Diagnostic approach to and treatment of thyroid nodules

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INTRODUCTION — Thyroid nodules come to clinical attention when noted by the patient, or as an incidental finding during routine physical examination, or during a radiologic procedure, such as carotid ultrasonography, neck computed tomography (CT), or positron emission tomography (PET) scanning. Several different disorders can cause thyroid nodules (table 1). Their clinical importance is primarily related to the need to exclude thyroid cancer, which accounts for 4.0 to 6.5 percent of all thyroid nodules in non-surgical series [1-4].

The prevalence of cancer is higher in several groups:

- Children
- Adults less than 30 years or over 60 years old
- Patients with a history of head and neck irradiation
- Patients with a family history of thyroid cancer

On the other hand, the prevalence of cancer may be lower in nodules within multinodular goiters, and virtually all autonomously hyperfunctioning ("hot") nodules are benign. (See "Overview of thyroid nodule formation", section on 'Multinodular goiters'.)

The diagnostic evaluation and treatment of thyroid nodules will be reviewed here. Fine needle aspiration techniques and common cytopathologic findings are reviewed elsewhere. (See "Thyroid biopsy" and "Atlas of thyroid cytopathology".)

EVALUATION — The clinical evaluation of the thyroid nodule is primarily related to the need to exclude thyroid cancer, which is present in 4.0 to 6.5 percent of thyroid nodules. Nonpalpable nodules (incidentalomas) have the same risk of malignancy as palpable nodules [5-9]. Thus, the initial evaluation in all patients with a thyroid nodule (discovered either by palpation or incidentally noted on a radiologic procedure, such as carotid ultrasonography, neck CT, MRI, or PET) includes a history, physical examination, and measurement of serum thyroid stimulating hormone (TSH). Ultrasound is also recommended for all patients to confirm the presence of nodularity, assess sonographic features, and to assess for the presence of additional nodules and lymphadenopathy.

Fine needle aspiration (FNA) biopsy is the most accurate method for evaluating thyroid nodules and identifying patients who require surgical resection [9]. If a serum TSH is normal or elevated, the next step in the evaluation of a thyroid nodule is a palpation or ultrasound-guided fine needle aspiration biopsy. If the nodule is complex or posterior, ultrasound guidance is strongly recommended to avoid nondiagnostic or incorrect cytology results. (See "Fine needle aspiration biopsy" below.)

Over the last decade, the use of thyroid scintigraphy to assess thyroid nodules has become less common. Although scintigraphy remains the only way to determine the functional status of a nodule, high-resolution thyroid ultrasonography provides anatomic definition superior to thyroid scintigraphy. (See "Overview of the clinical utility of ultrasonography in thyroid disease"). Scintigraphy is useful in patients with a low serum TSH concentration. It may be useful in patients with multiple thyroid nodules to select those that are hypofunctional and therefore may require FNA.

The figure summarizes our recommended evaluation of patients with thyroid nodules, beginning with TSH (algorithm 1). It is consistent with the American Thyroid Association guidelines [10].

History and physical examination — The history and physical examination have a low accuracy for predicting cancer. However, there are several features of the clinical evaluation that suggest an increased likelihood of malignancy, such as a history of rapid growth of a neck mass, childhood head and neck irradiation, total body irradiation for bone marrow transplantation, family history of thyroid cancer, or thyroid cancer syndromes (eg, multiple endocrine neoplasia 2, familial adenomatous polyposis, or Cowden syndrome). (See "PTEN hamartoma tumor syndrome, including Cowden syndrome" and "Clinical manifestations and diagnosis of familial adenomatous polyposis" and "Clinical manifestations and diagnosis of multiple endocrine neoplasia type 2").

A fixed hard mass, obstructive symptoms, cervical lymphadenopathy, or vocal cord paralysis all suggest the possibility of cancer.

Serum TSH — Thyroid function should be assessed in all patients with thyroid nodules.

- If the serum TSH concentration is low, indicating overt or subclinical hyperthyroidism, the possibility that the nodule is hyperfunctioning is increased and thyroid scintigraphy should be performed next. (See "Thyroid scintigraphy" below.)
- If the serum TSH concentration is normal or elevated, and the nodule meets criteria for sampling, then fine needle aspiration biopsy is indicated. In addition, patients with a high serum TSH concentration require an evaluation for hypothyroidism. (See "Indications" below and "Disorders that cause hypothyroidism".)

Serum TSH is an independent risk factor for predicting malignancy in a thyroid nodule. In a study of 1500 patients presenting to a thyroid practice, the prevalence of malignancy was 2.8, 3.7, 8.3, 12.3, and 29.7 percent for patients with serum TSH concentrations <0.4 mU/L, 0.4 to 0.9 mU/L, 1.0 to 1.7 mU/L, 1.8 to 5.5 mU/L, and >5.5 mU/L, respectively [11]. A similar study demonstrated that when cancer was diagnosed, a higher TSH was associated with a more advanced stage of cancer [12].

Thyroid ultrasonography — Thyroid ultrasound should be performed in all patients with a suspected thyroid nodule or nodular goiter on physical examination or with nodules incidentally noted on other imaging studies (carotid ultrasound, CT, MRI, or FDG-PET scan).

Thyroid ultrasonography is used to answer questions about the size and anatomy of the thyroid gland and adjacent structures in the neck. It provides considerably more anatomic detail than thyroid scintigraphy [13], CT [14], and physical examination [15,16]. In a retrospective study of 173 patients referred to a thyroid nodule clinic for an abnormal thyroid examination, the ultrasound findings were different from the physical examination done by the referring clinician in 63 percent of cases [16]. Of the 114 patients referred for a solitary nodule, 24 percent had additional nodules and 20 percent did not have a nodule of at least 1.0 cm that required aspiration. (See "Indications" below.)

There are several ultrasonographic findings that are suspicious for thyroid cancer (table 2). The predictive value of these characteristics varies widely, and we do not rely on thyroid ultrasound to diagnose cancer or to select patients for surgery. However, ultrasound findings can be used to select nodules for FNA biopsy. (See "Fine needle
Ultrasound can identify posteriorly located nodules or predominantly cystic nodules. The diagnostic accuracy of FNA performed by palpation is reduced in these nodules, and ultrasound-guided FNA is more effective. (See "Ultrasound-guided thyroid biopsy", section on 'Indications for ultrasound-guided FNA.') Apparent nodularity in Hashimoto's thyroiditis may represent focal enlargement from lymphocytic infiltrates, TSH-induced hyperplasia of follicular tissue, or a thyroid tumor. Ultrasonography may also help to distinguish among these possibilities.

