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REVIEW

The prognostic power of gene mutations in thyroid cancer

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Abstract

The introduction and generalization of next-generation sequencing techniques have significantly increased the identification of mutations in thyroid tumors from multiple patient cohorts. The understanding of the association between specific mutations and clinical outcomes is gradually leading to individualizing the care of patients with thyroid cancer. $BRAF^{V600}$ is the most common mutation seen in thyroid cancer patients and unequivocally predicts malignancy, but when considered in isolation, it is not recommended to be used as an independent prognostic factor. Mutations in *RAS* are the second most common alterations in thyroid cancer but can be found in benign and malignant lesions. Rearrangements involving receptor tyrosine kinases, primarily RET, are found in a subset of thyroid tumors without mutations in either *BRAF* or *RAS*. The assessment of additional mutations is increasingly employed in thyroid cancer prognostication. The coexistence of *BRAF* with alterations in genes such as *PIK3CA*, *TERT* promoter, or *TP53* is associated with less favorable outcomes. Similar studies have also shown that additional oncogenic mutations in *RAS*-mutant thyroid carcinoma, such as those affecting the *EIF1AX* gene, likely predict a more aggressive clinicopathologic behavior. Overall, emerging evidence suggests that the co-occurrence of specific alterations in defined genes with *BRAF* or *RAS* mutations can become prognostic tools and useful predictors of thyroid tumor aggressiveness.

Keywords: thyroid cancer; genomic; prognosis

Introduction

Thyroid cancer is the most common malignancy of the endocrine system. Papillary thyroid carcinoma (PTC) is the most common thyroid carcinoma, accounting for almost 80% of cases; 12% of thyroid carcinomas have follicular (FTC) or oncocytic (OC; previously Hurthle cell) histology, <3% are poorly differentiated thyroid carcinoma (PDTC) and <2% are anaplastic thyroid carcinoma (ATC) (1). Differentiated thyroid cancers (DTC) encompass PTC, FTC, and OC, whereas PDTC and ATC are less differentiated and more aggressive. Our knowledge of the genomic landscape of thyroid cancer has dramatically improved over the last decade. The landmark study by The Cancer Genome Atlas (TCGA) showed that PTC is dependent on the MAPK pathway activation via mutually exclusive mutations of *BRAF*, *RAS* or through gene rearrangements involving *RET* and other receptor tyrosine kinases (RTK) (2). Even though all these alterations activate MAPK signaling, *BRAF*-mutant, *RAS*-mutant, and *RET*-rearranged thyroid cancers have different behaviors. To date, several studies have aimed to establish genotype–phenotype correlations in patients with thyroid cancer, which has led to individualizing the care of patients with thyroid cancer, specifically patients with advanced thyroid cancer. This review article describes gene mutations in follicular cell-derived thyroid cancer with known prognostic power. Oncocytic

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carcinoma has a different molecular foundation, including widespread chromosomal haploidization and mutations in the mitochondrial genome, none of which have yet been assessed for their prognostic value and hence not included in this review article.

BRAF mutations

BRAF mutations predominantly occur at codon V600 and are the most common alterations of PTC, as they are identified in around 60% of cases (2). Mutations in the *BRAF* gene drive thyroid cancer transformation via activation of the MAPK pathway. The $BRAF^{V600E}$ mutation was initially associated with aggressive clinicopathologic features, including extrathyroidal extension, lymph node metastases (LNM), advanced stage, and poor clinical outcomes. In a meta-analysis of 19 studies on clinicopathologic features of papillary thyroid microcarcinoma (PTMC) with information on *BRAF* mutation, $BRAF^{V600E}$ mutation was significantly associated with extrathyroidal extension, multifocality, LNM, and advanced stage (3). In a retrospective multicenter study (16 medical centers in eight countries) on 2099 PTC patients with a median follow-up of 36 months, $BRAF^{V600E}$ mutation was associated with a higher risk of recurrence (47.71 vs 26.03 per 1000 person-years) with an unadjusted HR of 1.82. This remained significant after adjustment for patient age, sex, tumor size, extrathyroidal extension, LNM, and multifocality. Another retrospective multicenter study (11 centers in six countries) of 2,638 PTC patients with a median follow-up of 58 months showed synergism between LNM and $BRAF^{V600E}$; the disease recurrence rate was 10% vs 39.6% in non-LNM vs LNM patients, in the *BRAF*-positive group. The risk of mortality from cancer in this study was significantly higher in patients with LNM and $BRAF^{V600E}$ (2.9% in patients only with LNM, 1.2% in patients with only *BRAF* vs 7.8% in patients with both $BRAF^{V600E}$ and LNM; $P < 0.001$) (4).

