



Retrospective analysis of thyroid incidentalomas detected by [⁶⁸Ga] Ga-PSMA-11 PET/CT

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Abstract

Background Prostate cancer patients, undergo imaging procedures, with [⁶⁸Ga]Ga-PSMA-11 PET/CT (prostate-specific membrane antigen based positron emission tomography/computed tomography) utilized for primary and secondary staging. PSMA thyroid incidentalomas (PTI) are discovered in the thyroid gland while imaging prostate cancer patients with [⁶⁸Ga] Ga-PSMA-11 PET/CT.

Aims The aim of the study was to determine the clinical significance of PTIs detected on [⁶⁸Ga]Ga-PSMA-11 PET/CT. Another goal was to identify a possible threshold for the maximum standardized uptake value (SUVmax), above which a malignant growth could be suspected.

Study design A retrospective cross-sectional study.

Methods 769 patients with prostat cancer who underwent [⁶⁸Ga]Ga-PSMA-11 PET/CT scans in the nuclear medicine department of a tertiary care hospital between January 2020 and December 2022 were retrospectively screened in this study. We analyzed 67 patients in whom PTI was detected. Patients who exceeded the inclusion criteria had their thyroid ultrasonography and ultrasonography -guided fine needle aspiration findings analyzed.

Results PTI was discovered in 67 patients (8%). 42 patients who met the inclusion and exclusion criteria were included in the study. Of the 4 malignant patients (9.5%) in the study population, 2 were classified as TIRADS 3 and 2 were classified as TIRADS 4. The cut-off SUVmax value was found to be 5.6. With 100% sensitivity and 47.37% specificity, a cutoff SUVmax of 5.3 was determined through receiver–operator characteristic analysis in order to predict malignant cytology.

Conclusion PTI is a significant clinical finding; most of diffuse and focal uptakes are frequently related to benign diseases. Each center should establish its own a possible SUVmax cut-off over which a malignant lesion should be suspected.

Keywords Prostate cancer · PSMA (Prostate-specific membrane antigen) · PET (Positron emission tomography) · Thyroid · Thyroid incidentaloma

Introduction

Prostate cancer (PCa) is one of the most frequent cancers in men worldwide, and it is an important cause of mortality. Prostate cancer patients, like other cancer patients, undergo imaging procedures, with [⁶⁸Ga]Ga-PSMA-11 (prostate-specific membrane antigen) based positron emission tomography/computed tomography (PET/CT) being one of these

modalities utilized for primary and secondary staging [1]. PSMA is a transmembrane receptor protein that is expressed in normal prostate secretory epithelium and has been found to be greatly elevated in prostate cancer [2]. Despite its name, PSMA is not just found in prostate cancer; it can also be found in some benign situations and it is also seen in breast, thyroid, and lung cancers. The possible indications of this imaging modality in other solid tumors were

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established by in vitro and in vivo studies. According to recent investigations, PSMA is expressed in the neovascularity of numerous cancer types and regulates tumor angiogenesis and cell invasion. The identification of PSMA expression in these non-prostatic solid tumors suggests potential diagnostic and radioligand-based treatment options [3, 4]. PSMA thyroid incidentalomas (PTI) are discovered in the thyroid gland while imaging prostate cancer patients with [^{68}Ga]Ga-PSMA-11 PET/CT [5, 6]. Anaplastic and differentiated thyroid carcinomas also expressed PSMA [7]. PSMA positive thyroid lesions detected both metastases and primary thyroid cancers [6].

In our center, [^{68}Ga]Ga-PSMA-11 PET/CT is already used to stage and restaging for elevated PSA levels with prostate cancer patients, and there have been a few studies and case reports about PSMA thyroid incidentalomas in the literature. There is a need to evaluate PSMA thyroid incidentalomas while increasing the frequency of [^{68}Ga]Ga-PSMA-11 PET/CT for prostate cancer. Incidental thyroid PSMA neoplasms within our institution were illustrated and evaluated for the aim of this study. Another goal was to identify a possible threshold for the maximum standardized uptake value (SUV_{max}), above which a malignant growth could be suspected.

Materials and methods

Study protocol

This is a retrospective study. A local ethical committee approved the study, and the study was undertaken in accordance with the principles of the Declaration of Helsinki.

A total of 769 male prostate cancer patients aged 18 years or older who underwent [^{68}Ga]Ga-PSMA-11 PET/CT scans in the Nuclear Medicine department of a tertiary care hospital between January 2020 and December 2022 were retrospectively screened in this study.

The term “thyroid” was identified in 91 patients’ reports. The authors evaluated reports to determine the degree of uptake in the thyroid gland. [^{68}Ga]Ga-PSMA-11 uptake in the entire thyroid gland was labeled as diffuse, whereas [^{68}Ga]Ga-PSMA-11 uptake in clearly defined parts of the thyroid gland was labeled as focal. Individuals with increased [^{68}Ga]Ga-PSMA-11 uptake in the thyroid were enrolled in the study.

