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Evaluation and Management of Pediatric Thyroid Nodules

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1. Introduction

The prevalence of palpable thyroid nodules in patients less than 21 years of age is only .05-1.8% (American Cancer Society [ACS], 2009; Dinauer & Francis, 2007; Dinauer et al, 2008; Gosepath et al, 2007; Halac & Zimmerman, 2005, Niedziela, 2006; Ortel & Klinck 1965; Rallison et al 1991; Wartofsky, 2000; Wiersinga, 2007). However, the true incidence of incidental nodules may be higher than 13% in the pediatric and adolescent group based on autopsy studies. This is in comparison to the adult population where the rate of palpable thyroid nodules approaches 5% with autopsy studies showing up to 70% of adults harboring incidental thyroid nodules (Ezzat S et al, 1994; Guth et al, 2009). Risk factors for the development of malignant thyroid nodules in pediatric patients include female sex, puberty, family history of thyroid cancer, head and neck radiation exposure, and iodine-deficiency (Crom et al, 1997; Fleming, 1984; Fowler et al, 1989; Josephson & Zimmerman, 2008; Samaan, 1987; Solt et al, 2001).

Close to ten percent of all thyroid carcinomas occur in patients less than 21 years of age (Machens, 2010). Differentiated thyroid carcinoma (DTC) constitutes 3-8% of all childhood malignancies depending on the age group, and the numbers are thought to be increasing (ACS, 2009; Hameed & Zacharin, 2005; Hogan et al, 2009; Horner et al, 2010; Pacini, 2002; Ries et al, 2003; Waguespack et al, 2006). The majority of patients are adolescents between the ages of 15-19 with only 5% of cancers occurring in patients less than ten years of age (Hogan et al, 2009; Steliarova-Foucher et al, 2006). Familial thyroid carcinoma comprises 5% of all pediatric thyroid cancer, most commonly of the medullary subtype as part of the Multiple Endocrine Neoplasia 2 (MEN2) syndrome (Halac & Zimmerman, 2005; Loh, 1997; Nose, 2001). About 25% of pediatric thyroid nodules are malignant which is four- to five-fold the incidence compared to adults, and up to 30-50% in strictly surgical series (Canadian pediatric thyroid nodule study group [Canadian], 2008; Corrias et al, 2010; Dinauer et al, 2001; Hung, 1999; Lafferty & batch, 1997; Niedziela, 2006; Wiersinga, 2007; Yip et al, 1994).

Patients less than 21 years of age can present with a palpable thyroid nodule discovered on physical examination. More recently, however, more thyroid nodules are discovered as incidental findings by ultrasound or other imaging studies performed for other reasons (Corrias et al, 2008 % 2010, Canadian, 2008). The main risk factor for thyroid malignancy in

these patients is a history of head and neck radiation therapy or exposure that is dose and age dependent, which carries a relative risk of 6-18.3 (Ceccarelli et al, 1988; Crom, 1997; Duffy & Fitzgerald, 1950; Faggiano, et al 2004; Gharib et al 2006; Goepfert et al, 1984; Harness et al, 1992; Pacini, 2002; Sklar et al, 2000; Tucker et al, 1991; Viswanathan et al, 1994, Winship & Rosvoll, 1970). Other risk factors consist of a history of bone marrow transplant preceded by radiation therapy, family history of MEN2, Cowden's disease, Carney's complex, and Familial Adenomatous Polyposis (FAP) (Brignardello et al, 2008; Camiel et al, 1968; Halac & Zimmerman, 2005; Smith & Kerr, 1973).

