ORIGINAL ARTICLE

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Thyroid Cancer Prevalence and Risk in Incidental Thyroid Lesions Detected with ^{18}F-FDG PET/CT

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Abstract

Objective: The aim of this study is to analyze the relationship between thyroid nodules detected in patients who were examined in our clinic for any indication and had ^{18}fluoro-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) scanning and thyroid cancer.

Methods: Results of patients who had FDG PET/CT scanning for any indication other than thyroid cancer during 2015 and 2016 in Okmeydani Training and Research Hospital were examined. Age and genders of patients, FDG PET scanning indications, FDG accumulation type (focal or diffuse), lesion maximum standard uptake value (SUV_{max}), histology, and pathology of the patient who had fine-needle aspiration biopsy (FNAB) or surgery were recorded. According to the results obtained from these values, the relationship between thyroid nodules and thyroid cancer was analyzed.

Results: Among the group of 50 patients, ^{18}F-FDG PET/CT scanning detected all as having thyroid nodules. Forty cases had benign diagnoses, whereas ten cases had malignant diagnoses either by FNAB or total thyroidectomy. According to the diagnosis results, the SUV_{max} average of the malignant group was higher than the SUV_{max} average of the benign group. However, no statistically significant result was obtained ($p>0.05$). The results also showed no statistically significant association regarding tumor size between the malignant and benign groups ($p>0.05$).

Conclusion: Thyroid incidentaloma was detected among patients who had ^{18}F-FDG PET/CT scanning for any reason other than thyroid cancer. Thyroid malignancy was detected in 20% of patients diagnosed with thyroid nodules by with focal ^{18}F-FDG accumulation. No statistically significant results concerning SUV_{max} value and lesion size were obtained among groups having benign and malignant diagnoses. Since no significant results were obtained between the SUV_{max} and malignancy, no threshold value for SUV_{max} was calculated.

Keywords: Thyroid nodules, incidentaloma, FDG PET/CT

INTRODUCTION

A nodule detected in the thyroid gland in imaging studies performed for different reason without PURPOSE imaging (1). ^{18}Fluoro-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) is a valuable imaging method used for diagnosis, staging, restaging, treatment response, and biopsy guidance in oncological diseases (2).

A normal thyroid gland does not exhibit any physiological ^{18}F-FDG uptake. However, in approximately 1.2% to 4.3% of the ^{18}F-FDG PET studies, diffuse, or focal ^{18}F-FDG uptake is observed incidentally (1-3). In this examination, 14% to 50% of cases with focal involvement have thyroid malignancy, and those with diffuse involvement have diffuse hyperthyroidism or thyroiditis (1-3). In a review article, the malignancy rate was 4.4% for diffuse involvement and 34.8% for focal involvement (4). Most

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studies conducted so far on this subject are retrospective and devoid of definite diagnostic algorithms. In the retrospective studies of incidental thyroid involvement, the final diagnosis has been reached in only 30% to 50% of cases (5-7). There are considerable limitations in systematic reviews on this subject, such as publishing bias and significant heterogeneity in studies (8).

We conducted this retrospective study to detect the rate of incidental involvement in the thyroid gland in ^{18}F-FDG PET/computed tomography (CT) examination in our clinic and to determine the rate of malignancy among these patients.

METHODS

Patients

In our study, 9,974 patients who underwent ^{18}F-FDG PET/CT imaging between January 2015 and December 2016 with indications other than thyroid diseases in the Nuclear Medicine Department of Okmeydani Training and Research Hospital were evaluated, and 50 patients with definitive histopathological diagnosis of incidental thyroid nodules were included in the study. Patients showing focal or diffuse FDG uptake in the thyroid gland in the ^{18}F-FDG PET/CT study were evaluated and recorded as incidental involvement. Age, gender, ^{18}F-FDG PET/CT imaging indication, ^{18}F-FDG involvement (focal or diffuse), lesions' maximum standard uptake value (SUV_{max}), and histopathology of those who underwent surgery or fine-needle aspiration biopsy (FNAB) were recorded. The histopathological diagnoses of patients who underwent FNAB were categorized as malignant, benign, and suspicious. Histopathological diagnoses of patients who underwent thyroidectomy and FNAB were examined and compared with ^{18}F-FDG PET/CT findings. The cases with FNAB results that were inadequate, uncertain, and suspicious for malignancy (unless confirmed by total thyroidectomy) were excluded from the study. The incidence of incidental thyroid lesions, malignancy potentials of these lesions, the correlation of SUV_{max} and ^{18}F-FDG uptake patterns of lesions, with histopathological results of patients who underwent ^{18}F-FDG PET/CT study were examined. A retrospective evaluation was made by obtaining ^{18}F-FDG PET/CT imaging results from the archive in the nuclear medicine department and histopathological results from the patient files and pathology archive. This retrospective study was conducted with the approval of the Medical Ethics Committee of Okmeydani Training and Research Hospital, with the decision dated March 14, 2018, and numbered 615. Informed consent was obtained from all individual participants included in the study.

