Review Article

pISSN: 2287-4208 / eISSN: 2287-4690
World J Mens Health Published online Mar 5, 2019
https://doi.org/10.5534/wjmh.180133

The World Journal of Men's Health

Performance and Impact of Prostate Specific Membrane Antigen-Based Diagnostics in the Management of Men with Biochemical Recurrence of Prostate Cancer and its Role in Salvage Lymph Node Dissection

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Up to 50% of patients initially treated for prostate cancer in a curative intent experience biochemical recurrence, possibly requiring adjuvant treatment. However, salvage treatment decisions, such as lymph node dissection or radiation therapy, are typically based on prostate specific antigen (PSA) recurrence. Importantly, common imaging modalities (*e.g.*, computed tomography [CT], magnetic resonance imaging, and bone scan) are limited and the detection of recurrent disease is particularly challenging if PSA is low. Prostate specific membrane antigen (PSMA) positron-emission tomography/computed tomography (PET/CT) is a novel and promising imaging modality which aims to overcome the incapability of early identification of distant and regional metastases. Within this review, we summarize the current evidence related to PSMA-PET/CT in prostate cancer men diagnosed with biochemical recurrence after local treatment with curative intent. We discuss detection rates of PSMA-PET/CT stratified by PSA-levels and its impact on clinical decision making. Furthermore, we compare different image-fusion techniques such as PSMA-PET *vs*. F-/C-Choline-PET scans *vs*. PSMA-single photon emission computed tomography/CT. Finally, we touch upon the contemporary role of radio-guided-PSMA salvage lymphadenectomy.

Keywords: Positron-emission tomography; Prostate-specific membrane antigen, human; Prostatic neoplasms; Salvage therapy

INTRODUCTION

Up to 50% of prostate cancer (PCa) patients experience recurrence or disease persistence following local therapy with curative intent. Certainly, some of these men are candidates for adjuvant or salvage local surgical or radiation therapy (RT) approaches including stereotactic/hypo fractionated radiotherapy, salvage lymphadenectomy or prostatectomy [1-3]. However, this clinical decision is typically based in the absence of image-detectable recurrent disease but on prostate specific antigen (PSA) dynamics after local therapy. Thus,

Received: Dec 31, 2018 **Accepted:** Jan 20, 2019 **Published online** Mar 5, 2019
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the clinical value of identifying distant or regional metastases by the common gold-standard imaging modalities (computed tomography [CT], magnetic resonance imaging, bone scan) is limited and the detection of (local) recurrent PCa is particularly challenging if PSA levels are low [4,5].

In the light of these considerations, new imaging techniques are progressively evolving. For example, fusion of positron-emission tomography (PET) and CT provide functional and morphologic information. This allows physicians to identify metabolic cancer activity in addition to their shape and size. The latest imaging technology used for PCa is ^{68}Gallium (^{68}Ga)-labelled prostate specific membrane antigen (PSMA) PET-CT. PSMA, a transmembrane glycoprotein, is largely expressed on prostate cells with a greater expression on poorly differentiated, metastatic, and castration-resistant cancer cells [6], making it an optimal target for small-molecule radiopharmaceuticals, such as ^{99m}Technetium (^{99m}Tc) or ^{68}Ga to visualize PCa recurrent cells.

This review summarizes the current evidence related to ^{68}Ga-labelled PSMA-PET/CT in PCa men diagnosed with PSA recurrence. First, detection rates of PSMA-PET/CT stratified by PSA-levels and its impact on clinical decision making are being discussed. Second, PSMA-PET *vs.* F-/C-Choline PET scans and the role of PSMA-single photon emission computed tomography (SPECT)/CT are compared. Finally, accuracy of PSMA-PET in men undergoing salvage lymphadenectomy as well as the contemporary role of PSMA-radio-guided salvage lymphadenectomy are elucidated.

MAIN BODY

1. Evidence acquisition

A review of the literature was conducted in October 2018 using PubMed to find articles evaluating the contemporary role of PSMA for men with possible biochemical recurrence (BCR). Specifically, we sought to identify studies which can help answer the questions outlined previously.

Included studies were original articles, investigating *patients with biochemical recurrence of PCa* after primary or secondary treatment (*e.g.*, radical prostatectomy [RP], RT, systemic, or local treatment).

In order to present consistent results, studies had to report detection rates as the number of positive scans-irrespective of site of recurrence-relative to the number of patients examined ($n[Patients_{positive}]/n[Patients_{examined}]$). To better understand the value of detection rates, it is important to notice that in PET/CT lesions suspicious for PCa are defined as *any* focal uptake of PSMA higher than the adjacent background that is not associated with physiological uptake and thus, detection rates do not provide information about the site or quality of the lesion. We included studies reporting accuracy, sensitivity, specificity, positive and negative predictive values for PSMA-PET/CT before salvage lymphadenectomy if their estimations were based on histopathological reports. We excluded studies that inferred these estimates based on findings from clinical follow-up (*e.g.*, PSA values, findings from follow-up imaging) in order to gain most valuable results.

The search strategy employed the following approach: Search terms were used but not restricted to the following: *PSMA PET, positron emission tomography, ^{68}Ga, choline, biochemical recurrence, recurrent prostate cancer, BCR, prostate cancer, prostatic neoplasm, prostate malignancy, salvage lymph node dissection, SPECT, single photon emission computed tomography, radio-guided therapy.*

References of considered studies were reviewed and included if inclusion criteria were met. After critical review of 258 titles, 133 abstracts, 60 full texts and their respective references, 32 publications remained eligible for this review (Fig. 1).

