Clinical Thyroidology / Original Paper

European Thyroid Journal

Eur Thyroid J
DOI: 10.1159/000490699

Received: November 3, 2017
Accepted after revision: June 4, 2018
Published online: ■■■

Evaluation of the Role of *BRAF*V600E Somatic Mutation on Papillary Thyroid Cancer Disease Persistence: A Prospective Study

Luca Damiani[a] Sabrina Lupo[b] Roberta Rossi[b] Stefania Bruni[b] Mirco Bartolomei[c] Stefano Panareo[c] Paola Franceschetti[b] Paolo Carcoforo[d] Giovanni Lanza[e] Stefano Pelucchi[f] Ettore degli Uberti[a, b] Maria Chiara Zatelli[a, b]

[a]Department of Medical Sciences, Section of Endocrinology and Internal Medicine, University of Ferrara, Ferrara, Italy; [b]Endocrine Unit, Azienda Ospedaliero-Universitaria di Ferrara, Cona/Ferrara, Italy; [c]Nuclear Medicine Unit, Azienda Ospedaliero-Universitaria di Ferrara, Ferrara, Italy; [d]Department of Morphology, Section of Surgery, Surgery and Experimental Medicine, University of Ferrara, Ferrara, Italy; [e]Department of Medical Sciences, Pathology Unit, University of Ferrara, Ferrara, Italy; [f]Department of Biomedical and Surgical Specialization Sciences, University of Ferrara, Ferrara, Italy

- Refs. 7+27 are the same, please amend.
- Please check the parts marked in yellow.

Keywords
BRAFV600E · Prognosis · Papillary thyroid cancer · Prospective study

Abstract
Background: *BRAF*V600E (c.1799T>A) somatic mutation evaluation in fine needle aspiration biopsies (FNAB) is a powerful diagnostic tool in the settings of papillary thyroid cancer (PTC). However, its prognostic value is still a matter of great debate and has been addressed mostly in retrospective studies. ***Objectives:*** To evaluate whether the somatic *BRAF*V600E mutation, assessed by direct sequencing in FNAB material of thyroid nodules, may correlate with disease persistence in PTC patients. ***Study Design:*** We conducted a prospective cohort study investigating 160 PTC patients previously assessed for the somatic *BRAF*V600E mutation, and submitted to total thyroidectomy, with a follow-up of 2–10 years. Patients were matched according to somatic *BRAF*V600E mutation (80 BRAF+ and 80 BRAF– patients) and to the presence (LN+, 40 patients each group) or absence (LN, 40 patients each group) of neck lymphnode metastases. Disease persistence was considered according to basal or TSH-stimulated Thyroglobulin (TG) levels, anti-TG antibodies, neck ultrasound, CT scan where applicable and whole body scan after radioiodine ablation treatment (RAI). ***Results:*** The presence of the somatic *BRAF*V600E mutation did not influence the indication for RAI. None of the enrolled patients showed disease recurrence or died due to disease-related causes. During follow-up, disease persistence did not correlate with the presence of somatic *BRAF*V600E mutation both in patients submitted to RAI nor in those treated more conservatively. ***Conclusions:*** The somatic *BRAF*V600E mutation does not associate with a worse prognosis in low risk PTC and, in our settings, may not be considered an independent risk factor for disease persistence.

KARGER

E-Mail karger@karger.com
www.karger.com/etj

Maria Chiara Zatelli, MD, PhD
Department of Medical Sciences, Section of Endocrinology and Internal Medicine, University of Ferrara
Via Ariosto 35, IT–44100 Ferrara (Italy)
E-Mail ztlmch@unife.it

