Chapter 15
Approach to the Patient with an Incidentally Discovered Thyroid Nodule

Ana Maria Chindris and Victor Bernet

Objectives

To review steps in evaluation of a newly discovered thyroid nodule, ultrasound characteristics and indications for fine needle aspiration, to understand cytology results and role of molecular analysis and to discuss management options and long-term follow-up based on nodule characteristics and cytology.

Case Presentation

A 71-year-old Caucasian male is referred to the endocrine department for a newly diagnosed right thyroid nodule found at palpation during a routine physical examination. He had no associated symptoms such as voice changes, hoarseness, and neck swelling. No systemic type symptoms were reported. The patient was without any history of radiation exposure or family history of thyroid cancer. At physical examination, thyroid was normal in size, with irregular surface and a 2 cm discrete nodule palpable in the right lower lobe. No cervical lymphadenopathy was noted. The remaining of the physical examination was unremarkable.

TSH was 1.6 μIU/mL [0.3–5.0 μIU/mL]. An ultrasound of the neck revealed two heterogeneous solid nodules in the mid and lower pole of the right lobe. The largest, located in the lower pole measured $3.0 \times 2.1 \times 2.3$ cm and had coarse internal calcifications, the second, located in the mid pole measured $1.3 \times 1.1 \times 1.1$ cm and had peripheral calcifications. A third nodule, hypoechoic and less than 1 cm in size, was located in the right upper pole. Left lobe contained a single solid nodule measuring $1.2 \times 0.9 \times 0.9$ cm without worrisome features.

A.M. Chindris (✉) • V. Bernet
Mayo Clinic, Jacksonville, FL, USA

T.F. Davies (ed.), *A Case-Based Guide to Clinical Endocrinology*,
DOI 10.1007/978-1-4939-2059-4_15

Based on ultrasound features it was decided to perform FNA on the two larger right lobe nodules. The cytology was assessed as being indeterminate (atypia) and molecular analysis using a gene expression classifier was requested. The molecular results were assessed as being suspicious for malignancy in the case of the 3 cm nodule, while in the case of the 1.3 cm nodule no result was obtained secondary to inadequate RNA in the sample.

The patient was referred for thyroid surgery, and the final pathology indicated a 0.5 cm papillary thyroid cancer in the right lobe and also three subcentimeter foci of PTC in the left lobe with findings consistent with Stage 1 differentiated thyroid cancer. After discussion it was decided to forego treatment with radioactive iodine and patient was started on suppressive doses of thyroxine.

How the Diagnosis Was Made

Thyroid nodules are very common, with 40 % of patients in their 50s having a thyroid nodule detected by ultrasound [1] and with autopsy studies reporting a prevalence ranging between 13 and 57 % [2]. As in our case, they are typically found during routine physical examination, noted by the patient or family, or incidentally diagnosed on radiological studies performed for unrelated reasons [carotid Doppler, neck/chest computed tomography (CT)]. Advances in imaging techniques and increased use of radiologic studies led to a further increase in rate of detection of thyroid incidentalomas, from about 5 % by palpation to ten times more frequently with the use of high resolution ultrasound [1, 2].

Ultrasound examination is the preferred imaging modality to evaluate newly discovered thyroid abnormalities. In one study, one in six thyroid abnormalities noted on palpation did not correspond to a defined thyroid nodule on the ultrasound. Conversely US uncovered additional non-palpable nodules over 1 cm in 27 % of patients [3]. Incidence in thyroid nodules appears to increase with age, female sex, history of iodine deficiency, and exposure to head and neck radiation [2]. Solitary nodules are about four times more common in women than in men [1].

Assessing for presence of malignancy followed by presence of autonomous overactivity are the main objectives in evaluating a thyroid nodule. The incidence of thyroid cancer has been rising over the past three decades, only partly due to increase in use and performance of imaging [4]. Estimates indicate that about 5–13 % of all thyroid nodules harbor malignancy [5]. Fine needle aspiration remains the gold standard in assessing thyroid nodules for presence of cancer, however, up to 20 % of cytology results fall into the “indeterminate” category where the presence of cancer remains in doubt. A growing number of investigations over the last 10–15 years have focused on the potential use of molecular markers to confirm or exclude the presence of cancer in thyroid nodules. Several molecular tests are now available for the evaluation of thyroid nodules.

