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Review Article

The Milan System for Reporting Salivary Gland Cytopathology and Updates

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Abstract

The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) was introduced into cytopathology practice more than 5 years ago. It classifies the salivary gland lesion into 6 diagnostic categories and provides the risk of malignancy (ROM) and clinical management guidelines for each category. More than 100 articles have confirmed the applicability of this reporting system in routine practice and its important role in providing a uniform reporting system for salivary gland fine-needle aspiration. At the same time, new questions and feedback for improvement have emerged, as well as opportunities for clarification. For example, questions related to the non-diagnostic category are multiple-fold. First, although the cytologic criterion of the non-diagnostic category is currently defined as "<60 lesional cells or normal salivary gland tissue within the clinical setting of an evident mass", this has not been established or validated in the literature. Second, the ROM for the non-diagnostic category is high. Another question surrounds the interesting topic of sub-classifying current MSRSGC categories, as the risk of malignancy could vary in tumors of the same category. The last one concerns the incorporation of the ever-increasing number of molecular markers and antibody detection of gene re-arrangements, so-called next-generation immunohistochemistry (IHC) markers, into routine cytopathology practice. The quick application of next-generation sequencing into pathology practice provides an exciting opportunity for salivary gland cytopathology diagnosis.

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Introduction

Salivary gland neoplasms (SGN) are a rare group of histologically diverse tumors with frequently overlapping morphological features. Fine-needle aspiration (FNA) has been widely used as an integral part of SGN pre-operational workup and is safe and cost-effective. There was no standardized reporting system of salivary gland lesions, however, until the Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) was published in 2018.[1] With guidelines for consistent and transferable diagnoses, this system has improved communication between clinical practices, resulting in improved patient care. Since its implementation, the MSRSGC has had a huge impact on FNA diagnosis for SGN not only in the United States but also in the rest of the world.

MSRSGC put forth a six-tiered framework for classifying and reporting SGNs, providing the risk of malignancy (ROM) for each category, as well as clear-cut management recommendations (see Table 1). As of now, over 100 articles about MSRSGC have been published, including many international collaborations. Various retrospective and prospective clinical scenarios have been examined, including inter-observer reproducibility;[2,3] salivary gland cystic lesions;[4] submandibular lesions;[5] retrospective studies evaluating the FNA diagnosis of resected specific entities such as pleomorphic adenoma (PA) or Warthin tumor (WT);[6] and lesions in pediatric patients.[7] All these studies confirm FNA's excellent diagnostic performance in differentiating between benign and malignant salivary gland lesions and effectively distinguishing low- from high-grade neoplasms. It is a valuable tool for preoperative risk stratification. In this article, we will review the MSRSGC and discuss potential questions with some updates in the field of salivary gland cytopathology.

The reporting system

Non-diagnostic (ND) (I)

Diagnostic criteria

- Insufficient cells (<60 lesional cells);
- Preparation artifacts;
- Benign salivary gland elements in a clinically or radiologically defined mass (Fig 1a);
- Non-mucinous cyst fluid with an absence of an epithelial component.

Differential diagnosis and potential pitfalls

- The presence of significant cytologic atypia should not be classified as "non-diagnostic";
- Mucinous cyst fluid contents with an absence of an epithelial component should be classified as "Atypia of Undermined Significance (AUS)";
- Abundant inflammatory cells can be interpreted as ad-

Keywords: Salivary gland; Milan system for reporting salivary gland cytopathology; Gene re-arrangement; next-generation IHC markers.
Abbreviations: ND, non-diagnostic; AUS, atypia of undetermined significance; ROM, risk of management; SM, suspicious for malignancy; PA, pleomorphic adenoma.
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Table 1. The Milan System for Reporting Salivary Gland Cytopathology: ROM and recommended clinical management

Diagnostic Category	% ROM	Management
I. Non-Diagnostic	25%	Clinical/radiologic correlation; repeat FNA
II. Non-Neoplastic	10%	Clinical follow-up; radiologic correlation
III. Atypia of Undetermined Significance (AUS)	20%	Repeat FNA or surgery
IV. Neoplasm		
IVA. Neoplasm: Benign	<5%	Clinical follow-up or conservative surgery
IVB. Neoplasm: Salivary Gland Neoplasm of Uncertain Malignant Potential (SUMP)	35%	Conservative surgery
V. Suspicious for Malignancy	60%	Surgery, decide low- vs. high- grade & manage accordingly
VI. Malignant	90%	Surgery, decide low- vs. high- grade & manage accordingly

ROM: risk of malignancy; FNA: fine needle aspiration.

equate regardless of the presence of an epithelial component;
- A matrix component suggestive of a neoplasm should not be classified as "non-diagnostic".

