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Incidence of PSMA PET thyroid incidentaloma depends on analysis method and tracer

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Abstract

Objective To investigate the incidences of prostate-specific membrane antigen (PSMA) thyroid incidentaloma (PTI) using different methods to define PTI, to compare the incidence of PTI among different PSMA PET tracers, and to evaluate the clinical consequences of PTI.

Methods PSMA PET/CT scans in consecutive patients with primary prostate cancer were analyzed for the presence of PTI using a structured visual (SV) analysis reporting any elevated thyroidal uptake; a semi-quantitative (SQ) analysis using a SUVmax thyroid/bloodpool (t/b) ratio ≥ 2.0 as cutoff; and an analysis of PTI incidence in the clinical reports (RV analysis).

Results A total of 502 patients were included. The incidence of PTIs was 22% in the SV analysis, 7% in the SQ analysis, and 2% in the RV analysis. PTI incidences differed significantly from 29 to 64% (SQ, resp. SV analysis) for [^{18}F]PSMA-1007, 7 to 23% for [^{68}Ga]PSMA-11, 2 to 8% for [^{18}F]DCFPyL, and to 0% for [^{18}F]PSMA-JK-7. The majority of PTI in the SV and SQ analyses consisted of diffuse (72–83%) and/or only slightly elevated thyroidal uptake (70%). Inter-observer agreement in the SV analysis was substantial (kappa = 0.76–0.78). During follow-up (median 16.8 months), there were no thyroid-related adverse events except in three patients.

Conclusions The incidence of PTI varies greatly among different PSMA PET tracers and is strongly dependent on the analysis method applied. PTI may safely be restricted to focal thyroidal uptake with a SUVmax t/b ratio ≥ 2.0. The clinical pursuit of a PTI must be weighed up to the expected outcome of the underlying disease.

Key Points

- *Thyroid incidentalomas (PTIs) are recognized in PSMA PET/CT.*
- *Incidence of PTI varies greatly among PET tracers and analysis methods.*
- *Incidence of thyroid-related adverse events in PTI cases is low.*

Keywords Positron emission tomography computed tomography · Incidence · Thyroid gland · Prostatic neoplasms

Abbreviations

AVL	Antoni van Leeuwenhoek hospital
FNAC	Fine needle aspiration cytology
IQR	Interquartile range
IRB	Institutional Review Board
ISUP	International Society of Urologic Pathologists
PCa	Prostate cancer
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
PTI	PSMA PET thyroid incidentaloma
RV	Retrospective visual
SQ	Semi-quantitative
SUVmax	Maximum standardized uptake value
SV	Structured visual
t/b	Thyroid/bloodpool

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TI Thyroid incidentaloma
VOI Volume of interest

Introduction

Prostate carcinoma (PCa) is the most common malignant tumor in men worldwide with an incidence rate of 13,665 patients in 2021 in the Netherlands [1, 2]. The PCa incidence steadily rises with an age-standardized incidence of prostate cancer over 60 per 100,000 men in the early 1990s and over 110 per 100,000 men in 2011 [2]. Positron emission tomography/computed tomography (PET/CT) imaging targeting the prostate-specific membrane antigen (PSMA) plays an important role in the staging of primary and recurrent PCa and has proven to be superior to conventional imaging methods [3, 4]. The clinical adoption of PSMA PET/CT has led to the detection of PSMA-ligand uptake in non-prostatic tissues as well, such as the thyroid gland [5]. These PSMA PET thyroid incidentalomas (PTIs) include benign and malignant thyroid lesions with retrospective analyzed incidences ranging from 1 to 2% [6–8].

It is of additional value to provide practical tools to clinicians who treat prostate cancer patients on how to handle a PTI. Most available literature concerns FDG PET/CT thyroid incidentaloma (TI), which by convention includes only focal lesions, whereas diffuse FDG uptake is interpreted as a form of thyroiditis [9]. Focal TIs appear to be malignant in up to one-third of the patients [10–13]. Our earlier study showed an FDG-PET/CT TI incidence rate of 1.9% in oncological patients and demonstrated that the patient's survival was predominantly determined by the primary cancer, not by the possible malignant TI [14]. In another retrospective study concerning PSMA PET thyroid incidentalomas, the patient's prognosis was also determined by the primary malignancy and not by the PTI [7].

