



Donna Morrison. *Which Way Did It Go?* Watercolor, 23" × 30".

The diagnosis and treatment of thyroid nodules require a risk stratification by history, physical examination, and ancillary tests.

Evaluation of the Thyroid Nodule

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Background: *Thyroid nodules are common, yet treatment modalities range from observation to surgical resection. Because thyroid nodules are frequently found incidentally during routine physical examination or imaging performed for another reason, physicians from a diverse range of specialties encounter thyroid nodules. Clinical decision making depends on proper evaluation of the thyroid nodule.*

Methods: *The current literature was reviewed and synthesized.*

Results: *Current evidence allows the formulation of recommendations and a general algorithm for evaluating the incidental thyroid nodule.*

Conclusions: *Only a small percentage of thyroid nodules require surgical management. Diagnosis and treatment selection require a risk stratification by history, physical examination, and ancillary tests. Nodules causing airway compression or those at high risk for carcinoma should prompt evaluation for surgical treatment. In nodules larger than 1 cm, fine-needle aspiration biopsy is central to the evaluation as it is accurate, low risk, and cost effective. Subcentimeter nodules, often found incidentally on imaging obtained for another purpose, can usually be evaluated by ultrasonography. Other laboratory and imaging evaluations have specific and more limited roles. An algorithm for the evaluation of the thyroid nodule is presented.*

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Abbreviations used in this paper: FNAB = fine-needle aspiration biopsy, MEN = multiple endocrine neoplasia, MTC = medullary thyroid carcinoma, TSH = thyroid-stimulating hormone, CT = computed tomography, MRI = magnetic resonance imaging, US = ultrasound.

Introduction

Fundamental to evaluation of the thyroid nodule is differentiating medical from surgical disease. Although not mutually exclusive, five categories of thyroid nodules classify this broad spectrum of pathology — hyperplastic, colloid, cystic (containing fluid), inflammatory, and neoplastic,¹ with the last being the most feared. The indications for surgical management of the thyroid are suspicion of malignancy, compressive symptoms, hyperthyroidism, airway control in anaplastic cancer, and cosmesis. Clinically significant airway compression, even for a benign goiter, indicates consideration of surgical treat-

ment because with time, the thyroid will grow, and in so doing will make surgery more difficult and risky. In contrast, primary therapy for clearly benign noncompressive thyroid lesions, such as a toxic multinodular goiter, remains medical, as the surgical risks to the parathyroids and recurrent laryngeal nerves are much greater than the risks of medical therapy. The steps leading to a decision for operative intervention are the most involved when evaluating a nodule with potential for malignancy. The challenge is largely because thyroid nodules are common, yet thyroid carcinoma is not. In the United States, approximately 275,000 new thyroid nodules are detected each year,² but only 1 in 20 palpable nodules is malignant,^{3,4} and the annual incidence of clinically detected thyroid carcinoma is only 2 to 4 per 100,000 population.⁵ This knowledge alone may be of some comfort to the patient whose asymptomatic nodule was unexpectedly identified by imaging, an operation, or routine physical examination. Nevertheless, three quarters of thyroid carcinomas are asymptomatic.⁶

About 5% of adults in the United States have a palpable thyroid nodule.⁴ Nodules are more common as age increases and as iodine intake decreases, and they occur more frequently in women. Including nonpalpable nodules detected by ultrasonography, increases nodule prevalence from 30% in patients younger than 50 years of age to 50% in patients greater than 60 years of age.³ Due to anatomic factors, approximately 90% of all thyroid nodules are not palpable.^{7,8} Furthermore, half of patients with clinically apparent solitary nodules are found to have nonpalpable multinodular goiters on ultrasonography⁹ or surgical thyroidectomy.¹⁰ An earlier perception that solitary nodules are more likely malignant than a nodule within a goiter is now replaced with a general acceptance that the risk of cancer is similar in patients with solitary or multiple nodules.¹¹⁻¹³ Other types of nodules previously considered to be of low risk for cancer (long-standing nodules, nodules present in the hyperthyroid patient, and cystic lesions) have also been demonstrated to have at least an average risk of cancer.^{12,14-16} Evaluating the thyroid nodule is an involved process that begins with taking a history, performing the physical examination, and then choosing appropriate additional tests.

History

The thyroid nodule is often discovered during a complete physical examination performed routinely or for another purpose. Thus, it is common for the patient to have no knowledge of its presence. Nevertheless, many important clues may be garnered during a properly taken history. This information can begin the process of assessing risk for carcinoma, and it guides the physician in the choice of ancillary tests.

