

Patient Age-Associated Mortality Risk Is Differentiated by BRAF V600E Status in Papillary Thyroid Cancer

Shen X, Zhu G, Liu R, Viola D, Elisei R, Puxeddu E, Fugazzola L, Colombo C, Jarzab B, Czarniecka A, Lam AK, Mian C, Vianello F, Yip L, Riesco-Eizaguirre, G, Santisteban P, O'Neill EJ, Sywak MS, Clifton-Bligh R, Bendlova B, Sykorova V, Xing M. *Journal of Clinical Oncology*, 2018;36(5):438-445.

Reviewer:

Iuliana Bobanga, MD, Cleveland Clinic

In Brief

Numerous studies have confirmed the unique prognostic role of patient age in papillary thyroid cancer (PTC), starting with Crile and Hazard in 1953, who described the unfavorable prognosis of advanced patient age at diagnosis¹. Unlike any other cancer, patient age is incorporated in the AJCC staging system for papillary thyroid cancer as a staging dichotomization at 55 years of age². However, little is understood of the particular reasons why age is such a strong adverse prognostic factor in PTC. A recent analysis by Adam et al of 31,802 patients with PTC in the SEER database evaluated cancer-specific mortality at 10 years and found a linear relationship between patient age and death from PTC without an age cutoff demarcating a survival difference, challenging the current staging system of PTC³.

In addition to age and other tumor characteristics, the presence of the BRAF V600E mutation has been well known to be an oncogenic driver of PTC, associated with increased recurrence and cancer-related mortality. However, this association is not independent of aggressive tumor features⁴. BRAF V600E is also associated with older patient age at diagnosis and occurs in approximately 45% of patients with PTC^{4, 5}. The present study by Shen et al seeks to evaluate whether patient age at diagnosis is a prognostic factor for all patients with PTC, or whether BRAF V600E receptor status alters the prognostic utility of age in cancer-specific mortality⁶.

Shen et al conducted a comparative study of the relationship between patient age at diagnosis of PTC and their BRAF V600E status in a large multicenter cohort of patients (2,638 patients at 11 medical centers in six countries). The primary outcome measure was PTC-specific mortality - "death as a result of incurable PTC disease that invaded and compromised vital organs, causing the patient to die". The patients were divided in two groups: patients with wild-type BRAF (n=1,524) and patients with BRAF V600E mutation (n=1,094). Twenty patients were excluded due to failed BRAF genetic testing. A separate sub-analysis was carried out for patients with conventional PTC (CPTC), with 996 patient with wild-type BRAF and 883 patients with BRAF V600E. All patients received conventional treatment, including total or near-total thyroidectomy and other treatments such as radioactive iodine ablation as clinically indicated. The BRAF mutation status was determined after patients were surgically and medically treated and did not affect management decisions. The median follow-up time was 58 months.

The results were strikingly distinct between the two groups based on BRAF mutation status. There was a linear relationship between patient age and PTC-specific mortality in all patients when the cohort was taken together, but a steeper linear relationship in patients with BRAF

V600E. However, in patients with wild-type BRAF, PTC-specific mortality remained flat with increasing patient age. Thus, the age-associated mortality risk in PTC patients without a BRAF V600E mutation was completely lost, making age not a significant risk factor in this patient population. The analysis was adjusted for patient sex, tumor size, extrathyroidal extension, lymph node metastasis, distant metastasis and radioactive iodine treatment, and the linear relationship in the BRAF V600E group persisted. When the same analysis was performed for CPTC patients with wild-type BRAF versus CPTC patients with BRAF V600E, the results mirrored those for the entire cohort, showing a similar BRAF-V600E-dependent relationship between age at diagnosis and increased mortality risk. Age was not a risk factor for worse prognosis in CPTC patients with wild-type BRAF.