2. Evidence synthesis

1) Performance and impact of prostate specific membrane antigen positron-emission tomography/computed tomography

(1) Detection rates stratified to prostate specific antigen-levels: Measurement of serum PSA is the cornerstone in follow-up after primary curative treatment for PCa. Rising PSA values are helpful to identify patients with recurrence and it is directly correlated with tumor burden [7]. However, it cannot distinguish between local and systemic recurrence, and thus continuously rises some degree of clinical interpretation difficulties. PSMA-PET has been proposed as a tool which overcomes these shortcomings in the post-treatment setting. The aim of this part is to answer the following questions: What are the detection rates of PSMA PET/CT and at which PSA-thresholds is PSMA PET/CT able to identify positive lesions in a reasonable number of pa-

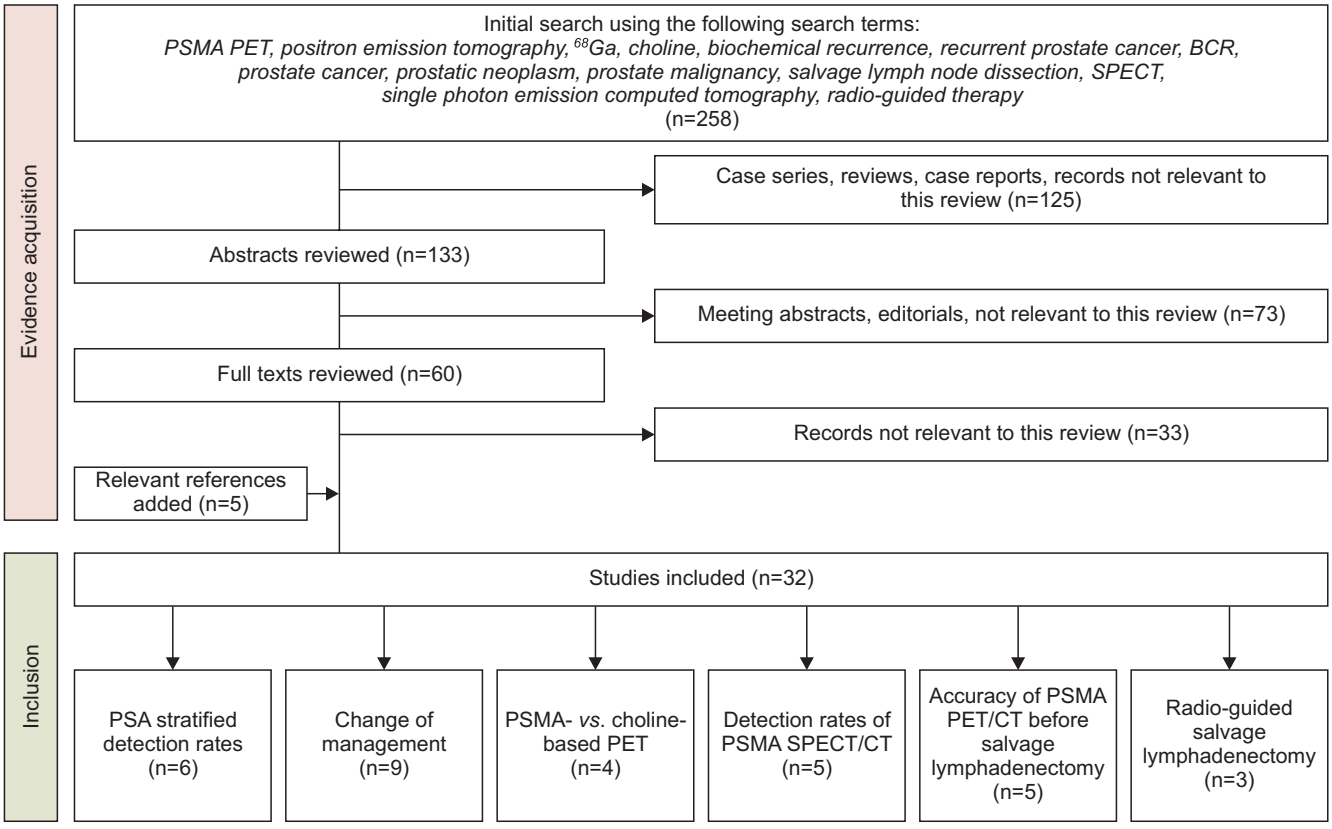

Fig. 1. Evidence acquisition. PSMA: prostate specific membrane antigen, PET: positron-emission tomography, BCR: biochemical recurrence, SPECT: single photon emission computed tomography, PSA: prostate specific antigen, CT: computed tomography.

tients? Do clinical parameters beyond PSA exist, that are associated with higher detection rates (Table 1)?

Looking at a broad spectrum of patients and a wide range of PSA values, PSMA PET/CT has detection rates ranging from 27.3% to 96% at PSA levels below 0.5 and ≥10 ng/mL, respectively. Afshar-Oromieh et al [8] evaluated PSMA PET/CTs of a large number of men (n=1,007) with BCR after different primary and secondary treatments (*i.e.*, RP, RT, androgen deprivation therapy [ADT], chemotherapy and/or high-intensity focused ultrasound). The overall detection rate of any lesion, including all PSA levels, was 79.5% – slightly lower than in previous studies of the same group, supposedly due to a lower median PSA level [9].

