Journal of Thyroid Disorders & Therapy

Feng Ye et al., Thyroid Disorders Ther 2016, 5:1
DOI: 10.4172/2167-7948.1000198

Research article Open Access

Analysis of BRAFV600E Mutation and Persistence of Papillary Thyroid Cancer after Total Thyroidectomy and Routine Central Neck Dissection

Feng liu[1], Zhi-hui li[1], Jing-qiang Zhu[1], Ri-xiang Gong[1],Wei Gao[2], Qian-qian Han[2],Ten-fei Xing[2], Lin-gao He[2], Libo Yang[3] and Feng Ye[3,4*]

[1]Department of Thyroid and parathyroid center, West China Hospital, Sichuan University, Chengdu 610041, China

[2]West China School of medicine, Sichuan University, Chengdu 610041, China

[3]Department of Pathology, West China Hospital, Sichuan University, Chengdu 610041, China

[4]Laboratory of Pathology, West China Hospital, Sichuan University, Chengdu 610041, China

[*]**Corresponding author:** Feng Ye, Department of Pathology, West China Hospital, Sichuan University, Guo Xue Xiang 37 Hao, Chengdu City, 610041, Sichuan Province, China,**Tel:** 13880608800; **E-mail** : fengye@scu.edu.cn

Rec date: November 24, 2015; **Acc date:** December 21, 2015; **Pub date:** December 28, 2015

Abstract

Purpose

The aim of this study is to investigate the predictive value of BRAF V600E mutation for the persistence of papillary thyroid cancer (PTC) after total thyroidectomy and routine central neck dissection.

Patients and Methods

We collect the clinicopathological data of 288 PTC patients with total thyroidectomy (TT) and routine central neck dissection (CND), and analyzed the relationship between BRAFV600E mutation status and the rate of elevated non-stimulated thyroglobulin (NSTg) value. And we also collect the clinicopathological data of 370 PTC patients who needed radio iodine ablation(RIA) after TT and routine CND, and analyzed the relationship between BRAFV600E mutation status and the rate of elevated stimulated Tg (STg)value before RIA. The clinicopathological data included gender, age at diagnosis, multifocality, bilaterality, tumor size, extrathyroidal invasion, and lymph node status of these patients. All the patents were diagnosis as PTC before operation by the combination with ultrasonograph and FNA (fine needle asperation).

Results

BRAFV600E mutation is not associated with the elevated rate of elevated Tg value after TT and routine CND.

Conclusions

BRAF V600E mutation is not an independent predictive factor for the persistence of papillary thyroid cancer (PTC) after TT and routine CND.

Keywords: Craniomandibular disorders; Temporomandibular disorders

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, the elevated serum Tg (thyroid globin) value is not rare after TT [3]. And the elevated serum Tg value usually indicate the persistence or recurrence of the disease if the patents received TT. Aggressive pathological behaviors of PTC, such as extrathyroidal extension, lymph node metastasis,distant metastasis, are usually the main cause of the elevated serum Tg value.

The association of BRAFV600E mutation with the clinicopathological characteristics of PTC patients and predictive value of this mutation for aggressive behaviors are extensively investigated [4-13]. A number of studies [4-8]demonstrated that BRAFV600E mutation was closely associated with aggressive pathological behaviors of PTC, such as extrathyroidal extension, lymph node metastasis, and high TNM stages. However, whether BRAFV600E mutation will increase the opportunity of disease persistence in the PTC patents after surgery is still unkown.

The aim of this study was to evaluate whether BRAFV600E mutation is an independent predictive factor for the persistence of papillary thyroid cancer (PTC) after TT and routine CND.

