# Clinico-pathological and Molecular Characteristics of Tall Cell Variant of Papillary Thyroid Microcarcinoma

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## ABSTRACT

**Background** Papillary thyroid microcarcinomas (PTMC) are papillary thyroid carcinomas (PTC) measuring ≤1 cm. Their prognosis is excellent. However, a subset of them behave aggressively with recurrence, metastasis and cancer-specific mortality of up to 2%. The tall cell variant (TCV) of PTC is a particularly aggressive tumor that generally presents in advanced stage and is associated with higher disease-related mortality. Recognizing this variant in PTMC may help select aggressive microcarcinomas for more intensive therapy.

**Methods** Clinico-pathological features of 23 TCV of PTMC in 21 patients were reviewed. DNA was extracted from tumor tissue and *BRAF* V600E mutational analysis was performed by single strand conformational polymorphism.

**Results** The patients included 17 women and 4 men aged 34 to 74 years (median 54 yrs). All patients underwent total thyroidectomy. Eleven of 21 thyroids (52%) contained multifocal PTMC but only in two patients was the additional PTMC of the TCV. The tumors ranged from 2 mm to 10 mm in size (median 7 mm). The majority of tumor cells were at least twice as tall as wide, had moderate to abundant eosinophilic cytoplasm, and classic nuclear features of PTC with frequent intranuclear inclusions. Four tumors showed lymphovascular invasion (17%) and seven exhibited extrathyroidal extension (pT3; 30%). Lymph nodes were dissected in fourteen patients, and showed metastases to level VI nodes (pN1a) in three (21%) and lateral cervical lymph nodes (pN1b) in two patients (14%). Nineteen of twenty-one tumors harbored *BRAF* V600E mutations (90%). Six of nineteen patients (31%) presented at advanced stage (III/IVA). These cases were compared with 23 age and size matched classic variants of PTMC which showed 26% (6/23) multifocality, no lymphovascular invasion or extrathyroidal extension, metastases to level VI nodes in 3 of 14 (pN1a, 21%) and metastasis to lateral cervical lymph nodes (pN1b) in one patient only (7.1%); and *BRAF* V600E mutation in 18/23 tumors (78%). Only three of 23 patients (13%) presented at an advanced stage (III/IVA).

**Conclusions** The tall cell variant of papillary microcarcinoma is frequently associated with multifocality, lymphovascular invasion, extrathyroidal extension, advanced stage at presentation, and *BRAF* V600E mutation. Their recognition may help select patients with PTMC for more aggressive treatment.

## BACKGROUND

Papillary thyroid microcarcinomas (PTMC) defined as papillary thyroid carcinomas (PTC) measuring ≤1 cm (1) are increasingly being identified due to the frequent use of thyroid ultrasound (2). While the vast majority of PTMC are curable, a small subset recur and metastasize. Recognition of these poorly behaving tumors will help triage PTMC for additional therapy. The TCV is a known aggressive subtype of PTC. Patients with TCV have a higher rate of extrathyroidal extension and distant metastases at presentation, and increased mortality when compared to the classic variant of PTC (3, 4). To our knowledge, the recognition of TCV among papillary thyroid microcarcinomas is generally not attempted in routine diagnostic surgical pathology as its significance remains unknown. In this study, we report the clinico-pathological characteristics of the tall cell variant of papillary thyroid microcarcinoma, and compare them to age and size matched classic variants of PTMC.

## METHODS

Twenty-three cases of TCV of PTMC were identified at the Department of Pathology at the Yale-New Haven Hospital after review of archival material. The criteria for diagnosis were: PTMC comprised of a majority (≥50%) of tall cells whose heights were at least twice that of their width (5). These tumors characteristically exhibited eosinophilic cytoplasm and classic nuclear features of PTC (Figures 3 & 4). These were compared with a similar number of age and size matched classic variants of PTMC (Figure 5). A subset of the TCV of PTMC were also reviewed with endocrine pathologists from other institutions.

The patient demographics and specifics of the resections were recorded in all cases. Clinical follow-up was obtained through the electronic medical record. Testing for *BRAF* V600E mutation was performed on DNA extracted from paraffin embedded tissue which was enriched for tumor cells by manual microdissection. The PCR product was obtained using assay specific reagents and was analyzed for the V600E mutation by Single Strand Conformation Polymorphism (SSCP) using appropriate positive and negative controls. The protocol was approved by the Yale-New Haven Hospital institutional review board for the study of human subjects.

## RESULTS

The clinico-pathologic and molecular characteristics of both the TCV PTMC and classic variant PTMC tumors are reported in Table 1. As the classic variants were age and size matched, no difference was expected in these two variables. A slightly higher male preponderance was noted in TCV compared to the classic variant of PTMC.

Twenty of the 21 patients with TCV of PTMC underwent a fine needle aspiration (FNA) biopsy of thyroid prior to resection, of whom eighteen were positive for PTC (Figure 1). Gross examination of most tumors showed a grey tan, firm, cut surface (Figure 2).