Of note, ADT was found to be significantly associated with positive PSMA PET/CTs (both p<0.001). ADT plays a relevant role in PSMA-based imaging since it is known to increase PSMA expression of PCa cells [6]. This phenomenon does not only increase the number of visualized lesions in patients on ADT compared to patients without ADT, but may also be of clinical importance regarding PSMA-targeting therapies. While the strength of this study lies in its large sample size, the rather heterogeneous spectrum of recurrent PCa patients represents a limitation regarding validity of PSMA-PET/CT detection rates. However, the results are being corroborated by the largest prospective study, conducted by Caroli et al [10], who examined PSMA PET/CTs from 314 men after RP or primary RT and without ADT within 6 months before imaging. If results from ^{18}flourine (F)-choline PET/CTs performed within one month prior to PSMA PET/CT were available, only patients with negative or "dubious" scans were included. In their study, the overall detection rate of any positive lesion was 62.7%, ranging from 27.3% for PSA values of 0–0.2 ng/mL to 94.8% for PSA values above 2 ng/mL. In comparison to the results from the previous mentioned retrospective study, the overall detection rate, as well as detection rates for PSA levels <0.5 and 1 to 2 ng/mL, was lower. These differences may be explained by the study design: results from prospective evaluations are less prone to unmeasured confounding. Also, the mean PSA was as low as 0.83 ng/mL, explaining the lower overall detection rate.

https://doi.org/10.5534/wjmh.180133

Table 1. PSA-stratified detection rates of PSMA PET/CT in men with biochemical recurrence of prostate cancer

Variable	Author					
	Afshar-Oromieh et al [8]	Caroli et al [10]	Eiber et al [12]	Einspieler et al [15]	Prado Júnior et al [13]	Rauscher et al [11]
Year	2017	2018	2015	2017	2018	2018
No. of patients	1,007	314	248	118	54	272
Study design	Retrospective	Prospective	Retrospective	Retrospective	Retrospective	Retrospective
Primary treatment	RP, RT, chemotherapy, ADT, HIFU	RP or RT	RP	RT	RP, RT, chemotherapy, ADT	RP
Median PSA range included (ng/mL)		<0.2 or two consecutive increases	≥0.2 (0.2–59.4)	2.2–158.4	0.02–39.00	0.2–1.0
Mean PSA (ng/mL)	2.2	0.83	1.99	6.4 (median)		
Detection rates (% of all patients with positive PET/CT) stratified by PSA (<0.5–≥10)						
Overall	79.5	62.7	89.5	90.7		65.0
Mean PSA (ng/mL)						
<0.5	46.0	29.4	57.9		38.5	55.0
0.5 to <1	73.0	47.1 (0.2–1.0)	72.7		71.0	74.0
1 to <2	80.0	75.0	93.0		85.7	
≥2	86.0	94.8	96.8		92.6	
2 to <5	88.5			81.8		
5 to <10	92.6			95.3		
10+	96.0			96.8		
Location of positive lesions (% of all scans)						
Mean PSA-stratification (ng/mL)						<0.5 0.5–1.0
Local recurrence	9.6		35.1	63.5		20.1 30.4
LN metastases	26.5			42.9		
~Pelvic			52.4			24.6 40.5
~Extrapelvic			5.2			3.7 5.0
Bone	13.0		35.9	42.1		13.4 21.7
Visceral/other	0.5		5.2	6.5		2.2 1.4
Predictors of positive scans	PSA, ADT	PSA		ADT		PSA, ADT

PSA: prostate specific antigen, PSMA: prostate specific membrane antigen, PET/CT: positron-emission tomography/computed tomography, LN: lymph node, RP: radical prostatectomy, RT: radiation therapy, ADT: androgen deprivation therapy, HIFU: high-intensity focused ultrasound.

Taken together, the study by Caroli et al [10] confirms higher PSA levels to be significantly associated with positive scans, while the impact of ADT could not be assessed due to study design.

When focusing on more homogeneous cohorts and low PSA levels for which reliable imaging modalities are desperately needed, PSMA-PET/CT still reveals lesions in more than 50% of the patients. A group from Munich investigated 272 patients with very low (0.2–0.5 ng/mL) and low (>0.5–1.0 ng/mL) PSA values after RP only [11]. Detection rates of any lesion in PSMA-PET/CT, stratified by PSA-levels, were as high as 55% *vs.* 74% for very low and low PSA values, respectively. These important findings were in line with other retrospective evaluations making the clinician understand that diagnostic PSMA PET/CT scans may be of use if imaging will have an impact in treatment strategy at PSA-levels below 0.5 ng/mL [12,13].

Interestingly, even in patients with very low PSA-values <0.5 ng/mL, two studies from Munich found distant lesions in ~18% of the patients. This finding suggests that clinicians are facing a rather palliative setting in almost every 5th to 6th patient with such low PSA levels. Furthermore, this finding underscores evidence from previous studies showing better outcomes only in 80% of patients undergoing salvage RT at low PSA levels [14].

Evidence for the value of PSMA PET/CT after RT as a primary treatment is low. Distinguishing between men who do and do not benefit from further – and to some extent morbid – treatment is exactly what diagnostic tools should be able to do. This is even more crucial in patients who had undergone RT as primary treatment since treatment options for patients with local recurrence after RT are associated with higher morbidity compared to those after primary RP. Unfortunately, to date there is only one study available that exclusively focused on patients with BCR after RT and found an overall detection rate of 90.7% for PSMA PET/CT at a comparatively high median PSA of 6.4 ng/mL. Evidence of distant disease in 59.8% of the patients suggests a certain potential to tailoring further treatment [15]. However, more in-depth investigations are needed to better understand the value and impact of PSMA PET/CT in the management of patients with BCR after RT.

In summary, the overall detection rates for patients with PSA-recurrence after primary local therapy for PCa range from 63% to 91%. Unsurprisingly, detection rates are higher among men with higher PSA levels. However, PSMA PET/CT demonstrates promising detection rates of >50% up to 74% for men with PSA levels <0.5 ng/mL and between 0.5 and <1 ng/mL, respectively. At these PSA levels, at which early salvage RT is recommended according to current guidelines, distant disease are found in ~18%.

For men with higher PSA ≥1 ng/mL detection rates were >80% in almost all studies. Besides higher PSA-level, ADT is significantly associated with positive scans which may be explained by its ability to increase PSMA expression on PCa cells. The major limitation of all of the aforementioned studies is the missing verification of positive lesions PSMA PET/CT: the true rate of positive lesions remains uncertain. More importantly, it remains unanswered whether the additional effort and expense translates into an alteration of the management and a clinical benefit in a long-term-perspective.

