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The Evaluation of Malignancy Rate of Incidental Thyroid Nodules Detected by FDG-PET/CT

FDG-PET/BT ile Saptanan İnsidental Tiroid Nodüllerinin Malignite Oranının Değerlendirilmesi

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Abstract

Objective: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) is widely used in investigating and staging malignancies. Malignancy rate is high in thyroid incidentalomas detected by FDG-PET/CT. The objective of this study was to evaluate the malignancy rate of incidental thyroid nodules in patients who had undergone FDG-PET/CT scan. **Material and Methods:** The reports of 10,197 FDG-PET/CT scans performed between January 2014 and May 2019 were analyzed retrospectively. The patients with incidental thyroid nodules and who underwent fine-needle aspiration biopsy (FNAB) were included in this study. Patients were stratified into two groups: malignant and non-malignant, according to FNAB cytological results. The association between maximum standardized uptake (SUV_{max}) values, ultrasonography (USG) findings, and cytological results of the biopsied nodules were investigated. **Results:** A total of 80 patients were included in the study. Forty (50%) of the patients were females, and the mean age was 63.2±11.4 years. Evaluation of FNAB results of 13 (16.3%) showed their malignant status. Of the patients in the malignant group, seven (53.8%) were females (mean age, 60.6±11.8 years). No statistically significant difference between the groups with or without malignancy in terms of gender distribution and mean age (p=0.762, p=0.401, respectively) was observed. The SUV_{max} value of the malignant group was 15.7 (5.1-29.7) and of the non-malignant group was 4.4 (1.6-24.1) (p<0.001). **Conclusion:** We found that the malignancy rate is high in patients with thyroid incidentaloma detected by FDG-PET/CT and those who underwent FNAB, confirming previous results in the literature. It is suggested to evaluate further thyroid incidentaloma cases with high SUV_{max} values.

Keywords: Positron emission tomography/computed tomography; fine-needle aspiration biopsy; thyroid nodule; ultrasonography

Özet

Amaç: Malignitelerin araştırılması ve evrelemesinde, ^{18}F-florodeoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografi (FDG-PET/BT) yaygın olarak kullanılmaktadır. FDG-PET/BT ile tespit edilen tiroid insidentalomalarında, malignite oranı yüksektir. Bu çalışma ile FDG-PET/BT yapılan hastalarda saptanan insidental tiroid nodüllerinde malignite oranının değerlendirilmesi amaçlanmıştır. **Gereç ve Yöntemler:** Ocak 2014 ve Mayıs 2019 tarihleri arasında gerçekleştirilen 10.197 adet FDG-PET/BT çekiminin raporları, retrospektif olarak incelendi. İnsidental tiroid nodülü saptanıp, ince iğne aspirasyon biyopsisi (İİAB) yapılan hastalar çalışmaya dâhil edildi. Hastalar, İİAB sitoloji sonuçlarına göre malign ve malign olmayan şeklinde 2 gruba ayrıldı. Biyopsi yapılan nodüllerin maksimum standart uptake (SUV_{maks}) değerleri, ultrasonografi (USG) bulguları ve patoloji sonuçları arasındaki ilişki araştırıldı. **Bulgular:** Çalışmaya toplam 80 hasta dâhil edildi. Bu hastaların 40'ı (%50) kadın olup, yaş ortalaması 63,2±11,4 yıl olarak bulundu. On üç (%16,3) hastanın İİAB sonucu, malign olarak değerlendirildi. Malign olan gruptaki hastaların 7'si (%53,8) kadın olup, yaş ortalaması 60,6±11,8 olarak hesaplandı. Malign olan ve olmayan gruplar arasında, cinsiyet dağılımı ve yaş ortalaması açısından anlamlı fark yoktu (sırasıyla p=0,762; p=0,401). Malign olan grubun SUV_{maks} düzeyi 15,7 (5,1-29,7), malign olmayan grubun ise 4,4 (1,6-24,1) saptandı (p<0,001). **Sonuç:** FDG-PET/BT ile tespit edilen ve İİAB uygulanan tiroid insidentaloma olgularında malignite oranını, literatür ile benzer şekilde yüksek bulduk. SUV_{maks} değeri yüksek tiroid insidentaloma olgularına, ileri tetkik yapılması gerekmektedir.

