Original Article

Relationship of Recurrence Rate with some Characteristics in Patients with Thyroid Carcinoma

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Abstract

Background: Determining the clinical and subclinical characteristics related to the recurrence status in patients with a thyroid carcinoma has great significance for prognosis, prediction of recurrence and monitoring of treatment outcomes. This study aimed to determine the association between recurrence rate and some characteristics in patients with thyroid carcinoma. **Patients and Methods:** The study was conducted by descriptive method with longitudinal follow-up on 102 thyroid carcinoma patients at 103 Military Hospital, Hanoi, Vietnam, from July 2013 to December 2016. **Results:** Univariate analysis showed that there was a relationship between the recurrence characteristics in the studied patients and the characteristics of lymph node metastasis (P = 0.026; OR = 15; 95% CI = 1.4–163.2) and BRAF V600E mutation status (P = 0.01; OR = 3.41; 95% CI = 1.31–8.88). When analysing the multivariable Logistic regression model, there was a positive correlation between the occurrence of BRAF V600E gene mutation (P = 0.032; OR = 17.649; 95% CI = 1.290–241.523) and male sex (P = 0.036; OR = 12.788; 95% CI = 1.185–137.961) and the occurrence of recurrence in study patients. The mean time to relapse was earlier in male patients than in female patients (P = 0.02). The mean time to relapse in patients with the BRAF V600E mutation (31.81 ± 1.14 months) was shorter than the mean time to relapse in the group without the mutation (57.82 ± 2.08 months) (P = 0.01). The group of patients with mutations in the BRAF V600E gene increased the risk of recurrence compared with the group without the mutation (HR = 9.14, P = 0.04). **Conclusion:** There is a positive correlation between recurrence and masculinity, lymph node metastasis and the occurrence of BRAF V600E mutations in thyroid carcinoma patients.

Keywords: BRAF V600E mutation, lymph node metastasis, recurrence rate, thyroid carcinoma

Introduction

Thyroid carcinoma is the most common endocrine cancer.[1] Thyroid carcinoma tends to increase globally. In 2018, according to data published by GLOBOCAN, there were 567,000 new cases of thyroid carcinoma worldwide, and thyroid carcinoma ranked 9th in general cancers.[2] In the US, there were 63,000 new cases of thyroid carcinoma in 2014, compared with 44,670 in 2010.[3,4] Differentiated thyroid carcinomas originate from follicular epithelial cells of the thyroid gland and include papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma.[3] Differentiated thyroid carcinoma develops slowly, usually grows locally and invades the thyroid cortex, surrounding tissues (oesophagus, trachea, larynx, skin infiltrates.), cervical lymph node metastases and distant metastases depending on the histopathological type and time of disease detection.[5] Tumours are usually small at first; if left unnoticed, they can go undetected.[6]

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Surgical removal of the thyroid gland is an effective measure in treating thyroid carcinoma.[7] In addition, radical dissection of the cervical lymph nodes in groups IIa, III, IV and Vb is recommended when indicated to optimise treatment effectiveness.[8-10] The disease has a good prognosis, and the rate of patients with a 5-year survival time is over 90%.[3] However, thyroid carcinoma has a certain recurrence rate; the rate of patients with metastases occurs in 5–30% of cases.[11]

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These patients often have a poor prognosis; the disease persists, invades and metastasizes faster, especially in the group that does not respond to treatment with I-131 (anti I-131).[12] Results from a number of studies showed that factors such as age, sex, tumour size and degree of distant metastasis are associated with the recurrence of thyroid carcinoma; however, some patients may have local recurrence.[13] Therefore, identifying clinical and laboratory features related to recurrence in patients with thyroid carcinoma has great significance for prognosis, recurrence prediction, and outcome monitoring. For this reason, we performed this study to determine the association of recurrence rate with some characteristics in patients with thyroid carcinoma.

Materials and Methods

Study population and design

The study subjects included patients who were operated on and diagnosed by post-operative histopathology with thyroid carcinoma at 103 Military Hospital, Hanoi, Vietnam, from July 2013 to December 2016. Exclusion criteria included patients with non-differentiated carcinoma of the thyroid gland, thyroid cancer secondary to metastases from other sites and extensively invasive differentiated thyroid cancer without total thyroidectomy.[14] All patients have been explained the study procedure and agreed to participate in the study.

