Evaluation of the Thyroid Nodule

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The evaluation and management of thyroid nodules remains an area of controversy. The past decade has witnessed two important advances. The increased availability and acceptance of fine-needle aspiration biopsy of thyroid nodules has dramatically altered the clinician's approach to this disease, and provides for the single most precise method for selecting appropriate patients for surgery. The introduction of high-resolution thyroid ultrasonography provides for anatomic definition that is clearly superior to thyroid scintigraphy. However, radionuclide imaging of the thyroid remains critical for determining the functional status of abnormal thyroid tissue. While aspiration, ultrasound, and scintigraphy all have appropriate indications, utility, and limitations, no single test or group of tests substitutes for careful clinical assessment and follow-up. This review attempts to provide a practical approach to the evaluation and management of the thyroid nodule.

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There are several peculiar aspects of goitrogenesis and thyroid neoplasia which are essential to understand in developing a reasonable approach to thyroid nodules. Thyroid nodularity is extremely common. In a population study (Framingham, MA) clinically apparent thyroid nodules were present in 6.4% of females and 1.5% of males (*1*). However, these figures significantly understate the problem. If one surveys apparently normal thyroid glands by sonography, 21% of women will have at least one thyroid nodule (*2*). Similarly, several autopsy surveys have found a prevalence of nodularity of 37%–57% (*3,4*). Therefore, while many nodules come to clinical attention because of their large size, their anterior position in the neck, or because of the skill of the physician performing the examination, most thyroid nodules are not clinically recognized.

Most clinically apparent nodules are benign. Surgical series do not provide a reliable estimate of cancer prevalence because of selection bias. Surgeons who report that 20%–40% of excised nodules are malignant have already excluded nodules which were of little clinical concern. Malignancy rates can be estimated by two recent surveys which also may not be totally void of selection bias. In a community hospital in North Carolina where most nodules were referred for surgery without benefit of aspiration biopsy, 6.5% of excised nodules were malignant (*5*). In Catania, Italy, 2,327 residents presenting with nodules were evaluated by fine-needle aspiration and 391 were selected for surgery; in adults, malignancy was found in 28% of surgical specimens, representing only 5% of all nodules (*6*). While these data assume no malignancies in the group who did not have surgery, they suggest that the malignancy rate may actually be lower than the 10%–12% rate suggested in recent literature analyses (*7,8*). Because thyroid nodules are so common, appropriate diagnostic evaluation must select a relatively small group of patients for surgery whose nodules are most likely to be malignant. Table 1 lists the common causes of thyroid nodules.

Fortunately, clinically apparent thyroid cancer is uncommon. Additionally, differentiated thyroid cancer (papillary and follicular), which presently account for about 80% of all primary thyroid malignancies, is generally associated with a good prognosis, especially in younger patients (*9*). Intrathyroidal papillary cancer in adults under age 40 is associated with a less than 2% prevalence of long-term (25-yr) mortality following primary surgical therapy (*10*). Occult papillary cancer of the thyroid, usually defined as lesions less than 1 cm, is extremely common. In the United States, recent autopsy series have reported that 5.7%–13% of all cadaver thyroids harbor an occult papillary cancer (*11,12*). The prevalence in some other countries is much higher; notably a recent series from Finland found occult papillary cancer in 36% of cadavers (*13*). These data suggest that a small papillary cancer may provide little threat to life, and its incidental finding may be inconsequential. However, the natural history of these lesions is still uncertain. A small proportion of differentiated thyroid cancers do behave in an aggressive manner (*9*). Invasive carcinomas and larger lesions, especially when they occur in older patients do have the capacity to metastasize and are more likely to be associated with a poorer long-term prognosis. Older patients with invasive papillary or follicular cancer have a 35%–65% long-term mortality (*10,14*). Poorly differentiated carcinoma, anaplastic carcinoma, some medullary cancer, and thyroid lymphoma are also aggressive, but fortunately are encountered less commonly than differentiated thyroid cancer (*9*).

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TABLE 1
Common Causes of Thyroid Nodularity

Benign	
Multinodular goiter ("colloid adenomas")	
Hashimoto's thyroiditis	
Cysts: colloid, simple, or hemorrhagic	
Follicular adenomas	
Macrofollicular adenomas	
Microfollicular adenomas (fetal)	
Trabecular adenomas (embryonal)	
Oxyphilic (Hürthle cell) types	
with cystic degeneration	
Malignant	
Papillary carcinoma	
Follicular variant	
Sclerosing variant	
Cystic adenocarcinoma	
Follicular carcinoma	
Widely invasive	
Minimally invasive	
Oxyphilic (Hürthle cell) type	
Medullary carcinoma	
Anaplastic and poorly differentiated carcinoma	
Primary lymphoma of the thyroid	
Metastatic carcinoma	
Especially breast and renal cell carcinoma	

Papillary cancer also may occur in young children, and despite a good overall prognosis, is more likely to metastasize than in adults (*15*). Since thyroid nodularity increases with age and is less common in children (*4*), the presence of a thyroid nodule in a child is twice as likely to represent a malignancy (*6*).

A history of radiation treatment to the head and neck region is also associated with an increased incidence of thyroid nodularity and malignancy (*16*). In two large series, 20%–27% of patients with exposure from predominately tonsillar or nasopharyngeal irradiation had thyroid nodularity, and 30%–33% of the nodularity represented malignancy, although some of the malignancies represented occult papillary cancers (*17,18*). There is no evidence that radiation-associated thyroid cancer is any more aggressive than other cancers (*16*).

