic suspicion, then FS evaluation is the preferred method to arrive at a more specific diagnosis.[4] Finally, involvement of subspecialized head and neck pathologists in the intraoperative consultation for SGTs results in a significant gain in sensitivity (up to 20%), underlining the importance of specialization in the complex field of salivary gland pathology.[18]

MAIN DIAGNOSTIC CHALLENGES AND LIMITATIONS OF SALIVARY GLAND FNA AND CNB

In 2022, the World Health Organization (WHO) classification system of tumors of the salivary glands contained 36 benign and malignant epithelial tumors along with several emerging entities.[2] According to the WHO, compared with tumors of other organs or systems, SGTs display one of the

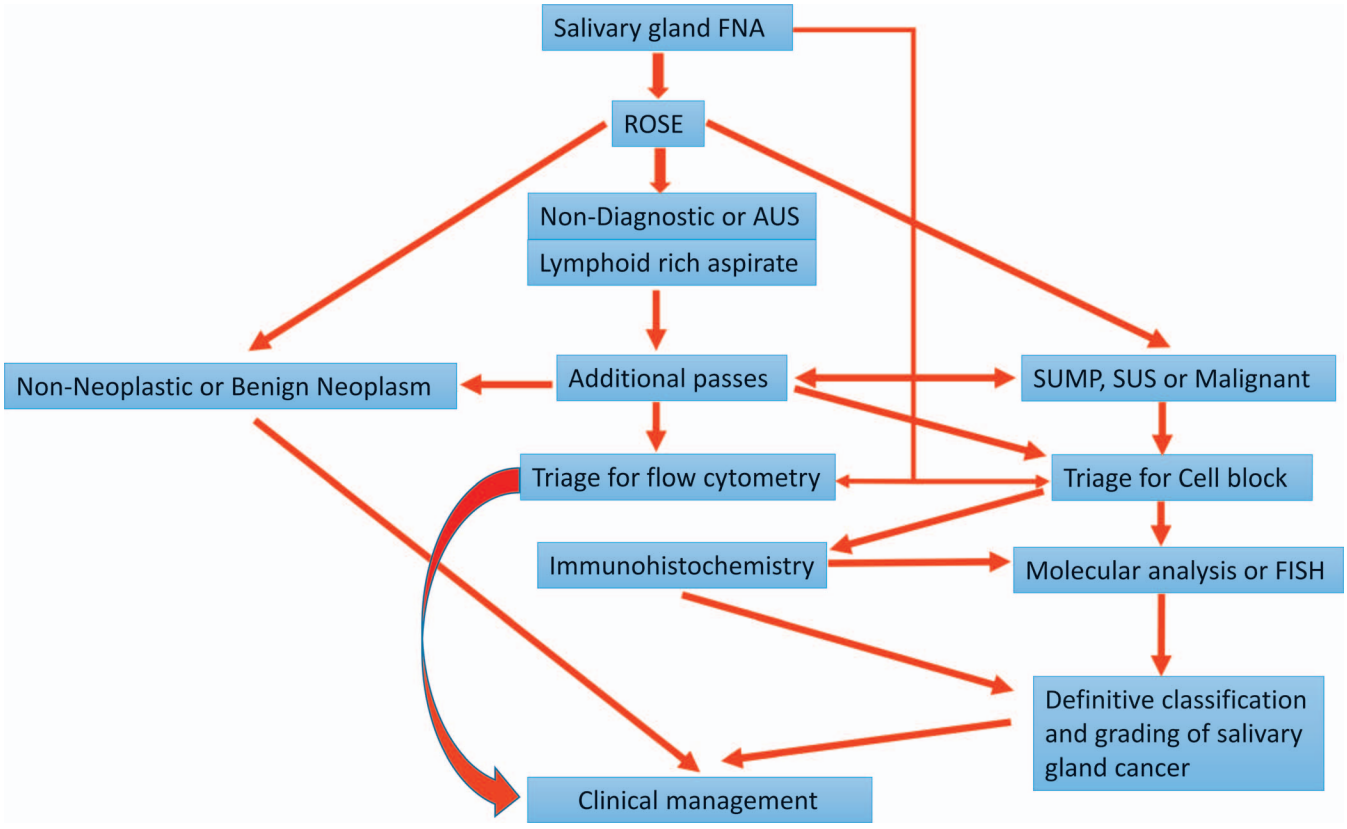

Figure 1. *Algorithm for salivary gland fine-needle aspiration (FNA) triage. Based on the Milan system category assigned during rapid on-site evaluation (ROSE), aspirated material from additional passes can be subsequently triaged to prepare extra smears or cell blocks for immunohistochemical studies, flow cytometry, molecular testing, and microbiologic evaluation. Abbreviations: AUS, atypia of undetermined significance; FISH, fluorescence in situ hybridization; SUMP, salivary gland neoplasm of uncertain malignant potential; SUS, suspicious for malignancy.*

highest morphologic, phenotypic, and genotypic diversities encountered in any single-organ system, representing one of the most difficult areas for cytology and pathology.[2] There is considerable overlap of histologic and immunohistochemical features between different SGTs, making definitive diagnosis challenging, even on some resection specimens.[2] Specific limitations, problems, and pitfalls pertaining to the FNA diagnosis of salivary gland lesions have attracted considerable interest and are extensively covered in the literature and textbooks.[1,5,8,19–22] Akin to the thyroid gland, a subset of SGTs require the assessment of histologic parameters (ie, invasion) of the whole tumor for definitive diagnosis and grading, which cannot be addressed by FNA and CNB. Salivary gland FNA and CNB are further complicated by the fact that masses that appear clinically within the parotid or submandibular gland may originate from the gland itself (intrinsic) or represent an intraglandular or peri-glandular lymph node, cyst of the neck, or soft tissue mass (extrinsic). Thus, the differential diagnosis of a mass in a major salivary gland area can be broad. While PA and WT are common and generally straightforward to diagnose by FNA, there is a minor subset of salivary gland lesions that are very difficult to interpret based on cytologic features alone, even for expert cytopathologists. These include several cellular basaloid neoplasms, cystic lesions (mucinous and nonmucinous), lymphoid lesions, and spindle cell lesions, along with a subset of oncocytic lesions and clear cell tumors.[1,5,8,21,22] Each of these groups is associated with a differential diagnosis that includes benign and malignant neoplasms; for some of them, the differential diagnosis also includes NN entities (Table 1).[1,5,8,21,22] Depending on many other factors such as (available) clinico-radiologic findings, adequacy of specimen cellularity, preparation quality, and most importantly, the availability of cell block (CB) material and ancillary studies (see below), the cytopathologist's degree of confidence in the most likely diagnosis and the way to report the findings may vary considerably. Because of significant morphologic overlap of some entities, it is unavoidable that at times only a morphological description of the FNA specimen will be provided to the treating clinician without a specific diagnosis. In the past, this was further complicated by the inconsistent use and overuse of modifying terms such as "atypical," "suggestive," or "suspicious," and/or in wordy descriptive diagnoses (aka, "describe it to death and let it go…") that may be confusing or incomprehensible, even to other cytopathologists. In this setting, clinicians may not grasp the key content of vague, descriptive cytology reports or will interpret them in a way that best matches their clinical impression. For example, "mucinous cyst" may be interpreted as benign by the clinician, while there is a significant probability that it represents a mucinous neoplasm such as MEC.[5,23] Similarly, the presence of "benign salivary gland elements only" may be reported as "negative for malignancy" by some cytopathologists and interpreted as benign/NN by the clinician, while it most likely represents a sampling error (an ND specimen).[5] Historically, there has been inconsistency in the format and terminology used for reporting the

