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Is there a relationship between patient age, tumor multifocality, and capsular invasion in papillary thyroid carcinoma? Retrospective evaluation of pathology specimens

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Ethics Committee Approval
The study was approved by the ethical board of Istanbul University, Cerrahpasa Medical Faculty IRB review board (approval Number: 04.09.2014-02-173816).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Papillary thyroid carcinoma (PTC) is the most prevalent of thyroid gland cancers. Although PTC generally is successfully treated, risk factors such as age, tumor size, thyroid capsule invasion, multifocality, and presence of metastases can negatively affect the prognosis. We aimed to assess the relationship between multifocality, capsular invasion, and patient age (≤45 vs >45 years of age) in PTC, along with other relevant tumor characteristics.

Methods: In this retrospective cohort study, evaluation of pathology findings in patients with a PTC diagnosis or thyroid nodules suspicious for PTC, the frequency of multiple specimen related prognostic factors by age was compared. Only patients initially operated with papillary thyroid cancer suspicion or definite diagnosis without distant organ metastasis were included. All the other patients with recurrent disease were excluded.

Results: Between 2008 and 2014, 466 patients with PTC tumors were operated. Tumors were multifocal in 62 (13.3%) patients and unifocal in 404 (86.7%). When multifocality was compared in two patient groups (≤45 years vs. >45), it was slightly higher in patients >45 years old (14.4%) vs ≤45 (11.5%; P=0.374). The multifocality rate in patients with a tumor size of >1 to ≤2 cm was significantly higher (17.5%) than in all other tumor size groupings (0.0-13.7%; P=0.002). Thyroid capsule invasion occurred in 39.1% of patients in the younger group vs 33.6% in the older group (P=0.05).

Conclusion: In light of our study's findings, including confirmation by multivariate analysis, age, as represented by the >45 year cutoff value, should not be considered an independent prognostic risk factor in planning treatment of PTC. The individual patient, tumor characteristics, and local and distant metastases status should remain the most important criteria for treatment selection and follow-up care in all patient age groups.

Keywords: Papillary thyroid carcinoma, PTC, Multifocality, Age, Capsule invasion, Metastasis

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Introduction

Thyroid cancers are the most frequently detected malignancies of the endocrine system. Papillary thyroid carcinoma (PTC) is the most common of well-differentiated thyroid cancers and is associated with a favorable outcome compared to other cancers. The long-term survival rates for adults with PTC is 92% to 98% at 10 years. Unfortunately, between 5% and 20% of these patients develop local or regional recurrences that necessitate further treatment, and 10% to 15% may develop distant metastases [1-3].

There are several factors that determine the prognosis for PTC. Age has been thought to be the main prognostic factor to consider; however, in recent years, gender, tumor multifocality, and the presence of thyroiditis have been found to influence the course of PTC. While PTC frequently presents with multifocal tumors, unilateral or bilateral multifocal PTC is not uncommon. The prevalence of multifocal PTC ranges widely between 18% and 87%, depending on methodological factors [4]. In addition, tumor multifocality increases the risk of recurrence, and of distant metastases. Although accuracy in diagnosing PTC has greatly improved due to widespread use of ultrasound-guided fine-needle biopsy and point-of-care sonography with fine-needle aspiration biopsy (FNAB), multifocality, as yet, can only be detected definitively in pathology specimens after surgery [4-7].

Tumor size and capsular invasion are also crucial parameters for determining the prognosis of PTC. Some studies have found that when tumors are >1 cm in size, they tend to spread aggressively beyond the thyroid, causing distant metastases [8]. For this reason, we included these variables in our study of prognostic indicators to analyze their level of correlation with multifocality and patient age.

Although a correlation between older age and a poor PTC prognosis has been demonstrated [9-11], there is a dearth of evidence regarding the interactive nature of known PTC prognostic factors. In this study, we aimed to assess the relationships between patient age and tumor characteristics (size, multifocality, capsular invasion, presence of thyroiditis) through retrospective analysis of pathology reports of patients who underwent thyroidectomy due to a diagnosis of PTC.

