Application of the Milan System for Reporting Salivary Gland Cytopathology in pediatric patients: An international, multi-institutional study

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BACKGROUND: Pediatric salivary gland fine-needle aspiration (FNA) is uncommon with a higher frequency of inflammatory lesions and a small proportion of malignancies. This international, multi-institutional cohort evaluated the application of the Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) and the risk of malignancy (ROM) for each diagnostic category. **METHODS:** Pediatric (0- to 21-year-old) salivary gland FNA specimens from 22 international institutions of 7 countries, including the United States, England, Italy, Greece, Finland, Brazil, and France, were retrospectively assigned to an MSRSGC diagnostic category as follows: nondiagnostic, nonneoplastic, atypia of undetermined significance (AUS), benign neoplasm, salivary gland neoplasm of uncertain malignant potential (SUMP), suspicious for malignancy (SM), or malignant. Cytology-histology correlation was performed where available, and the ROM was calculated for each MSRSGC diagnostic category. **RESULTS:** The cohort of 477 aspirates was reclassified according to the MSRSGC as follows: nondiagnostic, 10.3%; nonneoplastic, 34.6%; AUS, 5.2%; benign neoplasm, 27.5%; SUMP, 7.5%; SM, 2.5%; and malignant, 12.4%. Histopathologic follow-up was available for 237 cases (49.7%). The ROMs were as follows: nondiagnostic, 5.9%; nonneoplastic, 9.1%; AUS, 35.7%; benign neoplasm, 3.3%; SUMP, 31.8%; SM, 100%; and malignant, 100%. Mucoepidermoid carcinoma was the most common malignancy (18 of 237; 7.6%), and it was followed by acinic cell carcinoma (16 of 237; 6.8%). Pleomorphic adenoma was the most common benign neoplasm (95 of 237; 40.1%). **CONCLUSIONS:** The MSRSGC can be reliably applied to pediatric salivary gland FNA. The ROM of each MSRSGC category in pediatric salivary gland FNA is relatively similar to the ROM of each category in adult salivary gland FNA, although the reported rates for the different MSRSGC categories are variable across institutions. ***Cancer Cytopathol* 2022;130:370-380**. © *2022 American Cancer Society*.

KEY WORDS: cytology; fine-needle aspiration; Milan System for Reporting Salivary Gland Cytology (MSRSGC); parotid; pediatric cytology; risk of malignancy; salivary gland; submandibular gland.

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INTRODUCTION

Pediatric salivary gland lesions, similar to their counterparts in adults, represent a diverse group of congenital, inflammatory, infectious, and neoplastic conditions, including both benign and malignant neoplasms. Tumor heterogeneity, metaplastic and cystic changes, and sampling issues may add to the complexity of diagnosing these lesions.[1-5] However, pediatric salivary gland cytology differs from adult salivary gland cytology in several ways, including the cellular type of neoplasms that manifest in this younger patient population. Moreover, secondary neoplasms involving salivary glands in the pediatric population are different from those that occur in an adult population. Fine-needle aspiration (FNA) is a well-accepted, minimally invasive, and cost-effective procedure for the evaluation of salivary gland lesions in the pediatric population,[6-10] and its clinical feasibility and utility are often dictated by the patient's age, suspected diagnosis, and need for sedation or anesthesia. For example, adequate tissue sampling where both FNA and concurrent core or excisional biopsy are desired is typically performed under anesthesia.

FNA biopsy of salivary gland lesions can effectively differentiate between most commonly encountered nonneoplastic and neoplastic lesions.[11] It is also highly specific for the diagnosis of neoplasia (98%) and malignant neoplasms (96%); however, it is less sensitive for these entities.[11] The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) is an evidence-based classification system composed of 6 diagnostic categories, with each associated with a defined risk of malignancy (ROM) and recommendation for management.[12-14] The diagnostic categories of the MSRSGC are as follows: 1) nondiagnostic (I); 2) nonneoplastic (II); 3) atypia of undetermined significance (AUS; III); 4) neoplasm, including benign neoplasm (IVa) and salivary gland neoplasm of uncertain malignant potential (SUMP; IVb); 5) suspicious for malignancy (SM; V); and 6) malignant (VI).

The MSRSGC was created to facilitate communication among pathologists and clinicians to improve patient care. A recent comprehensive review of the literature showed that the mean ROM was 16.9% for category I, 10.5% for category II, 39.3% for category III, 2.9% for category IVa, 39.4% for category IVb, 84.2% for category V, and 97.5% for category VI in adults.[15] The application of the MSRSGC has been studied in adult patients; however, few have evaluated the application of the MSRSGC in the pediatric population.[16] This multiinstitutional, international study retrospectively evaluated the application of the MSRSGC to the largest series of salivary gland FNA cases in a pediatric population to establish the ROMs for each diagnostic category.