Table 1. Main Morphologic Cell Types in Salivary Gland Cytopathology

Predominant Cell Morphology	Common Diagnostic Entities		
	Nature of Lesion	Salivary Gland Origin	Non–Salivary Gland Origin
Basaloid	Benign	Pleomorphic adenoma	Pilomatrixoma
		Basal cell adenoma	
		Myoepithelioma (rarely)	
	Malignant	Adenoid cystic carcinoma	Basal cell carcinoma
		Basal cell adenocarcinoma	Basaloid squamous cell carcinoma
		Myoepithelial carcinoma	Small cell carcinoma
		Epithelial-myoepithelial carcinoma	
		Polymorphous (low-grade) adenocarcinoma	
Oncocytic/oncocytoid	Benign	Warthin tumor	
		Oncocytoma	
		Nodular oncocytosis	
		Cystadenoma	
		Myoepithelioma (rarely)	
	Malignant	Myoepithelial carcinoma	Metastatic carcinoma
		Oncocytic carcinoma	
		Secretory carcinoma	
		Acinic cell carcinoma	
		Salivary duct carcinoma	
		Mucoepidermoid carcinoma	
Clear/granular/finely vacuolated cytoplasm	Benign	Normal salivary gland	Lipoma
		Sebaceous lymphadenoma	
		Myoepithelioma	
	Malignant	Myoepithelial carcinoma	Metastatic carcinoma (especially renal cell carcinoma)
		Oncocytic carcinoma	
		Secretory carcinoma	
		Epithelial-myoepithelial carcinoma	
		Acinic cell carcinoma	
		Mucoepidermoid carcinoma	
		Sebaceous (lymphadeno)carcinoma	
Spindle	Benign	Pleomorphic adenoma	Nodular fasciitis
		Myoepithelioma	Schwannoma
			Leiomyoma
	Malignant	Myoepithelial carcinoma	Angiosarcoma
			Metastatic melanoma
			Various sarcomas

results of salivary gland FNA between different institutions and pathologists.[5,8,9,22] This inconsistency has the potential to be confusing to treating clinicians and to result in errors in communication and loss of clinically meaningful data. It is in this context that a uniform reporting system for salivary gland cytology such as the Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) is most beneficial.

GENERAL BENEFITS OF A STANDARDIZED REPORTING (CLASSIFICATION) SYSTEM

The primary purpose of standardized reporting systems is clarity of communication.[5,24,25] A universally accepted, uniform, and consistent terminology establishes a standard of care, enabling a clinician, independent of geography, to immediately grasp the final diagnostic conclusion of the cytopathologist and better stratify patients according to the severity of their disease and the implied ROM to ensure that the patient receives the correct management.[24] Standardized reporting systems also enable the comparison of data among institutions and provide a reliable tool for research and for quality control.[24] When appropriately applied with concurrent clinician education, standardized reporting systems may reduce medicolegal issues arising from communication errors between cytopathologists and clinicians.[24] The many benefits of standardized reporting systems for diagnostic cytopathology, including the MSRSGC, are summarized in Table 2.[5,24] Akin to the classification of diseases, these standardized classification systems are dynamic, continually evolving, and improve with time and experience. Significant advances that may impact the diagnosis, terminology, or management in a given field are incorporated in updated versions.

THE MILAN SYSTEM FOR REPORTING SALIVARY GLAND CYTOPATHOLOGY

Building on the success of prior cytology reporting systems for other organs, including the Bethesda System for Reporting Thyroid Cytopathology,[25] the MSRSGC was developed as a joint effort by an international task force of cytopathologists, surgical pathologists, and head and neck surgeons that first met in 2015 in Milan, Italy, with the endorsements of the American Society of Cytopathology

Table 2. Main Advantages of the Milan System for Reporting Salivary Gland Cytopathology (and Other Reporting Systems)[a]

Standardizes reporting and clarity of communication among cytopathologists, surgeons, radiologists, and other health care providers
Correlates and stratifies the cytologic diagnosis with a risk of malignancy
Facilitates the use of clinical management algorithms
Is relevant, transferable, and practical for institutions with variable experience and expertise in salivary gland cytology (ie, user-friendly)
Facilitates quality assurance and clinical audits by setting standards (eg, < 20% of nondiagnostic samples or <10% of atypia of undetermined significance samples)
Allows easy and reliable sharing of data from different laboratories for national and international collaborative studies and facilitates research into salivary gland lesions

[a] The Milan system does not intend to change any of the well-known cytomorphologic criteria for salivary gland lesions. Rather, it is a tool to provide a uniform format for reporting the interpretation of cytomorphologic criteria for salivary gland lesions or the way to approach salivary gland fine-needle aspiration cytology.

and the International Academy of Cytology.[5,8,26–30] The objective of the MSRSGC was to standardize reporting of salivary gland cytology, promote better communication between clinicians and institutions, and ultimately improve patient care by providing a uniform reporting system.[5,26–30] The MSRSGC consists of 6 diagnostic categories (summarized below and in Table 3), which incorporate the morphologic heterogeneity and overlap among various NN, benign, and malignant lesions of the salivary glands.[5] In addition, each diagnostic category of the MSRSGC corresponds to an inherent ROM that may be used to guide decision making and patient counseling.[5] The ROM for each category was based on rigorous review of the published literature at the time of development in 2018.[5]

The first *MSRSGC Atlas*, published in 2018, includes definitions, morphologic criteria, diagnostic category explanations, and sample reports for each of the diagnostic categories.[5] The *MSRSGC Atlas* also dedicates specific chapters to the application of ancillary studies, clinical management, and current histologic considerations. The MSRSGC is designed to be transferable and practical for institutions with all levels of expertise in salivary gland cytology. Since its implementation, the MSRSGC gained widespread international acceptance among cytologists and clinicians. It is currently used to report cytology results at many institutions worldwide and has been endorsed by the 2021 ASCO guidelines for the management of patients with salivary gland cancer[3,31] and by the 2022 WHO Classification of Head and Neck tumors.[2] The ASCO guidelines recommend that pathologists should report the ROM using a risk stratification scheme for salivary FNAs with particular attention to high-grade features.[3] The MSRSGC is designated as the current standard reporting scheme. Since its introduction, numerous FNA studies including meta-analyses have been published using the MSRSGC diagnostic criteria, confirming the value and role of the Milan system as a practical and useful classification system.[10,23,32–46] In a recent PubMed search, more than 200 studies using or referring to the MSRSGC have been published, including studies from North America, Europe, Africa, Australia, and several Asian countries. The reported mean ROM for each category in most studies is within the recommended range published by the MSRSGC.[10,32] The large amount of data from published studies using the MSRSGC since 2018 served as a basis for a recent update of the Milan system. The second edition of the MSRSGC, which is expected in early 2023, will include refined ROMs for each diagnostic category, a new chapter on imaging studies for salivary glands, and updates on the application of ancillary studies to salivary gland FNA, as well as updated nomenclature and entities in keeping with the latest 2022 WHO classification. Finally, Japanese and Chinese versions of the MSRSGC were published in 2019 and 2022, respectively.

Summary of the Diagnostic Categories in the Updated MSRSGC

The MSRSGC[5] consists of 6 diagnostic categories, which are summarized below and in Table 3.

Nondiagnostic.—The ND category should be used when the entire FNA material has been processed and examined, and yet in the judgment of the cytopathologist there is insufficient quantitative and/or qualitative cellular material to make a cytologic diagnosis. Currently, a quantitative adequacy criterion (ie, an absolute number of cells to define adequacy) for salivary gland FNA specimens has not been validated in studies.[5] Even obtaining an acellular fluid should not necessarily be considered inadequate in all cases. For example, FNAs of hemangioma or lymphangioma are composed of red blood cells only or serous fluid with mature lymphocytes. The interpretation of the result (ie, defining adequacy for any given specimen) must take into account the clinical impression and the radiologic and/or US aspects (including whether the lesion is reduced or disappears after aspiration).

Salivary gland FNA specimens that fall into the ND category include those with (1) rare or absent cells, (2) poorly prepared slides with artifacts (eg, air-drying, obscuring blood, and poor staining), (3) normal salivary gland elements only in the setting of a clinically or radiologically defined mass, (4) presence of fibrous stroma alone without any cellular component, (5) nonmucinous cyst fluid without epithelial cells (should be designated ''ND, cyst fluid only''), or (6) necrotic debris only (without any epithelial or inflammatory cells).