Lessons Learned

Clinical Evaluation of a Newly Discovered Thyroid Nodule

When evaluating a newly diagnosed thyroid nodule, the physician should start by obtaining a careful history with emphasis on risk factors for malignancy (exposure to radiation, family history of thyroid cancer, MEN 2a or 2b syndromes or, familial adenomatous polyposis) along with a description of nodule growth and of abnormal cervical lymph nodes if present. A review of systems should address symptoms consistent with hypo- and hyperthyroidism along with any compression related symptoms such as: dysphagia, positional dyspnea, voice changes/hoarseness, and/or cervical lymphadenopathy.

Physical examination should focus on location, size, mobility, and firmness of the nodule, presence of cervical lymphadenopathy, as well as signs of hypo- or hyperthyroidism.

Biochemical Tests

A serum thyroid-stimulating hormone (TSH) should be obtained. A TSH in the upper half of normal range or above has been correlated with increased risk of thyroid malignancy [6]. If suppressed, an elevated free thyroxine would confirm hyperthyroidism, and radioactive iodine uptake and scan are indicated as to determine the presence of a toxic/hyperfunctioning nodule or nodules [6]. In the case of hyperfunctioning nodules, fine needle aspiration (FNA) is not typically recommended as the risk of malignancy is extremely rare, although in the face of concerning ultrasound characteristics FNA may be appropriate in select cases. Measurement of serum thyroglobulin levels is not recommended as it is not specific for thyroid cancer in the presence of an intact thyroid and can be elevated secondary to benign conditions such as thyroiditis. A consensus does not exist with respect to routine measurements of unstimulated serum calcitonin levels for the evaluation of thyroid nodules. Selective use in case of family history of thyroid cancer or family history of MEN syndromes is indicated. Although the two-site, two step chemiluminiscent immunometric assays used currently are much less susceptible to interferences, they still display significant inter assay variability, and heterophilic antibodies have been described to cause falsely elevated, and occasionally low, calcitonin levels. However, it is generally accepted that values above 100 pg/mL are suggestive of medullary thyroid cancer, in which case surgery is indicated [6].

Ultrasound Characteristics and Malignancy Risk

All newly diagnosed or suspected thyroid nodules should be evaluated by ultrasound, as it provides the most accurate imaging technique in evaluating the structure of the thyroid gland. In the case of substernal extension, additional CT evaluation is appropriate.

A thyroid nodule typically represents thyroid tissue that has become distinct from surrounding parenchyma. Nonthyroidal entities can also appear as thyroid nodules such as: metastases from other primary malignancies, sarcoma, lymphoma, and intrathyroidal parathyroid. Likewise, chronic lymphocytic thyroiditis can appear on ultrasound as hyper- or hypoechoic areas separated by fibrotic strands, which may be mistakenly diagnosed as nodules. These areas also called pseudonodules do not have a halo or a sharp border and are not visualized in both longitudinal and transverse views.

Thyroid ultrasound should document the appearance and size of the thyroid lobes and any nodules or cysts and abnormal cervical lymph nodes, if noted. Sonographic features of thyroid nodules include: size (AP, transverse, and longitudinal diameter), shape (round, taller than wide), margins (borders/halo), echogenicity (hypo-, iso-, or hyperechoic), echostructure (homogenous vs. mixed solid/cystic vs. spongiform), presence of calcifications and internal vascularity. Several studies focused on identifying associations between certain US characteristics and malignancy, as summarized in Table 15.1. As seen, certain ultrasound features can be suggestive, but not definitively characterize a thyroid nodule as malignant or benign, for this purpose the gold standard remains FNA.

The size of the nodule does not predict risk of malignancy in a linear fashion. In a recent study including over 7,300 thyroid nodules the incidence of malignancy was 10.5 % in those measuring 1–1.9 cm and 15 % in thyroid nodules over 2 cm, incidence that remained relatively stable for sizes above 2 cm. Histopathology however, did change significantly, with follicular and Hurthle cell cancers being notably more frequent as the nodules got larger [9]. Micronodules (less than 1 cm) have a reported malignancy rate ranging between 2.1 and 7 % [10]. The American Thyroid