Materials and methods

Study design

We conducted a retrospective study of PTC patients who underwent total thyroidectomy (TT) and CND in West China Hospital, Sichuan University from January 2013 to December 2014. The Institutional Ethics Committee of the West China Hospital approved this study. The clinicopathological features such as Gender, age at diagnosis, multifocality, bilaterality, extrathyroidal invasion, Tumor size, lymph node metastases (LNM), AJCC stage, TSH(thyroid stimulating hormone), Tg and TGAB (thyroglobulin antibody) value in serum were collected. The stimulated Tg value was tested after the patients stopped to take levo-thyroxin for 3 weeks, and at the same time, the TSH values of all the patients were above 30mIU/L, usually more than 100 mIU/L. The non-stimulated Tg value was tested after the patients had taken levo-thyroxin for at least for 4 weeks after the operation and the TSH values were suppressed lower than 0.5 mIU/L.

We tested the BRAFV600E mutation status of 543 PTC patients who underwent thyroidectomy and routine ipsilateral CND. 255 patients were excluded because of high serum TgAb values or none total thyroidectomy or distant metastasis or lack the data of non-stimulated Tg values before RIA. Distant metastasis was accessed by CT scan of chest and Tg value. If either of them suggests distant metastasis we took whole body scan with 131I to evaluate. At last we got 288 patients and analyzed the relationship between BRAFV600E mutation and the rate of elevated non-stimulated Tg value. These 288 patients defined as group 1 (non-stimulated group).

173 patients of the 543 were excluded because of high serum TgAb concentration, none total thyroidectomy, distant metastasis, or lack of stimulated Tg values, at last we got 370 patients and analysed the association between BRAFV600E mutation and the rate of elevated stimulated Tg value. We defined these 370 patients as group 2 (stimulated group).

The procedure of DNA extraction and BRAFV600E analysis was the same as Li-Bo Yang' paper[14]. The surgical stratagem of these patents with TT and CND was as follows: TT and routine prophylactic ipsilateral CND was firstly performed, if there was metastasis at pretracheal lymph nodes or prelaryngeal lymph nodes (LN) confirmed by intraoperative frozen-section examination, or obviously enlarged LN in contra lateral central neck area, we performed the bilateral CND. If there was any evidence of metastasis in lateral neck lymph node, such as ultrasonogragh, CT, FNAC (fine needle aspiration cytology), we performed bilateral CND and lateral neck lymph node dissection.

We define non-stimulated Tg value within 1 ng/ml as unelevated, and higher than 1 ng/ml as elevated. And we define stimulated Tg value within 10 ng/ml as unelevated, and higher than 10 ng/ml as elevated.

Statistical analysis

Statistical analysis was performed with SPSS 16.0 (SPSS, Inc., Chicago, IL). Pearson 2test and Fisher's exact test were used to calculate the bivariate analysis

Independent samples t-tests were used for analysis. The two-sided significance level was set at $P<0.05$.

Results

The data of group 1 is shown in Table 1. In the group 1 (non-stimulated), bivariate analysis showed that elevated rate of elevated non-stimulated Tg value is only associated with lymph node metastasis. There is no significant association of the serum Tg value with gender, age at diagnosis, BRAFV600E mutation, multifocality, bilaterality ,extrathyroidal invasion, Tumor size, and AJCC stage in our study. But the relationship between the serum Tg value and LNM were not confirmed by t-test.

	Total n ()	non-stimulated Tg group		x^2	P value
		Unelevated (239)	Elevated (49)		
Gender				0.487	0.485
male	70 (24.3)	60(85.7)	10(14.3)		
Female	218 (75.7)	179(82.1)	39(17.9)		
Age at diagnosis				1.195	0.274
< 45	180 (62.5)	146(81.1)	34(18.9)		
≥ 45	108(37.5)	93(86.1)	15(13.9)		
BRAFV600E				3.79	0.052
mutation	95(33.0)	73(76.8)	22(23.2)		
wide type	193(67.0)	166(86.0)	27(14.0)		
Multifocality				2.411	0.12
no	164(56.9)	141(86.0)	23(14.0)		
yes	124(43.1)	98(79.0)	26(21.0)		
Bilaterality				0.634	0.426
no	224(77.8)	188(83.9)	36(16.1)		
yes	64(22.2)	51(79.7)	13(20.3)		
Extrathyroidal invasion				0.309	0.578
no	196(68.1)	161(82.1)	35(17.9)		
yes	92(31.9)	78(84.8)	14(15.2)		
LNM				6.715	0.01
yes	176(61.1)	138(78.4)	38(21.6)		
no	112(38.9)	101(90.2)	11(9.8)		
Tumor size (cm)				0.062	0.804
≤ 1	175(60.8)	146(83.4)	29(16.6)		
> 1	113(39.2)	93(82.3)	20(17.7)		
AJCC stage				1.675	0.643
	235(81.6)	197(83.8)	38(16.2)		
	3(1.0)	3(100.0)	0(0)		
	35(12.2)	27(77.1)	8(22.9)		

