Application of the Milan System for Reporting Salivary Gland Cytopathology: A Retrospective 12-Year Bi-institutional Study

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ABSTRACT

OBJECTIVES

Multi-institutional studies are required for the validation of the Milan System for Reporting Salivary Gland Cytopathology (MSRSGC).

METHODS

A total of 1,560 fine-needle aspirations of the salivary glands were retrieved from two institutions for a 12-year period. The diagnoses were reclassified based on the MSRSGC. Risk of malignancy (ROM) for each category was calculated based on 694 histologic follow-up cases.

RESULTS

The ROM for each category was: 18.3% for nondiagnostic, 8.9% for nonneoplastic, 37.5% for atypia of undetermined significance (AUS), 2.9% for benign neoplasm, 40.7% for salivary gland neoplasm of uncertain malignant potential (SUMP), 100% for suspicious for malignancy, and 98.3% for malignant. The sensitivity, specificity, positive predictive rate, and negative predictive rates were 89%, 99%, 98%, and 96%, respectively.

CONCLUSIONS

The results of the current study are in keeping with the MSRSGC. The indeterminate categories of AUS and SUMP showed intermediate ROMs at 37.5% and 40.7%, respectively.

Fine-needle aspiration (FNA) biopsy is a safe and cost-effective technique for the preoperative evaluation of salivary gland lesions. It is useful to differentiate between neoplastic and nonneoplastic lesions and to provide specific diagnoses for common benign and malignant neoplasms. However, cytologic interpretation of salivary gland FNAs can be challenging due to the diverse morphology of salivary gland tumors, including tumor heterogeneity and overlapping morphologic features between different tumor subtypes. The addition of new entities recognized by the updated 2017 World Health Organization classification of head and neck tumors also contributes to this challenge.1 In the past, the FNA diagnoses of salivary gland lesions were often descriptive and sometimes lacked clarity for management guidance. For these reasons, the Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) has been recently developed to standardize the terminology for reporting FNA cytology of salivary gland and to improve the communication between clinicians and pathologists.2,3 The MSRSGC is a seven-tiered classification system comprising: I, nondiagnostic; II, nonneoplastic; III, atypia of undetermined significance (AUS); IVA, benign neoplasm; IVB, salivary gland neoplasm of uncertain malignant potential (SUMP); V, suspicious for malignancy (SM); and VI, malignant. It also provides estimated risk of malignancy (ROM) and clinical management recommendations for each category. Since the inception of the MSRSGC, there have been a few studies addressing institutions' experiences with this classification system.4-13 Multi-institutional studies with a large number of cases and surgical pathology follow-up are necessary to validate the clinical utility of this classification scheme. The objectives of this study were to retrospectively reclassify consecutive salivary gland FNAs from a 12-year period at two institutions, to assess the ROM for each category with surgical pathology follow-up, and to compare the differences for diagnostic frequency, follow-up biopsy or resection rate, and ROM in each category between these two institutions to further validate the MSRSGC in real-world practice.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board (IRB) of Indiana University (IU, IRB No. 1802116631) and Taipei Veterans General Hospital (TVGH, IRB No. 2018-07-009AC). A retrospective search for all salivary gland FNAs from a 12-year period (2006-

2017) in the pathology databases of the two institutions was carried out. The FNA aspirates were performed by radiologists, pathologists, or surgeons with or without ultrasound guidance. Two to four passes were routinely obtained from each lesion. Rapid on-site evaluation was performed for most of the IU cases but for none of the TVGH cases. The direct smears were prepared with conventional methods. An air-dried slide stained with Romanowsky-type stains (either Liu or Diff-Quik) and an alcohol-fixed slide stained with Papanicolaou stain was prepared for each pass. Based on the cytology reports and selective review of microscope slides when information from the report was insufficient (H. H. W. reviewed the slides from IU and J.-F. H. reviewed the slides from TVGH), the final diagnosis of each case was reclassified based on the MSRSGC. The histology follow-up (core biopsy or resection) of these cases was retrieved. The ROM of cases from each category was calculated. The ROM is defined as the ratio of FNAs with malignant follow-up to the total number of FNA cases with histology follow-up for that category. For calculation of the sensitivity, specificity, positive predictive rate, and negative predictive rate for the malignancy, we grouped the SM and malignant cases together as positive, and the nonneoplastic and benign neoplasm cases as negative. The calculations with and without the inclusion of AUS and SUMP were performed. To compare diagnostic frequency, follow-up biopsy or resection rate, and ROM for each category between the two institutions, Fisher exact tests were applied. Student t test was performed to compare differences between mean ages of two groups. Two-sided P values less than .05 were considered to be statistically significant. Statistical analyses were performed using R software (version 3.5.0; R Foundation, Vienna, Austria).

