Impact of tall cell variant histology on predicting relapse and changing the management of papillary thyroid carcinoma patients

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Keywords: Papillary thyroid cancer -Tall cell variant-Recurrence risk -High risk papillary thyroid carcinoma -Management of tall cell variant of papillary thyroid carcinoma

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Received:
27 March 2017
Accepted revised:
27 April 2017

Abstract

Objectives: There has been much discussion recently about the risk category of tall cell variant (TVC) histology and its effects on the management of papillary thyroid carcinoma (PTC). We, therefore, undertook a retrospective study to compare stage-matched risk factors and recurrence rates between classical PTC (cPTC) patients and patients with TCV histology. **Subjects and Methods:** A total of 3128 well-differentiated thyroid carcinoma patients who were treated and followed-up for more than 5 years in our clinic from 1995 to 2016 were included in this study. There were 2783 PTC (89%) patients, 1113 (40%) of them were cPTC and 56 (2%) of them were TCV patients. **Results:** In all stages, the stage-matched incidence of extrathyroidal extension (ETE), lymphovascular invasion and initial lymph node metastases were significantly higher in TCV patients than in cPTC patients (P<0.001). Recurrence was in 10 of 27 patients (37%) with TCV and in 91 of 890 (10%) patients with cPTC diagnosed in stage I (odds ratio (OR)=5.16); in 4 of 6 patients with TCV and 18 of 84 (21%) patients with cPTC in stage II (OR=7.33); in 5 of 6 patients with TCV and 11 of 46 (23%) patients with cPTC in stage III (OR=15.90); and in 13 of 17 patients with TCV and 31 of 93 (33%) patients with cPTC in stage IV (OR=6.50). Stage-matched recurrence rates were found significantly higher in all stages of TCV patients than in cPTC patients (OR=8.49, P<0.001). Recurrence with distant metastases was seen more frequently in TCV patients than in cPTC patients (P<0.001) and treatment of metastatic disease was more difficult in TCV patients. **Conclusion:** Tall cell variant was an independent poor prognostic factor in papillary thyroid carcinoma patients even if they were diagnosed at early stages of the disease. Patients with tall cell variant histology required more aggressive therapeutic approach and closer follow-up than classical patients.

Hell J Nucl Med 2017; 20(2): 122-127 *Epub ahead of print: 12 July 2017* *Published online: 8 August 2017*

Introduction

Until now, there has been no clear consensus on the prognostic impact of tall cell variant (TCV) in papillary thyroid carcinoma (PTC). Unlike the overall good prognosis of classical PTC (cPTC) [1], TCV is generally reported as an independent poor prognostic factor [1-6], but some studies do not support the view [7-10] The higher rate of recurrence of TCV patients in these studies is attributed to the older age, bigger tumor size, extrathyroidal extension (ETE) and higher stage and grade of the tumor at the time of diagnosis rather than to TCV histology [7-10]. International guidelines also do not consider TCV as a high-risk factor. Tall cell variant histology is categorized as a low-risk factor according to the European Thyroid Association (ETA) guidelines [11] and as an intermediate risk factor according to the American Thyroid Association (ATA) guidelines [12]. The aim of this study was to determine the risk category of TCV histology by comparing recurrence rates of TCV histology in PTC patients, with the same stage of cPTC patients.

Subjects and Methods

We retrospectively reviewed 56 consecutive TCV histology patients and 1113 cPTC patients who were treated and followed up for more than 5 years in our clinic between 1995 and 2016. Their distribution to various stages, of TCV and of cPTC patients is found in Table 1. The distribution of TCV and of cPTC patients according to gender and other variables is found in Table 2. If pre-surgical ultrasound examination revealed lymph nodes

involvement, these patients underwent total thyroidectomy and lymph nodes dissection. All surgical specimens were analyzed by the same pathologist who was an expert on thyroid tumors. Tall cell variant was defined by the World Health Organization as a variant of PTC, in which the tumor is being composed predominantly (>50%) of tall cells with a height at least twice their width, with eosinophilic cytoplasm and basilar oriented nuclei, in addition to the characteristic nuclear features of PTC [10]. The patients were staged according to the 7th edition of the American Joint Committee on Cancer (AJCC). The numbers of TCV and of cPCT patients in every stage are mentioned in Table 2. All patients underwent ^{131}I ablation therapy if only residual normal thyroid tissue was present or ^{131}I therapy if residual tumor at thyroid bed plus initial cervical lymph nodes metastases or if distant metastases were detected. After primary treatment, all patients received a suppressive dose of thyroxine were followed up at 3, 6, and 12 months intervals and then yearly by measurement of serum thyroglobulin (Tg), anti-Tg, thyroid stimulating hormone and neck ultrasonography.

