Original Article

Validation of the Milan System for Reporting Salivary Gland Cytopathology and the diagnostic accuracy of FNA cytology for submandibular gland lesions

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BACKGROUND: The Milan System for Salivary Gland Cytopathology (MSRSGC) is a categorical system for salivary gland fine-needle aspiration cytopathology (FNAC) developed to aid clinicians in the management of salivary gland lesions. This classification is widely studied and validated, especially in cohorts that consist of mostly parotid gland lesions. However, only sparse literature describes the use of this classification for submandibular gland lesions in particular. **METHODS:** All patients in the Netherlands that underwent a submandibular gland resection between January 1, 2006, and January 1, 2017, with a FNAC before resection were identified with the use of the Dutch Pathology Registry database (PALGA). All FNAC results were retrospectively classified according to the MSRSGC. The risk of malignancy was calculated for all the MSRSGC categories. The sensitivity and specificity of the MSRSGC classification were calculated for submandibular gland FNAC. **RESULTS:** A total of 837 patients who underwent 975 FNAC aspirates from the submandibular glands were included in the analysis. Risks of malignancy for each of the MSRSGC categories were 14.4% in nondiagnostic, 4.4% in nonneoplastic, 37.0% in atypia of unknown significance, 3.9% in benign neoplasms, 40.7% in salivary gland neoplasms of unknown malignant potential, 76.2% in suspected malignant, and 91.3% in malignant cytology results. The sensitivity for diagnosing malignant submandibular gland tumors was 71.6% and specificity was 98.4%. **CONCLUSIONS:** The results of the present study validate the use of this classification for submandibular gland lesions. Risks of malignancy vary according to the anatomical subsites of the salivary gland lesions. ***Cancer Cytopathol* 2022;130:189-194**.

LAY SUMMARY:

- The risks of malignancy of the various Milan System for Salivary Gland Cytopathology (MSRSGC) categories vary according to the anatomical subsite of the salivary gland lesion.
- The proposed management techniques of the MSRSGC are valid for use with submandibular gland lesions.

KEY WORDS: biopsy; fine-needle; salivary glands submandibular gland; submandibular gland diseases; submandibular gland neoplasms.

INTRODUCTION

The submandibular gland is the second largest major salivary gland, as well as the second most frequent anatomical location for salivary gland tumors of the major salivary glands. Approximately 8% to 11% of all salivary gland tumors occur in the submandibular glands, compared to 61% to 85% in the parotid gland,

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0.3% to 1.4% in the sublingual glands, and 8% to 28% in the minor salivary glands.[1-7] Malignant tumors are more frequently encountered in the submandibular gland compared to the parotid gland; approximately 24% to 37% of all submandibular gland tumors are malignant compared to 9% to 32% of all parotid gland tumors. Minor salivary gland tumors (40% to 62% malignant) and sublingual gland tumors (86% to 100% malignant) are known for their even higher prevalence of malignancy.[1-7]

Fine-needle aspiration cytology (FNAC) helps to discriminate between benign and malignant submandibular gland tumors and nonneoplastic submandibular gland lesions. The diagnostic accuracy of this procedure is frequently debated. The accuracy of the procedure depends on the experience of the operator (clinician or radiologist) and (cyto-)pathologist. Recently, a systematic review evaluated the diagnostic accuracy of FNAC for parotid gland lesions and found a sensitivity of 78% and specificity of 98% for correctly diagnosing the tumor dignity.[8] Unfortunately, only 1 study has previously assessed the diagnostic accuracy of FNAC, specifically in submandibular gland lesions, reporting a sensitivity of 71% and a specificity of 94% for correctly diagnosing the tumor dignity.[9]

The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) is a categorical system for salivary gland FNAC results. Its founders believed that the lack of uniformity in the evaluation of salivary gland FNAC limited the effectiveness.[10,11] The MSRSGC was developed to address this exact issue. This diagnostic tool comprises different diagnostic categories, accompanied by an evidence-based risk of malignancy (ROM) and a suggested clinical management strategy.

