BRAFV600E mutation in papillary thyroid microcarcinoma: a meta-analysis

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Abstract

The prognostic value of the BRAFV600E mutation, resulting in poor clinical outcomes of papillary thyroid carcinoma, has been generally confirmed. However, the association of BRAFV600E with aggressive clinical behaviors of papillary thyroid microcarcinoma (PTMC) has not been firmly established in individual studies. We performed this meta-analysis to examine the relationship between BRAFV600E mutation and the clinicopathological features of PTMC. We conducted a systematic search in PubMed, EMBASE, and the Cochrane library for relevant studies. We selected all the studies that reported clinicopathological features of PTMC patients with information available on BRAFV600E mutation status. Nineteen studies involving a total of 3437 patients met these selection criteria and were included in the analyses. The average prevalence of the BRAFV600E mutation was 47.48%, with no significant difference with respect to patient sex (male versus female) and age (younger than 45 years versus 45 years or older). Compared with the WT *BRAF* gene, the BRAFV600E mutation was associated with tumor multifocality (odds ratio (OR) 1.38; 95% CI, 1.04–1.82), extrathyroidal extension (OR 3.09; 95% CI, 2.24–4.26), lymph node metastases (OR 2.43; 95% CI, 1.28–4.60), and advanced stage (OR 2.39; 95% CI, 1.38–4.15) of PTMC. Thus, our findings from this large meta-analysis definitively demonstrate that BRAFV600E-mutation-positive PTMC are more likely to manifest with aggressive clinicopathological characteristics. In appropriate clinical settings, testing for the BRAFV600E mutation is likely to be useful in assisting the risk stratification and management of PTMC.

Key Words

- ▶ BRAFV600E mutation
- ▶ thyroid cancer
- ▶ papillary thyroid microcarcinoma
- ▶ meta-analysis
- ▶ prognosis

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Introduction

A papillary thyroid carcinoma (PTC) measuring ≤ 1.0 cm or less in size is defined as papillary thyroid microcarcinoma (PTMC) by the World Health Organization Histological Classification of Tumors, and is often an incidental finding on histopathologic examination after thyroid surgery (LiVolsi *et al.* 2004). Owing to the widespread application of high-resolution thyroid ultrasound (US) and US-guided fine-needle aspiration biopsy (FNAB), PTC has been increasingly discovered at early stages in recent years. PTMC thus has become the most common form of PTC, accounting for almost half of all PTCs in large series reported in recent years (Davies & Welch 2006). According to the United States' Surveillance, Epidemiology, and End Results (SEER) data, the proportion of PTMC patients among all PTC cases has been rising rapidly since the 1980s; for example, it rose from 30% in 1988 to 40% in 2003 (Ries *et al.* 2007). The clinical management of patients with PTMCs, however, remains variable and controversial, because these tumors generally have a clinically indolent and innocuous course with excellent clinical prognosis. Some cases of PTMC, however, do exhibit aggressive clinicopathological characteristics and poor clinical outcomes (Roti *et al.* 2008). Therefore, identification of markers capable of distinguishing these aggressive tumors, especially in the phase before surgery, would be very useful in guiding appropriate clinical management of PTMC.

The BRAFV600E mutation, a point mutation at codon 600 of BRAF, results in substitution of valine to glutamate (V600E), leading to constitutive activation of the BRAF kinase and consequent uncontrolled activation of the MAPK pathway signaling (Davies *et al.* 2002). It is the most common genetic event in PTC and has been identified in about 45% of PTC cases and 25% of anaplastic thyroid cancer; but it does not occur in other thyroid cancers and benign tumors (Xing 2005, 2007). PTMCs have also been shown to harbor BRAFV600E mutations, which are considered to be the early stage of PTCs (de Biase *et al.* 2014). In recent years, the BRAFV600E mutation has emerged as a highly specific diagnostic marker and a useful prognostic factor in the risk stratification of PTC (Xing 2007). Results from many studies have indicated that BRAFV600E mutation is significantly associated with aggressive clinicopathological features of PTC, such as multifocality, extrathyroid extension, lymph node metastases (LNM) at presentation, and advanced stage (Xing 2007, Mathur *et al.* 2010, Moses *et al.* 2010). Recent large meta-analyses of studies on general PTC

