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Preoperative, operative, and postoperative pathological features in thyroid papillary carcinoma with and without capsule invasion

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ABSTRACT

Aims: Approximately 80-85% of thyroid malignancies are papillary thyroid cancer (PTC). This study evaluated the relationship between thyroid capsule invasion (TCI) in PTC and macroscopic histopathological findings.

Methods: A single-center, retrospective study was conducted using the medical records of adult patients who underwent PTC surgery. The patients were classified as TCI (+) or TCI (-) based on the postoperative pathological examination. Tumor localization, calcification, and multifocality were evaluated between the two groups.

Results: The study included 236 patients (mean age: 44.3±12.0 years, female sex: 76.7%). Preoperative basic characteristics, comorbidities, thyroid function status, nodule calcification, halo border irregularity, and nodule diameter on ultrasonography were similar between the two groups. However, more TCI (+) patients had positive or suspicious fine needle aspiration biopsy findings preoperatively. The duration of surgery was longer in TCI (+) patients (86 minutes vs. 75 minutes, p<0.001), whereas the length of hospital stay was similar. Surgical margin >1 mm was more common in TCI (+) vs. TCI (-) patients (47.3% vs. 81.8%, p<0.001). Postoperative macroscopic pathological reports showed that middle lobe tumor localization was more common in TCI (+) (38.2%) than in TCI (-) (23.2%) patients (p=0.028), whereas tumor localization in the upper pole, lower pole, and isthmus was not different. Multifocal involvement (41.8% vs. 38.1%) was also similar between the two groups.

Conclusions: This study showed that fine needle biopsy positivity and nodule localization in the middle thyroid gland were more common in TCI (+) PTC patients as detected postoperatively. The other macroscopic pathological findings were not different.

Introduction

The thyroid gland, which consists of two connected lobes, is one of the largest endocrine glands in the human body, weighing 20-30 g in adults. Malignant diseases of the endocrine system are common, and the thyroid lesions are the most frequent by 4-7% (1). Approximately 80-85% of thyroid malignancies are papillary thyroid cancer (PTC) (2). 'Papillary microcarcinomas' of ≤10 mm, classified as a subgroup of PTCs, comprise 30% of all papillary cancers and are considered more moderate than PTCs of >10 mm (3). Despite high survival rates, local recurrence and metastases may still occur and radical surgery may be required in such patients (4). Treatment of PTC is usually bilateral total thyroidectomy (BTT) and based on the tumor size and lymph node involvement, central or lateral lymph node dissection is performed (5).

Similar to tumor characteristics such as lymphovascular invasion and extrathyroidal extension, capsule invasion is also associated with clinical outcomes in PTC (6).

The relationship between capsule invasion and clinicopathological characteristics has been previously studied in thyroid follicular cancer (6). However, the data in this regard are sparse in PTC (6). Therefore, this study aimed to investigate the relationship of capsule invasion with preoperative clinical and laboratory parameters and postoperative histopathological findings in PTC.

Methods

Study population and recruitment

This was a retrospective analysis in a tertiary-care training and research hospital. This study was conducted in accordance with the Declaration of Helsinki as revised in 2013 and, was approved by the University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Clinical Research Ethics Committee (decision no: 2022/145, date: 24.11.2022).

A total of 236 patients who were above eighteen years old and operated with the diagnosis of PTC in the general surgery clinic of a single center between January 2017 and June 2022 were included in this study. Patients under 18 years of age and those who were operated on for recurrence were excluded from this study.

Variables and data collection

In addition to demographic variables, comorbidities, the American Society of Anesthesiologists (ASA) score, and body mass index (BMI) were recorded. Biochemical parameters were analyzed, including preoperative thyroxine levels (T4, ng/dL) and thyroid-stimulating hormone levels (mU/mL) and postoperative calcium (Ca) (Ca, mg/dL), thyroglobulin (Tg) (Tg, ng/mL) and anti-Tg antibody (anti-Tg, IU/mL). Preoperative ultrasonography (USG) findings and histopathological reports of fine-needle aspiration biopsies (FNAB) were investigated. Postoperative first-day Ca values were analyzed. In addition, Tg and anti-Tg levels were assessed in the third month in high-risk patients and in the sixth month in low-intermediate-risk patients. Surgical findings, postoperative complications, and histopathological findings were examined. Based on capsule invasion on pathological examination, the patients were grouped into thyroid capsule invasion (TCI) (+) and TCI (-).