Anahtar kelimeler: Pozitron emisyon tomografisi/bilgisayarlı tomografi; ince iğne aspirasyon biyopsisi; tiroid nodülü; ultrasonografi

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Introduction

The thyroid nodule, a lesion within normal thyroid tissue, is radiologically distinguished from the surrounding thyroid tissue. A thyroid nodule is a common clinical condition, and its prevalence has been reported around 5% in women and 1% in men in epidemiological studies (1). However, in randomly selected individuals, thyroid nodule prevalence ranged from 19 to 68% in ultrasonography (USG) evaluations (2). Evaluating thyroid nodules becomes primarily important for clinicians to detect thyroid cancer in 7-15% of thyroid nodules (3).

Thyroid nodules can be observed routinely during physical examination, as well as incidentally during a radiological procedure such as neck USG, neck and thorax computed tomography (CT), magnetic resonance imaging, and ^{18}F-fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) scan. Thyroid incidentalomas are non-palpable thyroid nodules that are detected incidentally during imaging procedures (1). The malignancy risk of both non-palpable and palpable nodules is almost similar (4).

In recent years, FDG-PET/CT has often been used in the diagnosis and staging of malignancies. Resultantly, clinicians encounter FDG-PET/CT scans that show incidentally diffuse or focal increased 2-[Florin-18] fluoro-2-deoxy-D-glucose (FDG) uptake in the thyroid gland (5). Diffuse FDG uptake of the thyroid gland is generally found compatible with benign inflammatory processes, such as thyroiditis, while focal uptake indicates a benign or malignant nodule - incidentaloma (6). Thyroid incidentalomas are observed in 1-4% of FDG-PET/CT images (7). Malignancy rate is reported as 26-50% in thyroid nodules detected with FDG-PET/CT and further investigated (5).

Determining the predictive value of FDG uptake of thyroid nodules for the malignancy risk may guide clinicians in deciding on further examination and treatment of the thyroid incidentalomas. The objective of the current study was to investigate the malignancy risk of thyroid nodules detected incidentally by FDG-PET/CT scan and the relationship between the FDG uptake level and the malignancy rate of these nodules.

Material And Methods

FDG-PET/CT scan reports of 10,197 patients in Necmettin Erbakan University Meram Faculty of Medicine, Meram, Turkey, admitted between January 2014 and May 2019 were retrospectively analyzed. Eighty (0.78%) of these 10,197 patients who underwent fine-needle aspiration biopsy (FNAB) upon detection of incidental thyroid nodules by FDG-PET/CT were included. Individuals younger than 18 years and those who underwent FDG-PET/CT scan for malignant diseases of the thyroid gland were excluded from the current study.

The Ethics Committee of the Necmettin Erbakan University Meram Medical School approved this study (Approval no: 2019/2023, 12.7.2019). The study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki.

Required data such as age, gender, thyroid function test, ultrasonographic nodule characteristics, and nodule dimensions of patients who underwent FNAB were collected. FNAB cytology reports of the patients and the final histopathology reports of those who underwent thyroid surgery were obtained, and the rate of malignancy was investigated. The patients were stratified into two groups according to the FNAB cytology results: malignant and non-malignant. The relationship between maximum standardized uptake (SUV_{max}) values in FDG-PET/CT reports, USG findings, and FNAB cytology results of the biopsied nodules were investigated.

Statistical Analysis

Statistical analyses were done using the Statistical Package for Social Sciences, SPSS version 21.0 software. Continuous variables were expressed as median (minimum-maximum) if the distribution was not normal and mean±standard deviation if the distribution was normal. The Mann-Whitney U test was performed to compare the independent group differences when the parametric test assumptions were not

provided; the significance test of the difference between the two means (independent samples t-test) was used when the parametric test assumptions are given. P value <0.05 was considered for statistically significant differences.

Results

Demographic, Radiological and Laboratory Findings of the Study Group

Of the total 80 patients, 40 (50%) were female, and 40 (50%) were male, and the mean age was 63.2±11.4 years. Considering the laboratory findings of the patients; the mean thyroid-stimulating hormone (TSH) value was 1.6±1.4 mU/L, median thyroglobulin antibody (TgAb) value was 0 (range, 0-225) U/mL, and median thyroid microsomal antibody (TMA) value was 2.2 (0-705) U/mL (Table 1). Evaluation of the FDG-PET/CT scans of patients showed following common indications: malignancy of unknown primary origin (n=39, 48.8%), lymphoma (n=12, 15%), lung cancer (n=11, 13.8%), breast cancer (n=5, 6.3%), colon cancer (n=3, 3.8%) and multiple myeloma (n=2, 2.5%). As per the FDG-PET/CT results, the median SUV_{max} value of thyroid nodules was 5.2 (2.1-29.7).

