The Incidental Thyroid Nodule

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Abstract: Incidental thyroid nodules that are found on an imaging study performed for reasons other than thyroid pathology represent a common scenario encountered by health care providers. The initial workup for these nodules comprises a thorough history and physical examination, thyroid function tests, a dedicated thyroid ultrasound, and fine-needle aspiration of any suspicious lesions. Management ranges from observation and reassurance to surgical resection and depends on the cytologic diagnosis. In cases of cytologically indeterminate or discordant nodules, surgical excision (lobectomy) offers a definitive diagnosis, although molecular testing or a reasonable period of observation may be useful as less invasive adjuncts. CA Cancer J Clin 2018;68:97-105. © 2018 American Cancer Society.

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Introduction

Incidental thyroid nodules (ITNs) are common presenting scenarios for medical providers. Defined as discrete, nonpalpable lesions radiologically distinct from the surrounding parenchyma, ITNs are found on anatomic imaging studies performed for reasons other than planned assessment of thyroid disease.1 Large population-based studies estimate that the prevalence of thyroid nodules identified by palpation is between 4% and 7%,2,3 with imaging studies identifying up to 10 times more nodules, most of which are benign.2 Autopsy studies estimate that thyroid nodules may be present in up to 50% to 60% of all adults.4 Women are more frequently affected than men (4:1), and the prevalence of thyroid nodules increases with age to 50% in women older than 70 years.2 As medical technology continues to evolve and the societal demand for imaging continues to increase,5 the incidence of ITNs will also continue to rise,6 making the risk stratification of patients with ITNs and the identification of those who need further evaluation, biopsy, and surgical intervention essential.

The primary goal in managing ITNs is to differentiate malignant lesions from benign conditions. Population-based studies estimate that the risk of malignancy is 1.6% among patients with ITNs,7 whereas studies of patients undergoing biopsy have estimated that the risk is 12%;8 these studies are influenced by selection bias, with the actual risk of malignancy unknown but likely falling in between. The rate of identification and the subsequent rate of malignancy of ITNs depend on both the initial imaging modality and the number of patients in whom further evaluation is pursued, as well as the clinical characteristics of the population studied. Incidental thyroid nodules are found on 20% to 67% of ultrasound (US) examinations, up to 25% of contrast-enhanced thoracic computed tomography (CT) scans, 16% to 18% of magnetic resonance imaging (MRI) scans, and 1% to 2.3% of positron emission tomography (PET) scans.9,11 When using surgical registries or identifying patients based on referral for US or fine-needle aspiration (FNA), the true number of patients with ITN is likely underestimated, as not all patients with ITNs undergo additional workup, with percentages ranging from 8% to 44%.12,13 Current reporting practices among radiologists,9 guidelines for further imaging (Table 1),1,3,14-16 and subsequent management strategies for ITN are variable, due
| INDICATIONS | AMERICAN THYROID ASSOCIATION (HAUGEN 2016) | NATIONAL COMPREHENSIVE CANCER NETWORK (HOANG 2012) | SOCIETY OF RADIOLOGISTS IN ULTRASOUND (TANPITUKPOONGSE 2015) | THREE-TIERED SYSTEM (FRATES 2005) | WHITE PAPER OF THE AMERICAN COLLEGE OF RADIOLOGY (HOANG 2015) |
|-------------|---------------------------------------------|-----------------------------------------------|-------------------------------------------------|---------------------------------|--------------------------------------------------|
| Indications for ultrasound | All patients with suspected thyroid nodule(s) | All patients with suspected thyroid nodule(s) | Not applicable | Nodules with high-risk features (suspicious lymph nodes, local invasion, or PET avidity) | Nodules with suspicious findings (abnormal lymph nodes, local invasion, or PET avidity) |
| | | | | OR nodules ≥ 1 cm in patients aged < 35 y | OR nodules ≥ 1 cm in patients aged ≥ 35 y |
| | | | | OR nodules ≥ 1.5 cm in patients aged ≥ 35 y | OR nodules ≥ 1.5 cm in patients aged ≥ 35 y |
| Indications for FNA | Solid hypoechoic nodules ≥ 1 cm with or without one or more: irregular margins, microcalcifications, taller than wide shape, rim calcifications with soft tissue extrusion, or extrathyroidal extension | Solid hypoechoic nodules ≥ 1 cm with microcalcifications, infiltrative margins, or taller than wide in the transverse plane | Solid nodules ≥ 1 cm with microcalcifications | Solid nodules ≥ 1 cm with microcalcifications, hypoechoic features, increased vascularity, infiltrative margins, or taller than wide dimensions | Any PET-avid nodule |
| | OR solid isoechoic or hyperechoic nodules ≥ 1.5 cm without the above features | OR solid nodules without the above features ≥ 1.5 cm | OR solid nodules ≥ 1.5 cm | OR PET-avid nodules | OR biopsy based on US characteristics (not further specified) |
| | OR spongiform or partially cystic nodules ≥ 2 cm without the above features | OR spongiform nodules ≥ 2 cm | OR mixed solid-cystic nodules ≥ 2 cm | OR any nodule associated with lymphadenopathy, extrathyroidal spread, lung metastases, or signs of ipsilateral vocal cord palsy | |

