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ORIGINAL ARTICLE

Mucoepidermoid carcinoma, acinic cell carcinoma, and adenoid cystic carcinoma on fine-needle aspiration biopsy and The Milan System: an international multi-institutional study

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Social Media: The overall diagnostic accuracy was 76.6% for mucoepidermoid carcinoma, 71.8% for acinic cell carcinoma and 88.9% for adenoid cystic carcinoma according to the Milan System for Reporting Salivary Gland Cytology (MSRSGC) in an international multi-institutional study.

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KEYWORDS
Salivary gland;
Fine-needle aspiration;
Mucoepidermoid carcinoma;
Acinic cell carcinoma;
Adenoid cystic carcinoma;
The Milan System for Reporting Salivary Gland Cytology;
Risk of malignancy;
Risk of neoplasm

Background We evaluated the diagnostic accuracy (DA), risk of neoplasm (RON), and risk of malignancy (ROM) for the commonly encountered malignant salivary gland tumors mucoepidermoid carcinoma (MECa), acinic cell carcinoma (ACCa), and adenoid cystic carcinoma (ADCa) applying The Milan System for Reporting Salivary Gland Cytology (MSRSGC).

Materials and methods The cytology archives from 2007 to 2017 of 9 academic institutions were searched for salivary gland FNAs for the following key words mentioned either in the principal and/or differential diagnosis: MEC, ACCa, and ADCa. The original cytology diagnosis was retrospectively classified according to the MSRSGC. Patient demographics, biopsy site, and available surgical follow-up were recorded. The final analysis included only cases with surgical follow-up.

Results A total of 212 salivary gland FNAs were included. Based on retrospective reclassification according to MSRSGC, 97 of 212 (46%) FNA cases carried a diagnosis of malignancy specific for either MECa, ACCa, or ADCa. In the remaining 115 cases, 24 of 212 (11%) were reclassified as suspicious for malignancy (SM) and 91 of 212 (43%) as salivary gland neoplasm of uncertain malignant potential (SUMP). The DA for MECa, ACCa, and ADCa was 78.7%, 75% and 89%, respectively. The RON was 100% for all 3 tumors and the ROM was 93.6% for MECa, 96.8% for ACCa, and 94.4% for ADCa.

Conclusions The DA of 78.7% for MECa, 75% for ACCa, and 89% for ADCa is reasonable in FNA specimens. Although the management of definitive cases of malignancy remains unchanged, the MSRSGC provides a ROM for SM and SUMP categories, which can improve patient management.
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Introduction

Fine-needle aspiration (FNA) is a valuable tool to evaluate and manage salivary gland lesions.[1] From the patient's perspective, it is a safe, cost-effective, and easily tolerable diagnostic procedure that can be performed by palpation or under ultrasound guidance in an outpatient clinical setting.[2,3] It has been shown that the surgical management and even the extent of surgical procedure of the salivary gland lesions is dependent on cytology interpretation. Furthermore, preoperative salivary gland FNA can affect the number of intraoperative frozen sections.[4,5] Therefore, it is important to differentiate benign from malignant lesions preoperatively. It is well-documented in the literature, however, that differentiating between a non-neoplastic, benign, and/or malignant salivary gland lesions is not always feasible in FNA specimens due to morphologic overlap, tumor heterogeneity, metaplastic changes (commonly encountered in non-neoplastic lesions), and sampling issues.[6]

Mucoepidermoid carcinoma (MECa), (Fig. 1), acinic cell carcinoma (ACCa), (Fig. 2), and adenoid cystic carcinoma (ADCa), (Fig. 3), are the most common malignant salivary gland neoplasms. These malignant neoplasms share cytomorphologic features with other benign and malignant salivary gland neoplasms and even with non-neoplastic lesions. Therefore, only a fraction of these commonly encountered malignant neoplasms is diagnosed with certainty in cytology material. A majority are diagnosed as either suspicious for malignancy or included in the differential diagnosis of a generic cytology diagnoses such as "Salivary Gland Neoplasm" or "Salivary Gland Lesion".[6]

The recently introduced Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) comprises 6 diagnostic categories termed as 1) non-diagnostic, 2) non-neoplastic, 3) atypia of undetermined significance (AUS), 4) neoplasm including benign and salivary gland neoplasm of uncertain malignant potential (SUMP), 5) suspicious for malignancy (SM), and 6) malignant (M).[7] Each category is associated with the risk of malignancy (ROM) and a recommendation for clinical management. The MSRSGC takes into account the diagnostic challenges faced in the interpretation and reporting of salivary gland lesions.