The definition of the recently recognized PTI is still under debate: whereas some would only include focal lesions on PSMA PET, others have regarded PTI to include diffusely elevated thyroid uptake as well [6–8]. Recently, the E-PSMA guidelines were developed to aid standardized interpretation and reporting of PSMA PET, which includes a system of grading the PSMA expression of PCa lesions in relation to reference tissues such as the bloodpool, liver, and parotid glands [15]. The thyroid gland is generally not taken into account in describing the physiological distribution of PSMA PET tracers, and thus, elevated thyroid uptake may not always be reported. This might be due to its presumed clinical irrelevance in the setting of PCa staging. These factors may have led to varying reporting rates of PTI in literature and possibly an underestimation of the incidence of PTI. Furthermore, the PTI incidence may be related to the applied PSMA tracer with higher reported incidences in the [^{18}F]PSMA-1007 tracer [7].

In this study, we aimed to investigate the incidence of PTI by reassessing a cohort of patients that underwent PSMA PET/CT using different methods to define PTI. A structured visual (SV) assessment of thyroidal uptake and a semi-quantitative (SQ) analysis were deployed and compared with the PTI incidence rates in the clinical reports of the scans, i.e., the retrospective visual (RV) analysis. Furthermore, the PTI incidence was assessed for four commonly applied PSMA tracers: [^{18}F]DCFPyL, [^{18}F]PSMA-1007, [^{18}F]PSMA-JK-7, and [^{68}Ga]PSMA-11. Lastly, the clinical consequences of these PTIs were evaluated.

Materials and methods

Patients

This study was approved by the Institutional Review Board of the Antoni van Leeuwenhoek hospital (AVL) (IRBd21-019). A cohort of consecutive patients who underwent PSMA PET/CT between August 2016 and May 2021 was selected from a prospectively maintained database at the AVL, a tertiary oncological referral hospital in the Netherlands. Patients underwent a PSMA PET/CT before prostatectomy because of intermediate/high-risk primary PCa ($\geq$ cT3, International Society of Urologic Pathologists grade 2/Gleason score $\geq 4+3$ or PSA ≥ 20 ng/mL) as per protocol. Patient characteristics and follow-up data were retrieved from the medical records.

PSMA PET imaging

PSMA PET imaging was performed in AVL or in one of the referring external centers using multiple tracers, according to local protocols. The applied PSMA tracers included the ^{18}F bound tracers: [^{18}F]DCFPyL, [^{18}F]PSMA-1007, [^{18}F]PSMA-JK-7, and the ^{68}Ga bound tracer [^{68}Ga]PSMA-11. The ^{18}F bound tracers were synthesized via direct radiofluoration at an on-site cyclotron facility and [^{68}Ga]PSMA-11 was produced on-site using a fully automated system (Scintomics GmbH), compliant to the Good Manufacturing Practices guidelines. PET images were acquired from mid-thigh to skull-base, median 118 min (interquartile range (IQR) 60–120) post-injection after a median dose of 288 MBq (IQR 204–312) for [^{18}F]DCFPyL, 50 min (IQR 45–60) post-injection after a median dose of 105 MBq (IQR 96–148) for [^{68}Ga]PSMA-11, a median of 90 (IQR 90–120) min post-injection after a median dose of 284 MBq (IQR 251–313) for [^{18}F]PSMA-1007, and a median of 77 min (IQR 60–90) after a median dose of 201 MBq (IQR 194–265) for [^{18}F]PSMA-JK7. PSMA PET/CT imaging was performed on

Siemens Truepoint, Philips Ingenuity/Gemini TF or Philips Vereos integrated PET/CT systems. PET images were combined with either a low-dose CT scan (120–140 kV, 40–80 mAs with dose modulation) or a full-dose CT scan (130 kV, 110mAs) with or without intravenous contrast enhancement. All PET images were corrected for scatter, decay, and random coincidences. All PSMA PET/CTs, whether performed in AVL or in one of the referring centers, were (re)assessed and reported by a nuclear medicine physician in the AVL.