RESULTS

A total of 1,560 salivary gland aspirates were retrieved, of which 885 cases originated from IU and 675 cases from TVGH, including 707 female and 853 male patients, with an average age of 55.2 years (range, 1-98). Of the 1,560 lesions, 980 were in the parotid gland, 272 in the submandibular gland, three in the palate, and a specific anatomic site was not documented in 302 of the FNA reports. The size of the lesions measured 2.4 cm on average (range, 0.5-9.4 cm).

The diagnostic frequency, biopsy or resection rate, and ROM for each category from the two institutions are summarized in Table 1. Overall, the final diagnosis of each FNA was reclassified based on the MSRSGC resulting in 294 (18.8%) cases classified nondiagnostic, 336 (21.5%) nonneoplastic, 60 (3.8%) AUS, 581 (37.2%) benign neoplasm, 92 (5.9%) SUMP, 19 (1.2%) SM, and 178 (11.4%) malignant. Based on 694 cases with histologic follow-up, the ROM for each category was: 18.3% (number of malignancies/total number, 13/71) for nondiagnostic, 8.9% (7/79) for nonneoplastic, 37.5% (15/40) for AUS, 2.9% (9/315) for benign neoplasm, 40.7% (24/59) for SUMP, 100% (15/15) for SM, and 98.3% (113/115) for malignant.

TABLE 1

Reclassification of Salivary Gland Aspirates From Two Institutions in the 12-Year Period 2006-2017 Based on the MSRSGC

Overall				**IU**			**TVGH**		
MSRSGC	**No. (Overall, %)**	**No. of Histology Follow-up (%)**	**No. of Malignant (ROM, %)**	**No. (Overall, %)**	**No. of Histology Follow-up (%)**	**No. of Malignant (ROM, %)**	**No. (Overall, %)**	**No. of Histology Follow-up (%)**	**No. of Malignant (ROM, %)**
I. Nondiagnostic	294 (18.8)	71 (24.1)	13 (18.3)	99 (11.2)	24 (24.2)	4 (16.7)	195 (28.9)	47 (24.1)	9 (19.1)
II. Nonneoplastic	336 (21.5)	79 (23.7)	7 (8.9)	251 (28.4)	49 (19.5)	4 (8.2)	85 (12.6)	30 (35.3)	3 (10)

Overall			IU			TVGH			
MSRSGC	No. (Overall, %)	No. of Histology Follow-up (%)	No. of Malignant (ROM, %)	No. (Overall, %)	No. of Histology Follow-up (%)	No. of Malignant (ROM, %)	No. (Overall, %)	No. of Histology Follow-up (%)	No. of Malignant (ROM, %)
III. AUS	60 (3.8)	40 (66.7)	15 (37.5)	37 (4.2)	26 (70.3)	11 (42.3)	23 (3.4)	14 (60.9)	4 (28.6)
IVA. Benign neoplasm	581 (37.2)	315 (54.2)	9 (2.9)	276 (31.2)	154 (55.8)	3 (1.9)	305 (45.2)	161 (52.8)	6 (3.7)
IVB. SUMP	92 (5.9)	59 (64.1)	24 (40.7)	58 (6.6)	37 (63.8)	17 (45.9)	34 (5%)	22 (64.7)	7 (31.8)
V. SM	19 (1.2)	15 (78.9)	15 (100)	7 (0.8)	4 (57.1)	4 (100)	12 (1.8)	11 (91.7)	11 (100)
VI. Malignant	178 (11.4)	115 (64.6)	113 (98.3)	157 (17.7)	98 (62.4)	96 (98)	21 (3.1)	17 (81.0)	17 (100)
Total	1,560 (100)	694 (44.5)	196 (28.2)	885 (100)	392 (44.2)	139 (35.5)	675 (100)	302 (44.7)	57 (18.9)

