



Tall Cell Variant of Papillary Thyroid Carcinoma: Impact of Change in WHO Definition and Molecular Analysis

Kristine S. Wong¹ · Sara E. Higgins¹ · Ellen Marqusee² · Matthew A. Nehs³ · Trevor Angell² · Justine A. Barletta¹

Published online: 18 December 2018
© Springer Science+Business Media, LLC, part of Springer Nature 2018

Abstract

The morphologic criteria for tall cell variant (TCV) of papillary thyroid carcinoma (PTC) were modified in the 2017 WHO Classification of Tumors of Endocrine Organs, with a decrease in the requirements for both the height of cells and in the percentage of tumor demonstrating a tall cell morphology. The aim of this study was to determine if the change in criteria would result in a significant increase in the percentage of tumors that meet criteria for TCV. In addition, we evaluated the correlation between morphology, molecular alterations, and clinical behavior of TCV. We studied three cohorts to evaluate the above stated questions. The first cohort was comprised of 97 PTC consecutively resected over a 12-month period that were originally diagnosed as classic PTC, PTC with tall cell features, or TCV. Tumor slides of each case were reviewed to determine the percentage of the tall cell component (< 30%, 30–49%, and \geq 50%) and the height of the cells in this component. This cohort was evaluated to determine if the change in WHO criteria would result in a significant increase in the percentage of tumors that meet criteria for TCV. Our second cohort consisted of nine consecutively resected PTC with a tall cell component \geq 30% (with tall cells defined as at least 2–3 \times as tall as wide) that had molecular characterization through a targeted, next-generation sequencing (NGS) assay. The molecular characteristics were correlated with the percentage of the tall cell component. Finally, a third cohort comprised of seven clinically aggressive TCV (defined as those with T4 disease, disease recurrence, or subsequent tumor dedifferentiation) was evaluated to determine histologic and molecular characteristics. In cohort 1, the number of cases classified as TCV increased significantly with the change in definition of TCV: 8 (8%) cases met the previous criteria for TCV (cells 3 \times as tall as wide in \geq 50% of the tumor), whereas 24 (25%) cases met the new 2017 WHO criteria (cells 2–3 \times as tall as wide in \geq 30% of the tumor) ($p = 0.0020$). Molecular analysis of cohort 2 revealed that all 9 cases harbored a *BRAF* V600E mutation. Pathogenic secondary mutations were absent in cases with < 50% tall cells, but they were detected in 2 (33%) of 6 cases with \geq 50% tall cells (2 cases with *TERT* promoter mutations, including 1 that also had an *AKT2* mutation). Histologic and molecular analysis of the clinically aggressive cohort (cohort 3), revealed that all cases had \geq 50% tall cells and 3 (43%) had secondary oncogenic mutations (all *TERT* promoter mutations). We found that the modified morphologic criteria put forth in the 2017 WHO tripled the number of cases that would be classified as TCV. Moreover, clinically aggressive tumors and those harboring secondary oncogenic mutations all had a tall cell component \geq 50%. Additional large multi-institutional studies incorporating clinical outcome and molecular data would be valuable to determine the best histologic definition of TCV.

Keywords Tall cell variant · Papillary thyroid carcinoma · Molecular profile

Kristine S. Wong and Sara E. Higgins contributed equally to this work.

