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Malignant risk of indeterminate pediatric thyroid nodules - an institutional experience

(Running title: malignant risk of pediatric thyroid nodules)

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Abstract

Background: Few studies focus on pediatric thyroid nodules categorized under indeterminate diagnostic categories. The current study was conducted to assess the risk of malignancy of indeterminate pediatric thyroid nodules.

Methods: A search of the institutional electronic pathology database from 01/2011 to 09/2018 was performed to identify pediatric (< 21 years old) thyroid nodules which were interpreted as follicular lesion of undetermined significance (FLUS), suspicious for follicular neoplasm (SFN) or suspicious for malignancy (SFM) and subsequently managed with surgery, repeat FNA, or ≥ 6 months of clinical/imaging monitoring. Results of follow-up (F/U) surgical resections and repeat FNA/Afirma tests, and clinical and radiologic data were collected.

Results: We identified 46 cases from 42 patients (11 to 20 years old, 33 females and 9 males), including 30 FLUS, 10 SFN and 6 SFM. Twenty-five FLUS, 10 SFN and 6 SFM cases underwent surgery. The histology revealed carcinomas in 36% of FLUS, 20% of SFN, and 100% of SFM categories; follicular adenomas in 32% of FLUS and 80% of SFN categories; and benign nodules in 32% of FLUS category. All 5 non-surgically treated FLUS cases were considered benign based on the findings of repeat FNA/Afirma tests (n=3, 3-22 months F/U) or clinical/radiologic exams (n=2, 8-12 months F/U).

Conclusions: Based on a limited study cohort, malignancy was identified in 36%, 20% and 100% of surgically managed pediatric thyroid nodules categorized as FLUS, SFN and SFM, respectively; suggesting a markedly higher malignant rate than the implied malignant risk for FLUS and SFM categories in adults.

Key words: Pediatric thyroid nodule, follicular lesion of undetermined significance, follicular neoplasm/suspicious for follicular neoplasm, suspicious for malignancy, risks of malignancy

Introduction

Although thyroid nodules are less common in children than adults, an overview of the literature has showed that pediatric thyroid nodules are more likely to be malignant and carry a 1.6 fold higher cancer risk compared to that of adult population.(1) The Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer from The American Thyroid Association recommends fine needle aspiration (FNA) as an essential tool for the assessment and management of pediatric thyroid nodules, and utilizing The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) as a guideline to categorize FNA cytologic findings.(2, 3) Among the six categories of TBSRTC, three are considered indeterminate, namely atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm/suspicious for follicular neoplasm (FN/SFN) and suspicious for malignancy (SFM). In spite of many published studies on cytologic, histologic and molecular findings of adult

indeterminate thyroid nodules, there are few publications focusing on pediatric thyroid nodules categorized under the indeterminate diagnostic categories of TBSRTC. The current study was conducted to assess the risk of malignancy and/or outcomes of pediatric thyroid nodules interpreted as indeterminate using TBSRTC criteria at a single center.

Methods

The retrospective study was approved by the Institutional Review Board (IRB) of the University of Michigan. A search of the Michigan Medicine institutional electronic pathology database from 01/2011 to 09/2018 was performed to identify pediatric (< 21 years old) thyroid nodules which were previously aspirated and interpreted as FLUS, SFN or SFM, and subsequently managed with surgery, repeat FNA, or ≥ 6 months of clinical/imaging monitoring. Interventional radiologists performed ultrasound-guided FNAs with cytopathologist-assisted rapid on-site evaluation (ROSE). Briefly, two conventional smears were made for each pass. One smear was air-dried and stained with Diff-Quik protocol to be evaluated immediately for specimen adequacy while the other smear was fixed with Sprayfix™ and subsequently stained with Papanicolaou stain. The needle was then rinsed in Cytolyt solution for a ThinPrep or a cell block. When repeat FNA was performed in nodules previously interpreted as FLUS, additional passes may be collected for Afirma testing at the treating clinician's discretion. For each case, age and gender of the patient, size of the targeted nodule, number of passes, and original cytologic interpretation were recorded. Further, results of subsequent surgical resections, repeat FNA, and

Afirma testing, as well as clinical and follow-up (F/U) radiologic data were collected. Re-review of slides prepared from the follow-up surgical specimens was performed to identify the cases that fulfilled the newly published diagnostic criteria of non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).(4)