Rapidity of growth can be telling and is worth the time to elicit in detail. Very rapid enlargement over hours with pain suggests hemorrhage into an existing nodule. Although 90% of hemorrhagic nodules are benign, this finding should not be reassuring — the remaining 10% are malignant, a rate even higher than the average nonhemorrhagic nodule.¹⁶ Nonneoplastic goiters tend to develop over years. Alternatively, rapid growth over weeks is more strongly associated with malignancy, and rapid growth during levothyroxine therapy is especially suggestive of cancer.¹⁷ Similarly, a sudden change in the size of a preexisting nodule implicates malignancy. Lymphoma, anaplastic thyroid carcinoma, and metastasis to the thyroid are the most frequent causes of thyroid nodules greater than 3 cm developing within 2 months.¹⁸ Some forms of thyroiditis share the rapid time course of neoplasms but may be differentiated by other characteristics. Pain, for example, suggests thyroiditis, such as subacute (de Quervain's) thyroiditis, which is of viral etiology. The rare pyogenic thyroiditis typically involves over days to weeks, but by involving rubor, calor, tumor, and dolor, it is easily distinguished from a neoplasm. Riedel's thyroiditis may more closely mimic a neoplasm, appearing most consistent with anaplastic thyroid carcinoma by developing rapidly, being nonpainful, and feeling firm on examination. Its intense fibrosis extends to adjacent structures and therefore duplicates several behaviors of anaplastic thyroid carcinoma. Riedel's thyroiditis lacks lymph node involvement, whereas nodal spread is the norm in anaplastic thyroid carcinoma. Biopsy is usually required to definitively diagnose Riedel's thyroiditis.

Symptoms of invasion such as airway compression, hoarseness, and dysphagia require prompt evaluation for malignancy as well. Finally, symptoms of hypo- or hyperthyroidism are less likely to accompany malignancies. Certainly, patients with Hashimoto's thyroiditis (which progresses to hypothyroidism) are predisposed to developing thyroid lymphoma, but in general, alterations in thyroid states do not coincide with malignant disease.

Although it is common for the above historical features to be unknown, even the asymptomatic patient can usually produce many historical and family history features of great use in stratifying their cancer risk and thus their need for thyroidectomy. Extremes of age are telling because 20% to 50% of solitary nodules in patients younger than 20 years of age are malignant.¹⁹⁻²² Pediatric thyroid carcinoma (diagnosed at age 18 years or younger) presents most commonly in the teenage years (with a mean age of 16 years) and in girls 5.6 times more often than in boys.²³ In patients greater than 70 years old, malignant disease is not as common, but when present it has a considerably worse prognosis.²⁴ Gender is also important: when a thyroid nodule is present, the risk of malignancy in

men is twice that of women.¹² Natural prevalence of dietary iodine significantly affects thyroid pathology. Nearly one third of the world's population is estimated to live in iodine-deficient areas — predominantly in the mountainous regions such as the Himalayas, the European Alps, and the Andes, where iodine has been washed out of the soil by glaciation and flooding, and in lowland regions far from the oceans, such as central Africa and eastern Europe. Thyroid nodules in patients from iodine-sufficient areas (such as the United States, Canada, and most of Central America) have a higher rate of malignancy than those from iodine-deficient areas (5.3% vs 2.7%). Nevertheless, follicular and anaplastic carcinomas are relatively more common (as a percentage of totals) in iodine-deficient areas.¹²

Radiation exposure to the neck places the patient at high risk for the development of both benign and malignant thyroid masses. Thirty percent of patients who have been previously radiated develop palpable nodules. Among this group, the risk of carcinoma is 30% to 50%.²⁴⁻²⁶ Fully 70% to 95% of thyroid cancers occurring after radiation exposure are papillary thyroid carcinoma.²⁷ Young age at exposure is a primary risk factor for cancer after irradiation, as risk increases with the duration since exposure. Women are two to three times as likely to develop radiation-induced thyroid neoplasms as men.²⁷ The potentially long latent period between radiation exposure and the development of thyroid cancer indicates long-term evaluation among these individuals.²⁸ The Chernobyl nuclear accident on April 26, 1986, spread radiation throughout much of Europe, with short-lived iodine isotopes deposited primarily in Russia, Ukraine, and Belarus. Thyroid cancer incidence in these regions has increased 12- to 34-fold since then, particularly among those exposed as children.²⁹ Eliciting a history of this environmental exposure is therefore important in immigrants from these regions. Therapeutic radiation ranging from 150 mGy to 25 Gy to the neck for skin infections, enlarged tonsils, adenoids, or thymus was common practice in the mid-1950s and 1960s,³⁰ continuing even into the 1970s,²⁷ and is likewise relevant. Given the high risk in this radiated population, a more aggressive approach is advisable, including a low threshold for hemithyroidectomy if malignancy cannot be ruled out otherwise. The risk of cancer in a thyroid after high-dose irradiation greater than 20 Gy is diminished because of increased cell death — a factor accounting for the usual hypothyroidism in this group.²⁷

