Management of Thyroid Nodules

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The Hospital Physician Endocrinology Board Review Manual is a study guide for fellows and practicing physicians preparing for board examinations in endocrinology. Each manual reviews a topic essential to the current practice of endocrinology.

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INTRODUCTION

Thyroid nodules are a common clinical problem presenting to both endocrinologists and general practitioners. Palpable thyroid nodules are found in 4% to 7% of U.S. residents.\(^1,^2\) A large population-based study in Framingham, Massachusetts, reported palpable nodules in 6.4% of females and 1.5% of males.\(^3\) Autopsy studies, however, report much higher rates of thyroid nodules, approaching 50%.\(^4\) With the introduction and widespread use of more sensitive imaging techniques, nonpalpable thyroid nodules are identified in patients with no prior history of thyroid disease. It is reported that incidental nodules found by ultrasound show a prevalence ranging from 19% up to 67%.\(^5\) Risk factors for development of thyroid nodules include advanced age, female gender, iodine deficiency, and prior radiation exposure.

The discovery of a thyroid nodule imparts concern for underlying malignancy, although only 5% to 10% of nodules harbor neoplastic cells.\(^1,^6\) According to American Cancer Society estimates, approximately 33,550 new cases of thyroid cancer were diagnosed in 2007, 75% of which involved women.\(^7\) Cancerous nodules are most likely to occur in patients between the ages of 20 and 55 years.\(^7\) Differentiated thyroid cancer carries a good prognosis, with a 5-year survival of 97%.\(^7\) Only malignant or large symptomatic nodules require surgical treatment. However, a systematic approach to the evaluation of thyroid nodules is important to avoid unnecessary surgery. Fine-needle aspiration (FNA) biopsy has resulted in substantial improvements in diagnostic accuracy, cost reductions, and higher malignancy yield at time of surgery.

It is important for endocrinologists to understand the historical and physical examination data that are helpful in evaluating thyroid nodules as well as the appropriate tests to consider in the workup of these lesions. This manual reviews the differential diagnosis and approach to evaluation of clinically or incidentally discovered thyroid nodules. Options for treatment, which are dependent on results of the clinical evaluation, are discussed as well.

DIFFERENTIAL DIAGNOSIS AND EVALUATION OF THYROID NODULES

CASE PRESENTATION

A 50-year-old woman is referred for evaluation after her primary care physician discovers a palpable mass in the patient’s left upper thyroid on routine physical examination.

The patient was previously unaware of the mass and has had no neck pain, dysphagia, hoarseness, or symptoms suggesting thyroid dysfunction or compression. She has no history of head or neck irradiation and takes no medications. Family history is negative for thyroid disease.

Physical examination reveals an enlarged and irregular thyroid gland with a 1-cm nodule in the left upper lobe. The nodule is firm, mobile, and nontender.

- What is the differential diagnosis of a thyroid nodule?

DIFFERENTIAL DIAGNOSIS

A simple way to classify thyroid nodules is to describe them as neoplastic or non-neoplastic (Figure 1). Neoplastic nodules can be benign or malignant.

Benign nodules include nonfunctioning adenomas. Patients with functioning nodules may present with symptoms of hyperthyroidism.

Malignant neoplastic nodules include those of thyroid origin and metastatic disease from other primary tumors. Differentiated thyroid cancers arising from follicular cells include papillary and follicular carcinoma, while anaplastic carcinoma is an undifferentiated form of thyroid cancer. Medullary carcinoma arises from C cells or parafollicular cells of the thyroid and present either in sporadic form or as part of a familial multiple endocrine neoplasia type 2 (MEN2) syndrome. The most common thyroid malignancy is papillary, comprising 75% to 80% of new cases of thyroid cancer, followed by follicular (10%–20%), medullary (3%–5%), and anaplastic (1%–2%) malignancies.\(^8,^9\) Hürthle cell
carcinoma, a variant of follicular carcinoma, is another possible thyroid malignancy. Some cancers may metastasize to the thyroid, including breast cancer, melanoma, lung cancer, and gastrointestinal and renal carcinoma. However, metastasis to the thyroid gland is a rare occurrence.

Non-neoplastic nodules commonly include colloid nodules or a dominant nodule of benign multinodular goiter. Hyperplastic nodules may develop after thyroid lobectomy, where an area of remaining thyroid gland hypertrophies. Finally, nodules in the neck are not always thyroid in origin and may represent thyroglossal duct cysts, parathyroid cysts, and vascular aneurysms. Regenerating areas associated with Hashimoto’s disease can also present as thyroid nodules.