Papillary Thyroid Carcinoma (PTC) incidence is increasing worldwide; despite excellent prognosis, 30% of patients may present persistent disease (PoD) or relapse [1–4]. The identification of novel prognostic markers is a matter of great interest. The somatic *BRAF*V600E mutation has a consolidated diagnostic role [5, 6], but its prognostic role is debatable. *BRAF*V600E correlates with many clinical and pathological PTC characteristics associated with high recurrence risk (HRR) and worse prognosis [7–12]. The Integrated Genomic Characterization of PTC study [13] indicates that "BRAF-like" tumours, showing a significant gene expression variation possibly accounting for the uncertainty regarding the prognostic and predictive power of *BRAF*V600E mutation, are predominantly less differentiated and may display a lower iodine up-take. A significant relationship was found between *BRAF*V600E, decreased disease-free survival rate [14–16] and increased mortality [17]. Two meta-analyses [12, 18] highlighted the relationship between *BRAF*V600E and a higher PoD risk or recurrence. However, the high prevalence of *BRAF*V600E (30–80%) and the not so low recurrence rate (30%) among PTCs [19] do not rule out the possibility that the association between these 2 variables may represent a coincidence, suggesting that they may not depend on each other. Russo et al. [20] retrospectively showed that *BRAF*V600E was not an independent predictor of unfavourable outcome, discouraging the use of this marker for prognostic purposes. In 185 unselected PTC patients followed up prospectively for ~5 years, *BRAF*V600E did not significantly associate with PoD/recurrence [21], suggesting the lack of prognostic value for this mutation. Another study [22] reported that *BRAF*V600E did not significantly correlate with patients (age, gender) or tumour (multicentricity, lymphocytic infiltration, stage) characteristics, showing a similar recurrence rate in both mutated and wild type patients. These conclusions are supported by the results of the most extensive retrospective study in the United States [23], showing the lack of any significant relationship between somatic *BRAF*V600E mutation and recurrence-free survival as well as disease-specific survival. The retrospective nature of these studies does not allow to possibility to draw definitive conclusion on the prognostic role of *BRAF*V600E somatic mutation. Therefore, the aim of our study was to prospectively evaluate the possible correlation between *BRAF*V600E somatic mutation and PTC persistence.

Materials and Methods

Patients

We selected 80 patients submitted to thyroidectomy for PTC with *BRAF*V600E somatic mutation, operated on between 2007 and 2014, for a prospective follow-up. This study is in accordance with the principles set out in the Declaration of Helsinki and informed consent was obtained from the participants to disclose their personal anonymous information.

A group of 80 patients submitted to thyroidectomy for PTC without *BRAF*V600E mutation was selected to match the patients displaying the mutation concerning gender, age, TNM, histotype. Each group (BRAF+ and BRAF–) included 40 patients with neck LN metastases (LN+) and 40 patients without neck LN metastases (LN–), according to the 8th TNM edition of the American Joint Committee on Cancer (AJCC) [24]. The 4 groups (BRAF+LN–; BRAF+LN+; BRAF–LN–; BRAF–LN+) were comparable in terms of sex, age, histotype and disease stage at diagnosis (Table 1).

Patients underwent a visit 3 months after surgery (Fig. 1) evaluating basal and recombinant human TSH-stimulated thyroglobulin (TG) levels, anti-TG antibody (ATG) levels, neck ultrasound (US), whole-body I^{131} scan. On the basis of disease stage, patients were submitted to radioiodine ablation treatment ablation (RAI) with 50–100 mCi. TG and ATG levels were evaluated by the TG Kit (33860; sensitivity = 0.1 ng/mL) and the TG Antibody II kit (A32898; sensitivity <0.9 IU/mL) respectively (Beckman Coulter). Follow-up is detailed in Figure 1. Patients with PoD were followed up at shorter time-points, depending on the clinical characteristics.

Biochemical PoD was defined when TSH-stimulated TG levels were >2 ng/mL or ATG were measurable (with undetectable basal TG levels). Morphological PoD was considered the detection of pathological LN at neck US, with histological confirmation. Imaging studies (i.e., computed tomography, MRI, whole-body I^{131} scan or FDG-PET) were performed where indicated. Clinical follow-up ranged from 2 to 10 years. Before surgery, all patients underwent US-guided FNAB and aspirates were evaluated for cytology and submitted to *BRAF*V600E somatic mutation analysis as previously described [25].

Statistical Analysis

The chi-square (χ^2) test was performed to evaluate the presence of statistically significant differences among the evaluated groups in terms of clinical and pathological characteristics and clinical outcome. The paired Student *t* test was employed to compare the mean age. A p value <0.05 was considered significant.

