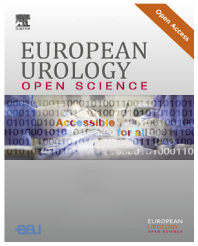
available at www.sciencedirect.com
journal homepage: www.eu-openscience.europeanurology.com



European Association of Urology

Prostate Cancer

The Probability of Metastases Within Different Prostate-specific Antigen Ranges Using Prostate-specific Membrane Antigen Positron Emission Tomography in Patients with Newly Diagnosed Prostate Cancer

Wietske I. Luining[a,b,c,*], *Marinus J. Hagens*[a,c,d], *Dennie Meijer*[a,b,c], *Joanneke B. Ringia*[d], *Tessa de Weijer*[a], *Huseyyin O. Bektas*[a], *Rosemarijn H. Ettema*[a,c], *Remco J.J. Knol*[e], *Ton A. Roeleveld*[c,d,f], *Sandra Srbljin*[g], *Saskia Weltings*[h], *Jose C.C. Koppes*[b], *Reindert J.A. van Moorselaar*[a,c], *Pim J. van Leeuwen*[c,d], *Daniela E. Oprea-Lager*[b], *André N. Vis*[a,c]

[a] *Department of Urology, Amsterdam University Medical Centers, Amsterdam, The Netherlands;* [b] *Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, Cancer Center Amsterdam, Amsterdam, The Netherlands;* [c] *Prostate Cancer Network the Netherlands, Amsterdam, The Netherlands;* [d] *Department of Urology, Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, The Netherlands;* [e] *Department of Nuclear Medicine, Noordwest Hospital, Alkmaar, The Netherlands;* [f] *Department Urology, Noordwest Hospital, Alkmaar, The Netherlands;* [g] *Department of Nuclear Medicine, Zaans Medical Center, Zaandam, The Netherlands;* [h] *Department of Urology, Zaans Medical Center, Zaandam, The Netherlands*

Article info

Article history:
Accepted December 3, 2023

Associate Editor:
Roderick van den Bergh

Keywords:
Metastatic disease
Prostate cancer
Prostate-specific antigen
Prostate-specific membrane antigen positron emission tomography/computed tomography

Abstract

Background and objectives: The association between prostate-specific antigen (PSA) level and probability of metastatic disease on prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) has not yet been established in patients with newly diagnosed prostate cancer (PCa). Our objective was to assess the probability of metastatic disease within different PSA ranges using PSMA PET/CT for initial staging of PCa, and to identify both the anatomical distribution and the predictors of metastases on PSMA PET/CT.
Methods: In total, 2193 patients with newly diagnosed PCa were retrospectively studied. PSMA PET/CT was performed for staging purposes between January 2017 and May 2022. The proportion of patients with PSMA-avid metastases, stratified by PSA level, was studied. A vast majority of patients in whom at least one high-risk prognostic factor was present underwent PSMA PET/CT. A multivariable logistic regression analysis was performed to identify the predictors of metastases on PSMA PET/CT using clinical, biochemical, radiological, and pathological variables.
Key findings and limitations: The median PSA level at PSMA PET/CT was 14.1 ng/ml. Any metastatic disease (miN1-M1a-c) was observed in 34.7% (763/2193) of all patients and distant metastases (miM1a-c) in 25.4% (557/2193) of patients. The presence of any metastatic disease increased with PSA levels, being 15.4% in men with PSA levels <10 ng/ml and 87.5% in men with PSA levels >100 ng/ml. The

* Corresponding author. Amsterdam UMC, Location VUmc, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands. Tel. +31 20 444 3289; Fax: +31 20 444 6031.
E-mail address: w.i.luining@amsterdamumc.nl (W.I. Luining).

https://doi.org/10.1016/j.euros.2023.12.001
2666-1683/© 2023 The Author(s). Published by Elsevier B.V. on behalf of European Association of Urology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

multivariable logistic regression analysis found significant associations between the presence of any metastatic disease and PSA subgroups, clinical tumor stage ≥T2, grade group >3, and radiological tumor stage ≥T3b.
Conclusions and clinical implications: This is the first large epidemiological study in patients with PCa demonstrating the association between PSA subgroups and metastatic disease on modern imaging PSMA PET/CT. Data from this study can be used to counsel patients on the probability of metastatic disease at the time of PSA screening and to provide guidance on existing guidelines.
Patient summary: The prostate-specific antigen level could be used to assess the risk of metastases on prostate-specific membrane antigen positron (PSMA) emission tomography/computed tomography (PET/CT). This knowledge is valuable for selecting patients who will benefit most from metastatic screening with PSMA PET/CT.
© 2023 The Author(s). Published by Elsevier B.V. on behalf of European Association of Urology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Introduction

Accurate staging of men diagnosed with (clinically significant) prostate cancer (PCa) is of paramount importance, as the treatment for PCa relies heavily on the presence of metastatic disease. The management of PCa ranges from active surveillance for carefully selected patients and curative therapies for locally confined disease to palliative regimens for patients with metastatic disease. Recently, prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) has emerged as a promising imaging modality with demonstrated superior diagnostic accuracy in detecting metastatic disease to conventional imaging modalities such as CT and bone scintigraphy [1–3]. However, further research is needed to evaluate the performance of the PSMA PET/CT across different prostate-specific antigen (PSA) ranges.