A history of tumors elsewhere in the body may indicate the presence of a tumor syndrome and raise the clinical suspicion for thyroid carcinoma. Gardner's and Cowden's syndromes (both with autosomal dominant inheritance) are associated with well-differentiated thyroid cancer. Gardner's syndrome involves multiple tumors of soft tissue and bone, and intestinal adenoma-

tous polyposis. Cowden's syndrome consists of multiple hamartomas, fibrocystic disease of the breast, and breast cancer. The syndromic features of multiple endocrine neoplasia (MEN) types IIa and IIb may also trigger consideration of medullary thyroid carcinoma (MTC). MEN inheritance is autosomal dominant, but penetrance is variable. MEN IIa consists of MTC (in all patients) as well as pheochromocytoma (in 50% of patients), and hyperparathyroidism from all-gland hyperplasia (in 10% to 30%). MEN IIb consists of MTC in about 85% of patients, but it is a more aggressive cancer than MEN IIa. This syndrome also involves mucosal neuromas (in all patients) and pheochromocytomas (in about half), and patients tend to have a marfanoid body habitus. Widespread neuromas within the gastrointestinal tract often cause constipation, which is a common lead symptom for MEN IIb. Thus, the manifestations of syndromes associated with thyroid carcinoma — ranging from diarrhea to depression — are myriad, and a new diagnosis of such a syndrome requires clinical acumen.

More common than diagnosing an inheritable syndrome by putting together a variety of signs and symptoms is making the determination through family history. Many patients have only vague recollections of their family history, and so it is often fruitful to ask them to gather a family history focusing on the thyroid for their second clinic visit. Because MTC, parathyroid hyperplasia, and pheochromocytoma are uncommon, any patient with a thyroid nodule and a family history of one or more of these disorders should undergo RET protooncogene testing. Similarly, the diagnosis of MEN 2 indicates RET mutation testing in all family members. Familial MTC is considered among the subtypes of MEN 2, but it occurs without other types of endocrine tumors. Like MEN 2, however, it is inherited in an autosomal dominant fashion and is caused by the same mutations as MEN 2a as well as by some less common mutations. Currently, genetic testing identifies >98% of MEN 2 and familial MTC cases. In the few families in whom a heritable cause for MTC cannot be excluded, evaluation must proceed as in the era before RET testing with frequent pentagastrin biochemical screening in patients at risk.³¹

Physical Examination

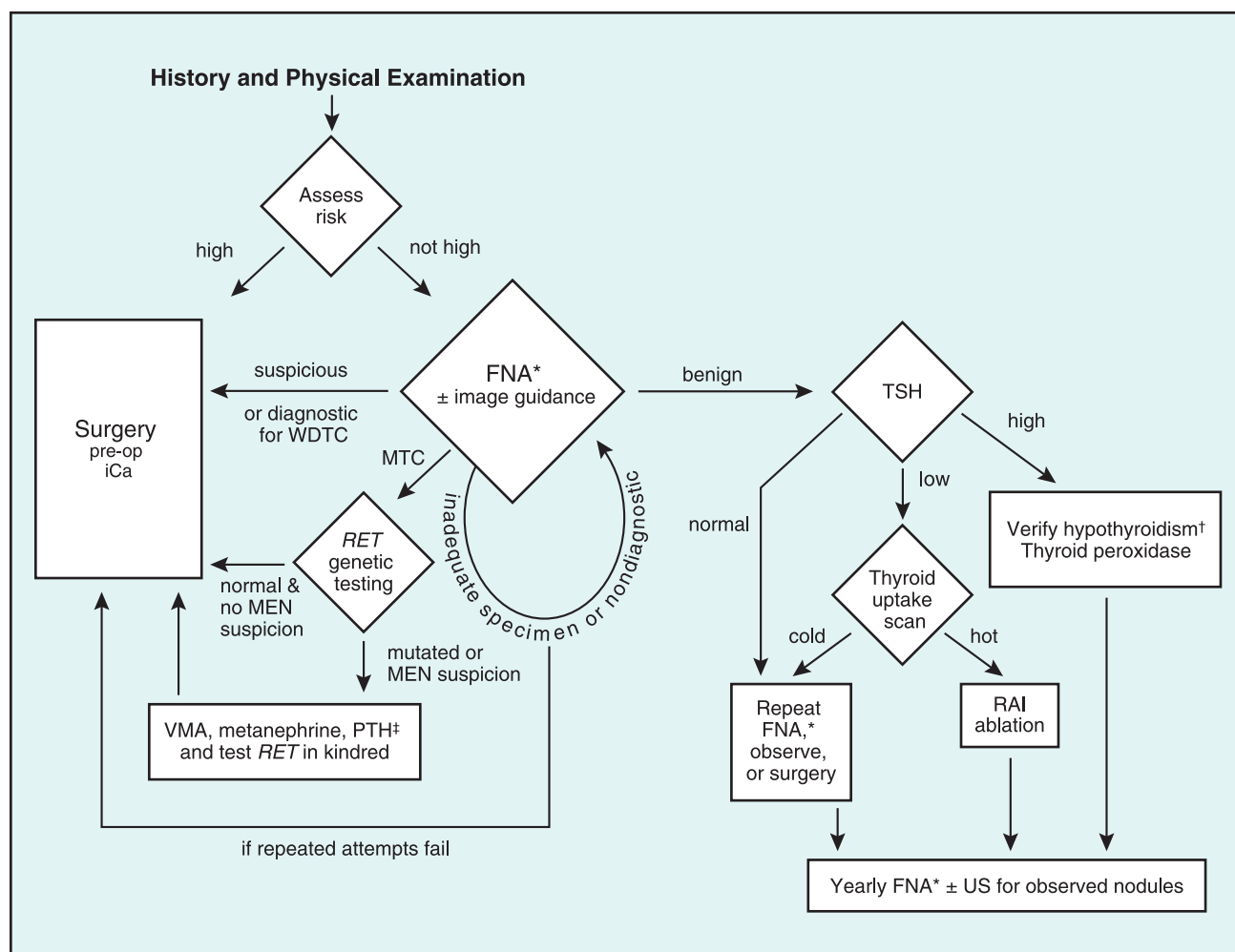
Following a thorough history, the next step in evaluating a patient with a thyroid nodule is a complete head and neck examination. The thyroid gland and nodules within it move upon swallowing, whereas masses external to the thyroid do not. The size and presence of any other palpable nodules should be noted. Its consistency (eg, firm, cystic, or rubbery) must be noted as the firmer the nodule, the greater the concern for carcinoma. Fixation suggests cellular invasion and malignancy.