Imaging

PET/CT imaging of patients included in the study was done with a Siemens Biograph 6 LSO HI-RES integrated PET/CT device (Siemens Medical Solutions, Knoxville, TN, USA). After four to six hours of fasting, patients waited in a quiet and dark room just before their exam. Blood glucose was measured with a glucometer just before the radiopharmaceutical injection. All patients used an oral contrast agent before imaging. Patients with blood glucose levels below 150 mg/dL were injected intravenously with 0.15-0.20 mCi/kg ^{18}F-FDG. After a 60-minute waiting period, the patient's bladder was emptied, and the patient was placed in the supine position on the bed of the PET/CT scanner. First guideline topogram CT images were acquired, then subsequent PET images of body parts from the vertex to the proximal thigh were acquired. The images of the patients were completed in approximately 20 to 25 minutes, with an average of 7 to 8 bed positions. The CT portion of the PET/CT study was non-diagnostic and used for attenuation correction and anatomical localization of ^{18}F-FDG PET images.

Histopathological Evaluation

The biological material obtained while performing the diagnostic and treatment procedures (FNAB or thyroidectomy) was examined histopathologically in our hospital's pathology department, and immunohistopathological staining was performed as necessary.

Statistical Analysis

IBM SPSS Statistics 22 for statistical analysis (SPSS IBM, Turkey) program was used to evaluate the findings of the study. The appropriateness of the parameters to normal distribution was evaluated with the Shapiro-Wilk test. In addition to descriptive statistical methods (mean, standard deviation, frequency), in the comparison of quantitative data, Student's t-test was used for comparing the parameters that showed normal distribution, and the Mann-Whitney U test was used for parameters that did not show normal distribution. Fisher's exact test was used to compare qualitative data. Significance was evaluated at the level of $p<0.05$.

RESULTS

Incidental involvement in the thyroid gland was observed in 401 (4%) of patients who underwent ^{18}F-FDG PET/CT (focal 2.3%, diffuse 1.6%). Diffuse involvement was observed in 162 (41%) (Figure 1) and focal uptake in 239 (59%) of these patients. Histopathological diagnosis was obtained by FNAB in 43 patients, and surgery in 7 patients. The average patient

age was 60.84±13.01 (34-86) years. Ten (20%) were male, and 40 (80%) were female. Our study parameters included were SUV_{max}, histopathological diagnosis and incidental lesion tumor size (Table 1). SUV_{max} range from 2.73 to 29.27 with an average of 8.39±5.83. The average SUV_{max} for benign and malignant lesions were 7.56±3.81 (mean, 6.15) and 11.72±10.34 (mean, 7.18).

Tumor sizes ranged from 6 to 43 mm, and the average size was 19.47±9.27 mm. The size of the nodules, either malignant or benign, was ≤15 mm in 23 cases (46%) and ≥15 mm in 27 cases (54%). While 40 (80%) of 50 cases were diagnosed as benign, (Figure 2) 10 (20%) were diagnosed as malignant (Figure 3). When the size assessment was made in malignant cases, 6 of 10 were 15 mm and below. Although the malignancy rate was higher in nodules smaller than 15 mm, it was statistically insignificant. In benign nodules, 17 of 40 cases had a size of 15 mm or less.

Six out of 23 nodules (26%) smaller than 15 mm were found to be malignant. This finding was higher than the malignancy rate in all ^{18}F-FDG positive nodules (20%) but was not statistically significant. The average SUV_{max} were higher in the malignant group, but there was no statistically significant difference regarding SUV_{max} ($p>0.05$). Since there was no statistically significant difference between the SUV_{max} averages of malignant and benign nodules, a cut-off point could not be calculated.

