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

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Abstract

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 evaluates the application of the Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) and the risk of malignancy (ROM) for each diagnostic category.

Methods: Pediatric (0-21-year-old) salivary gland FNA specimens from 22 international institutions of seven countries including the United States, England, Italy, Greece, Finland, Brazil, and France were retrospectively assigned to a 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 calculated for each MSRSGC diagnostic category.

Results: The cohort of 477 aspirates was reclassified according to the MSRSGC as: 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 (49.7%) cases. 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 (18/237, 7.6) followed by acinic cell carcinoma (16/237, 6.7%). Pleomorphic adenoma was the most common benign neoplasm (95/237, 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 adult salivary gland FNA, although these reported rates for the different MSRSGC categories were variable across institutions.

Key words: salivary gland, cytology, fine needle aspiration, the Milan System for Reporting Salivary Gland cytology (MSRSGC), risk of malignancy, pediatric cytology, parotid, submandibular gland

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] [7-10] and it's clinical feasibility and utility is often dictated by patient age, suspected diagnosis, and need for sedation or anesthesia. For example, adequate tissue sampling where both FNA and concurrent core or excisional biopsy is desired is typically performed under anesthesia.

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

MSRSGC is a 6-tier diagnostic scheme including the fol-
lowing categories: 1) nondiagnostic, 2) nonneoplastic, 3)
atypia of undetermined significance (AUS), 4) neoplasm
(including benign neoplasms and salivary gland neoplasms
of uncertain malignant potential [SUMPs]), 5) suspicious
for malignancy (SM), and 6) malignant

The MSRSGC was created to facilitate communication among pathologists and clinicians in order to improve patient care. A recent comprehensive review of the literature showed that the mean of 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 MSRSGC has been studied in adult patients, however, only few have evaluated the application of the MSRSGC in the pediatric population [16]. This multi-institutional, international study retrospectively evaluates the application of MSRSGC to the largest series of salivary gland FNA cases in 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 with the age range of 0-21 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 on-site evaluation (ROSE) was not included since the data was not available and there were cases that 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 retrieved data from each institution were collected as a spreadsheet of de-identified cases. They were further reviewed and analyzed by 2 pathologists (Zahra Maleki and Jerzy Klijanienko) in a master spreadsheet. The ROM and 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 (50.1%) males and 238 (49.9%) females **(Figure 1).** Their age ranged from 2 weeks to 21 years (mean age =13.14 years, median age=14.00, and SD=5.30). The parotid gland was the most common site (348, 73.0%), followed by submandibular gland (72,15.1%), oral/minor salivary glands (9,1.9%), and unspecified neck mass (13, 2.7%) **(Figure 2)**. FNA site was not available in 35 (7.3%) of the cases. Tumor size was available in 305/477 (64%) cases and ranged from 0.4 cm to 8.0 cm (Mean size: 2.54 cm, Median size: 2.40 cm, SD: 1.35).

The 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 2-4**.

Pleomorphic adenoma was the most common neoplasm and the most common benign neoplasm (95/116, 82%), followed by benign vascular/lymphatic conditions (5/116, 4.3%), neurofibroma (4/116, 3.4%), two of each of Warthin tumor, schwannoma, and desmoid tumor, as well as one of each of myofibroma, myoepithelioma, nodular fasciitis, oncocytoma, Langerhans cell histiocytosis, and pilomatrixoma.

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

Risk of Malignancy (ROM) and Risk of Neoplasm (RON)

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 ROM for each individual institution because of low case volumes. The histopathologic follow-up with risk of malignancy (ROM) and risk of neoplasm (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) (89/91, 97.8%) and was 100% for SUMP (IVB), SM (V) and malignant (VI) categories. RON was also high for AUS

(10/14, 71.4%). However, RON was intermediate for non-diagnostic categories (6/17, 35.3%) and low for the nonneoplastic category (8/33, 24.2%).

Discussion

FNA is a well-established procedure for evaluation of neck masses, thyroid lesions and salivary gland lesions in pediatric patients similarly to the 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 upon cytology-histology correlation [20]. Pediatric salivary gland- lesions encompass a wide range of diagnosis (**Table 4**). This range of diagnoses also diverges from the adult population [18, 21, 22]. Pediatric salivary gland lesions may require urgent attention and immediate morphology evaluation when there is a suspicion for high grade lymphomas, sarcomas and small round blue cells tumors to allow for timely intervention [23-26]. In this study, MSRSGC was highly sensitive for high grade tumors such as sarcoma, small round blue cell tumor, and neuroblastoma (**Table 3**). Rapid on-site evaluation can improve triaging of samples and tests.