Materials and methods

Study design and approval

This study was designed as a retrospective cohort evaluation of pathology data obtained from specimens of patients operated due to suspicious thyroid nodules, or patients who were diagnosed with PTC. Only patients initially operated with papillary thyroid cancer suspicion or definite diagnosis without distant organ metastasis were included. All the other patients with recurrent disease were excluded. This study was approved by the ethical board of Istanbul University Cerrahpasa Medical Faculty. (approval date: 04.09.2014 and number: 02-173816).

Surgical technique

Each patient underwent total or near subtotal thyroidectomy performed by one of five surgeons. This is the standard approach in our clinic for patients diagnosed with multinodular bilateral disease, or PTC diagnosed with FNAB. Total, or near total thyroidectomies were preferred for patients with suspicious thyroid nodules on sonography findings who had an insufficient sample or benign findings in their FNAB results. Central lymph node dissection was performed if there was evidence of lymph node metastases, or if palpable lymph nodes were detected on examination.

Data collection and PTC groups

Demographic data and pathology findings were obtained. Patients were classified for study into two age groups (≤45 and >45 years old), and into five distinct subgroups in accord with PTC pathology: papillary microcarcinoma (PMC), follicular variant papillary carcinoma (FVPC), classical papillary thyroid cancer (CPAP), oncolytic variant papillary thyroid cancer (OVPC), and Warthin-type papillary thyroid cancer (WTPTC).

Tumor characteristics

PTC tumor data were classified further into: dominant tumor size; anatomic location (isthmus, left thyroid lobe, right thyroid lobe, tumor behavior (thyroid capsular invasion, extra-thyroidal invasion, lymph node metastasis (LNM) [n<1 and n≥1]); and tumor morphology (capsular, non-capsular, presence or absence of necrosis, Hashimoto or lymphocytic thyroiditis). Tumor staging was determined by the 'tumor, node, metastasis' (TNM) classification system characterized by the AJCC-TNM 2018 Cancer Staging Manual [12].

Statistical analysis

The SPSS statistical package version 22.0 (IBM, Armonk, NY, USA) was used for all analyses. Continuous variables were presented using means and standard deviations, and group comparisons were made using the independent samples t-test. Qualitative variables were presented as frequency and percentage, and analyzed using the chi-square test, or Fisher's exact test, as appropriate. Multivariate analysis was carried out using logistic regression. All statistical tests were two-sided, and a *P*-value of <0.05 was considered statistically significant

Results

The descriptive characteristics of 466 patients operated between 2008-2014 due to suspicious thyroid nodules or who had been diagnosed with PTC, histological subgroups of tumor types, multifocality, presence or absence of LNM, and results of FNAB are summarized in Table 1. The sample was comprised of 374 (80.3%) females and 92 (19.7%) males; mean age was 49.6 (13.4) years. The two most common PTC subtypes were PMC (39.5%) and CPAP (28.8%). Tumors were multifocal in 62 patients (13.3%) and unifocal in 404 patients (86.7%). Mean tumor size was 1.54 (1.24) cm, with 283 (60.7%) patients diagnosed with a maximum tumor size >1 cm. Thirty-two patients (6.8%) were positive for LNM, and 34 (7.3%) PTC patients were also diagnosed with Hashimoto thyroiditis (Table 1).

Patients were classified into two age groups (i.e., ≤45 years [n=174, 37.3%] vs. >45 years [n=292, 62.7%]) and evaluated for proportional differences in PTC prognostic factors. Both age groups were fairly well matched with respect to frequency distributions of tumor subtypes (Table 2) and tumor size categories (Table 3). However, there was a significant difference between age groups in mean tumor size, with the

younger patient group diagnosed with slightly larger tumors, on average (1.7 (1.0) cm vs 1.4 (1.3) cm; $P<0.05$). Also, there was a significant between-group difference in gender composition, with males comprising 12.6% of patients ≤45 years of age and 24.0% of patients >45 ($P<0.05$). Multivariate analysis revealed that none of the aforementioned between-group difference variables were independent predictors of multifocality (Table 4).

