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Article

ARTICLE

BRAF V600E Mutation-Assisted Risk Stratification of Solitary Intrathyroidal Papillary Thyroid Cancer for Precision Treatment

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Abstract

Background: Precise risk stratification-based treatment of solitary intrathyroidal papillary thyroid cancer (SI-PTC) that is larger than 1.0 cm and 4.0 cm or less is undefined.

Methods: A genetic-clinical risk study was performed on *BRAF* V600E in 955 patients (768 women and 187 men) with SI-PTC, with median age of 46 years and median clinical follow–up time of 64 months at 11 medical centers in six countries. The chi-square test or, for analyses with small numbers, Fisher's exact test was performed to compare recurrence rates. Recurrence-free probability was estimated by Kaplan-Meier (KM) analysis, and the independent effect of *BRAF* mutation on the recurrence was analyzed by Cox regression and Cox proportional hazard analyses. All statistical tests were two-sided.

Results: Recurrence of SI-PTC larger than 1.0 cm and 4.0 cm or less was 9.5% (21/221) vs 3.4% (11/319) in *BRAF* mutation vs wild-type *BRAF* patients, with a hazard ratio (HR) of 3.03 (95% confidence interval [CI] = 1.46 to 6.30) and a patient age- and sex-adjusted hazard ratio of 3.10 (95% CI = 1.49 to 6.45, $P = .002$). Recurrence rates of SI-PTC larger than 2.0 cm and 4.0 cm or less were 16.5% (13/79) vs 3.6% (5/139) in mutation vs wild-type patients (HR = 5.44, 95% CI = 1.93 to 15.34; and adjusted HR = 5.58, 95% CI = 1.96 to 15.85, $P = .001$). Recurrence rates of SI-PTC larger than 3.0 cm and 4 cm or less were 30.0% (6/20) vs 1.9% (1/54) in mutation vs wild-type patients (HR = 18.40, 95% CI = 2.21 to 152.98; and adjusted HR = 14.73, 95% CI = 1.74 to 124.80, $P = .01$). Recurrences of mutation-positive SI-PTC were comparable with those of counterpart invasive solitary PTC,

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around 20% to 30%, in tumors larger than 2.0 cm to 3.0 cm. *BRAF* mutation was associated with a statistically significant decrease in recurrence-free patient survival on KM analysis, particularly in SI-PTC larger than 2.0 cm and 4.0 cm or less. Similar results were obtained in conventional SI-PTC. The negative predictive values of *BRAF* mutation for recurrence were 97.8% (95% CI = 96.3% to 98.8%) for general SI-PTC and 98.2% (95% CI = 96.3% to 99.3%) for conventional SI-PTC.
Conclusions: *BRAF* V600E identifies a subgroup of SI-PTC larger than 1.0 cm and 4.0 cm or less, particularly tumors larger than 2.0 cm and 4.0 cm or less, that has high risk for recurrence comparable with that of invasive solitary PTC, making more aggressive treatment reasonable.

Papillary thyroid cancer (PTC) is a common endocrine malignancy, accounting for about 90% of all thyroid malignancies (1–3). PTC consists of several histological variants, and conventional PTC (CPTC) is the major one, accounting for the majority of PTCs (2,4). PTC is generally highly curable, but some patients have an aggressive disease course (5–7). As PTC-related mortality is generally low but disease recurrence is common, an important goal of the initial treatment of PTC is to prevent disease recurrence by eliminating the cancer. Effective risk stratification is vital for appropriate treatment of patients to optimally balance the treatment-associated benefits and harms, which is currently based on the assessment of clinicopathological risk characteristics. This practice has been profoundly influenced by the American Thyroid Association's (ATA's) guidelines on the management of thyroid cancer (8,9). The 2009 ATA guidelines recommended total thyroidectomy for PTC larger than 1.0 cm regardless of clinicopathological characteristics (8). The recent 2015 ATA guidelines recommended lobectomy as an option for solitary intrathyroidal PTC (SI-PTC; lacking lymph node metastasis, extrathyroidal invasion, and distant metastasis) of tumor size larger than 1.0 cm and 4.0 cm or less (9). This recommendation is having a worldwide impact on the treatment of thyroid cancer. While the outcomes of this treatment strategy for PTC remain to be seen, it has become controversial (10–13). A particular debate is whether total thyroidectomy can be avoided in all SI-PTC larger than 1.0 cm and 4.0 cm or less and, if not, which patients with SI-PTC larger than 1 cm and 4.0 cm or less should be treated with total thyroidectomy as recommended previously (8). This controversy originates from the fact that the intrinsic risk of poor clinical outcomes is not equal in all SI-PTC, and it is often difficult to decide the right treatment extent (eg, total thyroidectomy vs lobectomy) based on clinical grounds. A novel prognostic system is thus needed in tackling this dilemma by more effectively risk-stratifying patients for precision management.

