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REVIEW

Equivocal bone lesions on PSMA PET/CT: systematic review and meta-analysis on their prevalence and malignancy rate

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Abstract

Purpose Prostate-specific membrane antigen (PSMA) PET/CT has an established reliable diagnostic performance for detecting metastases in prostate cancer. However, there are increasing instances of scans demonstrating equivocal bone lesions, with non-specific uptake and without a definite benign or malignant CT correlate. To date, the prevalence, malignancy rate, and relationship with radioligand type ([^{18}F] PSMA-1007 vs. others ([^{68}Ga]Ga-PSMA-11 and [^{18}F] DCFPyL) for these equivocal lesions have not been extensively established.

Methods A systematic review and meta-analysis was conducted on equivocal bone lesions. Pubmed and EMBASE were searched up to December 11, 2023. Quality of the studies was evaluated using QUADAS-2. The following proportions were pooled using random-effects model: (1) prevalence of equivocal bone lesions (i.e., number of patients with one or more equivocal bone lesions/number of patients with PSMA PET/CT) and (2) their malignancy rates (i.e., number of metastases/number of equivocal bone lesions). Subgroup analyses based on radioligand type, clinical setting, and definition of equivocal bone lesion were performed.

Results Twenty-five studies (4484 patients) were included. Pooled prevalence of equivocal bone lesions was 20% (95%CI, 12–31%). [^{18}F]PSMA-1007 was associated with a greater prevalence of equivocal lesions compared with other radioligands: 36% (95%CI 26–48%) vs. 8% (95%CI, 4–14%), respectively, $p < 0.01$. Pooled malignancy rate of equivocal bone lesions was 14% (95%CI, 7–25%). [^{18}F]PSMA-1007 was associated with a lower malignancy rate compared to other radioligands: 8% (95%CI, 3–19%) vs. 29% (95%CI, 17–44%), respectively, $p = 0.01$. There were no signficant difference in prevalence or malignancy rate between subgroups stratified to clinical setting or definition of equivocal bone lesions ($p = 0.32$–0.60).

Conclusions Equivocal bone lesions are often encountered on PSMA PET/CT but exihibit a low malignancy rate. Compared to other radioligands, [^{18}F]PSMA-1007 requires special attention as it is associated with a higher frequency and lower rate of metastasis.

Keywords Prostate specific membrane antigen · Positron emission tomography · Prostate cancer · Equivocal bone lesion · Unspecific bone uptake · [^{18}F]PSMA-1007

Introduction

Prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) has revolutionized the way prostate cancer is diagnosed and managed. The high level of PSMA expression in prostate cancer cells allows PSMA PET/CT to outperform conventional imaging in detecting not only recurrent and metastatic disease in the setting of biochemical failure, but also for initial staging of newly diagnosed intermediate- and high-risk prostate cancer [1]. Over the past decade, multiple clinical trials have demonstrated high accuracy of PET/CT using various PSMA-targeted radioligands and studies have shown that PSMA PET/CT findings impact the clinical management in approximately half of prostate cancer patients evaluated with such studies [2–7]. As a result, there

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has been widespread adoption of PSMA PET/CT across the globe along with integration into clinical practice guidelines [8, 9].

Despite its initial success, there is increasing awareness of several pitfalls of PSMA PET/CT, one of which is the presence of equivocal bone lesions with PSMA uptake. These often lead to further workup, and it has been suggested that many are ultimately benign (or represent a "false positive" finding for metastasis) [10]. There is also concern that certain PSMA-targeted radioligands such as [^{18}F]F-PSMA-1007 – which was initially considered advantageous for better assessing the prostate (or prostatectomy bed) due to its predominant excretion through the liver, are associated with a higher frequency of indeterminate bone lesions due to "unspecific bone uptake" [11]. Ambiguity of the significance of these equivocal lesions interpreted as being malignant may in some cases exclude such patients from receiving curative-intent local definitive therapy (e.g., prostatectomy or radiation treatment). As a means to address this issue, standardized reporting schemes such as PSMA Reporting and Data System (PSMA-RADS), Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE), and European Association of Nuclear Medicine PSMA (E-PSMA) standardized reporting guidelines have been proposed to improve the interpretation and communication of findings on PSMA PET [12–15]. In PSMA-RADS, a bone lesion is assigned a score of "3B" if it demonstrates equivocal uptake on PET along with CT appearance which is not definitive but also not atypical for malignancy [12]. These lesions are recommended to undergo additional imaging, biopsy, or follow-up to determine their clinical significance. Nevertheless, the clinical significance of equivocal bone lesions on PSMA PET/CT and how to best use this information to manage the patient's clinical treatment is still unclear.

Therefore, we conducted a systematic review and meta-analysis to evaluate (1) the prevalence of equivocal bone lesions on PSMA PET/CT, (2) the malignancy rate of equivocal bone lesions, and (3) the relationship between type of radioligand and equivocal bone lesions.

Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [16]. A study protocol was registered a priori to the Prospective Register of Systematic reviews (no. CRD42023486697) [17].

Search strategy

PubMed and EMBASE databases were searched up to December 11, 2023 to identify studies investigating equivocal bone lesions on PSMA PET/CT. The search query constructed based on key words ("prostate", "PSMA", "PET", "equivocal", and "bone") and their synonyms was as follows: Prostate AND ((PSMA OR prostate-specific membrane antigen) AND ("positron emission tomography" OR PET)) AND ("PSMA-RADS" OR ((unspecific OR nonspecific OR equivocal OR indeterminate) AND (bone OR skeletal OR osseous))). The study selection process was performed by two reviewers (S.W. and H.A.V.) in consensus.

Inclusion and exclusion criteria

Studies were included if they were relevant to the Patient, Intervention, Comparator, Outcome framework [18]: (1) "patients" with prostate cancer (regardless of clinical setting), (2) PSMA PET/CT as "intervention" (regardless of type of PSMA-targeted radioligand) and interpretation with or without using PSMA-RADS, (3) No "comparator", and (4) proportion of patients with equivocal bone lesions and their malignancy rates as "outcome". We excluded studies if they met any of the following criteria: (1) publication types other than original articles or conference abstracts (e.g., review articles, editorials, and case reports), (2) cohort of <10 patients, (3) insufficient information in the study to extract proportion relevant to the research question (i.e., prevalence of equivocal bone lesions and their malignancy rates), and (4) overlapping cohorts. When two or more studies were based on overlapping (or identical) cohorts, the one with more comprehensive and/or updated data was selected.

Data extraction and quality assessment

The following characteristics of the studies were tabulated using a standardized form: (1) study – author name(s), publication year, patient enrollment period, institution, country, design (prospective vs. retrospective); (2) clinical – age, clinical setting (e.g., primary staging, biochemical recurrence), Gleason score, prostate-specific antigen (PSA) level, reference standard for determining if equivocal bone lesions were malignant or not; and (3) PET – vendor, model, type of radioligand, injected dose, uptake time, acquisition time, definition of equivocal bone lesion (e.g., based on PSMA-RADS vs. other in-house criteria), number of patients with equivocal bone lesions, number of equivocal bone lesions, and number of equivocal bone lesions that were deemed malignant.

Assessments of the quality of the studies and their risk of bias were done based on Quality Assessment of Diagnostic

Accuracy Studies-2 (QUADAS-2) [19]. All 4 domains (*patient selection, index test, reference standard*, and *flow and timing*) were assessed for studies evaluating the malignancy rates. However, only two domains (*patient selection and index test*) were assessed for studies that evaluated the prevalence of equivocal bone lesions. As evaluating the prevalence of equivocal bone lesions does not directly involve correlating them to a "reference standard", the other two domains (*reference standard* and *flow and timing*) were not relevant for assessing quality and bias specifically for these studies. Both the data extraction and quality assessment were first done independently by two authors (S.W. and D.F.) and discrepancies were resolved by consensus with a third author (H.A.V.).