It is critical to have a good clinical and radiologic correlation in the diagnosis of "non-diagnostic" cases, and, as such, commenting about a possible sampling error is warranted in many cases.

Risk of malignancy and clinical management recommendation

The average ROM for aspirates of salivary gland lesions classified as "non-diagnostic" is approximately 25% with studies ranging from 0 to 67%. Repeat FNA under radiologic guidance is recommended. If the clinical and radiologic information is sufficiently suspicious for neoplasms, an open biopsy or surgical resection may be warranted after a repeated "non-diagnostic" diagnosis.

Non-neoplastic (II)

Diagnostic criteria

Specimen with benign non-neoplastic changes, including acute and chronic inflammation and infection.

Representative entities and cytomorphologic features

Reactive lymph node hyperplasia:
- Polymorphic lymphocytes with predominantly small and mature forms;
- Tingible body macrophages;
- Lymphohistiocytic aggregates which represent the cytological correlate of germinal centers;
- Background lymphoglandular bodies.

Acute sialadenitis (Fig 1b):
- Abundant neutrophils ± bacteria;
- Histiocytes;
- Necrosis and inflammatory debris;
- Granulation tissue (at later stages).

Granulomatous sialadenitis:
- Hypocellular (scant acinar and ductal cells) specimen;
- Groups of epithelioid histiocytes;
- Variable amounts of acute and chronic inflammatory cells;
- ± multinucleated giant cells and necrotic background debris.

Differential diagnosis and potential pitfalls

The major pitfall in the category of "non-neoplastic" is a sampling error. A careful clinical and radiologic correlation is, therefore, necessary to avoid a false negative FNA. In cases with atypical cytomorphologic features, a diagnosis of "AUS" is more appropriate, which will likely trigger a repeat FNA for further definitive diagnosis.

Risk of malignancy and clinical management recommendation

The average ROM for aspirates of salivary gland lesions classified as "non-neoplastic" is approximately 10% with studies ranging from 0 to 20%. Recommend correlation with microscopic studies or flow cytometry analysis and clinical follow-up.

Atypia of undetermined significance (III)

Diagnostic criteria

AUS is an indeterminate category that includes cases indefinite between the non-neoplasm and neoplasm. There are 6 major subgroups based on their cytomorphologic findings:

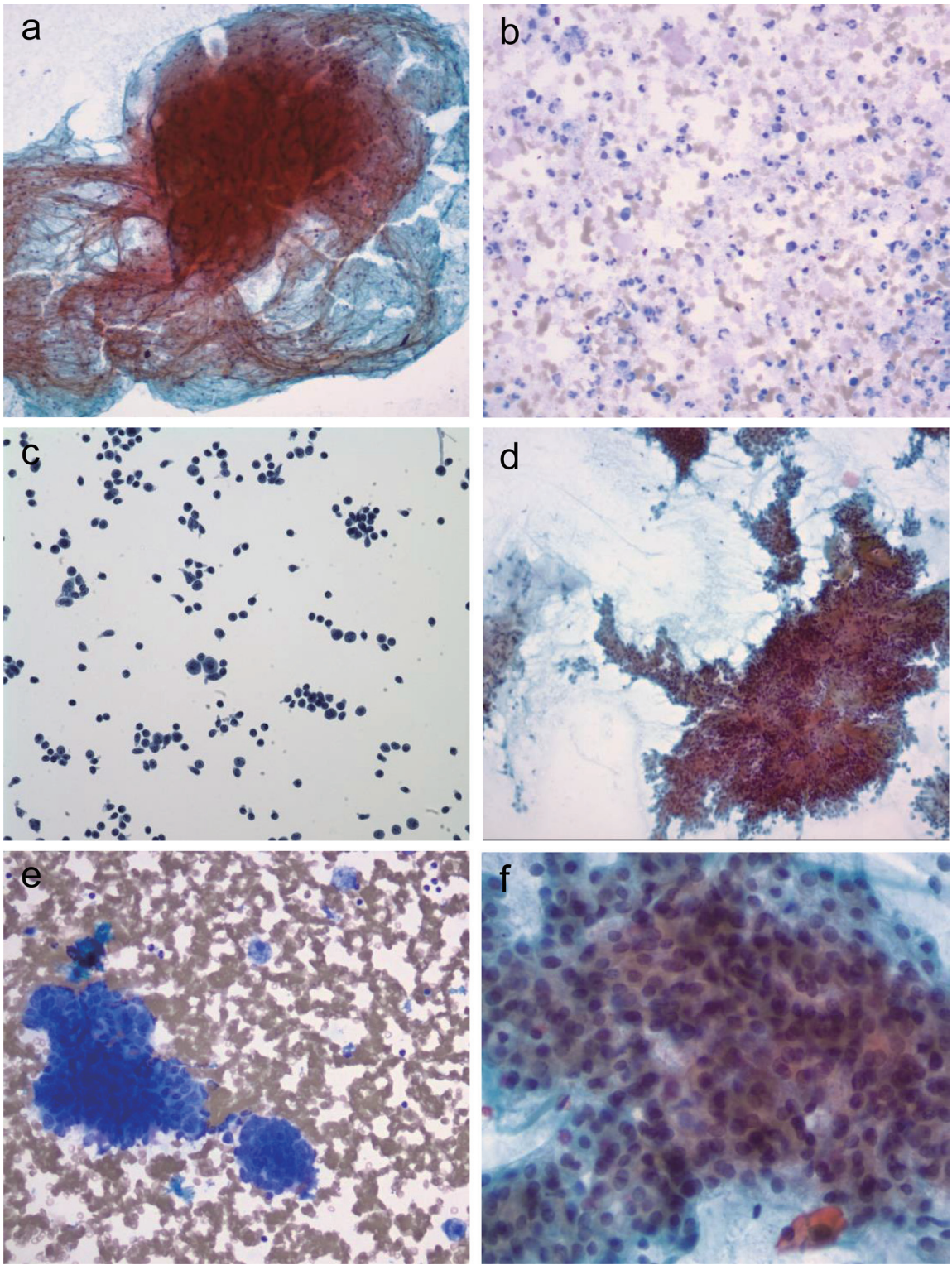

Fig. 1. Representative examples in each diagnostic category of the MSRSGC. (a) Non-diagnostic: FNA of a right parotid gland "lesion" showed only scant salivary gland parenchymal cells (Papanicolaou stain). (b) Non-neoplastic: FNA of a right parotid gland showed abundant neutrophils and histiocytes, consistent with abscess (Diff-quik stain). (c) AUS: FNA of a right parotid gland lesion showed single large atypical cells in the background of lymphoid tissue (Papanicolaou stain). Follow-up surgical resection revealed low-grade Non-Hodgkin B-cell lymphoma. (d) Neoplastic-benign: Classic cytomorphologic features of PA showed by Papanicolaou stain. (e) SUMP: A cellular specimen with basaloid appearing cells diagnosed as SUMP (Diff-Quik stain). Follow-up surgical specimen revealed basal cell adenoma. (f) SM: Clusters of epithelial cells including scattered mucin-filled cells, suspicious for neoplasm. Overall cellularity was low. Follow-up surgical specimen showed low-grade mucoepidermoid carcinoma (Papanicolaou stain).

- Reactive and reparative atypia indefinite for a neoplasm;
- Metaplastic changes (squamous, oncocytic, etc.) indefinite for a neoplasm;
- Hypocellular specimen suggestive of, but not diagnostic of a neoplasm;
- Preparation artifacts obscuring the distinction between a non-neoplastic and neoplastic process;
- Mucinous cystic lesion with absent/scant epithelial component;
- Lymphoid lesions indefinite for a lymphoproliferative disorder (Fig 1c).