MATERIALS AND METHODS

This study was conducted in accordance and compliance with all statutes, directives, and guidelines of the Code of Federal Regulations (Title 45, Part 46) and the Code of European Commonwealth Regulations and with institutional review board approval at all sites. The electronic cytology archives of 22 academic institutions were searched for all pediatric salivary gland FNA cases within the age range of 0 to 21 years. Cases were then retrospectively analyzed by each institution and assigned to the appropriate MSRSGC diagnostic categories. The following information was collected and recorded for each case: sex, age, FNA diagnosis, and surgical pathology follow-up diagnosis. Rapid onsite evaluation (ROSE) was not included because the data were not available, and there were cases in which FNA was performed by palpation. Various methods of specimen preparation (including conventional smears, liquid-based cytology [ThinPrep 5000 method; Hologic Co, Marlborough, Massachusetts], cytospins, and cell blocks) and staining (including Diff-Quik staining on air-dried slides for ROSE and Papanicolaou staining on conventional slides fixed with an alcohol-based fixative) were used according to the different protocols and preferences of each institution. The data retrieved from each institution were collected in a spreadsheet of de-identified cases. They were further reviewed and analyzed by 2 pathologists (Z.M. and J.K.) in a master spreadsheet. The ROM and the risk of neoplasm (RON) were calculated for each MSRSGC diagnostic category.

RESULTS

Patient Demographic and Mass Characteristics

A total of 477 cases were analyzed from 22 institutions. There were 239 males (50.1%) and 238 females (49.9%) (Fig. 1). Their ages ranged from 2 weeks to 21 years (mean age, 13.14 years; median age, 14.00 years; SD, 5.30 years). The parotid gland was the most common site (348; 73.0%), and it was followed by the submandibular

gland (72; 15.1%), the oral/minor salivary glands (9; 1.9%), and unspecified neck masses (13; 2.7%) (Fig. 2). FNA site was not available in 35 of the cases (7.3%). The tumor size was available for 305 of the 477 cases (64%) and ranged from 0.4 to 8.0 cm (mean size, 2.54 cm; median size, 2.40 cm; SD, 1.35 cm).

MSRSGC Classification

The 477 cases were classified according to the MSRSGC as follows: nondiagnostic (I), 49 (10.3%); nonneoplastic (II), 165 (34.6%); AUS (III), 25 (5.2%); benign neoplasm (IVa), 131 (27.5%); SUMP (IVb), 36 (7.5%); SM (V), 12 (2.5%); and malignant (VI), 59 (12.4%). Table 1 shows patient demographics and clinicopathologic characteristics for each category in the Milan system.

Histopathologic Follow-Up

Surgical pathology follow-up was available for 237 cases (49.7%), and these details are depicted in Tables 2 to 4.

Pleomorphic adenoma was the most common neoplasm and the most common benign neoplasm (95 of 116; 82%); it was followed by benign vascular/lymphatic conditions (5 of 116; 4.3%), neurofibroma (4 of 116; 3.4%), Warthin tumor (2 of 116), schwannoma (2 of 116), desmoid tumor (2 of 116), myofibroma (1 of 116), myoepithelioma (1 of 116), nodular fasciitis (1 of 116),

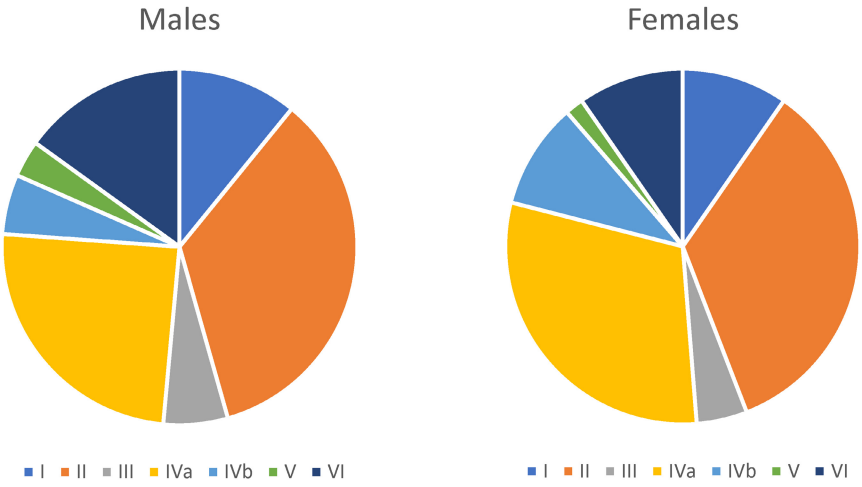

Figure 1. Distribution of pediatric fine-needle aspiration cases for each gender for each category.