Various studies have described the successful application of the MSRSGC for parotid gland lesions.[12-22] However, only 1 previous study has evaluated the application of the MSRSGC exclusively for submandibular gland lesions.[23]

This study set out to test the validity of the ROMs and proposed management techniques of the MSRSGC classification for submandibular gland FNAC. Another objective of this study was to assess the diagnostic accuracy of submandibular gland FNAC with the use of the MSRSGC classification, because current literature regarding this subject is relatively sparse.

MATERIALS AND METHODS

A retrospective cohort study was performed using the Dutch Pathology Registry (PALGA) database, "The Dutch nationwide network and registry of histo- and cytopathology." The study was approved by the PALGA scientific and privacy committee before execution. The informed consent was waived because the study did not fall within the remit of the Medical Research Involving Human Subjects Act.

The PALGA database was searched for excerpts of patients who had a salivary gland resection between January 1, 2006, and January 1, 2017. All excerpts included age of the patient, date of examination, and type of cytopathological examination (eg, cytopathological or histopathological study). All excerpts were manually checked for anatomical location of the lesion and the cytopathological or histopathological diagnosis according to the World Health Organization classification of 2005, considering that this classification system was the most appropriate to the search period used.

All salivary gland tumors of other tumor sites than the submandibular gland were excluded. Benign or malignant epithelial submandibular gland tumors, borderline tumors, other epithelial lesions of the submandibular glands, soft tissue lesions of the submandibular glands, and metastatic tumors to the submandibular glands were included in this study. Lymphomas were excluded because these are generally not surgically resected and therefore lack histopathological results. Revisions of FNAC were excluded. Patients who had FNAC more than 1 year before the resection were excluded because this might be an indicator of change in the clinical course of the disease or because of the possible occurrence of malignant transformation over this period of time.

All cytopathological results were retrospectively categorized to an MSRSGC category with the use of the MSRSGC guideline.[11] The FNAC results were compared with the histopathological diagnosis after resection of the lesion to estimate the ROM for each of the diagnostic categories. The sensitivity and specificity for the diagnosis of a malignant submandibular gland tumor were calculated. The categories of the suspected malignant (MSRSGC V) and malignant (MSRSGC VI) groups were classified as "positive" cytopathological tests, and the nonneoplastic (MSRSGC II) and benign salivary gland neoplasms (MSRSGC IVa) groups were categorized as "negative"

TABLE 1. Distribution of FNAC Aspirates Among MSRSGC Categories and Their Corresponding ROMs Compared With the Estimated ROMs of the MSRSGC Classification

Diagnostic Category	Distribution, %	ROM, %	MSRSGC ROM,[11] %
I. Nondiagnostic	22.1	14.4	25
II. Nonneoplastic	11.7	4.4	10
III. AUS	2.8	37.0	20
IVa. Neoplasm: benign	47.3	3.9	<5
IVb. SUMP	9.3	40.7	35
V. Suspected malignant	2.2	76.2	60
VI. Malignant	4.7	91.3	90

Abbreviations: AUS, atypia of unknown significance;FNAC, fine-needle aspiration cytopathology; MSRSGC, Milan system for reporting salivary gland cytopathology; ROM, risk of malignancy; SUMP, salivary gland neoplasm of unknown malignant potential.

tests for the diagnosis of malignancy. The indeterminate categories, eg, atypia of unknown significance (AUS) and salivary gland neoplasm of unknown malignant potential (MSRSGC III and IVb), and the nondiagnostic results (MSRSGC I) were excluded from the sensitivity and specificity analysis and separately reported. Sensitivity and specificity were reported alongside their respective 95% confidence intervals (CI).

RESULTS

A total of 837 unique patients underwent 975 FNAC aspirates from the submandibular gland. The cohort consisted of 331 male patients (39.5%) and 506 women patients (60.5%). Of all FNACs, 51.3% were taken from the left submandibular gland, 47.6% were taken from the right submandibular gland, and the side was unknown in 1.2% of all cases. The final histopathological diagnosis was a benign tumor in 60.8% of cases, a malignant tumor in 15.3%, and a nonneoplastic lesion in 23.9%.