### Thyroid scintigraphy

Thyroid scintigraphy is used to determine the functional status of a nodule. A low serum TSH, indicating overt or subclinical hyperthyroidism, increases the possibility that a thyroid nodule is hyperfunctioning. Thus, thyroid scintigraphy should be performed in patients with a low serum TSH concentration.

Thyroid scintigraphy can be used to select nodules for FNA. It cannot be used to select patients for surgical resection.

Scintigraphy utilizes one of the radioisotopes of iodine (usually 123I) or technetium-99m pertechnetate. If available, radiiodine scanning is preferred. These radioisotopes are handled differently by thyroid follicular cells. Normal thyroid follicular cells take up both technetium and radiiodine, but only radiiodine is organified and stored (as thyroglobulin) in the lumen of thyroid follicles [17]. Most benign and virtually all malignant thyroid nodules concentrate both radioisotopes less avidly than adjacent normal thyroid tissue (image 1). However, 5 percent of thyroid cancers concentrate pertechnetate, but not radiiodine [17]. These nodules may appear hot or indeterminate ("warm") on pertechnetate scans and cold on radiiodine scans. Although most are benign nodules [18-20], a few are thyroid cancers [19,21,22]. As a result, patients with nodules that are functioning on pertechnetate imaging should undergo radiiodine imaging to confirm that they are actually functioning [19,23].

#### Nonfunctioning

Nonfunctioning nodules appear cold (uptake less than surrounding thyroid tissue) (image 1), and they may require further evaluation by FNA. (See "Indications" below.)

- **Autonomous** — Autonomous nodules may appear hot (uptake greater than surrounding thyroid tissue) (picture 1) if they are hyperfunctioning. Autonomous nodules that do not make sufficient thyroid hormone to suppress serum TSH concentrations will appear indeterminate on thyroid scintigraphy (see 'Indeterminate' below). Autonomous nodules account for only 5 to 10 percent of palpable nodules. Only a few patients with autonomous nodules have been found to have thyroid cancer [24-26], and only a few of these cancers were aggressive [27]. Furthermore, in some of these patients, the cancer was adjacent to the autonomous nodule rather than within it. Since hyperfunctioning nodules rarely are cancer, a nodule that is hyperfunctioning on radiiodine imaging does not require FNA.

- **Indeterminate** — Because scintigraphy is two-dimensional, its limitations result from the superimposition of abnormal nodular tissue and normally functioning thyroid tissue (image 2). Thus, while over 80 percent of nonautonomous nodules greater than 2 cm appear cold, smaller nodules present as a filling defect in less than one-third of cases [24]. The remaining majority of smaller nodules are indeterminate on thyroid scintigraphy [28]. They could represent either small non-functioning nodules anterior or posterior to normally functioning thyroid tissue, or autonomous nodules that do not produce sufficient thyroid hormone to suppress TSH (image 3). These indeterminate nodules should not be referred to as warm or functioning since the majority are in fact non-functioning nodules. Most indeterminate nodules should be evaluated by FNA. (See 'Fine needle aspiration biopsy' below.)

The nature of an indeterminate nodule can be assessed by suppression scanning. This test is most commonly indicated in patients who have an indeterminate nodule and an FNA that was interpreted as a follicular neoplasm (microfollicular), or a follicular lesion of uncertain malignant potential, since these cytologic findings may be associated with autonomous nodules. (See "Atlas of thyroid cytopathology", section on 'Follicular neoplasm/microfollicular cytology'.) Rarely, this test may be indicated in a patient with an indeterminate nodule who refuses FNA. Patients with autonomously functioning nodules may become hyperthyroid with even small doses of T4 and should be warned of hyperthyroid symptoms [29]. Therefore, this test should not be done in older patients or in those with angina or cardiac arrhythmias.

Patients are given thyroid hormone in a dose sufficient to suppress TSH secretion, and a second scan is done once TSH suppression is documented, which may occur in one to two weeks or may require several dose adjustments. Suppression can usually be accomplished by administering T4 (2 mcg/kg for 10 days) [30]. Uptake of radioidine will be low or undetectable in nonautonomous tissue, but persist in autonomous tissue (image 1). If the region of nonsuppressible uptake corresponds to the palpable nodule, then the nodule can be assumed to be autonomous and benign.

#### Fine needle aspiration biopsy

The American Thyroid Association recommends FNA biopsy as the procedure of choice for evaluating thyroid nodules and selecting candidates for surgery [13]. FNA biopsy has resulted in improved diagnostic accuracy, a higher malignancy yield at the time of surgery, and significant cost reductions [31,32].

- **Overview** — The American Thyroid Association recommends FNA biopsy as the procedure of choice for evaluating thyroid nodules and selecting candidates for surgery [13]. FNA biopsy has resulted in improved diagnostic accuracy, a higher malignancy yield at the time of surgery, and significant cost reductions [31,32].

- **Indications** — There is increasing evidence that the presence of suspicious ultrasound features is more predictive of malignancy than nodule size alone [7,33]. A decision analysis of thyroid node biopsy criteria for nodules measuring 1.0 to 1.5 cm favors the approach of selecting nodules with suspicious ultrasonographic characteristics for biopsy of all nodules ≥1 cm [34]. The American Thyroid Association has taken such an approach, and our approach is consistent with ATA guidelines [10].

In patients without risk factors for thyroid cancer, we perform FNA biopsy for solid hypoechoic nodules (palpable or nonpalpable) measuring >1 cm. This recommendation is based upon observational studies that show similar rates of cancer in nonpalpable nodules >1 cm and palpable nodules of similar size [6,8]. FNA is also recommended for solid nodules that are isoechogenic or hyperechoic, if they are ≥1.0 to 1.5 cm, and for mixed cystic-solid nodules without suspicious features on ultrasound, if they are ≥2.0 cm (table 3) [10]. Spongiform nodules, defined as an aggregation of multiple microcystic components in more than 50 percent of the nodule volume, may not require FNA regardless of size, although it may be prudent to biopsy spongiform nodules ≥2.0 cm. Purely cystic nodules (no mural component) do not require a biopsy.

