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ORIGINAL ARTICLE – ENDOCRINE TUMORS

Papillary Thyroid Cancers with Focal Tall Cell Change are as Aggressive as Tall Cell Variants and Should Not be Considered as Low-Risk Disease

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ABSTRACT

Background. The tall cell variant of papillary thyroid carcinoma (PTC) is as an aggressive histological variant. The proportion of tall cells needed to influence prognosis is debated.

Methods. Patients with PTC and tall cells, defined as having a height-to-width ratio of $\geq$ 3:1, seen at a high-volume center between 2001 and 2015, were reviewed. Specimens were classified as (1) focal tall cell change, containing $<$ 30% of tall cells; (2) tall cell variant, $\geq$ 30% of tall cells; and (3) control cases selected from infiltrative classical PTCs without adverse cytologic features. Univariate, sensitivity, and multivariate analyses were performed with persistent/recurrent disease as the primary outcome.

Results. We identified 96 PTCs with focal tall cell change, 35 with the tall cell variant and 104 control cases. Factors associated with poor clinical prognosis were significantly greater in those with focal tall cell change and tall cell variants. Regarding primary outcome, hazard ratios were 2.3 (95% confidence interval [CI] 1.0–5.7) for focal tall cell change, and 3.4 (95% CI 1.2–8.7) for tall cell variants compared with controls. Five-year disease-free survival was higher for the control group (92.7%, CI 87.4–98.0) compared with focal tall cell change (76.3%, CI 66.1–86.5) and the tall cell variant (62.2%, CI 43.2–81.2). When stratified in groups consisting of tall cell proportions ($<$ 10%, 10–19%, 20–29% and $\geq$ 30%), identification of $\geq$ 10% tall cell change was associated with worse outcome (p = 0.002).

Conclusions. PTCs with $\geq$ 10% tall cell change have worse prognosis than those without tall cells. Our data indicate that thyroid cancer management guidelines should consider PTCs with focal tall cell change outside of the low-risk classification.

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Papillary thyroid carcinoma (PTC) is generally indolent, with excellent 10-year survival rates > 95%.[1] However, some histologic variants of PTCs demonstrate more aggressive behavior, leading to higher rates of metastasis, recurrence, and resistance to radioactive iodine (RAI) therapy.[2] Among these, the tall cell variant of PTC has been recognized for its aggressive biology.

In 1976, Hawk and Hazard first reported the tall cell variant of PTC.[3] Tall cells are characterized by a cell height that is at least two or three times its width, eosinophilic cytoplasm, basal nuclei, and the classic nuclear features of PTC.[4,5] At a molecular level, a higher prevalence of *BRAFV600E* mutation (80–100%), *TERT* promoter mutations, somatic copy number alteration of 1q, and oncogenic microRNA-21 (miR-21) have been identified in this variant.[6–9]

There is noticeable variability in descriptive reports of the tall cell variant of PTC, with a wide range of prevalence (3–19% of PTCs), recurrence (0–66.3%), and disease-specific death rates (1.5–42.9%).[10–15] Some of the variability is attributed to the thresholds for pathological identification of tall cell change. These criteria are ultimately used to define the tall cell variant, which include a ratio of 2 or 3 for height:width, and the proportion of tall cell change ranging from 30 to 75%.[4,15–21] Most experts have adopted a 30% proportion, rather than the previously more common 50%, as diagnostic criteria for a tall cell variant PTC.[22] The 4th edition of the World Health Organization (WHO) classification of endocrine tumors revised the cut-off value for tall cell change as ≥ 30% for tall cell variant designation.[23] The most recent 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer (ATA guidelines) included the tall cell variant as an independent factor indicating intermediate-risk rather than low-risk PTCs.[24] Interestingly, Beninato et al.[25] found that aggressive behavior can be seen in PTCs with ≥ 10% tall cell change, while other researchers also reported increased risk in those with other proportions of tall cell change.[8,26,27] The outcome implications of focal tall cell change (< 30%) in a classical variant PTC remains unaddressed in the risk stratification of most guidelines.