AUS, atypia of undetermined significance; IU, Indiana University; MSRSGC, Milan System for Reporting Salivary Gland Cytopathology; ROM, risk of malignancy; SM, suspicious for malignancy; SUMP, salivary gland neoplasm of uncertain malignant potential; TVGH, Taipei Veterans General Hospital.

TABLE 2

False-Positive Cases in the Malignant Category

Age	Sex	MSRSGC	FNA Diagnosis	Histologic Diagnosis
16	M	Malignant	Low-grade mucoepidermoid carcinoma	Pleomorphic adenoma
62	M	Malignant	Adenoid cystic carcinoma	Basal cell adenoma

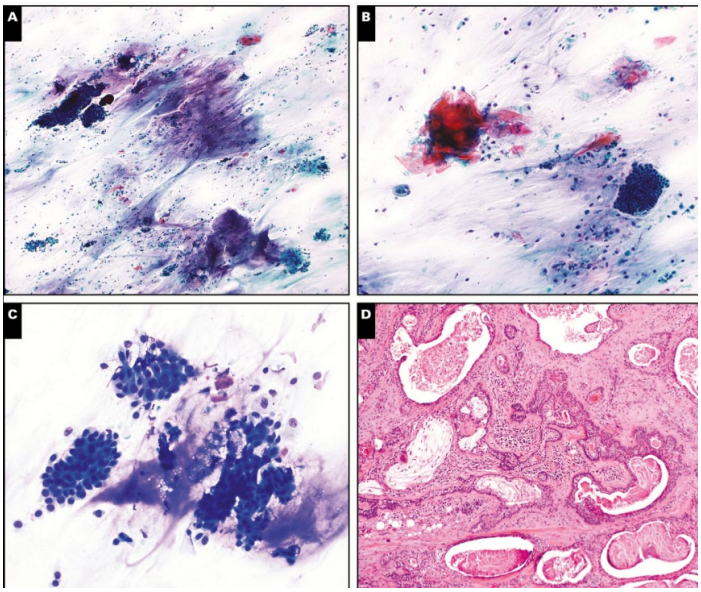
FNA, fine-needle aspiration; MSRSGC, Milan System for Reporting Salivary Gland Cytopathology.

Comparing the two institutions, IU had a significantly higher diagnostic frequency in nonneoplastic (28.4% vs 12.6%, $P < .05$) and malignant (17.7% vs 3.1%, $P < .05$) categories, while TVGH had much higher diagnostic frequency in nondiagnostic (28.9% vs 11.2%, $P < .05$) and benign neoplasm category (45.2% vs 31.2%, $P < .05$). The follow-up biopsy or resection rate was significantly higher in TVGH for the nonneoplastic category (35.3% vs 19.5%, $P < .05$). There were no differences in ROM for each category between these two institutions.

On histologic follow-up, the most common benign neoplasm was pleomorphic adenoma (226/694, 32.6%), followed by Warthin tumor (114/694, 16.4%). The most common malignancy was metastatic squamous cell carcinoma (40/694, 5.8%), followed by lymphoma (35/694, 5.0%). In the malignant category, patients with metastatic squamous cell carcinoma were much older than patients with other malignancies (mean age, 71.0 vs 56.4 years, $P < .001$). The most common primary site was the skin of head and neck.

