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[68Ga]Ga-PSMA Versus [18F]PSMA Positron Emission Tomography/Computed Tomography in the Staging of Primary and Recurrent Prostate Cancer. A Systematic Review of the Literature

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Abstract

Context: In the past 10 yr, several agents based on prostate-specific membrane antigen (PSMA) for positron emission tomography imaging have been introduced in clinical practice for the management of patients with prostate cancer (PCa).

Objective: To analyse the available data in the literature to clarify the advantages and disadvantages of [68Ga]Ga-PSMA and [18F]PSMA in different settings of PCa.

Evidence acquisition: A systematic literature search was made by using two main databases. Only studies published in the past 5 yr (2016–2021) in the English language with >20 enrolled patients were selected. Two reviewers independently appraised each article using a standard protocol. All the studies were analysed using a modified version of the Critical Appraisal Skills Programme checklist for diagnostic test studies.

Evidence synthesis: The systematic evaluation was made in 12 papers. Based on the quality assessment, the analysed studies demonstrated different methodologies. Three papers focused on the head-to-head comparison between 18F- and [68Ga]Ga-PSMA (n = 123 patients). A matched-pair comparison between 18F- and [68Ga]Ga-PSMA was reported in three papers, including 715 patients. The remaining papers used indiscriminately either 68Ga-PSMA or [18F]PSMA (n = 1.157 patients). [18F]PSMA-1007 is superior to [68Ga]Ga-PSMA-11 for the identification of local recurrence (less activity close to the bladder for [18F]PSMA-1007). Nonspecific/equivocal bone lesions are often recognised at [18F]PSMA-1007. [18F]DCFPyL is more reproducible for the identification of lymph nodes, and it shows fewer equivocal skeletal lesions and higher inter-reader agreement on skeletal lesions.

Conclusions: Despite a large body of literature on PSMA radiopharmaceutical agents labelled with 68Ga or 18F, there are limited head-to-head or matched-pair comparative data. Certain clinical indications could trigger a preference, whilst caution is needed in interpreting potential false-positive findings, especially with [18F]PSMA-1007. Given the excellent performance of all accessible radiopharmaceuticals, the availability of specific tracers will likely guide choice.

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Patient summary: In this systematic review, we analysed the currently available literature focused on [^{68}Ga] and [^{18}F]-labelled prostate-specific membrane antigen. Our purpose is to identify which tracers would be correctly employed for the management of patients with prostate cancer.

1. Introduction

In the past few years, with the introduction of new radiopharmaceutical agents, molecular imaging has deeply evolved with important changes in the oncologic field, either for diagnosis or for therapy, in the so-called theragnostic era. Foremost, is the introduction of prostate-specific membrane antigen (PSMA) agents for the management of prostate cancer (PCa). The first PSMA agent was introduced in the late 1990s, but the real revolution started at the beginning of 2012. From this date, several agents have been introduced in clinical practice, radiolabelled with gallium-68 [^{68}Ga] and later with fluoride-18 [^{18}F].

[^{68}Ga]Ga-PSMA-11 was the most employed tracer for imaging of PCa [1,2]; many studies, either retrospective or prospective trials, were published describing the advantages of this agent over conventional imaging or other radiopharmaceuticals, such as [^{11}C]choline or [^{18}F]choline [3]. However, due to its physical characteristics and availability (ie, production, delivery, and demand), an increasing interest for [^{18}F]-labelled PSMA compounds has been reported. Unlike [^{68}Ga]Ga-PSMA, several different [^{18}F]-labelled products are available [4]. Some differences were observed between [^{18}F]DCFPyL and [^{18}F]PSMA-1007. From a clinical point of view, the main dilemma is to understand whether there is a difference between [^{68}Ga]Ga-PSMA and [^{18}F]PSMA in terms of biodistribution, interpretation, and efficacy. In recent years, many papers have been published regarding patients' selection for PSMA, mainly for [^{68}Ga]Ga-PSMA [5–8].

On these premises, the present systematic review aimed to analyse the available data in the literature to clarify the pros and cons of [^{68}Ga]Ga-PSMA and [^{18}F]PSMA in different settings of PCa.

2. Evidence acquisition

2.1. Literature search

A systematic literature search was made by using two main databases (Web of Science and PubMed) to systematically retrieve papers by using the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines. The following keywords were used: "prostate" or "prostate cancer" or "prostate neoplasm"; "positron emission tomography" or "PET"; "prostate-specific membrane antigen" or "PSMA" or "[^{68}Ga]Ga-PSMA" or "[^{18}F]PSMA"; and "staging" or "restaging" or "biochemical recurrence". Studies assessing the diagnostic utility of [^{68}Ga]Ga-PSMA and [^{18}F]PSMA positron emission tomography (PET) in PCa primary staging (before definitive treatment) and restaging (for biochemical recurrence) were included for the assessment.

All types of studies were considered, such as head-to-head comparative series, matched-pair studies, clinical trials, prospective studies, and retrospective cohorts. Case reports, conference proceedings, editorial comments, and letters to the editor were excluded. Only studies published in the past 5 yr (2016–2021) in the English language with >20 enrolled patients were selected. In the case of duplicate study populations or analyses of repeated data, the publication reporting a larger sample size was used for the analysis.

Two reviewers (R.L. and L.E.) independently appraised each article using a standard protocol. The following information was extracted from each study: sample size, location of the study, year, median patient age, indication for PET (primary staging or recurrent disease staging), median prostate-specific antigen (PSA), type of comparative tracer, PSMA PET protocol, and standard of reference (ie, histopathology or conventional imaging modalities).

2.2. Quality of the selected papers

All the studies were analysed using a modified version of the Critical Appraisal Skills Programme (CASP) checklist for diagnostic test studies [9]. Critical appraisal was performed by two reviewers (R.L. and L.E.), and discrepancies, if any, were resolved by discussion with a senior author (F.A.).