However, other studies have questioned the value of the $BRAF^{V600E}$ mutation as an independent prognostic factor (5, 6, 7, 8, 9). In a retrospective multicenter study (13 medical centers in 7 countries) of 1849 patients with PTC and a median follow-up of 33 months, $BRAF^{V600E}$ mutation was associated with increased cancer-related mortality. However, when LNM, extrathyroidal extension, and distant metastases were included in the model, the association of $BRAF^{V600E}$ with mortality was no longer statistically significant (10). In a retrospective study of 101 patients with PTMC (72 $BRAF^{V600E}$ positive), there was no statistically significant association between $BRAF^{V600E}$ and extrathyroidal extension, multifocality, and LNM (7). In another retrospective study of 631 PTC patients (38.4% $BRAF^{V600E}$ positive), with an average of 83 months follow-up, $BRAF^{V600E}$ mutation was not associated with extrathyroidal extension, lymph node, and distant metastases. Disease-free survival was not different in patients with vs without *BRAF* mutation (6). In a retrospective study, 40 patients with PTMC with clinically significant lateral neck LNM and 71 patients with PTMC and no LNM were included. *BRAF* alterations were detected in 61% of the tumors. $BRAF^{V600E}$ mutation did not predict clinically significant lateral neck LNM (8). Another retrospective study of 429 patients with PTC (9) showed no significant association between $BRAF^{V600E}$ and more aggressive disease.

Although the association reported in multiple studies between $BRAF^{V600E}$ and disease recurrence, the clinical application of $BRAF^{V600E}$ alone as a prognostic marker is limited due to low specificity. Boucai *et al.*, in a study using TCGA data, showed that *BRAF* mutant tumors are heterogeneous. This study compared two subgroups of $BRAF^{V600E}$ mutant tumors based on their thyroid differentiation score (TDS): those with a preserved expression of thyroid differentiation genes (BRAF-TDS^{hi}) vs their counterparts with decreased expression of thyroid differentiation genes (BRAF-TDS^{lo}). $BRAF^{V600E}$ PTC tumors with downregulation of iodine metabolism genes (BRAF-TDS^{lo}) were larger ($P = 0.002$) and had higher T stage ($P = 0.002$) and more LNM ($P = 0.042$) and distant metastases ($P = 0.043$). There was no significant survival difference between the two groups ($P = 0.62$). Two out of 21 (9.5%) BRAF-TDS^{hi} patients had an incomplete response to therapy, whereas in the BRAF-TDS^{lo}, 28/76 (37%) patients had an incomplete response to therapy ($P < 0.01$) (11).

Overall, the 2015 American Thyroid Association guidelines recommended not using $BRAF^{V600E}$ in isolation to guide the management of patients with low-risk thyroid carcinoma due to low positive predictive value (PPV) (1). However, the coexistence of *BRAF* with other oncogenic mutations, such as those in *PIK3CA*, *TERT* promoter, or *TP53*, is associated with less favorable outcomes, as discussed later in this review.

RAS mutations

Point mutations in the *RAS* genes (*NRAS*, *HRAS*, and *KRAS* isoforms) are DTC's second most common genetic alterations. Mutations in *RAS* genes drive thyroid cancer transformation via activation of the MAPK pathway but have lower oncogenic potential than $BRAF^{V600E}$. $BRAF^{V600E}$-mutant thyroid cancers (enriched in classic and tall cell subtypes) are more frequently invasive than *RAS*-mutant tumors and show a tropism to regional lymph nodes. *RAS*-mutant DTCs are typically encapsulated and rarely spread; when they do, e.g. in metastatic FTCs and PDTCs, they bypass lymph nodes and instead they more frequently affect bone and lung sites (12, 13). *RAS* mutations can be found in different thyroid tumors, including 10–20% of PTC, particularly in the follicular variant of PTC (fvPTC), 40–50% of FTC, and 20–40% of PDTC and ATC (14). The lower allelic frequency of *RAS* mutations in follicular adenomas than carcinomas might explain why they are found in benign