As noted in **Table 2**, the ROM is higher than proposed by the Milan system for category 3 and 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 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-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, this data is collected by a very diverse group of cytopathologists, from diverse institutions, and even at each institution a diverse group of cytologists with a range of skills and a range of experience with SG FNA. This poses a huge challenge for the interpretation of the

data. The large size of the samples is considered as a strength of the study. However, this large number of cases reflects a broad spectrum of cytopathologists' skills and experience. The study is limited by the fact that the slides of cases with histology-cytology discrepancy were not reviewed due to the nature of the study (Figures 8A and 8B).

The proposed ROM for the non-diagnostic category in the MSRSGC is 25%. In our pediatric series, the non-diagnostic category comprised 10.3% (49/477) of all cases. Seventeen out of 49 cases (34.69%) had surgical follow-up; The ROM and RON were 5.9% and35.3% respectively. The ROM was lower than the MSRSGC proposal. However, ROM was reported as low as zero by onother studies both on pediatrics and adults for this category [27] [28]. In this category, one case of acinic cell carcinoma was the only malignant case identified on surgical follow-up and pleomorphic adenoma (1), neurofibroma (2), and two cases of benign vascular/lymphatic neoplasms were listed as benign neoplasms.

The proposed ROM for the non-neoplastic category in the MSRSGC is 10%. In this study, ROM was 9.1% and RON was 24.2% for the non-neoplastic category, respectively. The non-neoplastic category comprised 34.6% (165/477) of the cases. For 33 out of 165 (20%) cases they had surgical follow-up. Eight cases were neoplastic including five benign (two pleomorphic adenoma, one neurofibroma, two benign vascular/lymphatic lesions) and three malignant neoplasms (two mucoepidermoid carcinoma and one acinic cell carcinoma). Non-neoplastic category constitutes a large proportion of the cases (34%) and 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 comprised 5.2% (25/477) of the cases in this study which is within proposed range. ROM was 35.7% (5/14) for this category, which is significantly higher than original MSRSGC proposal of 20% and RON was 71.4% (10/14). Both benign and malignant neoplasms were diagnosed as AUS on aspirated material including mucoepidermoid carcinoma (3), lymphoma (2), pleomorphic adenoma (1), benign vascular and lymphatic neoplasms (1),

desmoid tumor (2), and nodular fasciitis (1). Two out of five AUS (40%) cases were diagnosed lymphoma on surgical follow-up. ROSE can improve the MSRSGC performance by means of triaging the specimens for instance concurrent collection of material for flow cytometry in cases with atypical lymphocytes, may improve the diagnosis of lymphomas and subsequently decrease the ROM in AUS category. ROSE can facilitate 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 by collection of material for microbiological studies. Overall, ROSE allows us to appropriately triage the cases for flow or cell block, which this could be a significant improvement for patient care to decrease atypia rate, avoid surgery or repeat biopsy for lymphoproliferative processes. Moreover, the ROM of 35.71% (5/14) of AUS category is high in a small sample size. This high ROM indicates that the pathologists may need to become more familiar with salivary gland cytology in pediatrics in order to more accurately classify them and subsequently lower the estimated ROM.

The proposed ROM for the benign neoplasm category in the MSRSGC is determined to be less than 5%. In this study, the benign neoplasm category comprised 27.5% (131/477) of all FNA cases. ROM was 3.29% and RON was 97.8% based upon cases with surgical follow-up, respectively. Pleomorphic adenoma was the most common benign neoplasm (81/86) in these cases. A case of each of the following tumors: mucoepidermoid carcinoma, acinic cell carcinoma, and adenoid cystic carcinoma were examples of malignant tumors misinterpreted as benign on FNA material.

The proposed ROM for SUMP category in the MSRSGC is 35%. The SUMP category comprised 7.5% (36/477) of the cases; surgical follow-up confirmed a neoplastic process in all cases. ROM was 31.8% (7/22) and RON was 100% in cases with surgical 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 cells features. One case displayed clear cell features on cytology and subsequent surgery confirmed secretory carcinoma. Pleomorphic adenoma was the most common benign neoplasm (10/15), and acinic cell carcinoma (4/7) was the most common malignant neoplasm.

The proposed ROM for the suspicious for malignancy category is 60% in the MSRSGC. The suspicious category comprised 2.5% (12/477) of the cases with a ROM of 100% (9/9). Mucoepidermoid carcinoma (4/9) was the most common malignant neoplasm in this category.