3. Evidence synthesis

3.1. Analysis of the evidence

From the systematic literature search, nine papers were selected. However, after careful evaluation of the references for each study, it emerged that three papers had a similar endpoint and were therefore included. The systematic evaluation was made in 12 papers (Fig. 1). In Table 1, the main information of the selected studies is listed [10–21]. Five papers comprised PCa patients who underwent radiolabelled PSMA PET for biochemical recurrence [10,12,13,15,17], one paper was related to patients with metastatic castrate-resistant PCa [11], two were related to the initial staging of disease [20,21], one was about the delineation of the intraprostatic dominant lesion (IDL) [14], and three articles assessed mixed cohorts (staging, restaging, and metastatic disease) [19–21].

Based on the quality assessment, the analysed studies demonstrated different methodologies. In fact, the majority of studies lacked a reference standard (eg, histopathology) to assess the validity of ^{68}Ga-PSMA or [^{18}F]PSMA PET results. The study design was unclear in several papers; also, the image interpretation was incomplete in some publications. However, the transferability of the data to the general pop-

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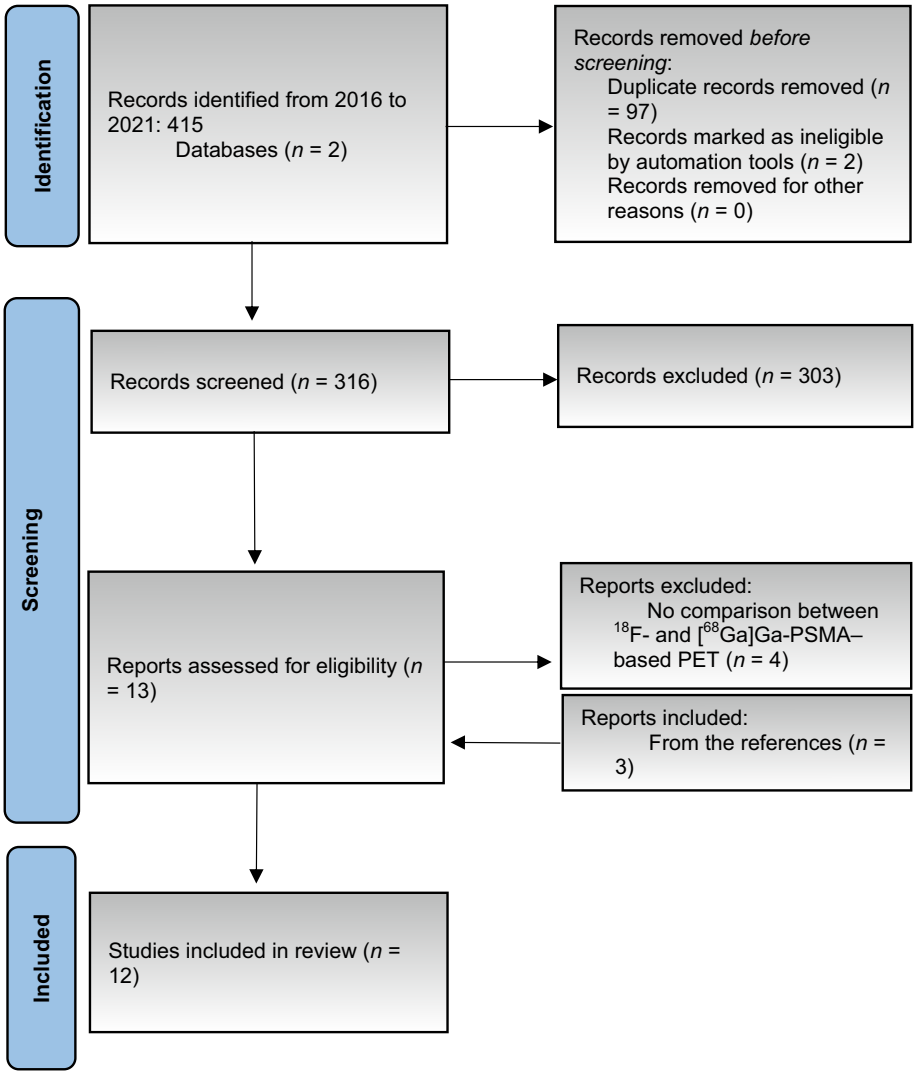

Fig. 1 – PRISMA flowchart for the selection of papers. PET = positron emission tomography; PRISMA = Preferred Reporting Items for Systematic reviews and Meta-analyses; PSMA = prostate-specific membrane antigen.

ulation was appropriate in many papers. The results of the CASP assessment are shown in Supplementary Table 1.

3.2. Head-to-head comparison

Three papers focused on the head-to-head comparison between ^{18}F- and [^{68}Ga]Ga-PSMA (n = 123 patients) [12,19,20]. However, the definition of head to head was somewhat compromised owing to different uptake periods (60 and 120 min, respectively, for ^{68}Ga- and ^{18}F-labelled PSMA) and the time between scans (ranging between 3 and 4 wk between the two tracers' scans), as reported in Table 1.