re-confirmed the association of the BRAFV600E mutation with prognostic factors and poor clinical outcomes of PTCs (Kim *et al.* 2012, Tufano *et al.* 2012). However, the value of the BRAFV600E mutation as a prognostic marker in PTMC is not entirely clear, although PTMC also belongs to the well-differentiated papillary carcinoma group. Results from some individual studies indicated that BRAFV600E mutation was significantly correlated with more aggressive characteristics of PTMCs (Lupi *et al.* 2007, Lee *et al.* 2009, Lin *et al.* 2010, Kurtulmus *et al.* 2012), while others did not show such a relationship (Kim *et al.* 2005, Kwak *et al.* 2009, Choi *et al.* 2013). A major limitation of these latter studies is the limited numbers of patients with PTMC. Thus, additional studies including larger numbers of patients are needed to determine whether the presence of the BRAFV600E mutation is a prognostic factor for patients with PTMC. To this end, we performed a comprehensive meta-analysis on a large number of patients to further examine the relationship between the BRAFV600E mutation and the clinicopathological features of PTMC.

Materials and methods

Search strategy and selection criteria

We searched PubMed, EMBASE, and the Cochrane Library databases to identify all potential clinical studies published before January 2014 that reported on BRAFV600E and aggressive clinical behaviors of PTMC. The following search terms were employed: PTMC, thyroid microcarcinoma, papillary microcarcinoma of the thyroid, micropapillary thyroid cancer, papillary microcarcinoma, and BRAF. In addition to the primary electronic search, we also reviewed the related citations in PubMed and examined the references of retrieved articles for any relevant articles. We screened and selected pertinent articles for inclusion by using the software EndNote X6 (Thomson Reuters (Scientific), Inc., Midtown Manhattan, New York, NY, USA). Any studies that reported the clinicopathological features of PTMC patients with information available on BRAFV600E mutation status were considered for inclusion. If a study reported data on both PTMC and PTC > 1.0 cm, only the former were used. The authors independently assessed articles for eligibility by screening all titles and abstracts and reviewing the full text of potentially relevant studies according to predefined inclusion and exclusion criteria. Any article was excluded i) if it only enrolled thyroid cancer subjects with tumor

Figure 1
The search strategy.

diameter >1.0 cm; ii) if it did not report any clinicopathological factors of the PTMC subjects (e.g., sex, age, multifocality, LNMs, extrathyroidal extension, and advanced stage); iii) if no *BRAF* mutation information was reported; iv) if it did not include PTMC defined by the WHO criteria; v) if only selected disease stages or only selected characteristics of PTMC were reported; and vi) if the study was published as an abstract, expert opinion, letter, conference article, editorial, case report, or review. When several papers were found analyzing the same population, only the most relevant was included. Only studies reported in English were included. Final selection of an eligible article was determined by consensus of the authors based on the above inclusion and exclusion criteria. Figure 1 summarizes the search strategy.

Data extraction

We extracted the following information from each study: the first author, year of publication, country, number of participants, patient sex and age, clinicopathological features (including multifocality, LNMs, extrathyroidal extension, and tumor stages), BRAFV600E mutation status, BRAFV600E mutation sequencing method, and sample source.

Data analyses and statistical methods

Statistical analysis was conducted using Stata software version 12.0 (StataCorp., College Station, TX, USA). The occurrence of BRAFV600E was treated as a dichotomous

variable and discrepancies between groups divided by clinicopathological factors were presented as odds ratios (ORs) with 95% CI, which were calculated using the Mantel-Haenszel method. Heterogeneity among the studies was tested using I^2 statistics, which are a quantitative tool of variability across studies. An I^2 value of 25, 50, and 75% indicates low, moderate, and high heterogeneity respectively (Higgins *et al.* 2003). We used a random effects model to synthesize the outcomes. To examine the robustness of the outcomes, we also performed sensitivity and subgroup analyses when heterogeneity was evident.