Akin to assessment of the thyroid gland, there is a good reason for cases demonstrating only cyst contents to be considered ND as opposed to negative, as some case series confirm that about 25% of these cases represent neoplasms, including poorly sampled MEC.[23,44,45] Except in rare settings such as sialadenosis or accessory parotid tissue, the finding of benign salivary gland elements by FNA cytology does not explain the presence of a clinically or radiologically defined mass and likely reflects a sampling error.[5] The presence of necrosis only in a salivary gland FNA specimen would be of concern given its association with high-grade malignancy (eg, metastatic squamous cell carcinoma); however, it may occur in benign neoplastic and NN conditions and is not diagnostically useful in isolation.[5]

There are certain exceptions to the ND category including the following: (1) Any specimen with significant cytologic atypia should be reported as ''atypia of undetermined significance'' (AUS). (2) Mucinous cyst fluid without epithelial cells should be categorized as AUS. (3) Inflammatory cells in large numbers in the absence of epithelial cells can be interpreted as NN in the appropriate clinicoradiologic context. (4) In the absence of neoplastic cells, the

Table 3. The Milan System for Reporting Salivary Gland Cytopathology[a]

Diagnostic Category and Definitions	Explanatory Notes	Average Prevalence, %	Average Risk of Malignancy, %	Usual Management
Nondiagnostic				
Reserved for FNA samples with insufficient cellular material for a cytologic diagnosis	This diagnostic category should only be used after all the material has been processed and examined. Exceptions include matrix material and mucinous cyst contents.	<20	15	Clinical and radiologic correlation; repeat FNA
Nonneoplastic				
Reserved for FNA samples that are diagnostic of benign nonneoplastic entities such as chronic sialadenitis, reactive lymph node, granulomas, and infection	Specimens lacking cytomorphologic evidence of a neoplastic process. Specimens with inflammatory, metaplastic, and reactive changes. Specimens showing evidence of reactive lymphoid tissue (flow cytometry is recommended based on clinical and morphologic suspicion).	13	11	Clinical follow-up and radiologic correlation
Atypia of undetermined significance				
Reserved for FNA samples containing limited atypia; indefinite for a neoplasm	Samples are indefinite for a neoplasm; a neoplastic process cannot be excluded after examination of all the material. A majority of these FNAs will represent poorly sampled neoplasms or reactive atypia.	<10	30	Repeat FNA or surgery
Neoplasm				
(A) Benign				
Reserved for benign neoplasms diagnosed based on established cytologic criteria	This category includes classic cases of pleomorphic adenoma, Warthin tumor, lipoma, etc.	60	<3	Conservative surgery or clinical follow-up
(B) Salivary gland neoplasm of uncertain malignant potential				
Reserved for FNA samples that are diagnostic of a neoplasm; however, diagnosis of a specific entity cannot be made	This diagnosis should be used for cases where a malignant neoplasm cannot be excluded. A majority of these cases will include cellular benign neoplasms, neoplasms with atypical features, or low-grade carcinomas.	<10	35	Conservative surgery[b]
Suspicious for malignancy				
Reserved for FNA samples showing features that are highly suggestive of, but not unequivocal for, malignancy	The FNA report should state which type of malignant tumor is suspected or provide a differential diagnosis. A majority of specimens in this category will be high-grade carcinoma on histopathologic follow-up. (An attempt should be made on histopathologic examination to subclassify the neoplasm following complete surgical excision into specific types and grades of carcinoma for cytologic-histologic correlation.)	<10	83	Surgery[b]
Malignant				
Reserved for FNA specimens that are diagnostic of malignancy	An attempt should be made to subclassify the neoplasm into specific types and grades of carcinoma: eg, low-grade (low-grade mucoepidermoid carcinoma) versus high-grade (salivary duct carcinoma). Other malignancies such as lymphomas, metastases, and sarcomas are also included in this category and should be specifically designated.	22	98	Surgery (extent dependent on type and grade of malignancy)

Abbreviation: FNA, fine-needle aspiration.

[a] Adapted from the Milan System for Reporting Salivary Gland Cytopathology[5] with permission from the Springer Nature Group.

[b] Intraoperative examination (frozen section) may be helpful to guide the extent of surgery.

presence of matrix material suggestive of a neoplasm should not be classified as ND.

Most ND salivary gland FNA specimens are due to sampling errors; in practice, the needle misses the lesion. Studies published after 2018 report a percentage of ND sampling ranging from 0% to 34.4%, with most of the studies reporting a ND rate less than 20%.[10,31,44,46] Importantly, the rate of ND FNA is significantly lower when performed at referral or tertiary centers (4.4% ± 2.3%) as compared to general hospitals (21.3% ± 17.5%).[44] Thus, it is recommended that the rate of ND salivary gland FNAs should be less than 20% and ideally much lower.[5,44] ND cases carry a ROM of 15%.[5,10,32,44] A repeat FNA can be used for ND specimens, preferably with the use of US guidance (if not originally used) and ROSE.[5] Alternatively, a follow-up CNB may be performed (depending on institutional preferences).[3] Nonetheless, an open biopsy or surgical resection may be required for repeated ND FNAs.

Nonneoplastic.—The NN category is used when the specimen lacks cytomorphologic evidence of a neoplastic process and consists of benign acinar and/or ductal epithelial cells, with or without inflammatory, metaplastic, and/or reactive changes. Entities belonging to this category include acute sialadenitis, chronic sialadenitis (including IgG4-related disease), granulomatous sialadenitis, sialolithiasis, and benign lymphoepithelial lesion or lymphoepithelial sialadenitis.[5] Correlation with clinical and radiologic findings is crucial to ensure that the FNA is representative of the salivary gland lesion and to minimize FN results.[5] Caution is also warranted since many NN salivary gland conditions can be secondary to a synchronous underlying neoplastic process. This is exemplified in the tumor-associated lymphoid proliferations that are often seen within and around a subset of SGTs, including MEC, WT, AciCC, and secretory carcinoma (SC), and may be prominently mimicking chronic sialadenitis. Enlarged intraparotid and peri-parotid lymph nodes due to reactive lymph node hyperplasia are also a common NN cause of a salivary gland mass. They are frequently sampled by FNA to confirm a benign process, to diagnose infection, or to rule out either metastatic disease or lymphoma (Figure 2, A). Since lymphoma is a common FN result,[11] flow cytometry is highly recommended for any case of a salivary gland lymph node aspirate in which lymphoma is in the differential diagnosis,[5,47] and ROSE can be very helpful to triage the material accordingly (Figure 1).[13]

The ROM for the NN category is approximately 11% (ranges from 0% to 20%).[5,10,32] Salivary gland FNA specimens designated as NN should be followed up clinically and/or radiologically. Any change in either the clinical or radiologic features should be an indication for a repeat FNA, given the risk of sampling error. Additional evaluation should be considered for patients with persistent lymphadenopathy.

Atypia of Undetermined Significance.—One of the primary indications for performing a salivary gland FNA is to determine whether the salivary gland lesion represents an NN or a neoplastic process, as this has implications for clinical management. However, in reality, confident designation as NN or neoplastic may not always be possible due to technical factors (eg, poor sampling with scant cellularity or poor slide preparation with artifacts) and/or because of the inherent characteristics of the lesion (eg, cystic, mucinous, fibrotic, or necrotic lesion or lymphoid lesion), potentially resulting in FP or FN diagnoses. Accordingly, the AUS category can be used for specimens that are indefinite for a neoplasm; in other words, when the cytomorphologic features (qualitative or quantitative) do not definitively fall into the ND or neoplasm categories of the MSRSGC.[5] In general, the AUS category favors a benign process, but a neoplasm cannot be excluded after examination of all the cellular material.[5] Evidence shows that the majority of cases in this category represent either reactive atypia or a poorly sampled neoplasm such as WT or low-grade MEC.[5,23,37]

The AUS category may be suitable in the following scenarios[5]: (1) reactive and reparative atypia indeterminate for a neoplasm; (2) squamous, oncocytic, or other metaplastic changes indeterminate for a neoplasm; (3) low-cellularity specimens that are suggestive, but not diagnostic, of a neoplasm; (4) specimens with preparation artifacts precluding distinction between NN and neoplastic processes; (5) mucinous cystic lesions with absent or very scant epithelial cells (raising a differential diagnosis between a mucus retention cyst and a low-grade MEC) (Figure 2, B); or (6) atypical lymphoid infiltrates, either from salivary gland lymph nodes or lymphoid lesions, in which a lymphoproliferative disorder cannot be excluded based on cytomorphology, and where additional investigations such as flow cytometry are warranted.