- What is an appropriate evaluation for a clinically or incidentally identified thyroid nodule?

**EVALUATION**

Most thyroid nodules are asymptomatic and discovered by physicians during physical examination. Non-palpable nodules found on routine imaging studies are known as “incidentalomas.” Some palpable lesions may not correspond to distinct nodules on ultrasound. It is recommended that nodules larger than 1 cm in diameter be evaluated because of their potential for clinically significant malignancies. Patients with risk factors for malignancy who are found to have nodules less than 1 cm in size may also require further evaluation. An algorithm for evaluation as well as treatment of thyroid nodules, developed by the American Thyroid Association Guidelines Taskforce, is shown in Figure 2.

- What historical data should be obtained?
- What are the appropriate techniques to examine the thyroid gland?

**History**

The majority of patients with thyroid nodules are euthyroid and asymptomatic. A minority of patients may complain of neck tenderness. Sudden onset of swelling should alert the physician to spontaneous hemorrhage into the nodule or, more rarely, to anaplastic carcinoma,
Figure 2. Algorithm for the evaluation and management of patients with one or more thyroid nodules. FNA = fine-needle aspiration biopsy; $^{123}$I = radioactive iodine; PE = physical examination; $^{99m}$Tc = technetium 99m; TSH = thyroid-stimulating hormone; U/S = ultrasound.

*If the scan does not show uniform distribution of tracer activity, ultrasound may be considered to assess for the presence of a cystic component. (Adapted with permission from Cooper DS, Doherty GM, Haugen BR, et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. The American Thyroid Association Guidelines Taskforce. Thyroid 2006;16:109–42.)
an overwhelmingly fatal thyroid malignancy. Most benign nodules will grow slowly over time. Alexander et al reported that 53% of nodules grew 15% or more in volume over their 5-year retrospective case series. Malignant nodules can follow this same indolent course or they may grow rapidly.

Risk factors for nodular development include iodine deficiency, advanced age, female gender, and a history of head or neck irradiation. In years past, it was common practice for patients to undergo radiation therapy for conditions such as acne, tonsillar or thymic enlargement, and tuberculous lymphadenopathy. This exposure may damage the thyroid, leading to mutagenesis and resultant malignancy years later. The most common risk factor for nodular development worldwide is iodine deficiency, and the prevalence of nodules in these areas is much higher than that in iodine-sufficient countries. Thiocyanate from tobacco smoke has been described as a goitrogen and stimulator of nodule formation. This compound is a metabolite of cyanide in tobacco smoke and it inhibits iodine uptake and organification, thereby stimulating goiter formation. Pregnancy often results in enlargement of nodule size, especially in geographic areas of iodine deficiency, and this is likely due to increased iodine demands by the fetus. Also, there are hereditary causes of nodule formation such as autosomal dominant activating mutations of the thyroid-stimulating hormone receptor (TSHR) gene, which is a rare cause of familial toxic multinodular goiter.

Historical data suggestive of cancer include history of hoarseness or rapid nodular growth, prior head or neck irradiation, whole body irradiation, or exposure to fallout from Chernobyl at age younger than 14 years. Family history of thyroid cancer, MEN2, familial polyposis coli, and Cowden disease also raise the suspicion of thyroid malignancy.

**Thyroid Examination**

The examination should include inspection and palpation of the thyroid as well as anterior and lateral neck compartments for lymphadenopathy. It is important to note the thyroid gland consistency (smooth or irregular), size, symmetry, firmness, mobility, and presence of tenderness. Examination of the thyroid can be inconsistent and inaccurate depending on the skill of the examiner. Nodules that are firm and fixed to the surrounding tissue are suspicious for malignancy. Some differentiated cancers are cystic and soft; furthermore, calcified benign colloid nodules may be firm to palpation. In general, nodules less than 1 cm in diameter are difficult to feel but can be seen on ultrasonography. A large nodular goiter can grow into the anterior mediastinum and obstruct venous outflow by compression of the thoracic inlet. When the patient extends his arms above the head, there is further narrowing of the inlet and facial plethora develops, a clinical sign referred to as Pemberton’s sign.

**Table 1. Clinical Features Suggestive of Thyroid Cancer**

<table>
<thead>
<tr>
<th>Feature</th>
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<tbody>
<tr>
<td>Rapidly enlarging nodule</td>
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<tr>
<td>Symptoms of local invasion (hoarseness, dysphagia)</td>
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<tr>
<td>Presence of cervical lymphadenopathy</td>
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<tr>
<td>Head or neck irradiation</td>
</tr>
<tr>
<td>Whole body irradiation</td>
</tr>
<tr>
<td>Exposure to fallout from Chernobyl at age &lt; 14 years</td>
</tr>
<tr>
<td>Family history of thyroid cancer</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 2</td>
</tr>
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</table>

- Which laboratory and radiologic tests should be included in the workup?

