Should tall cell thyroid cancers be evaluated differently from well-differentiated thyroid cancers?

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Kubilay Dalci*, Uğur Topal*, Ayşe Gizem Ünal*, Ahmet Gökhan Sarıtaş*, İsa Burak Güney**, Aysun Hatice Uğuz***, Gürhan Sakman*

Cukurova University Faculty of Medicine, Cukurova/Adana, Turkey
**Department of General Surgery*
***Department of Nucleer Medicine*
****Department of Surgical Oncology, Erciyes University , Melikgazuk, Turkey*

Should tall cell thyroid cancers be evaluated differently from well-differentiated thyroid cancers?

OBJECTIVE: *In this study, we aimed to investigate the clinical features of Papillary thyroid carcinoma(PTC) Tall cell variant(TCV), long-term outcomes and surgical experience in papillary thyroid carcinoma.*
MATERIAL-METHOD: *33 patients who were operated in our clinic between August 2012 and March 2018 and diagnosed as TCV in their pathology evaluation were included in the study. The demographic and clinical features of the patients, pathological features of the tumor and long-term results were examined.*
RESULTS: *A total of 33 patients were included in our study. The mean age was 55.2(18-85) years. The female sex was more dominant (75.8%). The most common presenting complaint was swelling in the neck (75.7%).Total thyroidectomy was performed in 84.8% and completion thyroidectomy after lobectomy was performed in 15.2%. Neck dissection was performed in 33% of the patients. The mean tumor diameter was 3.6 (1-10) cm. The tumor was multifocal in 36.3% of the patients. The capsule invasion rate of the tumors was present in 69.7% of the patients, extrathyroidal rate was 39.4%, Metastatic lymph nodes were detected in 30.3% of the cases. The mean follow-up duration was 39.3+22.4(5.25-78.63) months. 39.4% of patients had distant metastasis during follow-up. Disease free survival rate was 57.6%, total survival was 42.4 + 3.8 (34.7-50.0) months.*
CONCLUSION: *TCV is closely associated with larger tumor diameter, multifocal location, extrathyroidal spread and lymph node involvement, We believe that more aggressive surgery should be performed in the treatment of TCV cases and it is important to follow up the patients more closely.*

KEY WORD: Esophagus cancer, Neutrophil/lymphocyte ratio, Preoperative lymphocyte /neutrophil ratio, Prognosis

Introduction

Papillary thyroid carcinoma (PTC) is the most common malignancy of the thyroid gland. The Tall cell variant (TCV) of papillary thyroid carcinoma was first described by Hawk and Hazard in 1976 as a different subtype of papillary thyroid carcinoma (PTC) with cells twice the width in height [1]. In the same study, Hawk and Hazard noted that this subtype of papillary carcinoma has a larger tumor diameter than other forms of papillary carcinoma and occurs at an advanced age [1].
The amount of tall cell pattern has been controversial in the diagnosis of TCV. In the 2017 update, the World Health Organization (WHO) described PTC cases with 50% or more Tall cells as TCV [2]. Some controversy continues regarding the rate of Tall cell (30-75%) required for PTC-TCV diagnosis. The percentage of tall cells (TC) required to be considered as TCV of PTC may range from 30% to 50%, or even up to 75%. Many

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Correspondence to: Kubilay Dalcı, MD, Department of General Surgery, Cukurova University Faculty of Medicine, 01100 Sarıçam/Adana Turkey (e-mail: kubilaydalci@hotmail.com)

clinics consider the Tall Cell ratio needed to confirm PTC-TCV as >30% [3-6]. The incidence of TCV is reported to be between 3-10% in the literature [5,7]. The experience of pathologists is important in diagnosing TCV cases.

Most of the authors in the literature agree that TCV is more aggressive than classical PTC [7-10]. The TCV subtype is usually reported as an independent poor prognostic factor. Poor prognosis of TCV depends on advanced age at presentation, large tumor size and frequency of extrathyroidal extension [7-11]. However, there are also studies in the literature which do not support this view [6]. In addition, international guidelines do not consider TCV to be at high risk. Tall cell variant histology is categorized as a low risk factor according to European Thyroid Association (ETA) guidelines and as an intermediate risk factor according to American Thyroid Association (ATA) guidelines [12].