Table 1: Descriptive characteristics (n=466 patients)

	n	%
Gender		
Female	374	80.3
Male	92	19.7
Multifocality		
Multifocal	62	13.3
Unifocal	404	86.7
LNM		
Positive	32	6.8
Negative	434	93.2
Pathological subtypes		
PMC	184	39.5
FVPC	110	23.6
CPAP	134	28.8
OVPC	28	6.0
WTPTC	10	2.2
FNAB		
Not done	224	48
Positive	144	30.9
Negative	98	21.0
Papillary >1 cm	283	60.7
Micropapillary ≤1 cm	183	39.3
Thyroiditis		
Hashimoto	34	7.3
Lymphocytic	84	18.1

LNM: lymph node metastases, PMC: papillary microcarcinoma, FVPC: follicular variant papillary carcinoma, CPAP: classical papillary thyroid cancer, OVPC: oncolytic variant papillary thyroid cancer, WTPTC: Warthin-type papillary thyroid cancer, FNAB: fine-needle aspiration biopsy

Table 2: Tumor subtypes by age

	≤45 years old n (%)	>45 years old n (%)	*P*-value	Total n	%
PMC	56 (32.2)	128 (43.8)	<0.05	184	39.5
FVPC	42 (24.1)	68 (13.3)	0.677	110	23.6
CPAP	56 (32.2)	78 (26.7)	0.209	134	28.8
OVPC	16 (9.2)	12 (4.1)	<0.05	28	6.0
WTPTC	4 (2.2)	6 (2.1)	0.990	10	2.2
Total	174	292	—	466	100

PMC: papillary microcarcinoma, FVPC: follicular variant papillary carcinoma, CPAP: classical papillary thyroid cancer, OVPC: oncolytic variant papillary thyroid cancer, WTPTC: Warthin-type papillary thyroid cancer, FNAB: fine-needle aspiration biopsy

Table 3: Tumor size by age

	≤45 years old n (%)	>45 years old n (%)	*P*-value	Total n	%
≤1 cm	60	144	<0.05	204	43.8
>1≤2 cm	66	94	0.207	160	34.3
>2≤3 cm	34	24	<0.05	58	12.5
>3 cm	14	30	0.631	44	9.4
Total	174	292	–	466	100

Table 4: Multivariate analysis of multifocal and unifocal papillary thyroid cancer

	P-value	OR	%95 CI
Tumor size*	0.125	2.778	0.752-10.266
Age†	0.147	0.459	0.160-1.316
Tumor type§	0.304	0.335	0.041-2.699
Gender	0.919	1.071	0.282-4.077

*Tumor size >1 cm, †Age ≤45 years or >45 years, §Tumors with mixed types

Multifocal involvement in PTC tumors was found in 11.5% of patients ≤45 years and in 14.4% of the >45 group ($P=0.374$); capsular invasion was seen in 39.1% vs 33.6% ($P<0.05$), respectively. In addition, significantly higher rates of multifocality (17.5% vs 13.7%, 10.3%, 0.0%; $P<0.05$) (Figure 1) and capsular invasion (57.5% vs 18.6%, 41.4%, 27.3%; $P<0.001$) were found in tumors from >1cm to <2cm in diameter relative to other tumor size ranges (Figure 2). In turn, capsular invasion was found to be significantly correlated with LNM ($P<0.001$). When LNM and age were examined jointly, the LNM rate was found to be 11.5% in the ≤45 age group and 4.1% in the >45 age group ($P<0.05$).