As there is a paucity of evidence to support the clinical relevance of PTCs with < 30% of tall cells, we compared outcome and adverse tumor characteristics of PTCs with focal tall cell change (< 30% cell change in the entire tumor volume) and tall cell variant PTCs (≥ 30% cell change) in our series of thyroid cancers. We hypothesized that even small proportions of tall cell change within a PTC portend more aggressive tumor biology and, ultimately, worse clinical outcome.

MATERIALS AND METHODS

Case Selection and Pathology Review

We performed a retrospective review of all patients with any tall cell changes in PTC managed at a high-volume university hospital between 2001 and 2015. Patients were identified from the institutional pathology database. The institutional Research Ethics Board approved this study.

All tall cell variant PTCs and PTCs with focal tall cell change that were > 1 cm and had available follow-up data, were included. tall cell variants with a synchronous focus of other cytomorphology (e.g. columnar cell, hobnail cell change) and dedifferentiation were excluded. A control group consisted of all patients with classical PTCs > 1 cm with available follow-up from a 3-year period (2011–2013).

Tall cells were defined as cells with height three times their width, and having an eosinophilic cytoplasm with the characteristic nuclear features of PTCs. A PTC was classified as a tall cell variant when tall cell change accounted for at least 30% of the entire tumor volume, whereas a diagnosis of PTC with focal tall cell change was made when the PTC had focal tall cell change accounting for < 30% of the entire tumor volume. The pathologic definition for classical PTC as the control group was an infiltrative PTC with classical papillary architecture and with no evidence of adverse cytomorphological features, including the absence of all of the following: tall cell, columnar cell, or hobnail cell change, increased mitotic activity (> 3 per 10 high-power fields), tumor cell necrosis, and dedifferentiation.

Standard practice has been to submit the entire tumor for pathologic examination, as well as documentation of focal adverse cytomorphological features, including focal tall cell change. Two experienced endocrine pathologists (OM, SLA) independently reviewed all cases. The Pathology Department has used digital pathology routinely since 2011, and when a PTC displayed borderline tall cell-like changes, pathologists used whole slide images to confirm the height-to-width ratio. During re-review of cases for the purposes of this study, when a discordance was present with respect to focal tall cell change, the whole slide images were used to objectively estimate the volumetric extent of tall cell change within the entire tumor volume. By doing this, mutual agreement was achieved in all study cases.

Clinicopathologic Characteristics and Follow-Up

Demographic information, synoptic pathology reports, and clinical and imaging data were obtained from the electronic patient records. Persistent or recurrent disease

was defined as histologically or cytologically confirmed structural disease present or found after the initial surgery and RAI treatment. A serum thyroglobulin increase without structural disease, or small indeterminate lesions, were not considered recurrence for the purposes of this study. Follow-up time was defined as the time between surgery and the last clinical visit related to the thyroid cancer reported in the institutional electronic patient records up to 2017.

Statistical Analysis

Descriptive data were summarized using descriptive statistics. Differences in clinical and pathological features between each of the three groups (classical PTC without any adverse features, those with focal tall cell change, and tall cell variant groups) were tested using the Chi square, one-way analysis of variance (ANOVA) or Kruskal–Wallis tests as appropriate, with Sidak and Holm–Bonferroni corrections being applied once pairwise comparisons were made between the subgroups.

The relationship of PTC subgroups and persistent or recurrent disease was evaluated using univariate methods (Kaplan–Meier survival curve and log-rank test) and corrected for confounders using multivariate methods (Cox proportional hazards analysis). Forward stepwise regression was employed given the large amount of potential confounders and relatively low event rate (recurrence). The forward stepwise regression procedure included variables that both differed among the three subgroups of PTC and were univariately associated ($p < 0.10$) with persistent or recurrent disease. Those candidate confounders were entered step by step, starting with the highest p value in the univariate analysis, and eliminating non-significant variables until all variables in the model were statistically significant. Sensitivity analysis was performed to understand the thresholds of tall cell impact on outcome by stratifying patients with a specific reported percentage of tall cell features in groups consisting of a tall cell proportion of (1) $< 10\%$; (2) 10–19%; (3) 20–29%; and (4) $\geq 30\%$.