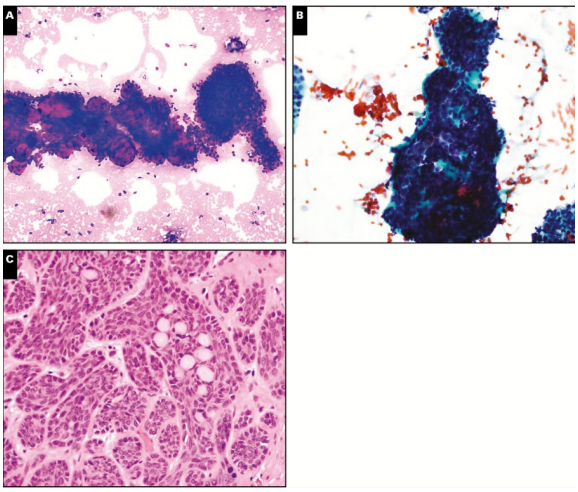
There were two false-positive cases in the malignant category Image 1. The second case was a basal cell adenoma, which was overdiagnosed as an adenoid cystic carcinoma on FNA Image 2. All 15 cases of SM that underwent surgery were malignant on histologic follow-up (ROM 100%).

Image 1



Fine-needle aspiration of right parotid gland mass was misinterpreted as a low-grade mucoepidermoid carcinoma. **A** and **B**, The smears show clusters of basaloid epithelial cells, occasional squamous cells, and abundant mucin in the background (Papanicolaou, ×200). **C**, Occasional cells demonstrate cytoplasmic vacuoles (Diff-Quik, ×400). **D**, Resection of the tumor revealed a pleomorphic adenoma with extensive squamous and mucinous metaplasia (H&E, ×200).

Image 2.



A basal cell adenoma was misinterpreted as adenoid cystic carcinoma on fine-needle aspiration. Cytologic smears show small hyaline globules within the basaloid epithelium (**A**, Diff-Quik, ×400; **B**, Papanicolaou, ×400). **C**, Histologic follow-up revealed a basal cell adenoma with focal cribriform growth pattern containing basophilic basement membrane-like material within the microcystic spaces (H&E, ×200).

Among the 394 benign aspirates categorized as nonneoplastic and benign neoplasm with histologic follow-up, there were 16 false-negative cases, which included seven cases of lymphoma, four cases of carcinoma ex pleomorphic adenoma, two cases of adenoid cystic carcinoma, and one case each of acinic cell carcinoma, adenocarcinoma, not otherwise specified (NOS), and secretory carcinoma Table 3.

TABLE 3

False-Negative Cases in the Nonneoplastic and Benign Neoplasm Categories

Age, y	Sex	MSRSGC	FNA Diagnosis	Histologic Diagnosis
33	M	Nonneoplastic	RLN	Lymphoma-classic Hodgkin

Age, y	Sex	MSRSGC	FNA Diagnosis	Histologic Diagnosis
32	M	Nonneoplastic	RLN	Lymphoma-follicular
71	M	Nonneoplastic	RLN	Lymphoma-follicular
83	M	Nonneoplastic	RLN	Lymphoma-follicular
39	F	Nonneoplastic	RLN	Lymphoma-follicular
47	F	Nonneoplastic	RLN	Lymphoma-MALT
16	M	Nonneoplastic	RLN	Lymphoma-T lymphoblastic
52	F	Benign neoplasm	WT	Acinic cell carcinoma
42	F	Benign neoplasm	PA	Adenoid cystic carcinoma
43	F	Benign neoplasm	PA	Adenoid cystic carcinoma
76	F	Benign neoplasm	PA	Carcinoma ex pleomorphic adenoma
29	F	Benign neoplasm	PA	Carcinoma ex pleomorphic adenoma

Age, y	Sex	MSRSGC	FNA Diagnosis	Histologic Diagnosis
60	M	Benign neoplasm	PA	Carcinoma ex pleomorphic adenoma
43	M	Benign neoplasm	PA	Carcinoma ex pleomorphic adenoma
63	F	Benign neoplasm	PA	Low-grade adenocarcinoma, NOS
66	M	Benign neoplasm	PA	Secretory carcinoma

FNA, fine-needle aspiration; MALT, mucosa-associated lymphoid tissue; MSRSGC, Milan System for Reporting Salivary Gland Cytopathology; NOS, not otherwise specified; PA, pleomorphic adenoma; RLN, reactive lymph node; WT, Warthin tumor.