Benign thyroid nodules may commonly occur in the thyroid by two processes. Benign monoclonal or oligoclonal thyroid adenomas have been well documented (*19*), however, they likely represent the minority of thyroid nodules (*20*). Most thyroid nodules are polyclonal and represent the expansion of relatively clonogenic cells which replicate in nodular fashion within a connective tissue framework forming multinodular glands (*21*). Adenomas have been subdivided according to morphology into predominately macrofollicular or simple adenomas, and microfollicular or cellular (atypical) adenomas. It may be difficult on histopathology, and impossible on needle biopsy, to distinguish a true monoclonal macrofollicular adenoma from polygenic nodules which are sometimes referred to as colloid adenomas. The distinction is felt to be of little importance to the patient, since both processes result in macrofollicle formation, and both processes are benign (*22,23*). Microfollicular (fetal) or cellular (embryonal or trabecular) adenomas, in contrast, do not form large follicles and are distinguished from follicular carcinoma only by their lack of capsular or vascular invasion (*22,23*). Since microfollicular and cellular adenomas are usually excised to exclude malignancy, their natural history is uncertain. It is possible that some cellular adenomas if examined with additional histopathologic sections would be reclassified as minimally invasive follicular carcinomas (*24*), while others might subsequently demonstrate invasion if left in situ, and rarely the potential to metastasize has been seen in the absence of apparent microinvasion (*24*).

Since the process involved in goitrogensis is felt to be distinct from true neoplasia (*20,21*), a general assumption has been that multinodular goiters are less likely to harbor a malignancy. This has become axiomatic with little definitive proof. Most autopsy surveys either exclude patients with known goiter, or classify thyroids as multinodular even though the nodularity would not have been clinically appreciated. Surgical series are not reliable at predicting true cancer prevalence because of patient selection. Older series suggest that the cancer prevalence in multinodular goiter is 28%–50% of that in solitary nodules (*25,26*); however, in two more recent series the prevalence of malignancy in solitary nodules was 17%–20%, while the prevalence of malignancy in multinodular glands was 13% in both (*27,28*). Such data can be used to support the concept that a dominant nodule in a multinodular gland should be evaluated as if it were a single nodule, since the risk of malignancy is not negligible.

It is therefore apparent that nodules in children and in patients exposed to head or neck irradiation are more likely to be malignant, and a solitary nodule is more likely to be cancerous than a dominant nodule in a multinodular goiter. While nodules in older patients are not more likely to be malignant, malignant nodules in older patients are more likely to show aggressive behavior. The clinical setting should thus influence the tempo and aggressiveness of diagnostic evaluation and management.

THYROID ASPIRATION AND BIOPSY

Although several centers have utilized cutting needle biopsy (CNB) or fine-needle aspiration (FNA) biopsy of the thyroid for several decades (*29–31*), only recently has this technique become accepted and widely available in North America. FNA is done with or without local xylocaine anesthesia by repetitively moving through the nodule a 21–27-gauge needle (most frequently 25 gauge) attached to a 10-ml syringe in a holder designed to facilitate the application of constant or intermittent suction. The aspirated material is smeared directly on slides, fixed, stained, and interpreted (Figs. 1–3). Biopsies may also be obtained with cutting needles which provide a core of tissue for histopathology. The use of 18–21-gauge needles during

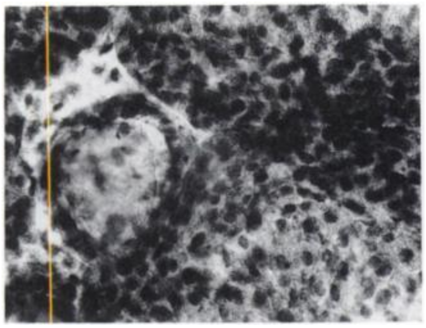

FIGURE 1. Typical cytologic appearance of a macrofollicular process showing benign macrofollicles with abundant colloid.

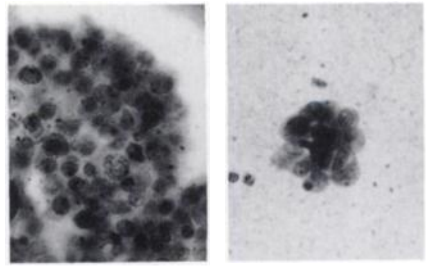

FIGURE 3. Papillary cancer demonstrating papillary structure, intranuclear inclusions, and psamomma body.

aspiration may also provide for histopathology of the material submitted as a cell block.

These techniques require expertise in obtaining, preparing, and interpreting the specimen. Many centers have reported marked improvement in both the percentage of diagnostic specimens, and the diagnostic accuracy after the first few years of utilizing these techniques. Commonly non-diagnostic rates as high as 30%–50% may be initially noted, but centers experienced in these techniques eventually are able to get adequate specimens in 90%–97% of patients (*32–39*). When FNA has been compared to CNB, some centers have reported better results with one technique or the other, while other centers have similar results for both methods, and many have commented that the techniques can be complementary (*36,37,40*). For example, colloid adenomas may be soft and difficult to cut with a core needle but provide diagnostic cytology with a fine needle, while lymphoma of the thyroid may be more readily assessed with histopathology. Assuming the availability of an experienced cytopathologist, FNA offers the advantages that the technique is virtually without complications, and can be done in an office setting by endocrinologists, cytopathologists, and other non-surgical specialists. CNB is more commonly done by trained surgeons, and rare complications such as bleeding, tracheal puncture, and recurrent laryngeal nerve injury have led some to suggest that it is more appropriately done in a hospital setting (*32*). Clinicians who evaluate nodular thyroids should first assess the available expertise in their community before selecting one method as primary over the other.

Conventional analysis of sensitivity and specificity of thyroid biopsy can be misleading and has created some confusion in the literature. The ideal test would determine whether a given nodule was benign or malignant. Unfortunately, both FNA and CNB techniques are limited by their inability to distinguish differentiated follicular thyroid cancer from a cellular or microfollicular adenoma (*41,42*). Therefore, there are four different results that one can obtain from a biopsy: malignant, benign, non-diagnostic, or indeterminate/suspicious. The latter category, which represents approximately 20% of all biopsy results, includes cellular or microfollicular neoplasms, which are classified as follicular carcinomas only if there is capsular or vascular invasion found at surgery (*41,42*). Invasion is only rarely detected by needle biopsy and surgical excision of the nodule is required to ascertain that it is noninvasive. About 18%–20% of all indeterminate/suspicious lesions will be classified as malignant after surgery because invasion is documented (*41,42*). The prevalence of malignancy is higher in larger nodules (>3 cm) (*40*). In analyzing the utility of thyroid biopsy, if one includes the indeterminate/suspicious category as "positive," then one should anticipate at least a 16% false-positive rate; if one includes this category as negative, then one would miss about 4% of thyroid cancers. As noted above, even if one had a non-surgical method to assess the presence of invasion, surgical excision of indeterminate/suspicious lesions is advocated because of their unknown natural history and potential for misclassification of a minimally invasive follicular carcinoma (*24*).