Table 15.1 Thyroid nodule ultrasound features

Ultrasound feature of the thyroid nodule	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Microcalcifications	26–59	85–95	24–77	42–94
Irregular borders	17–78	39–85	9–60	39–98
Increased intranodular vascularity	54–74	79–81	24–42	86–97
Solid	69–75	52–56	16–27	88–92
Hypoechogenicity	26–87	43–94	11–79	68–94
Taller than wide (transverse view)	33–40	91–93	68–77	67–75

Adapted from Frates [7], Moon [8]
PPV positive predictive value, *NPV* negative predictive value

Association (ATA) generally recommends biopsy of the nodules 1 cm and larger in size, with FNA of micronodules reserved for cases with high risk history, suspicious ultrasound findings or abnormal cervical lymph nodes [6].

Shape of the nodule was also assessed as predictor of malignancy; a taller than wide shape being found significantly specific for malignancy however with a low sensitivity.

Thyroid nodules may have either smooth or irregular margins. Most benign nodules will appear as well defined sonographically, while a blurred contour may indicate malignancy. The halo represents compressed perinodular blood vessels and appears as a thin iso- or hypoechoic rim surrounding usually a benign nodule. Absence of halo or a thick irregular halo (>2 mm) is, however, suggestive of follicular neoplasm [11, 12].

Echogenicity of a nodule describes its brightness compared to normal thyroid parenchyma. Solid nodules can therefore be hypo-, iso-, or hyperechoic. Hypoechogenicity has been associated with an increased risk of malignancy, although this feature is not specific [5]. Cystic fluid is anechoic. It may contain bright echogenic spots with reverberation artifact ("comet tail") which represent colloid crystal aggregates and signify a benign character. Pure thyroid cysts are rare; most thyroid nodules are complex, having both solid and cystic components. A particular mention should be made of "spongiform" or "honeycomb" nodules, which consist of multiple cystic areas, separated by septae, and are considered to be benign.

Calcifications can be divided in microcalcifications and macro (coarse) calcifications. Microcalcifications are echogenic foci without acoustic shadowing, considered to be the equivalent of psammoma bodies on histology and highly suggestive of papillary thyroid cancer. Coarse (eggshell) calcifications are associated mainly with benign disease; however, disruption of rim calcification may be seen in cases of malignancy [13].

Thyroid nodule vascularity is most commonly evaluated by Color Flow Doppler (CFD). In case of nodules with slow intranodular flow, Power Doppler, which is independent of velocity, can be used to better characterize internal vascularity. Several studies indicate that increased internal flow increases the probability that a thyroid nodule is malignant [11, 14, 15]. One suggested classification describes the pattern of nodular flow, as absent (grade I), perinodular (grade II), and peri and intranodular (grade III) [11]. In a study on over 200 thyroid nodules, Frates et al. [15] reports the nodule vascularity as absent (0), minimal internal flow without peripheral ring (1), peripheral ring of flow (defined as >25 % of the nodule's circumference) but minimal or no internal flow (2), peripheral ring of flow and small to moderate amount of internal flow, (3) and extensive internal flow with or without a peripheral ring (4).

Thyroid nodules that are hard to palpation have been recognized to have a higher malignant potential. Ultrasound elastography assesses tissue stiffness, by measuring the degree of distortion when a tissue is subjected to external pressure. It has been initially developed to evaluate other tissues including breast and prostate nodules, liver fibrosis and lymph nodes for malignancy. In recent years elastography has

been used in evaluation of thyroid nodules and emerging data suggest that, it could represent an independent predictor for thyroid nodule malignancy, to be used in conjunction with conventional ultrasound techniques [16].

Indications for FNA Sampling: Interpretation of the FNA Results—Role of Molecular Analysis

ATA 2009 guidelines summarize indications for biopsy of thyroid nodules based on various levels of evidence. Indications for FNA are based on a combination of patient's clinical history (e.g., exposure to radiation or personal or family history of thyroid cancer) and nodule size and appearance [6]. For example, a 1.5 cm nodule with increased intravascular flow and irregular margins would be favored for biopsy over a 2.5 cm spongiform nodule. Similarly, a 1.8 cm solid hypoechoic nodule with microcalcifications would take priority over a spongiform nodule (honeycomb appearance) 2 cm in size. Current guidelines recommend against FNA of completely cystic nodules.

