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ORIGINAL REPORT

Association Between *BRAF* V600E Mutation and Recurrence of Papillary Thyroid Cancer

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See accompanying editorial on page 7; listen to the podcast by Dr Haddad at www.jco.org/podcasts

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ABSTRACT

Purpose
To investigate the prognostic value of *BRAF* V600E mutation for the recurrence of papillary thyroid cancer (PTC).

Patients and Methods
This was a retrospective multicenter study of the relationship between *BRAF* V600E mutation and recurrence of PTC in 2,099 patients (1,615 women and 484 men), with a median age of 45 years (interquartile range [IQR], 34 to 58 years) and a median follow-up time of 36 months (IQR, 14 to 75 months).

Results
The overall *BRAF* V600E mutation prevalence was 48.5% (1,017 of 2,099). PTC recurrence occurred in 20.9% (213 of 1,017) of *BRAF* V600E mutation–positive and 11.6% (125 of 1,082) of *BRAF* V600E mutation–negative patients. Recurrence rates were 47.71 (95% CI, 41.72 to 54.57) versus 26.03 (95% CI, 21.85 to 31.02) per 1,000 person-years in *BRAF* mutation–positive versus –negative patients ($P < .001$), with a hazard ratio (HR) of 1.82 (95% CI, 1.46 to 2.28), which remained significant in a multivariable model adjusting for patient sex and age at diagnosis, medical center, and various conventional pathologic factors. Significant association between *BRAF* mutation and PTC recurrence was also found in patients with conventionally low-risk disease stage I or II and micro-PTC and within various subtypes of PTC. For example, in *BRAF* mutation–positive versus –negative follicular-variant PTC, recurrence occurred in 21.3% (19 of 89) and 7.0% (24 of 342) of patients, respectively, with recurrence rates of 53.84 (95% CI, 34.34 to 84.40) versus 19.47 (95% CI, 13.05 to 29.04) per 1,000 person-years ($P < .001$) and an HR of 3.20 (95% CI, 1.46 to 7.02) after adjustment for clinicopathologic factors. *BRAF* mutation was associated with poorer recurrence-free probability in Kaplan-Meier survival analyses in various clinicopathologic categories.

Conclusion
This large multicenter study demonstrates an independent prognostic value of *BRAF* V600E mutation for PTC recurrence in various clinicopathologic categories.

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INTRODUCTION

Papillary thyroid cancer (PTC) is a common endocrine malignancy, which accounts for 80% to 85% of all thyroid cancers, and can be classified into several subtype variants, including the common conventional PTC (CPTC), follicular-variant PTC (FVPTC), and a few uncommon variants.[1,2] Although PTC is generally a highly curable disease, disease recurrence is common, and a subgroup of patients die, particularly when disease recurrence occurs.[3-5] These patients need to be identified for appropriately more-aggressive treatments to reduce the chance of disease recurrence and progression. Clinical decisions regarding these patients are classically based on clinicopathologic risk criteria, which are often inaccurate, sometimes making the current risk stratification of PTC clinically challenging.

In recent years, prognostic molecular markers have been vigorously sought to improve risk stratification of PTC, among which *BRAF* V600E mutation has received the widest attention. *BRAF* V600E

is a major oncogenic mutation in PTC, which promotes PTC tumorigenesis by aberrantly activating the MAP kinase pathway.[6] Many studies have demonstrated an association of *BRAF* V600E mutation with aggressive clinicopathologic characteristics of PTC,[6-9] showing promise of this mutation as a prognostic molecular marker for PTC. The association of *BRAF* V600E mutation with PTC recurrence demonstrated in several previous studies has particularly important clinical relevance. However, these studies represented mostly single-institution studies with relatively small series of patients, and the results were sometimes inconsistent. This makes debatable the prognostic value of *BRAF* V600E mutation in the management of PTC. Also, the important issue of whether the prognostic value of *BRAF* V600E mutation holds in individual subtype variants of PTC, such as FVPTC, has not been established, because previous studies were mostly performed collectively in all PTC variants, and their sample sizes did not provide sufficient power to stratify by variant. Here, we investigated the role of *BRAF* V600E mutation in the recurrence of PTC in a large multicenter study with the goal of establishing its prognostic value for PTC recurrence.

PATIENTS AND METHODS

Study Countries and Centers

This study was conducted at 16 medical centers in eight countries, including the Johns Hopkins Medical Institution, University of Pittsburgh Medical Center, Memorial Sloan-Kettering Cancer Center, and Yale University in the United States; medical centers at the University of Pisa, University of Perugia, University of Milan, University of Padua, and University of Bologna in Italy; Kanagawa Cancer Center in Yokohama, Japan; Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology in Poland; medical centers at Griffith University and University of Sydney in Australia; Hospital La Paz Health Research Institute in Spain; the Institute of Endocrinology in Prague, Czech Republic; and the University of Ulsan in South Korea.

Study Patients

The same study patients and institutions from a recent study[10] plus additional patients and institutions participated in this study. Briefly, patients were consecutively selected at each center over differing time periods spanning 1978 to 2011. Patients with PTC of all types were selected at all centers, except for Memorial Sloan-Kettering Cancer Center and Kanagawa Cancer Center, where patients with relatively more advanced disease were treated. All patients had been treated for PTC with total thyroidectomy, and therapeutic neck dissection and dissection extents were performed as clinically indicated. Pathologic diagnoses of PTC and variants were made based on WHO criteria and documented in our peer-reviewed publications.[11-25] Postoperative treatments included standard thyroid-stimulating hormone suppression at appropriate levels and radioiodine (ie, iodine-131 [^{131}I]) ablation (Appendix Table A1, online only) in patients at all centers, except for Kanagawa Cancer Center, where no ^{131}I treatment was used. PTC recurrence was defined as recurrent or persistent disease per authoritative histologic, cytologic, radiographic, or biochemical criteria.[26,27] Local, regional, and distant recurrences were all included. Follow-up time was defined as the time from initial surgical treatment to discovery of PTC recurrence or, in cases of no recurrence, to the most recent clinic visit.