Herein, we evaluate diagnostic accuracy, risk of neoplasm (RON), and ROM for by retrospective application of MSRGC classification to a multi-institutional database comprising of FNA specimens salivary gland lesions with surgical pathology follow-up diagnosed as MECa, ACCa and ADCa.

Materials and methods

Data collection and categorization

The study was conducted after obtaining institutional research approval by each institution individually. The cytology archives of 9 academic institutions, including 6 in the United States (Johns Hopkins Hospital, Weill Cornell School of Medicine, University of Missouri School of Medicine, Virginia Commonwealth University, Perelman School of Medicine at the University of Pennsylvania, and Loyola University), 1 in Italy (Universita Cattolica del Sacro Cuore), 1 in Australia (St Vincent's Hospital), and 1 in Finland (Fimlab Laboratories) were retrospectively

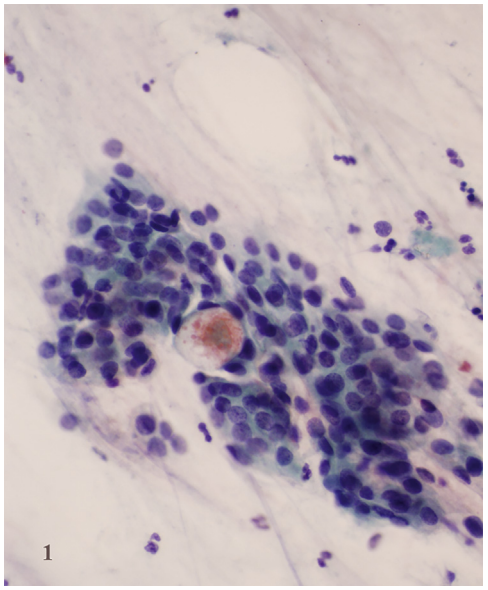

Figure 1 Mucoepidermoid carcinoma (x20, Papanicolaou stain).

searched for FNAs of salivary glands with the following key words: mucoepidermoid carcinoma, acinic cell carcinoma, or adenoid cystic carcinoma. The FNA cases were identified retrospectively between 2007 and 2017; cases without surgical pathology follow-up were excluded from this study. The case cohort chart was composed of 212 FNA cases of salivary glands identified among the 9 institutions, which were diagnosed as mucoepidermoid carcinoma, acinic cell carcinoma, or adenoid cystic carcinoma as a definitive diagnosis or in the differential diagnoses in cytopathology report and their correlated surgical follow-up. The following data points were recorded for each patient: tumor type, sex, age, biopsy site, FNA diagnosis, and surgical follow-up diagnosis. The FNA diagnoses were reclassified into the 3

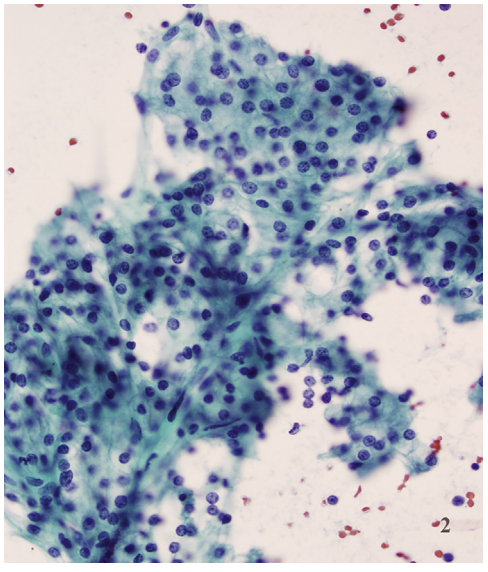

Figure 2 Acinic cell carcinoma (x20, Papanicolaou stain).

