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Editorial

EDITORIAL

Thyroid Cancer: Is It All in the Genes?

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Thyroid cancer represents one of the most biologically and clinically diverse solid malignancies. While most thyroid cancers originate from the follicular cells, the genetic alterations that drive these cancers are unique to each histologic subtype (1). Further, the behavior of thyroid cancer has a wide spectrum, from the commonly indolent and widespread papillary thyroid microcarcinoma (present in up to 35.6% of individuals at autopsy) to the uniformly rare and lethal undifferentiated thyroid cancer (2,3). Our understanding of the genetic events involved in thyroid cancer initiation and progression has grown, with some having translational implications for predicting thyroid cancer behavior and as therapeutic targets for advanced thyroid cancer (4).

In this issue of the Journal, two independent groups report interesting studies on the genetic alterations associated with radiation exposure–associated thyroid cancer in patients who had exposure to ^{131}I from the Chernobyl meltdown, and a second study reports on the prognostic utility of *BRAF V600E* mutation status—the most prevalent somatic oncogenic mutation in thyroid cancer—in patients with solitary isolated papillary thyroid cancer, which accounts for up to 80% of all thyroid cancer cases today (5,6).

A well-established risk factor for thyroid cancer is radiation exposure. While previous studies have established that certain recurrent genetic alterations occur in radiation exposure–associated thyroid cancer, the study by Efanov and colleagues provides a comprehensive analysis of gene mutations in a cohort in which thyroid radiation dose was measured (5). They report that 96.9% of 65 papillary thyroid cancers in patients from the Ukrainian-American cohort with a measurement of ^{131} I thyroid doses have somatic gene mutations (26.2% with point mutations and 70.8% with gene fusions). The type of gene mutation was also associated with the thyroid radiation dose. Gene fusions occurred at a higher frequency with a higher thyroid radiation dose (mean 1.4 Gy), and point mutations had a higher frequency in a lower thyroid radiation dose (mean 0.2 Gy). In a univariate analysis, cases with gene fusions had a lower mean age at exposure and surgery for papillary thyroid cancer and higher rates of histologic features of solid-trabecular and follicular growth pattern and extrathyroidal invasion. In a multivariable analysis, the association between the type of gene mutations and thyroid radiation dose was statistically significant. Some of the gene fusions identified (*POR-BRAF*, *MBP-BRAF*, *ZBTB8A-BRAF*, *SQSTM1-RET*, and *BANP-NTRK1*) were novel, and functional characterization of one of the gene fusions (*POR-BRAF*) showed oncogenic function in in vitro assays and activation of the MAPK pathway. This study in radiation-associated thyroid cancer provides new evidence on the pathobiology on how radiation leads to thyroid cancer. It may have therapeutic relevance given that most of the point mutations and gene fusions are known or likely to activate the MAPK pathway, which now can be targeted with various kinase inhibitors already approved for radioiodine-refractory thyroid cancer or that are currently being tested in clinical trials.

Huang and associates, in their multinational and -center study, characterized the association of somatic *BRAF V600E* mutations in thyroid cancer, building on their prior reports showing that *BRAF* mutation status is a prognostic factor for recurrence-free survival and thyroid cancer–specific mortality (6). In the current study, they focused on solitary intrathyroidal papillary thyroid cancer ($>$1 cm and $\leq$4 cm)—which accounted for 29% of the entire study cohort—and the implications of *BRAF* mutations' status to address a clinically important and controversial question on the extent of thyroidectomy alternatives (hemithyroidectomy, total, or near total thyroidectomy) currently recommended in such patients (7). The surgical treatment options are controversial because there is no level 1 clinical evidence that shows the superiority of any of the approaches relative to the risk of recurrent/persistent disease and, understandably, disease-specific mortality given the low rate of such an event in patients with low-risk papillary thyroid cancer. The primary end point in this retrospective study was disease recurrence as defined by serum thyroglobulin, structural recurrence on ultrasound imaging, and/or pathology. Huang and associates report a higher rate of locoregional thyroid cancer recurrence in tumors with *BRAF V600E* mutations as

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compared with wild-type tumors in patients who all had total thyroidectomy with or without lymph node dissection and postoperative ^{131}I. Interestingly, in comparison with high-risk papillary thyroid cancer, solitary intrathyroidal papillary thyroid cancer with *BRAF V600E* mutation had similar rates of recurrence. Further, the association between *BRAF V600E* mutation and higher recurrence was seen in all tumor size increments analyzed. A high negative predictive value of 97% to 100% was observed for recurrence when there was no *BRAF V600E* mutation. Based on their findings, Huang and colleagues concluded that a personalized or tailored treatment approach could be undertaken based on *BRAF V600E* mutation testing in patients with solitary intrathyroidal papillary thyroid cancer. Given that the entire cohort in this retrospective study had a total thyroidectomy, it is difficult to propose that individuals with no mutation can have a hemithyroidectomy and be sure their risk of recurrence would be low or nil based on the negative predictive value. Similarly, given the locoregional recurrences in both the thyroid bed and lymph node (it was not specified whether in the central neck and/or lateral neck), how does one then use this information to perform prophylactic lymph node dissection in individuals with solitary intrathyroidal papillary thyroid cancer that is positive for *BRAF* V600E mutation, expect a lower recurrence rate as a result of aggressive treatment (or vice versa, not perform lymph node dissection in *BRAF* wild-type cases), and be certain that patients will have similar locoregional recurrence as in this study? The same can be said for selecting patients who would require radioiodine ablation with ^{131}I.

In summary, both studies provide new, important information on the pathobiology and clinical relevance of gene mutations that may impact patient care—if future well-designed studies validate these findings and exploit these genetic changes for prognostication and as treatment targets.

Note

The author has no conflicts of interest to disclose.

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