Title

Diagnostic utility of fine needle aspiration cytology in pediatric thyroid nodules based on Bethesda Classification

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Authors

Jiang, Wen
Phillips, Susan A
Newbury, Robert O
et al.

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Abstract

Background
The Bethesda system for reporting cytopathology (TBSRTC) has been widely adopted in the management of thyroid nodules. Based on the limited pediatric data available, the implied malignancy risk for each of the categories may be significantly different in pediatrics versus adults, especially in the indeterminate categories (Bethesda Class III or IV). We aim to report the diagnostic accuracy of fine needle aspiration (FNA) biopsy at our institution based on the Bethesda system and the risk of malignancy in each category.

Methods
We retrospectively reviewed all patients who underwent a thyroid FNA at our tertiary pediatric hospital from 12/1/2002 to 11/30/2018. FNA results were classified according to TBSRTC. Patient demographics, cytology, histopathology, radiological and clinical follow-ups were examined.

Results
A total of 171 patients were included with 203 cytological samples. Average age at initial FNA was 14.7 years (range 6.9-18.6 years). The numbers of nodules reported for Bethesda categories I-VI were 29, 106, 22, 14, 6 and 26 respectively, and the rate of malignancy was: 13.8%, 4.7%, 22.7%, 35.7%, 83.3% and 100% respectively. Use of ultrasound guidance reduced the non-diagnostic rate from 38.1% to 11.5%. Introduction of on-site adequacy testing further reduced the non-diagnostic rate to 6.5% since 2014.

Conclusion
The risk of malignancy for thyroid nodules in this pediatric cohort is higher than reported in adults. However, rates described here are much closer to adult ranges than previously published pediatric cohorts. The addition of adequacy testing improved the non-diagnostic rate of FNA procedures performed with ultrasound guidance.

Keywords: Fine needle aspiration, cytology, pediatric, thyroid nodule, Bethesda classification

Introduction

The incidence of thyroid nodules in pediatrics is relatively low compared to adults, with a reported range of 1-2% (1,2). However, the incidence of thyroid cancer worldwide has been rising dramatically (3). According to the Surveillance, Epidemiology, and End Results (SEER) database, in the United States from 1974-2013, the overall incidence of thyroid cancer has increased 3% annually (4). With advances in ultrasound technology, our ability to detect thyroid nodules has improved over time. Recent studies suggest that the prevalence of pediatric thyroid nodules is much higher than previously estimated, with baseline incidence ranging from 0.64% to 2.69% (5). According to the American Thyroid Association (ATA) guideline, the diagnostic work-up requires ultrasound (US) imaging of thyroid nodules followed by fine needle aspiration (FNA) biopsy based on US characteristics and clinical context (6). Subsequent cytologic diagnosis plays a critical role distinguishing those that are benign and may be safely observed versus malignant nodules that require surgical intervention.

The Bethesda system of reporting thyroid cytopathology (TBSRTC) has been widely adopted by the thyroid community for the classification of cytologic diagnoses, ensuring consistent and comparable results across institutions. Since its initial publication in 2009 (7), there has been abundant literature in adults that link each diagnostic category to a well-defined range of malignancy risks as summarized in the most recent 2017 update (8). The estimated rates of malignancy in children however are not as well established. FNA also presents unique challenges in children with younger patients having difficulty tolerating the procedure without sedation as well as low volume of these procedures performed at pediatric centers. Rates of non-diagnostic samples are generally higher compared to adults (9). In the adult ATA guideline, indeterminate cytology generally warrants molecular testing or a repeat FNA (10). However, in children,

molecular testing has not been validated in large cohorts to be reliably utilized in clinical practice. Therefore, surgical lobectomy is recommended following an indeterminate cytology (6). Lastly, TBSRTC has not been as widely adopted in pediatric literature, resulting in a paucity of data with respect to the risk of malignancy, especially in the indeterminate categories (9,11). We report on our institutional experience with ultrasound guided FNA, diagnostic accuracy based on TBSRTC and the risk of malignancy in each category.

Methods

Subjects & Data collection

We obtained institutional review board approval for the retrospective review of all individuals ≤18 years that underwent a thyroid FNA from 12/1/2002 to 11/30/2018 at Rady Children's Hospital in San Diego. FNA results were categorized according to the Bethesda classification: Non-diagnostic (I), Benign (II), Atypia of undetermined significance (AUS) or Follicular lesion of undetermined significance (FLUS) (III), Follicular neoplasm (FN) or Suspicious for Follicular Neoplasm (SFN) (IV), Suspicious for malignancy (V), and Malignant (VI). We recorded patient's age, sex, ethnicity, cytologic diagnosis, surgical histopathology, and any available radiologic and clinical follow-ups.