2. Clinical evaluation

2.1 History

There are important questions the clinician should ask when evaluating a thyroid nodule in a pediatric patient. The most important risk factor for DTC is a history of head and neck radiation therapy or exposure (Harness, 1992). Radiation is a known risk factor for developing papillary thyroid cancer (PTC) (DeGroot & Paloyan, 1973; Sigurdson 1985). Today, many PTC patients are cancer survivors, having received internal γ radiation as part of a treatment protocol for lymphoma, especially Mantle radiation for Hodgkin's disease (HD), non-Hodgkin's lymphoma (NHL), leukemia, in preparation for a bone marrow transplant, or retinoblastoma. In a study of 16,500 leukemia survivors, thyroid carcinoma was the most common second malignancy in patients with a history of HD and NHL and the third most common after leukemia (Maule et al, 2007). High risk patients with thyroid nodules may have also received radiation forty to fifty years ago at very young ages for an enlarged thymus, acne, enlarged tonsils and adenoids, tinea capitis, or shoe size measurement (Mehta et al, 1989). Another type of high dose exposure that should be considered is external β radiation seen secondarily from such nuclear accidents as Chernobyl in 1986 and Japan in 2011. As a consequence, Japanese clinicians may see an increase in the number of pediatric thyroid cancers in the next three to ten years. These cancers are exclusively of the papillary subtype, have different RET/PTC rearrangements, and behave somewhat differently than sporadic tumors (Demidchik et al, 2006; Dinauer et al, 2008; Pacini, 2002).

An equally important risk factor for pediatric thyroid cancer is a family history of MEN2 or medullary thyroid cancer (MTC). An inquiry about family history of pheochromocytoma or a family member that may have had an unexpected complication during an operation of an unknown cause should also be performed. Penetrance of MTC is 100% in patients that have any of the responsible genes, and all of these patients will need, at a minimum, total thyroidectomy with central compartment lymph node dissection.

For solitary thyroid nodules, duration, growth and/or previous signs of infection such as erythema, pain or swelling are important. A thyroid nodule that varies in size over a period of time may be indicative of a cyst, and a thyroid cyst that has been previously drained or infected should make the clinician think of a thyroglossal duct cyst. The significance of nodular growth has been debated in the literature with some studies reporting that it is a risk factor for thyroid carcinoma (Canadian, 2008; Corrias et al, 2001; Degroot & Paloyan, 1973; O'Kane, 2010). Nevertheless, a thyroid nodule that has enlarged requires further diagnostic evaluation.

For both solitary thyroid nodules and multinodular goiters, symptoms of compression, including shortness of breath or coughing while lying down in the supine position and/or dysphagia are indications for surgical resection. Additionally, one must ask about a permanent change in voice, which, although rare, may indicate recurrent laryngeal nerve compression or involvement by a thyroid cancer.

The clinician should also inquire about symptoms of hypo- or hyperthyroidism such as weight loss or gain, palpitations, nervousness, excitability, or fatigue. Additionally, male gender itself is a risk factor for thyroid cancer, although less so in those patients less than ten years of age (Harach & Williams, 1985).

2.2 Physical exam

When evaluating any child or adolescent with thyroid nodules, a complete head and neck physical examination should be performed. This clinical exam entails palpating the thyroid gland for the presence of multiple nodules and/or diffuse glandular enlargement as well as the cervical lymph node basins for adenopathy. Any thyroid nodule or lymph node should be characterized as soft or firm, mobile or fixed, and for any tenderness to palpation. While soft and mobile thyroid nodules are usually associated with benignity, firm and fixed thyroid nodules are usually associated with malignancy. Although there is some controversy over whether solitary palpable nodules have an increased risk for cancer compared to those nodules that are discovered incidentally or part of a multinodular goiter, most studies in both adult and pediatric populations report similar rates of thyroid malignancy regardless of clinical presentation (AACE/AME, 2006; Cooper et al, 2009; Corrias et al, 2001; Frates et al, 2006; Gandolfi et al, 2004; Gharib, 2007; Leenhardt et al, 1999; Papini, 2002). Similar to nodular growth, tenderness is a finding with conflicting reports in the literature as to its significance in predicting thyroid cancer (Canadian, 2008; Lugo-Vicente, 1998).

For the rare patient with or a family history of MEN2, an examination for marfanoid habitus, pectus excavatum, mucosal neuromas and skin lesions should also be performed.

