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Tumor Genotype Determines Phenotype and Disease-related Outcomes in Thyroid Cancer:

A Study of 1510 Patients

Linwah Yip, MD[†], Marina N. Nikiforova, MD[†], Jenny Y. Yoo, MD^{*}, Kelly L. McCoy, MD^{*}, Michael T. Stang, MD^{*}, Michaele J. Armstrong, PhD^{*}, Kristina J. Nicholson, MD^{*}, N. Paul Otori, MD[†], Christopher Coyne, MD[‡], Steven P. Hodak, MD[‡], Robert L. Ferris, MD, PhD[§], Shane O. LeBeau, MD[‡], Yuri E. Nikiforov, MD, PhD[‡], and Sally E. Carty, MD[†]

^{*}Department of Surgery, Division of Endocrine Surgery, University of Pittsburgh, Pittsburgh, PA

[†]Department of Pathology, University of Pittsburgh, Pittsburgh, PA

[‡]Department of Medicine, Division of Endocrinology, University of Pittsburgh, Pittsburgh, PA

[§]Department of Otolaryngology, University of Pittsburgh, Pittsburgh, PA

Abstract

Objectives—To correlate thyroid cancer genotype with histology and outcomes.

Background—The prognostic significance of molecular signature in thyroid cancer (TC) is undefined but can potentially change surgical management.

Methods—We reviewed a consecutive series of 1510 patients who had initial thyroidectomy for TC with routine testing for *BRAF*, *RAS*, *RET/PTC*, and *PAX8/PPARG* alterations. Histologic metastatic or recurrent TC was tracked for 6 or more months after oncologic thyroidectomy.

Results—Papillary thyroid cancer (PTC) was diagnosed in 97% of patients and poorly differentiated/anaplastic TC in 1.1%. Genetic alterations were detected in 1039 (70%); the most common mutations were *BRAFV600E* (644/1039, 62%), and *RAS* isoforms (323/1039, 31%). *BRAFV600E*-positive PTC was often conventional or tall cell variant (58%), with frequent extrathyroidal extension (51%) and lymph node metastasis (46%). Conversely, *RAS*-positive PTC was commonly follicular variant (87%), with infrequent extrathyroidal extension (4.6%) and lymph node metastasis (5.6%). *BRAFV600E* and *RET/PTC*-positive PTCs were histologically similar. Analogously, *RAS* and *PAX8/PPARG*-positive PTCs were histologically similar. Compared with *RAS* or *PAX8/PPARG*-positive TCs, *BRAFV600E* or *RET/PTC*-positive TCs were more often associated with stage III/IV disease (40% vs 15%, $P < 0.001$) and recurrence (10% vs 0.7%, $P < 0.001$; mean follow-up 33 ± 21 mo). Distant metastasis was highest in patients with *RET/PTC*-positive TC (10.8%, $P = 0.02$).

Reprints: Linwah Yip, MD, Department of Surgery, Division of Endocrine Surgery, University of Pittsburgh, 3471 Fifth Ave, Kaufman Bldg, Ste 101, Pittsburgh, PA 15213. yipl@upmc.edu.

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Conclusions—In this large study of prospective mutation testing in unselected patients with TC, molecular signature was associated with distinctive phenotypes including cancers, with higher risks of both distant metastasis and early recurrence. Preoperative genotype provides valuable prognostic data to appropriately inform surgery.

Keywords

BRAF; molecular testing; *RAS*; thyroid; thyroid cancer

Because of the rising incidence of thyroid cancer (TC) and its unique diagnostic challenges, the costs associated with TC are escalating.¹ TC is typically diagnosed during the evaluation of thyroid nodules, and fine needle aspiration biopsy (FNAB) classifies thyroid nodules by cytologic characteristics into 1 of the categories defined by the 6-tiered Bethesda System for Reporting Thyroid Cytopathology.² Currently, up to 25% of FNAB specimens are diagnosed into 1 of the indeterminate Bethesda categories (III, IV, and V), and surgery is often required for definitive diagnosis.^{3,4} Molecular testing for a panel of 7 genetic markers that are associated with TC has been demonstrated to improve diagnostic specificity, to appropriately direct extent of initial thyroidectomy, and to reduce health care costs but is still considered controversial.^{5–7}

Available staging systems to predict disease-specific outcomes such as recurrence and survival are imperfect and rely on variables that are typically available only after resection.⁴ Enhanced preoperative risk stratification can potentially reduce the need for reoperative surgery, which can be associated with a higher rate of operative complications. In routine preoperative use of the 7-gene panel as a diagnostic adjunct, we have previously reported that particular markers can be associated with specific histologic characteristics.