Significance was determined at a p-value < 0.05, and statistical analyses were performed using SPSS version 22 (IBM Corporation, Armonk, NY, USA).

RESULTS

Overall, 131 patients with tall cell change were identified; 96 patients had focal tall cell change and 35 patients had tall cell variant PTC. We collected 104 patients to serve as a control group with classical PTC.

Table 1 summarizes the clinical and pathological features of the tumor subgroups. Control group patients with classical PTC, and those with focal tall cell change, were younger compared with those with tall cell variant PTC (mean age $\pm$ standard deviation 45.6 $\pm$ 13.5, 48.5 $\pm$ 14.7 and 55.3 $\pm$ 17.2 years, respectively). The median tumor size differed between the control group, PTC with focal tall cell change, and tall cell variant PTC {median size 17.0 mm (interquartile range [IQR] 13.0–31.5), 26.0 mm (IQR 16.0–39.5), and 40.0 mm (IQR 21.0–48.0), respectively}. Median follow-up time among tumor groups was 49.5 months (IQR 28.0) for the control group, 43.5 months (IQR 31.0) for PTC with focal tall cell change, and 35.0 months (IQR 87.0) for tall cell variant PTC. These differences were not statistically significant ($p = 0.521$). Factors significantly associated with both tall cell variant and focal tall cell change, but not the control group, included vascular invasion, gross extrathyroidal extension, positive resection margins, and distant lung metastasis. Lymph node metastases at the time of initial diagnosis were more frequent in patients with PTCs displaying focal tall cell change (68.8%) than those with classical PTC (53.8%) [$p = 0.031$].

Disease-Specific Outcome

Within the entire cohort, one patient died of disease. This patient had a tall cell variant PTC with lymph node metastasis and positive resection margins, and died of disease after rapid progression with extensive local invasion into the trachea and distant metastases to bone and brain.

The likelihood of persistent or recurrent disease was higher in patients with PTC displaying focal tall cell change (21.9%, $p = 0.002$) and tall cell variant PTC (37.1%, $p = 0.001$) compared with the control group with classical PTC (6.7%). Of the control group, 6.7% had locoregional lymph node metastasis and none had distant metastasis, whereas these rates were 14.6% and 8.9% for PTCs with focal tall cell change, and 14.3% and 22.9% for tall cell variant PTCs.

Table 2 shows the final multivariate Cox proportional hazards model for persistent or recurrent disease after the forward stepwise selection procedure. The hazard ratio (HR) for the PTC subgroup with focal tall cell change was 2.3 (95% confidence interval [CI] 1.0–5.7; $p = 0.062$), and 3.3 (95% CI 1.2–8.7; $p = 0.020$) for the tall cell variant PTC, adjusted for tumor size and gross extrathyroidal extension.

TABLE 1 Baseline clinicopathologic features per subgroup of papillary thyroid cancer

	Infiltrative classical PTC (control group) [*N* = 104]	PTC with focal tall cell change [*N* = 96]	Tall cell variant PTC [*N* = 35]	*p* Value
Age, years [mean (SD)]	45.6 (13.5)	48.5 (14.7)	55.3 (17.2)	0.003[a]
Female	77 (74.0)	63 (65.6)	19 (54.3)	0.083
Tumor size, mm [median (IQR)]	17.0 (13.0–31.5)	26.0 (16.0–39.5)	40.0 (21.0–48.0)	< 0.001[b]
Vascular invasion	14 (13.5)	30 (31.3)	14 (40.0)	0.001[c]
Gross extrathyroidal extension	1 (1.0)	13 (13.5)	7 (20.0)	< 0.001[c]
Positive margins	25 (24.0)	43 (44.8)	22 (62.9)	< 0.001[c]
Lymph node metastasis at diagnosis	56 (53.8)	66 (68.8)	25 (71.4)	0.047[d]
Distant metastasis at diagnosis	0	5 (5.2)	3 (8.6)	0.024[c]
Hemithyroidectomy as definitive treatment	7 (6.7)	2 (2.1)	1 (2.9)	0.241
RAI remnant ablation	64 (61.5)	80 (83.3)	31 (88.6)	< 0.001[c]