(2) Does prostate specific membrane antigen positron-emission tomography change clinical decision-making?: Even a highly accurate diagnostic test is only useful if it impacts clinical management. Thus, in addition to defining the accuracy of this test, one clinical relevant question is whether PSMA PET/CT influences clinical decision-making of men with BCR of PCa. Decision making might be particularly challenging when treatment recommendations before and after PSMA PET/CT are conflicting, boiling down to the question whether or not a therapy should be changed based on the results of PSMA PET/CT scans. For example: Does a men with BCR after primary RP and negative results on PSMA PET/CT still require salvage RT? Another rising debate addresses the management of oligometastatic diseases. The treatment of solitary or few metastases in patients with PCa showed longer ADT-free survival in a randomized phase II clinical trial [16]. However, do clinical decisions change in patients with oligometastatic disease seen in PSMA PET/CT? Table 2 summarizes the results of six retrospective and three prospective studies that observed changes in the management of recurrent PCa following PSMA PET/CT [17-25].

In patients planned for salvage RT after primary RP, results from PSMA PET/CT lead to modification of the initially planned RT strategy in up to one third of the patients: Calais et al [17] aimed to determine how

https://doi.org/10.5534/wjmh.180133

Table 2. Studies reporting change in management following PSMA-PET/CT in men with biochemical recurrence of prostate cancer

Variable	Author								
	Afaq et al [19]	Albisinni et al [20]	Calais et al [17]	Calais et al [21]	Farolfi et al [18]	Henkenberens et al [22]	Mattiolli et al [23]	van Leeuwen et al [25]	Zacho et al [24]
Year	2018	2017	2018	2018	2019	2018	2018	2015	2018
No. of patients	100	131	270	161 (101 respondents)	119	39	125	70	70
Study design	Retrospective	Retrospective	Retrospective	Prospective survey-based	Retrospective	Retrospective	Retrospective	Prospective	Prospective
Primary treatment	RP, RT	RP, EBRT, HIFU/ brachytherapy or both	RP	RP, RT	RP	RP	RP, RT	RP	RP, RT, RP+RT
Median PSA (ng/mL)		2.2	0.44	1.7	0.32	1.2	1.8	0.2	0.55
PSA range (ng/mL)		0.72–6.70	0.03–1.00	0.05–140	0.2–0.5	0.25–6.96	0.003–395	0.05–1.00	0.2–11.3
Overall detection rate (%)	47.0	75.0	49.0	75.0	34.4	84.6	64.0	54.0	53.0
Location of positive sites (% of all scans)									
Local recurrence	17.0		17.5	23.0	2.5	21.0	30.9	31.3	7.1
LN metastases						50.0			58.0
~Pelvic	9.0		30.5	47.0	17.6	29.0	44.4	18.6	
~Extrapelvic			3.5	21.0	3.4	21.0	30.0	8.6	
Bone			8.5	19.0	17.6	26.0	29.6	5.0	25.7
Visceral/other/multiple	21.0		1.0	7.0	0	2.0	13.6		7.1
Change of management based on PSMA PET/CT results (%)									
% of management changed in total	39.0	76.6	19.0	53.0	30.2	59.0	63.4 (of 104, 21 lost to follow-up)	28.6	43.5
% of management changed due to positive scans		69.4	39.0		87.8		85.5		
% of management changed due to negative scans		93.9			2.6		20.0		
Predominant changes	Avoidance or change of hormonal therapy (11%), active treatment instead of surveillance (9%)	Avoidance of ADT (64%), avoidance of salvage RT (22%), treatment of oligometastatic disease (34%)		Conversion to focal (29%) or systemic treatment (13%)	Modification of planned radiation therapy	Individualization of treatment concepts (59.0%)	Definitive treatment in local recurrence, avoidance of surgery in patients with visceral/bone metastases	Enlarging the volume of salvage RT, ADT	From curative – noncurative (26.6%); abandonment/ avoidance of salvage RT

PSMA: prostate specific membrane antigen, PET/CT: positron-emission tomography/computed tomography, PSA: prostate specific antigen, LN: lymph node, RP: radical prostatectomy, RT: radiation therapy, EBRT: external beam radiation therapy, HIFU: high-intensity focused ultrasound, ADT: androgen deprivation therapy.

often positive lesions seen in PSMA PET/CTs were covered by the prostate fossa clinical target volume for post-prostatectomy RT. This volume is defined by the Radiation Therapy Oncology Group and represents a minimum volume to be irradiated in a common post-operative scenario [26]. Calais et al [17] examined 270 men with BCR after RP and PSA levels of less than 1 ng/mL, who were planned for RT according to current guidelines [3,27,28]. A total of 19% were identified to harbor at least one positive lesion that was not covered by the consensus clinical target volume. Of those, 12% had extrapelvic lesions (mostly bone lesions) and thus salvage RT as initially planned would not lead to curative treatment. Seven percent had positive lesions within the pelvis, which could have led to an extension of the radiated field. Unfortunately, due to lack of follow-up, the question whether or not these results ultimately led to a change of management remains unclear. However, the true clinical impact was examined in a prospective setting by van Leeuwen et al [25] Positive lesions were detected in 54% of 70 consecutive men with PSA levels between 0.05–1.0 ng/mL following RP. The management was altered in 28.6% because of lesions that were located in either regional lymph nodes or bones that would not have been included in a conventional salvage RT field to the prostatic bed. Notably, the authors emphasize that in 18 men (25%) with positive lesions within the pelvis, consideration might also have been given to focused treatment to a higher dose, using the ^{68}Ga-PSMA fused with the planning CT to allow a simultaneous integrated boost or dose painting.