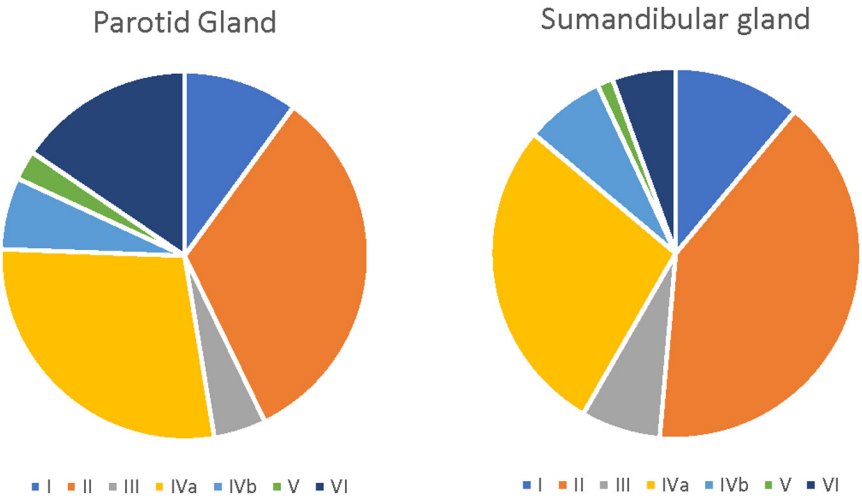

Figure 2. Distribution of pediatric fine-needle aspiration cases for each Milan category for the parotid gland and the submandibular gland.

oncocytoma (1 of 116), Langerhans cell histiocytosis (1 of 116), and pilomatrixoma (1 of 116).

Mucoepidermoid carcinoma was the most common malignant neoplasm (18 of 79; 23%), and it was followed by acinic cell carcinoma (16 of 79; 20%), rhabdomyosarcoma (11 of 79; 14%), lymphoma (10 of 79; 13%), retinoblastoma (10 of 79; 13%), neuroblastoma (3 of 79; 4%), adenoid cystic carcinoma (2 of 79; 2.5%), and secretory carcinoma (2 of 79; 2.5%) as well as 1 of each of the following tumors: nasopharyngeal carcinoma, melanoma, squamous cell carcinoma, sebaceous carcinoma, angiosarcoma, atypical teratoid/rhabdoid tumor, and epithelial myoepithelial carcinoma (Figs. 3-7).

ROM and RON

The ROM was calculated for each diagnostic category of the MSRSGC with the total number of cases in each MSRSGC category. It was not feasible to calculate the ROM for each individual institution because of low case volumes. The histopathologic follow-up with ROM and RON was available for each diagnostic category and is presented in Table 2. RON was high in the neoplasm categories (IV), including benign neoplasms (IVa; 89 of 91; 97.8%), and was 100% for the SUMP (IVb), SM (V), and malignant (VI) categories. RON was also high for AUS (10 of 14; 71.4%). However, RON was intermediate for nondiagnostic categories (6 of 17; 35.3%) and low for the nonneoplastic category (8 of 33; 24.2%).

DISCUSSION

FNA is a well-established procedure for the evaluation of neck masses, thyroid lesions, and salivary gland lesions in pediatric patients (similarly to adult populations) with good to excellent sensitivity and specificity.[7-9,17-19] A recent study about FNA of salivary gland lesions from children found a sensitivity of 92% and a specificity of 86% based on cytology-histology correlation.[20] Pediatric salivary gland lesions encompass a wide range of diagnoses (Table 4). This range of diagnoses also diverges from the adult population.[18,21,22] Pediatric salivary gland lesions may require urgent attention and an immediate morphology evaluation

TABLE 1. Shows Patient Demographics and Clinicopathologic Characteristics for Each Category in the Milan System

Milan System Diagnostic Category	Total Cases, No.	Cases With Surgical Follow-Up, No.	Malignant Cases, No.	Benign Neoplasm, No.	Nonneoplastic, No.	ROM, %
Nondiagnostic	42	13	1	5	7	7
Nonneoplastic	150	37	3	10	24	8
AUS	21	13	3	6	4	23
Neoplasm–benign	98	66	2	62	2	3
Neoplasm–uncertain malignant potential (SUMP)	22	15	3	12	0	20
Suspicious for malignancy	9	8	8	0	0	100
Malignant	56	49	48	0	1	98
Total	398	201	68	95	38	33.8

Abbreviations: AUS, atypia of undetermined significance; no, number; ROM, risk of malignancy; SUMP, salivary gland neoplasm of uncertain malignant potential.

TABLE 2. Distribution of Cases According to Their Milan System Categories and Comparison of Their ROMs According to the Milan Reference ROM

Milan Category	No. (%)	Cases With Surgical Follow-Up, No. (%)	Malignant Neoplasm on Surgical Follow-Up, No.	Benign Neoplasm on Surgical Follow-Up, No.	Diagnosis of Nonneoplastic Process, No.	RON on Surgical Follow-Up, %	ROM on Surgical Follow-Up, %	Milan Reference ROM, %
I	49 (10.3)	17 (34.69)	1	5	11	35.3	5.88	25
II	165 (34.6)	33 (20)	3	5	25	24.2	9.09	10
III	25 (5.2)	14 (56)	5	5	4	71.4	35.71	20
IVa	131 (27.5)	91 (69.46)	3	86	2	97.8	3.29	<5
IVb	36 (7.5)	22 (61.11)	7	15	0	100	31.81	35
V	12 (2.5)	9 (75)	9	0	0	100	100	60
VI	59 (12.4)	51 (86.44)	51	0	0	100	100	90
Total	477 (100)	237 (49.69)	79 (33.33)	116 (48.94)	42 (17.72)	NA	NA	NA

Abbreviations: NA, not applicable; no, number; ROM, risk of malignancy; RON, risk of neoplasm.