Data synthesis and analysis

The primary outcomes of this meta-analysis were: (1) the prevalence of equivocal bone lesions defined as the proportion of patients that had one or more equivocal bone lesions among all patients that underwent PSMA PET/CT and (2) the malignancy rate of equivocal bone lesions defined as the proportion of lesions that were deemed to be metastasis based on the reference standard among all evaluated equivocal bone lesions. The secondary outcomes were to explore heterogeneity by performing subgroup analyses, most importantly stratified to the type of PSMA-targeted radioligand ([18 F]PSMA-1007 vs. others [[68Ga]Ga-PSMA-11 or [18 F]DCFPyL], [18 F]PSMA-1007 vs. [68Ga]Ga-PSMA-11, and [18 F]PSMA-1007 vs. [18 F]DCFPyL]), but also by additionally relevant subgroups such as clinical setting (e.g., primary staging, biochemical recurrence, etc.) or definition of equivocal bone lesions (e.g., based on PSMA-RADS).

Pooling of the proportions and calculation of their 95% confidence intervals (CI) were done using a random-effects model with the "meta" package in statistical software R (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria) [20]. Heterogeneity was assessed with the Higgins I^2 test [21]. Heterogeneity was explored by comparing pooled proportions of the subgroups [22]. Publication bias was assessed with the Egger test and visualized using the funnel plot [23]. P values < 0.05 were considered statistically significant.

Results

Literature search

Three-hundred and twenty-two articles were initially identified from the systematic database search. After removal of 96 duplicates and exclusion of 168 papers by screening of titles and abstracts, 44 articles were considered potentially eligible. Upon full-text review, 19 of these studies were excluded for the following reasons (Supplementary Table 1): study does not deal with equivocal bone lesions ($n = 3$); equivocal bone lesions and equivocal soft tissue lesions were not separately documented ($n = 6$); overlapping patient cohort ($n = 8$); and topic deals with equivocal bone lesions on PSMA PET/CT but details of neither their prevalence nor malignancy rates were provided ($n = 2$). Ultimately, 25 studies (4484 patients) were included in the systematic review and meta-analysis (24–48). Flowchart for study selection is shown in Fig. 1.

Characteristics of included studies

The characteristics of the included studies are summarized in Tables 1, 2 and 3. Among all 25 studies, 8 (32%) evaluated the prevalence of equivocal bone lesions only [28, 30–32, 35, 40, 42, 48], 3 (12%) the malignancy rate of equivocal bone lesions only [34, 45, 47], and the remaining 14 (56%) both the prevalence and the malignancy rates of equivocal bone lesions [24–27, 29, 33, 36–39, 41, 43, 44, 46]. Most studies were retrospective in design ($n = 22$, 88%) [24–26, 28–35, 37–39, 41–48] and performed at single centers ($n = 23$, 92%) [24–28, 30–33, 35–48]. PSMA PET was performed for primary staging in 6 studies (24%) [27, 33, 35, 37, 43, 48], biochemical recurrence in all or most of the patients in 6 (24%) [25, 26, 30, 34, 41, 45], and a mixed cohort in 9 (36%) [24, 28, 29, 32, 38–40, 46, 47]. In the remaining, one study (4%) specifically included patients with non-detectable PSA levels after RP and the remaining 3 (12%) did not report cohort characteristics [36]. [^{18}F]PSMA-1007 was used in 13 studies (52%) [24–30, 32, 35–37, 44, 45], [^{68}Ga]Ga-PSMA-11 in 6 (24%) [31, 34, 39, 42, 43, 48], [^{18}F]DCFPyL in 3 (12%) [35, 38, 47], and a combination of [^{18}F]PSMA-1007 and non-[^{18}F]PSMA-1007 radioligands in 3 (12%) [33, 41, 46]. In 9 studies (36%), PSMA PET/CT was interpreted and equivocal bone lesions were accordingly defined per PSMA-RADS version 1.0 [24, 26, 33–35, 38, 43, 46, 47]. In the 16 remaining studies, various definitions were used (or details were not provided), most common being PSMA uptake without a morphologic correlate on CT ($n = 5$, 20%) [27, 32, 36, 37, 41]. Most of the studies that evaluated the malignancy rate of equivocal bone lesions (13/17 [76.5%]) used the best value comparator (BVC; a combination of imaging, clinical, histopathologic, or biochemical evaluations such as response to therapy) as the reference standard for determining whether the equivocal bone lesion was malignant or not [24, 25, 27, 29, 33, 34, 37–39, 41, 43, 46, 47]. The other studies used the following reference standards: biopsy ($n = 1$, 5.9%) [45], magnetic

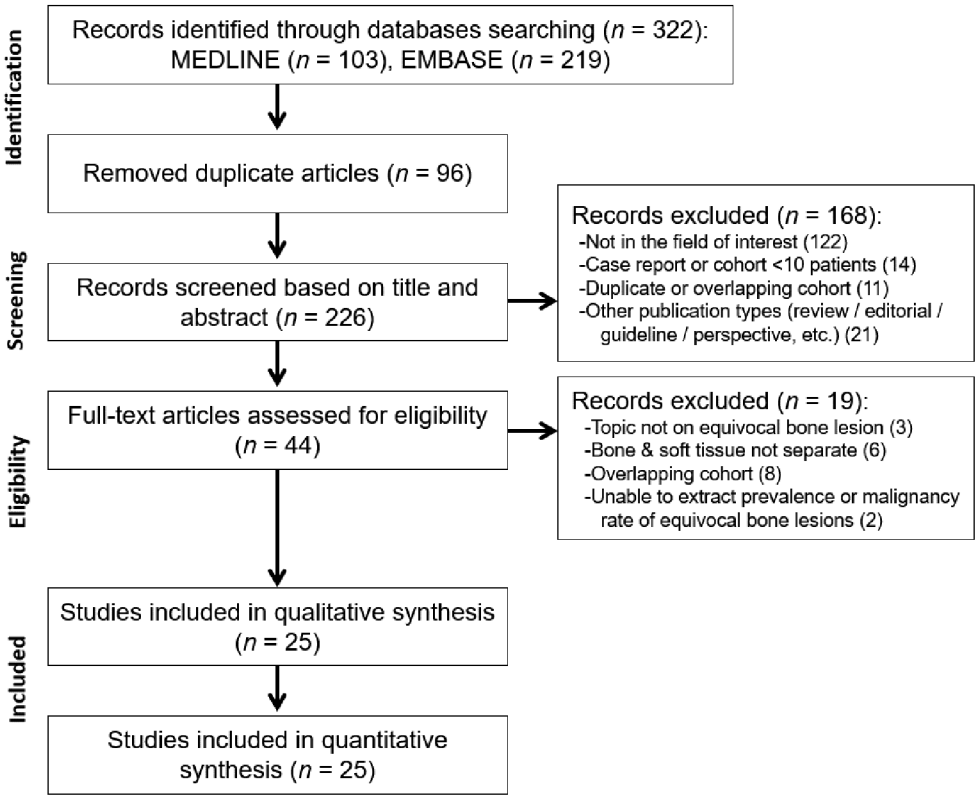


Fig. 1 PRISMA flowchart summarizing study selection process. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

resonance imaging (MRI) ($n = 2$, 11.8%) [26, 44], and PSA kinetics ($n = 1$, 5.9%) [36].

Quality and risk of bias

The overall quality of the included studies was considered moderate to good, with 13 (76.5%) of the 17 studies evaluating malignancy rate of equivocal bone lesions satisfying 4 or more of the 7 QUADAS-2 domains and 5 (62.5%) of the 8 studies only evaluating the prevalence of equivocal bone lesions satisfying 3 or more of the 4 evaluated QUADAS-2 domains. The detailed breakdown of QUADAS-2 assessments are provided in Fig. 2.