Data collection and image analysis

All PSMA PET/CT images were viewed using the Osirix Dicom Viewer (Pixmeo). For the SV analysis, three nuclear medicine physicians (M.D., M.W., Z.C.) with ample experience in reading PSMA PET/CT scans were instructed to visually analyze the PET/CT images and to indicate whether a PTI was present. Observers were blinded from clinical information including the clinical reports of the scans. The visual definition of PTI was defined as any focal uptake in the thyroid gland above the average thyroid tracer uptake, or diffuse uptake exceeding the normal background activity in the soft tissues in the head-neck area, as adapted from Gossili et al [6]. In any case, the PTI had to be discernable from noise and soft-tissue background activity in the head-neck area on a PET whole-body maximum intensity projection (MIP) (Fig. 1). Furthermore, observers were asked to describe the pattern

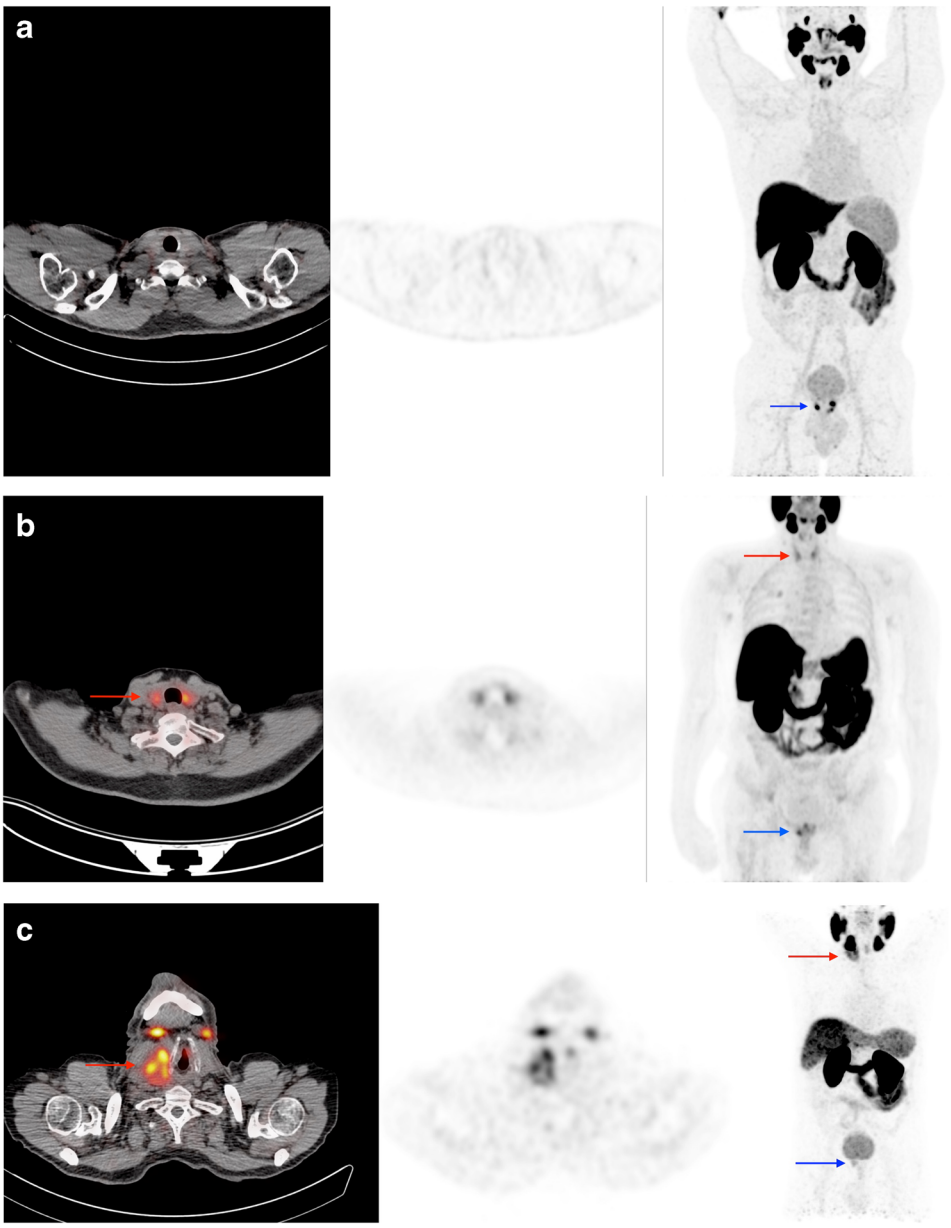

Fig. 1 Example images of prostate-specific membrane antigen (PSMA) thyroid incidentaloma (PTI) with focal, irregular, and diffuse patterns and varying level of intensity. Transverse, transverse fused to low-dose CT, and maximum intensity projection (MIP) images of PSMA PET scans are shown. Applied window with SUV-max 0–7. **a** [^{18}F]PSMA-JK-7 PET/CT showing no elevated tracer uptake in the thyroid. The primary prostate cancer is visible as multiple intense spots in the prostate (blue arrow, MIP). **b** [^{18}F]PSMA-1007 PET/CT showing moderately, diffusely elevated tracer uptake in the thyroid (red arrows). The primary prostate cancer is visible as multiple moderately intense spots in the prostate (blue arrow, MIP). **c**. [^{68}Ga] PSMA-11 PET/CT showing intensely, irregularly elevated tracer uptake in the thyroid (red arrows). The primary prostate cancer is visible as a relatively faint spot in the prostate (blue arrow, MIP)

Table 1 Overall comparison of PTI incidence between the different tracers [^{68}Ga]PSMA-11, [^{18}F]DCFPyL, [^{18}F]PSMA-1007

	Method	Uptake pattern	Tracer					*p* value
			[^{68}Ga]PSMA-11	[^{18}F]DCFPyL	[^{18}F]PSMA-1007	[^{18}F]PSMA-JK-7	Total	
PTI incidence (%)	SV	Diffuse	39 (15%)	8 (5%)	32 (57%)	0	79 (16%)	
		Focal	13 (5%)	2 (1%)	3 (5%)	0	18 (4%)	
		Irregular	10 (4%)	2 (1%)	1 (2%)	0	13 (3%)	
		Total	62/266 (23%)	12/154 (8%)	36/56 (64%)	0/26	110/502 (22%)	<0.001*
PTI incidence (%)	SQ	Diffuse	14 (5%)	3 (2%)	14 (25%)	0	31 (6%)	
		Focal	4 (2%)	0	2 (4%)	0	6 (1%)	
