TITLE:

Histologic and Clinical Follow-up of Thyroid Fine Needle Aspirates in Pediatric Patients

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RUNNING TITLE: Pediatric thyroid FNA

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Precis: In our experience, the risk of malignancy of thyroid FNA for the pediatric population (≤18 years old), not including papillary microcarcinoma, was 2% for benign aspirates, 21% for AUS, 57% for FN, and 100% for suspicious or malignant aspirates.

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ABSTRACT:

BACKGROUND: Although fine needle aspiration (FNA) has an important role in evaluating thyroid nodules in adults, there is little published data regarding its utility in the pediatric population.

METHODS: A retrospective analysis of thyroid FNAs on patients ≤18 years of age at two institutions was conducted. Aspirates were retrospectively categorized using the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). These diagnoses were then correlated with either final histopathology or clinical follow-up.

RESULTS: A total of 186 thyroid FNAs from 154 patients (122 females, 32 males), ranging from 9 months to 18 years (median 16 years, mean 14 years), were identified. FNA was performed to evaluate one to three nodules for each patient. Aspirates were classified as follows: non-diagnostic (n=27), benign (n=114), atypia of undetermined significance (AUS, n=21), follicular neoplasm (FN, n=8), suspicious for malignancy (n=3), and malignant (n=13). 61 samples had histologic correlation, 68 were followed clinically for ≥2 years, and 57 had either no follow-up or were followed for <2 years. For statistical purposes, FNA diagnoses of suspicious and malignant were considered positive, and benign lesions were negative. The accuracy was 99%, and the sensitivity and specificity were 94% and 100%, respectively. The risk of malignancy, not including papillary microcarcinoma, was 2% for benign aspirates, 21% for AUS, 57% for FN, and 100% for suspicious or malignant aspirates.

CONCLUSIONS: This analysis demonstrates that FNA is a sensitive and highly specific modality for evaluating thyroid nodules in pediatric patients. Each diagnostic category can facilitate communication and guide appropriate management.

KEYWORDS: thyroid, FNA, cytology, the Bethesda System, pediatric

TEXT:

Background:

Thyroid nodules are relatively uncommon in the pediatric population, with an estimated prevalence ranging from 1-2%.[1,2] However, the rate of malignancy in these nodules is higher in children compared to adults.[3-7] The average incidence of thyroid carcinoma in patients with thyroid nodules ranges from 9.2-50% in various studies with an overall reported risk of 26.4%.[8] This data can lead to a more aggressive approach to the clinical management of thyroid nodules in pediatric patients. Total thyroidectomies and diagnostic lobectomies are associated with an inherent risk of complications. Thyroid fine needle aspiration (FNA) has gained widespread acceptance as a useful modality for selecting appropriate patients for surgery while also identifying those who can be safely monitored by clinical follow-up. FNA has an important and proven role in evaluating thyroid nodules in adults, but it has been used less extensively in children. There is very little published data regarding its diagnostic utility in the pediatric population. Despite some concerns regarding its limitations, FNA is a safe and effective method, and it can be utilized to guide clinical decisions.[9] FNA should play a central role in the assessment and management of pediatric patients who present with thyroid nodules.

MATERIALS AND METHODS:

The study was approved by the Institutional Review Boards of Indiana University and University of California, Davis (UC Davis). A retrospective analysis of thyroid FNAs performed at Indiana University Health (IU Health) and UC Davis Medical Center on patients ≤18 years of age was conducted. It spanned a 20-year period from 1995-2014 at IU Health and a 10-year period from 2005-2014 at UC Davis Medical Center. All aspirates were retrospectively categorized into six groups using the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC).[10] A computer search of the anatomic pathology archives and the electronic medical record was performed to document the final histopathology of patients who underwent surgery. Also, the electronic medical record was utilized to track those patients who were monitored with close clinical follow-up alone. Clinical follow-up

consisted of neck ultrasounds and clinic notes with documented histories and physical examinations. The cytologic diagnoses were then correlated either with the pathology reports or with the clinical follow-up.

