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Clinical impact of PSMA PET in biochemically recurrent prostate cancer; a review of the literature

Maurits Wondergem · Friso M. van der Zant · Wouter A. M. Broos · Remco J. J. Knol

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Abstract PSMA PET is increasingly used for localising biochemical recurrent prostate cancer (BCR) and is incorporated in European and national guidelines. Nevertheless, clinical implications of PSMA PET need to be clarified. In this report, the available literature on the clinical impact of PSMA PET in patients with BCR is reviewed. A comprehensive literature search was performed using the MEDLINE® database. All studies reporting data on PSMA PET directed patient management were considered relevant. In the review, 16 studies were included. Change of management was 45% for the pooled data (861/1899 patients), of which 50% changed from non-targeted to targeted approach. Change from targeted to non-targeted approaches was found in 17% of patients. High heterogeneity was found between presently available studies. It can be concluded that PSMA PET induces change of management in almost half of the patients with BCR. After PSMA PET more patients are selected for metastasis targeted therapies. Potential beneficial effects of metastasis directed therapies require further evaluation.

Keywords prostate cancer · prostate specific membrane antigen · PSMA PET · biochemical recurrence

M. Wondergem, MD, PhD (✉) · F. M. van der Zant, MD, PhD · W. A. M. Broos, MD · R. J. J. Knol, MD, PhD
Department of Nuclear Medicine, Noordwest Ziekenhuisgroep, Alkmaar, The Netherlands
m.wondergem@nwz.nl

Klinische waarde van PSMA PET bij biochemisch recidiefprostaatcarcinoom; een review van de literatuur

Samenvatting PSMA PET wordt steeds vaker gebruikt voor het lokaliseren van biochemisch recidiefprostaatkanker (BCR). Het gebruik ervan is opgenomen in Europese en nationale richtlijnen. Desondanks zijn de klinische implicaties van PSMA PET onduidelijk. In deze review wordt de beschikbare literatuur over de klinische impact van PSMA PET bij patiënten met BCR besproken. Met behulp van de MEDLINE®-database werd een literatuuronderzoek uitgevoerd, waarbij artikelen zijn geïncludeerd die gegevens over therapeutische consequenties van PSMA PET bij BCR rapporteerden. In de review werden 16 artikelen opgenomen. Uit de gepoolde data bleek dat het beleid op grond van PSMA PET was aangepast bij 45% van de patiënten (861/1899), waarbij in 50% van de gevallen het beleid veranderde van niet-gerichte naar op metastasen gerichte behandeling. Verandering van gerichte naar niet-gerichte behandeling werd gevonden bij 17% van de patiënten. De beschikbare studies waren sterk heterogeen. De conclusie is dat PSMA PET bij bijna de helft van de patiënten met BCR leidt tot wijziging van het behandelbeleid. Na PSMA PET worden meer patiënten geselecteerd voor op metastasen gerichte behandelingen. Potentieel gunstige effecten van deze behandelingen dienen verder in kaart te worden gebracht.

Trefwoorden prostaatkanker · prostaatspecifiek membraanantigeen · PSMA PET · biochemisch recidief

Introduction

Prostate cancer (PCa) is the most common cancer in men in the Western world [1, 2]. Between 28% and 53% of patients treated with curative intention will develop biochemically-recurrent prostate cancer (BCR) [3]. BCR is defined as two consecutive prostate-specific antigen (PSA) values ≥0.2 ng/mL after radical prostatectomy, or any PSA increase of 2.0 ng/ml above the nadir following radiation therapy and brachytherapy, however in recent clinical trials other definitions have been applied [4–6]. Accurate imaging studies are desired for patients with BCR as early lesion localisation directs further treatment, which might include stereotactic metastasis-directed radiotherapy, salvage radiotherapy, salvage lymph-node dissection, or the initiation of systemic treatment [3].

Since more than a decade, positron emission tomography (PET) is one of the cornerstones of oncologic imaging and has been proven useful for a large variety of malignancies. However, the most frequently used tracer [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG) has a relatively low sensitivity for prostate cancer and therefore PET has had little impact on prostate cancer imaging and patient management, until recently [7]. In the last decade, the introduction of [^{18}F]-fluorocholine and [^{11}C]-choline PET has proven useful for detection and localisation of prostate cancer. In clinical practice it was used especially for detection of a biochemical relapse after therapies with curative intent. The relatively low positive predictive values of [^{18}F]-fluorocholine and [^{11}C]-choline, particularly due to false positive inflammatory lymph nodes, has prevented the wide clinical use of those tracers in primary staging of prostate cancer. Another known drawback of choline tracers is the moderate sensitivity for lymph node metastases [8].

