Jacques-Enguérrand Gourgue. *Houngan.* From the collection of Mr. and Mrs. J. Roderick Heller, III.

Distinguishing between malignant and benign thyroid nodules is necessary to ensure proper management of malignant nodules.

Evaluation of the Thyroid Nodule

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Background: *Clinically detectable thyroid nodules occur in up to 4% of the population in the United States. With ultrasound, nodules may be found in up to 50% of those over 50 years of age.*

Methods: *The author reviews his own experience as well as that of others to define a sound clinical approach to the differential diagnosis and detection of thyroid cancer.*

Results: *Prior neck irradiation is a risk factor for thyroid malignancy. The association of a thyroid nodule with enlarged lymph nodes or fixation of the nodule to strap muscles or the trachea suggests malignancy. A diffusely multinodular gland is usually benign.*

Conclusions: *Thyroid function tests rarely help a differential diagnosis. Fine-needle aspiration is the "gold standard" for diagnosis. Tiny "incidentalomas" are often followed with repeat monitoring for change of size or character.*

Introduction

Thyroid cancer accounts for only 0.4% of all cancer deaths and approximately 5 deaths per million population in the United States each year.[1] However, its clinical importance is disproportionate to its incidence because cancers of the thyroid must be differentiated from the much more frequent benign nodules (adenomas and multinodular goiters). Clinically detectable thyroid nodules occur in up to 4% of the population. With ultrasound, nodules may be found in up to 50% of the population over 60 years of age.

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Clinical History of Nodules

Conditions that should be considered in the differential diagnosis of a thyroid nodule are listed in Table 1. They include adenoma, cyst, multinodular goiter, an area of thyroiditis, irregular regrowth of tissue if surgery has been performed, and thyroid cancer. Factors that must be considered in determining the need for further workup include age, sex, and family history of the patient, history of the lesion, a history of neck irradia-

Table 1. — Differential Diagnosis of the Thyroid Nodule

Adenoma
Cyst
Carcinoma
Multinodular goiter
Hashimoto's thyroiditis
Subacute thyroiditis
Effect of prior operation or ^{131}I therapy
Thyroid hemiagenesis
Metastasis
Parathyroid cyst or adenoma
Thyroglossal cyst
Nonthyroidal lesions:
- Inflammatory or neoplastic nodes
- Cystic hygroma
- Aneurysm
- Bronchocele
- Laryngocele

tion, physical characteristics of the gland, local symptoms, and laboratory evaluation.

The age of the patient is an important consideration since the ratio of malignant-benign nodules is higher in youth. Men also carry a higher risk of malignancy.[2] Nodules are less frequent in men, but a greater proportion of them are malignant. Patients with the heritable multiple endocrine neoplasia (MEN) type 2 syndrome have pheochromocytomas, medullary thyroid carcinomas, hyperparathyroidism, and mucosal neuromas.

Prior neck irradiation is a risk factor for thyroid malignancy. Any irradiation above 0.5 Gy to the thyroid during the first 3 or 4 years of life has been associated with a 1% to 7% incidence of thyroid cancer occurring 10 to 30 years later.[3] Because of the high prevalence (20% to 40%) of carcinoma in nodules resected from irradiated glands, the finding of one or more clear-cut nodules in a radiated gland or a cold area on scan requires consideration for removal. In this case, multiple nodules do not assure that the lesions are benign.

The history of the neck lump itself is important. Recent onset, growth, hoarseness, pain, nodes in the supraclavicular fossae, symptoms of brachial plexus irritation, and local tenderness all suggest malignancy. The usual cause of sudden swelling and tenderness in a nodule is hemorrhage into a benign lesion. Although the presence of a nodule for many years suggests a benign process, some cancers grow slowly. A listing of the most common thyroid neoplasms is shown in Table 2.

Physical Findings

A thyroid nodule is typically felt as a discrete lump in an otherwise normal gland, and it moves with the thyroid. The association of a thyroid nodule with enlarged lymph nodes, particularly anterior triangle adenopathy, suggests malignant disease. Fixation of the nodule to strap muscles or the trachea also suggests malignancy. Pain, tenderness, or sudden swelling of the nodule usually indicates hemorrhage into the nodule but can also indicate an invasive malignancy. Hoarseness may arise from pressure or by infiltration of a recurrent laryngeal nerve by a neoplasm and is usually associated with malignancy. Fluctuance in the lesion suggests the presence of a cyst that is most likely benign.