Dietlein et al [12] retrospectively assessed 27 patients who were first submitted to [^{68}Ga]Ga-PSMA-11 (n = 16 patients), [^{18}F]DCFPyL (n = 5 patients), or [^{18}F]JK-PSMA PET/computed tomography (CT; n = 6 patients) for the identification of biochemical recurrent disease, but showing an equivocal or negative result for oligometastatic disease. Therefore, within 3 wk, the same population was studied with an [^{18}F]PSMA-1007 PET/CT. In comparison with the previous scan, only the semiquantitative differences between [^{68}Ga]Ga-PSMA-11 and [^{18}F]PSMA-1007 reached statistical significance (maximum standardised uptake value [SUVmax], 16 ± 19 for [^{68}Ga]Ga-PSMA-11 vs 23 ± 28 for ^{18}F-based tracers, p = 0.05 in ten lesions). The authors observed that [^{18}F]PSMA-1007 may increase the confidence in interpreting small locoregional lesions adjacent to the urinary tract but may decrease the interpretability of skeletal lesions. Considering the results of this study, the authors affirmed that CT-negative skeletal/bone marrow findings detected with [^{18}F]PSMA-1007 required further validation by magnetic resonance imaging (MRI) or PET/MRI scans, independently of PSA values. They concluded that [^{18}F]PSMA-1007 may therefore apply primarily to patients with a high probability of locally restricted disease or as a follow-up test in cases with equivocal findings adjacent to the urinary tract. When one is searching for distant metastases, particularly in the bone marrow, [^{68}Ga]Ga-PSMA-11 or [^{18}F]DCFPyL may be more suitable because of their higher specificity for bone marrow lesions.

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Table 1 – Main characteristics of selected papers

Authors	Ref.	Country	Year of publication	Nature of the study	Study design	Type of PSMA tracer	Sample size	Age (yr), median or mean ± SD (range)	Indication for PET	PSA (ng/ml), median (range),	Protocol type	Time between the two PET agents	Main endpoint
Dietlein et al	[12]	Germany	2020	R	Head-to-head analysis	[^{18}F] PSMA-1007 and [^{68}Ga]Ga-PSMA-11or [^{18}F] DCFPyL or [^{18}F]JK-PSMA-7	27 [^{18}F] PSMA-1007 + 16/27 [^{68}Ga] PSMA-11 + 5/27 [^{18}F] DCFPyL + 6/27 [^{18}F]JK-PSMA-7	67.2 ± 7.8	BCR	1.76 (0.3–27.7)	[^{68}Ga]Ga-PSMA-11 (159 ± 31 MBq), [^{18}F] DCFPyL (343 ± 52 MBq), [^{18}F]JK-PSMA-7 (323 ± 54 MBq), [^{18}F]PSMA-1007 (2 h after injection of 343 ± 49 MBq)	[^{18}F]PSMA-1007 within 3 wk after [^{68}Ga]Ga-PSMA-11or [^{18}F]DCFPyL or [^{18}F]JK-PSMA-7	To compare readers' confidence in interpreting PSMA-positive lesions; to assess the performance of [^{18}F]PSMA-1007 in the whole-body PET scan
Hoberück et al	[19]	Germany	2021	R	Head-to-head analysis	[^{68}Ga]Ga-PSMA-11 and [^{18}F] PSMA-1007	46 Both [^{68}Ga] Ga-PSMA-11 and [^{18}F] PSMA-1007	71 ± 8	Staging (22%), BCR (65%), FU (13%)	3.76 (0.32–113.7)	[^{68}Ga]Ga-PSMA-11 (106 min after injection of 149 MBq) and [^{18}F]PSMA-1007 PET (103 after injection of 154 MBq)	45/46 ^{68}Ga and then ^{18}F (within 12 ± 8 d)	Intraindividual comparison for malignant lesions, molecular imaging TNM staging, and unspecific lesions
Pattison et al	[20]	Australia	2022	P	Head-to-head analysis	[^{68}Ga]Ga-PSMA-11 and [^{18}F] PSMA-1007	50 Both [^{68}Ga] Ga-PSMA-11 and [^{18}F] PSMA-1007	71.8 ± 6.7	Staging (24%), BCR (54%), metastatic PCa (32%)	12 (staging), 0.8 (BCR), 9.7 (metastatic PCa)	[^{68}Ga]Ga-PSMA-11 (45–60 min after injection of 100–150 MBq) and [^{18}F]PSMA-1007 (120–180 min after injection of 250 MBq)	^{68}Ga and then ^{18}F (within 4 wk)	Concordance of [^{18}F] PSMA-1007 and [^{68}Ga] Ga-PSMA-11 for TNM with the American Joint Committee on Cancer prognostic stage and assess differences in tracer uptake
Dietlein et al	[10]	Germany	2017	R	Match-paired analysis	[^{68}Ga]Ga-PSMA-11 and [^{18}F] DCFPyL	191 [^{68}Ga]Ga-PSMA-11 (n = 129) and [^{18}F]DCFPyL (n = 62)	68.4–72.1	BCR	2.5 (^{68}Ga-prostatectomy), 2.7 (^{18}F-prostatectomy), 8.5 (^{68}Ga-radiotherapy), 4.1 (^{18}F-radiotherapy)	[^{68}Ga]Ga-PSMA-HBED-CC (60 min after injection of 158.9 MBq) and [^{18}F] DCFPyL (120 min after injection of 269.8 MBq)	Independent	Detection rate comparison between ^{68}Ga- and [^{18}F]PSMA-based agents
Rauscher et al	[13]	Germany	2020	R	Match-paired analysis	[^{68}Ga]Ga-PSMA-11 and [^{18}F] PSMA-1007	204 [^{68}Ga]Ga-PSMA-11 (n = 102) and [^{18}F]PSMA-1007 (n = 102)	71 ± 8	BCR	0.87 (0.2–13.6) for [^{18}F]PSMA-1007 and 0.91 (0.18–30) for [^{68}Ga]Ga-PSMA-11	[^{18}F]PSMA-1007 (94 ± 22 min after injection of 325 ± 40 MBq) and [^{68}Ga]Ga-PSMA-11 (54 ± 7 min after injection of 147 ± 27 MBq)	Independent	To assess potential differences in the frequency of non–tumour-related PSMA-ligand uptake; to compare detection efficacy of [^{68}Ga]Ga-PSMA-11 and [^{18}F] PSMA-1007 PET/CT
Kroenke et al	[21]	Germany	2021	R	Match-paired analysis	[^{18}F] rhPSMA-7 and [^{68}Ga]Ga-PSMA-11	320 [^{68}Ga]Ga-PSMA-11 (n = 160) and [^{18}F] rhPSMA-7 (n = 160)	72 ± 7	Staging (21%), BCR (79%)	14 (1.37–81)/0.87 (0.2–13.6) for staging/BCR [^{18}F] rhPSMA-7; 10.35 (3.8–81.5)/2.05 (0.2–30) for staging/BCR	[^{18}F]rhPSMA-7 (80 ± 20 min after injection of 329 ± 48 MBq) and [^{68}Ga]Ga-PSMA-11 (55 ± 9 min after injection of 143 ± 31 MBq)	Independent	To compare frequency of non–tumour-related uptake and tumour positivity in patients with primary or recurrent PCa