Lack of specificity of conventional imaging techniques has encouraged researchers to screen prostate cancer cells for suitable antigens in order to develop agents capable of specific binding. This resulted in the development of monoclonal antibodies (mAbs) to target prostate specific antigen (PSA) and prostatic acid phosphatase (PAP) [9]. Secretion of those antigens preclude cell-associated binding and presence of PSA and PAP in the plasma effectively blocks specific antibody binding at the tumour site. Thereafter, prostate specific membrane antigen (PSMA) was discovered, which is a 750 amino acid transmembrane protein and a highly specific prostate epithelial cell membrane antigen [10, 11]. Physiological expression of PSMA in normal cells is 100-1000 fold less than baseline expression in prostate cancer, expression increases as tumour grade increases with concurrent increase in metastatic sites and castrate refractory prostate cancer (CRPC) [7, 8]. Furthermore, PSMA is internalised and endosomally recycled, which increases the deposition of radiopharmaceuticals into the cell over time [9].

In 2006, ^{111}In-capromab, a mAb for targeting PSMA, was reported. However, this tracer has a poor efficacy associated with binding to the intracellular domain of PSMA, resulting in binding to nonviable cells that have damaged cell membranes only [10]. A few years later, mAbs targeting the external domain of PSMA were reported. Due to their relatively large mass, these ligands show slow clearance from background and slow target recognition, prohibiting their success as radiopharmaceuticals for imaging. Furthermore, they require superior safety profiles, since mAbs have potential side effects including allergic reactions [11–13]. From the late 2000s small molecule PSMA inhibitors, which are approximately 350 fold smaller than mAbs, have been reported [14–17]. Those tracers have rapid target recognition and background clearance and no adverse effects have been reported.

In comparison with choline, these PSMA-tracers have shown to detect more lesions at lower PSA levels, which not only increases the sensitivity for prostate cancer, but also increases the clinical impact of PET in prostate cancer [17, 18]. Furthermore, the specific binding to PSMA increases specificity for prostate cancer and positive predicting values.

At present, several PSMA tracers are available for clinical use including tracers labelled with ^{68}Ga or ^{18}F. ^{18}F-labeled tracers have some potential benefits since positrons emitted by ^{18}F decay have lower kinetic energies compared to those emitted by ^{68}Ga, resulting in a higher resolution of PET images acquiring ^{18}F tracers. Furthermore, the 110 min half-life of ^{18}F compared to 68 min half-life for ^{68}Ga, enables imaging at later timepoints without significant deterioration of image quality or the need for administration of higher dosages. However, for both ^{68}Ga and ^{18}F labelled tracers, high detection rates are reported in literature (Tab. 1; [19–23]). As a result, PET imaging with PSMA tracers for prostate cancer has found its way into standard clinical practice and is already incorporated in European and national guidelines (https://uroweb.org/guideline/prostate-cancer/and https://richtlijnendatabase.nl/richtlijn/prostaatcarcinoom/diagnostiek/beeldvormend_onderzoek/psma_pet_ct_bij_prostaatcarcinoom.html). The Dutch guidelines recommend the use of PSMA PET when screening for metastases in primary staging is indicated and for detection of BCR after radical prostatectomy and radiation therapy. Nevertheless, clinical implications of PSMA PET need to be clarified. Therefore, in this report, the available literature on the clinical impact of PSMA PET in patients with BCR has been reviewed.

Methods

Identification of studies

A comprehensive literature search was performed using the MEDLINE® database to identify relevant studies by the following strategy: (''rostate'' [MeSH Terms]

Table 1 Detection rates of different PSMA tracers for biochemical recurrent prostate cancer

Author	Year	Publication type	Tracer	*N*	Detection rates (%) per PSA category (ng/ml)			
					<0.5	0.5–1.0	1.0–2.0	>2.0
Giesel et al. [19]	2018	Original article	[^{18}F]-PSMA-1007	251	62	74	91	94
Mena et al. [20]	2019	Original article	[^{18}F]-DCFPyL	90	48	50	89	94
Perera et al. [21]	2019	Meta-analysis	[^{68}Ga]-PSMA-11	4790	45	59	75	95
Rahbar et al. [22]	2018	Original article	[^{18}F]-PSMA-1007	100	86	89	100	100
Song et al. [35]	2019	Original article	[^{18}F]-DCFPyL	72	50	69	100	91–96
Wondergem and Jansen et al. [23]	2019	Original article	[^{18}F]-DCFPyL	248	59	69	85	96