For patient selection, 2 studies were considered at high risk for bias and had high concern for applicability: in one study, PSMA PET/CT was performed in patients that had undetectable PSA after prostatectomy [36] and another study only evaluated patients who were referred for PSMA PET-guided biopsies [45]. Another study had an unclear risk of bias as it was not explicitly mentioned whether patient enrollment was consecutive or not [37].

Regarding the index test, in the aforementioned study where patients had undetectable PSA after prostatectomy, readers were not blinded and were aware of this unique clinical setting, resulting in a high risk of bias [36]. In another study, PSMA PET was interpreted alone – *specifically without correlation with CT* – which not only negatively influences the diagnostic accuracy of PSMA PET (*high risk of bias*), but also is not applicable to current day practice where they are interpreted simultaneously (*high concern for applicability*) [39]. Most other studies ($n = 12$) were at unclear risk of bias as it was not explicitly stated whether PSMA PET/CT was interpreted blinded to the outcome.

In the reference standard domain, only one study had low risk of bias, as it exclusively was based on histopathological assessment of PSMA-PET guided biopsy [45]. However, this was considered to have high concern for applicability, as it would not be feasible to biopsy all equivocal bone lesions in daily practice. Three studies had high risk of bias as they were based on only MRI correlation ($n = 2$) [26, 44] or only PSA kinetics ($n = 1$) [36]. All 13 other studies were considered at unclear risk as they were based on the BVC.

Finally, in the flow and timing domain, those 13 studies (at unclear risk in the reference standard domain) were considered to be at high risk of bias since individual patients in the study had different reference standard by definition (i.e., BVC). Two additional studies were at unclear risk of bias as the interval between PSMA PET/CT and the reference standard was not explicit [26, 44].

Prevalence of equivocal bone lesions

Twenty-two studies reported the prevalence of equivocal bone lesions on PSMA PET/CT. The prevalence in each

Table 1 Study and patient characteristics

First author	Institution	Enrollment period	Prospective design	No. of patients	Age (years)	Clinical setting (No. of patients in subgroup)	PSA (ng/ml)	Grade group
Arnfield [24]	Royal Brisbane and Women's Hospital	2018–2019	No	214	70, SD 7	Primary 100; BCR 114	5.0*, 0.95–10	NR, 1–5
Bohil [25]	Royal Liverpool University Hospital	NR (12 months)	No	203	64*, 49–82	Primary 14; Restaging 189	NR, 0.04–299	NR, 1–5
Dietlein [26]	University Hospital of Cologne	2017–2018	No	27	67, SD 8	Primary 2; BCR 25	3.3, 0.3–27.7	3, 1–5
Ettala [27]	University of Turku and Turku University Hospital	2018–2019	Yes	79	70, SD 7	Primary	12*, 3–2000	4, 1–5
Foley [28]	Royal United Hospitals Bath	2019–2020	No	16	NR	Primary 7; BCR 9	72, NR (Primary); 3.8, NR (BCR)	NR
Grunig [29]	University Hospital Zurich, Cantonal Hospital Lucerne, Cantonal Hospital St. Gallen, Cantonal Hospital Baden	2019–2020	No	348	71*, IQR 66–76	Primary 120; BCR 227	2.5*, IQR 0.5–9.3	3, 1–5
Hoberück [30]	University Hospital Carl Gustav Carus	NR	No	40	71*, SD 8	Primary 6; BCR 28; Follow-up 6	3.8*, 0.3–113.7	4, 1–5
Janssen [31]	Charité	2013–2017	No	54	70, NR	NR	38.4, SD 77.9	NR
Knappe [32]	Bern University Hospital	2019–2021	No	36	NR	NR	NR	NR
Kuten [33]	TelAviv Sourasky Medical Center	2015–2020	No	406	65, SD 11	Primary	0.5, 0–2.9	3, 2–4
Letang [34]	Institut Bergonié & Institut de Cancerologie de l'Ouest	2018–2020	No	298	71, 58–87	BCR	2.9, SD 2.5	NR, 1–5
Mihatsch [35]	University Hospital of Würzburg	2018–2021	No	18	70, SD 8	Primary	180.4, 4.8–1690.0	4, 2–5
Orevi [36]	Hadassah Medical Center	2020–2021	Yes	17	66, 53–74	Non-detectable PSA after RP	11.9, range 3.4–41 (pre-RP)	NR, 3–5
Paone [37]	Imaging Institute of Southern Switzerland	NR	No	80	NR	Primary	23.7*, NR	NR
Phelps [38]	National Cancer Institute	2017–2021	No	243	66*, 53–79	Primary 13; BCR 35	4.0*, 0.4–203.8	3, 1–5
Pyka [39]	Technical University of Munich	2012–2015	No	126	69, range 49–89	Primary 37; BCR 49; mCRPC 40	43.5, 2.7–500 (Primary); 20.9, 0.3–490 (BCR); 446, 0.97–3333 (mCRPC)	NR
Rowe [40]	Johns Hopkins University School of Medicine	2016–2016	Yes	16	66, 52–77	Mixed	4.4*, 0.2–224.5	4, 2–5
Seifert [41]	University Hospital Essen	2020–2020	No	792	71*, IQR 70–74	BCR	0.5*, IQR 0.2–1	3, 1–5
Shanmugasundaram [42]	Nepean Hospital	2015–2018	No	532	69*, IQR 63–73	NR	9.6*, IQR 6.2–17	4, IQR 2–5
Simsek [43]	Istanbul University	2015–2019	No	356	68, 47–91	Primary	16.42*, 1.29–7013	4, 1–5
Spurr [44]	Bristol Royal Infirmary	2021	No	112	NR	NR	NR	NR
Vollnberg [45]	Bern University Hospital	2019–2020	No	11	67*, 51–79	Primary 2; BCR 9	1.8, 0.3–5.2 (BCR); 110 ($n=1$, Primary)	2, 2–4
Wondergem [46]	Noordwest Ziekenhuisgroep	2019	No	240	NR	Primary 169; BCR 21; Follow-up 30	12*, 0.1–577	NR

Table 1 (continued)

First author	Institution	Enrollment period	Prospective design	No. of patients	Age (years)	Clinical setting (No. of patients in subgroup)	PSA (ng/ml)	Grade group
Yin [47]	Johns Hopkins University School of Medicine	2016–2017	No	110	63, SD 6	Primary 6; BCR 16	13.0, 0.3–37.8	NR
Zacho [48]	Aalborg University Hospital	2016–2018	No	112	68, 48–78	Primary	34.5, 1.7–276	5, 2–5

BCR = biochemical recurrence; IQR = interquartile range; mCRPC = metastatic castration-resistant prostate cancer; Primary = primary staging; PSA = prostate specific membrane antigen; RP = radical prostatectomy; SD = standard deviation

Continuous data are summarized as mean (age, PSA) or median (grade group) and ranges unless otherwise specified (e.g., median, standard deviation, or interquartile range)

*median

study ranged from 0 to 78% and the pooled prevalence across all 22 studies was 20% (95% CI: 12–31%) (Fig. 3). Substantial heterogeneity was present ($I^2 = 95.8\%$). There was no significant publication bias according to the Egger's test ($p = 0.21$) and funnel plot (Supplementary Fig. 1A). At subgroup analyses, type of PSMA-targeted radioligand was associated with heterogeneity ($p < 0.01$), but not the clinical setting ($p = 0.32$) or how equivocal bone lesions were defined ($p = 0.42$) (Table 4). Specifically, studies that used [^{18}F]PSMA-1007 ($n = 14$) were associated with a greater prevalence compared to those that used other radioligands ([^{68}Ga]Ga-PSMA-11 and [^{18}F]DCFPyL, $n = 10$): 36% (95% CI 26–48%) vs. 8% (95% CI 4–14%), respectively (Fig. 4). Subgroup analysis comparing [^{18}F]PSMA-1007 with each of the radioligands are shown in Supplementary Fig. 2.