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Table 1 (*continued*)

Authors	Ref.	Country	Year of publication	Nature of the study	Study design	Type of PSMA tracer	Sample size	Age (yr), median or mean ± SD (range)	Indication for PET	PSA (ng/ml), median (range),	Protocol type	Time between the two PET agents	Main endpoint
										[^{68}Ga]Ga-PSMA-11			
Fendler et al	[11]	Germany	2019	R	Observational study	[^{68}Ga]Ga-PSMA-11 and [^{18}F]DCFPyL	200 [^{68}Ga]Ga-PSMA-11 (n = 195) and [^{18}F]DCFPyL (n = 5)	71 (46–94)	nmCRPCa	5.3 (1.3–263.8)	[^{68}Ga]Ga-PSMA-11 (147 MBq) and [^{18}F]DCFPyL (316 MBq)	Independent	Detection of PCa metastases in patients considered nonmetastatic at conventional imaging
Baas et al	[16]	The Netherlands	In press	R	Observational study	[^{68}Ga]Ga-PSMA-11 and [^{18}F]PSMA-1007	213 [^{68}Ga]Ga-PSMA-11 (n = 38) and [^{18}F]PSMA-1007 (n = 175)	67 (62–71)	Initial staging (intermediate-to high-risk PCa)	9.3 (6.6–15.1)	NA	Independent	Predictive value of lymph node disease at PSMA PET on early BCR or persistence of PCa
Jansen et al	[15]	The Netherlands	2021	R	Observational study	[^{68}Ga]Ga-PSMA-11 and [^{18}F]DCFPyL	315 (the type of tracer for each patient not specified)	70 (68–75)	BCR after RT	1.3 (1.1–1.8)	NA	Independent	Detection rate of BCR after RT in patients not meeting the Phoenix criteria
Koerber et al	[18]	Germany	2021	R	Observational study	[^{68}Ga]Ga-PSMA-11 and [^{18}F]PSMA-1007	335 [^{68}Ga]Ga-PSMA-11 (n = 272) and [^{18}F]PSMA-1007 (n = 63)	67 (38–84)	Initial staging (all risk-type PCa)	11 (1.2–511)	[^{68}Ga]Ga-PSMA-11 (60 min after injection of 223 MBq) and [^{18}F]PSMA-1007 (90–120 min after injection of 254 MBq)	Independent	Identification of metastasis at PSMA PET in patients with PCa
Scobioala et al	[14]	Germany	2021	R	Observational study	[^{68}Ga]Ga-PSMA-11 and [^{18}F]PSMA-1007	35 [^{68}Ga]Ga-PSMA-11 (n = 9) and [^{18}F]PSMA-1007 (n =16)	68 (58–77)	Delineation of intraprostatic lesions	15.4 (0.6–57.9)	[^{68}Ga]Ga-PSMA-11 (60 min after injection) and [^{18}F]PSMA-1007 (120 min after injection)	Independent	Accuracy of PSMA PET/CT or PSMA PET/MRI compared with MRI for the identification of intraprostatic dominant lesion
Morawitz et al	[17]	Germany	2021	R	Observational study	[^{68}Ga]Ga-PSMA-11 and [^{18}F]PSMA-1007	59 [^{68}Ga]Ga-PSMA-11 (n = 36) and [^{18}F]PSMA-1007 (n = 23)	71 ± 8.5	BCR	1.96 (± 1.64)	[^{68}Ga]Ga-PSMA-11 (60 min after injection of 182 MBq) and [^{18}F]PSMA-1007 (120 min after injection of 229 MBq)	Independent	Detection rate of BCR after radical prostatectomy

BCR = biochemical recurrence; CT = computed tomography; FU = follow-up; MRI = magnetic resonance imaging; NA = not applicable; nmCRPCa = nonmetastatic castrate-resistant prostate cancer; P = prospective; PCa = prostate cancer; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; R = retrospective; rhPSMA = radiohybrid PSMA; RT = radiotherapy; SD = standard deviation.

