

# Effects of preoperative fine needle aspiration biopsy on surgical strategy in patients with papillary thyroid carcinomas

## Papiller tiroid karsinomlu hastalarda ince iğne aspirasyon biyopsinin cerrahi strateji üzerine etkileri

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### Abstract

**Aim:** Papillary thyroid carcinomas (PTCs) usually have good prognosis. In the presence of lymph node metastasis, capsular invasion and extra-thyroidal extension, some PTCs may display aggressive behavior. Early diagnosis of these cases is extremely important. Ultrasound-guided fine needle aspiration biopsy (FNAB) is an important diagnostic procedure and may identify the PTC likely to behave aggressively. Our study aimed to examine the effects of FNAB on surgical strategy in patients with PTC.

**Methods:** The data of 269 patients who underwent total thyroidectomy were evaluated in our retrospective cohort study. FNAB had been performed in 188 (70%) patients. Patients with non-incidentally diagnosed PTCs were compared with patients who had incidentally diagnosed PTCs in terms of parameters likely to be related to aggressive PTC.

**Results:** Patients  $\leq 45$  years old were more common in the non-incidentally diagnosed group ( $P=0.041$ ). Incidental diagnoses were common in females ( $P=0.014$ ), those with nodules larger than 2 cm in diameter and in patients with  $\geq 2$  nodules ( $P=0.001$ ). Postoperative remnant thyroid tissue was observed more commonly in incidental cases ( $P=0.008$ ). Lymph node metastasis ( $P=0.044$ ), capsular invasion ( $P=0.009$ ), and extra-thyroidal extension ( $P=0.022$ ) were more common in the non-incidentally diagnosed group.

**Conclusion:** It is difficult to estimate the behavior of PTCs preoperatively. Only a small number of PTCs can be preoperatively diagnosed with ultrasound-guided FNAB. The extent of surgery generally is defined by FNAB results. Detailed examination of all suspicious nodules is of great importance for earlier detection of aggressive PTCs and avoiding surgical over-treatment.

**Keywords:** Papillary thyroid carcinoma, FNAB, Incidental, Non-incidentally

### Öz

**Amaç:** Papiller tiroid karsinomları (PTK) genellikle iyi prognozludur. Lenf nodu metastazı, kapsül invazyonu ve ekstratiroidal yayılım varlığında, bazı PTK'lar agresif seyir gösterebilir. Bu vakaların erken teşhisi son derece önemlidir. Ultrason eşliğinde ince iğne aspirasyon biyopsi (İİAB) önemli bir tanı prosedürüdür ve agresif davranış gösteren muhtemel PTK'ları erken tanıyabilir. Çalışmamız, PTK'lı hastalarda İİAB'nin cerrahi strateji üzerindeki etkilerini incelemeyi amaçlamıştır.

**Yöntemler:** Retrospektif kohort çalışmamızda total tiroidektomi uygulanan 269 hastanın verileri gözden geçirildi. Preoperatif İİAB 188 (%70) hastaya uygulanmıştı. Non-incidental tanı konan hastalar, incidental tanı konan hastalar ile PTK'nın agresif davranışına bağlı olabilecek parametreler açısından istatistiksel olarak karşılaştırıldı.

**Bulgular:** Non-incidental grupta yaşı  $\leq 45$  olan hastalar daha sıkı ( $P=0,041$ ). İnsidental vakalar kadınlarda ( $P=0,014$ ), çapı 2 cm'den büyük nodüllerde ve nodül sayısı  $\geq 2$  olan hastalarda daha sıkı ( $P=0,001$ ). Postoperatif rezidü tiroid dokusu insidental grupta daha sık gözlemlendi ( $P=0,008$ ). Lenf nodu metastazı ( $P=0,044$ ), kapsül invazyonu ( $P=0,009$ ) ve ekstratiroidal yayılım ( $P=0,022$ ) non-incidental grupta daha sıkı.

**Sonuç:** PTK'ların biyolojik davranışlarını preoperatif olarak tahmin etmek zordur. Ameliyat öncesi ultrason eşliğinde İİAB kullanılarak PTK'ların az bir kısmı teşhis edilebilir. Genellikle ameliyatın kapsamı İİAB sonuçlarıyla belirlenmektedir. Tüm şüpheli nodüllerin detaylı muayenesi, agresif davranış gösteren PTK'ların daha erken tespiti ve aşırı cerrahi tedavinin önlenmesi açısından çok önemlidir.