In patients with risk factors for thyroid cancer (eg, childhood head and neck irradiation, family history of thyroid cancer), the ATA guidelines suggest that the nodule threshold size for FNA biopsy is smaller. The ATA guidelines recommend ultrasonography-guided FNA biopsy for all nodules ≥5 mm in high-risk patients (table 3) [10]. There are no data to support such an approach, and we prefer to biopsy subcentimeter nodules in both high and low risk patients, only if they have highly suspicious characteristics on ultrasound (table 2). (See "Overview of the clinical utility of ultrasonography in thyroid disease", section on 'Criteria for identifying cancer'.) Preliminary studies suggest the potential use of an imaging staging system similar to that used for breast imaging. The TIRADS system rates ultrasound findings on a
score of 1 to 5 based upon ultrasonographic characteristics; malignancy was found in 0 percent of category 2, 3.4 percent of category 3, 14 percent of category 4, and 86.5 percent of category 5 [35]. Studies are needed to assess the costs associated with the routine use of ultrasound to detect nonpalpable thyroid cancers, and the clinical impact of early detection.

**Multiple nodules** — Patients with multiple nodules have the same risk of malignancy as those with a single nodule [16,33]. Thus, the sonographic features of each nodule should be assessed independently to determine the need for FNA biopsy. If there are multiple coalescent nodules and none have suspicious sonographic features, FNA biopsy of the largest nodule is reasonable [19]. The nodules that are not biopsied should be monitored with periodic ultrasonography.

**Monitoring of small nodules that are not biopsied** — In patients without risk factors for thyroid cancer or suspicious ultrasound findings, routine FNA is not recommended for nodules <1 cm. We perform periodic ultrasonography (initially at 6 to 12 months, then at increasing intervals over time assuming stability, eg, at one to two year intervals, then three to five years) to evaluate for growth. If the nodule grows to ≥1 to 2 cm and demonstrates the ultrasound characteristics discussed above, ultrasound-guided FNA should be performed.

Indirect evidence for an observational approach to subcentimeter nonpalpable nodules comes from a Japanese study of 162 patients with small papillary cancers diagnosed by ultrasound-guided needle biopsy [38]. The average nodule size was 6.9 mm. The patients were among a group of 732 patients with positive biopsies; the remaining 570 patients chose surgery. During follow-up (half the patients were followed three to four years, 35 percent later opted for surgery), 70 percent were stable or were reduced in size, 1.2 percent developed lymph node metastases, and no one developed distant metastases.

**Diagnostic categories** — The National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference (“Bethesda Conference”) suggests the following classification scheme [37]:

- **Benign** — this includes macrofollicular or adenomatoid/hyperplastic nodules, colloid adenomas, nodular goiter, and Hashimoto’s thyroiditis
- **Follicular lesion or atypia of undetermined significance** — this includes lesions with atypical cells, or mixed macro- and microfollicular nodules
- **Follicular neoplasm** — this includes microfollicular nodules, including Hürthle cell lesions
- **Suspicious for malignancy**
- **Malignant**
- **Nondiagnostic**

The terms used by different cytopathologists to describe follicular thyroid nodules vary (table 4). It is essential that clinicians interpreting these reports be familiar with the terminology used by their cytopathologist. (See "Atlas of thyroid cytopathology" and "Thyroid biopsy", section on Diagnostic categories.)

**Molecular markers** — When cytologic results show follicular lesion/atypia of undetermined significance or follicular neoplasm, the results are often called indeterminate. The risk of malignancy with these cytologic classifications ranges from 5 to 32 percent, and the majority of these patients undergo thyroid surgery. However, most patients (75 to 95 percent) undergoing surgery for what is ultimately confirmed to be benign disease (see 'Follicular lesion or atypia of undetermined significance' below and 'Follicular neoplasm' below).

Improvement in the assessment of indeterminate FNA results may allow better risk stratification. There are two approaches to the molecular characterization of FNA aspirates that are commercially available in the United States: identification of particular molecular markers of malignancy, such as BRAF and RAS mutational status, and use of high density genomic data for molecular classification (an FNA-trained mRNA classifier) [39]. The mRNA classifier measures the activity level of 167 genes within the nodule (using the FNA aspirate). We favor using an mRNA classifier system (gene expression classifier), when available, based upon the following findings:

- In a study of 513 indeterminate samples from 479 patients tested for BRAF, RAS, RET/PTC, and PAX8/PPARgamma mutations prior to surgery, the detection of any mutation conferred a risk of histologic malignancy of 88 and 87 percent for samples showing follicular lesion/atypia of undetermined significance and follicular neoplasm, respectively [30]. However, 6 and 14 percent of nodules with FNA showing follicular lesion/atypia of undetermined significance and follicular neoplasm, respectively, were negative for these mutations and proved to be cancer on surgical histology. Thus, this approach misses a significant proportion of malignant samples that do not contain one of the mutations being tested.
- In a study of 265 indeterminate nodules (85 of which were malignant), using mRNA expression analysis and a gene expression classifier trained on FNA samples to detect benign thyroid nodules, the classifier had a negative predictive value for malignancy of 95 and 94 percent for samples showing follicular lesion/atypia of undetermined significance and follicular neoplasm, respectively [40,41]. It is suggested that application of this classifier would save over 60 percent of patients from diagnostic thyroid surgery, which would result in overall lower costs [42].

Where available, we suggest using this classifier for evaluating patients with FNA cytology showing follicular lesion/atypia of undetermined significance or follicular neoplasm. The decision to observe a patient with a benign molecular profile using this classifier should be reassessed as more data become available. (See Follicular neoplasm below.)

**Serum calcitonin concentration** — The routine measurement of serum calcitonin in patients with nodular thyroid disease is controversial [43]. Several reports have suggested that serum calcitonin should be measured routinely in patients with nodular thyroid disease in order to identify those who have medullary thyroid cancer at an earlier stage and to improve survival [44-49]. However, controversy remains about the routine use of serum calcitonin measurements because of the absence of uniform calcitonin thresholds to distinguish sporadic occur MTC [49-51], the high false-positive rate (59 percent or higher) in some studies, and the uncertain importance of small tumors [9,52]. (See"Medullary thyroid cancer: Clinical manifestations, diagnosis, and staging" and "Clinical manifestations and diagnosis of multiple endocrine neoplasia type 2", section on 'Medullary thyroid cancer'.)

Data on the utility of routine serum calcitonin measurement in patients with nodular thyroid disease are largely from prospective cohort studies [44-49,53-57]. In various reports, basal serum CT was increased in 0.5 to 5 percent of patients with thyroid nodules [48,54,57]. In a study of 1167 French patients with nodular thyroid disease, the prevalence of MTC in patients with elevated versus normal basal CT levels was 41.1 and 0.17 percent, respectively [49].

