Consultation with the Specialist : Thyroid Nodules

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CONSULTATION WITH THE SPECIALIST

Thyroid Nodules

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Educational Gap

Although most pediatric thyroid masses are benign, some are malignant; thus, pediatricians must be able to assess for risk of malignancy and order appropriate diagnostic tests in conjunction with consultation with an endocrinologist.

Objectives

After completing this article, readers should be able to:

1. **Develop a differential diagnosis and initial evaluation plan for a child or adolescent presenting with a thyroid mass.**
2. **List the risk factors associated with malignant thyroid nodules.**
3. **Understand the limitations of ultrasonography and fine-needle aspiration biopsy in the assessment of a thyroid nodule.**
4. **Recognize the risk factors inherent in surgical thyroidectomy.**
5. **Appreciate the current controversies in the management of pediatric thyroid nodules.**

Author Disclosure

Drs Osipoff and Wilson have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Abbreviations

FNAB:	fine-needle aspiration biopsy
I-131:	a radioactive isotope of iodine
MTC:	medullary thyroid carcinoma
PTC:	papillary thyroid carcinoma
rh-thyrotropin:	recombinant human thyrotropin
WDTC:	well-differentiated thyroid carcinoma
WBS:	whole-body scan

Introduction

Whether as part of a well-child examination, or in response to a patient or parent concern, it is important for the pediatrician to feel comfortable examining the thyroid gland. Although most pediatric thyroid masses are benign (Table 1 and Fig 1), in the event that a lesion is discovered, the pediatrician should be able to assess risk factors for malignancy and order appropriate diagnostic tests while awaiting consultation from the pediatric endocrinologist.

Epidemiology

Palpable thyroid nodules in the pediatric and adolescent population are relatively rare, having an estimated prevalence of 0.2% to 1.4%, which is 5 to 10 times less than in adults. (1) Despite their lower occurrence, studies estimate 9% to 50% (mean, 26.4%) of thyroid nodules in children and teenagers are cancerous, significantly higher than the estimated 10% to 14% of lesions in adults. (2) In fact, thyroid cancers are the third most common solid tumor in children and adolescents, with an annual incidence of 1.75 per 100,000. (3) The female-to-male ratio of malignant thyroid disease is age specific, with a ratio of 1 to 6 in children 5 to 9 years old, 1 to 1 in 10- to 14-year-olds, and 5 to 2 in 15- to 19-year-olds. (4) Well-differentiated thyroid carcinomas (WDTCs) comprise the vast majority of pediatric thyroid malignancies, with papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma accounting for 80% to 95% and 5% to 15% of these tumors, respectively. (5)(6)

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Clinical Aspects

The History: Assess for High-Risk Factors

Most patients who have a malignant thyroid nodule present with an incidentally found, painless thyroid mass

and are clinically and biochemically euthyroid. A thorough history is essential in assessing the likelihood of malignancy once a thyroid nodule is discovered. A history of ionizing radiation to the head or neck is an independent risk factor for the development of thyroid malignancies. Several decades may pass between the radiation exposure and the development of thyroid cancer. Historically, radiation was used to treat tonsillar hypertrophy, thymic enlargement, facial acne, and hemangiomas of the face and neck. Although these treatment modalities are not used today, irradiation of the head and neck is relatively common in children undergoing treatment for other forms of childhood cancer; thus, screening for thyroid malignancies should be a routine part of their posttreatment follow-up care.

The family history is of particular significance during the evaluation of a thyroid nodule because there are several syndromes (Table 2) associated with thyroid cancer that follow an autosomal dominant mode of inheritance. A family history of thyroidectomies, thyroid malignancies, or other cancers suggests that the child with the thyroid nodule has a genetic predisposition to the development of thyroid carcinoma. Although extremely rare in the United States, iodine deficiency has been linked to thyroid cancers, and determining if the child originates from an area of endemic iodine deficiency is crucial. Thyroid nodules in prepubertal children have a higher risk of malignancy. A thyroid nodule found in a male younger than 15 years old has the greatest chance of being malignant.