The MSRSGC recommends the AUS category for those cases demonstrating only mucinous cyst contents because of the known risk of MEC in this group (up to 60%–80% in the parotid for cases with histologic follow-up).[5,23] Indeed, even when the epithelial elements of a low-grade MEC are sampled by FNA, the mucous cells may mimic histiocytes within a mucinous background and thus lead to a FN interpretation.[1] The use of the AUS category should be low (<10% of all salivary gland FNA specimens), with every attempt made to classify specimens into a more specific category wherever possible.[5] The average ROM for this category is estimated to be 30%.[10,32] Careful clinical and radiologic correlations are recommended for specimens categorized as AUS. Depending on the overall risk assessment, a repeat FNA, CNB, open biopsy, or surgical excision may be required.[5] Flow cytometry and immunohistochemical staining to rule out a lymphoproliferative disorder should be considered for specimens containing atypical lymphoid cells.[5,47]

Neoplasm.—*Neoplasm: Benign.*—The neoplasm: benign category is reserved for clear-cut benign neoplasms diagnosed based on established cytologic criteria of a specific benign epithelial or mesenchymal neoplasm of the salivary gland.[5] The most common benign SGTs of epithelial origin include PA and WT (Figure 2, C), both of which can be diagnosed by FNA with high specificity (>98%).[1,9,11] Examples of benign SGTs of mesenchymal origin include lipoma, schwannoma, lymphangioma, and hemangioma. The ROM for this category is less than 3%.[5] For cases classified as neoplasm: benign, cross-sectional imaging should be performed to assess the extent of the tumor prior to proceeding to complete surgical excision with facial nerve preservation.[5] In certain situations, asymptomatic benign SGTs such as WT or a deep-lobe PA in an elderly patient may be managed by clinical observation. PAs harbor a small risk of malignant transformation (3.3%–8.5% of cases) that increases with time and tumor size, and evolution to carcinoma ex-PA is associated with significant morbidity and mortality.[2,6] Thus, even though excision is warranted in almost all PA cases, the management should be

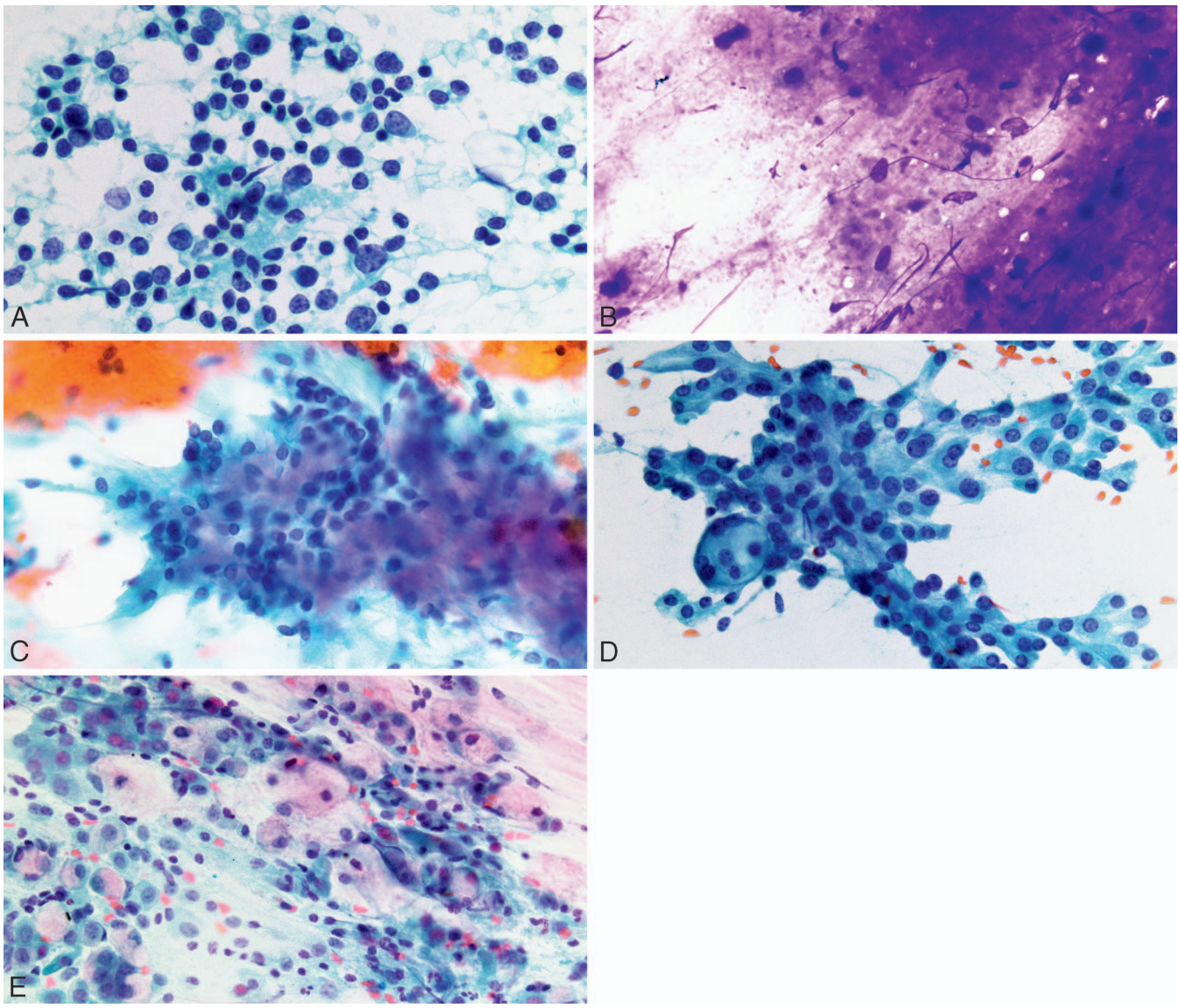

Figure 2. *Cytomorphologic features of selected Milan system diagnostic categories. A, Polymorphous population of lymphocytes associated with a reactive lymph node from the parotid gland and classified as nonneoplastic. Corresponding flow cytometry was benign. B, Hypocellular cystic lesion with abundant background mucin, admixed debris, and histiocytes classified as atypia of undetermined significance. C, Characteristic cytologic features of a classic pleomorphic adenoma consisting of fibrillar matrix material with embedded bland, uniform myoepithelial cells classified as neoplasm: benign. D, Low-grade neoplasm consisting of cells with abundant delicate cytoplasm and uniform bland nuclei classified as neoplasm: salivary gland tumor of uncertain malignant potential. The corresponding resection specimen revealed a secretory carcinoma. E, Characteristic cytologic features of low-grade mucoepidermoid carcinoma consisting of goblet-type mucinous cells admixed with epidermoid cells in a mucoid background classified as malignant (Papanicolaou stain, original magnifications ×600 [A] and ×400 [B through E]).*

individualized based on shared patient and physician decision making.

Neoplasm: Salivary Gland Neoplasm of Uncertain Malignant Potential.—The salivary gland neoplasm of uncertain malignant potential (neoplasm: SUMP) category is reserved for specimens that have cytologic features diagnostic of a neoplasm, but where distinction between a benign and malignant neoplasm cannot be made with certainty.[5] Many of the cases in this category include cellular benign neoplasms, neoplasms with atypical features, and low-grade carcinomas (Figure 2, D).[5] Further subcategorization of a specimen designated into the neoplasm: SUMP category as "cellular basaloid neoplasm" (ie, specimens characterized by a predominant population of cells with scant cytoplasm that confers an immature "basaloid" cytomorphology), "cellular oncocytic/oncocytoid neoplasm" (ie, specimens characterized by a predominant population of cells with moderate amounts of oncocytic granular cytoplasm), or "cellular neoplasm with clear cell features" (specimens characterized by a predominant population of cells with clear or vacuolated cytoplasm) can be helpful for refining the differential diagnosis.[5,48] The ROM for this category is 26%.[5,11,32] Surgical excision is indicated for most cases categorized as neoplasm: SUMP.[5] Preoperative cross-sectional imaging should be performed to evaluate the extent of the tumor, and an intraoperative FS may be used to help guide the extent of surgery (see above). Early-stage low- and intermediate-grade parotid cancers have been

shown to have excellent disease control when managed with complete surgical resection, even with narrow surgical margins, in the absence of adverse features such as perineural or lymphovascular invasion or pathologic nodal disease.[3,4,6] A subset of SUMP cases that appear to be benign based on their clinico-radiologic presentation could undergo repeat FNA after a period of observation.[5]

Suspicious for Malignancy.—The suspicious for malignancy (SUS) category is used for cases that show a higher degree of atypia than the AUS and neoplasm: SUMP categories; specifically, where the cytologic features are highly suggestive of, but not unequivocal for malignancy.[5] The purpose of separating this category from the malignant category is to ensure that the positive predictive value of the malignant category remains high, approaching 100%. It is recommended that an attempt should be made to further subcategorize the cases classified as SUS as suspicious for a primary salivary gland malignancy, metastasis, or lymphoma. The majority of the specimens in the SUS category will be suboptimal samples of a high-grade malignancy.[5,35] The SUS category may be used when the following conditions exist: (1) markedly atypical cells in a background obscured by blood or inflammation, or where there is poor cellular preservation or poor smear preparation that limits cytomorphologic assessment; (2) paucicellular sample with limited cytologic features of a specific malignant neoplasm; (3) markedly atypical cells, but admixed with features of a benign salivary gland lesion; (4) samples suspicious for lymphoma, but lacking sufficient material for ancillary studies for diagnostic confirmation.

