

A Comparison of Clinicopathological Characteristics and Short-Term Outcome of Papillary Thyroid Carcinoma with Tall Cell Histology and Classic Papillary Thyroid Carcinoma: A Single-Institution Experience

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Abstract

Context: Papillary thyroid carcinoma with tall cell histology (PTC-TCH) is an aggressive subtype in terms of clinicopathological features and outcome. Even 10% of tall cells can show aggressive features. **Aims:** The aim of this study is to investigate the behavior of PTC-TCH, to compare with classic PTC (cPTC), and evaluate the short-term outcome. **Settings and Design:** This is a retrospective analysis of patients with cPTC and those with TCH (PTC-TCH) seen from January 2010 to May 2017 seen in our Thyroid Cancer Clinic. **Materials and Methods:** A total of 40 patients with TCH were compared with 352 cPTC and evaluated for age, gender, tumor size, presence of multifocality, capsular, vascular invasion, extrathyroid extension, and appearance of metastases. Short-term response to therapy was assessed using the 2015 American Thyroid Association guidelines. **Statistical Analysis:** $P < 0.05$ was considered statistically significant. All analyses were performed with SPSS software (Version 21.0, Chicago, IL, USA). **Results:** PTC with TCH presented at a younger age, had larger tumors, and more extrathyroid extension. Seven out of 40 cases developed lung metastases, (17.5% vs. 4.5% in cPTC), within a year of diagnosis. **Conclusion:** PTC-TCH irrespective of percentage of tall cells showed aggressive features and early metastases. They should be recognized early as an aggressive subtype and treated intensively. Close follow-up must be instituted to look for metastases, especially to the lungs.

Keywords: Differentiated thyroid carcinoma, lung metastasis, papillary thyroid carcinoma with tall cell histology, prevalence

INTRODUCTION

Tall cell variant of papillary thyroid carcinoma (TCV-PTC) was first recognized in 1976.^[1] Recently, it has gained attention because of its aggressive nature in terms of pathological characteristics and patient outcome.^[2] In addition, 24% of deaths from thyroid cancer is attributed to TCV-PTC, being second only to poorly differentiated thyroid carcinoma (DTC).^[3] The American Thyroid Association (ATA) places it in the intermediate risk in terms of recurrence.^[4]

Controversy exists in the definition. It is not clear whether the percentage of tall cells influence the outcome. There have been reports where even 10% tall cells have shown poor prognosis (tall cell features) similar to those with >50% tall cells (TCV).^[5]

Objectives

At our institute, we have begun to see increasing numbers of thyroid cancer, mainly PTC and also tall cell histology (TCH), we undertook a study to evaluate the prevalence, characteristics, and outcome of these cases compared with classic PTC (cPTC) and also whether the percentage of tall cells influence the prognosis.

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MATERIALS AND METHODS

This study evaluated the prevalence, clinicopathological characteristics, and short-term outcome in patients with PTC with TCH. Clinicopathological features were compared with cPTC for any significant differences. In addition, although small in numbers, we compared those with >50% tall cells and those with <50%, to see if they differed in any of the variables studied. We also analyzed the few cases which developed lung metastases.

Amrita institute thyroid carcinoma database

The Thyroid Cancer Clinic was setup at our institute in January 2010. Patients seen there were consecutively entered into a database. From the outset, the management was based on the ATA guidelines published in 2009.^[4] After initial surgery and radioactive iodine (RAI) ablation, all patients were begun on appropriate suppressive doses of thyroxine. Six months later, they underwent a diagnostic whole-body scan, ultrasonography of the neck, stimulated thyroglobulin (Tg), and Tg antibody (TgAb) when thyroid-stimulating hormone was above 30. When indicated, they were given RAI ablation. Accordingly, they were classified into low-, intermediate-, and high-risk categories for recurrence (ATA, 2009). The follow-up initially used the response to therapy categories outlined by Tuttle and Leboeuf^[6] later modified according to the ATA 2015 recommendations.

Data from January 2010 to May 2017 were collected. At the time of data collection, our database contained 742 consecutive patients with DTC. We excluded all other variants of PTC, micro-PTC (MPTC), follicular, Hurthle cell, anaplastic, poorly differentiated types (ATC and PDTC), and children with PTC. The remaining 392 patients formed subjects of this study. Clinical and histopathological information were obtained from the electronic medical records.