The review of systems is invaluable in stratifying the risk of malignancy and guiding the evaluation. If a patient has symptoms consistent with hyperthyroidism, such as tachycardia or tremulousness, the thyroid mass is likely a solitary toxic adenoma or a multinodular goiter, both of which secrete thyroid hormone autonomously. Caution must be exhibited when a patient presents with a discrete thyroid mass and symptoms of hypothyroidism, such as cold intolerance or constipation. Although the nodule in this situation likely represents inflammatory change in the setting of Hashimoto thyroiditis, some literature suggests that the presence of chronic lymphocytic thyroiditis raises the risk for thyroid cancers. (7) Although rare in young patients with thyroid nodules, voice changes, symptoms of airway compression, or rapid growth of the lesion are worrisome for malignancy. However, if the patient complains of pain or tenderness over the nodule, hemorrhage into a cyst, thyroid abscess, or an inflammatory process should be considered before malignancy.

Table 1. Benign Thyroid Masses

Simple colloid cyst
Follicular adenoma
Multinodular goiter
Thyroglossal duct cyst
Ectopic thymic tissue
Inflammatory changes
Unilateral thyroid agenesis
Thyroid abscess
Teratoma

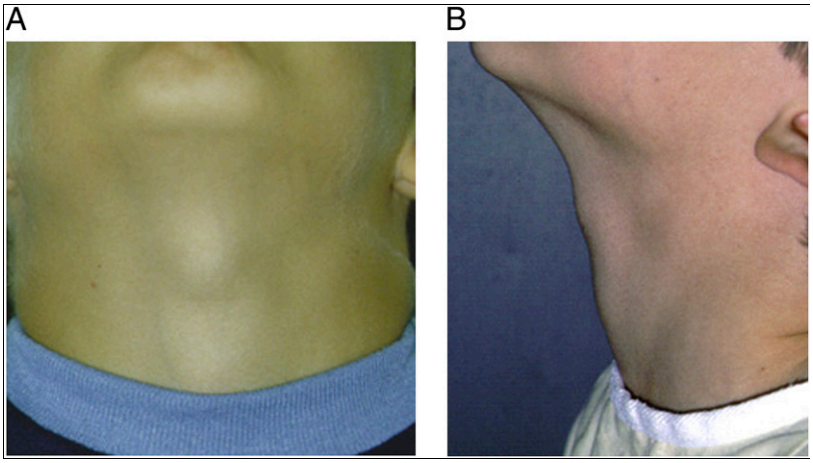

Figure 1. A. A patient with an ectopic thyroid gland (upper protuberance) before treatment. B. The same patient a few months after starting levothyroxine. Note how the gland has shrunk in response to treatment.

The Physical Examination

The physical examination also provides clues to help differentiate between a benign and malignant process. The size of the nodule does not have any diagnostic value. (1)(2)(3) A nodule that is firm to palpation, irregularly shaped, fixed to the surrounding tissue, or associated with regional lymphadenopathy is concerning for malignancy (Fig 2). However, if the mass is painful to the touch or associated with overlying erythema, a suppurative thyroiditis is higher on the differential and should be treated appropriately.

Occasionally, thyroid carcinoma will present as a peripheral, nontender lymph node enlargement without a detectable thyroid nodule being present. Therefore, it is imperative to consider thyroid malignancy in the differential diagnosis of all painless cervical lymphadenopathy, especially if the patient has any other risk factors.

Table 2. Autosomal Dominant Syndromes With Predisposition to Thyroid Malignancy

Medullary thyroid carcinoma (MTC)
Multiple endocrine neoplasia type 2a: MTC, pheochromocytoma, and parathyroid adenoma
Multiple endocrine neoplasia type 2b: MTC, pheochromocytoma, mucosal neuromas, marfanoid habitus
Familial MTC: isolated MTC
Non-MTC
Gardner syndrome: thyroid, breast, and colon cancers; lipomas; intestinal polyposis; osteomas
Cowden disease: thyroid and breast cancers, multiple hamartomas
Familial adenomatoid polyposis

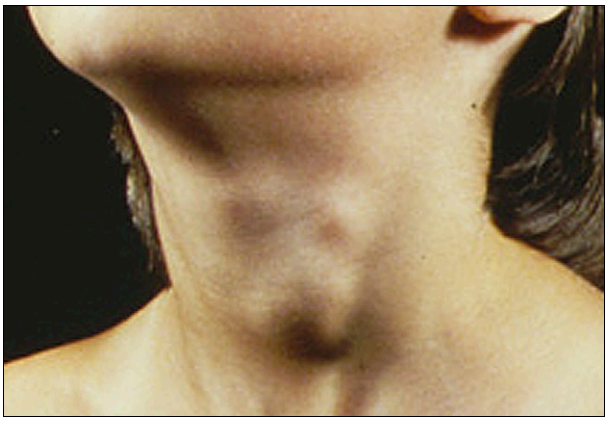

Figure 2. A patient with marked cervical lymphadenopathy (all protuberances) before diagnosis of PTC.