Malignancy rate of equivocal bone lesions

Seventeen studies reported the malignancy rate of equivocal bone lesions on PSMA PET/CT. The prevalence in each study ranged from 0 to 77% and the pooled prevalence across all 17 studies was 14% (95% CI: 7–25%) (Fig. 5). Substantial heterogeneity was present ($I^2 = 90.1\%$). There was no significant publication bias according to the Egger's test ($p = 0.52$) and funnel plot (Supplementary Fig. 1B). At subgroup analyses, type of PSMA-targeted radioligand was associated with heterogeneity ($p = 0.01$), but not the clinical setting ($p = 0.32$) or how equivocal bone lesions were defined ($p = 0.60$) (Table 4). Specifically, studies that used [^{18}F]PSMA-1007 ($n = 12$) were associated with a lower malignancy rate compared to those that used other radioligands ([^{68}Ga]Ga-PSMA-11 and [^{18}F]DCFPyL, $n = 8$): 8% (95% CI 3–19%) vs. 29% (95% CI 17–44%), respectively (Fig. 6). Subgroup analysis comparing [^{18}F]PSMA-1007 with each of the radioligands are shown in Supplementary Fig. 3.

Discussion

In this systematic review and meta-analysis, we investigated the prevalence of equivocal bone lesions on PSMA PET/CT in patients with prostate cancer and how often they are malignant. Overall, equivocal bone lesions were often encountered, approximately in 1 of 5 patients (pooled prevalence = 20%, 95% CI: 12–31%). However, the rate of malignancy was low with approximately 1 in 7 equivocal bone lesions deemed to be metastatic disease (pooled malignancy rate = 14%, 95% CI: 7–25%). The results of our study substantiate on a larger scale, the trends we have been observing in smaller individual reports. Although PSMA PET/CT has revolutionized how we manage patients with prostate cancer, our study highlights that we need to keep in mind this important pitfall of equivocal bone lesions. There needs to be increased awareness to all stakeholders involved, including expert and community nuclear medicine physicians and radiologists who interpret PSMA PET/CT, referring physicians, and patients and caregivers in order to further optimize clinical recommendation based on the most accurate or reliable information which is clinically available [49].

Type of radioligand was a significant factor of heterogeneity between the included studies. Specifically, the prevalence of equivocal bone lesions was higher and their malignancy rate was lower in studies using [^{18}F]PSMA-1007 (pooled estimate = 36%, 95% CI 26–48%) and 8%, 95% CI 3–19%, respectively) compared with other radioligands (pooled estimate = 8%, 95% CI 4–14% and 29%, 95% CI 17–44%, respectively). The reason for this difference between type of PSMA-targeted radioligand is not yet clearly understood. It has been suggested that the lower positron energy (and greater spatial resolution) and the longer half-life (and superior signal-to-background ratio) of [^{18}F] compared to [^{68}Ga] may partly explain this [29]; however, [^{18}F]DCFPyL also is synthesized with [^{18}F] and therefore this explanation cannot be considered valid. Others have suggested that it may be related to the higher binding affinity to

Table 2 PSMA PET/CT characteristics

First author	Scanner vendor (model)	Radioligand	Dose (MBq)	Uptake time (min)	Interpreter	Reporting	Reference standard †
Arnfield [24]	Siemens (Biograph mCT)	[^{18}F]PSMA-1007	250, 218–272	126*, 119–137	2 experienced NM	PSMA-RADS v1.0	BVC
Bohil [25]	GE (Discovery 690)	[^{18}F]PSMA-1007	4/kg	~120	2 experienced NM	NR	BVC
Dietlein [26]	Siemens (Biograph mCT 128 Flow)	[^{18}F]PSMA-1007	343, SD 49	120	NR	PSMA-RADS v1.0	MRI
Ettala [27]	NR	[^{18}F]PSMA-1007	NR	NR	2 experience NM	Avid without anatomical correlate	BVC
Foley [28]	NR	[^{18}F]PSMA-1007	238, SD 27	120	NR	NR	
Grunig [29]	GE (Discovery 600, Discovery 690, Discovery MI, Signa PET/MR), Siemens (Biograph mCT Flow)	[^{18}F]PSMA-1007	3–4/kg	60–90	1 double board-certified radiologist/NM	Focal mild-moderate uptake (SUV_{max} <10) not obviously related to a benign or malignant cause	BVC
Hoberück [30]	Siemens (Biograph Vision 600)	[^{18}F]PSMA-1007 [^{68}Ga]Ga-PSMA-11	154, 123–175 149, 111–161	104, SD 11 110, SD 18	2 experienced NM & 2 experienced radiologists	Decided in consensus considering uptake intensity, lesion size and morphologic appearance	
Janssen [31]	Phillips (Gemini Astonish TF 16)	[^{68}Ga]Ga-PSMA-11	120.3, SD 20.4	61.7, SD 32.2	2 readers	NR	
Knappe [32]	NR	[^{18}F]PSMA-1007	NR	NR	NR	Uptake without morphologic correlate in CT	
Kuten [33]	GE (Discovery 690, Discovery MI)	[^{18}F]PSMA-1007 [^{68}Ga]Ga-PSMA-11	4/kg 1.8–2.2/kg	~90 ~60	1 experienced NM	PSMA-RADS v1.0	BVC
Letang [34]	Siemens (Biograph mCT), GE (IQ5, MI DR, Discovery 700)	[^{68}Ga]Ga-PSMA-11	2.2/kg, 1.3–3.7	63, 51–90	1 senior & 1 resident NM	PSMA-RADS v1.0	BVC
Mihatsch [35]	Siemens (Biograph mCT 64, Biograph mCT Flow 128 Edge)	[^{18}F]PSMA-1007	301, SD 15	91, SD 10	1 resident radiologist, 1 expert radiologist, & 1 expert NM	PSMA-RADS v1.0	
Orevi [36]	GE (Discovery MI digital, Discovery MI DR)	[^{18}F]PSMA-1007	3.4/kg, SD 0.3	67, SD 8	2 experienced NM physicians	Avid foci with no corresponding abnormality on CT	PSA kinetics
Paone [37]	NR	[^{18}F]PSMA-1007	NR	NR	NR	Low-to-moderate uptake without a correlate lesion on CT	BVC
Phelps [38]	GE (Discovery MI DR)	[^{18}F]DCFPyL	262.7, SD 37.9	120	2 expert NM	PSMA-RADS v1.0	BVC
Pyka [39]	Siemens (Biograph mCT, Biograph mMR)	[^{68}Ga]Ga-PSMA-11	151, 95–217	60	2 expert NM	NR	BVC
Rowe [40]	Siemens (Biograph mCT 128), GE (Discovery RX 64)	[^{18}F]DCFPyL	333, SD 9	60	2 expert NM	NR	
Seifert [41]	Siemens (Biograph Vision, Biograph mCT, Biograph mMR)	[^{18}F]PSMA-1007 [^{68}Ga]Ga-PSMA-11	350.6, SD 61.8 133.3, SD 81.2	111, SD 20 67, SD 14	2 NM	Focally increased uptake (SUVmax > 4) and clear visualization in maximum intensity projection images without CT correlate	BVC
Shanmugasundaram [42]	NR	[^{68}Ga]Ga-PSMA-11	NR	NR	NR	NR	
Simsek [43]	Siemens (Biograph TruePoint)	[^{68}Ga]Ga-PSMA-11	~185	45–60	2 experienced NM	PSMA-RADS v1.0	BVC

Table 2 (continued)