Biopsy Procedure

Some of the earlier biopsies were performed without ultrasound guidance. Beginning in 2012, all FNA procedures were performed using US guidance by one of three experienced pediatric radiologists using a LOGIQe9 US system (GE Healthcare, Chicago, IL). Procedures were performed with either local or general anesthesia when clinically indicated (e.g. younger patients, developmental delay). High-frequency linear transducers optimized for soft tissue

technique were used, either the ML6-15 probe or the L8-18i probe in smaller patients. Under US guidance, a 25G needle was advanced into the nodule, and samples were obtained using capillary action or gentle aspiration technique. Four to five passes were performed for each nodule, or until the pathologist confirmed adequacy. For predominantly cystic nodules, the fluid was aspirated to completion and submitted for cytologic analysis.

Cytologic Methods

The pathologist prepared 3-5 slides per pass, depending on the volume received. Starting in 2014, we instituted adequacy testing in the biopsy suite where one smear was air dried and stained with DiffQuik per standard protocol to assess for adequacy prior to conclusion of the procedure. Minimum adequacy is defined by at least 6 groups of 10 well-visualized follicular cells according to TBSRTC (7). Additional passes were performed when necessary. The other slides were either alcohol fixed and stained with Papanicolaou or Hematoxylin and Eosin stain or air dried and Wright stained. Given the relatively low volume of biopsies, it has been our hospital policy that after pathologic analysis, all cytology slides were sent to University of California San Diego (UCSD) adult cytologists for second-opinion confirmation. We reported on the concordance of the diagnoses.

Statistical Analyses

Malignancy rate for each cytologic category was defined as the number of histologically malignant nodules divided by the total number of nodules in that category. Chi square test was used to compare the rate of non-diagnostic samples between the FNA performed with or without ultrasound, as well as before and after the use of on-site adequacy assessment. P-values < 0.05 were considered significant.

Results

A total of 171 patients with 203 biopsied nodules were included in this cohort. Patient characteristics are outlined in Table 1. The average age was 14.7 years (range 6.9-18.6 years). The cohort was comprised of predominantly female (81.9%), children older than 10 (93%), and predominantly of Hispanic ethnicity (48%). Thyroid antibody data was available for 108 patients, and 36 (33.3%) had at least one positive antibody, consistent with Hashimoto's thyroiditis.

Table 2 outlines the cytologic diagnoses according to TBSRTC. Data are presented as the number of biopsies in each category and as a percentage of the entire cohort. The malignancy risk is expressed as the percentage of malignant cases within each category. Of the 171 patients, 50 had a malignant diagnosis on surgical pathology, resulting in an overall rate of malignancy of 29.2% for the entire cohort.

Table 3 provides the clinical follow-up data with subsequent steps in diagnosis and management after the initial FNA. There were 28 patients in category I. Of the 28 patients, 2 were lost to follow-up, 7 chose observation without repeat FNA, and 12 had repeat biopsies. Of these, one cystic nodule remained non-diagnostic, but the nodule resolved on follow-up US. Of the remaining 11 repeat biopsies, 8 were benign, 1 was FLUS and 2 were malignant. All three patients with non-benign cytology underwent surgery. These combined with 9 other patients resulted in a total of 12 patients with histologic follow-up for category I.

In category II, of the 75 patients, six were lost to follow-up. Fourteen patients (18.7%) underwent repeat FNA during the study period when indicated, with 11patients having two biopsies and 3 patients having three biopsies each. One of the repeat biopsies was positive for malignancy and the patient underwent total thyroidectomy. All the remaining repeat biopsies stayed benign. Nineteen patients in this category underwent surgery with 5 malignancies on final

histopathology. Of the 19 that underwent surgery, five patients had nodules ≥ 4cm, and six had nodules between 3-4cm. Among the 5 malignancies, one nodule was ≥ 4cm, and two were between 3-4cm. The mean follow-up for patients without surgery was 1.7 years with a range of 8 months to 6 years.