Nonpalpable nodules have the same risk of malignancy as the palpable ones of similar size [17]. Similarly, solitary thyroid nodules carry the same risk of malignancy as individual nodules from a multinodular goiter [3]. Deciding which of the nodules to choose for FNA can represent a challenge. In the setting of multiple nodules without worrisome characteristics, it is generally accepted that the largest nodule should be biopsied. Radioactive iodine scan can be used in case of multinodular goiters in the setting of low or low–normal TSH. In this case, hypofunctioning nodules are identified for FNA.

FNA is a simple and safe procedure essential for thyroid nodule evaluation, with an overall accuracy exceeding 95 %. There are several techniques currently employed [parallel vs. perpendicular approach, free hand or with a needle guide, closed suction aspiration vs. "needle only"], all regarded as equally effective. It can be performed by palpation or under US guidance. Two to six passes with 27 or 25G needles are usually done, dictated by technique and operator's preference. Specimen adequacy can be assessed on site. Complications are rare, and consist of local pain and hemorrhage/hematoma. Isolated case reports in the literature note infection, acute thyroid inflammation, tumor seeding (needle tract), and recurrent laryngeal nerve injury with vocal cord paralysis. Anticoagulants should be preferentially discontinued 4–7 days prior to the procedure if possible, although cases of massive hematomas with airway obstruction are exceedingly rare, and hemostasis can be usually obtained by compression against the trachea.

Cytology results are currently reported using Bethesda system for reporting thyroid cytopathology [18]. At least 6 groups of benign follicular cells, with at least 10 follicular cells per group are required in order for the pathologist to make a benign diagnosis. In our institution, 10 follicular groups with ~10 cells per group are required for an adequate specimen with cells being present on two slides being preferred. The following diagnostic categories are reported [18] (Table 15.2):

Table 15.2 Bethesda diagnostic categories

Bethesda 2007 diagnostic category	Risk of malignancy (%)	Management previously recommended	Management currently recommended
Nondiagnostic	1–4	Repeat FNA with US	Repeat FNA with US
Benign	0–3	Clinical follow-up	Clinical follow-up
Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS)	5–15	Repeat FNA	GEC/mutation analysis
Follicular neoplasm (FN) or suspicious for a follicular neoplasm (SFN)	15–30	Surgical lobectomy	GEC/mutation analysis
Suspicious for malignancy (SMC)	60–75	Near total thyroidectomy or surgical lobectomy	Mutation analysis
Malignant	97–99	Near total thyroidectomy	Near total thyroidectomy

Although most biopsies are adequate for a cytologic diagnosis, 5–20 % will be nondiagnostic or unsatisfactory [19]. Reported causes include large cystic component [19]; colloid nodules that are acellular or hypocellular or artifacts. In case of a nondiagnostic FNA performed by palpation; the ATA recommends use of ultrasound guidance for the repeated procedure. In case of mixed nodules with large cystic component, sampling the solid portion of the nodule will yield a better specimen. Likewise, in case of large nodules with cystic degeneration, sampling the periphery of the nodule may avoid obtaining a nondiagnostic sample. In a series of 189 nodules with indeterminate cytology at first biopsy, Alexander et al. reports a success rate of 48 % (cystic nodules) to 76 % (solid nodules) with the second attempt [19]. Some advocate ultrasound guided core needle biopsy in cases where repeat FNA remains nondiagnostic, with one study on 21 nodules showing 86 % diagnostic yield by core biopsy following two or more nondiagnostic FNAs [20]. If repeat cytology remains nondiagnostic, surgical excision should be taken into consideration, as the risk of malignancy can be as high as 10 % [18].

Although small (about 5 %), false-negative rates are not negligible therefore clinical and sonographic follow-up in 6–18 months is essential [6]. The causes are sampling error, which occurs mainly with very small (<1 cm) or very large (>4 cm) nodules [1] and interpretation error. Significant growth (50 % in volume or at least 2 mm in two diameters) should prompt repeat FNA [6].

