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Thyroid Nodules in Children and Adolescents

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Introduction

Thyroid nodules (TN) and differentiated thyroid cancers (DTC) are reported in increasing numbers of children and adolescents. In part, this results from increased use of thyroid ultrasound (US) surveillance and diagnosis using fine needle aspiration (FNA)[1]. However, large TN and DTC are also increasingly common, suggesting a true rise in incidence[2]. Several factors increase the risk for TN, including genetic syndromes, radiation exposure, iodine deficiency, autoimmune thyroid disease (AIT), and Graves' disease (GD). This review will address recent advances in knowledge regarding TN prevalence, risk factors, differential diagnosis, evaluation, and management.

Question 1. How Common Are Pediatric TN?

Older data suggest that 0.2 – 5% of children and 13% of adolescents have TN[1], but newer studies identify sub-groups at much greater risk based on genetic predisposition or coexistent thyroid disease[1,3]. The Fukushima Health Management Survey Group performed US on asymptomatic children and adolescents and found TN in 1% of males and 1.7% of females[4]. Radiation exposure and obesity were significant risk factors[5]. Radetti, et. al. found that after 10 years of autoimmune thyroid disease (AIT), 43.9% of children and adolescents had TN[6]. Thyroid cysts have been detected in as many as 57% of children[7]. In addition, studies by Vergamini, et. al. confirm an increase in DTC as well[8].

Question 2. Which Patients Have Greater Risk for TN?

Genetic risk factors

Several genetic disorders predispose to TN and DTC which may be the presenting finding for familial adenomatoid-polyposis, Carney complex (PRKAR1A), endonuclease Dicer 1 (DICER1) syndrome, phosphatase and tensin homolog hamartoma tumor syndrome (PTEN, Cowden Syndrome), and Werner syndrome[9]. Familial, early-onset multinodular goiter (MNG) especially in males should prompt thyroid US and history focused on DICER1-associated tumors[10].

Radiation exposure

Radiation exposure is a known risk factor for TN, especially in children < 5 years of age[11]. In childhood cancer survivors who received radiation therapy (XRT), 2% develop TN each year, with a peak incidence of 15–25 years after XRT. Risk of DTC is greatest among those treated for Hodgkin lymphoma, leukemia, central nervous system tumors, and neuroblastoma. Patients prepared for

bone marrow transplant using XRT are also at increased risk[1]. Screening recommendations range from routine palpation to annual US. Routine US may detect DTC of smaller size, with fewer lymph node metastases (23.2% vs. 65.6%), and less extra-thyroidal extension (20.9 vs. 56.2%). However, Tonorezos et al. found no DTC within one year of normal physical examination in adults who had received XRT as children, suggesting physical examination may be adequate[12]. Some groups champion discussion of the risks and benefits of both options with each family[13].

Iodine deficiency

In the US, 5% of children and adolescents across all socioeconomic groups are iodine deficient and at increased risk for thyroid dysfunction, TN, and DTC[14].

Autoimmune thyroid disease, Graves' disease, and Goiter

AIT, GD, and goiter are associated with increased risk for TN and DTC in children[15-17]. In a recent study, 22.4% of children with Hashimoto thyroiditis were found to have TN, 7.9% of which were DTC[18]. Furthermore, the prevalence of TN increases over time from 9.3% at diagnosis to 43.9% after 10 years[6]. Allen, et al. found that palpation and history could identify some patients with TN, particularly when the gland was small, soft, and asymmetric[19]. However, the prevalence of TN discovered with this approach was much less than in all studies using US. In children who received surgical intervention for Graves' disease, TN were found in 41% and 22% had DTC[17]. The prevalence of TN in children with goiter ranges widely, up to 63.7% in Korea, suggesting strong regional, genetic, or environmental factors[16,20].

Question 3. What is the Risk that a Pediatric TN is Malignant?