Differential diagnosis and potential pitfalls

Cases diagnosed as AUS could be either non-neoplastic or neoplastic. Common differential diagnoses among lymphocyte-predominant aspirates range from chronic inflammation and reactive lymph node hyperplasia to malignant lymphoma, Warthin tumor, mucoepidermoid carcinoma, acinic cell carcinoma, etc. For cystic lesions, this could represent benign cysts such as a salivary duct cyst, branchial cleft cyst, and mucocele, or cystic neoplasms including Warthin tumor, pleomorphic adenoma, cystadenoma, low-grade mucoepidermoid carcinoma, or metastatic carcinoma in a lymph node. Wangsiricharoen *et al*.[8] recently reviewed surgical follow-ups in over 100 AUS cases and identified a wide variety of entities after the follow-up procedure, including metastatic melanoma, carcinoma, or mesenchymal tumors in addition to the common salivary gland tumors. As always, it is wise to have a clinical correlation and include a broad differential.

Ancillary testing

When there is sufficient material, ancillary testing may help change the diagnostic category, especially when differential diagnosis includes entities with specific immunochemistry and molecular/genetic characteristics. If there is a concern for a lymphoproliferative disorder, flow cytometry analysis is beneficial.

Risk of malignancy and clinical management recommendation

The ROM is expected to be within the range between that of the non-neoplastic and neoplastic categories, which is estimated to be around 20%. In further studies, the ROM was higher and ranged from 34% to 44%,[8,9] which is not unexpected as this is not a well-defined entity. Repeat FNA is recommended after the diagnosis of AUS. If there is a concern for malignancy based on the clinical presentation, it is recommended to perform a core needle biopsy, open biopsy, or surgical resection.

Neoplasm (IV)

Neoplasm: Benign

Diagnostic criteria

Cytomorphologic findings of a benign epithelial neoplasm (such as pleomorphic adenoma, Warthin tumor, or oncocytoma), or mesenchymal neoplasm (such as lipoma, schwannoma, lymphangioma, or hemangioma).

Representative entities with cytomorphologic features and differential diagnosis

- *PA*: variable admixtures of ductal epithelial cells, myoepithelial cells, and chondromyxoid matrix (Fig. 1d); differential diagnosis includes adenoid cystic carcinoma (AdCC) and low-grade mucoepidermoid carcinoma;
- *WT*: groups of oncocytes with background lymphocytes and dirty proteinaceous cystic appearance. Intraparotid lymph nodes, lymphoepithelial sialadenitis, oncocytoma, and lymphoepithelial cysts are in the differential;
- *Oncocytoma*: sheets/clusters of oncocytes without nuclear pleomorphism. Differential diagnosis includes diffuse oncocytosis; WT and Acinic cell carcinoma (ACC).

Ancillary testing

Immunochemistry stains may help with the differential diagnosis between benign and malignant neoplasms (see below). For specific entities such as PA, myoepithelial markers (smooth muscle actin, calponin, p63, p40, S100) in combination with Pleomorphic Adenoma Gene 1 (PLAG1) or High Mobility Group AT-Hook 2 (HMGA2) stain is helpful. Fluorescent in situ hybridization (FISH) analysis, if applicable (enough cellularity), may help rule out entities with specific translocation.

Risk of malignancy and clinical management recommendation

The benign category carries an estimated ROM of <5%, which can be followed up with complete resection with nerve preservation or clinically.

Neoplasm: Salivary gland neoplasm of uncertain malignant potential (SUMP)

Diagnostic criteria

- Cytomorphologic features of a neoplasm, in which a malignant entity cannot be excluded, including cellular basaloid neoplasm (Fig. 1e), oncocytic/oncocytoid neoplasm, and neoplasm with clear cell features;
- Lacking high-grade cytomorphologic features (marked atypia, highly mitotic, and necrosis).

Differential diagnosis

- Basaloid neoplasm: Cellular PA, epithelial-myoepithelial carcinoma, basal cell adenoma/carcinoma, AdCC, polymorphous adenocarcinoma;
- Oncocytic neoplasm: WT, cystadenoma, oncocytoma, ACC, metastatic renal cell carcinoma (RCC);
- Clear cell neoplasm: ACC, metastatic RCC.

Risk of malignancy and clinical management recommendation

The average ROM for aspirates of salivary gland lesions classified as "SUMP" is approximately 35%. Recommend nerve-sparing surgical resection.

