Clinical Diagnostic Gene Expression Thyroid Testing

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KEYWORDS

• Biopsy • Fine-needle aspirate • Gene expression • Genomics
• Molecular diagnostic techniques • DNA mutational analysis • Thyroid nodule

KEY POINTS

- Fifteen to 30% of thyroid fine-needle aspiration biopsies are cytologically indeterminate.
- When cytologically indeterminate thyroid nodules undergo diagnostic surgery, approximately three-quarters prove to be benign.
- The Afirma Gene Expression Classifier (GEC) achieved a risk of malignancy of 6% or less on an independent set of 265 prospectively collected cytologically indeterminate nodules when the molecular results were compared with the blinded gold standard central expert histopathology diagnosis.
- The National Comprehensive Cancer Network Thyroid Carcinoma Guideline states that cytologically indeterminate thyroid nodules determined to have a malignancy risk of ~5% or less with a molecular test can be clinically observed.
- For GEC-tested patients, published clinical utility studies demonstrate that approximately half of those with indeterminate cytology (Bethesda III/IV) avoid diagnostic thyroid surgery.

THYROID CANCER MULTIGENE EXPRESSION CLASSIFIERS: WHAT THE SURGEON SHOULD KNOW

Introduction

Before the advent of thyroid nodule fine-needle aspiration biopsy (FNAB), thyroid nodules were routinely referred for diagnostic surgery because of their 5% to 15% risk of malignancy (ROM).[1] FNAB decreased diagnostic thyroidectomies by one-half

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because most FNABs are diagnosed as cytologically benign.[2] Still, 15% to 30% of thyroid FNABs are cytologically indeterminate (ie, not clearly benign nor malignant).[1,3] When cytologically indeterminate thyroid nodules undergo diagnostic surgery, approximately three-quarters prove to be histologically benign.[4,5] Therefore, patient care could be significantly improved with genomic diagnostic technologies that accurately reclassify these samples as benign with high enough negative predictive value (NPV) to safely avoid the costs and risks of diagnostic thyroid surgery. In choosing which genomic test to order, the surgeon should insure that peer-reviewed publications exist that define the test's clinical and analytical validity, and most importantly, its clinical utility.

Currently, the Afirma gene expression classifier (GEC) (Veracyte Inc, South San Francisco, CA, USA) is used in cytologically indeterminate nodules (Bethesda III and IV) to reclassify them as benign nodules and to avoid diagnostic surgery. **Table 1** lists the Bethesda cytologic category definitions. By accurately excluding malignancy when the test result is benign, the Afirma GEC is known as a "rule-out" test.[6] In addition, it identifies rare neoplasms that are often difficult to diagnose accurately with cytology, such as medullary thyroid cancer (MTC), parathyroid neoplasms, and certain metastases to the thyroid. Given the wealth of published data regarding the Afirma GEC's clinical validity,[7,8] analytical validity,[9] and clinical utility,[10,11] patients should not undergo thyroid surgery for solely diagnostic reasons for lower risk cytologically indeterminate thyroid nodules (Bethesda III and IV) without the physician and patient considering the role of Afirma GEC testing. In the surgical author's practice, approximately half of the patients with cytologically indeterminate nodules chose to pursue surgery over additional testing. Younger patients, and those with a higher ROM based on cytology (Bethesda V vs Bethesda III/IV), were more likely to elect surgery.[12] For those who chose GEC testing, half avoided thyroid surgery, similar to what was found in 2 multicenter clinical utility studies of Afirma.[10,11]

Cost, Morbidity, and Risk of Mortality from Surgery

The average direct costs of hemithyroidectomy and total thyroidectomy are conservatively estimated at greater than $6000 and $11,000, respectively.[13] However, the range of costs for these procedures at various inpatient facilities exceeds $20,000 and $25,000, respectively.[13] Nevertheless, the costs of diagnostic surgery include more than just the direct cost of the procedure. Estimates of costs of diagnostic thyroidectomy should include surgical complications, as well as indirect costs due to time lost from work and responsibilities of daily living (eg, child care, cooking, cleaning), impaired quality of life (the fear of potentially having cancer and the anxiety of undergoing diagnostic surgery, postoperative pain and recovery, and the potentially impaired quality of life from iatrogenic hypothyroidism with,[14] or without,[15] a normal serum TSH).

Although thyroid lobectomy is increasingly performed as an outpatient procedure with excellent outcomes in experienced hands, the outcomes from thyroidectomy overall can be sobering. Thyroid surgery is associated with a perioperative mortality of 0.1% to 0.2%, with rates as high as 0.5%.[16–18] Serious or permanent nonlethal complications of thyroidectomy include hypocalcemia, recurrent and/or superior laryngeal nerve damage, rebleeding, and wound infection.[19,20] The frequency of these complications is underappreciated and is strongly related to surgeon experience (volume) and expertise. One study reported that 11% of patients undergoing thyroidectomy or parathyroidectomy required a visit to the emergency room at least once within 30 days of surgery, and nearly one-quarter of these patients required hospitalization.[21] Complication rates from thyroid surgery may be much higher in