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In brief

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Thyroid nodules are common and are detected in up to 68% of the population. Medical advances, like the widespread use of ultrasound, have improved our capability to detect thyroid nodules and thyroid cancer. Over the last decade, the incidence of thyroid cancer has increased by 4.5% per year, faster than any other cancer, but without a corresponding change in the mortality rate. However, a closer examination of this increased incidence revealed that the rise was almost completely attributed to the increasing use of neck ultrasonography and diagnosis of incidental subcentimeter papillary thyroid cancers (microcarcinomas). In addition, mounting evidence showed that the majority of these microcarcinomas were indolent in nature and had little potential to cause significant morbidity and mortality for patients. In response to increasing concern for the overdiagnosis and treatment of small papillary thyroid cancers, a US Preventative Task Force was commissioned in 2017 to evaluate the effectiveness and safety of thyroid cancer screening. They found that although thyroid cancer screening itself was not harmful to patients, it often led to treatment of small, insignificant microcarcinomas that were associated with a small but not insignificant rate of permanent nerve damage and hypoparathyroidism. In addition, surgical treatment conferred a higher chance of recommending adjuvant radioactive iodine ablation that was associated with harm to the salivary glands and a small but real risk of second primary cancers. Given these issues, the main goal of the initial and long-term follow-up of thyroid nodules is the identification of the subgroup of nodules that harbor a clinically significant cancer, cause compressive symptoms, are enlarging significantly, and/or progress to functional disease. Current management guidelines recommend a combination of ultrasonography, fine needle aspiration biopsy (FNAB), and molecular profiling to provide a safe and personalized approach.

Ultrasonography is the most widely used imaging modality for thyroid nodules and provides an inexpensive, safe, and reliable tool for the characterization of thyroid nodules and risk strat-

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ification for malignancy. Although it should not be used to screen for thyroid nodules in otherwise asymptomatic patients, patients with a thyroid abnormality on physical examination (such as a suspected nodule or goiter) or with an incidentally discovered nodule on another imaging modality (such as computed tomography, magnetic resonance imaging, or fluorodeoxyglucose-positron emission tomography) should undergo evaluation with an ultrasound that comprehensively examines the thyroid parenchyma, size of the isthmus and each lobe, location, and characteristics of thyroid nodules, and the evaluation of central and lateral lymph node compartments. Several studies have demonstrated that certain ultrasound findings have a high specificity for malignancy (>90%) and include the presence of microcalcifications, a shape that is taller than wide, and irregular margins (spiculated, infiltrative, or microlobulated). Additionally, a nodule with an interrupted peripheral calcification is more likely to be malignant. Another characteristic that is associated with thyroid cancer is hypoechogenicity; however, up to 55% of benign nodules are also hypoechoic. Although these individual characteristics may have high specificity, their individual sensitivities are less than 70% to 77%, limiting their utility to predict malignancy. However, a combination of 2 or more of these characteristics confers a higher sensitivity for the prediction of malignancy and therefore the 2 most commonly used risk stratification systems based on suspicious sonographic findings, the American Thyroid Association Risk Stratification System (ATA) and the American College of Radiology Thyroid Imaging, Reporting Data System (ACR TI-RADs), both emphasize using a combination of these suspicious features. Both systems have been shown to reliably risk stratify thyroid nodules for cancer, decreasing the number of unnecessary FNABs without missing clinically significant thyroid cancers.

FNAB has long been the cornerstone for the diagnosis of thyroid cancer. The Bethesda System for Reporting Thyroid Cytopathology was first developed in 2009 to improve communication between cytopathologists, endocrinologists, surgeons, and radiologists, and to facilitate research. The Bethesda system has been widely adopted and, recently, revised in 2017. The Bethesda system recommends that each report begin with 1 of 6 diagnostic categories: (1) nondiagnostic/unsatisfactory, (2) benign, (3) atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), (4) follicular neoplasm/suspicious for a follicular neoplasm (FN-SFN), (5) suspicious for malignancy (SM), and (6) malignant. Each category confers a certain risk of malignancy and is linked to evidence-based guidelines for clinical management. The 2017 revisions updated the risk of malignancy of each category and factored in the reclassification of encapsulated, noninvasive follicular variant of papillary thyroid carcinoma to noninvasive follicular thyroid neoplasm with papillary-like nuclear features, a subset of PTC that behaves similarly to follicular adenoma. The revised Bethesda system also accounts for the advent of molecular testing and its role in further refining the estimate of malignancy in indeterminate thyroid nodules. Indeterminate thyroid nodules include Bethesda III, IV, and V lesions and account for up to 40% of thyroid nodules. Ultimately, 60% of indeterminate lesions end up being resected despite the fact that the majority (85% of AUS-FLUS, 75% of FN-SFN, and 35% of SM) show histopathologic evidence of benign disease. Given the high rate of benign disease in indeterminate lesions that were surgically resected based on cytology alone, new methodologies have evolved to help fine-tune the prediction of malignancy.