The appropriateness of metastatic screening is driven by the presence of adverse prognostic factors, such as elevated initial PSA, higher International Society of Urological Pathology (ISUP) grade group (GG), and advanced clinical tumor (cT) stage, which are known to increase the likelihood of having metastatic disease [4,5]. Consequently, the European Association of Urology (EAU) and American Urological Association guidelines on PCa recommend performing any metastatic screening in patients with (unfavorable) intermediate- and high-risk PCa [5–7].

Pretreatment parameters have been shown to be associated with the presence of metastatic disease on PSMA PET/CT [8–11]. However, the majority of studied men had relatively low PSA levels (ie, below 20 ng/ml) and varying risk profiles. As a result, these studies lack real-world data and might therefore be of less clinical relevance. Owing to the increasing utilization of PSMA PET/CT in urological practice, this study aims to provide epidemiological data on the prevalence of metastatic disease in patients with newly diagnosed PCa using PSMA PET/CT, and to identify the anatomical distribution of PCa metastases within different PSA ranges.

2. Methods

2.1. Study design and patients

This multicenter retrospective cohort study was carried out as a collaboration among four centers from the Prostate Cancer Network in The Netherlands, including the Amsterdam University Medical Centers (Amsterdam UMC), The Netherlands Cancer Institute—Antoni van Leeuwenhoek, the Zaans Medical Center, and the Noordwest Hospital (NWZ). The study received approval from the local institutional review board at the Amsterdam UMC, incorporating an opt-out procedure where participants were provided with a letter containing study information and the options to decline participation (protocol no. 2021.0746).

2.2. Patient data

Patients with newly diagnosed, biopsy-proven PCa who underwent PSMA PET/CT imaging for primary staging between January 2017 and May 2022 were retrospectively included. Patients with an active secondary malignancy within the past 5 yr and those receiving testosterone-lowering therapies at the time of PSMA PET/CT were excluded from analysis.

For all patients, baseline clinical, biochemical, radiological, and histopathological data were obtained from the electronic medical record systems. The following data were collected per patient: age, cT stage based on digital rectal examination, PSA level at PSMA PET/CT, magnetic resonance imaging (MRI) findings (eg, Prostate Imaging Reporting and Data System [PI-RADS] classification and radiological tumor [rT] stage), and pathological biopsy features (highest ISUP GG and percentage positive cores on systematic biopsy) [4,12]. MRI and biopsy data were analyzed within a 1-yr time frame prior to or within 3 mo following PSMA PET/CT. Moreover, PSMA PET/CT findings were assessed for each patient, that is, the presence of molecular imaging (mi)-positive locoregional lymph nodes (miN1) or distant metastases (miM1a-c). The EAU risk classification system was used to stratify patients into those with low-, intermediate-, or high-risk PCa [5].

2.3. Magnetic resonance imaging

The rT staging was based on the MRI findings. Lesions were classified using the PI-RADS classification system, version 2.1 [12]. Magnetic resonance images showing no significant abnormalities (PI-RADS classifica-

tion 1–2) were defined as radiological T1 (rT1) and PI-RADS classification 3–5 lesions were classified as rT2 (localized tumor), rT3a (extracapsular extension), rT3b (seminal vesicle invasion), or rT4 (evidence of extension in organs adjacent to the prostate other than seminal vesicles).

2.4. Pathological assessment of prostate biopsy cores

MRI-targeted and/or systematic prostate biopsies were performed according to hospital standards. Both the transperineal and the transrectal approach were performed. The number of cores with cancer was assessed for each participant, as was the highest biopsy ISUP GG.

2.5. PSMA PET/CT imaging and assessment

According to a clinical agreement within all the hospitals of the Prostate Cancer Network in The Netherlands, PSMA PET/CT imaging was indicated in all biopsy-proven PCa patients with at least one adverse prognostic factor (initial PSA >20 ng/ml, ISUP GGs ≥3, and clinical or radiological T stage ≥3). Patients underwent PSMA PET/CT as the single staging imaging modality.

Several PSMA radiotracers were used for metastatic screening during this study's time frame, including ^{18}F-DCFPyL, ^{18}F-PSMA-1007, ^{18}F-JK-PSMA-7, and ^{68}Ga-PSMA-11. The ^{18}F tracers were synthesized via direct radiofluoration and the ^{68}Ga tracer using a semiautomated or fully automated synthesis module, both compliant to Good Manufacturing Practices [13,14]. PET images were obtained from midthigh to skull base, and combined with either a non–contrast-enhanced low-dose CT scan (30–110 mAs at 120 kV) or a diagnostic CT scan (110 mAs at 130 kV) with or without an intravenous contrast. All PET images were corrected for attenuation, decay, scatter, and random coincidences. Owing to local protocols, the dose and the incubation period (ie, the time between tracer administration and scan acquisition) varied among tracers and per scan site.