*BRAF*V600E can be associated with central compartment lymph node metastasis (CLNM) and other aggressive features.^{8,9} Preoperative detection of *RAS* was associated with an 83% risk of histologic malignancy and particularly with follicular variant papillary thyroid cancer (FV-PTC, 88%).^{10,11} FV-PTC is also commonly associated with preoperative detection of the *PAX8/PPARG* rearrangement.¹² Whether disease outcomes are associated with the specific mutation results from the 7-gene panel has not yet been comprehensively evaluated. The study objective was to correlate TC genotype to histology and to disease-related outcomes including recurrence and survival.

METHODS

Patients

After Quality Initiative/Quality Assurance institutional review board approval, we conducted a single institution retrospective study of the perioperative data retrieved from the systemwide electronic medical record for all consecutive patients who received thyroidectomy for histologic papillary thyroid cancer (PTC) from February 1, 2007 to July 1, 2013 (QIRB #1057). Preoperative cervical ultrasound with lymph node mapping and ultrasound-guided FNAB were routinely performed for thyroid nodules per the American Thyroid Association (ATA) guidelines.^{4,13} Thyroidectomy was performed algorithmically for clinical, radiographical, cytological, and molecular results as previously described.⁶

Extent of lymphadenectomy was determined by assessment of malignancy potential on preoperative ultrasonography and by intraoperative findings. Lateral compartment (levels 2–5) lymph nodes with suspicious ultrasound features including rounded appearance, cystic changes, loss of fatty hilum, and/or microcalcifications were biopsied preoperatively. If the results were positive for metastatic disease, selective compartment-oriented lymph node dissection was performed. Postoperative radioactive iodine ablation and degree of thyroid stimulating hormone (TSH) suppression were determined by clinical and histologic results per the ATA guidelines.^{4,13} Frequency and modality of surveillance including serum thyroglobulin and thyroglobulin antibody levels, cervical ultrasonography, and whole body I-131 imaging were directed by clinician's concern for recurrence and guideline recommendations.^{4,13}

Protocol for Prospective Molecular Testing

Molecular testing for a panel of markers that included *BRAFV600E*, *BRAFK601E*, *NRAS* codon61, *HRAS* codon61, *KRAS* codons12, and 13-point mutations, *RET/PTC1*, *RET/PTC3*, and *PAX8/PPARG* rearrangements was prospectively performed in all study patients for the following indications: (1) preoperatively for all in-house FNAB results that were positive for malignancy or in the indeterminate Bethesda cytology categories of atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS, III), follicular neoplasm (FN, IV), and suspicious for malignancy (V); (2) preoperatively by request for selected nodules with either benign or nondiagnostic cytology results; and (3) postoperatively in all histologic malignancies larger than 3 mm in size in the absence of previous molecular testing of FNAB cytology. In patients who had multifocal TC and mutation testing of more than 1 lesion, only the focus with more aggressive histologic features such as larger size or presence of extrathyroidal extension was included in further analysis.

Disease Outcomes

Pathologic confirmation of regional or distant metastatic disease after either reoperation or FNAB was classified as persistent (<6 months after initial surgery) or recurrent (≥ 6 months after initial surgery) disease.

Data Analysis

χ^2 was used to examine associations between categorical variables and unpaired 2-tailed Student *t* test was used to identify correlation between continuous variables. Kaplan-Meier and logistic regression analysis was performed using GraphPad Prism (GraphPad Software, La Jolla, CA).