Benign lesions account for 74-78% of pediatric TN. These may be diagnosed as follicular adenoma (FA), multinodular goiter (MNG), and non-invasive follicular thyroid neoplasm with papillary-like features (NIFTP)[21]. A much larger proportion of pediatric TN are malignant (22-26%) compared to adults (7-15%)[1]. It is rare for thyroid cancer in children or adolescents to be poorly differentiated or anaplastic. Most malignant lesions are DTC including papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and medullary thyroid carcinoma (MTC). The majority of PTC cases manifest classic histology (58.8%), but variants of PTC also occur. Follicular variant PTC comprises 23% of PTC cases and are further subdivided into encapsulated/non-invasive, encapsulated with vascular invasion, and non-encapsulated widely invasive variants. Less common variants of PTC include diffuse sclerosing variant, cribriform-morular variant (usually associated with *APC* mutations), solid variant, and tall cell variant[22]. FTC (10.1% of DTC) are sub-divided into minimally-invasive (<4 microscopic areas of capsular invasion) and widely invasive (≥4 sites of invasion)[23]. MTC is uncommon in children unless it develops in the context of multiple endocrine neoplasia type 2 (MEN2) but accounts for 8.1% of pediatric thyroid cancers[24].

Question 4. Which Children and Adolescents Without TN Warrant Routine US Surveillance for DTC?

The risk of DTC is greater for those with a family history of DTC or heritable cancer syndromes, and in these patients, annual US surveillance decreases TNM stage at the time of diagnosis[1,3].

For children and adolescents with AIT

Professional organizations disagree on whether to perform annual US in pediatric patients with AIT, or to perform US only when there is a palpable abnormality of the gland or lymph nodes[1,25]. The benefit of detecting small, clinically silent DTC in children is controversial and although recommended for those with a family history of DTC, there is no consensus for those with AIT[1]. However, 40% of DTC in children are discovered by the parent suggesting that infrequent palpation by a physician will miss many DTC[1]. Thyroid US may identify parenchymal changes in the thyroid that pre-date the onset of DTC in patients with AIT[26]. Serial US examination revealed increasing echogenicity in all AIT patients and that DTC developed in glands with a normo- or hypoechogenic background.

Question 5. What Should be Done Once a TN is Detected?

Perform a detailed history

The risk for DTC is 2.5-fold higher for children with a family history of benign thyroid disease and 4-fold higher if the family history includes DTC[3].

Obtain a serum thyrotropin (TSH) level

TSH in the upper tertile of the reference range may confer a greater risk for DTC[1]. Conversely, when a nodule is hyper-functioning and TSH is suppressed, there is a lower risk for DTC[1].

Perform a dedicated thyroid and neck US

US features of PTC frequently include solid composition, taller-than-wide shape, hypo-echogenic, invasive margins, increased intra-nodular blood flow, and micro-calcifications. In contrast, features most consistent with benign TN include small size, iso-echogenicity, partially or completely cystic structure, sharp or non-infiltrative margins, absent Doppler flow and absent calcifications. The risk for DTC also increases with abnormal cervical lymph node size, architecture, or shape. For that reason,

lymph nodes should be examined when thyroid US is performed[1]. Overall, US correctly identifies benign TN in 80.9% of cases[27].

Question 6. Which TNs Warrant FNA?

No clinical or imaging criteria are sufficiently robust to identify all malignant TN in children, so FNA is warranted for most TN in children. The 2015 ATA Guidelines recommend US-guided FNA in all TN >10 mm in children unless the lesion is purely cystic, and on all TN 5-10 mm that show any suspicious US features[1]. FNA should also be performed on any suspicious lymph nodes in the lateral neck so as to confirm the presencee of DTC prior to a lateral neck dissection[1].

Attempts to identify TN that might not warrant FNA have generated several scoring systems. The Thyroid Imaging Reporting and Data System (TI-RADS) was developed to decrease the frequency of FNA in adults with TN. It utilizes US features to assign TN into point-based categories with increasing risk of DTC[28]. The TI-RADS system has good concordance with the Bethesda System for Reporting Thyroid Cytopathology, with TI-RADS 1-2 TN prospectively followed and TI-RADS 3-5 TN referred for FNA[29]. In children, TI-RADS provides a positive predictive value of 71.7% and a negative predictive value of 80.0%[30]. However, relying on TI-RADS alone in pediatric TN results in an unacceptable false-negative rate of up to 22%[31].

Incidental TN (iTN) have the same risk for DTC as do palpable TN of similar size[1]. In part, this is because palpation fails to detect the majority of TN in children[32]. A direct comparison by Agrawal, et. al. found only 2 TN by palpation but 33 by US[32]. Furthermore, TN size has not predicted malignancy in pediatric US series whereas TN margins, echogenicity, and calcification are significant associations[33,34]. A study by Hammond, et al. specifically examined childhood and adolescent cancer survivors who had iTN detected by computerized tomography (CT) performed for other reasons[35]. Ultimately, 7.4% were proven to be DTC and they recommended US and FNA for iTN in this high-risk population.

