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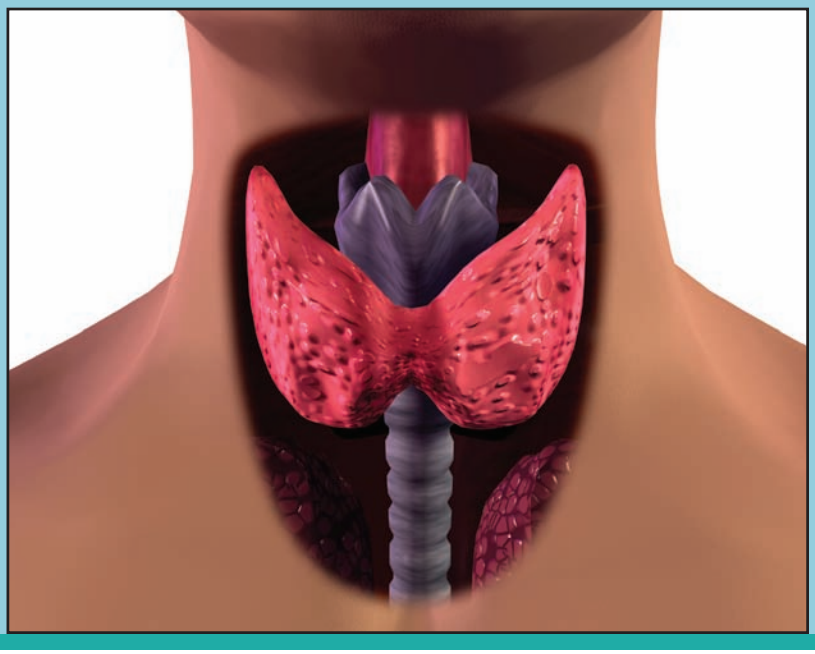

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FOCUS: Thyroid Cancer

Treatment & Research Updates

[INSIDE]

Thyroid Nodule Genetic Testing Found as Valuable, But Guidelines Lacking

BY HEATHER LINDSEY

While a valuable tool, genetic testing of thyroid nodules does generate some controversy among physicians because there are as yet no guidelines.

Emad Kandil, MD, the Edward G. Schlieder Chair in Surgical Oncology and Chief of the Endocrine Surgery Section at Tulane University School of Medicine, explained that before genetic testing was readily available, patients with thyroid nodule biopsy results of indeterminate significance would usually choose to undergo surgery to avoid the risk of missing a cancer.

"Most of the thyroid surgery being done was for benign disease," he said. Overall, an indeterminate nodule with benign genetic test results means physicians may want to observe the patient. While malignant results may indicate surgery, whether this means that half the thyroid should be removed, for example, or that more aggressive treatment is needed is open to discussion.

Physicians are still learning how to best use a commercially available gene expression classifier (GEC: Afirma Thyroid FNA Analysis, Veracyte; South San Francisco) and a genetic panel test (miR*Inform* Thyroid Panel, Asuragen, Austin, Tex.) for the evaluation and management of thyroid nodules, said Michael Mingzhao Xing, MD, PhD, Professor of Medicine and Oncology, Co-Director of the Johns Hopkins Thyroid Tumor Center, and Chief of the Laboratory for Cellular and Molecular Thyroid Research at the Johns Hopkins University School of Medicine.

EMAD KANDIL, MD, explained that before genetic testing was readily available, patients with thyroid nodule biopsy results of indeterminate significance would usually choose to undergo surgery to avoid the risk of missing a cancer.

Each has its merits and drawbacks, "but these two tests are among the best available tools at this time and are very useful," said Xing, who has no financial relationship with these companies but receives royalties on a licensed U.S. patent related to the BRAF mutation in thyroid cancer.

Molecular testing should be used to help answer clinical questions, said Robert L. Ferris, MD, PhD, FACS, Endowed Professor and Chief of the Division of Head and Neck Surgery, Associate Director for Translational Research, and Co-Leader of the Cancer Immunology Program at the University of Pittsburgh Cancer Institute. The American Thyroid Association (ATA) is creating a position paper on this topic, noted Ferris, who is chair of the writing group for the ATA surgical affairs committee.

