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Thyroid Nodules

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INTRODUCTION

Thyroid nodules are common entities, frequently discovered in clinical practice, either during physical examination, but also incidentally, during various imaging procedures. They are clinically important primarily due to their malignant potential. For this reason the initial evaluation should always include a history and physical examination focusing on features suggestive of malignancy. Serum thyrotropin (TSH) and thyroid ultrasonography (US) are pivotal in the evaluation of thyroid nodules, as they provide important information regarding thyroid nodule functionality and the presence of features suspicious for malignancy, respectively. Fine needle aspiration (FNA) biopsy is the most accurate and reliable tool for diagnosing thyroid malignancy and selecting candidates for surgery, particularly if performed under ultrasound guidance. The cytology findings from FNA biopsies will fall into an indeterminate category in approximately 25% of the cases, in which case malignancy cannot be safely excluded. The recent use of panels of gene mutations and molecular markers, when combined with the cytologic diagnosis, show promising results in improving the preoperative diagnosis of indeterminate thyroid nodules, thus reducing the number of unnecessary surgeries. Other tools for predicting the malignant potential of thyroid nodules still under investigation include elastography and 18F-fluorodeoxyglucose positron emission tomography (18FDG-PET) scanning. An approach to the initial evaluation and management of single nodules, functioning nodules, multinodular glands, incidental nodules, and cysts are discussed. Therapeutic interventions for benign nodules, when needed, may include surgery, radioiodine (131-I) therapy, or percutaneous ethanol injection (PEI), as indicated. Levothyroxine (T4) suppressive therapy is currently controversial and usually not recommended. The evaluation of thyroid nodules discovered during pregnancy is generally the same as for non-pregnant patients, except for the contraindication to radionuclide scanning. Thyroid cancer discovered during pregnancy may be safely managed by thyroidectomy after delivery in most of the cases, but if aggressive features are present, surgery should be ideally performed during the second trimester.

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DEFINITION, CLINICAL IMPORTANCE, EPIDEMIOLOGY

- Thyroid nodules are most common in women and older populations
- The purpose of thyroid nodule evaluation is to determine which nodules are malignant or require surgical attention

Thyroid nodules have been defined by the American Thyroid Association (ATA) as "discrete lesions within the thyroid gland, radiologically distinct from surrounding thyroid parenchyma."[1] They may be discovered by palpation during a general physical examination or with radiographic studies performed for medical evaluations, such as carotid duplex ultrasound (US), computed tomography (CT) scans, magnetic resonance imaging (MRI) studies, or 18FDG-PET scanning. The latter entities are called "thyroid incidentalomas" and they generally do not correspond to palpable thyroid lesions. Conversely, clinicians may identify palpable thyroid lesions that do not correspond to distinct radiological entities, and therefore would not be defined as thyroid nodules.[2]

Thyroid nodules are common, their prevalence being largely dependent on the identification method. The estimated prevalence by palpation alone ranges from 4% to 7%,[3,4] whereas US detects nodules in 20% to 76% of the adult population,[4–6] particularly with the current use of high-resolution US techniques.[7] The reported frequencies detected by US correlate with the prevalence reported at surgery and autopsy with ranges between 50% and 65%.[8]

The estimated annual incidence of thyroid nodules in the United States is approximately 0.1% per year, conferring a 10% lifetime probability for developing a thyroid nodule.[6] Thyroid nodules are 4 times more common in women than men and their frequency increases with age and low iodine intake.[4] The gender disparity is perhaps explained by the hormonal influences of both estrogen and progesterone, as increasing nodule size and new nodule development have been demonstrated to be related to pregnancy and multiparity.[9,10] Exposure to ionizing radiation, either during childhood, or as an occupational exposure, will cause a rate of development of thyroid nodules of 2% per year, reaching a peak incidence in 15 to 25 years.[11,12]

Thyroid nodules are clinically important for several reasons. They may cause thyroid dysfunction and, rarely, compressive symptoms, but they are primarily important because of the need to exclude thyroid cancer. The reported prevalence of malignancy in thyroid nodules evaluated by biopsy ranges from 4.0% to 6.5% and is largely independent of the nodule size.[13,14] Despite this, papillary microcarcinomas (smaller than 1 cm) incidentally found at the time of surgery are much more common (up to 36%),[15,16] but it is controversial whether or not a survival benefit exists with the diagnosis and treatment of such entities, given their generally benign course.[17,18] Importantly, the incidence of thyroid nodules discovered incidentally during 18FDG-PET imaging is small (1%–2%), but the risk of malignancy may be as high as 27%, thus such nodules require immediate evaluation.[19]

HISTORY AND PHYSICAL EXAMINATION

- History and physical examination should focus on detecting features particularly suggestive of malignancy

The spectrum of disorders associated with thyroid nodules ranges from benign etiologies to malignant conditions that may either have an indolent course or a very aggressive behavior (**Box 1**). Therefore, clinical evaluation is best tailored to identification of clues suggestive of malignant disease. A careful history and physical examination should include information regarding previous radiation treatment of the head and neck area; growth of a neck mass; location, size, and consistency of the thyroid nodule; cervical lymphadenopathy; associated

local symptoms such as pain, hoarseness, dysphagia, dysphonia, and dyspnea; and symptoms of hypothyroidism or hyperthyroidism.