Results

At diagnosis, 85.6% of patients had Stage I disease, indicating a very low risk of disease recurrence (LRR); none of the evaluated patients displayed disease recurrence during follow-up. Among the 160 PTC patients, 126 were submitted to RAI (74LN+ and 52LN–). LN status significantly associated with RAI therapy ($p < 0.01$), indicating that the choice to submit the patient to RAI was influenced by nodal status. Of these 126 patients, 65 were

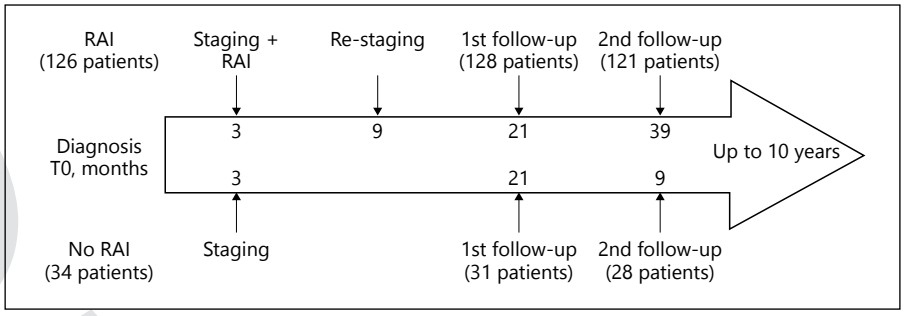

Fig. 1. Study design and follow-up structure. RAI, radioiodine ablation treatment.

Table 1. Patients' characteristics at diagnosis

Patients/tumour characteristics	BRAF+		BRAF–	
	LN+	LN–	LN+	LN–
Number	40	40	40	40
Mean age ± SE	50.20±2.53 (25 aged <55 years)	48.45±2.05 (29 aged <55 years)	50.73±2.55 (25 aged <55 years)	47.50±1.92 (27 aged <55 years)
Gender, male/female ratio	13/27 = 0.48	6/34 = 0.18	13/27 = 0.48	6/34 = 0.18
Classic histology PTC, %	92.5	87.5	92.5	86.1
Follicular variant PTC, %	7.5	12.5	7.5	13.9
MicroPTC (≤1 cm)	35	31	34	26
PTC >1 cm	5	9	6	14
Multifocal disease	11	6	18	9
Bilateral disease	7	3	9	6
T1a	35	31	34	25
T1b	3	3	4	6
T2	1	4	1	3
T3	1	1	1	4
T4a	0	0	0	2
T4b	0	1	0	0
Stage I	37	31	37	32
Stage II	0	0	0	0
Stage III	3	1	3	1
Stage Iva	0	7	0	6
Stage IVb	0	1	0	1

BRAF+ (60 received 100 mCi and 5 received 50 mCi) and 61 were BRAF– (52 received 100 mCi and 9 received 50 mCi), indicating that BRAF status did not influence the choice to submit the patient to RAI and the dose to be used. Among LN+ patients, 6 were not submitted to RAI (noRAI) due to the presence of co-morbidities. Among the 80 LN– patients, 28 did not undergo RAI and were free of disease (FoD) at the last follow-up.

Follow-Up and Outcome of Patient not Undergoing RAI

At first follow-up, among the 34 noRAI patients, 6LN+ patients had co-morbidities; among these, one died due to kidney cancer (BRAF–LN+), one for ischemic stroke and one due to cardiovascular disease (both BRAF+LN+), while the other 3 (2BRAF+LN+ and 1BRAF–LN+) patients showed PoD with stable TG levels. These 3 noRAI patients due to kidney failure. The other 28 patients were FoD (11BRAF+LN– and 17BRAF–LN–) at last follow-up.

At second follow-up, 3 patients with PoD (2BRAF+LN+ and 1BRAF–LN+) were lost at follow-up (LaF). All the 28LN– patients (11BRAF+ and 17BRAF–) were confirmed as FoD.

At last follow-up, among the 28 patients who continued to be followed up at our centre, 6 patients were LaF (1BRAF+LN– and 5BRAF–LN–), 1 (BRAF+LN–) died