There were 22 patients with category III cytology. Two patients transferred care to adult facility and were lost to follow-up. Two patients declined surgery and elected to be observed with serial US. Two patients elected for repeat biopsy, resulting both in benign cytology. Sixteen patients underwent surgical lobectomy with 5 malignancies detected, and all 5 underwent completion thyroidectomy.

In category IV, there were 14 patients and 13 of them underwent surgery, and one patient elected to monitor the nodule with serial US. That patient had a 2.4 cm hypoechoic homogeneous nodule without any suspicious features on US. The nodule was unchanged at the last follow-up 45 months after the initial biopsy. The remaining 13 patients underwent diagnostic lobectomy with 5 malignancies, and all underwent subsequent completion thyroidectomy.

A total of 6 patients had category V cytology. Five patients underwent total thyroidectomy. One patient who had bilateral nodules with benign cytology on the left, and suspicious for malignancy on the right, elected to have a right lobectomy. Histology was benign nodular goiter, and the left side was followed clinically.

In the final Bethesda category VI, there were 26 patients, and all underwent total thyroidectomy and 19 had either central and/or lateral neck dissection due to clinical and/or radiographically positive nodal disease. All were positive for malignancy on the final pathology.

Table 4 details the histopathologic diagnoses based on surgical specimens. The malignant pathologies included papillary thyroid carcinoma (PTC), follicular variant of papillary thyroid

carcinoma (FVPTC) and follicular carcinoma (FC). PTC comprised of the majority of the malignancies, 35/50 or 70% (Table 4). As expected, those with FN or SFN cytology, histology was mostly follicular carcinoma (4/5) and the one remaining case was FVPTC. Category III had 3 PTC and 2 FVPTC, whereas category I and II had a mix of all three malignant histologic types. The overall non-diagnostic rate for the entire cohort was 14.3%. Prior to 2011, before the publication of the ATA guideline, ultrasound guidance was not consistently used. Among the 203 biopsies, 21 were performed without US guidance. Of these, the non-diagnostic rate was 38.1% which is significantly higher than the non-diagnostic rate of 11.5% for the 182 performed with US guidance ($p=10^{-10}$).

In order to further reduce the non-diagnostic rate; starting in 2014 we instituted on-site adequacy testing where the pathologist reported the adequacy of the sample prior to the conclusion of the procedure. A total of 89 biopsies were performed under US guidance prior 2014 with a non-diagnostic rate of 16.9%, which is significantly higher than the 6.5% in the 93 cases performed after 2014 ($p=0.007$) (Figure 1).

When we examined the concordance rate of the second opinion diagnoses, there was only one case where the Rady and UCSD cytologic diagnoses differed. The initial cytology was read as category V, suspicious for malignancy and UCSD reported it as category IV, follicular neoplasm. That patient elected to have a total thyroidectomy and final pathology was follicular carcinoma with histologic features of angio-invasion.

Discussion

For the initial evaluation of thyroid nodules, FNA has proven to be a rapid and reliable way to achieve a possible diagnosis that guides subsequent medical and surgical management. First published in 2009 and updated in 2017, TBSRTC has enabled clinicians and researchers to

gather and publish a large body of information regarding the implied risk of malignancy in adults. On the other hand, the adoption of TBSRTC has been slow and somewhat variable in pediatrics despite recommendations by the ATA (4). Data is relatively limited regarding the risk of malignancy in pediatrics with most series being small with reported rates significantly higher than adults (12,13).

This case series represents a fairly large cohort of pediatric patients with thyroid nodules with complete cytologic diagnoses and subsequent histologic follow-up. The mean age of 14.7 years for this cohort is almost identical to other pediatric series with predominantly adolescent subjects (9,11). The distribution of the cytologic diagnosis according to TBSRTC also has similarities to previous pediatric series with the majority being benign nodules, 52.2% (9,11,14). Although slightly higher than the rate of 0-3% reported in adults (8), the malignancy rate is still quite low at 4.7% for category II. Many patients who elected to proceed with surgery had large nodules. Although in the past, the accuracy of FNA in nodules larger than 4cm were questionable (15), more recent meta-analysis in adults reported that rate of malignancy and false-negative FNA in most studies are not higher in larger nodules (16). We believe that a benign cytologic diagnosis is quite reliable, and with adequate follow-up, these patients may be safely observed. There is a debate on how aggressive benign nodules should be followed in a pediatric patient, but the overall literature is reassuring that malignancy rate remains low over time (17).

