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THYROID CANCER

Papillary Thyroid Cancer with Focal Tall-Cell Changes Have Similar Disease Characteristics and Outcomes as Tall-Cell Variants of Papillary Thyroid Cancer

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Review of: Bongers PJ, Kluijfhout WP, Verzijl R, Lustgarten M, Vermeer M, Goldstein DP, Devon K, Rotstein LE, Asa AL, Brierley JD, Tsang RW, Ezzat S, Vriens MR, Mete O, Pasternak JD 2019 Papillary thyroid cancers with focal tall cell change are as aggressive as tall cell variants and should not be considered as low-risk disease. Ann Surg Oncol. Epub 2019 May 21. PMID: 31115855.

SUMMARY

Background

Despite the excellent outcomes for most patients with papillary thyroid carcinoma (PTC), some histologic variants demonstrate more aggressive behavior, as defined by higher rates of metastasis, recurrence, and resistance to treatment with radioactive iodine (RAI). The tall-cell variant of PTC, first reported in 1976, is characterized by cell height that is at least two to three times its width, eosinophilic cytoplasm, basal nuclei, and classic nuclear features of PTC and has been shown to have a higher prevalence of *BRAF* V600E mutations. There has been significant variability in its description, including the proportion of cells required to make the diagnosis of tall-cell PTC; the 4th edition of the World Health Organization classification of endocrine tumors revised the threshold value of tall-cell change as ≥30%. The intent of the current study was to compare the outcome and adverse tumor characteristics of PTCs with focal tall-cell change (<30%)with tall-cell variant PTCs (≥30%) (1).

Methods

This was a retrospective review of all patients with any reported tall-cell changes in PTC at a single institution between 2001 and 2015; only tumors >1 cm and with available follow-up data were included. Patients were compared to a control group of patients with classical PTC >1 cm with available follow-up. For this study, tall cells were defined as cells with height three times their width, an eosinophilic cytoplasm, and characteristic nuclear features of PTC. Tall-cell variants were defined as tall-cell changes occupying at least 30% of the entire tumor volume. All cases were independently reviewed by two expert pathologists. Disease persistence or recurrence was defined as histologically or cytologically confirmed structural disease present after initial treatment; increases in serum thyroglobulin without structural disease, or small indeterminate lesions, were not considered to be disease recurrence in this study.

Results

The final cohort consisted of 131 patients: 96 (73%) with focal tall-cell change and 35 (27%) with tall-cell variant PTC; 104 patients with classical PTC served as the control group. Patients with classical PTC and focal tall-cell change were younger than those with tall-cell variant PTC (mean age, 45.6, 48.5, and 55.3, years, respectively; P = 0.003), and there were differences in median tumor size (17.0 mm, 26.0

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mm, and 40.0 mm; P<0.001). The tall-cell variant and focal tall-cell group had higher rates of vascular invasion, gross extrathyroidal extension, and lymph node metastases. In the control group, 6.7% had locoregional lymph node metastasis, as compared with 14.6% in patients with focal tall-cell change and 14.3% in patients with tall-cell variant.

In a multivariate analysis, when adjusted for tumor size and gross extrathyroidal extension, the hazard ratio for persistent or recurrent disease for patients with focal tall-cell change was 2.3 (95% confidence interval [CI], 1.0–5.7; P = 0.062) and for those with tall-cell variant 3.3 (95% CI, 1.2–8.7; P = 0.020). When stratified by percent tall-cell change, the rates of persistent or recurrent disease were 2.9% (<10% change), 29.4% (10–19% change), 37.5% (20–29% change), and 37.1% (≥30% change); PTC with >10% tall-cell change had lower rates of persistent or recurrent disease as compared with those with ≥10% change (P = 0.002).

Patients with classical PTC also had a higher 5-year disease-free survival rate (92.7%) as compared with those with focal tall-cell change (76.3%; P = 0.010) and tall-cell variant (62.2%; P = 0.001). There was no difference in 5-year disease-free survival rates between patients with focal tall-cell change or tall-cell variant.

Conclusions

In this cohort, patients with PTC and focal tall-cell change had worse prognostic features as compared with patients with classical PTC and had comparable disease characteristics and rates of persistent or recurrent disease as those with tall-cell variant PTC. Furthermore, rates of persistent or recurrent disease were significantly higher in patients with ≥10% tall-cell change.

COMMENTARY

In this study, the authors demonstrate that PTC with focal tall-cell change (specifically, 10–29%) may behave as aggressively as the tall-cell variant (defined as ≥30% change) and should not routinely be considered as "low-risk" PTC (1). Based on these findings, patients with focal tall-cell change had similar rates of persistent or recurrent disease, as well as 5-year disease-free survival. Previous studies had demonstrated that tall-cell change of 30–49% had similar characteristics to tall-cell change of ≥50%; these studies provided the basis for the reclassification of the tall-cell variant of PTC to those tumors with ≥30% change by the WHO in 2017 (2,3).

The current study further supports the findings of a recent meta-analysis, which studied the characteristics of PTC with tall-cell features and compared these to classical PTC and tall-cell variant PTC (defined as ≥50% change).(4) The analysis consisted of nine studies, including 403 tall-cell variants, 325 with focal tall-cell features, and 3552 classical PTC. While the study used the former definition of a tall-cell variant (at ≥30% change), the authors did find, in a subgroup analysis, that tall-cell features of as low as 10% resulted in PTC that behaved more like the tall-cell variant than classical PTC.

Limitations of the current study include the lack of testing for mutations, such as *BRAF* V600E, that may be associated with more aggressive behavior rather than the presence of tall-cell features (5). In addition, the authors were strict with their definitions of

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tall-cell change (height greater than three times width, whereas many studies use a definition of two to three times greater) and of disease persistence or recurrence. Therefore, this study may have underestimated both the number of patients with tall-cell change and the rate of persistent or recurrent PTC.

Overall, the study suggests that continued follow-up of patients with any tall cell change should be continued and that pathologists should consider more accurate reporting of the exact percentage of tall-cell change in order to facilitate patient follow-up and the study of long-term outcomes.

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