Study Design

This was a retrospective study, as described recently,[10] which was approved by the institutional review board of each center, and informed patient consent was obtained where required. Patient consent was waived in some cases after institutional review board review, because the study only involved the use of thyroid tumor tissues and collection of clinicopathologic information. Disease stages of PTC were defined based on the American Joint Committee on Cancer staging system. Genomic DNA isolated from primary PTC tumors was sequenced at exon 15 of the *BRAF* gene to identify *BRAF* V600E mutation, as described in our previously published studies.[11-25] In all cases, *BRAF* V600E mutation status was examined after the surgical and radioiodine treatments and had no impact on the selection of treatments for patients. A uniform protocol designed for this study was used at all centers to obtain clinicopathologic information from the medical records. Data from all 16 centers were pooled for the analysis of the relationship between *BRAF* V600E mutation and recurrence of PTC.

Statistical Analyses

Recurrence rates per person-year were calculated by dividing the number of recurrences by the total follow-up time, and Poisson regression was used to calculate the 95% CIs and compare across *BRAF* V600E mutation status. Kaplan-Meier survival curves and log-rank tests, censoring patients at the time of last follow-up or 15 years, and Cox proportional hazards regression analysis, censoring patients at the time of last follow-up, were used to compare recurrence by *BRAF* V600E mutation status. A second proportional hazards regression model adjusted for patient age at diagnosis, sex, and medical center, along with a third model that additionally adjusted for tumor size, extrathyroidal invasion, lymph node metastasis, multifocality, and PTC subtype, was used to examine the independent effect of *BRAF* V600E mutation. The covariates were tested for the proportional hazards assumption using the assess statement in SAS software (version 9.3; SAS Institute, Cary, NC). The covariate medical center violated the proportional hazards assumption, and consequently, stratified models were used. A sensitivity analysis, excluding patients who did not experience recurrence but were observed for < 3 years, was performed to address concerns of shorter follow-up times at some centers. Synergy indexes (SIs), as described by Hosmer and Lemeshow,[28] were calculated to examine the additive interactions of *BRAF* V600E mutation with classical clinicopathologic risk factors in affecting the recurrence of PTC. All analyses were performed using SAS software (version 9.3). All reported *P* values were two sided, and significance was set at $P < .05$.

RESULTS

Patient Demographics

We studied a total of 2,099 patients (1,615 women and 484 men) across the 16 centers, with a median age of 45 years (interquartile range [IQR], 34 to 58 years). Patient age, sex, *BRAF* V600E mutation status, PTC recurrence, and follow-up time are summarized overall, by medical center, and by country in Table 1. The overall *BRAF* V600E mutation prevalence was 48.5%, and the overall PTC recurrence was seen in 16.1% of patients, comparable to the literature.[6-8] The overall median follow-up time for all patients was 36 months (IQR, 14 to 75 months). The median follow-up time was 35 months (IQR, 15 to 78 months) in the *BRAF* V600E–positive group and 36 months (IQR, 13 to 72 months) in the *BRAF* V600E–negative group ($P = .37$). ^{131}I doses used in the initial treatment of patients were not different between *BRAF* mutation–positive and –negative groups at most individual centers, but they were higher in *BRAF* mutation–positive patients at some centers and in the overall analysis of all patients (Appendix Table A1, online only).

Relationship Between BRAF V600E Mutation and Recurrence of PTC

The number of patients and proportion with recurrence, recurrence rates per 1,000 person-years, and hazard ratios (HRs) for all patients with PTC and by subtype are listed in Table 2. For all patients,

Table 1. Demographic and Clinical Characteristics, *BRAF* V600E Mutation, Recurrence, and Follow-Up Time by Medical Center and Country