All patients with a thyroid mass must have their vocal cord mobility assessed to rule out vocal cord paralysis, which would suggest invasion of the recurrent laryngeal nerve. For large or inferiorly located thyroid lesions, Pemberton's sign should be sought to evaluate the degree of substernal extension. This maneuver involves the patient raising his or her arms over the head, which results in enlargement of the mass or subjective airway compression by venous congestion when a large substernal component is present. Inspection for mucosal neuromas and marfanoid habitus should be made as this finding is suggestive of MEN IIb. Finally, thorough and careful palpation of the neck should be performed to evaluate for palpable lymphadenopathy. Large, multiple, firm, or even fixed lymph nodes are suggestive of metastatic carcinoma, from the thyroid or elsewhere. After the history and physical examination are complete, risk stratification guides the choice of ancillary tests (Figure and Table).

Ancillary Tests

Fine-Needle Aspiration Biopsy

The single most important diagnostic evaluation for a thyroid mass is the fine-needle aspiration biopsy (FNAB). It is the safest, most cost-effective, and most reliable technique available to differentiate between benign and malignant diseases of the thyroid.³² It is highly accurate, inexpensive and has low morbidity. Processing time is usually only a few days. It is estimated that its use reduces the number of thyroidectomies by half and the overall cost of thyroid nodule medical care by one quarter while doubling the surgical confirmation of carcinoma.³³ Cytopathologic evaluation has improved significantly over the past two decades, but good aspiration technique and an experienced cytopathologist are necessary to reach the modern high standards. Immediate on-site evaluation of FNA specimens dramatically increases the adequacy of



Algorithm for evaluation of the thyroid nodule. Surgery broadly includes open biopsy (eg, to obtain tissue for diagnosis if needed), partial and total thyroidectomies. VMA = vanillylmandelic acid, PTH = parathyroid hormone level, RAI = radioactive iodine, iCa = ionized calcium level.

* FNA is used on nodules >1 cm in maximal dimension. Subcentimeter nodules may be observed, including yearly serial ultrasonography, or biopsied if suspicious.

† Verify hypothyroidism with T4 and T3.

‡ A vasoactive tumor or primary hyperparathyroidism alters the surgical plan.