The PTI study excluded participants having a history of thyroid nodule or thyroid malignancy, involvement on repeated imaging and nodule without enhanced uptake. Patients with repeated imaging were based on the images obtained by ultrasound (US) or cytology at the time of presentation to the endocrinology clinic.

Of the remaining 67 patients, 42 patients who had thyroid function tests such as thyroid-stimulating hormone (TSH) and free thyroxine (fT4) evaluated in the Endocrinology Department of our center and underwent thyroid US by an endocrinologist were included in the study. One patient with a thyroid nodule and increased [^{68}Ga]Ga-PSMA-11 uptake was excluded from the study because he refused the biopsy. One patient was excluded because the biopsy result was non-diagnostic and he refused re-biopsy.

The initial [^{68}Ga]Ga-PSMA-11 PET/CT scans were evaluated by Nuclear Medicine specialists in accordance with the European Nuclear Medicine Association guidelines [8]. ^{68}Ga was obtained by a germanium-68-gallium-68 ($^{68}\text{Ge}/^{68}\text{Ga}$) generator for labeling [^{68}Ga]Ga-PSMA-11 ligand An Agilent 1260 Infinity HPLC system (including dual pump, degasser and UV detector, Agilent Technologies, Santa Clara, CA, United States) with an ACE-5-C18 column (150 × 3 mm, affinity capillary electrophoresis [ACE]) and a NaI radio detector (Type: B-FC-3500, Eckert & Ziegler) was used to decide the radiochemical purity. The elution was monitored both by detecting UV (at 220 nm) and radioactivity. Water, acetonitrile, and trifluoroacetic acid (78/22/0,1 v/v/v) mixture was used as the mobile phase and flow rate was maintained at 0,6 mL/min. Radiochemical purity was greater than 97% as a result. [^{68}Ga]Ga-PSMA-11 PET/CT scans were obtained 45–60 min after injection of approximately 185 MBq (5 mCi) [^{68}Ga]Ga-PSMA-11 using an integrated PET/CT scanner (Siemens, Biograph True Point 6 PET/CT, Germany). A low dose whole-body CT scan was performed without intravenous contrast administration with 120 kV, 30–413 mAs, a pitch of 0.8, a section thickness of 3 mm, and a field of view of 78 cm. A PET scan was acquired from the skull base to the upper thigh with a 2-minute acquisition per bed position using a three-dimensional acquisition mode. The semi quantification results “standardized uptake value” as presented SUV_{max} were recorded. The maximum SUVs for thyroid lesions (thyroid SUV_{max}) and mean liver SUVs were recorded, and the ratio of the thyroid lesions SUV_{max} to the mean liver SUV (thyroid-to-liver SUV ratio) was obtained. Diagnostic performances for the thyroid SUV_{max}, thyroid lesions-to-liver SUV ratio were compared.

The thyroid incidentalomas which are the thyroid nodules with corresponding focal or diffuse radiotracer accumulation that were not determined previously by another imaging examination were defined from the PET/CT results. All nodules were classified by US examination in accordance with the European Thyroid Imaging Reporting and Data System (EU-TIRADS), which was implemented in 2017 [9]. 42 patients were assigned EU-TIRADS scores by an expert endocrinologist. If [^{68}Ga]Ga-PSMA-11 uptake was increased, fine needle aspiration cytology (FNAC) followed the American Thyroid Association

Table 1 Characteristics of patients with thyroid incidental findings on ⁶⁸Ga-PSMA PET/CT

| Variable | <i>N</i> = 42 (%) |
|------------------------------|-------------------|
| Median age (min-max) | 71 (50–82) |
| US Nodule | |
| Yes | 29 (69) |
| None | 13 (31) |
| Nodule involvement | |
| Diffuse | 6 (14.3) |
| Focal | 36 (85.7) |
| Distribution PSMA uptake | |
| Right lobe | 14 (33.3) |
| Left lobe | 16 (38.1) |
| Isthmus | 2 (4.8) |
| Both lobes | 10 (23.8) |
| TIRADS staging | |
| Tirads 2 | 9 (31.1) |
| Tirads 3 | 17 (58.6) |
| Tirads 4 | 3 (10.3) |
| Scintigraphy uptake | |
| Yes | 5 (11.9) |
| None | 37 (88.1) |
| Anti-thyroid peroxidase | |
| Positive | 9 (21.4) |
| Negative | 21(50) |
| Thyroid function test result | |
| Subclinical hyperthyroidism | 3 (7.1) |
| Overt hyperthyroidism | 3 (7.1) |
| Euthyroid | 36(85.7) |
| FNAC results | |
| Bethesda II | 12 (70.6) |
| Bethesda III | 4 (23.5) |
| Bethesda IV | 1 (5.9) |
| Final diagnosis | |
| Benign | 38 (90.5) |
| Malignant | 4 (9.5) |

standards. Thyroid nodules with higher uptake on [⁶⁸Ga]Ga-PSMA-11 PET/CT scans were subjected to ultrasound-guided fine needle aspiration (US-FNA), provided the nodule's longest diameter measured 10 mm on US. Biopsies were not performed on nodules less than 1 cm in size unless there were signs such as cervical lymphadenopathy or other abnormalities linked with a higher cancer risk [10]. A 23-gauge needle linked to a 5 mL disposable syringe was used to perform US-FNA on each thyroid nodule at least twice. Before performing FNAC, written consent was obtained from every patient. Thyroid cytopathologists assessed FNAC results in accordance with the Bethesda System for Thyroid Cytopathology [11].