✉ Justine A. Barletta
jbarletta@bwh.harvard.edu

Kristine S. Wong
kwong21@partners.org

Sara E. Higgins
sehiggins@bwh.harvard.edu

Ellen Marqusee
emarqusee@bwh.harvard.edu

Matthew A. Nehs
mnehs@bwh.harvard.edu

Trevor Angell
trevor.angell@usc.med.edu

¹ Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA

² Division of Endocrinology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

³ Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Introduction

Tall cell variant (TCV) of papillary thyroid carcinoma (PTC) accounts for approximately 6% of PTC and is considered an aggressive PTC subtype [1, 2]. It has double the rate of extrathyroidal extension and nearly triple the rate of distant metastases compared to classic PTC; moreover, the recurrence rate and cause-specific death rate of TCV are 22% and 8% compared to 7% and < 1% for classic PTC [2]. There are studies demonstrating that the more aggressive clinical behavior of TCV is not simply secondary to the higher rates of extrathyroidal extension and distant metastases of TCV [3–5]. For example, two SEER studies showed that the aggressive behavior of TCV was independent of factors such as patient age, extrathyroidal extension, or metastases [4, 5]. Additionally, in a study by Ito and colleagues evaluating 1700 PTC patients with slides re-reviewed to identify cases of TCV, the authors found a significantly worse disease-free survival and cause-specific survival for TCV compared to classic PTC in multivariate analysis [3]. The morphologic criteria for TCV were recently modified in the 2017 WHO Classification of Tumors of Endocrine Organs, with a decrease in both the required height of cells (3× as tall as wide modified to 2–3× as tall as wide) and in the percentage of tumor demonstrating a tall cell morphology (a “predominance of tall cells” suggesting a cutoff of $\geq 50\%$ modified to $\geq 30\%$) [6, 7]. This change was based on studies which demonstrated that tumors possessing a tall cell component comprising less than 50% of the tumor behave more aggressively than classic PTC [8–11]. In addition to the height of the tumor cells, TCV also demonstrates additional cytologic characteristics including eosinophilic cytoplasm and nuclei with pronounced nuclear features of PTC [7]. Although the molecular profile of TCV overlaps with that of classic PTC, TCV has been shown to have a higher mutation density than classic PTC, consistent with its more aggressive clinical behavior [12]. The *BRAF* V600E mutation, present in approximately 70% of classic PTC, is present in > 90% of TCV [12]. *TERT* promoter mutations have been linked to aggressive clinical behavior in thyroid carcinomas, especially when found together with a *BRAF* V600E mutation [13]. *TERT* promoter mutations are present in approximately 30% of TCV compared to 12% of classic PTC [14]. The aim of this study was to determine if the change in criteria put forth in the 2017 WHO would result in a significant increase in the percentage of tumors that meet criteria for TCV. In addition, we evaluated the correlation between morphology, molecular alterations, and clinical behavior of TCV.

Materials and Methods

Study Population and Data Acquisition

Approval from the Brigham and Women’s Hospital (BWH) institutional review board was obtained. Three different cohorts were investigated to evaluate our study questions. For each cohort, all available tumor slides for cases were reviewed to determine the percentage of the tall cell component (< 30%, 30–49%, and $\geq 50\%$) and the height of the cells in this component (2–3× as tall as wide versus 3× as tall as wide) (Fig. 1). No tumors in any cohort had an anaplastic or poorly differentiated component (as defined by the 2017 WHO). Additionally, for each cohort, patient demographics and histopathologic features were recorded, including patient age, sex, tumor size, presence of extrathyroidal extension, lymph node status, and margin status.

Cohort 1 was comprised of 97 PTC consecutively resected within a 12-month period at BWH that were initially