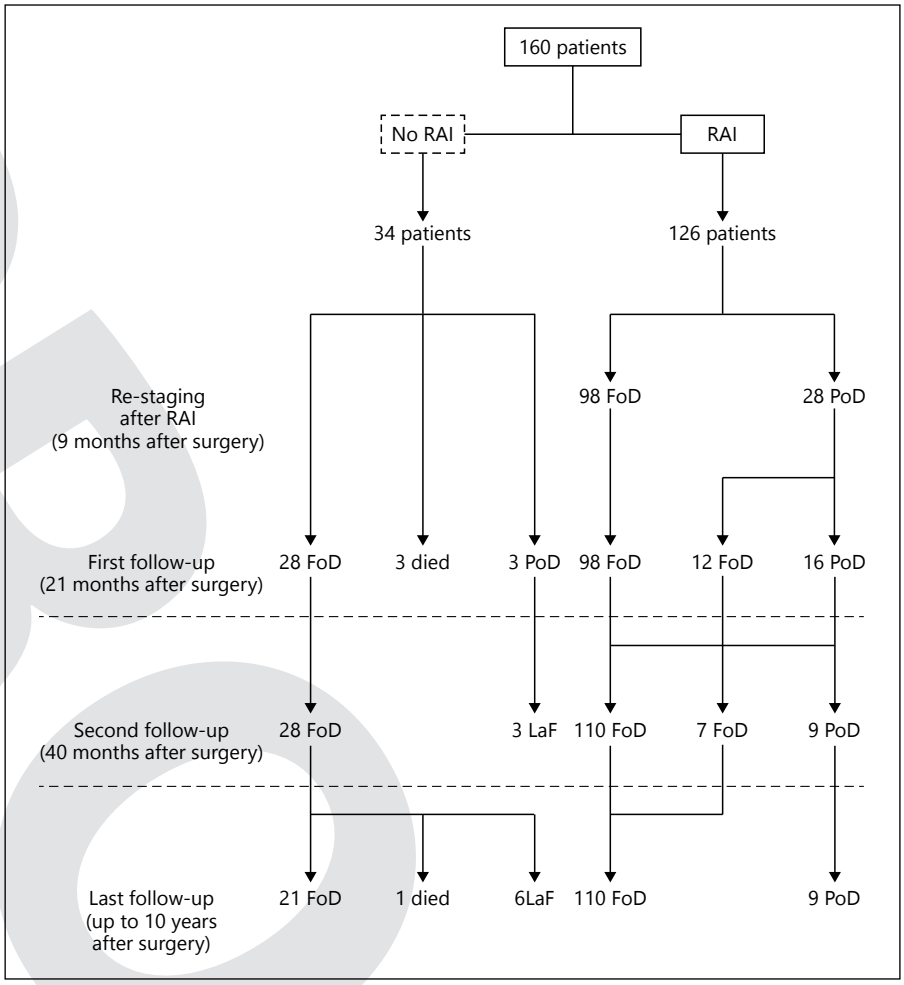

Fig. 2. Patients' outcome during follow-up. RAI, radioiodine ablation treatment; FoD, disease free; PoD, disease persistence; LaF, lost at follow-up.

due to other causes, while the other 21 (9BRAF+LN– and 12BRAF–LN–) were confirmed as FoD (mean follow-up = 69.7 ± 4.5 months; Fig. 2).

Follow-Up and Outcome of Patient Undergoing RAI

At re-staging, among the 126 patients submitted to RAI, 28 showed PoD, while 98 were considered FoD, including all the 14 patients that received 50 mCi. Sixteen patients were BRAF+ and 12 were BRAF–, indicating that PoD was independent of BRAF status ($p = 0.52$). In addition, 20 were LN+ and 8 were LN–, but no statistically significant association was found between nodal status and PoD ($p = 0.13$). More than 70% of these patients displayed biochemical persistence (14 with measurable Tg and 6 with measurable ATG levels), while 8 displayed structural persistence (Table 2 for BRAF status description). These results indicate that BRAF and nodal status do not predict PoD 6 months after RAI.

At first follow-up, lack of PoD was confirmed in the 98 patients who were FoD at re-staging. Among the 28 patients showing PoD at re-staging, at first follow-up, 16 showed PoD, while 12 were considered FoD, mainly due to the normalization of previously elevated ATG levels. Among the 16 patients with PoD, 8 were BRAF+ and 8 BRAF–, indicating that PoD was once again independent of BRAF status. In addition, 12 were LN+ and 4LN–, but no statistically significant association was found between nodal status and PoD at first follow-up ($p = 0.68$). These results indicate that BRAF and nodal status do not predict PoD 18 months after RAI.