Molecular-based risk stratification of thyroid cancer has shown promise in recent years (14,15). In this regard, the prognostic genetic marker *BRAF* V600E mutation, the most robust oncogene in PTC (16), has drawn particular attention (17–20). In addition to its widely observed association with aggressive clinicopathological characteristics of PTC, large studies have also demonstrated a strong association between *BRAF* mutation and PTC recurrence (21) and PTC-related mortality (19,22). However, all these previous studies looked at the prognostic potential of *BRAF* V600E in PTC in general without dissociation from classical clinicopathological risk characteristics; its prognostic value in PTC without aggressive pathological characteristics at the initial diagnosis is unknown. Also, although the prognostic potential of *BRAF* V600E in PTC has been known from these general studies, there is no known particular example of clinical setting to which the prognostic utility of *BRAF* V600E can be specifically applied to guide precision management. In the present study, we investigated the risk-stratifying utility of *BRAF* V600E mutation specifically in assisting the treatment of a unique and important clinical entity of PTC—SI-PTC, which lacks classical pathological risk characteristics at diagnosis but has inhomogeneous progression risk, thus imposing a challenge in defining the right initial treatment.

Methods

Study Medical Centers, Countries, and Patient Subjects

We selected 2638 consecutive patients with PTC from 11 medical centers in six countries (Table 1), as described previously (4,21,22). Exclusion of 56 patients with incomplete information left 2582 cases with complete information on clinicopathological outcomes, including disease recurrence and patient mortality. From these, we identified 955 cases (768 women and 187 men), with a median age of 46 years (interquartile range [IQR] = 36 to 57 years) and median clinical follow–up time of 64 months (IQR = 30 to 116 months), who, at the initial treatment, lacked multifocality, lymph node metastasis, extrathyroidal invasion, and distant metastasis (Table 1). PTC in these patients was defined as solitary intrathyroidal PTC (SI-PTC). From the remaining 1627 patients, we identified 406 cases with solitary invasive PTC (unifocal and with lymph node metastasis or extrathyroidal invasion, without distant metastasis) as the counterpart of SI-PTC. All patients received total thyroidectomy as the initial treatment. Neck dissection, radioiodine ablation, and thyroid-stimulating hormone suppression were pursued as clinically indicated, as described previously (4,21,22). Disease recurrence was defined as either recurrent or persistent disease per standard histological/cytological/radiographic/biochemical criteria (8,23), including collectively structural and biochemical recurrences. Follow-up time was defined as the time from the initial surgical treatment to the discovery of PTC recurrence or, in the case of no recurrence, to the most recent clinic follow-up (21).

Study Design

The study was approved by the institutional review board of each center, and informed patient consent was obtained where required. For *BRAF* V600E mutation analysis, genomic DNA was isolated from primary PTC tumors and sequenced at exon 15 of the *BRAF* gene as described previously (21,22,24–34). *BRAF* mutation status was not used to affect the treatment decision-making. Pooled data were analyzed to examine the relationship between *BRAF* mutation and recurrence of SI-PTC.

Statistical Analyses

Categorical data were presented as frequencies and percentages and analyzed using the chi-square test; for small case numbers,

Table 1. Demographic characteristics by medical center and country*

Medical center (country)	No. of patients	Age at diagnosis, y Median (IQR)	Follow-up time, mo Median (IQR)	Male sex No. (%)
1. Johns Hopkins Hospital (USA)	442	47 (37–57)	83 (41–140)	105 (23.8)
2. Department of Clinical and Experimental Medicine, World Health Organization Collaborating Center, University of Pisa (Italy)	82	40 (30–51)	120 (36–180)	10 (12.2)
3. University of Perugia (Italy)	31	49 (38–60)	36 (19–52)	9 (29.0)
4. University of Milan (Italy)	59	46 (39–58)	57 (25–92)	10 (16.9)
5. Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology (Poland)	94	48 (37–59)	67 (48–87)	9 (9.6)
6. Griffith University (Australia)	37	42 (34–53)	54 (9–88)	8 (21.6)
7. University of Padua (Italy)	26	43 (36–54)	25 (20–28)	3 (11.5)
8. University of Pittsburgh (USA)	48	53 (36–62)	18 (10–25)	10 (20.8)
9. Hospital La Paz Health Research Institute, Madrid (Spain)	24	41 (31–51)	46 (36–58)	4 (16.7)
10. University of Sydney (Australia)	33	46 (35–58)	104 (63–152)	8 (24.2)
11. Institute of Endocrinology, Prague (Czech Republic)	79	48 (34–59)	55 (40–97)	11 (13.9)
Overall	955	46 (36–57)	64 (30–116)	187 (19.6)

*IQR = interquartile range.