Family history of thyroid disorders should always be investigated. Rare but important familial thyroid syndromes include familial medullary thyroid cancer (MTC), derived from calcitonin-producing C-cell tumors, and familial nonmedullary thyroid cancer, which is derived from follicular cells. History of papillary thyroid cancer (PTC) in a parent or sibling increases the patient's risk of developing PTC by threefold and sixfold, respectively.[20] Familial MTC may be a component of multiple endocrine neoplasia (MEN) IIA (pheochromocytoma, MTC, and primary hyperparathyroidism) and IIB (pheochromocytoma, MTC, marfanoid habitus, and mucosal and digestive neurofibromatosis), or may occur as the sole component. Follicular cell–derived familial thyroid cancer has been described in several syndromes, such as Cowden disease, Carney complex, Werner syndrome, and familial polyposis, as well as occurring in isolation. Cowden disease is an autosomal dominant condition, resulting from a mutation in the PTEN gene, and is characterized by hamartomatous neoplasms of the skin, oral mucosa, gastrointestinal tract, central nervous and genitourinary systems, with breast and thyroid cancers being the most commonly encountered malignancies.[21,22] Carney complex, another autosomal dominant condition, is characterized by cardiac and cutaneous myxomas, spotty skin pigmentation, various endocrinopathies, and malignancies of endocrine and nonendocrine origin.[23] Less commonly, thyroid cancer can be encountered in patients with Werner syndrome, of which the main characteristic is premature aging, and familial polyposis, which is primarily associated with colon cancer.

A personal history of head and neck irradiation, particularly as a child, young age (<20 years), or advanced age (>70 years), and male sex are demographic features associated with increased likelihood of malignancy in a patient with a thyroid nodule. **Table 1** summarizes clinical features that should alert the clinician to the possibility of thyroid carcinoma in a patient with a thyroid nodule.[13] It is important to know that symptoms, such as hoarseness, dysphagia, and cough, are rarely related to thyroid conditions, and a thorough workup should be pursued to exclude other, more common etiologies related to gastrointestinal and respiratory systems.

DIAGNOSTIC STUDIES

A spectrum of diagnostic studies is available to aid in the evaluation of a thyroid nodule (**Fig. 1**). These include serum markers, such as serum thyrotropin (TSH) and calcitonin. Fine-needle aspiration (FNA) cytology is the cornerstone of thyroid nodule evaluation. Genetic markers of thyroid cancer risk, such as the BRAF mutation, can also be determined using cytology samples. In addition, immunohistochemical markers, such as galectin-3, cyclooxygenase 2, and cyclin D2, may have potential use. Ultrasonography plays a pivotal role in the evaluation of thyroid nodules, and elastography may prove to be a valuable addition. Other imaging studies, including MRI, CT, and 18FDG-PET scans may be helpful in certain circumstances.

Serum Markers

- The risk of malignancy in thyroid nodules increases as the serum TSH increases

TSH measurement should be part of the initial workup in every patient with a thyroid nodule and be used as a guide for further management (**Fig. 2**).[1,24,25] A normal or high TSH level should raise concerns for possible malignant potential of a nodule, whereas a low TSH is an indicator of benignity in most cases. Therefore, the next step in the evaluation of a patient with a low TSH would be an iodine-123 (123-I) or pertechnetate scintigraphy scan, to

explore the possibility of an autonomously functioning nodule. Hyperfunctioning thyroid nodules are almost always benign and generally do not require further cytologic investigation,[26,27] but a nonfunctioning or "cold" nodule in a patient with low TSH may indicate malignant potential. Recent studies have investigated the relationship between serum TSH concentration and thyroid cancer. TSH was found to be an independent predictor of malignancy in thyroid nodules.[28] The risk of malignancy rises in parallel with serum TSH, even within the normal range, and higher TSH levels were found to be associated with advanced-stage thyroid cancer.[26,29–31]

Calcitonin is a sensitive marker for detection of C-cell hyperplasia and MTC, as well as for surveillance and prognosis of MTC.[32] Calcitonin levels of more than 10 pg/mL were found to have high sensitivity for the detection of MTC,[33] with the specificity being enhanced by pentagastrin stimulation, when calcitonin levels exceed 100 pg/mL. Even though calcitonin screening was proved to be cost-effective and a useful tool in the evaluation algorithm for thyroid nodules,[34] it is not widely recognized in US,[1] partly because of the low prevalence of medullary thyroid cancer and lack of pentagastrin availability.

Serum thyroglobulin measurement is neither sensitive nor specific for the diagnosis of thyroid cancer in nodular thyroid disease, being more influenced by iodine intake and thyroid gland size.[35] Therefore, it is not recommended to be routinely measured in the initial evaluation of a thyroid nodule.[1]

Thyroid Ultrasonography

- Thyroid US allows targeting of nodules with suspicious appearance for biopsy

Thyroid US is an important technique widely used in the detection and evaluation of thyroid nodules. It is a noninvasive, inexpensive procedure that provides information with regard to nodule dimensions, structure, and thyroid parenchymal changes. Nowadays, the use of brightness-mode US and high-frequency transducers may detect lesions as small as 2 to 3 mm, which raises the question of which thyroid nodules are clinically relevant for further evaluation.

Previous studies have investigated the ability of thyroid US to differentiate between benign and malignant lesions to avoid the unnecessary use of invasive procedures.[36–39] As a result, several US features have been found to be indicative of malignant potential. Microcalcifications (**Fig. 3**), irregular or microlobulated margins, hypoechogenicity, taller-than-wide shape, and increased intranodular vascularity (**Fig. 4**) were found to be independent risk factors for malignancy.[38,40,41] Even though these suspicious features are characterized by high specificity, their positive predictive value is lowered by their relatively low sensitivity (**Table 2**). It is important to know that none of these US features alone is sufficient to differentiate benign from malignant tumors, but a combination of at least 2 of them better succeeds in pointing out a subset of lesions at high risk for malignancy.[42,43] Papini and colleagues[38] demonstrated that nodules with a hypoechoic appearance and one of the other suspicious US characteristics successfully identifies thyroid lesions that need to undergo further cytologic examination. For example, a predominantly solid nodule with micro-calcifications has a 31.6% likelihood of malignancy, whereas a predominantly cystic lesion (**Fig. 5**) with no microcalcifications lowers the probability for being cancer to 1.0%.[44] US findings such as isoechogenicity and spongiform appearance (defined as aggregations of multiple microcysts in more than 50% of the nodule) are features highly suggestive of benignity.[41]