Location	No. of Patients	Age at Diagnosis (years)		Male Sex		*BRAF* V600E Mutation		Recurrence, n (%)						Follow-Up Time (months)			
								All		*BRAF* V600E Positive		*BRAF* V600E Negative		All Patients		Patients With No Recurrence	
		Median	IQR	No.	%	No.	%	No.	%	No.	%	No.	%	Median	IQR	Median	IQR
Medical Center																	
Johns Hopkins Hospital	387	45	35 to 57	101	26	151	39	53	14	33	22	20	9	12	1 to 28	11	1 to 28
University of Pittsburgh	169	52	38 to 63	42	25	101	60	10	6	9	9	1	2	19	11 to 26	18	10 to 25
Memorial Sloan-Kettering Cancer Center	135	50	35 to 63	44	33	64	47	35	26	26	41	9	13	96	1 to 144	78	1 to 132
Yale University	18	36	32 to 49	4	22	8	44	3	17	2	25	1	10	5	1 to 14	3	1 to 14
University of Pisa	189	38	28 to 51	47	25	65	34	44	23	22	34	22	18	72	16 to 180	132	48 to 192
University of Perugia	117	49	37 to 59	32	27	76	65	23	20	12	16	11	27	21	6 to 39	18	5 to 40
University of Milan	110	42	34 to 55	24	22	38	35	23	21	7	18	16	22	48	24 to 64	58	26 to 70
University of Padua	135	48	39 to 57	32	24	87	64	17	13	10	12	7	15	26	22 to 30	26	22 to 31
University of Bologna	35	40	32 to 52	8	23	20	57	7	20	5	25	2	13	29	15 to 40	29	22 to 40
Kanagawa Cancer Center	49	55	41 to 65	16	33	33	67	19	39	15	45	4	25	68	28 to 75	73	61 to 78
Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology	99	49	33 to 59	10	10	42	42	4	4	2	5	2	4	48	42 to 53	48	43 to 54
Griffith University	76	40	34 to 56	20	26	34	45	4	5	3	9	1	2	42	4 to 82	40	2 to 79
University of Sydney	95	44	34 to 59	20	21	55	58	21	22	11	20	10	25	103	63 to 135	114	74 to 150
Hospital La Paz Health Research Institute	66	42	32 to 54	11	17	28	42	13	20	9	32	4	10	41	30 to 57	45	30 to 57
Institute of Endocrinology, Prague	222	47	31 to 60	39	18	71	32	22	10	12	17	10	7	50	29 to 85	50	30 to 84
University of Ulsan	197	43	35 to 52	34	17	144	73	40	20	35	24	5	9	105	58 to 120	109	69 to 121
Country																	
United States	709	47	36 to 58	191	27	324	46	101	14	70	22	31	8	16	2 to 35	15	1 to 30
Italy	586	44	34 to 55	143	24	286	49	114	19	56	20	58	19	32	18 to 63	36	23 to 75
Japan	49	55	41 to 65	16	33	33	67	19	39	15	45	4	25	62	28 to 75	73	61 to 78
Poland	99	49	33 to 59	10	10	42	42	4	4	2	5	2	4	48	42 to 53	48	43 to 54
Australia	171	43	34 to 57	40	23	89	52	25	15	14	16	11	13	74	32 to 118	78	35 to 120
Spain	66	42	32 to 54	11	17	28	42	13	20	9	32	4	10	41	30 to 57	45	30 to 57
Czech Republic	222	47	31 to 60	39	18	71	32	22	10	12	17	10	7	50	29 to 85	50	30 to 84
South Korea	197	43	35 to 52	34	17	144	73	40	20	35	24	5	9	105	58 to 120	109	69 to 121
Overall	2,099	45	34 to 58	484	23	1,017	48	338	16	213	21	125	12	36	14 to 75	37	15 to 79

Abbreviation: IQR, interquartile range.

20.9% (213 of 1,017) of *BRAF* mutation–positive patients and 11.6% (125 of 1,082) of *BRAF* mutation–negative patients experienced recurrence. Recurrence rates were significantly higher for *BRAF* mutation–positive compared with –negative patients (47.71 v 26.03 per 1,000 person-years), with an unadjusted HR of 1.82 (95% CI, 1.46 to 2.28), which remained significant after adjustment for patient age and sex and stratification by medical center (HR, 1.63; 95% CI, 1.29 to 2.06) and after additional adjustment for tumor size, extrathyroidal invasion, lymph node metastasis, multifocality, and PTC subtype (HR, 1.38; 95% CI, 1.07 to 1.80).

Restricting the analysis to patients with CPTC (Table 2), *BRAF* V600E mutation prevalence was 56.1% (813 of 1,448). In CPTC, 20.7% (168 of 813) of *BRAF* mutation–positive patients and 12.4% (79 of 635) of *BRAF* mutation–negative patients experienced recurrence. Recurrence rates were significantly higher for *BRAF* mutation–positive compared with –negative patients (44.92 *v* 25.63 recurrences per 1,000 person-years), with an unadjusted HR of 1.75 (95% CI, 1.34 to 2.29), which remained significant after adjustment for patient age and sex and stratification by center (HR, 1.48; 95% CI, 1.11 to 1.96) and after additional adjustment for pathologic characteristics (HR, 1.46; 95% CI, 1.08 to 1.99).

Restricting the analysis to patients with FVPTC (Table 2), the *BRAF* V600E mutation prevalence was 20.6% (89 of 431). In FVPTC, 21.3% (19 of 89) of *BRAF* mutation–positive patients and 7.0% (24 of 342) of *BRAF* mutation–negative patients experienced recurrence. Recurrence rates were significantly higher for *BRAF* mutation–positive compared with –negative patients (53.84 *v* 19.47 per 1,000 person-years), with an HR of 2.76 (95% CI, 1.51 to 5.06), which increased after adjustment for patient age and sex and stratification by center (HR, 4.02; 95% CI, 1.95 to 8.28) and remained significant after additional adjustment for pathologic characteristics (HR, 3.20; 95% CI, 1.46 to 7.02).

A sensitivity analysis excluding patients who did not experience recurrence but were observed for < 3 years was performed. The resulting person-year rates were slightly higher for both *BRAF* V600E mutation–positive and –negative patients,

Table 2. Relationship Between *BRAF* V600E Mutation and Tumor Recurrence in PTC of Various Subtype Variants