RESULTS

A total of 1510 patients with TC were examined. Women comprised the majority of the cohort (77%) and mean age at surgery was 49.2 ± 15.8 years. Histologic PTC was diagnosed in 97% of patients. Poorly differentiated and anaplastic TCs were present in only 0.5% and 0.6% of patients, respectively. Five patients (0.3%) had medullary TC that was nonhereditary in each case. Multifocal disease or extrathyroidal extension was present in

51% and 30% of patients, respectively. The majority (66%, 1003 patients) had at least 1 central compartment lymph node histologically evaluated (mean number of central compartment lymph nodes evaluated, 5.4 ± 5.1), and 40% of the 1003 patients had CLNM. Lateral compartment lymph node metastasis (LLNM) was identified preoperatively in 138 patients (9%), and selective lateral neck dissection was performed concurrently with initial thyroidectomy in all 138 patients (Table 1).

Molecular testing using the 7-gene panel identified an alteration in 69% of patients ($n = 1039$) and no tumor had more than 1 mutation. TC positive for *BRAFV600E* was identified in 42.6% (644) of patients (Fig. 1). Other *BRAF* variants were identified including K601E in 12 patients (0.9%) and a codon 582–598 duplication in 1 patient. After *BRAFV600E*, *RAS* mutations were the next most common genetic alteration and included mutations in *NRAS* 61 (225 patients, 14.9%), *HRAS* 61 (89 patients, 5.9%), and *KRAS* 12/13 (9 patients, 0.9%). Rearrangements were less frequently identified and the incidence of *RET/PTC1*, *PAX8/PPARG*, and *RET/PTC3* was 1.9% (29), 1.1% (16), and 0.5% (8), respectively (Fig. 1).

TCs associated with *BRAFV600E*, *RET/PTC*, and *PAX8/PPARG* were almost all PTCs. The exceptions were 3 *BRAFV600E*-positive TCs that were anaplastic TCs. Although 97% of TCs associated with *RAS* mutations were also PTC, *RAS* was associated with other histologies including follicular TC and oncocytic (Hurthle) cell cancer (Table 2). Of the 5 *RAS*-positive poorly differentiated/anaplastic TCs, mutations in *NRAS* 61 were identified in 4 patients and mutations in *HRAS* 61 in 1 patient. Two patients had sporadic medullary TCs that were associated with *HRAS* 61 and *KRAS* 12/13 mutations.

Specific mutations were also associated with PTC subtypes (Table 2). PTCs that were positive for *BRAFV600E* and *RET/PTC* were often conventional (39% and 54%) or tall cell variant (19% and 5.4%). On the contrary, *RAS*-, *PAX8/PPARG*-, and *BRAFK601E*-positive PTCs were frequently follicular variant (87%, 94%, and 92%, respectively). There were no significant associations between mutation and mean tumor size or multifocality (Table 3).

Similar histologic features were observed between *BRAFV600E*- and *RET/PTC*-positive PTC including the likelihood of extrathyroidal extension (51% vs 49%, $P = 0.9$) and CLNM (55% vs 70%, $P = 0.13$). However, LLNM was more likely in *RET/PTC* than in *BRAFV600E*-positive PTC (35% vs 14%, $P = 0.001$). Distant metastasis at presentation was also diagnosed in 3 of 37 (8%) patients with *RET/PTC*-positive PTC compared with 13 of 644 (2%) patients with *BRAFV600E*-positive PTC ($P = 0.05$). Similar, less aggressive histologic features were observed for *RAS*-, *PAX8/PPARG*-, and *BRAFK601E*-positive PTCs that had equivalently low rates of extrathyroidal extension (4.6% vs 0% vs 0%, $P = 0.5$) and CLNM (10% vs 0% vs 0%, $P = 0.6$). LLNM was present in 4 patients with *RAS*-positive TCs and all 4 were *NRAS* 61 positive. Distant metastasis at presentation did not differ significantly between patients with *RAS*-positive tumors (7/323, 2%), or with *PAX8/PPARG* and *BRAFK601E*-positive tumors (0%, $P = 1$). Advanced American Joint Committee on Cancer Tumor (AJCC) stage III or IV disease at presentation was as frequent with *BRAFV600E*-positive TC as with *RET/PTC*-positive TC (41% vs 35%, $P = 0.11$) and was also as frequent with *RAS*-, *PAX8/PPARG*-, and *BRAFK601E*-positive TCs (17% vs 19% vs 0%, $P = 0.3$). Thus, *BRAFV600E*- and *RET/PTC*-positive PTCs were

phenotypically similar and *RAS*-, *PAX8/PPARG*-, and *BRAF*K601E-positive PTCs were phenotypically analogous.

