

Use of gallium-68 prostate-specific membrane antigen positron-emission tomography for detecting lymph node metastases in primary and recurrent prostate cancer and location of recurrence after radical prostatectomy: an overview of the current literature

Henk B. Luiting* , Pim J. van Leeuwen[†], Martijn B. Busstra*, Tessa Brabander[‡], Henk G. van der Poel[†], Maarten L. Donswijk[§], André N. Vis[¶], Louise Emmett*^{*,††}, Phillip D. Stricker^{‡‡,§§,¶¶}  and Monique J. Roobol* 

*Department of Urology, Erasmus University Medical Centre, Rotterdam, [†]Department of Urology, Netherlands Cancer Institute, Amsterdam, [‡]Department of Radiology and Nuclear Medicine, Erasmus University Medical Centre, Rotterdam, [§]Department of Nuclear Medicine, Netherlands Cancer Institute, [¶]Department of Urology, Amsterdam UMC, Location VUmc, Amsterdam, The Netherlands, ^{**}Department of Nuclear Medicine, St Vincent's Hospital, ^{††}University of New South Wales, Sydney, ^{‡‡}St. Vincent's Prostate Cancer Centre, ^{§§}Garvan Institute of Medical Research, Kinghorn Cancer Centre, Darlinghurst, and ^{¶¶}St Vincent's Clinical School, UNSW, Sydney, NSW, Australia

Objectives

To review the literature to determine the sensitivity and specificity of gallium-68 prostate-specific membrane antigen (⁶⁸Ga-PSMA) positron-emission tomography (PET) for detecting pelvic lymph node metastases in patients with primary prostate cancer (PCa), and the positive predictive value in patients with biochemical recurrence (BCR) after initial curative treatment, and, in addition, to determine the detection rate and management impact of ⁶⁸Ga-PSMA PET in patients with BCR after radical prostatectomy (RP).

Materials and Methods

We performed a comprehensive literature search. Search terms used in MEDLINE, EMBASE and Science Direct were '(PSMA, ⁶⁸Ga-PSMA, ⁶⁸Gallium-PSMA, Ga-68-PSMA or prostate-specific membrane antigen)' and '(histology, lymph node, staging, sensitivity, specificity, positive predictive value, recurrence, recurrent or detection)'. Relevant abstracts were reviewed and full-text articles obtained where possible. References to and from obtained articles were searched to identify further relevant articles.

Results

Nine retrospective and two prospective studies described the sensitivity and specificity of ⁶⁸Ga-PSMA PET for detecting

pelvic lymph node metastases before initial treatment, which ranged from 33.3% to 100% and 80% to 100%, respectively. In eight retrospective studies, the positive predictive value of ⁶⁸Ga-PSMA PET in patients with BCR before salvage lymph node dissection ranged from 70% to 100%. The detection rate of ⁶⁸Ga-PSMA PET in patients with BCR after RP in the PSA subgroups <0.2 ng/mL, 0.2–0.49 ng/mL and 0.5 to <1.0 ng/mL ranged from 11.3% to 50.0%, 20.0% to 72.7% and 25.0% to 87.5%, respectively.

Conclusion

The review results showed that ⁶⁸Ga-PSMA PET had a high specificity for the detection of pelvic lymph node metastases in primary PCa. Furthermore, ⁶⁸Ga-PSMA PET had a very high positive predictive value in detecting lymph node metastases in patients with BCR. By contrast, sensitivity was only moderate; therefore, based on the currently available literature, ⁶⁸Ga-PSMA PET cannot yet replace pelvic lymph node dissection to exclude lymph node metastases. In the salvage phase, ⁶⁸Ga-PSMA PET had both a high detection rate and impact on radiotherapy planning in early BCR after RP.

Keywords

⁶⁸Ga-PSMA PET/CT, pelvic lymph node dissection, detection rate, pelvic lymph node metastases, #ProstateCancer, #PCSM

Introduction

Prostate cancer (PCa) has the second-highest incidence of all cancers in men worldwide [1]. Disease staging at primary diagnosis and at early biochemical recurrence (BCR) after initial curative treatment is important in determining optimal treatment strategy, and prognosis. Traditionally, CT or MRI is used for nodal staging, and bone scintigraphy (using ^{99m}Tc-labelled bisphosphonates) is used to detect bone metastases; however, all techniques have limited sensitivity for detecting lymph node and/or bone metastases [2]. In current practice, therefore, an extended pelvic lymph node dissection (PLND) is performed to accurately stage patients with a risk of > 5% of having nodal metastases [3].

The use of gallium-68 (⁶⁸Ga)-prostate-specific membrane antigen (PSMA) for positron-emission tomography (PET) in patients with PCa was first described in 2012 [4]. PSMA is a type 2 transmembrane glycoprotein that is highly overexpressed in PCa tumours and PCa metastasis. PSMA represents a large extracellular domain which can be targeted by ligands for imaging and treatment purposes [5]. Expression of PSMA is increased in more aggressive PCa [6]. Since the first report of the use of ⁶⁸Ga-PSMA PET in 2012, there has been a growing body of evidence that this technique is superior to other imaging approaches, both in the primary as well as in the recurrence setting [7,8]. ⁶⁸Ga-PSMA PET has demonstrated a significantly higher detection rate than choline PET/CT and a high overall impact on management [9]. The 2019 European Association of Urology guideline recommends performing a PSMA PET at early BCR (>0.2 ng/mL) after initial treatment if the result will influence subsequent treatment decisions (level of evidence 2b; weak recommendation) [3].

The primary aim of the present review was to obtain insight into the sensitivity and specificity of ⁶⁸Ga-PSMA PET for the detection of pelvic lymph node metastases in patients with primary PCa. In addition, we aimed to evaluate the positive predictive value of ⁶⁸Ga-PSMA PET for the detection of lymph node metastases in patients with BCR after initial curative treatment. The secondary aim was to assess the detection rate of ⁶⁸Ga-PSMA PET in patients with BCR after radical prostatectomy (RP), the location of PCa recurrence and the impact of ⁶⁸Ga-PSMA PET outcome on the planning of salvage treatment in these patients.