Type of PTC	*BRAF* Mutation		Tumor Recurrence						Person-Years of Follow-Up	Recurrence Rates					Model One*		Model Two†		Model Three	
			Overall		*BRAF* V600E Positive		*BRAF* V600E Negative			*BRAF* V600E Positive		*BRAF* V600E Negative								
	No.	%	No.	%	No.	%	No.	%		Per 1,000 Person-Years	95% CI	Per 1,000 Person-Years	95% CI	*P*§	HR	95% CI	HR	95% CI	HR	95% CI
All types	1,017 of 2,099	48.5	338 of 2,099	16.1	213 of 1,017	20.9	125 of 1,082	11.6	9,266.1	47.71	41.72 to 54.57	26.03	21.85 to 31.02	< .001	1.82	1.46 to 2.28	1.63	1.29 to 2.06	1.38	1.07 to 1.80
CPTC	813 of 1,448	56.1	247 of 1,448	17.1	168 of 813	20.7	79 of 635	12.4	6,822.2	44.92	38.62 to 52.26	25.63	20.56 to 31.95	< .001	1.75	1.34 to 2.29	1.48	1.11 to 1.96	1.46	1.08 to 1.99
FVPTC	89 of 431	20.6	43 of 431	10.0	19 of 89	21.3	24 of 342	7.0	1,585.7	53.84	34.34 to 84.40	19.47	13.05 to 29.04	< .001	2.76	1.51 to 5.06	4.02	1.95 to 8.28	3.20	1.46 to 7.02

Abbreviations: CPTC, conventional papillary thyroid cancer; FVPTC, follicular-variant papillary thyroid cancer; HR, hazard ratio; PTC, papillary thyroid cancer.
*Model one was unadjusted.
†Model two was adjusted for patient age and sex and stratified by medical center.
‡Model three was additionally adjusted for tumor size, extrathyroidal invasion, lymph node metastasis, and multifocality (and PTC subtypes for all-types group).
§ *P* values from Poisson regression comparing *BRAF* mutation–positive and –negative groups.

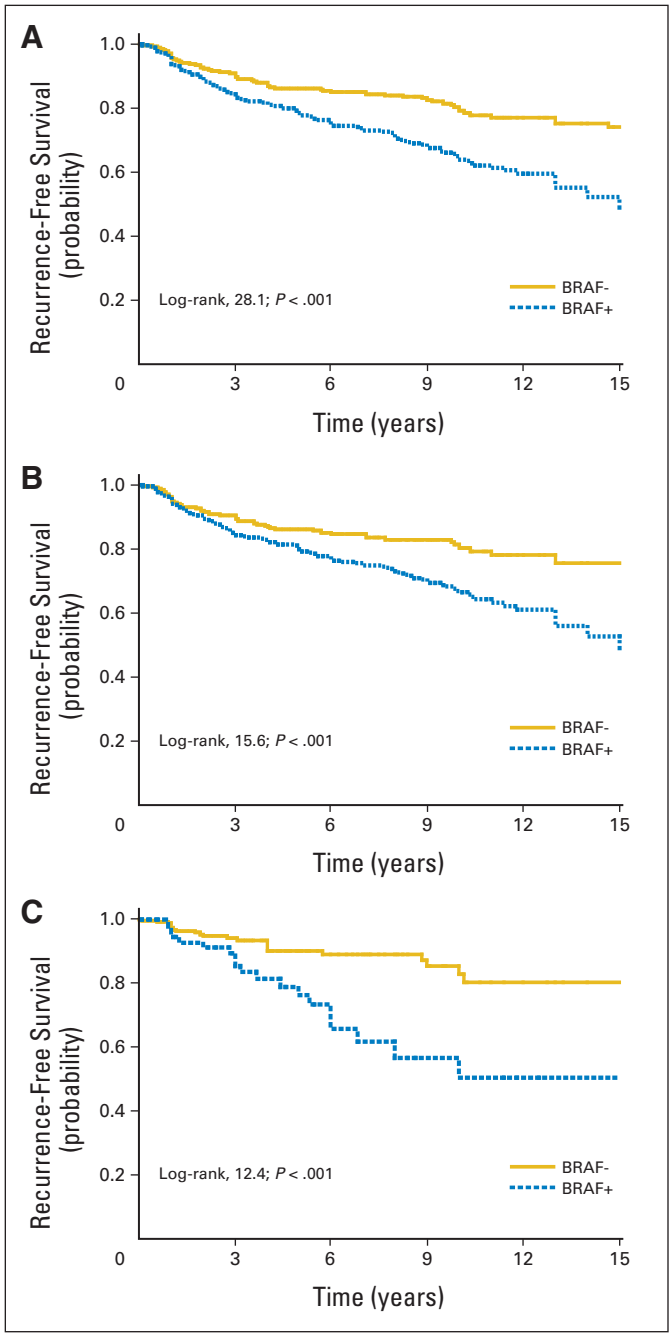

Fig 1. Kaplan-Meier survival curves of effect of *BRAF* V600E mutation status on disease recurrence–free probability in patients with various types of papillary thyroid cancer (PTC). Comparison of recurrence-free survival of patients, represented by indicated log-rank and *P* values in each panel, was performed between *BRAF* V600E–negative and –positive groups for (A) all patients, (B) those with conventional PTC, and (C) those with follicular-variant PTC. Follow-up time truncated at 15 years.