Although the specimens in this category are highly suggestive of a malignant neoplasm with a ROM approaching 80%,[10,32] the SUS category should not be used as a basis for radical surgery (including facial nerve sacrifice), chemotherapy, or radiotherapy. An additional procedure may be needed for a specific diagnosis, and cross-sectional imaging is needed to evaluate the extent of disease and staging prior to resection. FSs can have a beneficial role in this category, as discussed previously.

Malignant.—The malignant category is used for specimens that have cytomorphologic features, either alone (Figure 2, E) or in combination with ancillary studies (see below), that are diagnostic of malignancy.[5] Furthermore, an attempt should be made to provide the specific tumor type and, in cases of malignant primary SGTs, the grade of the tumor (ie, low-grade or high-grade) when feasible.[5,12] In addition to malignant primary SGTs, secondary (metastatic) tumors (with cutaneous squamous cell carcinoma being the most commonly diagnosed secondary tumor of the parotid gland, followed by melanoma) and hematolymphoid malignancies (with extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue being the most common salivary gland lymphoma) are also included in the malignant category. The estimated ROM for this category is 98%.[5,9,10,32] The clinical management strategy for specimens in this category will be determined by the type of malignancy diagnosed.[3,4,6] For malignant primary SGTs, the grade will often determine the extent of surgery, including the need for a neck dissection or the potential need to sacrifice a large nerve.[3,4,6] Although the grade and biologic behavior are often intrinsic to the specific tumor type, limited data indicate that cytopathologists are fairly accurate in subcategorizing low-grade and high-grade malignancies, with an overall grading accuracy approaching 90%.[12] For metastatic lesions with a confirmed origin, management should follow the standard of care based on primary tumor type.[3,4,6]

The reported distribution of FNA specimens among the diagnostic categories varies depending on individual institutions and patient populations.[10,32] As expected, the neoplasm: benign and NN categories are consistently among the most frequently used, while the frequency of the malignant diagnostic category ranges from 5% to 22%, depending on the study.[10,32] The average rate of AUS for salivary aspirates is 4% based on retrospective studies, with its wide range (0%–73%) highlighting the vast differences in salivary gland FNA practices across different institutions,[10,32,37] including the use of ROSE and ancillary studies (including flow cytometry), which have been shown to reduce the rate of AUS.[13,37,47] Similarly, the rate of SUMP and SUS are both low (<10%).[10,32]

The ROM associated with each diagnostic category is based on calculations from the available literature. Actual values for ROM are likely to vary depending on the characteristics of the patient population at any given institution, the anatomic site, radiologic features, and other characteristics of the individual tumor.[5] The cited ROMs from published studies may represent an overestimation, particularly for low-risk diagnostic categories, because ROM is based on the subset of patients with corresponding cytologic and histologic specimens.[49] The ROM may be further impacted by publication bias, patient demographics, and institutional referral patterns.[49]

Report Format in the MSRSGC

The MSRSGC does not intend to change any of the well-known diagnostic cytomorphologic criteria for salivary gland lesions or the way to approach salivary gland FNA cytology. Rather, it is a tool to provide a uniform format for reporting the FNA interpretation with the ultimate result of better communication and improved patient care. The implementation of the MSRSGC at a given institution should definitely be undertaken jointly with the treating clinicians who are the recipients for these reports, and the dissemination of information about the MSRSGC is essential for the success of the MSRSGC.[50] Pathologists should present the standardized terminology to clinicians, including how it will affect the clinical utility of the test and the potential benefit of risk stratification and management guidelines. In particular, the indeterminate categories of AUS and SUMP need to be carefully explained and compared with any prior diagnostic terminology.[50] Finally, the MSRSGC is intended as a flexible framework that can be modified to suit the needs of the particular laboratory and the patients it serves.

In the MSRSGC, the cytology report should include a statement on adequacy, the diagnostic category, a specific diagnosis as to the nature of the NN process or neoplasm present, and a brief description of the cytologic features.[5] If providing the above-mentioned information is not possible, a concise comment on the reason for the categorization of the lesion is recommended. When a specific diagnosis cannot be made for any reason, this should be clearly stated and explained. Concurrent with the use of diagnostic categories, pathologists are strongly encouraged to make a definitive diagnosis, rather than a descriptive diagnosis.[50] Pathologists should further process the specimen, use ancillary studies when appropriate, and seek expert consultation to establish a definitive diagnosis whenever possible.[50] The *MSRSGC Atlas*, soon in its second edition, is