Results

The basic characteristics of the eligible studies are summarized in Table 1. Nineteen studies (Kim *et al.* 2005, Lupi *et al.* 2007, Rodolico *et al.* 2007, Frasca *et al.* 2008, Min *et al.* 2008, Kwak *et al.* 2009, Lee *et al.* 2009, Basolo *et al.* 2010, Jung *et al.* 2010, Lin *et al.* 2010, Kurtulmus *et al.* 2012, Marchetti *et al.* 2012, Schulten *et al.* 2012, Choi *et al.* 2013, Chung *et al.* 2013, Mussazhanova *et al.* 2013, Rossi *et al.* 2013, Virk *et al.* 2013, Zheng *et al.* 2013), including 3437 patients, fulfilled the eligibility criteria and were included in the meta-analysis. Overall, 1632 (47.48%) of these patients had BRAFV600E-mutation-positive PTMCs. Sample sizes of these studies ranged from 13 to 977 patients. The earliest study was published in November 2005 and the most recent study was published in July 2013. Not all of the studies had all of the variables of our interest and some studies contained variables not needed for this analysis. Therefore, for each study, we only analyzed data for the relevant variables. Virtually all of the included studies were retrospective studies. Four studies established BRAF status from FNAC materials, 11 studies from paraffin-embedded tissues, and the rest used a mixture of FNAC and paraffin-embedded tissues.

Sex

Eight studies (Kim *et al.* 2005, Kwak *et al.* 2009, Lee *et al.* 2009, Basolo *et al.* 2010, Choi *et al.* 2013, Mussazhanova *et al.* 2013, Virk *et al.* 2013, Zheng *et al.* 2013), involving 456 male and 1800 female patients, were analyzed for the association between BRAFV600E mutation and patient sex. BRAFV600E mutation was detected in 235 (51.54%) of the 456 male and 819 (45.50%) of the 1800 female PTMC patients. No significant association was found between sex and BRAFV600E mutation (Fig. 2; OR 1.36; 95% CI, 0.98–1.90). The heterogeneity among the studies was low ($I^2=30.6\%$).

Table 1 Characteristics of the included studies

Study	Country	No. of cases	Sex (F/M)	Mean age (years)	BRAFV600E mutation		
					Sample	Method	No. (%)
Kim <i>et al.</i> (2005)	Korea	60	56/4	46.3 ± 10.2	FFPE tissues	Sq	31 (51.67)
Rodolico <i>et al.</i> (2007)	USA	214	171/43	41.3 ± 9.9	FFPE tissues	ASA	88 (41.12)
Lupi <i>et al.</i> (2007) ^a	Italy	230	171/59	46.1 ± 12.7	FFPE tissues	SSCP and Sq	90 (39.13)
Min <i>et al.</i> (2008)	Korea	60	NA	NA	FFPE tissues	SSCP	32 (53.33)
Frasca <i>et al.</i> (2008)	Italy	103	NA	NA	FFPE tissues	Sq	25 (24.27)
Lee <i>et al.</i> (2009)	China	64	56/8	46.6 ± 11.0	FFPE tissue (n=40), fresh tissue (n=24)	Sq	24 (37.5)
Kwak <i>et al.</i> (2009)	Korea	339	295/44	45.4	FNAC	Sq	213 (62.83)
Basolo <i>et al.</i> (2010) ^a	Italy	578	435/143	<45, 48.09%	FFPE tissues	SSCP and Sq	229 (39.62)
Jung <i>et al.</i> (2010)	Korea	147	126/21	<45, 39%	FFPE tissues	Sq	110 (74.83)
Lin <i>et al.</i> (2010)	China	61	52/9	49.0 ± 12.4	FNAC	Sq	21 (34.43)
Marchetti <i>et al.</i> (2012)	Italy	85	NA	NA	FNAC	Sq	63 (74.12)
Kurtulmus <i>et al.</i> (2012)	Turkey	64	NA	38.7 ± 9.9	FFPE tissues	FMCA	19 (29.69)
Schulten <i>et al.</i> (2012)	Saudi Arabia	56	48/8	36.4 ± 13.5	FFPE tissues, FNAC	Sq	10 (17.86)
Rossi <i>et al.</i> (2013)	Italy	50	NA	NA	FNAC	Sq	34 (68)
Choi <i>et al.</i> (2013)	Korea	101	90/11	<45, 24.75%	FFPE tissues	Sq	72 (71.29)
Virk <i>et al.</i> (2013) ^b	USA	124	103/21	NA	FNAC (n=51), FFPE tissue (n=78)	SSCP	87 (70.16)
Mussazhanova <i>et al.</i> (2013)	Japan	13	11/2	45.9 ± 6.0	FFPE tissues	Sq	6 (46.15)
Zheng <i>et al.</i> (2013)	China	977	754/223	45.95 ± 10.5	FFPE tissues	Sq	392 (40.12)
Chung <i>et al.</i> (2013)	Korea	111	95/16	47.9 ± 13.6	FNAC (n=85), FFPE tissues (n=26)	Sq	86 (77.48)
Total	19 studies	3437					1632 (47.48)