Suspicious for malignancy (SM) (V)

Diagnostic criteria

Some but not all the criteria for malignant diagnosis are present, thus the overall cytologic features are suggestive of malignancy, including:

- Marked atypia with poor preparation, or obscuring inflammation and blood;
- Limited cytologic features of a specific malignant lesion;
- Marked atypia admixed with features of a benign salivary gland lesion;
- Scant sample with atypical features suggestive of a neuroendocrine tumor.

Representative entities and cytomorphologic features

Suboptimal samples of a high-grade malignancy constitute a

significant proportion of SM. Additionally, low-grade tumors with characteristic cytologic features, but not sufficient quantitatively or qualitatively to be diagnostic also fall into SM (Fig 1f). Examples include low-grade mucoepidermoid carcinoma, acinic cell carcinoma, and adenoid cystic carcinoma. For lymphoid lesions, SM can be used if lymphoma is suggested while ancillary studies for definitive diagnosis are lacking.

Differential diagnosis and potential pitfalls

The degree of atypia in the SM category should be higher than that in AUS or SUMP, as the latter has significantly lower ROM. Ancillary testing including immunochemistry and molecular tests may be needed in challenging cases, which can help upgrade SM cases to the "malignant" category (see below).

Risk of malignancy and clinical management recommendation

The average ROM for "suspicious for malignancy" approaches 60%. Assess the extent of the lesion and staging before surgery. Classification for low- versus intermediate- versus high-grade helps determine the extent of the surgery.

Malignant (VI)

Diagnostic criteria

Cytomorphologic features, sometimes combined with ancillary studies, are diagnostic of malignancy.

Representative entities and cytomorphologic features

- Acinic cell carcinoma (Fig. 2a-b): "Monotonous" population of epithelial cells with vacuolated cytoplasm and zymogen granules (PAS-D stain positive);
- Secretory carcinoma (Fig. 2c-d): Polygonal cells in tubular, follicular, or papillary structures, with eosinophilic vacuolated cytoplasm and background mucoproteinaceous material;
- Adenoid cystic carcinoma: Basaloid monotonous tumor cells surrounding pale basement membrane-like materials;
- Salivary duct carcinoma (SDC): Pleomorphic cells with overtly malignant cytologic features; frequent mitosis and background necrosis;
- Mucoepidermoid carcinoma (MEC): Admixture of goblet-type mucus cells, intermediate and epidermoid cells; cystic background with extracellular mucin;
- Myoepithelial carcinoma: Cells with myoepithelial differentiation with variable morphology and atypia;
- Epithelial-myoepithelial carcinoma: Ductal and myoepithelial cells arranged in pseudopapillary tubules or sheets;
- Carcinoma ex Pleomorphic adenoma: High-grade carcinoma (usually SDC), with focal classic PA components;
- Intraductal Carcinoma (IDC) (Fig. 2e-f): Usually low-grade morphology with low nuclear/cytoplasmic ratio and finely distributed chromatin; cytoplasmic granules or yellow-brown pigment can be seen;[10,11]
- Others: Carcinoma with high-grade transformation; metastatic tumors; malignant mesenchymal tumors.

Differential diagnosis and ancillary testing

Histochemical stains have limited utility in differentiating the tumor type with overlapping morphology. PAS and PAS-D may highlight zymogen granules in the cytoplasm of ACC. Mucicarmine helps demonstrate mucin production in mucoepidermoid carcinoma.[12] In comparison, immunochemistry stains, particularly myoepithelial markers, are helpful in challenging cases.[13–16] Recently, it has become well-known that many salivary gland tumors harbor specific genetic alterations, thus providing a good opportunity to refine the differential diagnosis with the help of ancillary testing. In addition, several potential protein surrogate markers have been identified, although may not be available except in big academic centers (Tables 2 and 3).[17–20]

Risk of malignancy and clinical management recommendation

The MSRSGC implies 90% ROM in the category of malignant. Surgical resection is usually warranted. The classification including its grade will be helpful to the clinician in determining the extent of surgery.

Perspectives

Widely used application usually leads to new questions and feedback for improvement, as well as opportunities for clarification. With recent advancements in salivary gland cytopathology, important discoveries could also potentially be included in future discussions of updated guidelines.