Results

We identified a total of 46 cases from 42 patients with the average age of 15.1 years old (11 to 20 years old), including 33 females and 9 males. The original cytologic interpretations included 30 FLUS, 10 SFN and 6 SFM. Twenty-five FLUS, 10 SFN, and 6 SFM cases underwent surgery. Hemi-thyroidectomies were performed in 14 FLUS and 8 SFN cases while total thyroidectomies were performed in 11 FLUS, 2 SFN, and 5 SFM cases; one FLUS case and one SFM case underwent lobectomy followed by completion thyroidectomy. As can be seen in Table 1, the surgical specimens revealed malignancy in 9 of 25 (36%) FLUS, 2 of 10 (20%) SFN, and 6 of 6 (100%) SFM categories; Follicular adenomas were identified in 8 of 25 FLUS (32%) and 8 of 10 (80%) SFN categories. Benign nodules were diagnosed in 8 of 25 (32%) FLUS cases. Papillary thyroid carcinoma (PTC) represents the majority of malignancy (15/17), including 10 conventional and 5 follicular variants (Figures 1-3) and all were managed by total thyroidectomy. The remaining 2 malignant cases were diagnosed as Hurthle cell carcinomas, one received hemithyroidectomy while the other one was treated with hemithyroidectomy followed by completion thyroidectomy. Re-review of the surgical specimens did not identify any cases

which fulfilled the diagnostic criteria of NIFTP and could be reclassified as such.(4) Among the 25 surgically-treated FLUS cases, 2 received Afirma testing preoperatively and one patient was aspirated once while the other patient was aspirated twice with repeat FLUS categorization. Afirma testing in both 2 cases was interpreted as suspicious and the corresponding histologic examination revealed benign nodular hyperplasia in one patient and follicular variant of PTC in the other patient. Three out of the five non-surgically treated FLUS cases underwent repeat FNA which were interpreted as lymphocytic thyroiditis, nodular hyperplasia, and FLUS following 15 months, 22 months and 3 months of follow-up, respectively; the concurrent Afirma testing in the repeat FLUS case was interpreted as benign. The findings of clinical and/or radiologic follow up (8-12 months) were considered benign in the remaining 2 non-surgically managed cases. Overall, malignancy was identified in 30%, 20% and 100% of pediatric thyroid nodules categorized as FLUS, SFN and SFM, respectively.

Discussions

FNA as an important tool in the cytologic assessment of pediatric thyroid nodules, provides 94% sensitivity, 81% specificity and 77.2-98.6% diagnostic accuracy.(5) Similar to the management of adult thyroid nodules, the real challenge is identification of malignancy among the indeterminate categories. Based on the first edition of TBSRTC, the implied risk of malignancy was 10-30%, 25-40% and 50-75% for AUS/FLUS, FN/SFN and SFM category, respectively.(3) In the most recently published edition of TBSRTC, the implied risk of malignancy for the

indeterminate categories has been modified as a result of introduction of the new diagnostic terminology ”non-invasive follicular neoplasm with papillary thyroid nuclear features (NIFTP)”.(4) Accordingly, the newly implied risks of malignancy are 6-18%, 10-40% and 45-60% for AUS/FLUS, FN/SFN and SFM categories, respectively.(6) It is noteworthy to mention that the these results were generated from the adult population.

In our current study, all nodules categorized as SFN and SFM underwent surgeries. The corresponding histology demonstrated carcinomas in all SFM cases and 20% of SFN cases. The majority (25/30) of the FLUS cases underwent surgeries and benign non-neoplastic nodules, follicular adenoma and carcinomas (PTC or Hurthle cell carcinoma) were confirmed in 8, 8, and 9 cases, respectively. Re-review of the surgical specimens did not identify any cases which fulfilled the diagnostic criteria of NIFTP and could be reclassified as such. The remaining 5 non-surgically treated FLUS cases were considered benign based on the results of repeat FNA, Afirma testing, and/or clinical/radiological findings. Taken together, FLUS, SFN and SFM categories had a malignant rate of 30%, 20% and 100%, respectively in our investigation. It appears that pediatric indeterminate thyroid nodules, particularly nodules categorized as SFM and FLUS, carry a greater risk of malignancy than that of adult population after excluding NIFTP from malignant category. However, while interpreting these differences, one should note possible selection or sampling bias due to the limited pediatric case cohort contained in the current study. Although NIFTP has not been thoroughly investigated yet in pediatric patients,

this study and that of Rossi, et al which demonstrated that NIFTP comprised only 1.9% of resected pediatric thyroid nodules,(7) suggest that NIFTP in the pediatric population is rare.

There is limited data on histology-confirmed malignancy within indeterminate categories from other institutions (Table 2).(8-14) Similarly to our data, all these previously published studies contained limited number of cases in each of the indeterminate categories, i.e. 4 to 25 cases in AUS/FLUS, 4 to 19 cases in FN/SFN, and 2 to 6 cases in SFM category. The majority of the studies from the other institutions demonstrated 100% of malignant rate in SFM category. The risk of malignancy for FLUS (36%) and SFN (20%) observed in our study falls within the ranges documented by other institutions, namely 8-50% for AUS/FLUS and 10-100% for FN/SFN category. In contrast with our finding that FLUS category carried a higher malignant rate than SFN category, a greater rate of malignancy had been seen in FN/SFN rather than AUS/FLUS category in several of the aforementioned studies.(9, 12, 13) It is noteworthy to mention that these previous published studies were conducted prior to the introduction of NIFTP terminology. It is unclear if some of the specimens could actually be recategorized as NIFTP and therefore the malignant rate for each indeterminate category may be altered. Nonetheless, many factors may attribute to the variation in malignant rate, i.e. prevalence of malignant pediatric thyroid nodules, diagnostic thresholds for assessing cytologic and/or histologic specimens. It is crucial for pathologists, endocrinologists, and surgeons to have a clear understanding of practice patterns in their own institutions in order to provide an appropriate management of pediatric thyroid nodules.

