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Is *BRAF* mutation associated with lymph node metastasis in patients with papillary thyroid cancer?

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Abstract

Background—Some have proposed using V600E BRAF mutation status to dictate the surgical management of patients with papillary thyroid cancer (PTC). However, well-designed studies examining BRAF association with aggressive clinicopathologic features of PTC, including the presence of lymph node metastases (LNM), in patients who have undergone routine central lymph node dissection (CLND), are lacking.

Methods—Under institutional review board approval, 63 patients diagnosed with PTC on fine-needle aspiration who underwent total thyroidectomy and CLND were included. BRAF mutation status was determined in fresh frozen or intraoperative fine-needle aspiration samples with a colorimetric assay. Associations between BRAF mutation status and clinicopathologic features of PTC were examined using Chi-square and multivariate logistic regression analyses.

Results—BRAF mutation was found to be significantly associated with race only on Chi-square analysis. BRAF mutation was not found to be significantly associated with the presence of LNM (P = .167). On multivariate analysis, only size and venous/lymphatic invasion were significantly associated with LNM.

Conclusion—This small series underscores the prematurity in utilizing BRAF mutation status to determine the surgical management of patients with PTC, specifically whether or not to perform a CLND.

Many researchers have investigated the clinical role of *V600E BRAF* mutation in patients with papillary thyroid cancer (PTC). The *BRAF* mutation constitutively activates the RAS/RAF/mitogen-activated protein kinase signal transduction pathway and results in the malignant transformation of cells. This mutation is found in ≤70% of PTCs, is highly specific, and is easily detected in thyroid fine-needle aspirate biopsy samples.[1] In recent years, there has been an increased focus in the literature on the prognostic value and the potential clinical role of *BRAF* mutation in patients with PTC.[2,3] However, the true association of *BRAF* with poor clinicopathologic features, particularly, lymph node metastasis (LNM) that could affect the surgical approach to these patients, remains controversial. With the exception of 2 studies,[4-6] the remaining studies, including one that we have co-authored, examining *BRAF* association with LNM do not include patients who have undergone routine central lymph node dissection (CLND).[1,7] The largest study, by Basolo et al,[8] as an example, examined 1,060 patients with PTC and found correlation with *BRAF* mutation and LMN. However, in this study, only tumors <2 cm were included and patients only underwent CLND if there

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were intraoperative abnormalities identified.[8] By including only patients who underwent CLND and have likely more advanced disease and known lymph node status and, by excluding those who have not undergone CLND, there may exist potential bias by including only those patients with larger, more aggressive tumors and/or those who have clinically evident LNM at presentation. Additionally, many studies evaluate the association of *BRAF* with presence of LNM overall, rather than only central LNM. Many studies also report a significant association between the *BRAF* mutation and LNM on univariate analysis only.[4,9,10] However, this significance is lost in the few studies that perform multivariate analysis, adjusting for all variables known to be associated with aggressive PTC (age, gender, extrathyroidal extension, multifocality, and PTC variants and size). Studies maintaining significance on multivariate analysis either adjust only for age and gender or do not specify adjusted variables. Table I includes the 2 studies that adjusted for a majority of variables known to be associated with aggressive features and none demonstrated an association of BRAF status with LMN.[3,6,11]

Despite the controversy that exists in the literature and conflicting reports, some have proposed that *BRAF* status should be incorporated into the surgical algorithmic management of patients with PTC with respect to extent of surgery, specifically, whether or not the patient should undergo a CLND.[12] Additional multi-institutional studies in which the surgeons perform routine CLND and therefore include evaluable patients are needed to determine whether the measurement of *BRAF* status does or does not independently predict the presence of nodal metastases. In a small study, we therefore chose to examine whether BRAF mutation status is associated with LNM in patients with PTC by retrospectively examining consecutive patients who underwent routine CLND as part of an endocrine surgery practice, adjusting for confounding factors that included age, gender, tumor size, multifocality, PTC variant, and extrathyroidal extension.

METHODS

Study population

Under institutional review board approval, 63 consecutive patients diagnosed preoperatively with PTC on fine-needle aspiration (FNA) and operated on at The Johns Hopkins Hospital between January 2008 and October 2011 were identified from a thyroid tumor database that includes >5,000 patient records with 1,630 patients having a diagnosis of PTC. Because our goal was to examine *BRAF* as a prognostic marker and not as a diagnostic marker, only patients who had known PTC on FNA were included and, only patients operated on by a single surgeon (MAZ) who routinely performed CLND for tumors ≥1 cm, reflecting a change in clinical practice beginning January 2008, were included. All patients underwent total thyroidectomy and CLND as part of routine surgical practice. Patients with biopsy-proven lateral neck disease also under-went therapeutic lateral neck dissection. Patient demographics, including age, race, and sex, preoperative cytopathology, and surgical pathology reports were reviewed. CLNDs consisted of either both prophylactic and therapeutic dissections. All patients underwent unilateral CLND if they had only limited or no clinically detectable lymphadenopathy at the time of operation. Patients with extensive unilateral lymphadenopathy underwent bilateral CLND.