The study was conducted using a descriptive and longitudinal follow-up method. A total of 102 patients were recruited for the present study. All patients who met the inclusion and exclusion criteria were selected during the study period.

Research process

The characteristic information (name, age, gender, address and occupation), medical history and current diseases, examination of clinical signs and symptoms, laboratory tests and BRAF gene mutation tests were collected on the patient's record.

The stage of thyroid cancer was identified based on the tumor node metastasis (TNM) classification of the American Cancer Society (2014).

Serum levels of FT3 and FT4 were quantified by an automatic chemiluminescence system. Tg concentration was quantified by an Immuno Radio-Metric Assay technique at the Department of Biochemistry, 103 Military Hospital.

All patients were tested for BRAF gene mutations by Real-Time PCR. All post-operative specimens were stained for immunohistochemistry with markers HBME-1, CK19, RET, P53, Ki67 and COX-2. Immunohistochemical staining using the ABC method was conducted at the Department of Pathology, Military Hospital 103.

After surgery, the patient was re-examined at 1 month and received adjuvant treatment with I-131. The patient was then followed up and evaluated for recurrence status. The recurrence time was counted from the date of surgery to the date of examination and the detection of recurrent disease.

Evaluation of recurrence

After adjuvant treatment with iod-131 (I-131), patients were followed up every 3 months. At the time of re-examination, the patients were examined by clinical checking, ultrasound, thyroid function measurement, thyroglobulin concentration, and thyroid scintigraphy. The results of the recurrence assessment were as follows:

- No recurrence: after adjuvant therapy with I-131, the patient was determined to be disease-free during follow-up visits (complete thyroid tissue, negative whole-body scintigraphy and Tg concentration < 10 ng/ml) until the last follow-up visit.
- Relapse: after adjuvant therapy with I-131, the patient was determined to be free of the disease in the next follow-up (thyroid tissue was gone, whole body scintigraphy was negative and Tg concentration < 10 ng/ml) but then re-emergence at a follow-up visit (based on clinical or scintigraphy findings) in the neck or distant metastases, confirmed by FNA or other appropriate methods.
- Existing disease: after adjuvant therapy with I-131, it was still determined that the disease had not been cured in follow-up visits (thyroid tissue was still present, whole-body scintigraphy showed lymph node invasion or distant metastases and the concentration of Tg >10 ng/ml). The disease persisted at the last follow-up.

Ethical considerations

The Ethical Review Committee of Military Medical University, Vietnam, approved the protocol of the study. The study was in line with the Declaration of Helsinki. Written informed consent has been signed by all participants after a full explanation.

Statistical analysis

All results are presented as mean (SD) or, if biased, as median (interquartile range) for continuous variables and as percentages for categorical variables. Differences between groups were tested by the T-test. The Chi-square test or Fisher's exact test was used to assess whether there was a relationship between two categorical variables. The association between the recurrence rate and some characteristics was determined using multivariable logistic regression, using the VIF coefficient to assess whether there was multicollinearity between variables or not. P value < 0.05 was considered statistically significant. All data were processed using SPSS software version 26 (64-bit) for Windows (SPSS Inc., Chicago, IL).

Ethical Clearance Statement

The study was approved by the Ethical Review Committee of Vietnam Military Medical University vide letter number: 168/2014/IRB-VMMUI dated 06/03/2014. All participants were provided with written informed consent and agreed to join our study and use the patient data only for research and educational purposes.The study was also conducted using good clinical practice following the Declaration of Helsinki of 1964, as revised in 2013.