Statistical analysis

The Shapiro–Wilk test was used to determine whether the collected data conformed to a normal distribution, which confirmed the normal distribution. For continuous data, summary statistics including the average and standard deviation were supplied, whilst categorical variables were illustrated using frequency and percentage figures. The Student's *T* Test was used to compare mean measures between benign and malignant patients. The chi-square test was used to assess associations between categorical variables in both benign and malignant groups. Furthermore, the instances' capacity to differentiate between benign and malignant occurrences was assessed by examining the receiver operating characteristic (ROC) curve. The statistical significance was determined using a *P* < 0.05 significance level.

Results

[⁶⁸Ga]Ga-PSMA-11 PET/CT was administered to a total of 769 patients. Thyroid was identified in the reports of 91 patients. The PTI analysis excluded patients who had established thyroid disease or malignancy, nodules that did not exhibit increased [⁶⁸Ga]Ga-PSMA-11 uptake, or involvement on repeated extractions. PTI was discovered in 67 patients (8%).

The study comprised 42 individuals having thyroid US conducted by an endocrinology specialist among 67 patients who had thyroid function tests such as TSH and fT4 analyzed in our center's Endocrinology department. Characteristics of patients with thyroid incidental findings on [⁶⁸Ga]Ga-PSMA-11 PET/CT are presented in Table 1.

All of the patients were male gender; the median age was 71 (50–82) with a mean of 69.7 (±8.4).

In six patients, the TSH test was suppressed. Three of them had subclinical hyperthyroidism, while the other three had overt hyperthyroidism.

Five patients who presented with hyperthyroidism underwent [^{99m}Tc]Tc-Perchnetate thyroid scintigraphy. With enhanced [⁶⁸Ga]Ga-PSMA-11 uptake, the nodule showed higher tracer uptake. The hyperactive nodules' mean SUVmax was 7.48(±5.51). The SUVmax of non-hyperactive nodules was 6.94(±3.88), with no significant difference (*P*:0.783) detected. One patient with hyperactive nodules refused scintigraphy. Thirty-six patients were hypothyroid.

Of the 42 patients who underwent thyroid US, 36 patients had focal (85.7%) and 6 patients had diffuse (14.3%) [⁶⁸Ga]Ga-PSMA-11 uptake.

Nodules were detected in 29 (80.5%) of 36 patients with focal uptake. Fine needle aspiration biopsy was performed

Table 2 Chart of comparison of means with SD of SUVmax between benign and malignant cases

| Final diagnosis | Count | SUVmax (mean \pm SD) | P^a |
|-----------------|-------|------------------------|-------|
| Benign | 38 | 6.47 \pm 2.68 | 0.007 |
| Malignant | 4 | 12.02 \pm 9.76 | |

SUVmax maximum standardized uptake value, SD standard deviation

^aIndependent T Test

in 17 (58%) of 29 patients. Patients who underwent FNA were 40.47% (17/42) of the patients included in the study. 6 patients had nodules less than 1 cm and 6 nodules were hyperactive, so there was no indication for FNAC. In the results of 17 patients who underwent FNAC, 1 (5.8%) nodule was benign (TIRADS 2), 13 (76.4%) were Low-Risk Category (TIRADS 3). 3 Nodules were Intermediate-Risk Category (17%) (TIRADS 4).

FNAC results were Bethesda II in 12 patients (70.5%), Bethesda III in 4 patients (23.5%) and Bethesda IV in 1 patient (5.8%).

Two patients underwent thyroid surgery due to nodule size of 42 mm and 35 mm, and Bethesda III, IV cytology scores, respectively, and the pathology result was reported as papillary thyroid carcinoma.

FNAC results of the other 2 patients with Bethesda III and 20 mm nodules were found to be Bethesda VI (thyroid papillary carcinoma) and these 2 patients refused surgery.

While the probability of benign FNAC (Bethesda II) was 100% in TIRADS category 2, it was 88.2% and 33.3% in other categories (TIRADS 3, 4) respectively and it was statistically significant ($p = 0.028$).

Of the 4 malignant patients (9.5%) in the study population, 2 were classified as TIRADS 3 and 2 were classified as TIRADS 4. The prevalence of malignancy as final diagnosis was 11.8% in EU-TIRADS 3 and 66.6% in EU-TIRADS 4.