**Thyroid Function Studies**

Serum thyroid-stimulating hormone (TSH) is an important test for all patients with thyroid nodules. Currently available third-generation TSH assays are quite sensitive in detecting subtle thyroid dysfunction. If the TSH is normal or elevated, the patient should proceed with FNA, whereas patients with suppressed TSH should undergo radioiodine scanning to further evaluate the nodule. In general, thyroid antibodies, such as thyroid-stimulating immunoglobulins, antithyroperoxidase, and anti-microsomal antibodies, are not helpful in the workup of thyroid nodules. Thyroglobulin is a useful tumor marker for patients diagnosed with differentiated thyroid cancer after thyroidectomy; however, its routine measurement in the initial workup of thyroid nodules is not recommended.

The decision whether to routinely measure calcitonin levels in all patients with thyroid nodules is controversial. Elevated calcitonin is seen in medullary thyroid cancer. Nonrandomized studies have shown that early medullary thyroid cancer (C cell hyperplasia) may be detected by routine calcitonin measurements. Questions exist regarding the sensitivity and specificity of calcitonin as well as the cost-benefit ratio of routine screening, considering medullary thyroid cancer accounts for a very small portion of thyroid cancers. Unstimulated
levels greater than 100 pg/mL are highly suggestive of medullary thyroid cancer, but false-positive results are common in renal dysfunction or in patients taking proton pump inhibitors. The American Thyroid Association guidelines could not recommend for or against routine screening of calcitonin for patients with thyroid nodules.\textsuperscript{11} Patients diagnosed with medullary thyroid cancer may be offered genetic testing for mutations in the RET proto-oncogene.

**Imaging Studies**

Diagnostic ultrasonography is a useful tool to evaluate thyroid nodules. Some authors have suggested using ultrasound in screening patients with a history of familial thyroid cancer, MEN2, or radiation exposure.\textsuperscript{22} Ultrasound can help determine nodule size, location in the gland, presence of cystic components, and nodule amenability to FNA. Tan et al\textsuperscript{23} reported that out of 151 patients with a palpable solitary nodule, 48% were found to have multiple nodules by ultrasound. Ultrasound cannot be used to distinguish benign from malignant nodules. Nevertheless, there are sonographic features of nodules that may suggest malignancy. These include the presence of microcalcifications, hypoechogenicity, irregular margins, increased intranodular vascularity, and an incomplete peripheral halo.\textsuperscript{24}

Nuclear imaging is useful for patients with suppressed TSH. Like ultrasound, nuclear scintigraphy cannot distinguish benign from malignant lesions but can reveal the nodule’s ability to take up the nuclear tracer. Cold nodules have little or no tracer uptake and are nonfunctioning. Functioning nodules may be warm, with uptake similar to the surrounding thyroid tissue, or hot, with increased tracer uptake compared with the rest of the thyroid gland. Hot nodules are rarely malignant and do not warrant biopsy.\textsuperscript{14} Up to 94\% of nodules will be cold on nuclear imaging, and only 5\% to 15\% of these will be malignant.\textsuperscript{13,25} Commonly used isotopes are technetium pertechnetate (\textsuperscript{99m}TcO\textsubscript{4}\textsuperscript{+}) and radioiodine (\textsuperscript{123}I). Technetium is less expensive and more readily available than \textsuperscript{123}I. However, it has a higher false-positive rate of hot nodules. Technetium is trapped in the thyroid cell but not organified, and as a result, potentially cold nodules on \textsuperscript{123}I scans will appear hot with technetium. One disadvantage of \textsuperscript{123}I over \textsuperscript{99m}TcO\textsubscript{4}\textsuperscript{+} is that it requires a 24-hour delay after dosing before images can be obtained.\textsuperscript{15}

Magnetic resonance imaging and computed tomography are typically not useful in the routine workup of thyroid nodules. These radiologic studies may be utilized in patients with large multinodular goiters with compressive features.

**CYTOLOGIC DIAGNOSIS AND TREATMENT OPTIONS**

**CASE CONTINUED**

Thyroid function testing reveals a TSH level of 1.2 \(\mu\)U/mL (within the normal range). Ultrasound of the thyroid shows multiple subcentimeter nodules throughout the gland. The left upper lobe nodule is solid and hypoechoic without calcifications and measures 2.2 \(\times\) 1.3 \(\times\) 1.0 cm.