TABLE 3. Histologic Diagnoses of the Cases on Surgical Follow-Up

Milan Category	Histology Diagnoses on Surgical Follow-Up	
I (17/237)	Malignant (1)	• Acinic cell carcinoma (1)
	Benign (5)	• Pleomorphic adenoma (1) • Neurofibroma (2) • Benign vascular/lymphatic lesions (2)
	Nonneoplastic (11)	• Dermoid/epidermal inclusion cyst (2) • Acute, chronic, or granulomatous sialadenitis (3) • Mucocele-like cyst (1) • Reactive lymph node (2) • Benign duct cyst (3)
II (33/237)	Malignant (3)	• Acinic cell carcinoma (1) • Mucoepidermoid carcinoma (2)
	Benign (5)	• Pleomorphic adenoma (2) • Neurofibroma (1) • Benign vascular/lymphatic lesions (2)
	Nonneoplastic (25)	• Lymphoepithelial cyst (3) • Acute, chronic, or granulomatous sialadenitis (15) • Reactive lymph node (5) • Benign duct cyst (1) • Dermoid/epidermal inclusion cyst (1)
III (14/237)	Malignant (5)	• Mucoepidermoid carcinoma (3) • Lymphoma (2)
	Benign (5)	• Pleomorphic adenoma (1) • Benign vascular/lymphatic lesions (1) • Desmoid tumor (2) • Nodular fasciitis (1)
	Nonneoplastic (4)	• Dermoid/epidermal inclusion cyst (2) • Benign duct cyst (1) • Hyaline vascular Castleman disease (1)
IVa (91/237)	Malignant (3)	• Mucoepidermoid carcinoma (1) • Adenoid cystic carcinoma (1) • Acinic cell carcinoma (1)
	Benign (86)	• Pleomorphic adenoma (81) • Warthin tumor (2) • Schwannoma (2) • Myoepithelioma (1)
	Nonneoplastic (2)	• Benign duct cyst (1) • Lymphoepithelial cyst (1)
IVb (22/237)	Malignant (7)	• Acinic cell carcinoma (4) • Mucoepidermoid carcinoma (2) • Secretory carcinoma (1)
	Benign (15)	• Pleomorphic adenoma (10) • Neurofibroma (1) • Myofibroma (1) • Oncocytoma (1) • Langerhans histiocytosis X (1) • Pilomatrixoma (1)
V (9/237)	Malignant (9)	• Nasopharyngeal carcinoma (1) • Acinic cell carcinoma (1) • Sebaceous carcinoma (1) • Mucoepidermoid carcinoma (4) • Lymphoma (2)
VI (51/237)	Malignant (51)	• Mucoepidermoid carcinoma (6) • Rhabdoid tumor–AT/RT (1) • Rhabdomyosarcoma (11) • Lymphoma (6) • Secretory carcinoma (1) • Adenoid cystic carcinoma (1) • Epithelial myoepithelial carcinoma (1) • Retinoblastoma (10) • Neuroblastoma (3) • Melanoma (1) • Squamous cell carcinoma (1) • Acinic cell carcinoma (8) • Angiosarcoma (1)

Abbreviation: AT/RT, atypical teratoid/rhabdoid tumor.

when there is a suspicion for high-grade lymphomas, sarcomas, and small round blue cell tumors to allow for timely intervention.[23-26] In this study, MSRSGC was highly sensitive for high-grade tumors such as sarcomas, small round blue cell tumors, and neuroblastomas (Table 3). ROSE can improve the triaging of samples and tests.

As noted in Table 2, the ROM is higher than proposed by the Milan system for category III and is within the proposed range or lower for the other categories. However, the higher than expected ROM may be influenced by a selection bias in which lesions underwent subsequent surgical excision for a definitive pathologic evaluation. The true ROM for the MSRSGC categories may thus be lower than calculated. Even though the ROM is higher than expected for the Milan reference range or what might be desired for clinical decision-making, the types of malignancies miscategorized in MSRSGC I to IV are primary salivary gland carcinomas and lymphomas. Obtaining adequate material for ancillary studies such as flow cytometry in suspected cases for lymphomas may prevent a misdiagnosis and expedite patient treatment for lymphomas. Importantly, these data are collected by a very diverse group of cytopathologists from diverse institutions, and even at each institution, there is a diverse group of cytologists with a range of skills and a range of experience with salivary gland FNA. This poses a huge challenge for the interpretation of the data. The large size of the sample is considered a strength of the study. However, this large number of cases reflects a broad spectrum of cytopathologist skills and experience. The study is limited by

the fact that the slides of cases with histology-cytology discrepancies were not reviewed because of the nature of the study (Fig. 8A,B).