Evaluation

Laboratory Tests

The function of the thyroid gland should be assessed by measuring thyrotropin, thyroxine, and, in cases where hyperthyroidism is suspected, triiodothyronine. Any endocrinologic abnormalities should be corrected before surgical intervention. Although laboratory tests cannot differentiate a benign process from a malignant one, a suppressed thyrotropin level is suggestive of a hyperfunctioning nodule. In this situation, an iodine-123 thyroid uptake and scan is warranted to evaluate for a toxic adenoma or a multinodular goiter. Anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies also should be measured because their presence may signify an increased risk of malignancy.

Calcitonin is used to screen for medullary thyroid carcinoma (MTC), a cancer that originates from the parafollicular or C cells of the thyroid gland. Although an elevated level is highly suggestive of MTC, a normal level does not rule out microscopic disease. Although less sensitive than calcitonin, a serum carcinoembryonic antigen is useful for detecting MTC and monitoring for disease recurrence. Sporadic MTC is rare in the pediatric population, and MTC usually clusters in families. The inherited forms of MTC, either as part of multiple endocrine neoplasia or familial MTC, are due to an activating mutation in the RET gene. If such a condition is suspected, genetic analysis should be performed. Additionally, evaluation for a concomitant pheochromocytoma with a 24-hour urinary catecholamine collection is imperative, because this tumor would need to be removed before thyroid surgery to prevent hypertensive crisis.

Ultrasonography

Ultrasonography of the thyroid gland and regional lymph nodes offers a radiation-free method of characterizing thyroid nodules and assessing for local metastasis. Although carcinoma cannot be diagnosed by ultrasonography alone, certain imaging findings are more commonly seen in malignant lesions (see Table 3 and Fig 3). Ultrasonography can detect changes in the cervical lymph nodes, a finding that greatly increases the likelihood of malignancy. Nonpalpable thyroid nodules, which carry the same risk for malignancy as palpable nodules, may be detected. (3) Studies have found that, if there are multiple nodules, the individual risk of malignancy in each nodule decreases, but the overall cancer risk remains the same as for a patient with a solitary nodule. (8)

Fine-Needle Aspiration Biopsy

Fine-needle aspiration biopsy (FNAB) is considered the gold standard for preoperative diagnosis of thyroid nodules in adults. Three recent studies (1)(5)(9) investigated the utility of FNAB in pediatrics, and each concluded that FNAB is a highly sensitive test that should be utilized in all pediatric patients presenting with a thyroid nodule. A meta-analysis of 12 studies of pediatric FNAB found the pooled sensitivity to be 82% and specificity 91%. (9) Assuming that 20% of pediatric thyroid nodules are malignant, the meta-analysis determined the accuracy, positive predictive

Table 3. Ultrasonographic Findings Suspicious for Malignancy

Hypoechoic lesions
Intranodal microcalcifications
Intranodular central vascularization
Lesions that are more tall than wide
Lymph nodes alterations: irregular margins, increased size, lack of echogenic hilum, calcifications, irregular vascularity

There is considerable overlap between ultrasonographic findings of benign and malignant lesions.

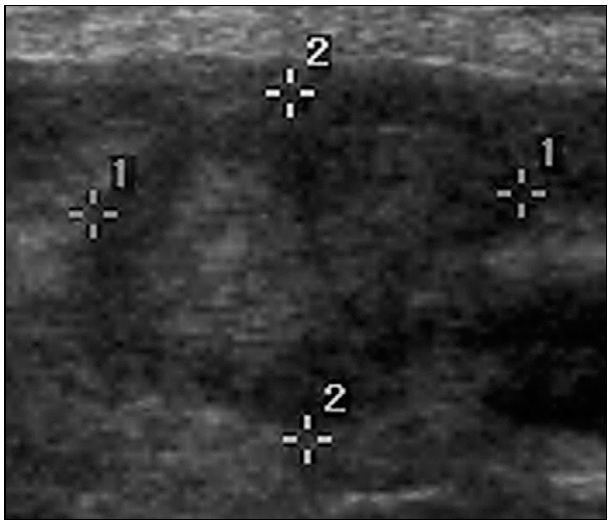

Figure 3. Ultrasonographic imaging of a thyroid nodule. Note the internal calcifications. The patient was diagnosed ultimately as having PTC and underwent a total thyroidectomy followed by radioactive iodine ablation.