Tall cell variants have been associated with higher extrathyroidal extension, multifocality, nodal metastasis and distant metastasis in previous studies (p: 0.0001). Extrathyroidal extension was found to be more frequent in the Tall Cell variant, with 54.7% versus 20.1%, compared to PTC (p<0.001). Multifocality was more common in the Tall cell variant than PTC, with 29.3% versus 26.7% (p<0.001). Nodal metastasis was higher in TCV compared to classical PTC (66.8% TCV and 56.3% PTC) (p<0.001). Distant metastasis was higher in TCV (11.1% vs. 4.3% PTC, p <0.001). Yearly overall survival was shorter in tall cell (80.6% vs. 93.5% PTC, p<0.001).Tumor size independently predicted worse prognosis for TCV (HR 1.29, p<0.001) [13].

The aim of this study was to evaluate the clinicopathologic features and outcomes of patients with TCV.

Material and Method

Thirty-three patients who underwent thyroid surgery between August 2012 and March 2018 at the Department of General Surgery of Çukurova University Faculty of Medicine were included in the study. Approval was obtained from the Ethics Committee of Çukurova University Faculty of Medicine dated and numbered 08.03.2019-86/38. Patient data were analyzed retrospectively. Patients who were younger than 18 years of age and whose data could not be accessed were excluded from the study.

TCV classification was made if it contained 50% or more Tall Cells without tumor necrosis or significant mitotic activity (>5mitoses/10 high-power fields, 400x) according to the WHO diagnostic criteria [(2)]. Tall Cell is defined as cells with an eosinophilic cytoplasm with a low nuclear cytoplasmic ratio, has characteristic nuclear properties of PTC and has twice the width in height. Mitotic velocity of the tumor was determined by counting 10 contiguous high-power fields (400x) using an Olympus microscope (U-DO model BX-40; Olympus America Inc., Melville, NY).

Tumor necrosis was defined by a ''comedo-like'' appearance composed of degenerating cytoplasm and punctate, karyorrhectic nuclear debris.Extrathyroidal extension (ETE) was defined as tumor cells invading the perithyroidal soft tissue or organs outside the thyroid capsule. The number of lymph nodes examined microscopically and the number of nodes with metastatic carcinoma were recorded.

Tumor staging was made according to AJCC 8th edition [14]. Radioactive iodine treatment was performed after surgical treatment in patients with residual tissue in the thyroid bed, multifocal carcinoma, capsule invasion, extrathyroidal lymph node spread or distant metastasis. All patients were given thyroxine treatment at suppression doses.

During routine follow-up, physical examination was done, serum thyroglobulin (sTg) and Thyroid Stimulating Hormone (TSH) levels were measured and regular neck ultrasonography was performed. When necessary, iodine-131 (^{131}I) whole body scintigraphy was performed.

Age, sex, presenting complaints, thyroid function tests, Preoperative Thyroid Fine Needle Aspiration Biopsy (TFNAB), type of operation, TNM stage, tumor diameter, lymphatic invasion, vascular invasion, capsule invasion, neuronal invasion, multifocality, extrathyroidal extension, whether they received radioactive iodine treatment, if so received dose and how many sessions, postoperative thyroglobulin (TG) level, last measured TG level, presence of distant metastasis, mortality, disease-free survival, total survival, follow-up duration, current clinical status, and current clinical follow-up status of the patients were recorded.Current clinical status was recorded as disease-free survival, recurrence and survival, mortality due to other causes and cancer-related mortality. Surgical notes, patient file information and electronic record information were evaluated retrospectively.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 24 package program(IBM Corp., Armonk, N.Y., USA). Categorical variables were summarised as numbers and percentages, continuous measurements were given as mean ± standard deviation (SD) (minimum-maximum when necessary). Kaplan-Meier and Log Rank tests were used for survival analysis.