Clinical Indicators of Thyroid Carcinoma Risk and Surgical Indication

Finding	Risk	Remarks
MEN 2/ <i>RET</i> protooncogene mutation	high	Prophylactic total thyroidectomy indicated
Airway compression	high	Iodine ablation usually ineffective
Vocal cord paralysis	high	Preoperative FNA useful for counseling and preparation
History of neck irradiation	high	History may reveal exposure
Pediatric or elderly patient	high	Preoperative FNA optional
FNA read as malignancy	high	FNA is 80% accurate overall
FNA read as follicular neoplasm	high	FNA cannot distinguish follicular adenoma vs carcinoma; surgery recommended
Metastatic disease on isotope scan	high	Pathognomonic for carcinoma
Rapid growth over days/weeks	moderate-high	Consistent with neoplasm
Cystic nodule	moderate	Malignancy rate is double that for solid nodules, but FNA is often inaccurate
FNA non-diagnostic more than once	moderate	Evaluate technique, consider other risk factors and surgery
Euthyroid state	moderate	See text
Rapid growth over hours	moderate	Suggests hemorrhage and 10% chance of cancer
Male gender	moderate	A nodule is twice as likely to be cancer in men
Neck lymphadenopathy	moderate	Consider other causes, consider thyroglobulin and calcitonin assay of lymph node FNA
Hot or cold nodule on isotope scan	low	See Figure
Hyper- or hypothyroid state	low	Consider medical thyroidopathies

specimens compared with specimens not evaluated immediately.³⁴ Current sensitivity and specificity generally exceed 90% and 70%, respectively.^{25,35} Accuracy of 80%, a positive predictive value of 46%, and a negative predictive value of 97% are reported.³⁶ This high negative predictive value is notable and will provide reassurance to the clinician and patient. However, negative cytologic result should never override strong clinical suspicion of malignancy. With use of small needles (21 to 24 gauge), earlier concerns for needle-track seeding of malignancy have not materialized. The false-negative rate varies from 1% to 5% and is associated with cysts or nodules smaller than 1 cm or masses greater than 3 cm.³⁷ For patients who proceed to an operation, prior use of FNAB reduces the need for frozen section analysis for diagnosis, reducing operative time and pathology fees.³⁸ Altogether, the use of FNAB results in savings of \$500 to \$1300 per patient.^{39,40}

In general, FNABs are reported as clearly malignant, clearly benign, suspicious, or nondiagnostic. A nondiagnostic result should never be interpreted as benign; rather, it represents a lack of diagnosis, usually due to insufficient cells for evaluation. Papillary thyroid carcinoma is the easiest to diagnose microscopically with evidence of papillary fronds and fibrovascular cores. The nuclei are grooved and have eccentric nucleoli. Anaplastic carcinoma is also easy to identify due to its high degree of cellular atypia. Lymphoma can be suggested by FNAB, but formulating a diagnosis often requires greater amounts of tissue via open biopsy for evaluation of cytoarchitecture and flow cytometry studies. MTC is also easily identified by calcitonin

immunohistochemistry performed on the aspirate. The difficulty with thyroid FNABs occurs in reports categorized as suspicious. Usually, this represents a follicular neoplasm that is indeterminate for adenoma vs carcinoma — a diagnosis requiring identification of tumor invading the thyroid capsule or blood vessel lumens. This is impossible with an FNA specimen. However, an FNA specimen that is densely cellular, lacks colloid, and has a microfollicular pattern suggests follicular carcinoma over adenoma. Microfollicular aspirates harbor carcinoma up to 25% of the time. Benign masses typically have an abundance of colloid, small numbers of follicular cells in a macrofollicular pattern, and abundant macrophages. Follicular neoplasms are generally treated with hemithyroidectomy and isthmusectomy, a conservative procedure that may be followed by completion thyroidectomy if the final pathology confirms carcinoma.

The recent development of molecular methods applied to FNA specimens offers improved diagnostic accuracy^{41,42} and may become a more commonly available component of needle aspirate evaluation in the future. Reverse transcription-polymerase chain reaction to detect thyroglobulin mRNA and thyrotropin-receptor mRNA from a lymph node is accurate for diagnosing metastatic thyroid cancer.⁴³ When mutations in the *BRAF* gene are detected in the aspirate sample, this finding is specific for papillary thyroid carcinoma and can yield the correct diagnosis of papillary thyroid carcinoma in approximately 10% of otherwise indeterminate FNAs.⁴² Whether using these special laboratory processes or standard cytopathology, FNA of a lymph node has an advantage because the presence of any thy-

roid tissue in a lymph node lateral to the carotid is diagnostic for a thyroid malignancy, while other causes for lymphadenopathy (such as lymphoma or squamous cell carcinoma) are simultaneously evaluated.