The number of nodules and their size are not predictive of malignancy, as a nodule smaller than 1 cm is as likely as a larger nodule to harbor neoplastic cells in the presence of

suspicious US features.[44,45] Choosing an arbitrary size as cutoff for the likelihood of cancer or stratifying the risk in a multinodular goiter based on the "dominant" nodule has fallen into disfavor.[38]

US identification of cervical lymph nodes demonstrating microcalcifications, increased vascularity, cystic changes, and rounded shape, along with coexisting ipsi-lateral thyroid nodules, are also very important clues for malignant etiology.[42] Evidence of extracapsular growth, which may range from invasion of the thyroid capsule to perithyroidal muscle infiltration and recurrent laryngeal nerve extension, is another strong indicator of malignancy.[42,43]

Screening for thyroid nodules by US, or by any other types of imaging studies, is not recommended in the general population because of the minimal aggressiveness and indolent course of most of the thyroid cancers. Current ATA guidelines[1] recommend diagnostic thyroid sonography to be performed only in patients with known or suspected thyroid nodules, or in the presence of risk factors.[24,46]

Other diagnostic imaging techniques, such as MRI and CT scans, are not indicated for routine thyroid nodule evaluation, but they may be helpful for the assessment of nodule size, substernal extension of a nodular goiter, and airway compression.[25]

Elastography

- Elastography is a promising tool for predicting the malignant potential of thyroid nodules

A recent advancement in the diagnosis of thyroid nodules has been brought by the use of elastography. This is a dynamic technique that assesses the hardness of the tissue as an indicator of malignancy.[47] This technique was demonstrated to be highly specific (96%–100%) and sensitive (82%–97%) in the diagnostic evaluation of thyroid nodules, independent of nodule size, or location within the thyroid gland.[48,49] It was also found to be reliable in the diagnostic evaluation of indeterminate/follicular lesions, but this aspect of its use still needs to be confirmed.[50] The diagnostic yield of elastography is impaired in nodules with a calcified shell, cystic lesions, and multinodular goiter with coalescent nodules, because the margins need to be well demarcated for proper interpretation.[51] It is not suitable for diagnosis of follicular carcinoma and its use is restricted to high-end US devices. Although more data from larger prospective studies is needed to establish the accuracy of this diagnostic technique, it remains a promising tool in selecting nodules for FNA.

FNA Biopsy

- FNA, in conjunction with US, forms the cornerstone of thyroid nodule evaluation

Thyroid FNA biopsy is the most reliable, safe, and cost-effective diagnostic tool used in the evaluation of thyroid nodules.[52,53] FNA under US guidance is preferred over the palpation-guided approach because of lower rates of false-negative and nondiagnostic cytology.[54] This is particularly true for nodules that are nonpalpable, located deeply in the thyroid bed, or have a predominantly cystic component.[1]

The decision to pursue FNA sampling should be based on a risk-stratifying approach that includes history, US characteristics, and nodule size (**Table 3**). Sub-centimeter nodules should be biopsied only if there is more than 1 suspicious US characteristic, extracapsular growth, abnormal cervical lymph nodes, or high-risk history (see **Table 1**). Otherwise, a cutoff size of 1 cm can be used for solid nodules that have only 1 suspicious sonographic feature, such as microcalcifications or hypoechoic appearance. Mixed cystic-solid nodules

should undergo biopsy if they are more than 1.5 cm in size and the solid component should be targeted for biopsy. Purely cystic and spongiform lesions are considered to have low risk for malignancy; therefore, they could be either monitored or biopsied if larger than 2 cm (see **Table 3**).

Cytologic diagnosis

- FNA based on an adequate sample is 95% accurate for diagnosing thyroid cancer

Almost 20% of FNA results are nondiagnostic, because of sampling error or poor preparation technique.[55] In such cases, it is recommended that a repeat FNA be performed under US guidance, and if available, on-site cytologic examination for better cytologic adequacy.[56,57] Approximately 7% of the nodules will still yield unsatisfactory cytologic results on repeated biopsies. In this situation, surgery is strongly recommended for solid nodules and close observation or surgery for partially cystic lesions, as they may harbor neoplastic potential.[1,58]

Diagnostic FNA results are divided into 5 categories, based on the recent Bethesda System for Reporting Thyroid Cytopathology[59]: benign (70%), malignant (5%), suspicious for malignancy, follicular or Hurthle cell neoplasm, and follicular lesions of undetermined significance or atypia. The last 3 cytologic diagnoses, which represent 25% of the total cases, have been previously classified as indeterminate lesions. They have a predicted probability for cancer of 50% to 75%, 20% to 30%, and 5% to 10%, respectively.[59]

The most common benign lesions include colloid nodule, macrofollicular adenoma, and lymphocytic thyroiditis, among others.[24] The most prevalent malignant lesions by far are represented by PTC, followed by follicular thyroid cancer (FTC), MTC, anaplastic carcinoma, and high-grade metastatic neoplasms.[60] Suspicious lesions may represent PTC that lacks definitive diagnostic criteria, follicular neoplasm, Hurthle cell neoplasm, lymphoma, or PTC-follicular variant.