The malignancy rate was (4/29) 13.7% in patients with focal [⁶⁸Ga]Ga-PSMA-11 PET/CT uptake confirmed by US. When the association between thyroid lesions-to-liver SUV ratio and variables was investigated, no significant findings were found. Therefore, it was not used in the evaluation. For this reason, only SUVmax was used in the evaluation. The SUVmax of patients with malignant final diagnosis was 12.02 \pm 9.76, while the SUVmax of patients with benign final diagnosis was 6.47 \pm 2.68 (Independent T Test $p = 0.007$) (Table 2). The discriminative power of SUVmax parameter on benign and malignant cases was analyzed by Receiver Operating Curve analysis. The success of the parameter in classification was statistically significant ($P = 0.044$). Area under the curve ROC = 0.734(0.575–0.858). The cut-off SUV max value was found to be 5.6 (100% sensitivity and 47.37% specificity). According to this model, individuals with SUVmax parameter values above 5.6 were classified as malignant (Fig. 1). PET/CT image example of one patient with incidental

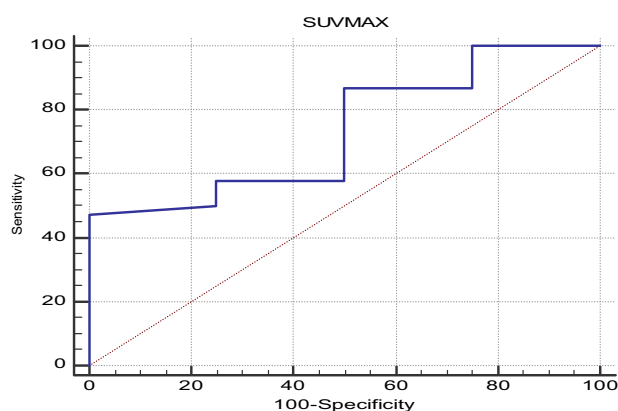


Fig. 1 SUVmax value ROC curve

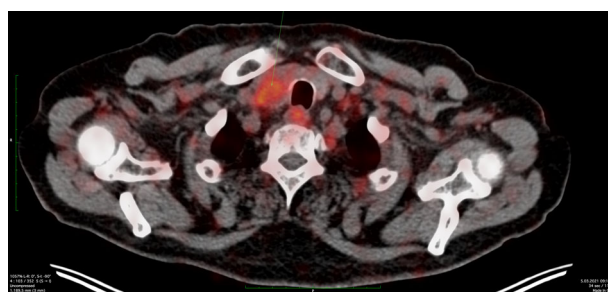


Fig. 2 Transaxial PET/CT fusion image of a malignant right thyroid incidentaloma in a 73-year-old man with SUVmax 5.8, biopsied to reveal a papillary carcinoma

thyroid uptake, with SUVmax 5.8 and his biopsy result, is provided in Fig. 2.

Discussion

Investigations in patients diagnosed with cancer usually aim to evaluate the patient's primary disease and the association of malignant or benign incidental lesions may be missed. The prevalence of concomitant primary neoplasms should not be underestimated.

Incidental thyroid focal uptake detected on 2- [¹⁸F] Fluoro-2-deoxy-D-glucose ([¹⁸F]FDG) PET/CT has been extensively studied in the literature [12–15].

PTIs were analyzed substantially less in the review, most likely due to the low utilization of [⁶⁸Ga]Ga-PSMA-11 PET/CT versus [¹⁸F]FDG PET/CT. However, because PSMA tracers are not totally selective for prostate cancer, other than PCa results are likely to become more common.

[¹⁸F]FDG TIs are commonly thought of as focally increased thyroid uptake. The frequency of FTI varied amongst investigations, ranging from 0.16 to 11.74% [15]. Cancer prevalence in [¹⁸F]FDG PET/CT has been shown to range between 20 and 40% among focal TIs [12, 14].

Approximately 30% [^{18}F]FDG TIs are malignant, with papillary thyroid cancer being the most common histologic subtype linked with malignant thyroid incidentalomas [12–14].

PSMA is not limited to prostate but is also expressed in some other malignancies such as breast, thyroid and lung [4]. This could be attributable to the fact that PSMA is prevalent in cancers that rely on angiogenesis and regulates the adhesion and invasion mechanisms of angiogenic endothelial cells [16].

Existing evidence suggests that thyroid cancer may exhibit PSMA activity, which could potentially facilitate the detection of the disease using PET/CT imaging [17]. This issue was addressed by a recent review in the literature [18].

Due to its presence not only in malignant tumors but also in the neovascularity of benign tumors, the focal thyroid uptake observed in [^{68}Ga]Ga-PSMA PET/CT scans could indicate either malignant or benign conditions [19]. Although PSMA is found primarily in the micro vessels of thyroid tumors, it is not expressed by normal thyroid cells or neoplastic cells, whether benign or well-differentiated malignant. The expression of PSMA in tumor capillaries was more pronounced in high-grade carcinomas compared to adenomas, with the most significant expression seen in thyroid cancer resistant to radioiodine treatment [20].

Similarly, a study described the immunohistochemical expression of PSMA in the neovascularity of various subtypes of thyroid cancer, especially those resistant to radioiodine in metastatic lesions [7]. Analyzing patients with metastatic differentiated thyroid cancer (DTC), [^{68}Ga]Ga-PSMA PET/CT identified 93.75% of the total lesions. [^{68}Ga]Ga-PSMA PET/CT is a valuable imaging modality that can be employed to detect metastasized DTC. Additionally, it could be crucial in the identification of patients who are untreated and could potentially benefit from PSMA-targeted radionuclide therapy [20].

