DIAGNOSIS

Test spots low-risk thyroid nodules

A novel gene expression classifier test can help identify subpopulations of patients with cytologically indeterminate thyroid nodules who have a low risk of thyroid cancer and could potentially be spared surgery, say US researchers.

Thyroid nodules are common and most are benign. For nodules of ≥ 1 cm in diameter, fine-needle aspiration (FNA) cytology is the method of choice to distinguish benign lesions from those at high risk of malignancy. Although FNA cytology can be used to accurately classify the majority of samples as benign, 15–30% of samples fall within the category of cytologically indeterminate. “Most patients with cytologically indeterminate FNA samples are recommended for surgery,” explains lead researcher Erik K. Alexander of Harvard Medical School. “However, only about 30% have cancer. For the remainder, this was unnecessary surgery, which carries risk, cost and morbidity. For these reasons a new diagnostic test is needed.”

Attempts to improve preoperative diagnostic evaluation of patients with indeterminate test results include genetic mutation analysis of FNA cytology samples; single gene mutations or translocations associated with thyroid cancer are tested for, such as mutations in *RAS* and *BRAF*. The flaw in currently available molecular testing systems is that the negative predictive value of these tests is insufficient to definitively exclude cancer.

The test assessed by Alexander *et al.* evaluates the expression of 167 genes to classify samples from a cytologically indeterminate nodule as either benign or suspicious. “This is the first approach to identify benign samples in the cytologically indeterminate FNA category,” comments Ralf Paschke of Universität Leipzig, Germany, who was not involved in this study. “By contrast, previous molecular diagnostic approaches for FNA primarily concentrated on the identification of malignant samples.”

The prospective validation study involved 49 clinical centres in the USA. The researchers collected 4,812 FNA samples from 3,789 patients with thyroid nodules ≥ 1 cm in diameter over a 19-month period. Of the 4,812 samples, 577 were cytologically indeterminate, and histopathological specimens from resected lesions were available for 413 of these. 265 cytologically indeterminate nodules met inclusion criteria for the final analysis. 85 of 265 nodules (32%) were malignant, according to blinded, expert histopathological review. 78 of these 85 nodules were also classified as suspicious by the gene expression classifier test (sensitivity 92%). The investigators suggest insufficient nodule sampling as a possible reason for the seven false-negative results. Of the 180 nodules determined to be benign by the histopathological review, only 93 were benign according to the gene expression classifier test (specificity 52%). Negative predictive values for the three subtype categories of indeterminate cytology were 95% for atypia (or follicular lesion) of undetermined significance, 94% for follicular neoplasm or lesion suspicious for follicular neoplasm, and 85% for lesions suspicious for malignancy.

“Patients with an indeterminate cytology, but benign gene expression classifier test results have a very low risk of cancer,” Alexander comments. “The prospective, blinded and multicenter nature of this study support the rapid translation of the test into the clinic.” However, Paschke cautions that the test required two additional needle insertions during FNA biopsy and that it is costly. The next step, he suggests, is to develop methods for molecular diagnostics using routinely obtained FNA smears or liquid-based cytology material that does not require additional needle insertions and storage of the obtained material for all patients in order to then select just the cytologically indeterminate samples for further molecular analysis.

Alexander reasons that patients with thyroid nodules that are cytologically indeterminate on FNA cytology and benign according to the gene expression classifier test may be better served by following a more conservative, nonoperative approach. “The findings suggest that care can be optimized (and cost and risk reduced) for a significant number of patients,” he concludes.

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