The presence of a diffusely multinodular gland, ascertained on the basis of palpation or sonography, usually can be interpreted as a sign of a benign goiter. If there is one area within a multinodular goiter that is distinctly different from the remainder of the gland on the basis of palpation or function or has demonstrated rapid growth, or if there are two discrete nodules in a gland that is otherwise normal, then there is the possibility of a malignant neoplasm rather than a benign multinodular goiter.[4] Although multinodularity reduces the possibility of malignancy, malignancy can occur in the multinodular gland.

In addition to a nodule, the gland occasionally has the diffuse enlargement and firm, irregular con-

Table 2. — Neoplasms of the Thyroid

Adenomas
• Follicular
Colloid variant
Embryonal
Fetal
Hürthle cell variant
• Papillary
• Teratoma
Malignant Tumors
• Differentiated
Papillary adenocarcinoma:
Pure papillary adenocarcinoma
Mixed papillary and follicular carcinoma (variants including tall cell, follicular, oxyphil, solid)
Follicular adenocarcinomas (variants: "malignant adenoma," Hürthle cell carcinoma or oxyphil carcinoma, clear cell carcinoma, insular carcinoma)
• Medullary carcinoma
• Undifferentiated
Small cell (to be differentiated from lymphoma)
Giant cell
Carcinosarcoma
• Miscellaneous
Lymphoma, sarcoma
Squamous cell epidermoid carcinoma
Fibrosarcoma
Mucoepithelial carcinoma
Metastatic tumor

sistency of chronic thyroiditis, a palpable pyramidal lobe, and antibody test results that may be positive. These findings strongly suggest thyroiditis but do not disclose the nature of the nodule, which must be evaluated independently. It should be remembered that 14% to 20% of thyroid cancer specimens contain diffuse or focal thyroiditis.

Thyroid Function Tests

Patients with a thyroid nodule are usually euthyroid. Normal values for the serum T_4 and thyroid-stimulating hormone (TSH) levels support this impression. Low thyroxine (T_4) results or elevated TSH levels should raise the question of thyroiditis. The serum thyroglobulin concentration may be elevated, as in all other goitrous conditions, and therefore is not a valuable tool in differential diagnosis of thyroid malignancy. Calcitonin assay is indicated in the presence of a family history or features of the MEN type 2 syndromes. A chest radiograph should be taken if a normal film has not been reported in the prior 6 months. Soft-tissue radiographs of the neck may disclose indentation or deviation of the trachea if the tumor is more than 3 or 4 cm in diameter. Fine, stippled calcifications through the tumor (psammoma bodies) are virtually pathognomonic of papillary cancer. Patchy or "signet ring" calcification occurs in old cysts and degenerating adenomas.

Calcitonin Assays

Although medullary thyroid cancer constitutes a small fraction of thyroid malignancies and an even smaller proportion of thyroid nodules, several reports suggest that routine screening of nodular goiters by calcitonin assay is an appropriate approach. Such screening offers the possibility of finding tumors before they have metastasized. Whether the considerable expense is justified remains unclear, and routine screening has not been adopted as a measure in most clinics.

Fine-Needle Aspiration Cytology

Fine-needle aspiration (FNA) cytologic examination has been widely adopted after numerous favorable reports of its accuracy. FNA has now become the standard for the determination of the significance of a thyroid nodule. The procedure is technically simple and acceptable to patients, but it requires an experienced operator and collaboration with a skilled cytopathologist who is knowledgeable in interpreting thyroid aspirations. Significant complications such as bleeding, infection, induced necrosis, or cyst formation are rare. Adequate specimens can be obtained in more than 90% of patients when two or three passes are prepared for analysis. When FNA is used in experienced hands, false-negative and false-positive diagnoses occur in less than 5%. Currently, FNA is viewed as the "gold standard" for diagnosis in most cases, and it plays a crucial role in the selection of patients for operation. Gharib and coworkers[5] recently analyzed data on 10,000 FNAs and found the procedure to be the preferred first step in diagnosis. The diagnostic accuracy was nearly 98%, with less than 2% false-positive and false-negative results.