Table 2. Comparison of disease recurrence rates of papillary thyroid cancer in various settings

	Recurrence of solitary intrathyroidal PTC, n/N (%)				Recurrence of solitary invasive PTC, n/N (%)	
Tumor size	Overall	Wild-type	*BRAF* V600E	*P**	Overall	*P*†
PTC						
All sizes (n = 955)	40/955 (4.2)	14/634 (2.2)	26/321 (8.1)	<.001	65/406 (16.0)	.001
>4.0 cm (n = 65)	4/65 (6.2)	1/49 (2.0)	3/16 (18.8)	.04	6/35 (17.1)	1.00
>3.0, ≤4 cm (n = 74)	7/74 (9.5)	1/54 (1.9)	6/20 (30.0)	.001	10/49 (20.4)	.39
>2.0, ≤4 cm (n = 218)	18/218 (8.3)	5/139 (3.6)	13/79 (16.5)	.001	28/132 (21.2)	.40
>1.0, ≤4 cm (n = 540)	32/540 (5.9)	11/319 (3.4)	21/221 (9.5)	.003	48/285 (16.8)	.02
≤1.0 cm (n = 350)	4/350 (1.1)	2/266 (0.8)	2/84 (2.4)	.24	11/86 (12.8)	.02
CPTC						
All sizes (n = 646)	28/646 (4.3)	7/384 (1.8)	21/262 (8.0)	<.001	54/325 (16.6)	.002
>4.0 cm (n = 25)	3/25 (12.0)	1/15 (6.7)	2/10 (20.0)	.54	6/24 (25.0)	1.00
>3.0, ≤4 cm (n = 26)	4/26 (15.4)	0/15 (0.0)	4/11 (36.4)	.02	8/38 (21.1)	.43
>2.0, ≤4 cm (n = 115)	12/115 (10.4)	2/57 (3.5)	10/58 (17.2)	.03	24/106 (22.6)	.42
>1.0, ≤4 cm (n = 333)	22/333 (6.6)	5/151 (3.3)	17/182 (9.3)	.03	38/229 (16.6)	.03
≤1.0 cm (n = 288)	3/288 (1.0)	1/218 (0.5)	2/70 (2.9)	.15	10/72 (13.9)	.03

*Chi-square test and, for small case numbers, Fisher's exact test were used for comparison between wild-type *BRAF* and *BRAF* V600E intrathyroidal PTC. All *P* values are two-sided. CPTC conventional papillary thyroid cancer; PTC = papillary thyroid cancer.

†Chi-square test and, for small case numbers, Fisher's exact test were used for comparison between *BRAF* V600E–positive intrathyroidal PTC and solitary invasive PTC. All *P* values are two-sided.

Fisher's exact test was used. Continuous variables of patient age and follow-up time, which were not normally distributed in this study, were summarized using medians and interquartile ranges (IQRs). The Kaplan-Meier log-rank test was used to analyze recurrence-free survival. Cox proportional hazards regression analysis was performed to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for comparison of disease recurrence by *BRAF* V600E status with adjustment for confounding factors. The assumption of proportionality was verified by plotting Schoenfeld residuals. Data were analyzed using Statistical Package for Social Sciences for Windows (SPSS) version 16.0 (IBM SPSS, Inc. New York, NY). All *P* values were two-sided, and a *P* value of less than .05 was considered statistically significant.

Results

Comparison of Disease Recurrences Between *BRAF* V600E–Positive SI-PTC and Counterpart High-Risk Invasive Solitary PTC

The overall prevalence of *BRAF* V600E mutation in SI-PTC was 33.6% (321/955). Only three (0.3%) deaths occurred in 955 patients (one with wild-type *BRAF* and two with *BRAF* V600E). While the overall recurrences of SI-PTC were generally modest, recurrences of *BRAF* mutation–positive SI-PTC rose sharply to become comparable with recurrences of the counterpart solitary invasive PTC, particularly in larger tumors (Table 2). Specifically, the recurrence rates in *BRAF* mutation–positive

Table 3. Hazard ratios and negative predictive values of *BRAF* V600E mutation for recurrence of solitary intrathyroidal papillary thyroid cancer

Tumor size	Unadjusted		Adjusted*		Negative predictive value % (95% CI)
	HR (95% CI)	P†	HR (95% CI)	P†	
All PTC					
All sizes (n = 955)	3. 89 (2.03 to 7.46)	<.001	4.01 (2.09 to 7.70)	<.001	97.8 (96.3 to 98.8)
>4.0 cm (n = 65)	8.18 (0.85 to 78.72)	.07	7.14 (0.71 to 71.57)	.10	98.0 (89.2 to 99.95)
>3.0, ≤4 cm (n = 74)	18.40 (2.21 to 152.98)	.007	14.73 (1.74 to 124.80)	.01	98.1 (90.1 to 99.95)
>2.0, ≤4 cm (n = 218)	5.44 (1.93 to 15.34)	.001	5.58 (1.96 to 15.85)	.001	96.4 (91.8 to 98.8)
>1.0, ≤4 cm (n = 540)	3.03 (1.46 to 6.30)	.003	3.10 (1.49 to 6.45)	.002	96.6 (93.9 to 98.3)
≤1.0 cm (n = 350)	3.35 (0.47 to 23.78)	.23	3.60 (0.51 to 25.56)	.20	99.2 (97.3 to 99.9)
CPTC					
All sizes (n = 646)	4.72 (2.00 to 11.09)	<.001	4.88 (2.07 to 11.51)	<.001	98.2 (96.3 to 99.3)
>4.0 cm (n = 25)	2.64 (0.24 to 29.36)	.43	3.40 (0.21 to 55.42)	.39	93.3 (68.1 to 99.8)
>3.0, ≤4 cm (n = 26)	–	–	–	–	100.0 (78.2 to 100.0)
>2.0, ≤4 cm (n = 115)	5.90 (1.29 to 26.97)	.02	6.45 (1.40 to 29.72)	.02	96.5 (87.9 to 99.6)
>1.0, ≤4 cm (n = 333)	3.24 (1.19 to 8.78)	.02	3.38 (1.24 to 9.19)	.02	96.7 (92.4 to 98.9)
≤1.0 cm (n = 288)	6.55 (0.59 to 72.26)	.13	6.37 (0.58 to 70.32)	.13	99.5 (97.5 to 99.99)