Statistical Analysis

All analyses were performed using the IBM Statistical Package for the Social Sciences Statistics® Statistical Software Program version 22.0 (IBM Corporation, 1 New Orchard Road, Armonk, New York, United States). Descriptive statistics are expressed as numbers, percentages, mean, standard deviation, and median (minimum-maximum). The conformity of the variables to the normal distribution was examined using visual (histograms and probability graphs) and analytical methods ("Kolmogorov-Smirnov", "Shapiro-Wilk tests"). Numerical variables with normal distribution were analyzed using the independent samples t-test between the two groups, and non-normally distributed variables were analyzed using the Mann-Whitney U test". Chi-square analysis and Fisher's exact test were used to compare the categorical data. A p-value of <0.05 was considered statistically significant.

Results

Basic characteristics of the sample and prevalence of TCI

The mean age of 236 patients included in the study was 44.3±12.0 years (18-75 years), and 76.7% were female. In the whole sample, most of the nodules were solid on preoperative USG evaluation (n=175, 74.2%), whereas most nodules were malignant on FNAB (n=162, 68.6%). The ratio of TCI in the whole sample was 23.3% (n=55).

Preoperative characteristics of TCI (+) versus TCI (-) patients

As shown in Table 1, age, sex, BMI, chronic comorbidities, USG nodule classification, diameter, calcification, and halo border irregularity were similar in the two groups. Preoperative thyroid function status was also not different; however, malignant FNAB findings were more frequent in TCI (+) (80.0%) than in TCI (-) (65.2%) (0.015). The preoperative ASA classification was similar in the two groups.

Intraoperative and postoperative clinical characteristics

As shown in Table 2, BTT + central lymph node dissection (CLND) was performed more frequently in TCI (+) (63.6%) vs. TCI (-) (38.1%) (p=0.001). The duration of surgery was longer in patients with TCI. As expected, increased Tg and RAI therapy were more common in TCI (+) patients, but serum Ca levels were not different. Surgery-related complications, length of hospital stay, duration of follow-up, and lymph node metastasis during follow-up were similar in the two groups (Table 2).

Macroscopic and histopathological examination characteristics

As shown in Table 3, the middle lobe localization of tumors was more frequent in TCI (+) patients. Lower pole localization was also more frequent, but the difference was not significant. In contrast, although there was no significance, isthmus and upper pole tumors were more frequent in TCI (-) patients. Multifocal involvement was not different between the two groups. The tumor type was papillary microcarcinoma by 44.1% in the whole group and was not different between the two groups, as were tumor grade and tumor pattern. The rate of lymphovascular invasion was 13.9% in the whole group, which was similar in TCI (+) and TCI (-) patients. More patients with TCI had surgical margins <1 mm. The number of metastatic lymph nodes was significantly lower in TCI (+) patients (Figures 1, 2, Table 3).

Table 1. Demographic and preoperative characteristics of patients with and without thyroid capsule invasion

	Total (n=236)	TCI (+) (n=55)	TCI (-) (n=181)	p-value
Age, mean±SD	44.3±12.0	44.6±12.3	44.2±12.0	0.841
Sex, female, n (%)	181 (76.7)	40 (72.7)	141 (77.9)	0.427
BMI (kg/m^2)	26 (16-42)	26 (16-38)	26 (18-42)	0.437
Hypertension, n (%)	53 (22.5)	14 (25.5)	39 (21.5)	0.543
Diabetes mellitus, n (%)	26 (11.0)	7 (12.7)	19 (10.5)	0.644
Coronary artery disease, n (%)	2 (0.8)	0	2 (1.1)	0.587
USG nodule classification, n (%)				
Solid	175 (74.2)	38 (69.1)	137 (75.7)	0.309
Semisolid	48 (20.3)	14 (25.5)	34 (18.8)	
Cystic	8 (3.4)	3 (5.5)	5 (2.8)	
Solid with cystic areas	5 (2.1)	0	5 (2.8)	
USG nodule diameter (millimeter), median (minimum-maximum)	14 (2-59)	13 (3-48)	15 (2-59)	0.781
Nodule calcification (+)	61 (25.8)	13 (23.6)	48 (26.5)	0.669††
Halo border irregularity (+)	62 (26.2)	16 (29.1)	46 (25.4)	0.587††
Preoperative TSH, median (minimum-maximum)	1.57 (0.01-24.5)	1.47 (0.02-7.70)	1.61 (0.01-24.5)	0.666
Preoperative T4, median (minimum-maximum)	0.88 (0.12-1.77)	0.88 (0.12-1.41)	0.92 (0.41-1.77)	0.440
Preoperative TSH classification, n (%)				
Euthyroid	211 (89.4)	48 (87.3)	163 (90.1)	0.462
Hyperthyroid	18 (7.6)	4 (7.3)	14 (7.7)	
Hypothyroid	7 (3.0)	3 (5.5)	4 (2.2)	
FNAB, n (%)				
Malignant	162 (68.6)	44 (80.0)	118 (65.2)	**0.015**
Suspicion of malignancy	40 (16.9)	7 (12.7)	33 (18.2)	
AUS-FLUS	6 (2.5)	0	6 (3.3)	
Benign	23 (9.7)	2 (3.6)	21 (11.6)	
Follicular lesion	2 (0.8)	2 (3.6)	0	
Atypia of undetermined significance	3 (1.3)	0	3 (1.7)	
ASA classification, n (%)				
I	140 (59.3)	32 (58.2)	108 (59.7)	0.899
II	74 (31.4)	17 (30.9)	57 (31.5)	
III	22 (9.3)	6 (10.9)	16 (8.8)	