While current EAU guidelines recommend PSMA PET/CT in patients with PSA values ≥ 1 ng/mL after RP [3], better long-term outcomes have been observed following early salvage RT in patients with PSA levels <0.5 ng/mL [3,28].

Astonishingly, Farolfi et al [18] found similar modification rates in patients at these PSA levels. For example 24% became candidates for stereotactic body radiation therapy ([SBRT], compared to 0% before PSMA PET/CT), while ADT was avoided in 14.3%. SBRT is currently under debate as a treatment option for oligometastatic PCa. It constitutes a non-invasive high-dose external beam radiotherapy, typically delivered in only a few fractions that allow for relative sparing of nearby normal tissues [29]. While there is evidence for a benefit in progression free survival from the treatment of oligomeatastatic disease, studies also show high distant failure rates over time [30].

Active treatment of local recurrence and/or oligometastatic disease and avoidance of definitive treatment in patients with distant disease are common post-imaging changes. Findings from several retrospective and survey-based studies show that when investigating a broader spectrum of patients with BCR after different primary treatment modalities, changes occur in up to three quarters of patients [19-21,23]. The largest retrospective study revealed that >90% of all negative scans resulted mostly in surveillance instead of administration of ADT [20]. In 34% of the patients, oligometastatic disease was actively treated. These findings on the impact of PSMA PET/CT on management decisions are further supported by a prospective study by Zacho et al [24] In the setting of BCR after RP, RT or RP plus salvage RT, they found that the management changed in 30/69 patients (43.5%) according to results from PSMA PET/CT [24]. Likewise, the prevailing change was avoidance of ADT, favouring selective lymph node dissection in men found to have positive lymph node disease. Also, in six out of nine patients with negative scans, salvage RT was omitted. It is important to note that all patients had BCR and that surveillance is only recommended in patients with favourable risk factors, while salvage RT represents the standard of care in patients with BCR after RP [3]. One has to question the meaningfulness of changing management decisions based on PSMA PET/CT as long as no long-term clinical outcomes are available and as long as there is no intention to investigate these.

In our review, out of nine studies, positive and negative PSMA PET/CT results influenced clinical decision making in 19% to 76% of cases, mainly by steering patients away from ADT towards more individual treatment, as for example by altering the initially planned radiation strategy. To what, if any, extent these decisions might impact clinical outcomes in a long-term perspective is uncertain due to missing follow-up investigations. This said, patients facing changes in their management due to results from PSMA PET/CT must be informed that these must not necessarily translate into a long-term clinical benefit.

2) Comparison to alternative imaging modalities for recurrent prostate cancer

(1) Prostate specific membrane antigen- *vs.* Choline-

https://doi.org/10.5534/wjmh.180133

Table 3. Detection rates of ^{68}Ga PSMA PET/CT *vs*. Choline-PET/CT

Variable	Author								
	Afshar-Oromieh et al [40]		Bluemel et al [37]			Morigi et al [39]		Schwenck et al [38]	
Year	2014		2016			2015		2017	
No. of patients	37		125			38		103	
Study design	Retrospective		Retrospective			Prospective		Retrospective	
Primary treatment	RP, RT, chemotherapy, ADT		RP and/or RT, HIFU			RP and/or RT		RP and/or RT	
Mean PSA (ng/mL)	11.1		5.4			1.74		2.7 (median)	
PSA range (ng/mL)	0.01–116		0.2–126.6			0.04–12.0			
Detection rates (% of all patients with positive PET/CT) stratified by PSA (<0.5–≥2)									
Overall	F-choline 70.3	PSMA 86.5	F-choline 74.4	F-choline and PSMA 85.6	PSMA + in F-choline- 43.8	F-choline 32	PSMA 66	C-choline 71	PSMA 94
PSA (ng/mL)									
<0.5			F-choline 41.6	F-choline and PSMA 61.5	PSMA + in F-choline -28.6	F-choline 12.5	PSMA 50		
0.5 to <1						F-choline 36	PSMA 71	C-choline[a] 22 (≤1 ng/mL)	PSMA[a] 55 (≤1 ng/mL)
1 to <2			F-choline 66.7	F-choline and PSMA 81.8	PSMA + in F-choline -45.5			C-choline[a] 53	PSMA[a] 50
2+			F-choline 89.4	F-choline and PSMA 97.0	PSMA + in F-choline -71.4	F-choline 63	PSMA 88	C-choline[a] 56	PSMA[a] 65

^{68}Ga: ^{68}Gallium, PSMA: prostate specific membrane antigen, PET/CT: positron-emission tomography/computed tomography, PSA: prostate specific antigen, RP: radical prostatectomy, RT: radiation therapy, ADT: androgen deprivation therapy, HIFU: high-intensity focused ultrasound.
[a]Detection rates based on lymph nodes.

positron-emission tomography/computed tomography: Before PSMA PET/CT was introduced, choline PET/CT was the most sensitive imaging modality in the setting of biochemically recurrent PCa [31]. Choline based imaging takes advantage of key enzymes in choline metabolism being up-regulated in PCa cells such as choline kinase, leading to accumulation of radiolabelled ^{11}carbon- and ^{18}F-choline [32,33]. The most challenging aspect is the detection of recurrent PCa in low serum PSA values after primary curative treatment, as PSA-level correlates with outcome after salvage therapies [14,34]. So far, reported choline PET/CT detection rates are comparably low, ranging from 19% to 36% in PSA levels ≤1.5 ng/mL [35]. A recent study revealed a detection rate of 55% in a population with PSA values ≤2 ng/mL [36].

To date, we found four studies directly or indirectly comparing results of PSMA and choline based PET scans, consisting of three retrospective studies and one prospective trial (Table 3).