For the indeterminate categories, there were 40 cases that had histology correlation within the AUS category. Among these, 15 cases (37.5%) were malignant, one was atypical, nine were benign neoplasms, and 15 were nonneoplastic. The most common malignant diagnosis in the AUS category was lymphoma (seven cases), accounting for 47% of all malignant cases in AUS category Table 4. For the SUMP category, there were 59 cases with histologic follow-up. Among these, two (3.4%) were nonneoplastic, 33 (55.9%) were benign neoplasm, and 24 (40.7%) were malignant. Most of the follow-up cases within the SUMP category were neoplastic (57/59, 96.6%) with 33 benign and 24 malignant neoplasms Table 5.

TABLE 4

Histologic Correlation of Atypia in the Undetermined Significance (AUS) Category (40 Cases)

MSRSGC	Histology Category	Histologic Diagnosis	No.
AUS	Nonneoplastic, 15 cases (37.5%)	Reactive lymph node	5
		Acute or chronic sialadenitis	5
		IgG4-related sialadenitis	2
		Lymphoepithelial cyst	1
		Epidermoid cyst	1
		Mucocele	1
	Atypical, 1 case (2.5%)	Atypical lymphoid infiltrate	1
	Benign neoplasm, 9 cases (22.5%)	Warthin tumor	3
		Basal cell adenoma	2
		Pleomorphic adenoma	1
		Benign keratinizing lesion	1
		Oncocytic cystadenoma	1
		Paraganglioma	1

MSRSGC	Histology Category	Histologic Diagnosis	No.
	Malignant, 15 cases (37.5%)	Lymphoma	7
		Mucoepidermoid carcinoma	2
		Acinic cell carcinoma	1
		Leiomyosarcoma	1
		Lymphoepithelial carcinoma	1
		Metastatic melanoma	1
		Metastatic squamous carcinoma	1
		Papillary cystadenocarcinoma	1

MSRSGC, Milan System for Reporting Salivary Gland Cytopathology.

TABLE 5

Histologic Correlation of Salivary Gland Neoplasm in the Uncertain Malignant Potential (SUMP) Category (59 Cases)

MSRSGC	Histology Category	Histologic Diagnosis	No.
SUMP	Nonneoplastic, 2 cases (3.4%)	Chronic sialadenitis	1
		Salivary duct cyst	1

MSRSGC	Histology Category	Histologic Diagnosis	No.
	Benign neoplasm, 33 cases (55.9%)	Pleomorphic adenoma	16
		Basal cell adenoma	11
		Warthin tumor	3
		Oncocytoma	1
		Pilomatrixoma	1
		Myoepithelioma	1
	Malignant, 24 cases (40.7%)	Mucoepidermoid carcinoma	7
		Adenoid cystic carcinoma	5
		Carcinoma ex pleomorphic adenoma	2
		Epithelial-myoepithelial carcinoma	2
		Metastatic basaloid squamous carcinoma	2

MSRSGC	Histology Category	Histologic Diagnosis	No.
		Salivary duct carcinoma	2
		Acinic cell carcinoma	1
		Secretory carcinoma	1
		Myoepithelial carcinoma	1
		MALT lymphoma	1

MALT, mucosa-associated lymphoid tissue; MSRSGC, Milan System for Reporting Salivary Gland Cytopathology.

To distinguish between benign and malignant, with and without inclusion of AUS and SUMP, the sensitivity, specificity, positive predictive rate, and negative predictive rates were 91%, 86%, 73%, 96% and 89%, 99%, 98%, 96% respectively Table 6.

TABLE 6

The Performance of the Milan System for Reporting Salivary Gland Cytopathology for Detecting Malignancy

	With Inclusion of AUS and SUMP, %	Without Inclusion of AUS and SUMP, %
Sensitivity	91	89

	With Inclusion of AUS and SUMP, %	Without Inclusion of AUS and SUMP, %
Specificity	86	99
Positive predictive value	73	98
Negative predictive value	96	96

AUS, atypia of undetermined significance; SUMP, salivary gland neoplasm of uncertain malignant potential.