There are multiple questions regarding the non-diagnostic category. First, although the cytologic criterion of the non-diagnostic is tentatively defined as "<60 lesional cells or normal salivary gland tissue for a clinically or radiologically defined mass", this has not been validated nor established in the literature. There is disagreement among pathologists as to whether the criteria are adequate to address all potentially non-diagnostic scenarios. For example, aspirates consisting of abundant matrix material with an absence of a cellular component should not be classified as non-diagnostic. Future study is needed to address these questions regarding the non-diagnostic category.

A further question related to the ND category is the relatively high ROM. Several meta-analyses have demonstrated variable results; Hollyfield *et al* reported a ROM of 38% while the ROM was 25% in the study conducted by Wei *et al*.[21,22] More recent studies reported much lower ROMs in the ND category compared with the 25% ROM by MSRSGC. As we know, many factors may have contributed to the variability between ROMs in different studies, including sampling errors, sample size variation, and/or the low surgical resection rates of non-diagnostic specimens.[3] Accumulated experiences from multi-institutional studies will help modify the ROMs for the ND category.

Sub-classification of current categories is another interesting topic. Several studies have proposed suggestions to sub-classify certain categories of MSRSGC. Due to the differences in clinical management, it has been suggested that Category VI be divided into two subdivisions and one additional unique category (Category VII), proposed as follows:[23] VIa) a low-grade malignancy requiring complete surgical excision without concurrent neck dissection; VIb) a high-grade malignant neoplasm that requires more radical surgical excision with concurrent neck dissection. Lesions requiring draining the lymph node basin, such as high-grade primary salivary gland neoplasms and metastatic lesions to the parotid gland lymph nodes (such as squamous cell carcinoma, metastatic melanoma, and Merkel cell carcinoma) should be grouped together. Hematological malignancies could be classified separately as class VII, in an attempt to ensure that appropriate hematological consultation is obtained, and the specimen is sent fresh for flow cytometry. Another study also explored the possibility of subgrouping MSRSGC category III