DISCUSSION

Incidence of detecting thyroid nodules on the neck ultrasonography (USG) performed for a purpose other than the thyroid gland is between 14% and 46% (1). The nodule detection rate varies among different radiological imaging methods.

Table 1. SUV_{max}, nodule size, age, and gender distribution in benign and malignant nodule groups

	Diagnosis		p
	Benign	Malignant	
SUV_{max} Avg. ± SD (median)	7.56±3.81 (6.15)	11.72±10.34 (7.18)	[1]**0.689**
Tumor size (n, %)			
≤15 mm	17 (42.5%)	6 (60%)	[2]**0.480**
>15 mm	23 (57.5%)	4 (40%)	
Age mean ± SD	61.9±12.59	56.6±14.49	[3]**0.253**
Sex (n, %)			
Male	8 (20%)	2 (20%)	[2]**1.000**
Female	32 (80%)	8 (80%)	

[1]Mann-Whitney U test, [2]Fisher's exact test, [3]Student's t-test, SUV_{max}: Maximum standard uptake value, Avg.: Average, SD: Standard deviation

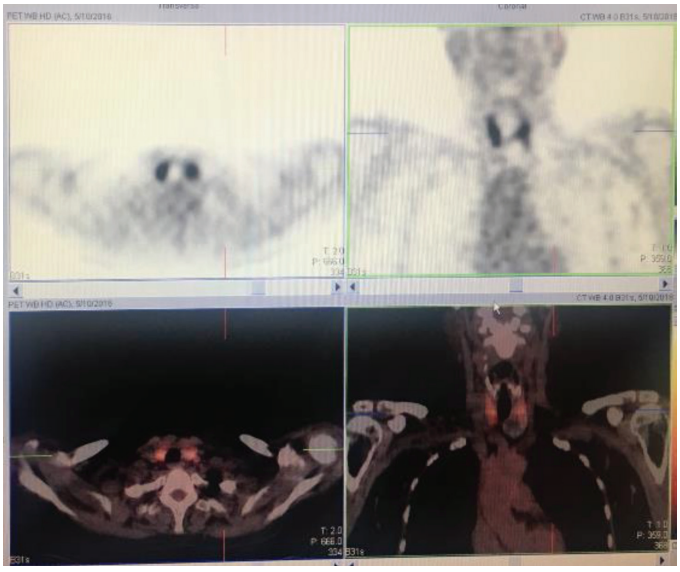

Figure 1. Chronic thyroiditis pattern showing diffuse FDG uptake. A 56-year-old female patient underwent ^{18}F-FDG PET/CT for restaging of cervical cancer. Axial PET and fusion images (left column) and coronal PET and fusion images (right column) show incidental diffuse FDG uptake in the thyroid gland (SUV_{max}: 14.69). The patient underwent FNAB, and her histopathology revealed lymphocytic thyroiditis

^{18}F-FDG: ^{18}Fluoro-fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography, SUV_{max}: Maximum standard uptake value, FNAB: Fine-needle aspiration biopsy

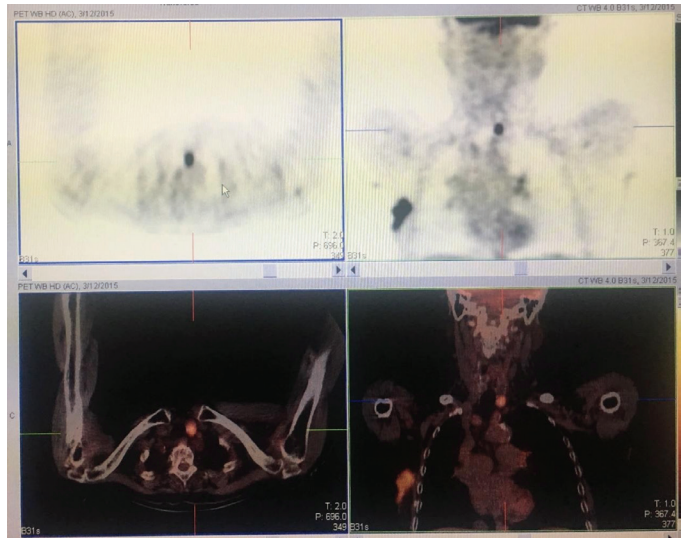

Figure 2. Benign thyroid nodule that shows focal FDG uptake. An 86-year-old female patient underwent an ^{18}F-FDG PET/CT study for the evaluation of cancer of unknown primary origin. Axial PET and fusion images (left column) and coronal PET and fusion images (right column) show focal FDG uptake in the left lobe of the thyroid gland. (SUV_{max}: 12.91). Correlation with USG showed a 15 mm nodule, and the FNAB results from this nodule were benign