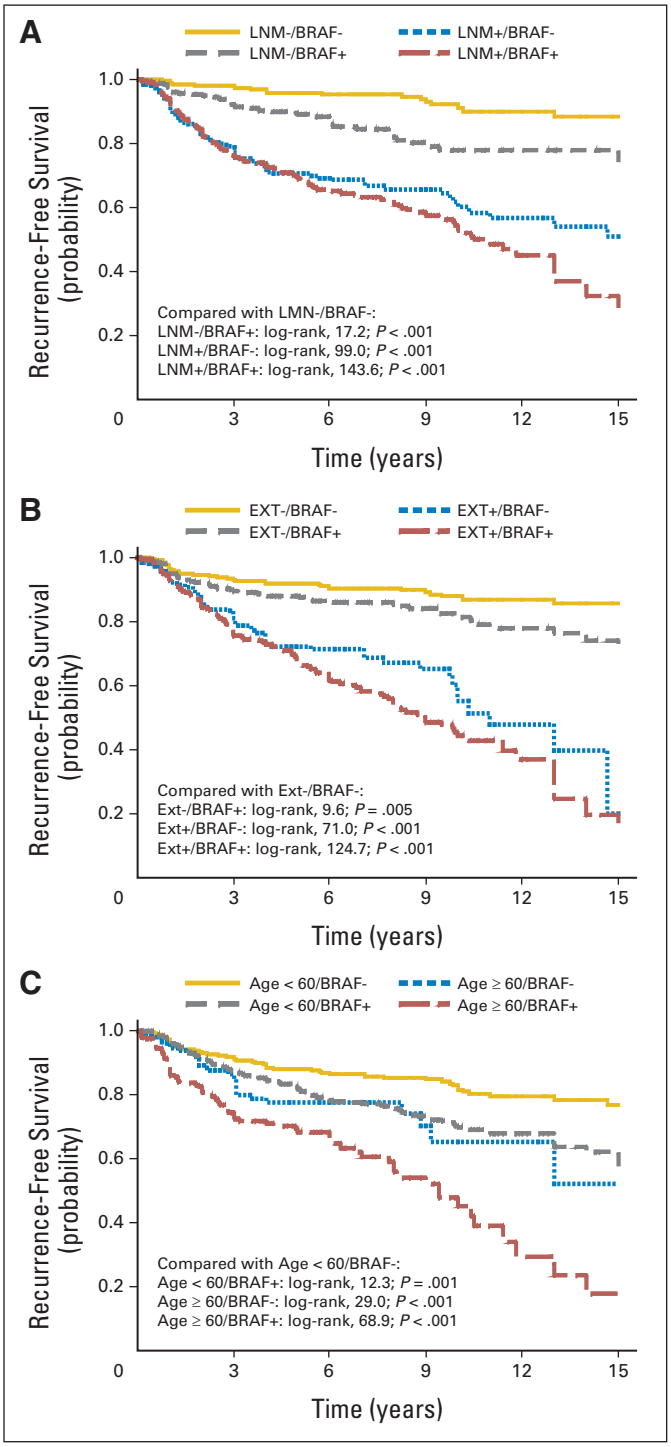

Fig 2. Kaplan-Meier survival curves of interaction of *BRAF* V600E mutation with clinicopathologic risk factors in affecting disease-free probability in patients with papillary thyroid cancer (all types). (A) Lymph node metastasis (LNM) and *BRAF* V600E mutation, (B) tumor extrathyroidal extension (EXT) and *BRAF* V600E mutation, and (C) patients age ≥ 60 years and *BRAF* V600E mutation. In each panel, *P* values were from log-rank tests, adjusted for multiple comparisons, comparing each stratum with patients negative for both *BRAF* V600E mutation and indicated clinicopathologic factor. Follow-up time truncated at 15 years.

but the risk ratios were similar to those reported for the full sample (data not shown).

Kaplan-Meier Analyses of PTC Recurrence-Free Probability

A significant association of *BRAF* V600E mutation with decreased recurrence-free probability is shown in Kaplan-Meier survival curves for all PTC (Fig 1A), CPTC only (Fig 1B), and FVPTC only (Fig 1C). We also compared the effects of *BRAF* V600E mutation and several classical clinicopathologic factors (Fig 2). In comparison with patients negative for both *BRAF* V600E mutation and lymph node

Table 3. Interactions of *BRAF* V600E With Conventional Risk Factors in Recurrence of PTC (all types): Synergy Test

Risk Factor for Interaction With *BRAF* V600E	Synergy Index*	95% CI
Patient age ≥ 45 years	3.22	0.69 to 15.01
Patient age ≥ 60 years	2.15	1.11 to 4.19
Lymph node metastasis	1.10	0.80 to 1.49
Extrathyroidal invasion	1.12	0.76 to 1.66

NOTE. Test method from Hosmer and Lemeshow.[28]
Abbreviation: PTC, papillary thyroid cancer.
*Synergy index different than 1 represents significant additive interaction; > 1 represents synergism; < 1 represents antagonism. There was significant synergistic interaction between *BRAF* V600E mutation and patient age ≥ 60 years in affecting recurrence of PTC. There were no significant interactions between *BRAF* V600E mutation and patient age ≥ 45 years, lymph node metastasis, or extrathyroidal invasion.

metastasis, those with either *BRAF* mutation or lymph node metastasis had a lower recurrence-free probability, and the probability was further reduced with coexisting mutation and lymph node metastasis (Fig 2A). Similarly, in comparison with patients negative for both *BRAF* mutation and extrathyroidal invasion, presence of either *BRAF* mutation or extrathyroidal invasion was significantly associated with a more rapid decline in the recurrence-free probability curve, and the curve declined further with coexisting mutation and extrathyroidal invasion (Fig 2B). Regarding patient age, in comparison with age < 60 years and *BRAF* mutation negativity, age < 60 years with *BRAF* mutation or age ≥ 60 years without *BRAF* mutation was significantly associated with a more rapid decline in the recurrence-free probability curve, and the curve declined further in patients age ≥ 60 years who were *BRAF* V600E mutation positive (Fig 2C).

To further examine the interactions of *BRAF* V600E mutation with clinicopathologic risk factors, we calculated the SI,[28] which tests for an additive interaction, representing synergism if the SI is > 1 and antagonism between the two factors if the value is < 1. We found a significant synergistic interaction between *BRAF* V600E mutation and patient age ≥ 60 years, with an SI of 2.15 (95% CI, 1.11 to 4.19; Table 3).