Results

A total of 33 patients were included in our study. The mean age of the patients was 55.2 (18-85) years and

TABLE I - *Demographic and clinical characteristics*

Variable	TCV (n=33)
Mean age (years)	55.2 (18-85)
Age (years)	
<55	13(39%)
>55	20(61%)
Sex	
Male	8(24.2%)
Female	25(75.8%)
Preoperative value of thyroid hormone	
TSH (mIU/L)	1.77(0.22-5.4)
T4	0.87(0.68-1.31)
T3	3.35(1.37-8.89)
Symptoms	
Neck swelling	25(75.7%)
Asymptomatic(incidental)	6(18.2%)
Dyspnea	2(6.1%)
Treatment Surgery	
Total thyroidectomy	28(84.8%)
Total thyroidectomy after lobectomy	5(15.2%)
Neck dissection	
Central	1(3%)
Lateral	4(12%)
Central and lateral	6(18%)
Not performed	22(67%)

TABLE II - *Pathological characteristics*

Variable	TCV (n=33)
Mean tumor size (cm)	3.6(1-10)
Multifocality	12(36.3%)
Capsule invasion	23(69.7%)
Extrathyroidal extension	13(39.4%)
Lymphatic invasion	14(42.4%)
Vascular invasion	13(39.4%)
Positive pathological lymph nodes	
N0	23 (69.7%)
N1	10(30.3%)
Stage (AJCC, 8th edition)	
I	20(60.6%)
II	8(24.2%)
III	0(0)
IV	5(15.2%)

most (61%) were over 55 years of age. The female sex was more dominant with 75.8%. Mean preoperative TSH level was 1.77(0.22-5.4)(mIU/L), mean T4 level was 0.87(0.68-1.31) (ng/dl), mean T3 level was 3.35(1.37-8.89) (pg/ml). The most common presenting symptom was swelling in the nect (75.7%). Total thyroidectomy was performed in 84.8% and completion thyroidectomy after lobectomy was performed in 15.2%. Neck dissection was performed in 33% of the cases. Central and lateral dissection was performed most frequently (18%). The demographic and clinical characteristics of the patients are given in Table I.

The mean tumor diameter was 3.6 [1-10] cm. 36.3% of the patients had multifocal tumors. Tumor capsule invasion was present in 23 cases (69.7%), extrathyroidal extension in 13 cases (39.4%), lymphatic invasion in 14 cases (42.4%) and vascular invasion in 13 cases (39.4%). The rate of metastatic lymph nodes was evaluated as N1 and was determined as 30.3%. Pathological stage of the patients (according to AJCC, 8th edition) were as follows, 20 cases of Stage I (60.6%), 8 cases of Stage II (24.2%), 0 cases of Stage III (0%), and 5 cases of Stage IV (15.2%). The findings including the pathological features of the tumor in the patients are presented in Table II.

Mean follow-up duration was 39.3±22.4 (5.25-78.63) months 81.8% of the patients were treated with radioactive iodine in the postoperative period. 22.3% of the patients who received radioactive iodine treatment received more than one dose treatment 39.4% of patients had distant metastasis during follow-up. The most common metastasis was lung with 27.3%.At their last follow-up, the current clinical status of the patients were as follows:alive without disease (57.6%), alive with metastasis (33.3%), died of thyroid carcinoma (9.1%), died of unrelated causes (0%). The clinical outcomes of the patients are presented in Table III. Disease free survival was 72.0±3.6 (64.9-79.1) months and overall survival was 42.4±3.8 (34.7-50.0) months and these results are shown in Figs. 1, 2.

TABLE III - *Clinical Outcome*

Variable	TCV (n=33)
Mean follow-up (months)	39.3+22.4 (5.25-78.63)
RAI treatment	
Absent	6(18.2%)
Present	27(81.8%)
Single dose	21(77.7%)
Multiple dose	6(22.3%)
Extent of metastases	
Lung	9(27.3%)
Cervical lymph node	2(6.1%)
Bone	1(3%)
Surrenal	1(3%)
None	20(60.6%)
Status at last follow-up	
Alive without disease	19(57.6%)
Alive with metastasis	11(33.3%)
Died of thyroid carcinoma	3(9.1%)
Died of unrelated cause	0
Disease-free survival (month)	38.8+4.8 (29.4-48.2)
Overall survival (month)	42.4+3.8 (34.7-50.0)