^{18}F-FDG: ^{18}Fluoro-fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography, SUV_{max}: Maximum standard uptake value, FNAB: Fine-needle aspiration biopsy, USG: Ultrasonography

Thyroid gland incidentalomas are seen in 16% of CT and magnetic resonance imaging studies and 27% of neck ultrasonographies (9,10). In an autopsy series, incidental nodules were more common in the thyroid gland. Mortensen et al. (11) reported that macroscopically at least one nodule was observed in half of the patients, and nodules were larger than 2 cm in approximately 33% of all cases.

The incidental detection rate of ^{18}F-FDG avid thyroid nodules in ^{18}F-FDG PET/CT studies has been reported between 0.1% and 4.3% (12). In our retrospective study, incidental uptake in the thyroid gland, either focal or diffuse, was observed in 401 (4%) of 9,974 patients who underwent ^{18}F-FDG PET/CT for evaluation of different malignancies. It is known that thyroid nodules are more common in women than in men. Also, ^{18}F-FDG PET/CT incidentalomas are more common in women (1). In our cohort, 74% of incidentalomas were detected in women. The nodule observed in the focal involvement area located incidentally in the thyroid gland is likely to be malignant. Therefore, the presence of nodules that show focal ^{18}F-FDG uptake should be evaluated with USG, and FNAB should be performed if necessary (13).

In our study, 60 of 239 patients with focal involvement underwent FNAB, and seven of them had a total thyroidectomy in addition to FNAB. Malignancy was detected in ten of the patients with malignancy-compatible cytology after total thyroidectomy and/or FNAB and was used as the gold standard to diagnose thyroid cancer. The risk of malignancy was calculated as 20% (10/50) for patients without FNAB. Inadequate and uncertain FNAB results and suspected malignant cases of FNAB (unless confirmed by total thyroidectomy) were excluded from the study. In a systematic review on this subject, the malignancy rates obtained with total thyroidectomy and FNAB in patients with incidental focal ^{18}F-FDG involvement in the thyroid gland were reported as 29.3%-33.2% (8). Bae et al. (7) reported the malignancy rate as 30.9% in patients with focal ^{18}F-FDG involvement in the thyroid gland. These rates are somewhat higher than the rates we found (20%). The probable reason for obtaining a rate below those cited in the literature is the low number of patients who had FNAB or total thyroidectomy, which is also a limitation of the study. However, cancer rates of focal incidentalomas were higher and were from 41.7% to 47% in some studies. However, these studies were limited and included a low number of patients in the study and made the histopathological diagnosis mostly by FNAB instead of an operation (14,15). Chen et al. (16) reported the malignancy rate of the ^{18}F-FDG positive thyroid nodules as 14%, a rate lower than that found in the literature. We think that the low risk of malignancy in this study may be due to bias in the evaluation of FNAB results on focal incidentalomas. In addition, geographical differences in which the study was conducted may be cause discordant malignancy risk.