		Total	18/266 (7%)	3/154 (2%)	16/56 (29%)	0/26	37/502 (7%)	<0.001*
PTI incidence (%)	RV	Diffuse	4 (2%)	1 (1%)	0	0	5 (1%)	
		Focal	3 (1%)	1 (1%)	2 (4%)	0	6 (1%)	
		Total	7/266 (3%)	2/154 (1%)	2/56 (4%)	0/26	11/502 (2%)	0.520

PTI prostate-specific membrane antigen PET thyroid incidentaloma, *SV* structured visual, *SQ* semiquantitative, *RV* retrospective visual

*Statistical significance ($p \leq 0.05$)

(focal, irregular, or diffuse) and intensity (slightly, moderately, or intensely elevated) of uptake. A random selection of 75 cases from each observer M.W. or Z.C. (in total 150 cases) was re-analyzed by observer M.D., blinded from clinical information and the results of the first analysis to determine inter-observer reliability.

For the SQ analysis, a volume of interest (VOI) was placed over the thyroid gland and the maximum standardized uptake value (SUVmax) thyroid corrected for body weight was determined. Subsequently, a VOI was placed over the ascending thoracic aorta and the SUVmax value of the bloodpool was measured. The SUVmax thyroid/bloodpool (t/b) ratio was determined in every patient. Based on previous studies reporting on a SUVmax lesion-to-background ratio discriminating borderline/malignant thyroid lesions on FDG PET/CT [16] and malignant lesions on PSMA PET/CT [17, 18], a SUVmax t/b ratio of ≥ 2.0 was determined as positive for PTI. In the case of a PTI, the pattern was visually determined and categorized as focal, diffuse, or irregular.

Lastly, for the RV analysis, all clinical reports of the PSMA PET/CTs were reviewed. Used tracer and the presence of PTI were noted. Any remark of elevated thyroid uptake on PSMA PET/CT in the clinical report was regarded as positive for PTI. Furthermore, the description of the PTI was categorized according to the pattern: focal or diffuse, and to intensity: slightly, moderately, or intensely elevated.

Statistical analysis

Incidences in PTI were calculated for the different analyses (SV, SQ, RV). To test for an overall difference in the incidence of PTI, Cochran's *Q* test was used, followed by pairwise comparisons of the methods using McNemar's test with Bonferroni adjustment. For every analysis, differences in PTI incidence rates were compared between the various PSMA tracers using Fisher's exact test followed by post hoc pairwise *Z*-tests with Bonferroni adjustment.

For the SV analysis, any difference in PTI incidence rates between the observers was tested using Fisher's exact test.