*Adjusted for patient age and sex. "-" indicates that a hazard ratio could not be calculated due to the zero recurrence in the *BRAF* mutation–negative group. CI = confidence interval; CPTC conventional papillary thyroid cancer; HR = hazard ratio; PTC = papillary thyroid cancer.
†Cox regression and Cox proportional hazard analyses were performed to examine the effects of *BRAF* mutation on recurrence using hazard ratios and 95% confidence intervals. All *P* values are two-sided.

SI-PTC vs invasive solitary PTC were 16.5% (13/79) vs 21.2% (28/132) for tumors larger than 2.0 cm and 4.0 cm or less ($P = .40$), 30.0% (6/20) vs 20.4% (10/49) for tumors larger than 3.0 cm and 4.0 cm or less ($P = .39$), and 18.8% (3/16) vs 17.1% (6/35) for tumors larger than 4.0 cm ($P = 1.00$). Similar comparable high recurrences of tumors larger than 1 cm and 4.0 cm or less, particularly tumors larger than 2.0 cm and 4.0 cm or less, were seen between *BRAF* mutation–positive SI-CPTC and invasive solitary CPTC (Table 2).

Analysis of the Relationship Between *BRAF* V600E Mutation and Recurrence of SI-PTC

As shown in Tables 2 and 3, recurrence in SI-PTC of all PTC variants and tumor sizes was 8.1% (26/321) in *BRAF* mutation–positive patients vs 2.2% (14/634) in wild-type *BRAF* patients, with a hazard ratio of 3.89 (95% CI = 2.03 to 7.46). In SI-PTC larger than 1 cm and 4.0 cm or less, recurrence was 9.5% (21/221) in *BRAF* mutation–positive patients vs 3.4% (11/319) in wild-type *BRAF* patients, with a hazard ratio of 3.03 (95% CI = 1.46 to 6.30) and a patient age- and sex-adjusted hazard ratio of 3.10 (95% CI = 1.49 to 6.45, $P = .002$). In SI-PTC larger than 2.0 cm and 4.0 cm or less, recurrence was 16.5% (13/79) in *BRAF* mutation–positive patients vs 3.6% (5/139) in wild-type *BRAF* patients, with a hazard ratio of 5.44 (95% CI = 1.93 to 15.34) and a patient age- and sex-adjusted hazard ratio of 5.58 (95% CI = 1.96 to 15.85, $P = .001$). In SI-PTC larger than 3.0 cm and 4.0 cm or less, recurrence was 30.0% (6/20) in *BRAF* mutation–positive patients vs 1.9% (1/54) in wild-type *BRAF* patients, with a hazard ratio of 18.40 (95% CI = 2.21 to 152.98) and a patient age- and sex-adjusted hazard ratio of 14.73 (95% CI = 1.74 to 124.80, $P = .01$) (Table 3). The recurrence rate was very low in solitary intrathyroidal papillary thyroid microcarcinoma (SI-PTMC; ≤1.0 cm), which was not affected by the *BRAF* mutation status (Table 2), with statistically nonsignificant hazard ratios (Table 3). The negative predictive values (NPVs) of *BRAF* mutation for recurrence of SI-PTC were mostly around 98% to 100% for various tumor sizes, being 97.8% (95% CI = 96.3% to 98.8%) for the overall analysis of all tumor sizes (Table 3).

With additional adjustment for radioiodine treatments, *BRAF* mutation–associated hazard ratios for PTC recurrence remained statistically significant (Supplementary Table 1, available online). When only structural recurrence was analyzed in the Johns Hopkins cases, similar robust effects of *BRAF* mutation were observed (Supplementary Table 2, available online). Structural recurrence was 18.2% (4/22) in *BRAF* mutation–positive SI-PTC larger than 2.0 cm and 4 cm or less vs 22.0% (11/50) in general invasive SI-PTC of the same tumor size ($P = 1.00$), with an NPV of 100.0% (95% CI = 95.1% to 100.0%). Most structural recurrence of SI-PTC occurred in neck lymph nodes, being 78.6% (11/14) vs 21.4% (3/14) in the thyroid bed.