**Anahtar kelimeler:** Papiller tiroid karsinomu, İİAB, İnsidental, Non-incidental

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## Introduction

Carcinoma of the thyroid gland is the most common endocrine malignancy. In the recent years, the incidence of papillary thyroid carcinomas (PTCs) has increased globally due to widespread utilization of high-resolution ultrasound-guided fine needle aspiration biopsy (FNAB) [1-8]. The clinical significance of this increase is controversial in terms of surgical strategy. One of the most common findings of thyroid disease is the presence of thyroid nodules. The prevalence of thyroid nodules ranges from 19% to 67% [9-11]. Some ultrasonographic findings, such as microcalcifications, hypoechogenicity, absence of a halo, increased intranodular vascularity, nodular shape or irregular margins indicate increased malignancy risk [12-14].

The prognosis of PTC is usually excellent and often does not require aggressive treatment. However, the presence of lymph node metastasis on the first admission of PTC patients indicates poor prognosis. Early diagnosis and formulation of the appropriate surgical strategy are very important in these patients. Ultrasound-guided FNAB is an important diagnostic method for early diagnosis of patients with PTC [14-19]. Our study aimed to examine the effects of results of FNAB on the surgical treatment of patients with PTC.

## Materials and methods

Ethics committee approval was obtained from Diskapi Yildirim Beyazit Training and Research Hospital, University of Health Sciences (No: 19.02.2018-46/11) and Declaration of Helsinki was complied. Our retrospective cohort study included 269 patients who underwent thyroidectomy between January 2014 and December 2018 and was diagnosed with PTC according to the final pathology report. All data including age, gender, nodule size, nodule findings (number, size, and presence of calcification), number of biopsies, FNAB results, extent of thyroidectomy, tumor diameter, subtype of tumor, multifocality, presence of residual thyroid tissue after thyroidectomy, lymph node metastasis, capsular invasion, and extra-thyroidal extension were recorded. Demographic features of the cases were detailed in Table 1. Ultrasound-guided FNAB was performed preoperatively in 188 (169 females and 19 males) patients. The mean age of these patients was 47.94 (11.60) (min=19, max=80) years. FNAB results were reported as malign in 32 (17%) patients and suspicious for malignancy in 37 (20%), who were included in the non-incident group. FNAB results of 119 patients, who constituted the incidental group, were preoperatively reported as benign in 31 (16%), non-diagnostic in 30 (16%) and atypia of undetermined significance (AUS) in 58 (31%) patients. Incidental and non-incident patients' data were compared. The presence, localization, and size of the postoperative residual tissue were evaluated with thyroid scintigraphy.

Technetium-99m (Tc-99m) pertechnetate thyroid scintigraphy was performed in all patients before the initiation of levothyroxine therapy. Anterior and oblique images were acquired 15 minutes after intravenous injection of 5 mCi  $\pm$  1 (185 MBq  $\pm$  37) Tc-99m pertechnetate. Prior to imaging, patients drank a glass of water to eliminate esophageal activity. Images were obtained by a gamma camera (Siemens ecam-signature;

Siemens, Hoffman Estates, Illinois, USA) in a 256x256 matrix, using a pinhole collimator with 1.78 zoom, over 100kcounts. The photopeak energy was 140 keV, with a 20% window width. Any increased activity distinguished from background activity was interpreted as a presence of residual thyroid tissue.

## Statistical analysis

Statistical Package for Social Sciences 18.0 (SPSS inc., Chicago, USA) program was used for statistical analysis. Descriptive statistics were presented as frequency and mean (standard deviation). Variables were compared with Chi-Square, Mann-Whitney U, and Kruskal-Wallis nonparametric tests. McNemar's test was used for the analysis of the dependent groups. *P*-value less than 0.05 was considered statistically significant.

