

Fine-Needle Aspiration Biopsy with BRAF Analysis and Elastography are Slightly More Efficient in Diagnosing Papillary Thyroid Cancers than FNAB and Thyroid Ultrasound

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Nacamulli D, Nico L, Barollo S, Zambonin L, Pennelli G, Girelli ME, Casal Ide E, Pelizzo MR, Vianello F, Negro I, Watutantrige-Fernando S, Mantero F, Ruge M, Mian C. Comparison of the diagnostic accuracy of combined elastosonography and BRAF analysis vs cytology and ultrasonography for thyroid nodule suspected of malignancy. Clin Endocrinol (Oxf) 2012;77:608-14.

SUMMARY ●●●●●●●●●●●●●●●●●●●●●●●●●●●●●●

Background

Diagnostic workup of thyroid nodules remains unsatisfactory, since 15% to 30% of samples obtained by fine-needle aspiration biopsy (FNAB) are classified as indeterminate. In these cases, thyroidectomy or lobectomy is indicated, even though a thyroid carcinoma is ultimately confirmed in less than 20% of these cases. In recent years many attempts at improving the diagnostic yield have been published. For instance, studies using the microarray technique to analyze a large number of genes show promise (1,2). Unfortunately, the test samples have to be shipped to specialized laboratories, and the investigation is still very expensive. In the present article, the authors analyze the performance of another approach that is available in regional centers. The authors combine elastography (ultrasound elastography [USE]), an improved ultrasound method measuring tissue stiffness, with measurement of the already well-established tumor marker BRAF in the FNAB. A total of 45% to 60% of papillary cancers harbor a point mutation of this gene, primarily the BRAF V600E mutation but other BRAF mutations (K601E and AKAP9-BRAF) mutations are also known to occur (3). However, BRAF mutations are rare in follicular thyroid cancers, and these tumors do not show increased tissue stiffness.

Methods

This retrospective study extended from 2009 to 2011. A total of 164 nodules were studied. Freehand USE

was done using a real-time scale of 1 to 5, where 5 corresponds to the highest tissue stiffness. BRAF mutations were identified through direct sequencing and by mutant allele-specific PCR amplification.

Results

The results of the histologic workup were as follows: 74 (45%) were benign nodules and 90 were malignant; 73 of the malignant nodules were classical papillary thyroid cancers, 10 were the follicular variant of papillary thyroid carcinoma (PTC), 5 were follicular cancers, and 2 were medullary cancers. Of these nodules, 37 had a diameter <1 cm and 58 were positive for BRAF mutations, 54 of which harbored the mutation V600E. BRAF mutation analysis was particularly useful in nodules with high elasticity (scale 1), in which the malignancy would have been missed without it. BRAF mutations were detected in 70% of all PTCs.

By combining BRAF analysis with USE, 105 nodules were classified as suspicious; 86 (82%) proved to be malignant. Using classical ultrasound and FNAB, 63% of the suspicious nodules that were operated on proved to be malignant. The predictive value of the combined tests turned out to be clearly superior for USE and BRAF as compared with ultrasound and FNAB. In particular, the specificity was markedly better (predictive value 74% as compared with 28%). Ultrasound and FNAB still left 50 cases in the “intermediate” group. Only 9 (18%) proved to be thyroid

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cancers at operation. When using USE and BRAF mutations, 15 of 31 (48%) turned out to be cancers.

Conclusions

This retrospective study concerns thyroidectomies and/or lobectomies carried out for 164 thyroid nodules, of which a very high percentage were revealed to be cancers. They were investigated by ultrasound, USE, FNAB and BRAF mutations. The

combined use of BRAF and USE was useful since in some elastic (scale 1) nodules BRAF mutations were positive; also some stiff (scale 4), but BRAF-negative, nodules were revealed to be malignant. Only the combination of the two results suggested the need for operation. Nevertheless, in a few cases BRAF analysis and USE failed to recognize the malignant nature of the nodule.

ANALYSIS AND COMMENTARY ● ● ● ● ●

The authors themselves suggest that this preliminary study should be followed by a prospective multicenter study. Other approaches, such as the gene microarray technique should be included. Yet, the cost of such an experiment would be very high and the success probably doubtful.

The present study, though interesting, has some clear shortcomings. For instance, only patients who underwent surgery are included in the study. This creates a considerable bias, since it is unlikely that in this center all patients underwent surgery. Moreover, although follicular cancers are mentioned, no separate results were given, despite the fact that they are known to be different in terms of BRAF mutation frequency and elasticity. Furthermore, it is not clear why the authors did not compare the combination of ultra-

sound and BRAF mutations instead of ultrasound and FNAB. Finally, even though not discussed specifically in the text, but shown in one figure, approximately 5% to 7% of nodules considered as benign based on USE scale 1 and absence of BRAF mutations were eventually identified as being malignant. Therefore, even in this situation, the clinical decision cannot rely fully on these two criteria.

However, the approach has the advantage of being easily feasible with a moderate increase in cost. Also, the technique of USE is still in a developing stage; at present, the more powerful, less subjective, and more objective shear wave elastography is becoming available (4). It is therefore likely that in the near future the information about the elasticity of thyroid nodules will become a routine addition to the present ultrasound techniques, although it brings only a small advantage over the currently available techniques.

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