Similar results were obtained in solitary intrathyroidal CPTC (SI-CPTC) (Tables 2 and 3). Specifically, the overall recurrence of all tumor sizes was 8.0% (21/262) in *BRAF* mutation–positive patients vs 1.8% (7/384) in wild-type *BRAF* patients ($P < .001$), with a hazard ratio of 4.72 (95% CI = 2.00 to 11.09). In SI-CPTC larger than 1 cm and 4.0 cm or less, recurrence was 9.3% (17/182) in *BRAF* mutation–positive patients vs 3.3% (5/151) in wild-type *BRAF* patients, with a hazard ratio of 3.24 (95% CI = 1.19 to 8.78). In SI-CPTC larger than 2.0 cm and 4.0 cm or less, recurrence was 17.2% (10/58) in *BRAF* mutation–positive patients vs 3.5% (2/57) in wild-type *BRAF* patients, with a hazard ratio of 5.90 (95% CI = 1.29 to 26.97). In SI-CPTC larger than 3.0 cm and 4.0 cm or less, recurrence was 36.4% (4/11) in *BRAF* mutation–positive patients vs 0.0% (0/15) in wild-type *BRAF* patients ($P = .02$). The hazard ratios in the above settings all remained statistically significant after adjustment for patient age and sex and radioiodine treatments (Table 3; Supplementary Table 1, available online). The recurrence of SI-CPTC 1.0 cm or less was extremely low, and *BRAF* mutation had no statistically significant effect (Tables 2 and 3). The NPVs of *BRAF* mutation for recurrence of SI-CPTC were mostly around 97% to 100% for various tumor sizes, being 98.2% (95% CI = 96.3% to 99.3%) on the overall analysis of all tumor sizes (Table 3).

Kaplan-Meier Analyses of Disease Recurrence-Free Survival of Patients With SI-PTC

On the analysis of patients with SI-PTC of all variants, *BRAF* mutation was associated with a statistically significant