FNA has substantially reduced the number of required thyroid surgeries for thyroid nodules with an expected increase in the number of malignancies diagnosed at surgery from 3.1 % to 34 % [21]. Still a significant number of thyroid surgeries are performed to obtain a definitive histopathology diagnosis. Research over the past years focused on identifying molecular markers that will identify all benign from

malignant thyroid nodules and make distinction between adenoma and carcinoma, therefore offering prognostic information and guiding management. There are three methods currently available:

Mutation detection (miRinform, Asuragen), "rules in" malignancy by using a panel of somatic mutations that collectively occur in about 70 % of thyroid cancers. They include point mutations (BRAF V600E, NRAS codon 61, HRAS codon 61, and KRAS codons 12/13) and rearrangements (RET/PTC1, RET/PTC3 and PAX8/PPARgamma). In a study of 1,056 FNA samples with indeterminate cytology, this method yielded a specificity ranging from 99 % (AUS/FLUS) to 96 % (SMC), with a corresponding PPV of 88–95 %, thus having the potential to correctly identify malignant nodules that would need total thyroidectomy. The authors propose a clinical algorithm for managing thyroid nodules with indeterminate cytology based on the results of this mutational analysis [22]. The main drawback of this method is the limited sensitivity of only 60 %, with as many as 40 % of thyroid cancers being missed at diagnosis, possibly due to lacking in the somatic mutations included in this panel [23].

Multigene expression classifier (Afirma, Veracyte)- is a "rule-out" test that measures expression levels of 167 genes using a thyroid gene microarray analyzed with a classification algorithm. The test reports the result as benign or suspicious and is designed to identify benign nodules within the "indeterminate cytology" category, therefore reducing the number of unnecessary surgeries. A validation trial on over 4,800 FNA samples from supracentimeter thyroid nodules, of which 265 were indeterminate, reported a sensitivity of 90–94 %, with a NPV ranging from 95 % (AUS/FLUS) to 85 % (SMC), respectively. The study reported false negative results in six cases of papillary carcinoma, and suggested that sampling method, especially in small nodules may be the culprit [24].

Thyrotropin Receptor mRNA (TSHR-mRNA) was developed at Cleveland Clinic as a molecular marker of thyroid cancer that is measured in the peripheral blood. In case of follicular neoplasm and suspicious for follicular neoplasm cytology, TSHmRNA in association with high quality neck ultrasound improved sensitivity to 97 %, with 84 % specificity. The data on using TSHR-mRNA for assessment of thyroid nodule cancer risk would benefit from confirmation as it is presently limited to a single institution.

Management Considerations: Intervention Versus Observation—Role of LT4 Suppressive Therapy

Management of a thyroid nodule is dictated by clinical presentation and cytology assessment.

(a) **Suspicious** cytology or molecular analysis results represent indications for surgery. In case of indeterminate cytology with suspicious mutation detection result (miRinform), proceeding with total thyroidectomy as opposed to standard diagnostic lobectomy may be considered.

(b) **Asymptomatic** thyroid nodules with benign cytology should be followed up for stability, with repeat ultrasound in intervals between 6 and 12 months (because of low but not negligible risk of a false-negative FNA result). Repeat biopsy is indicated in case of a volume increase ≥50 % or if the nodule increases by 2 mm in at least two dimensions. For large benign nodules >4 cm and nodules with associated compression symptoms, surgical removal with hemithyroidectomy is recommended. Newer methods of treatment of thyroid nodules include laser and radiofrequency ablation (RFA) and high-intensity focused ultrasound (HIFU) ablation however, at present they are mainly used in Europe and have not gained wide acceptance in the USA [5].

(c) **Management of thyroid cysts** management poses particular problems. As already mentioned, pure cysts do not require FNA, however drained fluid should be sent for cytology. Small asymptomatic cyst can be followed with periodic ultrasound. Large cysts that were drained should be followed for fluid reaccumulation. In such case, especially if associated with symptoms, a more definitive treatment is needed. Options include hemithyroidectomy and percutaneous ethanol ablation; in the latter case, more than one treatment may be required for successful nodule shrinkage.

(d) **Management of micro nodules (<1–1.5 cm)** continues to represent a particular challenge. The frequency of thyroid microcarcinoma is reported to be as high as 35 %. Although most cases are asymptomatic and diagnosed by chance, up to 43 % may have associated cervical lymphadenopathy, and up to 2.8 % are noted to have distant metastases [25]. Cytological malignancy rate reported in the literature for nodules <1.5 cm ranges between 7 and 13 %. Currently, ATA recommends FNA of nodules as small as 0.5 cm in the case of high risk history, concerning ultrasound characteristics in the presence of abnormal lymph nodes. Nodules <1.5 cm that are solid and hypoechoic or contain microcalcifications should also be biopsied.