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and malignant lesions (15). The use of *RAS* mutation as a molecular biomarker to diagnose thyroid cancer and to predict the prognosis is limited due to the heterogeneity described earlier. Instead, the identification of additional mutations in RAS-driven disease can inform prognosis. Some alterations, such as mutations in the *TERT* promoter and PI3K pathway effectors, occur across multiple DTCs, whereas others, such as mutations in *EIF1AX*, are strongly associated with *RAS*-mutant disease (16, 17). Studies assessing these additional alterations are summarized in the next section.

RET rearrangements

RET/PTC rearrangements generate fusion oncoproteins that reactivate RET. RET rearrangements are generated by the fusion of the catalytic domain of the tyrosine kinase receptor RET to the 5' terminal regions of heterologous genes. RET/PTC is associated explicitly with PTC and not with other types of thyroid cancer (18). Based on the TCGA study, the occurrence of RET/PTC in the PTC cohort is 6.8% (2).

Two groups of PTC harbor RET rearrangements: sporadic and radiation-induced. After the Chernobyl accident in 1986, there was a significant increase in the incidence of PTC in children, and the main driver was RET/PTC rearrangement (19, 20, 21, 22). Radiation-induced PTC with RET/PTC rearrangement has been reported to present at a more advanced T stage and have a higher probability of LNM. RET/PTC3 (NCOA4-RET) is predominant in radiation-induced PTC, and this rearrangement has been connected to the solid variant of PTC. RET/PTC1 (CCDC6-RET) is predominant in sporadic PTC and is strongly associated with the classic subtype (20, 23, 24). Radiation-induced PTC does not represent the general population with PTC and RET/PTC rearrangement. Studies on PTC with sporadic RET/PTC rearrangement have shown that these tumors are slow growing and do not usually progress toward more aggressive tumors like poorly differentiated thyroid carcinoma (25, 26). In pediatric patients, which are cohorts enriched for RTK fusions, RET/PTC-driven tumors have been associated with increased metastatic capacity and persistent disease compared to their *BRAF*- or *RAS*-mutant counterparts (27), whereas these differences are not observed in adult patients.

Additional mutations in thyroid cancer prognostication

Next-generation sequencing studies have shown that compared to DTC, PDTC and ATC display an extended set of mutations but typically harbor driver alterations in *BRAF*, *RAS*, or *RET* oncogenes (28, 29, 30). This suggests that PDTCs/ATCs can arise from PTCs/FTCs by accumulating key additional genetic abnormalities. The idea of a continuum in disease progression can thus be used to inform genomics-driven prognostication in DTC patients. Mutations in genes for which the most robust studies exist are discussed below, and a subset of them is highlighted in Table 1.

TERT promoter mutations

Mutations in the proximal promoter of the *TERT* (telomerase reverse transcriptase) gene were initially discovered in melanomas (31, 32) and shortly after identified as frequent events in various tumor types, such as gliomas, hepatocellular, urothelial, and thyroid carcinomas (33, 34, 35, 36). *TERT* promoter mutations occur in the noncoding portion of the gene at either c.-124C>T or c.-146C>T, reactivating *TERT* transcription in thyroid cancer cells (36, 37, 38). *TERT* promoter mutations are relatively frequent events in DTCs, suggesting they could serve as biomarkers of disease progression. The fact that they occur rather early in tumor evolution implies that they likely enhance the proliferative properties of *BRAF*- or *RAS*-driven thyroid cancer clones.