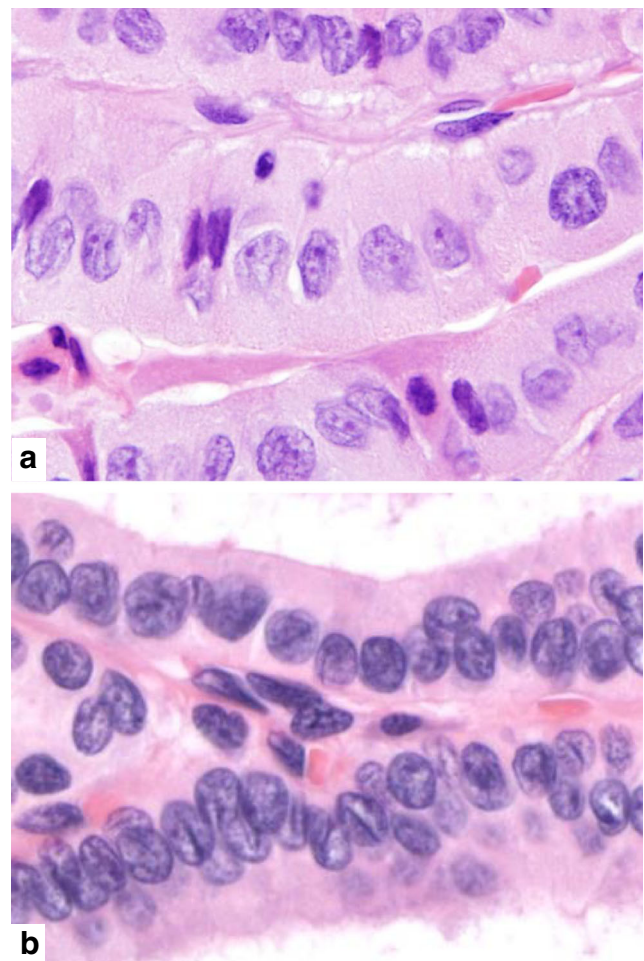


Fig. 1 Examples of papillary thyroid carcinoma with tall cells. **a** An example of a tumor with cells 3× as tall as wide. **b** An example of a tumor with cells 2–3× as tall as wide

diagnosed as classic PTC, PTC with tall cell features, or TCV. This cohort was evaluated to determine if the change in WHO criteria would result in a significant increase in the percentage of tumors that meet criteria for TCV. Cohort 2 consisted of nine consecutively resected PTC with a tall cell component $\geq 30\%$ (with tall cells defined as at least 2–3 \times as tall as wide) that had molecular characterization through a targeted, next-generation sequencing (NGS) assay (see below). Cohort 3 was comprised of seven clinically aggressive TCV (defined as those with T4 disease, disease recurrence, or subsequent tumor dedifferentiation). Cohorts 2 and 3 were evaluated to examine the correlation between morphology, molecular alterations, and clinical behavior of TCV.

Molecular Characterization by Targeted Next-Generation Sequencing

A subset of cases had molecular characterization via the OncoPanel assay developed at Brigham and Women's Hospital [15, 16]. OncoPanel molecular testing was performed using formalin-fixed paraffin-embedded tissue or freshly frozen tissue. Tumor DNA was isolated per standard methods (Qiagen, Valencia, CA) from macrodissected regions of tumor. Libraries were prepared from 50 ng of DNA using a customized solution-phase hybrid capture approach (Agilent Technologies, Santa Clara, CA). Bait sets covered 447 genes. Next-generation sequencing was performed using an Illumina HiSeq 2500 (Illumina, San Diego, CA). Sequencing was

analyzed by a variety of internally developed and publicly available tools, as previously described [16].

Statistical Analysis

A *t* test or Fisher exact test was used to compare differences in continuous and categorical variables, respectively. For all statistical methods, *p* values < 0.05 were considered significant.

Results

The clinicopathologic characteristics of cohort 1 are summarized in Table 1. A total of 97 consecutively resected PTC were identified from 71 (73%) women and 26 (27%) men, with a mean age of 48 years (range 21–81). The mean tumor size was 1.5 cm. Extrathyroidal extension, lymph node metastases, and positive surgical resection margins were present in 28 (29%), 46 (59%), and 16 (16%) cases, respectively. With tall cells defined as at least 3 \times as tall as wide, 1 (1%) had 30–49% tall cells, and 8 (8%) had $\geq 50\%$ tall cells. With tall cells defined as at least 2–3 \times as tall as wide, 9 (9%) had 30–49% tall cells, and 15 (16%) had $\geq 50\%$ tall cells. Overall, 8 (8%) cases met the prior WHO criteria for TCV (tall cells at least 3 \times as tall as wide in $\geq 50\%$ of cells), whereas 24 (25%) cases fulfilled the current WHO criteria for TCV (tall cells at least 2–3 \times as tall as wide in $\geq 30\%$ of cells) (*p* = 0.0020). There was no difference in tumor size or rates of extrathyroidal extension,

Table 1 Clinicopathologic characteristics of cohort 1

Characteristic	Entire cohort (<i>n</i> = 97)	TC: 3 \times in $\geq 50\%$ (<i>n</i> = 8)	TC: 2–3 \times in $\geq 30\%$ (<i>n</i> = 24)	<i>P</i> value
Sex (<i>n</i> (%))				
Female	71 (73)	4 (50)	18 (75)	0.22
Male	26 (27)	4 (50)	6 (25)	
Age (years)				
Mean	48	57	52	0.40
Range	21–81	31–81	21–81	
Mean tumor size (cm)	1.5	2.8	2.0	0.24
ETE (<i>n</i> (%))				
Present ^a	28 (29)	6 (75)	12 (50)	0.41
Absent	69 (71)	2 (25)	12 (50)	
LN metastases (<i>n</i> (%)) ^b				
Present	46 (59)	3 (43)	13 (65)	0.39
Absent	32 (41)	4 (57)	7 (35)	
Margin status (<i>n</i> (%))				
Positive	16 (16)	2 (25)	6 (25)	1.0
Negative	81 (84)	6 (75)	18 (75)	