Critique

This large multicenter cohort study by Shen et al brings a significant contribution to the understanding of age as a mortality risk factor in patients with PTC. It essentially shows that the increased risk of advanced age in PTC is completely BRAFV600E-dependent. If patients do not have this mutation, age is not a risk factor for poor prognosis. Importantly, it also shows a linear relationship between increasing age and PTC-specific mortality in patients with BRAF V600E mutations, without a dichotomous cutoff age. These two conclusions challenge the current AJCC staging system for PTC, which uses an age cutoff of 55 years for higher stage and currently does not incorporate BRAF mutation status. This study also has implications in how aggressively patients with PTC should be treated based on age and BRAF mutation status. Older patients with wild-type BRAF status may be able to avoid more aggressive treatment as their outcome is similar to younger patients with wild-type BRAF status. However, the ability to perform BRAF genetic testing on all patients with PTC will be extremely costly and challenging, and many years away from widespread implementation.

A limitation of this study is the lack of evaluating other mutations, such as the TERT promoter mutation, which also confers a poor prognosis to PTC. The TERT promoter mutation is known to coexist with BRAF V600E mutations and is more common in older patients, and could confer a confounding effect on mortality risk⁶. Another limitation is the absence of incorporating other thyroid cancer, such as follicular and Hurthle cell cancer that are also stages based on age in this study⁷. Although this was a robust cohort size, due to the low mortality risk of thyroid cancer, a larger cohort and longer follow-up duration may elucidate the effect of multiple molecular markers on age as a prognostic factor for various subtypes of thyroid cancer.

Future Directions

While the association between BRAFV600E and age is further elucidated by this study, the underlying mechanism is not well understood. Particularly why older patients with BRAFV600E do worse than younger patients with the same mutation remains to be clarified. Future studies are needed to confirm the results found by Shen et al, and would also include a larger variety of thyroid cancers and have long follow-up duration.

References:

1. Crile G Jr, Hazard HB. Relationship of the age of the patient to the natural history and prognosis of carcinoma of the thyroid. *Ann Surg* 138:33-38, 1953.
2. Amin MB, Edge S, Greene FL et al, *AJCC Cancer Staging Manual* (ed 8). New York, NY, Springer, 2016.

3. Adam MA, Thomas S, Hyslop T, et al. Exploring the relationship between patient age and cancer-specific survival in papillary thyroid cancer: Rethinking current staging systems. *J Clin Oncol* 34:4415-4420, 2016.
4. Xing M; Alzahrani AS, Carson, A; et al. Association Between BRAF V600E Mutation and Mortality in Patients With Papillary Thyroid Cancer. *JAMA*. 2013;309(14):1493-1501. doi:10.1001/jama.2013.3190
5. Xing M. BRAF mutation in thyroid cancer. *Endocr Relat Cancer*. 2005;12(2):245-262.
6. Shen X, Zhu G, Liu R, Viola D, Elisei R, Puxeddu E, Fugazzola L, Colombo C, Jarzab B, Czarniecka A, Lam AK, Mian C, Vianello F, Yip L, Riesco-Eizaguirre, G, Santisteban P, O'Neill EJ, Sywak MS, Clifton-Bligh R, Bendlova B, Sykorova V, Xing M. Patient Age-associated mortality risk is differentiated by BRAF V600E status in papillary thyroid cancer. *Journal of Clinical Oncology*, 2018;36(5):438-445.
7. Haymart MR. Is BRAF V600E mutation the explanation for age-associated mortality risk in patients with papillary thyroid cancer? *Journal of Clinical Oncology*, 2018;36(5):433-434.

Additional High Yield Reading:

1. Liu R, Bishop J, Zhu G, et al. Mortality risk stratification by combining BRAF V600E and TERT promoter mutations in papillary thyroid cancer: Genetic duet of BRAF and TERT promoter mutations in thyroid cancer mortality. *JAMA Oncol* 3:202-208, 2016.
2. Shen G, Kuo Y, Liu B, Huang R, Kuang A. BRAF V600E mutation does not significantly affect the efficacy of radioiodine therapy in patients with papillary thyroid carcinoma without known distant metastases. *Clin Nucl Med*, 2018, doi: 10.1097/RLU.0000000000002142. [Epub ahead of print]