Clinical THYROIDOLOGY



BRAF Mutation Is Not an Independent Predictor of Central- Lymph- Node Metastases in the Classical Variant of Papillary Thyroid Cancer

Jerome M. Hershman

SUMMARY • • • • • • • • •

Li C, Aragon Han P, Lee KC, Lee LC, Fox AC, Beninato T, Thiess M, Dy BM, Sebo TJ, Thompson GB, Grant CS, Giordano TJ, Gauger PG, Doherty GM, Fahey TJ 3rd, Bishop J, Eshleman JR, Umbricht CB, Schneider EB, Zeiger MA. Does BRAF V600E mutation predict aggressive features in papillary thyroid cancer? Results from four endocrine surgery centers. J Clin Endocrinol Metab 2013;98:3702-12. Epub August 22, 2013.

Background

The BRAF V600E mutation, found in a high proportion of papillary thyroid cancers (PTCs), results in constitutive activation of the mitogen-activated protein (MAP) kinase pathway and is generally believed to indicate that the tumor is aggressive (1). A controversial aspect of the surgical treatment of PTC is whether to perform routine prophylactic lymph-node dissection in the central compartment (level 6). The aim of this retrospective study was to determine the prognostic value of the BRAF mutation status as a predictor of lymph-node metastases to the central compartment, then mutation status could be used to justify prophylactic centrallymph-node dissection.

Methods

The study included 388 consecutive patients who underwent surgery for PTC between January 2009 and December 2011 at four tertiary endocrine surgery centers (Mayo Clinic, University of Michigan, Cornell, and Johns Hopkins). All patients had central-lymphnode dissections; in 76% of patients this was done on a prophylactic basis and in 24% there was preoperative evidence of central-lymph-node involvement.

The BRAF mutation was identified in DNA extracted from frozen or paraffin-embedded tissue samples by PCR amplification. The patients were divided into three groups: classical variant PTC (315 patients), follicular variant PTC (41 patients), and aggressive variant PTC (32, of whom 31 had tall-cell variant).

Statistical analysis included a bivariate analysis of the association between BRAF mutation status and patient and disease features, including age, sex, tumor size, lymph-node metastases, extrathyroidal extension, multifocality, lymphovascular invasion, involvement of surgical margins, and AJCC stage. Multivariate logistic-regression analyses of these features were conducted to examine which preoperative variables were independently associated with central-lymph-node metastases.

Results

The BRAF mutation prevalence was found to be 80.3% in the classical variant, 39% in the follicular variant, and 87.5% in the aggressive variant PTC. The bivariate analysis of all PTC subtypes showed a significant positive association between the BRAF mutation status and lymph-node metastases (P = 0.002) and advanced AJCC stage (P = 0.002). Multivariate logistic-regression analysis of all patients with PTC found that BRAF mutation (P = 0.001), tumor size >2 cm (P = 0.045), and extrathyroidal extension (P = 0.001) were independent predictors of lymph-node metastases. Age >45 years was negatively associated with the presence of lymph-node metastases (P = 0.001).

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When the bivariate analysis was performed for only the 315 classic variant PTCs, there was no significant association between BRAF mutation and lymph-node metastases or any of the other tumor variables. Multivariate logistic-regression analysis found that only age >45, tumor size >2 cm, and extrathyroidal extension were independent predictors of lymph-node metastases. There was no significant association between BRAF mutation status and lymph-node metastases in this group.

Conclusions

Although BRAF mutation was found to be an independent predictor of central-lymph-node metastases in the overall cohort of patients with PTC, this relationship lost significance when only classical variant PTC was included in the analysis. Prospective studies are needed before BRAF mutation can be considered a reliable factor to guide the treatment of patients with PTC with regard to performing prophylactic centrallymph-node dissection.

ANALYSIS AND COMMENTARY • • • • • •

This interesting study, concluding that BRAF mutation status is not a predictor of lymph-node metastasis for the classical variant of PTC, which occurred in 81% of the patients, is somewhat heretical with regard to the recent concern about the ominous prognostic value of this mutation. The finding that the BRAF mutation does not correlate with lymph-node metastasis is supported by a Japanese study of 613 patients with PTC of whom 38% had the BRAF mutation (2). In a meta-analysis of 32 studies including 6372 patients (written by some authors of the current study), BRAF mutation was associated with lymph-node metastases (3), but only 2 of the studies included prophylactic lymph-node dissection.

How can the contrary findings be reconciled? First, PTC has a very good prognosis in about 90% of patients, making it difficult to believe that the BRAF mutation indicates an ominous prognosis when it is currently found in such a high prevalence of PTC

patients. The finding that 80% of the classical variant PTCs had the mutation makes the statistical comparisons somewhat lopsided. If the large majority of patients with PTC have the BRAF mutation, then it becomes tough to prove that it predicts a poor outcome, including lymph-node metastases that correlates with more recurrence.

Second, the introduction of the current paper contains an excellent discussion about the controversial benefit of prophylactic central-lymph-node dissection, although it does not highlight the downside of the procedure, namely a higher incidence of surgical complications. It states that "most occult nodal micrometastases, although they occur in 31% to 62% of patients with PTC, remain clinically insignificant." Perhaps the use of the BRAF mutation will be as a marker of more aggressive PTC that should be treated more aggressively in patients who have gross lymphnode macrometastases that have been detected preoperatively. These patients are probably more likely to benefit from central-lymph-node dissection.

References

- Xing M. BRAF mutation in papillary thyroid cancer: pathogenic role, molecular bases, and clinical implications. Endocr Rev 2007;28:742-62. Epub October 16, 2007.
- 2. Ito Y, Yoshida H, Maruo R, Morita S, Takano T, et al. BRAF mutation in papillary thyroid carcinoma in a Japanese population: its lack of correlation

with high-risk clinicopathological features and disease-free survival of patients. Endocr J 2009;56:89-97. Epub October 8, 2008.

3. Li C, Lee KC, Schneider EB, Zeiger MA. BRAF V600E mutation and its association with clinicopathological features of papillary thyroid cancer: a meta-analysis. J Clin Endocrinol Metab 2012;97:4559–4570. Epub October 9, 2012.