The proposed ROM for the nondiagnostic category in the MSRSGC is 25%. In our pediatric series, the nondiagnostic category included 10.3% of all cases (49 of 477). Seventeen of 49 cases (34.69%) had surgical follow-up; the ROM and the RON were 5.9% and 35.3%, respectively. The ROM was lower than the MSRSGC proposal. However, the ROM for this category was reported to be as low as zero by other studies of both children and adults.[27,28] In this category, 1 case of acinic cell carcinoma was the only malignant case identified on surgical follow-up, and pleomorphic adenoma (1), neurofibroma (2), and 2 cases of benign vascular/lymphatic neoplasms were listed as benign neoplasms.

The proposed ROM for the nonneoplastic category in the MSRSGC is 10%. In this study, the ROM and the RON were 9.1% and 24.2%, respectively, for the nonneoplastic category. The nonneoplastic category included 34.6% of the cases (165 of 477). For 33 of 165 cases (20%), there was surgical follow-up. Eight cases, including 5 benign neoplasms (2 pleomorphic adenomas, 1 neurofibroma, and 2 benign vascular/lymphatic lesions) and 3 malignant neoplasms (2 mucoepidermoid carcinomas and 1 acinic cell carcinoma), were neoplastic. The nonneoplastic category constituted a large proportion of the cases (34.6%), and a 9% ROM is significant enough to create difficulty for clinical decision-making. This clinical issue has been described even in the adult population.[29]

The AUS category included 5.2% of the cases (25 of 477) in this study, which is within the proposed range. The ROM was 35.7% (5 of 14) for this category, which is significantly higher than the original MSRSGC proposal of 20%; the RON was 71.4% (10 of 14). Both benign and malignant neoplasms were diagnosed as AUS on aspirated material; they included mucoepidermoid carcinoma (3), lymphoma (2), pleomorphic adenoma (1), benign vascular and lymphatic neoplasms (1), desmoid tumor (2), and nodular fasciitis (1). Two of 5 AUS cases (40%) were diagnosed as lymphoma on surgical follow-up. ROSE can improve the performance of MSRSGC by triaging specimens; for instance, the concurrent collection of material for flow cytometry in cases with atypical lymphocytes may improve the diagnosis of lymphomas and subsequently decrease the ROM in the AUS category. ROSE can facilitate the collection of additional passes for preparing a cell block for ancillary studies for further characterization of the atypical cells. ROSE can also improve patient care in infectious/inflammatory cases through the collection of material for microbiological studies. Overall, ROSE allows us to appropriately triage cases for flow cytometry or cell blocks, and this could be a significant improvement for patient care by decreasing the atypia rate and preventing surgery or repeat biopsy for lymphoproliferative processes. Moreover, the ROM of 35.71% (5 of 14) for the AUS category is high for a small sample size. This high ROM indicates that the pathologists may need to become more familiar with

TABLE 4. Histologic Diagnoses of Cases in the Malignant, Benign, and Nonneoplastic Categories

Malignant Neoplasms (n = 79)	Benign Neoplasms (n = 116)	Nonneoplastic Conditions (n = 42)
Primary neoplasms (n = 47)	Pleomorphic adenoma (95)	Acute, chronic, or granulomatous sialadenitis (18)
Mucoepidermoid carcinoma (18)	Benign vascular/lymphatic lesions (5)	Reactive lymph node (7)
Acinic cell carcinoma (16)	Neurofibroma (4)	Benign duct cyst (6)
Adenoid cystic carcinoma (2)	Warthin tumor (2)	Dermoid/epidermal inclusion cyst (5)
Secretory carcinoma (2)	Schwannoma (2)	Lymphoepithelial cyst (4)
Epithelial myoepithelial carcinoma (1)	Desmoid tumor (2)	Hyaline vascular Castleman disease (1)
Sebaceous carcinoma (1)	Myoepithelioma (1)	Mucocele-like cyst (1)
Rhabdomyosarcoma (7)	Nodular fasciitis (1)	
Secondary neoplasms (n = 32)	Myofibroma (1)	
Rhabdomyosarcoma (4)	Oncocytoma (1)	
Lymphoma (10)	Langerhans histiocytosis X (1)	
Retinoblastoma (10)	Pilomatrixoma (1)	
Neuroblastoma (3)		
Melanoma (1)		
Squamous cell carcinoma (1)		
Angiosarcoma (1)		
Rhabdoid tumor–AT/RT (1)		
Nasopharyngeal carcinoma (1)		

Abbreviation: AT/RT, atypical teratoid/rhabdoid tumor.

salivary gland cytology in pediatrics to more accurately classify them and subsequently lower the estimated ROM.