FFPE, formalin-fixed, paraffin-embedded; FNAC, fine-needle aspiration cytology; Sq, sequencing; SSCP, single-strand conformational polymorphism; FMCA, fluorescence melting curve analysis; ASA, allele-specific amplification; NA, not available.

^aIn the two studies, the age at diagnosis of four patients from Lupi *et al.* (2007) and two patients from Basolo *et al.* (2010) was unknown.

^bBRAFV600E mutational analysis was performed in 129 tumors from 124 patients.

Age

To assess the relationship between BRAFV600E mutation and age, patients were divided into two groups based on age, one younger than 45 years and the other 45 years or older. Six studies were available for this analysis (Kim *et al.* 2005, Lupi *et al.* 2007, Basolo *et al.* 2010, Choi *et al.* 2013, Mussazhanova *et al.* 2013, Zheng *et al.* 2013), involving 1953 patients. Of the 1071 patients of 45 years age or older, 423 (39.50%) were BRAFV600E-mutation-positive, and 394 (44.67%) of the 882 patients younger than 45 years were BRAFV600E-mutation-positive. The association between BRAFV600E and patient age is close to significance (Fig. 3; OR 0.78; 95% CI, 0.60–1.00). The heterogeneity among the studies was low ($I^2 = 28.4\%$).

Thyroid multifocality

Ten studies (Kim *et al.* 2005, Lupi *et al.* 2007, Frasca *et al.* 2008, Kwak *et al.* 2009, Basolo *et al.* 2010, Lin *et al.* 2010, Kurtulmus *et al.* 2012, Marchetti *et al.* 2012, Choi *et al.* 2013, Zheng *et al.* 2013), including 2598 patients, were analyzed for the association between BRAFV600E

mutation and multifocality of PTMC. Of 1155 patients with BRAFV600E, 406 (35.15%) had multifocal disease, whereas 448 (31.05%) of the 1443 patients with WT BRAFV600E had multifocal disease. A significant association existed between the BRAFV600E mutation and multifocality (Fig. 4; OR 1.38; 95% CI, 1.04–1.82).

Figure 2

Random effect model of the odds ratios (ORs) with 95% CI of the frequency of BRAFV600E mutation associated with sex is shown.

Figure 3

Random effect model of the odds ratios (ORs) with 95% CI of the frequency of BRAFV600E mutation associated with age is shown.

The heterogeneity of the data was not significant and the I^2 estimate of the variance between the studies was 45.4%.

Extrathyroidal extension

Twelve studies (Kim *et al.* 2005, Lupi *et al.* 2007, Frasca *et al.* 2008, Lee *et al.* 2009, Basolo *et al.* 2010, Lin *et al.* 2010, Kurtulmus *et al.* 2012, Marchetti *et al.* 2012, Choi *et al.* 2013, Mussazhanova *et al.* 2013, Rossi *et al.* 2013, Zheng *et al.* 2013) involving 1006 patients with BRAFV600E and 1380 patients with WT *BRAF* were analyzed with regard to extrathyroidal extension. Extrathyroidal extension was detected in 393 (39.07%) of the 1006 patients with BRAFV600E, and was detected in 213 (15.43%) of the 1380 patients with WT *BRAF*. There was a significant association between BRAFV600E mutation and extrathyroidal extension (Fig. 5; OR 3.09; 95% CI, 2.24–4.26). No significant statistical heterogeneity was found among the studies ($I^2 = 36.3\%$).