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Hoberück et al [19] retrospectively compared [^{68}Ga]Ga-PSMA-11 and [^{18}F]PSMA-1007 intraindividually, identifying clinical situations in which one tracer outperforms the other (malignant lesions; molecular imaging tumour, node, metastasis [miTNM] staging; and presumable unspecific lesions). They included 46 PCa patients who underwent consecutive [^{68}Ga]Ga-PSMA-11 and [^{18}F]PSMA-1007 PET/CT or PET/MRI within a mean of 12 ± 8 d for the initial staging of disease (22%), biochemical recurrence assessment (65%), and follow-up (13%). In terms of miTNM staging, both tracers appeared widely exchangeable as no tracer relevantly outperformed the other. Differences in terms of miTNM stages in both studies occurred in nine of the 46 patients (19.6%). The miT stages differed in five patients (10.9%), the miN stages differed in three patients (6.5%), and different miM stages occurred only in one patient upstaged in [^{18}F]PSMA-1007 PET. There was no significant difference between [^{18}F]PSMA-1007 and [^{68}Ga]Ga-PSMA-11 SUVmax locally (31.5 vs 32.7; p = 0.658), in lymph node metastases (28.9 vs 24.9; p = 0.30), or bone metastases (22.9 vs 27.6; p = 0.286). The differences between the two tracers were far more common in presumable nonspecific lesions than in malignant sites: in [^{18}F]PSMA-1007 PET, more patients featured equivocal uptake in the lymph nodes (52.2% vs 28.3%; p < 0.001), bones (71.7% vs 23.9%; p < 0.001), and ganglia (71.7% vs 43.5%; p < 0.001). Probably unspecific, exclusively [^{18}F]PSMA-1007–positive lesions mainly occurred in the ribs (58.7%), axillary lymph nodes (39.1%), and cervical ganglia (28.3%). In addition, in [^{18}F]PSMA-1007 PET, a device-dependent difference in presumably unspecific uptake was observed between PET/CT and PET/MRI, with non–malignancy-associated uptake in bones and ganglia (77.5% vs 33.3%; p = 0.027 in both locations) more frequently and even exclusively observed, as in lymph nodes (60.0% vs 0%; p = 0.007), on PET/CT.

Pattison et al [20] prospectively enrolled 50 men who underwent both [^{68}Ga]Ga-PSMA-11 and [^{18}F]PSMA-1007 4 wk apart for staging (24%), biochemical recurrence assessment (54%), and metastatic disease evaluation (32%). The tracer [^{18}F]PSMA-1007 demonstrated higher uptake than [^{68}Ga]Ga-PSMA-11 within local recurrence, involved nodes, distant metastases, and most physiologic sites except the urinary bladder, which aided [^{18}F]PSMA-1007 in the local staging of the prostate primary/local recurrence and regional nodal disease assessment adjacent to ureters. The tracer [^{18}F]PSMA-1007 upstaged local prostate tumours in five of 17 patients, local recurrence in three of 33 patients, regional nodal disease in three of 50 patients, and distant metastasis in one patient (bladder). The tracer [^{68}Ga]Ga-PSMA-11 upstaged regional nodal disease in one of 50 patients and distant metastasis in one patient (right adrenal). Overall American Joint Committee on Cancer (AJCC) prognostic stage was concordant in 46/50 (92%) patients between [^{18}F]PSMA-1007 and [^{68}Ga]Ga-PSMA-11, with two patients upstaged for both tracers. However, [^{18}F]PSMA-1007 exhibited more equivocal results (one regional node and six equivocal bone lesions, one of which was subsequently confirmed metastatic) than [^{68}Ga]Ga-PSMA-11 (one equivocal local recurrence). SUVmax can be useful for discriminating between malignant and benign bone uptake. Indeed, in case of the absence of typical features on CT, a SUV_{max} cut-off point of <7.2 maximised the sensitivity and specificity for excluding bone metastasis. The tracer [^{18}F]PSMA-1007 has greater physiologic liver uptake than [^{68}Ga]Ga-PSMA-11, which obscured a solitary right adrenal metastasis.

3.3. Matched-pair comparison

A matched-pair comparison between ^{18}F- and [^{68}Ga]Ga-PSMA was reported in three papers [10,13,21]. A total of 715 patients were assessed with this method, with 391 [^{68}Ga]Ga-PSMA and 324 [^{18}F]PSMA scans. As emerged from the data (see Table 1), two out of three studies used the same number of patients [13,21].

Radiohybrid PSMA (rhPSMA) ligands are a new class of PSMA-targeting agents with rapid blood clearance and minimal urinary excretion (despite more frequent benign uptake), allowing fast and efficient ^{18}F-labelling as well as the use of radiometals such as ^{68}Ga or lutetium-177 (^{177}Lu).

Dietlein et al [10] retrospectively enrolled 191 consecutive patients who underwent [^{18}F]DCFPyL (n = 62, 120 min uptake period) and [^{68}Ga]Ga-PSMA-11 (n = 129, 60 min uptake period) for the evidence of biochemical recurrence from PCa. The authors made an iterative match-paired analysis, observing that for low PSA concentration, the PSA-stratified sensitivity curve was more robust and superior for [^{18}F]DCFPyL than for [^{68}Ga]Ga-PSMA-11: the average sensitivity was 80% for [^{18}F]DCFPyL and 68% for [^{68}Ga]Ga-PSMA-11 in patients with PSA levels ranging between 0.5 and 3.5 ng/ml. The authors concluded noninferiority for [^{18}F]DCFPyL. This was explained as follows: (1) a high kidney activity can mask nearby nodes, and (2) the different administered doses of tracers (higher for ^{18}F than for ^{68}Ga) can improve the ratio between tumour and background, thus enhancing the detection rate (mainly for [^{18}F]DCFPyL).

Rauscher et al [13] retrospectively enrolled 204 patients with biochemically recurrent PCa after radical prostatectomy undergoing [^{18}F]PSMA-1007 PET/CT (n = 102) compared with a similar group of patients (n = 102) who underwent [^{68}Ga]Ga-PSMA-11 PET/CT. The tracers [^{18}F]PSMA-1007 and [^{68}Ga]Ga-PSMA-11 PET revealed 369 and 178 PSMA-ligand–positive lesions, respectively. They also observed that the number of lesions with increased PSMA-ligand uptake attributed to a benign origin was considerably higher for [^{18}F]PSMA-1007 PET than for [^{68}Ga]Ga-PSMA-11 PET. Namely, [^{18}F]PSMA-1007 PET revealed almost five times more lesions attributed to a benign origin than [^{68}Ga]Ga-PSMA-11 PET (245 vs 52 lesions) most frequently observed in ganglia, nonspecific lymph nodes, and bone lesions (at a rate of 43%, 31%, and 24% for [^{18}F]PSMA-1007 and 29%, 42%, and 27% for [^{68}Ga]Ga-PSMA-11 PET, respectively). In addition, the SUVmax of lesions attributed to a benign origin was significantly higher (p < 0.0001) for [^{18}F]PSMA-1007 PET. These findings further support the need for sophisticated reader training, emphasising known pitfalls and reporting within the clinical context.