The proposed ROM for the benign neoplasm category in the MSRSGC was determined to be less than 5%. In this study, the benign neoplasm category included 27.5% of all FNA cases (131 of 477). The ROM was 3.29% and the RON was 97.8% on the basis of cases with surgical follow-up. Pleomorphic adenoma was the most common benign neoplasm (81 of 86) among these cases. Mucoepidermoid carcinoma, acinic cell carcinoma, and adenoid cystic carcinoma were examples of malignant tumors misinterpreted as benign on FNA material (1 case for each of these tumor types).

The proposed ROM for the SUMP category in the MSRSGC is 35%. The SUMP category included 7.5% of the cases (36 of 477); surgical follow-up confirmed a neoplastic process in all cases. The ROM was 31.8% (7 of 22) and the RON was 100% for cases with surgical

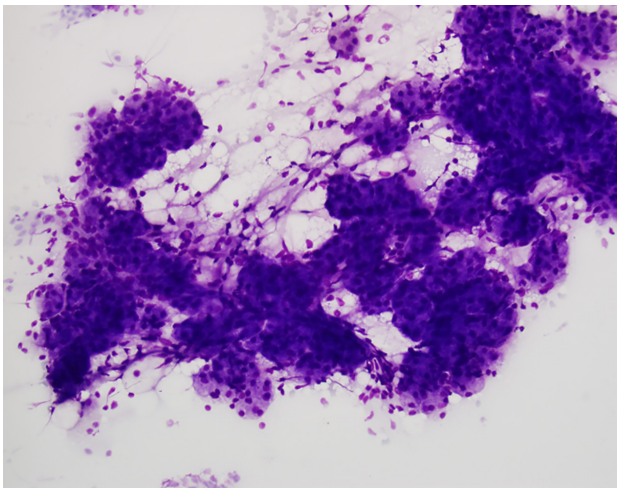

Figure 3. Nondiagnostic category: fine-needle aspiration shows benign-appearing acini (×200, Diff-Quik stain).

Figure 5. Neoplasm benign category: fine-needle aspiration shows a pleomorphic adenoma on ThinPrep (×400, Papanicolaou stain) confirmed by histology.

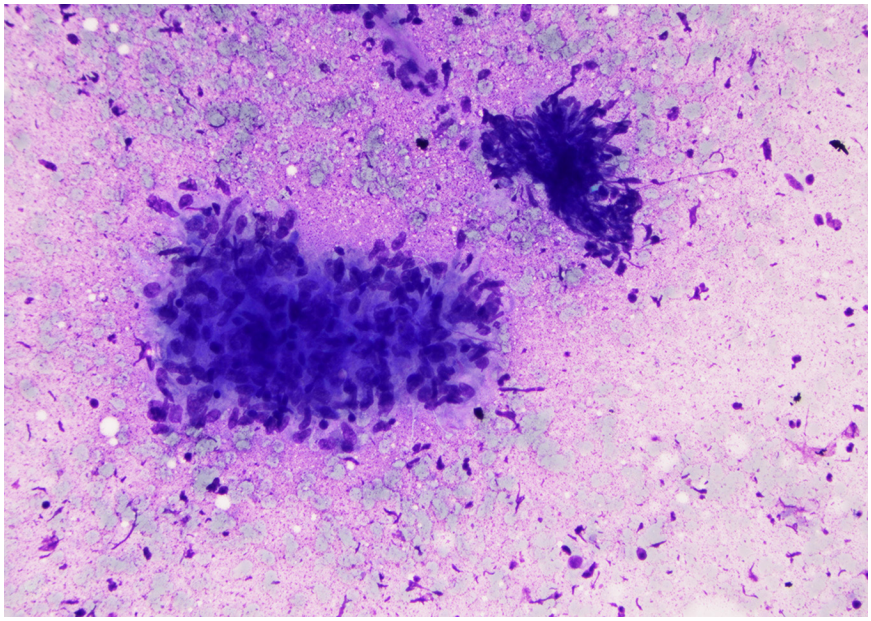

Figure 4. Nonneoplastic category: fine-needle aspiration shows granulomatous inflammation (×200, Diff-Quik stain) confirmed by core biopsy.