P values are based on comparison of the two tall cell subgroups

TC tall cell, ETE extrathyroidal extension, LN lymph node

^a Includes microscopic extrathyroidal extension

^b Lymph nodes were sampled in only 78 patients from the cohort

Table 2 Histopathologic and molecular characteristics of cohort 2

Case	% TC	H:W	Size (cm)	ETE	LN metastases	Margin status	Driver mutation	Secondary mutations
1	30–50	2–3	0.5	No	Yes	Negative	<i>BRAF</i> V600E	–
2	30–50	2–3	1.1	No	No	Negative	<i>BRAF</i> V600E	–
3	30–50	≥ 3	1.6	No	N/A	Negative	<i>BRAF</i> V600E	–
4	> 50	2–3	2.5	No	Yes	Negative	<i>BRAF</i> V600E	–
5	> 50	2–3	3.9	Yes	Yes	Negative	<i>BRAF</i> V600E	–
6	> 50	≥ 3	0.7	No	No	Negative	<i>BRAF</i> V600E	–
7	> 50	≥ 3	2.0	Yes	Yes	Negative	<i>BRAF</i> V600E	<i>TERT</i> , <i>AKT2</i>
8	> 50	≥ 3	2.2	Yes	No	Negative	<i>BRAF</i> V600E	<i>TERT</i>
9	> 50	≥ 3	2.6	No	Yes	Negative	<i>BRAF</i> V600E	–

ETE extrathyroidal extension, LN lymph node, TC tall cell, H:W height:width

lymph node metastases, or margin status between subgroups (Table 1).

Pathologic characteristics of cohort 2, i.e., PTC with a tall cell component $\geq 30\%$ (with tall cells defined as at least 2–3 \times as tall as wide) that had molecular characterization, are shown in Table 2. All cases had a *BRAF* V600E mutation. Two (22%) cases had secondary mutations involving the *TERT* promoter, with one of these tumors harboring an additional *AKT2* mutation (another known oncogenic mutation in thyroid carcinomas). Both cases with secondary mutations were in tumors with $\geq 50\%$ tall cells and a height to width ratio of at least 3. In cohort 3 (the cohort comprised of clinically aggressive TCV), 3 (43%) cases had pathogenic secondary mutations in addition to a *BRAF* V600E mutation (Table 3). All 3 of these cases had *TERT* mutations. Two of the cases with *TERT* mutations also demonstrated loss of function mutations in a second gene (*COL7A1* and *EWSR1*). Excluding 1 case where all slides were not available for review, all clinically aggressive cases had $\geq 50\%$ tall cells, with a height to width ratio of at least 3 in 2 (33%) cases and 2–3 in 4 (67%) cases.

Discussion

The aim of this study was to determine if the change in criteria put forth in the 2017 WHO Classification of Tumors of Endocrine Organs would result in a significant increase in the percentage of tumors that meet criteria for TCV. In addition, we evaluated the correlation between morphology, molecular alterations, and clinical behavior of TCV. We found that the number of cases classified as TCV increased significantly with the modification in criteria put forth in the 2017 WHO: 8% of cases met the old criteria for TCV (cells 3 \times as tall as wide in $\geq 50\%$ of the tumor), whereas 25% met the new criteria for TCV (cells 2–3 \times as tall as wide in $\geq 30\%$ of the tumor). In other words, the change in the WHO definition tripled the number of cases that would be classified as TCV. Additionally, we found that all clinically aggressive tumors (defined as those with T4 disease, disease recurrence, or subsequent tumor dedifferentiation) as well as those with secondary oncogenic mutations all had a tall cell component of $\geq 50\%$.