The presence of a *TERT* promoter mutation in material from fine needle aspiration biopsies has been shown to offer a diagnostic specificity for malignancy close to 100%. It can help refine the assessment of thyroid nodules with an indeterminate cytology (39, 40, 41, 42, 43). Furthermore, multiple studies provided evidence of the prognostic value that the assessment of *TERT* mutations, either alone or, most efficiently, combined with *BRAF* or *RAS*, can provide for DTC patients. In a group of 51 PTC patients, Liu and colleagues showed that *TERT* promoter mutations were associated with metastatic disease and decreased survival (44). Melo *et al.* studied a cohort of 332 PTCs and observed that *TERT* mutations had an independent prognostic value: they were associated with increased rates of distant metastases, persistent disease, and disease-specific mortality (45). The cooperative effects that the co-occurrence of a *BRAF* or *RAS* mutation plus a *TERT* promoter mutation has in predicting poorer clinical outcomes have been widely studied, and it is now firmly established. In a cohort of 507 PTC patients, Xing and colleagues reported that coexisting $BRAF^{V600E}$ and $TERT^{-124C>T}$ mutations were associated with high-risk clinicopathologic characteristics, including increased recurrence rates and decreased recurrence-free survival (46). Several other studies in independent PTC cohorts showed associations of *BRAF* + TERT mutations with disease recurrence, advanced tumor stage, presence of metastases, and higher mortality risk (16, 47, 48, 49, 50, 51). *TERT* promoter mutations have also been linked to lower thyroid differentiation levels and subsequent higher refractoriness to standard radioiodine therapy in $BRAF^{V600E}$-driven PTC (11, 52, 53). Finally, *TERT* mutations also cooperate with *RAS*-driven DTCs toward tumor aggressiveness. Song *et al.* retrospectively assessed a group of 690 patients with FTC and showed

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Table 1 Key studies using genomic characterization for differentiated thyroid cancer prognostication.

Reference	DTC type	DTC cohort, *n*	Gene(s) and mutations	Main findings
Ricarte-Filho *et al.* 2009 (66)	PTC, others	33	*AKT1*, *PIK3CA*	*AKT1* and *PIK3CA* mutations first reported in RAI refractory/metastatic PTCs, predominantly tall cell subtype
Melo *et al.* 2014 (45)	PTC + FTC	402	*TERT* promoter	*TERT* promoter mutations are associated with persistent and metastatic disease in PTC and FTC
Xing *et al.* 2014 (46)	PTC	507	$BRAF^{V600E}$ + *TERT* promoter	Co-occurrence of $BRAF^{V600E}$ and $TERT^{c.-124C>T}$ mutations associate with decreased recurrence-free survival of PTC patients
Song *et al.* 2016 (16)	PTC + FTC	551	$BRAF^{V600E}$ + *TERT* promoter; RAS + *TERT* promoter	Coexistence of *TERT* promoter mutations with either $BRAF^{V600E}$ or *RAS* alterations associate with increased disease-specific mortality
Pappa *et al.* 2021 (67)	PTC, $BRAF^{V600E}$ mutant	225	PI3K pathway (*PIK3CA*, *AKT1*, others)	Oncogenic mutations in PI3K pathway effectors are independent predictors of disease-specific mortality in $BRAF^{V600E}$-driven PTCs
Nguyen *et al.* 2022 (76)	PTC, metastatic	307	*TERT* promoter, *TP53*, *CDKN2A*, others	Pancancer analysis of metastatic tumors shows higher frequencies of mutations in *TERT*, *TP53* and *CDKN2A* in metastatic PTC (compared to PTC profiled by the TCGA)
Boucai *et al.* 2023 (68)	PTC, FTC, struma ovarii	21	*RBM10* and SWI/SNF gene mutations; chromosome 1q gain	Alterations in *RBM10*, SWI/SNF members and chromosome 1q are enriched in nonresponders to RAI (compared to exceptional responders)
Bikas *et al.* 2023 (17)	PTC + FTC, *RAS* mutant	69	*TERT* promoter, *PTEN*, SWI/SNF genes, others	Presence of oncogenic mutation in specific genes predict disease-specific mortality in *RAS*-driven DTCs

DTC, differentiated thyroid cancer; FTC, follicular thyroid cancer; PTC, papillary thyroid cancer; RAI, radioactive iodine; TCGA, The Cancer Genome Atlas.

that combined *RAS* and *TERT* promoter mutations showed a higher recurrence risk than either of those mutations in isolation (54). Shen and colleagues, on their part, led a multicenter effort and demonstrated that PTC patients whose tumors harbored RAS + TERT mutations showed worse clinicopathological outcomes, notably higher risks of recurrence (55). Song *et al.* later studied a cohort of 551 DTCs, including 48 *RAS*-mutant tumors, and showed that, similarly to their $BRAF^{V600E}$ + TERT counterparts, *RAS* + TERT mutations associated with decreased disease-free and disease-specific survival in DTC patients (compared to *RAS*-alone) (16).