PET images were acquired after a median of 117 min (interquartile range [IQR] 71–123 min) after injection following a median dose of 300 MBq (IQR 211–316) for ^{18}F-DCFPyL, 90 min (IQR 83–105 min) after injection following a median dose of 290 MBq (IQR 265–318 MBq) for ^{18}F-PSMA-1007, 69 min (IQR 60–90 min) after injection following a median dose of 203 MBq (IQR 195–216 MBq) for ^{18}F-JK-PSMA-7, and 54 min (IQR 45–60 min) after injection following a median dose of 135 MBq (IQR 100–161 MBq) for ^{68}Ga-PSMA-11.

PSMA PET/CT scans were interpreted by nuclear medicine physicians with abundant experience (>600 scans) in PSMA PET/CT reading. A scan was classified as positive if at least one lesion had PSMA expression suggestive of PCa according to the E-PSMA guidelines [15]. Lymph node metastases were categorized as either regional (miN1) or distant (miM1a) according to the PROMISE V2 criteria [16]. Regional lymph node metastases (miN1) were defined as those located in the true pelvis, within the surgical dissection template of the extended pelvic lymph node dissection. Likewise, lymph node metastases outside the surgical dissection template were defined as distant (miM1a). Bone metastases were defined as miM1b, and visceral metastases were considered as miM1c.

2.6. Statistical analysis

Descriptive statistics were reported for all patients (Supplementary Table 1). Categorical variables were reported as frequency distributions and percentages, and continuous variables were expressed as medians with IQR. The primary outcome of this study was the presence of metastatic disease observed on PSMA PET/CT at primary staging within different PSA ranges. Accordingly, patients were stratified into seven subgroups based on their PSA-levels: <10, ≥10–15, >15–20, >20–35, >35–50, >50–100, and >100 ng/ml. The cutoffs for these subgroups were determined based on their clinical usability.

Uni- and multivariable logistic regression analyses were employed to identify the predictors for detecting any (miN1-M1a-c) and distant metastatic disease (miM1a-c) on PSMA PET/CT. In the univariable analysis, several variables were included, namely, PSA subgroups, *c*T stage (ie, benign or suspected ≥*c*T2), highest ISUP GG, PI-RADS classification, and rT stage. A relaxed level of significance of $p < 0.10$ was used in univariable logistic regression analyses. Despite a significant proportion of missing values for MRI parameters, these were included in the multivariable analysis due to their frequent utilization in routine clinical practice [5]. A statistical analysis was performed using IBM SPSS statistics version 28 for Windows (IBM Corp., Armonk, NY, USA). Statistical significance was defined as $p < 0.05$.

3. Results

A total of 2193 patients underwent PSMA PET/CT for initial staging of PCa, of whom 28% had intermediate- and 70% high-risk disease (Table 1). PSMA-positive lesions within the prostate were found in 2133/2193 (97.3%) patients. PSMA PET/CT imaging was undertaken with ^{68}Ga-PSMA-11, ^{18}F-DCFPyL, ^{18}F-PSMA-1007, and ^{18}F-PSMA-JK7 in 929/2193 (42.4%), 839/2193 (38.3%), 264/2193 (12.0%), and 161/2193 (7.3%) patients, respectively. Any metastases on PSMA PET/CT were observed in 762/2193 patients (34.7%), while distant metastases (miM1a-c) were detected in 557/2193 patients (25.4%). Overall, the proportion of patients with metastatic disease on PSMA PET/CT was 9.3% (205/2193), 18.5% (406/2193), 16.9% (370/2193), and 2.0% (43/2193) for miN1 (ie, regional lymph nodes without distant metastases), miM1a, miM1b, and miM1c, respectively. The prevalence of any and distant metastatic disease on PSMA PET/CT was higher in patients who were scanned with ^{18}F-PSMA-1007 than in those scanned with other radiotracers ($p < 0.001$). Patient characteristics of all patients and PSMA PET/CT findings are listed in Tables 1 and 2, respectively.

3.1. PSMA PET/CT findings within different PSA subgroups

Patients had a median PSA level at PSMA PET/CT of 14.1 ng/ml (IQR 8.2–31.2 ng/ml). As illustrated in Figure 1, the proportion of patients with any (miN1-M1a-c) and distant (miM1a-c) metastatic disease increased progressively with higher PSA levels. Among men with a PSA level of ∼10 ng/ml (and who had at least one high-risk feature), approximately 15% had any metastatic disease, while <10% had distant metastases. In contrast, of men with PSA levels of ∼100 ng/ml and above, the vast majority had any metastatic disease and distant metastatic (∼90% and ∼80%, respectively). It is expected that the percentages equal 100% in those with even much higher PSA values. For those with other PSA values, any metastatic disease (miN1-M1a-c) was detected in approximately 25% (PSA 15), 30% (PSA 20), 35% (PSA 35), 50% (PSA 50), and 70% (PSA 100). As PSA levels increased, a correlation with the proportion of patients diagnosed with distant metastatic disease (miM1a-c) was observed. The cohort exhibiting a PSA level of 50–100 ng/ml consisted of a relatively small number of patients, leading to observable