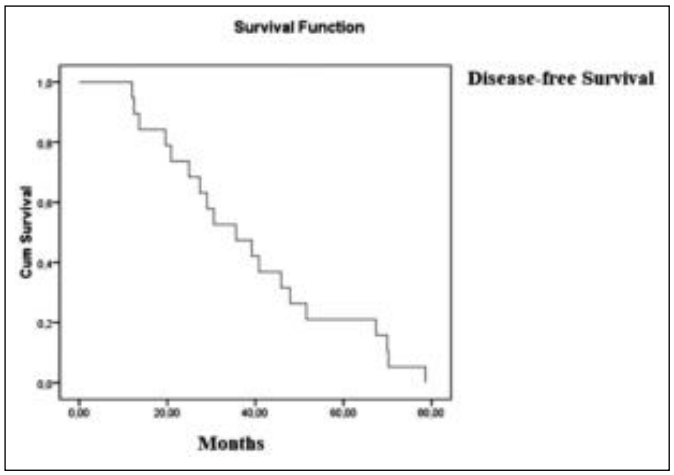

Fig. 1: Kaplan–Meier curves of Disease-free Survival.

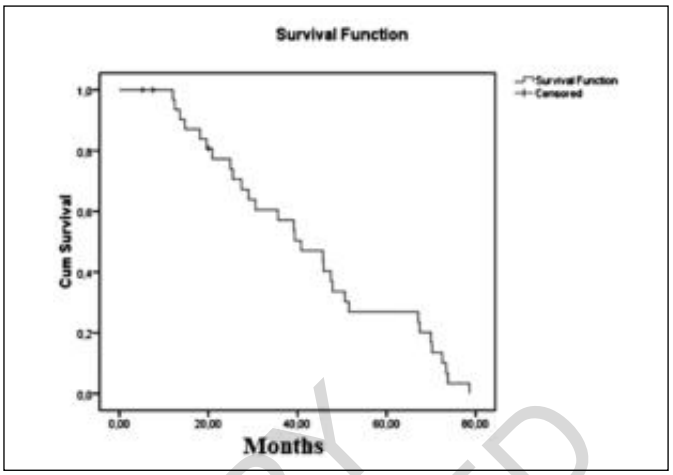

Fig. 2: Kaplan–Meier curves of Overall Survival.

Discussion

Although there is a consensus that TCV has higher tumor aggressiveness than classical PTC, there is still controversy about the prognostic significance of TCV [11,13].

Morris et al. compared 278 TCV and 278 PTC patients regarding age, sex, extrathyroidal extension, metastasis, clinical characteristics and year of diagnosis. In this study, it was found that TCV histology alone decreased 5-year disease-free survival [15]. In a study comparing 573 TCV cases and 42904 PTC cases, Kazaure et al. showed that the incidence of TCV increased and had a worse prognosis than classical PTC. They showed that patients with TCV should be treated aggressively with thyroidectomy and RAI, regardless of tumor size.

In contrast, there are publications in the literature indicating that the differences between the course of PTC and TCV do not depend on variant histology, but are related to high clinical stage and grade. Michels et al., in a study comparing 503 patients with conventional papillary carcinoma to 56 patients with TCV, the 10-year overall survival was 90% in PTC and 79% in TCV.In univariate analysis, the presence of TCV had a negative effect on prognosis, however this effect couldn't be demonstrated in multivariate analysis.Independent of histology, advanced age, distant metastases and positive lymph nodes were found to be significant negative prognostic factors of 40-45, the negative impact of age on prognosis gradually increases every decade [17,18]. Disease related mortality rates were found to be significantly higher in TCV patients over the age of fifty years compared to the control group [22]. In a 2010 series, Morris et al. found that TCV patients presented at a more advanced age (54.3 years - 46.3 years, p <0.0001) compared with classical PTC (15).Ganly et al. showed in their series that 57% of TCV patients were older than 45 years [8]. In our series, mean age was 55.2 [(18)] and 61% of the patients were over the age of 55.