The increase in the number of tumors diagnosed as TCV could potentially have significant clinical implications. Based

Table 3 Histopathologic and molecular characteristics of cohort 3

Case	% TC	H:W	Size (cm)	Aggressive features	Driver mutation	Secondary mutations
1	> 50	2–3	2.0	T4a, possible distant metastases	<i>BRAF</i> V600E	–
2	> 50	2–3	3.0	Recurrence as ATC	<i>BRAF</i> V600E	<i>TERT</i> , <i>COL7A1</i>
3	> 50	2–3	3.2	T4a	<i>BRAF</i> V600E	–
4	> 50	2–3	5.5	T4a	<i>BRAF</i> V600E	–
5	> 50	≥ 3	2.7	Recurrence	<i>BRAF</i> V600E	<i>TERT</i>
6	> 50	≥ 3	7.5	T4a	<i>BRAF</i> V600E	–
7	N/A ^a	N/A ^a	3.8	T4a, recurrence	<i>BRAF</i> V600E	<i>TERT</i> , <i>EWSR1</i>

^a Slides for 1 case were not available for review

TC tall cell, H:W height:width, ATC anaplastic thyroid carcinoma

on the classification of TCV as an aggressive PTC variant, the American Thyroid Association (ATA) characterizes it as an intermediate risk tumor in the absence of other high-risk features [1]. ATA guidelines indicate total thyroidectomy or lobectomy can be considered for low-risk tumors under 4 cm without extrathyroidal extension or clinical evidence of lymph node metastases; however, the guidelines indicate that intermediate-risk tumors should undergo total thyroidectomy and radioactive iodine treatment should be considered [1]. Compared to lobectomy, total thyroidectomy increases the risk of recurrent laryngeal nerve damage and permanent hypoparathyroidism and necessitates lifelong thyroid hormone replacement [17]. Additionally, radioactive iodine treatment can result in salivary gland dysfunction and has been linked to an increased risk of developing second malignancies [18–22]. Hence, increasing the number of patients diagnosed with TCV could put more patients at risk for complications. For biologically aggressive tumors, the clinical benefit of aggressive treatment outweighs potential complications; however, it is unclear if all tumors that would be included in the 2017 WHO definition of TCV warrant more aggressive management. For patients who underwent an initial lobectomy, a TCV diagnosis would potentially trigger a completion thyroidectomy; thus, exposing the patient to a second surgery and driving up healthcare costs [23]. Finally, a diagnosis of TCV also affects patient counseling given the increased risk of recurrence and mortality associated with TCV. Clearly, it is important to be as accurate as possible when counseling patients regarding these risks.

The change in WHO criteria for TCV was based on studies which demonstrated that tumors possessing a tall cell component comprising less than 50% of the tumor behave more aggressively than classic PTC [8–11]. In a study by Ganly and colleagues, they reported a decreased 10-year disease-specific survival for patients with tumors with tall cell features (defined as tumors with 30–49% tall cells, with tall cells 2–3× as tall as wide) compared to those with classic PTC [10]. In addition, they described subsequent dedifferentiation of three tumors with tall cell features. Beninato and colleagues reported higher rates of extrathyroidal extension, positive margins, and lymph node metastases in tumors with $\geq 10\%$ tall cells compared with classic PTC, though the recurrence rate was not significantly different between the two groups [8]. Oh and colleagues reported that tumors with tall cell features (defined as those with 10–49% tall cells, with the tall cells at least 3× as tall as wide) had similar T stage, extrathyroidal extension, N stage, lateral lymph node metastases, and *BRAF* status compared to tumors with a tall cell component $\geq 50\%$ [11]. Dettmer and colleagues showed that a 10% cutoff for tall cells was significantly associated with advanced tumor stage and lymph node metastases [9]. Additionally, they found that a tall cell component $> 10\%$ was the only significant factor for overall survival, tumor-specific, and relapse-free survival (and was

maintained in multivariate analysis). Although the study by Dettmer and colleagues showed significance in multivariate analysis, their cohort was enriched for patients with an adverse event, raising the question of whether this could potentially influence results. The two SEER studies showing that the aggressive behavior of TCV was independent of factors such as patient age, extrathyroidal extension, or metastases used an undefined definition for TCV (since slides are not re-reviewed centrally), but it is worth noting that TCV comprised $< 2\%$ of PTC in the study by Kazaure and colleagues [4, 5]. In the study by Ito and colleagues showing significantly worse disease-free survival and cause-specific survival for TCV compared to classical PTC in multivariate analysis, TCV was defined according to the former WHO criteria ($\geq 50\%$ of the tumor composed of tall cells with cells 3× as tall as wide) and TCV accounted for less than 4% of their cohort [3]. It is unclear whether the results from all of these studies taken together warrant the change of criteria put forth in the 2017 WHO given the number of patients potentially affected.