Table 1: Demographic features of the cases

	n (%)
Female/Male	169/19
Age of mean (SD), years	47.94 (11.60)
≤45 age	75 (40)
Solitary nodule	47 (25)
Nodule diameter ≤2cm	105 (56)
Preoperative FNAB results	
Malignancy/suspicious malignancy	69 (37)
AUS/non-diagnostic/benign	119 (63)
Type of Surgery	
Total thyroidectomy	99 (52.6)
Total thyroidectomy + CLND	89 (47.4)
Histopathological diagnosis	
PTMC	104 (55)
PTC	84 (45)
Mean tumor diameter (SD), mm	12.24 (10.96)
Residual thyroid tissue	135 (72)
Multifocality	75 (40)
Lymph node metastasis	13 (14.6)
Capsular invasion	22 (11.7)
Extrathyroidal extension	8 (4)
Recurrence	5 (2.6)

FNAB: fine needle aspiration biopsy, AUS: atypia of undetermined significance, CLND: central lymph node dissection, PTMC: papillary thyroid microcarcinoma, PTC: papillary thyroid carcinoma

## Results

Among patients who underwent FNAB (n=188), 104 (55%) were diagnosed with papillary thyroid microcarcinoma (PTMC) and 84 (45%) were diagnosed with PTC. Malignant or suspicious for malignant cells were detected in 24% of patients with PTMC, and 52% of patients with PTC (*P*=0.001). Among the incidental diagnosis group, 35% (n=42) were ≤45 years old. 48% (n=33) of patients younger than 45 years were in the non-incident group (*P*=0.041). There was a significant difference between the incidental and non-incident groups in terms of the extent of thyroidectomy. Extended thyroidectomy with central lymph node dissection (CLND) was carried out more commonly in non-incident group (*P*<0.001). Malignancy or suspicious for malignancy were more commonly reported in FNAB results of male patients (64%) compared to females (34%) (*P*=0.014). According to FNAB results, malignancy and suspicious for malignancy were more commonly reported in solitary nodules (*P*=0.001). Presence of a report of malignancy and suspicious for malignancy were significantly more common in nodules ≤2 cm (46%) compared to nodules larger than 2 cm (23%) (*P*=0.001). Capsular invasion was observed in 13% (n=9) of the incidental group and 19% (n=13) of the non-incident group (*P*=0.009). Extra-thyroidal extension was seen in a limited number of cases from each group, but was significantly higher in the non-incident group (*P*=0.022). Similarly, recurrences were observed in a few patients among both groups. Malignancy was not reported in 56% of calcified nodules in preoperative FNAB

examination ( $P=0.042$ ). Number of biopsies did not differ among the two groups. There was a significant difference between the incidental and non-incidental group patients in terms of thyroidectomy extension. Extended thyroidectomy (with CLND) was more commonly carried out in non-incidental group patients. The comparison of the parameters of the two groups is presented in Table 2.

Table 2: Demographic characteristics of incidental and non-incidental cases

	Incidental n (%)	Non-incidental n (%)	P-value
Age			
≤45	42 (35)	33 (48)	0.041
>45	77 (65)	36 (52)	
Gender			
Female	112 (66)	57 (34)	0.014
Male	7 (37)	12 (63)	
Nodule diameter			
≤2 cm	56 (54)	49 (46)	0.001
>2 cm	63 (77)	20 (23)	
Nodule number			
Single	22 (47)	25 (53)	0.001
>2	97 (69)	44 (31)	
Calcification			
Yes	47 (56)	37 (44)	0.042
No	72 (69)	32 (61)	
Biopsy number			
less than 2	100 (84)	59 (85.5)	0.514
2 and more	19 (16)	10 (15)	
Type of Surgery			
TT	75 (63)	24 (35)	0.001
TT+CLND	44 (37)	45 (65)	
Histopathological diagnosis			
PTMC	79 (76)	25 (24)	0.001
PTC	40 (48)	44 (52)	
Residual thyroid tissue	96 (81)	39 (56)	0.008
Multifocality	51 (43)	24 (35)	0.175
Lymph node metastases	5 (11)	8 (18)	0.044
Capsular invasion	9 (13)	13 (19)	0.009
Extrathyroidal extension	4 (3.4)	4 (5.8)	0.022
Recurrence	4 (3.4)	1 (1.4)	0.034