At second follow-up, lack of PoD was confirmed in the 110 patients who were FoD at first follow-up. Among the 16 patients showing PoD at the first follow-up, 9 showed PoD, while 7 were FoD, mainly due to the normalization of previously elevated ATG levels. Among the patients with PoD, 4 were BRAF+ and 5BRAF–, indicating that PoD was independent of BRAF status. In addition, 8 were

Table 2. Clinical characteristics of patients showing disease persistence at re-staging after RAI

Patient	BRAF status	Initial stage	N	M	Disease persistence at re-staging after RAI
1	+	Iva	0	0	Biochemical (Tg)
2	+	I	0	0	Biochemical (Tg)
3(A)	+	IVa	0	0	Biochemical (Tg)
4	+	IVa	0	0	Biochemical (Tg)
5	+	I	0	0	Biochemical (Tg)
6(B)	+	IVa	0	0	Biochemical (Tg)
7	+	I	0	0	Biochemical (Tg)
8(D)	+	I	0	0	Biochemical (Tg)
9	–	I	0	0	Biochemical (Tg)
10	–	I	0	0	Biochemical (Tg)
11(H)	–	IVb	0	0	Biochemical (Tg)
12	–	I	0	0	Biochemical (Tg)
13	–	I	0	0	Biochemical (Tg)
14	–	I	0	0	Biochemical (Tg)
15	+	III	0	0	Biochemical (ATG)
16	+	I	0	0	Biochemical (ATG)
17	+	I	0	0	Biochemical (ATG)
18	–	I	0	0	Biochemical (ATG)
19	–	I	0	0	Biochemical (ATG)
20(G)	–	III	0	0	Biochemical (ATG)
21(C)	+	IVb	1	0	Structural
22	+	IVa	1	0	Structural
23	+	I	1	0	Structural
24	+	I	1	0	Structural
25(F)	–	III	1	0	Structural
26(E)	–	IVa	1	0	Structural
27(I)	–	I	0	Lung	Structural
28	–	I	1	0	Structural

Letters indicate patients showing disease persistence at last follow-up (see Table 3 for details).

Table 3. Clinical characteristics of patients submitted to RAI showing disease persistence at last follow-up

Patient	BRAF status	Initial stage	N	M	Follow-up months
A	+	IVa	0	Lung	40
B	+	IVa	0	0	108
C	+	IVb	0	0	72
D	+	I	1	0	48
E	–	IVa	1	0	84
F	–	III	1	0	48
G	–	III	0	Tonsil	48
H	–	IVb	0	0	60
I	–	I	0	Lung	108

LN+ and 1LN–, but no statistically significant association was found between nodal status and PoD at second follow-up ($p = 0.07$). These results indicate that BRAF and nodal status do not predict PoD 21 months after RAI.

At last follow-up: all the 9 patients displaying PoD at second follow-up still showed PoD. Among the 4BRAF+ patients (follow-up range: 40–108 months), 2 showed the presence of metastases (1 in the lung and 1 in neck lymph nodes) and 2 received a second RAI treatment. Among the 5BRAF– patients (follow-up range: 48–108 months), 4 showed metastases (1 lung, 2 neck lymph nodes and 1 tonsil) and 4 received a second RAI treatment. In addition, the patient with lung metastases is currently treated with TKI due to progressive disease (Table 3). Among the 126 patients submitted to RAI, 117 patients did not show PoD/recurrence (follow-up range: 40–114 months; Fig. 2).

These results indicate that BRAF status in patients submitted to RAI does not seem to characterize patients with a worse prognosis. On the contrary, BRAF– patients in our series had a worse outcome, even though no definitive conclusion can be drawn due to the paucity of patients showing PoD.

Discussion

This prospective study demonstrates that BRAF status does not influence short-term prognosis in LRR PTCs, even with metastatic lymph nodes. Our data show that there is no significant difference between patients with BRAF+PTC and those with BRAF–PTC concerning PoD at any time during a 40–108 months follow-up after surgery. Our results suggest that *BRAF*V600E may not have a prognostic significance and are consistent with those of a prospective study evaluating an unselected series of 185 PTC patients [21], where *BRAF*V600E did not significantly associate with PoD/recurrence at the end of follow-up (~5 years). However, this study does not take into account PTC risk factors independently of *BRAF*V600E. At the opposite, our study has been designed to assess the impact of *BRAF*V600E mutation independently of other PoD/recurrence risk factors (age, gender, and disease stage). On the other hand, the criteria adopted to match BRAF+ with BRAF– patients do not take into account possible prognostic characteristics different from those indicated by current literature. Xing et al. [16] showed that *BRAF*V600E has an independent prognostic value, since it significantly associates with PTC recurrence. However, the latter study is retrospective (mean follow-up = 35 months) and evaluates disease recurrence, while

in our study none of the patients had a recurrence. This difference may be due to the different patients population in the 2 studies: patients having a PTC >2 cm in diameter at diagnosis were 55.5% in the study by Xing et al. ■■ and only 11.9% in our study. Moreover, in our study<30% of the patients had a multifocal disease, which is correlated with a higher recurrence rate [26], further indicating an LRR population in our study. Indeed, we observed PoD rather than recurrence, indicating that early diagnosis prevents PTC relapse. On the contrary, Fugazzola et al. [22] included a greater HRR patients' portion. They found that *BRAF*V600E tended to associate with a greater tumour diameter, and lymph-node metastases, but failed to reach statistical significance. Therefore, it appears that in our country, PTC patients' prognosis is not affected by *BRAF*V600E.