A couple of the aforementioned studies specified types of malignancies on the subsequent resections specimens. In this regard, Smith et al observed mainly follicular variants of PTC, followed by conventional PTC and follicular carcinoma.(9) Partyka et al saw almost even number of conventional and follicular variant of PTC.(13) However, the malignancies seen in our study included mainly conventional PTC and a subset of follicular variant of PTC. None of the studies encountered other variants of PTC, i.e. diffuse sclerosing variant, previously reported by others.(10)

In the current study, several patients with FLUS nodules underwent total thyroidectomies which revealed benign nodular hyperplasia. Clinically, these patients had multinodular goiter and at least one of the nodules exhibited continuous growth. Total thyroidectomy approach was chosen by the patient's parents. In this regard, public awareness on increased risk of malignancy in pediatric thyroid nodules may have an influence in the decision making. Molecular testing could be used as an adjunct to FNA for further stratification of pediatric indeterminate nodules. It has been reported that the detection of a molecular genetic abnormality fully correlated with malignancy and the authors pointed out that the molecular studies would change the management in 5% of the AUS/FLUS cases and 25% of the FN/SFN cases in terms of expediting surgery and decreasing the need for repeat FNA.(15). However, molecular test has not been routinely utilized in the preoperative assessment of pediatric thyroid nodules in our institution. A few FLUS nodules received concurrent Afirma testing and the results did not always correlate well with the follow-up histology diagnoses. Our overall findings on the limited case cohort suggest that

Afirma testing may be helpful to avoid unnecessary surgery in some patients with thyroid nodules categorized into AUS/FLUS category, while pediatric thyroid nodules categorized as FN/SFN and SFM may be managed with surgery without preoperative Afirma testing.

In conclusion, based on a limited study cohort, indeterminate pediatric thyroid nodules have a higher malignant rate compared with that of adult, particularly for FLUS and SFM categories. Furthermore, NIFTP appears to be rare in the pediatric population.

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Legends:

Figure 1. Follicular lesion of undetermined significance case

A. Disorganized follicular epithelial groups, mild nuclear enlargement and dense colloid in the background (Diff-Quik stain, 100x).
B. Cytological atypia with nuclear enlargement, chromatin clearing, and nuclear membrane folds (Papanicolaou stain, 400x).

C. Follow-up surgical specimen showing papillary thyroid carcinoma, conventional type, with papillary projections and psammoma bodies. (H&E stain, 40x).

D. Nuclear features of classical papillary thyroid carcinoma, i.e. powdery chromatin, intranuclear grooves and pseudoinclusion (H&E stain, 400x).

Figure 2. Suspicious for follicular neoplasm case

A. Hypercellular sample with microfollicular pattern (Diff-Quik stain, 100x).

B. Nuclear enlargement with prominent nucleoli and oncocytic cytoplasm (Papanicolaou stain, 400x).

C. Follow up surgical excision demonstrating Papillary thyroid carcinoma with follicular growth pattern lacking well defined capsule in a lymphocytic thyroiditis background. (H&E stain, 40x).

D. Nuclear features of papillary thyroid carcinoma are evident. Please note the psammoma bodies, which also excludes this tumor from NIFTP category. (H&E stain, 400x).

Figure 3. Suspicious for malignancy case

A. ThinPrep slide demonstrating cellular aspirate showing fragments of highly atypical follicular epithelial cells (Papanicolaou stain, 100x).

B. The group of cells with nuclear size variation, irregular nuclear outlines, nuclear grooves and occasional nucleoli (Papanicolaou stain, 400x).

C. Surgical excision sample demonstrating conventional papillary thyroid carcinoma growth pattern. (H&E stain, 40x).

D. High magnification showing classical nuclear features of papillary thyroid carcinoma with grooves and intranuclear inclusion (H&E, 400x).

Table 1. Cytologic-histologic correlation in pediatric indeterminate thyroid nodules

Category	Histologic Diagnoses					Total
	NH	LT	FA	HCA	PTC	
FLUS	7	1	8	1	8	25
SFN	-	-	8	-	2	10
SFM	-	-	-	1	5	6
Total	7	1	16	2	15	41