Abbreviations: FNA, fine-needle aspiration; PET, positron emission tomography; US, ultrasound. *Or mixed solid-cystic nodules with a solid component measuring the same. **Observation with serial ultrasound may be considered rather than biopsy if desired.
in part to a lack of a dominant set of comprehensive management guidelines (Table 1). Herein, we present a discussion of management strategies for patients with ITNs, including the supporting evidence for each management recommendation.

**Initial Evaluation**

The initial evaluation of a patient with an ITN should include a complete history and physical examination with an emphasis on prior thyroid-related concerns, including medications, previous biopsies, symptoms of hypothyroidism or hyperthyroidism, previous head and neck or whole-body irradiation, and previous surgery, particularly head and neck or upper esophageal/thoracic surgery. In addition, family history of thyroid disorders or syndromic patterns that suggest an increased risk of thyroid cancer (eg, multiple endocrine neoplasia type II, Cowden syndrome, Carney complex, familial adenomatous polyposis and/or Gardner syndrome, Werner syndrome, DICER1 syndrome) should be evaluated. Symptoms such as dysphagia, dysphonia, and dyspnea (at rest, positional, or nocturnal) should alert the clinician to the possibility of compression or invasion of surrounding structures by carcinoma, whereas pain is more likely with thyroiditis. The physical examination should include a thorough neck examination focusing on the thyroid and evaluation for central and lateral adenopathy. Initial laboratory workup should include measurement of serum thyrotropin and free thyroxine levels, which can confirm hypothyroidism or hyperthyroidism. If Hashimoto thyroiditis is suspected, then testing for the presence of antithyroid peroxidase antibodies can supplement the clinical diagnosis. The risk of concomitant differentiated thyroid cancer in the setting of Hashimoto thyroiditis is unclear, as thyroidectomy studies influenced by selection bias demonstrate a positive association between Hashimoto thyroiditis and thyroid cancer, whereas population-based studies do not support a causative relationship. In contrast, Hashimoto thyroiditis is strongly associated with primary thyroid lymphoma (pooled relative risk, 9.74; 95% confidence interval [95% CI], 3.93-24.13 [P < .001] compared with patients who have thyroid lymphoma without Hashimoto thyroiditis). The rarity of the disease overall (1%-5% of all thyroid cancers and 0.37% of patients with Hashimoto thyroiditis) means that thyroid lymphoma remains low on the differential for ITNs, even in patients with Hashimoto thyroiditis. More commonly, the lymphocytic infiltration seen in patients with Hashimoto thyroiditis can produce benign thyroid pseudonodules; as discussed below, FNA biopsy can help identify malignancy in this setting. Calcitonin levels should be measured in the rare patient in whom medullary thyroid cancer is suspected, but calcitonin should not be used as a screening test for the general population. Thyroglobulin level measurement in patients with an intact thyroid is not sensitive or useful in the screening process for thyroid cancers.

**Imaging**

US is the preferred imaging modality for thyroid complaints, because other imaging modalities are less sensitive in diagnosing thyroid malignancies. CT is useful for evaluating invasion into surrounding structures or the extent of a subternal goiter but often underestimates thyroid nodule size; in addition, the presence of microcalcifications on CT scans, unlike on sonograms, does not correlate with the risk of malignancy. The overall risk of malignancy for an ITN found on a CT scan is from 3.9% to 11.3%. MRI features suggestive of malignancy are even less defined, although some researchers suggested that low mean apparent attenuation coefficients on diffusion-weighted MRI scans may predict malignancy with high sensitivity, specificity, and accuracy rates (98%, 92%, and 99%, respectively). The rate of malignancy in patients with ITNs identified on PET scans is markedly higher than that in patients with nodules identified on CT scans or MRI. In one large systematic review of more than 55,000 patients in 18 studies undergoing PET scans, researchers found a pooled rate of ITN detection of 1%, but 33% of those ITNs were malignant, most often papillary thyroid cancer (82%). Although the resolution for nodules on PET scan is lower than that of CT or MRI, the radiotracer used for PET is specific for metabolically active tissue, leading to a higher rate of malignancy within detected abnormalities. This is due in part to the characteristics of the patient population (most patients undergoing PET have a current or prior nonthyroid malignancy and are more likely than the general population to have been exposed to radiation) and in part because of the specific metabolic characteristics of PET. The pattern of standardized uptake value (SUV) on PET is important: diffuse tracer uptake within the thyroid gland generally represents benign disease, whereas focal uptake is associated with malignancy in 30% to 50% of cases. The maximum SUV on PET appears to be associated with an increased risk of malignancy, but a specific SUV cutoff to determine benign versus malignant is not defined. Clinical characteristics, such as age, sex, and tumor size, have not been associated with the risk of malignancy in nodules identified on PET. Finally, in patients with hyperthyroidism, radionuclide thyroid scans can demonstrate characteristics of the nodule in question compared with the surrounding thyroid parenchyma. It is generally accepted that hyperfunctioning nodules are rarely malignant (3.1% in surgically resected series influenced by selection bias), and either observation with medical management (as in the case of diffuse uptake across the gland) or surgical management (as in the case of a solitary hyperfunctioning adenoma) can be safely pursued.
Regardless of the initial imaging modality, all patients with suspected thyroid nodule(s) should undergo a dedicated thyroid/neck US that encompasses the thyroid as well as the central and lateral neck compartments. In addition to being the gold standard for size measurement, characteristics of the thyroid parenchyma on US increase or decrease suspicion for thyroid malignancy (Table 2). Lymph nodes that are sonographically abnormal (loss of fatty hilum, microcalcifications, hyperechoic change, round shape, or necrosis) may increase the level of suspicion and alter the planned operation in more than one-third of patients with ITNs.