RESULTS:

A total of 186 thyroid FNA samples from 154 patients (122 females, 32 males) with an age range of 9 months to 18 years (median 16 years, mean 14 years) were identified at IU Health and UC Davis Medical Center. FNAs were performed to evaluate one to three nodules for each patient. Among these subjects, 127 patients had 1 nodule with 1 FNA performed. 10 patients had 1 nodule with 1 initial FNA and 1 repeat FNA. 12 patients had 2 nodules with a single FNA performed on each nodule. Also, 1 patient had 2 nodules with an initial FNA on each nodule and 1 repeat FNA on one nodule. Lastly, 4 patients had 3 nodules with a separate FNA on each nodule. Among 11 patients with repeat FNA, the results showed 3 patients with a benign diagnosis in both initial and repeat aspirates. 7 patients were non-diagnostic on initial aspirates and benign on follow-up, and 1 patient showed benign on initial aspirate and AUS on repeat FNA. Surgical follow-up revealed a benign nodule in this patient who was diagnosed AUS on repeat FNA.

The aspirates were classified according to TBSRTC as follows: non-diagnostic (n=27, 14.5%), benign (n=114, 61.3%), atypia of undetermined significance (AUS, n=21, 11.3%), follicular neoplasm (FN, n=8, 4.3%), suspicious for malignancy (n=3, 1.6%), and malignant (n=13, 7.0%). Overall, 61 (32.8%) FNA samples had surgical follow-up with histologic correlation, and 68 (36.6%) FNAs were followed clinically for ≥2 years. 57 (30.6%) FNAs had either no follow-up or were followed for <2 years (Table 1).

For statistical purposes, FNA diagnoses of suspicious and malignant were categorized as positive, and all benign lesions were designated as negative. Clinical follow-up for ≥2 years with no documented

change in physical exam or neck ultrasound was considered a benign result. Also, those patients with no follow-up, follow-up for <2 years, or increased nodule size on ultrasound were not included in these calculations. Among the cases with surgical correlation, the pathology reports showed benign thyroid disease, follicular adenoma, papillary microcarcinoma, and malignancy (Table 2).

The overall accuracy of thyroid FNA in this population was found to be 99%, and the overall sensitivity and specificity were 94% and 100%, respectively. The risk of neoplasm was 9% for benign aspirates, 53% for AUS, 100% for FN, and 100% for suspicious or malignant aspirates (Figure 1). The risk of malignancy, not including papillary microcarcinoma, was 2% for benign aspirates, 21% for AUS, 57% for FN, and 100% for suspicious or malignant aspirates (Figure 1). The risk of malignancy including papillary microcarcinoma was 2% for benign aspirates, 26% for AUS, 57% for FN, and 100% for suspicious or malignant aspirates.

Among the 25 surgical results of malignancy, there were 18 cases (72%) of papillary thyroid carcinoma and 4 cases (16%) of follicular variant of papillary thyroid carcinoma. Two cases (8%) showed follicular carcinoma, and one case (4%) demonstrated metastatic germ cell tumor (Table 3).

DISCUSSION:

This retrospective analysis demonstrates that FNA is a sensitive and highly specific diagnostic modality for evaluating thyroid nodules found in pediatric patients. There is little data published on the use of FNA in children, and the available reports comprise only small patient cohorts. In our analysis, the sensitivity of thyroid FNA was 94%, and this is in agreement with previously published data showing a sensitivity ranging from 60-100%. Also, the specificity was 100%, which is concordant with reports of specificity ranging from 90-95%.[11-14] There is interest in refining the diagnostic approach to pediatric thyroid nodules, and this analysis lends support to that growing literature.

