Clinical THYROIDOLOGY



A Benign Gene Expression Classifier Result on an Indeterminate Thyroid FNA May Reduce the Need for Thyroidectomy

Duick DS, Klopper JP, Diggans JC, Friedman L, Kennedy GC, Lanman RB, McIver B. The impact of benign gene expression classifier test results on the endocrinologist-patient decision to operate on patients with thyroid nodules with indeterminate fine-needle aspiration cytopathology. Thyroid 2012;22:996-1001. Epub August 8, 2012; doi: 10.1089/thy.2012.0180.

Background

Nodules classified as "indeterminate" by cytology make up about 15% to 30% of biopsy results. This classification is much more common that that of overt malignancy, which is found in only 5% of biopsied nodules. The Bethesda classification system divides the indeterminate classification into follicular lesion of undetermined significance (FLUS), follicular neoplasm, and suspicious for malignancy, with the possibility of the nodule being malignant being about 10%, 25%, and 65%, respectively, in the three categories.

The Afirma gene expression classifier (AGEC) is claimed to have a 95% negative predictive value when it is applied to indeterminate nodules in the two lesslikely-to-be-malignant categories. The evaluation of this classifier, including its pitfalls, was reported in the August issue of Clinical Thyroidology (1). The purpose of the current study was to determine how the AGEC influenced the joint decision of the endocrinologist and patient to operate on an indeterminate nodule when AGEC reading of the nodule was benign. There was the tacit assumption that all patients with nodules classified cytologically as indeterminate would have been referred for surgery.

Methods

This retrospective multicenter study included patients of 51 endocrinologists at 21 practice sites

who obtained the AGEC on cytologic specimens of thyroid nodules >1 cm whose FNAs were read as indeterminate. When the AGEC was classified as negative for malignancy, the investigators determined whether patients were referred for surgery. In addition, the basis for surgery was determined.

Results

The study analyzed data on 368 patients (395 nodules) with a median size of 2.4 cm. Surgery was performed on only 28 patients (7.6%) of those whose FNA was cytologically indeterminate but whose AGEC was benign; the predicted number based on other data compiled by Veracyte investigators would have been 74% (2). The primary reasons that surgery was recommended to the 28 patients with benign results on AGEC were that the nodule was large in 13 patients, symptomatic in 7, rapidly growing in 3, symptomatic in 7, a second suspicious nodule in 3, suspicious on ultrasonography in 2, suspicious on cytology in 2, and not otherwise specified in 12. (Apparently, patients could have more than one reason.) Hemithyroidectomy was the surgery for 68% of the patients; the rest had a total thyroidectomy.

Conclusions

A benign Afirma gene expression classifier result led to a marked reduction in performing thyroidectomy in patients with cytologically indeterminate nodules. *continued on next page* A Benign Gene Expression Classifier Result on an Indeterminate Thyroid FNA May Reduce the Need for Thyroidectomy

ANALYSIS AND COMMENTARY • • • • •

This study has a number of significant shortcomings. It did not subdivide the nodules in the indeterminate category. The number whose cytology was either FLUS or follicular neoplasm was not stated. Apparently, only 2 were suspicious; another Afirma study has not recommended the use of the gene classifier for nodules that are suspicious for malignancy for two reasons; first, almost two-thirds of these nodules turn out to be cancers, and second, the classifier mistakenly classified 6% of a small group of suspicious nodules as benign when they were really malignant (3).

It would be interesting to know the number of patients whose cytology was in the indeterminate category and whose AGEC was classified as suspicious, but this was not stated; only those classified by AGEC as benign were the subject of the study.

The study does not state the number of malignant nodules found in the 28 patients who actually had thyroidectomy. The justification that the study focused only on how many patients were spared thyroidectomy is not a sufficient reason for this omission.

At the recent ATA meeting in Quebec, McIver and colleagues from the Mayo Clinic presented their additional experience with the AGEC. They reported that only 23% of indeterminate nodules were classified by AGEC as benign. Of the 27 AGEC "suspicious" nodules that went to surgery, only 4 (15%) were malignant (4).

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References

- Hershman JM. A gene-expression classifier on FNA biopsy of a thyroid nodule may be helpful to determine whether an indeterminate nodule is benign. Clin Thyroidol 2012;24(8):2-4.
- 2. Wang CC, Friedman L, Kennedy GC, Wang H, Kebebew E, Steward DL, Zeiger MA, Westra WH, Wang Y, Khanafshar E, et al. A large multicenter correlation study of thyroid nodule cytopathology and histopathology. Thyroid 2011;21:243-51. Epub December 29, 2010.
- 3. Alexander EK, Kennedy GC, Baloch ZW, Cibas ES, Chudova D, Diggans J, Friedman L, Kloos RT,

Livolsi VA, Mandel SJ, et al. Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. N Engl J Med 2012;367:705-15. Epub June 25, 2012; doi: 10.1056/NEJMoa1203208.

4. McIver B, Reddi HV, Kosok LL, Smallridge R, Jones AD, Bernet V. An independent study of a gene expression classifier (Afirma) in the evaluation of cytologically indeterminate thyroid nodules: initial report. Program of the 82nd Annual Meeting of the American Thyroid Association, Quebec, September 19-23, 2012, p. 171.