Surgery, with lobectomy or total thyroidectomy is the treatment of choice for malignant and suspicious lesions.[1] The same is true for follicular lesions, unless the nodule is found to be autonomous on a 123-I scan in the setting of low-normal TSH.[1] Thyroid nodules larger than 3 cm with mixed cystic/solid components should be strongly considered for surgery for diagnostic purposes, as FNA yields a high rate of false-negative results in these lesions.[61]

Indeterminate cytology

- The cytology findings from some FNA biopsies fall into an indeterminate category in which malignancy cannot reliably be excluded
- Panels of gene mutations may serve as markers of which patients with cytologically indeterminate nodules may safely avoid surgery

Current management for most patients with indeterminate cytology at FNA biopsy consists of diagnostic surgery to establish a histopathological diagnosis. However, only 10–40% of these cases will turn out to be malignant,[59,62] leading to more than 60% of surgeries being unnecessary, with their associated risks and costs. The evaluation of genetic markers associated with thyroid carcinoma (PTC: BRAF, RAS, RET/PTC; FTC: PAX8/PPARγ1) in the cytology specimen has been shown to improve preoperative diagnosis of thyroid nodules in large prospective studies, particularly when used in combination with cytologic features.[63,64] For example, in a Korean population, the combination of both cytology and BRAF mutation status increased the specificity of testing from 36% to 95% compared with FNA cytology alone.[65] The use of molecular markers, in the form of a panel of gene mutations, in patients with indeterminate cytology on FNA samples has been shown to

increase the probability of cancer from 24% to 89% if any mutation is identified, whereas the lack of any mutation decreases the risk to 11%.[66] Cost-effectiveness analysis using a molecular panel of gene markers, coupled with classical cytologic findings, to increase the predictive power of diagnostic interpretations shows promising results when compared with the surgical approach, and is likely to be used in the future in clinical practice.[67]

Currently, there are 2 commercially available assays that provide molecular testing of the thyroid cytologic specimens from FNA biopsy. Veracyte Afirma Gene Expression Classifier, promoted by Genzyme (Cambridge, MA, USA), evaluates messenger RNA (mRNA) expression levels for 142 genes. It has a negative predictive value of 96% when evaluated in samples with indeterminate cytology, thus helping patients with benign lesions to avoid unnecessary surgeries.[68] The recent cost-effectiveness analysis by Li and colleagues[67] predicts that routine application of the gene expression classifier lowers the rate of surgeries for benign nodules from 57% (with current practice) to 14%. miRInform Thyroid is another commercially available assay provided by Asuragen (Austin, TX, USA), which analyzes a panel of 7 molecular markers most commonly encountered in thyroid cancers (BRAF, KRAS, HRAS, NRAS, RET/PTC1, RET/PTC3, PAX8/PPARγ). In contrast to the Veracyte product, it is thus designed to improve the preoperative cytologic diagnosis of indeterminate thyroid nodules by predicting which nodules are most likely to be malignant. Its clinical validation still needs to be determined, but the analytical specificity was found to be 99%, and the sensitivity 95%.

In addition to genetic markers, immunohistochemical staining of cytology specimens and other novel serum markers may be of use. With respect to immunohistochemical markers, galectin-3 is a protein marker that was also shown to improve preoperative diagnosis in indeterminate follicular lesions when used in combination with conventional cytomorphological diagnostic procedures.[69,70] However, recent data have shown that galectin-3 is more useful for diagnosing PTC than FTC.[71] Measurement of serum TSH receptor mRNA, which serves as an indicator of circulating thyroid cancer cells, may be useful for helping determine which nodules with indeterminate cytology are malignant. TSH receptor mRNA concentrations greater than 1 ng/μg had a positive predictive value of greater than 90% for carcinoma.[72]

The use of 18FDG-PET scan in the preoperative diagnosis of thyroid nodules with indeterminate cytology has high sensitivity, but histologic diagnosis is still required to distinguish benign from malignant etiology in 18FDG-PET–positive nodules.[73–76] However, the use of 18FDG-PET could potentially reduce the number of unnecessary thyroidectomies by 39% to 46%.[73,74] It has limited value in selecting candidates for surgery among patients with the cytologic diagnosis of follicular neoplasm, as the glucose metabolic activity is similar in benign and malignant nodules with follicular pattern cytology.[45]

INITIAL EVALUATION OF SINGLE NODULES, FUNCTIONING NODULES, MULTINODULAR GLANDS, INCIDENTAL NODULES, AND CYSTS

- A patient with a multinodular thyroid has the same risk of having a malignancy as a patient with a single thyroid nodule

An algorithm for the initial evaluation of a thyroid nodule is shown in **Fig. 2**. Tests that direct the evaluation along different pathways depending on their results include TSH values, US findings, FNA results, scintigraphy findings, and results of molecular testing. Most nodules will be found to be benign based on cytology. Such nodules do not require immediate further diagnostic evaluation or treatment,[1] but can simply be monitored.

With respect to TSH values, a scintigraphy scan (123-I or technetium 99mTc pertechnetate) should be performed in patients with thyroid nodules and serologic evidence of low or low-normal TSH concentration for further evaluation of nodule functionality. Nodules that are interpreted as “hot” on scintigraphy represent hyperfunctioning nodules and should not be considered for FNA biopsy because they are very rarely malignant.[25] The isofunctioning or nonfunctioning nodules, also named “cold” nodules, have a risk for cancer between 5% and 15%, and therefore should be aspirated for further evaluation. The ability to assess nodular functioning with radio-isotope scanning is generally limited in lesions smaller than 1 cm.[35]

US examination, in addition to providing information about the appearance and size of nodules, will also document the number of nodules. Of note, the prevalence of thyroid cancer in patients with a multinodular goiter is the same as in patients with a solitary nodule and is independent of the number of nodules. However, the likelihood of malignancy per nodule decreases as the number of nodules increases.[77] If 2 or more nodules larger than 1 cm are present, the selection of nodules for FNA biopsy should be made on the basis of the previously described suspicious US characteristics. Otherwise, the largest nodule should be targeted for biopsy.[1]

Thyroid incidentalomas discovered by CT or MRI should initially undergo US evaluation, with further management being guided based on the sonographic characteristics, as mentioned previously. In contradistinction, incidentalomas detected by 18FDG-PET examination have a high risk of malignancy, and US evaluation, along with FNA biopsy, should be performed.[25]

Totally cystic lesions are generally considered benign and, unless a solid component is present, further diagnostic investigation is not required (see **Table 3**).