All of these corroborate that PSMA PET/CT has better detection rates as choline-based PET scans, especially at low PSA-levels. The largest study was conducted by Bluemel et al [37], analysing 125 men who underwent sequential imaging beginning with ^{18}F-choline PET/CT followed by PSMA PET/CT, in case F-choline PET/CTs was negative. The overall detection rate was 85.6% for the sequential scans and 74.4% for F-choline alone. Detection rates increased with higher serum PSA levels. In choline-negative patients (n=32), PSMA-PET/CT detected sites of recurrence in 43.8%, indicating improvement in detection of recurrent PCa using PSMA PET/CT. However, due to the study design, a direct comparison of choline to PSMA-based PET scans was not feasible as there is no information if F-choline positive lesions may have been PSMA PET/CT negative. Similar findings were described in other studies that are summarized in Table 3 [38-40]. In brief, Schwenck et al [38] found that PSMA-PET-scans had a significantly higher (lesion-based) detection rate compared to choline-PET-scans (94% *vs.* 71%, respectively, p<0.001). In 13 of 67 positive scans (19.4%), lesions were only found in PSMA PET/CT, whereas only 2 patients (3.0%) had positive lesions in choline-based imaging only. Interestingly, most patients who had PSMA-only positive lesions presented with PSA levels <1 ng/mL, corroborating the results from a prospective evaluation of 38 patients with BCR after primary treatment by Morigi et al [39]. Here, the detection rate at PSA-levels <0.5 ng/mL, was four times higher in PSMA PET/CT than in choline PET/CT (50% *vs.* 12.5%). Moreover, of all 26 patients with positive lesions, more than 50% were only recorded in PSMA-PET/CT. Histopathological evaluation of nine PSMA- and two choline-detected positive lesions revealed true positive lesions for all PSMA-detected lesions, whereas one of the choline-detected lesions was false-positive (and true negative in PSMA PET/CT).

Taken together, these studies clearly support the superiority of PSMA-PET/CT over choline-based PET-scans in term of detection rates, with a focus on low PSA levels. However, most results remain unconfirmed and lack histological confirmation. Moreover, long-term outcomes are unavailable and awaited.

(2) Prostate specific membrane antigen as a target protein for single photon-emission tomography/computed tomography: Similar to PET, SPECT is another functional imaging modality depicting the nuclear radiation emitted from the radiolabeled PSMA ligand (in this case ^{99m}Tc labeled MIP-1404). The main difference between SPECT and PET/CT modalities is the type of the used radioactive tracer: Whereas PSMA PET relies on emission of positrons from ^{68}Ga, SPECT measures the emission of gamma rays from ^{99m}Tc. While the qualities of the images produced differ, with lower resolution in SPECT, it benefits from being regarded as more economic [41]. In addition, SPECT is gaining attraction due to the fact that resolution improvements can be achieved when SPECT is combined with common imaging modalities such as CT or X-ray [42].

Studies aiming to investigate the role of PSMA SPECT/CT in men with BCR are scarce. Here, we will discuss the five available retrospective studies, all of which investigating detection rates of PSMA SPECT/CT in heterogeneous cohorts of patients with BCR after different primary and/or secondary treatment of PCa (Table 4).

These studies provide a rough idea about SPECT/CT being comparatively effective at higher PSA levels. However, at lower PSA levels, for which imaging improvements are more desperately needed, PET/CT clearly outperforms SPECT/CT. The only available large-scale study, including 225 patients was conducted by Schmidkonz et al in 2018 [43]. While the overall detection rate of PSMA SPECT/CT of 77% was comparable to PET diagnostics, it is important to note that for

https://doi.org/10.5534/wjmh.180133

Table 4. Detection rates of PSMA SPECT/CT in patients with biochemical recurrence of prostate cancer

Variable	Author				
	Liu et al [44]	Rauscher et al [47]	Reinfelder et al [45]	Schmidkonz et al [43]	Su et al [46]
Year	2018	2016	2017	2018	2017
No. of patients	208	22[a]	60	225	50
Study design	Retrospective	Retrospective	Retrospecitve	Retrospective	Retrospective
Primary treatment	RP and/or RT, chemotherapy, ADT, LND	RP, RT, HIFU	RP+/- LND, RT, ADT	RP, RT +/-ADT	RP, RT, or ADT
PSA range included (ng/mL)	0.2–36.0	0.2–7.2	0.2–520.6	0.01–93	>0.2
Median PSA (ng/mL)	4.6[b]	1.03[b]	2.6	3.5	7.6
Detection rates (% of all patients with positive PET/CT) stratified by PSA (<0.5–≥10)					
Overall	72.6	59	70	77	78
PSA (ng/mL)					
<0.5	48.6				
0.5 to <1	55.6		36.4 (PSA <1)		30 (PSA <1)
1 to <2	60.9		74.4 (PSA 1 to 3)	54 (PSA <2 ng/mL)	80 (PSA 1-4)
2+			91.4	90	
2 to <5	83.0				
5 to <10	86.7				100 (PSA 4–10)
10+	81.3				100
Location of positive lesions (% of all scans)					
Reference	Positive scans		Positive scans	Total cohort	Total cohort
Local recurrence	8.6		33.3	24.9	36
LN metastases	28.5		47.6	46.7	42
Bone	38.4		45.2	26.7	50
Visceral/other	24.5 (including multiple sites)		2.4	5.3	12 (soft tissue)
Predictors of positive scans	PSA-level, PSA doubling time			PSA level, Gleason score, ADT	

PSMA: prostate specific membrane antigen, SPECT/CT: single photon emission computed tomography/computed tomography, PSA: prostate specific antigen, PET: positron-emission tomography, LN: lymph node, RP: radical prostatectomy, RT: radiation therapy, ADT: androgen deprivation therapy, LND: lymph node dissection, HIFU: high-intensity focused ultrasound.
[a]Patients with known positive lesions in PSMA PET/CT. [b]Mean.