DNA extraction and *BRAF* mutation detection assay

Depending on availability, DNA was obtained from either frozen or paraffin-embedded thyroid tumor samples using DNeasy Blood & Tissue Kit (Qiagen, Valencia, CA). If thyroid tumor was unavailable, FNA samples from the corresponding PTC were used. Each specimen was verified for the presence of PTC using a corresponding 5-μm-thick, hematoxylin-eosin–stained slide. For analysis of the *v600E BRAF* mutation, a colorimetric

mutation detection assay or shifted termination assay (Mutector; TrimGen, Baltimore, MD) was used. Exon 15 of the *BRAF* gene containing the site where V600E mutation occurs was first amplified by colorimetric assay using Taqman DNA polymerase and Mutector kit. The Mutector kit utilizes a detection primer that is complementary to the *BRAF* exon 15 antisense strand. The primer extension reaction allows for primer extension only when the target base is mutated. Primer extension involves multiple labeled nucleotides. After the enzymatic color development reaction, the labeled nucleotides generate a color signal. Color was quantified by a microplate reader at a wavelength of 405 nm to confirm the results.

Statistical analysis

Associations between *BRAF* mutation status and clinicopathologic features of PTC were examined using Chi-square analysis. Multivariable logistic regression analyses were used to ascertain possible independent association of clinicopathologic parameters with central LNM in PTC, including *BRAF* mutation status, patient age, gender, race, size, PTC variant, the presence of venous/lymphatic invasion, surgical margins, and extrathyroidal extension. Multivariate logistic regression analyses were also used to ascertain possible independent association of those clinicopathologic parameters that would be preoperatively available to the clinician. $P < .05$ was considered significant. Statistical analysis was performed with STATA 12 SE Software (StataCorp LP, College Station, TX).

RESULTS

All patients underwent total thyroidectomy and CLND (level VI); 9 patients also had a lateral neck dissection (levels II–V) for the presence of biopsy proven lateral neck metastases. Only patients undergoing initial operation for PTC were included. Of the patients who underwent only CLND without lateral neck dissection, 48 underwent a unilateral CLND, and 6, a bilateral CLND; of the patients who only had a CLND, 25 underwent therapeutic CLND and 29 underwent prophylactic CLND. With the exception of patients who were thin and had no evidence of deep cervical lymphadenopathy, all had a deep CLND (8.4 ± 8.3 lymph nodes). Of the 63, 28 had multifocal PTC, the majority of which were 1–2 mm in size. There were 50 women and 13 men with a mean age of 44.8 years (SD, 10.8) and mean tumor size of 2 cm (SD, 0.8); 50 (79%) were white (for the remainder of the races too few were in any one category to be considered separately); 44 (70%) had *BRAF* positive tumors; 33 (52%) had lymphovascular invasion; 12 (19%) had positive surgical margins; and 38 (60%) had positive lymph nodes. Postoperatively, 16 of the 63 (25%) had temporary hypocalcemia; 1 patient had a hematoma and 1 patient had a unilateral vocal cord paralysis. The latter patient had an intact and functioning recurrent laryngeal nerve (measured by nerve monitoring) at the time of surgery; postoperatively, this patient was lost to follow-up.

BRAF mutation status was found to be significantly associated with race only on Chi-square analysis (Table II). *BRAF* mutation status was not associated with any other clinicopathologic features of PTC. Specifically, of the 44 *BRAF*-positive tumors, 29 (66%) had LNM; of the 19 *BRAF*-negative tumors, 9 (47%) had metastases ($P = .167$). Neither multivariate logistic regression analyses performed to examine all clinicopathologic predictors of central LNM in PTC (Table III) nor only variables that would be preoperatively available (Table IV) showed significant association between the *BRAF* mutation and LNM. Only size and venous/lymphatic invasion were significantly associated with LNM on multivariate logistic regression (Table III).

DISCUSSION

Controversy about whether patients should undergo prophylactic CLND notwithstanding, attempting to identify those patients who would benefit from a neck dissection has been at the forefront of the endocrine surgical literature for decades.[13-15] Because of this controversy, many have investigated potential prognostic variables that could help the clinician to tailor appropriate treatments schemes for patients with PTC. Herein, we have attempted to closely examine the role of *BRAF* as a prognostic variable with a study that included consecutive and evaluable patients.