On the contrary, we cannot draw any conclusion concerning the association between BRAF status and mortality, since none of our patients died due to PTC-related causes. A much longer follow-up is necessary in order to observe an impact on mortality, as found in the multicentre retrospective study by Xing et al. [17], which encompasses 46 years of follow-up. In the latter study, *BRAF*V600E significantly associates with increased PTC-related mortality, even though this association was not independent of tumour features.

In our study, BRAF status did not influence the choice of submitting the patients to RAI, which was rather guided by initial disease stage, and in particular, by nodal status, in keeping with the indications issued by the ATA 2009 guidelines [27]. Nodal status could have been influenced by the surgical approach [28], but we controlled for this variable taking into account 2 groups of wild-type and mutated patients, matched also according to the presence or the absence of LN. In light of the ATA 2015 guidelines, a much lower number of patients would have been addressed to RAI. However, the outcome of these patients might not have been different, since the majority of our patients belong to the LRR category.

In addition, among patients submitted to RAI, BRAF status was not significantly associated with prognosis in terms of PoD, which seems rather to be correlated with nodal status. In keeping with our results, a previously published study has shown that RAI outcome in PTC patients without distant metastases is not significantly influenced by BRAF status, even in patients with HRR at diagnosis [29]. Similarly, a retrospective study taking into account patients with a PTC >1 cm showed that mutant and wildtype BRAF subgroups did not differ in radioiodine sensitivity [30]. On the contrary, the presence of a *BRAF*V600E mutation in the primary tumour seems to predict a worse RAI up-take in distant metastases, and, consequently, a poorer prognosis [31]. However, our study did not include patients with distant metastases at diagnosis and the difference in PoD among LN+ patients and that in LN– patients did not reach statistical significance at any follow-up time point, preventing us from drawing any definitive conclusions on this issue. The majority of our patients was diagnosed and treated at a very early stage, allowing them to be FoD at the end of follow-up. The lack of PoD, at the same time, indicates that follow-up intervals could be extended in patients with LRR. Similarly, none of the patients not submitted to RAI showed PoD, in both BRAF+ and BRAF– groups. Therefore, a definitive conclusion cannot be drawn as to the prognostic role of BRAF status in this patient group, even though our data may suggest that the presence of *BRAF*V600E does not associate with a worse prognosis. On the other hand, our data shows that patients were correctly addressed to a conservative management, confirming that a less aggressive management of LRR PTC results in the lack of PoD. In a previous report on low-risk PTCs, BRAF was predictive of a worse outcome [32]. However, in the examined unselected population, patients with BRAF+ PTCs differed from those with BRAF– PTCs at diagnosis as concerns several characteristics. In our study, on the contrary, initial patients and tumour characteristics perfectly match in the groups of mutated as compared to wild-type BRAF patients.

In conclusion, our results, which are deeply influenced by the very strict inclusion criteria leading to a limited patients' sample, show that BRAF status does not have a prognostic role in the short term in LRR patients, indicating that *BRAF*V600E may not represent an independent prognostic factor. Large prospective case-control studies recruiting patients with PTC at high or intermediate risk of recurrence at diagnosis are necessary to clarify the prognostic role of BRAF status in PTC patients.

Disclosure Statement

M.C.Z. has received consultant fees from Novartis and Genzyme. E.d.U. has received consultant fees from Novartis and grant support from Sanofi. The other authors have nothing to disclose.

Funding Source

This work has been supported by funds from the Italian Ministry for University and Research PRIN 2015 (2015HPMLFY).