Question 7. What is Appropriate Treatment for TNs in Children and Adolescents?

Appropriate treatment is individualized and based on the results of FNA in consultation with patient and parent that incorporates their anxiety and concerns. The sensitivity, specificity, and accuracy of FNA in children are similar to that of adults [overall accuracy (91%), sensitivity (100%), and specificity (88%)][36] but the risk of malignancy in each Bethesda category is greater in children than in adults[37]. FNA results are categorized into one of six diagnostic categories according to the Bethesda System[38]:

1. Nondiagnostic or unsatisfactory
2. Benign
3. Atypia or follicular lesion of undetermined significance (AUS/FLUS)
4. Follicular/Hürthle neoplasm or suspicious for follicular/Hürthle neoplasm (FN or SFN)
5. Suspicious for malignancy (SUSP)
6. Malignant

Bethesda 1

For children with non-diagnostic/unsatisfactory cytopathology, repeat FNA is an option. Repeat aspiration should be postponed for 3-6 months[39]. Because repeat FNA may not be an acceptable option for a child, lobectomy may be considered instead.

Bethesda 2

Follow-up is warranted for children with benign cytopathology (malignancy rate 5%), and surgery should be considered if the nodule grows or the patient experiences compressive symptoms[1]. Frequency and duration of follow up are still debated, but many centers perform annual US for at least 10 years. Given the higher rate of false negative interpretations in lesions > 4 cm, lobectomy should be considered in these children even if the FNA reveals benign cytopathology[1].

Bethesda 3-4

About 35% of pediatric FNA are classified as indeterminate (AUS/FLUS or FN/SFN), and 50-58% of these are malignant[40]. Repeat FNA fails to clarify diagnosis in as many as 10-30% adults[39].

In children with AUS/FLUS or FN/SFN, there appears to be 50-58% risk for DTC[41]; and lobectomy with completion thyroidectomy upon confirmation of DTC is an option[42]. Molecular testing with oncogene panels can rule out or rule in DTC in some indeterminate specimens[40]. For example, detection of a *BRAF* mutation or a fusion gene (*RET/PTC* or *NTRK3/ETV6*) warrants total thyroidectomy[43]. However, pediatric TN lacking recognized mutations still carry a substantial DTC risk, and lobectomy continues to be recommended for all children with FN/SFN[42]. Total thyroidectomy should be considered for bilateral TN.

Bethesda 5-6

For children with FNA diagnosis of SUSP or malignant cytopathology, the risk for DTC nears 100%[37,41]. In these cases, total thyroidectomy with or without central neck dissection should be performed[1]. The surgical risks of total thyroidectomy are significantly reduced when surgery is performed by a high volume thyroid surgeon[44].

Follow-Up

Follow-up for patients with DTC is outlined in current treatment guidelines[1]. However, follow-up for those with benign FNA remains under study. Published guidelines recommend annual thyroid US and either repeat FNA or removal for TN that grow or develop suspicious US features[1,45,46]. However, Singh, et. al. found that TN growth was not predictive of malignancy in adults[47]. Nou, et. al. suggests a repeat US after 2-4 years in adults [48] while Lee, et. al. suggests that follow up for benign FNA in adults can be discontinued after 3 years [49]. However the risk of false negative FNA appears greater in children and for that reason, most pediatric centers follow benign FNA for several years[37].

Summary

In summary, TN are increasing in incidence among children and adolescents. The probability that a TN is malignant in children and adolescents is around 22-26%, but criteria developed for classification of nodules in adults cannot be used to predict malignancy risk in pediatric TN. A detailed history can significantly increase the clinician's suspicion of malignancy. Molecular diagnostics can be helpful in determining the malignancy risk in TNs with indeterminate FNA diagnoses.

Conflict of Interest

The authors have no financial interests or commercial support relevant to this material and attest that the material is original and has not been previously published or submitted in part or whole. Furthermore, the authors attest that all authors have substantively contributed to the writing of this material, have reviewed and approve of the final version as submitted.

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