First author	Scanner vendor (model)	Radioligand	Dose (MBq)	Uptake time (min)	Interpreter	Reporting	Reference standard †
Spurr [44]	NR	[^{18}F]PSMA-1007	NR	NR	NR	NR	MRI
Vollnberg [45]	Siemens (mCT, Vision 600, Vision Quadra)	[^{18}F]PSMA-1007	240, 213–254	90	1 dual board-certified radiologist/NM & 1 NM	NR	Biopsy
Wondergem [46]	Siemens (Biograph 16 TruePoint)	[^{18}F]PSMA-1007 [^{18}F]DCFPyL	324, 239–363 319, 231–367	90 120	2 experienced NM	PSMA-RADS v1.0	BVC
Yin [47]	Siemens (Biograph mCT), GE (Discovery RX)	[^{18}F]DCFPyL	~333	60	2 experienced readers	PSMA-RADS v1.0	BVC
Zacho [48]	Siemens (Biograph mCT Flow 64), GE (VCT Discovery True 64)	[^{68}Ga]Ga-PSMA-11	2/kg	60	3 experienced NM	NR	

BVC = best value comparator; MRI = magnetic resonance imaging; NM = nuclear medicine physician; NR = not reported; PSMA-RADS = Prostate Specific Membrane Antigen Reporting and Data System; SD = standard deviation; SUV_{max} = maximum standardized uptake value

Continuous data are summarized as mean (age, PSA) or median (grade group) and ranges unless otherwise specified (e.g., median, standard deviation, or interquartile range)

*median

† Studies that only evaluated prevalence of equivocal bone lesions have empty cells for reference standard

Table 3 Subgroup analyses on the prevalence of equivocal bone lesions and their malignancy rates stratified to type of PSMA-targeted radioligand, methods for reporting PSMA PET/CT, and clinical setting

	Variable	Category	No. of studies (or sub-studies)	Pooled estimate (95% confidence interval)	p value
Prevalence	Radioligand	[^{18}F]PSMA-1007	14	0.36 (0.26–0.48)	0.01
		Others *	10	0.08 (0.04–0.14)	
	Reporting	PSMA-RADS	7	0.15 (0.06–0.33)	0.42
		Others	15	0.23 (0.12–0.38)	
	Clinical setting	Initial staging	6	0.10 (0.03–0.31)	0.32
		Biochemical recurrence	4	0.37 (0.16–0.65)	
		Mixed	8	0.24 (0.14–0.39)	
		Others †	4	0.14 (0.02–0.60)	
Malignancy rate	Radioligand	[^{18}F]PSMA-1007	12	0.08 (0.03–0.19)	0.01
		Others *	8	0.29 (0.17–0.44)	
	Reporting	PSMA-RADS	8	0.16 (0.06–0.37)	0.60
		Others	9	0.11 (0.04–0.28)	
	Clinical setting	Initial staging	4	0.31 (0.05–0.80)	0.32
		Biochemical recurrence	5	0.12 (0.07–0.19)	
		Mixed	6	0.13 (0.05–0.32)	
		Others †	2	0.03 (0.00-0.03)	

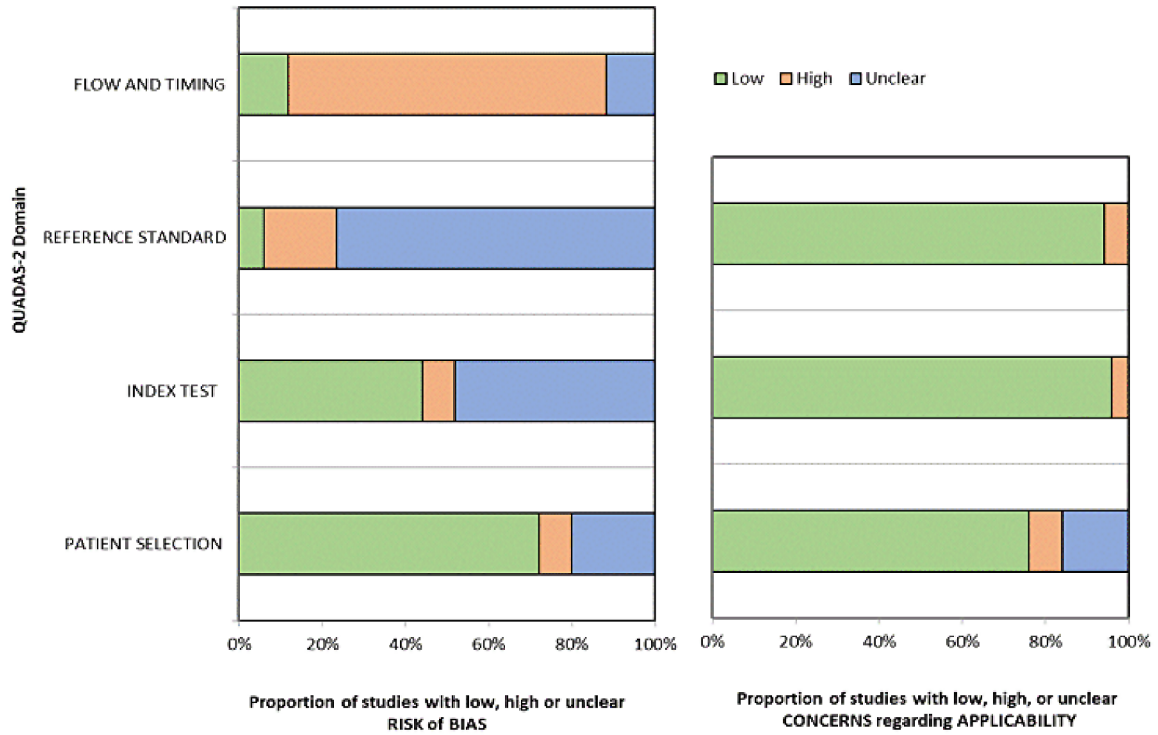
PSMA = prostate specific membrane antigen; PSMA-RADS = PSMA Reporting and Data System;

* [^{68}Ga]Ga-PSMA-11 or [^{18}F]DCFPyL

† Non-detectable prostate-specific antigen level after radical prostatectomy ($n = 1$) or not reported ($n = 3$ for prevalence and $n = 1$ for malignancy rate)

receptors and internalization rate of [^{18}F]PSMA-1007 [50, 51]. Regardless, the difference between [^{18}F]PSMA-1007 and other radioligands has important clinical implications. [^{18}F]PSMA-1007 has been considered advantageous for delineating the primary tumors and local recurrence after radical treatment and for radiotherapy planning (e.g., dose painting) due to its lack of urinary excretion compared with other radioligands [52–54]. Therefore, these characteristics related to radioligand type should be taken into consideration when choosing which one to use, and how to interpret them (in addition to jurisdictional constraints and access issues such as [^{18}F]PSMA-1007 not yet approved in the United States and whether there is a cyclotron on site). Moreover, additional training may be needed before using [^{18}F]PSMA-1007 to avoid overcalling these equivocal bone lesions.

Other factors such as clinical setting or how equivocal bone lesions were defined were not a substantial source of heterogeneity ($p = 0.32$–0.60). As bone metastases can virtually occur in any clinical setting, across the broad categories of primary staging, biochemical recurrence, and even during systemic treatment for known metastatic disease, the



Study (1st author, publication year)	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Arnfield, 2021	Low	Unclear	Unclear	High	Low	Low	Low
Bohil, 2021	Low	Unclear	Unclear	High	Low	Low	Low
Dietlen, 2020	Low	Low	High	Unclear	Low	Low	Low
Ettala, 2023	Low	Low	Unclear	High	Low	Low	Low
Foley, 2021	Low	Unclear			Low	Low	
Grunig, 2021	Low	Unclear	Unclear	High	Low	Low	Low
Hoberück, 2021	Low	Low			Low	Low	
Janssen, 2018	Unclear	Unclear			Unclear	Low	
Knappe, 2022	Unclear	Unclear			Unclear	Low	
Kuten, 2021	Low	Low	Unclear	High	Low	Low	Low
Letang, 2022	Low	Low	Unclear	High	Low	Low	Low
Mihatsch, 2022	Low	Unclear			Low	Low	
Orevi, 2022	High	High	High	Low	High	Low	Low
Paone, 2022	Unclear	Unclear	Unclear	High	Low	Low	Low
Phelps, 2023	Low	Low	Unclear	High	Low	Low	Low
Pyka, 2016	Low	High	Unclear	High	Low	High	Low
Rowe, 2020	Low	Low			Low	Low	
Seifert, 2023	Low	Unclear	Unclear	High	Low	Low	Low
Shanmugasundaram, 2020	Unclear	Low			Unclear	Low	
Simsek, 2021	Low	Unclear	Unclear	High	Low	Low	Low
Spurr, 2022	Unclear	Unclear	High	Unclear	Unclear	Low	Low
Vollnberg, 2022	High	Low	Low	Low	High	Low	High
Wondergem, 2021	Low	Low	Unclear	High	Low	Low	Low
Yin, 2019	Low	Unclear	Unclear	High	Low	Low	Low
Zacho, 2020	Low	Low			Low	Low	