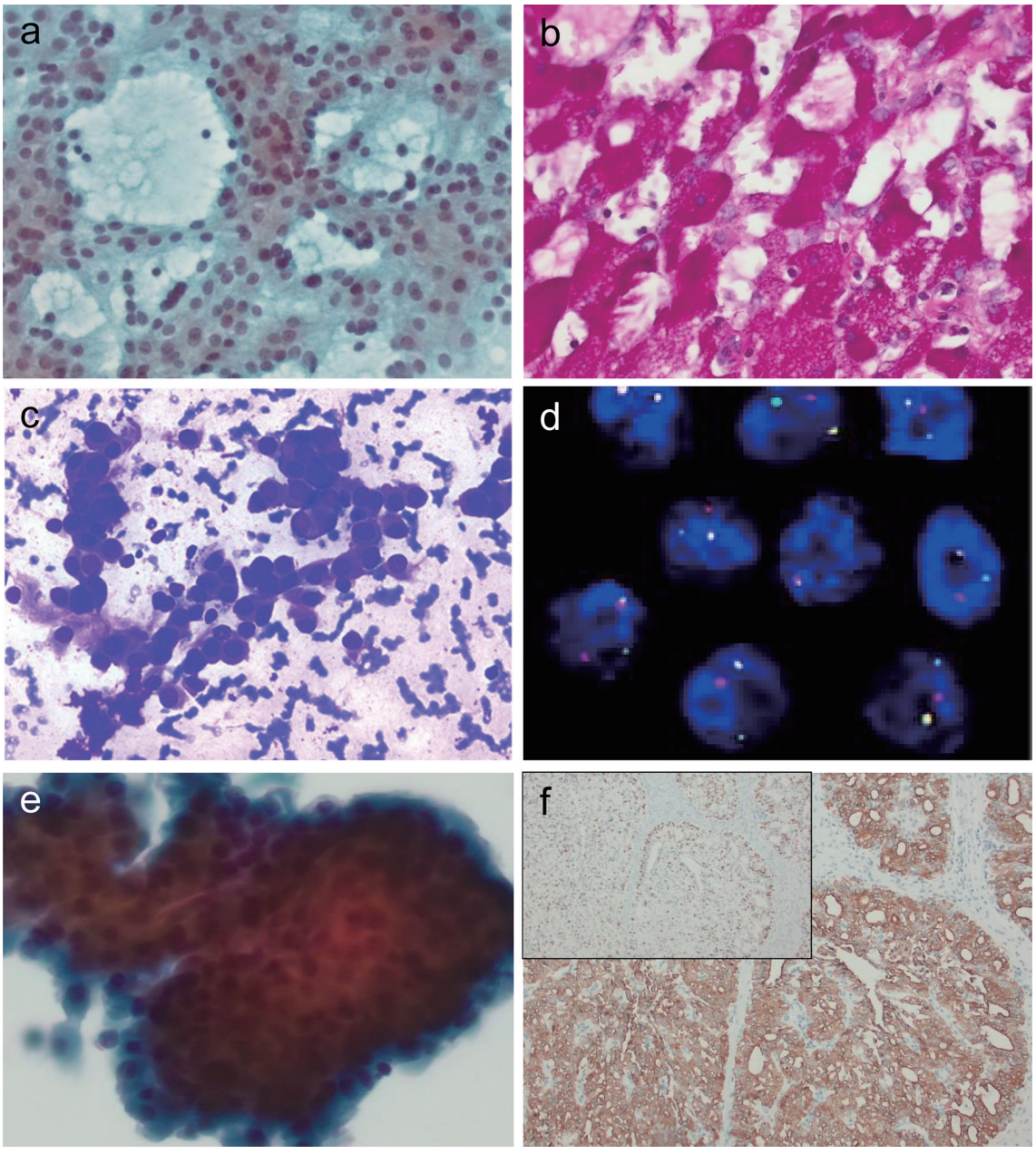

Fig. 2. Cytomorphologic features and ancillary tests of malignant salivary gland tumors. (a-b) Acinic cell carcinoma: (a) Papanicolaou stain showed round/oval nuclei, evenly dispersed fine chromatin, and low nuclear-cytoplasmic ratios. The cytoplasm appears granular with occasional vacuolization and indistinct cell borders. (b) Special stain of PAS-D showed strong diffuse cytoplasmic staining. (c-d) Secretory carcinoma: (c) Diff-quik stained showed intermediate-sized, polygonal uniform cells with bland-looking round eccentric nuclei and vacuolated or granular cytoplasm. (d) FISH demonstrated the chromosomal translocation leading to the fusion gene between the ETV6 gene on chromosome 12 and the NTRK3 gene on chromosome 15, confirming the diagnosis of secretory carcinoma. (e-f) Low-grade oncocytic-type salivary intraductal carcinoma: (e) Papanicolaou-stain showed small cellular groups with abundant oncocytic cytoplasm and centrally placed round/oval nuclei with inconspicuous nucleoli. (f) Immunohistochemical staining showed the larger ductal cells are positive for CK7 and surrounding myoepithelial cells are positive for p63 (inset).

(AUS) and found that ROMs varied within the same category. While specimens obscured by preparation artifacts have the highest ROMs, those with reactive and reparative atypia thus indefinite for neoplasm carried the lowest ROMs. There appears a need to sub-classify AUS.[8]

The third question is the ever-increasing number of molecular markers and antibody detection of gene re-arrangements, so-called next-generation IHC markers. The rapidly evolving molecular cytopathology of SGNs not only holds promise for specific diagnostic markers but also potential targets for precision medicine. Table 3 demonstrates genetic markers of common salivary gland tumors to date. Fluorescence in situ hybridization can be used to detect these molecular alterations, enhancing the specificity and accuracy. One barrier to implementing advanced molecular techniques, such as FISH and next-generation sequencing, is

Table 2. Common IHC markers of common salivary gland tumors

	NR4A3	Muc4	MGB	DOG1	CD117	CK5/6	P40/p63	SMA, calponin	Sox-10	AR
ACC	+	–	–	+	–	–	–	–	+	–
AdCC	–	–	–	–	+	+	+/–	+	+	–
SC	–	+	+	–	–	–	–	–	+++	–
SDC	–	–	+/–	–	–	–	–	–	–	+
MEC, HG	–	–	+/–	+/–	–	–	+	–	+/–	–
IDC	–	–	–	+	–	+	+	+	+	–

MGB: mammaglobin; AR: Androgen receptor; ACC: acinic cell carcinoma; AdCC: adenoid cystic carcinoma; SC: secretory carcinoma; SDC: salivary duct carcinoma; MEC: mucoepidermoid carcinoma; HG, high-grade; IDC: intraductal carcinoma.