Kroenke et al [21] performed a retrospective matched-pair comparison of 160 [^{18}F]rhPSMA-7 with 160 [^{68}Ga]Ga-PSMA-11 PET/CT studies for primary staging (n = 33) and

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biochemical recurrence (n = 127). All primary tumours were positive with both agents (n = 33 each), whilst slightly more metastatic lesions were observed with [^{68}Ga]Ga-PSMA-11 in both disease stages (113 for [^{18}F]rhPSMA-7 and 124 for [^{68}Ga]Ga-PSMA-11), with no significant differences in terms of SUVmax (p > 0.05); however, the tumour-to-bladder ratio was significantly higher for [^{18}F]rhPSMA-7 (4.9 ± 5.3 vs 2.2 ± 3.7, p = 0.02 for local recurrence; 9.8 ± 9.7 vs 2.3 ± 2.6, p < 0.001 for primary PCa). The tumour positivity rate was consistently high for [^{18}F]rhPSMA-7 as well as [^{68}Ga]Ga-PSMA-11: [^{18}F]rhPSMA-7 and [^{68}Ga]Ga-PSMA-11 PET revealed 566 and 289 PSMA-ligand–positive lesions, respectively. Of these, 379/566 (68%) and 100/289 (34.6%) lesions were considered benign with similar anatomical distribution (42%, 24%, and 25% in [^{18}F]rhPSMA-7 vs 32%, 24%, and 38% in [^{68}Ga]Ga-PSMA-11 for ganglia, bone, and unspecific lymph nodes, respectively). Moreover, a higher number of local recurrences were observed with [^{18}F]rhPSMA-7 than with [^{68}Ga]Ga-PSMA-11 (42 vs 32 lesions), potentially due to the lower urinary excretion of [^{18}F]rhPSMA-7 that improved the detection rates in regions directly adjacent to the urinary bladder. The authors concluded that adequate reader training can allow physicians to differentiate benign uptake from disease, thus benefiting from the logistical and clinical advantages of [^{18}F]rhPSMA-7.

By considering the abovementioned papers [10,12,13,19–21], on the basis of the clinical indications, three studies were related to the biochemical recurrence of disease [10,12,13], and three considered both initial staging and biochemical recurrence of PCa [19–21]. According to Dietlein et al [10,12] and Rauscher et al [13], in patients with biochemical recurrence of PCa, ^{18}F-labelled PSMA was more efficient in detecting the recurrence of disease, both for PSA ranging between 0.5 and 3.5 ng/ml and for the identification of local recurrence (mainly for the lower bladder activity in the case of [^{18}F]PSMA-1007). However, the increase in the detection rate for ^{18}F-labelled PSMA was also correlated with a high rate of false-positive findings, mainly in celiac ganglia and bone lesions. Therefore, a careful interpretation was suggested by all the authors. Data from the papers of Hoberük et al [19], Pattison et al [20], and Kroenke et al [21] underlined the advantages of [^{18}F]PSMA-1007 for the identification of the primary tumour (useful also for radiotherapy planning), but reduced detectability for liver and adrenal lesions, due to the tracer's biliary excretion. In Table 2, a summary of detection rates for ^{68}Ga- and ^{18}F-labelled PSMA is reported, based on the abovementioned studies. As illustrated, based on the patient analysis, no great differences emerged from ^{68}Ga- and ^{18}F-labelled PSMA in terms of detection rate. Conversely, in the lesion-based analysis, ^{18}F-labelled PSMA identified more local soft tissue and bone lesions than [^{68}Ga]Ga-PSMA-11, but [^{68}Ga]Ga-PSMA-11 was able to detect more local and distant lymph node metastases. However, the data are scarce for a correct comparison among the available ^{68}Ga- and ^{18}F-labelled PSMA.

3.4. *Indiscriminate use of ^{68}Ga or ^{18}F*

Finally, the majority of the papers included in this review (n = 6) [11,14–18] used indiscriminately either ^{68}Ga-PSMA or [^{18}F]PSMA in patients at different settings of disease (from the initial diagnosis to castration-resistant disease). Therefore, 1157 patients were studied with both tracers, independently of their different biodistribution and biochemical characteristics.

In the studies by Baas et al [16], Jansen et al [15], and Fendler et al [11], [^{68}Ga]Ga-PSMA and [^{18}F]PSMA were used indiscriminately for the same endpoints. In the first study, 213 patients were enrolled to evaluate the predictive value of preoperative PSMA PET assessment for lymph nodes suspicious for metastases in the biochemical persistence or early biochemical recurrence settings [16]. The authors concluded that extended lymph node dissection should be planned in patients with intermediate- to high-risk PCa and a positive preoperative PSMA PET, to avoid an incorrect nodal stage and incomplete tumour burden removal. In their experience, Jansen et al [15] reported that with the introduction of PSMA PET, the Phoenix criteria used for the definition of recurrent PCa after radiotherapy should be reassessed. Indeed, the authors, by using both [^{68}Ga]Ga-PSMA and [^{18}F]PSMA PET/CT, found that 84% of PCa

Table 2 – PSA-based detection rates for ^{18}F-labelled PSMA and [^{68}Ga]Ga-PSMA-11