## 3. Diagnostic procedures

3.1 Neck ultrasound

Neck ultrasound has become an extension of the physical exam for many clinicians. This imaging modality has been shown to be cost-effective and accurate in the evaluation of thyroid nodules in adult patients (Milas et al, 2005; Solorzano et al, 2004). Neck ultrasound provides information on the size, shape, and composition of thyroid nodules, evaluates the contralateral thyroid lobe for additional nodules, and allows the clinician to examine the cervical lymph node chains for suspicious adenopathy. This is especially important in the pediatric age group since up to 50% of these thyroid cancer patients in contemporary series present with positive lymph nodes (Hay et al, 2008; Hogan et al, 2009; Pacini, 2002). Since the 1980s, neck ultrasound has been used to evaluate thyroid nodules in pediatric and adolescent patients with a history of head and neck radiation therapy or exposure (Corrias et al, 2001; Crom et al, 1997; Dorzd et al, 2009; O'Kane, 2010; Poyhonen & Lenko, 1986; Solt et al, 2001). In the past decade, the use of ultrasound in guiding FNA biopsy has also led to a decreased rate of insufficient samples (Danese et al, 1998; Izquierdo et al, 2009, Kim MJ et al, 2008).

To evaluate the thyroid gland and surrounding lymph nodes, a 10-14 MHz linear array transducer is used. Appropriate technique entails examination of the thyroid gland and any nodules in both the transverse and longitudinal view, and identifying landmarks such as the trachea, internal jugular vein and carotid artery. Each thyroid nodule should be measured in three dimensions and individual characteristics documented including regular vs. irregular borders, solid vs. cystic architecture, hypo-, iso- or hyperechogenicity, presence of microcalcifications, and the presence of taller greater than wider dimensions. Cervical lymph nodes should similarly be evaluated for elongated vs. rounded shape, regular vs. irregular borders, absence of a fatty echogenic hila, heterogeneous echogenicity, calcifications, and irregular blood flow throughout the node vs. normal central hilar vessels.

Although individual ultrasound characteristics are not reliable in predicting benignity or malignancy of thyroid nodules, certain combinations of ultrasound features do have a predictive value. One study demonstrated that hypoechoic thyroid nodules with irregular borders and microcalcifications carry a 30X risk for malignancy (Jabiev et al, 2009). (Figure 1) Other studies have shown similar ultrasound features predict thyroid malignancy in addition to intrinsic vascularity, taller greater than wider dimension (Figure 2), irregular halo, and elastography (Moon et al, 2011; Chan et al, 2003). Conversely, thyroid nodules with regular borders, cystic component, iso- or hyperechogenicity and no

A
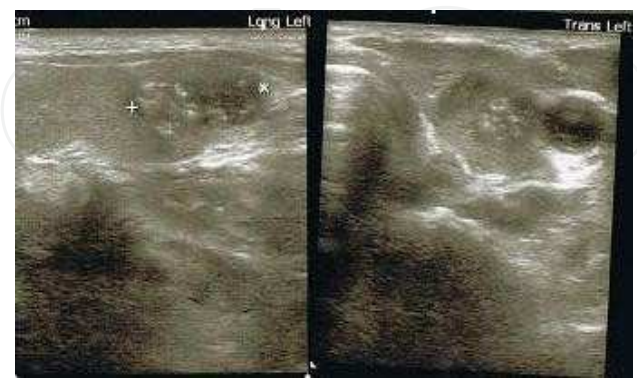
B

Fig. 1. Ultrasound features of malignant thyroid nodules. **Figures 1A & B** Ultrasound nodule characteristics include irregular borders, hypoechoic echogenicity, and microcalcifications

microcalcifications can predict benignity in patients without a history of radiation or thyroid cancer (Figure 3) (Goldfarb et al, 2011). In one study of pediatric patients, malignant thyroid nodules were more likely to have microcalcifications, lymphadenopathy and altered nodular vascular pattern, although each characteristic was only present in 47-73% of patients. Furthermore, a subset of patients deemed to have benign ultrasound findings, namely nodules with regular borders, normal vasculature, no calcifications, and no suspicious lymph nodes were followed without any change in exam for at least one year (Corrias et al, 2010).