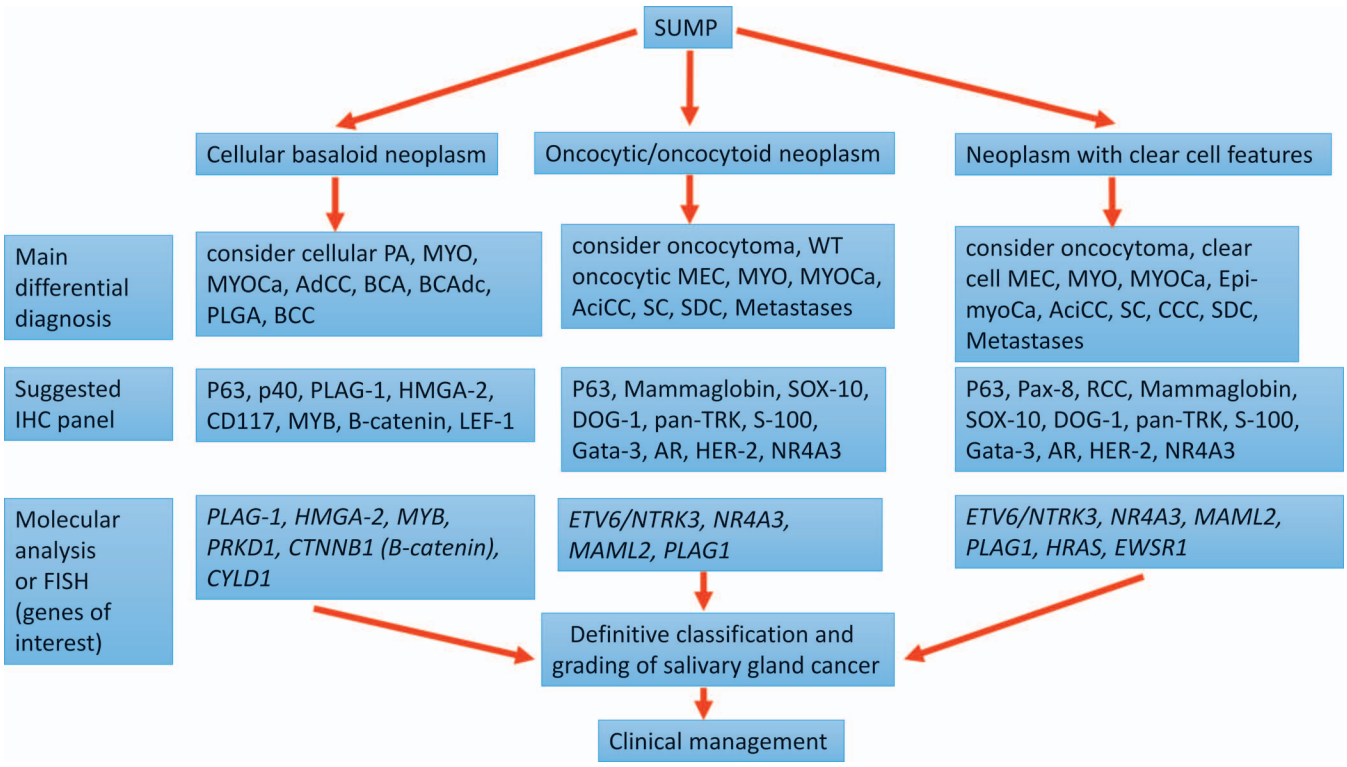

Figure 3. *Diagnostic algorithm for salivary gland tumor of uncertain malignant potential (SUMP) cases including the most common diagnostic entities in the differential diagnosis and ancillary studies to consider. Abbreviations: AciCC, acinic cell carcinoma; AdCC, adenoid cystic carcinoma; BCA, basal cell adenoma; BCAdc, basal cell adenocarcinoma; BCC, basal cell carcinoma; CCC, clear cell carcinoma; Epi-myoCa, epithelial-myoepithelial carcinoma; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; MEC, mucoepidermoid carcinoma; MYO, myoepithelioma; MYOCa, myoepithelial carcinoma; PA, pleomorphic adenoma; PLGA, polymorphous (low-grade) adenocarcinoma; RCC, renal cell carcinoma; SC, secretory carcinoma; SDC, salivary duct carcinoma; WT, Warthin tumor.*

designed to be user-friendly and incorporates many examples of reports with explanatory notes. The implied ROMs and management within a category or subcategory of the MSRSGC can vary substantially, and the additional information in a description or explanatory note can significantly impact patient management.[50]

ROLE OF ANCILLARY STUDIES

As discussed above, the primary goal of salivary gland FNA is facilitating appropriate clinical management. The MSRSGC stratifies salivary gland FNAs into 6 diagnostic categories with subcategories that are generally sufficient to guide clinical management, including the type and extent of surgery.[5] Ancillary studies, including immunohistochemistry (IHC), for salivary gland FNA are needed only in a minority of cases since most cases (eg, PA, WT) can be accurately diagnosed by cytomorphology alone. Therefore, ancillary studies should be considered primarily for aspirates in which the results would modify clinical management or clinical risk within the MSRSGC.[51] For cases that are definitely neoplastic but in which there is uncertainty regarding the specific diagnosis, the added value of ancillary studies depends on the specific diagnostic concerns and potential impact and clinical management. Akin to thyroid FNAs, ancillary studies are most useful for some aspirates in the indeterminate categories of SUMP or SUS, as they can help to refine the differential diagnosis and potentially place the specimen in a more definitive diagnostic category (Figure 3) with implications for management. While approximately half of AdCC, AciCC, SC, and MEC cases are diagnosed as malignant by cytomorphology alone (46%) (Figure 2, E), many of these cases are diagnosed as SUMP (43%) or SUS (11%).[52] In a study from the Memorial Sloan Kettering Cancer Center, 33.3% of AciCC and 50% of AdCC cases were in a SUMP category.[23] Based on their specific genetic alterations and/or immunoprofiles,[2] ancillary studies can readily confirm the diagnosis for these entities, allowing them to be placed in a definitive malignant category (Figure 3).[43,51,53–59] The application of ancillary studies for aspirates classified as AUS is often limited by the scant cellularity of these specimens, and a repeat FNA with or without ROSE (or a CNB) may be more helpful for these cases (Figure 1).

Over the past decade, the importance of ancillary studies for improving diagnostic accuracy of salivary gland FNA, especially within the framework of the MSRSGC, has been strongly emphasized.[43,51,53–59] A majority of SGTs are characterized by specific genetic alterations that can be used for diagnostic purposes.[2] The characteristic immunophenotypic and cytogenetic features of various SGTs are well described in the literature and now have significant diagnostic (and sometimes therapeutic) implications.[2,3] The most common molecular alterations were included in the latest WHO definitions of several SGTs, including MEC, AdCC, SC, polymorphous adenocarcinoma, and hyalinizing clear cell carcinoma.[2] The 2021 ASCO guidelines recommend that pathologists may perform ancillary testing (IHC or molecular studies) on FNAs and CNBs to support diagnosis and ROM.[3,31] Several new immunomarkers have been developed and can be very useful to refine the differential diagnostic list or to favor a specific entity when

cytomorphology alone is not sufficient.[43,51,53–59] This is especially true in the SUMP subcategories of basaloid neoplasms and oncocytic/oncocytoid/clear cell neoplasms, which includes many AdCC, AciCC, SC, and MEC cases along with benign SGTs such as PA, oncocytoma, or basal cell adenoma (Figure 3).[43,51,53–59] Currently, several antibodies are available to identify protein surrogates of specific genetic alterations that are overexpressed in a subset of SGTs, including MYB (*MYB*::*NFIB* fusion in AdCC), PLAG-1 (*PLAG-1* rearrangement in PA and carcinomas-ex-PA), and more recently pan-TRK and NR4A3 expression for SC and AciCC, respectively.[43,51,53–55] In general, some of these so-called molecular immunomarkers are more sensitive but less specific than their corresponding genetic alterations, which can be demonstrated by various methods such as fluorescence in situ hybridization (FISH) or next-generation sequencing (NGS).[51,53–59] Recently, some institutions have developed their own comprehensive customizable NGS SGT-specific panels to detect specific gene alterations, including mutations, fusions, and RNA gene expression alterations, in order to facilitate the diagnosis and classification of SGTs. For example, the SalvGlandDx panel is an all-in-one RNA-based NGS panel suitable for the detection of mutations, fusions, and gene expression levels of 27 genes involved in SGTs.[57] This promising approach covers most of the common molecular alterations of SGTs in a single test and can be reliably performed on formalin-fixed CB specimens.[57] However, in contrast to the thyroid gland, where molecular testing with commercially available molecular tests is commonly performed for indeterminate thyroid nodules,[60] NGS for salivary gland FNA is less common and lacks the specific, targeted, and commercially available panels as in thyroid FNA. With the continuous discovery of additional specific genetic alterations in SGTs and the increasing availability of diagnostic markers that can be applied on FNA material, the diagnostic accuracy of salivary gland FNA will continue to improve, leading to better patient management.

THE UTILITY OF CBS FOR SALIVARY GLAND FNA

CBs are a collection of sediments and visible pieces of tissue from cytologic specimens that are concentrated and processed into formalin-fixed, paraffin-embedded blocks, and stained with hematoxylin-eosin like histologic specimens.[56,59] Various techniques can be used to prepare CBs, with each method having its advantages and disadvantages. The preparation of FNA material using the CB technique essentially represents a diluted version of a CNB, which is equivalent to microbiopsies or mini-cores, facilitating the use of ancillary studies.[43] CBs are therefore complimentary to conventional cytology. A wide array of ancillary studies such as IHC, special stains (eg, mucin), FISH, DNA or mRNA in situ hybridization, and NGS can be performed on CBs.[5,43,56,59] While IHC (and other ancillary studies) can be performed on any form of cytologic preparations including CBs, cytospins, smears, and liquid-based preparations,[59] the use of CBs is the preferred method in most institutions as it has the advantage over other cytologic preparations in producing several nearly identical sections on which an IHC panel can then be applied. This is essential for cases in which several immunostains are typically needed for the diagnosis (eg, SC, AciCC, salivary duct carcinoma, metastases, etc).[5,43] CB material can thus provide easy access to additional IHC and/or molecular tests for cases with diagnostic difficulty, and judicious and case-based ancillary studies performed on FNA CBs with sufficient material can improve the diagnostic yield by further characterization of the atypical or neoplastic cells, particularly in MSRSGC neoplastic categories, as demonstrated by several studies.[43,56,59] However, CBs are not routinely prepared for all salivary gland FNA cases due to utilization of (most) aspirated material for direct smears and/or liquid-based cytology, and when CBs are available, they may be insufficient (hypocellular) for ancillary studies.[56,59] Therefore, ROSE of salivary gland FNA specimens for adequacy, if performed, can play a key role in triaging the material for ancillary studies, including flow cytometry (for saline or Roswell Park Memorial Institute medium), if there is lymphoma suspicion, or CBs (ideally in formalin to alleviate the need for a specific IHC validation) in order to optimize the diagnostic yield of the material for difficult cases (Figure 1).[13,59] While an FNA sample with both cytologic preparations and CB is strongly preferred, some institutions where ROSE is not routinely available process all the FNA material directly for CBs with excellent results in order to anticipate the use of ancillary studies for difficult cases.[34,43] Behaeghe et al[34] retrospectively analyzed 359 salivary gland samples processed only as a Cellient CB, with an overall accuracy of 92.9%, sensitivity of 75.9%, specificity of 97.9%, positive predictive value of 91.7%, and negative predictive value of 95%, respective to the diagnostic categories (excluding ND, AUS, and SUMP categories). Morand et al[43] analyzed 230 FNA samples processed only as Histogel CBs, with similar results. The ROMs based on surgical follow-up for the ND, NN, AUS, neoplasm: benign, SUMP, SUS, and malignant categories were 21.4%, 0%, 50%, 0%, 30%, 100%, and 100%, respectively.[43]