Authors [Ref.]	[^{68}Ga]Ga-PSMA-11 DR		[^{18}F]PSMA DR	
	Per patient	Per lesion/site	Per patient	Per lesion/site
Dietlein et al [12]	PSA <0.5 ng/ml: 89% PSA 0.5–3.5 ng/ml: 66% PSA >3.5 ng/ml: 91%	NA	PSA <0.5 ng/ml: 87% PSA 0.5–3.5 ng/ml: 88% PSA >3.5 ng/ml: 84%	NA
Rauscher et al [13]	80.4%	Global: 70.8% Abdominopelvic LNM: 34% Local recurrence: 26% Supradiaphragmatic LNM: 17% Bone mets: 21% Soft tissue mets: 2%	80.4%	Global: 33.6% [a] Abdominopelvic LNM: 29% Local recurrence: 22% Supradiaphragmatic LNM: 27% Bone mets: 18% Soft tissue mets: 4%
Kroenke et al [21]	PSA <0.5 ng/ml: 56% PSA 0.5–1 ng/ml: 77% PSA 1–2 ng/ml: 64% PSA >2 ng/ml: 95%	Local recurrence: 32% Pelvic LNM: 54% Nonpelvic LNM: 26% Bone mets: 22% Visceral mets: 1%	PSA <0.5 ng/ml: 56% PSA 0.5–1 ng/ml: 77% PSA 1–2 ng/m: 64% PSA >2 ng/ml: 95%	Local recurrence: 42% Pelvic LNM: 44% Nonpelvic LNM: 17% Bone mets: 29% Visceral mets: 6%

DR = detection rate; LNM = lymph node metastases; mets = metastases; NA = not applicable; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen.
[a] [^{18}F]PSMA-1007.

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had a metastatic disease below the Phoenix PSA threshold. Finally, Fendler et al [11] demonstrated that PSMA PET was able to detect the presence of metastases in patients otherwise classified as bearing nonmetastatic castration-resistant PCa, paving the way for the introduction of this new imaging modality in the therapeutic management of this subset of patients.

Koerber et al [18] enrolled 335 men with primary PCa who underwent PSMA PET ([^{68}Ga]Ga-PSMA-11 or [^{18}F]PSMA-1007 indiscriminately) for the detection of metastasis. By comparing the areas under the curve (AUCs) of [^{68}Ga]Ga-PSMA-11 and [^{18}F]PSMA-1007, the authors obtained better results for the ^{18}F-based ligand than for [^{68}Ga]Ga-PSMA for the detection of metastases in patients with intermediate- to high-risk PCa (AUC: 0.71 vs 0.63).

Scobioala et al [14] enrolled 35 patients who underwent [^{18}F]PSMA PET/CT or [^{68}Ga]Ga-PSMA-11 PET/CT or PET/MRI, and multiparametric MRI (mpMRI) for the identification of IDLs before radical radiotherapy. The authors found that PSMA-based PET was more accurate than mpMRI for the definition of IDLs and that a trend towards higher specificity was reported for [^{68}Ga]Ga-PSMA-11 PET/MRI (97%) compared with [^{18}F]PSMA-1007 PET/CT (93%) and [^{68}Ga]Ga-PSMA-11 PET/CT (91%). Moreover, they reported that [^{18}F]PSMA-1007 PET/CT showed higher diagnostic performance than [^{68}Ga]Ga-PSMA PET/CT for lesions localised in the transition zone of the base region (0.67 vs 0.56).

Finally, Morawitz et al [17] determined that in patients with biochemical recurrence of PCa, [^{18}F]F-PSMA-1007 PET/CT was able to detect more recurrent lesions than [^{68}Ga]Ga-PSMA-11 PET/CT and CT, both at patient- and lesion-based analysis (87% vs 83.3% vs 49.2%, and 100% vs 98.8% vs 50.7%, respectively).

3.5. Discussion

From the careful analysis of the selected papers, some comments about the different radiopharmaceutical PSMA agents can be made:

1. Currently, data from definitive head-to-head comparisons are lacking and therefore definitive conclusions are difficult to be drawn.
2. Matched-pair analyses are a sort of "trick" for the comparison between the radiopharmaceuticals and are subject to a significant bias.
3. Most papers are retrospective, but in many cases, the data demonstrated similar outcomes for both tracers in staging and biochemical recurrence.
4. The tracer [^{18}F]PSMA-1007 is superior to [^{68}Ga]Ga-PSMA for the identification of local recurrence (less activity close to the bladder for [^{18}F]PSMA-1007).
5. Nonspecific/equivocal bone lesions are often recognised in [^{18}F]PSMA-1007 PET scans [22]. In this regard, Arnfield et al [23] recently suggested an SUVmax threshold of 7.2. Below this threshold, lesions could be interpreted as likely benign.

In Table 3, we summarise the pros and cons of each tracer (^{68}Ga- vs ^{18}F-labelled PSMA).

In current clinical practice, the choice of the best radiopharmaceutical is often determined by local availability. Local choice of [^{68}Ga]Ga-PSMA, [^{18}F]PSMA-1007, or [^{18}F]