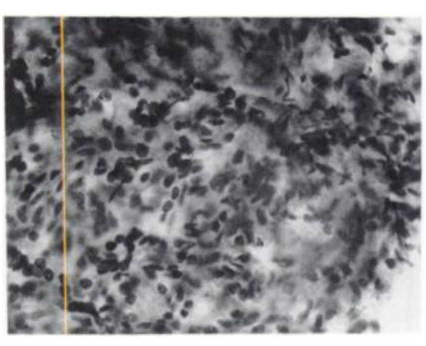

FIGURE 2. Cytologic appearance of a microfollicular adenoma showing clumps of small follicles and scant colloid.

Follicular neoplasms of the oxyphilic cell type (Hürthle cell neoplasms) are also considered suspicious and warrant surgical excision especially if the cytologic pattern is cellular or microfollicular (*38,41*). Hürthle cell carcinoma appears to have a more aggressive natural history than differentiated follicular thyroid cancer; however, this may possibly relate to their decreased propensity to accumulate radioiodine, making invasive and metastatic tumor resistant to post-surgical therapy (*43*). Management of macrofollicular oxyphilic neoplasms is controversial, since some advocate excision of all Hürthle cell neoplasms (*38,41*), while others have emphasized their benign natural history (*44*). There is considerable oxyphilic change in Hashimoto's thyroiditis, and it is essential that the cytopathologist distinguish true Hürthle cell neoplasms from chronic thyroiditis to avoid unnecessary surgery (*45*).

Management of indeterminate/suspicious cytology is further complicated by the finding of this cytologic pattern in biopsies of autonomous (hyperfunctioning) nodules. In one study, patients with well-documented hyperfunctioning thyroid nodules were subjected to FNA, and suspicious cytology was found in 7 of the 12 nodules (*46*). Since autonomous nodules are almost never malignant, it has been argued that nodules with indeterminate/suspicious cytology should subsequently be scanned with ^{123}I to exclude autonomous nodules from further surgical consideration (*46*).

Since most patients with cold nodules and either malignant or indeterminate/suspicious cytopathology will be referred for surgery, the major benefit of thyroid biopsy is to exclude surgical intervention in patients with benign macrofollicular lesions (simple or colloid adenomas) and patients with lymphocytic thyroiditis and other benign lesions. Since 65%–80% of patients will have a benign cytopathology (*36,38,39,42*), one should assess the utility of thyroid biopsy by determining the number of false-negatives, i.e., the number of patients with benign cytopathology who have malignant or cellular lesions. In most series from centers with several years experience with FNA, there are 0%–5% false-negatives (*32,33,35–37,39,40,42*). Most false-negatives occur because of sampling error (*34*), and they can be minimized by careful sampling and interpretation. Depending upon the nodule size, it may be prudent to make up to five passes through the nodule with the fine needle to assure representative sampling. Cytopathologists usually require six to eight clusters of cells on at least two different smears for adequate diagnosis.

Since most false-positives are cellular adenomas for which surgical excision cannot be avoided for accurate diagnosis, one could instead define false-positive as a benign (macrofollicular lesion) which was incorrectly diagnosed as a malignant or a microfollicular or cellular (trabecular) adenoma. Using this definition, false-positive specimens are seen in less than 5% of patients, usually due to focal hyperplasia in a macrofollicular lesion or cellular atypia in a degenerating lesion (*38,39,47*). Thus if one concedes the need for surgical intervention in cellular lesions, the accuracy of thyroid biopsy should exceed 95% (*32,34,38,47*).

It is important to emphasize that non-diagnostic lesions are not negative. The absence of malignant cells in an aspirate that does not provide for a cytopathologic diagnosis indicates an unsatisfactory specimen, not a negative specimen, and the biopsy should be repeated.

Considerable confusion has also occurred because of a nonuniform nomenclature for cytopathologic descriptions (*39*). Table 2 lists the cytopathologic categories, description, and representative surgical pathology of follicular neoplasms. It is essential that the clinician be familiar with the nomenclature used in the local cytopathology laboratory. For example, the term follicular neoplasm is useful if it indicates a cellular lesion in the indeterminate/suspicious category. However, if the term encompasses any lesion composed of thyroid follicular cells, it is useless for distinguishing macrofollicular from cellular lesions. The term follicular adenoma has been used in some laboratories to designate a benign macrofollicular neoplasm, while others have used this term to indicate an indeterminate cellular/suspicious lesion. Specific descriptive terms are essential to avoid misunderstanding.

TABLE 2
Cytopathologic Diagnosis of Follicular Lesions

Cytologic pattern	Description	Histopathology
Macrofollicular	Abundant colloid Predominately large follicles and flat sheets of follicular cells	Nodular goiter (colloid adenoma) Macrofollicular adenoma
Microfollicular	Scant colloid Small microfollicles	Microfollicular (fetal) adenoma Follicular carcinoma
Cellular	Scant colloid Clusters and clumps of cells with varying pleomorphism Cells have intranuclear inclusions and clefts	Trabecular (embryonal) adenoma Microfollicular adenoma Follicular carcinoma Follicular variant of papillary carcinoma

Cystic lesions are more difficult to diagnose by thyroid aspiration (*39,48*). While the patient may be considerably reassured when an easily palpable lesion is aspirated and the transfer of fluid from his neck to the syringe results in virtual disappearance of the palpated lump, the aspirated material is frequently old blood mixed with degenerated follicular cells and stromal elements that are unsuitable for cytologic examination. Almost all cystic lesions of the thyroid represent degenerating thyroid nodules, and the use of high-resolution ultrasonography will demonstrate the degenerating neoplastic tissue adjacent to or in the wall of the cystic structure (*49*). Following aspiration of the cyst, if the adjacent tissue is palpable, aspiration of the solid component will frequently yield a diagnosis. If a small solid component is identified by ultrasonography, ultrasound-guided needle aspiration may provide for a diagnostic specimen.

