Retrospective Analysis of PSMA PET/CT Thyroid Incidental Uptake in Adults: Incidence, Diagnosis and Treatment/outcome in a Tertiary Cancer Referral Center and an Academic Hospital

Marceline W Piek
Antoni van Leeuwenhoek Netherlands Cancer Institute: Antoni van Leeuwenhoek Nederlands Kanker Instituut https://orcid.org/0000-0003-2216-1369
Lisa H. de Vries
UMC Utrecht: Universitair Medisch Centrum Utrecht
Maarten Donswijk
Antoni van Leeuwenhoek Netherlands Cancer Institute: Antoni van Leeuwenhoek Nederlands Kanker Instituut
Bart de Keizer
UMC Utrecht: Universitair Medisch Centrum Utrecht
Jan Paul de Boer
Antoni van Leeuwenhoek Netherlands Cancer Institute: Antoni van Leeuwenhoek Nederlands Kanker Instituut
Lutske Lodewijk
UMC Utrecht: Universitair Medisch Centrum Utrecht
Rachel S. van Leeuwaarde
UMC Utrecht: Universitair Medisch Centrum Utrecht
Menno R. Vriens
UMC Utrecht: Universitair Medisch Centrum Utrecht
Koen J. Hartemink
Antoni van Leeuwenhoek Netherlands Cancer Institute: Antoni van Leeuwenhoek Nederlands Kanker Instituut
Iris M.C. van der Ploeg (i.vd.ploeg@nki.nl)
Antoni van Leeuwenhoek Netherlands Cancer Institute: Antoni van Leeuwenhoek Nederlands Kanker Instituut

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Research Article

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Abstract

Purpose

A prostate-specific membrane antigen (PSMA) thyroid incidentaloma (PTI) is an unexpected, PSMA-avid thyroid lesion, newly detected during the investigation of an unrelated condition using PSMA PET/CT. The aim of this study is to examine the incidence and clinical significance of PTI and the associated management strategies since the implementation of the PSMA PET/CT scan.

Methods

This study involves a retrospective cohort study of 61 PTI cases depicted on PSMA PET/CT scans performed between January 2016 and July 2021, almost exclusively for (re)staging prostate cancer. The medical records of the included cases were retrospectively reviewed and data of the PSMA PET/CT scans, primary malignancy, thyroid diagnostics, treatment and follow-up were collected.

Results

PTI was reported in 1.1% of the oncologic PSMA PET/CT scans included in this study. Two PTI cases had a histologically proven thyroid cancer, one a benign thyroid lesion and one a metastasis of a renal cell carcinoma. In none of the cases in whom any form of further thyroid work-up was withheld, the PTI became clinically relevant during follow-up (median 1.8 years (1.1-3.3)). Six patients (10%) died due to their primary cancer.

Conclusion

The incidence of thyroid incidentalomas on PSMA PET/CT was low (1.1%) in this large, two-center experience. Less than half of the PTI cases were analyzed and the risk of malignancy, despite being low, was not negligible. The clinical outcome was good using a standard diagnostic work-up for PTI, while the prognosis of the patient was determined by the primary malignancy. The consideration to analyze and treat PTI cases should be part of the shared decision making in cancer patients.

Introduction

The incidence of many types of cancer has increased over the past decade and oncologists strive to improve tailor-made treatment options.[1] Imaging is an important part of staging cancer and essential to provide patient specific treatment. The role of positron emission tomography/computed tomography (PET/CT) has expanded in oncology and is performed as a routine investigation in a number of common cancers.[2, 3] An incidentaloma is an unexpected finding on imaging not related to the original diagnostic inquiry.[4] With the rising number of performed scans, the incidence of incidentalomas increases too.