PTI was identified in 0.9, 8, and 0.8% of patients undergoing [^{68}Ga]Ga-PSMA-11, [^{18}F]PSMA-1007, and [^{18}F]DCFPyL PET/CT, respectively [21].

Thyroid uptake occurred incidentally in 4% of patients undergoing [^{68}Ga]Ga-PSMA-11 PET/CT in the Gossili study. 15% of patients who presented with PSMA avid thyroid incidentaloma had malignancy detected [6].

In a meta-analysis using PSMA-targeting radiopharmaceuticals, the prevalence of TI in patients undergoing PET/CT was low (1.3%) but the risk of malignancy was significant, ranging from 3 to 19% in focal incidentalomas. Of the 96 incidentalomas, 6 were malignant. Five of the six malignant cases had a focal pattern, including three primary thyroid tumors and two metastatic renal carcinomas [17].

In our study, the prevalence of PTI was 8.7%, which was higher than in other PSMA studies, but similar to [^{18}F]FDG

PET/CT and the rate of focal involvement was higher than diffuse. Of the total patients in the study population, 9.5% were malignant with focal involvement and the rate of malignancy confirmed by US nodules was 13.7%.

The thyroid gland is often not taken into account in the explanation of the physiologic distribution of PSMA PET tracers and, accordingly, increased thyroid uptake may not always be evident. This may be because it is assumed to be clinically insignificant in PCa staging. The reason why the incidence of PTI varies widely between different PSMA PET tracers is mostly due to the method of analysis used. All of these may have led to different PTI reporting rates in the literature and possibly resulted in a low estimation of PTI incidence. For [^{68}Ga]Ga-PSMA-11PET/CT, the incidence of PTI ranged from 7 to 23% according to different analysis methods [22].

There is no study that determines a threshold value for SUV parameters, as with [^{18}F]FDG PET/CT, to guide with the early analysis of PTI during [^{68}Ga]Ga-PSMA-11PET/CT interpretation and reporting. Only one study displays the variance in SUVmax values between malignant and benign PTI in [^{68}Ga]Ga-PSMA-11PET/CT scans. The SUVmax was notably elevated in individuals with malignant findings (median SUVmax 9.2) in comparison to those with benign conditions (median SUVmax 5.2), revealing a statistically significant difference ($P = 0.039$). Even in cases with only focal lesions, a notable discrepancy in SUVmax between patients with and without cancer was observed, despite the study's limited participant count ($n = 7$, $P = 0.048$). As anticipated, benign PTIs exhibited a lower SUVmax [6]. Another study reported that the uptake value was higher in benign lesions [23]. Some of the mentioned studies are shown comparatively in Table 3.

However, PSMA expression in the neovascularity of differentiated thyroid cancer was shown to be significantly lower than in undifferentiated thyroid cancer [7].

Studies on FDG PET/CT have generally reported a lower SUVmax in benign nodules than in thyroid malignancies. Kang et al. reported that the mean SUVmax of benign nodules (6.5 ± 3.8) was significantly lower than that of malignant nodules (16.5 ± 4.7) and the cut-off value of SUVmax was 4.2 [24].

In another study with [^{18}F]FDG PET/CT, significantly higher SUV max was present in malignant lesions compared to benign lesions ($P = 0.013$). And similar to our study, in ROC curve analysis the cut-off value for SUVmax for differentiating malignant nodules from benign nodules was 5.3 (82% sensitivity, 65% specificity) [25].

Although the vast majority of [^{18}F]FDG PET/CT TIs are benign, the malignancy incidence cannot be ignored. As there is a dearth of conclusive evidence regarding the most effective management approach for TI, current guidelines endorse the utilization of fine needle aspiration cytology.

Table 3 Characteristics of thyroid incidentalomas in some studies

| Findings | Authors | | | |
|---------------------------|-------------------------------|-------------------------------|--|---------------------------------|
| | Our study | Gossili et al. [6] | Piek et al. [21] | Osman et al. [23] |
| SUVmax benign | 6.47 ± 2.68 | 5.2 ± 0.7 SD | – | 6.3 |
| SUVmax malignant | 12.02 ± 9.76 | 9.2 ± 0.9 SD | – | 1.9 |
| Cut-off SUVmax | 5.6 | – | – | – |
| Final diagnosis malignant | 4 | 2 | 3 | 1 |
| Total patients | 769 | 341 | 5434 | 764 |
| No. of TI | 67/769(%8) | 13/341(%4) | 61/5434(%1.1) | 6/764(%0.9) |
| Analyzed patient | 42 | 13 | 43 | – |
| Radiotracer | [⁶⁸ Ga]Ga-PSMA-11 | [⁶⁸ Ga]Ga-PSMA-11 | [¹⁸ F]F-DCFPyL [¹⁸ F]F-PSMA-1007 [⁶⁸ Ga]Ga-PSMA-11 | [⁶⁸ Ga]Ga-PSMA-HBED |
| FNAC | 17 | 7 | 22 | 2 |
| Focal pattern | 36 | 7 | 43 | – |
| Diffuse pattern | 6 | 5 | 18 | – |
| Mixed pattern | – | 1 | – | – |
| Ultrasound | 42 | 7 | 25 | – |

