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BRAF V600E Mutation and Papillary Thyroid Cancer—Letter

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To the Editor Our recent multicenter study¹ reported an association between *BRAF*V600E and PTC-related patient mortality. However, this association was not independent of tumor behaviors and the prognostic value of *BRAF*V600E was debated in an accompanying Editorial.² This issue warrants further discussion in several aspects.

First, the synergistic interaction between *BRAF*V600E and tumor behaviors demonstrated in our study¹ suggests that *BRAF*V600E promotes aggressive tumor behaviors to exert its effect on mortality. Thus, multivariable analyses adjusting for tumor behaviors would artificially nullify the association between *BRAF*V600E and mortality, underestimating its prognostic value.

Second, the strong synergism between *BRAF*V600E and patient age in affecting PTC mortality demonstrated in our study¹ not only represents a unique mechanism of *BRAF*V600E in affecting mortality, as the Editorial² pointed out, but is also a reason for the attenuation of the significance of *BRAF*V600E when the multivariable model included patient age. Adjusting for patient age underestimates the incremental prognostic value of *BRAF*V600E when its status can in fact distinguish patients of similar age into higher- and lower-risk groups.

Third, contrary to the statement in the Editorial,² our study supports the position that prognostic *BRAF*V600E testing should be performed in conventionally low-risk patients with PTC. Our study¹ demonstrated that in the *BRAF* mutation-negative and conventionally low-risk patients, particularly in patients with conventional PTC, mortality was virtually zero, whereas a few deaths did occur in the *BRAF* mutation-positive patients. This high negative predictive value of *BRAF*V600E for mortality is consistent with the high negative predictive value of *BRAF*V600E for PTC recurrence,^{3,4} particularly in conventionally low-risk patients.⁴

How to manage low-risk PTC has been debated and over-treatment of these patients is common. With this high negative predictive value, testing for *BRAF*V600E would help identify many mutation-negative patients who could be considered for conservative management.

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References

1. Xing M, Alzahrani AS, Carson KA, et al. Association between *BRAF*V600E mutation and mortality in patients with papillary thyroid cancer. *JAMA*. 2013; 309(14):1493–1501. [PubMed: 23571588]
2. Cappola AR, Mandel SJ. Molecular testing in thyroid cancer: *BRAF* mutation status and mortality. *JAMA*. 2013; 309(14):1529–1530. [PubMed: 23571594]
3. Xing M, Clark D, Guan H, et al. *BRAF* mutation testing of thyroid fine-needle aspiration biopsy specimens for preoperative risk stratification in papillary thyroid cancer. *J Clin Oncol*. 2009; 27(18):2977–2982. [PubMed: 19414674]
4. Elisei R, Viola D, Torregrossa L, et al. The *BRAF*V600E mutation is an independent, poor prognostic factor for the outcome of patients with low-risk intrathyroid papillary thyroid carcinoma: single-institution results from a large cohort study. *J Clin Endocrinol Metab*. 2012; 97(12):4390–4398. [PubMed: 23066120]