DISCUSSION

FNA has become widely accepted as a first-line diagnostic tool for the evaluation of salivary gland lesions and can provide useful information for clinical management of these patients. However, cytomorphologic interpretation can be challenging when dealing with tumors showing diverse morphology and metaplasia. The objective of the MSRSGC is to foster better communication between clinicians and pathologists and to improve patient care. It provides a standardized, tiered diagnostic framework with risk stratification for salivary gland FNA. The ROM for each category estimated by the authors of the MRSGC2 is as follows: 25% for nondiagnostic, 10% for nonneoplastic, 20% for AUS, less than 5% for benign neoplasm, 35% for SUMP, 60% for SM, and 90% for malignant. However, the actual ROMs for the MRSGC diagnostic categories that have been reported in the literature have ranged widely: 18% (0%-44.2%) for nondiagnostic, 8.6% (1.6%-33.3%) for nonneoplastic, 30.1% (0%-100%) for AUS, 3.4% (1.6%-7.9%) for benign neoplasm, 40.3% (26.7%-50%) for SUMP, 84.8% (50%-100%) for SM, and 97.5% (92.3%-100%) for malignant Table 7.4-14

TABLE 7

Summary of Risks of Malignancy for MSRSGC Categories in Studies With Pathologic Follow-up Published 2017-2019

		Risk of Malignancy, % (No. of Malignancies/Total No.)						
Author	**No.**	**Nondiagnostic**	**Nonneoplastic**	**AUS**	**Benign Neoplasm**	**SUMP**	**SM**	**Malignant**
Hollyfield et al[5]	77	37.5 (3/8)	16.7 (2/12)	33.3 (3/9)	3.8 (1/26)	33.3 (2/6)	66.7 (2/3)	100 (13/13)
Layfield et al[6]	162	13.8 (4/29)	5.3 (1/19)	20 (3/15)	3.6 (2/55)	44.4 (4/9)	60 (3/5)	93.3 (28/30)
Montezuma et al[7]	104	25 (1/4)	33.3 (2/6)	9.1 (1/11)	1.6 (1/61)	40 (6/15)	50 (1/2)	100 (5/5)
Pujani et al[8]	64	0 (0/1)	10 (1/10)	50 (1/2)	2.5 (1/40)	50 (1/2)	100 (2/2)	100 (7/7)
Rohilla et al[9]	94	0 (0/1)	17.4 (4/23)	100 (2/2)	7.3 (3/41)	50 (1/2)	(0/0)	96 (24/25)
Song et al[10]	429	17.8 (8/45)	14.3 (2/14)	30.6 (15/49)	2.2 (4/178)	46.4 (26/56)	78.9 (15/19)	98.5 (67/68)
Thiryayi et al[11]	283	8.5 (5/59)	1.6 (1/63)	0 (0/7)	1.9 (2/104)	26.7 (4/15)	100 (5/5)	100 (30/30)
Vallonthaiel et al[12]	190	44.2 (19/43)	7.7 (1/13)	0 (0/3)	7.9 (5/63)	44.4 (4/9)	81.5 (22/27)	100 (32/32)

		Risk of Malignancy, % (No. of Malignancies/Total No.)						
Author	**No.**	**Nondiagnostic**	**Nonneoplastic**	**AUS**	**Benign Neoplasm**	**SUMP**	**SM**	**Malignant**
Viswanathan et al13	373	6.7 (3/45)	7.1 (7/98)	38.9 (7/18)	5 (6/121)	34.2 (13/38)	92.9 (13/14)	92.3 (36/39)
Current study	694	18.3 (13/71)	8.9 (7/79)	37.5 (15/40)	2.9 (9/315)	40.7 (24/59)	100 (15/15)	98.3 (113/115)
Overall	2,470	18.3 (56/306)	8.3 (28/337)	30.1 (47/156)	3.4 (34/1,004)	40.3 (85/211)	84.8 (78/92)	97.5 (355/364)
MSRSGC estimation 3		25	10	20	<5	35	60	90

AUS, atypia of undetermined significance; MSRSGC, Milan System for Reporting Salivary Gland Cytopathology; SM, suspicious for malignancy; SUMP, salivary gland neoplasm of uncertain malignant potential.