A nodule that grows after FNA cytology is read as benign presents a challenge that should be addressed with a repeat FNAB and, if it still appears benign, consideration should be given to suppression vs excision.¹¹

Cystic lesions present a unique challenge because the fluid rarely contains adequate cellularity for cytologic diagnosis. When cystic fluid is encountered on FNAB, all of the fluid should be evacuated, and then the thyroid should be reexamined for any residual palpable mass. If present, this mass should undergo needle aspiration separately. Most thyroid carcinomas (85%) are solid, with 3% being cystic and 12% being mixed solid and cystic.⁴⁴ The rate of malignancy in thyroid nodules containing cystic fluid is 10.7%, which is twice the rate in solid nodules.¹⁶ Yet in one study, the correct diagnosis of carcinoma by FNAB was achieved in only 21% of cystic lesions compared with 45% of mixed solid and cystic lesions and 63% of solid lesions.⁴⁴ Although cystic and mixed cystic and solid lesions have a higher rate of false-negative and nondiagnostic FNAB, they also have a higher rate of malignancy (19% to 25%), making consideration of thyroid lobectomy advisable.⁶

When the cytopathologic diagnosis is indeterminate, FNAB should be repeated. Young children, however, may be unable to tolerate needle aspiration in their neck. Given the high rate of cancer in thyroid nodules of patients less than 20 years of age (20% to 50%), the failure to obtain an FNA diagnosis should not prevent consideration of thyroidectomy in this population.

The clinical scenario of a rapidly growing thyroid mass with direct extension to adjacent structures suggests either anaplastic thyroid carcinoma or Riedel's thyroiditis. FNAB can distinguish between the two in approximately 65% of cases, although the fibrotic changes in Riedel's thyroiditis may appear indistinguishable from the fibrotic reaction to anaplastic thyroid carcinoma on cellular smear. When also present, lymphadenopathy suggests anaplastic thyroid carcinoma as regional metastasis is the norm in this disease but absent in Riedel's thyroiditis. In this scenario, FNAB of the lymph node may provide the diagnosis. If this technique fails, open biopsy may be indicated to definitively differentiate between these two entities.

The older method of interpreting a shrinking nodule during a trial of thyroid-stimulating hormone (TSH) suppression with L-thyroxine as a sign of benignity has low sensitivity and specificity. Thus, the suppression method is replaced by FNAB and cytologic evaluation of the nodule.⁴⁵ The practice of treating cystic lesions and autonomously functioning nodules with sclerosing agents has gained some favor in recent years but is not widely accepted; before doing so, however, it is impor-

tant to evaluate for carcinoma by FNAB first.^{46,47} A nodule in a patient with a family history of MTC or a strong papillary thyroid carcinoma family history should also prompt FNAB and consideration of surgery.⁴⁸ Similarly, a nodule in a previously radiated neck, in the context of Graves' disease or one found on ultrasonography to have ill-defined margins, an absent sonolucent rim (a "halo"), or minute calcifications, indicates the use of FNAB,^{24,25,49,50} and thyroidectomy should be considered.

Serology and Biochemical Tests

After the history and physical examination, the degree of suspicion for malignancy can be categorized as low, moderate, or high. Appropriate laboratory studies can be chosen at this time. Although numerous tests are available, typically very few are necessary. An excellent screening test for all patients with a thyroid nodule is serum TSH level. Assuming no pituitary dysfunction or an acute illness, this sensitive assay will determine whether a patient is euthyroid, hypothyroid, or hypothyroid. Most often, patients with a thyroid nodule are euthyroid. If they are not euthyroid, this tends to point toward a benign diagnosis and a functional disorder, such as Hashimoto's thyroiditis or a toxic nodule. Patients with a high TSH level should have full thyroid function testing (T₄ and T₃). When hypothyroidism is confirmed, thyroid peroxidase (formerly called antimicrosomal) antibodies should be assayed to evaluate for Hashimoto's thyroiditis. If surgery is likely, a preoperative ionized calcium level test is helpful. If elevated, it may indicate the need for parathyroid surgery help the surgeon diagnose a parathyroid adenoma mimicking a thyroid nodule or identify primary hyperparathyroidism — which raises the possibility of MEN I or II and allows one to plan for combined thyroid-parathyroid surgery and avoid the unnecessary risk of returning for parathyroid surgery at a later date. In contrast, tests that should not be ordered at the initial evaluation include thyroglobulin and calcitonin levels. Although a high serum calcitonin level is both sensitive and specific for MTC, only 1 of 100 thyroid nodules have MTC, and this test is therefore not a cost-effective screening method for all individuals with a thyroid nodule.⁵¹ With a family history of MTC, however, a serum calcitonin should be included in the initial test as it is sensitive in detecting even small MTCs. If personal or family history of MTC exists, or if the FNA suggests this diagnosis, then mutational screening of the *RET* protooncogene should be employed. Thyroglobulin levels are appropriate as a surveillance test in well-differentiated thyroid carcinoma following total thyroidectomy but have no role in pretreatment evaluation.

Imaging Studies

Palpation is insensitive for detection of thyroid nodules, as shown by a study in which up to half of patients

with normal neck examinations were found to have nodules when imaged with ultrasonography.⁵² Furthermore, one third of these nonpalpable nodules were greater than 20 mm in diameter, underscoring limitations of palpation.