Medical advances in gene sequencing in the past decade have greatly facilitated increased knowledge of thyroid tumor biology and molecular genomics, leading to the development of a variety of molecular profiling methodologies to complement FNAB and the Bethesda Classification System for these indeterminate thyroid nodules. Gene expression classifiers, of which the most commonly used is Afirma (Veracyte Inc., San Francisco, CA), quantify the mRNA expression of multiple candidate genes within the entire transcriptome of the sample tissue from which an algorithm renders 1 of 2 molecular signatures: benign or suspicious. A large multicenter trial demonstrated that Afirma had a high sensitivity rate and overall negative predictive value (NPV) of 93% that could be useful as a “rule out” test for benign nodules. However, it had a low specificity of 52% and was not suitable as a “rule in” test to predict malignancy. Numerous independent validation studies have since highlighted how performance characteristics of the test are highly dependent on the prevalence of cancer in the patient population, but have generally confirmed the high NPV when the pretest probability of malignancy in a population

is less than 23%. Veracyte recently introduced the Afirma Genomic Sequencing Classifier that sequences nucleic acids and quantifies RNA expression in the context of 1115 core genes. A validation study examining 183 indeterminate FNAB samples from the initial prospective, blinded multicenter study found that this new test demonstrated a sensitivity of 91% and a specificity of 68% (NPV of 96% and PPV of ~50% in a population with 24% risk of malignancy).

Another approach to molecular profiling uses our increasing knowledge of the genetic background and mutations that are the oncogenic drivers of thyroid cancers. The most commonly used mutation panel, ThyroSeq, started as an initial 7-gene mutation panel that demonstrated a high specificity for thyroid cancer but low sensitivity and was known as the "rule in" test. This test has since been expanded twice to detect a total of 126 gene mutations and 42 gene rearrangements. ThyroSeq v3 demonstrated 98% sensitivity, 82% specificity, and 91% accuracy using specimens from a population with a pretest probability of malignancy between 5% and 15%. Importantly, the test had 93% sensitivity and 69% specificity in lesions with Hürthle cells, whose malignant potential are often difficult to predict using cytopathology alone.

MicroRNAs are small noncoding RNAs, whose expression is dysregulated in thyroid cancers and reflects changes in the expression of various oncogenes and tumor-suppression genes. MicroRNAs demonstrate relative molecular stability during handling and processing making it an attractive alternative for molecular profiling techniques. Classification algorithms using microRNA have demonstrated a high specificity and sensitivity. The most commonly used microRNA classifier (ThyraMIR) is offered in combination with a mutation panel (ThyGeNEXT). An algorithm combining the 2 methodologies yielded a sensitivity and specificity of 89% and 85%, respectively, and with a malignancy prevalence of 32%, NPV of 94%, and PPV of 74%.

Although there is some evidence that the use of molecular profiling can significantly decrease the number of nodules that undergo surgical excision, the use of these techniques is recommended only in situations where it would change the management and should be considered within the context of other relevant clinical risk factors for malignancy and indications for surgery.

The correlation between sonographic features and malignancy risk is also used to guide the follow-up strategy for nodules that do not meet FNAB criteria at the time of initial imaging. Subcentimeter nodules with very low-risk sonographic features have an extremely low risk of malignancy, and are highly unlikely to change during ultrasound follow-up. In comparison, nodules with high-risk sonographic patterns carry an estimated risk of malignancy of greater than 70%-90%. Therefore, surveillance ultrasonography for a nodule with high-risk sonographic features and associated increased risk of malignancy should be at a shorter interval than for a nodule with a very low-risk sonographic pattern. Similarly, the follow-up of thyroid nodules with benign FNABs is also based on the sonographic pattern. Studies indicate that many missed malignancies are found in nodules with high-risk sonographic patterns and that repeat ultrasound-guided FNAB of nodules with initial benign cytology shows a higher rate of missed malignancies in nodules with high-risk sonographic features than in nodules that display growth alone. In contrast, the risk of malignancy after 2 benign FNAB results is virtually zero. If a nodule has undergone a repeat ultrasound-guided FNAB with a second benign result, continued surveillance with ultrasonography is no longer indicated.

Tumor size has long been considered an important prognostic factor in differentiated thyroid cancer (DTC). Clinicians generally agree that DTC tumors that are larger than 4 cm in diameter or high risk (familial history, radiation exposure, or associated lymph node disease) should be treated with total thyroidectomy. However, for small (1-4 cm), low-risk DTC, the appropriate extent of surgery, whether it be total thyroidectomy or unilateral lobectomy, has been a longstanding subject of debate among experts. Several recent large, national database studies have demonstrated no difference in overall or disease-specific survival between thyroid lobectomy and total thyroidectomy for small, low-risk papillary thyroid cancers. In addition, institutional studies have shown low rates of locoregional recurrence and need for completion thyroidectomy after thyroid lobectomy. These findings have led the revised ATA and NCCN guidelines to recommend either total thyroidectomy or unilateral lobectomy as sufficient initial treatment for DTC between 1 and 4 cm in size without clinical evidence of extrathyroidal extension or lymph

node metastases. The decision between total thyroidectomy or unilateral lobectomy should be considered within the clinical context of age, contralateral thyroid nodules, history of radiation exposure, and familial DTC, as well as patient preferences.

The management of thyroid nodules continues to evolve at a rapid pace as our ability to detect disease with more precision and our understanding of the optimal treatment increases. The goal in managing thyroid nodules is to carefully balance the cost of evaluation and treatment with the benefits derived. A diagnostic algorithm that combines ultrasonography, FNAB, and molecular testing enables a personalized and safe approach to the management of thyroid nodules.