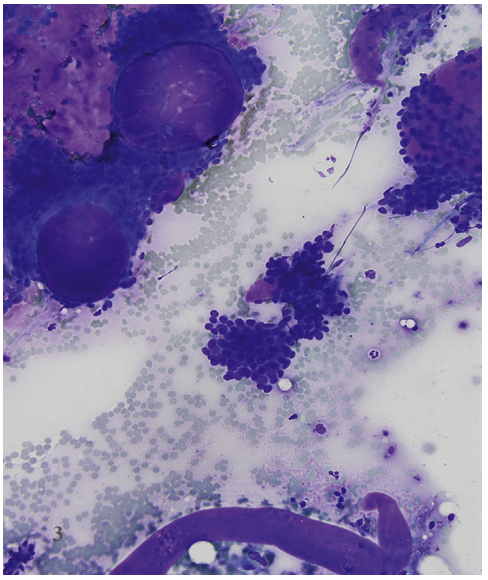

Figure 3 Adenoid cystic carcinoma (x20, Diff-Quik).

diagnostic categories of MSRSGC: malignant (M), suspicious for malignancy (SM), and salivary gland neoplasm of undetermined malignant potential (SUMP). The study included the pathology report review only. Each institution reviewed its own pathology reports individually and reclassified the cases into the MSRSGC categories. There were 2 or more pathologists in each institution to review the reports and consensus were reached for discrepant cases in each institution. The latter included FNA cases in which a malignant lesion was included in the differential diagnosis. Review of the surgical follow-up for each case was categorized as confirmed other malignant diagnosis, or benign diagnosis.

The risk of neoplasia (RON) and ROM were calculated with and without recategorization using MSRSGC. Data management and plotting were done using Python version 3.4 along with the Pandas package for data analysis.

Risk of neoplasm = number of neoplastic cases/total cases of the interest.
Risk of malignancy = number of malignant cases/total cases of the interest.
Diagnostic accuracy = Number of cases with a definitive diagnosis which was confirmed on histology/total number of cases with a definitive diagnosis of the interest.

The FNA/case data from all institutions were received in deidentified form for final review by J.A.M and Z.M. at the Johns Hopkins Hospital.

Specimen data

The cytology samples in this study were prepared with Diff-Quik staining on air-dried slides, Papanicolaou staining on

slides fixed with an alcohol-based fixative, or Thin-Prep preparation of alcohol fixed aspirations.

Results

A total of 212 salivary gland FNA cases represented 117 (55.2%) female patients and 95 (44.8%) male patients with a female:male ratio of (1.23:1). The average patient age was 53.8 years (range: 14 to 89 years). Parotid gland was the most common biopsy site (170, 80.2%) followed by submandibular gland (23, 10.8%); specified only as neck mass (6, 2.8%); parapharyngeal mass (4, 1.9%); cheek mass (3, 1.4%); sublingual gland (2, 0.9%); and one of each periauricular, mastoid area, maxilla, and tongue (1 each, 0.5%), respectively (Table 1). The 212 cases were distributed into 3 main groups based on FNA diagnosis: MECa 111 (52.4%), ACCa 55 (25.9%), and ADCa 46 (21.7%) cases. Based on the application of MSRSGC, 97 (45.7%) were diagnosed as malignant, 24 (11.3%) as SM, and 91 (43%) as SUMP.

Mucoepidermoid carcinoma

FNA cases in the MECa group

The 111 cases included 54 (48.7%) men, and 57 (51.3%) women. The average age was 53 years (range: 23 to 89 years). The parotid gland was the most common FNA site (88.3%); the other sites included submandibular gland (4, 3.6%), cheek masses (3, 2.7%), sublingual glands or neck masses (2, 1.8% each), and one each from the parapharyngeal space or periauricular region (0.9% each). A definitive diagnosis of malignant MECa was rendered in 47 and included in the differential diagnosis in 64 cases. On surgical pathology follow-up, 74 of 111 (66.66%) cases were confirmed as mucoepidermoid carcinoma and 28 of 111 (25.2%) cases were confirmed as other types of carcinomas of salivary gland origin. Nine of 111 cases (8.1%) were diagnosed as benign.

Based on MSRSGC reclassification, 47 cases (42.3%) were diagnosed as malignant MECa. Sixteen (14.4%) cases were diagnosed as SM/suspicious for mucoepidermoid carcinoma and 48 cases (43.3%) as SUMP. Histology–cytology correlation of cases is shown in Table 2.