THYROID SCINTIGRAPHY

The role of thyroid scintigraphy in the initial evaluation of the thyroid nodule has been questioned by several investigators (*8,23*). However, thyroid scanning remains critical for the determination of autonomously functioning thyroid tissue. Scintigraphy is usually done with one of the radioisotopes of iodine or technetium. There are minor but potentially significant differences in the handling of these two radiopharmaceuticals by thyroid follicular cells. Normal thyroid follicular cells will trap both [^{99m}TC]pertechnetate and radioiodine. However, only radioiodine is organified to the tyrosine residues of thyroglobulin and stored in the colloid space (*50*). Most benign and virtually all malignant neoplastic or nodular goitrous thyroid tissue concentrate both radiopharmaceuticals less avidly than adjacent normal thyroid tissue. This results in a "cold" appearance on the scintogram (Fig. 4). Autonomously functioning thyroid nodules will frequently concentrate both agents more avidly than normal adjacent thyroid tissue. This results in a "hot" or hyperfunctioning appearance on the scan (Fig. 5). Autonomous nodules are almost never malignant (*51*), so for practical purposes one excludes consideration of cancer if the nodule in question is shown to be autonomous. A handful of case reports demonstrate malignancy associated with autonomous nodules (*52–55*); however, in some of these, it is uncertain whether the area of autonomy was adjacent to a hypofunctioning cancer, while others represent a focus of occult papillary cancer of uncertain significance. Certainly, careful clinical follow-up of all thyroid nodules that are not excised will allow one to detect very rare hyperfunctioning thyroid cancer.

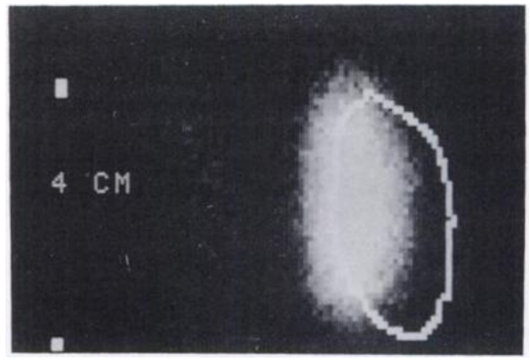

FIGURE 5. Iodine-123 scan demonstrating a large autonomous nodule with suppression of isotope concentration in the opposite lobe.

There are many well-documented discrepancies between ^{99m}Tc and radioiodine scintigraphy with regard to the function of nodular tissue. Approximately 3%–8% of benign or malignant thyroid nodules will concentrate [^{99m}Tc] pertechnetate well, but fail to organify radioiodine (*56*). Such nodules may appear "hot," "warm," or "indeterminate" on ^{99m}Tc scans and cold on radioiodine scans. While the majority of such discrepancies occur in benign lesions including cellular adenomas (*57–60*), several cases of thyroid cancer which concentrate [^{99m}Tc]pertechnetate but fail to organify radioiodine have been reported (*56,58,61–63*). Some authors have suggested therefore that functional nodules scanned with ^{99m}Tc should be rescanned with radioiodine (*58,64*).

Radioiodine scans may also be preferred because of lower backround and greater picture clarity (*65*). The lack of esophageal and salivary uptake contribute to clarity. However, in a recent crossover trial, despite reader preference for radioiodine scanning, the number of discrepant interpretations involved only 5%–8% of cases, and none of the malignant lesions were discrepant (*65*).

Radioiodine scanning is best done with ^{123}I because its short physical half-life (13 hr) and lack of beta emissions result in considerably less radiation dose to the patient than ^{131}I. However, the isotope is considerably more expensive, is produced in a cyclotron, and must be transported daily to hospitals for distribution to patients. Additionally, the tradition of obtaining 24-hr radioiodine uptakes makes scintigraphy a two-day procedure for the patient. Imaging at 4 hr allows the procedure to be done in a single day (*67*), but is still less convenient to schedule than ^{99m}Tc scans and may sacrifice some of the better imaging quality. Many investigators feel that the convenience, availability, and reduced cost of ^{99m}Tc make it an acceptable imaging agent, since the slightly better quality of radioiodine scans is of limited clinical significance, and only a rare thyroid cancer will concentrate [^{99m}Tc]pertechnetate, but fail to organify radioiodine (*65,67*).

Unlike thyroid aspiration or biopsy, scintigraphy is extremely limited as a tool to select appropriate surgical candidates. In one study, only slightly more than half of excised malignant thyroid nodules presented as "cold" defects on thyroid scintigraphy (*51*). Scintigraphy is a two-dimensional scanning technique. Its limitations result from the superimposition of abnormal nodular tissue and normally functional thyroid tissue (Fig. 6). Accordingly, over 80% of nonautonomous nodules greater than 2 cm

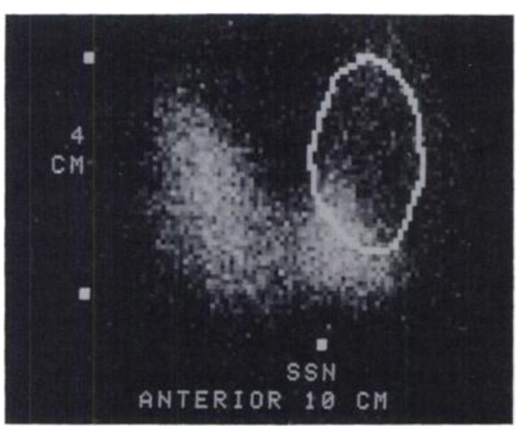

FIGURE 4. Iodine-123 scan demonstrating typical appearance of a large 3.5 cm hypofuncting ("cold") nodule.

FIGURE 6. Iodine-123 scan of a 2-cm papillary cancer that overlies normal isotope concentration in the uninvolved portion of the right lobe.

will appear "cold" on scan, while smaller nodules will present as a filling defect in less than one-third of scintigrams (*51*). The use of oblique views will improve the appropriate classification of smaller nodules. However, the majority of smaller nodules remain indeterminate on thyroid scans (*68*).