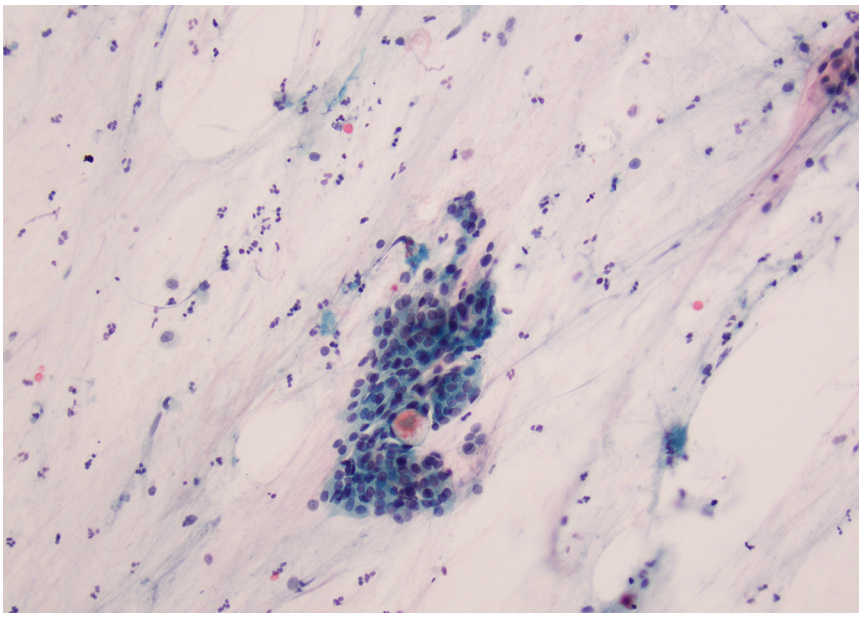

Figure 6. Suspicious for malignancy category: fine-needle aspiration shows a fragment of a neoplastic cell with a mucin-containing cell in a background of mucin and acute inflammation (×400, Papanicolaou stain). It was diagnosed as suspicious for mucoepidermoid carcinoma. The surgical follow-up diagnosis was mucoepidermoid carcinoma.

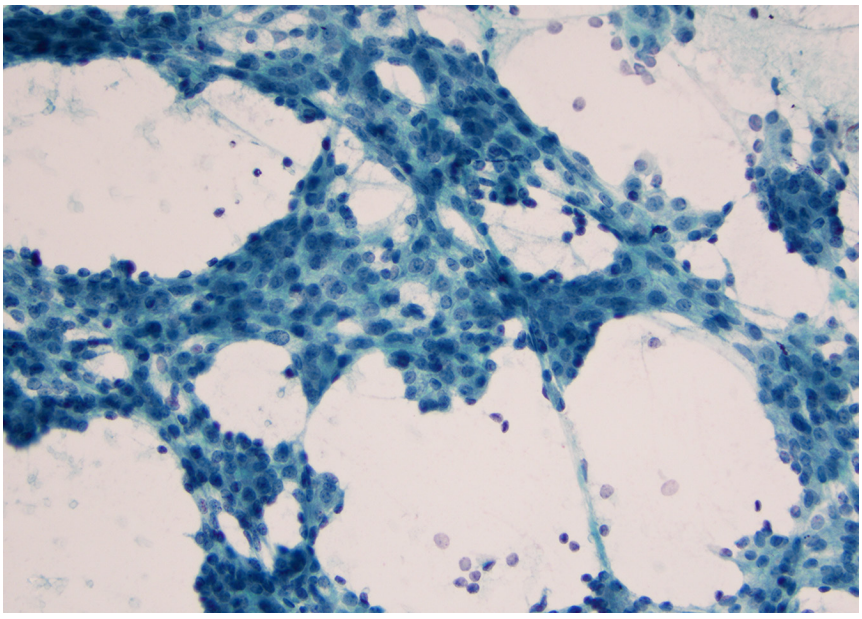

Figure 7. Malignant category: fine-needle aspiration shows fragments of neoplastic cells with relatively uniform nuclei and moderate to abundant granular cytoplasm (×400, Papanicolaou stain). It was diagnosed as acinic cell carcinoma, and this was confirmed by subsequent surgical diagnosis.

follow-up. SUMP with basaloid features was the most common reported morphology. Surgical follow-up confirmed pleomorphic adenoma. A few cases showed oncocytic features and spindle cell features. One case displayed clear cell features on cytology, and subsequent surgery confirmed secretory carcinoma. Pleomorphic adenoma was the most common benign neoplasm (10 of 15), and acinic cell carcinoma (4 of 7) was the most common malignant neoplasm.

The proposed ROM for the SM category is 60% in the MSRSGC. The suspicious category included 2.5% of the cases (12 of 477) with an ROM of 100% (9 of 9).

Mucoepidermoid carcinoma (4 of 9) was the most common malignant neoplasm in this category.