Lymph node metastasis

Seventeen studies (Kim *et al.* 2005, Lupi *et al.* 2007, Rodolico *et al.* 2007, Frasca *et al.* 2008, Min *et al.* 2008, Lee *et al.* 2009, Basolo *et al.* 2010, Jung *et al.* 2010, Lin *et al.* 2010, Kurtulmus *et al.* 2012, Marchetti *et al.* 2012, Choi *et al.* 2013, Chung *et al.* 2013, Mussazhanova *et al.* 2013, Rossi *et al.* 2013, Virk *et al.* 2013, Zheng *et al.* 2013) including 1385 cases with BRAFV600E and 1620 patients with WT *BRAF* were analyzed with regard to LNM. LNM was found in 486 (35.09%) of 1385 cases with BRAFV600E and in 171 (10.56%) of 1620 patients with WT *BRAF*. There was a significant association between BRAFV600E mutation and LNM (Fig. 6; OR 2.43; 95% CI, 1.28–4.60). Significant statistical heterogeneity was found among

the studies ($I^2 = 85.8\%$). Sensitivity analysis was performed and, as a result, the heterogeneity of the data markedly decreased to 41.3% when the study of Zheng *et al.* (2013) was excluded. We did not find any other major changes when sensitivity analysis was performed in other cases. Therefore, this study was a major contribution to the heterogeneity. With this treatment, a significant association still existed between BRAFV600E mutation and LNM after exclusion of this study (OR 1.94; 95% CI, 1.35–2.79).

Advanced stages

Nine studies (Kim *et al.* 2005, Frasca *et al.* 2008, Kwak *et al.* 2009, Lee *et al.* 2009, Basolo *et al.* 2010, Lin *et al.* 2010, Schulten *et al.* 2012, Choi *et al.* 2013, Zheng *et al.* 2013) including 1017 patients with BRAFV600E and 1320 patients with WT *BRAF* were analyzed with regard to advanced stage of PTMC. Advanced stage (defined as TNM III/IV) was found in 356 (35.00%) of the 1017 patients with mutant *BRAF* and in 213 (16.14%) of the 1320 patients with WT *BRAF*. There was a significant association between BRAFV600E and advanced stage (Fig. 7; OR 2.39; 95% CI, 1.38–4.15). Significant heterogeneity was found among the studies ($I^2 = 77.7\%$).

Analyses of the effects of BRAFV600E mutation on the aggressive clinicopathological features of PTMC according to country

Subgroup analysis was conducted according to the country of the study subjects to investigate the potential sources of heterogeneity and assess whether the effects of BRAFV600E on aggressive clinicopathological features of

Figure 4

Random effect model of the odds ratios (ORs) with 95% CI of the BRAFV600E mutation associated with thyroid multifocality is shown.

Figure 5
Random effect model of the odds ratios (ORs) with 95% CI of the BRAFV600E mutation associated with extrathyroidal extension is shown.

PTMC were associated with geographic regions (Table 2). The effect estimates were broadly consistent among the subgroups that were analyzed. The heterogeneity was significantly decreased in the subgroup analysis of extra-thyroidal extension and advanced stage. However, the results of the subgroup analyses also indicated that BRAFV600E is not significantly associated with high-risk tumor features (e.g., extra-thyroidal extension, LNM, and advanced stage) of PTMC in patients from Korea, where the prevalence of the BRAFV600E mutation was unusually high. It is also notable that the Korean subgroup has a significant odds ratio for tumor multimodality, while the other geographical subgroups do not.