OR ''prostate''[All Fields]) AND (''neoplasms''[MeSH Terms] OR ''neoplasms''[All Fields] OR ''cancer''[All Fields]) AND biochemical[All Fields] AND (''recurrence''[MeSH Terms] OR ''recurrence''[All Fields]) AND PET[All Fields]. The limit "humans" was used. The reference list of potential suitable studies was additionally searched to identify other relevant studies. This resulted in 535 potentially relevant studies.

Inclusion and exclusion criteria

All abstracts of relevant studies were reviewed with a set of predefined inclusion and exclusion criteria. All studies reporting data on PSMA PET directed patient management were considered relevant. No language restrictions were applied. The following studies were excluded from this review: studies presenting data on a patient population that was suspected to be used in earlier publications; studies of which no full text article was available; review studies; letters to the editor and case reports. This resulted in 36 included studies.

Data extraction

After initial assessment for inclusion the following data were extracted from the selected studies: study design, aim of the study, number of included patients; used PSMA tracer, used definition of biochemical recurrence, inclusion criteria, previous therapies, PSA at time of PET, number of patients with PET induced change in management, and kind of change in management. An additional 20 studies were excluded based on the extracted data: 15 did not report numbers on change of management, three studies also included patients with PSA persistence after radical prostatectomy and two studies also included patients with primary prostate cancer. For two studies it could not be ruled out that patients with PSA persistence were included; however, since inclusion of those patients was not mentioned explicitly, those studies were included in the further analysis.

Data structuring

PSMA PET induced change in management was divided in nine groups: systemic to targeted therapy, surveillance to targeted therapy, change of targeted strategy, targeted to systemic therapy, surveillance to systemic therapy, change of systemic therapy, targeted therapy to surveillance, systemic therapy to surveillance, and others. The data of studies that provided sufficient data to extract the exact numbers of change in therapy were pooled. Targeted therapies included: prostatectomy, lymph node dissection, local radiation therapy, pelvic lymph node radiation, and stereotactic radiation of oligometastatic disease.

Results

Ultimately 16 studies were included in the review (Tab. 2; [24–39]). Twelve studies reported outcomes using [^{68}Ga]-PSMA-11 PET, while four studies reported data on other PSMA-tracers. 14 studies used PET combined with computed tomography (CT), while two studies also included patients that received PET combined with magnetic resonance imaging (MRI). Large differences were found between included patient populations, including: patients with low PSA values versus patients without limitations for PSA values, oligometastatic disease on PSMA PET versus no restriction of number of metastases, only radical prostatectomy as previous therapy versus all kinds of previous therapies, normal or equivocal findings on conventional imaging before PSMA PET versus no restrictions on findings on previous imaging, and inclusion of patients found suitable for radiation therapy before PSMA PET versus patients without limitations on intended therapy before PSMA PET.

The reported rate of change of management ranged from 19–73% (Tab. 3). The pooled data of all patients included in this review show an overall change of management in 861 of 1899 patients (45%). Nine studies, including 729 patients, reported sufficient data to extract the kind of change in management [20, 24, 26, 27, 29, 33, 36, 38, 40]. In 332 (46%) of these 729 patients a change in management was seen. In 50% of them management changed to a targeted approach while systemic treatment or surveillance was scheduled without information from PSMA PET (Fig. 1). A change from targeted approaches to non-targeted was found in 17% of patients. As a result, PSMA PET directed more patients to targeted therapy strategies.