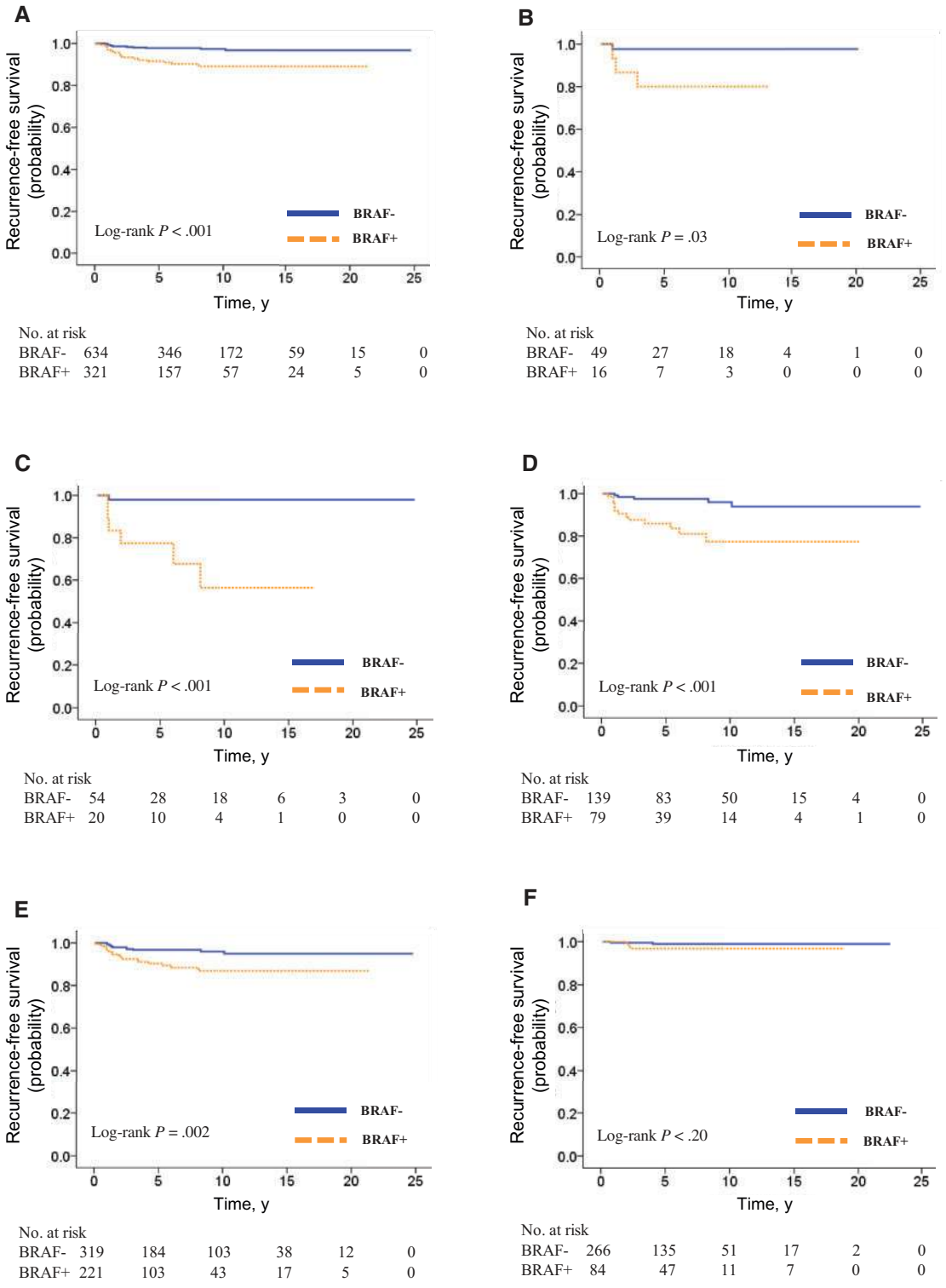

Figure 1. Kaplan-Meier analysis of the impacts of *BRAF* V600E mutation on disease recurrence–free survival of patients with solitary intrathyroidal papillary thyroid cancer. **A)** Tumors of all sizes. **B)** Tumors >4.0 cm. **C)** Tumors >3.0 and ≤4.0 cm. **D)** Tumors >2.0 and ≤4.0 cm. **E)** Tumors >1 cm and ≤4.0 cm. **F)** Tumors ≤1 cm. Log-rank *P* values from the comparison of recurrence-free survival between *BRAF* V600E mutation–positive and wild-type *BRAF* patients are shown in each panel. All statistical tests were two-sided.

decrease in recurrence-free patient survival in SI-PTC of all tumor sizes ($P < .001$) (Figure 1A), tumors larger than 4.0 cm ($P = .03$) (Figure 1B), tumors larger than 3.0 cm and 4.0 cm or less ($P < .001$) (Figure 1C), tumors larger than 2.0 cm and 4.0 cm or less ($P < .001$) (Figure 1D), and tumors larger than 1 cm and 4.0 cm or less ($P = .002$) (Figure 1E). The effect of *BRAF* mutation was most robust in tumors larger than 3.0 cm and 4.0 cm or less (Figure 1C). *BRAF* mutation had no effect