(e) **Suppressive treatment with thyroid hormone to induce shrinkage or halt growth of benign thyroid nodules in euthyroid patients is no longer advocated.** Widely used in the past, it is now out of favor as risks associated with excess thyroid hormone (e.g., osteoporosis and atrial fibrillation) outweigh the potential benefits. Use of LT4 is justified in hypothyroid patients in whom TSH normalization can be also associated with reduction in thyroid nodule size. In addition, LT4 suppressive therapy can shrink cancerous nodules offering a false sense of comfort and delay in diagnosis.

(f) **Autonomously functioning thyroid nodules** should be evaluated for the presence of clinical or subclinical hyperthyroidism and managed accordingly.

Questions

1. Which of the following thyroid nodules is more likely to be malignant on cytology? (nodule size reported as transverse × antero-posterior × longitudinal)

   (a) A 3 × 2 × 2 cm round nodule with honeycomb appearance in a multinodular goiter
   (b) A 2.5 × 2.8 × 2.8 cm solid hypoechoic nodule with irregular margins and punctate internal calcifications
   (c) A 1 × 1.5 × 1.5 cm mixed nodule with bright internal echogenic foci
   (d) A 1.5 × 1.5 × 1.2 cm nodule with eggshell calcification

2. A 43-year-old patient with a recently discovered TN during routine physical examination, has a TSH of 0.06 mIU/L, FT4 = 1.5 (0.6–1.6) FT3 = 3.9 (2.6–7.5). He is otherwise asymptomatic. What test would you order next? OK

   (a) Antithyroid peroxidase (TPO) antibody titers
   (b) Serum thyroglobulin
   (c) Radioactive iodine uptake and scan
   (d) Palpation-guided FNA

3. A 52-year-old patient with a palpable TN undergoes a neck ultrasound. This notes a heterogenous thyroid gland with a hypoechoic nodular area located in mid left lobe and measuring 2 × 1.5 cm on transverse view. Rotating the probe longitudinally fails to identify the nodule. Her TSH is 3.8 mIU/L, and she is otherwise asymptomatic. What would you recommend to the patient?

   (a) Repeat neck ultrasound in 3 months
   (b) Thyroglobulin level
   (c) Antithyroid peroxidase and thyroglobulin antibody levels
   (d) Radioactive iodine uptake and scan

4. A 44-year-old patient presents with an incidentally found thyroid nodule. Her TSH is 1.2 mIU/L and she is asymptomatic. Neck ultrasound reveals a 2.5 × 3.0 × 2.5 cm right lower lobe hypoechoic nodule with irregular margins and increased internal vascularity that pushes against the thyroid capsule. Ultrasound guided FNA yields indeterminate result and gene expression classifier returns as benign. What would you advise the patient?

   (a) Repeat FNA in 6 months
   (b) Start LT4 suppressive therapy
   (c) Reassure the patient and recommend repeat ultrasound and TSH in 1 year.
   (d) Perform thyroid lobectomy for histological diagnosis.

Answers to Questions

1. b: Explanation: Amongst ultrasound features associated with increased risk of malignancy, microcalcifications in a hypoechoic, taller-than-wide nodule, have been associated with a higher specificity for cancer. Spongiform nodules are almost always benign, continuous eggshell calcifications are also associated with benign nodules as well as the echogenic foci (comet tail artifact)
2. c: Explanation: In the setting of a suppressed TSH, the next step in evaluating a thyroid nodule is a radioactive iodine uptake and scan to assess whether the nodule is hyperfunctioning. In such case, FNA is not indicated. An ultrasound should, however be performed in every newly diagnosed thyroid nodule.
3. c: Explanation: Pseudonodules appear as nodular structures in one ultrasound view, but not on the other, and do not need FNA. They can be seen in Hashimoto thyroiditis, therefore it is reasonable to test for markers of autoimmunity, even if TSH is within normal range, as they may indicate if patient is a risk of developing hypothyroidism.
4. d: Explanation: The reported sensitivity of the gene expression classifier is 90–94 %. This nodule displays several ultrasound characteristics suggestive for malignancy therefore surgery for histological diagnosis, as opposed to follow-up in 1 year, is indicated. Repeat FNA would be indicated if the FNA was nondiagnostic/unsatisfactory. Suppressive therapy with thyroxine would not be beneficial in case the nodule is malignant.