Table 1 – Descriptive statistics of all patients undergoing primary staging using prostate-specific membrane antigen PET/CT

	All patients (*n* = 2193)
Age at scan, median (IQR)	70 (64–75)
PSA at PET (ng/ml), median (IQR)	14.1 (8.2–31.2)
PSA subgroups, *n* (%)	
<10	765 (34.8)
≥10–15	379 (17.3)
>15–20	203 (9.3)
>20–35	352 (16.1)
>35–50	139 (6.3)
>50–100	155 (7.1)
>100	200 (9.1)
Clinical tumor stage, *n* (%)	
T1	776 (35.4)
T2a-b	663 (30.2)
T2c	130 (5.9)
T3	437 (19.9)
T4	53 (2.4)
Unknown	134 (6.1)
EAU risk classification, *n* (%)	
Low	22 (1.0)
Intermediate	602 (27.5)
High	1535 (70.0)
Unknown	34 (1.6)
Biopsy findings	*n* = 2117
Highest grade group according to ISUP, *n* (%)	
1	95 (4.5)
2	383 (18.1)
3	539 (25.5)
4	461 (21.8)
5	624 (29.5)
Unknown	15 (0.7)
Percentage of systematic cores with PCa, median (IQR)	50.0 (25.0–90.0)
MRI findings	*n* = 1553
Radiological tumor stage, *n* (%)	
Negative (T1)—organ confined (T2)	805 (51.8)
Extracapsular extension (T3a)	322 (20.7)
≥Seminal vesicle invasion (T3b)	362 (23.3)
Unknown	64 (4.1)
PI-RADS score, *n* (%)	
1–3	94 (6.1)
4	319 (20.5)
5	999 (64.3)
Unknown	141 (9.1)

CT = computed tomography; EAU = European Association of Urology; IQR = Interquartile range; ISUP = International Society of Urological Pathology; MRI = magnetic resonance imaging; PCa = prostate cancer; PET= positron emission tomography; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen.

fluctuations in the figure with minor upward and downward deviations.

3.2. Association of clinical parameters with PSMA PET/CT findings

The univariable logistic regression analysis demonstrated significant associations between all tested variables and the presence of (any) metastatic disease on PSMA PET/CT ($p < 0.001$). The multivariable logistic regression analysis showed a significant association between PSA subgroups and the presence of any (miN1-miM1a-c) and distant metastatic disease (miM1a-c) on PSMA PET/CT, with higher odds ratios (ORs) observed in higher PSA subgroups ($p < 0.001$; Table 3). Especially, ISUP GGs 4 and 5 (OR 1.19, 95% confidence interval [CI] 1.20–3.05, $p = 0.007$ and OR 2.95, 95% CI 1.90–4.59, $p < 0.001$, respectively), and more advanced rT stages, that is, ≥rT3b (OR 3.81, 95% CI 2.59–5.62, $p < 0.001$) demonstrated a significant association with any metastatic disease on PSMA PET/CT. Similar results were found for distant metastatic disease, although suspected cT stages and ISUP GG 3 were also significantly predictive (OR 1.59, 95% CI 1.02–2.49, $p = 0.042$ and OR 2.11, 95% CI 1.64–3.84, $p = 0.014$, respectively).

4. Discussion

PSMA PET/CT imaging has shown increasing adoption for use in both staging and restaging of PCa [5,6]. However, the exact value of this modern imaging technique in detecting and assessing metastatic disease in PCa is yet to be fully understood. This study evaluated the association between PSA level and the prevalence of any metastatic disease detected by PSMA PET/CT in a large contemporary cohort of patients with newly diagnosed PCa (PSA level >20 ng/ml, ISUP GG ≥3, and/or ≥rT3). Our findings highlight that PSA level, as well as other pretreatment prognostic variables, are strongly associated with the probability of detecting metastatic disease on PSMA PET/CT. At a median PSA level of 14.1 ng/ml, approximately one-third of patients had any metastatic disease, and approximately one-fourth

Table 2 – Prostate-specific membrane antigen PET/CT findings per anatomical location for the entire study population and per applied PSMA radiotracer