Overall, the presence of a *TERT* promoter mutation is a bona fide marker of poor prognosis (for a detailed review and meta-analyses on this topic, see (56, 57, 58, 59)), and it is now gradually incorporated into the clinical guidelines for managing thyroid cancer patients (1).

RAS + *EIF1AX* mutations

Mutations in *EIF1AX*, a gene encoding a member of the translation initiation complex, were first reported in a small subset of the PTCs (2), and shortly after identified as much more frequent events in the PDTCs and ATCs (28, 29). The pattern of mutations of *EIF1AX* in advanced diseased showed a remarkable association with the presence of *RAS* mutations, suggesting a cooperativity among those two genetic lesions that were later mechanistically dissected (60). *EIF1AX* alterations also occur in uveal melanomas (61), but a specific mutation at a splice site at alanine 113 (A113splice) is exclusive of thyroid tumors.

Isolated *RAS* or *EIF1AX* mutations associate with follicular-patterned thyroid neoplasms, including benign follicular adenomas (FA), fvPTC, and FTC. The fact that the *RAS* + *EIF1AX* combination was enriched in PDTC and ATC prompted various groups to evaluate its role in the stratification of early disease. Karunamurthy and colleagues surveyed the prevalence of *EIF1AX* mutations across a series of thyroid specimens. They found that 4/4 carcinomas carrying an *EIF1AX* mutation did so at the A113splice position, and 3/4 had coexisting mutations in *NRAS* (62). More recently, three groups assessed the pattern of *EIF1AX* mutations in thyroid cancers. Gargano *et al.* reported, in a series of surgically removed nodules, a risk of malignancy of 100% for specimens with *EIF1AX* mutations (most of them at A113splice) when coexisting with additional mutations (overwhelmingly at *NRAS*, *HRAS*, or *KRAS*) (63). Karsogliu-French and colleagues evaluated 31 consecutive patients with *EIF1AX* mutations: the 18 specimens without coexisting mutations in *RAS* genes were enriched in benign disease (12/18 were FA, 3/18 hyperplastic nodules (HN) and 3/18 FTC), whereas the 13 *EIF1AX* + *RAS* samples showed primarily malignant phenotypes (6/13 PTC, 3/13 ATC, 2/13 NIFTP, 1/13 FA, and 1/13 HN) (64). Bandargal and colleagues, on their part, reported a multicenter series of 42 surgically resected nodules that harbored an *EIF1AX* mutation and showed that every single thyroid specimen with coexisting *EIF1AX* + *RAS* mutations was a carcinoma (65). Overall, there is growing evidence

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suggesting that, although *RAS* or *EIF1AX* mutations can be found in isolation in a subset of FA, their co-occurrence likely pushes these lesions toward malignancy, typically prompting FTC, encapsulated or infiltrative fvPTC histotypes. Because of their low frequency in DTCs, so far no large studies have comprehensively evaluated whether *EIF1AX*-mutant tumors behave significantly differently than their counterparts with alternative genomic alterations.

Other mutations in DTC prognostication

The presence in DTCs of additional mutations in pathways that have been shown to promote cancer progression is rare but conveys clear prognostic significance. Ricarte-Filho *et al.* reported mutations in *AKT1* and *PIK3CA* (key effectors of the PI3K/AKT pathway) in $BRAF^{V600E}$-driven radioiodine-refractory metastatic/recurrent DTCs. PI3K/AKT pathway mutations were predominantly found in biopsies obtained from recurrent or metastatic sites and were enriched in PTCs with tall cell histotypes (66). In a cohort of 225 $BRAF^{V600E}$-mutant PTCs, Pappa and colleagues showed that the presence of additional mutations in PI3K pathway effectors were independent predictors of disease-specific mortality (67). Song *et al.* confirmed the role of mutations in the PI3K pathway in increased mortality in a cohort of 50 $BRAF^{V600E}$-driven advanced PTCs and suggested that alterations in histone methyltransferase genes also had prognostic value (68). Bikas and colleagues, on their part, reported that additional mutations targeting several pathways predict disease-specific mortality in a cohort of 69 *RAS*-driven DTCs (17). In addition, two recent side-by-side publications from the same group demonstrated the power of comprehensive molecular testing in predicting tumor recurrence and refining the current methods for risk stratification of thyroid cancer patients (69, 70).