If the physician is planning on a total thyroidectomy because the patient already has indications for surgery, then testing is much less useful, he said. "If you're looking at indeterminate needle biopsy results, then molecular testing is potentially useful for seeing whether observation is safe or if surgery is indicated, what extent should be recommended to the patient."

Indeterminate Nodules

Genetic testing is particularly useful for atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS), as well as follicular neoplasm (FN) or those suspicious for follicular neoplasm (SFN), as defined by the Bethesda classification system, said Lawrence Kim, MD, an endocrine surgeon in the Division of Surgical Oncology at the University of North Carolina School of Medicine.

ROBERT L. FERRIS, MD, PHD: "If you're looking at indeterminate needle biopsy results, molecular testing is potentially useful for seeing whether observation is safe or if surgery is indicated, what extent should be recommended to the patient."

The categories of suspicious for malignancy or malignant do not usually require further genetic testing, he added.

According to the literature, about 15 to 25 percent of nodules on FNA cytology are indeterminate, meaning "we can't tell the patient with enough confidence whether they have cancer and we need to remove it or if we can follow it," said Christian Nasr, MD, Medical Director of Cleveland Clinic's Thyroid Center. "When a nodule is indeterminate, it puts physicians, cytologists, and patients in a corner."

Once these growths are removed, cancer is found up to 50 percent of the

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time, although this rate can vary based on the institution and nodule subtype, he said. At his institution, he noted, the rate is generally 25 to 30 percent if on cytology the nodule is SFN.

Ruling Out Cancer

If patients have an indeterminate nodule, physicians may recommend GEC testing, said Xing. The Afirma test evaluates the expression pattern of 142 genes, and indicates if a nodule is benign.

Writing in an email, Paolo Miccoli, MD, Professor of Surgical Anatomy and Surgery General, Director of the Department of Surgical Pathology, Medical & Molecular and Critical Area, and Associate Professor of Pediatric Surgery at the University of Pisa, said, "Although additional evidence supporting its analytical validity, clinical validity, and clinical utility is needed, this molecular approach could help to significantly reduce unecessary surgeries.

As demonstrated by the literature (***NEJM 2012;367:705-715*** and ***J Clin Endocrinol Metab 2014;99:119-125***), the negative predictive value with GEC is 95 percent for indeterminate nodules, meaning that a patient has only a five percent risk of cancer in specific cytologic diagnostic categories, Ferris explained. Based on this risk, patients and physicians are usually comfortable with watchful waiting.

LAWRENCE KIM, MD, said that genetic testing is particularly useful for AUS or FLUS, as well as for follicular neoplasms or those suspicious for follicular neoplasm.

If GEC results are benign and other clinical features are low risk, then physicians can comfortably recommend observation, agreed Xing. The low false-negative result, given the generally unaggressive nature of thyroid cancer, is acceptable to many physicians and patients. "Ideally, we would wish it was even a lower risk, but we don't have a test like that yet," he said.

Ferris said that physicians need to keep in mind that the test's predictive value is not going to be the same within various categories of indeterminate lesions at every institution, because cancer risk from one center to another will differ, sometimes substantially, based on cytopathologists' practice patterns and interpretation of the same specimen.

The frequency of thyroid cancer also varies by location and institution, said Ferris. To use a molecular test, you need a thorough knowledge of its performance and cancer risk as indicated by cytology performed at your center. For example, the rate of FLUS in Cincinnati may be 25 percent, but 10 percent elsewhere.

Also of note, while GEC results may state that a nodule is suspicious for cancer, the test is not conclusive regarding malignancy, said Kim, citing a recent report indicating a 52 percent specificity (***NEJM 2012;367:705-715***).

Because the GEC test has a poor positive predictive value, using it to make decisions about surgery is not advisable, Ferris said.

Another drawback, he continued, is that the Afirma test has not been validated—despite the *NEJM* paper. "It's very tightly controlled, and not many centers have done a performance evaluation with an independent cohort."