	All patients (*n* = 2193)	[18F]DCFPyL (*n* = 839)	[18F]PSMA-JK7 (*n* = 161)	[18F]PSMA-1007 (*n* = 264)	[68Ga]PSMA-11 (*n* = 929)	*p* value
PSMA PET findings, n *(%)*						
Prostate lesion(s)	2133 (97.3)	817 (97.4)	155 (96.3)	264 (100.0)	897 (96.6)	0.020
Any metastasis (miN1-M1a-c)	762 (34.7)	262 (31.2)	47 (29.2)	132 (50.0)	321 (34.6)	<0.001
Only regional lymph nodes (miN1)[a]	205 (9.3)	73 (8.7)	10 (6.2)	23 (8.7)	99 (10.7)	0.23
Distant metastases (miM1)	557 (25.4)	189 (22.5)	37 (23.0)	109 (41.3)	222 (23.9)	<0.001
Distant lymph nodes (miM1a)[b]	406 (18.5)	149 (17.8)	27 (16.8)	70 (26.5)	160 (17.2)	0.005
Bone (miM1b)	370 (16.9)	120 (14.3)	26 (16.1)	79 (29.9)	145 (15.6)	<0.001
Visceral (miM1c)	43 (2.0)	17 (2.0)	2 (1.2)	8 (3.0)	16 (1.7)	0.51

CT = computed tomography; mi = molecular imaging; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.
[a] Without M1 disease.
[b] Lymph node metastases outside the surgical template of the extended pelvic lymph node dissection.

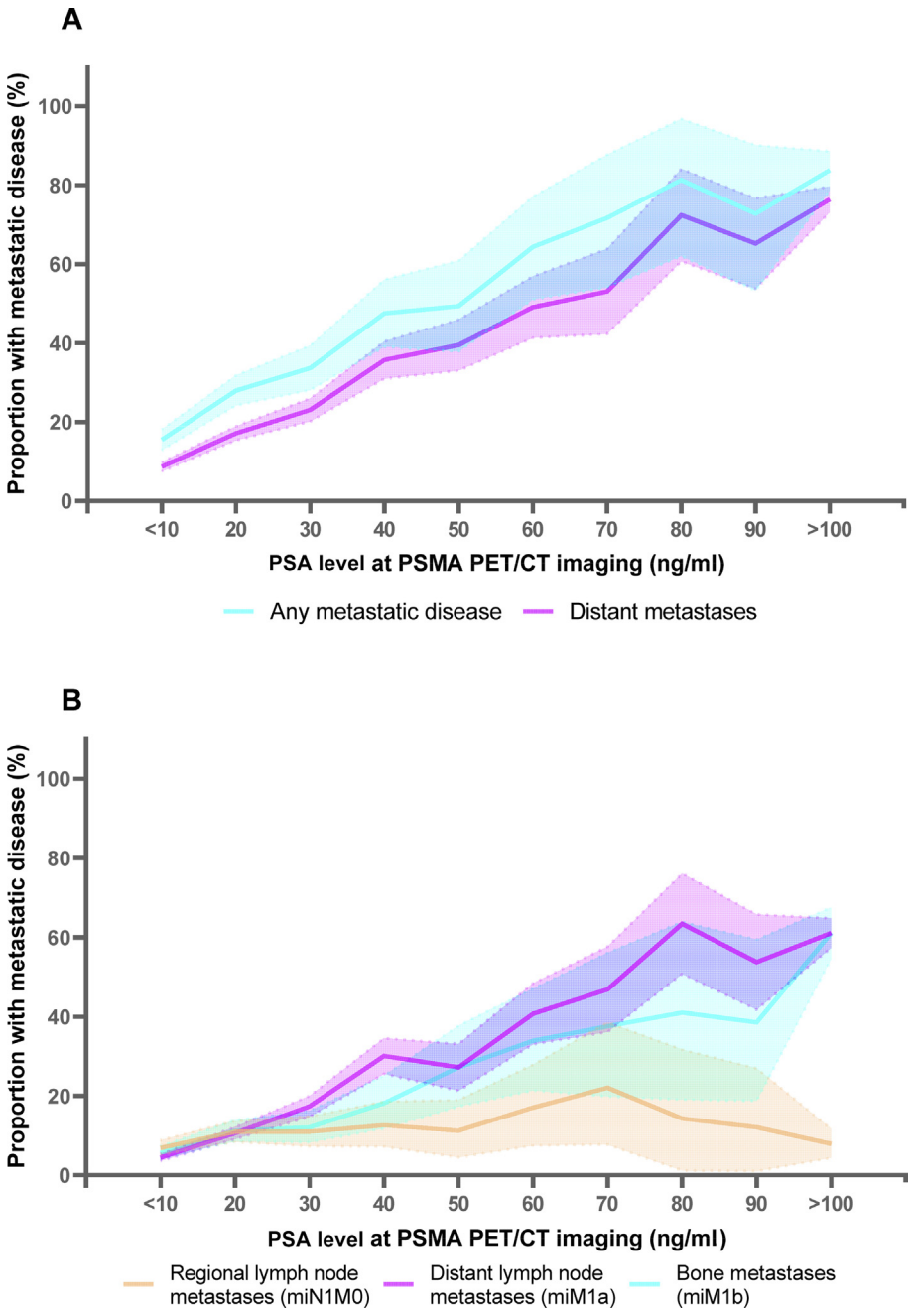


Fig. 1 – The proportion of patients with (A) any or distant metastatic disease and (B) the anatomical distribution of metastases shown by prostate-specific antigen (PSA) level on primary staging prostate-specific membrane antigen (PSMA) PET/CT. The proportion of patients with metastatic disease is displayed along with their 95% confidence interval. Patients were stratified into PSA subgroups with intervals of 10 ng/ml. The yellow line represents the patients with only regional lymph node metastases without the presence of any distant metastases. Owing to the limited prevalence of visceral metastases in the study, this figure does not include the proportion of patients with visceral metastases. mi = molecular imaging; PET/CT = positron emission tomography/computed tomography.

had distant metastatic disease detected at the time of initial diagnosis.