In general, 5% to 8% of aspirates are diagnostic of malignancy, 10% to 20% are considered suspicious but not diagnostic (demonstrating microfollicular cytology), 2% to 5% fail to provide an adequate specimen, and the remainder are considered benign, usually suggestive of a "colloid nodule" or thyroiditis.[6] An inadequate specimen should lead to reaspiration. A biopsy of nonpalpable nodules can be performed under ultrasound guidance. Nonpalpable thyroid nodules, typically less than 1 cm in size, are usually nonmalignant. Ultrasound-guided fine-needle aspiration biopsy may be appropriate in these individuals. A positive diagnosis of cancer leads to surgery. Patients with suspicious FNA histology should also undergo surgery since approximately 25% prove at surgery to be malignant. In the remainder of patients, continued observation and possibly suppressive thyroxine therapy are offered. Patients who do not undergo surgery are seen at 6- or 12-month intervals and examined for any sign such as pain, growth, hoarseness, or nodes that might indicate a change in the character of the tumor. Another biopsy is performed after 2 to 3 years and again after 5 to 8 years to document the benign nature of the lesion. The outcome of reaspiration of benign nodular thyroid disease was investigated by Erdogan et al[7] in studies on more than 200 patients. Three of 216 patients had a diagnosis changed from benign to papillary carcinoma at the time of the second biopsy. The authors conclude that a second aspiration of clinically suspicious nodules can correct some initial false-negative results, but routine reaspiration was not useful in clinically stable disease.

Thyroid Sonography

Sonographic examination of thyroid nodules is now commonly performed. Good technique demonstrates nodules more than 3 mm in size, indicates cystic areas, and may demonstrate a capsule around the nodule and the size of the lobes. Thyroid sonography often displays multiple nodules when only one is noted clinically. The technique is more sensitive than scintiscanning, is noninvasive, involves less time, allows serial examinations, and is usually less expensive. Three percent to 20% of lesions are found to be totally or partially cystic. Purely cystic lesions are

reported to have a lower incidence of malignancy than solid tumors (3% vs 10%).

Isotope Scans

The scintiscan received much attention in the past as an aid in the differential diagnosis of thyroid lesions. The scan can provide evidence for a diagnosis in a multinodular goiter, in Hashimoto's thyroiditis, and rarely in thyroid cancer when functioning cervical metastases are seen. The chance of malignancy is low if the scan demonstrates a hyperfunctioning nodule suppressing the remainder of the gland and if the patient is thyrotoxic as demonstrated by an elevated serum T_4 or T_3 level or by suppressed sensitive TSH (sTSH). Malignant tumors usually fail to accumulate iodide to a degree equal to that of the normal gland. However, most cold nodules are benign adenomas and cysts rather than cancers. The reported incidence of cancer in cold nodules is highly variable; a review of 400 cases found 10% to be cancer.[8] Tumors smaller than 1 cm in size are below the discriminating power of most of the available scanning devices. Thus, a nodule 1 cm or less in diameter that fails to collect radioactive iodine (cold nodule) might not be delineated at all on the scintiscan. Further, many nodules turn out to be neither cold nor hot (preferential isotope accumulation). The thyroid scintiscan has some value, primarily for the clearly toxic nodule. The thyroid scintiscan is not a reliable predictor as to whether a palpable nodule is malignant or benign.