FLUS: Follicular lesion of undetermined significance

SFN: Suspicious for follicular neoplasm

SFM: Suspicious for malignancy

NH: Nodular hyperplasia

LT: Lymphocytic thyroiditis

FA: Follicular adenoma

HCA: Hurthle cell carcinoma

PTC: Papillary thyroid carcinoma

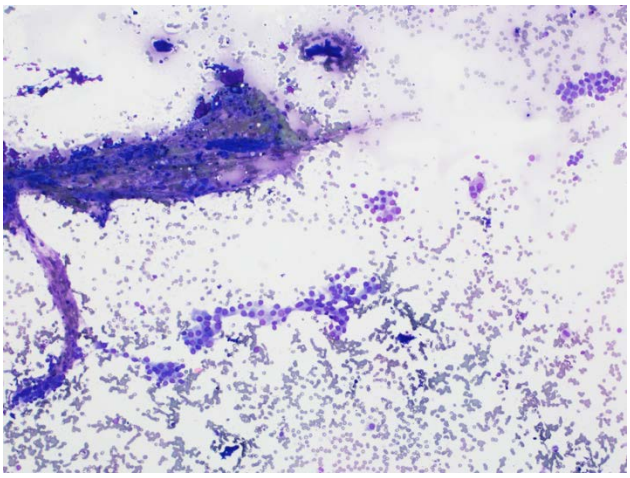
Table 2. Rate of histology-confirmed malignancy (%) in pediatric indeterminate thyroids from different institutions

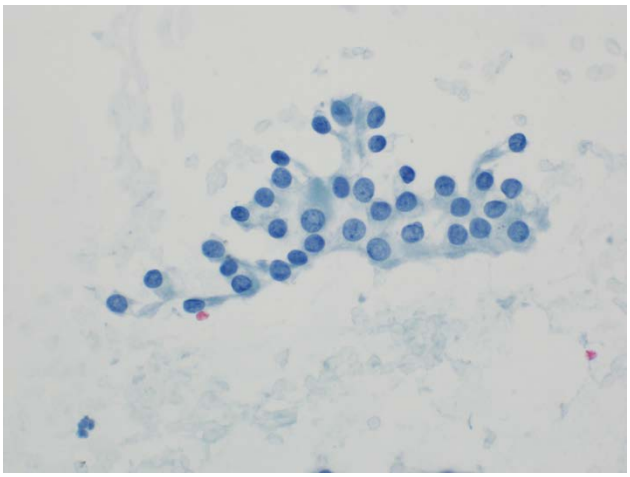
Studies	Current	Gupta	Smith	Rossi	Lale	Norlen	Partyka	Pantola
Year	present	2013	2013	2014	2015	2015	2016	2016
Categories								
AUS/FLUS	9/25 (36)	4/10 (40)	7/25 (28)	-	2/4 (50)	2/9 (22)	4/14 (29)	1/12 (8)
FN/SFN	2/10 (20)	6/6 (100)	11/19 (58)	-	7/18 (39)	4/4 (100)	4/7 (57)	1/10 (10)
SFM	6/6 (100)	4/10 (100)	6/6 (100)	9/11 (82)	4/4 (100)	3/3 (100)	3/3 (100)	2/2 (100)

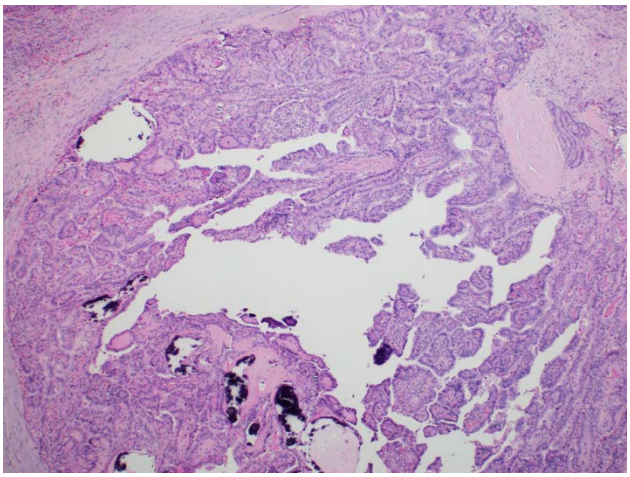
AUS/FLUS: Atypia of undetermined significance/Follicular lesion of undetermined significance

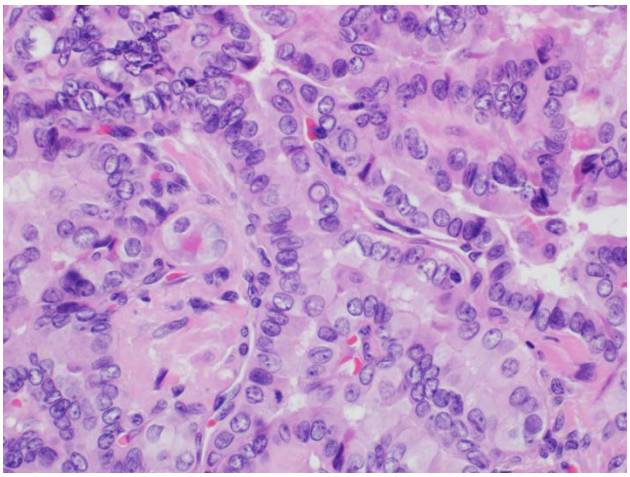
FN/SFN: Follicular neoplasm/Suspicious for follicular neoplasm