Data are expressed as *n* (%) unless otherwise stated

PTC papillary thyroid carcinoma, *IQR* interquartile range, *RAI* radioactive iodine, *SD* standard deviation

[a]Significant differences between classical PTC versus the tall cell variant

[b]Significant differences between all groups

[c]Significant differences between classical PTC versus focal tall cell change/tall cell variant

[d]Significant differences between classical PTC versus focal tall cell change

TABLE 2 Forward Cox regression analysis for persistent or recurrent disease

	HR (95% CI)	*p* Value
Subgroup of PTC		
Classical PTC	1.0 (reference)	
PTC with focal tall cell change	2.3 (1.0–5.7)	0.062
Tall cell variant PTC	3.4 (1.2–8.7)	0.020
Tumor size, mm	1.0 (1.0–1.1)	0.003
Gross extrathyroidal extension	2.6 (1.1–5.8)	0.024

Potential confounders that entered the forward stepwise selection procedure were tumor size, vascular invasion, gross extrathyroidal extension, positive resection margins, lymph node metastasis at the time of initial diagnosis, and RAI remnant ablation

PTC papillary thyroid carcinoma, *HR* hazard ratio, *CI* confidence interval

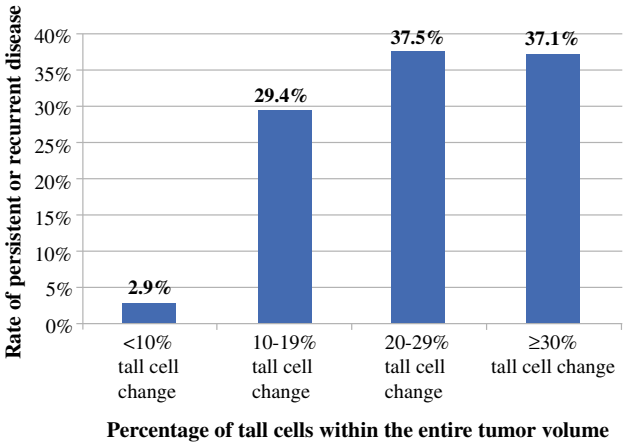


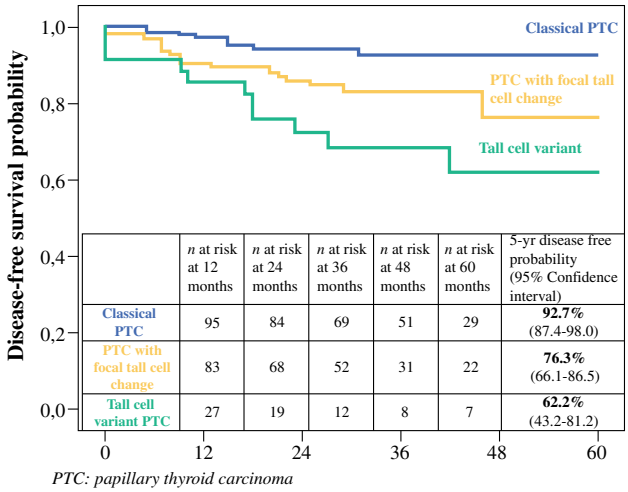
FIG. 1 Persistent or recurrent disease rate stratified per amount of tall cells present in the papillary thyroid carcinoma

Sensitivity Analysis

The relationship between the extent of tall cell change and persistent or recurrent disease is shown in Fig. 1. This included 35 cases with < 10% tall cell change, 17 between 10 and 19%, 24 between 20 and 29%, and 35 tall cell variants had recurrence rates of 2.9%, 29.4%, 37.5% and 37.1%, respectively. PTCs exhibiting < 10% tall cell change had less persistent or recurrent disease compared with PTCs with ≥ 10% tall cell change ($p = 0.002$).