In our study, the ROMs for the nonneoplastic and benign neoplasm categories were 8.9% and 2.9%, which are in keeping with the MSRSGC. The differences in ROM for these two categories between the two institutions were minimal (8.2% vs 10% for nonneoplastic and 1.9% vs 3.7% for benign neoplasm). A total of 16 false-negative cases were identified. Among these, all seven false-negative cases for the nonneoplastic category were lymphoma on follow-up biopsy. These cases were interpreted as reactive lymph nodes based on cytomorphology on FNA. Failure to recognize abnormal lymphoid cells and to

obtain additional aspirates for flow cytometry during the on-site evaluation was the main reason for these diagnostic errors. The reclassification of these cases was based on the original report. However, most of the cases could be better classified as AUS upon retrospective slide review. Reactive lymph node was the most common nonneoplastic diagnosis in our study, accounting for 43.8% (147/336) of the cases. Although seven cases of lymphoma were missed, the overall ROM for cytologic diagnosis of reactive lymph node in our study was still relatively low at 4.7% based on clinical and histologic follow-up. Lymphoma was also found to be the predominant cause of false-negative diagnosis in the nonneoplastic category in other studies.[13,15] Of the nine false-negative cases within the benign neoplasm category, carcinoma ex pleomorphic adenoma (four cases) and adenoid cystic carcinoma (two cases) accounted for the majority of errors. All of these cases had been misdiagnosed as pleomorphic adenoma on FNA. Carcinoma ex pleomorphic adenoma was also the main contributor to the increase in ROM in the benign neoplasm category in the study by Viswanathan et al.[13] In our study, the other two cases that were falsely diagnosed as pleomorphic adenoma due to the presence of focal metachromatic mesenchymal materials on FNA were one case of low-grade adenocarcinoma, NOS and one case of secretory carcinoma. The last false-negative case in the benign neoplasm category was an acinic cell carcinoma, which was misdiagnosed as Warthin tumor on FNA due to the coexistence of oncocytoid tumor cells and lymphocytes.

In our study, the most common benign neoplasm was pleomorphic adenoma, comprising 32.6% of all cases, while the most common malignant diagnoses were metastatic squamous cell carcinoma and lymphoma, comprising 5.8% and 5.0% of all cases, respectively. Rossi et al[15] also found that the most frequent benign and malignant lesions were pleomorphic adenoma and squamous cell carcinoma, while lymphoma was reported as the most common malignant neoplasm by Viswanathan et al.[13] Primary squamous cell carcinoma and lymphoma are rare. Most cases of squamous cell carcinoma and lymphoma in our study arose in lymph nodes located within or adjacent to the parotid glands or submandibular glands.

The ROMs of SM and malignant categories were 100% and 98.3% in our study, which is higher than suggested in MSRSGC. False-positive cases are rare, comprising only two cases in our study. The first false-positive case was a pleomorphic adenoma with extensive squamous and mucous cell metaplasia. The corresponding FNA was diagnosed as low-grade mucoepidermoid carcinoma due to the presence of squamoid cells in a background of abundant mucinous material (Image 1). The second case was a monomorphic basal cell adenoma, which was overdiagnosed as an adenoid cystic carcinoma due to the presence of small hyaline globules on FNA smears (Image 2). Basal cell adenoma misinterpreted as adenoid cystic carcinoma on FNA has been previously reported.16 The basement membrane-like material forming hyaline globules is known to be a characteristic feature of adenoid cystic carcinoma but can also be seen in other salivary gland neoplasms, including pleomorphic adenoma, basal cell adenoma, myoepithelioma, polymorphous adenocarcinoma, and epithelial-myoepithelial carcinoma.