The overwhelming majority of our patients with a benign diagnosis by FNA were monitored with clinical follow-up alone. There was a 2% risk of malignancy and a 9% risk of neoplasm among those patients with benign FNA diagnoses who subsequently underwent surgery or clinical follow-up for more than two years. With no documented changes in physical exam and/or neck ultrasound, there is some credence to monitoring these patients with clinical follow-up alone. On the opposite end of the spectrum, all of the patients with a suspicious or malignant aspirate had surgery. There was a 100% risk of neoplasm and a 100% risk of malignancy in this subset of patients.

Twenty-seven patients (14.5%) had a non-diagnostic aspirate in our study. Seven of these patients had repeat FNA and showed benign in the follow-up aspirates. A meta-analysis found 1.8% to 23.6% of all thyroid FNAs were non-diagnostic with an overall value of 12.9%.[15] It seems that our non-diagnostic rate is slightly higher, and this may be associated with the focus on the pediatric population.

The indeterminate categories of AUS and FN can often lead to uncertainties in clinical management. This retrospective analysis illustrates a 21% (excluding papillary microcarcinoma) and 26% (including papillary microcarcinoma) risk of malignancy in the group of AUS aspirates and a 57% risk of malignancy in the group of FN aspirates. A meta-analysis[15] showed FNA cases in the AUS category ranged from 3% to 27.2% with an overall value of 9.6% and an overall rate of malignancy of 15.9%. The FNA cases in the FN category ranged from 1.2% to 25.3% with an overall value of 10.1% and a risk of malignancy of 26.1%. There is an incremental risk of malignancy for the pediatric population within these categories, and this is consistent with most other reports in the literature.[6,16-18] FNA can be an effective means for clinicians to risk stratify thyroid nodules.[6] Overall, the accuracy of the thyroid FNA was 99% in this analysis, which is slightly superior compared to previous reports of 70-95% accuracy.[2,4,12]

The clinical management of thyroid nodules varies across institutions, and FNA is often underutilized in the pediatric population. Since the risk of malignancy is high in these lesions, a systematic approach to the management of these patients is warranted.[3] Total thyroidectomies and diagnostic lobectomies are established components of the multidisciplinary management of children who present with thyroid nodules. However, these surgical procedures carry a risk for perioperative complications, including hypoparathyroidism and recurrent laryngeal nerve injury.[4,19] In patients younger than 10 years of age, the risk of complications increases with repeat surgery.[16] Thyroid FNA has the potential to decrease the number of patients undergoing unnecessary operations while simultaneously increasing the percentage of patients with malignancy who are referred for surgery.[20,21]

FNA is a highly accurate, minimally invasive procedure that can add valuable information for clinical management of patients with thyroid nodules. This diagnostic technique can be safely and easily used in children with minimal discomfort.[5,12] It is well tolerated and can be performed with ultrasound guidance, local anesthetics, and pediatric distraction techniques.[5] This study shows that FNA is a sensitive and highly specific tool for the evaluation of thyroid lesions occurring in children. If a nodule is found to be malignant on FNA, the patient can be referred for definitive surgery, and the need for an intraoperative frozen section is usually obviated. When the cytology is benign, our results demonstrate a low risk of malignancy, and it is therefore reasonable to manage these patients with clinical follow-up alone. Additionally, if the FNA is indeterminate, our analysis shows a distinct incremental risk of malignancy in these categories. Although not performed in our series, molecular testing was proven to have value in management of these indeterminate thyroid aspirates in pediatric patients.[17] Detection of a molecular genetic abnormality is correlated with a 100% malignancy rate and would enable these patients to go directly to thyroidectomy without a need for repeat FNA. The FNA diagnosis should be correlated with nodule size, clinical symptoms, and radiologic findings.[6] Each diagnostic category can

hopefully facilitate communication with physicians and guide appropriate clinical management in these pediatric patients.

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FIGURE LEGEND:

Figure 1 Risk of Neoplasm and Malignancy associated with each Diagnostic Category