Statistical analysis

Stage-matched risk factors such as age, gender, tumor size, multifocality, ETE, vascular invasion, initial lymph node metastases, postoperative Tg levels and recurrence rates were analyzed by using the statistical package for the social science (SPSS 15.0; SPSS Inc., Chicago, Illinois, USA) software. Number, percentage, mean, median, SD, and minimum and maximum values were used for the description of data analysis. Concordance of continuous variables to a normal distribution was measured with the Kolmogorov-Smirnov test. The Mann-Whitney U-test was used for continuous variables and the χ^2-test was used for categorical variables in the comparisons between groups. Values of P less than 0.05 were accepted as statistically significant. This was a retrospective study using records, documents, and data of patients referred to our clinic for ^{131}I therapy and follow-up. Our institutional review ethics committee approved this study.

Results

Patients' distribution according to initial staging is summarized in Table 1. The diagnoses of multifocality, extra-thyroidal invasion (ETE), lymphovascular invasion and initial lymph node metastases were made by an experienced thyroid pathologist who reviewed the patients' histological specimens. Distant metastases were diagnosed in 71 (65%) of the patients by ultrasonography, CT, and MRI in the pre-therapeutic period and in 39 (35%) were detected by post-therapy I-131 whole body scan. There were two false positives of post therapeutic I-131 whole body scan due to one thymus hyperplasia and one pneumonia which were confirmed by radiological examinations and clinical follow-up.

Most of the patients with cPTC were diagnosed in the early stages [890 patients (80%) in stage I and 84 patients (7.5%) in stage II]. There were also significant numbers of patients with TCV in the early stages [27 patients (48.2%) in stage I and 6 patients (10.7%) in stage II]. This finding indicates that more than half (58.9%) of patients with TCV were diagnosed at the early stages of the disease. Stage-matched categorical variables in the groups of patients (cPTC and TCV) were compared in Table 2. Extrathyroidal extension, lymphovascular invasion, and initial lymph node metastases were found significantly higher in all stage-matched TCV, PTC patients than in cPTC patients (P<0.01). Gender and multifocality were not statistically significantly different between the two groups.

Table1. *The initial staging of the patients.*

Stage	Classic variant n (%)	Tall cell variant n (%)
I	890 (80)	27 (48.2)
II	84 (7.5)	6 (10.7)
III	46 (4.2)	6 (10.7)
IV	93 (8.3)	17 (30)
Total	1113 (100)	56 (100)

Among the continuous variables (Table 3) in stages II, III and IV, TCV patients were found significantly older than stage-matched cPTC patients (P=0.013, P=0.047 and P=0.029, respectively). Tumor size was bigger in stages II, III and IV in TCV, PTC patients (P=0.033, P= 0.037and P=0.003 respectively) and pre-ablation serum Tg levels were significantly higher in stages III and IV in TCV patients (P=0.024 and P= 0.037 respectively), total administered ^{131}I activity for the treatment of patients in all stage- matched TCV PTC patients was significantly higher than in cPTC patients.

Stage-matched recurrence rates, odds and odds ratios for TCV and cPTC patients were compared in Table 4. The odds ratio of recurrence was found significantly higher for TCV compared to stage-matched cPTC. The odds ratios for TCV were: 5.16 (P<0.001) in stage I, 7.33 (P=0.027) in stage II, 15.90 (P=0.016) in stage III, 6.50 (P=0.002) in stage IV and 8.49 (P<0.001) in all stages.

Recurrence with distant metastases (Table 5) was more frequently seen in TCV patients than in cPTC patients at all stages. Six of 56 TCV patients and 48 (4.3%) of the cPTC patients returned to iodine negative metastatic disease. De-differentiation/anaplastic transformation found significantly higher in TCV patients than in cPTC patients (OR=2.48, P=0.045).