The distribution of FNAC aspirates, the corresponding ROMs for every MSRSGC category, and the ROMs provided by the authors of the MSRSGC are provided in Table 1. Most of the FNAC results were categorized in the benign salivary gland neoplasms (MSRSGC IVa) category (47.3%), followed by the nondiagnostic category (22.1%), nonneoplastic category (11.7%), and the salivary gland neoplasm of unknown malignant potential (SUMP) category (9.3%). The highest risks of malignancy were found in the malignant (91.3%) and suspected malignant (76.2%) categories, respectively. The AUS and SUMP categories had ROMs of 37% and 40.7%.

TABLE 2. Most Frequent False-Negative Histopathological Diagnoses Arranged by Their False-Negative Rates

Type of Malignancy	False Negatives, No.	True-Positives, No.	False-Negative Rate, %[a]
Acinic cell carcinoma	2	0	100
Polymorphic adenocarcinoma	2	0	100
Myoepithelial carcinoma	2	2	50
Adenoid cystic carcinoma	12	16	42.9
Epithelial-myoepithelial carcinoma	1	2	33.3
Salivary duct carcinoma	1	7	12.5
Adenocarcinoma NOS	1	12	7.7
Muco-epidermoidcarcinoma	0	6	0
Carcinoma ex pleomorphic adenoma	0	6	0
Basal cell adenocarcinoma	0	2	0

Abbreviations: FNAC, fine-needle aspiration cytopathology;NOS, not otherwise specified.
[a]The false-negative rate is calculated as (false negatives on FNAC/false negatives + true positives) × 100. Only diagnoses with at least 2 false-negative results or 2 true-positive results are included.

The sensitivity of submandibular gland FNAC for diagnosing a malignant tumor was 71.6% (CI, 60.5, 81.1), the specificity was 98.4% (CI, 97.0, 99.3). Nondiagnostic results were found in 22.1% of all FNACs, and 12.1% yielded an indeterminate cytopathological result.

The false-negative rates for all histopathological tumor subtypes are listed in Table 2. Only subtypes with at least 2 false-negative or 2 true-positive cytopathological results are shown. The highest false-negative rates were found among acinic cell carcinomas (2/2), polymorphic adenocarcinomas (2/2), and myoepithelial carcinomas (2/4). The absolute most false-negative FNAC results were seen among the adenoid cystic carcinomas (12/28).

The exact cytopathological diagnosis of a pleomorphic adenoma was found to be malignant (false-negative result) in 3.5% of all cases (15 false-negative results on 428 diagnoses in total), whereas for Warthin tumors, this was 0% (zero false-negatives, 16 diagnoses in total).

Further analysis revealed the histopathological subtypes of the 9 false-positive results in the MSRSGC V and VI categories: 5 were pleomorphic adenomas and sialadenitis caused 4.

DISCUSSION

The MSRSGC is extensively studied, which has resulted in widespread support for this classification. However, only a few studied the use of this classification only for submandibular gland lesions. The found ROMs in this

TABLE 3. MSRSGC Diagnostic Categories and Their ROMs in Studies Regarding Submandibular Gland FNAC

	MSRSGC								
	No.	No.[a]	I	II	III	IVa	IVb	V	VI
Study	ROM (%)								
Current study	975	975	14.4	4.4	37	3.9	40.7	76.2	91.3
Maleki et al[23]	734	333	10.6	7.5	27.6	3.2	41.9	82.3	93.6

Abbreviations: FNAC, fine-needle aspiration cytopathology; MSRSGC, Milan system for reporting salivary gland cytopathology; ROM, risk of malignancy.
[a]Histopathologically correlated FNACs.

TABLE 4. Distribution of Lesions and ROM for the Different MSRSGC Categories for Submandibular Gland FNAC, Parotid Gland FNAC, and as Estimated by the MSRSGC Classification

		MSRSGC						
Study	No.	I	II	III	IVa	IVb	V	VI
				Distribution				
Submandibular gland FNAC[a]	975	22.1	11.7	2.8	47.3	9.3	2.2	4.7
Parotid gland FNAC[23]	12,898	19.0	2.2	3.2	61.4	6.4	3.0	4.7
				ROM				
Submandibular gland FNAC[a]	975	14.4	4.4	37	3.9	40.7	76.2	91.3
Parotid gland FNAC[23]	12,898	12.5	10.3	29	2.3	28.6	83	99.3
MSRSGC classification[11]	—	25	10	20	<5	35	60	90

Abbreviations: FNAC, fine-needle aspiration cytopathology; MSRSGC, Milan system for reporting salivary gland cytopathology; ROM, risk of malignancy.
[a]Current study.

study validate the proposed management techniques of the MSRSGC classification. However, the results also suggest that the ROMs of some of the MSRSGC categories may differ per anatomical subsite.