Acinic cell carcinoma

The 55 cases with language suggestive of ACCa were from 25 (45.5%) male patients, and 30 (54. 5%) female patients. The average age was 53 years (range: 14 to 85 years). Forty-six biopsies (83.6 %) were taken from the parotid gland, 4 (7.2%) from the submandibular gland, 3 (5.4%) from a neck mass, and 2 (3.6%) from the parapharyngeal space. ACCa was a definitive diagnosis in 32 cases and included in the differential diagnosis in the remaining cases (23). Overall, 37 of 55 (67.3%) cases were confirmed with a diagnosis of acinic cell carcinoma. Twelve of 55 (21.8%) cases were confirmed malignant, but categorized as other types of carcinoma. Six of 55 cases (10.9%) were diagnosed benign. Applying MSRSGC, 32 cases (58.2%) had a definitive diagnosis of ACCa on aspirated material and were categorized as malignant. Four (7.3%) cases were diagnosed suspicious for ACCa and were categorized as SM and 19 cases (34.5%) were diagnosed as SUMP in which ACCa was included in differential diagnosis. Histology–cytology correlation of cases is shown in Table 2.

Table 1 Patient sex, age, and biopsy site and the cytology–histology correlation for each malignant category.

Type	Age (y)	Sex	Biopsy site and number of cases
Mucoepidermoid carcinoma (n = 111)	23-89 y Average: 53	Male 54 Female 57	Parotid 98 Submandibular gland 4 Sublingual gland 2 Parapharyngeal 1 Periauricular 1 Cheek mass 3 Neck mass 2
Acinic cell carcinoma (n = 55)	14-85 y Average: 53	Male 25 Female 30	Parotid 46 Submandibular gland 4 Parapharyngeal 2 Neck mass 3
Adenoid cystic carcinoma (n = 46)	31-88 y Average: 58	Male 16 Female 30	Parotid 26 Submandibular gland 15 Parapharyngeal 1 Mastoid area 1 Neck mass 1 Maxilla 1 Tongue 1

Table 2 Cytology-histology correlation of the cases for each Milan category.

Type	Malignant	Suspicious for malignancy	SUMP
Mucoepidermoid carcinoma (n = 111)	**Mucoepidermoid carcinoma (37)** **Other carcinomas (7):** Squamous cell carcinoma (3) Salivary duct carcinoma (2) Carcinoma ex pleomorphic adenoma (1) Poorly differentiated carcinoma of the skin (1) **Benign (3):** Pleomorphic adenoma (3)	**Mucoepidermoid carcinoma (12)** **Other malignancies (3):** Carcinoma ex pleomorphic adenoma (1) Embryonic rhabdomyosarcoma (1) Salivary gland cystadenocarcinoma (1) **Benign (1):** Warthin tumor with cystic change (1)	**Mucoepidermoid carcinoma (26)** **Other carcinomas (16):** Squamous cell carcinoma (3) Salivary duct carcinoma (2) Carcinoma ex pleomorphic adenoma (1) Adenocarcinoma (3) High grade carcinoma (2) Acinic cell carcinoma (1) Secretory carcinoma (1) Lymphoepithelial carcinoma (1) Matastatic papillary thyroid carcinoma (1) Adenosquamous cell carcinoma likely metastasis (1) **Benign (6):** Basal cell adenoma (2) Warthin tumor (1) Benign salivary gland tissue (1) Pleomorphic adenoma (1) Duct ectasia (1)
	47	16	48
Acinic cell carcinoma (n = 55)	**Acinic cell carcinoma (24)** **Other carcinomas (7):** Mucoepidermoid carcinoma (2) High grade adenocarcinoma (2) Salivary duct carcinoma (1) Squamous cell carcinoma(1) Metastatic renal cell carcinoma (1) **Benign** (**1**): Pleomorphic adenoma (1)	**Acinic cell carcinoma (3)** **Benign (1):** Pleomorphic adenoma (1)	**Acinic cell carcinoma (10)** **Other carcinomas (5):** Salivary duct carcinoma (2) Secretory carcinoma (1) High grade carcinoma (1) Carcinoma with neuroendocrine features (1) **Benign (4):** Warthin tumor (1) Oncocytoma (1) Myoepithelioma (1) Pleomorphic adenoma (1)
	32	4	19
Adenoid cystic carcinoma (n = 46)	**Adenoid cystic carcinoma (16)** **Other carcinomas (1):** Epithelial-myoepithelial carcinoma (1) **Benign (1):** Pleomorphic adenoma (1)	**Adenoid cystic carcinoma (3)** **Other carcinomas (0)** **Benign (2):** Myoepithelioma (1) Pleomorphic adenoma (1)	**Adenoid cystic carcinoma (11)** **Other carcinomas (2):** Poorly differentiated carcinoma (1) Carcinoma ex pleomorphic adenoma (1) **Benign (10):** Pleomorphic adenoma (6) Basal cell adenoma (2) Lymphadenoma (1) Cystadenoma (1)
	18	5	23

Boldfaces represents the categories.