	15(5.2)	12(80.0)	3(20.0)	

Tabel 1: Tg value and clinicopathological factors in group 1(non-stimulated).

The data of group 2 is shown in table 2. In the group 2, bivariate analysis show that higher rate of elevated stimulated Tg is associated with Multifocality, Bilaterality, and LNM. But BRAFV600E mutation is not associated with higher rate of elevated stimulated Tg. Multivariate analysis showed that LNM had significant positive associations with elevated Tg value in group 2.

In all, the rate of the elevated serum Tg values, no matter TSH is suppressed nor stimulated, is not associated with BRAFV600E mutation after total thyroidectomy and routine CND. Only LNM had significant positive associations with higher rate of elevated Tg value in group 2.

Discussion

Elevated serum Tg level usually indicated that thyroid or tumor remnants, LNM or distant metastasis, it is usually to be a indicator of persistence of PTC after TT [3].

Some studies reported that the BRAFV600E mutation is related to older age, tumor size, thyroid capsular invasion, extrathyroidal extension, and LNM [15–20]. These features indicated a poor outcome in PTC patients [21–23]. Several studies further defined the relationship between the BRAFV600E mutation and the aggressiveness of thyroid tumor cells. Many studies have investigated the role of the mutation in the decision of the most optimal initial surgical extent, including prophylactic CND for PTC, but the results are controversial [24]. Lee et al. [25] conducted a small series that included only 63 patients with PTC and underscored the prematurity of utilizing BRAF V600E mutation status to determine the surgical management of patients with PTC, specifically whether or not to perform CND. They suggested that prospective, multi-institutional studies that include only patients preoperatively known to have PTC and centers in which routine CND is performed are therefore greatly needed before we can accurately assess whether BRAF V600E mutation status should be incorporated into critical decisions regarding the appropriate operative management of patients with PTC.

		Group 2		**2**	**P value**
	Totaln%	Unelevated298	Elevated72		
Gender				1.886	0.17
male	90 (24.3)	68 (75.6)	22 (24.4)		
female	280 (75.7)	230 (82.1)	50 (17.9)		
age				2.63	0.105
45	226 (61.1)	176 (77.9)	50 (22.1)		
≥ 45	144 (38.9)	122 (84.7)	22 (15.3)		
BRAFV600E				0.931	0.335
mutation	126 (34.1)	98 (77.8)	28 (22.2)		
wide type	244 (65.9)	200 (82.0)	44 (18.0)		
Multifocality				5.273	0.022
no	204 (55.1)	173 (84.8)	31 (15.2)		
yes	166 (44.9)	125 (75.3)	41 (24.7)		
Bilaterality				5.568	0.018
no	272 (73.5)	227 (83.5)	45 (16.5)		
yes	98 (26.5)	71 (72.4)	27 (27.6)		
Extrathyroidal invasion				1.064	0.302
yes	259 (70.0)	205 (79.2)	54 (20.8)		
no	111 (30.0)	93 (83.8)	18 (16.2)		
LNM				11.069	0.001
yes	247 (66.8)	187 (75.7)	60 (24.3)		
no	123 (33.2)	111 (90.2)	12 (9.8)		
Tumor size (cm)				2.771	0.096
≤ 1	227 (61.4)	189 (83.3)	38 (16.7)		
1	143 (38.6)	109 (76.2)	34 (23.8)		
AJCC stage				1.716	0.633
	291 (78.6)	236 (81.1)	55 (18.9)		
	3 (0.8)	3 (100.0)	0 (0)		
	50 (13.5)	40 (80.0)	10 (20.0)		
	26 (7.0)	19 (73.1)	7 (26.9)		

Table 2: TG and clinicopathological factors in group 2 (stimulated).