Disease-Free Survival

As demonstrated in Fig. 2, infiltrative classical PTCs (control group) had a higher 5-year disease-free survival of 92.7% compared with PTCs displaying focal tall cell change (76.3%, $p = 0.010$) and tall cell variant PTCs (62.2%, $p = 0.001$). There was no significant difference between PTCs with focal tall cell change and tall cell variant PTCs with respect to 5-year disease-free survival ($p = 0.120$).



	n at risk at 12 months	*n* at risk at 24 months	*n* at risk at 36 months	*n* at risk at 48 months	*n* at risk at 60 months	5-yr disease free probability (95% Confidence interval)
Classical PTC	95	84	69	51	29	**92.7%** (87.4-98.0)
PTC with focal tall cell change	83	68	52	31	22	**76.3%** (66.1-86.5)
Tall cell variant PTC	27	19	12	8	7	**62.2%** (43.2-81.2)

PTC: papillary thyroid carcinoma

FIG. 2 Five-year disease-free survival curve. *PTC* papillary thyroid carcinoma

DISCUSSION

This study highlights the elevated risk profile of PTCs with small percentages of tall cell change. Tumors with focal tall cell change (defined as < 30% of the entire tumor volume) had worse prognostic features than a control group of classical PTCs with no adverse cytomorphological features, and resembled those of tall cell variants. PTCs with focal tall cell change, and tall cell variant PTCs, had comparable rates of persistent or recurrent disease. Moreover, focal tall cell change showed a trend to be independently associated with persistent and recurrent disease. When the percentage of tall cells in the PTC was > 10%, the recurrence/persistence rate increased tenfold, from 3 to 30%.

The tall cell variant of PTC stands out as an aggressive variant. The extent of tall cell change required to negatively affect prognosis remains unclear.[3,4,15–21] The most recent 4th edition of the WHO classification adopted the cut-off of 30%, and a recent survey of expert thyroid pathologists showed that no consensus has yet been reached on the diagnostic criteria for this variant.[22,23] In that particular report, only 7 of 14 experts identified that they use the 30% cut-off to define a tall cell variant.[22] In recent years, there has been a tendency to use lower thresholds in defining tall cell variants. This has been influenced by studies that found adverse outcomes when only 10% tall cell change was seen in the sections examined.[8,25,27] Poor survival and higher rates of lymph node metastasis were independently associated with tall cell variant PTCs correlating with other known risk factors for poor outcome, such as patient age, tumor size, and extrathyroidal extension.[10,12,28,29] In this study, these risk factors were seen more commonly in both the tall cell variant and focal tall cell groups compared with the control group.

One ongoing difficulty in making a diagnosis of tall cell variant involves thyroid specimen evaluation. Currently, there are no evidence-based guidelines addressing the amount of thyroid tumor that needs to be submitted for histological examination when making a diagnosis of tall cell variant PTC.[22] In this study, all thyroidectomy specimens were submitted in toto for microscopic examination and were reviewed by two expert endocrine pathologists. This enabled us to determine the extent of the tall cell change within the entire tumor volume rather than the percentage of tall cells in representative sections, the latter being a method commonly used in most North American surgical pathology practices. In addition, this unique advantage secured accurate selection of the control group.

With the de-escalation of the treatment of thyroid cancer, further discussion on surgical approach for patients with tall cell change is warranted. Within the sensitivity analysis in this cohort, PTCs with < 10% tall cell change had a recurrence/persistent rate of 3%, consistent with low-risk disease that would likely be a candidate for lobectomy alone. In contrast, patients with ≥ 10% tall cell change (but < 30%) had a 30% chance of recurrence or persistence. This suggests a possible benefit of more aggressive management, including total thyroidectomy and RAI remnant ablation, usually reserved for higher-risk disease. At least 5 of the 41 patients (12.2%) with 10–30% tall cell features would be classified as 'low-risk' according to the recent ATA guidelines. It is important to note that these changes in management can only be applied after the initial surgical management, given that a diagnosis of tall cell containing PTC requires a histological examination.