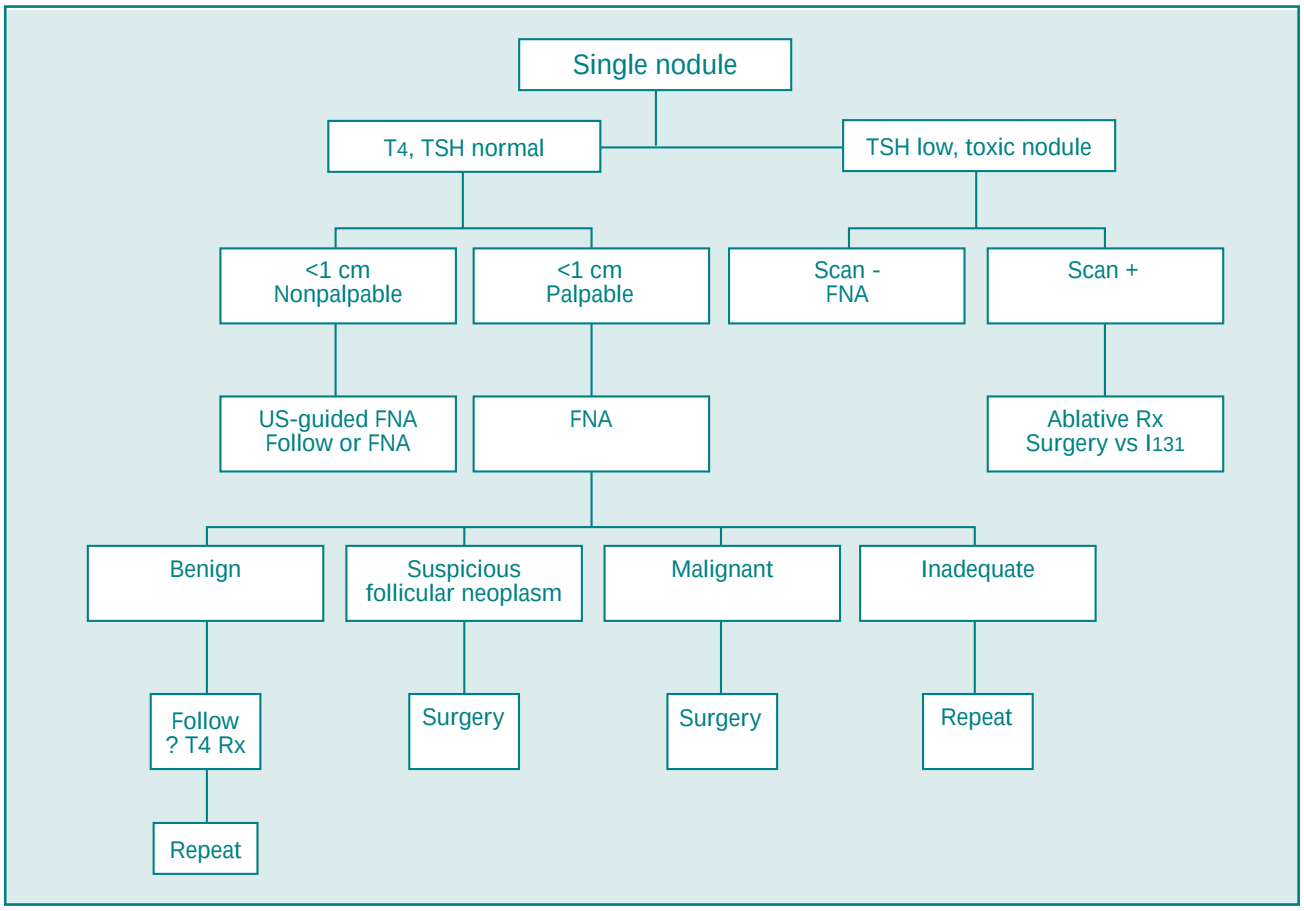
Algorithm for the Workup of the Thyroid Nodule

An algorithm for the workup of a thyroid nodule is provided in the Figure. The initial T_4 and TSH levels distinguish the toxic nodule from the much more common nonfunctioning nodules. The further evaluation of the nonfunctioning nodules is based primarily in the results of FNA.