A tumor was defined as TCV if it contained >50% tall cells. Tall cells were defined as those cells with a height greater than thrice its width, eosinophilic cytoplasm, and basilar-oriented nuclei besides the classic nuclear features of PTC. Both definitions for PTC and tall cell description were as recommended by the World Health Organization (WHO) Classification of Tumors (2004) and endorsed by the ATA guidelines in 2015 till modified recently. There were 352 patients with cPTC and 40 with TCV. We categorized these 40 patients (tall cells >10%) as TCH (PTC-TCH) [Figure 1]. Patients with <10% tall cells were excluded. These 40 patients were then subdivided into TCV (TCV-PTC) when tall cells were >50% ($n = 22$) and PTC with tall cell features or TCF-PTC ($n = 18$) with 10%–50% tall cells.

The following data were collected: age at diagnosis, presenting features, type of surgery performed (including reexploration of the neck), Tg, and TgAb levels serially and at the time of response to therapy evaluation and frequency of RAI therapy. Out of the 40 histopathology specimens/slides, 32 were read by a senior head-and-neck oncopathologist, 4 reported by another senior pathologist, and 4 were unfortunately operated

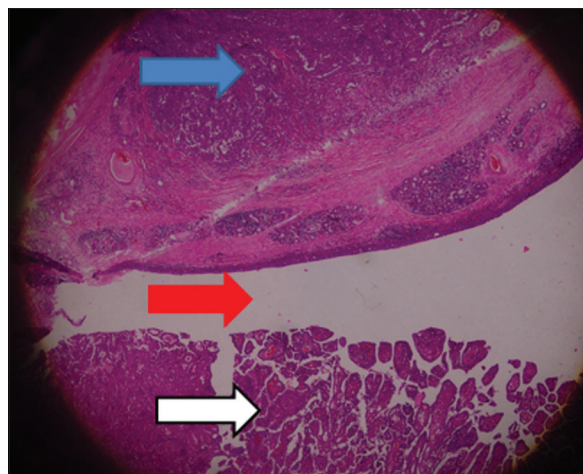


Figure 1: Histology showing (scanner view, H and E, $\times 4$) tall cell variant of papillary thyroid carcinoma. Section also shows anaplastic transformation of tall cells infiltrating trachea (blue arrow – anaplastic transformation, red arrow – tracheal lumen, white arrow – tall cell areas)

in other hospitals. Histopathology reporting was based on the Royal College of Pathologists (RC Path)^[7] and the College of American Pathologists (CAP) format.^[8]

The following histopathological parameters were assessed: tumor size, multifocality, vascular invasion, perineural infiltration, microscopic extrathyroidal extension (ETE) (into perithyroidal soft tissue), and presence of metastatic lymph nodes. Microscopic ETE was defined based on the RC Path/CAP guidelines. Lymph nodes were noted as positive on the basis of original histopathology reports or if they appeared in the reexplored tissue.

Assays

Tg level was determined by the electrochemiluminescence assay (Elecsys 2010), Roche, Switzerland. The first-generation kit used in the initial 5 years had a limit of detection (LOD) of <0.1 ng/ml. From 2015, the second-generation kit used in testing had a LOD of <0.040 and reference range of 0.04–500 ng/ml. TgAb was assessed using the ARCHITECT anti-Tg assay (Abbott, United States), a chemiluminescent microparticle 2-step immunoassay which quantifies the IgG class of TgAb in human serum and plasma on the ARCHITECT System. The lower LOD was 1.0 IU/mL. Reference range is 0.0–4.11 IU/mL. The lowest level exhibiting a 20% CV is 0.31 IU/mL.

Statistical analysis

Nonparametric statistics were used to compare the continuous variables. Continuous variables are reported as a mean \pm standard deviation or median values and ranges, while categorical variables are reported as absolute numbers and percentages. Multivariate regression analysis was done to assess the effect of the various parameters associated with PTC-TCH. $P < 0.05$ was considered statistically significant. All analyses were performed with IBM SPSS software (Version 21.0, Chicago, IL, USA).