References

1 Udelsman R, Chen H: The current management of thyroid cancer. Adv Surg 1999;33:1–27.
2 Paterson IC, Greenlee R, Adams Jones D: Thyroid cancer in Wales, 1985–1996: a cancer registry based study. Clin Oncol (R Coll Radiol) 1999;44:245–251.
3 Soares P, Trovisco V, Rocha AS, Lima J, Castro P, Preto A, Máximo V, Botelho T, Seruca R, Sobrinho-Simões M: BRAF mutations and RET/PTC rearrangements are alternative events in the etiopathogenesis of PTC. Oncogene 2003;22:4578–4580.
4 Omry-Orbach G: Risk stratification in differentiated thyroid Cancer: an ongoing process. Rambam Maimonides Med J 2016;7.
5 Xing M: BRAF mutation in papillary thyroid cancer: pathogenic role, molecular bases, and clinical implications. Endocr Rev 2007;28: 742–762.
6 Rossi M, Buratto M, Bruni S, Filieri C, Tagliati F, Trasforini G, Rossi R, Beccati MD, degli Uberti EC, Zatelli MC: Role of ultrasonographic/clinical profile, cytology, and BRAF V600E mutation evaluation in thyroid nodule screening for malignancy: a prospective study. J Clin Endocrinol Metab 2012;97:2354–2361.
7 Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM; American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer: Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167–1214.
8 Brown RL, de Souza JA, Cohen EE: Thyroid cancer: burden of illness and management of disease. J Cancer 2011;2:193–199.
9 Wang J, Wu GS, Ma XP, Liu YY, Chen HT, Huang W: Detection of BRAF mutation and its clinical significance in thyroid cancer. Chin J Exp Surg 2011;28:1102–1104.
10 Lee JH, Lee ES, Kim YS: Clinicopathologic significance of BRAF V600E mutation in papillary carcinomas of the thyroid: a meta-analysis. Cancer 2007;110:38–46.
11 Li C, Lee KC, Schneider EB, Zeiger MA: BRAF V600E mutation and its association with clinicopathological features of papillary thyroid cancer: a meta-analysis. J Clin Endocrinol Metab 2012;97:4559–4570.
12 Kim TH, Park YJ, Lim JA, Ahn HY, Lee EK, Lee YJ, Kim KW, Hahn SK, Youn YK, Kim KH, Cho BY, Park DJ: The association of the BRAF(V600E) mutation with prognostic factors and poor clinical outcome in papillary thyroid cancer: a meta-analysis. Cancer 2012; 118:1764–1773.
13 Cancer Genome Atlas Research Network: Integrated genomic characterization of papillary thyroid carcinoma. Cell 2014;159:676–690.
14 Kebebew E, Weng J, Bauer J, Ranvier G, Clark OH, Duh QY, Shibru D, Bastian B, Griffin A: The prevalence and prognostic value of BRAF mutation in thyroid cancer. Ann Surg 2007; 246:466–471.
15 Elisei R, Ugolini C, Viola D, Lupi C, Biagini A, Giannini R, Romei C, Miccoli P, Pinchera A, Basolo F: BRAF(V600E) mutation and outcome of patients with papillary thyroid carcinoma: a 15-year median follow-up study. J Clin Endocrinol Metab 2008;93:3943–3949.
16 Xing M, Alzahrani AS, Carson KA, Shong YK, Kim TY, Viola D, Elisei R, Bendlová B, Yip L, Mian C, Vianello F, Tuttle RM, Robenshtok E, Fagin JA, Puxeddu E, Fugazzola L, Czarniecka A, Jarzab B, O'Neill CJ, Sywak MS, Lam AK, Riesco-Eizaguirre G, Santisteban P, Nakayama H, Clifton-Bligh R, Tallini G, Holt EH, Sýkorová V: Association between BRAF V600E mutation and recurrence of papillary thyroid cancer. J Clin Oncol 2015;33:42–50.
17 Xing M, Alzahrani AS, Carson KA, Viola D, Elisei R, Bendlova B, Yip L, Mian C, Vianello F, Tuttle RM, Robenshtok E, Fagin JA, Puxeddu E, Fugazzola L, Czarniecka A, Jarzab B, O'Neill CJ, Sywak MS, Lam AK, Riesco-Eizaguirre G, Santisteban P, Nakayama H, Tufano RP, Pai SI, Zeiger MA, Westra WH, Clark DP, Clifton-Bligh R, Sidransky D, Ladenson PW, Sykorova V: Association between BRAF V600E mutation and mortality in patients with papillary thyroid cancer. JAMA 2013;309:1493–1501.