Kappa coefficient was used to estimate agreement between the observers. The agreement between two observers was evaluated by Cohen's kappa with standard error and percent agreement. To determine kappa (κ) values, response categories were dichotomized as 0, no PTI present, and 1, PTI present (focal, diffuse, or irregular). As conventionally classified, kappa values of 0–0.20 indicate a poor, 0.21–0.40 a fair, 0.41–0.60 a moderate, 0.61–0.80 a substantial, and 0.81–1.0 a nearly perfect agreement [19]. All statistical tests were two-tailed, and a value of $p \leq 0.05$ was considered statistically significant. Statistical analyses were conducted using R software, version 4.0.3, and Statistical Package for Social Sciences (SPSS, IBM; v27).

Table 2 Post hoc comparison of PTI incidence between the different tracers for the SV and SQ analyses: results of pairwise *Z*-tests corrected for multiple testing are shown as *p* values per tracer

SV analysis	Tracer					
		[^{68}Ga]PSMA-11	[^{18}F]DCFPyL	[^{18}F]PSMA-1007	[^{18}F]PSMA-JK-7	Totals
PTI present	yes	62	12	36	0	110
	no	204	142	20	26	392
p value		1.000	< 0.001*	< 0.001*	0.022*	
SQ analysis	Tracer					
		[^{68}Ga]PSMA-11	[^{18}F]DCFPyL	[^{18}F]PSMA-1007	[^{18}F]PSMA-JK-7	Totals
PTI present	Yes	18	3	16	0	37
	No	248	151	40	26	465
p value		1.000	0.008*	< 0.001*	0.558	

PTI prostate-specific membrane antigen PET thyroid incidentaloma, *SV* structured visual, *SQ* semiquantitative, *RV* retrospective visual

*Statistical significance ($p \leq 0.05$)

Table 3 Overall comparison of PTI incidence between the SV, SQ, and RV analyses using Cochran's *Q* test

	Method			*p* value
	SV	SQ	RV	
PTI incidence (%)	110/502 (22%)	37/502 (7%)	10/502 (2%)	< 0.001*

PTI prostate-specific membrane antigen PET thyroid incidentaloma, *SV* structured visual, *SQ* semiquantitative, *RV* retrospective visual

*Statistical significance ($p \leq 0.05$)

Table 4 Results of McNemar's post hoc pairwise comparisons with Bonferroni showing the *p* value per method comparison

	SV	SQ	RV
SV	–		
SQ	< 0.001*	–	
RV	< 0.001*	< 0.001*	–

PTI prostate-specific membrane antigen PET thyroid incidentaloma, *SV* structured visual, *SQ* semiquantitative, *RV* retrospective visual

*Statistical significance ($p \leq 0.05$)

Results

A total of 502 male patients with a mean age of 67 (± 6.5) years and PSMA PET/CT scans for intermediate/high-risk primary PCa were included in this analysis. The used PSMA tracers were [^{68}Ga]PSMA-11 ($n = 266$), [^{18}F]DCFPyL ($n = 154$), [^{18}F]PSMA-1007 ($n = 56$), and [^{18}F]PSMA-JK-7 ($n = 26$). The median (IQR) follow-up time from the first date of the PSMA PET/CT scan was 16.8 (8.4–32.4) months.

PTI incidence per PSMA tracer

The incidence of PTI ranged from 0% for [^{18}F]PSMA-JK-7 to 64% for [^{18}F]PSMA-1007 and differed significantly among tracers in the SV method and SQ analysis (Fisher's exact test $p < 0.001$), whereas the incidence of PTI did not differ significantly among tracers in the RV analysis ($p = 0.520$; Table 1). Post hoc pairwise comparisons using *Z*-tests with Bonferroni correction for the SV analysis showed significantly lower PTI incidences in [^{18}F]DCFPyL (8%; $p < 0.001$) and [^{18}F]PSMA-JK-7 (0%; $p = 0.022$), and higher PTI incidence in [^{18}F]PSMA-1007 (64%; $p < 0.001$; Table 2). Post hoc pairwise comparisons for the SQ method showed significantly lower PTI incidences in [^{18}F]DCFPyL (2%; $p = 0.008$), and higher PTI incidence in [^{18}F]PSMA-1007 (29%; $p < 0.001$).