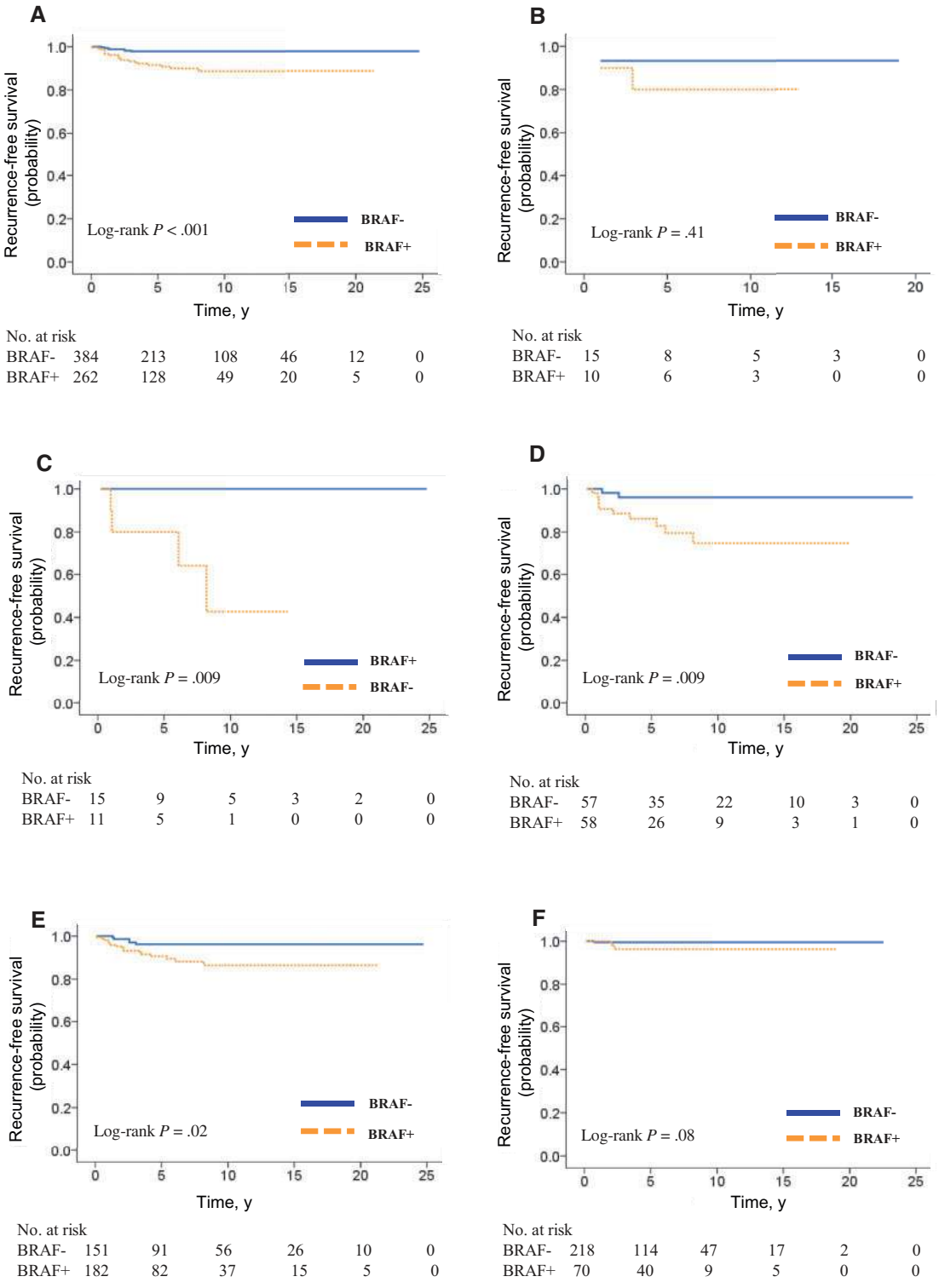

Figure 2. Kaplan-Meier analysis of the impact of *BRAF* V600E mutation on disease recurrence–free survival of patients with solitary intrathyroidal conventional papillary thyroid cancer. **A)** Tumors of all sizes. **B)** Tumors >4.0 cm. **C)** Tumors >3.0 and ≤4.0 cm. **D)** Tumors >2.0 and ≤4.0 cm. **E)** Tumors >1 cm and ≤4.0 cm. **F)** Tumors ≤1 cm. Log-rank *P* values from the comparison of recurrence-free survival between *BRAF* V600E–positive and wild-type *BRAF* patients are shown in each panel. All statistical tests were two-sided.

on recurrence-free patient survival in SI-PTMC ($P = .20$) (Figure 1F).

Similar results were obtained in SI-CPTC (Figure 2). *BRAF* mutation was associated with a statistically significant decrease in recurrence-free patient survival in most tumor size categories—tumors of all sizes ($P < .001$) (Figure 2A), tumors larger than 4.0 cm ($P = .41$) (Figure 2B), tumors larger than 3.0 cm and 4.0 cm or less ($P = .009$) (Figure 2C), tumors larger than 2.0 cm and

4.0 cm or less ($P = .009$) (Figure 2D), and tumors of larger than 1 cm and 4.0 cm or less ($P = .02$) (Figure 2E). As seen in the analyses of SI-PTC of all variants (Figure 1, C and F), *BRAF* mutation also showed the most robust effect in SI-CPTC larger than 3.0 cm and 4.0 cm or less (Figure 2C) and no effect in tumors 1.0 cm or smaller ($P = .08$) (Figure 2F).

We also analyzed the effect of *TERT* promoter mutation in the cohort of Johns Hopkins cases where *TERT* information was available. *TERT* promoter mutation alone had no effect while *BRAF* mutation consistently had a statistically significant effect on SI-PTC recurrence, whether alone or when coexisting with *TERT* promoter mutation (Supplementary Table 3, available online).

Discussion

The recent ATA guidelines (9) recommended lobectomy as a therapeutic option for SI-PTC larger than 1 cm and 4.0 cm or less, reversing a previous recommendation for total thyroidectomy in all patients with such PTC (8). Yet, while patients with SI-PTC generally have an excellent prognosis, some have disease recurrence and even disease-specific death, suggesting that the intrinsic risk of poor prognosis is not equally low in SI-PTC. It is not possible, however, to precisely identify those patients with SI-PTC who appear to be at low risk based on clinicopathological grounds but in fact have high intrinsic risk for poor prognosis and should therefore favor more aggressive treatment. On the other hand, intrinsically low-risk SI-PTC should be treated with lobectomy for the benefits of thyroid function preservation and decreased risk of surgical complications. Controversies have thus arisen as to how to apply the current ATA treatment recommendations for SI-PTC (eg, total thyroidectomy vs lobectomy) (10–13).

In this context, the present study investigated the risk stratification value of *BRAF* V600E specifically in SI-PTC. *BRAF* V600E clearly separated SI-PTC larger than 1 cm and 4.0 cm or less into different risk categories for disease recurrence; recurrence in larger *BRAF* mutation–positive tumors was especially high, particularly in SI-PTC larger than 2.0 cm and 4.0 cm or less or SI-PTC larger than 3.0 cm and 4.0 cm or less. These findings are consistent with the oncogenic role of *BRAF* mutation in the aggressiveness of PTC (15). A previous single-institution study on 319 patients also demonstrated an association between *BRAF* mutation and disease recurrence in noninvasive PTC (35), but this study included PTC with multifocality, which is a generally accepted indication for total thyroidectomy (8,9). The present large multicenter study focused on SI-PTC with specific stratified tumor sizes whose treatment mode is currently controversial. Given that recurrence occurred predominately in neck lymph nodes, a close preoperative, intraoperative, and posttreatment evaluation of neck lymph nodes is important in patients with *BRAF* mutation–positive PTC.