Table 2 Characteristics of included studies

Author	Year	*N*	Tracer	Definition BCR	Additional inclusion criteria[b]		Patient characteristics			
					PSA (ng/ml)	Other	Primary RP (+sRT)	Primary RT (+ADT)	Other	PSA (median, range)
Change of treatment										
Afaq et al. [38]	2018	100	[^{68}Ga]-PSMA-11	NR	–	–	68	32	–	NR
Bashir et al. [24]	2019	28	[^{68}Ga]-PSMA-11	NR	–	Oligometastatic disease	28 (11)	–	–	0.22 (0.3–2.3)[d]
Calais et al. [26]	2018	101	[^{68}Ga]-PSMA-11	RP: AUA RT: Phoenix	–	Initial RP or RT	87 (28)	14 (9)	–	1.7 (0.05–140)
Calais et al. [26]	2018	270	[^{68}Ga]-PSMA-11	AUA	<1.0	Initial RP without sRT	270	–	–	0.48 (0.03–1)
Farolfi et al. [37]	2019	119	[^{68}Ga]-PSMA-11	EAU	0.2–0.5	Initial RP without sRT	119	–	–	0.32 (0.2–0.5)
Grubmuller et al. [27]	2018	117	[^{68}Ga]-PSMA-11	EAU	–	Initial RP	117 (69)	–	–	1.04 (0.58–1.87)[d]
Hope et al. [28]	2017	126	[^{68}Ga]-PSMA-11	NR	<12 months[c]	–	76 (33)	41 (41)	–	5.9[e]
Kulkarni et al. [29]		68	[^{68}Ga]-THP-PSMA	Phoenix	–	–	NR	NR	–	4.44[e] (0.16–71.0)
Mattiolli et al. [30]	2018	125	NR[a]	RP: EAU RT: Phoenix	–	Initial RP or RT	107	62	–	1.8 (0.003–395)
Mena et al. [31]	2018	68	[^{18}F]-DCFBC	RP: EAU RT: any PSA rise	–	Initial RP or RT	59 (9)	9	–	4.4[e] (0.2–37.4)
Muller et al. [39]	2019	223	[^{68}Ga]-PSMA-11	NR	–	–	197 (69)	2	24	0.98 (0.03–99)
Roach et al. [32]	2018	312	[^{68}Ga]-PSMA-11	NR	–	Negative conventional imaging	NR	NR	NR	1.1 (0.01–75)
Rousseau et al.[a] [33]	2019	52	[^{68}Ga]-PSMA-11	NR	≤1.5	After RP, normal mpMRI and BS	52	–	–	0.44 (0.07–1.5)
Schmidt-Hegeman et al. [a] [34]		90	[^{68}Ga]-PSMA-11	NR	–	After RP, before sRT, no distant disease on PSMA PET	90	–	–	0.43 (0.10–6.24)
Song et al. [35]	2019	72	[^{18}F]-DCFPyL	RP: AUA RT: Phoenix	–	Initial RP or RT	42 (12)	30	–	3.0 (0.23–698.4)
Zacho et al. [36]	2018	70	[^{68}Ga]-PSMA-11	RP: PSA >0.2 RT: rise >2.0 above nadir	–	Initial RP or RT	64 (17)	6	–	0.55 (0.2–11.3)

RP radical prostatectomy, *RT* radiation therapy, *sRT* salvage radiation therapy, *ADT* androgen deprivation therapy, *NR* not reported
AUA: PSA >0.2 ng/ml >6 weeks post-surgery; Phoenix criteria: PSA rise ≥2 ng/ml above the nadir, EAU: two consecutive rising PSA values >0.2 ng/ml; ASTRO:
[a]Tracer labelled with ^{68}Ga not further specified
[b]Additional inclusion criteria besides biochemical recurrence
[c]PSA doubling time
[d]Interquartile range
[e]Mean

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Table 3 Change of management after PSMA PET

Afaq et al. [38]	2018	Retrospective	39/100	39%	8	6	5	3	3	2	1	1	10
Bashir et al. [24]	2019	Retrospective	12/28	43%	–	1	9	2	–	–	–	–	–
Calaiset al. [26]	2018	Prospective	54/101	53%	12	9	8	6	7	5	4	3	–
Calais et al. [26]	2018	Retrospective	52/270	19%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Farolfi et al. [37]	2019	Retrospective	36/119	30%	17	NR	NR	NR	NR	NR	NR	NR	NR
Grubmuller et al. [27]	2018	Retrospective	50/117	43%	23	18	2	–	–	5	1	1	–
Hope et al. [28]	2017	Prospective	67/126	53%	19	15	10	6	6	1	6	4	–
Kulkarni et al. [29]	2019	Prospective	23/68	34%	2	1	3	4	2	6	4	–	1
Mattiolli et al. [30]	2018	Retrospective	66/104	63%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mena et al. [31]	2018	Prospective	34/68	50%	–	18	–	–	3	–	13	–	–
Muller et al. [39]	2019	Retrospective	122/203	60%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Roach et al. [32]	2018	Prospective	192/312	62%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rousseau et al. [33]	2019	Prospective	38/52	73%	9	13	8	–	2	–	4	2	–
Schmidt-Hegeman et al. [34]	2019	Retrospective	18/90	20%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Song et al. [35]	2019	Prospective	43/72	60%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zacho et al. [36]	2018	Prospective	15/69	22%	7	4	2	2	–	–	–	–	–