In the studies that showed a diagnostic advantage to measuring basal serum calcitonin [45,48,58,59], however, serum calcitonin was repeated after pentagastrin (available only in some countries) stimulation to confirm medullary cancer or C cell hyperplasia in those with elevated calcitonin levels. As an example, in one report of 10,864 patients screened after 1991, 44 (0.4 percent) had an elevated calcitonin, all confirmed by an elevated pentagastrin-stimulated calcitonin, and all had medullary cancer [48]. Fifty-nine percent of these patients were in complete remission compared with only 2.7 percent of patients diagnosed with medullary cancer prior to the use of routine screening, suggesting a benefit to early diagnosis. In contrast, in a study of 10,158 patients with thyroid nodules, 5 percent had elevated basal calcitonin, but only 20 percent of these patients had elevated values after pentagastrin stimulation, and only 31 percent of these patients had medullary cancer [54]. In all of these studies, calcitonin was more accurate than FNA for indentifying medullary thyroid cancer, since many of the cancers were quite small. In the French study, only 2 of 12
patients diagnosed by calcitonin measurement had lesions that were 1.0 cm in diameter or larger, while four were less than 0.3 cm in diameter [45]. False-positive calcitonin results may be obtained in patients with hypercalcaemia, hypergastrinemia, neuroendocrine tumors, renal insufficiency, papillary and follicular thyroid carcinomas, goiter, and chronic autoimmune thyroiditis [9,69]. Furthermore, prolonged treatment with omeprazole (greater than two to four months), beta-blockers, and glucocorticoids have been associated with hypercalcitoninemia [61]. In addition, there are reports of rare medullary thyroid cancers that do not secrete calcitonin, and a false negative test result may be expected [62,63].

In countries where pentagastrin is available, basal serum CT testing (after renal insufficiency and use of proton pump inhibitor medication have been ruled out) [43,45,48,59,64]. At present, we agree with others that the routine use of basal calcitonin measurements in nodular thyroid disease is not warranted in countries (eg, United States) where the use of pentagastrin stimulation as a confirmatory test is not available [65,66]. The American Thyroid Association (ATA) notes the uncertainties surrounding calcitonin measurements and has not taken a position for or against calcitonin screening [10,67].

If pentagastrin stimulation testing were available, some thyroid experts would routinely measure serum calcitonin in patients with nodular thyroid disease, whereas others would not. If the basal serum calcitonin (CT) level is measured and exceeds 10 pg/mL, the CT measurement should be repeated after pentagastrin stimulation testing (after renal insufficiency and use of proton pump inhibitor medication have been ruled out) [59]. Calcium is also a calcitonin secretagogue, and owing to the unavailability of pentagastrin in many countries, there is a growing interest in using the calcium stimulation test as a confirmatory test in patients with elevated basal calcitonin levels. However, few standardized data using modern calcitonin assays are available [68]. Pentagastrin and calcium stimulation testing is reviewed separately. (See "Clinical manifestations and diagnosis of multiple endocrine neoplasia type 2", section on 'Pentagastrin stimulation test' and "Clinical manifestations and diagnosis of multiple endocrine neoplasia type 2", section on 'Calcium stimulation test'.)

Other lab tests — Routine measurement of serum anti-thyroid peroxidase (TPO) antibodies and thyroglobulin is not necessary. Measurement of TPO antibodies may be helpful in patients with a high TSH suggestive of chronic autoimmune (Hashimoto's) thyroiditis. However, the presence of a high titer of TPO antibodies does not negate the need for FNA biopsy of a thyroid nodule in a patient with Hashimoto's thyroiditis. Although rapid shrinkage of the nodule when T4 therapy is instituted may be sufficiently reassuring to mitigate further concern, thyroiditis and thyroid cancer coexist with sufficient frequency, especially after head and neck irradiation [55,69]. Thus, a definite nodule, even in the presence of a high serum antibody concentration, requires further evaluation. Serum thyroglobulin levels can be elevated in many thyroid diseases. An elevated level does not help discriminate benign from malignant thyroid nodules. Thus, we do not measure serum thyroglobulin levels as part of the evaluation of patients with a thyroid nodule.

Thyroid incidentalomas — Incidentalomas are nonpalpable thyroid nodules that are detected during other imaging procedures. Nonpalpable nodules have approximately the same risk of malignancy as palpable nodules [5-8]. In some settings, especially nodules discovered on PET scan (see "PET scans" below), the risk of malignancy may be higher, but in other settings (cysts/nodules), it may be lower.

Patients with a history of childhood head or neck irradiation — Radiation exposure of the thyroid during childhood is the most clearly defined environmental factor associated with benign and malignant thyroid tumors. There is a linear dose-response curve, with no evidence of a threshold at low doses. The risk reaches a plateau, and possibly tapers off, at high doses. (See "Radiation-induced thyroid cancer".)

Many patients with a history of radiation exposure during childhood have nonpalpable thyroid nodules. This was illustrated by a report in which 54 such patients underwent thyroid ultrasonography [70]. Although most of the patients had no palpable nodules, 47 had 157 nodules on ultrasonography. The nodules ranged in size from a few millimeters to 3.0 cm. Eleven nodules were 1.5 cm or larger, six of which could be palpated.

The arguments for and against the routine use of ultrasonography in patients with a history of radiation are reviewed in detail elsewhere. We recommend ultrasonography based upon an assessment of each patient's risk factors for thyroid cancer. (See "Radiation-induced thyroid cancer", section on 'Ultrasound'.)

Nonthyroid cancer — In patients with a nonthyroid cancer, there may be a higher than usual incidence of malignancy in incidentally discovered thyroid nodules. In one report of 41 such patients, 16 underwent surgery based upon the results of FNA, with four papillary thyroid cancers, four microscopic papillary thyroid cancers, two metastatic cancers, and seven benign lesions [71].

PET scans — Many incidentalomas found on PET scans are thyroid cancers; in two studies, 2.2 to 2.8 percent of patients had thyroid uptake, and 27 to 42 percent of those proved to be papillary cancer [72]. In a retrospective study of 87 incidentalomas identified by PET, 76 percent of those with suspicious ultrasonographic characteristics were malignant, while only 13 percent of those with benign ultrasonographic characteristics were cancers [73]. Medullary cancer has also been detected as an incidental finding on PET scan [74,75]. Thus, thyroid nodules discovered incidentally on PET scans require ultrasound-guided FNA biopsy.