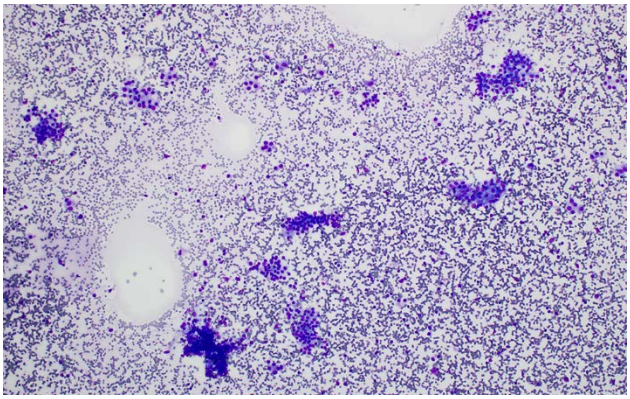
SFM: Suspicious for malignancy

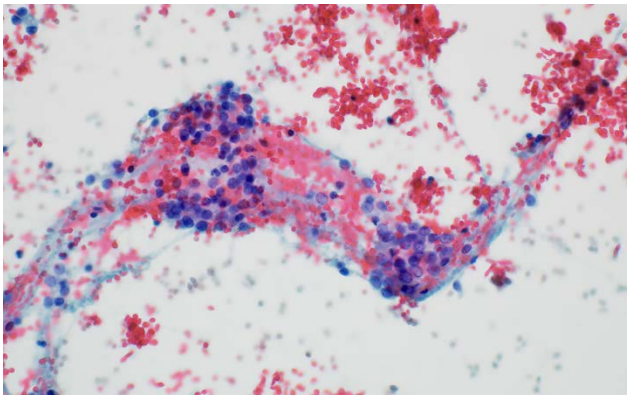


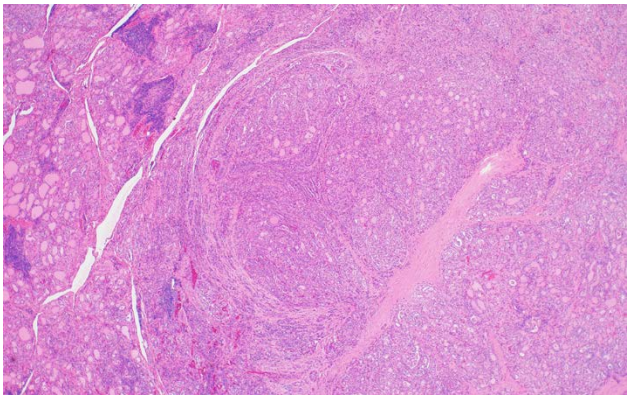


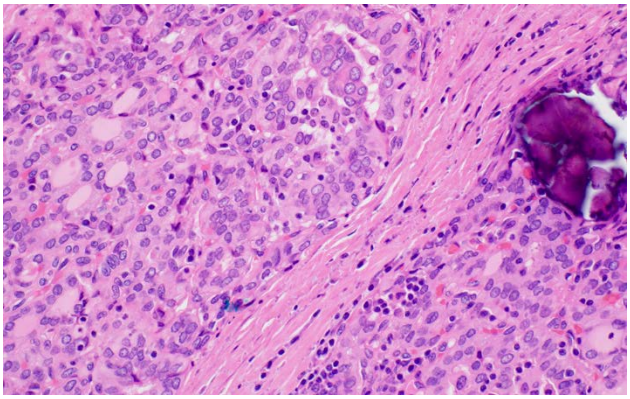


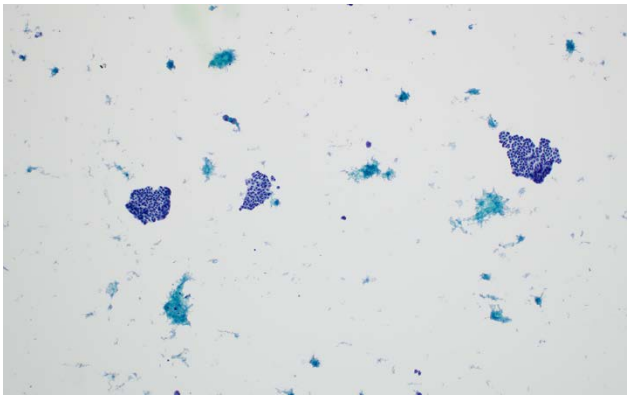


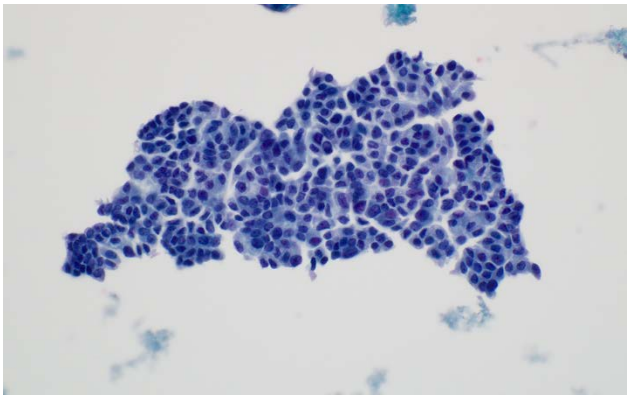


