

The frequency of thyroid incidental findings and risk of malignancy detected by ⁶⁸Ga-labeled prostate-specific membrane antigen PET/CT in prostate cancer

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Abstract

Objective: Gallium-68-prostate-specific membrane antigen positron emission tomography/computed tomography (⁶⁸Ga-PSMA PET/CT) has become a well-established imaging method for the evaluation of patients with prostate cancer. However, several cases have revealed PSMA uptake in a large variety of conditions other than prostate cancer. Prostate-specific membrane antigen uptake in thyroid cancer has also been reported. The aim of the present study was to systematically investigate the prevalence and clinical significance of thyroid incidental findings in patients undergoing ⁶⁸Ga-PSMA PET/CT. **Materials and Methods:** We retrospectively identified all patients referred for ⁶⁸Ga-PSMA PET/CT at the Department of Nuclear Medicine, Aalborg University Hospital, Denmark between May 2015 and May 2019. Patients with increased PSMA uptake in the thyroid gland were included in the analysis. Follow-up included imaging, biochemical, and/or histopathological collected over six months. **Results:** A total of 341 patients were included. Increased ⁶⁸Ga-PSMA uptake in the thyroid gland was observed in 13 patients (4%). Focal uptake was observed in seven patients, diffuse uptake in five patients and mixed focal and diffuse uptake in one patient. Malignancy was verified in two patients (2/13 patients, 15%), both patients with focal PSMA uptake. **Conclusion:** Gallium-68-PSMA thyroid incidental findings are rare in prostate cancer patients. However, cases of focal PSMA uptake in the thyroid gland should be further investigated, as these findings may represent metastatic or primary malignancy of the thyroid gland.

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Introduction

Gallium-68 (⁶⁸Ga) prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) is increasingly used for the localization of biochemical recurrence in prostate cancer (PCa) as well as the primary staging of high-risk PCa due to premium diagnostic characteristics [1, 2]. It is recommended by the European Association of Urology guidelines for patients with biochemical recurrence of PCa [3]. Despite the term “prostate-specific”, ⁶⁸Ga-PSMA uptake has been shown in numerous cancers other than PCa, including but not limited to thyroid, gastric, colon, breast, lung, adrenal, renal, and urothelial cell cancer. Expression of PSMA has also been shown in various benign conditions [4]. Some case reports have described ⁶⁸Ga-PSMA-positive thyroid lesions, including adenoma and carcinoma, as recently reviewed [5]. Additionally, a large series of consecutive patients reported the proportion of thyroid cancer as well as benign findings [6–8], but no study so far has reported the prevalence of incidental thyroid diffuse and focal uptake or the clinical significance. The aim of the present study was to systematically investigate the prevalence and clinical significance of any type (focal or diffuse) of thyroid incidental findings in patients undergoing ⁶⁸Ga-PSMA PET/CT stratified by pattern of uptake (focal or diffuse incidental ⁶⁸Ga-PSMA uptake).

Material and Methods

Patients

Consecutive patients who underwent ⁶⁸Ga-PSMA PET/CT at a single center between May 2015 and May 2019 were reviewed for the increased uptake of PSMA in the thyroid gland.

If a patient had more than one PSMA PET/CT scan, only the first PET/CT scan with incidental thyroid uptake was included in the analysis.

PSMA PET/CT

Prostate-specific membrane antigen PET/CT was performed with the ^{68}Ga -PSMA-11 ligand as described in detail previously [9-12]. The PSMA PET/CT scans were evaluated on a Syngo Via workstation (Siemens Healthineers GmbH, Erlangen/Germany). Incidental uptake was defined as any visual uptake (focal, diffuse or mixed) in the thyroid gland above the average thyroid PSMA uptake. The maximum standardized uptake value (SUVmax) was measured in patients with visual PSMA uptake in the thyroid.