With regard to the colorometric assay compared with other assays, when applied to detection of the *BRAF* mutation in a clinical study, it was able to correctly identify *BRAF* mutation status in all 90 samples, whereas polymerase chain reaction restriction enzyme analysis misclassified 10 wild-type samples as mutant and direct sequencing misclassified 1 mutant sample as wild type.[16] Because direct sequencing methods will also read wild-type DNA mixed within the clinical sample, a misreading occurs any time there is >80% wild-type DNA and <20% mutant DNA. Conversely, the colorimetric assay can detect mutant DNA in concentrations as low as 1%.[16]

The purpose of this study was to determine whether BRAF status is associated with LMN. The debate about whether or not to perform prophylactic CLND is beyond the scope of this study. However, it is important to know whether BRAF could be used to decide whether or not to perform a CLND. Almost all previous studies have not looked at only patients who have had CLND and are thus evaluable in terms of whether there is an association.[2] Studies include those patients who did and did not undergo CLND, thus biasing evaluation of the *BRAF* mutation analysis to include only those who underwent therapeutic CLND.

Our extensive review of the literature (unpublished) revealed that in patients who had undergone routine CND, a significant association between *BRAF* and LNM has been documented only for tumors ≤1 cm.

Our results showed no association between *BRAF* mutation and LNM on either univariate or multivariate logistic regression analyses. On multivariate logistic regression analyses, only size and the presence of lymphovascular invasion, both variables that have been shown by others to predict metastases, were positively associated with LNM.[17] Several studies have examined *BRAF* mutation and lymphovascular invasion.[10,18-20] However only Elisei et al[20] found a significant correlation on univariate analysis between *BRAF* and vascular invasion; Lee et al,[19] O'Neill et al,[18] and Sykorova et al[10] found the correlation to be insignificant. Herein we have reported a significant correlation on multivariate analysis between *BRAF* and venous/lymphatic invasion. For reasons that are unclear, only race seemed to be positively associated with *BRAF* mutation on univariate analysis, with whites more likely to harbor the mutation.

Our study is retrospective and limited in size, and thus subject to several limitations: Small number of patients, 1 surgeon's practice, inclusion of all patients with PTC and lymph node dissection, including lateral neck dissections, and the inclusion of patients with FVPTC. One might, for instance, argue that one should only include those who only underwent CLND, or prophylactic CLND, or only those with PTC to determine whether *BRAF* could predict LNM. However, we present a potential study design and statistical analysis method, if applied prospectively to a multi-institutional study, would ultimately determine the true association of *BRAF* mutation with LNM in patients with PTC. Specifically, we propose that a prospective, multi-institutional study that included only surgical practices where routine CLND be performed for patients with PTC be performed. Furthermore, by performing multivariate logistic regression analysis of preoperative clinicopathologic

predictors of LNM, we also put forth a clinically applicable analysis of the data; in this study, we evaluated only those variables that would be available to the clinician preoperatively and thus applied to make preoperative decisions and found no variable, including *BRAF*, that was associated with LMN (Table IV). With the small number of patients included in this study, it is likely to be subject to type II error. Although this study may be too small to accurately assess whether an association truly exists between *BRAF* mutation and LNM, it illustrates that existing evidence, consisting of mostly retrospective and possibly biased studies, is insufficient to measure the prognostic value of *BRAF* mutation and that similar prospective studies with larger numbers are needed before *BRAF* mutation may be used to guide the management of patients PTC.

Unlike the majority of existing literature, we examined a consecutive cohort of patients, diagnosed with PTC on preoperative cytopathology, who also underwent routine CLND and thus were evaluable for the association between *BRAF* mutation and the presence or absence of nodal metastases. Our study included 9 who had undergone lateral neck dissection and had clinically more aggressive disease, lending even more credence to the finding that *BRAF* was not associated with the presence of LNM. Furthermore, given the fact that the majority of patients with PTC already harbor LMN, studies that include only the group of patients who underwent neck dissections based on preoperative or intraoperative suspicion and excluded those who did not, introduce significant bias toward those patients with larger tumors or with clinically evident LNM.