TREATMENT FOR BENIGN NODULES

- Surgical treatment is recommended for nodules causing compressive symptoms, and can be considered for toxic nodular disease and thyroid cysts
- T4 suppressive therapy is controversial: it is associated with the risks of iatrogenic hyperthyroidism, but may prevent new nodule formation

Most benign thyroid nodules do not require any specific intervention, unless there are local compressive symptoms from significant enlargement, such as dysphagia, choking, shortness of breath, hoarseness, or pain, in which case thyroidectomy should be performed.

Other indications for surgery in benign nodules include the presence of a single toxic nodule, or a toxic multinodular goiter. Radioiodine (131-I) therapy is another option for treatment of toxic nodular goiters, but they are usually more radioresistant than toxic diffuse goiter and radioiodine is not the first-line therapy if compressive symptoms are present. Treatment with 131-I for larger nodules is not preferred either, as such nodules require high doses of 131-I with its associated side effects. Radioiodine therapy needs to be approached with caution in individuals with uncontrolled thyrotoxicosis. However, the only absolute contraindications to 131-I therapy are pregnancy and lactation.[78]

Aspiration is the treatment of choice in thyroid cysts, but the recurrence rates are high (60%–90% of patients), particularly with repeated aspirations and large-volume cysts.[79,80] Percutaneous ethanol injection (PEI) has been studied in several large randomized controlled studies, with reported success in 82–85% of the cases after an average of 2 sessions, with a volume reduction of more than 85% from baseline size.[79,80] PEI may also be considered for hyperfunctioning nodules, particularly if a large fluid component is present. It has a success rate ranging from 64% to 95%,[81–83] with a mean volume reduction of 66%,[81] but

recurrences are more common and the number of sessions required to achieve good response is higher (about 4 sessions per patient). PEI is a safe procedure, with the most common reported adverse effects being local pain, dysphonia, flushing, dizziness, and, rarely, recurrent laryngeal nerve damage.[79,80,84] Surgery, in addition to serving as a suitable option for treatment of single toxic nodules and toxic multinodular goiter, is also a reasonable therapy for cystic lesions, as an alternative to the previously mentioned procedures.

Levothyroxine (T4) therapy for benign thyroid nodules has been proposed with the aim of achieving nodule shrinkage and preventing further appearance of new nodules through TSH suppression. Although several randomized control trials and meta-analyses have demonstrated nodule shrinkage in patients from areas of iodine deficiency,[85–88] a clinically significant decrease in nodule volume is achieved only in a minority of patients with sufficient iodine intake.[85,88,89] Other predictive features of good response to T4 treatment are recent diagnosis, small nodule size, and colloid appearance at FNA.[90]

T4 suppressive therapy is not devoid of adverse effects, such as decreased bone density, particularly in postmenopausal women, atrial fibrillation, and increased overall morbidity and mortality from cardiovascular diseases.[91] Current guidelines[1] do not recommend routine use of T4 suppressive treatment in patients with benign thyroid nodules from areas with iodine sufficiency. A recent study conducted in Italy in individuals with nontoxic goiter. However, a recent study conducted in Italy in individuals with non-toxic goiter showed decreased goiter growth, decreased formation of new nodules, and decreased risk of developing PTC in a population receiving T4, compared with an untreated population.[92] Thus, this management technique may have some utility.

FOLLOW-UP

- A 50% increase in the volume of a previously biopsied thyroid nodule is a reasonable trigger for repeating an FNA

Benign thyroid nodules require further long-term follow-up because of the risk of false-negative results after initial FNA, which is about 5%.[93] Serial US at 6 to 18 months from the initial FNA is the recommended investigation for the follow-up examination of thyroid nodules to accurately detect significant changes in size[94] or discover changes in appearance (**Fig. 6**).

There is no consensus definition for nodule growth and threshold size to repeat an FNA. However, many investigators propose a cutoff value of 50% for nodule volume growth, or more than 20% increase in at least 2 dimensions of a solid nodule, or the solid portion of a mixed cystic-solid nodule to be reasonable and safe.[95] An online calculator to determine the change in volume of a thyroid nodule from its serial dimensions is available on the ATA Web site (http://www.thyroid.org/professionals/calculators/CINV.php). Although nodule growth is an indication for repeat biopsy,[1] growth is not pathognomonic for malignancy.[96] Repeated FNA biopsy is recommended to be performed under US guidance, as false-negative rates are higher with palpation-guided FNA, compared with US-guided FNA.[54] A recent retrospective analysis of value of repeated FNAs of benign thyroid nodules demonstrated high accuracy (98%) of the initial diagnosis.[97]

If no significant nodule growth is observed at repeated US, a follow-up interval of 3 to 5 years may be reasonable (see **Fig. 6**).[1]

THYROID NODULES IN PREGNANCY

- If a diagnosis of thyroid cancer is made during pregnancy, surgery usually may be delayed until after delivery
- In the case of aggressive or rapidly growing thyroid cancer, surgery during the second trimester is safest

The etiology and behavior of thyroid nodules discovered during pregnancy as compared with the general population is unknown.[98] As a consequence, the evaluation should be similar to that for nonpregnant patients, except for the contraindication to radionuclide scanning. If a patient is found to have persistently suppressed serum TSH levels after the first trimester, the radionuclide scan and possible subsequent FNA can be safely postponed until after delivery and cessation of lactation.[1] In euthyroid or hypothyroid pregnant women with thyroid nodules, consensus guidelines recommend that an FNA biopsy should be performed.[1] An argument can be made, however, for deferring the FNA until after delivery unless there are worrisome clinical features that would perhaps lead to a recommendation for a thyroidectomy during pregnancy. If a diagnosis of malignancy results from the FNA, but postponement of thyroidectomy until the patient is post partum is the intended plan before the FNA, this simply exposes the patient to anxiety regarding a diagnosis about which she can take no action.