value, and negative predictive value of FNAB to be 83.6%, 55.3%, and 98.2%, respectively. FNAB under ultrasonographic guidance allows for nonpalpable nodules to be biopsied and decreases the chance of a nondiagnostic biopsy. Benign FNAB results, such as the finding of a colloid nodule, can prevent unnecessary surgery. Atypical or malignant cytology guides the appropriate surgical intervention.

FNAB is not without limitations. The diagnostic yield depends on the person obtaining the biopsy to collect a sufficient sample and on the skill of the pathologist making the cytology report. It is difficult to obtain a diagnostic sample from nodules <1 cm. Although FNAB can identify PTC, follicular adenomas and carcinomas cannot be distinguished by FNAB alone and require surgical pathologic analysis to determine if the lesion invades the thyroid capsule. Nine to 20% of FNABs are nondiagnostic. (5) In that event, the physician must use other clinical criteria to decide whether to proceed with surgical resection or continued observation. The small neck size of young children and the need for sedation in most pediatric patients pose additional challenges in obtaining an FNAB. Adverse events, such as hemorrhage or abscess formation, are extremely rare after an FNAB.

Surgical Management

Although a consensus exists for early, prophylactic total thyroidectomy in children at risk for inheritable MTC, (10) the optimal surgical management of WDTC in the pediatric and adolescent population remains controversial. Proponents of lobectomy cite lower rates of surgical complications in comparison with total or near-total thyroidectomy. The most frequent complications of total thyroidectomy, permanent hypoparathyroidism with resultant hypocalcemia and permanent laryngeal nerve paralysis causing voice changes and dysphagia, occur in ~2% and 1% of patients, respectively. (11) Studies comparing the recurrence rate in children who underwent total thyroidectomy versus lobectomy are conflicting. Some authors refute that intergroup differences exist, whereas others have found recurrence rates up to 50% higher in the lobectomy group.

Although no official recommendations exist, most centers today support total or near-total thyroidectomy for pediatric WDTC. Despite a slightly higher surgical risk, total thyroidectomy allows radioiodine scanning and thyroglobulin levels to be used to detect metastases and disease recurrence (see next section). The majority of patients with PTC have microscopic foci of PTC in the contralateral thyroid lobe. Removing the entire gland eliminates these foci as potential sites of disease recurrence. This procedure decreases the need for a "completion thyroidectomy," a second surgery associated with higher rates of surgical complications. (6)

The extent to which cervical lymph nodes should be surgically explored and dissected remains debated; broad

exploration increases the risk of surgical complications, whereas less extensive investigation may miss disease. (12) After lobectomy, most individuals remain euthyroid without medication, but a total thyroidectomy will necessitate lifelong levothyroxine supplementation.

Postoperative Management

Assessing and Treating Metastases With Radioiodine

Pediatric patients afflicted with thyroid cancer have a higher incidence of lymph node involvement and distant metastases at initial presentation in comparison with adults. Each thyroid cancer metastasizes differently. PTC invades regional lymph nodes and the lungs, follicular thyroid carcinoma seeds hematologically to the lungs and liver, and MTC utilizes the lymphatic system to spread cancerous cells. WDTC cells, unlike those of MTC, are able to concentrate iodine. This property is utilized to identify WDTC metastases and remnant tissue in the thyroid bed by the use of a radioiodine whole-body scan (WBS).

WBS can be done only after a near-total or total thyroidectomy because iodine-avid thyroid tissue concentrates radioiodine more efficiently than cancerous cells, thereby limiting the detection and treatment of metastases. To maximize uptake, radiographic contrast must not have been administered in the previous 2 to 3 months, and high iodine content foods must be avoided for several weeks. Levothyroxine is replaced by triiodothyronine supplementation 4 to 6 weeks before the scan. Two weeks before all thyroid hormone support is withdrawn causing a rise in thyrotropin, ideally >30 mIU/L. Because this action renders the patient hypothyroid, some centers utilize recombinant human thyrotropin (rh-thyrotropin) injections instead, although its use in children does not have Food and Drug Administration approval.