While differentiated thyroid cancers are more commonly seen in women, they are more progressive in men [20]. The female sex ratio was found to be 64-87%in the literature [5,21,22]. When Ghossein et al compared classic papillary carcinoma with TCV in terms of sex, the female sex ratio was found to be 78.3% and 82.3% (p: 0.557), respectively, and female dominance was found in both groups [5]. In the series of Kazaure et al., male sex was found to be a risk factor(hazard ratio (HR) 1.6, confidence intervalCI, 1.4-1.7)with regards to mortality (p<0.0001) [13]. In our series, the rate of female patients was 75.8% and there was female sex dominance in accordance with the literature.

Well-differentiated thyroid cancers are generally asymptomatic and rarely cause any complaints. Patients with increased tumor size present with swelling in the neck. They may also present with shortness of breath due to the compression effect of the mass. In our series, the mean tumor diameter was 3.6 cm, and the most frequent complaint to the hospital was swelling of the neck with 75.7%. Two patients presented with shortness of breath. One of these ,Leung et al. showed that the general characteristics of normal thyroid tissue such as iodine uptake and thyroglobulin production were different from other well-differentiated thyroid carcinomas in TCV cases. They claimed that RAI treatment was ineffective becausecomplete body scans did not show radioactive iodine absorption in relapsed TCV patients. Therefore, they argued that RAI will have a very limited role in the systemic treatment of generalized disease. In the same study, it was shown that thyroglobulin sensitivity was less in detecting TCV relapse.

Thyroglobulin levels were not increased in approximately 30% of patients with relapse. They showed that RAI treatment in metastatic disease was ineffective in many cases. They suggested that initial treatment should be aggressive to minimize the possibility of distant metastasis. All patients in their series underwent total thy-

roidectomy and 92.9% of TCV patients underwent RAI [9]. Ganly et al. found that total thyroidectomy was performed at a 70% rate in classical PTC, and 87% in TCV (p = 0.001), and RAI treatment was more common in TCV patients (74%) than in classical PTC (52%)[8].

In our series, 85% of patients underwent total thyroidectomy in the first operation and 15% of them underwent completion thyroidectomy after lobectomy. Tumor size, RAI treatment plan, and multifocal factors were effective in this high total thyroidectomy rate 82% of the patients in the study were treated with RAI. The presence of residual thyroid tissue, multifocal carcinoma, capsule invasion, extrathyroidal extension, lymph node positivity and distant metastasis played a role in RAI treatment plan. Six patients who had recurrence and had increased thyroglobulin during their follow-up were treated with multiple courses of RAI.

Histological type of tumor, diameter of the tumor and lymph node involvement are important for neck dissection indication. Therefore, histological types of thyroid cancers have gained importance. Central lymph node dissection may be planned in the presence of clinically detected central LN according to the ATA 2015 guideline. Prophylactic central neck dissection may be planned in the absence of clinical central LN metastasis, however there is T3-4 tumor lateral LN metastasis (+) N1b is present [12]. Lateral neck dissection is recommended in the presence of biopsy-proven lateral LN metastasis [12]. In the literature, the rate of cervical lymph node metastasis of TCV varies between 40-70% [6,8]. In the study performed by Ghossein et al, regional lymph nodes were evaluated microscopically and 67.3% of TCV patients had LN metastasis at presentation, while 40% of classic PTC patients had positive lymph nodes (p<0.004). In multivariate analysis, histological subtype (TCV vs. classical PTC) was found to be an independent risk factor associated with LN metastases (p<0.007) [5]. Ganly et al. evaluated cervical lymph node metastasis as Prognostic Factors for Neck Recurrence-Free Survival (NRFS). Ten-year NRFS was found to be 97% in N0 cases and 80% in N1 cases (p <0,001). In our series, the rate of neck dissection was lower than in the literature and we related this to the lower rate of cervical lymph node metastasis (30%) than reported in the literature [8].

Many studies have shown that tumor diameter is a poor prognostic factor [7,5,11,25]. In addition, thyroid capsule invasion, nodal metastasis and distant recurrence may occur even in micro TCV. In a series of 453 patients, Ganly et al. found that tumor size was higher in TCV than classical PTC. 46% of TCV cases had tumor diameters > 2 cm (p = 0.05)[8]. Terry et al. found a higher risk of recurrence in tumors larger than 4 cm in diameter [26]. In this study, it was shown that each 1cm increase in tumor diameter, increases the risk of death by 29%. In multivariate analyses of survival of TCV cases, increased tumor size was associated with tumor aggressiveness [13]. In our series, the mean tumor diameter was 3.6 cm and there were tumor sizes reaching 10 cm.