Following initial evaluation, the use of selected radiographic studies can be helpful in managing thyroid masses. Specifically, thyroid ultrasound (US) is an invaluable instrument in evaluating thyroid nodular disease. It is noninvasive, may be more readily available than the FNAB in a primary care setting, and provides information that may suggest malignancy or benign disease. US can be used to follow a nodule found incidentally by another method, such as computed tomography (CT) or magnetic resonance imaging (MRI), when it cannot be palpated. If the lesion is less than 1 cm in maximal dimension, US is helpful for serial measurements during a period of conservative observation. Alternatively, if the lesion is greater than 1 cm but not palpable, US can guide an FNAB, reducing the incidence of missing the nodule of concern. While nodule size is not predictive of malignancy,^{13,53,54} the use of 1 cm as a size threshold for use of FNAB is based on the indolent process of most thyroid carcinomas and the lack of evidence suggesting that treatment of subcentimeter microcarcinomas improves outcomes. US can also evaluate the thyroid bed for local recurrence after treatment. In addition, ultrasonography is accurate in identifying metastatic neck and paratracheal lymph nodes. Although certain sonographic findings such as hypoechogenicity, solid composition, microcalcifications, irregular or ill-defined margins, an absent sonolucent rim (or "halo"), evidence of invasion or regional lymphadenopathy, and Doppler evidence of increased blood flow in the center of the nodule are associated with an increased risk of malignancy, US usually cannot distinguish between benign and malignant lesions accurately.^{52,55,56} Since the vast majority of papillary microcarcinomas do not grow during long-term follow-up and do not become clinically significant thyroid carcinoma,⁵⁷ modalities that increase test sensitivity could increase unnecessary worry and intervention significantly by lowering specificity. Thus, using screening US may increase detection of microadenomas but may not improve patients' outcomes. However, when US findings suggest carcinoma, further evaluation by FNAB is indicated.⁵⁸ Unless US is indicated for one of the above reasons, its use adds cost and time to the evaluation, potentially delaying therapy without adding benefit. Unfortunately, US cannot penetrate bone and is thus unable to evaluate substernal nodules. When indicated, CT or MRI can be used to image the substernal thyroid.

A thyroid "incidentaloma" is a nonpalpable thyroid nodule found incidentally in surgery or by imaging studies performed for another purpose. The high

prevalence of thyroid nodules and the low individual risk, as described above, make the management of incidentalomas both routine and potentially challenging. Inspection for locally aggressive characteristics and metastatic nodes on the original imaging study may help stratify risk. Nodules greater than 1 cm generally need some intervention, such as FNAB, depending on other risk factors (Figure and Table).

Routine use of CT or MRI is not indicated in the evaluation of a thyroid nodule, but each is useful in selected circumstances. Either CT or MRI can accurately determine substernal extension and invasion of surrounding structures, such as esophagus, larynx, or trachea,²⁴ and should be used only if invasion or substernal extension is suspected. Although more readily available at most centers, CT imaging with contrast dye delivers an iodine load that can delay postoperative thyroid scanning for 4 to 8 weeks and can also cause a subclinically hyperthyroid patient to enter thyroid storm⁵⁹; thus, it should be avoided.

Isotope Scanning

Although many patients with thyroid nodules undergo radioactive iodine or technetium 99 (^{99m}Tc) scanning, there are few modern indications for its use. Ninety-five percent of nodules are cold on radioactive iodine scanning. The frequency of malignancy in cold nodules is 10% to 15% vs 4% in hot nodules.⁵¹ Thus, both hot and cold nodules are likely to be benign, and malignancy is only slightly more likely in cold than hot nodules. This test is therefore not helpful in discriminating benign from malignant nodular disease. Furthermore, in a series of 158 consecutive patients with papillary thyroid carcinoma where thyroidectomy was preceded by radioactive iodine imaging, 41% had no lesion identified on scanning.⁶⁰ Indications for radioactive iodine scanning include use in the hyperthyroid patient, as it can help differentiate between a toxic nodule greater than 1 cm in maximal dimension and the diffuse pattern in Grave's disease. Additionally, when Hashimoto's is suspected, some clinicians use radioactive iodine scanning to evaluate a nodule because a small, firm lobe of Hashimoto's can otherwise be misdiagnosed as a nodule. This finding would circumvent the need for an FNAB with its high false-positive rate in this condition. The ability of isotope scanning to detect metastatic disease (when the cancer is iodine-avid) may be the greatest diagnostic utility of this modality.