Only 1 prior study performed by Maleki et al[23] validated the MSRSGC for only submandibular gland FNACs. The methodology of their study and the current study are different: Maleki et al[23] performed a global multi-institutional study, whereas the current study uses national data. Moreover, Maleki et al[23] also included lymphomas in their study cohort. The risks of malignancies of both studies are compared in Table 3.

Overall, the results are very similar. The most notable discrepancy is that the ROM of the AUS category was higher in the current study than what Maleki et al[23] observed in their study (37% vs 27.6%). This difference may be caused by the fact that the current study only includes cytopathological results that are correlated with a histopathological resection results, whereas Maleki et al[23] also compared their cytopathological results with the results of clinical follow-up in case of the absence of any histopathological results to compare these with. Other minor discrepancies include that the ROM in the nondiagnostic category was higher in the current study (14.4% vs 10.6%), and the observed ROM in the nonneoplastic category was lower in the current study as when compared to the other study (4.4% vs 7.5%).

The histopathological distribution and ROMs of the MSRSGC categories of the current study (that only includes submandibular gland FNAC) and our previous study (that included only parotid gland FNACs)[22] are compared in Table 4. These studies have nearly identical methods that only differ in the anatomical location studied. The histopathological distribution of histopathological lesions in the submandibular glands shows discrepancies as compared to the parotid gland: nonneoplastic lesions were more prevalent in the submandibular glands (23.9% vs 3.4%), malignant tumors were slightly more frequently seen in the submandibular glands (15.3% vs 12.4%), and benign tumors occurred more often in the parotid gland (84.2% vs 60.8%). The distribution of FNACs over the different MSRSGC categories follows a similar pattern; nonneoplastic lesions represented the larger part of the surgically removed lesions from the submandibular glands (11.7% vs 2.2%), and proportionally less benign tumors were removed from the submandibular glands (47.3% vs 61.4%).

Most interestingly, the ROMs of the indeterminate categories were higher for submandibular gland lesions as compared to the parotid gland lesions categories (MSRSGC III: 37% vs 29% and MSRSGC IVb: 40.7% vs 28.6%). Similarly, the ROM of the benign salivary gland neoplasms category was almost twice as high for submandibular gland lesions (3.9% vs 2.3%). These

observations are most probably related to the relatively higher occurrence of malignant tumors in the submandibular glands. The ROM of the nondiagnostic category was lower for submandibular gland lesions as compared to that of the parotid gland lesions (4.4% vs 10.3%). This may be caused by the larger number of nonneoplastic lesions that were removed from the submandibular glands. Preoperative malignant or suspect malignant diagnoses on submandibular gland FNAC had a lower ROM as compared to the ROM of these categories for parotid gland FNAC (MSRSGC V: 76.2% vs 83% and MSRSGC VI: 91.3% vs 99.3%). Nine diagnoses (5 pleomorphic adenomas and 4 sialadenitis diagnoses) were incorrectly considered as malignant in either of these categories. Sialadenitis is considered an arduous cytopathological diagnosis, the inflammation gives rises to atrophic acinic cells, which in combination with the sometimes present atypical ductal epithelia may cause suspicion for malignancy. In addition, the higher prevalence of malignancy in the submandibular glands may cause the pathologist to be biased and to be more cautious in defining a lesion with minor atypia as benign or nonneoplastic, thus causing a lower ROM of the (suspected) malignant categories.