Neck ultrasound showing a hypervascular nodule in a patient with biochemical hyperthyroidism is consistent with a toxic thyroid nodule. On a comparable note, a diffusely enlarged hypervascular and hypoechoic gland, especially in a patient with ophthalmopathy and biochemical hyperthyroidism, is consistent with Graves' disease. Additionally, multiple nodules in a hyperthyroid patient suggest a toxic multinodular goiter.

An important component of the information obtained with ultrasound is the evaluation of the contralateral thyroid lobe and the surrounding lymph nodes. (Figure 4) Multiple studies have shown that ultrasound allows the surgeon to plan for extent of thyroidectomy (Mazzaglia, 2010; Papini, 2002; Park et al, 2009; Stulak et al, 2006). The authors (M.G and J.I.L) believe that ultrasound should be used routinely in the evaluation of thyroid nodules in pediatric patients with reports in the literature suggesting its advantage for this specific purpose (Corrias et al, 2008; Stulak et al, 2006; Wada et al, 2009).
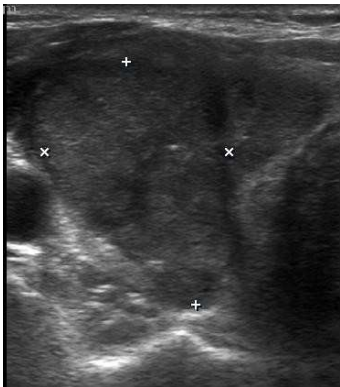
Fig. 2. Thyroid nodule with taller > wider dimensions

Fig. 3. Example of thyroid nodule with benign ultrasound features
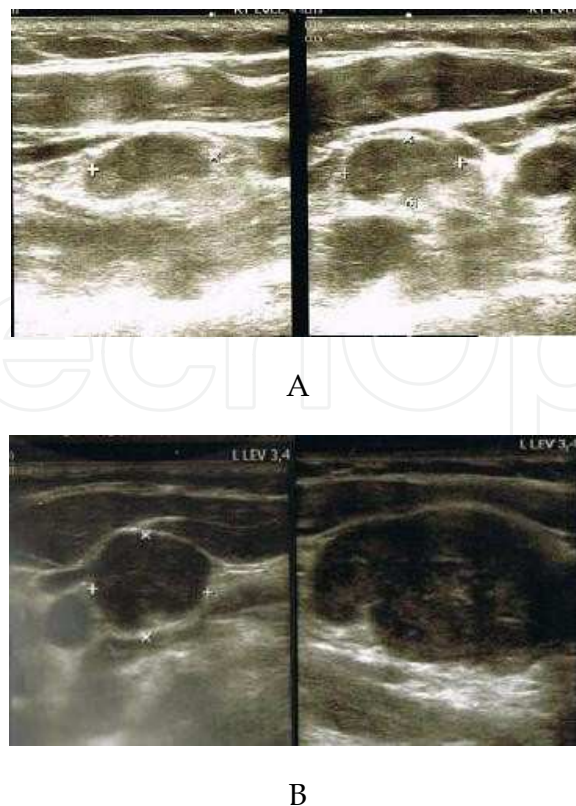Ultrasound nodule characteristics include regular borders, solid and cystic components, and no microcalcifications

A

B

Fig. 4. **Ultrasound features of abnormal lymph nodes**
Figure 4A &B Abnormal lymph nodes demonstrate an enlarged size, microcalcifications, irregular borders, and a solid component

3.2 Scintigraphy

Thyroid scintigraphy is mentioned mainly for historic purposes. Before ultrasound, radioisotope scans were utilized for evaluating thyroid nodules. "Hot" nodules were indicative of hyperfunctioning thyroid nodules or, if diffuse activity, Graves' disease, and unlikely to be malignant. Conversely, "cold" nodules were thought to be highly suspicious for thyroid malignancy (Corrias et al, 2001; Scholtz et al, 2011). Aside from its inaccuracy, patients who undergo thyroid scintigraphy are subjected to radiation that may be of concern in pediatric patients. As such, there are very few, if any, indications for routine thyroid scintigraphy in these younger patients with thyroid nodules.