Discussion

Our study clearly showed that TCV histology is an indepent

Table 2. *Categorical variables of stage-matched tall cell variant and classic variant PTC patients. The descriptive was expressed in positive cases numbers (n) with percentages (%).*

Variables		Stage I		Stage II		Stage III		Stage IV		Total	
Sex		Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
	cPTC	223 (25)	667 (75)	22 (26)	62 (74)	11 (24)	35 (76)	74 (80)	19 (20)	330 (30)	783 (70)
	TCV	5 (18)	22 (82)	2 (33)	4 (67)	4 (66)	2 (34)	8 (47)	9 (53)	19 (34)	37 (66)
	P value	0.475		0.680		0.067		0.063		0.321	
Multifocality	**cPTC**	316 (35)		48 (57)		22 (47)		25 (26)		411 (37)	
	TCV	11 (40)		4 (66)		1 (16)		10 (58)		26(46)	
	P value	0.587		0.709		0.216		0.145		0.414	
Extra-thyroidal invasion	**cPTC**	75 (8,4)		14 (16)		8 (17)		25 (26)		122	
	TCV	7(25)		4(66)		5(83)		13(76)		29	
	P value	0,034		0,011		0,006		0,004		<0,001	
	Odds ratio 95 % CI	3.80 1.55-9.28				23.75 2.43-23.83		8.84 2.63-29.66		4.72 2.90-7.62	
Lympho-vascular invasion	**cPTC**	130 (14)		9(10)		9 (19)		30 (32)		178 (15)	
	TCV	11 (40)		3(50)		4 (66)		11 (64)		29 (51)	
	P value	0.006		0.017		0.025		0.014		<0.001	
	Odds ratio 95% CI	4.01 1.82-8.85		8.33 1.45-47.63		8.22 1.29-52.4		3.85 1.30-11.4		5.64 3.26-9.76	
Initial lymph node metastases	**cPTC**	117 (13)		14 (16)		13 (28)		35 (37)		179 (16)	
	TCV	8 (29)		4 (66)		5 (83)		14 (82)		31 (55)	
	P value	0.018		0.011		0.026		0.002		<0.001	
	Odds ratio 95% CI	2.78 1.19-6.49		10.00 1.66-60.00		12.69 1.34-119.33		7.73 2.07-28.82		6.47 3.73-11.2	

cPTC:classicalpapillarythyroidcarcinoma,TCV:Tallcellvariant.(onlypositivecasesnumbers(n)withpercentages(%)wasgiven)

Table 3. *Continuous variables of stage-matched tall cell variant and classic variant. (n=number of patients)*

Variables	Stage I		Stage II		Stage III		Stage IV	
	(n= number of patients, Mean±SD)							
Age (years)	TCV (n=27)	38±13	TCV (n=6)	59±10	TCV (n=6)	56±4	TCV (n=17)	61±10
	cPTC (n=890)	37±12	cPTC (n=84)	42±15	cPTC (n=46)	41±8	cPTC (n=93)	46±12
	P=0.964		P=0.013		P=0.047		P=0.029	
	TCV (n=27)	18.5±6	TCV (n=6)	27.5±7.5	TCV (n=6)	55±11.5	TCV (n=17)	47±24
	cPTC (n=890)	15±5	cPTC (n=84)	18.5±8	cPTC (n=46)	32±17	cPTC (n=93)	22±10.5
	P=0.083		P=0.033		P=0.037		P=0.003	
	TCV (n=27)	49±3.8	TCV (n=6)	101.5±11.5	TCV (n=6)	154±33	TCV (n=17)	630±76
	cPTC (n=890)	24±4	cPTC (n=84)	64.5±18.5	cPTC (n=46)	12±9	cPTC (n=93)	105.5±16
	P=0.399		P=0.781		P=0.024		P=0.037	
	TCV (n=27)	8,77±0,55	TCV (n=6)	13,6±3,92	TCV (n=6)	15,65±8,5	TCV (n=17)	13,9±4,3
	cPTC (n=890)	5,55±3,4	cPTC (n=84)	7,7±4,2	cPTC (n=46)	7,5±2,5	cPTC (n=93)	8,2±5,2
	P=0.001		P=0.025		P=0.009		P=0.004	

Table 4. *The initial staging of the patients.*

Stage	Classic variant				Tall cell variant						
	n	R	RR (%)	Odds	n	R	RR (%)	Odds	Odds ratio	95%confidence interval	P value
I	890	91	10	0.11	27	10	37	0.58	5.16	2.29-11.61	<0.001
II	84	18	21	0.27	6	4	66	2	7.33	1.24-43.29	0.027
III	46	11	23	0.31	6	5	83	5	15.90	1.67-151.15	0.016
IV	93	31	33	0.50	17	13	76	3.25	6.50	0.95-21.59	0.002
Total	1113	151	13	0.15	56	32	57	1.33	8.49	4.86-14.81	<0.001

n:Numberofpatients,R:Numberofpatientsdevelopingrecurrence,RR:Recurrencerates

high-risk factor. Tall cell variant histology is responsible for the aggressive behavior of the tumor showing a higher incidence of extrathyroidal invasion (ETE), lymphovascular invasion and distant metastases, which are responsible for higher recurrence rates and poor prognosis in TVC, than in cPTC. Our study provides important evidence to clarify the controversy about whether TCV histology is associated with worse prognosis or not [13]. Histology of TCV was also found