Cytology in both categories V and VI were quite accurate in this series. There were no false positives when PTC features were seen on cytology (VI), and there was only one benign case among category V. The data supports the validity of our cytologic interpretations, and a recommendation of up-front total thyroidectomy as the initial surgical treatment.

The indeterminate categories of AUS/FLUS (III) and FN (IV) have always presented as diagnostic and management challenges both in adults and pediatrics. These two categories together accounted for only 17.7% of all the biopsies in this cohort which is comparable to many published large adult studies (18). According to a meta-analysis by Bongiovanni et al examining 8 articles with 25,445 FNA cases in adults, AUS/FLUS accounted for 9.6% and FN accounted for 10.1% of the total cases (19). Older pediatric series have reported significantly higher rates of indeterminate cytology which makes generalization of the result and subsequent management challenging (20). The malignancy rate of 22.7% for AUS/FLUS in this cohort is slightly higher than the reported adult range of 6-18%, and the malignancy rate of 35.7% for FN falls within the range of 10-40% referenced for adults according to TBSRTC (8). This is in contrast to the much higher malignancy rates reported in previous pediatric series. Cherella et al reported a malignancy rate of 44% for AUS and 71% for FN in their cohort which is almost the same as their suspicious for malignancy category (9). Amirazodi et al reported a 67% malignancy for "atypical" cytology, which combined categories III and IV (11). However, the rate of surgical resection for atypical cytology in that cohort was only 52.9%. The higher malignancy rate may reflect a surgical selection bias, with those who underwent surgery having more concerning clinical characteristics or suspicious sonographic features. In this current cohort, majority of the patients underwent surgical lobectomy as recommended by the ATA guideline: 16/22 (72.7%) patients with AUS/FLUS and 13/14 (92.9%) patients with FN. Therefore, the rate of malignancy is likely an accurate estimate of the true risk associated with these two categories in this cohort. The histopathology of the FN category was either FC or FVPTC which supports the validity of the cytologic interpretation.

Studies in adults have shown that molecular testing may be valuable in the management of thyroid nodules with indeterminate cytology (21, 22). Many report using gene expression classifiers as "rule out" tests in adults with indeterminate nodules where a benign molecular profile may avoid unnecessary surgery (22). However, with the malignancy rates between 22.7-35.7% for categories III and IV, a gene sequencing "rule in" test would be much more appropriate to determine which patients would benefit from total thyroidectomy instead of a lobectomy as the initial surgery (21, 23). Prospective pediatric studies with molecular testing on indeterminate FNA samples would be necessary to determine the most appropriate role of molecular testing in improving the diagnostic accuracy of FNA in children.

For the non-diagnostic samples, even though the TBSRTC update gave a malignancy rate of 5-10%, a large meta-analysis suggests that malignancy rate in adults may be as high 16.8% (18). The reported rate in this cohort (13.8%) falls well within this range, also comparable to rates reported in previous pediatric series (9,11,14). Adequate follow-up is essential in this population since the risk of malignancy is not trivial. Repeat FNA should be strongly recommended and surgical diagnostic lobectomy should be performed if the repeat biopsy fails to achieve an adequate diagnosis.

Our overall rate of non-diagnostic samples was 14.3% which is comparable to recent pediatric series (9), and lower than many of the earlier pediatric cohorts (11,12,13). The significantly higher rate of non-diagnostic biopsies performed without ultrasound guidance during the early years supports the ATA recommendations of routine use of ultrasound during the FNA process. Since 2014, the utilization of on-site cytologic adequacy assessment has been able to significantly reduce our non-diagnostic rate to the current 6.5%, which is comparable to rates published by high volume adult centers (18). On-site evaluation for thyroid FNA has been

shown to significantly improve specimen adequacy with a decreased number of passes necessary to achieve a diagnostic result (24, 25). The addition of adequacy assessment was a significant quality improvement measure for us especially in the context of a lower incidence of thyroid nodules in pediatric patients. Furthermore, the process of second-opinion confirmation gave us additional reassurance, drawing on the expertise of our high-volume adult cytopathologists. Although we reported an excellent concordance rate, in head and neck pathology, thyroid has the highest rate of diagnostic disagreement with considerable inter- and intra-observer variability. Second opinion reviews in thyroid cytology have been shown to improve diagnostic accuracy and decrease the rate of indeterminate cases that may significantly change clinical management (26, 27).