Suvmax maximum standardized uptake value, *SD* standard deviation, *FNAC* fine needle aspiration cytology

According to ultrasound findings, the occurrence of cancer was recorded at 0% in cases classified as EU-TIRADS 2, 2.9% in EU-TIRADS 3, 4.2% in EU-TIRADS 4, and remarkably high at 78.6% in EU-TIRADS 5. The EU-TIRADS system displays notable accuracy in distinguishing high-risk malignancies from lower-risk lesions in TIs observed through [¹⁸F]FDG PET/CT, adopting a cautious clinical approach. Moreover, establishing a center-specific threshold for SUV parameters is recommended to facilitate the initial assessment of these lesions during PET/CT interpretation and reporting [26].

In the assessment of patients having nodules categorized as EU-TIRADS 4 and EU-TIRADS 5, the research found cancer rates to be 16.7 and 60%, respectively. Incorporating [¹⁸F]FDG PET/CT alongside intermediate ultrasound evaluation could play a role in assessing the cancer likelihood of thyroid nodules. To be more precise, the study concluded that thyroid lesions falling under the EU-TIRADS 4 classification, but exhibiting no [¹⁸F]FDG uptakes, could potentially be excluded from further investigations [27].

In the study utilizing [¹⁸F]FDG PET/CT, an optimal threshold SUV value of 4.1 was determined. The malignancy rates for different TIRADS categories were as follows: 9% for category 3, 15% for category 4a, 39% for category 4b, 72% for category 4c, and 100% for category 5. These findings indicate an escalating risk of malignancy with higher TIRADS category assignments. Notably, TIRADS category 3 exhibited a malignancy rate of 9%, highlighting a clinically relevant malignancy risk even in thyroid incidentalomas lacking suspicious ultrasound characteristics. Consequently, it is advisable to conduct thyroid

imaging and aspiration biopsy for thyroid incidentalomas detected through [¹⁸F]FDG PET/CT if there is evident [¹⁸F]FDG uptake, irrespective of the absence of suspicious ultrasound features that might suggest mandatory US-FNA [28].

As far as we know, there are few studies on [⁶⁸Ga]Ga-PSMA-11PET/CT. In 10 cases (10/25), PSMA avid thyroid nodules greater than 10 mm were additionally visualized by ultrasound. In one study, the FNAC Bethesda II was 100% in TIRADS category 2 and 66.7, 33.3 and 57.1% in the other categories (TIRADS 3, 4, 5), respectively. For TIRADS 3, 4 and 5, the rate of malignant FNAC (Bethesda VI) was 0, 16.7 and 0%, respectively [21].

In our study, among 17 biopsied patients, 1 (5.8%) nodule was benign (TIRADS 2) and 13 (76.4%) were probably benign (TIRADS 3), 3 nodules were indeterminate for malignancy (17%) (TIRADS 4).

Of the patients who underwent biopsy, 12 were Bethesda II (70.5%), 4 (23.5%) were Bethesda III and 1 (5.8%) was Bethesda IV. The probability of benign FNAC (Bethesda II) was 100% in TIRADS category 2 and 88.2 and 33.3% in other categories (TIRADS 3, 4), respectively. The prevalence of malignancy as final diagnosis was 11.8% in EU-TIRADS 3 and 66.6% in EU-TIRADS 4.

We believe that the SUVmax value cut off we found in our study is important. These findings suggest that nodules with [⁶⁸Ga]Ga-PSMA-11 uptake require further investigation. Similar to our study each center should establish its own a possible SUVmax cut-off over which a malignant lesion should be suspected. Specifically, when a patient has a long-life expectancy and there is a focal thyroid

incidentaloma with a high SUVmax (>5.6), a pathological diagnosis should be made either by histology or by cytology testing.

This study has some limitations. The first is its retrospective design. Another constraint pertains to the fact that [⁶⁸Ga]Ga-PSMA-11PET/CT scans were predominantly conducted on male patients with prostate cancer, which hinders the applicability of the findings to a broader clinical context. Considering the higher incidence of thyroid cancer in women, the potential for thyroid incidentalomas to yield malignant outcomes might have been limited in our study. Additionally, the availability of a definitive histologic diagnosis was restricted to only a small subset of patients due to the limited number who underwent thyroid surgery.

As a result, the risk of malignancy in focal PSMA-avid thyroid lesions is not negligible. The importance of further investigation of incidental [⁶⁸Ga]Ga-PSMA-11 uptake to clarify the nature of PTIs and not to overlook a malignant tumor in particular has been confirmed. [⁶⁸Ga]Ga-PSMA-11 uptake in the thyroid nodule should be considered, as PSMA may be a new therapeutic target for the treatment of metastatic and RAI resistance thyroid cancers.