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

This study shows that ROM for the non-diagnostic category is lower than was originally proposed by the MSRSGC (5.9% vs 25%) while it is higher for the AUS (35.71% vs. 20%), suspicious (100% vs 60%), and malignant (100% vs 90%) categories. ROM for non-neoplastic (9.1% vs 10%), benign neoplasm (3.29% vs <5%), and SUMP (31.8% vs 35%) categories were similar to those proposed by the MSRSGC. The differences in ROM might be explained by differences in neoplasms involving pediatric salivary glands versus tumors arising in adult salivary glands, and 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 while metastatic carcinomas are more common in adults.

The ROM identified in the AUS and non-neoplastic groups creates a management decision challenge for clinicians managing patients with a salivary gland lesion[29]. This is particularly true in pediatric patients where the delay in diagnosis and treatment may have more significant implications [23-26]. The clinical context, associated imaging findings, and clinical suspicion may be the driving factor for clinical decision making, in AUS or non-neoplastic cases. A modified MSRSGC for pediatrics or a clinical decision tool, as seen in **Table 5**, may be needed to better assist the clinician in correctly interpreting the MSRSGC categories for pediatric patients. This

study is clearly proves that the salivary gland cytology in pediatrics can be improved. Further studies are warranted to investigate the preanalytical factors such as 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 to improve 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 which require additional studies to confirm its clinical validity and as a clinical decision tool in the management of pediatric salivary gland lesions.

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Figure legends

Figure 1. Shows the distribution of the pediatric FNA cases for each gender for each category.

Figure 2. Shows the distribution of pediatric FNA cases for each Milan category for parotid gland and submandibular gland.

Figure 3. Non-diagnostic category, FNA showing benign appearing acini (X200, Diff-Quik stain).

Figure 4. Non-neoplastic category, FNA showing granulomatous inflammation (X200, Diff-Quik stain), confirmed by core biopsy.

Figure 5. Neoplasm benign category, FNA showing pleomorphic adenoma on ThinPrep (X400, Papanicolaou stain), confirmed by histology.

Figure 6. Suspicious for malignancy category, FNA showing a fragment of neoplastic cell with a mucin containing cell in a background of mucin and acute inflammation (X400, Papanicolaou stain). It was diagnosed as suspicious for mucoepidermoid carcinoma. The surgical follow-up diagnosis was mucoepidermoid carcinoma.

Figure 7. Malignant category, FNA showing fragments of neoplastic cells with relatively uniform nuclei and moderate to abundant granular cytoplasm (X400, Papanicolaou stain). It was diagnosed as acinic cell carcinoma and it was confirmed by subsequent surgical diagnosis.

Figures 8A and 8B. An example of a discrepant case. 8A) Aspirated material showed scattered mature squamous cells in a background of debris and rare macrophages (four passes). It was diagnosed non-neoplastic consistent with squamous cell lined developmental cyst. 8B) Surgical follow-up was pleomorphic adenoma (benign neoplasm) with squamous metaplasia.

Milan System diagnostic category	Total cases	Cases with surgical follow up	Malignant cases	Benign neoplasm	Non-neoplastic	ROM
Non-diagnostic	42	13	1	5	7	7%
Non-neoplastic	150	37	3	10	24	8%
Atypia of undetermined significance (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%

Milan Category	N (%)	Cases with Surgical follow-up (%)	Malignant neoplasm on surgical follow up	Benign neoplasm on surgical follow up	Diagnosis of non-neoplastic process	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 (49.68)	79 (33.33)	116 (48.94)	42 (17.72)	NA	NA	NA

Table 2. Distribution of cases according to their Milan System categories and comparison of their ROM according to the Milan reference ROM.

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)
	Non-neoplastic (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)
	Non-neoplastic (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)
	Non-neoplastic (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)
	Non-neoplastic (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)

Table 3. Shows histologic diagnoses of the cases on surgical follow-up.

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

Table 4. Shows histologic diagnosis of cases in malignant, benign, and non-neoplastic categories.

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

Table 5. Milan Category ROM and possible clinical management options.
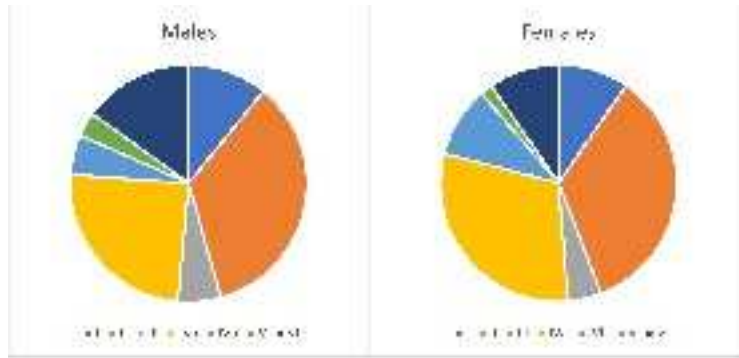
Figure 1. Shows the distribution of the pediatric DNA cases by each gender for each category.