- What is the significance of these findings?
- What is the appropriate next step in this patient’s management?

This patient presents with a previously undiagnosed thyroid nodule. She is euthyroid and has a multinodular goiter with a dominant left upper lobe nodule measuring 2.2 cm in its largest dimension. The patient’s risk for malignancy is statistically 5\% to 10\% but likely is less, considering that she has no worrisome risk factors. Because of the size and hypoechogenicity of the nodule, FNA biopsy is indicated. Because the patient is clinically and biochemically euthyroid, radioiodine imaging is not indicated. However, if she was hyperthyroid, radioiodine uptake scanning should be considered to identify whether or not the nodule is functional.

**FINE-NEEDLE ASPIRATION**

The most accurate and cost-effective method for evaluation of thyroid nodules is FNA. It is recommended as the procedure of choice in the workup of thyroid nodules.\textsuperscript{11} All nodules greater than 1 cm in size or any nodule with sonographic features suggestive of malignancy should be evaluated by FNA. Even if the TSH is elevated, FNA is recommended because the rate of malignancy in nodules is similar in glands affected with Hashimoto’s thyroiditis as in normal glands.\textsuperscript{26} FNA has a reported sensitivity of 68\% to 98\% and a specificity of 72\% to 100\%.\textsuperscript{27} False-negative results may occur from sampling errors or mistakes in the cytopathologic analysis. Rarely is a malignant FNA result a false-positive. Many surgeons will request FNA of any thyroid nodule prior to surgery for suspected nonmalignant lesions, as the cytology assists the surgeon in planning the operative approach.\textsuperscript{28} The procedure is quite simple with relatively little risk.
It involves making several passes through the nodule with a 25- or 27-gauge needle with or without mild suction. The aspirated contents are subsequently expelled onto glass slides and fixed in alcohol for cytopathologic analysis. Complications are possible, albeit very rare.29 In most cases, bleeding is minimal and patients tolerate the procedure without difficulty.

Patients with multinodular goiter who present with multiple nodules over 1 cm in size may require biopsy of several different nodules within the gland. Rather than simply biopsying the largest nodules, those with suspicious ultrasound appearance should be biopsied preferentially. In the case of multinodular goiter with low TSH, radionuclide scanning should be performed and FNA considered in those nodules deemed nonfunctioning.11

FNA Categories

There are 4 possible results of FNA biopsy: benign, malignant, indeterminate or suspicious, and inadequate or nondiagnostic (Table 2). The overwhelming majority of thyroid aspirations are benign. Inadequate samples occur in 10% to 20% of biopsies, while 10% will be indeterminate or suspicious for malignancy and 5% will return as malignant.13 Excessive blood or few cellular components (often seen with cystic lesions) in an aspirate will yield an inadequate result. All such biopsies should be repeated with ultrasound guidance.30 Even with excellent technique, there is a 5% chance the second biopsy will be nondiagnostic as well.13 In these cases, the patient should undergo surgical resection of the nodule. When ultrasound is used to guide FNA, the incidence of nondiagnostic samples decreases significantly. One study reported an 11% decrease in nondiagnostic biopsies with ultrasound guidance.31 Two European studies showed that ultrasound guidance decreased nondiagnostic rates from 8.7% and 16% to 3.5% and 7%, respectively.32,33 This technique is especially useful in evaluation of cystic nodules located posteriorly in the gland.

Indeterminate nodules may be reported as suspicious or as a follicular neoplasm. Unless found to be autonomously functioning or hot by radionuclide scanning, these nodules should be considered for surgical evaluation since histologic evaluation for capsular or vascular invasion is required to distinguish between follicular adenoma versus carcinoma.11 Molecular markers have been considered for use in the accurate diagnosis of indeterminate nodules but have not yielded conclusive results.34

Table 2. Fine-Needle Aspiration Results and Appropriate Therapies

<table>
<thead>
<tr>
<th>Results</th>
<th>Treatment Option(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>Follow</td>
</tr>
<tr>
<td></td>
<td>Surgery for compressive symptoms</td>
</tr>
<tr>
<td>Malignant</td>
<td>Lobectomy or total thyroidectomy</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Consider surgical evaluation</td>
</tr>
<tr>
<td>Inadequate</td>
<td>Repeat biopsy with ultrasound guidance</td>
</tr>
</tbody>
</table>

• What options are available for treatment of thyroid nodules?