Additional research with a substantial sample size is necessary to elucidate the genuine clinical implications of PTIs, their characteristics, significance in clinical contexts, and the potential contribution of radioactively labeled [⁶⁸Ga]Ga-PSMA-11PET/CT in the diagnostic pathway for thyroid cancer.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by İ.Ç.K., P.P.Ö., Z.P.K., and E.A. The first draft of the manuscript was written by İ.Ç.K., M.S. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethics approval and consent to participate The study was conducted in accordance with the Declaration of Helsinki. Patients gave informed consent to these investigations (as part of their normal medical care both at diagnosis and follow-up). The study was approved by the ethics committee of our institution (Decision date: 09.11.2022 No: 2022/744).

References

1. M. Perera, N. Papa, M. Roberts et al. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. *Eur. Urol.* **77**, 403–417 (2020). <https://doi.org/10.1016/j.eururo.2019.01.049>
2. R.G. Lapidus, C.W. Tiffany, J.T. Isaacs, B.S. Slusher., Prostate-specific membrane antigen (PSMA) enzyme activity is elevated in prostate cancer cells. *Prostate.* **45**, 350–354 (2000). [https://doi.org/10.1002/1097-0045\(20001201\)45:4<350::aid-pros10>3.0.co;2-u](https://doi.org/10.1002/1097-0045(20001201)45:4<350::aid-pros10>3.0.co;2-u)
3. A. Rizzo, S. Dall'Armellina, D.A. Pizzuto et al. PSMA Radioligand Uptake as a Biomarker of Neoangiogenesis in Solid Tumours: Diagnostic or Theragnostic Factor? *Cancers* **14**, 4039 (2022). <https://doi.org/10.3390/cancers14164039>
4. D. Malik, A. Sood, B.R. Mittal et al. Nonspecific Uptake of ⁶⁸Ga-Prostate-Specific Membrane Antigen in Diseases other than Prostate Malignancy on Positron Emission Tomography/Computed Tomography Imaging: A Pictorial Assay and Review of Literature. *Indian J. Nucl. Med.* **33**, 317–325 (2018). https://doi.org/10.4103/ijnm.IJNM_81_18
5. F. Bertagna, D. Albano, L. Giovanella et al. ⁶⁸Ga-PSMA PET thyroid incidentalomas. *Hormones* **18**, 145–149 (2019). <https://doi.org/10.1007/s42000-019-00106-8>
6. F. Gossili, L.J. Petersen, H.D. Zacho, The frequency of thyroid incidental findings and risk of malignancy detected by ⁶⁸Ga-labeled prostate-specific membrane antigen PET/CT in prostate cancer. *Hell J. Nucl. Med.* **23**, 240–245 (2020). <https://doi.org/10.1967/s002449912202>
7. M. Moore, S. Panjwani, R. Mathew et al. Well-Differentiated Thyroid Cancer Neovasculature Expresses Prostate-Specific Membrane Antigen-a Possible Novel Therapeutic Target. *Endocr. Pathol.* **28**, 339–344 (2017). <https://doi.org/10.1007/s12022-017-9500-9>
8. F. Ceci, D.E. Oprea-Lager, L. Emmett et al. E-PSMA: the EANM standardized reporting guidelines v1.0 for PSMA-PET. *Eur. J. Nucl. Med. Mol. Imaging* **48**, 1626–1638 (2021). <https://doi.org/10.1007/s00259-021-05245-y>
9. G. Russ, S.J. Bonnema, M.F. Erdogan, C. Durante, R. Ngu, L. Leenhardt, European Thyroid Association Guidelines for Ultrasound Malignancy Risk Stratification of Thyroid Nodules in Adults: The EU-TIRADS. *Eur. Thyroid J.* **6**, 225–237 (2017). <https://doi.org/10.1159/000478927>
10. B.R. Haugen, E.K. Alexander, K.C. Bible et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* **26**, 1–133 (2016). <https://doi.org/10.1089/thy.2015.0020>
11. K. Kaliszewski, D. Diakowska, B. Wojtczak, Z. Forkasiewicz, Evaluation of selected ultrasound features of thyroid nodules with atypia of undetermined significance/follicular lesion of undetermined significance for the Bethesda reporting system for thyroid cytology. *Cancer Manag. Res.* **10**, 2223–2229 (2018). <https://doi.org/10.2147/CMAR.S168409>
12. G. Treglia, F. Bertagna, R. Sadeghi, F.A. Verburg, L. Ceriani, L. Giovanella, Focal thyroid incidental uptake detected by ¹⁸F-fluorodeoxyglucose positron emission tomography. Meta-analysis on prevalence and malignancy risk. *Nuklearmedizin* **52**, 130–136 (2013). <https://doi.org/10.3413/Nukmed-0568-13-03>
13. F. Bertagna, G. Treglia, A. Piccardo et al. F18-FDG-PET/CT thyroid incidentalomas: a wide retrospective analysis in three Italian centres on the significance of focal uptake and SUV value. *Endocrine* **43**, 678–685 (2013). <https://doi.org/10.1007/s12020-012-9837-2>
14. F. Bertagna, G. Treglia, A. Piccardo, R. Giubbini, Diagnostic and clinical significance of F-18-FDG-PET/CT thyroid incidentalomas. *J. Clin. Endocrinol. Metab.* **97**, 3866–3875 (2012). <https://doi.org/10.1210/jc.2012-2390>
15. J.F. de Leijer, M.J.H. Metman, A. van der Hoorn et al. Focal Thyroid Incidentalomas on ¹⁸F-FDG PET/CT: A Systematic Review and Meta-Analysis on Prevalence, Risk of Malignancy