Fig. 2 Grouped bar charts summarizing risk of bias (left) and concern for applicability (right) in 25 included studies according to the QUADAS-2 tool. Individual study results are shown at the bottom. For 8 studies that only reported the prevalence of equivocal bone lesions on PSMA PET/CT (but not their malignancy rates), a modified approach using only 2 of the 4 domains (*patient selection* and *index test*) were assessed as the other 2 domains (*reference standard* and *flow and timing*) were not relevant

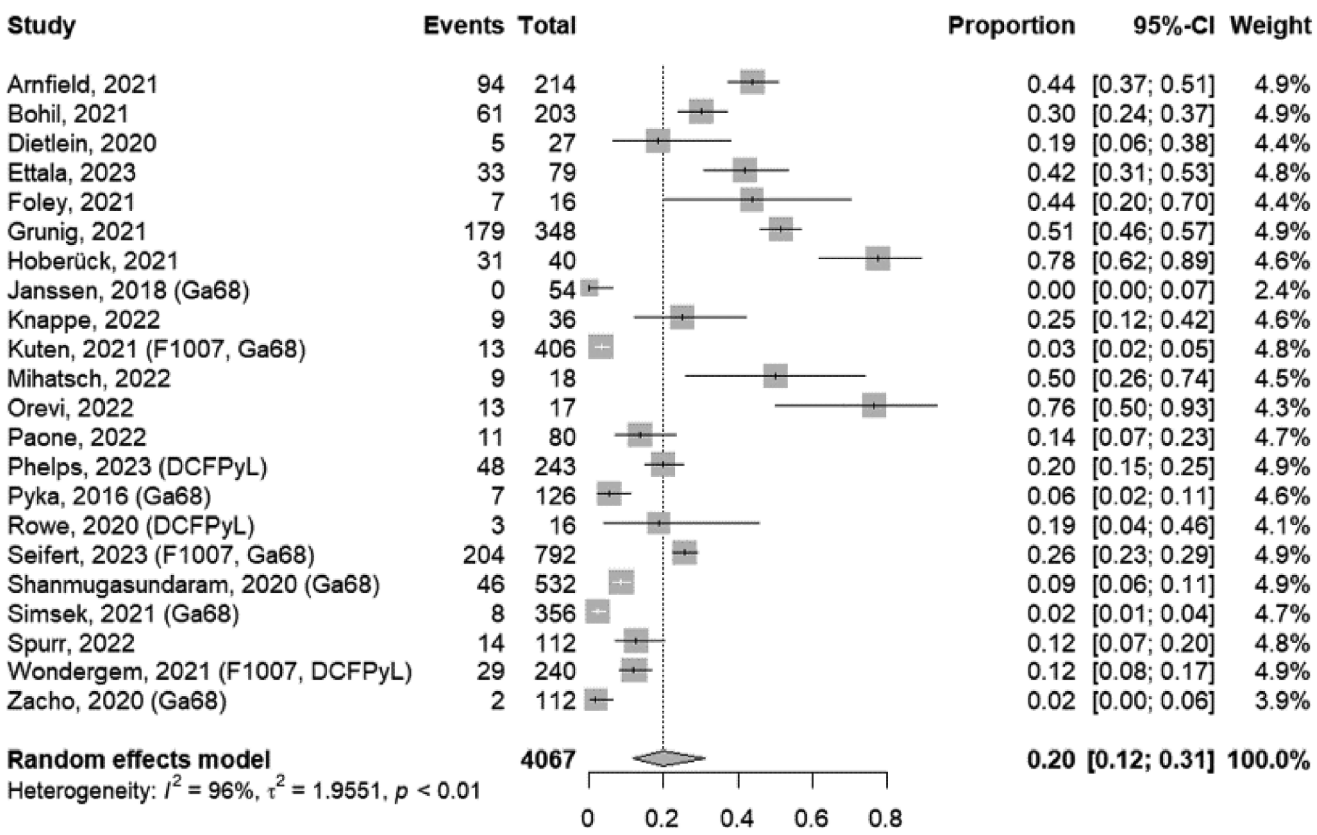


Fig. 3 Forest plot showing pooled prevalence of equivocal bone lesions in all 22 studies. Events = number of patients with equivocal bone lesions. Total = number of patients in the study

risk stratification itself (e.g., PSA level, PSA kinetics, or Gleason grade group) may be more important in determining whether the equivocal bone lesion is metastatic or not. For example, while the overall pooled malignancy rate was 14% (95% CI: 7–25%), few of the studies at the extreme ends warrant mention to illustrate this point. For example, two studies in which PSMA PET/CT was performed in predominantly high-risk patients – Paone et al. [37] (high risk in 58.8% [47/80], median PSA 23.7 ng/ml) and Simsek et al. [43] (high risk in 81.2% [289/356], median PSA 16.4 ng/mL) had very high malignancy rates of 76.9% (70/91) and 70.0% (7/10), respectively, substantially higher than the overall pooled malignancy rate of 14%. These data support tailoring the workup of equivocal bone lesions on PSMA PET/CT depending on the pretest likelihood of bone metastasis. They can be considered metastasis and managed accordingly in patients at high risk for metastasis (or with co-existing additional sites of *definite* metastasis elsewhere); on the contrary, in a patient at low risk for metastasis (especially who is a candidate for locoregional definitive treatment), higher thresholds should be applied for calling equivocal bone lesions as metastases so that the patient will not be denied potentially curative intent treatment. If risk is truly indeterminate, additional imaging, biopsy, or follow-up to confirm their significance may still be required. Further investigation is needed to see whether quantitative analysis of PSMA PET (e.g., maximum standardized uptake value [SUV_{max}] such as cutoff of > 7.2 suggested by Arnfield et al. [24]), secondary PSMA uptake patterns (e.g., focality and changes in late-phase acquisition [55]), more in-depth morphological analysis of CT correlates, or using additional tools such as genomic classifiers (e.g., Decipher test) will help identify metastasis or not in such scenarios [56, 57].