Table 1: Characteristics of research subjects

Characteristics	n	%
Sex		
Female	84	82.4
Male	18	17.6
Age groups		
<45	51	50
≥45	51	50
(Mean ± SD)	45.1 ± 13.4	
Tumour detection time		
<1 year	63	61.8
1 - <5 years	24	23.5
≥5 years	15	14.7
T		
T_1	14	13.7
T_2	86	84.3
T_3	2	2.0
N		
N_0	90	88.2
N_1	12	11.8
Stage		
I	53	52.0
II	45	44.1
III	4	3.9
Cytological results		
Negative	36	35.3
Positive	66	64.7
Instant biopsy		
Papillary thyroid carcinoma	90	88.2
Histopathological results		
Papillary thyroid carcinoma	86	84.3
Papillary thyroid carcinoma/hashimoto	7	6.9
Micropapillary thyroid carcinoma	4	3.9
Papillary thyroid carcinoma, follicular variant	5	4.9
Mutation of the BRAF V600E gene		
Yes	62	60.8
No	40	39.2
HBME-1		
≤3+	56	62.2
4+	34	37.8
CK19		
1+ và 2+	19	21.1
3+ và 4+	71	78.9
COX-2		
Negative	33	36.7
Positive	57	63.3
p53		
Negative	43	47.8
Positive	47	52.2
Ki67		
Negative	61	67.8
Positive	29	32.2
RET		
Negative	10	11.1
Positive	80	88.9
FT3		
Normal	86	84.4
Increase	16	15.6
FT4		
Normal	96	94.1
Increase	6	5.9
TSH		
Decrease	6	5.9
Normal	93	91.1
Increase	3	3
Tg		
Normal	66	64.7
Increase	36	35.3
Anti -Tg		
Normal	88	86.2
Increase	14	13.8
Surgery method		
Thyroid lobectomy with tumour	4	3.9
Total thyroidectomy	98	96.1

Table 2: Results of follow-up of recurrence in patients with thyroid carcinoma

Time after surgery	Number of patients with recurrence	Number of patients re-examination	Rate (%)
6 months	0	52	0.0
12 months	6	52	11.5
18 months	3	52	5.8
24 months	2	42	4.8
36 months	1	28	3.6
48 months	0	16	0.0
60 months	0	6	0.0
Total	12	52	11.8

Results

The average age of patients was 45.14 ± 13.42, in which female patients accounted for the majority with 82.4% (ratio female/male = 4.7/1). Most of the study patients had the disease detected within 1 year of the time of symptoms (61.8%). The majority of patients have the disease in stages I and II. Histopathological examination results showed that PTC accounted for 84.3%. Total thyroidectomy was the main treatment method applied to the patients in this study.

At the end of data recording, there were 50 cases of lost track in patients who had only 1 or 2 follow-up visits or did not re-examine. After 60 months (5 years) of follow-up and evaluation of recurrence, it was found that 11/52 (18.8%) patients were recorded and monitored for recurrence after surgery (clinical examination, ultrasound appearance of thyroid tissue and the presence of cervical lymphadenopathy was confirmed by fine-needle aspiration cytology, thyroid function measurement, blood thyroglobulin concentration > 10 ng/ml, thyroid scintigraphy, whole-body scan with positive results).

Research results from Table 3 show that in the group of patients, 27.3% relapsed after treatment at stage N1 (with