### Tissue Diagnosis and Management

Patients with an ITN that is clinically or radiographically suspicious for malignancy (Tables 1 and 2) should undergo FNA biopsy. Although guidelines and clinical practice patterns vary, most physicians agree that FNA biopsy is indicated for any solid or hypoechoic nodule greater than 10 mm in diameter or with suspicious sonographic features (microcalcifications, extrathyroidal extension, irregular borders, and greater height than width) (Table 1). FNA results in a nondiagnostic specimen 15% to 20% of the time, with US-guided FNA decreasing the rate of nondiagnostic specimens by approximately one-half (ie, from 16% to 7% in a study of 497 nodules). US further allows for the performing clinician to focus the biopsy on the most suspicious area of a nodule or lymph node or, in patients with multiple thyroid abnormalities, allows for the assessment of each site. Immediate cytopathologic assessment for specimen adequacy may further improve diagnostic yield by allowing additional passes in a single setting and thereby decreasing inadequate sampling. For those patients with initial nondiagnostic results, a repeat FNA or US-guided FNA may yield diagnostic material in 50% and 63%, respectively. Core-needle biopsy is rarely necessary, and the authors recommend against it, because it is more likely to cause bleeding and patient discomfort. The false-negative rate for FNA biopsy (including US-guided and FNA by palpation) ranges between 1.3% and 11.5%, with most centers reporting between 1% and 6%. Repeat biopsy may be necessary in the case of nondiagnostic or indeterminate specimens or to obtain specimens for additional molecular testing, as discussed below.

The management of ITNs depends on the cytopathologic diagnosis as reported using The Bethesda System for Reporting Thyroid Cytopathology (Table 3). Patients with initial nondiagnostic results should undergo a repeat US-guided FNA biopsy. If the FNA biopsy results are still indeterminate, then surgical resection (thyroid lobectomy) can be considered for diagnostic purposes versus continued close observation. For a clinically or cytologically overt or suspected malignancy (Bethesda category V or VI), either total thyroidectomy or lobectomy may be performed, depending on the tumor size, the presence of high-risk

### Table 2. Ultrasound Features Suggestive of Malignancy in the Primary Tumor and Within Lymph Nodes

| Thyroid Nodule Features | Lymph Node Features |
|-------------------------|--------------------|
| Microcalcifications     | Microcalcifications|
| Hypoechoogenicity       | Hypoechoogenicity  |
| Irregular margins       | Peripheral vascularity|
|                          | Rounded shape      |
| Shape taller than wide  | Cystic aspect      |

### Table 3. The Bethesda System for Reporting Thyroid Cytopathology With Suggested Management and Corresponding Risk of Malignancy

| Diagnostic Category      | Suggested Management | Predicted Risk of Malignancy | Actual Risk of Malignancy in Surgically Excised Nodules, Median (Range), % |
|--------------------------|----------------------|------------------------------|----------------------------------------------------------------------------|
| I. Nondiagnostic/unsatisfactory | Repeat FNA with US guidance | NIIFTP ≠ Cancer, %<sup>a</sup> | NIIFTP = Cancer, %<sup>a</sup> | 20 (9-32) |
| II. Benign                | Clinical and sonographic follow-up | 5-10                          | 5-10                          | 2.5 (1-10) |
| III. Atypia or follicular lesion of undetermined significance | Repeat FNA, molecular testing, and/or lobectomy | 6-18                          | 10-30                         | 14 (6-48) |
| IV. Follicular neoplasm or suspicious for follicular neoplasm | Molecular testing and/or lobectomy | 10-40                         | 25-40                         | 25 (14-34) |
| V. Suspicious for malignancy | Lobectomy or thyroidectomy<sup>b</sup> | 45-60                         | 50-75                         | 70 (53-97) |
| VI. Malignancy            | Lobectomy or thyroidectomy<sup>b</sup> | 94-96                         | 97-99                         | 99 (94-100) |