With the exception of 4 studies[9,21-23] that focused on only classical variants of PTC, the majority of studies either does not specify or explicitly includes a mixture of different histologic subtypes of PTC. Because different subtypes have varying disease patterns and *BRAF* mutation prevalence, the results of these past studies may be skewed depending on the composition of the tumor collection analyzed. Compounding this, current criteria for diagnosing follicular variant of PTC (FVPTC) is often unclear as Elsheikh et al[24] have demonstrated both significant inter-observer and intraobserver variation in the diagnosis of FVPTC. Complete agreement among experts in diagnosing FVPTC was observed in only 13% of cases and intraobserver agreement ranged from 17% to 100%.[24] As a result of the difficulty in diagnosing follicular lesions such as FVPTC, the inclusion of misdiagnosed follicular adenomas, for instance, which would exhibit extremely low rates of BRAF mutation, might also skew the results toward a stronger association between *BRAF* mutation and aggressive features. Therefore, a histologically homogenous population would be more informative. The inclusion criteria in this study included a diagnosis of PTC on cytopathology preoperatively and hence excluded a significant proportion of the clinically indolent or questionable subtypes of PTC, namely FVPTC. Accordingly, FVPTC prevalence within our cohort, 4.8%, is significantly lower than the numbers cited in the literature (9–22.5%). In addition, the *BRAF* mutation prevalence within our cohort lies at the higher end of the spectrum defined by the literature, further supporting the concept that less FVPTC or tumors with questionable diagnoses were included. Last, in our study the researchers performing the *BRAF* mutation analysis were not responsible for the final histopathologic results, thus eliminating any potential known or unknown biases.

In conclusion, although this series is small, with only 63 patients, its results underscore the prematurity in utilizing *BRAF* mutation status to determine the surgical management of patients, specifically whether a patient with PTC should have a CLND. Prospective, multi-institutional studies that include only patients who have known PTC preoperatively and centers in which routine CLND is performed are, therefore, greatly needed before we can accurately assess whether *BRAF* mutation status should be incorporated into critical decisions regarding the appropriate operative management of patients with PTC.

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Table I

Multivariable logistic regressions in the literature examining *BRAF* as a predictor of lymph node metastases, adjusting for variables associated with aggressive papillary thyroid cancer

Study	*No. of patients*	*Multivariate* P *values*	
Frasca et al25	323	.89	Adjusted for age, gender, multifocality, tumor size, extrathyroidal extension, and variant
Xing et al3	219	.13	Adjusted for age, gender, multifocality, tumor size, extrathyroidal extension, and variant

Table II

Associations between the *V600E BRAF* and clinicopathologic features of papillary thyroid cancer

Clinicopathologic features	***BRAF-positive*** **n = *44 (70%)*** **n (%)**	***BRAF-negative*** **n = *19 (30%)*** **n (%)**	**P *value***
Gender			
Female	34 (77)	16 (84)	.532
Male	10 (23)	3 (16)	
Age (yrs)			
<45	21 (48)	9 (47)	.979
≥45	23 (52)	10 (53)	
Race			
White	38 (86)	12 (63)	.037*
Non-white	6 (14)	7 (37)	
Tumor size (cm)			
<2	25 (57)	13 (68)	.388
≥2	19 (43)	6 (32)	
Multifocality			
No	27 (61)	8 (42)	.158
Yes	17 (39)	11 (58)	
Variant			
Conventional	40 (90)	16 (84)	.218
Follicular	2 (5)	3 (16)	
Tall cell	2 (5)	0	
Venous/lymphatic invasion			
Absent	20 (45)	13 (68)	.094
Present	24 (55)	6 (32)	
Surgical margins			
Negative	36 (82)	15 (79)	.790
Positive	8 (18)	4 (21)	
Central lymph node metastasis			
Absent	15 (34)	10 (53)	.167
Present	29 (66)	9 (47)	
Extrathyroid extension			
Absent	39 (89)	18 (95)	.449
Present	5 (11)	1 (5)	
AJCC stage			
I + II	27 (61)	15 (79)	.174
III + IV	17 (39)	4 (21)	

*Statistically significant.

AJCC, American Joint Committee on Cancer.

Table III

Multivariate logistic regression analysis of clinicopathologic predictors of central lymph node metastases in patients with papillary thyroid cancer

	Odds ratio	*95% confidence interval*	P *value*
BRAF mutation	1.44	0.291–7.14	.654
Age (≥45)	0.572	0.139–2.37	.441
Gender (female)	0.829	0.159–4.34	.825
Race (white)	1.65	0.263–10.3	.593
Size (>2 cm)	5.21	1.15–23.7	.032*
Variant			
Follicular variant	0.743	0.0491–11.2	.830
Tall cell variant	0.0675	0.00195–2.33	.136
Multifocality	0.887	0.180–4.38	.883
Positive surgical margins	6.32	0.762–52.4	.088
Extrathyroidal extension	0.0704	0.00362–1.37	.080
Venous/lymphatic invasion	14.0	2.97–66.5	.001*

*Statistically significant.

Table IV

Multivariate logistic regression analysis of preoperative clinicopathologic predictors of central lymph node metastases in patients with papillary thyroid cancer

	Odds ratio	*95% confidence interval*	P *value*
BRAF mutation	1.94	0.604–6.25	.266
Age (≥45 yrs)	0.752	0.248–2.28	.615
Gender (female)	0.945	0.239–3.74	.936
Race (white)	1.15	0.280–4.70	.848
Size (>2 cm)	3.03	0.973–9.42	.056