Some promising novel techniques currently in the research and development stage, including multiplex biomarker analysis of single cells (eg, fast analytical screening technique FNA), have been shown to be effective on hypocellular FNA material with a rapid turnaround time and potential to alleviate the need to obtain a CB for ancillary studies (for both diagnostics and therapeutics).[61]

CONCLUSIONS

There is a significant clinical role for FNA and/or CNB in the preoperative assessment of salivary gland lesions, with both techniques being recently endorsed by the ASCO guidelines for the management of salivary gland cancer.[3,31] Evaluation of salivary gland lesions remains one of the most challenging areas of cytopathology. The MSRSGC was developed to provide a universally accepted and consistent reporting structure for salivary gland FNA.[5] The primary goals of the MSRSGC are to improve cytopathologist-clinician communication and provide assistance with clinical decision making.[5] Since its implementation, the MSRSGC has gained international acceptance as a tool to improve reporting standards and consistency in this complex diagnostic area. An updated version of the MSRSGC is expected in early 2023. Subsequent experience will lead to further refinements to this terminology framework. Ancillary testing has greatly enhanced the ability for more accurate classification as per the MSRSGC and allows for the definitive diagnosis of many salivary FNA specimens. With the continuous discovery of additional specific genetic alterations in SGTs and the increasing availability of diagnostic markers that can be applied on FNA material,

the diagnostic accuracy of salivary gland FNA will continue to be further improved, leading to better patient management.