Abbreviations: FNA, fine-needle aspiration; NIIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; US, ultrasound. <sup>a</sup>As predicted by the Bethesda system (McCoy 2007). <sup>b</sup>As summarized by Haugen 2016 and determined before the introduction of NIIFTP. <sup>c</sup>Based on tumor size, histopathologic characteristics, and anticipated need for postoperative radioactive iodine therapy.
pathologic features, and patient preference. Specifics regarding the extent of surgery for overt or suspected malignancy are outside the scope of this article but, in general, total thyroidectomy should be performed for tumors greater than 4 cm in diameter. Lobectomy can be considered for patients who have ITN with unifocal small (<1.5 cm) tumors, with no evidence of extrathyroidal extension or lymph node metastases, without a personal history of neck irradiation or family history of thyroid cancer, and who are unlikely to undergo postoperative radioactive iodine therapy. For patients with intermediate sized tumors (between 1.5 and 4 cm), most endocrine surgeons prefer total thyroidectomy, although lobectomy and isthmectomy also can be considered. Patients with imaging and FNA findings that indicate benign thyroid conditions (adenomas, colloid nodules, complex cysts, hyperplastic nodules, and thyroiditis with a pseudonodular appearance) harbor a risk of malignancy less than 3% and can be observed with serial examination and US at 6-month to 1-year intervals, lengthening the interval after documentation of stability. Serial FNA biopsy in the absence of changing imaging features over time in these patients is unlikely to be helpful. Surgical intervention should be considered, even with a benign cytology, for patients with large nodules (≥4 cm), because the false-negative rate for FNA biopsy increases with nodule size due to sampling error. In one study of 223 patients with thyroid nodules greater than 4 cm and initially benign cytology, the false-negative rate for FNA biopsy was 13%. Another group examined 323 thyroid nodules with benign cytologies and found an FNA biopsy false-negative rate of 11.7% for all nodules at least 3 cm in diameter. These findings support surgical resection (thyroid lobectomy) as a viable management strategy for thyroid nodules greater than 3 to 4 cm regardless of cytology versus observation, with patient preferences guiding therapy.

Atypia of undetermined significance (AUS) and follicular lesion of undetermined significance (FLUS) (Bethesda category III) are categories reflecting indeterminate cytologies that do not clearly meet the criteria for benign or malignant lesions, follicular neoplasms (FN), or suspicious for FN (SFN) (Bethesda category IV), or nodules suspicious for malignancy (category V). They may be dominated by Hurthle cells or have focal features suggestive of malignancy in an otherwise benign-appearing sample and are often impacted by poor fixation. Interpathologist variability is most pronounced in this diagnostic category. In one study, 7 board-certified cytopathologists with more than 5 years of clinical experience reviewed 75 cases of various thyroid pathologies collected from their respective institutions and chosen intentionally to include a high proportion of cases originally diagnosed as AUS/FLUS (n = 31). When blinded to the original institutional diagnosis and the clinical history, consensus review was consistent in one-third of cases, resulted in a benign diagnosis in another one-third, and was considered suspicious for malignancy in the remaining one-third. In addition, 21% of 19 originally benign cases were categorized as AUS/FLUS. Preparation quality and inadequate cellular adequacy were cited as major factors influencing the lower concordance between pathologists for AUS/FLUS samples. Others have documented an inverse relationship between the number of AUS/FLUS diagnoses and the number of nondiagnostic FNA biopsy samples when analyzed according to year, aspirator, and cytologist. Therefore, a repeat FNA biopsy after a diagnosis of AUS/FLUS is reasonable, with 50% to 60% of repeat biopsies resulting in benign diagnoses.

The Bethesda IV category of FN/SFN was originally created to denote lesions at risk for follicular carcinoma that thus should be triaged to surgical evaluation, although most will ultimately represent benign nodules (Table 3). While previously surgical lobectomy was recommended as a diagnostic procedure and remains the standard of care, molecular testing (as discussed below) may provide additional information and ease anxiety about observation in selected patients with nodules in this category.