Table 3 Risk of neoplasm (RON) and risk of malignancy (ROM) for each category, and the overall risk of neoplasm and risk of malignancy.

Type	Malignant RON ROM	Suspicious for malignancy RON ROM	SUMP RON ROM	Overall RON ROM
Mucoepidermoid carcinoma (n = 111)	47/47	16/16	46/48	109/111
	44/47	15/16	42/48	101/111
Acinic cell carcinoma (n = 55)	32/32	4/4	19/19	55/55
	31/32	3/4	15/19	49/55
Adenoid cystic carcinoma (n = 46)	18/18	5/5	23/23	46/46
	17/18	3/5	13/23	33/46
Overall (n = 212)	97/97	25/25	88/90	210/212
	92/97	21/25	70/90	183/212

SUMP; salivary gland neoplasm of uncertain malignant potential.

Adenoid cystic carcinoma

Forty-six cases were ADCa in 16 (34.8%) men and 30 (65.2%) women. The average age was 58 years (range: 31 to 88 years). The FNA site included 26 (56.5%) parotid gland, 15 (32.6%) submandibular gland, and 1 each of a neck mass, parapharyngeal space, mastoid area, maxilla, and tongue (2.2% each). ADCa was a definitive diagnosis in 18 cases and was included in the differential diagnosis in the remainder of cases (28 cases). Overall, 30 of 46 (65.2%) cases were confirmed with a diagnosis of ADCa. Three of 46 (6.5%) cases were confirmed malignant, however; they were categorized as other types of carcinoma. A benign diagnosis was rendered in 13 of 46 (28.3%) cases. Applying MSRSGC criteria, 18 cases (39.1%) had a definitive diagnosis of ADCa on aspirated material and were categorized as malignant. 5 (10.8%) cases were diagnosed as suspicious for ADCa and were categorized as SM and 23 cases (50%) were diagnosed as SUMP in which ADCa was included in differential diagnosis. Histology–cytology correlation of cases is shown in Table 2.

Diagnostic accuracy, risk of neoplasm, and risk of malignancy based on MSRSGC

The overall diagnostic accuracy was as follows: 78.7% for MECa, 75% for ACCa, and 89% for ADCa. Only 2 out of 212 cases showed benign non-neoplastic salivary gland tissue on histology and the rest were malignant or benign neoplasms; 86% (183 of 212) of the cases were confirmed as malignant on surgical follow up. The ROM was the highest in MECa category (91%) followed by the ACCa (89%) and ADCa (72%) categories. Table 3 shows RON and ROM for each category.

Discussion

In this retrospective multi-institutional international study, MECa was the most common primary malignant neoplasm of the salivary gland, followed by ACCa and ADCa. Our study results show that the diagnosis of MECa either rendered as a definitive diagnosis or included in differential diagnosis carries a higher ROM, followed by diagnosis of ACCa and ADCa. Similarly, upon stratifying the original diagnoses into the MSRSGC categories, the ROM remained highest in all malignant, suspicious, and SUMP categories for mucoepidermoid carcinoma, followed by ACCa and ADCa. Although the MSRSGC applied for these 3 most common primary malignant neoplasms of the salivary glands, the ROM and RON were influenced by these specific entities. The RON was 100% and the ROM varied between 94% and 97% for cases diagnosed as MECa, ACCa, or ADCa; these results are in agreement with other published studies.[8] The RON was 100% for all 3 carcinomas diagnosed as suspicious for malignancy; ROM, however, was quite variable for each neoplasm. The ROM in the SM category was 94% for MECa, followed by 75% for ACCa and dropping to 60% for ADCa. This lower value of ROM for cases diagnosed as suspicious for ADCa is considerably lower than other published studies.[8,9]

In the SUMP category, RON was 96% for cases with MECa included in the differential diagnosis, whereas the RON was 100% where ACCa or ADCa were included in differential diagnosis. The ROM in SUMP category varied from 87.5% for MEC to 78.9% and 56.5% for ACCa and ADCa, respectively. The RON for SUMP falls in the same range reported by Song et al,[8] however, in our study the ROM is significantly higher than other studies (reported range: 24.1% to 50%).[10-15] These findings show that, depending on what tumors are listed in the differential diagnosis, the ROM for suspicious and SUMP categories may be different.