Persistent disease requiring neck reoperation for less than 6 months after initial surgery occurred in 12 patients—4 patients with *RET*/PTC mutations who had lateral neck dissection ($n = 2$) and reoperative central compartment neck dissection ($n = 2$) and 8 patients with *BRAF* mutations who had mediastinal exploration ($n = 2$), lateral neck dissection ($n = 5$), or both reoperative central and lateral neck dissection ($n = 1$). Metachronous metastatic disease occurred in 6 patients; 4 with *BRAF*V600E PTC, 1 with *RET*/PTC PTC, and 1 with *NRAS* 61 positive PTC. Compared with *RAS*-, *PAX8/PPARG*-, or *BRAF*K601E-positive TC, the TCs expressing *BRAF*V600E or *RET*/PTC were more often associated with AJCC stage III/IV at presentation (40% vs 15%, $P < 0.001$) and early recurrence (10% vs 0.7%, $P < 0.001$; mean follow-up 33 ± 21 mo). Distant metastasis was highest in patients with *RET*/PTC-positive TC (10.8%, $P = 0.02$).

Mean follow-up for the entire cohort was 33 ± 21.2 months. More than 6-month follow-up was available for 89% (1349) of patients, and overall 79 patients (5.8%) required reoperation for recurrent disease (Table 4). Among the 1039 patients who had positive 7-gene mutation testing results, recurrences were most common in patients with *BRAF*V600E- (9.7%) or *RET*/PTC- (9.4%) positive TC. By Kaplan-Meier analysis, type of mutation helped stratify disease-free survival (DFS) (Fig. 2). DFS at 5 years for patients with *RAS*-, *PAX8/PPARG*-, and *BRAF*K601E-positive TCs (96%, 100%, and 100%, respectively) was higher than that for patients with *BRAF*V600E- and *RET*/PTC-positive TCs (80% and 77%; $P < 0.001$).

Overall disease-specific survival at 5 years was 99.7% and was not dependent on mutation ($P = 0.9$).

DISCUSSION

Many of the genetic changes that lead to thyroid carcinogenesis have been recently elucidated and involve alterations in the MAPK and PI3K pathways such as mutations in *BRAF* and *RAS*.^{14,15} Using accurate and cost-effective techniques, the alterations can be readily detected in preoperative FNAB and pathology specimens. In 2007, we initiated a prospective clinical management algorithm that implemented routine molecular testing for a 7-gene panel of all FNAB specimens that were either cytologically indeterminate or from nodules with other clinically concerning characteristics such as large size. We also tested histologic PTC tumors larger than 3 mm that did not have testing performed preoperatively using the same 7-gene panel.⁵ In this consecutive, unselected, and large series of histologic TCs with long-term follow-up, we demonstrate here that TC genotype correlates to tumor phenotype including histologic features and DFS.

We have previously shown that molecular testing of FNAB specimens classified into 1 of the 3 indeterminate Bethesda categories can be used to accurately diagnose TC preoperatively. In the study by Nikiforov et al,⁵ 513 FNAB indeterminate specimens with cytology, molecular results from the 7-gene panel, and histology were analyzed. When any one of the mutations was identified, the risk of cancer was 87% to 95%, depending on the cytology

category. Because of the high risk of malignancy, a positive molecular testing result was an indication for initial total thyroidectomy, which is the recommended surgical procedure for patients with a known diagnosis of TC.⁴ In contrast, when no mutation was identified, the risk of cancer was reduced in the AUS/FLUS, FN, and suspicious categories to 6%, 14%, and 28%, respectively, and thus, initial lobectomy was recommended.⁵ The high performance of a similar molecular panel was also validated by Cantara et al.¹⁶ In a subsequent cohort study, we observed that a clinical algorithm that used molecular testing results to guide extent of thyroidectomy led to a 30% increase in appropriate total thyroidectomy for a clinically significant TC while also resulting in a 33% increase in lobectomy alone for either papillary thyroid microcarcinoma or benign histology.⁶