Graves' disease — The prevalence of thyroid nodules and cancer in patients with Graves' disease has been investigated in a prospective study in which 245 patients with Graves' disease underwent screening ultrasonography. Thirty-five percent had nodules and 3.3 percent had thyroid cancers (one of eight cancers was palpable) [76]. The authors did not recommend routine ultrasonography in patients with Graves' disease, but noted the risk of malignancy was higher in patients over age 45. We limit ultrasonography to Graves' patients with palpable abnormalities or heterogeneous or focal decreased uptake on thyroid scintigraphy.

Cystic nodules — There is disagreement concerning the risk of cancer in a cystic nodule. Several series have reported few (0.5 to 3 percent) or no cancers in these nodules, while others have reported rates of cancer only slightly lower than those for solid nodules. (See "Cystic thyroid nodules".) As a result, aspiration of cyst fluid for cytologic analysis is almost always indicated for complex cysts >2cm in diameter without suspicious features. FNA is not necessary for pure cysts unless it is for therapeutic reasons. Cancer is uncommon in cystic nodules that are no longer palpable after aspiration [77]. Larger nodules, nodules with bloody aspirates, or nodules that reaccumulate after repeated aspiration are more likely to contain cancer [78,79]. Reaspiration should be performed if the nodule remains palpable after aspiration and the cytology is nondiagnostic [80,81].

Ultrasonography after aspiration is useful for determining the nature, size, and location of the solid portion of the nodule, which then can be aspirated under ultrasound guidance [82].

For patients who refuse FNA, or when there is concern about a hematoma in patients taking anticoagulants, clinical follow-up of the nodule is reasonable if there is evidence of extensive cystic degeneration on ultrasonography.

Pregnancy — Thyroid radionuclide scanning is contraindicated during pregnancy. Otherwise, a pregnant woman found to have a thyroid nodule should be evaluated in the same way as if she were not pregnant. Thus, fine needle aspiration biopsy of the nodule should be done (as it would be for most nonpregnant patients). (See "Overview of thyroid disease in pregnancy", section on 'Goiter'.)
are usually followed without surgery. There is still controversy concerning the efficacy of T4 therapy for these patients. In the absence of a history of childhood neck irradiation, patients with benign nodules should not be treated with T4. (See "Thyroid hormone suppressive therapy for thyroid nodules and benign goiter".)

We perform periodic ultrasound monitoring of benign thyroid nodules, initially at 6 to 12 months, then at increasing intervals over time. Cystic degeneration and hemorrhage are the most common causes of sudden enlargement, and can be detected by ultrasoundography or repeat aspiration [79]. Reseption of thyroid nodules that are unchanged clinically is not warranted, because detection of malignancy is uncommon in routine repeat biopsies [63-67]. This was illustrated in two studies of 250 patients who had routine repeat FNA; only one previously benign nodule was found to be malignant on repeat aspiration (0.4 percent) [65,66]. In a third report, 3 of 216 patients (1.4 percent) had papillary cancer on a repeat biopsy [68]. Malignancy is rare even in benign thyroid nodules that have grown. In an observational study of 268 patients with 330 benign thyroid nodules, most nodules (89 percent) increased in volume (defined as ≥15 percent increase on ultrasound) over a mean of 20 months (range 1 to 65 months) [69]. However, only 1 of the 74 nodules that were rebiopsied was malignant (1.4 percent).

Thus, small changes in nodule size on serial ultrasonography do not require a repeat aspiration. However, reassessment is warranted when there is substantial growth (more than a 50 percent change in volume or 20 percent increase in nodule diameter with a minimum increase in two or more dimensions of at least 2 mm) or change in the texture of a nodule, or new symptoms are attributed to a nodule [10].

**Follicular lesion or atypia of undetermined significance** — This category includes lesions with mild nuclear atypia, mixed macrofollicular and microfollicular lesions where the proportion of microfollicles and macrofollicles is similar, lesions with extensive oncocytic (Hürthle cell) change, and specimens that are compromised because of poor fixation or obscuring blood. These cytologic findings are common, especially in nodular goiters. The risk of malignancy with this cytotologic classification ranges from 5 to 32 percent [37,69-91]. There is no definite consensus as to which of these should be excised to exclude follicular cancer.

One approach is to follow patients with nodules that are greater than 50 percent macrofollicular fragments (flat sheets with uniform non-crowded cells), unless they are clinically suspicious or present in patients with a higher risk of cancer. Nodules that are less than 50 percent macrofolliclar fragments, nodules with similar proportions of macrofollicles and microfollicles, and nodules with cellular atypia are frequently reaspirated after a three to six month interval, or earlier, before making a decision whether to monitor or excise [37]. If repeat aspirates continue to show atypical cells or microfollicularity, thyroid scintigraphy (for microfollicularity), surgery, or molecular testing (as for follicular neoplasm) should be considered (see 'Follicular neoplasm' below).

Previously, the response of a nodule to T4 suppressive therapy was used to select nodules that required excision: nodules that shrank were assumed to be benign, and those that failed to shrink were excised to exclude malignancy. However, this approach is not very specific since only 17 to 25 percent of nodules regress when T4 is administered. (See "Thyroid hormone suppressive therapy for thyroid nodules and benign goiter".) Furthermore, 13 percent of subsequently proven papillary cancers in one series decreased in size during T4 treatment [92].

**Follicular neoplasm** — In patients with cytology suggesting follicular neoplasms (microfollicular, cellular, or indeterminate), we typically perform thyroid scintigraphy, particularly if the TSH is in the lower end of the normal range. Patients with hyperfunctioning (autonomous) nodules are followed, or if the patient is hyperthyroid, radioiodine therapy or surgery is advised. (See "Treatment of toxic adenoma and toxic multinodular goiter".)

From 15 to 25 percent of microfollicular or cellular adenomas prove to be cancers, depending upon the cytologic pattern [37]. Thus, most patients without nonautonomous microfollicular adenomas should undergo diagnostic surgery with pathology evaluation for capsular or vascular invasion. Patients with surgical histology specimens showing benign follicular adenoma (ie, the absence of capsular or vascular invasion) do not require further treatment. However, patients whose surgical histology shows follicular thyroid cancer (or follicular variant papillary thyroid cancer) will need to have a completion thyroidectomy.

Several approaches are under investigation to improve upon cytology alone for the assessment of follicular neoplasm and follicular lesion/atypia of undetermined significance. The routine use of molecular analysis on indeterminate FNA aspirates (follicular neoplasm or follicular lesion/atypia of undetermined significance) may reduce substantially the number of patients who require diagnostic thyroid surgery. (See 'Molecular markers' above.)