Methods

In May 2019, we performed a comprehensive literature search. Relevant manuscripts were found through searches of Medline, EMBASE and Science Direct databases. To review the sensitivity, specificity and positive predictive value of ⁶⁸Ga-PSMA PET, the following search terms were used: '(PSMA, ⁶⁸Ga-PSMA, ⁶⁸Gallium-PSMA, Ga-68-PSMA or prostate-specific membrane antigen)' in combination with

'(histology, lymph node, staging, sensitivity, specificity or positive predictive value)'. To review the detection rate of ⁶⁸Ga-PSMA PET in patients with BCR after RP the following search terms were used: '(PSMA, ⁶⁸Ga-PSMA, ⁶⁸Gallium-PSMA, Ga-68-PSMA or prostate-specific membrane antigen)' in combination with '(recurrence, recurrent or detection)'. Studies were initially selected based on title, followed by screening on abstract. References to and from obtained articles were searched to identify further relevant articles. Only articles in the English language were included.

For the first section of the present review, we included all studies that determined the diagnostic ability of ⁶⁸Ga-PSMA PET for preoperative lymph node staging of PCa, using histopathology as the 'gold standard'. The sensitivity, specificity and positive predictive value were retrieved from the studies included in our review. The studies were divided into two categories: (1) patients undergoing a ⁶⁸Ga-PSMA PET before initial treatment consisting of RP with extended PLND, i.e. the primary diagnosis and (2) patients with BCR after initial treatment undergoing ⁶⁸Ga-PSMA PET, followed by salvage PLND, i.e. salvage therapy. We excluded studies that included a mixed group of patients (primary diagnosis and salvage therapy) and did not present the results separately. Studies reporting only the per-region sensitivity and specificity were also excluded.

For the second section of this review, we included studies that reported the detection rate of the ⁶⁸Ga-PSMA PET in patients with BCR after RP and a PSA value < 1.0 ng/mL. The detection rates were subdivided into three PSA categories: 0.01–0.19 ng/mL; 0.20–0.49 ng/mL; and 0.50 to <1.00 ng/mL. Finally, the sites of PCa recurrence were collated when reported in patients with BCR after RP without additional treatment after RP. Therefore, studies describing patients who received radiotherapy and/or androgen deprivation therapy (ADT) before ⁶⁸Ga-PSMA PET were excluded.

The results of the included studies are reported in the text as ranges; a meta-analysis was not performed. The individual reported results are provided in Tables 1–4.

Results

Diagnostic Performance of ⁶⁸Ga-PSMA PET for Pelvic Lymph Node Metastases

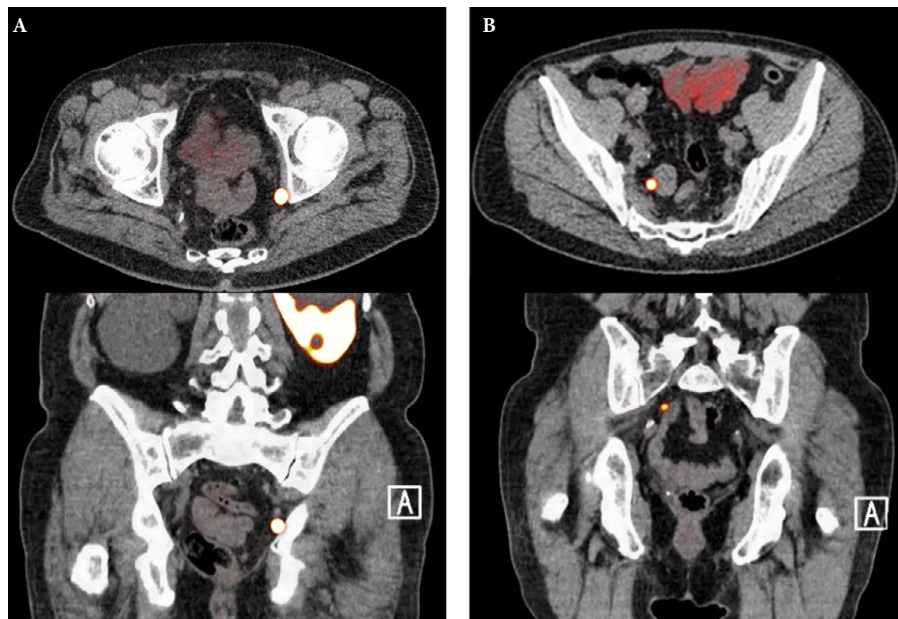
Eleven studies were included in this review that presented data on the sensitivity and specificity of ⁶⁸Ga-PSMA PET for detection of pelvic lymph node metastases in men with newly diagnosed PCa (Table 1, Fig. 1) [8,10–19]. Two prospective studies, including a total of 63 patients, showed a per-patient sensitivity (range) and specificity (range) of 64–100% and 90–95%, respectively. The per-node sensitivity and specificity were 50–58% and 96–100%, respectively [15,18]. Nine retrospective studies, including 696 patients, showed a per-

Table 1 The per-patient and per-node sensitivity and specificity of gallium-68 prostate-specific membrane antigen positron-emission tomography/CT in patients undergoing radical prostatectomy with extended lymph node dissection (primary diagnosis).

Author (year)	Total number of patients (patients with LNM)	Number of lymph nodes dissected Mean \pm sdMedian (IQR)	Per-patients sensitivity, %	Per-patients specificity, %	Per-node sensitivity	Per-node specificity
Budaus (2016) [10]	30 (12)	20.3 18.5 (13.5–27.5)	33.3	100	–	–
Gupta (2017) [8]	12 (7)	20.25 20	100	80	66.67%	98.61%
Maurer (2016) [11]	130 (41)	– 21 (12–30)	65.9	98.9	–	–
Obek (2017) [12]	51 (15)	20.2 \pm 8.5 18.5	53.3	86.1	–	–
Thalgott (2018) [13]	73 (25)	26.1 \pm 16.9 23 (17–29)	60	100	–	–
Van Leeuwen (2018) [14]	140 (51)	– 16 (12–21)	53	88	–	–
Van Leeuwen (2017) [15]	30 (11)	17.8 \pm 7 16 (12–20)	64	95	58%	100%
Yaxley (2019) [16]	208 (55)	– 13	38.2	93.5	24.4%	99.5%
Zhang (2017) [17]	42 (15)	7.095 –	93.3	96.3	96.08%	99.65%
Park (2018)* [18]	33 (3)	11.6 –	100	90	50%	98.38%
Yilmaz ([19])	10 (2)	– –	100	100	–	–

IQR, interquartile range; LNM, lymph node metastases. *Gallium-68 prostate-specific membrane antigen positron-emission tomography (^{68}Ga -PSMA PET)/MRI was used instead of ^{68}Ga -PSMA PET/CT.