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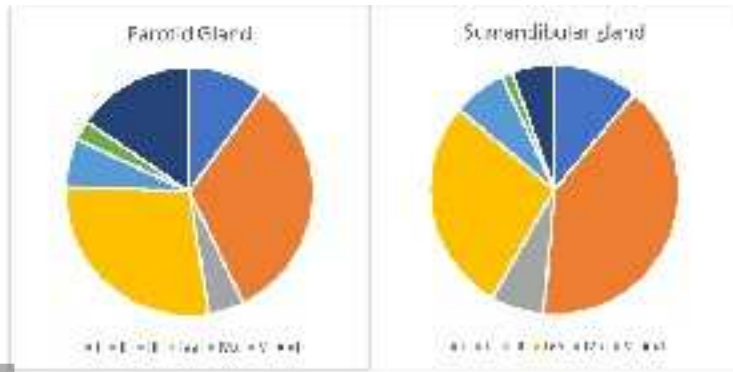
Figure 2. Shows the distribution of pediatric metastases in each Milan category for parotid gland and submandibular gland.
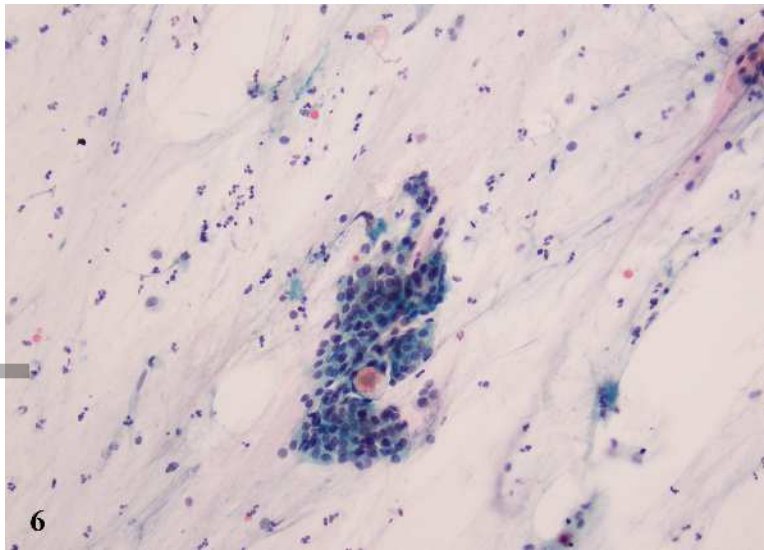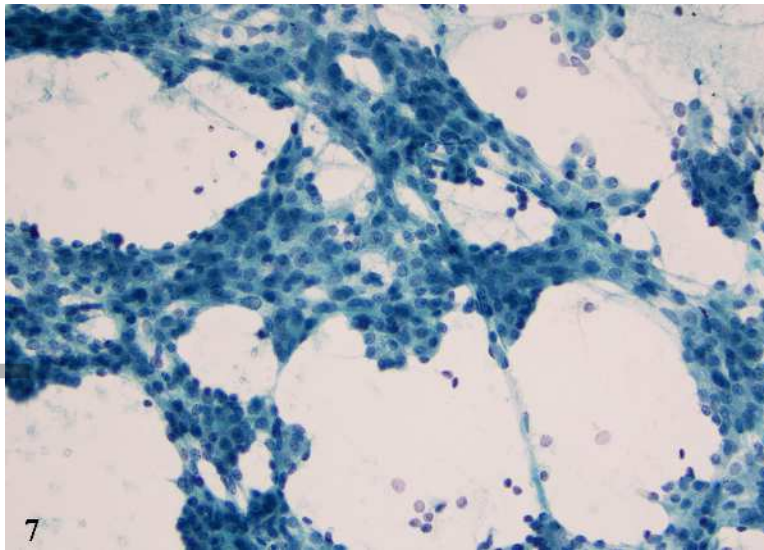