References

1. Faquin WC, Powers CN. *Salivary Gland Cytopathology*. New York: Springer; 2008. *Essentials in Cytopathology Series*, vol. 5.
2. El-Naggar AK, Chan J, Takata T, Grandis J, Blootweg P. *WHO Classification of Tumours. Pathology and Genetics of Head and Neck Tumours*. 4th ed. Lyon, France: IARC Press; 2022.
3. Geiger JL, Ismaila N, Beadle B, et al. Management of salivary gland malignancy: ASCO guideline. *J Clin Oncol*. 2021;39(17):1909–1941.
4. Sood S, McGurk M, Vaz F. Management of salivary gland tumours: United Kingdom national multidisciplinary guidelines. *J Laryngol Otol*. 2016;130(S2): S142–S149.
5. Faquin WC, Rossi ED, Baloch Z, et al, eds. *The Milan System for Reporting Salivary Gland Cytopathology*. Cham, Switzerland: Springer; 2018.
6. Mantravadi AV, Moore MG, Rassekh CH. AHNS series: do you know your guidelines? Diagnosis and management of salivary gland tumors. *Head Neck*. 2019;41(2):269–280.
7. Eytan DF, Yin LX, Maleki Z, et al. Utility of preoperative fine needle aspiration in parotid lesions. *Laryngoscope*. 2018;128(2):398–402.
8. Pusztaszeri M, Rossi ED, Baloch ZW, Faquin WC. Salivary gland fine needle aspiration and introduction of the Milan reporting system. *Adv Anat Pathol*. 2019;26(2):84–92.
9. Schmidt RL, Hall BJ, Wilson AR, Layfield LJ. A systematic review and meta-analysis of the diagnostic accuracy of fine-needle aspiration cytology for parotid gland lesions. *Am J Clin Pathol*. 2011;136(1):45–59.
10. Jalaly, JB, Farahani, SJ, Baloch, ZW. The Milan system for reporting salivary gland cytopathology: a comprehensive review of the literature. *Diagn Cytopathol*. 2020;48(10):880–889.
11. Hughes JH, Volk EE, Wilbur DC, Cytopathology Resource Committee College of American Pathologists. Pitfalls in salivary gland fine-needle aspiration cytology: lessons from the College of American Pathologists Interlaboratory Comparison Program in Nongynecologic Cytology. *Arch Pathol Lab Med*. 2005; 129(1):26–31.
12. Johnson DN, Onenerk M, Krane JF, et al. Cytologic grading of primary malignant salivary gland tumors: a blinded review by an international panel. *Cancer Cytopathol*. 2020;128(6):392–402.
13. Kakkar A, Kumar M, Subramanian P, et al. Utility of the Milan system for reporting salivary gland cytopathology during rapid on-site evaluation (ROSE) of salivary gland aspirates. *Cytopathology*. 2021;32(6):779–788.
14. Li S, Baloch ZW, Tomaszewski JE, LiVolsi VA. Worrisome histologic alterations following fine-needle aspiration of benign parotid lesions. *Arch Pathol Lab Med*. 2000;124(1):87–91.
15. Eom HJ, Lee JH, Ko MS, et al. Comparison of fine-needle aspiration and core needle biopsy under ultrasonographic guidance for detecting malignancy and for the tissue-specific diagnosis of salivary gland tumors. *AJNR Am J Neuroradiol*. 2015;36(6):1188–1193.
16. Schmidt RL, Hall BJ, Layfield LJ. A systematic review and meta-analysis of the diagnostic accuracy of ultrasound-guided core needle biopsy for salivary gland lesions. *Am J Clin Pathol*. 2011;136(4):516–526.
17. Schmidt RL, Hunt JP, Hall BJ, Wilson AR, Layfield LJ. A systematic review and meta-analysis of the diagnostic accuracy of frozen section for parotid gland lesions. *Am J Clin Pathol*. 2011;136(5):729–738.
18. Mantsopoulos K, Bessas Z, Sievert M, et al. Frozen section of parotid gland tumours: the head and neck pathologist as a key member of the surgical team. *J Clin Med*. 2022;11(5):1249.
19. Jain R, Gupta R, Kudesia M, Singh S. Fine needle aspiration cytology in diagnosis of salivary gland lesions: a study with histologic comparison. *CytoJournal*. 2013;10:5.
20. Colella G, Cannavale R, Flamminio F, Foschini MP. Fine-needle aspiration cytology of salivary gland lesions: a systematic review. *J Oral Maxillofac Surg*. 2010;68(9):2146–2153.
21. Tyagi R, Dey P. Diagnostic problems of salivary gland tumors. *Diagn Cytopathol*. 2015;43(6):495–509.
22. Griffith CC, Pai RK, Schneider F, et al. Salivary gland tumor fine needle aspiration cytology. A proposal for a risk stratification classification. *Am J Clin Pathol*. 2015;143(6):839–853.
23. Lubin D, Buonocore D, Wei XJ, et al. The Milan System at Memorial Sloan Kettering: utility of the categorization system for in-house salivary gland fine-needle aspiration cytology at a comprehensive cancer center. *Diagn Cytopathol*. 2020;48(3):183–190.
24. Sundling KE, Kurtycz DFI. Standardized terminology systems in cytopathology. *Diagn Cytopathol*. 2019;47(1):53–63.
25. Ali SZ, Cibas ED, eds. The Bethesda system for reporting thyroid cytopathology: definitions, criteria and explanatory notes. New York: Springer; 2017.
26. Rossi ED, Faquin WC, Baloch Z, et al. The Milan System for Reporting Salivary Gland Cytopathology: analysis and suggestions of initial survey. *Cancer Cytopathol*. 2017;125(10):757–766.
27. Rossi ED, Baloch Z, Pusztaszeri M, Faquin WC. The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC): an ASC-IAC-sponsored system for reporting salivary gland fine-needle aspiration. *J Am Soc Cytopathol*. 2018;7(3):111–118.
28. Barbarite E, Puram SV, Derakhshan A, Rossi ED, Faquin WC, Varvares MA. A call for universal acceptance of the Milan system for reporting salivary gland cytopathology. *Laryngoscope*. 2020;130(1):80–85.
29. Rossi ED, Faquin WC. 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. *Cancer Cytopathol*. 2018;126(9):756–766.
30. Rossi ED, Wong LQ, Bizzarro T, et al. The impact of FNAC in the management of salivary gland lesions: institutional experiences leading to a risk based classification scheme. *Cancer Cytopathol*. 2016;124(6):388–396.
31. Pusztaszeri M, Deschler D, Faquin WC. The 2021 ASCO guideline on the management of salivary gland malignancy endorses FNA biopsy and the risk stratification scheme proposed by the Milan system for reporting salivary gland cytopathology. *Cancer Cytopathol*. 2023;131(2):83–89.
32. Wei S, Layfield L, LiVolsi VA, Montone KT, Baloch ZW. Reporting of fine needle aspiration (FNA) specimens of salivary gland lesions: a comprehensive review. *Diagn Cytopathol*. 2017;45(9):820–827.
33. Layfield LJ, Baloch ZW, Hirschowitz SL, Rossi ED. Impact on clinical follow-up of the Milan system for salivary gland cytology: a comparison with a traditional diagnostic classification. *Cytopathology*. 2018;29(4):335–342.
34. Behaeghe M, Vander Poorten V, Hermans R, Politis C, Weynand B, Hauben E. The Milan System for Reporting Salivary Gland Cytopathology: single center experience with cell blocks. *Diagn Cytopathol*. 2020;48(11):972–978.
35. Maleki Z, Miller JA, Arab SE, et al. "Suspicious" salivary gland FNA: risk of malignancy and interinstitutional variability. *Cancer Cytopath*. 2018;126(2):94–100.
36. Viswanathan K, Sung S, Scognamiglio T, Yang GCH, Siddiqui MT, Rao RA. The role of the Milan system for reporting salivary gland cytopathology: a 5-year institutional experience. *Cancer Cytopath*. 2018;126(8):541–551.
37. Wang H, Malik A, Maleki Z, et al. "Atypical" salivary gland fine needle aspiration: risk of malignancy and interinstitutional variability. *Diagn Cytopathol*. 2017;45(12):1088–1094.
38. Rohilla M, Singh P, Rajwanshi A, et al. Three-year cytohistological correlation of salivary gland FNA cytology at a tertiary center with the application of the Milan system for risk stratification. *Cancer Cytopath*. 2017;125(10):767–775.
39. Thiryayi SA, Low YX, Shelton D, Narine N, Slater D, Rana DN. A retrospective 3-year study of salivary gland FNAC with categorisation using the Milan reporting system. *Cytopathology*. 2018;29(4):343–348.
40. Liu H, Ljungren C, Lin F, Zarka MA, Chen L. Analysis of histologic follow-up and risk of malignancy for salivary gland neoplasm of uncertain malignant potential proposed by the Milan system for reporting salivary gland cytopathology. *Cancer Cytopath*. 2018;126(7):490–497.
41. Maleki Z, Baloch Z, Lu R, et al. Application of the Milan system for reporting submandibular gland cytopathology: an international, multi-institutional study. *Cancer Cytopath*. 2019;127(5):306–315.
42. Kurtycz DFI, Rossi ED, Baloch Z, et al. Milan interobserver reproducibility study (MIRST): Milan System 2018. *J Am Soc Cytopathol*. 2020;9(3):116–125.
43. Morand GB, Alsayegh R, Mlynarek AM, et al. Application of the Milan system for reporting salivary gland cytopathology using cell blocks. *Virchows Arch*. 2022;481(4):575–583.
44. Rossi ED, Faquin WC. The Milan system for reporting salivary gland cytopathology: the clinical impact so far. Considerations from theory to practice. *Cytopathology*. 2020;31(3):181–184.
45. Maleki Z, Allison DB, Butcher M, Kawamoto S, Eisele DW, Pantanowitz L. Application of the Milan system for reporting salivary gland cytopathology to cystic salivary gland lesions. *Cancer Cytopath*. 2021;129(3):214–225.
46. Lui SK, Tenney T, Mullane PC, Viswanathan K, Lubin DJ. Nondiagnostic salivary gland FNAs are associated with decreased risk of malignancy compared with "all-comer" patients: analysis of the Milan system for reporting salivary gland cytopathology with a focus on Milan I: nondiagnostic. *Cancer Cytopath*. 2022;130(10):800–811.
47. Stacchini A, Aliberti S, Pacchioni D, et al. Flow cytometry significantly improves the diagnostic value of fine needle aspiration cytology of lymphoproliferative lesions of salivary glands. *Cytopathology*. 2014;25(4):231–240.
48. Pusztaszeri MP, Baloch ZW. Subcategorizing salivary gland neoplasm of uncertain malignant potential (SUMP) in the Milan system for reporting salivary gland cytopathology. *Cancer Cytopath*. 2022;130(7):484–487.
49. Pusztaszeri M, Baloch Z, Vielh P, Faquin WC. Application of the Milan system for reporting risk stratification in salivary gland cytopathology. *Cancer Cytopath*. 2018;126(1):69–70.
50. Van Zante A. Ha P. Pusztaszeri MP. The Milan system for reporting salivary gland cytopathology: benefits and cautions. *AJSP Rev Rep*. 2010;25(5):235–242.
51. Jo VY, Krane JF. Ancillary testing in salivary gland cytology: a practical guide. *Cancer Cytopath*. 2018;126 Suppl 8:627–642.
52. Miller JA, An D, Shafique K, et al. Mucoepidermoid carcinoma, acinic cell carcinoma, and adenoid cystic carcinoma on fine-needle aspiration biopsy and the Milan system: an international multi-institutional study. *J Am Soc Cytopathol*. 2019;8(5):270–277.
53. du Jour KP, Griffith CC. The role of ancillary techniques in salivary gland cytopathology specimens. *Acta Cytol*. 2020;64(1–2):92–102.

54. Pusztaszeri MP, Faquin WC. Update in salivary gland cytopathology: recent molecular advances and diagnostic applications. *Semin Diagn Pathol*. 2015;32(4):264–274.

55. Pusztaszeri MP, García JJ, Faquin WC. Salivary gland FNA: new markers and new opportunities for improved diagnosis. *Cancer Cytopath*. 2016;124(5): 307–316.

56. Tabibi S, Gabrielson M, Saoud C, et al. Ancillary studies on cell blocks from fine needle aspiration specimens of salivary gland lesions: a multi-institutional study. *Diagn Cytopathol*. 2022;50(5):235–252.

57. Freiberger SN, Brada M, Fritz C, et al. SalvGlandDx— a comprehensive salivary gland neoplasm specific next generation sequencing panel to facilitate diagnosis and identify therapeutic targets. *Neoplasia*. 2021;23(5):473–487.

58. Tommola E, Kalfert D, Hakso-Mäkinen H, Kholová I. The contributory role of cell blocks in salivary gland neoplasms fine needle aspirations classified by the Milan system for reporting salivary gland cytology. *Diagnostics (Basel)*. 2021; 11(10):1778.

59. Dubucs C, Basset C, D'Aure D, Courtade-Saïdi M, Evrard SM. A 4-year retrospective analysis of salivary gland cytopathology using the Milan system for reporting salivary gland cytology and ancillary studies. *Cancers (Basel)*. 2019; 11(12):1912.

60. Rajab M, Payne RJ, Forest VI, Pusztaszeri M. Molecular testing for thyroid nodules: the experience at McGill University teaching hospitals in Canada. *Cancers (Basel)*. 2022;14(17):4140.

61. Pai SI, Faquin WC, Sadow PM, Pittet MJ, Weissleder R. New technology on the horizon: fast analytical screening technique FNA (FAST-FNA) enables rapid, multiplex biomarker analysis in head and neck cancers. *Cancer Cytopathol*. 2020;128(11):782–791.