3.3 Fine Needle Aspiration (FNA)

Fine needle aspiration (FNA) has been extensively studied in adults. In general, FNA is a safe, cost-effective procedure that can be performed in the office or clinic setting. When positive for cancer, FNA is 90-98% sensitive for predicting thyroid cancer depending on institution (Tee et al, 2007). With an FNA diagnosis of malignancy, the appropriate surgical procedure can be performed that usually involves total thyroidectomy for all nodules greater than one cm, and central and/or lateral neck dissection when involved lymph nodes are identified either preoperatively and/or intraoperatively. In pediatric patients, however, there remains disagreement over the accuracy of FNA with some groups reporting high sensitivity and specificity whereas others suggesting the opposite; one group reported a

sensitivity as low as 70% (Amriki et al, 2005; Arda et al, 2001; Bargen et al, 2010; Canadian, 2008; Corrias et al, 2001; Hosler et al, 2006; Izquierdo et al, 2009; Lugo-Vicente, 1998; Willgerodt et al, 2006). Additionally, "indeterminate" FNA biopsies may have up to a 50% chance of malignancy in multiple series with their malignant potential determined only on final pathology (Bargen et al, 2010; Brooks, 2001; Gharib, 2007; Kim E et al, 2003; Mandell, 2001; Raab, 1995). In one surgical series, benign FNA biopsy carried up to a 17% risk of thyroid malignancy (Tee, 2007).

The imprecision of FNA, seemingly equal to ultrasound evaluation, becomes more important when considering FNA in pediatric patients. While FNA is safe and easily accomplished in pediatric patients, other factors should be taken into account (Willgerodt et al, 2006). For those patients, especially in the younger age groups, clinicians must take into consideration the potential inability or maturity for such patients to sit still for the procedure, an increased sensitivity to or fear of needle sticks, and a smaller space to maneuver both the ultrasound and FNA needle with precision.

As such, the authors suggest a more selective use of FNA in pediatric patients, and ultrasound may be used to identify those patients who require further FNA diagnosis. The main role for FNA is making a definitive diagnosis of cancer in a thyroid nodule or lymph node with very suspicious ultrasound characteristics for preoperative planning (Lugo-Vicente, 1998).

FNA is performed with a 22-25 gauge needle in young adult and pediatric patients. Local anesthetic can be used at the discretion of the clinician. Studies have shown that multiple passes at different areas within the nodules as well as multiple slides give the most accurate biopsy results (Alexander et al, 2002). Aspirated contents should immediately be placed in fixative, and in an ideal setting, reviewed immediately by a cytopathologist for adequacy of sample. In general, thyroid nodules in the superior pole and/or anteriorly located are most easily biopsied in the office setting, whereas those nodules residing in a posterior location are more easily biopsied by interventional radiology.

3.4 Other imaging

In patients with a diagnosis of thyroid cancer, many advocate a preoperative chest X-ray to exclude for obvious pulmonary metastases (Hung, 1999; Waugepack et al, 2006). Another consideration is a non-contrast CT or MRI to identify pathologic lymphadenopathy or extensive thyroid disease preoperatively. Care must be taken not to order an intravenous contrast scan so as not to interfere with postoperative radioactive iodine scanning and treatment.

3.5 Laboratory testing

If not done already, laboratory evaluation should include thyroid-stimulating hormone (TSH) to determine if patients are euthyroid, hypothyroid or hyperthyroid. In patients that are suspected to have medullary thyroid carcinoma, calcitonin, CEA, and calcium levels should be obtained, and urine or plasma free metanephrines and normetanephrines to exclude underlying pheochromocytoma associated with MEN2.

4. Initial management

4.1 Cystic nodules

Whereas cystic thyroid nodules in adults are generally thought to be benign, there is some evidence to suggest the same does not hold true in pediatric patients (Yastovich et al, 1998). In adults, thyroid nodules with a cystic component can have a malignancy rate of at least 13% (Chan et al, 2003). For purely cystic thyroid nodules with regular borders, a reasonable initial management approach is FNA under ultrasound guidance. The fluid should be sent for cytology and the patient should be monitored with serial ultrasound exam at six months and then yearly thereafter for three years. Although FNA may be repeated a second time, the patient should be advised to undergo surgical resection, usually diagnostic thyroid lobectomy with isthmusectomy if the thyroid cyst recurs. Thyroid lesions with mixed solid and cystic components should be evaluated based on a combination of ultrasound characteristics as outlined below.