Effects of BRAF V600E Mutation on Recurrence of Conventionally Low-Risk PTC

BRAF V600E mutation was also significantly associated with PTC recurrence in conventionally low-risk patients (Table 4). In patients with stage I PTC, 12.1% (66 of 547) of *BRAF* mutation–positive patients and 7.3% (53 of 726) of *BRAF* mutation–negative patients experienced recurrence. Recurrence rates were significantly higher for *BRAF* mutation–positive versus –negative patients (25.61 *v* 15.75 per 1,000 person-years; $P = .008$), with an HR of 1.61 (95% CI, 1.12 to 2.31), which remained significant at 1.56 (95% CI, 1.04 to 2.34) after adjustment for patient age, sex, medical center, tumor size, extrathyroidal invasion, lymph node metastasis, and multifocality. In patients with stage II PTC, 20.7% (19 of 92) of *BRAF* mutation–positive patients and 9.2% (13 of 142) of *BRAF* mutation–negative patients experienced recurrence. Although these numbers were relatively small, *BRAF* mutation was still significantly associated with higher recurrence rates (54.99 *v* 22.65 per 1,000 person-years; $P = .01$) and risk (fully adjusted HR, 4.45; 95% CI, 1.70 to 11.67). In patients with micro-PTC, 17.8% (39 of 219) of *BRAF* mutation–positive patients and 5.7% (18 of 315) of *BRAF* mutation–negative patients experienced recurrence. Again, *BRAF* mutation was significantly associated with higher recurrence rates (43.85 *v* 13.04 per 1,000 person-years; $P < .001$) and risk (fully adjusted HR, 2.40; 95% CI, 1.00 to 5.75).

Significant effects of *BRAF* V600E mutation on PTC recurrence were also found with various tumor sizes (Appendix Tables A2 and A3, online only). When examined in various patient sex and age categories (Appendix Table A4, online only), significant effects of *BRAF* mutation on PTC recurrence were observed in both male and female patients and patients age ≥ 60 or ≥ 45 years. These effect patterns of *BRAF* mutation were reproduced in CPTC and FVPTC variants. Among most of these categories, the impact of *BRAF* V600E mutation on PTC recurrence was greatest in men age ≥ 60 years (Appendix Table A4, online only).

DISCUSSION

It is often a challenging task to risk stratify patients with PTC for optimal treatments. In recent years, promise for better prognostication of PTC has come from molecular markers.[9] The *BRAF* V600E mutation has emerged as one such promising molecular marker that has attracted considerable attention.[6-9] However, previous studies, which were relatively small and mostly single institution oriented, yielded inconsistent results, making *BRAF* V600E mutation debatable as a prognostic marker for PTC.[29-31]

In this study, we demonstrated a significant association of *BRAF* V600E mutation with recurrence of PTC, which was independent of conventional clinicopathologic risk factors, representing an incremental prognostic value of *BRAF* V600E mutation beyond the power of conventional clinicopathologic risk factors. We also observed a synergistic interaction between *BRAF* V600E mutation and older patient age in affecting PTC recurrence, which was similar to their synergistic effect on PTC-associated patient mortality.[10] It is worth noting that even in conventionally low-risk stage I or II disease and micro-PTC, *BRAF* V600E mutation was strongly associated with recurrence, confirming the findings in a recent smaller study.[32] Management of these patients is highly controversial.[33] The prognostic value of *BRAF* V600E mutation may help improve the risk stratification and treatment of these patients.

The prognostic value of *BRAF* V600E mutation in specific individual subtype variants of PTC has been rarely investigated in previous studies.[6-9] With the large size of this study, we were able to examine CPTC and FVPTC individually and similarly demonstrated a strong prognostic value of *BRAF* V600E mutation. It was particularly interesting to see, for the first time to our knowledge, a strong association of *BRAF* V600E mutation with recurrence of FVPTC. In fact, *BRAF* V600E mutation showed the most significant association and highest HRs for recurrence of FVPTC compared with CPTC and all PTCs. *BRAF* V600E mutation was previously reported to be most common in infiltrative FVPTC with lymph node metastases and extrathyroidal invasion,[34] consistent with the association of *BRAF* V600E mutation with FVPTC recurrence found in this study. FVPTC has been increasingly documented, and some studies have suggested an overall better prognosis than other PTC variants,[35] whereas other studies have suggested a prognosis for FVPTC similar to that for CPTC,[36] which tends to promote under-treatment in some practices, whereas unnecessary over-treatments may occur in other practices. The prognostic value of

Table 4. Relationship Between *BRAF* V600E Mutation and Tumor Recurrence in Low-Risk Clinicopathologic Categories of PTC

Clinicopathologic Category	Tumor Recurrence				Person-Years of Follow-Up	Recurrence Rates					Model One*		Model Two†		Model Three‡	
	BRAF V600E Positive		*BRAF* V600E Negative			*BRAF* V600E Positive		*BRAF* V600E Negative								
	No.	%	No.	%		Per 1,000 Person-Years	95% CI	Per 1,000 Person-Years	95% CI	*P*§	HR	95% CI	HR	95% CI	HR	95% CI
Stage I	66 of 547	12.1	53 of 726	7.3	5,941.8	25.61	20.12 to 32.60	15.75	12.03 to 20.62	.008	1.61	1.12 to 2.31	1.58	1.07 to 2.34	1.56	1.04 to 2.34
Stage II	19 of 92	20.6	13 of 142	9.2	919.5	54.99	35.08 to 86.22	22.65	13.15 to 39.00	.01	2.44	1.20 to 4.97	3.22	1.41 to 7.34	4.45	1.70 to 11.67
Tumor ≤ 1.0 cm	39 of 219	17.8	18 of 315	5.7	2,270.2	43.85	32.04 to 60.02	13.04	8.21 to 20.69	< .001	3.33	1.90 to 5.84	2.74	1.50 to 5.02	2.40	1.00 to 5.75

Abbreviations: HR, hazard ratio; PTC, papillary thyroid cancer.
*Model one was unadjusted.
†Model two was adjusted for patient age and sex and stratified by medical center.
‡Model three was additionally adjusted for tumor size, extrathyroidal invasion, lymph node metastasis, and multifocality (and PTC subtypes for all-types group).
§*P* values from Poisson regressions comparing *BRAF* mutation–positive and –negative groups.