RESULTS

Out of 392 patients included, 352 were cPTC and 40 PTC-TCH. Baseline features of PTC-TCH were as follows: the mean age at diagnosis was 42.9 years (range 23–71) with 52.5% females. About 62.5% of patients were <45 years of age. The mean tumor size was 30.3 mm (\pm 16.1 mm). When we compared the pathological features of cPTC and PTC-TCH, we found that tall cell tumors were larger than cPTC (30.3 mm vs. 18.2 mm, $P = 0.001$) [Figure 1]. The two groups were not statistically different in terms of age of presentation (42.9 years vs. 43.1 years, $P = 0.886$) and duration of neck swelling (20.73 vs. 21.8 months, $P = 0.861$). There was a male predilection for tall cell tumors (47.5% vs. 33.5%, $P = 0.081$). Tall cell tumors had more of statistically significant ($P < 0.05$) capsular invasion (54.1% vs. 37.7%, $P = 0.270$), ETE (55% vs. 30.4%, $P = 0.224$), and distant metastasis (20% vs. 6.5%, $P = 0.751$) (predominantly lung metastasis – 17.5% vs. 4.5%, $P = 0.477$) when compared to cPTC [Figure 2]. Tall cell tumors were more often multifocal (57.9% vs. 47%, $P = 0.443$), had slightly more association with lymphocytic thyroiditis (48.4% vs. 44.7%, $P = 0.973$), more lymph nodal metastasis (25% vs. 14%, $P = 0.795$) with perinodal spread (36.8% vs. 21.2%, $P = 0.312$). However, these differences were not statistically significant. Vascular invasion was unusually lower in tall cell group than cPTC (24.3% vs. 29.8%, $P = 0.142$). Furthermore, multivariate analysis showed a significant correlation between PTC-TCH and lung metastasis ($P = 0.004$).

We compared the two groups: TCV-PTC (>50% tall cells) and TCF-PTC (10%–50% tall cells) for any difference in behavior. However, the two groups were not statistically different in terms of clinical or histopathological characteristics ($P > 0.05$) [Table 1].

Follow-up and response to therapy

The mean duration of follow-up was 1.6 years. Out of those with follow-up >6 months, 72% have an incomplete/indeterminate response to therapy at their last follow-up. Surprisingly, more patients in focal tall cell group had incomplete/indeterminate response compared to TCV.

DISCUSSION

To the best of our knowledge, there has been no publication on TCH-PTC from India so far. In a review from Chennai, India, which analyzed the types of PTC, only one out of 377 patients belonged to TCV-PTC.^[9] A meta-analysis on TCV-PTC by Liu *et al.*^[10] in 2017 found only a few Asian studies from Korea and China and none from India.

Prevalence of TCH among PTC in our study was 10.2%, comparable with other published reports. Our prevalence was much higher than reported in the Chennai study and more in keeping with the Western and South Asian data. ATA guidelines report a 1.3%–13.3% prevalence for TCV-PTC.^[6] The wide range is due to the use of varying criteria (tall cell percentage).

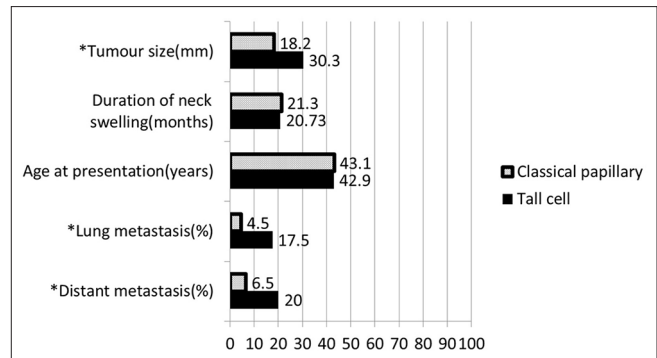


Figure 2: Bar diagram showing a comparison of histopathological characteristics of classical papillary carcinoma and papillary thyroid carcinoma with tall cell histology