Table 3: Factors associated with recurrence in patients with thyroid carcinoma

Characteristics	Recurrence				OR; 95%CI	p*
	No (n = 41)		Yes (n = 11)			
	n	%	n	%		
T						
T_1	7	17.1	1	9.1	-	0.739
T_2	33	80.5	10	90.9		
T_3	1	2.4	0	0		
N						
N_0	40	97.6	8	72.7	15;	0.026
N_1	1	2.4	3	27.3	[1.4 – 163.2]	
Stage						
I	22	53.7	5	45.5	–	0.061
II	19	46.3	4	36.4		
III	0	0	2	18.2		
Sex						
Female	37	90.2	7	63.6	5.2;	0.051
Male	4	9.8	4	36.4	[1.1 – 26.3]	
Age groups						
< 45	20	48.8	5	45.5	1.1;	1.0
≥ 45	21	51.2	6	54.5	[0.3 – 4.3]	
BRAF V600E mutation						
Yes	18	43.9	10	90.9	12.8;	0.007
No	23	56.1	1	9.1	[1.5 – 109.3]	
HBME-1						
≤ 3+	27	65.9	6	54.5	1.6;	0,503
4+	14	34.1	5	45.5	[0.4 – 6.2]	
CK19						
1+ và 2+	11	26.8	1	9.1	3.7;	0.421
3+ và 4+	30	73.2	10	90.9	[0.4 – 32.1]	
COX-2						
Negative	21	51.2	4	36.4	1.8;	0.503
Positive	20	48.8	7	63.6	[0.5 – 7.2]	
p53						
Negative	22	53.7	4	36.4	2.0;	0,499
Positive	19	46.3	7	63.6	[0.5 – 8.0]	
Ki67						
Negative	30	73.2	7	63.6	1.6;	0.709
Positive	11	26.8	4	36.4	[0.4 – 6.4]	
RET						
Negative	2	4.9	1	9.1	0.5;	0.518
Positive	39	95.1	10	90.9	[0.04 – 6.2]	
FT3						
Normal	37	92.5	10	90.9	1.2;	1.0
Increase	3	7.5	1	9.1	[0.6 – 1.9]	
FT4						
Normal	14	34.1	5	45.5	0.6;	0.503
Increase	27	65.9	8	54.5	[0.2 – 2.4]	
TSH						
Decrease	5	12.5	1	9.1	-	1.0
Normal	8	20.0	2	18.2		
Increase	27	67.5	8	72.7		
Tg						
Normal	35	97.2	8	80.0	8.7;	0.115
Increase	1	2.8	2	20.0	[0.7 – 108.8]	

Contd...

Table 3: Contd...

Characteristics	Recurrence				OR; 95%CI	p*
	No (n = 41)		Yes (n = 11)			
	n	%	n	%		
Anti -Tg						
Normal	35	94.6	10	90.9	1.8;	0.551
Increase	2	5.4	1	9.1	[0.1 – 21.3]	
Surgery method						
Thyroid lobectomy with tumor	2	4.9	0	0	1.3;	1.0
Total thyroidectomy	39	95.1	11	100	[1.1 – 1.5]	
Tumor detection time						
< 1 year	23	56.1	9	81.8	-	0.390
1 - < 5 years	12	29.3	1	9.1		
≥ 5 years	6	14.6	1	9.1		

Table 4: Multivariable logistic regression model of factors associated with recurrence rate in patients with thyroid carcinoma

Factors	B	p - value	OR	95% C.I.		VIF
				Lower	Upper	
BRAF V600E mutation	2.871	0.032	17.649	1.290	241.523	1.080
Sex	2.549	0.036	12.788	1.185	137.961	1.009
N	2.005	0.124	7.428	.576	95.806	1.086
Constant	-6.677	0.003	0.001			

Table 5: Time of recurrence with some related characteristics

Characteristic	Time of recurrence (months)	p*
BRAF V600E mutation		
Yes	31.81 ± 1.14	0.01
No	57.82 ± 2.08	
Sex		
Male	39.45 ± 7.24	0.02
Female	55.59 ± 1.6	

cervical lymph node metastasis), while the rate of patients with cervical lymph node metastasis in the group of patients who did not relapse after treatment was only 2.4% ($P = 0.026$; OR = 15; 95% CI = 1.4–163.2), and 90.9% of patients with BRAF V600E gene mutation had relapsed after treatment, while the rate of disease recurrence in the group of patients without BRAF V600E gene mutation was 9.1% ($P = 0.01$; OR = 3.41; 95% CI = 1.31–8.88). There is a relationship between the recurrence characteristics in the studied patients and the features of lymph node metastasis and the BRAF V600E gene mutation status. At the same time, the association of immune markers, hormone levels, surgical methods, and disease detection time with recurrence characteristics in the studied patients has not been found.

When analysing the association of recurrence status in thyroid carcinoma patients with some characteristics by using a multivariable logistic regression model, the results showed that there is a positive correlation between the occurrence of gene mutations BRAF V600E ($P = 0.032$; OR = 17,649; 95% CI = 1.290–241.523) and male sex ($P = 0.036$; OR = 12,788; 95% CI = 1,185–137,961) with the occurrence of recurrence in study patients.