BRAF V600E mutation in FVPTC may now help better define the vigorous levels of treatment for this cancer.

The aggressive role and prognostic value of *BRAF* V600E mutation in PTC can be explained by several molecular mechanisms, including its aberrant regulation of various signaling pathways, such as the MAP kinase pathway, NFκB pathway, and RASSF1A pathway; upregulation of various pro-oncogenic molecules; and downregulation of various tumor suppressor genes in thyroid cancer.[37] *BRAF* V600E mutation also uniquely downregulates thyroid iodide–metabolizing genes, such as sodium-iodide symporter (NIS),[37] thus explaining the initial finding of the association of *BRAF* V600E mutation with the loss of radioiodine avidity and hence radioiodine treatment failure in PTC.[13] The molecular mechanism for the silencing of NIS by *BRAF* V600E mutation was recently demonstrated to involve histone deacetylation at the *NIS* promoter.[38]

One weakness in this study was the potential patient inhomogeneity, as is often seen in multicenter studies. Some centers treated patients with more-advanced diseases, but the number of such patients was relatively small. Center stratification performed in this study helped minimize the effect of variations among centers. Also, the large multicenter study with worldwide geographic reach makes the findings highly generalizable. The median follow-up time of 36 months was relatively short, but this should have captured most recurrence events, because PTC recurs mostly within the first several years after the initial treatments. Treatment doses of radioiodine varied at different centers. However, within most centers, there was no significant difference in dose between *BRAF* mutation–positive and –negative patients. A higher overall dose of radioiodine was received by *BRAF* mutation–positive patients, presumably because these patients had more aggressive disease, which prompted more-aggressive treatments. This may have caused an underestimation of the effect of *BRAF* V600E mutation on PTC recurrence, because radioiodine treatment has been shown to reduce recurrence of PTC, particularly in patients with high-stage disease.[27]

In summary, this was a large multicenter study that provided sufficient power to address the prognostic value of *BRAF* V600E mutation for the recurrence of PTC in various clinicopathologic categories. These results, together with the recent demonstration of the strong association of *BRAF* V600E mutation with PTC-associated patient mortality, help establish a prognostic value of *BRAF* V600E mutation in PTC.

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Disclosures provided by the authors are available with this article at www.jco.org.

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Association Between *BRAF* V600E Mutation and Recurrence of Papillary Thyroid Cancer

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Appendix

Table A1. Initial Radioiodine Treatment Doses by *BRAF* V600E Mutation Status in PTC (all types)

Location	No. of Patients	*BRAF* Mutation Positive		*BRAF* Mutation Negative		
		Median	IQR	Median	IQR	*P**
			Medical Center			
Johns Hopkins Hospital	387	76	0 to 100	30	0 to 100	.03
University of Pittsburgh	162	135	106 to 161	105	0 to 134	< .001
Memorial Sloan-Kettering Cancer Center	90	104	30 to 197	75	0 to 150	.05
Yale University	17	158	51 to 243	100	0 to 209	.38
University of Pisa	189	30	30 to 30	30	30 to 30	.60
University of Perugia	117	100	50 to 100	100	50 to 100	.37
University of Milan	110	80	50 to 80	50	0 to 80	.07
University of Padua	135	100	100 to 150	100	100 to 150	.57
University of Bologna	32	100	50 to 100	100	98 to 100	.86
Kanagawa Cancer Center	49	0	0 to 0	0	0 to 0	1.0
Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology	98	100	100 to 100	100	100 to 100	.84
Griffith Medical School	0	—		—		—
University of Sydney	84	143	108 to 162	162	135 to 270	.26
Hospital La Paz Health Research Institute	66	120	100 to 150	100	100 to 150	.13
Institute of Endocrinology, Prague	221	100	0 to 102	100	0 to 119	.93
University of Ulsan	197	150	150 to 150	150	150 to 150	.008
			Country			
United States	656	100	0 to 140	53	0 to 103	< .001
Italy	583	100	30 to 100	50	30 to 100	< .001
Japan	49	0	0 to 0	0	0 to 0	1.0
Poland	98	100	100 to 100	100	100 to 100	.84
Australia	84	143	108 to 162	162	135 to 270	.26
Spain	66	120	100 to 150	100	100 to 150	.13
Czech Republic	221	100	0 to 102	100	0 to 119	.93
South Korea	197	150	150 to 150	150	150 to 150	.008
Overall	1954	100	50 to 150	100	27 to 103	< .001

Abbreviations: IQR, interquartile range; PTC, papillary thyroid cancer.
**P* value from Wilcoxon signed-rank test.

Table A2. Recurrence and HRs for *BRAF* V600E Mutation–Positive Versus -Negative Patients in Various Tumor Size Groups of PTC (all types)

Tumor Size Category (cm)	Recurrence						
	BRAF Mutation Positive		*BRAF* Mutation Negative				
	No.	%	No.	%	HR	95% CI	*P*
1.0 to 2.0	68 of 472	14.4	40 of 451	8.9	1.69	1.14 to 2.50	.009
2.0 to 3.0	60 of 292	20.6	37 of 263	14.1	1.66	1.09 to 2.50	.02
3.0 to 4.0	49 of 164	29.9	34 of 171	19.9	1.41	0.90 to 2.19	.13
≥ 4.0	55 of 129	42.6	29 of 146	19.9	1.88	1.20 to 2.95	.006

Abbreviations: HR, hazard ratio; PTC, papillary thyroid cancer.