Table 1: Comparison of tall cell variant (50% tall cells) (papillary thyroid carcinoma-tall cell variant) versus focal tall cell features (10%–50% tall cells) (papillary thyroid carcinoma-tall cell features)^a

Characteristics	TCV (%) (n=22)	Focal TCF (%) (n=18)	P
ETE	63.6	44.4	0.224
Perithyroidal fat	71.4	87.5	
Skeletal muscle	28.6	12.5	
Lymphocytic thyroiditis	45	44.4	0.97
Multifocality	52.4	64.7	0.44
Capsular invasion	61.9	43.8	0.27
Vascular invasion	33.3	12.5	0.14
Lymph node metastasis	42.9	47.1	0.795
Perinodal spread	27.3	50	0.31
Distant metastasis	18.2	22.2	0.75
Lung metastasis	16.7	22.2	0.477
Gender	Male 45.5 Female 54.5	Male 50 Female 50	0.08

^aNone of the parameters were significant. TCV: Tall cell variant, TCF: Tall cell features, ETE: Extrathyroidal extension

SEER database shows a 158% increase in TCV from 1988 to 2008.^[11] The reason for this is unclear.

The more aggressive features in our patients such as ETE, capsular invasion, larger tumor size, and distant metastasis, especially to lungs compared with cPTC [Figures 2 and 3] are in keeping with other reports.^[2] Ganly *et al.* showed that TCV was common in elderly. However, our cohort was younger, 62.5% were <45 years. He also showed that TCV-PTC and TCF-PTC (tall cells 30%–50%) were both aggressive.^[2] Comparison between TCV-PTC and TCF-PTC showed no statistically significant differences [Table 1] in our cohort, suggesting that the lack of influence for tall cell percentage in their aggressive behavior. This is perhaps the only series where response to therapy was defined using the latest ATA guidelines.

The median follow-up for TCH-PTC was 12 months (range 1–5 years).

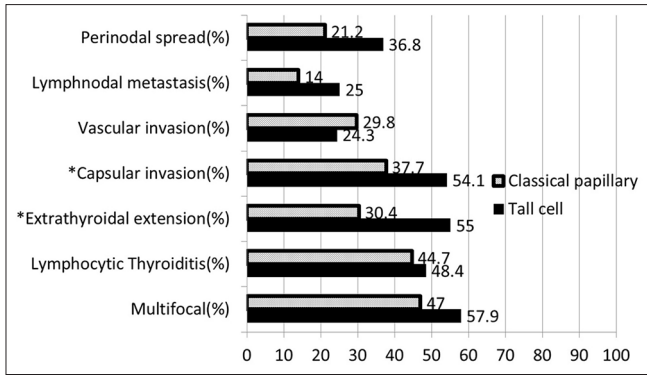


Figure 3: Bar diagram showing a comparison of clinical characteristics of classical papillary carcinoma and papillary thyroid carcinoma with tall cell histology

Short-term outcome in our series was similar between TCV-PTC and TCF-PTC. Out of the 15 patients with TCV-PTC, six had excellent response, whereas nine had incomplete response. TCF-PTC group did not behave differently in this aspect (excellent – 3 and incomplete – 11). These results suggest that percent tall cells do not influence the prognosis.

Metastasis from PTC is uncommon as these tumors have an indolent course. The most common metastatic site is lungs followed by bone and other organs. Certainly, none of the large series reporting lung metastasis from PTC recently looked at the contribution among them from TCF/TCV.^[12,13]

In our series, seven out of 40 (17.5%) showed lung metastases, significantly higher than in cPTC [Table 2]. These were documented by the first diagnostic/posttherapy iodine scan [Figure 4], chest CT, or PET/CT. Histopathological confirmation was available in only one patient who developed lobar collapse and underwent lobectomy. As noted in our study, Kazaure *et al.*^[11] reported distant metastases from PTC to be 4.3% as against 11.1% from TCV. Machens *et al.*^[14] reported a 4.8% prevalence of TCV, of which 31% had distant metastasis, predominantly pulmonary. The authors pointed out the high incidence and cautioned the need for close follow-up in these cases.