TREATMENT OPTIONS

Patients presenting with 1 or more thyroid nodules and suppressed TSH should be evaluated and treated for hyperthyroidism with antithyroid drugs, radioiodine therapy, or surgery. A detailed review of treatment of hyperthyroidism is beyond the scope of this review. Briefly, antithyroid medications control the hyperthyroidism, but to shrink the goiter 131I therapy or surgery would be appropriate options. Surgery may be necessary for large nodular goiters with compressive symptoms.

Radioiodine therapy is an alternative treatment for patients with hyperfunctioning nodules from a single toxic adenoma or toxic multinodular goiter. Goals of therapy are to destroy the autonomously functioning area and to re-establish euthyroidism from the surrounding normal thyroid tissue.35 Patients may be rendered euthyroid or hypothyroid depending on the extent of normal thyroid tissue remaining after treatment.

Radioiodine may also be used to reduce the volume of nodules in nontoxic multinodular goiter after establishing benign cytologic results. Several studies have demonstrated a mean decrease in thyroid volume of 40% after 1 year36,37 and 50% to 60% after 3 to 5 years.38,39 Studies are currently being done to increase the efficacy of radioiodine using recombinant TSH.40

Benign fluid-filled nodules are usually treated with aspiration. An alternative therapy for cystic nodules is percutaneous ethanol injection. This technique involves applying ethanol directly into the nodule with ultrasound guidance. The procedure can be painful but is effective in reducing nodular volume.13,41

In an effort to decrease the size of nodules and prevent further nodular growth, some practitioners advocate suppressive treatment with thyroxine. This practice
has fallen out of favor due to lack of demonstrated efficacy in clinical trials and may result in subclinical hyperthyroidism with increased risk for cardiac arrhythmias and bone loss. Gharib and Mazzaferri reviewed the literature on suppressive therapy and found that thyroxine fails to shrink most nodules. A meta-analysis of 6 randomized controlled clinical trials concluded that a slight but insignificant reduction in nodule size was seen with suppressive therapy. The decrease in nodule size may be more pronounced in iodine-deficient areas of the world.

Those patients with nodules deemed malignant by FNA should be referred to an experienced endocrine surgeon for lobectomy or total thyroidectomy and possible lymph node dissection. More extensive surgeries may be required for patients with medullary thyroid cancer and poorly differentiated tumors. As previously described, patients with indeterminate pathology on repeat FNA should be offered thyroidectomy to obtain a definitive diagnosis.

CASE CONCLUSION

FNA biopsy of the left thyroid nodule is performed. The sample is satisfactory, and cytologic interpretation is “nodular goiter.” The patient is instructed to return for repeat ultrasonography in 6 to 12 months to reassess nodule size and in 1 year for TSH measurement.

- What follow-up is necessary in patients with thyroid nodules?

FOLLOW-UP

Nodules that are benign by FNA and do not require surgery based on size or absence of compressive symptoms should be followed clinically and with serial ultrasound to monitor nodule size and rate of growth. There are no defined guidelines for the rapidity of growth or nodule size that requires repeat biopsy. One definition of growth is a 20% increase in nodule diameter with an increase of at least 2 mm in 2 or more dimensions. Patients with benign nodules should have yearly TSH measurements and follow-up ultrasound 6 to 12 months after the initial aspiration. The frequency of serial ultrasounds thereafter depends on the nodule size stability.

SUMMARY POINTS

- Thyroid nodules are common. Although the prevalence of palpable nodules has been estimated at 4% to 7%, the rate of nodules found on autopsy or discovered incidentally on ultrasound is significantly higher.
- Only 5% to 10% of thyroid nodules are malignant, and only malignant or large symptomatic nodules require surgical treatment. However, a systematic approach to evaluation is important to avoid unnecessary surgery.
- Most patients are euthyroid and asymptomatic, making it important to review risk factors for malignant disease, including radiation exposure, family history of thyroid cancer, and history of MEN2. Clinical features suggesting thyroid cancer include a rapidly enlarging nodule, hoarseness, dysphagia, and cervical lymphadenopathy.
- Workup begins with a serum TSH measurement. If normal or elevated, the next step is FNA; if suppressed, radioiodine scanning is needed for further evaluation. Diagnostic ultrasound is useful for determining nodule size, location, presence of cystic components, and amenability to FNA.
- All nodules greater than 1 cm in size or with sonographic features suggesting malignancy should be evaluated with FNA. FNA is reliable and safe.
- The large majority of FNA results are benign. Patients with benign nodules should undergo follow-up; malignant or suspicious nodules should be treated surgically.

REFERENCES

5. Tan GH, Gharib H. Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. Ann Intern Med 1997;


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