Regarding the molecular determinants of response to radioactive iodine (RAI) treatment, Boucai *et al.* compared a unique cohort of metastatic thyroid cancer patients with exceptional structural responses to RAI therapy vs matched nonresponders. Exceptional

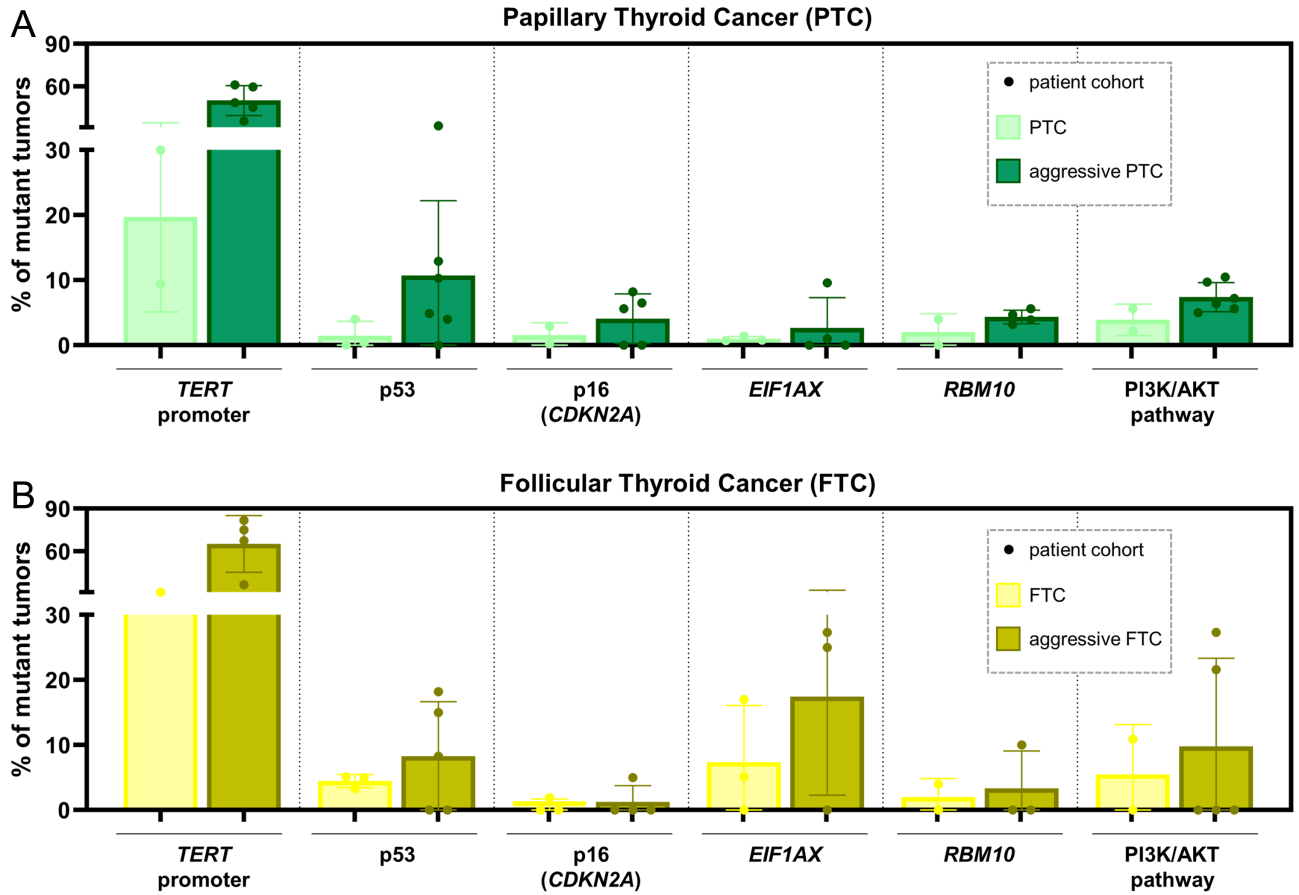

Figure 1

Comparison of the prevalence of mutations in key genes and pathways in differentiated thyroid cancer (DTC) patients vs DTC cohorts with aggressive/metastatic behavior in (A) papillary thyroid cancer (PTC) and (B) follicular thyroid cancer (FTC). Each dot represents an independent patient cohort. Data were obtained from studies employing next-generation sequencing technologies in nonoverlapping thyroid cancer cohorts between 2014 and 2022 (2, 30, 72, 73, 74, 75, 76, 77, 78, 79, 80). Only studies with at least ten patients were included to avoid small sample size bias.