Fig. 1 Axial and sagittal plane gallium-68 prostate-specific membrane antigen positron-emission tomography /CT images of two patients with locoregional lymph node recurrence after initial curative treatment. The metastasis in patient A is located in the obturator area and the metastasis in patient B is located in the presacral area.



patient sensitivity and specificity of 33.3–100% and 80–100%. The per-node sensitivity and specificity was 24.4–96.1% and 98.6–100%, respectively [8,10–14,16,17,20].

In this review, eight retrospective studies were included, reporting the positive predictive value of ^{68}Ga -PSMA PET in detecting pelvic lymph node metastases in patients with BCR

after initial curative treatment [21–28]. All patients underwent salvage PLND, and histopathology was used as the gold standard reference. The positive predictive value, among the total of 290 patients included, ranged from 70% to 100% (Table 2) [21–28].

Detection Rate of ⁶⁸Ga-PSMA PET in Patients with Biochemical Recurrence after Radical Prostatectomy

The detection rates of ⁶⁸Ga-PSMA PET in men with BCR after RP are shown per PSA subgroup in Table 3. Eight studies reported the detection rate of ⁶⁸Ga-PSMA PET in patients with a PSA value <0.2 ng/mL [29–36]. This included 286 patients. Eighty-six of the 286 patients (30.1%) had a positive ⁶⁸Ga-PSMA PET, with the detection rate ranging from 11.3% to 50.0% [29–36].

Eighteen studies reported the detection rate of ⁶⁸Ga-PSMA PET in patients with a PSA 0.20–0.49 ng/mL [21,29–45]. Combined, this involved 1078 patients. Of the 1078 patients, 507 (47.0%) had a positive ⁶⁸Ga-PSMA PET. At this PSA range, the detection rate varied from 20.0% to 72.7% [21,29–45].

Fifteen studies described the detection rate of ⁶⁸Ga-PSMA PET in patients with a PSA level of 0.50 to <1.0 ng/mL [21,29–33,35–38,41–45]. Collectively, these studies included 567 patients. Of these 567 patients, 367 (64.7%) had a positive ⁶⁸Ga-PSMA PET. The detection rate ranged from 25% to 87.5% [21,29–33,35–38,41–45].

Location of Prostate Cancer Recurrence Based on the ⁶⁸Ga-PSMA PET

In total, three studies reported the anatomical sites of ⁶⁸Ga-PSMA-positive lesions in patients with BCR after RP in the absence of treatment between RP and ⁶⁸Ga-PSMA PET.

The location of PCa recurrence in the different PSA groups is shown in Table 4. Emmett et al. [36] and van Leeuwen et al. [30], combined, identified 254 patients with a PSA <1 ng/mL detecting a local recurrence only in 63 patients, pelvic lymph node metastases ± local recurrence in 55 patients, and distant metastases ± local recurrence in 39 patients. Boreta et al. [34] included 125 patients with a PSA <2.0 ng/mL. ⁶⁸Ga-PSMA PET detected a local recurrence only in eight patients, pelvic lymph node metastases ± local recurrence in 33 patients, and distant metastases ± local recurrence in 25 patients.

Discussion

Recently, the ability of imaging to detect PCa metastases and PCa recurrence at very low PSA values has notably improved after the introduction of the PSMA PET. We conducted this review to determine the sensitivity, specificity and positive predictive value of ⁶⁸Ga-PSMA PET in detecting pelvic lymph node metastases. Furthermore, we assessed the detection rates of ⁶⁸Ga-PSMA PET and the location of PCa recurrence in patients with early BCR after RP. On the basis of the current

Table 2 The positive predictive value of gallium-68 prostate-specific membrane antigen positron-emission tomography/CT in patients undergoing salvage lymph node dissection (salvage phase).

Author (year)	Total number of patients	Initial treatment (n)	Number of lymph nodes dissected Mean ± sd Median (IQR)	PPV per patient, %	PPV per region, %
Fendler (2019)* [21]	87	RP and/or RT	–	84	84
Linxweiler (2018) [22]	25	RP (25)	–	92	–
Mandel (2018)* [23]	23	RP (23)	9 (5–14)	70	87.5
Pfister (2016) [24]	28	RP (23) RT (3)	15	82	75.7 (per node)
Rauscher (2016) [25]	48	RP (45) RT (3)	11	93	94.6
Siriwardana (2017) [26]	35	RP (28) Brachytherapy (5) ERBT (1) ERBT + brachytherapy (1)	–	91	–
Jilg (2017) [27]	30	RP (29) RT (1)	9 (3–14)	100%	98.3
Herlemann (2016) [28]	14	RP (14)	33 (25.5–41.5)	–	86

EBRT, external beam radiation therapy; HIFU, high-intensity focused ultrasonography; IQR, interquartile range; PPV, positive predictive value; RP, radical prostatectomy; RT, radiation therapy. *Patients underwent either gallium-68 prostate-specific membrane antigen positron-emission tomography (PET)/CT or PET/MRI.

Table 3 Detection rate of gallium-68 prostate-specific membrane antigen (PSMA) positron-emission tomography in different PSMA subgroups.

Author (year)	Number of patients (percentage positive scans) PSA 0.50 to <1.00 ng/mL	Number of patients (percentage positive scans) PSA 0.01–0.19 ng/mL (%)	Number of patients (percentage positive scans) PSA 0.20–0.49 ng/mL
Kranzbühler (2018) [29]	9 (44.4)	11 (72.7)	8 (87.5)
Van Leeuwen (2016) [30]	35 (40.0)	28 (71.4)	7 (57.1)
Meredith (2016) [31]	124 (11.3)	79 (26.6)	45 (53.3)
Gupta (2017) [32]	11 (45.5)	16 (43.8)	17 (29.4)
Schmuck (2017) [33]	18 (38.9)	34 (55.9)	28 (60.7)
Emmett (2017) [36]	64 (50.0)	81 (67.9)	24 (79.2)
Boreta (2019) [34]	9 (33.3)	75 (52.0)	–
Yilmaz (2019) [35]	16 (43.8)	17 (52.9)	14 (64.3)
Habl (2017)* [45]	–	42 (50.0)	21 (85.7)
Fendler (2019) [21]	–	136 (38.2)	79 (57.0)
Berliner (2017) [37]	–	33 (51.5)	11 (54.5)
McCarthy (2019) [38]	–	63 (50.8)	21 (76.2)
Bashir (2019)* [39]	–	28 (60.7)	–
Farolfi (2019) [40]	–	119 (34.5)	–
Calais (2018) [41]	–	153 (40.5)	117 (59.8)
Sanli (2017) [42]	–	10 (20)	4 (25.0)
Eiber (2015) [43]	–	19 (57.9)	33 (72.7)
Rauscher (2018) [44]	–	134 (55.2)	138 (73.9)
Total	286 (30.1)	1078 (47.0)	546 (63.9)

*PSA level between 0.01 and 0.5 ng/mL.