PTI incidence per analysis

The incidence of PTI varied considerably between the different analyses (Table 3). The incidence of PTI was 22% ($n = 110$) according to the SV analysis, 7% ($n = 37$) according to the SQ analysis, and 2% ($n = 11$) according to the RV analysis. Comparing the various analyses, Cochran's *Q* test indicated a significant overall difference in the incidence of PTI ($p < 0.001$). Post hoc pairwise comparisons of the several analyses using McNemar's test with Bonferroni adjustment showed significant differences in PTI incidence for all comparisons ($p < 0.001$), meaning that the three different analyses differed from each other in PTI incidence (Table 4).

PTI patterns and intensity

The majority of PTIs showed a diffuse uptake pattern, both in the SV analysis ($n = 79/110$; 72%) and in the SQ analysis

Table 5 Numbers of PTI (total $n=110$) subdivided according to uptake pattern and intensity

		PTI intensity			
		Slight	Moderate	Intense	Total
PTI uptake pattern	Diffuse	56	20	3	79
	Focal	15	2	1	18
	Irregular	6	5	2	13
	Total	77	27	6	110

PTI prostate-specific membrane antigen PET thyroid incidentaloma

($n=31/37$; 83%). According to the SV analysis, most of the PTIs consisted of only slightly elevated thyroidal uptake ($n=77$, 70% of all PTI) (Table 5). Non-diffuse, moderately-intensely elevated thyroid uptake consisted of 10/110 PTIs (9%) and 10/502 of all patients (2%).

PTI inter-observer agreement

The incidence of PTI did not differ significantly between observers in the SV analysis (range 19–25%; Fisher's exact test $p=0.459$; Table 6). There was a substantial agreement between the observers with Cohen's kappa values ranging from 0.76 to 0.78 and an overall level of agreement ranging from 91 to 93% (Table 7).

Clinical consequences

Thirty-one patients with PTIs who were identified with the SV method had follow-up PSMA PET/CT performed within a median (IQR) of 12 (8.4–24) months of the initial study. In nineteen patients (61%), the thyroidal PSMA uptake resolved on follow-up PSMA PET/CT, in twelve patients (39%) the PTI persisted (Fig. 2).

Twelve patients, of which seven (58%) were identified in the SV or SQ analysis, underwent thyroid function screening and were assessed for presence of clinical thyroid disease. Two patients with diffuse thyroidal uptake in the SV and SQ analyses had hypothyroidism and elevated TSH levels (8.0 mU/L), respectively. The other patients had normal TSH levels.

Ultrasonography was performed in five patients who were identified in the SV analysis with either focal ($n=1$), diffuse ($n=3$), or irregular ($n=1$) thyroidal uptake. These patients were diagnosed with multinodular goiter with cystic areas. One of these patients had an acute tracheal compression due to sudden hemorrhage of a cystic thyroid nodule which needed surgical intervention. Two patients received fine needle aspiration cytology (FNAC) (Fig. 2). One patient had a focal PTI in the right thyroid lobe and a Bethesda IV score at FNAC. The patient underwent a hemithyroidectomy and the final pathology result showed pT1 papillary thyroid cancer. The other patient had a focal PTI in the left lobe and a Bethesda IV score as FNAC result with a difficult distinction between thyroid and parathyroid tissue. This patient had the final diagnosis of primary hyperparathyroidism based on elevated plasma levels of parathyroid hormone and received no thyroid surgery. In none of the patients in whom any form of further thyroid workup was withheld, the PTI became clinically relevant during a median (IQR) follow-up of 16.8 (8.4–39.6) months.

Discussion

The increasing clinical adoption of PSMA PET/CT for the staging of PCa has led to a rising detection of PSMA PET PTIs. This study aimed to investigate the incidences of PTI comparing several analysis methods and different PSMA PET tracers, to assess the inter-observer agreement, and to investigate the clinical consequences of PTI in PCa patients.