There are several limitations to this study. Data regarding mortality may be missing as follow-up data were collected retrospectively and information regarding mortality outside of the electronic hospital record is unavailable. Furthermore, since our center is a tertiary care endocrine surgery referral center, selection bias may explain why our control group of infiltrative classical PTCs had a somewhat worse outcome compared with the literature.[30,31] If true, this bias would underestimate the aggressiveness of focal tall cell change compared with controls.

We did not perform molecular profiling of tumor subgroups. While tall cell variants of PTC are frequently associated with *BRAFV600E* mutations, data from The Cancer Genome Atlas (TCGA) showed that these tumors are also enriched in synchronous *TERT*-promoter mutations, somatic copy number alterations and gain of 1q (*SCNA-low-1q amp*), as well as a distinct epigenetic signature including *miR-21* expression.[9,27] Future studies will

employ genetic testing that may allow clinicians to have indications on aggressive tumors, possibly within a pre-operative fine needle aspiration.

CONCLUSIONS

As treatment of thyroid cancer becomes less aggressive and more targeted to higher-risk patients, selecting those in lower- and higher-risk categories is imperative to minimize recurrence and optimize quality of life. Patients with PTCs displaying focal tall cell change without other intermediate- or high-risk characteristics are currently classified as low risk. The 5-year recurrence rate of 23.7% in our study indicates that patients with focal tall cell change have a risk association that is more consistent with tall cell variant PTCs than classical variant PTCs. Furthermore, those patients with $> 10\%$ tall cell composition of PTCs had recurrence rates in the range of 30%, compared with 3% for those with $< 10\%$ of components. Our data suggest a potential re-classification of low-risk PTCs with at least 10% composition of tall cells.