Prostate carcinoma (PCa) is the most common malignancy in men worldwide with annual age-adjusted rates of 59.3 per 100.000 in Europe.[5] Diagnosis and treatment response in prostate cancer is

challenging because the clinical course of the disease is often heterogeneous.[6] Prostate-specific membrane antigen (PSMA) is a transmembrane protein with significantly increased expression in prostate cancer cells compared to normal prostate tissue.[7] PET/CT targeting the PSMA receptor (PSMA PET/CT) plays an increasingly important role in the detection and staging of primary and recurrent PCa [8, 9]. PSMA is also expressed in tumor associated neovasculature of a wide spectrum of malignant neoplasms, including various thyroid carcinoma.[10–17] As a result, PSMA may be used as target for nuclear imaging and therapy in different advanced tumors such as thyroid, prostate, head and neck and breast cancer.[18–24] PSMA expression was observed in differentiated thyroid cancer (DTC) as well as in undifferentiated (anaplastic) thyroid cancer.[14, 17] The expression of PSMA was seen more frequently in DTC with distant metastases (100%) compared to DTC with lymph node metastases only (67%).[14] The expanding use of PSMA PET/CT has led to the identification of PSMA incidentalomas, also depicted in the thyroid gland.[25–27] PSMA thyroid incidentaloma (PTI) is defined as an unexpected PSMA-avid thyroid lesion, newly detected on PSMA PET/CT. The clinical significance of PTIs has not been investigated extensively.

The aim of this study is to evaluate the incidence and clinical significance of PTIs revealed by PSMA targeting PET/CT in a tertiary cancer referral center and an academic hospital. The intention was to describe the different possible management strategies, the results and the clinical relevance of these different approaches to PTIs in patients with a non-thyroid primary cancer.

Methods

Ethical

This study was approved by the Institutional Review Board from the Netherlands Cancer Institute-Antoni van Leeuwenhoek (NCI-AvL) Hospital and the University Medical Center Utrecht (UMCU) (IRBd21-019).

Imaging

All cases scanned between January 2016 and July 2021 with PSMA PET/CT in the AVL or UMCU or referred with an externally performed PSMA targeting PET/CT (using either ^{68}Ga-PSMA-11, ^{18}F-PSMA-1007 or ^{18}F-DCFPyl as tracer) were identified from the medical records. A total of 2510 and 894 patients underwent ^{68}Ga-/^{18}F-PSMA PET/CT scan and ^{18}F-DCFPyL PET/CT scans, respectively in our two centers. In total, 2030 patients who underwent externally performed PET/CT scans using either the ^{68}Ga-/^{18}F-PSMA tracer or the ^{18}F-DCFPyL tracer were included in the study. The incidence of PTI was calculated using the data from the scans performed in our hospitals and the data from the externally performed scans. The PSMA targeting PET/CTs had been performed for diagnosis, staging or treatment response measurements for a known or suspected non-thyroidal malignancy, almost exclusively PCa. The imaging reports were searched for the word “thyroid”. The reports were then manually screened by authors M.W.P. and L.H.d.V. to assess whether focal or diffuse PSMA uptake in the thyroid gland was reported. Diffuse uptake was defined as PSMA uptake in the whole thyroid gland, whereas focal uptake was defined as

PSMA uptake in well circumscribed areas of the thyroid gland. Cases with known thyroid disease or thyroid cancer were excluded. Medical records of included cases were reviewed and data on the primary malignancy, tumor stage, PSMA avidity, extent of thyroid investigation, treatment and follow-up was collected.

Analyses/evaluation of thyroid nodules

The initial PSMA PET/CT scans were analyzed by specialized nuclear medicine physicians according to the European Association of Nuclear Medicine (EANM) guidelines.[28] The Thyroid Imaging Reporting and Data System (TIRADS) published in 2017 served as a guidance for ultrasound analysis.[29] In most cases the American Thyroid Association guidelines (ATA) were followed to refrain from FNAC in thyroid nodules < 1 cm unless there was cervical lymphadenopathy or another finding associated with a higher cancer risk.[30] FNAC results were analyzed by dedicated pathologists based on the Bethesda System for Thyroid Cytopathology.[31] Clinical and pathological staging was reported according to the 8th edition TNM classification by the American Joint Committee on Cancer (AJCC).

Statistical analysis

Baseline values of continuous variables were visually checked for normality with histograms, q-q plots and the Shapiro-Wilk normality test. For normally distributed numeric data, the mean and standard deviation were reported. Non-normally distributed numeric data were reported as median with interquartile range (IQR, 25th-75th percentile). For categorical data frequencies and percentages were reported. All statistical tests were two-tailed, and a value of $p \leq 0.05$ was considered statistically significant. Statistical analysis was conducted using R software, version 4.0.3.