Song et al suggested that their overestimation of ROM in SUMP could be due to factors such as patient demographics, tumor characteristics, or referral practice to each institution. Our study is multi-institutional and international, which shows the highest ROM in the SUMP category.

The ROM in the SUMP category is higher when MECa, ACCa, or ADCa is included in the differential diagnosis. This may reflect the importance of including the differential diagnosis on ROM in the SUMP category.

Overall, pleomorphic adenoma, the most common tumor of the salivary glands, was also the most common diagnostic pitfall for malignancy, likely due to heterogeneity of these tumors[6,16-18] Chondromyxoid or fibrillary matrix admixed with epithelial cells and myoepithelial cells constitutes pleomorphic adenoma in most cases.[19] Our previous study and slide review illustrated that abundance of matrix material in pleomorphic adenoma does not usually cause a diagnostic problem. Nonetheless, scarcity of matrix in cellular pleomorphic adenoma with prominent myoepithelial cells or epithelial cells might be mistaken for malignant neoplasms.[6] This study was based on cytopathology reports and the cases that were misinterpreted as pleomorphic adenoma were all cellular per report. Of note, cases suspected to be pleomorphic adenoma or diagnostic of pleomorphic adenoma were not included in this study.

As aforementioned, the RON and ROM were highest in cases with a definitive diagnosis or the differential that included MECa. This might be explained by the diagnostic criteria in MECa, which are easily reproducible (including presence of extracellular mucin, mucinous cells, and squamous cells on aspirated material).[6,20,21] Moreover, MECa is the most commonly encountered malignancy of the salivary glands and there is less of an overlap with other benign lesions. The overall RON and ROM for ACCa were 100% and 89%, respectively. Myoepithelial rich pleomorphic adenoma, Warthin tumor, and oncocytoma can be mistaken for ACCa. ACCa is characterized by large delicate, vacuolated, or polygonal clear cells with ill-defined cell borders, abundant granular (zymogen granules) cytoplasm, bland nuclei, and occasional lymphocytes and naked nuclei,[15,22,23] while oncocytes in oncytoma and Warthin tumor display granular cytoplasm with well-defined cytoplasmic membranes.

The overall RON and ROM for ADCa was 100%, and 72%, respectively. Relatively large spheres or cylindrical, acellular, well-defined metachromatic hyaline matrix and monomorphic basaloid cells with round nuclei and angulated nuclear contour and occasional naked nuclei characterize ADCa.[24,25] Pleomorphic adenoma, basal cell adenoma, myoepithelioma, lymphadenoma, and cystadenoma were benign surgical follow-ups that masqueraded as ADCa in aspirated material. Presence of cells with high nuclear-to-cytoplasmic (N/C) ratio and matrix may contribute to misinterpretation of these lesions; for instance, basal cell adenoma can be mistaken for ADCa through the fragments of basal cells with high N/C ratio. Peripheral palisading and a rim of metachromatic stroma surrounding the fragments are helpful diagnostic features for basal cell adenoma when they are present.[16,26,27]

In conclusion, our analysis of the cytology and histologic follow-up of FNA cases of MECa, ACCa, and ADCa categories shows a high diagnostic accuracy rate for these tumors. The ROM is within the reported range for all salivary gland malignancies. The ROM for SUMP in the ADCa group was significantly higher, however. In addition, the ROM for suspicious and SUMP categories might be influenced by tumor types included in the differential diagnosis. Thus, familiarity with cytomorphologic features of these neoplasms and the diagnostic pitfalls can improve ROM and RON in The Milan System for Reporting Salivary Gland Cytology.

Disclosure statement

The authors have no financial conflicts of interest to declare.

Statement of ethics

The authors have no ethical conflicts to disclose.

Author's contributions

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