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REFERENCES

1. Clark O, Duh Q-Y, Kebebew E, Gosnell J, Shen W. Textbook of endocrine surgery, 3rd edn. Kathmandu: Jaypee Brothers Medical Publishers; 2016.
2. Lam AK, Lo C-YY, Lam KS. Papillary carcinoma of thyroid: A 30-yr clinicopathological review of the histological variants. *Endocr Pathol.* 2005;16(4):323–30.
3. Hawk WA, Hazard JB. The many appearances of papillary carcinoma of the thyroid. *Cleve Clin Q.* 1976;43(4):207–16.
4. Ghossein R, Livolsi VA. Papillary thyroid carcinoma tall cell variant. *Thyroid.* 2008;18(11):1179–81.
5. Solomon A, Gupta PK, LiVolsi VA. Distinguishing tall cell variant of papillary thyroid carcinoma from usual variant of papillary thyroid carcinoma in cytologic specimens. *Diagn Cytopathol.* 2002;27(3):143–8.
6. Erler P, Keutgen XM, Crowley MJ, et al. Dicer expression and microRNA dysregulation associate with aggressive features in thyroid cancer. *Surgery.* 2014;156(6):1342.
7. Min HS, Lee C, Jung KC. Correlation of immunohistochemical markers and BRAF mutation status with histological variants of papillary thyroid carcinoma in the Korean population. *J Korean Med Sci.* 2013;28:534–41.
8. Oh W, Lee Y, Cho U, et al. Classic papillary thyroid carcinoma with tall cell features and tall cell variant have similar clinicopathologic features. *Korean J Pathol.* 2014;48(3):201.
9. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. *Cell.* 2014;159(3):676–90.
10. van den Brekel MW, Hekkenberg RJ, Asa SL, Tomlinson G, Rosen IB, Freeman JL. Prognostic features in tall cell papillary carcinoma and insular thyroid carcinoma. *The Laryngoscope.* 1997;107(2):254–9.
11. Hunt JL. Unusual thyroid tumors: a review of pathologic and molecular diagnosis. *Expert Rev Mol Diagn.* 2005;5(5):725–34.
12. Ghossein RA, Leboeuf R, Patel KN, et al. Tall cell variant of papillary thyroid carcinoma without extrathyroid extension: biologic behavior and clinical implications. *Thyroid.* 2007;17(7):655–61.
13. Silver CE, Owen RP, Rodrigo JP, Rinaldo A, Devaney KO, Ferlito A. Aggressive variants of papillary thyroid carcinoma. *Head Neck.* 2011;33(7):1052–59.
14. Carling T, Ocal IT, Udelsman R. Special variants of differentiated thyroid cancer: does it alter the extent of surgery versus well-differentiated thyroid cancer? *World J Surg.* 2007;31(5):916–23.
15. Wang X, Cheng W, Liu C, Li J. Tall cell variant of papillary thyroid carcinoma: current evidence on clinicopathologic features and molecular biology. *Oncotarget.* 2016;7(26):40792–9.
16. Nikiforova MN, Kimura ET, Gandhi M, et al. BRAF mutations in thyroid tumors are restricted to papillary carcinomas and anaplastic or poorly differentiated carcinomas arising from papillary carcinomas. *J Clin Endocrinol Metab.* 2003;88(11):5399–404.
17. Akslen LA, LiVolsi VA. Prognostic significance of histologic grading compared with subclassification of papillary thyroid carcinoma. *Cancer.* 2000;88(8):1902–8.
18. Guan H, VandenBussche CJ, Erozan YS, et al. Can the tall cell variant of papillary thyroid carcinoma be distinguished from the conventional type in fine needle aspirates? A cytomorphologic study with assessment of diagnostic accuracy. *Acta Cytol.* 2013;57(5):534–42.
19. Michels JJ, Jacques M, Henry-Amar M, Bardet S. Prevalence and prognostic significance of tall cell variant of papillary thyroid carcinoma. *Hum Pathol.* 2007;38:212–9.
20. Terry JH SJS, Karkowski FJ, Suarez JR, Yassa NH, Platica CD, Marti JR. all cell papillary thyroid cancer: incidence and prognosis. *Am J Surg.* 1994;168(5):459–61.
21. Axelsson TA, Hrafnkelsson J, Olafsdottir EJ, Jonasson JG. Tall cell variant of papillary thyroid carcinoma: a population-based study in Iceland. *Thyroid.* 2014;25(2):216–220.
22. Hernandez-Prera JC, Machado RA, Asa SL, et al. Pathologic reporting of tall-cell variant of papillary thyroid cancer: Have we reached a consensus? *Thyroid.* 2017;27(12):1498–504.
23. Lloyd RV, Osamura RY, Klöppel G, Rosai J. WHO classification of tumours of endocrine organs, 4th edn. Lyon: IARC; 2017.
24. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid.* 2016;26(1):1–133.
25. Beninato T, Scognamiglio T, Kleiman DA, et al. Ten percent tall cells confer the aggressive features of the tall cell variant of papillary thyroid carcinoma. *Surgery.* 2013;154(6):1331.
26. Ganly I, Ibrahimpasic T, Rivera M, et al. Prognostic implications of papillary thyroid carcinoma with tall-cell features. *Thyroid.* 2014;24(4):662–70.
27. Dettmer MS, Schmitt A, Steinert H, et al. Tall cell papillary thyroid carcinoma: new diagnostic criteria and mutations in BRAF and TERT. *Endocr Relat Cancer.* 2015;22(3):419–29.

28. Morris LGT, Shaha AR, Tuttle MR, Sikora AG, Ganly I. Tall-cell variant of papillary thyroid carcinoma: a matched-pair analysis of survival. *Thyroid.* 2010;20(2):153–8.
29. Chung YJ, Lee JS, Park SY, et al. Histomorphological factors in the risk prediction of lymph node metastasis in papillary thyroid carcinoma. *Histopathology.* 2013;62(4):578–88.
30. Leung AK, Chow S-MM, Law SC. Clinical features and outcome of the tall cell variant of papillary thyroid carcinoma. *The Laryngoscope.* 2008;118(1):32–8.
31. Prendiville S, Burman KD, Ringel MD, et al. Tall cell variant: an aggressive form of papillary thyroid carcinoma. *Otolaryngol Head Neck Surg.* 2000;122(3):352–7.