A limited number of studies have explored the association between PSA level and the prevalence of metastatic disease detected by PSMA PET/CT, focusing on patients opting for curative treatments such as radical prostatectomy or external beam radiotherapy [8–11]. While recognizing the limited clinical impact of PSMA PET/CT in low- and favorable intermediate-risk patients, we deliberately included these patients to offer a comprehensive analysis of metastatic incidences across all PCa risk groups. This approach provides nuanced insights into the association between PSA levels and metastasis within the broader epidemiological context of real-world PCa scenarios. In comparison with our study, Yaxley et al. [11] found an overall lower prevalence of metastatic disease in newly diagnosed PCa patients subjected to ^{68}Ga-PSMA PET/CT (12.1% vs 34.7%). By stratifying patients based on PSA subgroups (<10, 10–20, and >20

Table 3 – Logistic regression analyses predicting any (miN1-M1a-c) and distant metastatic disease (miM1a-c) on prostate-specific membrane antigen PET/CT in patients with primary prostate cancer[a]

	Any (miN1-M1a-c)			Distant (miM1a-c)		
	OR	95% CI	*p* value	OR	95% CI	*p* value
PSA subgroups (ng/ml)						
<10	Reference			Reference		
≥10–15	1.83	(1.20–2.79)	0.005	2.13	(1.23–3.70)	0.007
>15–20	2.18	(1.34–3.56)	0.002	2.40	(1.28–4.47)	0.006
>20–35	2.27	(1.45–3.57)	<0.001	2.54	(1.43–4.50)	0.001
>35–50	2.31	(1.21–4.39)	0.011	3.60	(1.72–7.49)	<0.001
>50–100	5.84	(3.07–11.12)	<0.001	6.82	(3.36–13.83)	<0.001
>100	7.48	(3.41–16.41)	<0.001	10.64	(4.78–23.71)	<0.001
Clinical tumor stage based on DRE						
Benign (T1)	Reference			Reference		
Suspected (≥T2)	1.21	(0.86–1.70)	0.27	1.59	(1.02–2.49)	0.042
Highest grade group according to ISUP						
1–2	Reference			Reference		
3	1.5	(0.95–2.36)	0.79	2.11	(1.64–3.84)	0.014
4	1.91	(1.20–3.05)	0.007	1.97	(1.06–3.65)	0.031
5	2.95	(1.90–4.59)	<0.001	3.18	(1.80–5.64)	<0.001
PI-RADS classification						
PI-RADS 1–3	Reference			Reference		
PI-RADS 4	1.06	(0.41–2.75)	0.90	0.42	(0.14–1.34)	0.14
PI-RADS 5	1.85	(0.76–4.52)	0.18	0.84	(0.31–2.30)	0.73
Radiological tumor stage on MRI						
Negative (T1)—organ confined (T2)	Reference			Reference		
Extracapsular extension (T3a)	1.49	(0.98–2.47)	0.060	1.55	(0.89–2.70)	0.12
≥Seminal vesicle invasion (T3b)	3.81	(2.59–5.62)	<0.001	4.36	(2.67–7.11)	<0.001

CI = confidence interval; CT = computed tomography; DRE = digital rectal examination; ISUP = International Society of Urological Pathology; mi = molecular imaging; MRI = magnetic resonance imaging; OR = odds ratio; PET = positron emission tomography; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen.

[a] Univariate significant variables added to the analysis: PSA subgroups ($p < 0.001$), clinical tumor stage based on DRE ($p < 0.001$), highest ISUP grade group ($p < 0.001$), PI-RADS classification ($p < 0.001$), and radiological tumor stage ($p < 0.001$).

ng/ml), metastatic disease was detected in 8.2%, 14.9%, and 43.0% of patients, respectively. The lower prevalence of metastatic disease could be attributed to differences in baseline characteristics, with the patients having lower PSA levels (a median of 6.5 ng/ml) and more favorable prognostic risk factors (lower ISUP GGs and less advanced radiological tumor stages). Meyrick et al. [10], Klingenberg et al. [9], and Chikatamarla et al. [8], on the contrary, reported metastatic disease prevalence more in line with our study, with rates of, respectively, 34.3%, 35.3%, and 34.0% among newly diagnosed PCa patients. Confirming our data, the risk of metastatic disease increased with rising PSA levels, ranging from 18.5% to 28.7% for PSA levels <10 ng/ml and 50.2% to 55.8% for PSA levels >20 ng/ml. Their comparable prevalence of metastatic disease could be attributed to the similarity in patient cohorts and comparable baseline characteristics.