Treatment of the Thyroid Nodule

Toxic Nodules

Toxic nodules are treated by resection, by iodine-131 (^{131}I) therapy or, in some clinics, by ethanol injection. Surgery is safe, removes the lesion, provides his-



Algorithm for evaluation of the single thyroid nodule.

tologic diagnosis, avoids leaving a hard nodule in the thyroid gland, and avoids irradiation and possible hypothyroidism. Toxic nodules may also be treated by administration of single 30- to 60-mCi doses of ^{131}I. The ease and convenience of ^{131}I, lower expense, avoidance of a scar, and avoidance of hospitalization make it the preferable approach in older patients and those with coincident serious illness. This therapy usually spares the uninvolved parts of the gland because, at the time, they are inactive. Results are to some extent unpredictable. Smaller doses may be ineffective or may need to be repeated, and the remainder of the gland receives 10 to 80 Gy, which induces hypothyroidism in approximately 10% of cases.[9] Although in theory this radiation could induce tumor formation, this has not been reported. Furthermore, the patient receives 0.3 to 0.6 Gy of whole body irradiation. A nodule is usually left in the gland after treatment, but surgery is avoided.

Autonomous thyroid adenomas are currently being treated by some physicians through repeated percutaneous injection of ethanol under ultrasonic guidance. Volumes of 0.4 to 2 mL are injected, and patients may receive up to nine or more treatments at intervals of several days. The response is a gradual return to a euthyroid state and shrinking of the nodule.[10] Leakage of ethanol can cause local pain and tissue damage, fever, and occasionally transient dysphonia. Nodules less than 30 to 40 cubic mL respond with approximately 70% shrinkage in size, while larger lesions are not so successfully reduced. A firm or partially cystic nodule usually remains. An occasional by-product of ^{131}I treatment is the subsequent development of Graves' disease. This is probably induced by the released thyroid antigens stimulating autoimmunity.

Cysts

Cystic lesions are aspirated and often reaspirated one or more times. Possibly long-term suppression with thyroid hormone tends to prevent recurrence, although this outcome is uncertain. If the lesion is still clearly evident after repeated aspiration, it must be considered a mixed solid/cystic lesion and probably should be resected. The aspirated fluid should be cytologically examined, but the specimens are often not satisfactory for diagnosis. Some physicians attempt to sclerose cysts by aspirating fluid and then reinjecting one half volume of a 10/1 mixture of saline and an injectable form of tetracycline containing 100 mg/mL of the drug. Care must be taken to avoid subcutaneous leakage, which is very painful for the patient. The technique is not widely used but is reported to be effective.

Sclerotherapy is also possible using ethanol instillation. In a recent report,[11] recurrent cysts were aspirated and one third volume of ethanol was instilled and then removed after 5 minutes. Some patients were treated twice. The overall effect was a major reduction in cyst size.

Solid Nodules

Solid, mixed, functioning, and "cold" nodules constitute the remaining group and indeed the majority of cases. Major reliance is placed on aspiration cytology. If the results are positive for carcinoma, resection is performed. If no specimen is obtained, reaspiration is performed. If the specimen is suspicious, resection is recommended. A "suspicious" cytology should lead to resection, since approximately 25% of these nodules are carcinomas on final pathology.

Incidentalomas

Widespread use of ultrasound for the examination of any neck pathology has resulted in frequent recognition of thyroid nodules that are too small to be palpated on clinical examination. Usually, such nodules are <1 cm in largest diameter, are asymptomatic, and are not associated with lymph nodes or other suggestions of malignancy. Often incidentally found, such nodules are problematic because of the difficulty in achieving a specific diagnosis, which is desired by the patient.

The usual differential diagnostic possibilities described earlier are again present. The probability of malignancy is lower than that in larger lesions, although exactly how much so is uncertain. Tiny cystic lesions are especially unlikely to be malignant. Presence of neck adenopathy, local symptoms such as pain or dysphonia, growth under observation, a family history of thyroid cancer, or a history of external radiation to the neck are all causes for concern and suggest that resection should be performed. If the lesion can be palpated, it is appropriate to perform an FNA cytologic examination and proceed as for management of larger lesions. More typically, the nodule cannot be precisely demarcated on examination. Ultrasound-guided FNA is possible for lesions closer to 1 cm in size and in patients who clearly want diagnostic assurance. The smaller lesions are difficult to aspirate with certainty, even under ultrasonic guidance. Considering the probable benign nature of most such lesions, the slow growth and spread of differentiated thyroid cancers, and our ability to offer close surveillance via yearly (or more frequent) ultrasound examinations, a common alternative course is to observe such lesions periodically and to reserve resection for those that grow or produce other symptoms.

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