After confirming thyrotropin elevation, the patient drinks radioactive iodine (I-131) and 24 to 72 hours later undergoes WBS by the use of a scintillation camera designed to capture emitted radiation from the ingested isotope (Fig 4). Residual tumor or significant tissue in the thyroid bed warrants surgical reexploration. If WBS reveals metastases or minimal remnant thyroid tissue, a larger treatment dose of I-131 is given with the goal of destroying the cancerous cells or ablating the remaining tissue.

Dosing of I-131 is another area of debate in managing pediatric WDTC, because no research-driven guidelines exist regarding its administration. The benefits of I-131, namely decreased disease recurrence, need to be weighed against the risks of treatment. Acute, and generally transient, side effects of I-131 include nausea, sialadenitis, altered taste, leucopenia, thrombocytopenia, and menstrual irregularities. Potential long-term risks of I-131 include decreased fertility, pulmonary fibrosis, and an increased risk of secondary malignancy, such as leukemias and solid tumors. (3) A second WBS is completed 6 months after the initial administration of radioiodine therapy to assess if a second treatment dose of I-131 is warranted.

Thyroglobulin Levels

Thyroglobulin, a protein used in the production of endogenous thyroid hormone, is produced exclusively by the thyroid gland and thyroid cancers. This property allows thyroglobulin to be used in athyreotic patients as an adjuvant to WBS in disease surveillance for WDTC. Thyrotropin stimulation causes thyroglobulin to rise, and levels should be measured after levothyroxine withdrawal or following rh-thyrotropin injection. In general, thyroglobulin levels >8 ng/mL while the patient is hypothyroid

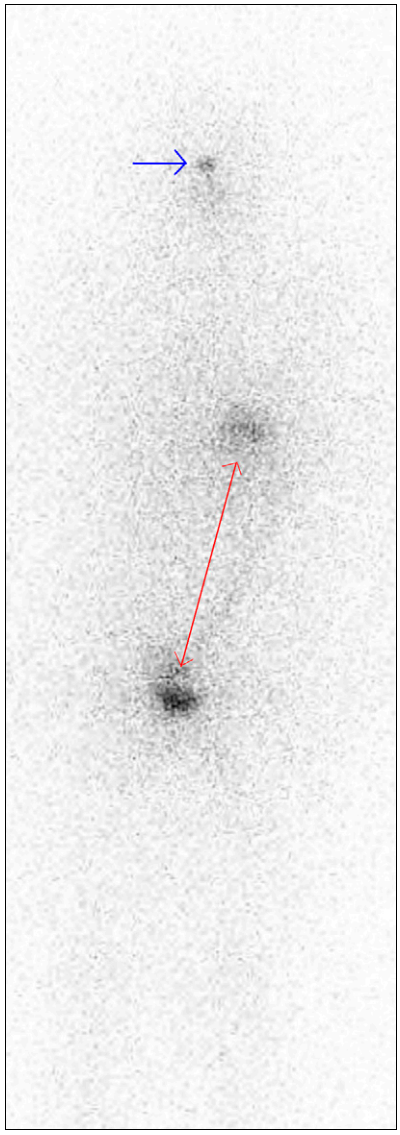

Figure 4. Example of a radioactive iodine whole body scan (WBS). Patient had a total thyroidectomy for papillary thyroid carcinoma (PTC). At the time of the scan, the patient's thyrotropin level was 39 mIU/L. The blue arrow points to remnant tissue in the thyroid bed. The red arrow points to the kidney and bladder. As the radioactivity is excreted through the urine, this pattern is a normal finding on a WBS. There is no evidence of metastases.

or >2 ng/mL after rh-thyrotropin injection suggest disease recurrence or a residual thyroid remnant. Levels of thyroglobulin should be undetectable when thyrotropin levels are not elevated. Antithyroglobulin antibodies interfere with the thyroglobulin assay, so it is important to screen patients for the presence of these antibodies.

Thyrotropin Suppression

Because thyrotropin promotes WDTC growth, it is believed that depriving the cancerous cells of this stimulation will limit their expansion. This deprivation is achieved by administering sufficient levothyroxine to suppress endogenous thyrotropin production. The degree of suppression is also under debate, with most advocating for thyrotropin levels of 0.1 to 0.4 μU/L in patients with low risk of recurrence and <0.02 μU/L in high-risk patients. The benefits of thyrotropin suppression need to be balanced against its potential risks. Long-term complications of excessive levothyroxine include headaches, insomnia, difficulty concentrating, and problems with skeletal maturation and mineralization.