responders were enriched in RAS-like alterations (e.g. mutations in *RAS* genes or in $BRAF^{K601E}$), whereas $BRAF^{V600E}$ drove tumors from nonresponders. The latter also harbored *RBM10* and SWI/SNF gene mutations and chromosome 1q gains (71).

Besides the prognostic role of mutations in *loci* such as the *TERT* promoter, *EIF1AX,* or in effectors of the PI3K/AKT pathway in the context of *BRAF*- or *RAS*-mutant tumors, there is indirect evidence of other genetic alterations as biomarkers of DTC severity. These come from tumor sequencing studies in which rare subsets of PTC and FTC with aggressive/metastatic properties were evaluated (*n* (PTC) = 18–379; *n* (FTC) = 11–60 patients) (30, 72, 73, 74, 75) as well as from a recent pan-cancer study of metastatic disease which included 307 PTCs (76). In Fig. 1, we compared the prevalence of selected mutations, typically more frequent in PDTC/ATC, in aggressive DTC cohorts vs unselected DTC counterparts (typically more indolent) (2, 30, 72, 73, 74, 75, 76, 77, 78, 79, 80). The former comparison suggests that mutations in other *loci*, such as *TP53*, *CDKN2A* (p16), and *RBM10*, likely prime a subset of PTCs (Fig. 1A) and FTCs (Fig. 1B) toward more aggressive behavior.

Finally, apart from gene mutations, differences in the expression of messenger RNAs (mRNAs) and microRNAs (miRNAs) have been suggested as potential tools to stratify PTC patients. As detailed in the previous section, Boucai and colleagues stratified, based on thyroid differentiation scores, the 227 *BRAF*-mutant PTCs from the TCGA study into the BRAF-TDS-high vs the BRAF-TDS-low subgroups. The authors showed that the transcriptomes of the BRAF-TDS-high tumors were more akin to RAS-like PTCs, which tend to maintain the thyroid follicular architecture better. They also showed that, compared to BRAF-TDS-low, the BRAF-TDS-high group overexpressed genes related to cell polarity, such as *CDH16* and *PDHD1-L1*, as well as miRNAs targeting nodes in the TGF-β signaling pathway (11). Nieto *et al.* also analyzed the TCGA dataset, associated mRNA levels of *FN1*, *ITGA3*, and *MET* genes, as well as of miRNAs miR-486 and miR-1179 with recurrence of BRAF-like PTCs, and provided functional validation *in vitro* systems (81). The latter builds upon the abundant literature assessing the clinical and biological implications of specific miRNAs in thyroid cancer (82, 83, 84, 85, 86, 87), although so far, this knowledge is not applied in routine prognostication.

In summary, alterations in *BRAF*, *RAS*, and *RET* are initiating events in thyroid tumors and determine some of their features. However, the use of genomic information for prognostication purposes typically requires the evaluation of a larger set of mutations in other genes which have been shown to play a role in thyroid cancer progression. In this regard, mutations in the *TERT* promoter, *EIF1AX* (in *RAS*-mutant disease) and in effectors of the PI3K/AKT pathway are good candidates to become useful routine biomarkers in thyroid cancer prognostication. Advancing knowledge in prognostic implications of different mutations has helped clinicians to individualize the care of patients with thyroid cancer. Intense follow-up visits and cross-sectional imaging are routinely recommended for patients whose tumors have specific combinations of oncogenic alterations, while less aggressive follow-up visits are usually recommended in patients with less aggressive mutations. Advancing knowledge on the genomic landscape of thyroid cancer has also led to the development of targeted systemic treatment in patients with advanced thyroid cancer in recent years.

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