Although the definition of equivocal bone lesions (or how PSMA PET/CT was interpreted) was not a substantial factor of heterogeneity, this issue deserves more in-depth discussion. Nine (36.0%) of the studies used PSMA-RADS version 1.0, while various other definitions were used (or details not provided) in the remaining studies. No studies up to now have evaluated the recently updated PSMA-RADS version 2.0 [13]; however, only minimal impact on the prevalence and malignancy rate of equivocal bone lesions is to be expected considering the content of the modifications. It is unclear whether the conduct of using PSMA-RADS (or any other standardized reporting system) will in itself improve assessment of bone lesion. However, lessons can be learned from the history of the debate between Prostate Imaging

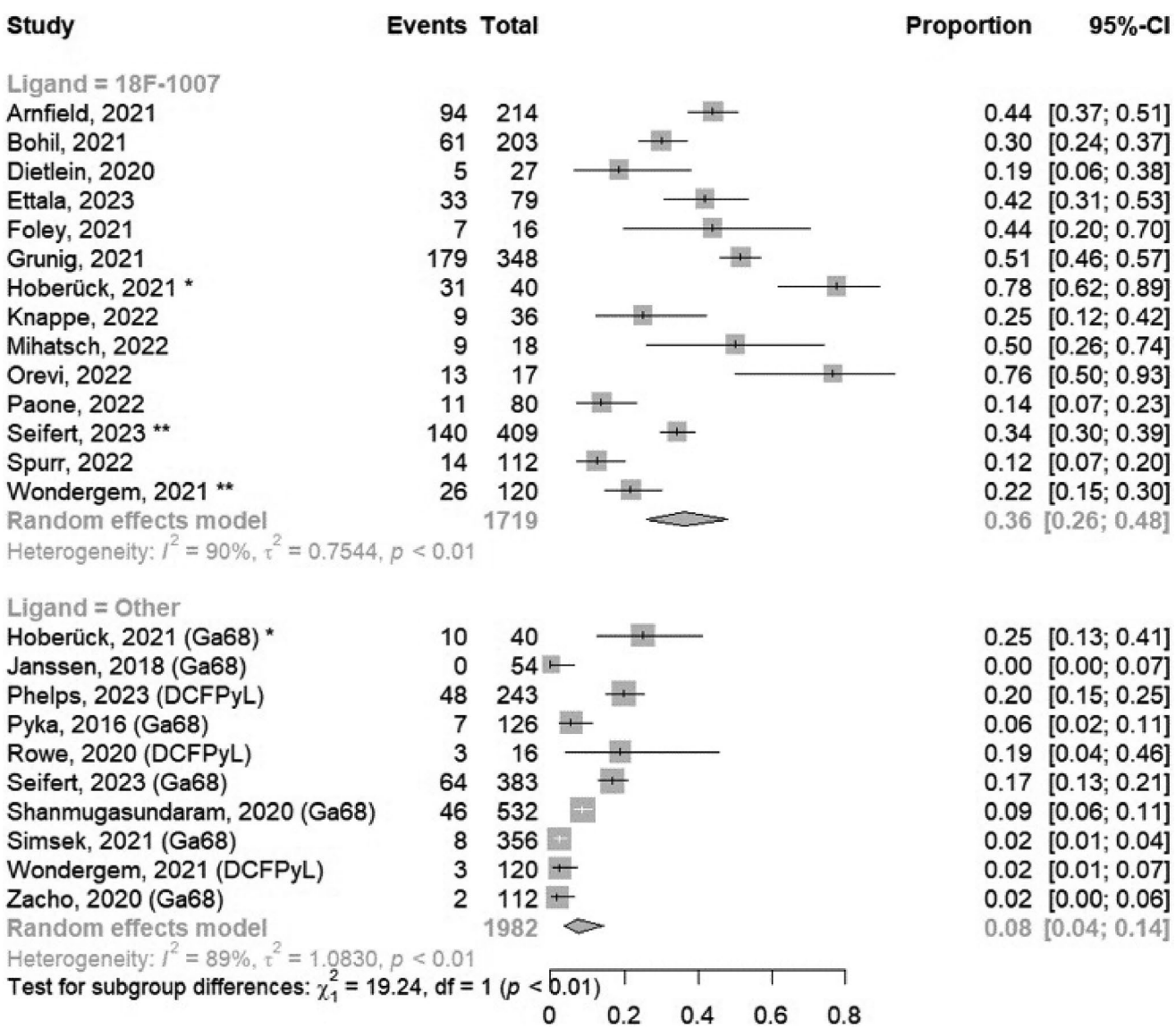


Fig. 4 Forest plots showing pooled prevalence of equivocal bone lesions stratified to subgroups based on type of PSMA-targeted radioligand. Studies that used [^{18}F]PSMA-1007 ($n = 14$) had a greater pooled prevalence compared to those that used other radioligands ([^{68}Ga]Ga-PSMA-11 and [^{18}F]DCFPyL, $n = 10$, $p < 0.01$)

Reporting and Data System (PI-RADS) versus Likert scale for interpreting MRI. While diagnostic performance was not significantly different (at least in high-volume tertiary centers), PI-RADS eventually became the standard for prostate MRI interpretation because it provided clear structure, standardization, and definition allowing the potential for decreasing inter-reader variability [58, 59]. PSMA-RADS could be used as a platform for research or utilized as part of clinical trials across different institutions and settings to help establish the clinical significance and most optimal way to manage equivocal bone lesions on PSMA PET/CT. Such structured reporting may also improve inter-reader agreement for PSMA PET/CT interpretation [60].

There were a few limitations in this systematic review and meta-analysis. First, there was substantial heterogeneity between the included studies. Nevertheless, we were able to demonstrate that at least some of this heterogeneity arises from the differences in type of PSMA-targeted radioligand ([^{18}F]PSMA-1007 vs. others [[^{68}Ga]Ga-PSMA-11 or [^{18}F]DCFPyL]). Secondly, most (13/17 [76.5%]) of the included studies used BVC as the reference standard for determining whether the equivocal bone lesion was malignant or not. Although we acknowledged that this is a potential source for unclear risk of bias in the QUADAS-2 assessments, it should be emphasized that BVC is not perfect. As a matter of fact, using BVC could lead to both false positive and negative conclusions. Nonetheless, biopsy

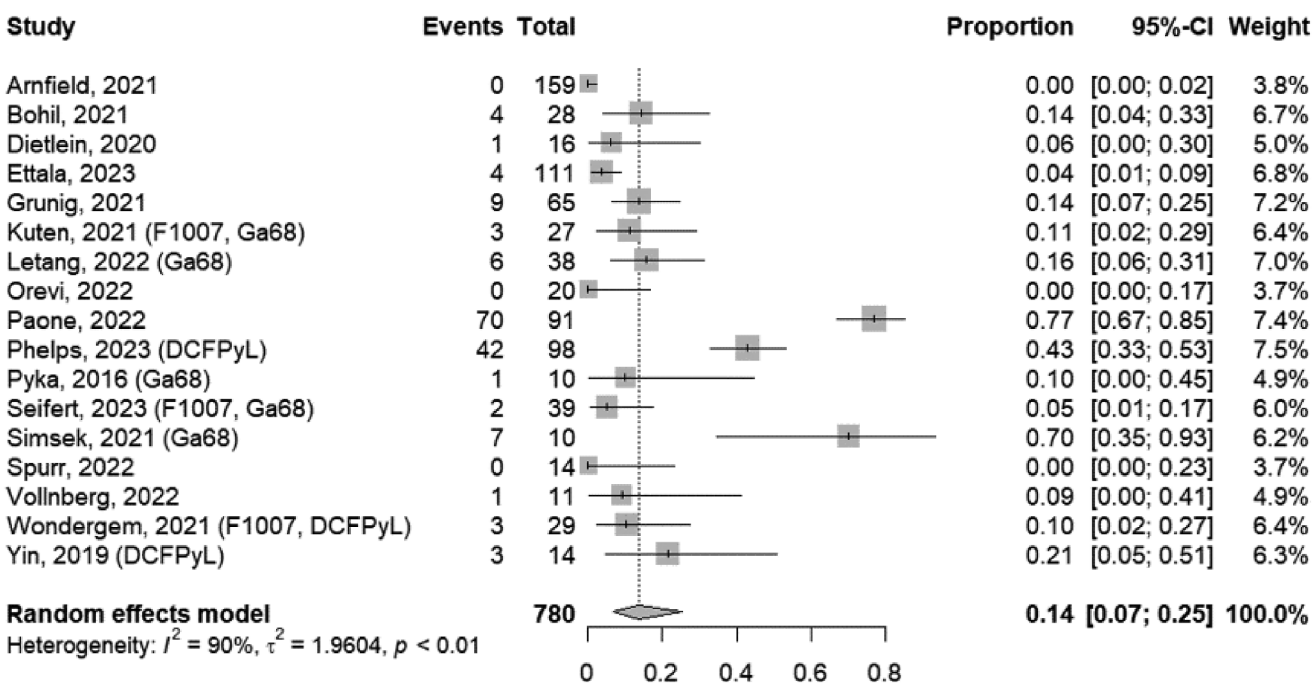


Fig. 5 Forest plot showing pooled malignancy rate of equivocal bone lesions in all 17 studies. Events = number of malignant bone lesions. Total = number of equivocal bone lesions