Occasionally, a patient may be referred for an incidental thyroid nodule noted only on 18-fluorodeoxyglucose positron-emission tomography (FDG-PET) scan obtained for another purpose, usually evaluation of another known or suspected malignancy. Among a group of 32 patients with a focal thyroid FDG-PET incidentaloma who then underwent FNAB, 16 (50%)

were found to be malignant — 14 were papillary thyroid carcinoma and 2 were metastatic from breast and esophagus.⁶¹ Thus, thyroid incidentalomas identified on FDG-PET scan have a high risk of malignancy and thus should be evaluated further, starting with FNAB.

Genetic Tests

Germline mutations in the *RET* protooncogene cause MEN 2a, MEN 2b, and familial MTC.^{62,63} The protein consists of an extracellular region, a transmembrane region, and an intracellular domain terminating in a catalytic core. Mutational screening of the *RET* protooncogene serologically is the current best method for screening individuals at risk for MTC. An FNAB suggestive or diagnostic of MTC or a family history of MEN or MTC indicates *RET* screening. Not only does the presence of a mutation predict MTC, but the disease phenotype is correlated with the position and type of mutation in the *RET* gene.^{64,65} Germline mutations involving the substitution of threonine for methionine due to an A-to-C transition at codon 918 in the tyrosine kinase domain cause up to 95% of classic MEN 2b cases. Classic MEN 2a is caused by mutation at codons 634, 609, 611, 618, or 620.^{66,67} Other point mutations, found in the extracellular domain, also account for MEN 2a and familial non-MEN MTC substituting a cystine residue at codon 609, 611, 618, 620, 630, or 634. Mutational analysis must include some of the less common codons as well, including 768, 790, 791, 804, 883, 891, and 922, lest a false diagnosis of sporadic MTC be rendered and family members not screened. Thus, by direct DNA analysis from a peripheral blood sample, it is possible to identify patients with these syndromes who have inherited a mutated *RET* allele and in whom MTC will develop. Even if MTC is diagnosed by FNAB, preoperative knowledge of this syndrome is essential to avoid a potential hypertensive crisis or leave the necessary parathyroid operation for another setting fraught with scarring and altered anatomy. *RET* mutational testing is available at any time from birth, and thus the indication for prophylactic thyroidectomy is available earlier than with the formerly used pentagastrin stimulation test.⁶⁶ The optimal age for prophylactic thyroidectomy among children with a *RET* mutation depends on the specific mutation and, when available, calcitonin testing.⁶⁸ Progression from C-cell hyperplasia to MTC is dependent on both age and the position of the mutated *RET* codon, and pooled data support the use of a schedule for timing of surgery (ranging from before 6 months of age to before 5 years). Yet rare cases in which nodal metastases have occurred earlier than predicted support the additional use of yearly stimulated calcitonin level to prompt earlier surgical intervention. This supplemental practice may be impossible in some countries, including the United States, where pentagastrin has become limited.⁶⁸ The importance of this genetic information in evaluating

non-index cases is that prophylactic surgery can be performed earlier and the potential for cervical lymph node dissection can be avoided.

Conclusions

The primary question raised in evaluating a thyroid nodule is whether it is likely to require surgical treatment. Airway compression usually indicates thyroidectomy, and decision making for cosmetic issues is straightforward. Identifying surgical candidates due to concern of carcinoma is more involved. Only 1 in 20 thyroid nodules are malignant, but a thorough assessment allows the physician to stratify the degree of cancer risk. Historical risk factors include rapid growth or sudden change in size of a thyroid nodule, radiation exposure to the thyroid, male gender, age less than 20 or greater than 60 years, and family history of MEN 2, familial MTC, Cowden's syndrome, or Gardner's syndrome. Physical examination risk factors include lymphadenopathy and signs of invasion or compression, including vocal cord paresis or fixation of the nodule. The presence of pulmonary metastases or recurrence of a cystic nodule is also suggestive of malignancy.

The FNAB is central to stratification of cancer risk as it has overall good accuracy and low morbidity. A patient with an FNA result that is suspicious or clearly malignant should also be counseled to undergo surgery, even in the absence of other risk factors. A nodule with cystic fluid is more likely to be malignant than its solid counterpart yet is less likely to be correctly diagnosed as malignancy by FNA, making consideration of thyroid lobectomy advisable. Overall, the 97% negative predictive value of FNA is useful in selecting patients who do not require surgery. High clinical suspicion should, however, always supersede a negative FNAB result. If a nodule is followed, FNAB should be repeated annually. US plays an important role in assessing the size, location, and number of nodules. It is often useful in guiding the FNA for small or deep nodules or when multiple nodules are present. Occasionally, US, CT, or MRI adds to the preoperative evaluation, but iodinated contrast should be avoided. We currently recommend radionuclide imaging only for nodules identified as benign by FNAB in the hyperthyroid patient. Thyroglobulin has no preoperative role. A proposed evaluation algorithm is presented in the Figure.

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