Multifocal tumors (two or more foci) may originate from a single malignant source with intrathyroidal extension or may originate from multiple independent foci [26,27]. In the series Kazaure et al., where they compared 573 TCV cases to 42904 PTC cases, they detected multifocality in 29.3% of TCV cases and 26.7% of PTC cases (p<0.001). In the same study, multifocality was shown to be associated with low survival in multivariate analyses [13]. In the series of Okuyucu et al., 45.5% of TCV cases and 37.5% of cPTC cases were multifocal (p: 0.217) and they argued that multifocality was not a risk factor in TCV and classic PTC [7]. Many papillary cancer studies show a high rate of cancer in the other lobe in the presence of multifocal cancer. Therefore, in some cases, complete resection of multicentric disease and complementary thyroidectomy may be required for RAI treatment. In our series, 36.3% of the patients had multifocal localization.

In a study by Ghossein et al. comparing classic papillary carcinoma and TCV, they found capsule invasion in 69.6% of TCV patients and 43.2% in classical PTC (p: 0.047). Disease recurrence was detected in 20% of patients with thyroid capsule invasion. In the same study, multivariate analysis suggested that histologic subtype (TCV and classic PTC) and thyroid capsule invasion were not independent risk factors.In our study, capsule invasion was 69.7%, similar to the series of Ghossein et al. Recurrence was detected in 34.7% of patients with capsule invasion [5].

In a series of 573 TCV cases compared to 42904 PTC cases, Kazaure et al. found extrathyroidal extension to be 54.7% in TCV cases and 20.1% in PTV cases (p<0.001).Extrathyroidal extension was a risk factor for mortality in multivariate analysis (HR 1.7, 95% CI, 1.5-1.9) (p<0.0001) [14]. Ghossein et al. found the extrathyroidal extension rate in their series as 51.6% in TCV [3]. Extrathyroidal extension was found to be higher in TCV when compared to classical PTC, in many series in the literature [7,15]. In our series, the extrathyroidal extension rate was found to be 39.4%.

Günalp et al. compared the recurrence rates in TCV patients according to stages; found that lymphovascular invasion rate was higher in TCV than classical PTC. Recurrence rate was found to be 51% in TCV and 15% in PTC(p<0.001). Lymphovascular invasion was found to be 5.64 (Odds ratio 95% CI, 3.26-9.76) in multivariate analysis and it was found to be a risk factor for recurrence [28]. In our series, the rate of lymphovascular invasion was found to be 40% and recurrence was found in 60% of patients with lymphovascular invasion.

In the literature, the rate of stage III-IV disease in TCV varies between 30-70% [9,28]. Villar Taibo et al. found the stage III/IV disease ratio as 62.5% in TCV and 20.5% in PTC, in the TCV variant group compared to classi-

cal PTC groups (p:0.009) [29]. In a series conducted by Leung, the 10-year survival rate of stage IV patients was significantly lower in patients with TCV than in classical PTC (14.3% in TCV, 60.9% in PTC, p=005) [9]. In our study, stage 3-4 disease rate was 15.2% and this rate was lower than the literature. We attributed this low rate to the fact that the mean age of the patients in our series was younger and the number of positive lymph nodes was lower than reported in the literature. In our series, two patients with stage 3-4 disease died due to tumor-related complications, and three patients are being followed-up with lung metastasis.

It is known in the literature that TCV has a higher likelihood of local or distant metastasis and a higher mortality rate when compared to classical PTC [7,13,30]. In their series, Okuyucu et al. found local or distant metastasis as 60% in TCV and 16.2% in PTC (p<0.001)[7]. In the Kazaure series, multivariate regression analysis found the presence of distant metastasis as a risk factor for mortality (HR 3, 95% CI, 2.6-3.6) (p<0.0001)[13]. In accordance with the literature, the most common distant metastasis in our series was lung (27.3%). Two patients with lung metastasis died and one patient was using tyrosine kinase inhibitors.