Where available, we suggest mRNA expression analysis using an FNA-trained classifier for managing patients with FNA cytology showing follicular neoplasm or follicular lesion/atypia of undetermined significance. (See 'Molecular markers' above.) For patients with indeterminate FNA cytology who have a benign molecular pattern, we suggest observation, rather than diagnostic lobectomy. The negative predictive value for malignancy with this technique (94 to 95 percent) seems to be sufficiently high to warrant observation over diagnostic surgery [40,41]. However, the decision to observe a patient with a benign profile should be reassessed as more data become available. For patients with a suspicious pattern using this technique, we suggest a diagnostic lobectomy (however, an individual patient may prefer a total thyroidectomy if a high volume thyroid surgeon is available).

If the fine needle aspirate is analyzed for particular molecular markers of malignancy (rather than mRNA expression analysis using an FNA-trained classifier), surgical management depends upon the findings. For patients with indeterminate FNA cytology who test negative for a mutation using a molecular panel that tests for BRAF, RAS, RET/PTC, and PAX8/PPARgamma mutations, we diagnostic lobectomy, rather than observation. A significant proportion of malignant samples (6 to 14 percent) will be missed using this technique, if the aspirate does not contain one of the mutations being tested. (See 'Molecular markers' above.) For patients with indeterminate cytology who test positive for a mutation using this molecular panel, we suggest a total thyroidectomy rather than a diagnostic lobectomy. (See "Surgical treatment of differentiated thyroid cancer", section on 'Choice of procedure'.)

**Suspicious for malignancy** — This category includes lesions with some features suggestive of but not definitive for papillary thyroid cancer. Typically, nodules in this category have a 50 to 75 percent risk of malignancy. Such patients should be referred for surgery.

**Malignant** — The malignant category includes papillary cancer, medullary cancer, thyroid lymphoma, anaplastic cancer, and cancer metastatic to the thyroid. Patients with cytology diagnostic of malignancy should be referred for surgery.

**Nondiagnostic** — A nondiagnostic biopsy is cytologically inadequate. It is critical that the absence of malignant cells not be interpreted as a negative biopsy if no or scant follicular tissue is obtained. In a study of patients with a nondiagnostic cytology specimen after a palpation FNA, repeating the FNA under ultrasound guidance significantly improved the diagnostic yield for both solid and cystic nodules [93]. Thus, for patients with nondiagnostic FNA biopsies, we repeat the FNA using ultrasound-guidance. If repeated ultrasound-guided aspirations are nondiagnostic, ultrasound-guided core needle biopsy should be considered. In one study of patients who had one nondiagnostic FNA, a core-needle biopsy provided diagnostic results in 74 percent of patients, while a repeat FNA provided a result in only 52 percent of patients; after two non-diagnostic FNAs, the core needle provided a result in 86 versus 29 percent for FNA [94]. Surgical excision, especially for larger solid nodules with sonographically suspicious features [95], or observation, especially for smaller partially cystic nodules, are reasonable options.

**Autonomou nodule**— The optimal therapy of patients with autonomous nodules is controversial. Those in whom the nodule causes hyperthyroidism should be treated with radioiodine or surgery, possibly after a period of antithyroid drug therapy. (See "Treatment of toxic adenoma and toxic multinodular goiter".)

Patients with subclinical hyperthyroidism (low serum TSH and normal serum free T4 values) present a difficult problem. Subclinical hyperthyroidism is associated with an increased risk of atrial fibrillation in patients over age 60 to 65 years, and in postmenopausal women, a decrease in bone mineral density. Management depends upon clinical risk for complications of subclinical hyperthyroidism and the degree of TSH suppression. This topic is reviewed in detail elsewhere. (See "Subclinical
Cystic thyroid nodules — Cystic nodules also present difficult management issues. Many patients with small cystic nodules with nondiagnostic cytology can be followed with the assumption that the nodule is benign. In some patients, however, recurrent bleeding or cyst reformation may be a source of discomfort, anxiety, or rarely obstructive symptoms, mandating excision of the nodule. T4 therapy was not beneficial in a small randomized study of patients with cystic nodules [95]. (See "Cystic thyroid nodules").

Management — Benign, autonomous, and cystic thyroid nodules can be treated by ultrasound-guided injection of ethanol or sclerosing agents, and by ultrasound-directed physical energy. These approaches have not gained widespread acceptance in the United States because of potential complications, including occasional reports of prolonged pain after the procedure. This topic is reviewed elsewhere. (See "Ultrasound-guided thyroid biopsy").

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

• Basics topics (see "Patient information: Thyroid nodules (The Basics)") and "Patient information: Multinodular goiter (The Basics)"

• Beyond the Basics topics (see "Patient information: Thyroid nodules (Beyond the Basics)"

SUMMARY AND RECOMMENDATIONS

Evaluation

• The initial evaluation in all patients with a thyroid nodule (discovered either by palpation or incidentally noted on a radiologic procedure, such as carotid ultrasonography, neck CT, or PET) includes a history, physical examination, neck ultrasonography, and measurement of serum thyroid stimulating hormone (TSH). (See Evaluation above.)

• Thyroid scintigraphy should be performed in patients with a low serum TSH concentration. (See Thyroid scintigraphy above.)

• Fine needle aspiration (FNA) biopsy is the most accurate method for evaluating thyroid nodules and selecting patients for thyroid surgery (algorithm 1). We suggest FNA biopsy of palpable and incidentally discovered (nonpalpable) solid hypoechoic thyroid nodules >1 cm. Solid isoechoic or hyperechoic nodules ≥1 to 1.5 cm, mixed cystic and solid nodules with suspicious ultrasound characteristics ≥1.5 to 2 cm, and mixed cystic and solid nodules with no suspicious features ≥2 cm should also have FNA (table 3). Spongiform nodules ≥2 cm could also be evaluated by FNA, although observation without FNA is an alternative option. We perform FNA biopsy of subcentimeter nodules only if they have highly suspicious characteristics on ultrasound. (See Indications above.)

• FNA biopsy of thyroid nodules is commonly performed under ultrasound guidance. Ultrasound-guided FNA biopsy should be performed for nonpalpable nodules and for nodules that are technically difficult to aspirate using palpation methods alone, such as predominantly cystic or posteriorly located nodules. In patients with large nodules (>4 cm), ultrasound-guided FNA directed at several areas within the nodule may reduce the risk of a false negative biopsy. (See Fine needle aspiration biopsy above.)