Results

Incidence of PSMA PET/CT thyroid incidentalomas

A total of 5434 patients underwent PSMA PET/CT scan between 2016 and 2021 of which 61 PTIs (1.1%) were identified based on the exclusion criteria. The process for case selection is presented in Fig I.

Management strategies

The median age of all PTI cases (N = 61) was 71.0 years (IQR 68–75) and 98% were male (TABLE I). Imaging was performed due to PCa in most patients (98%) and parotid cancer in one female patient. The PSMA PET/CT scans showed focal PSMA uptake in the thyroid gland in 70% of PTI cases (Fig. IIIa). One case also had uptake in cervical lymph nodes (level VI). Laboratory testing including thyroid stimulating hormone (TSH), T4 levels was performed in 21% of cases and most of them were euthyroid.

Subsequent evaluation by ultrasound was performed in 25 (25/61) PTI cases (TABLE II). Five of these cases (5/25) had an advanced stage of PCa with lymph node metastasis or distant metastasis at the time of initial diagnosis. The majority of cases (20/25) who received ultrasound for PTI had a less advanced PCa stage (N0, M0). Consequently, the odds of receiving additional PTI diagnostics was

decreased (odds ratio 0.24; 95% CI: 0.05–0.86; $p = 0.01$) for the patients with an advanced stage of PCa compared to the patients with a less advanced stage of PCa.

Ten cases (10/25) who were additionally imaged by ultrasound had PSMA-avid thyroid nodules larger than 1 cm. In one case, ultrasound depicted both a thyroid lesion and pathological regional lymph nodes, as was also seen on PSMA PET/CT.

FNAC was performed in 21 of the 25 (84%) cases who underwent ultrasonography. In 4 cases, the thyroid gland showed multinodular disease with no defined nodules and therefore FNAC was not indicated. Bethesda I, II, III and IV was seen in 2 (14%), 14 (62%), 2 (14%) and 3 (14%) cases, respectively. Two of the Bethesda I cases had a second and third cytological puncture, showing a Bethesda II and a Bethesda VI lesion, respectively. One case with a Bethesda III score had significant growth of the thyroid nodule during ultrasound surveillance and had a Bethesda V score at the second cytological puncture.

In this study population, 4 patients (7%) received thyroid surgery due to a Bethesda IV, V or VI cytology score. One patient with a Bethesda IV score had a FNA cytology result with a difficult distinction between thyroid- and parathyroid tissue. This patient had the final diagnosis of primary hyperparathyroidism and received no thyroid surgery. Two patients underwent a hemithyroidectomy for a 1.9 and 3.6 cm thyroid nodule in the right lobe. The pathology result showed a papillary thyroid carcinoma (PTC) and a thyroid adenoma, respectively. Two other patients with multiple thyroid nodules in both lobes underwent a total thyroidectomy. Pathological examination showed a Hurthle cell carcinoma of 5.6 cm and a metastasis of 6.2 cm with lymph node metastasis of a previously unknown primary clear cell renal cell carcinoma. In Fig. II the final Bethesda scores and pathology results are shown.

Follow-up

The median follow-up for the total cohort of PTI cases was 1.8 years (IQR 1.1–3.3). During follow-up, 11 (18%) PTI cases had no cancer related event after the PSMA PET/CT scan, 44 (67%) PTI cases were treated for recurrent PCa, and 3 (5%) for a different cancer type (head- and neck cancer, neuroendocrine tumor). There were no thyroid disease related events in the group of PTI cases without additional thyroid imaging. Six (10%) patients died after a median follow-up period of 2.6 years (IQR 1.7–3.6) due to progression of disseminated PCa.

Discussion

This study showed that PTIs were found in 1.1% of patients who underwent PSMA PET/CT. Further diagnostic analysis with ultrasound was performed in less than half of the PTI cases (41%). Most of these cases (84%) underwent FNAC. In only few cases (7%) thyroid surgery was performed. Two patients had a histologically proven thyroid cancer, one patient a benign thyroid lesion and one patient a metastasis of a renal cell carcinoma. The majority of cases (20/25) who received additional PTI diagnostics had a less advanced stage of their primary malignancy. Six patients (10%) died due to their primary PCa.