Discussion

In recent decades, the incidence of thyroid cancer, especially that of PTMC, has been rapidly rising (Davies & Welch 2006). In the United States, it has been reported that PTMC is the most common thyroid malignancy in patients older than the age of 45 years (Hughes et al. 2011). Therefore, it has become a major challenge to appropriately manage the increasing number of PTMC cases. PTMCs seem to consist of two biologically distinct subpopulations: a population with indolent tumors that have minimal or no potential for progression and a second population that has more aggressive behaviors and poor prognosis (Guerra et al. 2012a). Currently, for low-risk PTMC cases which are often incidentally detected by imaging studies, such as ultrasound screening, limited treatment with appropriate clinical monitoring without aggressive interventions is considered to be a reasonable therapeutic strategy (Ito &

Miyauchi 2007, 2009). However, this strategy is not applicable to patients with high-risk characteristics, such as those with extrathyroidal extension, LNM, advanced stages and distant metastasis because these factors are usually associated with aggressive cancer and a poor prognosis (Ito & Miyauchi 2007, 2009). Both European Thyroid Association (Pacini et al. 2006) and American Thyroid Association guidelines (Cooper et al. 2009) recommended hemithyroidectomy for PTMCs in the absence of preoperative evidence of LNM. Unfortunately, it is often not a straightforward task to identify pre-operative LNM in PTMCs because of the limitations associated with ultrasonographic examinations, which diminish the detection sensitivities. Thus, LNM is frequently found during an operation or in the pathology postoperatively, with an incidence reported to be 30–65% (Guerra et al. 2012a). As in PTC in general, LNM is also associated with tumor recurrence of PTMC as demonstrated in a large meta-analysis (Roti et al. 2008). In order to decrease the overall recurrence rate and possibly improve the survival rate, it would be reasonable to remove metastatic lymph nodes in the neck, which is the most common source of recurrence of PTMC. Thus, if known preoperatively to be associated with LNM, it would be reasonable to treat PTMC with total or near-total thyroidectomy with the appropriate extent of central neck dissection. On the other hand, indiscriminate prophylactic central compartment neck dissection is associated with significant risks of surgical complications such as the damage to the recurrent laryngeal nerve and hypoparathyroidism (Brown et al. 2008, Witt 2008) and should be avoided. Therefore, identification of aggressive PTMC

Figure 6
Random effect model of the odds ratios (ORs) with 95% CI of the BRAFV600E mutation associated with lymph node metastasis is shown.

Figure 7

Random effect model of the odds ratios (ORs) with 95% CI of the BRAFV600E mutation associated with the advanced stage (TNM III/IV) is shown.

preoperatively and design of appropriate treatments have become an important yet often challenging issue.

BRAFV600E has provided the promise of better and practically helpful risk stratification for PTC, including PTMC, which can be applied as a prognostic molecular marker for preoperative testing of FNAB specimens (Xing et al. 2009, Joo et al. 2012). Several molecular mechanisms are well known to underly the aggressive role of BRAFV600E. It has been widely demonstrated that the BRAFV600E mutation can promote upregulation of many tumor-promoting genes and downregulation of tumor suppressor genes and aberrant silencing of thyroid iodide-handling genes, impairing the sensitivity of PTC to radioactive iodine treatment (Liu et al. 2007, Xing 2013). These results all indicate that, biologically, the BRAFV600E mutation plays a critical role in the tumorigenesis, progression, and aggressiveness of PTC. This explains well the role of the BRAFV600E mutation in the increased risk of aggressiveness of PTMC positive for this mutation. Given the heterogeneity of *BRAF* mutation in PTC as indicated by the results of studies by the Vitale group (Guerra et al. 2012a,b) and the recent elegant de Biase study (de Biase et al. 2014), multifocal PTMC lesions may not necessarily harbor *BRAF* mutations.

