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CORRESPONDENCE

Age-Associated Mortality Risk in Papillary Thyroid Cancer: Does *BRAF* Make a Real Difference?

TO THE EDITOR: The study by Shen et al[1] recently published in *Journal of Clinical Oncology*, together with the accompanying editorial by Haymart,[2] described the results of a large multicentric series of patients with papillary thyroid carcinoma (PTC). Shen et al tested whether age at diagnosis, a well-recognized predictor of poor outcome, especially disease-specific mortality, maintains its predictive value after controlling for the most frequent genetic alteration in PTC, the *BRAF* V600E mutation. They found that the age-associated mortality risk was present only in patients with tumors harboring the *BRAF* mutation, and they claimed that these findings will have a major impact on the clinical management of patients with PTC. Considering that the overall frequency of this mutation is 45% and the disease-specific mortality is quite low in the group of patients with wild-type *BRAF*, older patients with wild-type *BRAF* tumors could be spared from aggressive treatment procedures.[1]

The results are relevant and deserve a thoughtful analysis because the molecular landscape of PTC in older patients is known to be different from that in their younger counterparts,[3] and this difference was not taken into account. Furthermore, PTC mortality rates in both cohorts (1.0% in wild-type *BRAF* and 3.8% in *BRAF* V600E)[1] are low, which raises the question of whether a *BRAF*-modulated age stratification per se will be valuable in clinical practice.

The editorial by Haymart[2] stresses that the major limitation of the study is that only *BRAF* mutations were analyzed despite recognition that the genetic landscape of tumors is influenced by patients' age. TERT promoter (*TERTp*) mutations frequently coexist with *BRAF* mutations, and both TERT and *BRAF* mutations are more frequent in older patients.[1,3,4] Until now, these biomarkers were consistently associated with poorer outcome in patients with PTC. *TERTp* mutations were found to be a stronger predictor of disease-specific mortality than *BRAF* in most published series,[4-7] with the exception of the data previously published by the corresponding author's group.[8] Unfortunately, when discussing their results, Shen et al[1] disregarded all of the data available to the scientific community about the relationship between *TERTp* mutations (with or without coexisting *BRAF* mutations) and mortality.[4-7] Considering that *TERTp* mutations frequently coexist with *BRAF* mutations and may be a stronger predictor of disease-specific mortality, it may well be that the major factor driving mortality in patients with *BRAF*-mutated PTC is their *TERTp* status.

The association of age with poorer prognosis is also valid for follicular thyroid carcinoma,[3] a differentiated thyroid carcinoma in which *BRAF* mutations are not present. *TERTp* mutations are also associated with older age at diagnosis and with disease-specific mortality in follicular thyroid carcinoma.[4] These findings support our hypothesis that *TERTp* mutations may be a major molecular mediator of the relationship between age and mortality in thyroid carcinoma.

As Shen et al[1] mention, the frequency of *BRAF* mutation in PTC is higher in older patients. Considering that the overall frequency of *BRAF* mutation in PTC is approximately 45%, the frequency can be above 50% in older patients. This contradicts the authors' assumption that a *BRAF*-based therapeutic strategy in older patients may avoid a more aggressive treatment in the majority of the patients because most of the patients may indeed have *BRAF*-mutated PTC.

At variance with the limited importance of finding a BRAF mutation, we agree that, from the clinical standpoint, the negative predictive value of *BRAF* has the most relevant added value when stratifying patients' prognosis.[1] This should be emphasized because the proposed risk assessment tools still focus on the positive predictive value of finding a *BRAF*-mutated PTC,[9] which can be low.

We think it would have been helpful to have data on the causes of death. *BRAF* mutation has been associated with local but not distant metastases; some series even show a lower frequency of distant metastases in *BRAF*-mutated PTC,[10] whereas *TERTp* mutations have consistently been associated with distant metastases.[4] Because distant metastases are a major cause of disease-specific mortality, knowledge regarding the cause of death would improve our understanding of the mechanisms beyond the putative *BRAF*-modulated prognostic effect of age.

In summary, we agree that the negative predictive value of *BRAF* mutation (wild-type *BRAF*) for prognostic stratification of mortality may be of value for clinicians, particularly in older patients with PTC. In addition, it should be emphasized that mortality is quite low regardless of *BRAF* genotype. Therefore, we suggest adding *TERTp* status to the prognostic equation. *TERTp* status should be included with *BRAF* in the prognostic algorithm for PTC.

Miguel Melo
Instituto de Investigação e Inovação em Saúde, University of Porto, Porto; Centro Hospitalar e Universitário de Coimbra, University of Coimbra, Coimbra, Portugal

Adriana Gaspar da Rocha
Instituto de Investigação e Inovação em Saúde, University of Porto, Porto; ACeS Baixo Mondego, Coimbra, Portugal

Gustavo Cancela e Penna
Federal University of Minas Gerais; Hospital Mater Dei, Belo Horizonte, Minas Gerais; Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

Manuel Sobrinho-Simões
Instituto de Investigação e Inovação em Saúde, University of Porto, Hospital S. João, Porto, Portugal

Paula Soares
Instituto de Investigação e Inovação em Saúde, University of Porto, Porto, Portugal

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Miguel Melo
Consulting or Advisory Role: Bial, Genzyme, Shire, Boehringer Ingelheim
Speakers' Bureau: Bial, Boehringer Ingelheim, Eli Lilly, Sanofi, AstraZeneca

Adriana Gaspar da Rocha
No relationship to disclose

Gustavo Cancela e Penna
No relationship to disclose

Manuel Sobrinho-Simões
Consulting or Advisory Role: Eisai, Diaxonhit

Paula Soares
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