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Cytopathologic Diagnosis of Thyroid Nodules Varies Considerably

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SUMMARY

Background

The evaluation of a thyroid nodule depends on FNA and then cytopathology to classify it as benign, malignant, or if neither, to assign a probability of malignancy. The probability is based on the Bethesda system for reporting cytopathology (1). This paper examines the validity of the cytopathologic diagnosis by comparing the diagnostic classifications of "local cytopathologists" and "expert cytopathologist" on a large number of samples. In particular, concordance among the local versus expert cytopathologists and even the concordance of diagnoses by experts reviewing the blinded slides previously studied were evaluated. The results show that cytopathologic diagnosis of thyroid FNA specimens is variable and imprecise, even though it is the "gold standard" and is a cornerstone for the treatment of patients with thyroid nodules.

Methods

Patients were recruited from 14 academic centers and 35 community-based practices. FNA of nodules was performed under ultrasound. Histopathology reports and slides were obtained for 776 nodules from 653 patients, including 310 patients who had undergone thyroidectomy, but only 336 samples from 290 patients were actually used in the cytopathology study. The histopathology was reviewed by two study pathologists. Thyroid microcarcinomas that were found incidentally were excluded.

Because a high proportion of the local cytopathology reports did not use the Bethesda system, the reports were reclassified into this system by two of the three central cytopathology experts. The slide preparations varied by site; 74% were air-dried, and only 26% had alcohol-fixed or ThinPrep slides. Concordance between the local report and one expert was considered the final diagnosis. In discordant cases, the slides were sent to another expert; if the experts were concordant, that was considered the final diagnosis. If there was discordance between experts, a third expert reviewed the slides. Discordance among all three experts occurred in 26 cases, leaving 336 nodules that were the basis for the subsequent analysis. The degree of concordance was calculated using a k statistic.

Results

There was 91% concordance in the diagnosis of the 776 resected nodules with regard to their being benign or malignant in the comparison between the local and expert pathologists. Disagreement occurred most frequently with regard to follicular/Hürthle-cell carcinomas being called benign.

Using a compressed four-category cytopathology diagnosis (benign, indeterminate, malignant, inadequate), concordance between local and expert occurred in 74% of cases. When a six-category system was used that expanded indeterminate to AUS/FLUS, follicular neoplasm/suspicious for follicular

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neoplasm, or suspicious for malignancy, the concordance fell to 64%. The local pathologists tended to have more diagnoses in the indeterminate categories than the experts. The risk for cancer after a false benign diagnosis was similar for experts and local pathologists—about 10%.

When the same "blinded" cytopathology slides were read again by the same three experts more than 30 days after the previous reading, the proportion of identical diagnoses varied from 60% to 83%.

Conclusions

Substantial interobserver and intraobserver variability exists in the cytopathologic evaluation of thyroid nodules and this variability indicates the limitation of visual microscopic diagnosis.

ANALYSIS AND COMMENTARY

The authors of this study are leading authorities in cytopathology and the clinical management of thyroid cancer. Their striking observations in this carefully designed study confirm several other reports concerning the reproducibility, or lack of it, of thyroid cytopathology. Olson et al. recently reported that the cytopathology diagnosis according to the Bethesda system changed 32% of the time when the tertiary center reevaluated slides made by the referral institution (2). Davidov et al. reported that concordance between cytopathologists who evaluated 129 patients with indeterminate FNA biopsies was only 37% (48 of 129) using the Bethesda classification (3). A second opinion on 922 FNA slides found 122 disagreements (13%) in diagnosis, of which 44 were major with regard to a management decision (4).

In my personal reviews of cytopathology with our local experts, I see them struggle to be accurate, and I observe that there is a certain art to making the diagnosis that could lead to arbitrary decisions that might not have been made by others. Our department has had mandatory quality control. The outside experts often disagree on the diagnosis of "follicular neoplasm," with even more disagreement on the diagnosis of FLUS. The proportion of FNA that are diagnosed as FLUS/AUS varied between 3% and 27% among institutions, suggesting that the criteria for making this diagnosis are "soft" and that some cytopathologists avoid the diagnosis (5).

Unfortunately, the current study has some major limitations. First, the experts reviewed the local cytologic diagnosis and reclassified it into the Bethesda categories because 57% of the academic sites and 91% of the community sites did not use the Bethesda system. Formulating the classification pigeonhole from the written reports is one step removed from doing it on the slides themselves, especially in the somewhat murky indeterminate categories. Second, three fourths of the cytology slides on which the diagnosis was based were only air-dried, not alcohol-fixed. Alcohol-fixed slides are superior for evaluating nuclear details that are very important for diagnosis (6). Nevertheless, I believe that the message is valid: cytopathologic diagnosis is a somewhat uncertain science. The clinician must be wary and not forsake clinical judgment in the treatment of patients with thyroid nodules.

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References

1. Baloch ZW, LiVolsi VA, Asa SL, Rosai J, Merino MJ, Randolph G, et al. Diagnostic terminology and morphologic criteria for cytologic diagnosis of thyroid lesions: a synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference. Diagn Cytopathol 2008;36:425-37.
2. Olson MT, Boonyaarunnate T, Aragon Han P, Umbricht CB, Ali SZ, Zeiger MA. A tertiary center's experience with second review of 3885 thyroid cytopathology specimens. J Clin Endocrinol Metab 2013;98:1450-7.
3. Davidov T, Trooskin SZ, Shanker BA, Yip D, Eng O, Crystal J, et al. Routine second-opinion cytopathology review of thyroid fine needle aspiration biopsies reduces diagnostic thyroidectomy. Surgery 2010;148:1294-9.
4. Bajaj J, Morgenstern N, Sugrue C, Wasserman J, Wasserman P. Clinical impact of second opinion in thyroid fine needle aspiration cytology (FNAC): a study of 922 interinstitutional consultations. Diagn Cytopathol 2012;40:422-9. Epub September 30, 2011.
5. Bongiovanni M, Spitale A, Faquin WC, Mazzucchelli L, Baloch ZW. The Bethesda System for Reporting Thyroid Cytopathology: a meta-analysis. Acta Cytol 2012;56:333-9. Epub July 25, 2012; doi: 10.1159/000339959.
6. Kini SR. Thyroid cytopathology: an atlas and text. Philadelphia: Lippincott Williams & Wilkins, 2008.