Our study was not designed to evaluate the prognostic significance of the percentage of the tall cell component because we did not have clinical outcome data for our main cohort. However, we did correlate histologic findings and aggressive clinical behavior with molecular characteristics in tumors from a small number of patients. Consistent with the results reported by Dettmer and colleagues [9], we found that although *TERT* promoter mutations were present in some of the clinically aggressive TCV, not all clinically aggressive tumors harbored *TERT* promoter mutations (or secondary oncogenic mutations). However, it is possible that for tumors with tall cells, parameters such as presence of secondary oncogenic mutations, including but not limited to *TERT* promoter mutations, or gross extrathyroidal extension might be a better way to identify patients that would benefit from more aggressive treatment than the characteristics of the tall cell component. We also recognize that there is considerable interobserver variability in the diagnosis of TCV [24]. It may be that image analysis could help pathologists determine height of cells, though this ultimately would not provide insight into the biologic implications of the findings.

In conclusion, we found that the number of cases diagnosed as TCV would triple using the 2017 WHO criteria. Although this is a small, single institution, retrospective study, this finding is concerning given the potential clinical ramifications. In the last decade, there has been a call for efforts both to decrease overtreatment of thyroid carcinomas and to find ways to better predict the natural history of disease [25]. Additional large multi-institutional studies incorporating clinical outcome and molecular data would be valuable to determine the best histologic definition of TCV so that patients are risk stratified and treated appropriately.

