

Cytopathology in Focus: Managing adults with thyroid nodules and cancer—2015 guideline highlights



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May 2016—In January of this year, the American Thyroid Association published the 2015 update to its guidelines for the management of adults with thyroid nodules and differentiated thyroid cancer.¹ Separate guidelines were published for the pediatric population in July 2015.² Although the guidelines for adult patients were published as a “Special Article” in *Thyroid*, they run the length of a small book—133 pages in total.

A panel of experts contributed to the latest 2015 document, similar to the guidelines released in 2006 and 2009,^{3,4} with the addition for the first time of a pathologist (Yuri E. Nikiforov, MD, PhD, University of Pittsburgh Medical Center). The developers of the 2015 ATA guidelines used the methods of evidence-based medicine to search, select, and review relevant articles published in the English medical literature since the preceding 2009 guidelines were developed. They used the American College of Physicians guideline grading system to critically appraise the evidence and to grade the strength of their recommendations. Strength of evidence was graded as high-, moderate-, or low-quality, and in each case, based on the risk-benefit ratio, the panel made a strong recommendation (benefits clearly outweighed harms or vice versa), a weak recommendation (benefits and harms were comparable), or no recommendation at all (evidence insufficient to compare benefits and risks).

This comprehensive document, like the previous guidelines, is organized in a question-and-answer format, providing more than 100 recommendations, over 20 of which are new for the 2015 update. These include recommendations for the management of thyroid nodules (initial evaluation, clinical and ultrasound criteria for FNA, interpretation of FNA results, use of molecular markers, and management of benign thyroid nodules), initial management of thyroid cancer (screening, staging and risk assessment, surgery, radioiodine therapy, and thyrotropin suppression therapy), and long-term management of differentiated thyroid cancer (surveillance for recurrent disease, thyroid hormone therapy, management of recurrent and metastatic disease, consideration for clinical trials and targeted therapy, and directions for future research).

A new visual guide to the different ultrasonographic patterns of thyroid nodules and the risk of malignancy associated with each pattern may be of particular interest to those who interpret thyroid cytopathology. This welcome addition to the guidelines seems to be a part of bringing ultrasonography to the front lines of managing thyroid nodules. Based on high-quality evidence, all patients who are known or suspected to have thyroid nodules are strongly recommended to undergo thyroid ultrasound with survey of cervical lymph nodes. When clinically indicated, fine needle aspiration is still the procedure of choice for evaluating thyroid nodules. According to the new visual guide, the various sonographic patterns of thyroid nodules are categorized into high suspicion (with greater than 70 to 90 percent risk of malignancy), intermediate suspicion (10 to 20 percent malignant), low suspicion (five to 10 percent malignant), very low suspicion (less than three percent malignant), and benign (less than one percent malignant).

Minimum thyroid nodule size thresholds are defined to guide clinicians in when to consider sampling nodules in any of the preceding categories. For example, there is a strong recommendation that high or intermediate suspicion nodules undergo FNA if 1.0 cm or larger, while there are weak recommendations to consider FNA for low suspicion

nodules 1.5 cm or larger, or very low suspicion nodules 2.0 cm or larger. For nodules that do not meet these criteria or are purely cystic, there is a strong recommendation that they *not* undergo FNA. However, it is also stated that the patient's age (particularly under age 40) and personal preference may modify the decision-making in managing subcentimeter thyroid nodules with suspicious sonographical features. Referring to the visual schema may increase the disease detection rate of thyroid FNAs examined by cytopathologists and may affect the risk of malignancy associated with various Bethesda System diagnoses. (The ATA guidelines strongly recommend using the Bethesda System for Reporting Thyroid Cytopathology.)

In addition to FNA reporting, the basic principles of histopathologic evaluation are also outlined with a recommendation (No. 46). In this section, the encapsulated follicular variant of papillary thyroid cancer without invasion was specifically mentioned as a variant of thyroid carcinoma with a more favorable outcome. This will likely bring more attention to this specific lesion in the wake of the new proposed terminology by the Endocrine Pathology Society in 2015 and 2016, "Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFT-P)." The changes in thyroid FNA practice and malignancy risk stratification with individual FNA diagnoses are yet to be determined by the new terminology.⁵

The recommendations related to molecular testing of cytologically indeterminate thyroid nodules are another area that is likely to encourage more dialogue between clinicians and pathologists. Since this is an area where the science is still evolving rapidly, most of the recommendations are based on low-quality evidence. Nonetheless, the recommendations in this regard are mostly strong, albeit vague. For example: "If molecular testing is being considered, patients should be counseled regarding the potential benefits and limitations of testing and about the possible uncertainties in the therapeutic and long-term clinical implications of results." As can be seen in this recommendation, the guidelines are intentionally noncommittal on the topic of molecular testing because the science is ever-changing. This emphasizes the important role pathologists will probably be called upon to play in advocating for rational and judicious use of these novel molecular technologies. Pathologists should educate themselves on the nuances of thyroid molecular testing so they too can counsel their clinician colleagues about the benefits, limitations, and uncertainties of testing, and about the interpretation and clinical implications of test results.

The guidelines emphasize the importance of quality assurance in laboratory testing with this strong recommendation: "If intended for clinical use, molecular testing should be performed in Clinical Laboratory Improvement Amendments/College of American Pathologists (CLIA/CAP)-certified molecular laboratories, or the international equivalent, because reported quality assurance practices may be superior compared to other settings."

One of the most important aspects of any guidelines is that they are dynamic documents and meant to be updated regularly. Developing any set of evidence-based clinical guidelines requires striking a fine balance between being prescriptive for a large group of patients yet at the same time allowing for variations in individual patient characteristics. The American Thyroid Association task force has done a commendable job of trying to achieve that balance in developing its 2015 guidelines, given the large scope of what it covers, the evolving state of the science, and the ever-increasing focus on personalized medicine in modern health care.

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):1-133.
2. Francis GL, Waguespack SG, Bauer AJ, et al. Management guidelines for children with thyroid nodules and differentiated thyroid cancer. *Thyroid*.

2015;25(7):716-759.

3. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2009;19(11):1167-1214.
4. Cooper DS, Doherty GM, Haugen BR, et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines Taskforce. *Thyroid*. 2006;16(2):109-142.
5. Strickland KC, Howitt BE, Marqusee E, et al. The impact of noninvasive follicular variant of papillary thyroid carcinoma on rates of malignancy for fine-needle aspiration diagnostic categories. *Thyroid*. 2015;25(9):987-992.

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