††Fisher's exact test.
TCI: Thyroid capsule invasion, BMI: Body mass index, ASA: American Society of Anaesthesiologists, USG: Ultrasonography, FNAB: Fine needle aspiration biopsy, AUS/FLUS: Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance, TSH: Thyroid stimulating hormone, T4: Thyroxine, SD: Standard deviation

Discussion

Consistent with the literature, most PTCs were diagnosed as a solid or semisolid mass, and a minority were in cystic form. Approximately 10% of the patients may present with metastatic disease (7), but we observed a slightly higher rate of lymphovascular involvement of 13.9%, which can be explained by the level of the facility that accepts more complicated patients as a referral center.

The College of American Pathologists specifies that capsular invasion, extrathyroidal extension, and lymphovascular invasion in thyroid carcinomas are key features in malignancy based on histopathological classification and emphasizes the importance of reporting (8). Capsular invasion is among the gross pathophysiological findings and may affect the aggressive behavior pattern of the tumor, locoregional spread, and both central and lateral lymph node metastasis, particularly in follicular-patterned carcinomas (9,10). It may also be associated with many parameters during the postoperative period (11,12).

We observed no difference in demographic findings, co-morbidities and preoperative thyroid function tests between patients with and without TCI, which is consistent with the literature. However, consistent with the literature, more patients

Table 2. Intraoperative and postoperative clinical characteristics

	Total (n=236)	TCI (+) (n=55)	TCI (-) (n=181)	p-value
Surgical procedure				
Bilateral total thyroidectomy, n (%)	132 (55.9)	20 (36.4)	112 (61.9)	**0.001**††
Bilateral total thyroidectomy + Central lymph node dissection, n (%)	104 (44.1)	35 (63.6)	69 (38.1)	
Duration of surgery (minutes)[a]	80 (40-176)	86 (55-146)	75 (40-176)	**<0.001**[ŧ]
Postoperative calcium level[b]	8.4±0.6	8.4±0.6	8.5±0.6	0.265[†]
Postoperative Tg (>1 ng/mL), n (%)	14 (5.9)	7 (12.7)	7 (3.9)	**0.023**[ŧŧ]
Radioactive iodine therapy, n (%)	115 (48.7)	42 (76.4)	73 (40.3)	**<0.001**††
Complications				
Transient hypocalcemia, n (%)	79 (33.5)	18 (32.7)	61 (33.7)	0.893††
Transient hoarseness, n (%)	28 (11.9)	10 (18.2)	18 (9.9)	0.098††
Bleeding, n (%)	2 (0.8)	1 (1.8)	1 (0.6)	0.413[ŧŧ]
Presence of cheilosis leakage , n (%)	1 (0.4)	1 (1.8)	0	0.233[ŧŧ]
Length of hospital stay[a]	2 (2-10)	2 (2-10)	2 (2-7)	0.212[ŧ]
Follow-up duration (months)[a]	24 (12-54)	24 (12-54)	24 (12-52)	0.743[ŧ]
Lymph node metastasis during postoperative follow-up	9 (3.8)	3 (5.5)	6 (3.3)	0.439[ŧŧ]

[a]Median (minimum-maximum), [b]mean±standard deviation. [ŧ]Mann-Whitney U test, ††chi-square test, [ŧŧ]Fisher's exact test, Tg: Thyroglobulin, Anti-Tg: Anti-thyroglobulin antibody, TCI: Thyroid capsule invasion