Table A3. Recurrence per 1,000 Person-Years and Relative Risk in *BRAF* V600E Mutation–Positive Versus –Negative Patients in Various Tumor Size Groups of PTC (all types)

	Recurrence					
	BRAF Mutation Positive		*BRAF* Mutation Negative			
Tumor Size Category (cm)	Per 1,000 Person-Years	95% CI	Per 1,000 Person-Years	95% CI	Relative Risk	95% CI
1.0 to 2.0	31.71	25.00 to 40.22	18.36	13.47 to 25.03	1.73	1.17 to 2.55
2.0 to 3.0	45.33	35.20 to 58.39	27.36	19.82 to 37.76	1.66	1.10 to 2.50
3.0 to 4.0	64.02	48.39 to 84.71	46.48	33.21 to 65.05	1.38	0.89 to 2.13
≥ 4.0	91.92	70.57 to 119.73	49.28	34.25 to 70.92	1.87	1.19 to 2.92

Abbreviation: PTC, papillary thyroid cancer.

Table A4. Recurrence and HRs for *BRAF* V600E Mutation–Positive Versus –Negative Patients With PTC (all types) in Various Age and Sex Groups

	Recurrence					
	BRAF Mutation Positive		*BRAF* Mutation Negative			
Patient Age (years)	No.	%	No.	%	HR	95% CI
All PTCs						
All patients						
All ages	213 of 1,017	20.9	125 of 1,082	11.6	1.82	1.46 to 2.28
< 45	75 of 443	16.9	69 of 576	12.0	1.37	0.99 to 1.91
≥ 45	138 of 574	24.0	56 of 506	11.1	2.20	1.61 to 3.00
≥ 60	80 of 251	31.9	31 of 195	15.9	1.84	1.22 to 2.79
Women						
All ages	133 of 767	17.3	86 of 848	10.1	1.72	1.31 to 2.26
< 45	50 of 351	14.2	50 of 468	10.7	1.33	0.90 to 1.98
≥ 45	83 of 416	20.0	36 of 380	9.5	2.08	1.40 to 3.07
≥ 60	50 of 187	26.7	22 of 140	15.7	1.47	0.89 to 2.42
Men						
All ages	80 of 250	32.0	39 of 234	16.7	1.90	1.30 to 2.79
< 45	25 of 92	27.2	19 of 108	17.6	1.30	0.72 to 2.37
≥ 45	55 of 158	34.8	20 of 126	15.9	2.35	1.41 to 3.93
≥ 60	30 of 64	46.9	9 of 55	16.4	3.08	1.46 to 6.51
CPTC						
All patients						
All ages	168 of 813	20.7	79 of 635	12.4	1.75	1.34 to 2.29
< 45	64 of 368	17.4	46 of 345	13.3	1.26	0.86 to 1.85
≥ 45	104 of 445	23.4	33 of 290	11.4	2.33	1.57 to 3.46
≥ 60	56 of 193	29.0	18 of 111	16.2	1.90	1.11 to 3.24
Women						
All ages	104 of 612	17.0	50 of 501	10.0	1.74	1.24 to 2.44
< 45	43 of 296	14.5	30 of 281	10.7	1.35	0.84 to 2.16
≥ 45	61 of 316	19.3	20 of 220	9.1	2.23	1.34 to 3.70
≥ 60	34 of 143	23.8	13 of 81	16.0	1.41	0.74 to 2.70
Men						
All ages	64 of 201	31.8	29 of 134	21.6	1.70	1.09 to 2.65
< 45	21 of 72	29.2	16 of 64	25.0	1.01	0.53 to 1.95
≥ 45	43 of 129	33.3	13 of 70	18.6	2.47	1.32 to 4.63
≥ 60	22 of 50	44.0	5 of 30	16.7	3.90	1.47 to 10.32
FVPTC						
All patients						
All ages	19 of 89	21.4	24 of 342	7.0	2.76	1.51 to 5.06
< 45	6 of 35	17.1	15 of 175	8.6	2.06	0.79 to 5.38
≥ 45	13 of 54	24.1	9 of 167	5.4	3.50	1.49 to 8.23
≥ 60	8 of 16	50.0	4 of 60	6.7	3.43	0.97 to 12.13
Women						
All ages	12 of 70	17.1	21 of 266	7.9	2.17	1.06 to 4.45
< 45	4 of 28	14.3	15 of 143	10.5	1.43	0.47 to 4.36
≥ 45	8 of 42	19.0	6 of 123	4.9	3.50	1.21 to 10.12
≥ 60	5 of 12	41.7	3 of 41	7.3	4.86	0.90 to 26.37
Men						
All ages	7 of 19	36.8	3 of 76	4.0	5.60	1.44 to 21.76
< 45	2 of 7	28.6	0 of 32	0.0	*	
≥ 45	5 of 12	41.7	3 of 44	6.8	2.71	0.64 to 11.45
≥ 60	3 of 4	75.0	1 of 19	5.3	2.18	0.17 to 28.05

Abbreviations: CPTC, conventional papillary thyroid cancer; FVPTC, follicular-variant papillary thyroid cancer; HR, hazard ratio; PTC, papillary thyroid cancer.
*Could not be estimated.