NR not reported

Seven studies did not report sufficient data to extract the kind of management change; those are reviewed in a narrative way in the following paragraphs. Farolfi et al. reported change in management in 36/119 patients (30%) as a secondary outcome in a study that assessed the performance of [^{68}Ga]-PSMA-11 PET/CT in BCR after radical prostatectomy without salvage radiation therapy [37]. A similar study by Song et al. used the promising ^{18}F-labelled tracer ^{18}F-DCFPyL. They reported change of management in 43/72 patients (60%) in a heterogenous population of patients after RP and radiation therapy with BCR [35]. A study by Schmidt-Hegeman et al. primarily investigated the effect of [^{68}Ga]-PSMA-11 PET/CT guided radiation therapy on the biochemical recurrence free survival. They reported change in management in 18/90 patients (20%) with BCR who were scheduled for salvage radiation therapy before [^{68}Ga]-PSMA-11 PET/CT as a secondary finding [34].

A study by Roach et al. showed change in management in 192/312 patients (62%) with BCR and negative or equivocal conventional imaging [32]. [^{68}Ga]-PSMA-11 PET/CT resulted in a significant reduction in the number of men in whom the site of disease recurrence was unknown; besides there was significant increase in the detection of presumed oligometastatic and polymetastatic disease. In contrast to these results the authors reported no significant change in the intended overall treatment plan when categorized into surveillance, targeted/localized, or systemic therapy. However, since in this article those numbers are given only for the total population, changes in management for single patients cannot be extracted.

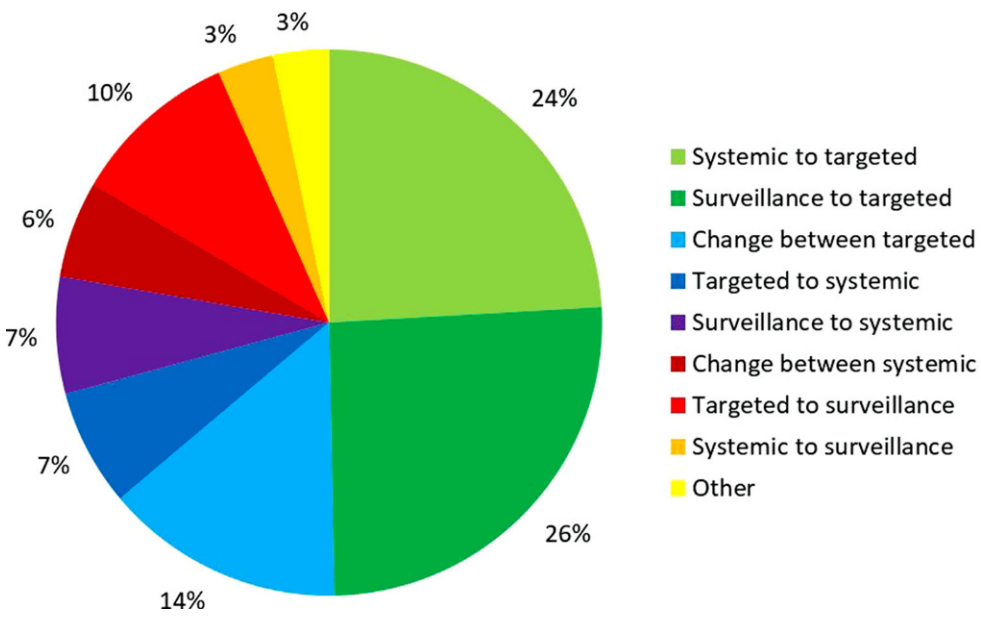

Fig. 1 Pooled data. Characteristics of change of management in 332/729 patients

Matiollo et al. evaluated the clinical impact of [^{68}Ga]-PSMA PET/CT and correlated potential treatment changes to age, Gleason score, PSA level and SUV_{max} [30]. A change in treatment was found in 66/104 patients. A significant change of treatment plan was found in patients with a higher Gleason score ($p = 0.0233$), higher SUV_{max} ($p = 0.0306$) and higher PSA levels ($p < 0.0001$; median PSA = 2.55 ng/ml); however, the clinical consequences of those correlations are not further discussed.