Table 4 Detection rate and location of recurrence in patients without treatment between radical prostatectomy and gallium-68 prostate-specific membrane antigen positron-emission tomography/CT at different PSA values.

	Emmett (2017) [36]	Van Leeuwen (2016) [30]	Boreta (2019) [34]
PSA range	0.01–0.19	0.01–0.19	0.01–0.19
Total patients (total positive, percentage positive)	77 (45, 58.4%)	35 (11, 31.4%)	9 (3, 33.3%)
Recurrence fossa only	12	5	0
Pelvic lymph nodes ± fossa	16	4	2
Distant metastases ± fossa	17	2	1
PSA range	0.2–0.49	0.2–0.49	0.20–0.59
Total patients (total positive; % positive)	82 (56; 68.3)	28 (18; 64.3)	80 (39; 48.8)
Recurrence fossa only	22	10	6
Pelvic lymph nodes ± fossa	23	5	22
Distant metastases ± fossa	12	3	11
PSA range	0.50 to <1.0	0.5 to <1.0	0.60–1.19
Total patients (total positive; % positive)	25 (19; 76.0)	7 (4; 57.1)	24 (13; 54.2)
Recurrence fossa only	9	5	2
Pelvic lymph nodes ± fossa	6	1	4
Distant metastases ± fossa	4	1	7

literature, we conclude that ^{68}Ga -PSMA PET has an excellent specificity and positive predictive value for the detection of pelvic lymph node metastases in primary and recurrent PCa, that the detection rate achieved by ^{68}Ga -PSMA PET in patients with BCR after RP increases in parallel with rises in PSA values, and that the impact of PSMA in these men with recurrent PCa is considerable.

The results of this review highlight the high specificity and positive predictive value of ^{68}Ga -PSMA PET in detecting pelvic lymph node metastases. Most studies report a per-patient specificity of 90% or higher [10,11,13,15–17,19]. This high specificity is a result of the high expression of PSMA in PCa and lymph node metastases, resulting in a high tumour to background ratio [46–49].

An extended PLND is the gold standard for lymph node staging in PCa, but lymph node metastasis can be missed during extended PLND or misclassified during histological examination. Increased sensitivity of extended PLND can further increase the specificity of ^{68}Ga -PSMA PET. This is demonstrated by Horn et al. [50], who detected metastatic tissue in 120 of 121 patients with a positive ^{68}Ga -PSMA PET using PSMA-targeted radioguided surgery. Owing to the high specificity and positive predictive value of ^{68}Ga -PSMA PET in detecting pelvic lymph node metastases, it is not always necessary to obtain histology to confirm lymph node metastasis in case of a positive ^{68}Ga -PSMA PET result.

The specificity of ^{68}Ga -PSMA PET for detecting local recurrence or bone metastases is unknown because

histopathological confirmation is often not obtained; however, the specificity of ⁶⁸Ga-PSMA PET in detecting a local recurrence is thought to be high because of the high efficacy of salvage radiotherapy with regard to local recurrence detected by ⁶⁸Ga-PSMA PET [36]. By increased PSMA expression, fractures and Paget's disease can mimic bone metastases on ⁶⁸Ga-PSMA PET, with high expression in the vasculature of neo-angiogenesis. The specificity of ⁶⁸Ga-PSMA PET for early bone metastases is almost certainly lower because of these benign conditions that also express low levels of PSMA [51–54].

The specificity and sensitivity of ⁶⁸Ga-PSMA PET for detecting intraprostatic lesions at diagnosis is calculated on the basis of whole prostate gland histology. The reported specificity and sensitivity range from 92% to 100% and 60.1% to 67%, respectively [55,56]. A high lesion to normal prostate tissue ratio is seen in lesions with Gleason score ≥ 7 [55]. The use of ⁶⁸Ga-PSMA PET in the diagnostic pathway of PCa is yet to be determined.

The sensitivity of ⁶⁸Ga-PSMA PET for detecting lymph node metastases, in contrast to the specificity, is only moderate. The reported per-patient sensitivity ranges from 33.3% to 100%. The fact that the ⁶⁸Ga-PSMA PET misses lymph node metastases is highlighted by a lower per-node sensitivity, which is in the range of 24.4–66.67%. Lymph node metastases can be missed because of the lack of PSMA expression in 0–9% of primary prostate tumours and lymph node metastases [57,58]. Moreover, ⁶⁸Ga-PSMA PET misses small lymph node metastases [10,12,15,25,27]. In the studies by van Leeuwen et al. [15], Budaus et al. [10] and Obek et al. [12] the ⁶⁸Ga-PSMA PET missed all lymph node metastases smaller than 2, 4 and 5 mm, respectively therefore, ⁶⁸Ga-PSMA PET cannot yet replace extended PLND to exclude pelvic lymph node metastases.

As extended PLND is used as the gold standard reference, the number of nodes removed influences the sensitivity of ⁶⁸Ga-PSMA PET. ⁶⁸Ga-PSMA PET results can wrongly be classified as true-negative if lymph node metastasis is missed during extended PLND. Although there is no consensus regarding the minimum number of lymph nodes that should be removed during extended PLND, studies in which a low number of lymph nodes are removed should be interpreted with caution.

In the salvage phase, the detection rate of ⁶⁸Ga-PSMA PET is strongly correlated to the PSA value at the time of the PET [59]. The high efficacy of blind salvage radiotherapy on the prostatic fossa at PSA values < 0.5 ng/mL demonstrates that most patients with BCR after RP at this PSA level actually experience a local recurrence [60]. In the present review, local recurrence was detected only in 22.1% (49/222) of all men at a PSA < 0.5 ng/mL, suggesting that ⁶⁸Ga-PSMA PET misses local recurrences (Table 4). This is confirmed by the high

efficacy of salvage radiotherapy (SRT) to the prostatic fossa in patients with a negative ⁶⁸Ga-PSMA PET result [36]. Failure to detect local recurrence is probably attributable to the inability to distinguish tumour activity from intense activity in the nearby bladder owing to urinary radiotracer excretion and to the fact that less aggressive PCa more often returns locally and less aggressive disease expresses less PSMA [46–49].