Thyroid USG reports showed that the mean largest diameter of nodules was 20.7±12.8 (4-70) mm; 29 (36.3%) of the thyroid nodules were localized in the right lobe; 20 (25%) in the left lobe; 16 (20%) in the right and left lobe, 9 (11.3%) in both lobes and isthmus (Figure 1).

The USG findings of thyroid nodules also revealed the following: 58 (72.5%) of the nodules were solid, 1 (1.3%) cystic, and 19 (23.8%) mixed. Sixty-four patients showed contours [regular: 59 (92.2%), irregular: 5 (7.8%)]. Nodule echogenicity data of 57 patients' USG report revealed that 25 (43.8%) nodules were hypoechoic, 17 (29.8%) isoechoic, and 2 (3.5%) hyperechoic (Figure 2).

Calcification status of nodules in USG report of 67 patients showed that 4 (6%) patients had nodules with microcalcification, 15 (22.4%) patients had nodules with macrocalcification, 2 (2.5%) patients had nodules with both micro and macrocalcification, and

Table 1. Demographic and laboratory findings.

Parameter	Value
Sex (female/male), n	40/40
Age, mean±SD	63.2±11.4
TSH (mU/L), mean±SD	1.6±1.4
TgAb (U/mL), median (minimum-maximum)	0 (0-225)
TMA (U/mL), median (minimum-maximum	2.2 (0-705)
Nodule diameter (mm), Mean±SD	20.7±12.8
SUVmax value, median (minimum-maximum	5.2 (2.1-29.7)

SD: Standard deviation; TSH: Thyroid-stimulating hormone; TgAb: Thyroglobulin antibody; TMA: Thyroid microsomal antibody; SUVmax: Maximum standardized uptake.

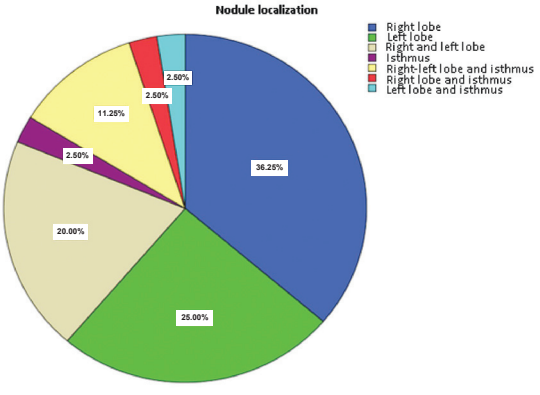

Figure 1. Localization of thyroid nodules.

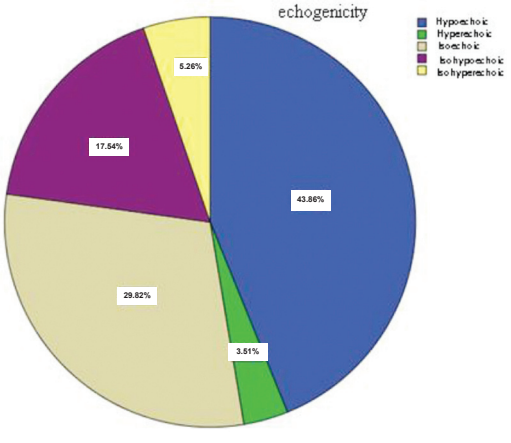

Figure 2. Evaluation of nodules according to their echogenicity.

46 (68.7%) patients showed nil calcification (Figure 3).

FNAB cytology results of the patients showed that the cytology findings were benign in 52 (65%) patients, malignant in 13 (16.3%) patients, suspicious in 4 (5%) patients, and nondiagnostic in 11 (13.8%) patients (Figure 4). Separate assessment of the results of malignant cytology revealed that 9 (69.2%) patients had papillary thyroid cancer, 1 (7.6%) non-Hodgkin lymphoma involvement, 1 (7.6%) undifferentiated carcinoma, 1 (7.6%) malignant cytology, and 1 (7.6%) had suspicious malignant cells in their FNAB results.