To our knowledge, no other study has investigated the probability of metastatic disease in larger series of patients with PSA subgroups exceeding 20 ng/ml. Previous studies have aggregated patients with PSA values of >20 ng/ml, but the prevalence of metastatic disease varies significantly within this range, ranging from 36.1% for PSA values 20–35 ng/ml to 87.5% for PSA values ≥100 ng/ml in the present study. Gaining insights into these specific subgroups and understanding their corresponding metastatic potentials hold paramount importance as we strive for more personalized management and diagnostic approaches for patients with newly diagnosed PCa [17]. In this context, it is noteworthy that PSMA-negative patients also occur with PSA values >20 ng/ml, warranting consideration for alternative screening methods to detect metastases. The fact that PSMA-directed targeted prostate biopsies have shown promising results opens the possibility of avoiding the need for MRI prostate in certain cases [18]. By focusing more on real-world data and a wider range of PSA subgroups, we can optimize the diagnostic process, expedite timely detection of metastatic disease, and maximize the efficient utilization of health care resources. Nevertheless, the clinical benefit of early metastasis detection is yet to be established.

In literature, a higher prevalence of nonspecific tracer uptake, particularly in osseous structures, has been reported for ^{18}F-PSMA-1007 than for other PSMA radiotracers. This uptake could be attributed to physiological uptake or benign conditions such as degenerative changes, fibrous dysplasia, or post-traumatic disorder [19–22]. This might potentially explain the increased detection rate of ^{18}F-PSMA-1007 for metastases on PET/CT, as reported in our study. However, it is important to acknowledge that other factors (eg, scan protocols) may also have an influence on these results. In addition to the PSA level, other clinical prognostic factors were also shown to be significantly associated with the detection of metastatic disease on PSMA PET/CT. Notably, both a higher ISUP GG and more advanced clinical/radiological T stages were found to be significantly associated with an increased prevalence of metastatic disease. This is consistent with the findings of previous studies [8–11]. Similar to previous studies, metastatic disease was predominantly present in men with ISUP GGs ≥4 and radiological tumor stages ≥rT3b, highlighting significant risk

factors for metastatic disease. Incorporating these clinical characteristics in PSMA PET/CT imaging decisions, regardless of PSA level, is essential for identifying patients at an elevated risk of metastasis and guiding appropriate management strategies effectively. The current findings may serve as the basis for improved risk stratification nomograms, enabling better patient selection for metastatic screening with PSMA PET/CT and, thereby, advancing personalized medicine.

This study is not devoid of limitations. First, given the retrospective nature of this study, the presence of a selection bias cannot be ruled out, meaning that results should be interpreted with caution. The outcome of this study depends highly on the indication for performing PSMA PET/CT imaging. All the selected patients had at least one adverse prognostic factor, so data regarding the probability of metastatic disease in those without any adverse prognostic factors are yet unknown. However, it is felt that the prevalence of metastatic disease in patients with no adverse prognostic factors is only very low. Second, recognizing the speculative nature of the PSA subgroups, our study emphasizes clinical relevance by focusing on PSA levels exceeding 20 ng/ml, facilitating a comprehensive analysis of the metastatic potential across diverse PCa cohorts. Third, due to the lack of histopathological confirmation, it remains unclear whether the suspected metastases detected on PSMA PET/CT were true PCa metastases. Finally, the use of different PSMA tracers and scan protocols across centers might have influenced our findings. Nevertheless, despite the aforementioned limitations, the real-world data obtained in this study offer valuable insights that can be applied in routine clinical practice.

5. Conclusions

This is the first epidemiological study in a large contemporary series of patients with newly diagnosed PCa that demonstrated the association between PSA level and metastatic disease using novel PSMA PET/CT imaging. A clear association was found between PSA level and the prevalence of metastatic disease at first diagnosis as well as with the extent of disease. Data from this study can be used to counsel patients and clinicians on the probability of metastatic disease at the time of PSA screening, provide guidance on existing guidelines, and form the basis of new risk group nomograms, thereby enhancing the appropriateness of PSMA PET.

***Author contributions*:** Wietske I. Luining had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Luining, Hagens, Meijer, Oprea-Lager, Vis.
Acquisition of data: Luining, Hagens, Ringia, de Weijer, Bektas, Knol, Roeleveld, Srbljin, Weltings, Koppes.
Analysis and interpretation of data: Luining, Hagens.
Drafting of the manuscript: Luining, Hagens.
Critical revision of the manuscript for important intellectual content: Hagens, Ettema, Meijer, van Moorselaar, van Leeuwen, Oprea-Lager, Vis.
Statistical analysis: Luining, Hagens.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Oprea-Lager, Vis.
Other: None.

Financial disclosures: Wietske I. Luining certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2023.12.001.

