**TERT** promoter mutations in thyroid cancer: growing evidence for a predictor of poor outcome

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In the paper “TERT promoter mutations identify a high-risk group in metastasis-free advanced thyroid carcinoma” published recently this year in *The European Journal of Cancer*, authors Bournaud *et al.* present a novel and interesting study investigating the relationship between telomerase reverse transcriptase (TERT) promoter mutations and clinical outcomes in intermediate and high-risk differentiated and poorly-differentiated thyroid cancers (1).

Since the discovery of telomeres and telomerase, large strides have been made towards understanding the relationship between telomeres, telomerase, and cancer. Telomerase is a complex consisting of TERT and an RNA template that is capable of extending telomeres, the TTAGGG tandem repeat found at the extreme ends of chromosomes. Telomeric sequences associate with telomere binding proteins to form a complex that cap and protect the ends of each chromosome, contributing to genomic stability (2). As DNA replication mechanisms cannot copy the ends of linear chromosomes, telomeres in normal human cells that do not have telomerase activity are progressively shortened with each cell replication cycle until a critical length is reached that triggers a DNA damage response and cell cycle arrest. Unsurprisingly, immortal cell lines and cancer cells have long been known to express telomerase and escape normal cell senescence (2-4).

More recently, mutations in the promoter region of TERT have been found in certain cancers, including thyroid cancer as first reported by Liu *et al.* in 2013 (5). Since then, TERT mutations have made its way into tumor genomic profiling panels such as ThyroSeq, and there has been increasing interest in determining its diagnostic utility as well as its prognostic value. While there have been previous publications that linked the presence of TERT promoter mutations with tumor aggressiveness and poor outcomes in thyroid cancers, the vast majority of these have been observational studies (6).

In the current paper, Bournaud *et al.* reported their prospective study enrolling 173 patients with “intermediate-to high-risk thyroid cancer”. This included papillary thyroid cancers (PTC), follicular thyroid cancers (FTC), and poorly differentiated thyroid cancers (PDTC) that were either stage pT3M0 with size ≥20 mm, pT4, or M1. This is a unique subgroup of patients who were at higher risk for recurrence and poorer outcomes. Patients underwent total or near-total thyroidectomy and were treated with radioactive iodine (RAI) according to American Thyroid Association guidelines. They were then restaged at about 15 months and followed yearly with biochemical and imaging tests. The mean duration of follow-up was 46 months. The tumor specimens were analyzed for the presence of TERT promoter mutations as well as BRAF exon 15, NRAS exon 3 and HRAS exon 3 mutations.

The overall prevalence of TERT promoter mutations in the study was 20.2%, which is slightly higher than previously reported rates and likely due to the selection of higher-risk patients. The authors reported a significantly higher prevalence of TERT promoter mutations in tumors with aggressive vs. nonaggressive histology (32.7% vs.
15.3%) as well as in patients with age >45 (27.5% vs. 10%). This is consistent with previous findings in the literature (5-7). Interestingly however, the prevalence of BRAF mutations was not found to be significantly different between aggressive vs. non-aggressive tumors (28.9% vs. 30.6%). A BRAF mutation was found in only 1 out of the 31 PDTCs in the cohort. In contrast, results from the sequencing of 84 PDTCs by Landa et al. showed that 33% had BRAF mutations (8). The BRAF V600E mutation is the most frequent genetic alteration in PTC, and while its utility as an independent prognosticator remains controversial, evidence exists suggesting that co-occurrence of BRAF mutations with TERT promoter mutations is associated with high clinicopathologic aggressiveness (9). The evidence presented in the current study did not suggest any association between BRAF mutations and tumor aggressiveness or outcomes, nor did it demonstrate synergistic effects with TERT promoter mutations. Therefore, it would have been interesting to look at tumors with concurrent BRAF and TERT promoter mutations.

The authors also found a significant association between TERT promoter mutations and incomplete initial response, lower probability of achieving no residual disease, and poorer event-free survival in the total study population. However, given that aggressive histological features had the same association with poor event-free survival, the authors concluded that the prognostic value of TERT promoter mutations was not independent of histology.

Unfortunately, there was no analyses that examined the surgical technique used. Some patients underwent near-total thyroidectomy, which leaves behind residual thyroid tissue that could be the source of persistent disease. It would be interesting to see if there is a significant difference between the surgical techniques used in TERT-promoter-mutated and non-mutated groups.

Recent work published by Yang et al. in the Journal of Nuclear Medicine reported that TERT promoter mutation was associated with decreased RAI avidity in distant metastatic differentiated thyroid cancer, suggesting that the difference in outcomes between TERT mutated and non-mutated groups may at least partially be explained by loss of RAI avidity in metastatic patients (10). However, this study did not consider histology, and future studies will be needed to determine whether RAI response can be predicted by presence of TERT mutation alone.

In the subgroup of patients without aggressive histology, TERT-promoter-mutated cases did have significantly more cancer-specific deaths, although the number of events was too low in this subgroup to reach statistical significance in the survival analyses (P=0.051). When analyzing only M0 patients without aggressive histology, the authors found an association between TERT promoter mutations and worse survival, though there was a lack of events in the non-mutated group to calculate a P value. This suggests that there may be a small subset of at-risk patients who have tumors with TERT promoter mutations that have not yet manifested an aggressive histopathologic appearance at the time of surgery. However, this will need to be supported with more evidence in further studies.

In conclusion, the results presented by Bouchard et al. is consistent with previous work on TERT promoter mutations in thyroid cancer and contributes to the evidence demonstrating that they are associated with poorer outcomes and more aggressive tumor histology. While it is still uncertain if its prognostic value is independent of histology, the evidence so far shows that TERT promoter mutation analysis is a useful element of tumor genomic profiles, especially in FNA samples where histology cannot be ascertained. However, the full story regarding TERT promoter mutations remains incomplete and further studies are needed to clarify their independent prognostic potential as well as their contribution to tumor aggressiveness alone and in conjunction with other cancer-associated mutations.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References