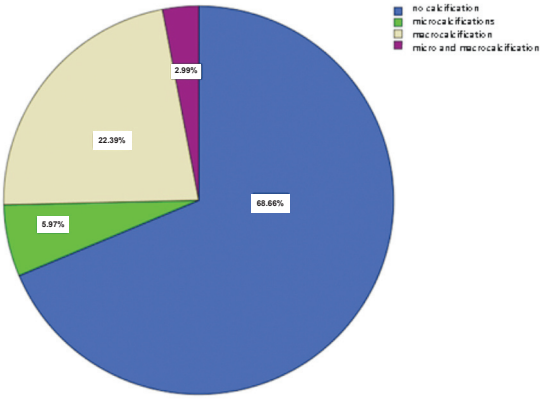

Figure 3. Evaluation of nodules according to their calcification status.

Comparison of Patients According to FNAB Cytology Results

Considering the FNAB cytology results, the patients were divided into two groups: malignant (n=13, 16.3%) and non-malignant (n=67, 83.7%); their demographic, laboratory, and radiological findings were compared. FDG-PET/CT indications in the malignant group were lymphoma in 3 (23%) patients, lung cancer in 1 (7.6%) patient, multiple myeloma in 1 (7.6%) patient, and malignancy of undefined primary origin in 8 (61.5%) patients.

Seven (53.8%) of the patients in the malignant group were female, and 6 (46.2%) were male; the mean age of the malignant group was 60.6±11.8 years. Of the non-malignant group patients, 34 (50.7%) were male, and 33 (49.3%) were female, with the mean age of 63.7±11.3 years. Patients in the malignant and non-malignant groups were of similar gender and age (p=0.762 and p=0.401, respectively).

Comparison of the laboratory findings of the groups showed no difference in serum TSH, TgAb, and TMA values between the groups (p=0.148, p=0.107, and p=0.694, respectively).

A comparison of the thyroid nodules of the groups using their USG findings demonstrated that the mean largest diameters of nodules in the malignant and non-malignant group were 22.1±17.8 and 20.5±11.8 mm, respectively (p=0.711). No difference between the groups in terms of cystic-solid nodules, nodule contour irregularity, and calcification status (p=0.626, p=0.585, and p=0.200, respectively) was observed (Table 2).

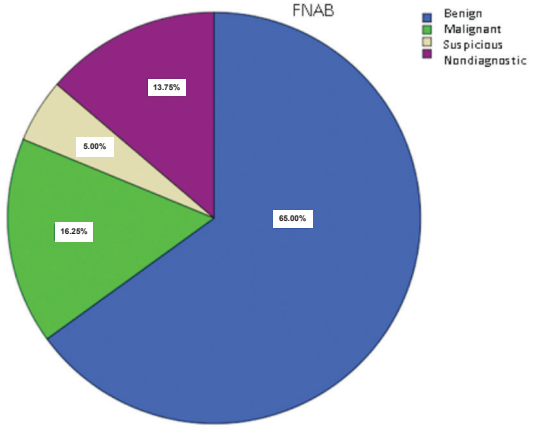

Figure 4. Fine-needle aspiration biopsy cytology results of thyroid nodules.

Comparing the SUV_{max} values of the nodules employing the FDG-PET/CT results showed the SUV_{max} values of the malignant group and the non-malignant group were 15.7 (5.1-29.7) and 4.4 (1.6-24.1), respectively, with a statistically significant difference (p<0.001) (Table 2).

Discussion

The rate of malignancy was 16.3%, according to FNAB cytology results of incidental thyroid nodules detected by FDG-PET/CT in the current study. The SU-

Table 2. Group-wise comparison of demographic, laboratory, and radiological findings.

Parameter	Malignant (n=13)	Non-malignant (n=67)	p value
Sex (female/male), n	7/6	33/34	0.762
Age, years, mean±SD	60.6±11.8	63.7±11.3	0.401
TSH, mU/L, mean±SD	2.1±1.2	1.5±1.4	0.148
TgAb, U/mL, median (minimum-maximum)	0 (0-0)	0 (0-225)	0.107
TMA, U/mL, median (minimum-maximum)	0 (0-705)	2.5 (0-288)	0.694
Nodule diameter, mm, mean±SD	22.1±17.8	20.5±11.8	0.711
Nodule structure, n (%)			
Cystic	0 (0)	1 (1.5)	
Solid	11 (84.6)	47 (72.3)	0.626
Mixed	2 (15.4)	17 (26.2)	
Nodule contour, n (%)			
Regular	9 (90)	50 (92.6)	0.585
Irregular	1 (10)	4 (7.4)	
Calcification status, n (%)			
None	7 (58.3)	39 (70.9)	
Microcalcification	2 (16.7)	2 (3.6)	0.200
Macrocalcification	2 (16.7)	13 (23.6)	
Micro-macro	1 (8.3)	1 (1.8)	
SUV_{max} value, median (minimum-maximum)	15.7 (5.1-29.7)	4.4 (1.6-24.1)	<0.001

SD: Standard deviation; TSH: Thyroid-stimulating hormone; TgAb: Thyroglobulin antibody; TMA: Thyroid microsomal antibody; SUVmax: Maximum standardized uptake.