In 2012, the National Cancer Institute recommended revision of terminology to replace the word “cancer” when data support patterns of indolent behavior to avoid overdiagnosis and overtreatment among multiple cancer types. A working group comprised of international experts subsequently reviewed and summarized 268 cases of encapsulated follicular variant of papillary thyroid cancer, and 109 patients had an encapsulated follicular variant of papillary thyroid cancer without any evidence of vascular or capsular invasion confirmed on central pathologic review. With a follow-up of between 10 and 26 years, all patients in this group were alive without evidence of disease; none received radioactive ablation therapy. As a result, the revised terminology of “noninvasive follicular thyroid neoplasm with papillary-like nuclear features” (NIFTP) was created. The diagnostic criteria for NIFTP include the absence of vascular and capsular invasion, which requires evaluation of the tumor-capsule interface and thus an inability to diagnose based on cytology alone, making NIFTP a surgical disease. As a result of reclassifying these lesions, the risk of malignancy across most Bethesda categories is expected to decrease (Table 3), with some authors reporting the largest decrease among indeterminate lesions (AUS/FLUS or FN/SFN) versus others reporting the largest decrease among suspicious lesions (Bethesda category V). Currently, investigators have attempted to better characterize preoperative characteristics of NIFTP on cytopathology, molecular studies, and US and, although some have suggested that malignant lesions can be accurately identified and segregated preoperatively from NIFTP, further work is necessary to reliably identify NIFTP preoperatively. If it can be identified reliably in the
preoperative setting, then the diagnosis of NIFTP may allow for an increase in nonoperative or limited operative management (ie, lobectomy rather than total thyroidectomy in suspicious lesions believed to favor NIFTP). Molecular testing may be used as an adjunct to guide decisions whether to observe versus operate, and perhaps guide decisions regarding the extent of the operation (lobectomy vs total thyroidectomy) in patients with indeterminate lesions. Either surgical excision of an ITN for diagnosis or close clinical and sonographic observation can be appropriate in the case of a persistently indeterminate nodule.

Molecular Testing
Several molecular panels aimed at increasing the accuracy of preoperative cytologic diagnosis of thyroid nodules are commercially available, each of which must be interpreted carefully. The Afirma Gene Expression Classifier (GEC) (Veracyte, South San Francisco, CA) assesses expression of 142 genes most likely to be associated with benign disease. Prospectively validated in 3789 patients with 4812 nodule aspirates, the assay is most useful in ruling out malignancy in cytologically indeterminate nodules. For example, for nodules characterized cytologically as AUS/FLUS or FN/SFN, the negative predictive value (NPV) for malignancy is 95% and 94%, respectively. In contrast, the positive predictive value (PPV) for these nodules is only 38% and 37%, respectively. These results have been further validated in a multi-institutional study in which overall sensitivity and specificity for nodules characterized as AUS/FLUS/FN/SFN or SUSP (suspicious) was 90% and 52%, respectively. Therefore, the Afirma GEC is considered a “rule-out” test: a negative result has a high concordance with benign histology, but its ability to predict malignancy is limited. Currently, in clinical practice, only a small percentage of patients who have indeterminate nodules with a GEC prediction of benign undergo resection (range, 6%-13%), resulting in the possibility that some of these patients have an underlying indolent malignancy that has not declared. The authors suggest regular annual follow-up of these patients and lengthening the surveillance interval with documented stability on US.

In contrast, the ThyroSeq next-generation sequencing assay (version 2.1; CBLPath, Rye Brook, NY) has a higher PPV and is considered a “rule-in” test. Initially developed using a 7-gene panel, the current version (2.1) has gone through several iterations and assesses for point mutations in 14 genes and/or rearrangements in 42 genes. An updated version examining point mutations and rearrangements in 112 thyroid-related genes as well as quantitative data regarding gene expression and copy number variation (version 3) was recently made available. In separate validation studies performed at the developing institution, the sensitivity, specificity, NPV, and PPV for lesions categorized as AUS/FLUS using ThyroSeq v2.1 were 90.9%, 92.1%, 97.2%, and 76.9%, respectively, and the same values for FN/SFN were 90%, 93%, 96%, and 83%, respectively. Independent validation of the assay outside of the developing institution is not currently available.