Table 3. Macroscopic and histopathological examination characteristics

	Total (n=238)	TCI (+) (n=55)	TCI (-) (n=181)	p-value
Location, n (%)				
Upper pole	100 (29.7)	21 (38.2)	79 (43.6)	0.473††
Lower pole	91 (27.2)	25 (45.5)	66 (36.5)	0.230††
Isthmus	82 (24.4)	14 (25.5)	68 (37.6)	0.098††
Middle	63 (19.4)	21 (38.2)	42 (23.2)	**0.028**††
Multifocal involvement (+)	92 (38.7)	23 (41.8)	69 (38.1)	0.623††
Tumor type, n (%)				
Papillary microcarcinoma	104 (44.1)	23 (41.8)	81 (44.8)	0.701††
Papillary carcinoma	132 (55.9)	32 (58.2)	100 (55.2)	
Tumor grade, n (%)				
T1a	103 (43.6)	22 (40.0)	81 (44.8)	0.652††
T1b	81 (34.3)	21 (38.2)	60 (33.1)	
T2	44 (18.6)	9 (16.4)	35 (19.3)	
T3	8 (3.4)	3 (5.5)	5 (2.8)	
Tumor pattern, n (%)				
Papillary	76 (32.2)	17 (30.9)	59 (32.6)	0.872††
Follicular	20 (8.5)	5 (9.1)	15 (8.3)	
Papillary and follicular	138 (58.5)	33 (60.0)	105 (58.0)	
Focal papillary and follicular	2 (0.8)	0	2 (1.1)	
Lymphovascular invasion	33 (13.9)	10 (18.2)	23 (12.7)	0.305††
Surgical margin, n (%)				
>1 mm	174 (73.7)	26 (47.3)	148 (81.8)	**<0.001**††
<1 mm	62 (26.3)	29 (52.7)	33 (18.2)	
Number total of lymph nodes[a]	2 (0-23)	6 (0-23)	2 (0-21)	**0.002**[ŧ]
Number of metastatic lymph nodes[a]	0 (0-18)	0 (0-13)	0 (0-18)	**0.008**[ŧ]

[a]Median (minimum-maximum). [ŧ]Mann-Whitney U test, ††chi-square test.
TCI: Thyroid capsule invasion

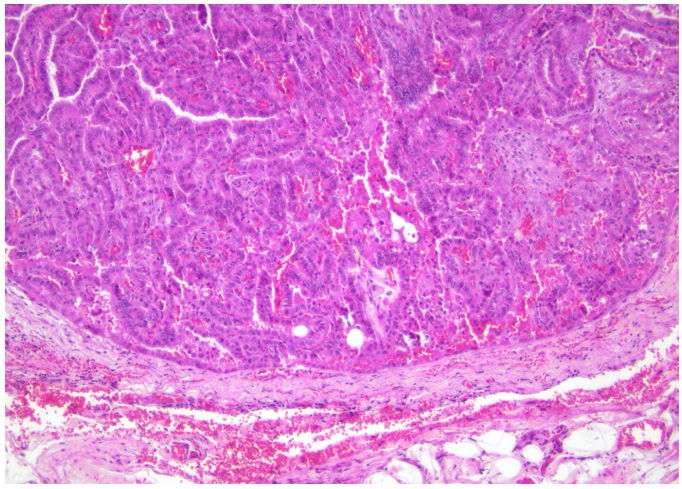

Figure 1. There is no capsular infiltration, although there is subcapsular localization of the tumor (hematoxylin and eosin staining, x100 magnification)

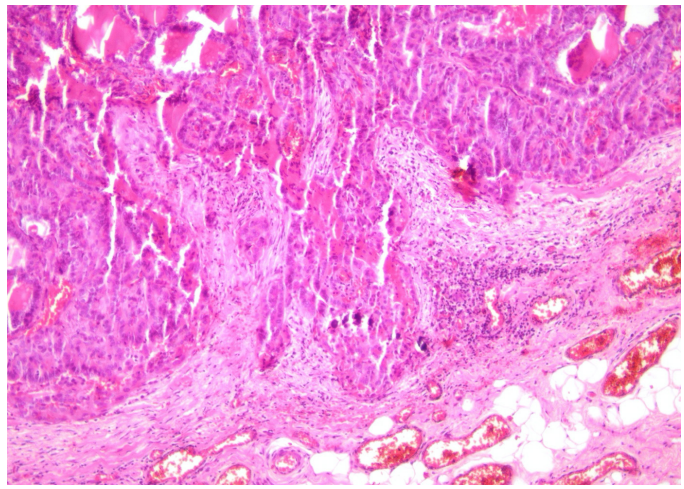

Figure 2. Tumor infiltration outside the capsule is seen (hematoxylin and eosin staining, x100 magnification)

with TCI had malignancy features in FNAB. Our findings suggest that the more malignant features in the pre-operative biopsy, the greater the probability of capsule invasion postoperatively. Although it is difficult to predict the behavior of papillary thyroid carcinomas using diagnostic methods in the pre-operative period (13), confirmation by FNAB may suggest postoperative local-advanced histopathological findings (13,14).