Follow-up

Follow-up was defined as any imaging, biochemical, and/or histopathological examinations performed within six months from the incidental PET finding. For the patients without any formalized follow-up, as well as the patients with a benign diagnosis obtained in the follow-up period, additional workup was performed. The unique Danish personal identifier system allowed tracking of medical information, irrespective of site of contact. The regional pathology file system was reviewed for any thyroid investigations. For patients with no malignant findings in the thyroid by cytology and/or histology at the time of follow-up (November 2020), the incidental findings on the PSMA PET was categorized as benign.

Statistical analysis

Descriptive statistics included the calculation of frequencies/proportions for categorical data, whereas quantitative values were expressed as medians and ranges. The SUVmax values in patients with malignant and benign findings were compared using a Mann-Whitney test, an unpaired, nonparametric analysis (GraphPad Prism version 9.0, GraphPad Prism Software, San Diego/USA).

Approval

This quality assessment study was approved by the Danish National Data Protection Agency, who provided a waiver for patient informed consent to access the patient files. According to national legislation, retrospective studies do not require approval from the ethical committee.

Results

Patients

Three hundred forty-one patients underwent 356 ^{68}Ga -PSMA PET/CT scans. The indications for the 356 scans were primary staging ($n=181$, 51%), biochemical recurrence ($n=148$, 41%) and miscellaneous, e.g., assessment of the response to anticancer treatment ($n=27$, 8%). Gallium-68-PSMA avid lesions in the thyroid gland were observed in 13 of the 341 patients (4%), who had a mean age of 70 years (range 48-77 years). Prostate-specific membrane antigen uptake was

categorized as focal in seven patients, diffuse in five patients and mixed in one patient (Table 1). The median SUVmax was 5.0 (range 4.8 to 9.8) in patients with focal PSMA-avid lesions and 6.1 (range 2.6 and 9.3) in patients with diffuse PSMA uptake in the thyroid.

Follow-up and findings

The majority of the patients (9 of 13 patients, 69%) underwent follow-up (Table 1). Generally, the follow-up was more comprehensive in patients with focal than diffuse lesions. Ultrasound with fine-needle aspiration (FNA) was the most frequently used follow-up modality. Cytopathology showed malignant findings in two patients and indeterminate findings in one patient among patients with focal PSMA uptake. Fine-needle aspiration findings were benign in four patients. Five patients underwent surgery (hemithyroidectomy), which showed cancer in two patients and benign findings in another three patients. Thus, the malignancy rate in the entire population was 15% (2/13 patients), it was 29% (2/7 patients) among patients with solitary focal lesions, and 22% among patients with follow-up. No malignancy was detected in the patients with diffuse ^{68}Ga -PSMA uptake in the thyroid gland: one patient had malignancy ruled out by cytology; the others had no signs of thyroid disease during follow-up.

Overall, eleven patients were diagnosed with a benign condition. Seven patients had follow-up for six months without being diagnosed with a thyroid malignancy during that period. In addition, four patients did not have any follow-up within 6 months according to our definition. Additional workup did not show any pathology evidence of thyroid malignancy 18 to 50 months after the ^{68}Ga -PSMA PET/CT. Among the seven patients with follow-up, no cancer was diagnosed on average for 34 months (range 22-50 months), the four patients with no follow-up were followed for 23 months (range 18-28) to validly exclude thyroid malignancies.

The SUVmax was significantly higher in patients with malignant findings (median SUVmax 9.2, two patients) than in patients with benign conditions (median SUVmax 5.2, 11 patients) ($P=0.039$). Among patients with focal lesions only, the significant difference in SUVmax in patients with or without cancer was confirmed despite the limited number of patients ($n=7$, $P=0.048$).

Pathology

Malignancy was confirmed in two patients; one patient had papillary thyroid cancer (Figure 1). Metastases were detected in 17 of 22 surgically removed lymph nodes, the largest of which was 6mm in diameter. Gallium-68-PSMA PET/CT showed a lesion in the thyroid but no increased PSMA uptake in any lymph nodes.