Papillary thyroid carcinoma (PTC) is the most common histologic type of differentiated thyroid cancer, which is characterized by early lymph node (LN) metastasis (1). Cervical LNM is frequently observed in PTC patients with an average incidence of 60% (2). The most common sites of metastases are the central lymph nodes (CLNs) of the neck (level VI). Therapeutic central compartment neck dissection is well accepted to perform for patients with known LN metastasis diagnosed by physical examination or preoperative ultrasonograph (US) scanning. In china main land, lobotomy/TT with prophylactic ipsilateral CND is a well accepted procedure for PTC if the surgeon can control the complications. TT and routine prophylactic CND for PTC was also reported by other authors (26). If the tumor size is more than 1cm, thyroid capsular invasion, extrathyroidal extension, TT with prophylactic ipsilateral central lymph node dissection is usually performed. In our center, we perform routine CND followed with TT to minimize the opportunity of disease persistence or recurrence, and the rate of permanent recurrent laryngeal nerve palsy or hypoparathyrodism is lower than 0.3%.

In group 2 (TSH stimulated), they all received the RIA (radio iodine ablation), because they had the pathological features of thyroid capsular invasion, extra thyroidal extension, and/or LNM. Interestingly we found that in this group, we do not find that the rate of BRAFV600E mutation was obviously higher than that in the total sample. This may indicate that even though BRAFV600E mutation is

associated with thyroid capsular invasion, extra thyroidal extension, and/or LNM in many studies (4-8), the association is not strong.

Our study compares the rate of elevated serum Tg value between the patients with BRAFV600E mutation and wide type after TT with routine CND, and shows no difference between two groups. Although BRAFV600E mutation is usually associated with tumor size more than 1cm, thyroid capsular invasion, extrathyroidal extension and LNM, it seems not to increase the possibility of tumor or LN remnant after TT and routine CND.

		95% confidence interval		
Features	Odds ratio	Lower bound	upper bound	P value
Multifocality+	1.423	0.699	2.897	0.331
Bilaterality+	1.375	0.651	2.905	0.404
LNM+	0.355	0.182	0.691	0.002

Table 3: Multivariate analysis of the association between clinicopathological features and Tg value in group 2.

Conclusion

In our study, we do not confirmed that the BRAFV600E mutation was an independent predictor for higher rate of elevated serum Tg values after TT and routine CND. This may indicate that TT and routine CND can minimize the disease persistence of the patients even with BRAFV600E mutation and maybe helpful to reduce the recurrence of the disease. If the complication of the surgery can be controlled, TT and routine CND can be considered for the patents at high risk of disease persistence or recurrence.

Acknowledgement

This work was funded by grants from the National Natural Science Foundation of China (31000601) and Young Investigator Scholar in Sichuan University (2012SCU04A14).