Muller et al. found a substantial increase in the use of metastasis-targeted treatment and a reduction in the use of systemic treatment in all patients imaged during the first year after introduction of [^{68}Ga]-PSMA-11 PET/CT for BCR into clinical routine [39]. The two most frequently selected therapy options were 'undergoing targeted radiotherapy only' (59/203 included patients; 29%), and 'undergoing targeted radiotherapy with hormonal therapy' (20/203 patients; 10%). The proportion of patients in whom systemic therapy was selected decreased from 60% (133/223 patients) to 34% (70/203 patients) based on the information provided by the [^{68}Ga]-PSMA-11 PET/CT scan. PSMA PET-directed metastasis-targeted treatment led to a complete response after six months in 45% of patients.

A study by Calais et al. determined how often salvage radiation therapy target volumes based on the Radiation Therapy Oncology Group guidelines covered [^{68}Ga]-PSMA-11 PET/CT-defined disease, and assessed the potential impact of [^{68}Ga]-PSMA-11 PET/CT on salvage radiation therapy in patients with early BCR (PSA <1.0 ng/ml) after radical prostatectomy [25]. They found that 122 of 270 patients (49%) had a positive [^{68}Ga]-PSMA-11 PET/CT result. Of these 122 patients, 52 had at least one PSMA positive lesion that was not covered by target volumes, which implied major impact on salvage radiation planning in all of those patients. For 24 patients extension of targeted volumes was possible to cover lymphatic metastases. 22 patients had oligometastatic diseases (≤5 metastases), potentially eligible for metastasis directed stereotactic body radiation. Six patients had extensive disease and would be unlikely to profit from salvage radiation therapy.

Discussion

The included studies in this review all show a substantial impact of PSMA PET on the management of patients with BCR. Some of these studies evaluated whether PSA values were a predictor for therapy change after PSMA PET. Afaq et al. found that higher PSA levels were significantly ($p = 0.024$) associated with management changes; 25.0%, 26.3%, 33.3%, 50.0%, 38.5%, and 50.0% for PSA values <0.2, 0.2–<0.5, 0.5–<1.0, 1.0 < 2.0, 2.0–<5.0, and ≥5.0 ng/ml respectively [38]. Mattiolli et al. also found a predictive value of higher PSA levels for change of management ($p < 0.0001$) [30]. In contrast to these findings, Calais et al. found no association between change of management and PSA levels at [^{68}Ga]-PSMA-11 PET/CT [26]. Hope et al. also found no significant management changes in 42%, 40%, 65%, 57%, and 56% for PSA values 0–0.2, 0.2–1.0, 1.0–2.0, 2.0–5.0, and ≥5.0 ng/ml, respectively. Furthermore, Roach et al. found no correlation between PSA levels and treatment changes; 67%, 60%, and 60% for PSA levels <0.2, 0.2–0.5, and >0.5 ng/ml, respectively [28, 32]. These data show that therapy changes may occur at all PSA levels and possibly even more frequently in patients with higher PSA levels. Therefore, in our opinion, no upper PSA limit should be used to select patients with BCR for PSMA PET/CT. No studies reported whether the character of change of treatment showed any relation with PSA values, since it could be hypothesised that therapy would change more towards systemic strategies in patients with higher PSA levels. Amongst other factors including PSA kinetics, Gleason grade, tumor stage, prior therapy, National Comprehensive Cancer Network risk groups, age and SUV_{max} of positive lesions, no other definite predictors of treatment change were found.

None of the included studies in this review provide data on the accuracy of PSMA PET/CT for detection of localisations of BCR. Most data are available from studies that used PSMA PET/CT before salvage lymphadenectomy. The largest of these available studies, by Rauscher et al., retrospectively evaluated 48 patients with biochemical recurrence who underwent [^{68}Ga]-PSMA-11 PET/CT or PET/MRI [41]. An analysis based on ten defined anatomical fields in the pelvis yielded a sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of 78%, 97%, 95%, 88% and 90% for PSMA PET and 27%, 99%, 95%, 69%, and 72% for morphological imaging (CT or MRI) while a patient based analysis yielded 100%, 50%, 93%, 100%, and 94% for PSMA PET and 34%, 83%, 93%, 84%, and 40% for morphological imaging. Other studies have confirmed these findings, including a meta-analysis by Kimura et al., that showed a high specificity and reasonable sensitivity for lymph node staging (specificity 95–97% and sensitivity 82–84%) [42]. Although PSMA PET is more sensitive than morphological imaging, the current sensitivity of PSMA PET/CT is still not high enough to justify salvage lymphadenectomy of solely the PET-positive regions. Furthermore, it remains unclear whether or not salvage lymphadenectomy based on PSMA PET findings will result in better survival outcomes. Siriwardana et al. found a biochemical free survival of 23% at 12 months after salvage lymph adenectomy in 35 patients with biochemical recurrence after radical prostatectomy with or without previous salvage radiation therapy to the prostate fossa [43].