The PTI incidence differed substantially between tracers, with the highest incidence in the [^{18}F]PSMA-1007 tracer in both the SQ and SV analyses (29%, resp. 64%), whereas lower incidences were found for [^{18}F]DCFPyL (2%, resp. 8%) and no PTI at all for [^{18}F]PSMA-JK-7. This is in line with our earlier two-center retrospective study in which we

Table 6 Overall comparison of PTI incidence between the observers in the reassessment visual (RV) method using Fisher's exact test

	Observer				***p* value**
	1	2	3	*Total*	
PTI incidence (%)	30/155 (19%)	50/203 (25%)	30/144 (21%)	110/502 (22%)	0.459

Table 7 PTI inter-observer agreement for the RV method shown as % agreement and Cohen's kappa value per observer pairwise comparison

Observer comparison	Kappa (standard error)	% agreement	Number of shared PTIs
Observer 1 vs observer 3	0.78 (0.1)	93	12
Observer 2 vs observer 3	0.76 (0.09)	91	16
Observer 1 + 2 vs observer 3	0.77 (0.06)	92	28

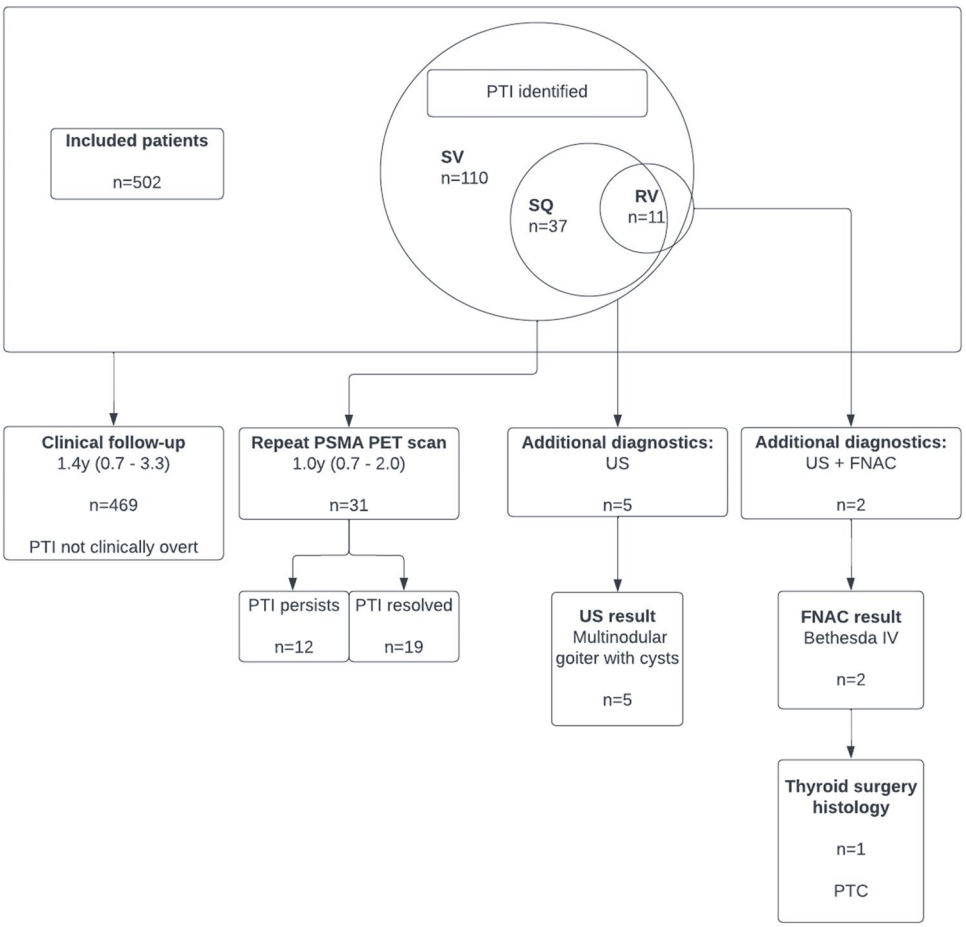

Fig. 2 Graphical representation of PTI detected per method and number of shared PTIs; flowchart of follow-up data. Follow-up duration displayed in years (y): median (interquartile range)

found a relatively high PTI incidence in [^{18}F]PSMA-1007 (8%) compared to [^{18}F]DCFPyL and [^{68}Ga]PSMA-11 (0.8, resp. 0.9%) [7].

The structured visual (SV) analysis yielded a significantly higher PTI incidence than the semi-quantitative (SQ) analysis (22% vs 7%). The PTI incidence rates in the clinical reports (RV analysis; 2%) were the lowest of the three analyses. Virtually, all PTIs described in the clinical reports (RV analysis) and detected using the SQ method were detected in the SV method as well, whereas the SQ and RV methods also had considerable overlap. The PTI incidence did not differ significantly between observers and the inter-observer agreement was substantial (kappa coefficient 0.76–0.78), indicating the robustness of PTI findings in the SV method.