• Where available, we suggest mRNA expression analysis using an FNA-trained gene classifier for further evaluating FNA aspirates with indeterminate cytology (follicular neoplasm or follicular lesion/atypia of undetermined significance). (See Molecular markers above.)

Management

• Patients with benign nodules (macrofollicular or adenomatoid/hyperplastic nodules, colloid adenomas, nodular goiter, and Hashimoto’s thyroiditis) are usually followed without surgery. We perform periodic ultrasound monitoring of benign thyroid nodules initially at 6 to 12 months, then at increasing intervals, and repeat FNA only when there is substantial growth (more than a 50 percent change in volume or 20 percent increase in at least two nodule dimensions), change in the echo texture of a nodule, or new symptoms are attributed to a nodule. (See Benign nodules above.)

• For patients with follicular lesions or atypia of undetermined significance (nodules with atypical cells or nodules with both macrofollicular and microfollicular features), we perform repeat FNA after a three to six month interval, or earlier. If repeat aspirates continue to show follicular lesion/atypia of undetermined significance, and thyroid scintigraphy does not show an autonomous nodule, we perform molecular testing (as for follicular neoplasm immediately below). If molecular testing is unavailable, we suggest surgical resection if repeat aspirates continue to show atypical cells (Grade 2C). For patients with nodules that are greater than 50 percent macrofollicular, we suggest monitoring, unless they are clinically suspicious or present in patients with a higher risk of cancer (Grade 2C). (See Follicular lesion or atypia of undetermined significance above.)

• For patients with nonautonomous (cold) follicular neoplasms (microfollicular adenomas), we send the FNA aspirate for mRNA expression analysis using an FNA-trained gene classifier (if available). If molecular testing is not available, we suggest diagnostic lobectomy, rather than observation (Grade 2B). In the absence of capsular or vascular invasion (on surgical histology), the lesion is classified as a benign adenoma, and no further treatment is required. For patients whose surgical histology shows follicular thyroid cancer (or follicular variant papillary thyroid cancer), completion thyroidectomy is necessary. (See Follicular neoplasm above and Molecular markers above.)

For patients with indeterminate FNA cytology who have a benign molecular pattern on mRNA expression analysis using an FNA-trained gene classifier, we suggest observation (Grade 2C). However, the decision to observe a patient with a benign profile should be reassessed as more data become available. Diagnostic lobectomy remains an alternative option for patients with a benign molecular pattern, depending upon the nodule’s clinical characteristics and patient preference. For patients with a suspicious molecular pattern using this technique, diagnostic lobectomy is necessary. However, an individual patient may prefer a total thyroidectomy if a high volume thyroid surgeon is available.

If the FNA aspirate (from a patient with indeterminate cytology) is tested for a mutation using a molecular panel that tests for BRAF, RAS, RET/PTC, and PAX8/PPARGamma mutations, and no mutations are detected, we suggest diagnostic lobectomy rather than observation (Grade 2B). A significant proportion of malignant samples will be missed using this technique if the aspirate does not contain one of the mutations being tested. For patients with indeterminate cytology this result should be treated as an equivocal test. If the FNA aspirate shows another abnormality (other than the absence of mutations), we suggest an FNA biopsy of benign molecular pattern, diagnostic lobectomy remains an alternative option for patients with a benign molecular pattern, depending upon the nodule’s clinical characteristics and patient preference. If a mutation is present, we recommend diagnostic lobectomy (Grade 2B).
who test positive for a mutation using this molecular panel, we suggest a total thyroidectomy, rather than a diagnostic lobectomy (Grade 2B).

- Patients with cytology suggesting cancer or suspicious for cancer should be referred for surgery. (See Malignant above and Suspicious for malignancy above.)
- For patients with nondiagnostic palpation or ultrasound-guided biopsies, we perform repeat FNA using ultrasound-guidance. For patients with solid nodules and nondiagnostic cytology after repeated biopsies, we typically perform an ultrasound-guided core needle biopsy. Careful clinical follow-up, repeat FNA biopsy, and surgical resection are alternative options. For cytologically nondiagnostic nodules that are partially cystic, we suggest careful clinical follow-up with ultrasound monitoring rather than surgical resection (Grade 2C). (See Nondiagnostic above and Cystic thyroid nodules.)

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REFERENCES


47. Hahm JR, Lee MS, Min YK, et al. Routine measurement of serum calcitonin is useful for early detection of medullary thyroid carcinoma in patients with nodular thyroid diseases. Thyroid 2001; 11:73.


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Causes of thyroid nodules

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
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</thead>
<tbody>
<tr>
<td>Multinodular (sporadic) goiter (&quot;colloid adenoma&quot;)</td>
<td>Papillary carcinoma</td>
</tr>
<tr>
<td>Hashimoto's (chronic lymphocytic) thyroiditis</td>
<td>Follicular carcinoma</td>
</tr>
<tr>
<td>Cysts: colloid, simple, or hemorrhagic</td>
<td>Minimally or widely invasive</td>
</tr>
<tr>
<td>Follicular adenomas</td>
<td>Oxyphilic (Hurthle-cell) type</td>
</tr>
<tr>
<td>Macrofollicular adenomas</td>
<td>Medullary carcinoma</td>
</tr>
<tr>
<td>Microfollicular or cellular adenomas</td>
<td>Anaplastic carcinoma</td>
</tr>
<tr>
<td>Hurthle-cell (oxyphil-cell) adenomas</td>
<td>Primary thyroid lymphoma</td>
</tr>
<tr>
<td>Macro- or microfollicular patterns</td>
<td>Metastatic carcinoma (Breast, renal cell, others)</td>
</tr>
</tbody>
</table>
Recommended management of thyroid nodules

Patient with thyroid nodule

- **TSH**
  - **TSH-N or ↑**
    - Ultrasound to assess need for FNA
    - Doesn’t meet criteria: Monitor
    - Meets criteria: Fine needle aspiration
  
  - **TSH ↓**
    - Radioscintigraphy and ultrasound
    - Cold: Observation
    - Hot: Treatment by evoking hypothyroidism and selected cases of subclinical hyperthyroidism

- **FNA:** fine-needle aspiration; **N:** normal; **TSH:** thyroid-stimulating hormone (thyrotropin); **US-FNA:** ultrasound-guided fine-needle aspiration.

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FNA: fine-needle aspiration; N: normal; TSH: thyroid-stimulating hormone (thyrotropin); US-FNA: ultrasound-guided fine-needle aspiration.

* Thyroid scintigraphy after suppressing TSH with thyroxine.