Previous studies have demonstrated similar cancer behavior in pregnant patients diagnosed with PTC when compared with the general population,[99,100] with no differences in survival rates or recurrences in pregnant women operated for PTC during or after delivery.[100] Rates of complications after thyroid surgery are higher in pregnant women than their nonpregnant counterparts, however.[101] Because additional retrospective data suggest that delaying surgery for less than 1 year from the time of the differentiated thyroid cancer diagnosis has no impact on patient outcome,[102] postponing the surgery until after delivery seems a reasonable approach. If more advanced or aggressive disease is present at the time of diagnosis, or a decision is made to pursue thyroidectomy for thyroid cancer discovered early in pregnancy, surgery should be ideally performed in the second trimester of pregnancy,[103] as this may decrease the risk of early miscarriage and premature delivery.

T4 suppressive therapy to maintain a serum TSH level between 0.1 and 1.0 mU/L is a reasonable approach in pregnant patients diagnosed with thyroid cancer on the basis of an FNA and who are awaiting thyroidectomy.[104]

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Box 1 Etiology of thyroid nodules

Benign etiology

Follicular adenoma

Hurthle cell adenoma

Colloid cyst

Simple or hemorrhagic cyst

Lymphocytic thyroiditis

Granulomatous thyroiditis

Infectious processes

Malignant etiology

Malignancy of follicular or C-cell origin

Papillary carcinoma

Follicular carcinoma

Hurthle cell carcinoma

Medullary thyroid carcinoma

Anaplastic carcinoma

Malignancy of other origin

Thyroid lymphoma

Malignancy metastatic to the thyroid

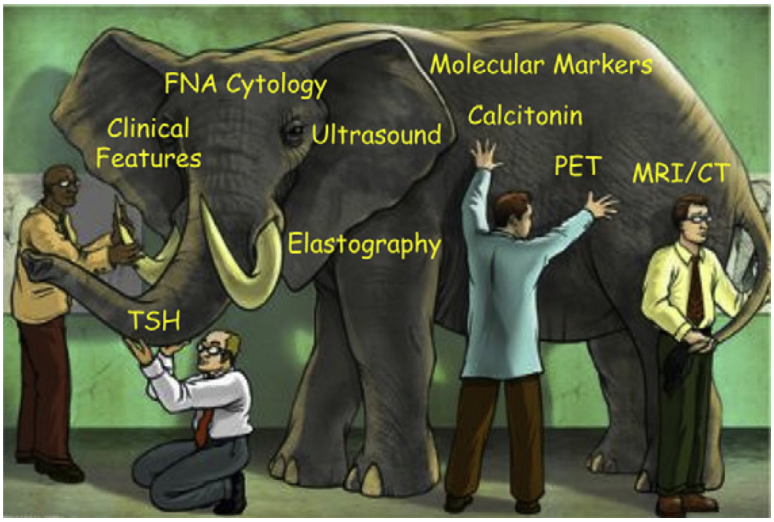

Fig. 1.
Diagnostic studies available for evaluating thyroid nodules. (*Modified from* figure provided by Dr BR Haugen, University of Colorado at Denver and Health Sciences Center, Aurora, CO; with permission.)

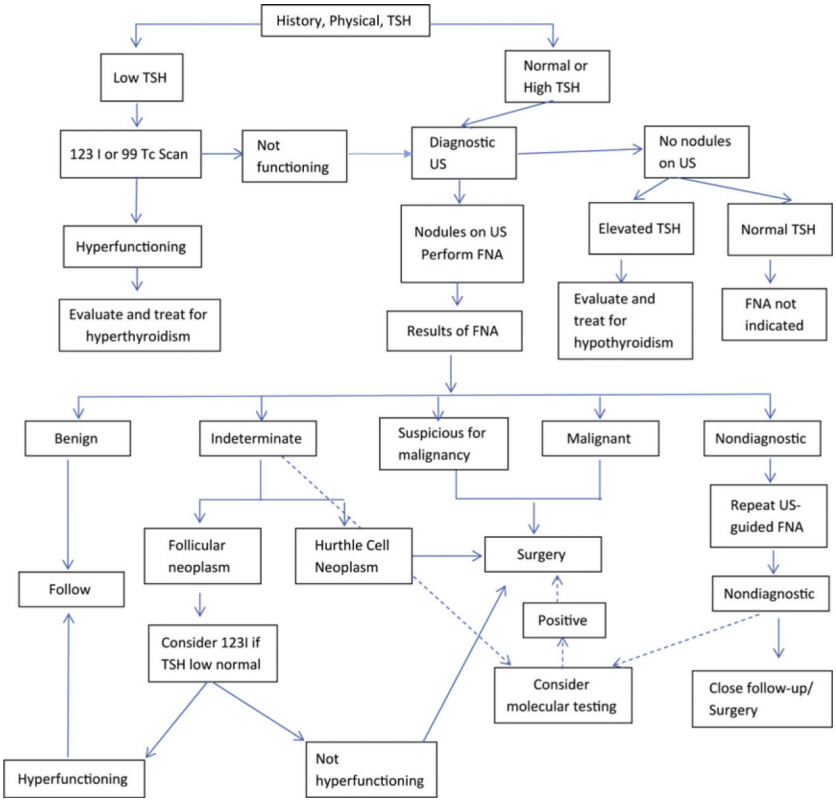

Fig. 2.