A major cause of misdiagnosis in scintigram interpretation is failure to adequately mark the nodule of clinical concern. As noted previously, there is a high prevalence of multinodularity associated with a clinically dominant nodule (*69*), and a high prevalence of occult papillary thyroid cancer (*11–12*). Therefore, it is extremely important when interpreting either individual scans or clinical series to be certain that the scintigraphic abnormality or the malignancy corresponds to the nodule that was of clinical concern. For example, in one study, 16% of the cancers detected by surgical pathologists were found in a region of the thyroid distant from the palpated nodule; almost all of these were occult papillary cancers less than 1 cm in diameter (*51*). Nodular tissue may distort thyroid architecture, resulting in a focal increased anterioposterior dimension of normal thyroid tissue which may then appear "warm" on scan. Small hypofunctioning thyroid cancers may also appear adjacent to autonomous nodular regions in a multinodular gland. Therefore, patients undergoing scintigraphy should have their glands palpated by an experienced clinician with markers superimposed upon the scintigram to accurately determine the location of the palpated abnormality.

A major cause for misunderstanding of scintigram interpretation is the use of the term "warm" to designate indeterminate nodules. The majority of thyroid cancers under 2 cm, as well as a minority of larger tumors, will fail to appear as a "cold" nodule on scan because they are located in front of or behind normally functioning thyroid tissue (*51*). Therefore, the designation "warm" nodule, which is frequently misinterpreted as a functioning nodule, is particularly inappropriate. Normal thyroid tissue requires the presence of TSH (thyroid-stimulating hormone) to stimulate the uptake of radioiodine or [^{99m}Tc]pertechnetate. When TSH is suppressed by either excessive endogenous or exogenous sources of thyroid hormone, little

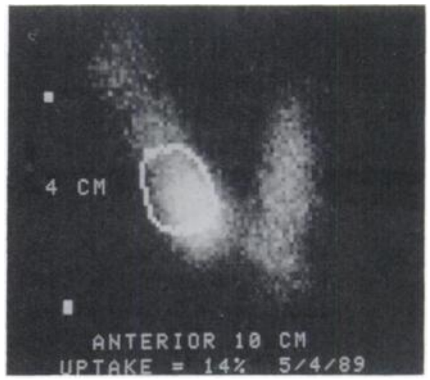

FIGURE 8. Iodine-123 scan of the same thyroid depicted in Figure 7, obtained after 4 wk of levothyroxine administration. The palpated right nodule marker overlies an area of relatively increased isotope concentration indicating autonomy since there is suppression of isotope concentration throughout the rest of the gland.

isotope concentration occurs in normal thyroid tissue. Autonomous tissue will concentrate iodine in the absence of TSH. An autonomous nodule may appear as a hot nodule on scintigraphy when the nodule itself is producing sufficient thyroid hormone to suppress pituitary TSH production, preventing isotope accumulation in the adjacent normal tissue (Fig. 5). If, however, the production of thyroid hormone by the nodule is insufficient to suppress pituitary TSH production, the nodule may appear "warm" or indeterminate on scan (Fig. 7). Nonautonomous nodules which concentrate and organify iodine poorly compared to normal thyroid tissue should appear "cold" on scan; however, as noted above, small nodules will frequently be indeterminate because of the unavoidable limitations of a two-dimensional scanning technique. Therefore the designation indeterminate is most appropriate for nodular tissue that is not unambiguously autonomous ("hot" or hyperfunctioning) or hypofunctional ("cold").

The true nature of an indeterminate nodule can be assessed by suppression scanning (*70*). Patients are given thyroid hormone to suppress serum TSH to undetectable levels, and the patient is rescanned. Uptake of tracer will be suppressed to low or undetectable levels in nonautonomous tissue, while autonomous tissue will have persistent uptake (Fig. 8). Assuming the nonsuppressible uptake corresponds to the clinically palpable nodule, then the potential for malignancy in that nodule is so low that it can be considered negligible. All indeterminate or warm nodules in which isotope uptake is suppressed by the administration of thyroid hormone are nonautonomous and should be further evaluated (e.g., with FNA) as if they had been "cold" on initial scan.

When one uses suppression scanning, one must document the adequacy of suppressive therapy. Suppression may be accomplished by administering either 1-triiodothyronine 25 μg tid for 10 days, or 1-thyroxine for 3–6 weeks. Because of the higher potential for adverse cardiac effects from excessive 1-triiodothyronine therapy, most endocrinologists prefer using 1-thyroxine to suppress serum TSH concentration. The availability of sensitive TSH tests al-

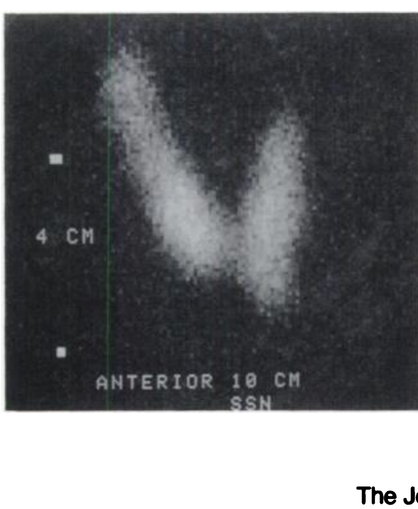

FIGURE 7. Iodine-123 scan obtained to assess a right nodule. Without a nodule marker, the location of the nodule is uncertain. A marker placed over the inferior right lobe (not shown) suggested indeterminate function.

lows for the accurate determination of subnormal serum TSH concentrations (*71*) and has made TRH testing unnecessary to document adequate TSH suppression. If the suppression scan shows persistent isotope concentration which is not clearly an area of focal uptake in an autonomous nodule, then a serum TSH should be determined coincident with the scan to validate adequate suppression of the pituitary-thyroid axis. The dose of l-thyroxine utilized depends upon the clinical setting. Average replacement doses in women are approximately 0.112 mg; they are probably higher in men and lower in the elderly, and they also vary with body mass (*72*). An appropriate dose of l-thyroxine should be selected based upon the patient's age, sex, and body mass, and should be about 0.025 mg more than the estimated replacement dose. Caution is necessary for older patients with angina or arrythmias in whom suppression scanning may be dangerous and inappropriate; some patients may require a gradual escalation of dose until TSH is suppressed. Finally, patients with autonomous nodules may become thyrotoxic with even small doses of l-thyroxine, and all patients should be warned of possible hyperthyroid symptoms (*73*).