References

1. Jemal A1, Bray F, Center MM, Ferlay J, Ward E, et al. (2011) Global cancer statistics. CA Cancer J Clin 61: 69-90.
2. Howlader N, Noone AM, Krapcho M (2013) SEER Cancer Statistics Review, 1975-2010. National Cancer Institute.
3. Yim JH, Kim EY, Bae Kim W, Kim WG, Kim TY, et al. (2013) Long-Term Consequence of Elevated Thyroglobulin in Differentiated Thyroid Cancer. Thyroid 23: 58-63.
4. Leenhardt L, Grosclaude P, Chérié-Challine L (2004) Increased incidence of thyroid carcinoma in france: a true epidemic or thyroid nodule management effects? Report from the French thyroid cancer committee. Thyroid 14:1056-1060.
5. Hundahl SA, Fleming ID, Fremgen AM, Menck HR (1998) A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985–1995. Cancer 83:2638-2648.
6. Nikiforov YE (2011) Molecular analysis of thyroid tumors. Mod Pathol 24 Suppl 2: S34–S43.
7. Xing M (2005) BRAF mutation in thyroid cancer. Endocr Relat Cancer 12: 245-262.
8. Jeong D, Jeong Y, Park JH (2013) BRAF (V600E) mutation analysis in papillary thyroid carcinomas by peptide nucleic acid clamp real-time PCR. Ann Surg Oncol 20: 759-766.
9. Zheng X, Xia T, Lin L (2012) BRAFV600E status and clinical characteristics in solitary and multiple papillary thyroid carcinoma: experience of 512 cases at a clinical center in China. World J Surg Oncol 10: 104.
10. Lin KL, Wang OC, Zhang XH,(2010) The BRAF mutation is predictive of aggressive clinicopathological characteristics in papillary thyroid microcarcinoma. Ann Surg Oncol 17: 3294-3300.
11. Kim YS, Kim JS, Bae JS, Park WC (2013) Clinical implication of the BRAFV600E mutation in papillary thyroid carcinoma. World J Surg Oncol 11: 99.
12. Ito Y, Yoshida H, Maruo R, (2009) BRAF mutation in papillary thyroid carcinoma in a Japanese population: its lack of correlation with high-risk clinicopathological features and disease-free survival of patients. Endocr J 56: 89-97.
13. Bozec A, Dassonville O, Chamorey E, (2011) Clinical impact of cervical lymph node involvement and central neck dissection in patients with papillary thyroid carcinoma: a retrospective analysis of 368 cases. Eur Arch Otorhinolaryngol 268: 1205-1212.
14. Yang LB, Sun LY, Jiang Y, (2015) The Clinicopathological Features of BRAF Mutated Papillary Thyroid Cancers in Chinese Patients. Int J Endocrinol 2015: 642046.
15. Howell GM, Nikiforova MN, Carty SE, (2013) BRAF V600E mutation independently predicts central compartment lymph node metastasis in patients with papillary thyroid cancer. Ann Surg Oncol 20: 47-52.
16. Lim JY, Hong SW, Lee YS, (2013) Clinicopathologic implications of the BRAFV600E mutation in papillary thyroid cancer: a subgroup analysis of 3130 cases in a single center. Thyroid, 23: 1423-1430.
17. Kim SJ, Lee KE, Myong JP, (2012) BRAFV600E mutation is associated with tumor aggressiveness in papillary thyroid cancer. World J Surg 36: 310-317.
18. Xing M, Clark D, Guan H, (2009) BRAF mutation testing of thyroid fine-needle aspiration biopsy specimens for preoperative risk stratification in papillary thyroid cancer. J Clin Oncol 27: 2977-82.
19. Nakayama H, Yoshida A, Nakamura Y, (2007) Clinical significance of BRAF (V600E) mutation and Ki-67 labeling index in papillary thyroid carcinomas. Anticancer Res 27: 3645-3649.
20. Fugazzola L, Puxeddu E, Avenia N, (2006) Correlation between B-RAFV600E mutation and clinico-pathologic parameters in papillary thyroid carcinoma: data from a multicentre Italian study and review of the literature. Endocr Relat Cancer 13: 455-464.
21. Turanli S (2007) Is the type of dissection in lateral neck metastasis for differentiated thyroid carcinoma important? Otolaryngol Head Neck Surg 136: 957-960.
22. Durante C, Haddy N, Baudin E, (2006) Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab 91: 2892-2899.
23. Mazzaferri EL, Jhiang SM (1994) Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 97: 418-428.
24. Lee, J. W., & Koo, B. S. (2013) The prognostic implication and potential role of BRAF mutation in the decision to perform elective neck dissection for thyroid cancer. Gland Surgery, 2(4), 206–211.
25. Lee KC, Li C, Schneider EB, (2012) Is BRAF mutation associated with lymph node metastasis in patients with papillary thyroid cancer? Surgery 152:977-83.
26. Dutenhefner SE, Marui S, Santos AB, (2013)BRAF, A tool in the decision to perform elective neck dissection? Thyroid 23: 1541–1546.