Algorithm for initial evaluation of a patient with thyroid nodule. (*Modified from* Cooper DS. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19(11):1167–214; with permission.)

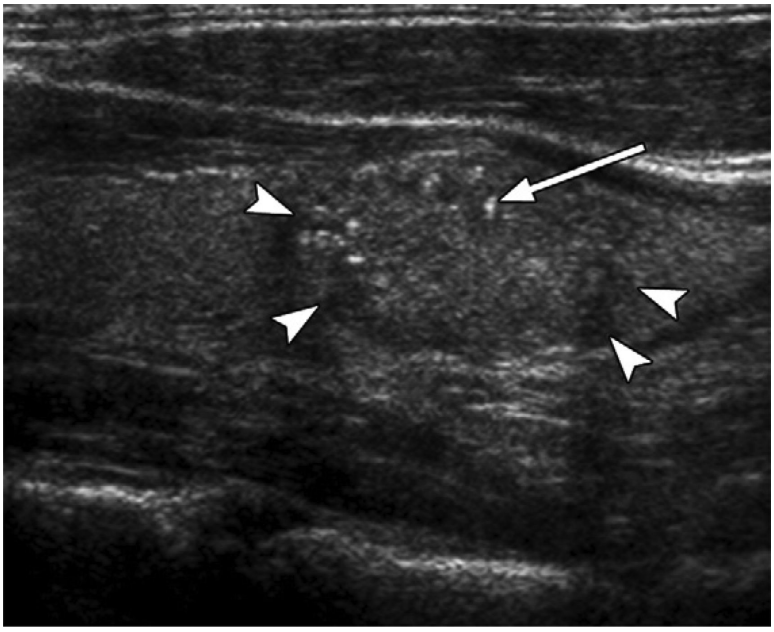

Fig. 3.
US image of a thyroid nodule (*arrowheads*) containing multiple fine punctuate echogenicities (*arrow*) with no comet-tail artifact, indicating high suspicion for malignancy. FNA and surgery confirmed PTC. (*Reproduced from* Frates MC. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. Radiology 2005;237:794–800; with permission.)

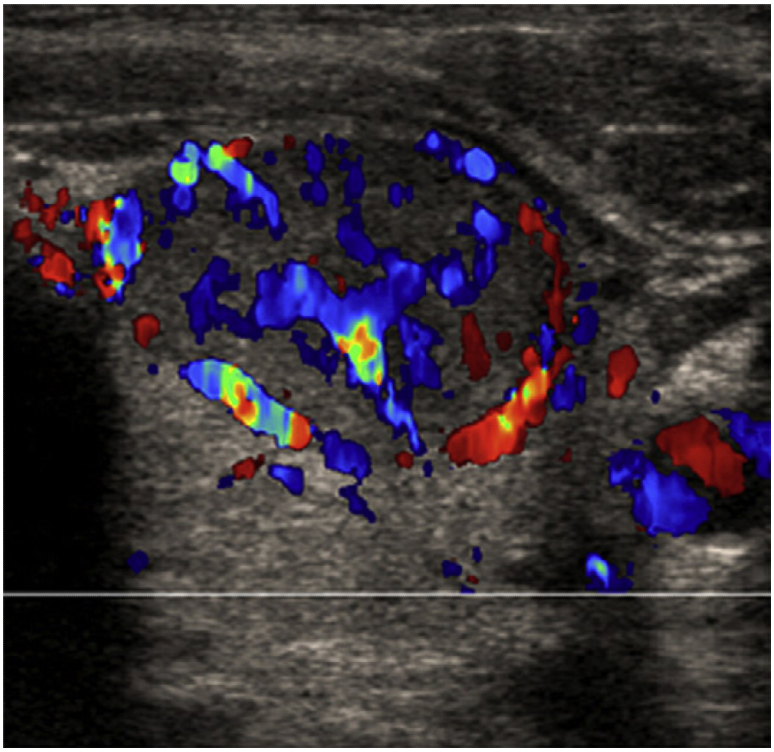

Fig. 4.

Color Doppler US of a thyroid nodule showing marked internal vascularity, indicating increased likelihood of malignancy. Histology demonstrated PTC. (*Reproduced from* Frates MC. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. Radiology 2005;237:794–800; with permission.)

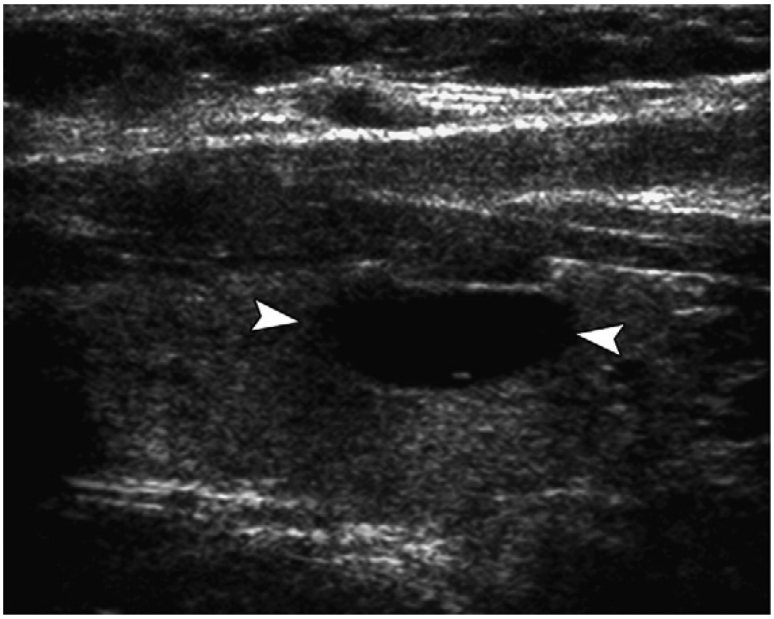

Fig. 5.