This study has several limitations. Although this is a relatively robust pediatric cohort, numbers are still small compared to adults. The follow-up period is relatively short with many patients transitioning to adult care soon after treatment, especially when diagnosed in late adolescence. Because of the nature of a tertiary referral center, selection bias exists where patients with nodules that have more suspicious clinical or radiographic features may be preferentially referred to us causing an overestimation of the malignancy rates. Given our proximity to the border between the United States and Mexico, Hispanic patients of Mexican descent comprised a significant portion of our cohort. Therefore, the malignancy rates described here may not be representative of pediatric populations in other regions of the country with different ethnic compositions.

In conclusion, our findings demonstrated that US guided FNA performed at a pediatric tertiary center provides reliable and accurate cytologic diagnoses in pediatric patients presenting with thyroid nodules despite significantly lower volumes when compared to adult centers. Although

the malignancy rates reported here are higher than adult ranges in several categories, they are much closer to TBSRTC expected rates than prior pediatric series (9,11,12,13).

The routine use of real-time ultrasonography combined with on-site adequacy assessment has helped decrease the overall non-diagnostic rate over the study period. These findings support the current ATA recommendation outlined for the management of pediatric nodules. Future studies examining the role of molecular testing on indeterminate cytologic samples may further improve the diagnostic accuracy of thyroid FNA in children.

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Table 1. Patient characteristics

Characteristic	No. (%)
Age at Diagnosis (years)	
Mean (SD) [range]	14.7 (±2.7) [6.9-18.6]
Age ≤ 10	12 (7.0)
Gender	
Male / Female	31(18.1) / 140 (81.9)
Ethnicity/race	
Caucasian/White	73 (42.7)
Hispanic (89.3% Female)	82 (48.0)
Other	16 (11.3)
Nodule size, cm	
< 2	102 (50.2)
2-4	81 (39.9)
> 4	20 (9.9)

Table 2: Cytologic categories of FNAB according to Bethesda Classification

	No. of Biopsies	Malignancy		TBSRTC* 2017 (adult)
Diagnostic Category	Total (%)	Cases	Risk (%)	Risk (%)
I Non-diagnostic	29 (14.3)	4	13.8	5-10
II Benign	106 (52.2)	5	4.7	0-3
III AUS or FLUS	22 (10.8)	5	22.7	6-18
IV Follicular neoplasm	14 (6.9)	5	35.7	10-40
V Suspicious for Malignancy	6 (3.0)	5	83.3	45-60
VI Malignant	26 (12.8)	26	100	94-96
Total	203 (100)	51		

* According to 2017 TBSRTC with reference risk used here assuming NIFTP ≠ CA, NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features (8).

Table 3: Patient clinical and surgical follow-up

		Total Patients	Repeat FNA	Surgery	Observation	Lost to Follow-up
Diagnostic Category						
I	Initial FNA	28		7	7*	2
	2nd FNA		12	5	7	
II	Initial FNA	75		18	37	6
	2nd FNA		14	1	10	
	3rd FNA		3		3	
III	Initial FNA	22		16	2	2
	2nd FNA		2		2	
IV		14		13	1	
V		6		6		
VI		26		26		
	Total	171		92		

* 6 of the 7 were complete cystic nodules that resolved after the FNA

Table 4: Surgical Histopathology

Diagnostic Category	I	II	III	IV	V	VI
FNA	Non-diagnostic	Benign	AUS/ FLUS	FN/SFN	Suspicious	Malignant
Histopathology						
Total Cases	12	19	16	13	6	26
Follicular Adenoma	1	4	3			
Benign Colloid Nodules		2			1	
Nodular Hyperplasia	4	3	5	3		
Lymphocytic thyroiditis	2	3	2	4		
Hürthle cell adenoma		1	1	1		
Benign epithelial cyst	1	1				
Papillary carcinoma	3	3	3		5	22
Follicular variant PTC		1	2	1		3
Follicular carcinoma	1	2*		4		1†

* One patient had FC with an incidental focus of papillary microcarcinoma in the contralateral lobe which was not counted as a PTC nodule

† Second opinion cytology disagreed with original diagnosis of papillary thyroid carcinoma, and called follicular neoplasm, with final pathology being follicular carcinoma

Figure 1: Non-diagnostic (ND) rate of 19.1% prior to 2014 is significantly higher than the 6.5% after 2014 when on-site adequacy testing was instituted. (p=0.002)