The other patient had thyroid metastases from clear-cell-type renal cell carcinoma (RCC). The patient was diagnosed with RCC in 2006 and had been followed for more than 10 years without any signs of recurrence. Gallium-68-PSMA PET/CT, which was performed due to the biochemical recurrence of PCa, showed increased PSMA uptake in the left thyroid lobe. The patients also showed PSMA uptake in a pathology-verified RCC lymph node in the retroperitoneum, located at the site of prior nephrectomy, as well as in the pelvis (PCa

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

Patient no.	Pattern of PSMA uptake	Age (years)	SUVmax	TSH level	Thyroid scintigraphy	Ultra-sound	FNA (cytology)	Pathology (histology)	Final Diagnosis
1	Focal	74	5.0	Elevated	-	Indeterminate	Indeterminate	Benign	Benign
2	Focal	74	9.8	-	-	Malignant	Malignant	Metastases from renal cell carcinoma	Malignant
3	Focal	52	8.7	Normal	-	Malignant	Malignant	Papillary thyroid carcinoma	Malignant
4	Focal	73	5.0	Normal	-	Benign	Benign	Benign	Benign
5	Focal	62	7.0	Low	Hot nodule	-	-	-	Benign
6	Focal	68	4.8	Normal	-	Benign	Benign	-	Benign
7	Focal	72	5.0	-	-	-	-	-	Benign
8	Diffuse	73	2.6	Normal	-	Benign	Benign	-	Benign
9	Diffuse	48	7.8	Normal	-	-	-	-	Benign
10	Diffuse	65	5.8	-	-	-	-	-	Benign
11	Diffuse	72	5.2	-	-	-	-	-	Benign
12	Diffuse	62	6.6	-	-	-	-	-	Benign
13	Mixed (Diffuse + Focal)	77	5.2 + 9.6	Normal	Cold nodule	Indeterminate	Benign	Benign	Benign

⁶⁸Ga PSMA PET/CT: Gallium-68 prostate-specific membrane antigen (PSMA)-based positron emission tomography/computed tomography (PET/CT); FNA: fine-needle aspiration; SUVmax: maximum standardized uptake value; TSH: thyroid-stimulating hormone; '-' means not conducted

cancer recurrence). This case was presented in detail previously [13].

An example of a PSMA-avid thyroid lesion with benign pathology is shown in Figure 2. This patient presented with a PSMA-avid mixed lesion. Ultrasound and FNA results indicated the absence of cancer, but thyroid scintigraphy showed a cold nodule. The patient underwent hemithyroidectomy, which showed benign pathology.

Discussion

Gallium-68-PSMA PET/CT has gained much clinical attention in recent years. Since PSMA tracers are not entirely specific for PCa, non-PCa findings will likely occur with increasing numbers along with increasing utility. Incidental PSMA-avid lesions