Due to the aggressive biological structure of TCV, survival rates are lower than PTC due to negative prognostic factors. In a study by Kazaure et al., 5-year disease-specific survival was 97.4% in PTC and 87.5% in TCV (p< 0.001). 5-year overall survival was 80.6% in TCV,and 93.5%in PTC (p<0.001) [13]. In the series of Leung et al., patients alive without disease were 83.3% in classic PTC and 50% in TCV(p<0.001). Patients who died of thyroid carcinoma were 7.0% in classic PTC and 42.9% in TCV (p<0.001)(9). The mean follow-up duration in our series was 39.3 (5.25-78.63) months. Disease-free survival (month) was found as 38.8±4.8 (29.4-48.2),overall survival (month) was found as 42.4 (34.7-50.0), those alive without disease was 57.6%, alive with metastasis was 33.3%, and those who died of thyroid carcinoma was 9.1%.Our alive without disease rates were higher than the literature, while our died of thyroid carcinoma rates were lower than those reported in the literature.

In conclusion, TCV is an aggressive behavioral subtype of papillary thyroid cancer with poor prognosis [15]. TCV is closely associated with larger tumor diameter, increased multifocality multicentricity, extrathyroidal extension, lymph node involvement, local recurrence and distant metastasis. Prognosis is directly related to these features [24]. In addition to total thyroidectomy, central site lymph node dissection should be routinely performed in the treatment of TCV, lateral neck dissection should be considered in the presence of suspected lymphatic metastasis and invasion of surrounding tissues should also be removed [27]. All patients should be treated with radioactive iodine irrespective of tumor diameter and should be followed up closely [13].

Our rsults were consistent with the literature. We think that it is important to be more aggressive in the treatment of TCV and it is important to follow up the patients more closely. Prospective studies with large patient series are needed on this topic.

Riassunto

Questo studio è finalizzato ad analizzare le caratteristiche cliniche del carcinoma papillare della tiroide (PTC), variante a cellule alte (TCV), gli esiti a lungo termine e l'esperienza chirurgica nell'ambito del carcinoma papillare della tiroide.

Nella nostra clinica tra agosto 2012 e marzo 2018 sono stati operati 33 pazienti, e diagnosticati come TCV dall'anatomo-patologo, e su questi si è rivolto in nostro studio retrospettivo, esaminando le caratteristiche demografiche e cliniche, le caratteristiche patologiche del tumore e i risultati a lungo termine.

L'età media dei 33 pazienti era di 55,2 (18-85) anni. Il genere femminile era più dominante (75,8%). Il sintomo più frequente è stato il gonfiore del collo (75,7%), la tiroidectomia totale è stata eseguita nell'84,8% e la tiroidectomia di completamento dopo la lobectomia è stata eseguita nel 15,2%. La dissezione del collo è stata eseguita nel 33% dei pazienti. Il diametro medio del tumore era 3,6 (1-10) cm. Il tumore era multifocale nel 36,3% dei pazienti. Il tasso di invasione della capsula dei tumori era presente nel 69,7% dei pazienti, il tasso di sviluppo extratiroideo era del 39,4%, i linfonodi metastatici sono stati rilevati nel 30,3% dei casi. La durata media del follow-up è stata di 39,3 + 22,4 (5,25-78,63) mesi, ed il 39,4% dei pazienti ho presentato metastasi a distanza nel corso del follow-up. Il tasso di sopravvivenza libera da malattia è del 57,6%, la sopravvivenza totale è di 42,4 + 3,8 (34,7-50,0) mesi.

In conclusione il TCV è strettamente associato a dimensioni maggiori del tumore maggiore, sviluppo multifocale, diffusione extratiroidea e coinvolgimento dei linfonodi. Riteniamo che si debba eseguire un intervento più aggressivo nel trattamento dei casi di TCV ed è importante seguire più da vicino i pazienti.