THYROID ULTRASOUND

Most investigators would agree that the routine use of thyroid ultrasound for the evaluation of thyroid nodules is not cost effective (*7,8,23*). Nonetheless, ultrasonography provides considerably more anatomic (but not functional) detail than thyroid scintigraphy (*69*) or computerized tomography (*74*), and it has an important role in certain situations. The high-resolution 10 MHz transducers are able to resolve thyroid cysts that measure only 2 mm, and solid lesions as small as 3–4 mm in size (*75*). Initially it was hoped that the ultrasound characteristics of solid nodules might be useful in distinguishing benign from malignant lesions. Hypoechoic lesions were more likely to be malignant than benign, but discrimination was modest with only 63% of hypoechoic lesions representing malignancy in one series (*69*). A hyperechoic lesion was more likely to be benign, however 4% of such lesions were malignant. The presence of a complete halo around the nodule was also more likely to be correlated with a benign lesion, however 6% of nodules with complete halos and 16% of those with incomplete halos were found in lesions that proved to be malignant (*69*). The specificity of sonography is clearly inadequate for the selection of patients for surgical intervention and should not be routinely done before FNA or biopsy. A possible exception would be a patient who either refused biopsy or was unsuitable for biopsy (e.g., a patient requiring anti-coagulation therapy); the additional information provided by the ultrasound might help to assign a more accurate clinical risk if postponing intervention was under consideration.

A possible use for thyroid ultrasound is in the determination of multinodularity. It is clear that 20%–40% of patients referred for ultrasonography for a single thyroid nodule will be found to have multiple nodules (*69,75,76*). However, it is not clear that such multinodularity, frequently including lesions under 1 cm, has the same significance as multinodularity determined clinically or by scintigraphy. The assumption that a nodule in a multinodular gland is less likely to be malignant than a solitary nodule (*23,25,26*) is controversial since in some surgical series the prevalence of cancer in a dominant nodule in a nodular goiter may be as high as 13%, only slightly less than that of a solitary nodule (*27,28*). Thus, while the ultrasonographic findings of multinodularity might be associated with a slightly smaller risk of malignancy, it should not prevent further evaluation of a dominant lesion. A possible exception would be a small clinically dominant nodule presenting in a nodular goiter. For example, a patient with multiple nodules ranging in size from 0.5–1.5 cm might come to clinical attention because one of the several nodules lies anterior and is more easily palpated than the others. If the scintigram suggests multinodularity, an ultrasound might be reassuring to document the absence of a truly dominant nodule. It is probably unnecessary to aspirate a superficial 0.7 cm isthmic nodule when the gland contains several 1.0 cm nodules deep in both lobes which were not appreciated on palpation.

One major utility of ultrasound is for the follow-up evaluation of cystic nodules. With the advent of high-resolution ultrasonography it is clear that pure thyroid cysts are quite rare and comprise probably fewer than 1% of predominately cystic nodules (*49*). Almost all "cysts" represent degeneration or hemorrhage of associated solid lesions which can frequently be seen on sonographic images as relatively small lesions in the wall of the cyst (Fig. 9), or as adjacent solid masses (*49,75*). Many such lesions are complex with multiple solid and cystic areas. There is disagreement in the literature as to the risk of a malignancy in a predominately cystic lesion. Several series have reported few (0.5%–3%) or no malignancies in this group (*77–80*), while others have reported rates of malignancy only slightly lower than those for solid lesions (*48,81,82*). Aspiration of cyst fluid for cytologic analysis is almost always indicated (*48,83*). If there is no palpable lesion after aspiration, the diagnostic procedure may also be curative if the cyst does not reaccumulate. Malignancy is uncom-

FIGURE 9. Iodine-123 scan obtained to assess bilateral thyroid nodules. The "nodules" represented the enlarged lobes of a patient with Hashimoto's thyroiditis.

mon in cystic nodules without palpable residual following aspiration. In one series, 1% of completely aspirated cystic nodules were proved to be malignant, while 10% of nodules which could not be completely decompressed by fluid aspiration harbored a malignancy (*84*). Additional risk factors for malignancy in predominately cystic lesions include lesions larger than 3 cm, bloody aspirates, and lesions which reaccumulate on repeated aspiration (*48, 83*).

Initial ultrasonographic evaluation of a small, potentially cystic lesion may be appropriate for patients with contraindications to needle aspiration. Otherwise, the appreciation of the nodule's cystic nature can be determined by aspiration. If a significant residual solid component is palpable following primary aspiration, it should be reaspirated or biopsied (*48,81,83*). If palpation is uncertain, or cytopathology non-diagnostic, an ultrasound following aspiration is useful for determining the nature, size, and location of any persistent lesion. Relatively small solid components of complex or higher-risk lesions can be aspirated under ultrasound guidance if palpation is inadequate (*2*).

While thyroid ultrasound has a limited role for the initial evaluation of the thyroid nodule, it may have a more important role in the follow-up management of thyroid lesions. Ultrasound can be used to accurately follow nodule size over time, it can be used preoperatively to identify lymph nodes or other intrathyroidal lesions following the needle biopsy diagnosis of papillary cancer, it can identify an occult focus of papillary cancer in a patient presenting with malignancy in a cervical node, and it can be used to monitor both lymph node and thyroid bed recurrence following surgery for thyroid cancer (*85*). It may also be used to establish the presence or absence of nodularity in patients with a history of neck irradiation, or to confirm the presence of a nodule for clinicians who are uncertain of a finding on palpation. Finally, it may be used to guide needle aspiration biopsy for small lesions, or lesions situated in difficult positions such as directly anterior to the carotid artery (*2*).