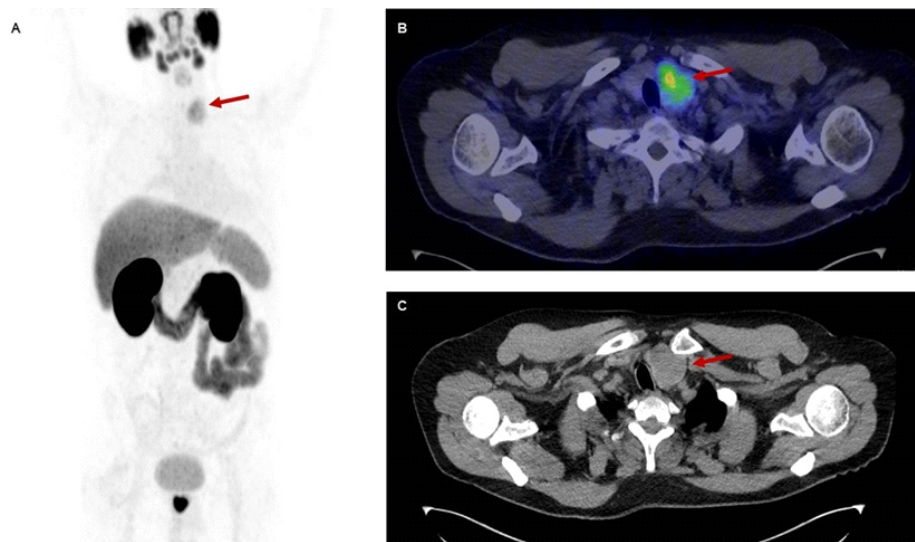


Figure 1. A 52-year-old man underwent a ^{68}Ga -PSMA PET/CT scan for staging of a high-risk cancer. Maximum-intensity projection (A) and fused axial PET/CT (B) showed an incidental finding in the left thyroid lobe (arrows) with increased ^{68}Ga -PSMA uptake (SUVmax 8.7) and no evidence of PSMA-positive lymph nodes. Computed tomography (C) showed left-sided enlargement of the thyroid. The patient underwent total thyroidectomy, and the diagnosis of papillary thyroid cancer was confirmed. Total thyroidectomy found metastasis of the right thyroid lobe as well as cervical lymph node level 6 (T3aN1aM0).

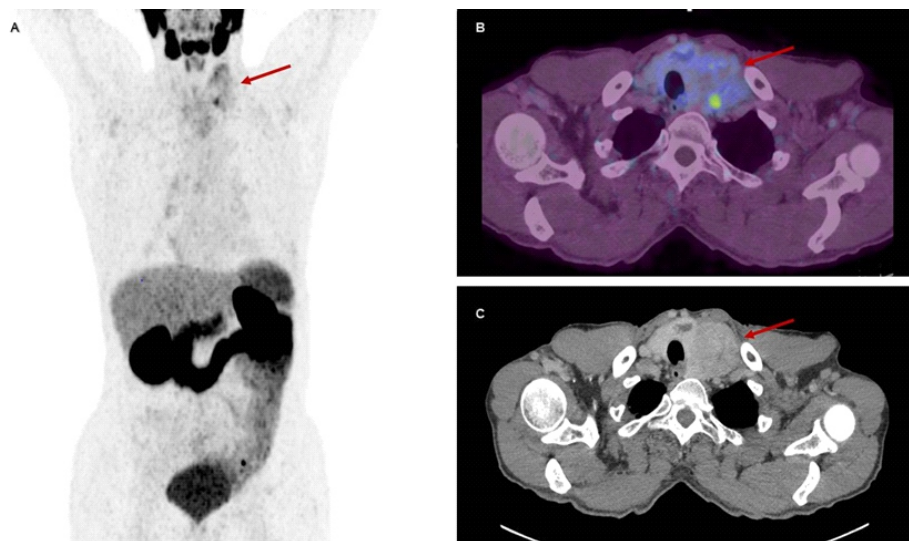


Figure 2. A 77-year-old man with biochemical recurrence of prostate cancer and incidental mixed (focal and diffuse) thyroidal uptake of PSMA. Maximum-intensity projection of ^{68}Ga -PSMA PET/CT (A) and fused axial PET/CT (B) and CT (C) showed focal PSMA uptake posteriorly and mild-moderate PSMA uptake in the rest of the left thyroid lobe (arrows). The patient underwent left-sided thyroidectomy. Histopathology showed a nodular goiter.

in the thyroid have been reported sporadically. To the best of our knowledge, this is the first study to systematically report the prevalence and clinical importance of unexpected PSMA-avid thyroid lesions. We found any incidental PSMA-avid thyroid lesions in 4% of consecutive patients. Cancer was confirmed in 15% of the patients with any incidental PSMA-avid thyroid lesion.

Gallium-68-PSMA PET/CT has premium diagnostic characteristics in PCa, as shown with biochemical recurrence [1] as well as primary staging [2]. However, PSMA is not explicitly localized in PCa since it may also be expressed in the neovasculature in some cancers, such as RCC, colon cancer, neuroendocrine tumors, melanoma, and breast cancer [14, 15]. A

number of benign conditions have also been associated with PSMA avidity [4, 16].