Figure 1: Tumor size and capsular invasion

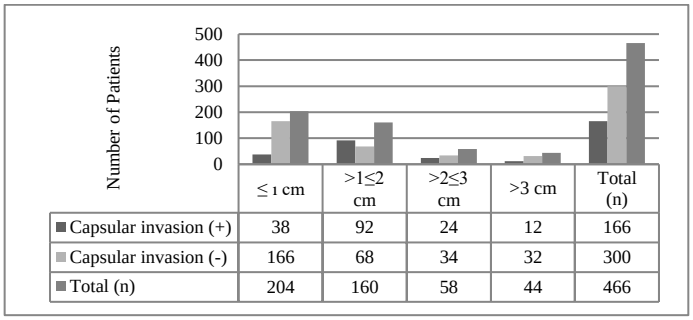
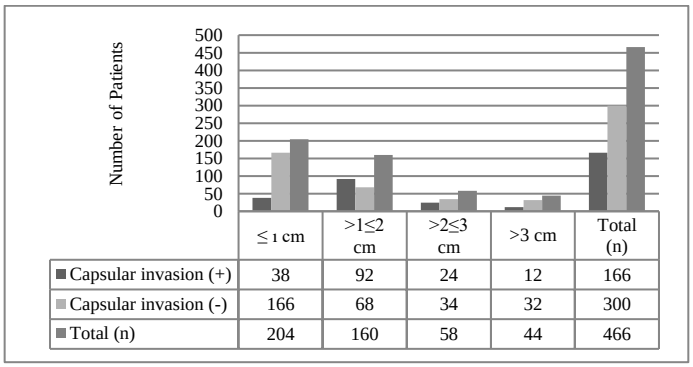


Figure 2: Tumor size and multifocality



When age groups were examined independently, capsular invasion was more prevalent when multifocal involvement was observed. Within the ≤45 age group, the capsular invasion rate in multifocal cases was 50.0% vs 37.7% in unifocal cases ($P<0.01$); within the >45 age group, the capsular invasion rate in multifocal cases was 38.1% vs 32.8% in unifocal cases ($P<0.05$). Capsular invasion in PTC was also found to be correlated with lymphocytic thyroiditis ($P<0.05$), but was unrelated to Hashimoto thyroiditis. The incidence rates of lymphocytic and Hashimoto thyroiditis within the ≤45 and >45 age groups were, respectively: 18.4%, 6.9%, and 17.8%, 7.5%, with no significant differences between groups.

Discussion

Age is often viewed as a central, independent, prognostic risk factor for well-differentiated thyroid cancers [13, 14]. Yet, the presence of other pathological risk factors (e.g., multifocality, thyroid capsule invasion, vascular invasion, extrathyroidal spread, and LNM) have been found in some studies to increase with patient age [15, 16]. Thus, the interrelationships between these factors in PTC require further elucidation.

In a retrospective study by Coburn et al. [17] of 318 patients with well-differentiated thyroid cancers, operated patients were examined in 3 different age groups (group 1, 21-50 years; group 2, 51-70 years; group 3, >70 years). Patients received postoperative adjuvant radioactive iodine (I-131) therapy if deemed necessary. In contrast to our findings, Coburn et al found that in the older age group, multifocality did not increase linearly with age (23%, 28%, and 15% in groups 1, 2, and 3, respectively) while capsular invasion was significantly increased (38%, 49%, and 74%) [17]. These data suggest that factors other than age (e.g., histological or morphological tumor characteristics) play meaningful roles in predicting cancer progression.

Tumor size has a marked impact on PTC prognosis. Numerous studies have shown that the prognosis for patients

with microcarcinomas, especially those with tumor sizes of ≤1 cm, is better than that for larger tumors [18, 19]. However, size alone is not a sufficient parameter to determine prognosis or optimum treatment. In the current study, when tumor size and capsule invasion were examined jointly, a significantly higher rate of capsule invasion (57.5%) was found for tumors between 1 and 2 cm in diameter relative to other tumor size groups. In addition, multifocality rate was also found to be significantly greater (17.5%) within this tumor size range.

In a related manner, a study by Pellegriti et al [20] of 299 patients with tumor sizes ≤1.5 cm, patients with tumor sizes of ≥1 cm had a 30.3% higher extrathyroidal spread than the other group (13%). Bilateral extrathyroidal spread and lymph node involvement have been found to be prevalent in thyroid capsule invasion, especially in patients with tumors of >1≤2 cm, providing evidence that these T1b tumors (as classified in the TNM staging system) may be more aggressive than micropapillary tumors [20].