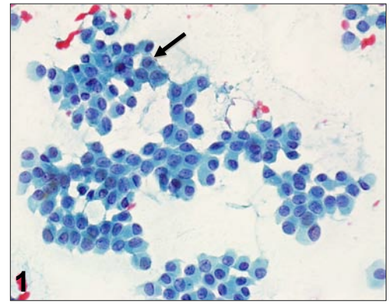
**Table 1. Clinico-pathologic and Molecular Characteristics of TCV and Classic Variant of PTMC (Age and Size matched)**

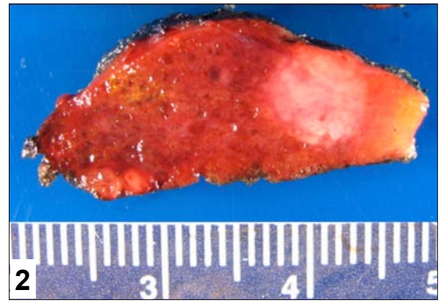
| | Tall Cell Variant Microcarcinoma (n=23 tumors, 21 patients) | Classic Variant Microcarcinoma (n=23 tumors) |
|---|---|---|
| Median age (years) | 54 (range: 34-74) | 51 (range: 32-80) |
| Age < 45years<br>Age ≥45 years | 4(19%)<br>17 | 5(22%)<br>18 |
| F:M | 17:4 (4.3:1) | 22:1 (22:1) |
| Size | | |
| ≤5mm<br>>5mm | 6 (26%)<br>17 (74%) | 6 (26%)<br>17 (74%) |
| Median tumor size in mm (range) | 7 (2-10) | 7 (2-10) |
| Extrathyroidal extension (ETE) | 7/23 (30%) | 0/23 (0%) |
| Lymphovascular Invasion | 4/23 (17%) | 0/23 (0%) |
| Multifocality | 11/21 (52.3%) | 6/23 (26.1%) |
| *BRAF* V600E mutation positive | 19/21 (90.4%) | 18/23 (78.2%) |
| pT | | |
| T1a | 12/19* (63.2%) | 23 (100%) |
| T3 | 7/19* (36.8%) | 0 |
| pN | | |
| N0 | 9/14* (64.3%) | 10/14 (71.4%) |
| N1a | 3/14* (21.4%) | 3/14 (21.4%) |
| N1b | 2/14* (14.2%) | 1/14 (7.1%) |
| AJCC Stage | | |
| I | 13/19* (68.4%) | 20/23 (87%) |
| III | 5/19* (26.3%) | 2/23 (8.7%) |
| IVA | 1/19* (5.3%) | 1/23 (4.3%) |

*Two of the patients were staged based on the larger non-TCV papillary thyroid carcinoma present within the thyroidectomy specimen (pT1b and pT2). These patients were excluded from analysis with respect to tumor size, nodal status and AJCC staging (n=19 patients).

## DISCUSSION & CONCLUSIONS

- TCV of PTMC is a morphologically distinct entity and can be recognized on routine microscopy following the usual definition.
- The majority of these tumors are >5 mm in size, and are characterized by a higher prevalence of extrathyroidal extension, lymphovascular invasion, multifocality, *BRAF* V600E mutation, and a more advanced stage at presentation.
- However, there was no significant difference in lymph node status when compared with age and size matched classic variant PTMC which may be reflective of the fact that three quarters of these tumors were greater than 5 mm.
- A larger case series is needed to fully explore these trends and understand their significance.



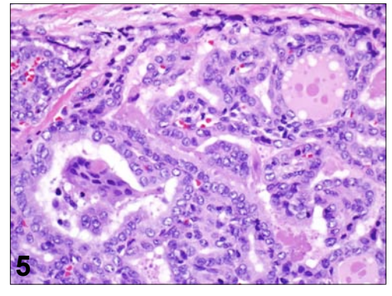




**Figure 1.** FNA biopsy of TCV of PTMC. Sheets of cells with nuclear grooves and intranuclear inclusion (arrow) with dense cytoplasm (Papanicolaou stain, X400).

**Figure 2.** Gross appearance of a 6 mm TCV of PTMC.

**Figure 3.** Extrathyroidal extension in a TCV of PTMC (H&E, x100).

**Figure 4.** Photomicrograph of a TCV of PTMC with intranuclear inclusion (arrow) (H&E, x400).

**Figure 5.** Photomicrograph of classic variant of PTMC for comparison (H&E, x400).

## REFERENCES

1. De Lellis RA, Lloyd RV, Heitz PU, Eng C, editors. World Health Organization. Classification of tumours. Pathology and genetics of tumours of endocrine organs. Lyon, France: IARC Press; 2004. p. 57–66.
2. Davies L, Welch HG. 2006. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 295:2164-7.
3. Jalisi S, Ainsworth T, LaValley M. 2010. Prognostic Outcomes of Tall Cell Variant Papillary Thyroid Cancer: A Meta-Analysis. J Thyroid Res 22: 325602.
4. Morris LG, Shaha AR, Tuttle RM, Sikora AG, Ganly I. 2010. Tall-cell variant of papillary thyroid carcinoma: a matched-pair analysis of survival. Thyroid 20:153–158.
5. Ghossein R and Livolsi V. 2008. Papillary Thyroid Carcinoma Tall Cell Variant. Thyroid. 18:1179-1181.

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