4.2 Toxic nodules

Thyroid lobectomy with isthmusectomy for a solitary toxic nodule in pediatric patients is currently performed (Astl et al, 2004; Canadian, 2008). Although radioactive iodine therapy and anti-thyroid medications are efficacious in a certain percentage of patients, many pediatricians believe that the benefits of surgical resection outweigh the risks of receiving radioactive iodine therapy (RAI), the substantial rate of permanent hypothyroidism, noncompliance with medication, and need for immediate relief of hyperthyroid symptoms (school and social performance) in this particular age group (Sherman et al, 2006). Thyroidectomy for benign disease can be performed by an experienced thyroid surgeon with minimal complications (Raval et al, 2009). When only removing half of a patient's thyroid gland, there is no risk of permanent hypoparathyroidism and rendering a patient hypothyroid is much abated. For toxic multinodular goiters, similar risks of non-surgical therapy apply with an even higher rate of failure for both RAI and medical therapy, as well as a greater chance for permanent hypothyroidism. These patients typically undergo total thyroidectomy due to bilateral thyroid nodules. While a risk for permanent hypoparathyroidism exists, the rate is very low in the hands of an experienced thyroid surgeon.

4.3 Solitary thyroid nodules

In the pediatric population, a significant number of patients will be referred for surgical consultation with clinical indications that necessitate thyroidectomy. These surgical indications include (but are not limited to) a history of head and neck radiation, history of MEN2, toxic nodule or multinodular goiter, obstructive symptoms, and fixed or firm nodule. In a pediatric patient with no evaluation, ultrasound examination should be performed based on the following recommendations.

4.3.1 Benign ultrasound features

Although large clinical studies with surgical cohorts have not been performed in the pediatric population, some clinicians have reported successful monitoring of pediatric

patients with serial ultrasound exams based on benign features alone (Corrias et al, 2010). Such benign thyroid nodules are iso- or hyperechoic, have regular borders, no microcalcifications, and no suspicious lymphadenopathy. Such nodules can be safely monitored with a neck ultrasound exam at six months and then yearly thereafter for three to five years as recommended by current ATA guidelines, or every two years by Korean consensus guidelines (Cooper et al, 2009; Moon et al, 2011). If thyroid nodule ultrasound characteristics change or new clinical factors develop that warrant surgical resection, FNA or diagnostic thyroid lobectomy with isthmusectomy should be considered. One long term study of 56 patients who were originally thought to have benign disease based on ultrasound and/or FNA were later found to have PTC (Ito et al, 2007). Only 5.3% of these patients developed recurrent disease and none died, suggesting that such thyroid cancers have an indolent course.

4.3.2 Malignant ultrasound features

Thyroid nodules that present with suspicious features such as irregular borders, microcalcifications, corresponding suspicious lymph nodes and hypoechogenicity may require surgical resection regardless of FNA results. Either diagnostic thyroid lobectomy with isthmusectomy and frozen section or total thyroidectomy depending on patient preference may be performed.

4.3.3 Equivocal ultrasound features

Since there are no large surgical series characterizing combinations of ultrasound features in the pediatric age group, nodules that have a mix of both benign and malignant features should be biopsied. Any FNA result other than benign should be regarded with suspicion since a 25% malignancy rate exists in such thyroid nodules of this pediatric age group. Benign FNA results in a patient with equivocal ultrasound features should at minimum receive close follow-up, and surgical resection should be considered for definitive diagnosis.

For pediatric patients with FNA results, subsequent management and following recommendations are made.

4.3.4 Benign FNA results

In patients with benign FNA results, benign ultrasound features, no worrisome aspect of the history or physical exam, and no indication for surgical resection, thyroid nodules can be safely monitored with serial ultrasound exams for the next three to five years. However, benign FNA results may have up to a 17% false negative rate. If there are other clinical indications for surgical resection, such as obstructive symptoms, fixed nodule, or a history of head/neck radiation therapy or exposure, thyroid lobectomy with isthmusectomy should be performed. For benign FNA results in a thyroid nodule with suspicious ultrasound characteristics and no other clinical indications for surgical resection, either diagnostic thyroid lobectomy and isthmusectomy or close monitoring with serial ultrasound exams may be indicated. In such situations, the patient should be counseled that thyroid malignancy cannot be entirely excluded, and surgical resection may be required for definitive diagnosis.