PHYSICAL EXAMINATION

The use of thyroid biopsy and aspiration has dramatically increased the percentage of malignant nodules excised in most surgical series by 60%–100% and has reduced the percentage of benign nodules excised by 34%–70% (*86–88*). It is therefore apparent that physical examination has a low accuracy for predicting malignancy. However, a subgroup of patients fit clinical criteria that are so suspicious for malignancy that surgical intervention is probably indicated despite questionable cytologic or scintigraphic findings (*89*). Patients with rapid growth of a large solid thyroidal mass require surgical treatment even if the lesion is benign. A preoperative aspiration or biopsy might be useful in planning the surgical approach, but should not prevent definitive diagnosis and treatment (*90*). However, sudden enlargement of a previously evaluated nodule may indicate hemorrhage, and may be treated more conservatively (*83*). A hard and fixed mass, obstructive symptoms, the presence of lympadenopathy or vocal cord paralysis all suggest malignancy, although in one report 40% of patients with recurrent laryngeal nerve palsy had benign disease (*27*). If the diagnosis of anaplastic carcinoma or thyroid lymphoma can be made on needle aspiration or biopsy, appropriate non-surgical treatment (e.g., radiotherapy) can be instituted (*91*).

THYROID FUNCTION TESTS AND ANTI-MICROSOMAL ANTIBODIES

There is little data available as to the effectiveness of ordering thyroid function tests as part of the routine evaluation of thyroid nodule; however, most physicians obtain this information. With the advent of sensitive TSH measurements, a TSH alone should provide for adequate screening of thyroid function (*92*). If the TSH is subnormal, indicating clinical or subclinical hyperthyroidism, the possibility that the nodule is hyperfunctioning is increased and a thyroid scan would seem the logical next step. An elevated TSH suggests hypothyroidism. In North America, in the absence of prior therapy for hyperthyroidism, hypothyroidism is generally due to Hashimoto's thyroiditis. Apparent nodules may represent thyroid tissue stimulated to enlarge under the influence of high serum TSH concentrations or might represent true thyroid neoplasms. A thyroid ultrasound might distinguish these possibilities, or a rapid shrinkage of the nodule when l-thyroxine therapy is instituted might be sufficiently reassuring to mitigate further clinical concern (*93*). While the presence of positive anti-microsomal antibodies in a patient with a normal TSH might indicate the existence of Hashimoto's thyroiditis, the coexistence of thyroiditis and thyroid cancer occurs with sufficient prevalence (*15*), especially after head and neck irradiation (*94*), that one should fully evaluate a true nodule despite the presence of positive antibodies.

APPROACHES TO THE PATIENT WITH A THYROID NODULE

There is considerable diversity in the approach to the patient with a thyroid nodule. Many centers routinely obtain both thyroid scintigrams and sonography as the initial work-up in all patients. For the reasons outlined above, it is clear that sonography will only rarely suggest that further evaluation is unnecessary, and as a result, its routine use should be discouraged. It is also clear that reliance upon physical examination will result in a rather low ratio of cancers excised in surgical thyroidectomy specimens. Trials of thyroid suppressive therapy are not very specific since only 20%–30% of nodules will suppress (*7*), and in one series 13% of subsequently proven papillary cancers were reduced in size preoperatively by thyroid hormone treatment (*95*). It is generally agreed that l-thyroxine is the preferred hormonal preparation for suppressive therapy (*93*).

An excellent case can be made for evaluating all thyroid nodules initially with thyroid aspiration. A cost effective analysis suggests that this approach is also the least expensive (*8*). Benign macrofollicular lesions are followed clinically, and nodules with cytology diagnostic of cancer would be excised. Patients with microfollicular or cellular (indeterminate/suspicious) lesions could then be referred for scintigraphy. Non-autonomous ("cold") lesions would be excised to exclude capsular invasion, and autonomous ("hot") lesions would be followed, or if toxic, treated with radioiodine or surgery.

Proponents of aspiration as the initial diagnostic test fail to consider several important variables. First, patients may be extremely apprehensive regarding the biopsy procedure. If one assumes that about 5% of solitary nodules in North America are autonomous (*96*), one can save a small percentage of patients the minimal physical trauma and greater psychologic trauma of this procedure if one first obtains thyroid function tests and thyroid scintigraphy to select appropriate patients for aspiration or biopsy. Additionally, patients may be quite apprehensive about "suspicious" biopsy results, and the subsequent documentation of autonomy on a thyroid scintigram may be insufficient reassurance to prevent surgery. Second, using thyroid aspiration as an initial diagnostic procedure assumes sufficient clinical expertise that one doesn't unnecessarily biopsy patients with Hashimoto's thyroiditis. This extremely common thyroid condition frequently results in goiter, which can be quite asymmetric. Approximately 4% of referrals for thyroid scinigraphy at the Massachusetts General Hospital to evaluate a "thyroid nodule" demonstrate that the questioned nodule corresponds to an entire functioning thyroid lobe (Fig. 7). An elevated TSH and/or positive anti-microsomal antibodies will frequently confirm the clinical impression of Hashimoto's thyroiditis in these patients. Additionally, the cytologic interpretation of Hashimoto's thyroiditis can be difficult due to the presence of oxyphil cell change (*45*), and an occasional patient with thyroiditis is referred for surgery because of a suspicious biopsy which suggests a Hürthle cell neoplasm. Finally, if one begins with thyroid scintigraphy, one can save an occasional patient further evaluation if the nodule appears to be a non-dominant lesion in a multinodular goiter, which can be confirmed with ultrasonography. The cost of thyroid surgery is very high relative to the cost of scintigraphy or needle aspiration, and the cost of needle aspiration exceeds that of scintigraphy. As a result, the cost advantage of beginning with needle aspiration is eliminated if thyroid function testing and scintigraphy prevent further evaluation in only a few cases of Hashimoto's thyroiditis or multinodular goiter, or if they prevent surgery in only 1%–2% of such patients. Similarly, if only an occasional patient with an autonomous nodule and a "suspicious" aspirate decides to have surgery, the cost savings from immediate aspiration are eliminated.

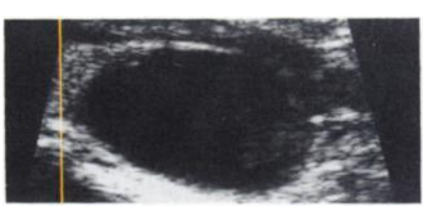

FIGURE 10. Sonographic appearance of a thyroid adenoma with cystic degeneration. The adenoma is seen within the wall of the predominately cystic structure on the right side of the photograph.