In our patients, the unusual feature was the appearance of lung lesions at diagnosis in two cases and within 1 year of detection of the primary in the rest. Ghossein *et al.*^[15] had reported 7 distant metastases in 62 TCV patients, out of which four were to the lungs, noted after 3 years of follow-up (3.4, 10.6, and 14.6 years). In a Saudi Arabia study^[16] on TCV-PTC defined as >10% tall cells, distant metastasis was seen in 8 out of 42 patients with TCV comparable with ours. Lung involvement was 11.9% much lower than ours. Male preponderance was noted (six out of seven) in our cases of lung metastases.

Although all our cases were ablated with RAI except one patient, all needed a second dose of RAI for persistent disease. Of these, three belonged to the TCV group and four were in the TCF group. Three of our patients required reexploration for local recurrence. These observations point to the intrinsic

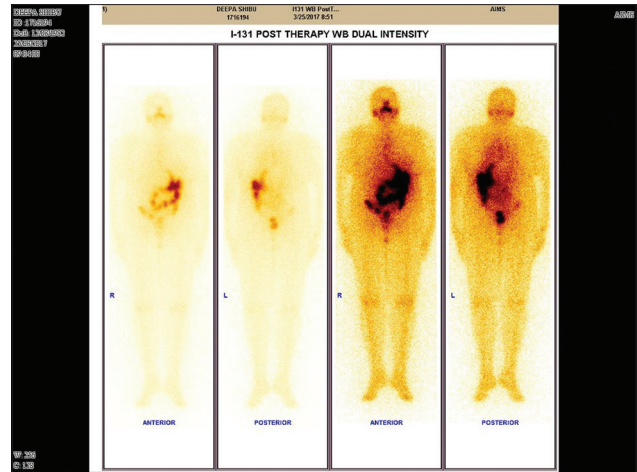


Figure 4: Whole-body I-131 posttherapy scan showing lung uptake

Table 2: Characteristics of papillary thyroid carcinoma-tall cell histology with lung metastasis (n=7)

Tumor size	Mean 3.3 (cm)
Age at presentation (years)	
>45	3
<45	4
Gender	
Males	5
Females	2
Multifocal	3
Lymphocytic thyroiditis	1
ETE	5
Capsular invasion	3
Vascular invasion	1
>5 lymph nodes	3

ETE: Extrathyroidal extension

aggressive behavior of PTC-TCH, perhaps irrespective of tall cell percentage.

Many mechanisms are postulated to explain the aggressive nature of TCV. TERT promoter mutations (TERTp) are prevalent in TCV more than in cPTC (30% vs. 10%).^[17] These mutations have been associated with recurrence of PTC and may even contribute to mortality.^[18] It is possible that these mutations account for the aggressive behavior of these tumors. We feel that it would be worthwhile looking for TERTp in TCH-PTC.

Shortcomings of our study include small numbers of TCH-PTC and short duration of follow-up. We could not use the new WHO definition (TCV-tall cells >30%) in this study as it became available only recently. Our advantage is the unique nature of the database and uniformity in management using the international standards. This feature adds to the credibility of our data. Our numbers are small to come to strong conclusions. Our results, however, do support the view that TCH-PTC is an aggressive subtype. The lack of importance for percent tall cells in the histology is

strongly suggested by the absence of significant differences between TCF and TCV, both in clinicopathological features or in the incidence of lung metastases. In patients with TCH, search for lung metastases early in the course of the disease, as recommended by Machens *et al.*^[14] should be encouraged and intensive therapy should be planned, irrespective of the number of tall cells. TERTp mutations or Ki-67 labeling index should be investigated as a marker for the aggressiveness of TCV. Anaplastic transformation must be looked for especially in the metastatic lesions irrespective of the type – TCV-PTC or TCF-PTC. Accurate histopathological analysis should be used so that these tumors are recognized at diagnosis.

CONCLUSION

We also suggest that TCV, irrespective of the percent tall cells, should be moved into high-risk category of the ATA risk stratification so that it receives initial aggressive therapy and close follow-up for recurrence either at locoregional sites or in distant organs, especially the lungs. In this context, we welcome the change in the definition of TCV to those having >30% of tall cells in the new edition of WHO classification of tumors. More studies in the future should evaluate the contribution of 10%–30% tall cells in determining the prognosis.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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