The incidence of thyroid incidentalomas (TIs) has been described before. ^{18}FDG PET/CT TIs have been widely studied.[32–35] FDG TIs are generally regarded as focally elevated thyroid uptake and up to one-third of the FDG TIs are malignant. The most frequent malignant histological subtype is PTC.[32–35] Because the PSMA PET/CT scan is a relatively new diagnostic tool, there is limited clinical experience with incidental detection of synchronous PSMA-avid malignancies. The incidental expression of PSMA was also shown in other cancers such as renal cell carcinoma, neuroendocrine tumors, melanoma, colon carcinoma, lung cancer or breast cancer.[36–39] Recently, PSMA uptake in thyroid cancer has been reported in case-reports and prospective studies. [19, 25–27] Bychkov et al. found that PSMA expression was observed in a wide spectrum of thyroid tumors and that thyroid cancers had significantly higher PSMA expression than benign tumors. However, the detection of PSMA uptake in the thyroid gland did not guarantee thyroid origin of these lesions.[15] The incidence of PTIs was studied by Kirchner et al. who found an incidental uptake of ^{68}Ga-PSMA by the thyroid gland in 22% of 55 patients with urological cancers.[44] This incidence is higher compared to our study population which can be related to a different study design. The current literature reveals one systematic review concerning ^{68}Ga-PSMA PTIs.[26] Most of the included studies were retrospective in nature and consisted of case-reports. This review concluded that the risk of a PTI being malignant is not negligible. Among 23 PTIs with focal uptake, 6 were malignant (5 primary thyroid carcinomas and one renal cell carcinoma metastasis), one was a follicular lesion of undetermined significance and the other lesions were benign. Gossili et al. studied 341 patients with a ^{68}Ga-PSMA PET/CT scan of which 7 patients (2%) had increased focal PSMA uptake in the thyroid gland of which two were confirmed malignant (2/7).[27] In our cohort, 43 PTIs (70%) with focal uptake were included of which 3 had a proven malignant pathology (2 thyroid carcinomas and one metastasis from renal cell carcinoma). The incidence of confirmed malignancy (7.0%) in the current cohort is lower compared to the above-mentioned study.[27] In general, the follow-up in our study was more comprehensive in cases with focal than diffuse PTIs which is similar to the findings of Gossili et al. Diffusely increased uptake of FDG in the thyroid is thought to be associated with autoimmune thyroiditis or hypothyroidism which may also explain the low rate of diagnostic follow-up for diffuse PTIs.[45]

The ATA guidelines for thyroid nodules suggests further workup in all thyroid nodules of 1 cm and larger, also when incidentally depicted on imaging, because they have a greater potential to be clinically significant malignancies.[30] According to the 2015 Dutch guideline, the advice is to analyze thyroid incidentalomas by ultrasound and FNAC in cases without relevant comorbidities.[40] The indication for PSMA PET/CT scan in this study was staging of the primary detected malignancy, predominantly PCa. This specific population therefore has relevant comorbidity. The strategy to actively pursue all PTIs of one cm and above in this cohort may lead to overtreatment of thyroid nodules that might never become clinically relevant. Surgical management of thyroid carcinoma consists of lobectomy or total thyroidectomy with or without neck dissection or radioactive iodine treatment. These strategies are associated with complications such as hypothyroidism (5% of patients), iatrogenic hypoparathyroidism, recurrent laryngeal nerve damage (1% of patients), dysphagia, hemorrhage and wound infection.[41, 42] The current use of additional imaging and treatment for PTIs detected by PSMA PET/CT scans must be critically evaluated to avoid such complications.

In both our hospitals, different types of management strategies were applied. A minority of 4 patients underwent thyroid surgery, of which 3 were histologically proven malignant. The patient's comorbidity and life expectancy based on the primary non-thyroid cancer should be taken into account while deciding the further evaluation of a PTI. This study indicates that most physicians have indeed considered this, since patients with a less favorable expected outcome, for example with local- or distant metastasis, received PTI workup significantly less often compared to patients with a more favorable prognosis. If more PTI workup was performed, more thyroid cancers may have been detected. However, analysis of the follow-up data indicates that these possible missed thyroid malignancies dit not become clinically relevant for the patients in our study cohort. However, our follow-up period was relatively short.