The proposed ROM for the malignant category is >90% in the MSRSGC. The malignant category included 12.4% of the cases (59 of 477) with an ROM of 100% (51 of 51). Acinic cell carcinoma was the most common primary malignant neoplasm (8 of 51), and retinoblastoma (10 of 79) and lymphoma (10 of 79) were the most common secondary neoplasms. Rhabdomyosarcoma was confirmed in 11 cases; 7 were primary, and 4 were secondary. The subtype was available only in 2 primary cases: 1 embryonal and 1 alveolar. The subtype of rhabdomyosarcoma plays a crucial role in a patient's treatment and prognosis, and its reporting is of paramount importance.[30]

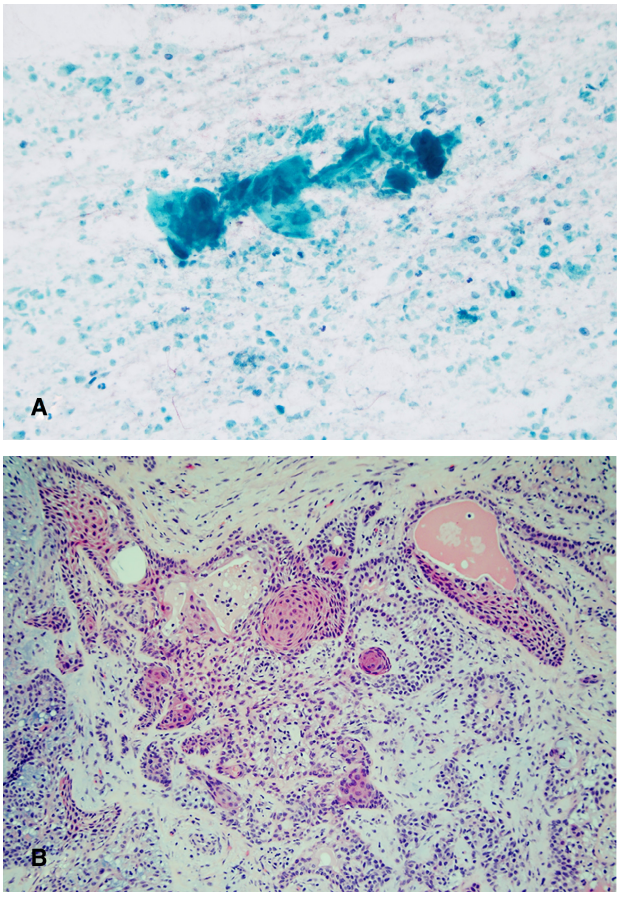

Figure 8. An example of a discrepant case. (A) Aspirated material showed scattered mature squamous cells in a background of debris and rare macrophages (4 passes). It was diagnosed as a nonneoplastic case consistent with a squamous cell–lined developmental cyst. (B) The surgical follow-up diagnosis was pleomorphic adenoma (benign neoplasm) with squamous metaplasia.

This study shows that the ROM for the nondiagnostic category is lower than originally proposed by the MSRSGC (5.9% vs 25%), whereas it is higher for the AUS (35.71% vs. 20%), suspicious (100% vs 60%), and malignant categories (100% vs 90%). The ROMs for the nonneoplastic (9.1% vs 10%), benign neoplasm (3.29% vs <5%), and SUMP categories (31.8% vs 35%) are similar to those proposed by the MSRSGC. The differences in the ROMs might be explained by differences between neoplasms involving pediatric salivary glands and tumors arising in adult salivary glands and by diagnostic challenges in distinguishing low-grade salivary malignancies in children. Entities involving the salivary glands in pediatrics differ vastly from those in adults; for instance, small round cell tumors and lymphomas are common in pediatrics, whereas metastatic carcinomas are more common in adults.

The ROM identified in the AUS and nonneoplastic groups creates a management decision challenge for clinicians managing patients with a salivary gland lesion.[29] This is particularly true for pediatric patients, for whom delays in diagnosis and treatment may have more significant implications.[23-26] The clinical context, associated imaging findings, and clinical suspicion may be the driving factors for clinical decision-making in AUS or nonneoplastic cases. A modified MSRSGC for pediatrics

TABLE 5. Milan Category ROMs and Possible Clinical Management Options

Milan Category	ROM on Surgical Follow-Up, %	Milan Reference ROM, %	Repeat FNA	Clinical Follow-Up (May Include Imaging)	Ancillary or Alternative Biopsy Techniques (Core)	Surgical Excision or Definitive Oncologic Treatment
I	5.88	25	X	X		
II	9.09	10		X	X	
III	35.71	20		X	X	X
IVa	3.29	<5		X		X
IVb	31.81	35			X	X
V	100	60			X	X
VI	100	90				X

Abbreviations: FNA, fine-needle aspiration; ROM, risk of malignancy.

or a clinical decision tool, as shown in Table 5, may be needed to better assist clinicians in correctly interpreting the MSRSGC categories for pediatric patients. This study clearly proves that salivary gland cytology in pediatrics can be improved. Further studies are warranted to investigate preanalytical factors such as the utility of ultrasound guidance, the FNA performer's experience, and the number of passes. The pathologist's experience and familiarity with salivary gland cytology are other key factors for improving the diagnostic accuracy.

In conclusion, the MSRSGC can be successfully applied for pediatric salivary gland cytology similarly to previously established adult salivary gland cytology. However, there are some notable differences that require additional studies to confirm its clinical validity and its use as a clinical decision tool in the management of pediatric salivary gland lesions.

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AUTHOR CONTRIBUTIONS

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