VALIDATION OF A MOLECULAR CLASSIFIER FOR PREOPERATIVE IDENTIFICATION OF MEDULLARY THYROID CANCER IN THYROID NODULE FINE-NEEDLE ASPIRATION BIOPSIES

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Objective: Cytopathological evaluation of thyroid fine-needle aspiration biopsy (FNAB) specimens may not raise preoperative suspicion of medullary thyroid cancer (MTC), as it misses over one-half of these uncommon, yet aggressive, neoplasms. Additionally, serum calcitonin screening for MTC has a high false positive rate, which results in a low positive predictive value (PPV). We report results from a large, prospective validation of an mRNA-based expression signature (MTC Classifier) to preoperatively identify MTC in FNAB samples.

Methods: Prospectively, we conducted cytology on 50,430 consecutively received thyroid nodule FNAB samples. Among the 15.5% indeterminate samples (Bethesda categories III and IV), we performed the Afirma Gene Expression Classifier (GEC) to reclassify samples as benign or suspicious, and also used the MTC Classifier to identify MTC. We similarly evaluated an additional 2,673 prospective FNAB samples identified as indeterminate, suspicious or malignant (Bethesda III-VI) by locally read cytopathology. Clinical details were obtained for patients with MTC signatures or cytological features that suggested MTC. The MTC Classifier was also performed on 215 consecutive likely malignant specimens (Bethesda V-VI) to calculate incidence of the MTC signature.

Results: The MTC Classifier identified an MTC signature in 0.2%, 0.5%, 1.0%, and 1.8% of consecutive nodules with Bethesda category III-VI cytologies, respectively. The PPV for the MTC Classifier was 98%, and the single false positive was another neuroendocrine tumor (paraganglioma). In MTC-confirmed patients, basal serum calcitonin was <20 pg/ml in 7.5%, and unsuspected MEN2 germline mutations were identified in 10%. No MTC was found in 5 cases where cytology raised suspicion for MTC but the MTC Classifier did not, suggesting a high negative predictive value (NPV).

Discussion: In the largest thyroid FNAB study evaluating the incidence of MTC to date, an MTC Classifier identified all 39 histologically confirmed MTC cases, whereas only 15 (38%) were suspected or diagnosed as MTC by cytology. The MTC Classifier has high PPV for preoperatively identifying MTC among indeterminate thyroid nodules when used with the Afirma GEC, and also among FNABs deemed suspicious or malignant by cytopathology.

Conclusion: The preoperative genomic identification of MTC is expected to alter patient care, solidifying the need for timely, more thorough surgery, and necessitating preoperative screening for life-threatening concomitant pheochromocytoma.