Other studies have shown that molecular testing for either single gene mutations such as *BRAFV600E* or the 7-gene panel as an adjunct to FNA biopsy adds diagnostic accuracy.^{17,18} But whether molecular testing provides additional information on tumor characteristics and prognosis is lesswell defined. *BRAFV600E* is the most common mutation identified in PTC and may be predictive of aggressive clinical features.^{19,20} However, in other studies, its presence does not always seem to be associated with aggressive histologic features.^{21,22} Retrospective selection of tumors that undergo mutation testing and geographic variation in the prevalence of TC subtypes may have contributed to the differential results observed. When compared with a consecutive series of histologic TCs in the present study, we observed a distinctive tumor phenotype that was associated with *BRAFV600E*. Almost all (99.5%) were PTCs and the majority were conventional or tall cell variant. *BRAFV600E*-positive PTC had a high incidence of extrathyroidal extension (51%), CLNM (55%), and 41% of patients presented with advanced AJCCTNM stage III/IV. We and others have previously shown that *BRAFV600E*-positive FNAB was often associated with cytologic findings that have either architectural or cellular atypia.^{21,23} However, in the study by Ohori et al.,²³ approximately 20% of *BRAFV600E*-positive FNA biopsy specimens were classified as being in the indeterminate category including AUS/FLUS, FN, or suspicious, and in these patients, preoperative *BRAF* testing helped avoid unnecessary repeat biopsy when indicated, facilitated preoperative patient counseling, and led to appropriate initial total thyroidectomy. Now with nearly 3 years of follow-up, we observed a DFS of 80% at 5 years that seems to plateau thereafter. With longer follow-up, we anticipate that we will be able to further determine optimal surveillance strategies for these patients using both comprehensive mutation status and histologic features to guide risk stratification.

In this study, TCs that were positive for *BRAFV600E* were phenotypically similar to those that were positive for *RET/PTC*. Conventional and tall cell PTCs that were the most common histologic subtypes for both mutations and aggressive histologic features were seen at equivalent rates in patients with *BRAFV600E*- and *RET/PTC*-positive PTCs. However, patients with *RET/PTC*-positive PTC had a high incidence of LLNM (35%) and distant metastasis (8%) at presentation.

Equally notable is that nearly 25% of the histologic TCs diagnosed here were positive for *RAS*, *PAX8/PPARG*, and *BRAFK601E*, and these tumors had a high likelihood of having encapsulated histologic features. *RAS*-positive FV-PTC can rarely also be infiltrative or be associated with multiple areas of capsular or vascular invasion, and careful histologic

examination is essential to accurately discriminate these more worrisome lesions from the well-demarcated, encapsulated FV-PTC.¹⁰ For all patients with *RAS*-, *PAX8/PPARG*-, and *BRAF*K601E-positive TCs, the clinical course was indolent and DFS was nearly 100% at 5 years. We believe that deescalated care, including initial lobectomy instead of total thyroidectomy and limiting the use of radioactive iodine may be indicated for the majority of patients with TC associated with *RAS*, *PAX8/PPARG*, and *BRAF*K601E mutations.

Further classification of PTC using molecular signature was also proposed in analysis of The Cancer Genome Atlas (TCGA) data.²⁴ Comprehensive whole genome sequencing that included miRNA, DNA methylation, and protein expression was performed for 496 submitted PTCs, and distinctive molecular features were observed that clustered into *BRAF*-like and *RAS*-like tumors. *BRAF*-like PTCs were genetically and phenotypically more heterogeneous but included the subset of tumors that were most likely to present at advanced stage and recur. The phenotype of the *RAS*-like PTC in TCGA was also similar to what we observed and was more likely to be FVPTC and have a low recurrence risk.²⁴ However, our series here also included non-PTC tumor types and we observed that 5/8 (40%) of the poorly differentiated/anaplastic TCs and 2 medullary thyroid cancers (MTC) had *RAS* mutations. Thus, we conclude that *RAS*-positive PTC may have a predictable phenotype, but preoperative detection of *RAS* should also take into account the possibility for the rarer, yet aggressive non-PTC malignancies.