The mean time to relapse in patients with the BRAF V600E mutation (31.81 ± 1.14 months) was shorter than the mean time to relapse in the group without the mutation (57.82 ± 2.08 months); this difference is statistically significant ($P = 0.01$). The mean time to relapse was earlier in male patients than in female patients ($P = 0.02$).

The Kaplan-Meier chart showed that the group of patients with the BRAF V600E gene mutation increased the risk of recurrence compared with the group without the mutation (HR = 9.14); this difference was statistically significant with $P = 0.04$ (Log-rank test) [Tables 1-5].

Discussion

To evaluate postoperative recurrence and supportive treatment with I-131. We applied the following diagnostic criteria for recurrence. After surgery and after adjuvant treatment with I-131, the patient was determined to be disease-free at the next follow-up (complete thyroid tissue, negative whole-body scan, and blood Tg < 10 ng/ml), but at the next follow-up visit, the recurrence site appeared (based on clinical findings, ultrasound examination or scintigraphy) in the thyroid, cervical lymph nodes, or distant metastases and was confirmed by a positive FNA result. Many factors can influence thyroid cancer recurrence; however, there is still some controversy.[13] The results of our study showed that sex, metastasis of cancer to lymph nodes in the neck region, and mutations in the BRAF V600E gene were associated with recurrence characteristics.

There have been many studies analysing the influence of the male gender on the risk of recurrence,[15-17] but the results are still controversial. In our study, the univariate analysis

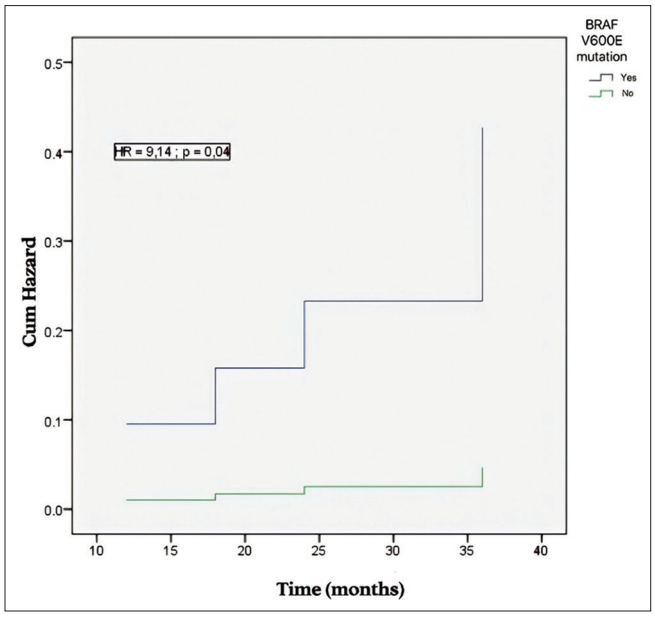

Figure 1: Risk of recurrence in patients with mutations in the BRAF V600E gene

of the relationship between sex and relapse showed that the male gender had a higher risk of recurrence than the female (OR = 5.2, 95% CI = 1.1–26.3); however, this difference is not statistically significant when analysing univariate with P = 0.051. However, after using the multivariable logistic regression model, the above difference was statistically significant, with P = 0.036. In addition, the mean time to relapse was earlier in male patients than in female patients (P = 0.02). The results of our study are consistent with the study of Oyer *et al*.,[18] which demonstrated that male gender is a risk factor for recurrence in thyroid cancer patients under 45 years of age. Some other studies also show that the male gender is associated with a higher risk of recurrence than the female.[13,15] However, results from other studies show that the recurrence rate in both sexes is similar.[19-21] There are differences in results between the above studies, partly due to the heterogeneity of the study population, differences in surgical scope, and a number of other factors.[22]

The presence of lymph node metastases is a risk factor for recurrence after treatment in patients with thyroid cancer.[23,24] Recently, many studies have demonstrated that in patients with thyroid carcinoma, adjacent lymph node metastasis is a predictor of recurrence in patients with PTC.[25,26] The results of our study also showed that the number of patients who relapsed after treatment was higher in the N1 stage than in the N0 group; this difference was statistically significant when analysing univariate (P = 0.026; OR = 15; 95% CI = 1.4–163.2), however, when analysing based on the multivariable logistic regression model, the influence of cervical lymph node metastasis on recurrence characteristics was not statistically significant (P = 0.124). The American Thyroid Association has also proposed a low, moderate and high-risk stratification system to predict recurrence risk.[12] This system recommended that the number and size of metastatic lymph nodes be considered risk factors for predicting recurrence.[12] Thus, the results of the above study showed that the metastasis of adjacent lymph nodes was one of the factors related to the recurrence status after treatment in patients with thyroid cancer.