Previous authors suggested that irregular borders and hypoechogenicity were the fundamental USG findings in PTC, and postoperative capsular invasion, extrathyroidal extension, and preoperative USG findings were correlated (15). However, we observed no difference in USG findings between patients with and without TCI in the current study, which may have been caused by the fact that a relatively higher ratio of advanced disease was observed.

Li et al. (16) reported that large tumor size, multifocality, and vascular invasion were significant risk factors for central lymph node metastasis and surgical time in PTC. In addition, a significant relationship was observed for capsular invasion in patients who underwent CLND in addition to BTT because of central lymph node metastasis. We also observed a significant correlation between TCI and total and malignant lymph node counts in the histopathological evaluation.

The tumor grade, tumor pattern, and multicentricity did not differ according to capsule invasion in PTC in our study. However, previous authors have shown associations of multifocal PTCs with lymph node metastasis, recurrence, and low survival (17). The association of multifocality with advanced pathological classification, capsule invasion, and extrathyroidal extension has been reported (17,18). Our findings which contradict these data in the literature warrant future observations.

Isthmus tumors, but not other regions, were found to be more likely to present with capsular invasion in PTC (19). We could not confirm this association. On the other hand, as a novel finding, we observed a significantly higher proportion of middle-localization nodules in PTC with capsular invasion. The upper pole, lower pole, and isthmus tumor localizations were not different in patients with and without capsular invasion. Nodules in the middle-lower pole were also associated with malignancy and nodule aggressiveness (20). However, to the best of our knowledge, this is the first study to show a relationship between the middle lobe localization of a nodule and capsular invasion in PTC. Nevertheless, these findings await confirmation in larger studies that perform adjusted comparisons.

Capsule invasion is a predictor of worse prognosis, even in low-stage PTCs (20,21). However, we observed no significant differences in surgery-related complications in patients with PTC with and without capsular invasion. This is also a new finding. On the other hand, higher postoperative Tg levels and RAI therapy were more frequent in TCI (+) patients, which agrees with previous studies that showed Tg levels are effective predictors of prognosis (22) and may correlate with histopathological parameters (22,23). In addition, a previous study showed that early complications after BTT and subtotal thyroidectomy in differentiated thyroid cancers are similar in the BTT and subtotal thyroidectomy groups (24).

Thyroid nodules with Bethesda categories III and IV have an overall malignancy risk of 15-40% (25,26). If Bethesda III or IV lesions are found malignant, the most common histopathological subtype is the follicular variant of PTC, which is generally less aggressive than the classical PTC (26). Furthermore, this subtype has a lower risk of lymph node metastases, recurrence, and local extension, especially when encapsulated (26). The findings of the current study are consistent with the literature showing that Bethesda III and IV tumors were more aggressive, as shown by the lower margin and Tg level.

Study Limitations

This study has some limitations. The design was retrospective and single-center. The sample size was relatively small, and the follow-up duration was short. Several variables, such as the risk factors for thyroid cancer, could not be obtained from the patient files. We were also not able to explore the potential variables that may be related to capsule involvement, such as radiation history, dietary iodine intake, a history of benign thyroid disease, and BRAF V600E mutation.

Conclusion

In patients with PTC, capsular invasion was significantly more common in tumors in the middle of the thyroid gland. Furthermore, metastatic lymph nodes and increased postoperative Tg levels, which determine aggressiveness and worse outcomes, were more frequent in patients with capsule invasion.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Clinical Research Ethics Committee (decision no: 2022/145, date: 24.11.2022).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: M.Ö., O.H., Concept: B.U., Design: B.U., M.Z.B., İ.A.Ö., E.Ç., O.H., Data Collection or Processing: B.U., M.S.Ç., Analysis or Interpretation: S.A.K., M.Ö., Literature Search: B.U., M.Z.B., Writing: B.U., M.Z.B.

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