In patients with BCR after RP ⁶⁸Ga-PSMA PET has been found to have a high management impact and detection rate [61]; however, the recommendation to perform ⁶⁸Ga-PSMA PET after RP to guide salvage treatment is only weak [3]. Although all patients in the different studies included in the present review underwent RP as primary therapy, not all treatments between RP and ⁶⁸Ga-PSMA PET were similar. Additional treatments after RP influence the outcome and detection rate of the ⁶⁸Ga-PSMA PET. First, ADT at the time of the PET influences the chance of having a positive ⁶⁸Ga-PSMA PET. In the nomogram presented by Rauscher et al. [44] for patients with BCR after RP, all patients with a PSA value > 0.2 ng/mL and on ADT at time of the PET have a $\sim 90\%$ chance of having a positive PET. The study by Emmett et al. [62] showed that the effect of androgen blockade depends on the patient's hormonal sensitivity, and impacts the scan results within 9 days of commencing treatment. In patients with hormone-sensitive metastatic PCa, androgen blockade reduces the PSMA intensity. In contrast, androgen blockade in patients with castrate-resistant PCa significantly increases PSMA intensity and the number of lesions detected [62]. There is a clear effect, therefore, of ADT on the performance of ⁶⁸Ga-PSMA PET, which needs further evaluation. Second, patients who underwent SRT after RP, but before ⁶⁸Ga-PSMA PET, have a decreased risk of having local recurrence detected on ⁶⁸Ga-PSMA PET. In most papers reporting the detection rate of ⁶⁸Ga-PSMA PET that are included in this review, both patients with or without ADT at time of or prior to the PSMA PET were included. Moreover, a selection of patients underwent radiotherapy to the prostatic fossa between RP and ⁶⁸Ga-PSMA PET. This should be considered when interpreting the results.

Salvage radiotherapy is the last curative treatment possibility for patients with BCR after RP, and is most effective at low PSA values [60]; however, SRT is unsuccessful if PCa has recurred outside the prostatic fossa. Only three studies describe a patient cohort without additional treatment between RP and ⁶⁸Ga-PSMA PET to determine the effect of ⁶⁸Ga-PSMA PET outcome on SRT planning [30,34,36]. By detecting PCa recurrence outside the prostatic fossa, the outcome of ⁶⁸Ga-PSMA PET changed SRT planning in 34.7% (42/121) and 39.1% (43/110) patients at PSA values < 0.2 and 0.2 – 0.49 ng/mL, respectively. In the study by Boreta et al. [34] ⁶⁸Ga-PSMA PET changed SRT planning in 41.3% (33/80) of all patients with a PSA value of 0.2 – 0.59 ng/mL. Therefore, the use of ⁶⁸Ga-PSMA PET to prevent

unsuccessful SRT seems indicated in patients considered for SRT, even at PSA values < 0.2 ng/mL.

The optimal time to perform ^{68}Ga -PSMA PET is unclear, but one conclusion can be drawn from the included studies, namely, ^{68}Ga -PSMA PET has poor sensitivity for local recurrences, especially at low PSA values. ^{68}Ga -PSMA PET should therefore be used to exclude metastases rather than to detect a local recurrence. In patients considered for SRT, the ^{68}Ga PSMA PET should be obtained at a PSA value where the detection rate is considered high enough to exclude metastases and a negative ^{68}Ga PSMA PET/CT triggers SRT.

The present review has some limitations. The first is inherent in its design. We did not perform a systematic review and meta-analysis as not all data were available; therefore, we were only able to show the reported results of the different studies. The second limitation is the lack of prospective and randomized controlled trials included. Most studies included were retrospective in design and therefore have a possible selection bias.

A strength of this review is the strict inclusion criteria of articles included. This enabled adequate assessment of the specificity and sensitivity of ^{68}Ga -PSMA PET in detecting lymph node metastases. Moreover, by excluding papers describing the location of PCa recurrence after RP and additional treatments, we presented a well-defined selected group of patients considered for SRT.

Future studies should focus on strategies to improve the sensitivity of ^{68}Ga -PSMA PET. To do so, different strategies could be considered. First, the stimulation of upregulation of PSMA in PCa cells might improve the sensitivity. *In vitro* models showed an upregulation of the PSMA surface levels in PCa cells by enzalutamide and dutasteride, although the effect of androgen blockage on the sensitivity of ^{68}Ga -PSMA PET seems to depend on the phenotype of the PCa [62,63]. More research is needed to evaluate the exact effect of androgen blockade on the ^{68}Ga -PSMA PET imaging. Second, next to the expression of the PSMA receptor, the detection of small lesions by PET scanners depends both on technical and tracer characteristics. Improvement of spatial resolution of PET systems and usage of tracers with higher positron yield and shorter positron range, such as ^{18}F , might improve the detection of small lesions [64,65]. In eight patients who underwent ^{18}F -PSMA-1007 PET/CT and subsequent RP with extended PLND, the sensitivity and specificity were 94.7% and 100%, respectively [66]. Moreover, decreased urinary clearance of ^{18}F -PSMA-1007 might reduce activity of radiotracer in the bladder and hence improve detection of local recurrence [66]. In patients with BCR after RP, the detection rate of ^{18}F -PSMA-1007 PET/CT was 61.5% (40/65) and 74.5% (35/47) for patients with PSA values of 0.2–0.49 ng/mL and 0.5–0.99 ng/mL, respectively [67]. The reported detection rates of ^{18}F -DCFPyL PET/CT in the PSA range of

0.2–0.49 ng/mL and 0.5–0.99 are 59% (17/29) and 69% (20/29), respectively [68]. In a recent matched-pair comparison, the accuracy of ^{68}Ga -PSMA PET and ^{18}F -PSMA-1007 PET was determined in patients with BCR after RP. Diagnostic performance was similar, however, ^{18}F -PSMA-1007 PET showed positive lesions that were benign in origin (e.g. ganglia) five times more often. Readers of ^{18}F -PSMA PET should be aware of these potential pitfalls. In addition, future studies should focus on determining the optimal time to perform PSMA PET and the effectiveness of SRT after negative PSMA PET at different PSA values. Lastly, studies with long-term follow-up are needed to determine the role of PSMA-guided salvage therapies in clinical practice.