Another “rule-in” test with high specificity is ThyGenX (Interpace Diagnostics, Parsippany, NJ), which was previously marketed as miRinform (Asuragen, Austin, TX) and also uses a 7-gene panel (v-Raf murine sarcoma viral oncogene homolog B1 [BRAF], Harvey rat sarcoma viral oncogene homolog [HRAS], neuroblastoma rat sarcoma viral oncogene homolog [NRAS], Kirsten rat sarcoma viral oncogene homolog [KRAS], rearranged in transformation/papillary thyroid carcinoma 1 [RET-PTC1], RET-PTC3, and paired box gene 8–peroxisome proliferator-activated receptor γ [PAX8-PPARG]) to assess for mutations associated with papillary thyroid cancer. By using this panel, the detection of mutations in BRAF or RET/PTC was 100% associated with malignancy regardless of initial cytologic diagnosis, whereas the rate of malignancy with the detection of other mutations depended on the initial cytologic assessment (ie, RET mutations were associated with a cancer diagnosis in 74% to 88% of specimens), and the absence of a detected mutation did not ensure a benign diagnosis. To improve the false-negative rate, ThyGenX is currently combined with a micro-RNA gene expression classifier (ThyraMIR; Interpace Diagnostics). This combination was initially evaluated by Labourier et al in 109 indeterminate nodules (AUS/FLUS or FN/SFN), with resulting sensitivity, specificity, NPV, and PPV of 89%, 85%, 94%, and 74%, respectively. Those authors concluded that the addition of the micro-RNA classifier improved sensitivity without compromising specificity. In the only external validation to date, industry-sponsored investigators reported that the incorporation of ThyraMIR increased the sensitivity to 94% versus 55% in their study for ThyGenX alone. The inclusion of multiple histopathologic categories in their series of 257 resected thyroid nodules makes it difficult to apply these data Specifically to indeterminate nodules. MicroRNA has also been used alone in the Rosetta GX Reveal assay (Rosetta Genomics, Rehovot, Israel), which uses quantitative reverse transcriptase–polymerase chain reaction on FNA smears. In the initial study of 201 smears, analysis was successful on 94% of smears and, when limited to AUS/FLUS and FN/SFN nodules only, sensitivity and specificity were both 74%, the NPV was 92%, and the PPV was 43%. This test has the additional advantage of circumventing any requirement for fresh tissue or special processing that other molecular studies may require and is best used as a rule-out test with a high NPV.

Molecular testing is meant not to replace clinical judgment but rather to augment discussion and clinical guidance. For example, the results of molecular testing may be
useful in counseling a patient with a high-risk but objectively indeterminate nodule who is hesitant to proceed with surgery, in which a rule-in test may support surgery, or in a patient with a low-risk but objectively indeterminate nodule who is hesitant to proceed with surveillance, for whom a rule-out test may support observation.

**Observation of Incidentally Detected Differentiated Thyroid Cancer**

Although observation of a known cancer is not routinely recommended, for some patients, surveillance of a small, incidentally found thyroid cancer may be clinically appropriate, with intervention performed at a later date, if necessary. For example, delaying surgery is appropriate in patients with extensive medical comorbidities for whom medical optimization is required before thyroid surgery. It is also appropriate in patients with unmodifiable comorbidities whose life expectancy is significantly reduced and thus may never be surgical candidates.

In contrast, the identification of a healthy patient with a small thyroid cancer who may safely avoid surgery is more complex. In a prospective study in Japan, researchers examined observation with semiannual US versus immediate surgery in patients with papillary thyroid microcarcinoma (≤10 mm on US) who had no evidence of nodal or distant metastasis and had primary tumors located away from the recurrent laryngeal nerve or trachea without signs or symptoms of invasion. Of the 1235 patients who chose observation, only 191 (15%) underwent surgery after an average of 60 months. The reasons for surgery included tumor enlargement, development of another thyroid pathology, and changes in patient or physician preference. Tumor growth was observed in 58 patients (4.6%), nodal metastases in 219 patients (18%), and 43 patients (3.5%) progressed to clinical disease (defined as a tumor size >12 mm and/or development of nodal metastases). No patient developed distant metastases or died of thyroid cancer during the study period. Compared with patients younger than 40 years, older patients were significantly less likely to experience disease progression; of the 496 patients older than 60 years, only 2.2% demonstrated an increase in tumor volume by greater than 50% preceded an increase in tumor size at a median of 8.2 months, suggesting that tumor kinetics may be useful in the early identification of patients who will progress to tumor growth. This experienced group at a tertiary referral center has also published their well elucidated selection criteria, which include tumor, patient, and medical team-specific characteristics.

The combination of all 3 of these factors is crucial to the successful nonoperative management of small low-risk cancers. Further study of the selection of patients with indolent, well-differentiated thyroid cancer; the ability to perform salvage operations in patients with disease progression; and long-term outcomes will be necessary before widespread implementation of a surveillance approach to well-differentiated thyroid cancer.

**Summary**

Incidental thyroid nodules represent a common problem encountered by surgeons. Initial evaluation of patients with ITNs should include a complete history and physical examination, thyroid function studies, a dedicated thyroid US that includes the central and lateral compartments of the neck, and FNA biopsy for cytologic diagnosis of any suspicious lesions. Management of clearly benign nodules consists of patient reassurance and observation, whereas clearly malignant nodules should be resected. In cases with indeterminate cytology, repeat FNA biopsy, thorough observation, and, if necessary, well selected molecular testing may guide the clinician. Surgical excision remains the standard for diagnosis in cases of persistent ambiguity. Further research regarding the feasibility and oncologic safety of surveillance for small, incidentally found thyroid cancers is needed.

**References**

1. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016;26:1-133.
2. Mazzaferri EL. Management of a solitary thyroid nodule. *N Engl J Med*. 1993;328:553-559.
3. Wilhelm S. Evaluation of thyroid incidentaloma. *Surg Clin North Am*. 2014;94:485-497.
4. Mortensen JD, Woolner LB, Bennett WA. Gross and microscopic findings in clinically normal thyroid glands. *J Clin Endocrinol Metab*. 1955;15:1270-1280.
5. Wagner J, Aron DC. Incidentomas: a “disease” of modern imaging technology. *Best Pract Res Clin Endocrinol Metab*. 2012; 26:3-8.