Although approximately 9% of *BRAF*V600E and *RET/PTC*-positive TCs had recurrent disease, the majority were disease-free at last follow-up. In multivariable analysis, the presence of *BRAF*V600E when all other histologic features are known was not an independent predictor of disease-related mortality, which limits its incorporation into commonly used staging systems such as the AJCC system.²⁰ On the contrary, *BRAF*V600E has been associated with an increased risk of recurrence, and we have previously observed that the risk was highest in patients who were 65 years of age or older.^{8,19} The presence of extrathyroidal extension and lymph node metastasis is also predictive of recurrent disease, and the association of these histologic features to recurrence may be augmented in *BRAF*V600E-positive PTC.¹⁹ However, histologic features cannot feasibly be used to guide initial surgical management. Additional genetic markers have already been identified that provide additional risk stratification and these include *TERT* promoter, *p53*, and *PIK3CA* mutations. *TERT* promoter mutations (C228T and C250T) are found in association with *BRAF*V600E or *RAS* mutations, are seen in PTC with aggressive clinicopathologic features, and are independently associated with disease-specific mortality.^{25,26} In addition to the presence of one of the mutations known to be associated with aggressive disease, the detection of more than 1 mutation can also be a marker of poorer prognosis. Multigene sequencing analysis such as next generation sequencing allows sensitive high-throughput evaluation of a broader panel of markers on FNA cytology that can further refine preoperative prognostication.²⁷

Knowing this correlation between tumor genotype and disease phenotype can now potentially help tailor cost-effective preoperative evaluation and further guide extent of initial surgery. When *BRAF*V600E or *RET/PTC* is detected preoperatively, cervical ultrasonography with lymph node mapping of the lateral and central compartments should

always be performed (Fig. 3). If no obvious disease is seen, prophylactic central compartment lymph node dissection by experienced surgeons at the time of initial total thyroidectomy may be considered because of the 56% incidence of CLNM reported here. Although not studied in an RET/PTC-specific cohort, aggressive surgical resection of occult lymph node metastasis in the lateral neck using either prophylactic lateral neck dissection or sentinel lymph node mapping has not to date resulted in improvements in rate of recurrence or survival and thus is not currently recommended as standard of care.⁴ Preoperative imaging of the chest to evaluate for metastatic disease should also be considered for patients with RET/PTC-positive TC, in particular, and patients should also be counseled on the 10% to 15% risk of recurrent disease at 5 years. On the contrary, when RAS, PAX8/PPARG, or BRAFV600E is detected preoperatively, the likelihood of FV-PTC is high and in the absence of concerning ultrasound features, lobectomy alone may be sufficient treatment for selected low-risk lesions. RAS-positive lesions may be either poorly differentiated/anaplastic or MTC, and clinical and radiographical features may be helpful in differentiating these aggressive TCs from the more indolent encapsulated FV-PTC.

Limitations of the present study include use of electronic medical record review without rereview of histology or cytology results. Second, treating physicians were not blinded to mutation testing results, which may have influenced decision making such as extent of surgery, need for radioactive iodine ablation, and intensity of surveillance. Thus, it was not possible to objectively evaluate whether genotype altered our threshold for postoperative treatment. Third, multifocal disease was identified in 51% of patients, and only the tumor with the most aggressive histologic features was included in the study, which may have led to some degree of bias. Finally, in analysis, we did not include the cohort that was 7-gene mutation panel negative as likely these tumors carry a genetic alteration that overlaps with the MAPK and PI3K pathways. The Cancer Genome Atlas analysis demonstrated that after whole genome sequencing, only 3.5% of the analyzed PTC failed to have an apparent driver mutation.²⁴ Our current molecular panel has already expanded to include additional genetic mutations such as PTEN and EIF1AX and rearrangements such as NTRK fusions that will help further stratify the 31% of patients with “mutation-negative” TC. The expanded multigene panel has higher diagnostic sensitivity, and in a recent study of FNA biopsies classified as follicular neoplasm, a mutation-negative result was associated with only a 4% risk of TC, and active surveillance may be a very reasonable consideration.²⁸

CONCLUSIONS

In this consecutive series of 1510 patients with TC who had mutation testing for a 7-gene panel, 69% had a mutation in BRAFV600E, BRAFK601E, NRAS codon 61, HRAS codon 61, KRAS codons 12/13 point mutations, RET/PTC1, RET/PTC3, or PAX8/PPARG rearrangements. Outcomes varied by mutation: BRAFV600E and RET/PTC-positive TCs tended to be more aggressive with 5-year DFS of 84% and 78%, respectively. But RAS-, PAX8/PPARG-, and BRAFK601E-positive TCs were indolent with 5-year DFS of more than 97%, and this phenotype can be equally informative at guiding patient care. Thus, tumor genotype was associated with histologic and clinical phenotype, and molecular signature should be a component of the preoperative and postoperative risk stratification of patients with TC.