In conclusion, ^{68}Ga -PSMA PET has a very high specificity and positive predictive value in detecting pelvic lymph node metastases, therefore, histological confirmation is not always necessary if ^{68}Ga -PSMA PET detects pelvic lymph node metastasis. In contrast, the sensitivity of the ^{68}Ga -PSMA PET in detecting pelvic lymph node metastases is only moderate and small lymph node metastases can be missed. ^{68}Ga -PSMA PET, therefore, cannot yet replace extended PLND to exclude pelvic lymph node metastases. Based on the available data, ^{68}Ga -PSMA PET seems to have a high management impact in patients considered for SRT at (early) BCR after RP. Future studies should focus on improving the sensitivity of ^{68}Ga -PSMA PET, and prospective studies focusing on long-term outcomes of PSMA-guided therapies are required.

Conflict of Interest

The authors declare to have no conflict of interest.

References

- 1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68: 394–424
- 2 Hövels AM, Heesakkers RA, Adang EM et al. The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis. *Clin Radiol* 2008; 63: 387–95
- 3 EAU Guidelines. Edn. Presented at the EAU Annual Congress Barcelona 2019. ISBN 978-94-92671-04-2.
- 4 Afshar-Oromieh A, Haberkorn U, Eder M, Eisenhut M, Zechmann CM. [^{68}Ga]Gallium-labelled PSMA ligand as superior PET tracer for the diagnosis of prostate cancer: comparison with ^{18}F -FECH. *Eur J Nucl Med Mol Imaging* 2012; 39: 1085–6
- 5 Sweat SD, Pacelli A, Murphy GP, Bostwick DG. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. *Urology* 1998; 52: 637–40
- 6 Schwarzenboeck SM, Rauscher I, Bluemel C et al. PSMA ligands for PET imaging of prostate cancer. *J Nucl Med* 2017; 58: 1545–52
- 7 De Visschere P, J, Standaert C, Futterer JJ et al. A systematic review on the role of imaging in early recurrent prostate cancer. *Eur Urol Oncol* 2019; 2: 47–76
- 8 Gupta M, Choudhury PS, Hazarika D, Rawal S. A comparative study of (^{68}Ga)Gallium-prostate specific membrane antigen positron emission tomography-computed tomography and magnetic resonance imaging for