<table>
<thead>
<tr>
<th>Ultrasound features associated with thyroid cancer risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ultrasonographic features that are associated with an increased risk of thyroid cancer</strong></td>
</tr>
<tr>
<td>Hypoechoic</td>
</tr>
<tr>
<td>Microcalcifications</td>
</tr>
<tr>
<td>&quot;Twinkling&quot; on B-flow imaging</td>
</tr>
<tr>
<td>Central vascularity</td>
</tr>
<tr>
<td>Irregular margins</td>
</tr>
<tr>
<td>Incomplete halo</td>
</tr>
<tr>
<td>Nodule is taller than wide</td>
</tr>
<tr>
<td>Documented enlargement of a nodule</td>
</tr>
<tr>
<td><strong>Ultrasonographic features that are associated with a low risk of thyroid cancer</strong></td>
</tr>
<tr>
<td>Hyperechoic</td>
</tr>
<tr>
<td>Large, coarse calcifications (except medullary cancer)</td>
</tr>
<tr>
<td>Peripheral vascularity</td>
</tr>
<tr>
<td>Resembles puff or Napoleon pastry</td>
</tr>
<tr>
<td>Spongiform appearance</td>
</tr>
<tr>
<td>Comet-tail shadowing</td>
</tr>
</tbody>
</table>
Nonfunctioning thyroid nodule: Appearance on thyroid scintigraphy

123-I thyroid scan demonstrating typical appearance of a large, 3.5 cm hypofunctioning ("cold") nodule in the left upper lobe of the thyroid. The position of the nodule is outlined in white. SSN: suprasternal notch.

Courtesy of Douglas Ross, MD.
Autonomous thyroid nodule: Appearance on thyroid scintigraphy

123-I thyroid scan demonstrating an autonomous ("hot") nodule with suppression of isotope uptake elsewhere. The total 24-hour isotope uptake was normal (12 percent).

SSN: suprasternal notch.

Courtesy of Douglas Ross, MD.
Indeterminate thyroid nodule: Appearance on thyroid scintigraphy

123-I thyroid scan of a 2 cm papillary cancer, which does not appear as a nonfunctioning nodule because it overlies normal isotope concentration in the uninvolved portion of the right lobe.

SSN: suprasternal notch.

Courtesy of Douglas Ross, MD.
Indeterminate thyroid scan: Appearance on thyroid scintigraphy

123-I thyroid scan obtained to assess a palpable right thyroid nodule. The function of the nodule could not be determined. SSN: suprasternal notch.

Courtesy of Douglas Ross, MD.
Thyroid suppression scan

123-I thyroid scan of the indeterminate thyroid nodule shown in the previous radiograph, after four weeks of T4 therapy. The nodule (outlined in white) overlies an area of relatively increased isotope concentration, indicating autonomy, since uptake is suppressed in the rest of the gland.

SSN: suprasternal notch.

Courtesy of Douglas Ross, MD.
<table>
<thead>
<tr>
<th>Nodule sonographic or clinical features</th>
<th>Recommended nodule threshold size for FNA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-risk history</strong></td>
<td></td>
</tr>
<tr>
<td>Nodule WITH suspicious sonographic features</td>
<td>&gt;5 mm  Recommendation A</td>
</tr>
<tr>
<td>Abnormal cervical lymph nodes</td>
<td>AllΔ  Recommendation A</td>
</tr>
<tr>
<td>Microcalcifications present in nodule</td>
<td>≥1 cm  Recommendation B</td>
</tr>
<tr>
<td>Solid nodule</td>
<td></td>
</tr>
<tr>
<td>AND hypoechoic</td>
<td>&gt;1 cm  Recommendation B</td>
</tr>
<tr>
<td>AND iso- or hyperechoic</td>
<td>≥1-1.5 cm  Recommendation C</td>
</tr>
<tr>
<td>Mixed cystic-solid nodule</td>
<td></td>
</tr>
<tr>
<td>WITH any suspicious ultrasound features</td>
<td>≥1.5-2.0 cm  Recommendation B</td>
</tr>
<tr>
<td>WITHOUT suspicious ultrasound features</td>
<td>≥2.0 cm  Recommendation C</td>
</tr>
<tr>
<td>Spongiform nodule</td>
<td>≥2.0 cm◊  Recommendation C</td>
</tr>
<tr>
<td>Purely cystic nodule</td>
<td>FNA not indicated§  Recommendation E</td>
</tr>
</tbody>
</table>

MEN: multiple endocrine neoplasia; FMTC: familial medullary thyroid cancer.

* High-risk history: History of thyroid cancer in one or more first degree relatives; history of external beam radiation as a child; exposure to ionizing radiation in childhood or adolescence; prior hemithyroidectomy with discovery of thyroid cancer, 18FDG avidity on PET scanning; MEN2/FMTC-associated RET protooncogene mutation, calcitonin >100 pg/mL.

• Suspicious features: microcalcifications; hypoechoic; increased nodular vascularity; infiltrative margins; taller than wide on transverse view.

◊ Sonographic monitoring without biopsy may be an acceptable alternative.

§ Unless indicated as therapeutic modality.

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<table>
<thead>
<tr>
<th>Cytologic pattern</th>
<th>Description</th>
<th>Histopathology</th>
</tr>
</thead>
</table>
| Benign macrofollicular fragments | Abundant colloid  
Predominantly large follicles and flat sheets of follicular cells | Nodular goiter (colloid adenoma)  
Macrofollicular adenoma |
| Follicular lesion or atypia of undetermined significance | Mixed macrofollicular and microfollicular nodules  
OR  
Cells with mild nuclear atypia  
OR  
Extensive oncocytic (Hurthle cell) change | Multinodular goiter  
Follicular adenoma  
Follicular cancer  
Papillary cancer (follicular variant)  
Hashimoto's thyroiditis |
| Follicular neoplasm  
(microfollicular) | Scant colloid  
Small microfollicles  
OR  
Clusters and clumps of cells with varying pleomorphism  
Cells have intranuclear inclusions and clefts | Microfollicular adenoma  
Follicular carcinoma  
Follicular variant of papillary carcinoma |
Evaluation of patients with a thyroid nodule

Schematic representation of the evaluation and management of patients with a thyroid nodule, beginning with fine-needle aspiration biopsy of the nodule.

TSH: thyroid-stimulating hormone (thyrotropin); US-FNA: ultrasound-guided fine-needle aspiration.

* Thyroid scintigraphy after suppressing TSH with thyroxine.