References

[1] Anttinen M, Ettala O, Malaspina S, et al. A prospective comparison of 18F-prostate-specific membrane antigen-1007 positron emission tomography computed tomography, whole-body 1.5 T magnetic resonance imaging with diffusion-weighted imaging, and single-photon emission computed tomography/computed tomography with traditional imaging in primary distant metastasis staging of prostate cancer (PROSTAGE). Eur Urol Oncol 2021;4:635–44.
[2] Hofman MS, Lawrentschuk N, Francis RJ, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet 2020;395:1208–16.
[3] Perera M, Papa N, Roberts M, 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 2020;77:403–17.
[4] Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma: definition of grading patterns and proposal for a new grading system. Am J Surg Pathol 2016;40:244–52.
[5] Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer—2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2021;79:243–62.
[6] Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part I: risk stratification, shared decision making, and care options. J Urol 2018;199:683–90.
[7] Hagens MJ, Luining WI, Jager A, et al. The diagnostic value of PSMA PET/CT in men with newly diagnosed unfavorable intermediate-risk prostate cancer. J Nucl Med 2023;64:1238–43.
[8] Chikatamarla VA, Okano S, Jenvey P, et al. Risk of metastatic disease using [(18)F]PSMA-1007 PET/CT for primary prostate cancer staging. EJNMMI Res 2021;11:128.
[9] Klingenberg S, Jochumsen MR, Ulhøi BP, et al. 68Ga-PSMA PET/CT for primary lymph node and distant metastasis NM staging of high-risk prostate cancer. J Nucl Med 2021;62:214–20.
[10] Meyrick DP, Asokendaran M, Skelly LA, Lenzo NP, Henderson A. The role of 68Ga-PSMA-I&T PET/CT in the pretreatment staging of primary prostate cancer. Nucl Med Commun 2017;38:956–63.
[11] Yaxley JW, Raveenthiran S, Nouhaud FX, et al. Risk of metastatic disease on (68) gallium-prostate-specific membrane antigen positron emission tomography/computed tomography scan for primary staging of 1253 men at the diagnosis of prostate cancer. BJU Int 2019;124:401–7.
[12] Turkbey B, Rosenkrantz AB, Haider MA, et al. Prostate Imaging Reporting and Data System version 2.1: 2019 update of Prostate

Imaging Reporting and Data System version 2. Eur Urol 2019;76:340–51.
[13] Bouvet V, Wuest M, Jans H-S, et al. Automated synthesis of [18F] DCFPyL via direct radiofluorination and validation in preclinical prostate cancer models. EJNMMI Res 2016;6:40.
[14] Cardinale J, Martin R, Remde Y, et al. Procedures for the GMP-compliant production and quality control of [18F] PSMA-1007: a next generation radiofluorinated tracer for the detection of prostate cancer. Pharmaceuticals 2017;10:77.
[15] Ceci F, Oprea-Lager DE, Emmett L, et al. E-PSMA: the EANM standardized reporting guidelines v1.0 for PSMA-PET. Eur J Nucl Med Mol Imaging 2021;48:1626–38.
[16] Seifert R, Emmett L, Rowe SP, et al. Second version of the prostate cancer molecular imaging standardized evaluation framework including response evaluation for clinical trials (PROMISE V2). Eur Urol 2023;83:405–12.
[17] Jochumsen MR, Bouchelouche K. PSMA PET/CT for primary staging of prostate cancer—an updated overview. Semin Nucl Med. In press. https://doi.org/10.1053/j.semnuclmed.2023.07.001.
[18] Bodar YJL, Jansen BHE, van der Voorn JP, et al. Detection of prostate cancer with (18)F-DCFPyL PET/CT compared to final histopathology of radical prostatectomy specimens: is PSMA-targeted biopsy feasible? The DeTeCT trial. World J Urol 2021;39:2439–46.
[19] Arnfield EG, Thomas PA, Roberts MJ, et al. Clinical insignificance of [(18)F]PSMA-1007 avid non-specific bone lesions: a retrospective evaluation. Eur J Nucl Med Mol Imaging 2021;48:4495–507.
[20] Grünig H, Maurer A, Thali Y, et al. Focal unspecific bone uptake on [(18)F]-PSMA-1007 PET: a multicenter retrospective evaluation of the distribution, frequency, and quantitative parameters of a potential pitfall in prostate cancer imaging. Eur J Nucl Med Mol Imaging 2021;48:4483–94.
[21] Hagens MJ, Oprea-Lager DE, Vis AN, et al. Reproducibility of PSMA PET/CT imaging for primary staging of treatment-naïve prostate cancer patients depends on the applied radiotracer: a retrospective study. J Nucl Med 2022;63:1531–6.
[22] Wondergem M, van der Zant FM, Broos WAM, Knol RJJ. Matched-pair comparison of (18)F-DCFPyL PET/CT and (18)F-PSMA-1007 PET/CT in 240 prostate cancer patients: interreader agreement and lesion detection rate of suspected lesions. J Nucl Med 2021;62:1422–9.