References

1. Mazzaferri EL. Management of a solitary thyroid nodule. N Engl J Med. 1993;328(8):553–9.
2. Dean DS, Gharib H. Epidemiology of thyroid nodules. Best Pract Res Clin Endocrinol Metab. 2008;22(6):901–11.
3. Marqusee E, et al. Usefulness of ultrasonography in the management of nodular thyroid disease. Ann Intern Med. 2000;133(9):696–700.
4. Chen AY, Jemal A, Ward EM. Increasing incidence of differentiated thyroid cancer in the United States, 1988–2005. Cancer. 2009;115(16):3801–7.
5. Sipos JA. Advances in ultrasound for the diagnosis and management of thyroid cancer. Thyroid. 2009;19(12):1363–72.
6. Cooper DS, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167–214.
7. Frates MC, et al. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. Ultrasound Q. 2006;22(4):231–8. discussion 239–40.
8. Moon WJ, et al. Benign and malignant thyroid nodules: US differentiation–multicenter retrospective study. Radiology. 2008;247(3):762–70.
9. Kamran SC, et al. Thyroid nodule size and prediction of cancer. J Clin Endocrinol Metab. 2013;98(2):564–70.
10. Butros R, et al. Management of infracentimetric thyroid nodules with respect to ultrasonographic features. Eur Radiol. 2007;17(5):1358–64.

11. Cerbone G, et al. Power Doppler improves the diagnostic accuracy of color Doppler ultrasonography in cold thyroid nodules: follow-up results. Horm Res. 1999;52(1):19–24.
12. Bonavita JA, et al. Pattern recognition of benign nodules at ultrasound of the thyroid: which nodules can be left alone? AJR Am J Roentgenol. 2009;193(1):207–13.
13. Kim BM, et al. Sonographic differentiation of thyroid nodules with eggshell calcifications. J Ultrasound Med. 2008;27(10):1425–30.
14. Papini E, et al. Risk of malignancy in nonpalpable thyroid nodules: predictive value of ultrasound and color-Doppler features. J Clin Endocrinol Metab. 2002;87(5):1941–6.
15. Frates MC, et al. Can color Doppler sonography aid in the prediction of malignancy of thyroid nodules? J Ultrasound Med. 2003;22(2):127–31. quiz 132–4.
16. Azizi G, et al. Performance of elastography for the evaluation of thyroid nodules: a prospective study. Thyroid. 2013;23(6):734–40.
17. Hagag P, Strauss S, Weiss M. Role of ultrasound-guided fine-needle aspiration biopsy in evaluation of nonpalpable thyroid nodules. Thyroid. 1998;8(11):989–95.
18. Cibas ES, Ali SZ. The Bethesda system for reporting thyroid cytopathology. Am J Clin Pathol. 2009;132(5):658–65.
19. Alexander EK, et al. Assessment of nondiagnostic ultrasound-guided fine needle aspirations of thyroid nodules. J Clin Endocrinol Metab. 2002;87(11):4924–7.
20. Samir AE, et al. Ultrasound-guided percutaneous thyroid nodule core biopsy: clinical utility in patients with prior nondiagnostic fine-needle aspirate. Thyroid. 2012;22(5):461–7.
21. Carpi A, et al. Aspiration needle biopsy refines preoperative diagnosis of thyroid nodules defined at fine needle aspiration as microfollicular nodule. Biomed Pharmacother. 1996; 50(8):325–8.
22. Nikiforov YE, et al. Impact of mutational testing on the diagnosis and management of patients with cytologically indeterminate thyroid nodules: a prospective analysis of 1056 FNA samples. J Clin Endocrinol Metab. 2011;96(11):3390–7.
23. Hodak SP, Rosenthal DS, For The American Thyroid Association Clinical Affairs Committee. Information for clinicians: commercially available molecular diagnosis testing in the evaluation of thyroid nodule fine-needle aspiration specimens. Thyroid. 2013;23(2):131–4.
24. Alexander EK, et al. Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. N Engl J Med. 2012;367(8):705–15.
25. Bernet V. Approach to the patient with incidental papillary microcarcinoma. J Clin Endocrinol Metab. 2010;95(8):3586–92.