low PSA levels (<2 ng/mL), SPECT/CT showed considerably lower detection rates of only 54% compared to PSMA PET/CT. The highest detection rate for SPECT/CT at very low PSA levels (<0.5 ng/mL) was described by Liu et al [44] with 48.6%. In patients with PSA relapse and PSA values <1 ng/mL after primary treatment, two smaller retrospective studies showed detection rates for PSMA SPECT/CT of only 36.4% and 30%, respectively [45,46]. The superiority of PSMA PET/CT over PSMA SPECT/CT in detecting positive lesions at low PSA levels using are further illustrated in a study by Rauscher et al [47]: In a preselected cohort of 22 patients with positive lesions in PSMA PET/CT and a median PSA of 1.03 ng/mL, SPECT/CT only detected 14/29 lesions (48.3%) and no additional lesions.

3) Accuracy of ^{68}Gallium-prostate specific membrane antigen positron-emission tomography/computed tomography before salvage lymphadenectomy

Along with higher detection rates of recurrent PCa, salvage lymphadenectomy, has gained increasing interest. There is a growing body of literature analyzing the sensitivity, specificity, positive and negative predictive value, and accuracy of PSMA PET diagnostics for patients undergoing salvage lymphadenectomy [48-52]. Compared to the above mentioned detection rates, these investigations additionally aim to analyze the accuracy for the detection of lymph node metastases by comparing the results seen in PSMA PET/CT with histopathologic findings. Are lesions seen in PSMA PET/CT actually positive in histopathology? Or even more crucial: Are negative lesions truly negative? To answer these questions, it is most important to not exclusively remove positive lesions when undertaking a lymph node dissection (as done in some of the aforementioned studies), but to perform a bilateral extended lymph node dissection beyond positive lesions [50].

When performing standardized lymph node dissections, the current sensitivity and specificity of PSMA-PET/CT are not high enough to justify a salvage lymphadenectomy solely of the PET-positive regions, instead a complete (extended) bilateral salvage lymphadenectomy may be performed.

In the largest retrospective study conducted by Rauscher et al [52], standardized predefined lymph node template fields in 48 patients with positive results in PSMA PET/CT, PET/MR of morphologic imaging were evaluated. Regarding the predefined fields (so called field-based), sensitivity, specificity, positive predictive value, negative predictive value and accuracy of ^{68}Ga-PSMA PET were 77.9%, 97.3%, 94.6%, 87.8%, and 89.9% whereas these results were 100%, 50%, 93.3%, 100%, and 93.8% on a patient-based analysis. PSMA based results outclassed morphologic imaging results especially in terms of sensitivity, which was <35% in both field- and patient-based analysis. Hence, PSMA PET/CT identifies patients with negative results more reliably compared to morphologic imaging, but still doesn't reach levels to which selective lymph node dissection only should be suggested as almost ¼ of negative lesions in PSMA PET/CT were ultimately positive in histological evaluation. The field-based results seen in Rauscher et al's study [52], however, are comparable to those seen in smaller studies (Table 5) [48,49,51]. Interestingly, the results also translated into results seen in a real world investigation by Mandel et al [50]. While most other investigators looked at imaging results from their home institution, Mandel et al [50] evaluated PSMA PET/CT or PET/MR from 13 different nuclear medicine centers. Often, study settings largely differ from real world settings: When investigating imaging results, differences may occur throughout the process due to different imaging policies across practices and institutions. By including results from different nuclear medicine centers the results yield in a higher generalizability.

Difficulties in comparing the results from the above-mentioned studies arise from discrepancies in used references for the analyses (number of patients, number of lymph nodes removed or the anatomic boundaries). Moreover, it is of note that in many cases only patients with positive results underwent surgery resulting in selection bias due to imaging-derived pre-selection and possible overestimation of sensitivity results. Furthermore, it remains debatable whether or not salvage lymphadenectomy should be performed based on findings from PSMA PET/CT at all. Of note, according to current guidelines, any kind of salvage lymphadenectomy should only be offered to highly selected patients and its impact on long-term oncologic outcomes is still controversial [3,53].

4) Radio-guided salvage lymphadenectomy

With the attempt to further tailor therapy, new PSMA-targets have lately been developed to possibly

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Table 5. Accuracy of ^{68}Ga PSMA PET diagnostic in men undergoing salvage lymph node dissection for recurrent prostate cancer

Variable	Author					
	Herlemann et al [48]	Jilg et al [49]	Mandel et al [50]		Pfister et al [51]	Rauscher et al [52]
Year	2016	2017	2018		2016	2016
No. of patients	14	30	23		28	48
Study design	Retrospective		Retrospective		Retrospective	Retrospective
Primary treatment	RP	RP, RT	RP		RT, RP, HIFU	RT, RP
Median PSA (ng/mL)		1.7	3.9 (mean)		2.4	1.31
PSA range included (ng/mL)		0.11–12.16			0.04–8	>0.2
Reference	Field-based[a]	Field-based[a]	Field-based[a]	Side-based[b]	Patient-based	Patient-based	Field-based[a]
Accuracy	77	95.6	84.4	80.4	91.9	93.8	89.9
Sensitivity	83	93.2	75.9	89.5	86.9	100	77.9
Specificity	63	100	87.5	74.1	93.1	50	97.3
PPV	86	100	68.8	70.8	75.7	93.3	94.6
NPV	56	88.9	90.9	90.9	96.6	100	87.8

^{68}Ga: ^{68}Gallium, PSMA: prostate specific membrane antigen, PET: positron-emission tomography, PSA: prostate specific antigen, PPV: positive predictive value, NPV: negative predictive value, RP: radical prostatectomy, RT: radiation therapy, HIFU: high-intensity focused ultrasound.
[a]Based on predefined lymph node fields. [b]Left/right.

guide salvage treatment in oligometastatic patients: Instead of labeling PSMA with positron emitting isotopes for imaging purposes, it can also be targeted by gamma-radiation emitting isotopes [54]. The emitted radioactivity can be detected during surgery with the use of gamma probes giving an acoustic feedback. In an experimental setting, radio guided salvage lymph node dissection might be a promising approach for the future as it can lead to a beneficial BCR-free survival compared to "standard" salvage lymphadenectomy.