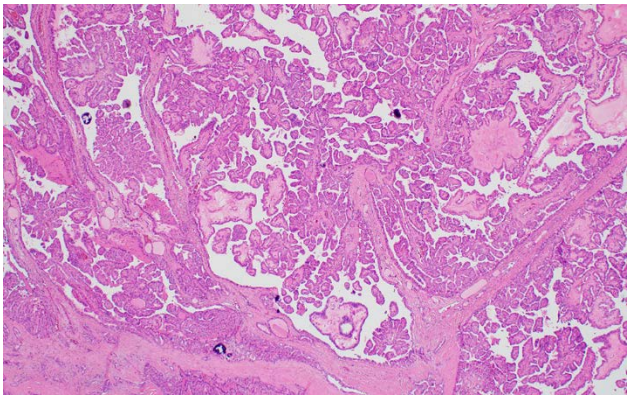


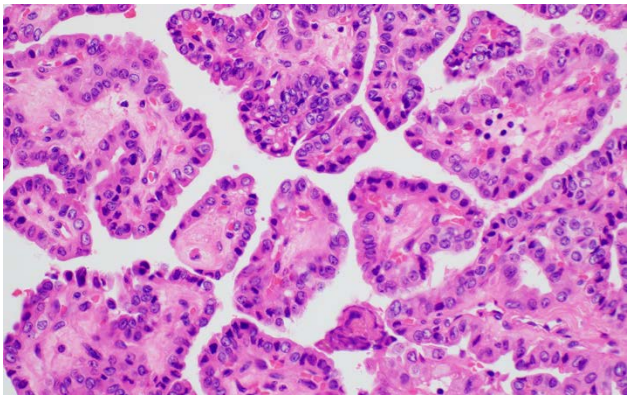


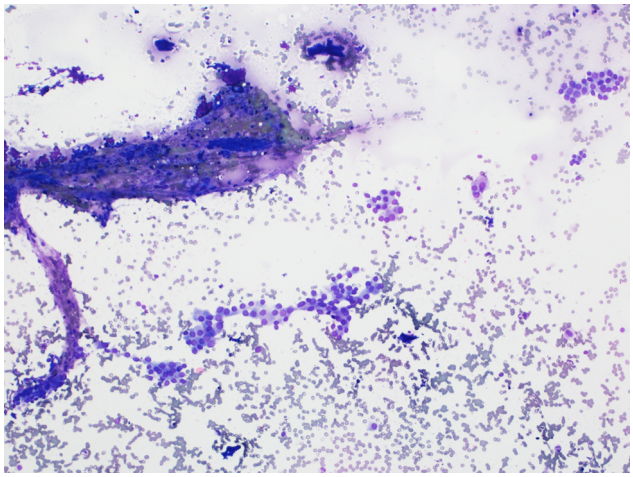












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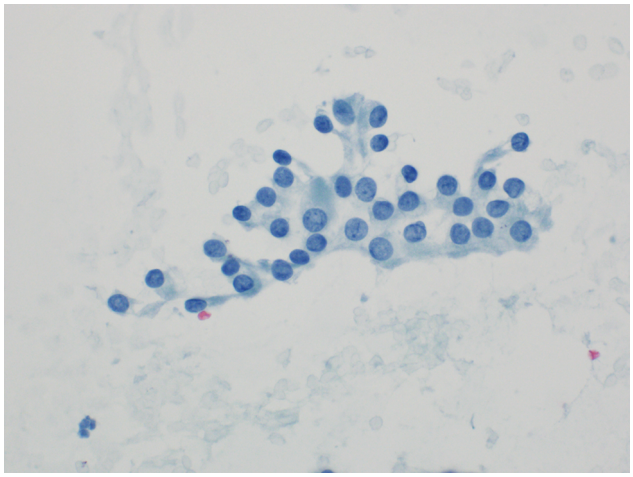

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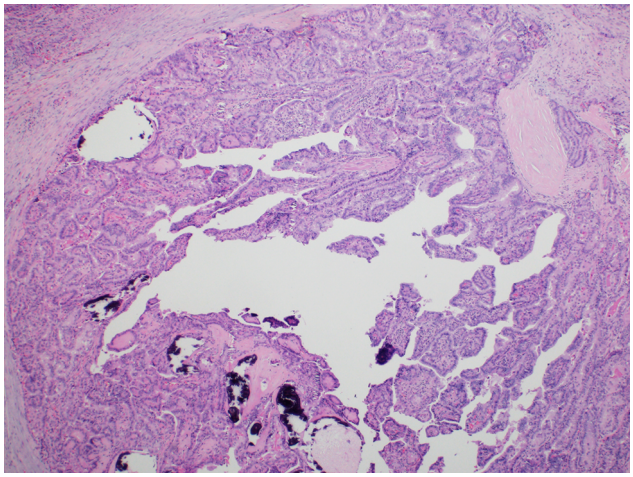