- and Inconclusive Fine Needle Aspiration. *Front. Endocrinol.* **12**, 723394 (2021). <https://doi.org/10.3389/fendo.2021.723394>
16. R.E. Conway, N. Petrovic, Z. Li, W. Heston, D. Wu, L.H. Shapiro, Prostate-specific membrane antigen regulates angiogenesis by modulating integrin signal transduction. *Mol. Cell Biol.* **26**, 5310–5324 (2006). <https://doi.org/10.1128/MCB.00084-06>
 17. K.K.S. Godê, F.A. Mourato, A.F.F. Sales et al. Thyroid incidentalomas in PSMA PET/CT: a systematic review and meta-analysis. *Clin. Transl. Imaging* **11**, 263–269 (2023). <https://doi.org/10.1007/s40336-022-00537-1>
 18. A. Rizzo, M. Racca, S. Dall'Armellina et al. Potential Role of PSMA-Targeted PET in Thyroid Malignant Disease: A Systematic Review. *Diagnostics* **13**, 564 (2023). <https://doi.org/10.3390/diagnostics13030564>
 19. A. Bychkov, U. Vutrapongwatana, S. Tepmongkol, S. Keelawat, PSMA expression by microvasculature of thyroid tumors - Potential implications for PSMA theranostics. *Sci. Rep.* **7**, 5202 (2017). <https://doi.org/10.1038/s41598-017-05481-z>
 20. P. Verma, G. Malhotra, R. Agrawal, S. Sonavane, V. Meshram, R.V. Asopa, Evidence of Prostate-Specific Membrane Antigen Expression in Metastatic Differentiated Thyroid Cancer Using 68Ga-PSMA-HBED-CC PET/CT. *Clin. Nucl. Med.* **43**(8), e265–e268 (2018). <https://doi.org/10.1097/RLU.0000000000002161>
 21. M.W. Piek, L.H. de Vries, M.L. Donswijk et al. Retrospective analysis of PSMA PET/CT thyroid incidental uptake in adults: incidence, diagnosis, and treatment/outcome in a tertiary cancer referral center and University Medical Center. *Eur. J. Nucl. Med. Mol. Imaging* **49**(7), 2392–2400 (2022). <https://doi.org/10.1007/s00259-022-05679-y>
 22. M.L. Donswijk, M.W. Piek, Z. Cheung et al. Incidence of PSMA PET thyroid incidentaloma depends on analysis method and tracer. *Eur. Radiol.* **33**, 3377–3385 (2023). <https://doi.org/10.1007/s00330-023-09492-5>
 23. M.M. Osman, A. Iravani, R.J. Hicks, M.S. Hofman, Detection of Synchronous Primary Malignancies with 68Ga-Labeled Prostate-Specific Membrane Antigen PET/CT in Patients with Prostate Cancer: Frequency in 764 Patients. *J. Nucl. Med.* **58**, 1938–1942 (2017). <https://doi.org/10.2967/jnumed.117.190215>
 24. K.W. Kang, S.K. Kim, H.S. Kang et al. Prevalence and risk of cancer of focal thyroid incidentaloma identified by 18F-fluorodeoxyglucose positron emission tomography for metastasis evaluation and cancer screening in healthy subjects. *J. Clin. Endocrinol. Metab.* **88**, 4100–4104 (2003). <https://doi.org/10.1210/jc.2003-030465>
 25. Ö. Demir, N. Köse, E. Özkan, U. Ünlütürk, G. Aras, M.F. Erdoğan, Clinical significance of thyroid incidentalomas identified by 18F-FDG PET/CT: correlation of ultrasonography findings with cytology results. *Nucl. Med. Commun.* **37**, 715–720 (2016). <https://doi.org/10.1097/MNM.0000000000000495>
 26. P. Trimboli, G. Paone, G. Treglia et al. Fine-needle aspiration in all thyroid incidentalomas at ¹⁸F-FDG PET/CT: Can EU-TIRADS revise the dogma? *Clin. Endocrinol.* **89**, 642–648 (2018). <https://doi.org/10.1111/cen.13819>
 27. P. Trimboli, A. Piccardo, M. Alevizaki et al. Dedicated neck ¹⁸F-FDG PET/CT: An additional tool for risk assessment in thyroid nodules at ultrasound intermediate risk. *Clin. Endocrinol.* **90**, 737–743 (2019). <https://doi.org/10.1111/cen.13949>
 28. S.R. Chung, Y.J. Choi, C.H. Suh et al. Thyroid Incidentalomas Detected on ¹⁸F-Fluorodeoxyglucose Positron Emission Tomography with Computed Tomography: Malignant Risk Stratification and Management Plan. *Thyroid* **28**, 762–768 (2018). <https://doi.org/10.1089/thy.2017.0560>

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