Strengths and limitations

A strength of this study includes the large study population for a rarely described finding. Study limitations include the retrospective nature of this study. Another limitation is that the PSMA PET/CT scans were predominantly performed in male patients with prostate cancer. Therefore the conclusions cannot be extrapolated to general clinical practice.The physician dependent choices for PTI workup might also be a potential study bias. The nuclear medicine reports were generated by different nuclear medicine physicians in different hospitals, which might have led to heterogenous reporting. Also, only a minority of patients underwent thyroid surgery. Therefore, a final histological diagnosis was only available in few patients.

Conclusion

PTIs were found in 1.1% of the performed PSMA PET/CT scans included in this study. Less than half of the PTI cases were analyzed and the risk of malignancy, despite being low, was not negligible. Of the remaining PTI cases without additional diagnostics, the PTI did not become clinically relevant during follow-up. The threshold for additional PTI diagnostics was logically higher in this population with significant comorbidities. No patients died from thyroid cancer and the strategy to withhold from thyroid diagnostics in PTI seems valid for a large group of patients with an unfavorable prognosis of their primary cancer based on this study. Though, in our opinion, in case of a well treatable underlying malignancy, diagnostic workup and treatment according to the ATA guidelines should be considered. These considerations should be part of the shared decision making in cancer patients with a PTI.

Declarations

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Conflicts of interest/Competing interests: not applicable

Availability of data and material: not applicable

Code availability: not applicable

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Tables

TABLE I. Clinical characteristics and PSMA PET/CT data

Variable	N = 61 (%)
Women	1 (2)
Age in years	67
Men	60 (98)
Age in years, median (IQR)	71 (68-75)
PSMA tracer/thyroid uptake	
^{68}Ga-PSMA^{2}-11	
Focal uptake	26 (43)
Diffuse uptake	14 (23)
^{18}F-DCFPyl	
Focal uptake	6 (10)
^{18}F-PSMA-1007	
Focal uptake	11 (18)
Diffuse uptake	4 (7)
Indication for PSMA PET/CT^{3}	
Staging prostate cancer	60 (98)
Staging salivary gland cancer	1 (2)
AJCC stage prostate cancer (primary malignancy)	
Stage I	8 (13)
Stage IIa	4 (7)
Stage IIb	4 (7)
Stage IIc	7 (12)
Stage IIIa	5 (8)
Stage IIIb	7 (12)
Stage IIIc	2 (3)
Stage IVa	12 (20)
Stage IVb	11 (18)
AJCC stage head-neck cancer (primary malignancy)	
Stage III	1 (2)

Distribution PSMA uptake	
Right lobe	26 (43)
Left lobe	25 (41)
Both lobes	10 (16)
Suspected lymph nodes	
Level VI	1 (2)
Thyroid function test results	13 (22)
Euthyroid	12 (20)
Subclinical hyperthyroidic	1 (2)

[2]PSMA = Prostate-specific membrane antigen

[3]PET/CT = Positron emission tomography/computed tomography

TABLE II. Workup characteristics and treatment of PSMA thyroid incidentalomas

Variable	N = 61 (%)
Repeated PSMA[4] PET/CT[5] result[a]	21 (34)
No uptake	7 (33)
Less uptake	2 (10)
Same uptake	0 (0)
More uptake	14 (67)
Number of US[6]	25 (41)
US size thyroid nodule (cm)[b]	
<0.5	2 (8)
<1	8 (32)
1-2	6 (24)
2-3	1 (4)
3-4	3 (12)
Size not mentioned	5 (20)
US distribution thyroid nodule[b]	
Left lobe	9 (36)
Right lobe	7 (28)
Both lobes	7 (28)
Not mentioned	2 (8)
Suspected lymph nodes on US[b]	1 (2)
Level IV	
Cytology thyroid incidentalomas	21 (34)
Number of punctures	
1	12 (57)
2	5 (24)
3	4 (19)
Bethesda classification (final) [c]	
Category I	0 (0)
Category II	15 (71)