6. Sosa JA, Hanna JW, Robinson KA, Lamman RB. Increases in thyroid nodule fine-needle aspirations, operations, and diagnoses of thyroid cancer in the United States. *Surgery*. 2013;154:1420-1426; discussion 1426-1427.

7. Smith-Bindman R, Lebda P, Feldstein VA, et al. Risk of thyroid cancer based on thyroid ultrasound imaging characteristics: results from a population-based study. *JAMA Intern Med*. 2013;173:1788-1796.

8. Nam-Goong IS, Kim HY, Gong G, et al. Ultrasonography-guided fine-needle aspiration of thyroid incidentaloma: correlation with pathological findings. *Clin Endocrinol*. 2004;60:21-28.

9. Hoang JK, Langer JE, Middleton WD, et al. Managing incidental thyroid nodules detected on imaging: white paper of the ACR Incidental Thyroid Findings Committee. *J Am Coll Radiol*. 2015;12:143-150.

10. Starker LF, Prieto PA, Liles JS, et al. Endocrine incidentalomas. *Curr Probl Surg*. 2015;52:219-246.

11. Shie P, Cardarella S, Sprawls K, Fulda KG, Taur A. Systematic review: prevalence of malignant incidental thyroid nodules identified on fluoroine-18 fluorodeoxyglucose positron emission tomography. *Nuc Med Commun*. 2009;30:742-748.

12. Uppal A, White MG, Nagar S, et al. Benign and malignant thyroid incidentalomas are rare in routine clinical practice: a review of 97,908 imaging studies. *Cancer Epidemiol Biomarkers Prev*. 2015;24:1327-1331.

13. Tamptuopongse TP, Grady TA, Sosa JA, Eastwood JD, Choudhry KR, Hoang JK. Incidental thyroid nodules on CT or MRI: discordance between what we report and what receives workup. *AJR Am J Roentgenol*. 2015;205:1281-1287.

14. Frates MC, Benson CB, Charboneau JW, et al. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. *Radiology*. 2005;237:794-800.

15. Hoang JK, Raduazo P, Yousem DM, Eastwood JD. What to do with incidental thyroid nodules on imaging? An approach for the radiologist. *Semin Ultrasound CT MR*. 2012;33:150-157.

16. National Comprehensive Cancer Network. NCCN Guidelines, Version 1.2017: Thyroid Carcinoma. Fort Washington, PA: National Comprehensive Cancer Network; 2016. nccn.org/professionals/physician_gls/pdf/thyroid.pdf. Accessed April 22, 2017.

17. Petr EJ, Else T. Genetic predisposition to endocrine tumors: diagnosis, surveillance and challenges in care. *Semin Oncol*. 2016; 43:582-590.

18. Topliss DJ. Clinical update in aspects of the management of autoimmune thyroid diseases. *Endocr Pract (Seoul)*. 2016;31:493-499.

19. Resende de Paiva C, Grionho C, Feldt-Rasmussen U, von Buchwald C. Association between Hashimoto’s thyroiditis and thyroid cancer in 64,628 patients. *Front Oncol*. 2017;7:53.

20. Choi JS, Choi Y, Kim EK, et al. A risk-adapted approach using US features and FNA results in the management of thyroid incidentalomas identified by 18F-FDG PET. *Ultraschall Med*. 2014;35:51-58.

21. Boeckmann J, Bartel T, Siegel E, Bodenner D, Stack BC Jr. Can the pathology of a thyroid nodule be determined by positron emission tomography? *Laryngol Head Neck Surg*. 2012;146:906-912.

22. Mirfakhraee S, Mathews D, Peng L, Woodruff S, Zigman JM. A solitary hyper-functioning thyroid nodule harboring thy- roid carcinoma: review of the literature (serial online). *Thyroid*. 2013;6:7.

23. Wu LM, Gu HY, Xu QH, et al. The accuracy of ultrasonography in the preoperative diagnosis of cervical lymph node metastasis in patients with papillary thyroid carci- noma: a meta-analysis. *Eur J Radiol*. 2012; 81:1798-1805.

24. Nahban F, Ringel MD. Thyroid nodules and cancer management guidelines: compar- isons and controversies. *Endocr Relat Cancer*. 2017;24:R13-R26.

25. Chabir H, Goellner JR. Fine-needle aspiration biopsy of the thyroid: an appraisal. *Ann Intern Med*. 1993;118:282-289.

26. Carmeci C, Jeffrey RB, McDougall JR, Nowels KW, Weigel RJ. Ultrason-guided fine-needle aspiration biopsy of thyroid masses. *Thyroid*. 1998;8:283-289.