V_{max} values of patients in the malignant group were noticed to be remarkably higher than those of non- malignant patients. No significant difference was observed between the malignant and non-malignant groups in terms of nodule size, structure, contour, and microcalcification status.

Several previous studies have investigated the highly variable malignancy rates (8-64%) in incidental thyroid nodules detected in FDG-PET/CT scans (8,9). Also, the 2015 American Thyroid Association guideline recommended performing FNAB because of an increased risk of malignancy in thyroid nodules larger than 1 cm detected with FDG-PET/CT and confirmed by USG (1). Several reasons were cited for this highly variable malignancy rate. First, most of these studies were retrospective. In many studies, not all patients with a thyroid nodule were examined in detail. The most important reason for this situation is that FDG-PET/CT scan in some patients indicated an advanced stage or disseminated metastatic cancer. It appears that diagnosing new cancer or the presence of metastases in the thyroid gland does not affect survival and may prevent clinicians from performing FNAB in this group. In our study, this malignancy rate could not be determined since the same was not investigated in patients detected with thyroid nodules. Comparison with similar studies should involve the terminology used. Reported malignancy rate "Is the malignancy rate of thyroid nodules that have been examined in detail?" or "the malignancy rate of all detected nodules?" may impact the study results.

For example, the meta-analysis by Soelberg et al. on evaluating 22 studies showed that 125,754 FDG-PET/CT scans revealed 1,994 (1.6%) patients with incidental thyroid nodules and approximately two-thirds (1,051 people, 62.7%) were examined in detail.

Primary thyroid cancer was detected in 366 (34.8%) of the patients who underwent detailed examination (10). In a study reported from our country, focal uptake in the thyroid gland was detected in 221 (1.7%) of 12,796 patients who underwent FDG-PET/CT scan for about ten years; of them, 126 (57%) patients were applied FNAB. Thyroid cancer was detected in 43 (34.1%) of these patients after the FNAB test (11). Our findings show conformity with the literature. In this study, 0.78% of FDG-PET/CT scans showed focal uptake in the thyroid gland and FNAB was applied. The malignancy rate was 16.3% in the biopsied thyroid nodules.

Focal incidental thyroid lesions detected by FDG-PET/CT scan showed higher malignancy rates than those detected by other methods (12). In one study, the malignancy rate was 7.6% in patients detected by physical examination, 4-12.6% in those detected by USG, and 1.8-10.5% in those who underwent surgery for benign reasons (13). The relatively higher ratio in those detected by FDG-PET/CT can be explained by two reasons. First, malignant lesions have increased glycolysis and glucose uptake, so increased FDG uptake is observed with FDG-PET/CT scan, which evaluates thyroid nodules for metabolic activity. Free fatty acids are used as an energy source in the thyroid gland, and FDG uptake is not expected under normal conditions since there is no glucose transporter 1 (GLUT1) expression in the thyroid tissue (14). However, GLUT1 expression has been evidenced by immunostaining in differentiated and anaplastic thyroid cancers (15). Diagnosing thyroid cancer by FDG uptake alone is impossible because focal FDG uptake has also been reported in nodules from autonomic functional thyroid or adenomatous goiter (16,17). The finding of not diagnosing malignancy in all thyroid nodules with focal FDG uptake in our study corroborates the above situation. Relatively greater malignancy rate could also be due to reason that evaluated patients generally consisted of cancer patients who were directed to FDG-PET/CT for reasons such as primary cancer staging, treatment response evaluation, or radiotherapy planning, and higher probability of a second primary tumor in these patients (18).