TT: total thyroidectomy, CLND: central lymph node dissection, PTMC: papillary thyroid microcarcinoma, PTC: papillary thyroid carcinoma

## Discussion

Despite the increasing incidence of PTC, there is no consensus about the optimal treatment. It is widely accepted that PTC has excellent prognosis [6,15,20]. Some non-incidental tumors behave more aggressively and tend to recur [21]. Many authors suggest that early detection and aggressive treatment are necessary in these cases [22]. The incidence of incidental PTMCs have increased in the recent years [23]. Patients incidentally diagnosed with PTC are reported to comprise about 45-75% of all PTC patients [21-24]. It has been known that factors such as slow growth rate, absence of specific symptoms, clinical characteristics and potential co-occurrence with benign thyroid disease make diagnosis difficult.

FNAB is considered the most accurate procedure to identify malignant nodules. However, nodule characteristics are not reliable enough to diagnose malignancy. PTC was more frequently diagnosed incidentally in nodules larger than 2 cm, which can be explained by increased heterogeneity in larger nodules. FNAB is not always applicable in terms of cost effectiveness and results are usually obscure. Positive prediction of malignant thyroid nodules is restricted due to limited diagnostic methods, such as FNAB [24]. Currently, only 10-25% of patients with PTC can be diagnosed preoperatively with FNAB. In our study, the incidence of incidental diagnosis was 63%.

Presence of lymph node metastasis, capsular invasion and extra-thyroidal extension on admission indicates aggressive PTC. Surgical treatment of these patients requires a different

surgical strategy. It is extremely difficult to preoperatively predict malign and aggressive cases. FNAB is recommended in presence of suspicious or intermediate ultrasonographic findings.

Higher incidence of non-incidental diagnosis may be explained by the wide application of screening programs. Compared to results of other studies in the literature, malignancy and suspicious for malignancy findings were more commonly reported in our series due to the examination of the specimens by a single expert pathologist.

Pisanu et al. [22] showed that age and gender are not significant factors in terms of incidental or non-incidental diagnosis, whereas capsular invasion and lymph node metastasis were significantly more common in patients with non-incidental diagnosis ( $P<0.001$  and  $P<0.001$ , respectively). Chow et al. [25] reported that age has no effect on the aggressiveness and metastasis of PTMC. Our study showed that age was an independent significant factor for non-incidental diagnosis. Non-incidental diagnosis of PTC patients ≤45 years were more common compared with the others.

Wang et al. [26] showed that microcalcification was present in nearly half of the PTMC nodules. Microcalcification in a nodule is associated with a higher probability of malignancy. It was observed in 45% of our patients and more frequently encountered in nodules of incidental group patients; however, preoperative FNAB was not definitive in this group.

Lombardi et al. [21] showed that lymph node metastasis and extra-thyroidal extension are significant factors for non-incidental diagnosis of the patients with PTC, with which our findings were consistent.

In a cross-sectional study, tumor size of non-incidentally diagnosed tumors was found significantly higher than incidentally diagnosed tumors (7.5mm vs. 4.2mm) [22]. Difference in tumor size remains one of the most important parameters. A consensus is yet to be reached. In our series, the rate of incidental diagnosis of PTMCs was higher than PTCs (76% vs 24%, respectively). Diameter of the tumor was a significant factor in our study.

Vlassopoula et al. [27] reported that tumor subtype (papillary or micropapillary) and/or capsular invasion was not effective on the course and outcome of the PTC. Our study showed that incidental diagnosis affects surgical strategy. Patients with non-incidentally diagnosed PTC more commonly underwent extended thyroidectomy with CLND, as expected. Total thyroidectomy was more commonly observed in patients with incidental PTC.

### Limitations

Our study was conducted retrospectively on patients who were referred to our department for postoperative thyroid scintigraphy. Further prospective research involving a larger number of patients is needed.

### Conclusions

Although the prognosis of PTC is generally excellent, some may behave aggressively, particularly those with a lymph node metastasis on first admission. The early, preoperative detection of potentially aggressive PTCs is crucial for formulating the appropriate surgical strategy. Unfavorable risk factors should be sought in all patients and if possible, all nodules should be evaluated with ultrasound-guided FNAB.

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