As the utility of BRAFV600E mutation assessment in the management of PTC has been increasingly appreciated (Xing 2007, 2013, Kim et al. 2012, Xing et al. 2013a), mutational analysis may also be useful in the preoperative management of patients with PTMC. In this meta-analysis, we found a strongly significant association of BRAFV600E mutation with extrathyroidal invasion, multifocality, LNM, and advanced disease stages of PTMC, confirming that the presence of BRAFV600E is a risk for

increased aggressiveness of PTMC. Therefore, BRAFV600E may be a useful prognostic molecular marker to help identify PTMCs with increased risk of aggressive clinicopathological behaviors, including LNM and hence increased risk of disease recurrence. Xing et al. (2013b) carried out a study of 1849 patients to investigate the association between BRAFV600E and PTC-related mortality and found that the BRAFV600E mutation was significantly associated with increased cancer-related mortality among patients with PTC compared with the WT *BRAF* group. Many studies on PTC have also demonstrated a strong association between the BRAFV600E mutation and tumor recurrence (e.g., Xing et al. 2005, 2014, Elisei et al. 2012). There have been few studies that have assessed the relationship between patient survival or tumor recurrence of PTMC and the BRAFV600E mutation, and no reliable conclusions could be reached due to the relatively small number of cases in most studies. Subgroup analyses in two recent large multicenter studies demonstrated a significant association of the BRAFV600E mutation with tumor recurrence and patient mortality in PTMC (Xing et al. 2013b, 2014). However, larger studies could be even more helpful to definitively address the role of BRAFV600E in tumor recurrence and patient mortality of PTMC.

Table 2 Subgroup analyses of the effects of BRAFV600E mutation on the aggressive clinicopathological features of PTMC according to country

Subgroup	Total no. of patients	OR (95% CI)	I^2 (%)
Multifocality			
Korea (three studies)	500	1.54 (1.02–2.32)	0
Italy (four studies)	996	1.26 (0.84–1.90)	34.8
China (two studies)	1038	1.78 (0.42–7.55)	81.7
Turkey (one study)	64	2.75 (0.91–8.27)	0
Extrathyroidal extension			
Korea (two studies)	161	1.09 (0.56–2.12)	0
Italy (five studies)	1046	3.64 (2.59–5.12)	0
China (three studies)	1102	3.97 (2.46–6.40)	19.7
Others (two studies)	77	2.90 (0.70–12.00)	0
Lymph node metastasis			
Korea (five studies)	479	1.18 (0.67–2.08)	43.4
Italy (five studies)	1046	2.65 (1.56–4.50)	6.5
China (three studies)	1102	5.52 (1.02–29.91)	91.2
USA (two studies)	301	2.24 (1.23–4.11)	0
Others (two studies)	77	2.08 (0.23–18.79)	52.7
Advanced stage			
Korea (three studies)	500	0.97 (0.66–1.43)	0
China (three studies)	1102	3.98 (2.48–6.37)	20.7
Italy (two studies)	679	4.09 (2.34–7.17)	0
Saudi Arabia (one study)	56	2.44 (0.20, 29.94)	0

Although cancer-related mortality rate among patients with PTMC is extremely low, recurrence is relatively common and occurs in 4.0–13.4% of patients (Davies *et al.* 2002, Ross *et al.* 2009, Joo *et al.* 2012, Tufano *et al.* 2012), which is associated with an increase of fivefold in the risk of cancer-related death (Liu *et al.* 2007). Therefore, Xing (2009) suggested that the primary management goal for this cancer is to prevent its progression and to identify, prevent, and manage its recurrence. To this end, more aggressive treatment of BRAF-mutation-positive PTMC in appropriate clinical settings may be reasonable. This seems to be the case particularly in areas where the prevalence of BRAFV600E was low. In contrast, BRAFV600E may have relatively limited prognostic utility in areas, such as Korea, where the BRAFV600E mutation has an extremely high prevalence (Jung *et al.* 2010, Choi *et al.* 2013, Chung *et al.* 2013).

Conclusion

In conclusion, the results of this large meta-analysis demonstrate that the BRAFV600E mutation is strongly associated with aggressive clinicopathologic behaviors of PTMC, including extrathyroidal extension, LNM, and advanced stage. The BRAFV600E mutation may prove to be a useful prognostic molecular marker in assisting the risk stratification and management of PTMC in appropriately defined clinical settings.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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