The diagnostic category of AUS in the MSRSGC is defined as a salivary gland FNA that lacks either qualitative or quantitative cytomorphologic features to be diagnosed with confidence as either nonneoplastic or neoplastic. It encompasses a heterogeneous group of lesions ranging from nonneoplastic to malignant. The histologic follow-up of our 40 AUS cases showed 37.5% nonneoplastic, 37.5% malignant, 22.5% benign neoplasm, and 2.5% atypical. The most common malignant diagnosis was lymphoma, accounting for 47% of all malignant cases in the AUS category (Table 4). In a recent study, Wang et al17 reported a high ROM (61%) for “atypical” salivary gland FNA based on a multi-institutional study with 154 cases having histologic follow-up. Lymphoma also accounted for the most common malignant diagnosis, comprising the same rate of 47% as noted in our study. The ROM for the AUS category in our study was 37.5%, which is higher than 20% suggested by the MSRSGC,3 lower than the report by Wang et al,17 and similar to the reports by the others.5,10,13

SUMP is a category reserved for FNA samples that are diagnostic for a neoplasm but cannot be further classified as a specific histopathologic entity. The ROM for SUMP in our study was 40.7%, which is in keeping with most reported data.4-7,10,12,13 Most of the histologic follow-up diagnoses of the SUMP cases were neoplasms (96.6%), including

33 benign neoplasms and 24 malignant neoplasms (Table 5). Among these, the most common benign neoplasms were pleomorphic adenoma (17 cases, 49%) and basal cell adenoma (11 cases, 31%), while the most common malignant neoplasms were mucoepidermoid carcinoma (seven cases, 30%) and adenoid cystic carcinoma (five cases, 22%).

There might be geographic differences between eastern and western countries in the distribution of diagnoses among each of the MSRSGC categories. In our study, IU recorded a significantly higher diagnostic frequency in the nonneoplastic (28.5% vs 12.6%) and malignant (17.7% vs 3.1%) categories ($P < .05$), while TVGH recorded a much higher diagnostic frequency in nondiagnostic (28.9% vs 11.1%) and benign neoplasm (45.2% vs 31.2%) categories ($P < .05$). However, there were no significant differences in ROM for each category between these two institutions. At IU, we provide on-site evaluation for most of the salivary gland FNAs, which might explain the lower nondiagnostic rate at IU compared to that of TVGH, where on-site evaluation of the FNA was not routinely performed.

To the best of our knowledge, here we report the largest retrospective series of salivary gland FNA reclassified based on the newly established MSRSGC. The MSRSGC appears to be a useful tool to provide uniform terminology for the salivary gland lesions sampled by FNA. Without the inclusion of AUS and SUMP categories, our study demonstrated high sensitivity, specificity, positive predictive rate, and negative predictive rate for detecting malignancy at 89%, 99%, 98%, and 96%, respectively. The AUS and SUMP categories accounted for only small proportions of cases (3.8% for AUS and 5.9% for SUMP). The ROMs were intermediate at 37.5% for AUS and 40.7% for SUMP, respectively. Although both AUS and SUMP showed similar ROM in our study, the lesions in the AUS group were more heterogeneous. Nonneoplastic lesions accounted for 37.5% of the cases in the AUS group, while only 3.4% of the cases in SUMP. Because most lesions diagnosed as SUMP turn out to be neoplastic with a moderate ROM, the management recommendation of conservative surgery and frozen section seems to be appropriate. For AUS cases, a careful clinicoradiologic correlation, ideally discussed in a multidisciplinary team meeting, is warranted. If the image study suggests an epithelial

neoplasm, conservative surgery should be considered. If lymphoma is suspected, core or excisional biopsy with flow cytometry study might be the management of choice. Otherwise, clinical follow-up with repeat FNA is also a viable option for patients with AUS diagnosis. The limitation of this study is its retrospective design and we did not review slides from all of the cases; in particular, nondiagnostic, nonneoplastic, and most pleomorphic adenoma and Warthin tumor cases were not included. Future prospective studies with clinical follow-up are necessary to assess the performance of this new classification scheme.

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