- lymph node staging in high risk prostate cancer patients: an initial experience. *World J Nucl Med* 2017; 16: 186–91
- 9 Morigi JJ, Stricker PD, van Leeuwen PJ et al. Prospective comparison of ¹⁸F-fluoromethylcholine versus ⁶⁸Ga-PSMA PET/CT in prostate cancer patients who have rising PSA after curative treatment and are being considered for targeted therapy. *J Nucl Med* 2015; 56: 1185–90
 - 10 Budaus L, Leyh-Bannurrah SR, Salomon G et al. Initial experience of ⁶⁸Ga-PSMA PET/CT imaging in high-risk prostate cancer patients prior to radical prostatectomy. *Eur Urol* 2016; 69: 393–6
 - 11 Maurer T, Gschwend JE, Rauscher I et al. Diagnostic efficacy of ⁶⁸Ga-PSMA positron emission tomography compared to conventional imaging for lymph node staging of 130 consecutive patients with intermediate to high risk prostate cancer. *J Urol* 2016; 195: 1436–43
 - 12 Obek C, Doganca T, Demirci E et al. The accuracy of ⁶⁸Ga-PSMA PET/CT in primary lymph node staging in high-risk prostate cancer. *Eur J Nucl Med Mol Imaging* 2017; 44: 1806–12
 - 13 Thalgot M, Duwel C, Rauscher I et al. One-stop-shop whole-body ⁶⁸Ga-PSMA-11 PET/MRI compared with clinical nomograms for preoperative T and N staging of high-risk prostate cancer. *J Nucl Med* 2018; 59: 1850–6
 - 14 van Leeuwen PJ, Donswijk M, Nandurkar R et al. Gallium-68-prostate-specific membrane antigen (⁶⁸Ga-PSMA) positron emission tomography (PET)/computed tomography (CT) predicts complete biochemical response from radical prostatectomy and lymph node dissection in intermediate- and high-risk prostate cancer. *BJU Int* 2019; 24: 62–8
 - 15 van Leeuwen PJ, Emmett L, Ho B et al. Prospective evaluation of ⁶⁸Gallium-prostate-specific membrane antigen positron emission tomography/computed tomography for preoperative lymph node staging in prostate cancer. *BJU Int* 2017; 119: 209–15
 - 16 Yaxley JW, Raveenthiran S, Nouhaud FX et al. Outcomes of primary lymph node staging of intermediate and high risk prostate cancer with ⁶⁸Ga-PSMA positron emission tomography/computerized tomography compared to histological correlation of pelvic lymph node pathology: can preoperative ⁶⁸Ga-PSMA positron emission tomography/computerized tomography replace pelvic lymph node dissection for prostate cancer staging? *J Urol* 2019; 201: 815–20
 - 17 Zhang Q, Zang S, Zhang C et al. Comparison of ⁶⁸Ga-PSMA-11 PET-CT with mpMRI for preoperative lymph node staging in patients with intermediate to high-risk prostate cancer. *J Transl Med* 2017; 15: 230
 - 18 Park SY, Zacharias C, Harrison C et al. Gallium ⁶⁸PSMA-11 PET/MR imaging in patients with intermediate- or high-risk prostate cancer. *Radiology* 2018; 288: 495–505
 - 19 Yilmaz B, Turkay R, Colakoglu Y et al. Comparison of preoperative locoregional Ga-68 PSMA-11 PET-CT and mp-MRI results with postoperative histopathology of prostate cancer. *Prostate* 2019; 79: 1007–17
 - 20 Tulsyan S, Das CJ, Tripathi M, Seth A, Kumar R, Bal C. Comparison of ⁶⁸Ga-PSMA PET/CT and multiparametric MRI for staging of high-risk prostate cancer. *Nucl Med Commun* 2017; 38: 1094–102
 - 21 Fendler WP, Calais J, Eiber M et al. Assessment of ⁶⁸Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer: a prospective single-arm clinical trial. *JAMA Oncol* 2019; 5: 856–63
 - 22 Linxweiler J, Saar M, Al-Kailani Z et al. Robotic salvage lymph node dissection for nodal-only recurrences after radical prostatectomy: perioperative and early oncological outcomes. *Surg Oncol* 2018; 27: 138–45
 - 23 Mandel P, Tilki D, Chun FK et al. Accuracy of ⁶⁸Ga-prostate-specific membrane antigen positron emission tomography for the detection of lymph node metastases before salvage lymphadenectomy. *Eur Urol Focus* 2018; <https://doi.org/10.1016/j.euf.2018.07.025>. [Epub ahead of print]
 - 24 Pfister D, Porres D, Heidenreich A et al. Detection of recurrent prostate cancer lesions before salvage lymphadenectomy is more accurate with ⁶⁸Ga-PSMA-HBED-CC than with ¹⁸F-Fluoroethylcholine PET/CT. *Eur J Nucl Med Mol Imaging* 2016; 43: 1410–7
 - 25 Rauscher I, Maurer T, Beer AJ et al. Value of ⁶⁸Ga-PSMA HBED-CC PET for the assessment of lymph node metastases in prostate cancer patients with biochemical recurrence: comparison with histopathology after salvage lymphadenectomy. *J Nucl Med* 2016; 57: 1713–9
 - 26 Siriwardana A, Thompson J, van Leeuwen PJ et al. Initial multicentre experience of ⁶⁸ gallium-PSMA PET/CT guided robot-assisted salvage lymphadenectomy: acceptable safety profile but oncological benefit appears limited. *BJU Int* 2017; 120: 673–81
 - 27 Jilg CA, Drendel V, Rischke HC et al. Diagnostic accuracy of Ga-68-HBED-CC-PSMA-ligand-PET/CT before salvage lymph node dissection for recurrent prostate cancer. *Theranostics* 2017; 7: 1770–80
 - 28 Herlemann A, Wenter V, Kretschmer A et al. ⁶⁸Ga-PSMA positron emission tomography/computed tomography provides accurate staging of lymph node regions prior to lymph node dissection in patients with prostate cancer. *Eur Urol* 2016; 70: 553–7
 - 29 Kranzbühler B, Nagel H, Becker AS et al. Clinical performance of ⁶⁸Ga-PSMA-11 PET/MRI for the detection of recurrent prostate cancer following radical prostatectomy. *Eur J Nucl Med Mol Imaging* 2018; 45: 20–30
 - 30 van Leeuwen PJ, Stricker P, Hruby G et al. ⁶⁸Ga-PSMA has a high detection rate of prostate cancer recurrence outside the prostatic fossa in patients being considered for salvage radiation treatment. *BJU Int* 2016; 117: 732–9
 - 31 Meredith G, Wong D, Yaxley J et al. The use of ⁶⁸Ga-PSMA PET CT in men with biochemical recurrence after definitive treatment of acinar prostate cancer. *BJU Int* 2016; 118 (Suppl. 3): 49–55
 - 32 Gupta SK, Watson T, Denham J et al. Prostate-specific membrane antigen positron emission tomography-computed tomography for prostate cancer: distribution of disease and implications for radiation therapy planning. *Int J Radiat Oncol Biol Phys* 2017; 99: 701–9
 - 33 Schmuck S, Nordlohne S, von Klot CA et al. Comparison of standard and delayed imaging to improve the detection rate of [⁶⁸Ga]PSMA I&T PET/CT in patients with biochemical recurrence or prostate-specific antigen persistence after primary therapy for prostate cancer. *Eur J Nucl Med Mol Imaging* 2017; 44: 960–8
 - 34 Boreta L, Gadzinski AJ, Wu SY et al. Location of recurrence by Gallium-68 PSMA-11 PET scan in prostate cancer patients eligible for salvage radiotherapy. *Urology* 2019; 129: 165–71
 - 35 Yilmaz U, Komek H, Can C, Altindag S. The role of (⁶⁸Ga)PSMA I&T in biochemical recurrence after radical prostatectomy: detection rate and the correlation between the level of PSA, Gleason score, and the SUVmax. *Ann Nucl Med* 2019; 33: 545–53
 - 36 Emmett L, van Leeuwen PJ, Nandurkar R et al. Treatment outcomes from ⁶⁸Ga-PSMA PET/CT-informed salvage radiation treatment in men with rising PSA after radical prostatectomy: prognostic value of a negative PSMA PET. *J Nucl Med* 2017; 58: 1972–6
 - 37 Berliner C, Tienken M, Frenzel T et al. Detection rate of PET/CT in patients with biochemical relapse of prostate cancer using [⁶⁸Ga]PSMA I&T and comparison with published data of [⁶⁸Ga]PSMA HBED-CC. *Eur J Nucl Med Mol Imaging* 2017; 44: 670–7
 - 38 McCarthy M, Francis R, Tang C, Watts J, Campbell A. A multicentre prospective clinical trial of ⁶⁸Gallium PSMA HBED-CC PET-CT restaging in biochemically relapsed prostate carcinoma: oligometastatic rate and distribution, compared to standard imaging. *Int J Radiat Oncol Biol Phys* 2019; 104: 801–08
 - 39 Bashir U, Tree A, Mayer E et al. Impact of Ga-68-PSMA PET/CT on management in prostate cancer patients with very early biochemical recurrence after radical prostatectomy. *Eur J Nucl Med Mol Imaging* 2019; 46: 901–7
 - 40 Farolfi A, Ceci F, Castellucci P et al. ⁶⁸Ga-PSMA-11 PET/CT in prostate cancer patients with biochemical recurrence after radical prostatectomy and PSA <0.5 ng/ml. Efficacy and impact on treatment strategy. *Eur J Nucl Med Mol Imaging* 2019; 46: 11–9