It is worth noting that the prognostic power (ie, HR) of *BRAF* mutation demonstrated here in SI-PTC, particularly in large tumors, was much higher than that demonstrated for *BRAF* mutation in general PTC (21). It is also important to note that in tumors larger than 2.0 cm and 4.0 cm or less or larger than 3.0 cm and 4.0 cm or less, the high recurrence rates in *BRAF* mutation–positive SI-PTC were comparable with those in their counterpart invasive solitary PTCs. Because total thyroidectomy is generally accepted for invasive solitary PTCs (8.9), given the similarly high recurrence rates, total thyroidectomy should be favored over lobectomy for *BRAF* mutation–positive SI-PTC larger than 2.0 cm and 4 cm or less, particularly tumors larger than 3.0 cm and 4.0 cm or less, which would be consistent with the 2009 ATA recommendations (8). In such patients, total thyroidectomy may facilitate radioiodine remnant ablation to enhance the specificity of thyroglobulin testing in the surveillance of disease recurrence and possibly reduce recurrence. This treatment strategy would be practical as only the minority of patients with SI-PTC were positive for *BRAF* V600E mutation; specifically, mutation-positive SI-PTC of any size account for 33.6% (321/955), mutation-positive SI-PTC larger than 1 cm and 4.0 cm or less account for 23.1% (221/955), and mutation-positive SI-PTC larger than 2.0 cm and 4.0 cm or less account for 8.3% (79/955) of all cases of SI-PTC. In contrast, the nearly zero mortality and extremely low recurrences of *BRAF* mutation–negative SI-PTC (NPVs 98%–100%) make it reasonable to treat these PTCs with thyroid lobectomy, which, except for tumors larger than 4.0 cm, would be consistent with the recent recommendations of the ATA guidelines (9). Given the low recurrence, even *BRAF* mutation–negative SI-PTC larger than 4.0 cm could be treated with lobectomy. These *BRAF* mutation–negative patients who can be treated with lobectomy represent the majority of SI-PTC, accounting for 66.4% (634/955) of all cases. This number becomes 75.2% (718/955) if including the 84 cases of *BRAF* mutation–positive SI-PTMC that can also be treated with lobectomy (see below).

A common clinical scenario for a solitary PTC larger than 1 cm and 4.0 cm or less is that preoperative ultrasonography shows no suspicious lymph nodes and extrathyroidal invasion. With the current ATA recommendations (9), lobectomy is a standard treatment option for these patients. The present study may call into question the general application of such treatment of patients with *BRAF* mutation–positive tumors, particularly tumors larger than 2.0 cm and 4.0 cm or less. As preoperative ultrasonography has a limited sensitivity in detecting central lymph node metastasis and extrathyroidal invasion (8,9), many patients in the above scenario may have occult lymph node metastasis and extrathyroidal invasion, which can synergize *BRAF* V600E in promoting PTC recurrence and mortality (21,22). If such patients are treated with lobectomy, which is generally associated with conservative neck dissection and no radioiodine ablation, when the tumor was positive for *BRAF* mutation, the recurrence risk could be higher than that observed in the present study, in which only SI-PTC surgically proven to lack lymph node metastasis and extrathyroidal invasion were studied.

The present study also demonstrated a very low recurrence in SI-PTMC, which was not statistically significantly affected by *BRAF* mutation. Thus, lobectomy for SI-PTMC regardless of the *BRAF* mutation status seems to be generally reasonable, which would be consistent with the ATA guidelines (8,9). Previous studies demonstrated an association between *BRAF* mutation and disease recurrence as well as patient mortality in PTMC (16,21,22,36). These studies, however, were on general PTMC, which often had lymph node metastasis and extrathyroidal invasion, unlike the present study, which focused on SI-PTMC. The positive effects of *BRAF* mutation in these studies on PTMC in fact reflect a synergism between *BRAF* mutation and aggressive clinicopathological risk factors as shown previously (21,22). Interestingly, the present study demonstrated a very low recurrence in *BRAF* mutation–negative SI-PTC larger than 4.0 cm, with a high NPV of *BRAF* mutation for disease recurrence. This finding seems to question the current practice of indiscriminative total thyroidectomy for PTCs larger than 4.0 cm recommended by the ATA (8,9).

A limitation of the present study was the lack of direct comparison of the prognostic effects of *BRAF* V600E between total thyroidectomy and lobectomy. However, the fact that all the patients received total thyroidectomy in the present study may have actually caused an underestimate of the effect of *BRAF* mutation on clinical outcomes because total thyroidectomy was shown to result in decreased disease recurrence and patient mortality of PTC compared with lobectomy, albeit more so in high-risk patients (37,38). Another limitation is the lack of information on other mutations, such as *RAS* and *TERT* promoter mutations. *RAS* mutations alone have no prognostic risk in thyroid cancer (39) while *TERT* promoter mutation is a recently emerged prognostic genetic marker in thyroid cancer (40,41). *TERT* promoter mutation alone, however, had limited prognostic risk (42,43). Indeed, in the Johns Hopkins cases, we found that *TERT* promoter mutation alone had no effect while *BRAF* mutation consistently had a statistically significant effect on SI-PTC recurrence, whether alone or when coexisting with *TERT* promoter mutation. Thus, testing *BRAF* V600E alone in assisting risk stratification of SI-PTC seems to be sufficient.

In summary, *BRAF* V600E mutation clearly differentiates SI-PTC into low- and high-risk categories. Recurrence rates are sufficiently high in patients with *BRAF* mutation–positive SI-PTC larger than 1 cm and 4.0 cm or less, particularly tumors larger than 2.0 cm and 4.0 cm or less, to favor total thyroidectomy as the surgical treatment. Conversely, thyroid lobectomy is favored for *BRAF* mutation–negative SI-PTC given the high NPV of *BRAF* mutation for disease recurrence, which is applicable to the vast majority of patients with SI-PTC. Thus, including *BRAF* V600E mutation as a prognostic genetic marker in risk stratification may help more precisely manage patients with SI-PTC. This study has broad clinical implications.

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Notes

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