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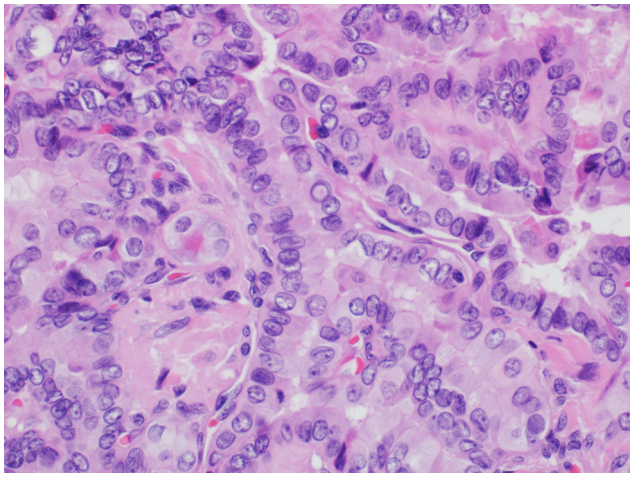

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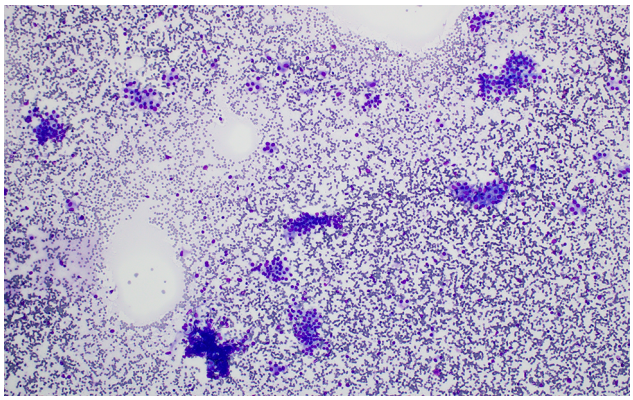

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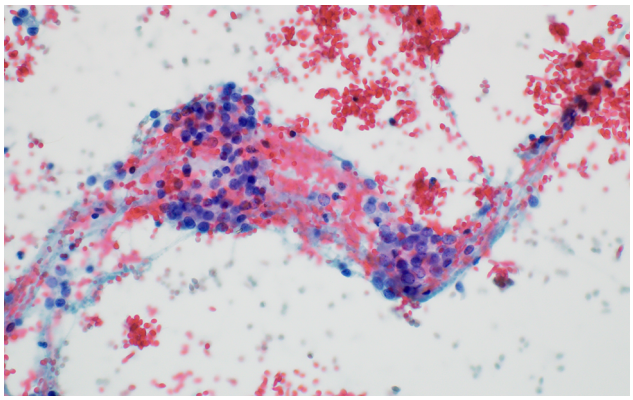

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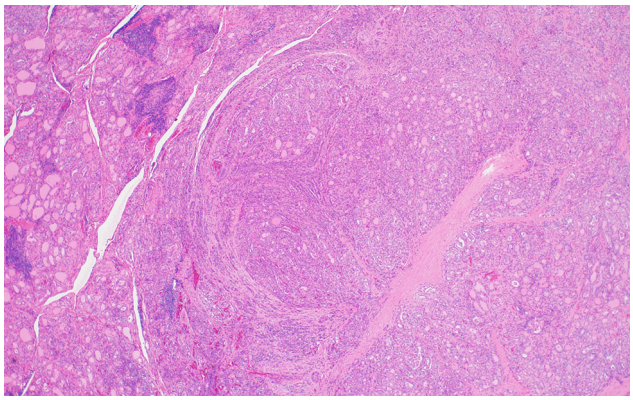

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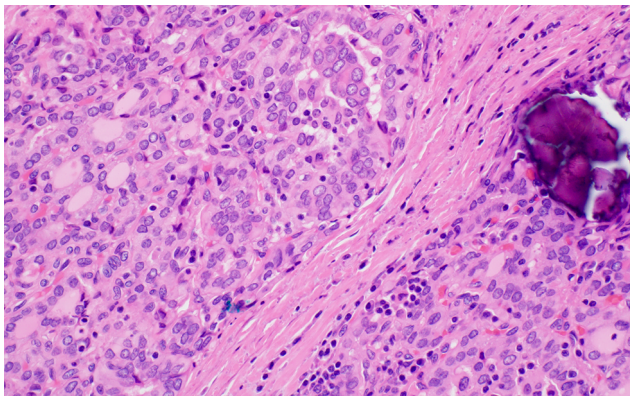