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Commento e Commentary

Prof. Guglielmo Ardito, MD, FACS
General Surgery and Endocrine Surgery - UCSC Roma

Differentiated Thyroid Cancer?" by Kubilay Dalci and colleagues. The Authors should be congratulate; their surgical review on Tall Cell Variant (TCV), a subtype of Papillary thyroid carcinoma (PTC), is very interesting and deserves appreciation for the accurate and rigorous methodologic approach.
The authors referred a single-center retrospective, non randomized study with the primary aim of assessing the incidence of TCV and confirming the poorer clinical outcome of this subtype. Their results agree with previous studies suggesting that TCV is a rare and high-risk PTC, biologically and clinically aggressive form, still underdiagnosed, that warrants individualized therapeutic strategies. The A.A., according to most authorities, believe that TCV's worse prognosis is related to its older age at presentation, larger tumor size, and high frequency of extrathyroid extension. However, it has been suppossed that the aggressive behavior could be related to the higher prevalence of B-RAF mutations when compared to the classical PTC.
According to our experience we would like to point out that despite the significance of TCV with respect to risk stratification and therapeutic decision making, its diagnosis depends on pathologist expertise and is subject to pathologist variability. We have performed from 1990 to 2015 more than 9000 thyroidectomies and rarely experienced TCV. Actually, pathologic reporting of PTV varies among observers. This disagreement is a result of the lack, to date, of unanimous diagnostic criteria and variation in individual pathologists' interpretation. These discrepancies lead to over- and- under diagnosis of TCV, wich has significant implication in patient management. Therefore it is mandatory to understand this variability in diagnosis of TCV as it relates to risk stratification and interpretation of clinical studies related to this histologic subtype of PTC.
The data provided by Kubilay and colleagues, albeit with the limitations of a nonrandomized study, highlight the ongoing challenges and unknowns about TCV and argue in favor of the importance of future work to reach consensus on the diagnostic criteria of TCV and into the biologic diffferencies that might contribute to the different behavior between TCV and classical PTC.

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Leggiamo con interesse l'articolo di Kubilay Dalci e colleghi. Bisogna congratularsi con gli Autori; la loro revisione chirurgica su Tall Cell Variant (TCV), un sottotipo di carcinoma papillare della tiroide (PTC), è molto interessante e merita apprezzamento per l'approccio metodologico accurato e rigoroso.
Gli autori hanno fatto riferimento a uno studio retrospettivo a centro singolo, non randomizzato, con l'obiettivo primario di valutare l'incidenza di TCV e confermare l'esito clinico più scarso di questo sottotipo. I loro risultati concordano con studi precedenti che suggeriscono che il TCV è una PTC rara e ad alto rischio, biologicamente e clinicamente aggressiva, ancora sotto-diagnosticata, che richiede strategie terapeutiche individualizzate. Gli AA, secondo la maggior parte delle autorità, ritengono che la peggiore prognosi del TCV sia correlata alla età più avanzata dei pazienti, alle dimensioni maggiori del tumore e all'alta frequenza di estensione extratiroidea. Tuttavia, è stato supposto che il comportamento aggressivo potrebbe essere correlato alla maggiore prevalenza delle mutazioni B-RAF rispetto al PTC classico.
Secondo la nostra esperienza vorremmo sottolineare che, nonostante l'importanza del TCV rispetto alla stratificazione del rischio e al processo decisionale terapeutico, la sua diagnosi dipende dall'esperienza del patologo ed è soggetta alla sua variabile esperienza. Abbiamo eseguito dal 1990 al 2015 più di 9000 tiroidectomie e raramente incontrato TCV. In realtà, la segnalazione patologica di PTV varia tra gli osservatori. Questo disaccordo è il risultato della mancanza, fino ad oggi, di criteri diagnostici unanimi e di variazioni nell'interpretazione dei singoli patologi. Queste discrepanze portano a una diagnosi eccessiva di TCV, che ha implicazioni significative nella gestione del paziente. Pertanto è obbligatorio comprendere questa variabilità nella diagnosi di TCV in quanto si riferisce alla stratificazione del rischio e alla interpretazione degli studi clinici relativi a questo sottotipo istologico di PTC.
I dati forniti da Kubilay e colleghi, sebbene con i limiti di uno studio non randomizzato, evidenziano le sfide e le incognite in corso sul TCV e sostengono a favore dell'importanza del lavoro futuro per raggiungere il consenso sui criteri diagnostici del TCV e nelle differenze biologiche che potrebbe contribuire al diverso comportamento tra TCV e PTC classico.