For other PSMA PET targeted treatments after BCR including salvage radiation therapy to pelvic

Table 4 Characteristics of studies presenting data on survival outcomes after PSMA PET directed salvage therapies

Author	Year	*N*	Tracer	Definition BCR	Additional inclusion criteria[b]		Patient characteristics			
					PSA (ng/ml)	Other	Primary RP (+sRT)	Primary RT (+ADT)	Other	PSA (median, range)
Artigas et al. [44]	2019	20	^{68}Ga-PSMA-11	NR	–	Oligometastatic disease	20	–	–	1.4 (0.2–15.0)
Emmett et al. [46]	2017	164	^{68}Ga-PSMA-11	Rising PSA	≥0.05; <1.0	Initial RT suitable for sRT	164	–	–	0.23 (0.14–0.35)
Emmett et al. [45]	2019	186	^{68}Ga-PSMA-11	Rising PSA	≥0.05; <5.0	Initial RP, suitable for sRT	186	–	–	0.26 (0.15–0.59)[c]
Henkenberens et al. [47]	2016	29	^{68}Ga-PSMA I&T	PSA ≥0.3	–	–	28 (16)	1	–	1.47 (0.52–32.01)
Kneebone et al. [48]	2018	57	NR	EAU	–	Oligometastatic disease	50 (20)	7 (2)	–	NR
Kroeze et al. [49]	2019	305	NR[a]	NR	–	Oligometastatic disease	293	12	–	1.05 (0.04–47.5)
Marzec et al. [50]	2019	19	^{68}Ga-PSMA-11	Other	–	Oligometastatic disease	19	–	–	2.2 (0.2–10.1)
Ong et al. [51]	2019	20	NR[a]	NR	–	Oligometastatic disease	20 (5)	–	–	1.3 (0.2–30)
Schmidt- Hegeman et al.[34]	2019	90	^{68}Ga-PSMA-11	NR	–	After RP, before sRT, no distant disease on PSMA PET	90	–	–	0.43 (0.10–6.24)
Siriwardana et al. [43]	2017	35	NR[a]	NR	–	Oligometastases lymph node only	28 (14)	2	5	2.2 (0.5–5.6)
Soldatov et al. [52]		108	^{68}Ga-PSMA I&T	RP: PSA >0.2 RT: rise >2.0 above nadir	–	Oligometastatic disease	97 (62)	11 (6)	–	NR

RP radical prostatectomy, *RT* radiation therapy, *sRT* salvage radiation therapy, *ADT* androgen deprivation therapy, *NR* not reported, *AUA* PSA >0.2 ng/ml > 6 weeks post-surgery, *Phoenix criteria* PSA rise ≥2 ng/ml above the nadir, *EAU* two consecutive rising PSA values >0.2 ng/ml