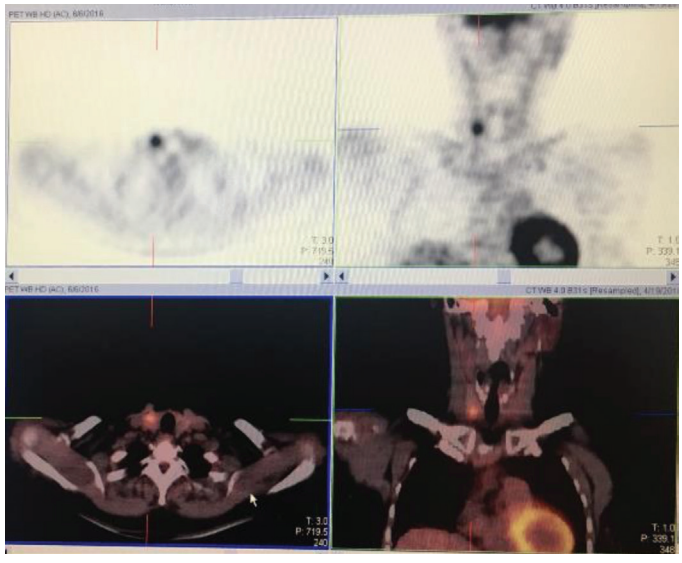

Figure 3. Malignant thyroid nodule that shows focal FDG uptake. A 46-year-old female patient underwent an ^{18}F-FDG PET/CT study for the evaluation of cancer of unknown primary origin. Axial PET and fusion images (left column) and coronal PET and fusion images (right column) show focal FDG uptake in the right lobe of the thyroid gland. (SUV_{max}: 7.8). Ultrasonography showed an 11 mm nodule corresponding to the focal uptake. FNAB from the nodule revealed atypia of unknown significance. Subsequently, the patient underwent a total thyroidectomy, and the pathology results revealed papillary thyroid carcinoma

^{18}F-FDG: ^{18}Fluoro-fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography, SUV_{max}: Maximum standard uptake value, FNAB: Fine-needle aspiration biopsy

Determining a specific SUV_{max} cut-off value for the discrimination of benign and malignant thyroid nodules is another concern. Makis and Ciarallo (12) reported a statistically significant difference between the median SUV_{max} of benign thyroid incidentalomas (SUV_{max}: 4.8) vs malignant (SUV_{max}: 6.3). However, due to the wide range of overlap between the two groups, the authors did not find it reliable to determine the malignancy with this SUV_{max} threshold value. Pagano et al. (17) stated that malignant lesions have a higher SUV_{max} than benign lesions, and this has a positive correlation when SUV_{max}: >5. The meta-analyses also reported a significant difference between SUV_{max} of benign lesions and malignant lesions. However, no particular SUV_{max} cut-off value was identified because of the overlap between the two groups (4,8,18). In our study, the average SUV_{max} was higher in the group diagnosed as malignant. Still, the difference between benign and malignant nodules regarding SUV_{max} averages was not statistically significant ($p>0.05$).

In a study conducted by Shi et al. (19) with 5,216 patients, the malignant thyroid incidentalomas were significantly larger than benign lesions (malignant 1.8±0.8 cm, benign 1.3±0.5 cm, p=0.006). They had higher SUV_{max} (11.3 vs. 4.8, p<0.001). We chose a 1.5 cm cut-off value arbitrarily. There was no statistically significant difference regarding the distribution rates between the tumor size groups (p>0.05).

The 2015 American Thyroid Association (ATA) guideline suggests that if the uptake is diffuse, it is confirmed by USG or clinical findings regarding the ^{18}F-FDG involvement in the thyroid gland. There is no need for further imaging examination (strong recommendation medium level of evidence). In focal ^{18}F-FDG uptake, if the nodule is confirmed with USG and the size of the nodule is >1 cm, thyroid FNAB is recommended because the risk of malignancy increases (strong advice medium evidence) (20). Similarly, the 2016 Agency for Care Effectiveness (ACE) guideline recommends FNAB for increased risk of malignancy in thyroid nodules that show focal ^{18}F-FDG uptake on PET. However, if the involvement is diffuse, they do not recommend further investigation. Unlike the ATA guideline, the ACE guideline does not make any recommendations regarding the nodule size for performing a biopsy of the nodule that shows ^{18}F-FDG uptake (21).

CONCLUSION

Thyroid incidentaloma was detected in 4% of patients who underwent ^{18}F-FDG PET/CT for non-thyroid cancer. The pattern of FDG uptake in these patients was focal in 59% and diffuse in 41%. Thyroid malignancy was detected in 20% of patients with ^{18}F-FDG PET/CT with focal FDG uptake. There was no significant difference between the groups diagnosed benign and malignant concerning SUV_{max} and lesion size. The cut-off value for SUV_{max} could not be calculated because there was no relationship between SUV_{max} and malignancy.

It was thought that thyroid incidentalomas that show focal ^{18}F-FDG uptake on ^{18}F-FDG PET/CT studies should be correlated with USG. Because of the high risk of malignancy, analysis of histopathologies should be performed with FNAB.

Ethics

Ethics Committee Approval: This retrospective study was conducted with the approval of the Medical Ethics Committee of Okmeydani Training and Research Hospital, with the decision dated March 14, 2018, and numbered 615.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.F.C., Concept: İ.F.C., T.Ö., Design: İ.F.C., T.Ö., Data Collection or Processing: İ.F.C., Analysis or Interpretation: İ.F.C., T.Ö., Literature Search: İ.F.C., Writing: İ.F.C., F.Ö., S.S.K.

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

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