Ultrasound Characteristics Predict BRAF V600E Mutational Status

Kabaker AS, Tublin ME, Nikiforov YE, Armstrong MJ, Hoak SP, Stang MT, McCoy KL, Carty SE, Yip L. Suspicious ultrasound characteristics predict BRAF V600E-poisitive papillary thyroid carcinoma. Thyroid. February 23, 2012 [Epub ahead of print]. doi:10.1089/thy.2011-0274.

SUMMARY • • • • • •

Background

The ATA guideline (1) and recent Society of Radiologists in Ultrasound consensus statement (2) recommend ultrasound (US) assessment of all thyroid nodules with biopsy of those that are larger 1 cm with worrisome sonographic features. The BRAF V600E mutation has been associated with an increased risk of extrathyroidal extension (ETE) and nodal metastases with a higher risk of persistent disease (3) but may not indicate a worse prognosis (4). This study investigated whether specific US characteristics can reliably detect papillary thyroid carcinoma (PTC) with a BRAF V600E mutation.

Methods and Results

This was a blinded retrospective study of a cohort of 106 patients with a histologic diagnosis of PTC ≥1 cm who had a cervical US, initial thyroid surgery, and molecular testing for BRAF V600E on the fine-needle aspiration prior to surgery or histologic sections after surgery. There were 55 patients who had BRAF-positive PTC and 51 patients had BRAF-negative PTC. Preoperative US images were evaluated by a single radiologist who was unaware of BRAF status for nodule size and suspicious sonographic features (taller-than-

wide shape, ill-defined margins, hypoechogenicity, calcifications, noncystic composition. and absence of halo). The BRAF V600E mutation was associated with suspicious US findings, including taller-than-wide shape (47% vs. 7%, P<0.001), ill-defined margins (42% vs. 9%, P<0.001), hypoechogenicity (83% v. 36%, P<0.001), microcalcifications/macrocalcifications (87% vs. 24%, P<0.001), and absent halo (85% vs. 27%, P<0.001). BRAF mutation was not associated with solid composition. BRAF-positivity was predicted with a positive predictive value of 82% when ≥3 suspicious US features were present. The absence of suspicious US features together with negative BRAF testing predicted PTC without extrathyroidal extension or lymph-node metastasis (negative predictive value [NPV], 88%).

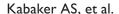
Conclusions

This study demonstrates that a combination of suspicious sonographic features is associated with an increased risk of a BRAF mutation, and the lack of suspicious US features and negative BRAF testing have a good NPV (88%) for ETE and metastatic nodes. This information may assist in the planning of the initial surgical management and risk stratification of patients with PTC.

ANALYSIS AND COMMENTARY • • • • •

The 2009 American Thyroid Association Guideline for Thyroid Nodules and Cancer (1) suggests using both the TMN AJCC/UICC staging plus risk factors to completely assess risk for death and persistence/recurrence of the tumor. These risk categories state that microscopic ETE (stage 3 in patients >45 years old) and metastatic nodes (stage 3 or 4a if >45 years)

place patients at increased risk of recurrence and death. Classic PTC histology, ETE, and metastatic nodes are associated with the BRAF V600E mutation. Although the ATA guidelines suggest consideration of using molecular markers, including BRAF V600E, in the management of thyroid nodules with an indeterminate FNA biopsy, it is not yet in the current 2009 guidelines as a risk factor to alter therapy of a continued on next page



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patient with PTC. It is clear that three or more suspicious features greatly increase the risk of PTC (2) in a nodule. This study suggests that three or more features increase the risk of the BRAF V600E mutation, ETE, and metastatic nodes. At this point, I would not use the US appearance to infer BRAF V600E status. If multiple suspicious sonographic features are seen in a nodule, I would consider testing for the mutation on the FNA biopsy and performing a careful sonographic evaluation for metastatic neck nodes and extension of the tumor outside the thyroid. Although some

investigators (3,4) have suggested using the presence of BRAF V600E mutation to direct surgery (level VI node dissection, total vs. lobectomy), this has not yet been tested and shown to impact patient outcomes. A future large multi-institution study showing the utility of using preoperative BRAF V600E status to direct surgery will be needed before current guidelines for the management of thyroid cancer are altered.

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