- 41 Calais J, Czernin J, Cao M et al. (68)Ga-PSMA-11 PET/CT mapping of prostate cancer biochemical recurrence after radical prostatectomy in 270 patients with a PSA level of less than 1.0 ng/mL: impact on salvage radiotherapy planning. *J Nucl Med* 2018; 59: 230–7
- 42 Sanli Y, Kuyumcu S, Sanli O et al. Relationships between serum PSA levels, Gleason scores and results of 68Ga-PSMAPET/CT in patients with recurrent prostate cancer. *Ann Nucl Med* 2017; 31: 709–17
- 43 Eiber M, Maurer T, Souvatzoglou M et al. Evaluation of hybrid 68Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. *J Nucl Med* 2015; 56: 668–74
- 44 Rauscher I, Duwel C, Haller B et al. Efficacy, predictive factors, and prediction nomograms for (68)Ga-labeled prostate-specific membrane antigen-ligand positron-emission tomography/computed tomography in early biochemical recurrent prostate cancer after radical prostatectomy. *Eur Urol* 2018; 73: 656–61
- 45 Habl G, Sauter K, Schiller K et al. (68) Ga-PSMA-PET for radiation treatment planning in prostate cancer recurrences after surgery: Individualized medicine or new standard in salvage treatment. *Prostate* 2017; 77: 920–7
- 46 Bostwick DG, Pacelli A, Blute M, Roche P, Murphy GP. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. *Cancer* 1998; 82: 2256–61
- 47 Prasad V, Steffen IG, Diederichs G, Makowski MR, Wust P, Brenner W. Biodistribution of [(68)Ga]PSMA-HBED-CC in patients with prostate cancer: characterization of uptake in normal organs and tumour lesions. *Mol Imaging Biol* 2016; 18: 428–36
- 48 Ananias HJ, van den Heuvel MC, Helfrich W, de Jong IJ. Expression of the gastrin-releasing peptide receptor, the prostate stem cell antigen and the prostate-specific membrane antigen in lymph node and bone metastases of prostate cancer. *Prostate* 2009; 69: 1101–8
- 49 Woythal N, Arsenic R, Kempkensteffen C et al. Immunohistochemical validation of PSMA expression measured by (68)Ga-PSMA PET/CT in primary prostate cancer. *J Nucl Med* 2018; 59: 238–43
- 50 Horn T, Kronke M, Rauscher I et al. Single lesion on prostate-specific membrane antigen-ligand positron emission tomography and low prostate-specific antigen are prognostic factors for a favorable biochemical response to prostate-specific membrane antigen-targeted radioguided surgery in recurrent prostate cancer. *Eur Urol* 2019; 76: 517–23
- 51 Hoberuck S, Michler E, Kaiser D, Rohnert A, Zophel K, Kotzerke J. Prostate-specific membrane antigen expression in distal radius fracture. *Clin Nucl Med* 2018; 43: 611–3
- 52 Jochumsen MR, Dias AH, Bouchelouche K. Benign traumatic rib fracture: a potential pitfall on 68Ga-prostate-specific membrane antigen PET/CT for prostate cancer. *Clin Nucl Med* 2018; 43: 38–40
- 53 Panagiotidis E, Paschali A, Giannoula E, Chatzipavlidou V. Rib fractures mimicking bone metastases in 18F-PSMA-1007 PET/CT for prostate cancer. *Clin Nucl Med* 2019; 44: e46–8
- 54 Rowe SP, Deville C, Paller C et al. Uptake of (18)F-DCFPyL in Paget's disease of bone, an important potential pitfall in clinical interpretation of PSMA PET studies. *Tomography* 2015; 1: 81–4
- 55 Fendler WP, Schmidt DF, Wenter V et al. 68Ga-PSMA PET/CT detects the location and extent of primary prostate cancer. *J Nucl Med* 2016; 57: 1720–5
- 56 Donato P, Roberts MJ, Morton A et al. Improved specificity with (68)Ga PSMA PET/CT to detect clinically significant lesions "invisible" on multiparametric MRI of the prostate: a single institution comparative analysis with radical prostatectomy histology. *Eur J Nucl Med Mol Imaging* 2019; 46: 20–30
- 57 Chakraborty PS, Tripathi M, Agarwal KK, Kumar R, Vijay MK, Bal C. Metastatic poorly differentiated prostatic carcinoma with neuroendocrine differentiation: negative on 68Ga-PSMA PET/CT. *Clin Nucl Med* 2015; 40: e163–6
- 58 Zacho HD, Nielsen JB, Haberkorn U, Stenholt L, Petersen LJ. ⁶⁸Ga-PSMA PET/CT for the detection of bone metastases in prostate cancer: a systematic review of the published literature. *Clin Physiol Funct Imaging* 2017; <https://doi.org/10.1111/cpf.12480>. [Epub ahead of print]
- 59 Perera M, Papa N, Roberts M et al. Gallium-68 prostate-specific membrane antigen positron emission tomography in advanced prostate cancer—updated diagnostic utility, sensitivity, specificity, and distribution of prostate-specific membrane antigen-avid lesions: a systematic review and meta-analysis. *Eur Urol* 2019; <https://doi.org/10.1016/j.eururo.2019.01.049>. [Epub ahead of print]
- 60 Tendulkar RD, Agrawal S, Gao T et al. Contemporary update of a multi-institutional predictive nomogram for salvage radiotherapy after radical prostatectomy. *J Clin Oncol* 2016; 34: 3648–54
- 61 Han S, Woo S, Kim YJ, Suh CH. Impact of (68)Ga-PSMA PET on the management of patients with prostate cancer: a systematic review and meta-analysis. *Eur Urol* 2018; 74: 179–90
- 62 Emmett LM, Yin C, Crumbaker M et al. Rapid modulation of PSMA expression by androgen deprivation: serial (68)Ga PSMA-11 PET in men with hormone sensitive and castrate resistant prostate cancer commencing androgen blockade. *J Nucl Med* 2019; 60: 950–4
- 63 Kranzbühler B, Salemi S, Umbricht CA et al. Pharmacological upregulation of prostate-specific membrane antigen (PSMA) expression in prostate cancer cells. *Prostate* 2018; 78: 758–65
- 64 Omami G, Tamimi D, Branstetter BF. Basic principles and applications of (18)F-FDG-PET/CT in oral and maxillofacial imaging: a pictorial essay. *Imaging Sci Dent* 2014; 44: 325–32
- 65 Sanchez-Crespo A. Comparison of Gallium-68 and Fluorine-18 imaging characteristics in positron emission tomography. *Appl Radiat Isot* 2013; 76: 55–62
- 66 Giesel FL, Hadaschik B, Cardinale J et al. F-18 labelled PSMA-1007: biodistribution, radiation dosimetry and histopathological validation of tumor lesions in prostate cancer patients. *Eur J Nucl Med Mol Imaging* 2017; 44: 678–88
- 67 Giesel FL, Knorr K, Spohn F et al. Detection efficacy of (18)F-PSMA-1007 PET/CT in 251 patients with biochemical recurrence of prostate cancer after radical prostatectomy. *J Nucl Med* 2019; 60: 362–8
- 68 Wondergem M, Jansen BHE, van der Zant FM et al. Early lesion detection with (18)F-DCFPyL PET/CT in 248 patients with biochemically recurrent prostate cancer. *Eur J Nucl Med Mol Imaging* 2019; 46: 1911–8

Correspondence: Henk B. Luiting, Department of Urology, Erasmus University Medical Center, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands.

e-mail: h.luiting@erasmusmc.nl

Abbreviations: 68Ga-PSMA, gallium-68 prostate-specific membrane antigen; PSMA, prostate-specific membrane antigen; PET, positron-emission tomography; PCa, prostate cancer; BCR, biochemical recurrence; RP, radical prostatectomy; PLND, pelvic lymph node dissection; ADT, androgen deprivation therapy; SRT, salvage radiotherapy.