[a]Tracer labelled with ^{68}Ga not further specified

[b]Additional inclusion criteria besides biochemical recurrence

[c]Interquartile range

Table 5 Response and survival after PSMA directed targeted therapies

Author	Year	Intervention	Biochemical response			BCR-free survival			Distant PFS		ADT-free survival	
			Definition	%	ToM (months)	Definition BCR	%	ToM (months)	%	ToM (months)	%	ToM (months)
Artigas et al. [44]	2019	sRT OM	PSA decline >50%	15; 70	1; 4	Two PSA increases at least 1 month apart	79; 53	12; 24	–	–	74	24
Emmett et al. [45]	2017	sRT PF, PF+PL or OM	PSA decline >50% or PSA ≤0.1 ng/ml	72	10.5 (median FU)	–	–	–	–	–	–	–
Emmett et al. [45]	2019	sRT PF, PF+PL or OM	–	–	–	PSA >0.2 ng/ml above nadir	65	36	–	–	–	–
Henkenberens et al. [47]	2016	sRT PF or OM	–	–	–	NR	100	9	–	–	–	–
Kneebone et al. [48]	2018	sRT OM	Any PSA decline/PSA <0.03 ng/ml	70/14	16 (median FU)	PSA >0.2 ng/ml above nadir	46; 23; 16	12; 18; 24	–	–	–	–
Kroeze et al. [49]	2019	sRT ± ADT	–	–	–	PSA >0.2 ng/ml above nadir	78[a] 53[b]	24	–	–	93; 83	12; 24
Marzec et al. [50]	2019	sRT OM ± ADT[c]	PSA decline >50%	84	17 (median FU)	PSA >0.2 ng/ml above nadir	66; 41	12; 24	–	–	–	–
Ong et al. [51]	2019	sRT OM	Any PSA decline/> 50% PSA decline	60/40	During FU	–	–	–	62	12	70	12
Schmidt-Hegeman et al. [34]	2019	sRT PF or PF+PL ± ADT	PSA ≤0.1 ng/ml	81	23 (median FU)	PSA >0.2 ng/ml above nadir	78	23 (median FU)	–	–	–	–
Siriwardana et al. [43]	2017	sLND	PSA <0.2/PSA <0.05	54/39	1.5	PSA >0.2 ng/ml or PSA >nadir	23	12	–	–	–	–
Soldatov et al. [52]		sRT OM	Any PSA decline	97	18 (median FU)	Two consecutive PSA increases	56	18 (median FU)	–	–	–	–

BCR biochemical recurrence, *PFS* progression free survival, *ADT* androgen deprivation therapy, *ToM* time of measurement after salvage therapy, *sRT* salvage radiation therapy, *OM* oligometastatic disease, *PF* prostatic fossa, *PL* pelvic lymph nodes, *FU* follow-up, *NR* not reported, *sLND* salvage lymph node dissection

[a]With ADT

[b]Without ADT

lymph nodes or stereotactic radiation therapy to oligometastatic disease, several studies have analysed survival outcomes of patients treated for BCR after PSMA PET/CT (Tab. 4 and 5) [34, 44–52]. Three studies reported ADT-free survival after salvage radiation therapy for local or oligometastatic disease, which ranged from 70–93% and 74–83% at 12 and 24 months, respectively. However, no predefined indications for initiation of ADT were reported. BCR-free survival after salvage radiation therapy was reported in eight studies and ranged between 46–79% at 12 months (reported in 3 studies) and 16–53% at 24 months (reported in 4 studies). PSA decline >50%, reported in four studies, ranged between 40 and 84%. Most studies included heterogenous cohorts including patients that previously underwent radical prostatectomy and/or radiation therapy and with different PSA values at the time of PSMA PET and had a retrospective design. Furthermore, survival outcomes are not uniformly reported in available literature, since definitions of survival outcomes and time points of measurement of these outcomes differ greatly between available studies. None of these studies were properly randomised controlled trials. Therefore, the impact of PSMA PET initiated targeted therapies on survival remains largely unknown.

However, there is some evidence that imaging guided metastasis directed therapy may have effect on survival. A prospective randomized controlled Phase II trial by Ost et al. showed a prolonged median ADT-free survival of 21 months in a group treated with metastasis directed therapy after choline PET/CT (surgery or stereotactic body radiotherapy) compared to 13 months in the surveillance group [53]. These data suggest that metastasis directed therapy should be explored further in randomized clinical trials. An interesting initiative is a randomized prospective phase III trial, in which 193 patients will be randomized 1:1 to standard salvage radiation therapy based on conventional imaging and salvage radiation therapy based on [68Ga]-PSMA-11 PET/CT [54]. The primary end-point of the study will be biochemical progression-free survival, with progression defined by PSA ≥0.2 ng/ml and rising.

Conclusion

Although high heterogeneity is found between presently available studies, in general, PSMA PET shows promising results as a diagnostic tool in BCR of PCa and induces change of management in almost half of the patients with BCR (45% pooled data). After PSMA PET more patients are selected for metastasis targeted therapies; however, the potential beneficial effects of metastasis directed therapies, including improved survival outcomes, require further evaluation in prospective randomised clinical trials.

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Maurits Wondergem, nuclear medicine physician

Friso M. van der Zant, nuclear medicine physician

Wouter A.M. Broos, nuclear medicine physician

Remco J.J. Knol, nuclear medicine physician