Incidental findings can be detected with different imaging modalities, such as neck ultrasonography, CT, magnetic resonance imaging and PET/CT, and in many organs, such as the adrenal gland, colon, and thyroid gland [17]. The thyroid is a common site of incidental findings [18, 19]. Several studies have reported the prevalence and the malignancy risk of incidental thyroid findings by PET/CT with fluorine-18-fluorodeoxyglucose (^{18}F -FDG) [20, 21], carbon-11/fluorine-18 choline [22] and, recently, ^{68}Ga -PSMA PET/CT as summarized in a systematic review [5]. To date, ^{68}Ga -PSMA-11 uptake in the thyroid has been shown to be due to primary benign or malignant

thyroid conditions as well as sporadic cases of metastatic spread from other cancers, e.g., prostate cancer [23, 24]. Some studies have described the proportion of incidental thyroid nodules on the PET and/or CT part of ^{68}Ga -PSMA PET/CT but without differentiation of diffuse or focal PSMA uptake patterns, frequencies of malignancy, and/or established follow-up criteria in order to declare malignant versus benign findings [6-8].

We analyzed a consecutive sample of prostate cancer patients referred for ^{68}Ga -PSMA imaging, primarily for biochemical recurrence or primary staging. The proportion of incidental thyroid ^{68}Ga -PSMA uptake findings in our study corresponded well with the data from ^{18}F -FDG PET/CT studies [20, 21, 25, 26]. Keidar et al. (2018) reported thyroid nodules in 9% of studies, of which two-thirds had focal uptake; no final assessment of malignancy was reported [7]. The present malignancy rate for incidental PSMA-avid thyroid lesions is also in line with the malignancy rates for incidental ^{18}F -FDG-avid lesions [26].

The follow-up rate was high in patients with focal lesions compared to diffuse or mixed lesions. Lack of follow-up for incidental thyroid lesions found by PET/CT is not uncommon. Trials with ^{18}F -FDG uptake in the thyroid have shown a median follow-up rate of 48% among patients with focal ^{18}F -FDG-avid thyroid lesions, ranging from 11% to 100% [20, 21, 25, 26]. We found cancer among 29% of all patients with a focal PSMA-avid thyroid lesion, cancer among 40% of patients undergoing any imaging and/or pathology follow-up, and cancer in 50% of patients with a pathology assessment. These data were in line with the summary data from 23 patients with PSMA-avid thyroid lesions, showing cancer in 26% of the patients with focal uptake [5]. Corresponding data with ^{18}F -FDG-avid focal lesions showed that the malignancy rate increased from 14% among all patients to 32% among patients with any follow-up and 50% among patients with a final pathology assessment [26]. We concluded that the frequency and malignancy rates of PSMA and ^{18}F -FDG appeared quite similar despite the different populations and modes of action of the tracers.

Despite the limited number of patients with confirmed malignancy in our series, the SUVmax was significantly higher in patients with malignant versus benign findings. This was true for the entire cohort as well as for the subset of patients with focal lesions. In parallel, SUVmax values are generally higher in malignant than in benign focal ^{18}F -FDG-avid thyroid nodules [27-29].

We identified one case of papillary thyroid carcinoma showing a PSMA-avid lesion corresponding to the affected thyroid lobe. Uptake of PSMA has been observed in follicular, papillary and medullary thyroid cancers, and some authors have raised the question of using ^{68}Ga -PSMA PET/CT in the management of thyroid cancer [30-32]. Lutetium-177 PSMA targeted therapy for thyroid cancer has recently been presented [33]. However, the observation that numerous lymph node metastases in patients with thyroid cancer were not seen on ^{68}Ga -PSMA PET/CT raised the question of the importance of the theranostic use of PSMA in thyroid cancer. A lack of PSMA uptake in verified thyroid cancer has also been re-

ported by others [6].

In conclusion, approximately one in every three patients with focal PSMA-avid thyroid lesions was diagnosed with a malignant condition in our population. Thus, we suggest that incidental, focal PSMA-avid thyroid lesions, despite being rare, require further investigations to exclude malignancy.

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The authors declare that they have no conflicts of interest.

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