It should be apparent from the foregoing discussion that the most cost-efficient evaluation of the thyroid nodule may be dependent upon available clinical expertise. This author considers either approach (initial aspiration or initial scintigraphy and TSH measurement) reasonable and of equivalent cost. The initial diagnostic procedure(s) can be chosen based upon patient and physician preference, expertise in and availability of the procedure, and overall clinical assessment.

For example, needle aspiration may be the most appropriate initial test in the following situations: a patient with an extremely suspicious nodule, especially with coexistent lymphadenopathy or cord paralysis; a patient who cannot be adequately scanned because of a recent contrast dye load or because of pregnancy; a patient with a suspicious small lesion which is likely to be indeterminate on scintigraphy; a patient evaluated in a clinic without nuclear medicine facilities; or a patient in whom the diagnosis needs to be made rapidly because of travel or other considerations.

Thyroid scintigraphy and TSH measurement may be more appropriate as the initial diagnostic procedure in other clinical situations: a patient with a family history of Hashimoto's thyroiditis, especially if the TSH is elevated or there is an abnormal lobe contralateral to the apparent nodule; a patient with hyperthyroid symptoms or known subnormal serum TSH concentration; a patient who is anxious about the needle aspiration; a patient who is anticoagulated; or a patient evaluated in a center where expertise in fine needle aspiration is unavailable.

MANAGEMENT

The management of thyroid cancer is beyond the scope of this review. Clearly, almost all patients with cytology diagnostic of malignancy, and most patients with indeterminate/suspicious cytology will be referred for surgery and appropriate follow-up care. A recent review suggested that microfollicular and cellular adenomas could be followed on l-thyroxine suppressive therapy for growth without undue excess morbidity due to the late diagnosis of malignancy (*7*). Because of the uncertainty regarding the natural history of cellular adenomas and the ability of some differentiated cancers to regress on l-thyroxine (*70,95*), the author finds this approach unacceptable in young patients. However, in elderly patients who have significant operative risk or who have life expectancies that are limited because of non-thyroidal disease, it is reasonable to follow suspicious adenomas or even an occasional carcinoma (*40*) by administering suppressive doses of l-thyroxine.

Macrofollicular nodules are usually followed without surgery. Presently there is considerable controversy as to whether 1-thyroxine suppression should be instituted, and some have advocated clinical follow-up of benign nodules without further treatment (*97*). Only 2%–30% of nodules will regress on suppressive therapy (*7,32,70*); however, it is unknown to what extent 1-thyroxine will prevent further growth of macrofollicular lesions. While some have advocated periodic re-biopsy of macrofollicular lesions, only an occasional macrofollicular lesion will enlarge on 1-thyroxine therapy, and it would seem most appropriate to reserve repeat biopsy (or surgical excision) for such lesions. Cystic degeneration and hemorrhage is the most common cause of sudden nodular enlargement, and this can be appreciated by sonography or aspiration (*70,83*).

A recently appreciated disadvantage to suppressive doses of 1-thyroxine is the association of overzealous therapy with significant reductions in bone density (*98*). It is presently uncertain whether carefully monitored doses of 1-thyroxine, which result in minimal TSH suppression and avoid hyperthyroxinemia, are of any threat to skeletal integrity. Until prospective studies are available, it is recommended that 1-thyroxine therapy be monitored closely with sensitive TSH assays to avoid overtreatment. Using a third generation TSH assay, subnormal TSH values between 0.05–0.5 MU/liter are rarely associated with hyperthyroxinemia, while values below 0.05 MU/liter are associated with hyperthyroxinemia in 53% of patients (*92*).

Management of autonomous nodules is also controversial. Toxic nodules which result in clinical hyperthyroidism require treatment with radioiodine or surgery, and many patients are first treated with antithyroid drugs. Radioiodine is effective for toxic nodules, is rarely associated with hypothyroidism, and usually results in a significant reduction in nodule size (*99*). Autonomous nodules which result in subclinical hyperthyroidism (subnormal TSH with normal levels of thyroid hormone) present a difficult management problem. Twenty percent of autonomous nodules over 3 cm will become toxic (*96*). Such patients are at risk for iodine-induced hyperthyroidism, and some centers prophylactically ablate such nodules with radioiodine (*100*). The association of subclinical hyperthyroidism with reduced bone density, cardiac arrythmias, and exacerbation of angina suggest that a more aggressive approach to such nodules may be appropriate especially in the elderly (*101*). Autonomous nodules have TSH receptors, and those that are not associated with TSH suppression may be partly dependent upon TSH for growth (*102*). It is possible that 1-thyroxine suppressive therapy may be of benefit in preventing further growth and toxicity of such nodules (*102*), however, care must be taken to avoid clinical hyperthyroidism (*73*).

Cystic nodules present some of the greatest challenges to management. Many smaller cystic nodules are followed with negative but nondiagnostic cytology with the assumption that they are benign. Recurrent hemorrhage or slow reaccumulation of cyst contents may be a source of discomfort, anxiety, and rarely obstructive symptoms; this may lead to surgical excision despite benign cytopathology. One could argue that suppression of the underlying adenoma might reduce the frequency or growth-related degeneration and hemorrhage, however, in a small randomized study there was no benefit of 1-thyroxine therapy (*103*). Recently, investigators have reported success with sclerosing of cystic lesions by instillation of tetracycline (*104*), however, because of occasional reports of prolonged pain following this procedure, it has not gained widespread acceptance in North America.

CONCLUSIONS

Thyroid nodules are extremely common, and clinically significant thyroid cancer is relatively uncommon. The initial evaluation of thyroid nodules should effectively select patients for surgery who are likely to have a malignancy. While thyroid aspiration biopsy is the single most precise test for selecting appropriate patients for surgery, thyroid scintigraphy is essential if one wishes to exclude patients with autonomous nodules from surgical intervention. Many physicians prefer to use the results of thyroid function testing and scintigraphy to select appropriate patients for biopsy, while other physicians choose to use scintigraphy in patients with suspicious cytopathology to exclude patients with autonomous nodules from surgery. The optimal approach depends upon the clinical setting, patient preference, and available expertise. Nonexcised nodules require careful clinical follow-up. Suppression of serum TSH concentration by administering 1-thyroxine to shrink nodules or prevent their further growth remains a commonly accepted clinical practice, although the long-term efficacy and risks of such therapy remain poorly defined.

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