Moreover, not all experts agree that using GEC for all indeterminate nodule types is advantageous. In Nasr's view, the test is most useful for FN nodules, which carry a 25 to 30 percent cancer risk based on the literature, and previously required diagnostic lobectomy. A benign result essentially takes this cancer risk down to five percent.

However, because AUS and FLUS nodules carry a cancer risk of only five to 15 percent, he said that rather than undergoing GEC and as an alternative to removing the nodule, he recommends that patients undergo a repeat biopsy in three months. The results prove to be benign about 50 percent of the time.

CHRISTIAN NASR, MD: "When a nodule is indeterminate, it puts physicians, cytologists, and patients in a corner."

"If I try to apply GEC to AUS or FLUS, I could be fooling myself or fooling the patient," he said. The test does not have enough power to rule in cancer and for physicians to recommend having the nodule removed.

Ruling in Cancer

The miR*Inform* Thyroid Panel can be used for ruling in cancer, he continued, explaining that the test is very good for detecting papillary cancer and follicular cancer, for which surgery can be easily recommended.

This test is based on oncogenic markers and reflects basic science knowledge of each oncogene's function, Ferris said. For example, BRAF and KRAS, which are included on the Asuragen panel, have been studied in the lab, and the malignant behavior they impart is understood. However, almost every academic center now tests for BRAF and RAS, so a commercial product is not necessary.

With the Asuragen panel, the positive predictive value is more than 87 percent, depending on what particular genetic alteration tests positive, making this a good tool for making decisions about

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total thyroidectomy he said, citing ***J Clin Endocrinol Metab 2011;96:3390-3397***. If the patient has decided upon a lobectomy, the test may indicate the need for a second surgery.

However, the test only covers mutations present in about 75 percent of thyroid cancers, so if the results are negative, recommending observation is difficult, he noted.

Specifically, the negative predictive value of the miR*Inform* Thyroid Panel is 94 percent for AUS and FLUS categories, which is as good as Afirma, but only 86 percent for the FN diagnosis, so patients have a 14 percent risk of having cancer with this diagnosis. He said that with the noncommercial genetic panels used in Pittsburgh, the risk of malignancy is 27 percent for the FN category. Consequently, physicians are generally not comfortable with observation based on this type of testing.

Xing said that overall, he considers Asuragen's genetic panel to be a good diagnostic tool, and it is particularly helpful for making decisions about whether patients should undergo surgery for a potential malignancy and if so, how aggressive the surgery should be. This is especially the case if BRAF mutation status is revealed.

Then, depending on whether there are high-risk clinical factors and positive test indicators for particular genetic markers on the panel, physicians may decide to pursue more aggressive surgery such as total thyroidectomy accompanied with neck dissection. If the genetic panel test comes back negative, physicians may decide on less aggressive treatment.

> Physicians are still learning how to best use the commercially available gene expression classifier and genetic panel test. "Each has its merits and drawbacks, but they are considered to be among the best available tools at this time and are very useful."

Practical Use in the Clinic

Xing said that given the merits and drawbacks of the two tests, a reasonable approach in the clinic may be to use the GEC test first. Patients with a benign diagnosis can be conservatively followed, and those with results suspicious for malignancy can subsequently undergo genetic panel testing, particularly a BRAF mutation test, to help determine the type and extent of thyroid surgery, he said, pointing to a study he coauthored last year with Bryan Haugen and Martin Schlumberger (***Lancet 2013;23:1058-1069***).

Currently, though, these tests are not widely used, partly due to lack of awareness as well as to their high cost, Xing noted. "However, it is expected that the combination of conventional clinicopathological risk factors with the use of these molecular tests will greatly improve the current management of thyroid nodules." Further development of even more efficient and effective molecular tests is welcome.

Nasr agreed: "It would be nice to combine the qualities of both of these tests to rule in benignity and rule out cancer," he said.

Veracyte's President and CEO, Bonnie Anderson, said that to complement its GEC test, the company is planning to develop molecular classifiers for likely malignant nodules. These are intended to give physicians better preoperative information to help guide what kind of surgery they should perform and may also help to prevent completion surgeries, she said.