Table 3 – Pros and cons of ^{18}F-labelled PSMA and [^{68}Ga]Ga-PSMA-11

	[^{68}Ga]Ga-PSMA [a]	[^{18}F]-PSMA [b]
Pros	1. Experience: most widely studied tracer, and thus has most experience with handling and image interpretation 2. Availability: on-site availability (^{68}Ga generator's availability) at some centres may increase access at some sites 3. Availability: lack of intellectual property protection enabled widespread access at a low cost 4. Physical characteristics: short half-life results in low radiation dose to patients and staff 5. Biodistribution: less unspecific tracer accumulation in benign findings compared with [^{18}F]PSMA tracers 6. Authorisation: FDA approved	1. Physical characteristics: long radioactive half-life of 110 min, enabling central manufacture for distribution to satellite centres and more efficient labour manufacture costs [27–29] 2. Physical characteristics: low positron energy (0.65 MeV) with high spatial resolution; this has been shown in phantom studies, but the difference may not be clinically relevant 3. Biodistribution: biodistribution studies demonstrated reduced accumulation in the bladder for [^{18}F]-PSMA-1007 (due to a mainly liver excretion) offering potential improvements for locoregional staging adjacent to the urinary bladder and ureters. 4. Authorisation: EMA approved in France
Cons	1. Availability: short half-life of 68 min limits ability to distribution commercial production 2. Availability: ^{68}Ge/^{68}Ga generator yield may limit the number of patients that can be scanned 3. Availability: although cyclotron-based production of [^{68}Ga]GaCl3 is possible, the reports of the amount of radiopharmaceutical produced are currently similar to the activity when multiple 68Ge/68Ga generators are eluted in serial to a labelling platform [30] 4. Physical characteristics: high positron energy (1.9 MeV) that may determine lower image resolution 5. Biodistribution: urinary excretion of [^{68}Ga]Ga-PSMA-11 radiotracer may limit the identification of small-volume disease adjacent to the ureters, bladder, and prostatic urethra requiring the need of contrast or diuretics [31], with potential side effects [32] 6. Biodistribution: intense urinary uptake in the bladder and kidneys may also lead to a fair/halo artefact, limiting the detection of disease in adjacent pelvic tissues [33,34] 7. Image interpretation: incorrect ^{68}Ga dose calibration may impact quantitative accuracy [33,34]	1. Experience: less published data compared with [^{68}Ga]Ga-PSMA-11 2. Availability: intellectual property protection may increase costs; may be more relevant for [^{18}F]-DCFPyL 3. Physical characteristics: longer half-life and administered radioactivity may increase patient and staff radiation dose 4. Image interpretation: nonspecific/equivocal bone lesions are more often recognised with [^{18}F]-PSMA-1007 [18] but not with [^{18}F]-DCFPyL 5. Image interpretation: higher liver accumulation with [^{18}F]-PSMA-1007 may obscure visceral metastases or change assessment for suitability for radioligand therapy if a liver threshold is used

EMA = European Medicine Agency; FDA = Food and Drug Administration; PSMA = prostate-specific membrane antigen; rhPSMA = radiohybrid PSMA.
[a] [^{68}Ga]Ga-PSMA-11.

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DCFPyL may depend on the availability of on-site ^{68}Ga generator, radiopharmaceutical scientist, and the cost of purchasing from a commercial provider. Regulatory approval and reimbursement are also important factors. Both [^{68}Ga]Ga-PSMA and [18F]DCFPyL are now approved in the USA by the Food and Drug Administration. US National Comprehensive Cancer Network guidelines now refer to these agents, whereas other guidelines such as E-PSMA standardised reporting guidelines [35] remain agnostic with regard to the choice of radiotracer. In Australia, a recommendation by the relevant health technology assessment authority for reimbursement has been made; this is radiotracer agnostic and would enable each centre to choose its preferred radiotracer. In this landscape of increasing global availability, approval, and reimbursement, it seems that high-level data such as randomised controlled trials or more robust prospective head-to-head comparisons are unlikely to be performed.

However, in defined clinical situations, certain specific information is of utmost importance to clinicians:

1. The tracers [^{18}F]PSMA-1007 and [^{18}F]rhPSMA-7 may be preferable for the evaluation of the prostate primary or prostate bed due to lower urinary uptake.
2. The tracer [^{18}F]PSMA-1007 should be interpreted carefully for the identification of bone metastases. However, [^{18}F]DCFPyL showed fewer equivocal skeletal lesions and higher inter-reader agreement on skeletal lesions, as reported by Wondergem et al [24] in a matched-pair analysis comprising 120 patients.
3. The evaluation of suitability for radioligand therapy with [^{177}Lu]PSMA studies has used physiologic liver uptake as a reference standard. Patients with tumour uptake greater than liver without sites of measurable PSMA-negative disease were deemed suitable in the VISION trial [25,36]. Physiologic liver uptake is higher with [^{18}F]PSMA-1007, which decreases the proportion of patients deemed suitable. The use of quantitative criteria as performed in the TheraP trial [22,26] may overcome this limitation.

The main limitation of the present systematic review is the lack of real comparative data. Only three studies really provided a head-to-head comparison, with a total of 123 patients; one of these three studies included 46 patients and it was purely retrospective, and there was no real gold standard available; one study was prospective with 50 patients, again lacking gold standard; and one study used a mix of PET tracers as a comparator, lacked gold standard, and was also retrospective.

4. Conclusions

The verdict on the optimal usage of the different PSMA-targeted radiopharmaceutical agents labelled with ^{68}Ga or ^{18}F is not determined. In this regard, the current literature comparing the different tracers is still limited. Certain clinical indications could trigger a preference (ie, [^{18}F]PSMA-1007 would be used in case of primary lesions or suspected prostatic fossa recurrence, but caution is needed in interpreting bone uptake given the higher incidence of benign uptake. Pragmatically, however, the availability of a tracer will probably most likely determine which radiopharmaceutical will be considered. Reporter expertise may also be a significant factor in the interpretation and ultimately accuracy of the reported study rather than the choice of a radiopharmaceutical. Having said this, it must be stated once more that PSMA PET imaging has revolutionised PCa imaging, and all the above-discussed small-molecular PSMA tracers represent outstanding options for this novel molecular imaging method.

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Study concept and design: Evangelista, Hofman.
Acquisition of data: Evangelista, Laudicella.
Analysis and interpretation of data: Evangelista, Laudicella, Maurer.
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Appendix A. Supplementary data

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