Category III	1 (5)
Category IV	3 (20)
Category V	1 (5)
Category VI	1 (5)
Thyroid surgery[d]	4 (7)
Hemithyroidectomy	2 (50)
Total thyroidectomy	2 (50)
Neck dissection[d]	1 (2)
Lateral neck dissection (levels II-V)	1 (100)
PA thyroid surgery[d]	
Follicular thyroid carcinoma	1 (25)
Hurthle cell thyroid carcinoma	1 (25)
Thyroid adenoma	1 (25)
Metastasis different cancer	1 (25)
PA neck dissection[e]	
Metastasis different cancer	1 (100)

[4]PSMA = Prostate-specific membrane antigen

[5]PET/CT = Positron emission tomography/computed tomography

[6]US= ultrasound

[a] = Percentage of patients with repeated PSMA PET/CT scan [b] = Percentage of patients who underwent ultrasound, [c] = Percentage of patients who underwent FNAC, [d] = Percentage of patients who underwent thyroid surgery, [e] = Percentage of patients who underwent neck dissection

Figures

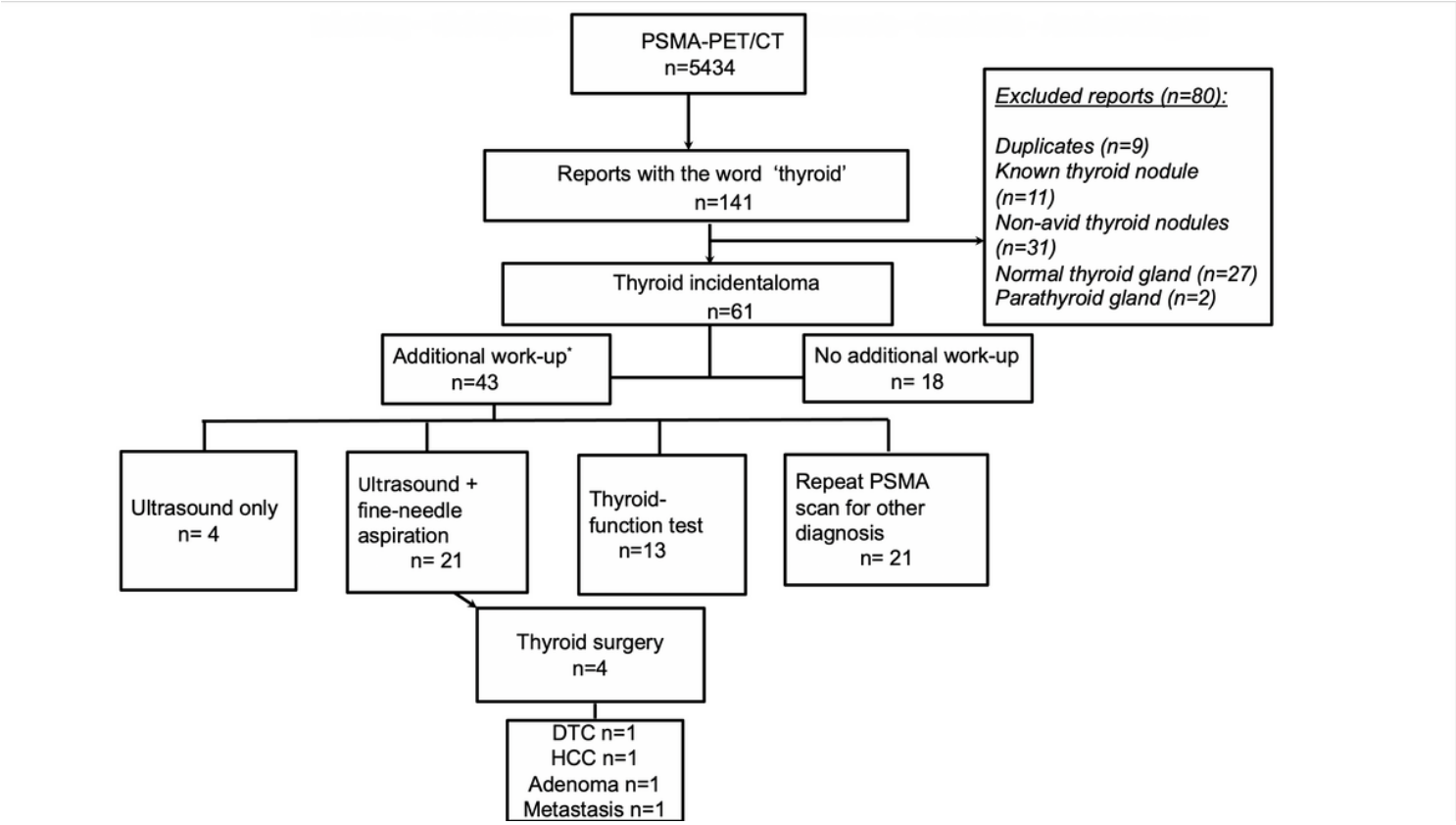


Figure 1

Flowchart of patient-selection. * 18 patients received a combination of ultrasound, thyroid function test and/or a repeated PSMA scan for other diagnosis PSMA = Prostate-specific membrane antigen PET/CT = Positron emission tomography/computed tomography DTC = Differentiated thyroid carcinoma, HCC = Hurthle cell carcinoma

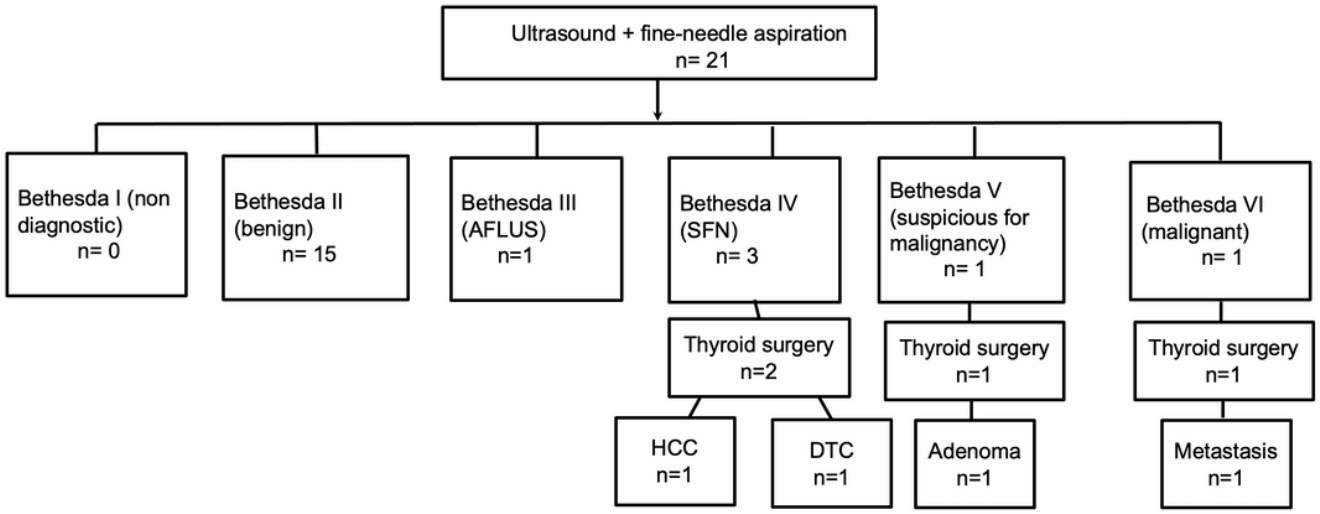
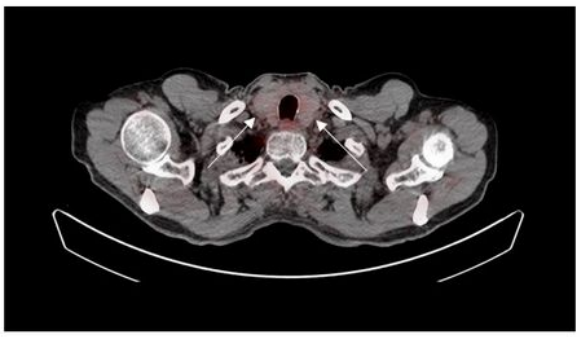
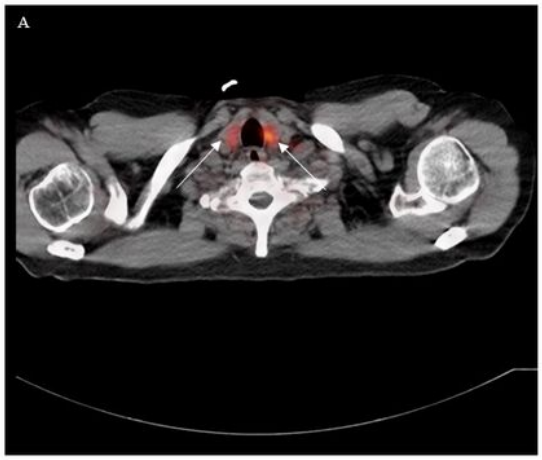