The BRAF gene mutation was considered to be one of the important mutations related to the invasiveness, advanced stage, recurrence rate, and metastatic degree of thyroid carcinoma.[27] The results of our study showed that the occurrence of the BRAF V600E gene mutation increases the risk of recurrence compared with the group without the mutation (HR = 9.14, P = 0.04). At the same time, the mean time to relapse in patients with the BRAF V600E mutation was earlier than the mean time to relapse in the group without the mutation (P = 0.01). Our results were similar to those of other studies.[28-30] Several other studies have shown that the BRAF mutation rate is high—about 80–85% in recurrent thyroid carcinomas.[31,32] The cause of the greater recurrence in patients with BRAF mutations is the loss of affinity of the follicular cells for radioactive iodine and the consequent PTC unresponsiveness to therapy with radioactive iodine.[33,34] Abnormal activation of the MAPK signalling pathway is responsible for altering the iodine capture mechanism of thyroid follicular cells.[35] Through the activation of the MAPK signalling pathway in thyroid carcinoma, The BRAF V600E mutation inhibits the expression of thyroid function-specific genes. As a result, the thyroid cells lose their iodine tolerance mechanism. As a result, iodine is only partially tolerated in thyroid cells carrying the BRAF V600E mutation, and iodine is sparsely accumulated in the lumen of the thyroid follicle.[35] This is the key molecular mechanism by which BRAF mutations induce radioiodide loss in PTC and, consequently, radioiodine therapy failure and increased disease recurrence rates. Ge J *et al*.[36] noticed that *the* BRAF mutation may be a predictor of the efficacy of iodine-131 treatment for papillary thyroid cancer. However, it should be noted that several other studies have not linked BRAF V600E mutations with tumour recurrence in patients with PTC with small sizes [Figure 1].[37,38]

There are still some limitations in our study; our sample size is not large; in this study, we only consider the number of patients with relapse or not, regardless of the location of recurrence, whether it is the same or bilateral, single or multiple recurrences or multiple sites.

Conclusion

This study found that in patients with thyroid carcinoma, the recurrence rate is related to sex characteristics, lymph node metastasis characteristics and BRAF V600E gene mutation characteristics. Male patients with cervical lymph node metastasis and the BRAF V600E mutation have a higher recurrence rate and an earlier relapse time.

Abbreviations

BRAF, B-type Raf kinase; COX, Cyclooxygenase; CK, Cytokeratin; FT3, Free triiodothyronine; FT4, Free thyroxine;

HBME, Hector Battifora mesothelial; PTC, Papillary thyroid carcinomas (PTC); TSH, Thyroid stimulating hormone.

Ethical statement

All participants were provided with written informed consent and agreed to join our study, and the protocol was approved by the Ethical Review Committee of Vietnam Military Medical University (Reference No. 168/2014/IRB-VMMU). The study was also conducted using good clinical practice following the Declaration of Helsinki of 1964, as revised in 2013.

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Author contributions

Bui Dang Minh Tri, Bui Tung Hiep: Conceptualization, Project Administration, Supervision, Validation.

Nguyen Thanh Hiep: Writing – Review and Editing; Corresponding; Last endorsement of the adaptation to be distributed.

Bui Dang Minh Tri, Bui Dang Phuong Chi, Bui Duc Thanh and Tran Quoc Viet: Data Curation, Formal Analysis and Investigation.

Bui Dang Minh Tri, Bui Dang Phuong Chi, Tong Duc Minh, Nguyen Hoang Trung and Nguyen Thi Ngoc Dung: interpretation of data, Methodology, writing – Original Draft Preparation.

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Conflicts of interest

There are no conflicts of interest.

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