In a retrospective study of 174 patients by Cheema et al [21], patients with tumor sizes of ≥2 cm had 20% more LNM than patients with tumor sizes of <2 cm, and one-third of these patients had LNM at the time of diagnosis. In addition, the rate of disease recurrence in all tumor sizes was determined to be equivalent. As a result, LNM status at diagnosis, rather than tumor size, determined the rate of recurrence [21]. In our study, patient age and LNM rate were examined jointly. The LNM rate was 11.5% in patients ≤45 years of age vs 4.1% in patients >45 years old. In addition, LNM was found to be significantly correlated with capsular invasion.

Although Pelizzo et al. [22] did not identify capsular invasion as a prognostic factor, a number of studies have done so [23, 24], and there appear to be strong relationships between capsular invasion, multifocality, extrathyroidal spread, and LNM. Mercante et al. [25] found that extrathyroidal spread and LNM were important risk factors in disease progression in a study of 445 patients with PTC. Still other studies define detection of thyroid capsule invasion as having a similar prognostic value as that of extrathyroidal extension, even in the absence of invasion of the surrounding soft tissue. In our study, we examined the inter-relationship between multifocality and capsular invasion with respect to age group. Interestingly, capsular invasion was significantly greater in multifocal cases relative to unifocal cases within each age group studied. That is, in the ≤45-year-old group, capsular invasion rate in multifocal cases was 50.0% vs 37.7% in unifocal cases. Similarly, but less significantly, the capsular invasion rate in multifocal cases in patients >45 years old was 38.1% vs 32.8% in unifocal cases.

In a corroborative study by Lin et al. [26] covering 1682 PTC patients, multifocality was seen in 337 patients, and extrathyroidal spread was seen in 28% of multifocal cases and 21% of unifocal cases. In consideration of these data, in conjunction with our own, the greater presence of capsule invasion and extrathyroidal extension in multifocal cases suggest that a more aggressive treatment strategy is needed in multifocal cases in patients of all ages.

In recent years, a number of studies were conducted that evaluated cancer development and prognosis in patients with chronic lymphocytic thyroiditis and Hashimoto thyroiditis [27, 28]. Although predominantly, Hashimoto thyroiditis has been associated with an increased risk of PTC, there is some evidence suggesting that patients with Hashimoto thyroiditis and PTC appear to have a more favorable prognosis [29]. In our study, the incidence of lymphocytic thyroiditis in patients ≤45 years old was 18.4%, and the incidence of Hashimoto thyroiditis was 6.9%. In >45-year-olds, the rate of lymphocytic thyroiditis was 17.8%, while the rate of Hashimoto thyroiditis was 7.5%: these rates did not significantly differ between age groups. Interestingly, in our study, capsular invasion was found to correlate with lymphocytic thyroiditis, and PTC patients without Hashimoto thyroiditis, had slightly higher rates of LNM (6.9% vs 5.9%).

Limitations

A limitation of the study was that it was retrospective. Also, while the large sample size was study strength, the lack of follow-up data precluded estimation of survival findings. In addition, study outcomes would have been strengthened by inclusion of a patient sample more evenly distributed between unifocal and multifocal carcinomas.

Conclusions

The current study aimed to assess the relationship between multifocality, capsular invasion, and patient age (≤45 vs >45 years of age) in PTC, along with other relevant tumor characteristics. PTC patients >45 years of age were found to have only slightly higher rates of multifocal involvement, and significantly lower rates of capsular invasion. However, capsular invasion rates were significantly higher in multifocal cases within each age group, and, capsular invasion was independently related to LNM. This study also indicated that capsular invasion and multifocal involvement in PTC were significantly related to tumor size, which was independent of age. In light of our study's findings, including confirmation by multivariate analysis, age, as represented by the >45 year cutoff value, should not be considered an independent prognostic risk factor in planning treatment of PTC. The individual patient, tumor characteristics, and local and distant metastases status should remain the most important criteria for treatment selection and follow-up care in all patient age groups.

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