A considerable majority of PTIs concerned PTIs with a diffusely elevated thyroidal uptake (72–83%) and contributed substantially to the higher incidence of PTI in the SV and SQ analyses. High incidences of diffuse thyroidal uptake were seen especially in [^{18}F]PSMA-1007, and to a lesser extent in [^{68}Ga]PSMA-11 (15%), which is in line with an earlier study reassessing PSMA PET/CTs for physiological tracer distribution patterns and incidental uptake [20]. However, diffuse uptake patterns may be regarded as benign and may be ignored by observers because of their presumed clinically irrelevance in the setting of staging PCa[21]. Furthermore, in the SV analysis, slightly elevated thyroidal uptake was regarded as positive for PTI, while in clinical practice of staging PCa this may easily be overlooked. These factors may attribute to the considerable differences in PTI incidence between the SV, SQ, and RV analyses. When excluding PTIs with a diffuse uptake pattern and/or only slight intensity from the SV analysis, the incidence of PTI was substantially lower (2%) and comparable to the incidence in the RV analysis and our earlier retrospective studies concerning PTI and FDG PET TI [7, 14].

An argument to restrict the definition of PTI to focal thyroidal uptake with substantial intensity (moderately or intensely elevated uptake) may be the analogy with FDG PET, in which only focal uptake has been associated with the risk of malignancy [22, 23]. Furthermore, the intensity of TI uptake (SUVmax) in FDG PET may be associated with an increased risk of malignancy and high PSMA expression has been shown in cases of differentiated thyroid carcinoma as well [22–26]. On the other hand, diffuse thyroidal uptake without any structural abnormalities on

CT may reflect a physiologic phenomenon that is typical for tracers such as [^{18}F]PSMA-1007 and [^{68}Ga]PSMA-11. Kirchner et al. reported unremarkable thyroid function tests or imaging follow-up in 11/12 patients with diffusely elevated thyroid uptake on [^{68}Ga]PSMA-11 PET/CT [20]. Still, the clinical relevance of diffuse thyroidal PSMA-ligand uptake needs to be elucidated.

During the clinical follow-up, there were no thyroid-related adverse events except for a small minority of patients with clinically reported PTI who received additional diagnostics. In our earlier retrospective study, the patient's prognosis during a median follow-up of 1.8 years was also determined by the primary malignancy and not by the PTI [7]. However, clear criteria for PTI and long-term follow-up data are lacking. Applying a SUVmax thyroid/SUVmax bloodpool ratio of 2.0 or more may serve as a threshold to qualify a focal PTI as clinically relevant. Prospective studies are needed to refine this SUVmax ratio criterion for clinically relevant PTIs. The possible benefits of (early) detection of thyroid cancer must be weighed against increased costs, risks, and patients' anxiety about additional diagnostics and treatment in the setting of the underlying PCa, especially given the increasing recognition of low-risk thyroid cancer [27–31].

Strengths and limitations

The main strength of this study is the large consecutive cohort of patients that could be formed from a prospective institutional database. Furthermore, a comparison could be made between multiple clinically used PSMA tracers as well as an inter-observer comparison of PTI incidence reported by three different experienced nuclear medicine physicians, which has not been described before. Lastly, this study gives unprecedented insight into the uptake patterns and intensity levels of PTI.

A limitation is the retrospective design of the study and a relatively short clinical follow-up period. Furthermore, there is no clear consensus on what a clinically relevant PTI is; therefore, the results of this study may be less reproducible in other centers.

Conclusion

The incidence of PTI varies greatly among different PSMA PET tracers with the highest incidence in the [^{18}F]PSMA-1007 tracer, and is strongly dependent on the analysis method applied. The structured visual assessment of thyroidal uptake showed a substantial inter-observer agreement and a considerably higher incidence of PTI, which may be attributed to a large proportion of PTIs with diffuse and/or slightly elevated uptake. Although the definition of clinically relevant PTI needs to be further refined, the current and former study results suggest that a PTI may safely be restricted to focal thyroidal uptake with a SUVmax t/b ratio ≥ 2.0. The clinical pursuit of a PTI must be weighed up to the expected outcome of the underlying disease by implementing a shared decision strategy.

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Declarations

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Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- diagnostic or prognostic study
- performed at one institution

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