18 Tufano RP, Teixeira GV, Bishop J, Carson KA, Xing M: BRAF mutation in papillary thyroid cancer and its value in tailoring initial treatment: a systematic review and meta-analysis. Medicine (Baltimore) 2012;91:274–286.
19 Czarniecka A, Kowal M, Rusinek D, Krajewska J, Jarzab M, Stobiecka E, Chmielik E, Zembala-Nozynska E, Poltorak S, Sacher A, Maciejewski A, Zebracka-Gala J, Lange D, Oczko-Wojciechowska M, Handkiewicz-Junak D, Jarzab B: The risk of relapse in Papillary Thyroid Cancer (PTC) in the context of BRAFV600E mutation status and other prognostic factors. PLoS One 2015;10:e0132821.
20 Russo M, Malandrino P, Nicolosi ML, Manusia M, Marturano I, Trovato MA, Pellegriti G, Frasca F, Vigneri R: The BRAF(V600E) mutation influences the short- and medium-term outcomes of classic papillary thyroid cancer, but is not an independent predictor of unfavorable outcome. Thyroid 2014;24:1267–1274.
21 Galuppini F, Pennelli G, Vianello F, Censi S, Zambonin L, Watutantrige-Fernando S, Manso J, Nacamulli D, Lora O, Pelizzo MR, Rugge M, Barollo S, Mian C: BRAF analysis before surgery for papillary thyroid carcinoma: correlation with clinicopathological features and prognosis in a single-institution prospective experience. Clin Chem Lab Med 2016;54:1531–1539.
22 Fugazzola L, Mannavola D, Cirello V, Vannucchi G, Muzza M, Vicentini L, Beck-Peccoz P: BRAF mutations in an Italian cohort of thyroid cancers. Clin Endocrinol (Oxf) 2004;61: 239–243.
23 Henke LE, Pfeifer JD, Ma C, Perkins SM, DeWees T, El-Mofty S, Moley JF, Nussenbaum B, Haughey BH, Baranski TJ, Schwarz JK, Grigsby PW: BRAF mutation is not predictive of long-term outcome in papillary thyroid carcinoma. Cancer Med 2015;4:791–799.
24 Edge SB, Compton CC: The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471–1474.
25 Rossi M, Buratto M, Tagliati F, Rossi R, Lupo S, Trasforini G, Lanza G, Franceschetti P, Bruni S, degli Uberti E, Zatelli MC: Relevance of BRAF(V600E) mutation testing versus RAS point mutations and RET/PTC rearrangements evaluation in the diagnosis of thyroid cancer. Thyroid 2015;25:221–228.
26 Hay ID, Hutchinson ME, Gonzalez-Losada T, McIver B, Reinalda ME, Grant CS, Thompson GB, Sebo TJ, Goellner JR: Papillary thyroid microcarcinoma: a study of 900 cases observed in a 60-year period. Surgery 2008;144:980–988
27 Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM; American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer: Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167–1214.
28 Carcoforo P, Portinari M, Feggi L, Panareo S, De Troia A, Zatelli MC, Trasforini G, degli Uberti E, Forini E, Feo CV: Radio-guided selective compartment neck dissection improves staging in papillary thyroid carcinoma: a prospective study on 345 patients with a 3-year follow-up. Surgery 2014;156:147–157.
29 Li J, Liang J, Zhao T, Lin Y: Noninferior response in BRAF(V600E) mutant nonmetastatic papillary thyroid carcinoma to radioiodine therapy. Eur J Nucl Med Mol Imaging 2016;43:1034–1039.
30 Zoghlami A, Roussel F, Sabourin JC, Kuhn JM, Marie JP, Dehesdin D, Choussy O: BRAF mutation in papillary thyroid carcinoma: predictive value for long-term prognosis and radioiodine sensitivity. Eur Ann Otorhinolaryngol Head Neck Dis 2014;131:7–13.
31 Yang K, Wang H, Liang Z, Liang J, Li F, Lin Y: BRAFV600E mutation associated with non-radioiodine-avid status in distant metastatic papillary thyroid carcinoma. Clin Nucl Med 2014;39:675–679.
32 Elisei R, Viola D, Torregrossa L, Giannini R, Romei C, Ugolini C, Molinaro E, Agate L, Biagini A, Lupi C, Valerio L, Materazzi G, Miccoli P, Piaggi P, Pinchera A, Vitti P, Basolo F: The BRAF(V600E) mutation is an independent, poor prognostic factor for the outcome of patients with low-risk intrathyroid papillary thyroid carcinoma: single-institution results from a large cohort study. J Clin Endocrinol Metab. 2012;97:4390–4398.