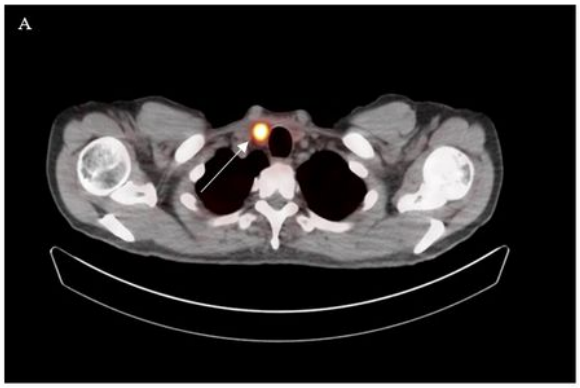
Figure 2

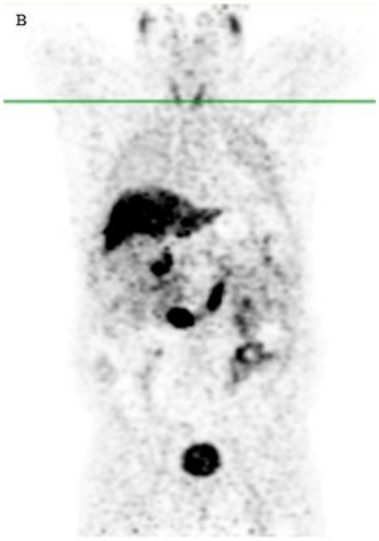
Flowchart of final pathology results. AFLUS = atypical follicular lesion of undetermined significance, SFN = suspicious for follicular neoplasm, DTC = differentiated thyroid carcinoma, HCC = Hurthle cell carcinoma



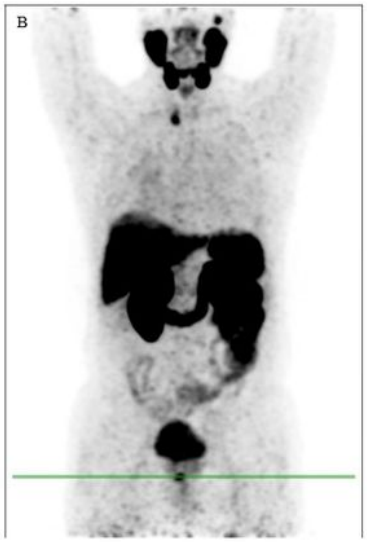
a)







b)



c)

Figure 3

Images PTI1. a. Thyroid without PSMA uptake on 68Ga-PSMA PET/CT fused image b. Diffuse thyroidal PSMA uptake on both sides on A) 68Ga-PSMA PET/CT fused image and B) 68Ga-PSMA PET/CT maximum intensity projection (MIP) image c. Focal thyroid PSMA uptake on the right side on A) 68Ga-PSMA PET/CT fused image and B) 68Ga-PSMA PET/CT maximum intensity projection (MIP) image PTI

= PSMA thyroid incidentaloma, PSMA = Prostate-specific membrane antigen, PET/CT = Positron emission tomography/computed tomography 1PTI = PSMA thyroid incidentaloma