4.3.5 Indeterminate FNA results (Bethesda III-Atypical cells and Bethesda IV-Follicular neoplasm

Current ATA guidelines recommend surgical resection for any Bethesda IV follicular neoplasm (Cooper et al, 2009). For Bethesda III lesions, the current recommendation is repeat FNA. However, in pediatric patients, the next course of action should also be based on thyroid nodule ultrasound features and other risk factors. In the absence of any definite risk factors, management options include close monitoring with serial ultrasound exams if the nodule has benign features or diagnostic thyroid lobectomy with isthmusectomy for thyroid nodules with suspicious ultrasound characteristics or patient preference.

4.3.6 Suspicious/malignant FNA results (Bethesda V and VI)

Any thyroid nodule with an FNA diagnosis of cancer (Bethesda VI) requires surgical resection that usually consists of total thyroidectomy with or without neck dissection. Pediatric patients have a high rate of multifocality and a higher risk of recurrent disease if a lesser operation is performed (Cooper et al, 2009; Demidchik et al, 2006; Hay et al, 2010; Hung, 1999; Jarzab et al, 2000; Thompson & Hay, 2004; Welsh-Danaher et al, 1998). In addition, total thyroidectomy allows for the potential use of RAI therapy to treat metastatic disease. Total thyroidectomy also allows patients to be monitored with serum TG and TG antibodies for recurrent disease. Careful examination of the central and lateral neck compartment lymph nodes should be undertaken with preoperative ultrasound for potential neck dissection. Suspicious appearing lymph nodes associated with malignant thyroid nodules confirmed by FNA are considered cancerous until proven otherwise. Such suspicious lymph nodes may warrant FNA preoperatively for surgical planning or frozen section in the operating room.

The sensitivity of "suspicious" or Bethesda V FNA results is somewhat institutional dependent. Rate of malignancy can be upward of 95% for such FNA biopsies. If, however, the clinician's respective institution has a lower rate of malignancy in Bethesda V specimens, an approach with diagnostic thyroid lobectomy with isthmusectomy may be undertaken. Frozen section may play a role in determining a definitive diagnosis of thyroid cancer in the operating room, allowing for total thyroidectomy at the first operation.

4.4 Multinodular goiter

Multiple thyroid nodules discovered on ultrasound examination in pediatric patients is important for surgical planning. Ultrasound features for each thyroid nodule should be evaluated, and further management undertaken as outlined for solitary thyroid nodules. If there is an indication for surgical resection for any single nodule based on risk factors, ultrasound features or FNA results, the presence of bilateral thyroid nodules should prompt consideration for total thyroidectomy. Small and less than one cm thyroid nodules with benign features can usually be monitored with serial ultrasound exams. An informed discussion should be carried out with the pediatric patient and parents.

5. Conclusion

Thyroid nodules in the pediatric patient require careful and vigilant evaluation. Since elements of a patient's history, physical exam, or risk factors may be indications for surgical

resection, ultrasound should be further utilized as a key diagnostic tool to help evaluate any thyroid nodule in the pediatric population.

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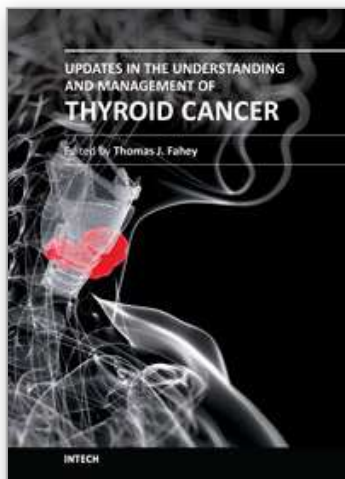
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Edited by Dr. Thomas J. Fahey

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