Minimizing Unnecessary Surgery for Thyroid Nodules

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Thyroid follicles remodel continuously, responding to stimuli such as thyrotropin, growth factors, cytokines, and iodine. Nodules develop when these growth signals drive hyperplasia or when a follicular cell acquires a genetic mutation that confers autonomous growth. Thyroid nodules are commonly seen in clinical practice. With the use of ultrasonography, nodules can be detected in at least 25 to 50% of adults and are more common in women and with increasing age.

When a patient presents with a thyroid nodule, the primary concern is whether it is benign or malignant. Findings on fine-needle aspiration, ideally performed with ultrasonographic guidance, are the mainstay of clinical decision making. If the diagnosis is in doubt, most physicians and patients opt for hemithyroidectomy or total thyroidectomy, hedging against the risk of a potential cancer and allowing a thorough pathological examination.

The quest for better diagnostic tests for patients with thyroid nodules has been a long but successful journey. In addition to fine-needle aspiration, valuable tests have included radionuclide scanning with iodine-123 or technetium-99m, ultrasonography, and positron-emission tomography. In recent years, genetic abnormalities associated with thyroid cancer have offered promise as a more definitive means of distinguishing benign and malignant lesions. Unfortunately, most thyroid nodules do not contain one of these high-risk mutations, necessitating lobectomy or thyroidectomy in nodules with mutation-negative cytologic findings.

Alexander et al. now provide evidence in the Journal that a new gene-expression classifier test can be used to identify low-risk thyroid nodules among cytologically indeterminate fine-needle aspirates. This test was based on an empirical assessment of more than 247,000 mRNA transcripts associated with pathologically proven benign or malignant thyroid lesions. The primary finding is that the gene-expression classifier test has a high negative predictive value for cytologically indeterminate nodules (95% for an atypical or follicular lesion of undetermined significance, 94% for a follicular neoplasm or lesion suggestive of follicular neoplasm, and 85% for a lesion suggestive of cancer). It bears emphasizing that this test does not have sufficient specificity to inform decision making for samples with clear-cut cytologic results (i.e., benign or malignant).

Can this new gene-expression test reduce unnecessary surgery? The answer is seemingly “yes,” but with important caveats. Approximately 75,000 operations are performed for cytologically indeterminate nodules in the United States each year. If results of the gene-expression classifier test were used to inform clinical decision making (Fig. 1), it might be possible to reduce surgery for nodules with indeterminate cytology by at least one third, or about 25,000 operations per year. Even with the added cost of the test, this approach could result in substantial cost savings.

However, the risk of this approach is that 5 to 10% of nodules classified as benign (false negatives) are likely to be malignant, particularly those that are cytologically indeterminate but suggestive of cancer. Because this group is at high risk for cancer, it might be reasonable to repeat the fine-needle aspiration biopsy or perform a diagnostic hemithyroidectomy even when the gene-expression classifier indicates a benign profile.
For patients being monitored, it will be important to have a low threshold to repeat fine-needle aspiration if ultrasonographic findings indicate rapid growth or characteristics suggestive of cancer. Over time, we can anticipate that additional molecular tests will further refine diagnostic accuracy. For example, when known mutations are present (e.g., BRAF V600E, RET/PTC, and PAX8–PPARγ [peroxisome proliferator–activated receptor gamma 1]), the risk of malignancy is close to 100%. In this era of focusing on high-quality outcomes at lower cost, this new gene-expression classifier test is a welcome addition to the tools available for informed decision making about the management of thyroid nodules.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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