27. de Koster EJ, Choudhry KR, Hoang JK, Taur A. Systematic review: prevalence of malignant incidental thyroid nodules identified on fluoroine-18 fluorodeoxyglucose positron emission tomography. *Nuc Med Commun*. 2009;30:742-748.

28. Alexander EK, Heering JP, Benson CB, et al. Assessment of non-diagnostic ultrasound-guided fine needle aspirations of thyroid nodules. *J Clin Endocrinol Metab*. 2002;87:4924-4927.

29. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. *Thyroid*. 2017;27:1341-1346.

30. McCoy KL, Jabbour N, Ogilvie JB, Ohori NP, Carty SE, Yim JH. The incidence of cancer and other thyroid malignancies among patients referred for ultrasound-guided fine needle aspirations of thyroid nodules. *Acta Cytol*. 2016; 60:39-45.

31. Alexander-EK, Heering-JP, Benson-CB, et al. Asssessment of non-diagnostic ultrasound-guided fine needle aspirations of thyroid nodules. *J Clin Endocrinol Metab*. 2002;87:4924-4927.

32. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. *Thyroid*. 2017;27:1341-1346.

33. McCoy KL, Jabbour N, Ogilvie JB, Ohori NP, Carty SE, Yim JH. The incidence of cancer and other thyroid malignancies among patients referred for ultrasound-guided fine needle aspirations of thyroid nodules. *Acta Cytol*. 2016; 60:39-45.

34. Alexander EK, Heering JP, Benson CB, et al. Assessment of non-diagnostic ultrasound-guided fine needle aspirations of thyroid nodules. *J Clin Endocrinol Metab*. 2002;87:4924-4927.

35. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. *Thyroid*. 2017;27:1341-1346.

36. Nikiforov YE, Ohori NP, Hodiak SP, et al. Impact of mutational testing on the diagnosis and management of patients with cyto logically indeterminate thyroid nodules: a prospective analysis of large samples. *J Clin Endocrinol Metab*. 2011;96:3390-3397.
49. Nikiforov YE, Carty SE, Chiosea SI, et al. Highly accurate diagnosis of cancer in thyroid nodules with follicular neoplasm/ suspicious for a follicular neoplasm cytology by ThyroSeq v2 next-generation sequencing assay. *Cancer*. 2014;120:3627-3634.

50. Nikiforov YE, Carty SE, Chiosea SI, et al. Impact of the multi-gene ThyroSeq next-generation sequencing assay on cancer diagnosis in thyroid nodules with atypia of undetermined significance/ follicular lesion of undetermined significance cytology. *Thyroid*. 2015;25:1217-1223.

51. Yip L, Sosa JA. Molecular-directed treatment of differentiated thyroid cancer: advances in diagnosis and treatment. *JAMA Surg*. 2016;151:663-670.

52. Cantara S, Capezzone M, Marchisotta S, et al. Impact of proto-oncogene mutation detection in cytological specimens from thyroid nodules improves the diagnostic accuracy of cytology. *J Clin Endocrinol Metab*. 2010;95:1365-1369.

53. Labourier E, Shifrin A, Busseniers AE, et al. Molecular testing for miRNA, mRNA, and DNA on fine-needle aspiration improves the preoperative diagnosis of thyroid nodules with indeterminate cytology. *J Clin Endocrinol Metab*. 2015;100:2743-2750.

54. Wylie D, Beaudenon-Huibregtse S, Haynes BC, Giordano TJ, Labourier E. Molecular classification of thyroid lesions by combined testing for miRNA gene expression and somatic gene alterations. *J Pathol Clin Res*. 2016;2:93-103.

55. Lithwick-Yanai G, Dromi N, Shtabsky A, et al. Multicentre validation of a microRNA-based assay for diagnosing indeterminate thyroid nodules utilising fine needle aspiration smears. *J Clin Pathol*. 2017;70:500-507.

56. Ito Y, Miyauchi A, Kihara M, Higashiyama T, Kobayashi K, Miya A. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. *Thyroid*. 2014;24:27-34.

57. Sugitani I, Toda K, Yamada K, Yamamoto N, Ikenaga M, Fujimoto Y. Three distinctly different kinds of papillary thyroid microcarcinoma should be recognized: our treatment strategies and outcomes. *World J Surg*. 2010;34:1222-1231.

58. Tuttle RM, Fagin JA, Minkowitz G, et al. Natural history and tumor volume kinetics of papillary thyroid cancers during active surveillance. *JAMA Otolaryngol Head Neck Surg*. 2017;143:1015-1020.

59. Brito JP, Ito Y, Miyauchi A, Tuttle RM. A Clinical framework to facilitate risk stratification when considering an active surveillance alternative to immediate biopsy and surgery in papillary microcarcinoma. *Thyroid*. 2016;26:144-149.