Table 5. *Recurrence with distant metastases.*

	Recurrence rates n(%)				
Stage	**Classical PTC**	**Tall cell variant**	**Odds ratio**	**95% Confidence interval**	**P value**
I	75 (8)	10 (37)	6.39	2.049-9.424	<0.001
II	13 (15)	4 (66)	10.92	1.810-65.912	0.009
III	8 (17)	5 (83)	23.75	2.433-231.830	0.006
IV	25 (26)	13 (76)	8.84	2.633-29.668	<0.001
Total	121 (10)	32 (57)	10.93	6.232-19.173	<0.001

n=number of patients

as an independent risk factor which affects the recurrence and survival on multivariate analysis in a number of other studies [3, 7, 14-16]. Some studies suggested that the worse prognosis which is associated with TCV was attributed to the older age of patients with bigger tumor size, extrathyroidal extension, and higher TNM stage at the time of diagnosis [4, 8, 10]. In this study, we showed that recurrence risks and metastatic ratios at early stages of TCV histology patients were higher than at stage-matched cPTC patients. Our findings are in accordance with previous studies which demonstrated that TCV histology is an independently poor prognostic factor in PTC patients [1-4, 7, 8]. Similar with our study, Kazaure et al. (2012) [17] also compared cPTC patients matched for age, sex, presence of gross extrathyroidal disease, regional and distant metastatic stage based on SEER database with TCV histology and PTC patients and found that TCV histology had significantly shorter by 5 years, overall survival (80.6% TCV vs. 93.5% cPTC, P<0.01). It is interesting that using the same database (SEER) another retrospective study of 97 TCV and 18260 cPTC (1998-2009) patients with <1cm tumor, by Kuo et al (2013) [18] did not find significant differences in overall and disease-specific survival between these two groups of patients. In this study, we found that TCV histology presents 5.19 and 7.33 times greater odds than cPTC in stages I and II, respectively and that TCV histology is an independent risk factor for PTC patients. The importance of our findings is on patient management especially at early initial stages of the disease, since we showed that in patients with TCV histology, recurrence rates are much higher than in cPTC patients even at the early stages of the disease. Ghossein et al (3) investigated the biological behavior and clinical implications of TCV without the extrathyroid extension but our study is the first one in the literature which compares stage-matched recurrence rates of TCV patients with cPTC patients. We recommend more aggressive treatment to TCV patients than to cPTC patients especially when TCV is diagnosed at the early stages of the disease. In addition to bilateral total thyroidectomy, prophylactic central lymph node dissection should be considered and if pre-operative neck ultrasound shows suspicious lateral lymph nodes, lateral lymph node dissection should be considered. Post-operative radioiodine ablation therapy should be given even if tumor remnant size is less than 1 cm.

Advantages and limitations

The advantage of this study is that by using our database we were able to compare stage-matched risk factors and recurrence rates of cPTC and TCV patients in a rather large number of PTC patients. There is no stage-matched risk factors and recurrence rates comparison, of cPTC and TCV patients in previously published reports.

One of the limitations of this study arises from the fact that it is a retrospective investigation and we didn't investigate molecular and genetic features of TCV histopathology which could provide further insight into the aggressive behavior of TCV. High expression of Muc1 in TCV could be responsible for the aggressive behavior of TCV [19]. Muc1 is a transmembrane epithelial cell surface glycoprotein. Its over-expression interferes with integrin-mediated adhesion to the extracellular matrix and with cadherin-mediated cell-cell adhesion. Increased Muc1 expression thereby promotes cellular dissociation and oncogenic progression [20, 21]. The higher prevalence of activating point mutations of the BRAF serine/threonine kinase in TCV histology when compared to cPTC histology may also be related to the aggressive behavior of TCV [22].

Another limitation of our study is that we didn't compare disease-specific survival rates of the stage-matched cPTC and TCV histology PTC patients since this comparison needs longer follow-up and detailed death reports.

In conclusion, Tall cell variant histopathology is an independent, poor prognostic factor for papillary thyroid carcinoma recurrence even if it is diagnosed at early stages of the disease and a more aggressive initial treatment approach and close follow-up of these patients are necessary.

The authors of this study declare no conflict of interest

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From Kostas Ph. Grammatikos, A fish named clown anemonefish, aged about 1 year, in a private aquarium lying insigde a tropical anemone which is aged 200-300 years. These anemones are poisonous to all fishes except the clown anemonefish.