Management of Thyroid Nodules
Case Study and Commentary, Jocelyn Hewitt, MD, and Sumathi Srivatsa, MD

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Program Audience
Primary care physicians.

Educational Needs Addressed
Thyroid nodules are very common lesions, frequently detected by modern imaging methods. Only malignant or large symptomatic nodules require surgical treatment, and a systematic approach to the evaluation of thyroid nodules is important to avoid unnecessary surgery. Fine-needle aspiration biopsy has resulted in substantial improvements in diagnostic accuracy, cost reductions, and higher malignancy yield at time of surgery. It is important for physicians to understand the historical and physical examination data that are helpful in evaluating thyroid nodules and which tests to consider in their workup.

Educational Objectives
After participating in this CME activity, primary care physicians should be able to
1. Describe the clinical presentation and risk factors for thyroid nodule
2. Know the differential diagnosis of thyroid nodule
3. Describe the tests and procedures used for workup of thyroid nodules
4. Describe treatment options for patients with thyroid nodule

CASE STUDY
Initial Presentation
A 56-year-old woman presents to her primary care physician for a routine physical examination and is found to have a 1-cm thyroid nodule in the left upper thyroid lobe. Her thyroid is enlarged and irregular and the nodule is firm, mobile, and nontender. She has no family history of thyroid disease.

• How common are thyroid nodules?

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 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 much larger prevalence of 19% to 67% [5]. The discovery of a thyroid nodule imparts concern for underlying malignancy, although only 5% to 10% of nodules harbor neoplastic cells [1,6]. The American Cancer Society projects that approximately 30,000 new cases of thyroid cancer will be diagnosed in 2006 and 75% of these cases will be in women [7]. Differentiated thyroid cancer carries a good prognosis, with a 5-year survival of 97%.

• What historical data should be obtained during evaluation of a clinically or incidentally discovered nodule?

Most thyroid nodules are asymptomatic and discovered by physicians during physical examination. Nonpalpable nodules found on routine imaging studies are known as “ incidentalomas.” Some palpable lesions may not correspond to distinct nodules on ultrasound [8]. 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 [9].

The majority of patients with thyroid nodules are

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Risk factors for nodular development include iodine deficiency, advancing 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 tuberculosis lymphadenopathy [13]. 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 [14]. Pregnancy often results in enlargement of nodule size, especially in iodine-deficient areas, 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 [15].

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 [16] (Table 1). Familial history of thyroid cancer, multiple endocrine neoplasia type 2 (MEN2), familial polyposis coli, and Cowden disease also raise the suspicion of thyroid malignancy [17].

Table 1. Clinical Features Suggestive of Thyroid Cancer

<table>
<thead>
<tr>
<th>Feature</th>
<th>Example</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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<td>Head or neck irradiation</td>
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<td>Whole body irradiation</td>
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<tr>
<td>Exposure to fallout from Chernobyl under 14 years of age</td>
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<tr>
<td>Family history of thyroid cancer</td>
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<tr>
<td>Multiple endocrine neoplasia type 2</td>
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A simple way to classify thyroid nodules is to describe them as neoplastic or non-neoplastic (Figure). Neoplastic nodules can be benign or malignant. Benign nodules include nonfunctioning and functioning 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 either present in sporadic form or as a part of familial MEN2 syndromes. 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 [18,19]. 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, as well as gastrointestinal and renal carcinoma, but 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

- What are the appropriate techniques to examine the thyroid gland?

When examining the thyroid, inspect and palpate the thyroid as well as anterior and lateral neck compartments for lymphadenopathy. 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 [2]. 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 [13]. 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 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.

- What is the differential diagnosis of a thyroid nodule?

Euthyroid and asymptomatic [10]. 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, an overwhelmingly fatal thyroid malignancy [11]. Most benign nodules will grow slowly over time. Alexander et al [12] 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.

Differentiated cancers are cystic and soft; furthermore, calcification is usually not present in differentiated thyroid carcinomas. Hürthle cell carcinomas, which tend to be more differentiated, may have a different histological appearance with dense cytoplasm and less distinct nuclear membranes, but the diagnosis is still usually made on the basis of clinical and imaging findings. Other poorly differentiated thyroid cancers, such as medullary carcinoma, are less common but have a worse prognosis. Small, well-differentiated tumors may have a more indolent course, while larger or more advanced tumors may be more aggressive. The presence of cervical lymphadenopathy suggests metastatic disease and is an important factor in determining the need for surgery. The presence of local invasion (hoarseness, dysphagia) or rapid growth is also highly suggestive of malignancy. However, some cancers may metastasize to the thyroid, including breast cancer, melanoma, lung cancer, as well as gastrointestinal and renal carcinoma, but 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.

• Which laboratory tests should be considered?