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FIGURE 1.
Distribution of molecular testing results.

FIGURE 2.
Disease-free survival differs according to mutation by Kaplan-Meier analysis.

FIGURE 3.

Phenotypic characteristics of associated thyroid cancer by mutation. DM indicates distant metastasis; ETT, extrathyroidal extension; MTC, medullary thyroid cancer.

TABLE 1

Patient and Thyroid Cancer Characteristics (n = 1510)

Men	343 (23%)
Mean age, yr	49.2 ± 15.8
Mean tumor size, cm	2.1 ± 1.6
Type of thyroid cancer	
Papillary	1468 (97%)
Follicular	10 (0.7%)
Oncocytic (Hurthle) cell	10 (0.7%)
Poorly differentiated	8 (0.5%)
Anaplastic	9 (0.6%)
Medullary	5 (0.3%)
Multifocal	775 (51%)
Extrathyroidal extension	453 (30%)
CLN evaluated	1003
Mean no. of CLN evaluated	5.4 ± 5.1
No. with CLNM	405 (40%)
LLNM	138 (9%)
Mutation positive	1039 (69%)
Mean follow-up, mo	33 ± 21.2
No. with >6-mo follow-up	1349 (89%)
Recurrence	78 (5.8%)

CLN indicates central lymph nodes.

TABLE 2

Thyroid Cancer Distribution by Mutation

	BRAF V600E	RAS	RET/PTC	PAX8-PPARG	BRAFK601E
Papillary TC	641 (99.5%)	312 (97%)	37 (100%)	16 (100%)	12 (100%)
Conventional	250 (39%)	9 (3%)	20 (54%)	—	—
Follicular variant	78 (12%)	270 (87%)	1 (2.7%)	15 (94%)	11 (92%)
Tall cell variant	123 (19%)	2 (0.6%)	2 (5.4%)	—	—
Other	15 (2.3%)	5 (1.6%)	2 (5.4%)	—	—
Not specified	174 (27%)	26 (8%)	13 (35%)	1 (6%)	1 (8%)
Follicular TC	—	3 (0.9%)	—	—	—
Hurthle cell TC	—	1 (0.3%)	—	—	—
Poorly differentiated and anaplastic TC	3 (0.5%)	5 (1.5%)	—	—	—
Medullary TC	—	2 (0.6%)	—	—	—

TABLE 3**Histologic Characteristics by Mutation**

	BRAF V600E	RAS	RET/PTC	PAX8-PPARY	BRAFK601E
Mean tumor size, cm	1.7 ± 1.2	2.3 ± 1.6	2 ± 1.5	3.2 ± 1.6	2.4 ± 3.1
Multifocal	360 (56%)	153 (47%)	23 (63%)	7 (44%)	9 (75%)
Extrathyroidal extension	327 (51%)	15 (4.6%)	18 (49%)	0	0
No. with CLND	523 (81%)	156 (48%)	33 (89%)	8 (50%)	7 (58%)
CLNM	286 (55%)	16 (10%)	23 (70%)	0	0
LLNM	92 (14%)	4 (1.2%)	13 (35%)	0	0
Distant metastasis at presentation	13 (2%)	7 (2%)	3 (8%)	0	0
TNM stage					
1	56%	67%	57%	69%	100%
2	4%	15%	8%	13%	0%
3	32%	13%	22%	19%	0%
4	9%	3%	14%	0%	0%

CLND indicates Central compartment lymph node dissection.

TABLE 4

Disease Outcomes by Mutation

	BRAF V600E	RAS	RET/PTC	PAX8-PPARG	BRAFK601E
Mean follow-up, mo	33 ± 20.6	31 ± 21.7	27 ± 19.8	30 ± 18.4	20.5 ± 15.3
Persistence	16 (2.6%)	7 (2.3%)	5 (15.6%)	0	0
Recurrence	57 (9.7%)	2 (0.7%)	3 (9.4%)	0	0
Deceased	16 (2.5%)	7 (2.2%)	1 (2.7%)	1 (6.3%)	0