The most notable differences between the ROMs of the current study and the ROMs provided by the MSRSGC classification are found in 3 categories (Table 4): the ROM in the nondiagnostic category was considerably lower than estimated by the MSRSGC (14.4% vs 25%), the ROM for nonneoplastic lesions was slightly lower than estimated (3.3% vs 10%), and the ROM in the AUS category was higher than the estimated value by the MSRSGC (37% vs 20%). Again, these observations are likely to be caused by the differences in occurrence of benign and malignant tumors in the submandibular glands. More importantly, they do not necessarily change the proposed management strategies for the nonneoplastic and nondiagnostic categories (clinical and radiological correlation and follow-up/repeat FNAC). Because of the relatively high ROM found in the AUS category for submandibular gland FNACs in both this study (37%) and the study performed by Maleki et al[23] (27.6%), clinicians may favor surgery in case of a submandibular gland lesions with an AUS result rather than repeating the FNAC. Reasons for this preference may be to prevent diagnostic delay, because of the relative low morbidity of a submandibular gland resection, and because of the certainty of the histopathological diagnosis afterwards.

The sensitivity of submandibular gland FNAC for the diagnosis of malignant tumors was almost 10% lower than the sensitivity of parotid gland FNAC (71.6% vs 81.2%), whereas the specificity was nearly the same (98.4% vs 99.1%).[22] A lower sensitivity translates to a proportionally higher number of false-negative results after submandibular gland FNAC. The technique of acquiring cells for submandibular and parotid gland FNAC is similar, making it an unlikely cause of the difference in diagnostic accuracy. Likewise, the evaluation of submandibular gland cytopathology does not pose any additional challenges compared to parotid gland FNAC. Treating clinicians should be aware of the possible lower accuracy of submandibular gland FNAC.

The diagnostic accuracy (sensitivity and specificity) was calculated using a similar methodology as prior studies.[12,16,19,20,22] This was done to compare these studies and provide a measure of the diagnostic accuracy of the MSRSGC classification. This methodology, however, has several limitations. The first limitation is that this method excludes indefinite and nondiagnostic results from the analysis of diagnostic accuracy. The second limitation is that the MSRSGC classification is not designed to achieve a specific diagnosis, but it is designed to guide clinical management. Diagnostic accuracy is a measure of the discrimination between diagnoses (in this case: malignant vs. nonmalignant), which is not the essence of the MSRSGC. Therefore, for a correct estimation of the accuracy of the MSRSGC, diagnostic accuracy might not be the most appropriate measure. Therefore, a future study should look into whether or not the correct treatment was commenced with the use of the MSRSGC.

The sole inclusion of surgically treated patients with submandibular gland lesions in this study causes a selection bias. Moreover, this may cause overestimation of the ROMs, because people with nonneoplastic or benign lesions are sometimes not surgically treated. Also, the histopathological distribution of submandibular gland lesions in the actual population might be different from what we have found, because our cohort only includes submandibular gland lesions that had a cytopathological evaluation before resection, whereas some lesions might be resected without FNAC before the procedure. Nonetheless, this study was not set up to study the histopathological distribution of submandibular gland lesions.

The results of this study validate the proposed management techniques of the MSRSGC classification for

use with submandibular gland lesions, however, due to the relatively higher ROM in the AUS category, clinicians may favor surgery over a repeat FNAC for submandibular gland lesions with an AUS result. The ROMs of some MSRSGC categories differ between parotid gland lesions and submandibular gland lesions. Because of this, we would propose the authors of the MSRSGC to provide a bandwidth for each of the diagnostic categories (eg, 4% to 10% for II, 30% to 40% for MSRSGC III and IVb, and 90% to 99% for VI) and state that the ROM may differ per anatomical subsite. Future MSRSGC validation studies should focus on subsites for which the MSRSGC has not yet been specifically tested, such as the sublingual glands and accessory salivary glands. In all, the results of this study strongly endorse the use of the MSRSGC classification for submandibular gland lesions.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Sam T.H. Reerds: Conceived and designed the study, collected the data, performed the statistical analysis, interpreted the data, and wrote the first draft of the article. **Jimmie Honings:** Conceived and designed the study, interpreted the data, and wrote the first draft of the article. **Henri A.M. Marres:** Conceived and designed the study. **Adriana C.H. van Engen-van Grunsven:** Conceived and designed the study and interpreted the data. All authors revised and finalized the article.

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