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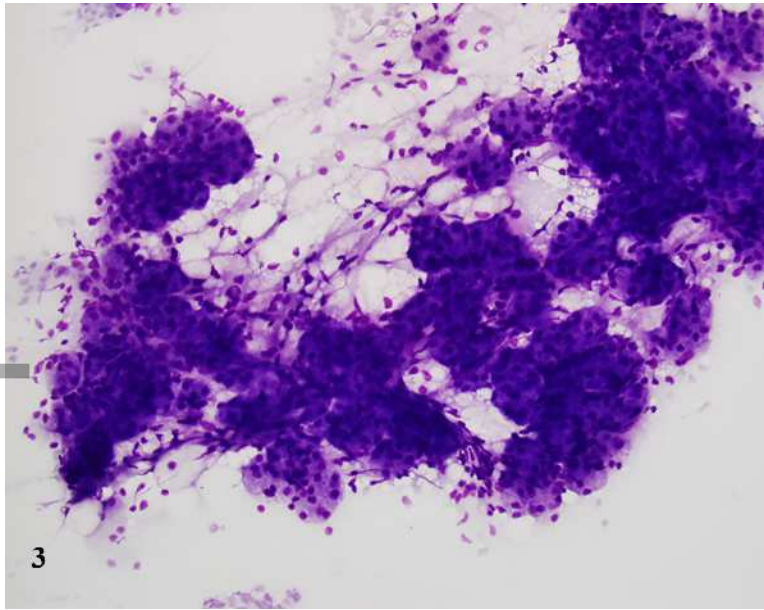
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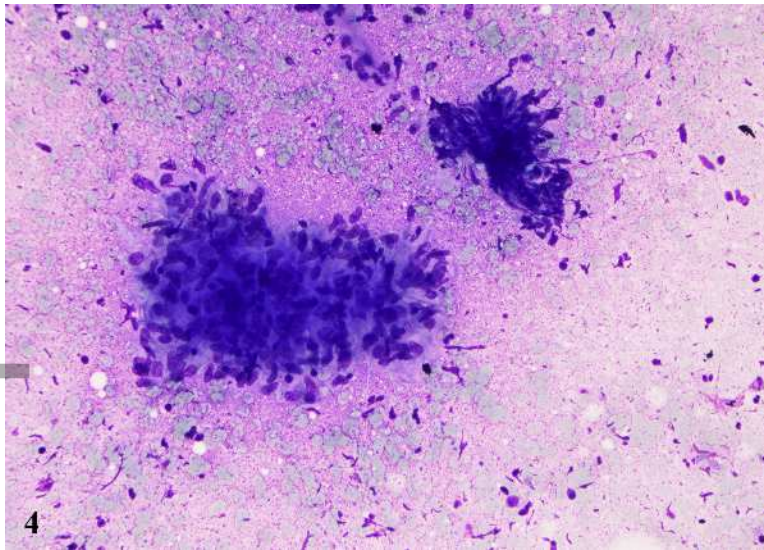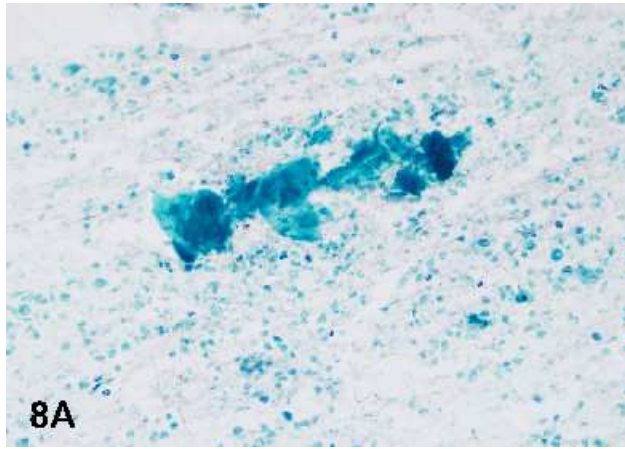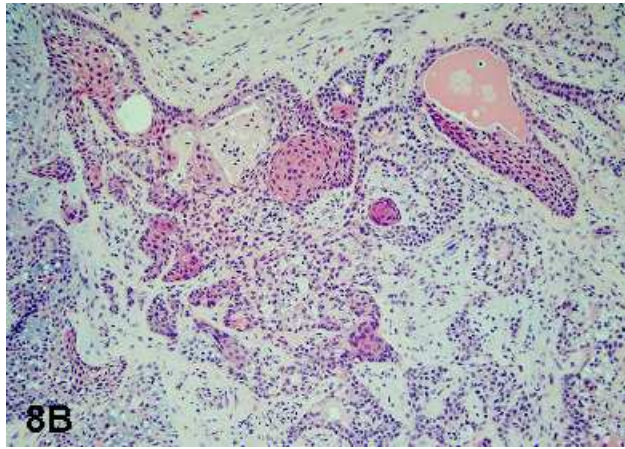
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