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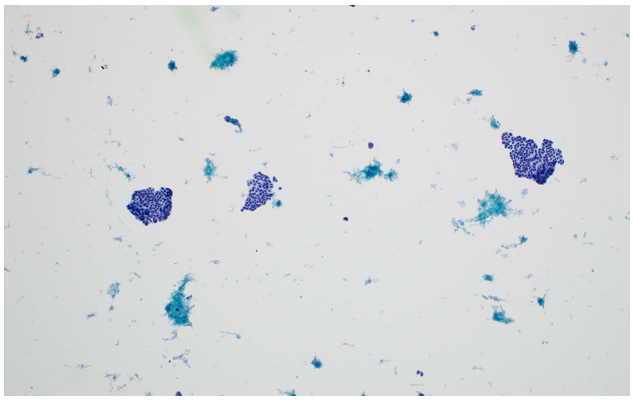

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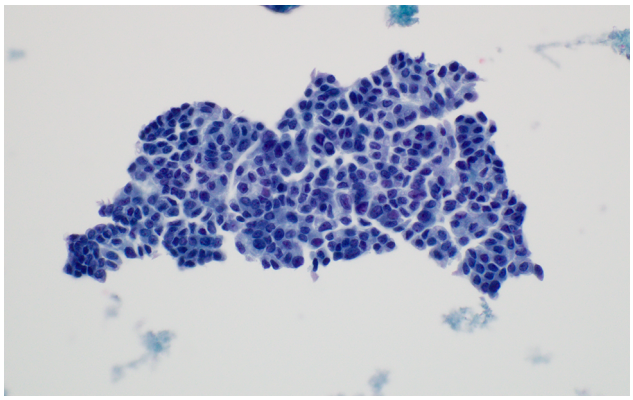

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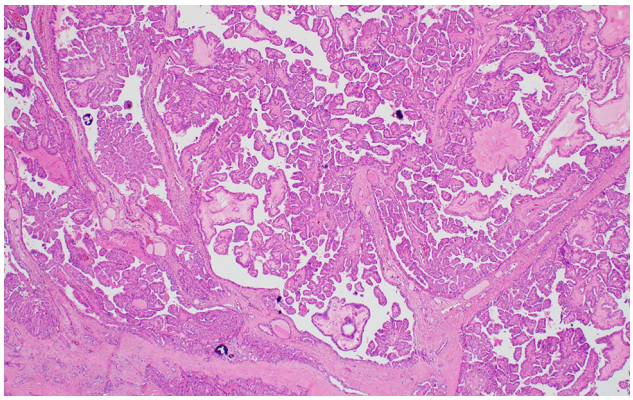

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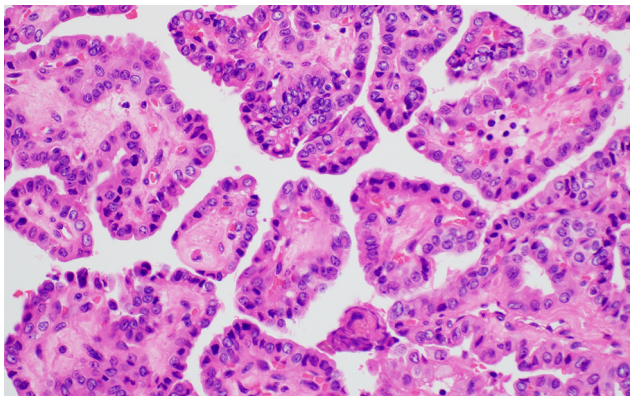

DC_24266_Fig3D.tif

Table 1. Cytologic-histologic correlation in pediatric indeterminate thyroid nodules

Category	Histologic Diagnoses					Total
	NH	LT	FA	HCA	PTC	
FLUS	7	1	8	1	8	25
SFN	-	-	8	-	2	10
SFM	-	-	-	1	5	6
Total	7	1	16	2	15	41

FLUS: Follicular lesion of undetermined significance

SFN: Suspicious for follicular neoplasm

SFM: Suspicious for malignancy

NH: Nodular hyperplasia

LT: Lymphocytic thyroiditis

FA: Follicular adenoma

HCA: Hurthle cell carcinoma

PTC: Papillary thyroid carcinoma

Table 2. Rate of histology-confirmed malignancy (%) in pediatric indeterminate thyroids from different institutions

Studies	Current	Gupta	Smith	Rossi	Lale	Norlen	Partyka	Pantola
Year	present	2013	2013	2014	2015	2015	2016	2016
Categories								
AUS/FLUS	9/25 (36)	4/10 (40)	7/25 (28)	-	2/4 (50)	2/9 (22)	4/14 (29)	1/12 (8)
FN/SFN	2/10 (20)	6/6 (100)	11/19 (58)	-	7/18 (39)	4/4 (100)	4/7 (57)	1/10 (10)
SFM	6/6 (100)	4/10 (100)	6/6 (100)	9/11 (82)	4/4 (100)	3/3 (100)	3/3 (100)	2/2 (100)

AUS/FLUS: Atypia of undetermined significance/Follicular lesion of undetermined significance

FN/SFN: Follicular neoplasm/Suspicious for follicular neoplasm

SFM: Suspicious for malignancy