US image of a cystic thyroid nodule (*arrowheads*). (*Reproduced from* Frates MC. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. Radiology 2005;237:794–800; with permission.)

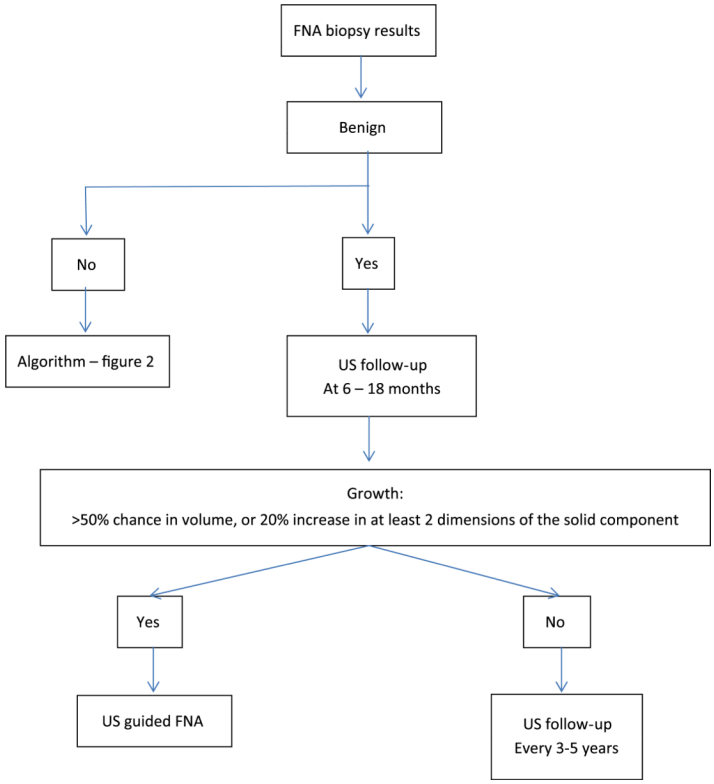

Fig. 6.
Algorithm for follow-up of benign thyroid nodules.

Table 1

Features suggestive of increased potential for thyroid carcinoma in a patient with thyroid nodule

Patient History or Characteristics	Findings on Physical Examination	Findings Seen on Imaging
Family history of MEN, MTC, and PTC	Firm nodule	Suspicious ultrasound features
History of head and neck irradiation	Nodule fixed to adjacent structures	Lymphadenopathy
History of Hodgkin and non-Hodgkin lymphoma	Growth of nodule, especially during therapy to suppress serum TSH	
Age <20	Abnormal cervical lymphadenopathy	
Age >70	Paralysis of the vocal cords	
Male sex		
Symptoms of compression: hoarseness, dysphagia, dysphonia, dyspnea, cough		

Abbreviations: MEN, multiple endocrine neoplasia; MTC, medullary thyroid cancer; PTC, papillary thyroid cancer; TSH, serum thyrotropin.

Table 2

Ultrasound characteristics of thyroid nodules predictive of malignancy

Ultrasound Feature	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %
Microcalcifications	26.1–59.1	85.8–95.0	24.3–70.7	41.8–94.2
Hypoechogenicity	26.5–87.1	43.4–94.3	11.4–68.4	73.5–93.8
Irregular margins or no halo	17.4–77.5	38.9–85.0	9.3–60.0	38.9–97.8
Solid	69.0–75.0	52.5–55.9	15.6–27.0	88.0–92.1
Intranodule vascularity	54.3–74.2	78.6–80.8	24.0–41.9	85.7–97.4
More tall than wide	32.7	92.5	66.7	74.8

Reproduced from Frates MC. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. Radiology 2005;237(3):794–800; with permission.

Table 3

Sonographic and clinical features of thyroid nodules and recommendations for FNA

Nodule Sonographic or Clinical Features	Recommended[a] Nodule Threshold Size for FNA	
High-risk history		
Nodule with suspicious sonographic features	>5 mm	Recommendation A
Nodule without suspicious sonographic features	>5 mm	Recommendation I
Abnormal cervical lymph nodes	All	Recommendation A
Microcalcifications present in nodule	≥1 cm	Recommendation B
Solid nodule		
And hypoechoic	>1 cm	Recommendation B
And iso- or hyperechoic	≥1–1.5cm	Recommendation C
Mixed cystic-solid nodule		
With any suspicious ultrasound features	≥1.5–2.0cm	Recommendation B
Without suspicious ultrasound features	≥2.0 cm	Recommendation C
Spongiform nodule	≥2.0 cm[b]	Recommendation C
Purely cystic nodule	FNA not indicated[c]	Recommendation E

Abbreviation: FNA, fine-needle aspiration.

Modified from Cooper D. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19(11):1167–214; with permission.

[a]Explanation of Recommendations: A, strongly recommends based on good evidence; B, recommends, based on fair evidence; C, recommends based on expert opinion; E, recommends against based on fair evidence; I, recommends neither for nor against, evidence insufficient.

[b]Sonographic monitoring without biopsy may be an acceptable alternative.

[c]Unless indicated as therapeutic modality.