that they are not currently widely available outside of major academic medical centers. Furthermore, the limited materials commonly seen in FNA specimens create an additional challenge. An alternative solution could be developing immunohistochemical surrogates for those diagnostic genetic tests. Earlier efforts seemed to have failed using IHCs in SGN cytopathology. MYB protein is expressed in both adenoid cystic carcinomas and other diagnostic mimickers; pleomorphic adenomas usually express PLAG1 protein, which is also expressed in carcinoma ex-pleomorphic adenoma. Nevertheless, an increasing number of promising studies have recently been reported. Skaugen and colleagues[24] revealed that NR4A3 immunostaining is highly specific for the diagnosis of acinic cell carcinoma, which is more sensitive than both DOG1 immunostaining and NR4A3 FISH. Acinic cell carcinoma is often diagnostically challenging in FNAs because the routinely used acinar markers DOG1 and SOX10 cannot help differentiate between tumor and normal salivary acini. Skaugen *et al*. demonstrated that NR4A3 immunostaining is negative in normal acini, which easily solved the diagnostic dilemma.[25–27] NR4A3 immunostaining is particularly helpful when the specimen has low cellularity insufficient for molecular diagnosis. It serves as an important diagnostic marker for ACC with adequate cell block material. Another promising example in SGN immunostaining is amphiregulin (AREG), which is an epidermal growth factor receptor (EGFR) ligand and also a downstream target of CRTC1-MAML2 fusion. AREG protein expression, detected by immunohistochemistry, helps identify fusion-positive MECs.[17] Future studies are needed to further develop immunohistochemical surrogates of genetic signatures to help with the diagnosis of challenging cases.

Lastly, with the considerable progress achieved with immune checkpoint inhibitors (e.g., atezolizumab, nivolumab, and pembrolizumab), requests for testing PD-L1 expression have become routine for many entities such as head and neck squamous cell carcinoma. Although there are no established guidelines for SGNs, clinical studies are ongoing with promising results after PD-L1 inhibitor treatment.[28] Traditionally, PD-L1 expression is determined by IHC testing histologically. Given that the first-line diagnostic modality for SGN is usually the FNA, it is surprising that reports exploring the possibility of PD-L1 staining in salivary gland FNA are lacking. Ongoing studies by the authors' group will soon aid in providing answers to this important question.

Conclusion

The widespread application of MSRSGC coupled with important clinical factors related to patient management has made significant progress in the characterization and diagnosis of salivary gland lesions. We are very excited to learn that the second edition of the MSRSGC reporting guidelines is expected to be published in early 2023, which will update ROMs based on new evidence in the literature and incorporate other significant advances in salivary gland cytopathology.

Table 3. Genetic markers of common salivary gland tumors[17–20]

Tumor	Translocation	Genes involved	Prevalence
PA	t(3;8)	PLAG1-fusions or HMG2-fusions	55%; 10–20%
MEC	t(11;19)(q21;p13); t(11;15)(q21;q26)	MECT1-MAML2 or MECT3-MAML2	30–80%; 5%
AdCC	t(6;9)(q22-23;p23-24)	MYB-NFIB; MYBL1-NFIB	30–85%; 10%
SC	t(12;15)(p13;q25)	ETV6-NTRK3	95%
Acinic cell Ca	t(4;9)(q13;q31)	*SCPP* gene clusters-NR4A3	84%
Basal cell adenoma		*CTNNB1* mutations	60%
Intraductal Ca		NCOA4-RET; TRIM27-RET	47%
Salivary Duct Ca		*AR* gene alteration; Her2 amplification	40–70%; 35%
Polymorphous adenocarcinoma		*PRKD1/2/3* mutation	70–80%
CCC	t(12;22)(q13;q12)	EWSR1-ATF1	80–90%
Myoepithelial Ca		EWSR1 rearrangement	35%
Epithelial-myoepithelial Ca		*HRAS* mutation	33–83%

PA: pleomorphic adenoma; MEC: mucoepidermoid carcinoma; AdCC: adenoid cystic carcinoma; SC: secretory carcinoma; CCC: clear cell carcinoma

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Conflict of interest

The authors have no conflicts of interest related to this publication.

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