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 [11]. If the TSH is normal or elevated, the patient should proceed with fine-needle aspiration (FNA), whereas those patients with suppressed TSH should undergo radioiodine scanning to further evaluate the nodule. In general, thyroid antibodies, such as thyroid-stimulating immunoglobulins, antithyroperoxidase, and antimicrosomal 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 [9,11].

The decision on 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 [20,21]. 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 published this year could not recommend for or against routine screening of calcitonin for patients with thyroid nodules [9]. Patients diagnosed with medullary thyroid cancer may be offered genetic testing for mutations in the RET proto-oncogene.

• Which radiologic tests should be included in the work-up of thyroid nodules?

Diagnostic ultrasound 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 a history of radiation exposure [22]. Ultrasound can help determine nodule size, location in the gland,
presence of cystic components, and nodule amenability to FNA. Tan et al [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, hypoehocogenicity, irregular margins, increased intranodular vascularity, and an incomplete peripheral halo [24].

Nuclear imaging is useful for patients with suppressed TSH. Like ultrasound, nuclear scintigraphy cannot distinguish benign from malignant lesions but can reveal the nodules 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 [9]. Up to 94% of nodules will be cold on nuclear imaging and only 5% to 15% of these will be malignant [11,25]. Commonly used isotopes are technetium pertechnetate (\(^{99m}\)TcO\(_4\)) and radiiodine (\(^{123}\)I). Technetium is less expensive and more readily available than \(^{123}\)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 \(^{123}\)I scans will appear hot with technetium. One disadvantage of \(^{123}\)I over \(^{99m}\)TcO\(_4\) is that it requires a 24-hour delay after dosing before images can be obtained [11].

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.

**Patient Workup**

Thyroid function testing reveals a TSH level of 1.2 μU/mL. 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 × 1.3 × 1.0 cm.

**What is the significance of these findings?**

The patient presents with a previously undiagnosed thyroid nodule. She is euthyroid and has a multinodular goiter with a dominant left upper lobe nodule measuring more than 1 cm in size. Because she is clinically and biochemically euthyroid, radiiodine imaging is not indicated. However, if she was hyperthyroid, radiiodine 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 [9]. 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 [26]. FNA has a reported sensitivity of 68% to 98% and a specificity of 72% to 100% [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 [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 [9].

There are 4 possible results of a FNA: 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 [11]. 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 [11]. 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 reports an 11% decrease in nondiagnostic biopsies with...
ultrasound guidance [31]. Two European studies show 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 [9]. Molecular markers have been considered for use in the accurate diagnosis of indeterminate nodules but have not yielded conclusive results [34].

**What options are available for treatment of thyroid nodules?**

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 article. Briefly, antithyroid medications control the hyperthyroidism, but to shrink the goiter 131I therapy or surgery are 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 year [36,37] 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 [11,41].

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 [42] 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 nodular size was seen with suppressive therapy [43]. 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 [11]. As previously described, patients with indeterminate pathology on repeated FNA should be offered thyroidectomy to obtain a definitive diagnosis.

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

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 nodular size and rate of growth [9]. 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 at least 2-mm increase in 2 or more dimensions [9]. 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.

**What is the appropriate next step in this patient’s management?**
In this patient, FNA of the thyroid nodule is indicated. Her risk for malignancy is statistically 5% to 10% but likely less considering she has no worrisome risk factors. Assuming the nodule is benign, follow-up should include yearly measurements of TSH and repeat ultrasonography in 6 to 12 months to reassess nodular size.

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References


CME EVALUATION: Management of Thyroid Nodules

DIRECTIONS: Each of the questions below is followed by several possible answers. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. Which of the following diagnostic modalities is the most accurate and cost-effective method for evaluating thyroid nodules?
   (A) Ultrasonography
   (B) Radioactive scintigraphy
   (C) Fine-needle aspiration
   (D) None of the above

2. Which of the following characteristics of thyroid nodules would warrant evaluation by biopsy?
   (A) Microcalcifications on ultrasound
   (B) Nodular diameter of 0.8 cm
   (C) Hot nodule on $^{123}$I radioiodine scan
   (D) None of the above

3. Which of the following features are suspicious for thyroid malignancy?
   (A) Rapidly enlarging thyroid nodule
   (B) Hoarseness
   (C) History of radiation therapy for acne in childhood
   (D) None of the above
   (E) All of the above

4. Family history of thyroid cancer is most significant in which of the following cancers?
   (A) Papillary carcinoma
   (B) Medullary carcinoma
   (C) Follicular carcinoma
   (D) Anaplastic carcinoma
   (E) Lymphoma

5. For patients with a clinically significant thyroid nodule and low thyroid-stimulating hormone measurement, which of the following is the diagnostic test of choice?
   (A) Fine-needle aspiration
   (B) Ultrasonography
   (C) Radioactive scintigraphy
   (D) Measurement of anti-thyroidperoxidase antibodies
   (E) None of the above
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