References

- 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. ed.[^], eds.: Mary Ann Liebert, Inc. 140 Huguenot Street, 3rd Floor New Rochelle, NY 10801 USA, 2016; 1–133.
- Wang X, Cheng W, Liu C, Li J Tall cell variant of papillary thyroid carcinoma: current evidence on clinicopathologic features and molecular biology. *Oncotarget* 7: 40792–40799, 2016.
- Ito Y, Hirokawa M, Fukushima M, Inoue H., Yabuta T., Uruno T., Kihara M., Higashiyama T., Takamura Y., Miya A., Kobayashi K., Matsuzuka F., Miyauchi A. Prevalence and prognostic significance of poor differentiation and tall cell variant in papillary carcinoma in Japan. *World journal of surgery* 32: 1535–1543- discussion 1544–1535, 2008.
- Kazaure HS, Roman SA, Sosa JA Aggressive variants of papillary thyroid cancer: incidence, characteristics and predictors of survival among 43,738 patients. *Annals of surgical oncology* 19: 1874–1880, 2012.
- Morris LGT, Shaha AR, Tuttle RM, Sikora AG, Ganly I Tall-cell variant of papillary thyroid carcinoma: a matched-pair analysis of survival. *Thyroid : official journal of the American Thyroid Association* 20: 153–158, 2010.
- DeLellis RA, Lloyd R, Heitz PU, Eng C World Health Organization Classification of Tumours: Pathology and Genetics Tumours of Endocrine Organs, 2004.
- Lloyd RV, Osamura R, Kloppel G, Rosai J WHO Classification of Tumours of Endocrine Organs, 2017.
- Beninato T, Scognamiglio T, Kleiman DA, Uccelli A, Vaca D, Fahey III TJ, Zarnegar R Ten percent tall cells confer the aggressive features of the tall cell variant of papillary thyroid carcinoma. *Surgery* 154: 1331–1336- discussion 1336, 2013.
- Dettmer MS, Schmitt A, Steinert H et al. Tall cell papillary thyroid carcinoma: new diagnostic criteria and mutations in BRAF and TERT. *Endocrine-related cancer* 22: 419–429, 2015.
- Ganly I, Ibrahimspasic T, Rivera M, Nixon I, Palmer F, Patel SG, Tuttle RM, Shah JP, Ghossein R Prognostic implications of papillary thyroid carcinoma with tall-cell features. *Thyroid : official journal of the American Thyroid Association* 24: 662–670, 2014.
- Oh WJ, Lee YS, Cho U, Bae JS, Lee S, Kim MH, Lim DJ, Park GS, Lee YS, Jung CK Classic papillary thyroid carcinoma with tall cell features and tall cell variant have similar clinicopathologic features. *Korean journal of pathology* 48: 201–208, 2014.
- Cancer Genome Atlas Research Network Integrated genomic characterization of papillary thyroid carcinoma. *Cell* 159: 676–690, 2014.
- Liu R, Bishop J, Zhu G, Zhang T, Ladenson PW, Xing M Mortality Risk Stratification by Combining BRAF V600E and TERT Promoter Mutations in Papillary Thyroid Cancer: Genetic Duet of BRAF and TERT Promoter Mutations in Thyroid Cancer Mortality. *JAMA oncology* 3: 202–208, 2016.
- Liu X, Bishop J, Shan Y, Pai S, Liu D, Murugan AK, Sun H, el-Naggar AK, Xing M Highly prevalent TERT promoter mutations in aggressive thyroid cancers. *Endocrine-related cancer* 20: 603–610, 2013.
- Sholl LM, Do K, Shivdasani P et al. Institutional implementation of clinical tumor profiling on an unselected cancer population. *JCI insight* 1: e87062, 2016.
- Garcia EP, Minkovsky A, Jia Y, Ducar MD, Shivdasani P, Gong X, Ligon AH, Sholl LM, Kuo FC, MacConaill LE, Lindeman NI, Dong F Validation of OncoPanel: A Targeted Next-Generation Sequencing Assay for the Detection of Somatic Variants in Cancer. *Archives of pathology & laboratory medicine* 141: 751–758, 2017.
- Kandil E, Krishnan B, Noureldine SI, Yao L, Tufano RP Hemithyroidectomy: a meta-analysis of postoperative need for hormone replacement and complications. *ORL; journal for oto-rhinolaryngology and its related specialties* 75: 6–17, 2013.
- Alexander C, Bader JB, Schaefer A, Finke C, Kirsch CM Intermediate and long-term side effects of high-dose radioiodine therapy for thyroid carcinoma. *J Nucl Med* 39: 1551–1554, 1998.
- Almeida JP, Sanabria AE, Lima EN, Kowalski LP Late side effects of radioactive iodine on salivary gland function in patients with thyroid cancer. *Head & neck* 33: 686–690, 2011.
- Brown AP, Chen J, Hitchcock YJ, Szabo A, Shrieve DC, Tward JD The risk of second primary malignancies up to three decades after the treatment of differentiated thyroid cancer. *J Clin Endocrinol Metab* 93: 504–515, 2008.
- Iyer NG, Morris LG, Tuttle RM, Shaha AR, Ganly I Rising incidence of second cancers in patients with low-risk (T1N0) thyroid cancer who receive radioactive iodine therapy. *Cancer* 117: 4439–4446, 2011.
- Sandeep TC, Strachan MW, Reynolds RM et al. Second primary cancers in thyroid cancer patients: a multinational record linkage study. *J Clin Endocrinol Metab* 91: 1819–1825, 2006.
- Agrawal N, Abbott CE, Liu C, Kang S, Tipton L, Patel K, Persky M, King L, Deng FM, Bannan M, Ogilvie JB, Heller K, Hodak SP Noninvasive Follicular Tumor with Papillary-Like Nuclear Features: Not a Tempest in a Teapot. *Endocr Pract* 23: 451–457, 2017.
- Hernandez-Prera JC, Machado RA, Asa SL, Baloch Z, Faquin WC, Ghossein R, LiVolsi VA, Lloyd RV, Mete O, Nikiforov YE, Seethala RR, Suster S, Thompson LD, Turk AT, Sadow PM, Urken ML, Wenig BM Pathologic Reporting of Tall-Cell Variant of Papillary Thyroid Cancer: Have We Reached a Consensus? *Thyroid* 27: 1498–1504, 2017.
- Welch HG, Doherty GM Saving Thyroids - Overtreatment of Small Papillary Cancers. *The New England journal of medicine* 379: 310–312, 2018.