Long-Term Follow-up

Specific guidelines for long-term follow-up of pediatric thyroid carcinomas do not exist and recommendations are based on the individual institution's experiences. Most centers advocate that, for the first 18 to 24 months after thyroidectomy, patients should undergo WBS and thyroglobulin measurement twice a year. I-131 can be administered every 6 months until WBS and thyroglobulin levels suggest that the WDTC has been eliminated. When there has been no evidence of disease for 12 consecutive months, these studies can be performed annually for the next 2 years, and then again 3 years later. Assuming that there has been no disease recurrence, these surveillance studies should be conducted every 5 years. As the child grows older, it is important to arrange for continuity of care with an adult endocrinologist.

Prognosis

Fortunately, even when there is advanced tumor staging and metastases at presentation, pediatric and adolescent patients with WDTC have an excellent prognosis, having higher survival rates than their adult counterparts who have less invasive disease. The overall survival rate is ~99% at 10 years, 95% at 20 years, and 90% at 30 years. Although thyroid carcinoma is rarely fatal in children and teenagers, this population is at an increased risk for disease recurrence. Historically, the progression-free survival rates are markedly lower, being 65% to 70% at 5 years, 61% at 10 years, and 46% at 20 years. (6)(12) Thyroid capsule invasion, soft-tissue invasion, positive surgical margins, presence of distant metastases at diagnosis, and presentation at <15 years old have been cited as risk factors for disease recurrence. (12) The impact of more aggressive surgical treatment, use of radioiodine, and thyrotropin suppression remains to be seen.

Summary

- Based on strong research evidence, thyroid nodules in children and teenagers are more likely to be malignant than in adults.
- Based on strong research evidence, a history of ionizing radiation to the head or neck is an independent risk factor for the development of thyroid malignancies.
- There is strong research evidence, including a recent meta-analysis, (9) supporting the use of fine-needle aspiration biopsy in the evaluation of all pediatric and adolescent patients presenting with a thyroid nodule.
- The surgical management and postoperative care of pediatric and adolescent patients who have well-differentiated thyroid carcinomas remains controversial, because the rarity of the disease limits the ability to conduct randomized, prospective research studies.
- Numerous studies have demonstrated that, despite presenting with more advanced disease, pediatric and adolescent patients with thyroid carcinoma have a higher survival rate than adults.
- The American Thyroid Association has issued strong evidence-based recommendations for the management of medullary thyroid carcinoma, including RET mutation testing and early prophylactic total thyroidectomy in children with high-risk mutations. (10)

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1. A 17-year-old boy is noted to have a palpable thyroid nodule on a routine examination. Which of the following findings makes it more likely that his nodule is malignant?
   - A. Age >15 years
   - B. Cervical lymphadenopathy
   - C. Male gender
   - D. Nodule is tender
   - E. Tachycardia

2. The boy's mother has had thyroid carcinoma, a risk factor for his having a malignancy. He undergoes ultrasonography. Which of the following ultrasonographic findings is most consistent with malignancy?
   - A. A lymph node having a sharp margin is noted
   - B. Intranodal microcalcifications are present
   - C. Lesion is hyperechoic
   - D. Lesion is wider than tall
   - E. Nodule lacks central vascularization

3. The decision is made to perform a fine-needle aspiration biopsy (FNAB). Which of the following statements about FNAB is true?
   - A. Fifty percent of FNABs are nondiagnostic
   - B. FNAB is specific but not sensitive
   - C. FNAB is straightforward and performed easily
   - D. Hemorrhage and abscess formation are common complications
   - E. It is difficult to obtain a diagnostic sample from nodules <1.0 cm

4. The boy is found to have a well-differentiated thyroid carcinoma. Most medical centers would recommend the following therapy:
   - A. Chemotherapy
   - B. Radiation therapy
   - C. Radioactive iodine
   - D. Thyroid lobectomy
   - E. Total thyroidectomy

5. After surgery, the boy and his parents ask about his prognosis. Given his age, lack of metastases, and absence of local invasion, you feel comfortable telling them that the probability of 10-year survival is approximately:
   - A. 55%
   - B. 67%
   - C. 75%
   - D. 85%
   - E. 99%

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