In this study, SUV_{max} values of thyroid incidentalomas with malignancy were significantly higher than those without malignancy. However, there are contradictory results in studies investigating the relationship between SUV_{max} value in thyroid incidentalomas and the risk of malignancy. Only about half of the previous studies have documented a significant difference between benign and malignant lesions in terms of SUV_{max}, while the other half did not. Are et al. evaluated FDG-PET/CT results of 8,800 patients and detected malignancy in 24 (42%) of 57 patients who underwent FNAB; and observed no significant difference between SUV_{max} values of malignant and benign lesions (9.2 vs. 8.2), respectively (p=0.7) (19). Hagenimana et al., in their evaluation of FDG-PET/CT scans, detected thyroid incidentaloma in 0.74% of 40.914 patients; they observed thyroid malignancy in 8.2% of patients with thyroid incidentaloma and noticed no significant difference between malignant and benign lesions in terms of SUV_{max} values [4.90 (2.95-8.65) and 4.40 (3.55-7.73), respectively, p=0.499] (20). In a meta-analysis performed by Qu et al., involving one of the highest numbers of patients in 29 studies, the PET/CT results of 196,298 patients were evaluated. In that study, 2,559 patients had focal uptake in the thyroid gland; 1,549 underwent FNAB or thyroid surgery; SUV_{max} values of the 862 malignant patients after pathology were found to be higher than 430 benign patients (p=0.001) (21). Furthermore, Soelberg et al., in their meta-analysis, reported a significantly higher SUV_{max} value of the malignant lesions (6.9±4.7) than that in benign lesions (4.8±3.1) (p<0.001) (10).

Thyroid nodules are reported more common in women than in men (1). Similarly, incidental thyroid lesions detected in FDG-PET/CT are more common in women than in men (22). In a study conducted in our country, 65% of patients with thyroid incidentaloma detected by FDG-PET/CT were reported to be female and 35% male (23). In the current study, the number of men and women was found to be equal, unlike in previous studies.

Few studies investigating the relationship between nodule size and malignancy in thyroid nodules detected by FDG-PET/CT normally did not report a significant difference in this regard. In the meta-analysis of 28 studies by Qu et al., 29 studies, no significant difference was found between the diameters of malignant and benign lesions (p=0.07) (21). Bae et al., in their study of 99 thyroid incidentaloma patients detected by FDG-PET/CT, reported that no statistically significant difference was observed between the nodule diameters (1.81±1.08 cm) of patients with benign pathology results (n=76) and nodule diameters (1.54±0.90 cm) of patients with malignant pathological results (n=23) (p=0.289) (24). This finding, similar to those in other studies, is also supported in the current study that showed no significant difference between malignant and non-malignant nodules in terms of nodule diameter.

In the ultrasonographic evaluation of thyroid nodules, findings such as the solid structure of the nodule, contour irregularity, and presence of microcalcification were associated with increased risk of malignancy (1). However, few more studies have investigated the relationship between these parameters and malignancy in thyroid incidentaloma cases detected by FDG-PET/CT. Demir et al. observed a significant difference between the SUV_{max} values of malignant and benign nodules (10.2±8.9 vs. 5.6±3.0, p=0.013), respectively but reported that the difference between the size of malignant and benign nodules was not statistically significant (20.0±7.3 vs. 16.7±7.4, p=0.923). Demir et al. also noticed that the presence of suspicious USG findings and the high elastography score (≥4) was also statistically significant for malignancy (p<0.001, p=0.035, respectively) (25). Oven et al. reported no association between malignancy and the presence of microcalcification or solid structure of the nodule with similar p values, but a relationship between contour irregularity and malignancy (p=0.007) was observed (23). No significant relationship could be established between these parameters and malignancy in the current study, probably because of the low number of patients with thyroid malignancy in the study group.

Papillary thyroid carcinoma has been reported as the most common histological type (84-100%) in malignant thyroid incidentalomas in few studies on thyroid incidentalomas that were detected by FDG-PET/CT (21,26). Incidence of papillary thyroid carcinoma was found most frequently as in other studies in the literature.

Conclusion

In conclusion, the malignancy rate of thyroid incidentalomas detected by FDG-PET/CT and then biopsied with FNAB was found to be 16.3%, similar to the literature. SUV_{max} values of thyroid incidentalomas diagnosed with malignancy were significantly higher than those without a diagnosis of malignancy. Due to the increased malignancy potential, detailed diagnostic evaluations, especially using USG and FNAB, should be done for focal thyroid lesions detected incidentally in FDG-PET/CT scan.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Leyla Turgut; Design: Melia Karaköse; Control/Supervision: Mustafa Kulaksızoğlu, Feridun Karakurt; Data Collection and/or Processing: Leyla Turgut, Mustafa Can; Analysis and/or Interpretation: İlker Çordan, Muhammet Kocabaş; Literature Review: Muhammet Kocabaş; Writing the Article: Muhammet Kocabaş, Mustafa Can; Critical Review: Melia Karaköse; References and Fundings: Mustafa Can; Materials:Leyla Turgut.

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