(used as the sole reference standard in 1 study [45]) cannot be used for all patients nor would that be ethically justified. Furthermore, interpretation of bone biopsies can be challenging especially when lesions are sclerotic, which is often the case in the setting of patients with prostate cancer, with approximately 1 in 4 biopsies yielding nondiagnostic results [61]. BVC is commonly used in clinical practice to decide whether equivocal bone lesions are metastasis or not. Therefore, the pooled estimates derived from this meta-analysis probably reflect real world evidence. Finally, we were unable to directly analyze the relationship between the location of the equivocal bone lesion and malignancy rate. Yet, it is well known from extensive literature that the likelihood of metastasis is different between locations – not only between axial and non-axial bones but even within axial bones (e.g., ribs vs. vertebrae or pelvic bones) [62, 63]. Although further investigation will be needed in this specific context, we can speculate that equivocal bone lesions on PSMA PET/CT will less likely be metastasis in the ribs, especially when in isolation without additional sites of disease in the pelvis or vertebrae.

In conclusion, equivocal bone lesions are often encountered on PSMA PET/CT but exhibit a low malignancy rate. Compared to other radioligands, [^{18}F]PSMA-1007 requires special attention as it is associated with a higher frequency and lower rate of metastasis.

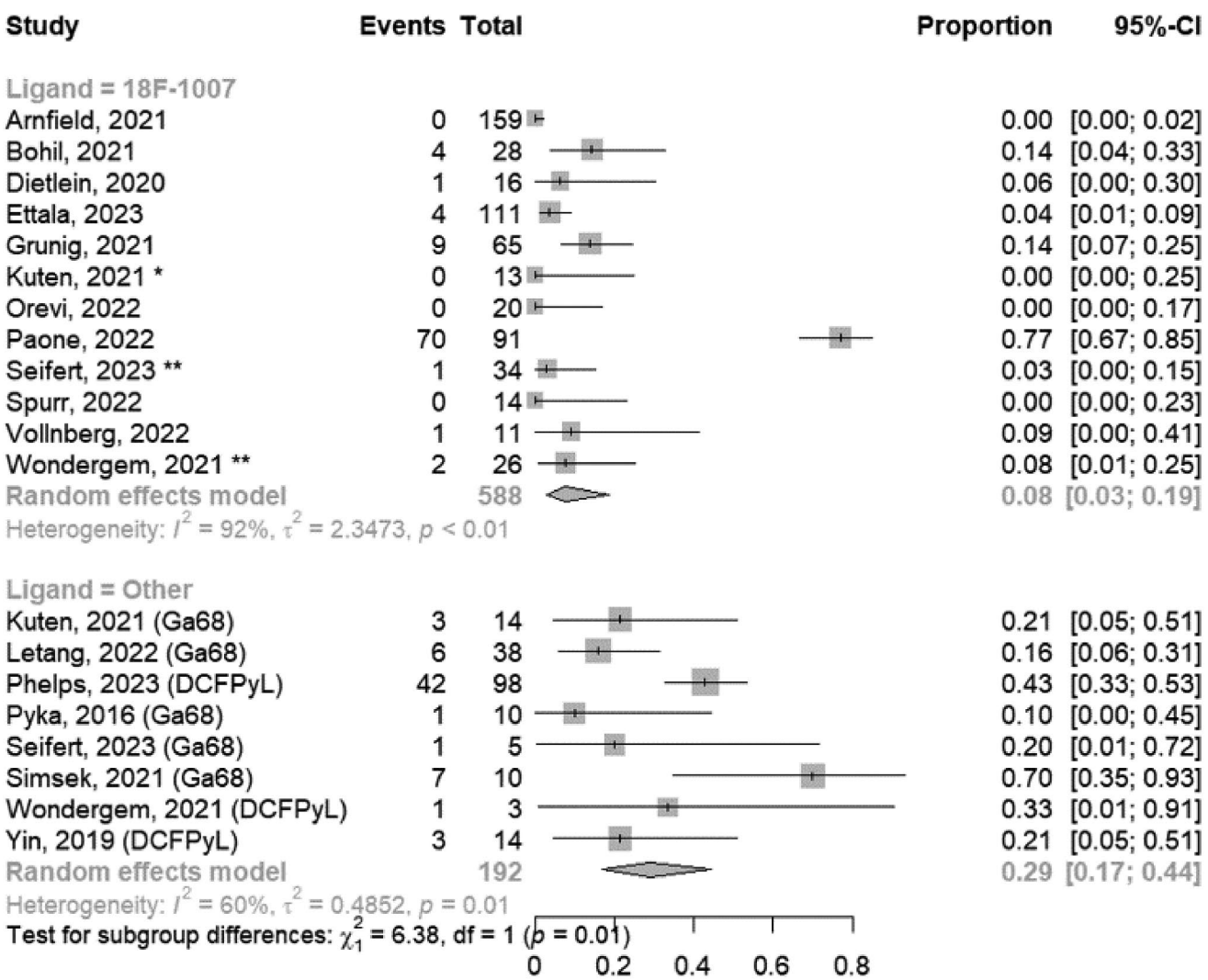


Fig. 6 Forest plots showing pooled malignancy rate of equivocal bone lesions stratified to subgroups based on type of PSMA-targeted radioligand. Studies that used [^{18}F]PSMA-1007 (n = 12) had a lower pooled malignancy rate compared to those that used other radioligands ([^{68}Ga]Ga-PSMA-11 and [^{18}F]DCFPyL, n = 8, p = 0.01)

Abbreviations

BVC	best value comparator
MRI	magnetic resonance imaging
PET/CT	positron emission tomography/computed tomography
PSA	prostate-specific antigen
PSMA	Prostate-specific membrane antigen
PSMA-RADS	PSMA Reporting and Data System
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2

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Author contributions Study conceptualization: SW, HAV. Data acquisition: SW, DF, HAV. Data analysis: SW. Data interpretation: SW, ASB, DL, MEM, KPF, YA, SH, IAB, SST, DRW, MJZ, HAV. Drafting of manuscript: SW. Critical revision of manuscript: SW, ASB, DL, MEM, KPF, YA, SH, IAB, SST, DRW, MJZ, HAV. Supervision: HAV.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval This study did not involve individual human participant data as it was a systematic review and meta-analysis using only *study-level summary data* provided openly in the literature. Nevertheless, it was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki, its subsequent amendments, or comparable ethical standards.

Informed consent This study did not involve individual human participant data as it was a systematic review and meta-analysis using only *study-level summary data* provided openly in the literature. As

such, the need for informed consent was not applicable.

Competing interests MEM received honoraria for lectures from Siemens, GE, and BM but unrelated to the current work. KPF is a co-investigator on "Optimizing timing of rhPSMA-7.3 (18F), for assessing site(s) of recurrent disease following radical prostatectomy" (PI Herbert Lepor) but does not receive any salary support and was unrelated to the current work. IAB has received research support from GE Healthcare and Bayer, speaker honorarium from GE-Healthcare, Baer, Astellas, Janssen and Novartis, and institutionally compensated advisory role for Novartis, Merck & Cie and Ratio Radiotherapeutics but unrelated to the current work. DRW has received consulting fees from Leap Therapeutics, Foundation Medicine, Pfizer, Janssen, Sanofi, Lilly, Labcorp, Myovant, Bayer, AstraZeneca, Accutar and has received travel funding from Pfizer and Bayer but unrelated to the current work. The other authors have nothing to disclose.

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