Clinical outcomes and safety of this new and experimental procedure were first evaluated by a group from Munich, Germany [55]. The investigators compared intra-operative gamma probe radioactivity with histopathological results of dissected specimen of 31 men with oligometastatic recurrence within the pelvic or retroperitoneal lymph nodes. *Ex vivo* measurements (positive *vs.* negative) with gamma probes resulted in a sensitivity, specificity and accuracy of 92.3%, 93.5% and 93.1%, respectively. The positive and negative predictive values were 88.9% and 95.6%. Of all men with complete follow-up information, a PSA reduction of >50% and 90% were observed in 76.6% and 53.3%, respectively. Two thirds remained without therapy after a median follow-up of 337 days. Another 31 men were analyzed in a similar setting, but using ^{99m}Tc based PSMA to guide surgery [56]. Sensitivity was lower (83.6%) with a specificity of 100% in 132 tissue specimen removed. Accuracy reached 93%. After surgery, PSA-reduction to ≤0.2 ng/mL was seen in 20 patients (64.5%) of whom 13 (65%) stayed BCR free after 13 months. In concordance with the aforementioned results, 20 men (64.5%) continued being therapy-free after a median follow-up of 12.2 months. These results are further strengthened by a short term follow-up study by Knipper et al [57] PSA reduction >50% and >90% within six weeks of surgery was significantly higher in 13 patients who underwent radio guided salvage lymph node dissection compared to 29 patients who underwent surgery based on PSMA PET/CT results only ($p<0.01$). These findings underscore the potential of radio guided salvage lymph node dissection in the future. However, one must bear in mind that the studies examined very small and highly-selected patients. Furthermore, the follow-up time of a maximum of 13 months has to be considered as rather short. Before a final evaluation of this new procedure can be made, further, larger cohorts with longer follow-up need to be investigated.

SUMMARY AND CONCLUSION

In this narrative review, we summarize literature relating to the use of PSMA-based nuclear medicine studies in a variety of clinical scenarios including the performance of PSMA PET/CT in patients with BCR of PCa, its impact on clinical decision-making, its value compared to other available imaging modalities, and its accuracy in patients undergoing salvage lymphadenectomy. Finally, we demonstrated current experimental approaches using PSMA as a target for radio-guided salvage lymphadenectomy.

We found that overall detection rates of PSMA-PET/CT range from 63% to 91%. Especially in men with low PSA values <1 ng/mL and <0.5 ng/mL, for which visualization is most urgently needed, detection rates are promising and outrange those seen in other imaging modalities such as F/C-choline PET/CT or PSMA SPECT/CT. In men with PSA ≥1 ng/mL detection rates were consistently >80% across almost all studies. Detection rates were repeatedly shown to be associated with rising PSA as well as in patients under ADT which may be explained by its ability to increase PSMA expression on PCa cells. Positive and negative PSMA scans impacted clinical decision-making in up to 76% of patients, leading predominantly to avoidance of ADT or changes in the planned radiation strategy.

From a clinical point of view, the sensitivity of ~75% of PSMA-PET does not seem to be high enough to justify a salvage lymphadenectomy of the PET-positive regions alone. Instead, if salvage lymphadenectomy is considered, a complete (extended) bilateral salvage lymphadenectomy should be performed. Conversely, outcomes of radio-guided salvage lymphadenectomy seem to be better compared to "standard" salvage lymphadenectomy but must be considered as a rather experimental strategy.

There are some limitations our review has to address; first, most studies include very heterogeneous cohorts including patients who underwent RP and/or RT, for whom PSA thresholds for detecting metastases in BCR, based on PSMA PET/CT may differ. Second, many of the studies were performed in academic centers whose populations may not be generalizable to the overall public. The fundamental limitation of these studies is their lack of long-term clinical outcomes. Evidence to back up the theoretical benefits is still lagging behind the rapid advancement of this novel diagnostic tool and patients must be informed that decisions made based on PSMA PET/CT do not necessarily translate into a survival benefit. Given this lack of evidence regarding the benefit in clinical outcomes, one has also to question whether the expenses for this high-cost imaging modality are worth the investment. Unfortunately, to date there is no study investigating the cost-effectiveness of PSMA PET/CT.

Kasivisvanathan et al [58] demonstrated that designing a randomized trial of imaging modalities is feasible and has the potential to change clinical practice in the right scenario.

Overall, PSMA PET/CT shows promising results as a diagnostic tool in BCR of PCa. However, in order to implement PSMA-based diagnostics and therapies into individualized medicine in the future, prospective randomized clinical trials are required.

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contribution

Conceptualization: Krimphove MJ, Mandel PC, Preisser F, Chun FKH. Methodology: Krimphove MJ, Mandel PC, Preisser F, Chun FKH. Project administration: Krimphove MJ, Mandel PC, Chun FKH. Supervision: Mandel PC, Cole AP, Chun FKH. Visualization: Krimphove MJ, Theissen LH, Cole AP. Writing–original draft: Krimphove MJ, Theissen LH, Cole AP, Mandel PC, Preisser F. Writing–review & editing: Krimphove MJ, Theissen LH, Cole AP, Preisser F, Mandel PC, Chun FKH.

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