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BRAF V600E Mutation and Papillary Thyroid Cancer—In Reply

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In Reply I disagree with Dr Ciarrocchi and colleagues that *BRAF*V600E has no role in the aggressiveness of PTC because of its dependence on tumor behaviors, including local and distant metastases and invasion. It is clear that PTC would not cause patient death without aggressive tumor behaviors.

Our study demonstrated a strong synergism between *BRAF*V600E and aggressive clinicopathological behaviors, as reflected by the strong synergy indices and the fact that the association of mortality with *BRAF*V600E or clinicopathological behavior alone was only moderate but increased when the 2 were considered jointly. Thus, *BRAF*V600E does have a significant association with mortality, which likely occurs through promoting aggressive tumor behaviors and would be misleadingly lost using conventional multivariable models. Further efforts are needed to define how to specifically use the prognostic value of *BRAF* V600E clinically.

Some studies have not shown an association of *BRAF*V600E with aggressive behaviors of PTC. However, most have, as shown in large meta-analyses.^{1,2} Many factors could bias the conclusion about the prognostic value of *BRAF*V600E. For example, in a large study of 631 patients with PTC that failed to show an association of aggressiveness of PTC with *BRAF* V600E,³ many patients (41.5%) had only partial thyroidectomy, making thorough pathological characterization difficult. In addition, the majority of the patients in this study did not receive radioiodine ablation, potentially masking an effect of *BRAF*V600E on clinical outcomes given that *BRAF* mutation-negative PTC is more sensitive to radioiodine ablation.^{1,2}

Ciarrocchi and colleagues' statement that a previous study⁴ showing no aggressive role of *BRAF*V600E in PTC confirms our study is incorrect. However, the 2 studies are not comparable; the former was a single institution study focused on a small number of highly selected cases and the latter was a large multicenter study of consecutive cases.

The study by Sancisi et al⁴ selected patients with distant metastases who only had well-differentiated primary cancer; cases of PTC with distant metastases and high-grade disease or poorly differentiated or undifferentiated components were excluded. This biased case selection misrepresents the real metastatic behaviors of PTC, in which cases with high-grade disease or aggressive pathological components tend to metastasize distantly. This exclusion criterion is problematic, particularly when the role of *BRAF*V600E is studied because the *BRAF* mutation promotes dedifferentiation of PTC.⁵

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It is also unclear whether the control patients were matched with respect to factors that may potentially affect *BRAF*V600E. For example, only the mean age of patients and the mean and range of the follow-up time were provided, without detailed information on patient age distribution and the chronological time of recruitment. This is an important issue because *BRAF*V600E displays a lower prevalence in younger vs older patients and in patients treated earlier compared with more recently.⁶

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