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ORIGINAL ARTICLE

Prospective comparison of whole-body MRI and ^{68}Ga-PSMA PET/CT for the detection of biochemical recurrence of prostate cancer after radical prostatectomy

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Abstract

Purpose To assess whole-body magnetic resonance imaging (wb-MRI) for detection of biochemical recurrence in comparison to ^{68}Ga-prostate-specific membrane antigen positron emission tomography/computed tomography (^{68}Ga-PSMA PET/CT) in prostate cancer (Pca) patients after radical prostatectomy.

Methods This was a prospective trial including 28 consecutive patients (mean age 65.3 ± 9.0 years) with newly documented biochemical recurrence of Pca (mean prostate-specific antigen, PSA, 2.09 ± 1.95 ng/ml) following radical prostatectomy. All patients underwent both wb-MRI including a dedicated pelvic imaging protocol and PET/CT with 166 ± 35 MBq ^{68}Ga-PSMA within a time window of 11 ± 10 days. PET/CT and MRI datasets were separately evaluated regarding Pca lesion count, type, localization and diagnostic confidence (three-point Likert scale, 1–3) by two nuclear medicine specialists and two radiologists, respectively. The reference standard was based on histopathological results, PSA levels following targeted salvage irradiation and follow-up imaging. Lesion-based and patient-based detection rates were compared using the chi-squared test. Differences in diagnostic confidence were assessed using the Welch test.

Results A total of 56 Pca lesions were detected in 20 of the 28 patients. ^{68}Ga-PSMA PET/CT detected 56 of 56 lesions (100%) in 20 patients (71.4%), while wb-MRI detected 13 lesions (23.2%) in 11 patients (39.3%). The higher detection rate with ^{68}Ga-PSMA PET/CT was statistically significant on both a per-lesion basis ($p < 0.001$) and a per-patient basis ($p = 0.0167$). In 8 patients (28.6%) no relapse was detectable by either modality. All lesions detected by wb-MRI were also detected by ^{68}Ga-PSMA PET/CT. Additionally, ^{68}Ga-PSMA PET/CT provided superior diagnostic confidence in identifying Pca lesions (2.7 ± 0.7 vs. 2.3 ± 0.6, $p = 0.044$).

Conclusion ^{68}Ga-PSMA PET/CT significantly out-performed wb-MRI in the detection of biochemical recurrence in Pca patients after radical prostatectomy.

Keywords Recurrent · Prostate · Cancer · PSMA · PET/CT · MRI

Introduction

Prostate cancer (Pca) is the most common malignancy and one of the leading causes of cancer-related death in men worldwide [1]. Despite advances in Pca therapy, up to 40% of patients develop biochemical recurrence after radical prostatectomy, particularly men with a history of high-risk Pca [2]. However, the detection and localization of Pca recurrence is challenging as conventional imaging modalities such as ultrasonography, computed tomography (CT) and bone scintigraphy have only limited sensitivity, especially at low serum prostate-specific antigen (PSA) levels (<10 ng/ml) [3, 4].

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Early localization of the site of recurrent Pca is crucial because resection or targeted salvage radiotherapy can be performed with curative intent in patients with locally limited disease, thereby often helping to prolong the time to long-term androgen-deprivation therapy (ADT) [5–7]. Prostate-specific membrane antigen (PSMA) is a type-II transmembrane protein that is overexpressed on Pca cells [8].

Over the last 5 years, ^{68}Ga-PSMA PET/CT has become an essential method for imaging Pca for primary staging and restaging, and in patients with biochemical recurrence. Multiple studies have already indicated that ^{68}Ga-PSMA PET/CT is able to identify pathological Pca lesion uptake even in patients with very low PSA levels (<2 ng/ml) and with better diagnostic accuracy than previous PET tracers such as ^{18}F-choline or ^{11}C-acetate [9–12]. However, there are some pitfalls with ^{68}Ga-PSMA PET/CT such as false-negative scans due to low PSMA expression (about 5% of Pca) or masking of Pca lesions in or adjacent to organs with high background activity [13]. Incidental radiotracer uptake by noncancerous bone remodelling processes may lead to false-positive radiotracer uptake [14]. Moreover, as ^{68}Ga-PSMA is mainly excreted via the kidneys and accumulates in the urinary bladder, small local recurrences adjacent to the bladder can be missed [15]. Magnetic resonance imaging (MRI) has also been used for identifying Pca recurrence. Based on the unparalleled soft-tissue contrast and benefits of diffusion-weighted imaging (DWI), MRI is regarded as a valuable tool for the detection of Pca recurrence, especially in patients with altered pelvic anatomy following radical prostatectomy [16, 17]. However, with regard to the diagnostic performance of whole-body MRI (wb-MRI) compared to ^{68}Ga-PSMA PET/CT, the few studies that are available did not focus on patients with disease relapse. Hence, the purpose of this study was to prospectively compare the diagnostic performance of wb-MRI with that of ^{68}Ga-PSMA PET/CT for the detection of biochemical recurrence in Pca patients.

Materials and methods

Patients

The institutional review board (IRB) approved this single-centre study, and all patients provided signed informed consent prior to enrolment (University Dusseldorf IRB number 2014082777). A total of 28 consecutive male patients (age 65.3 ± 9.0 years) with newly documented biochemical recurrence of Pca (PSA ≥0.2 ng/ml) who had undergone radical prostatectomy were prospectively included in the study. All patients underwent both wb-MRI with a dedicated pelvic imaging protocol and PET/CT with ^{68}Ga-PSMA (also known as ^{68}Ga-PSMA-11). There was no fixed order or randomization schedule, but wb-MRI and PET/CT had to be performed within a limited time-window of 3 weeks (mean 11 ± 10 days). The average PSA level in the patients at the time of imaging was 2.09 ± 1.95 ng/ml (range 0.2–9.9 ng/ml). All 28 patients had undergone curative radical prostatectomy with pelvic lymphadenectomy (n = 27) or without pelvic lymphadenectomy (n = 1). The mean pretherapeutic PSA level was 12.6 ± 8.0 ng/ml and the median Gleason score was 7. The initial tumour stage was pT2 in 15 patients (53.6%) and pT3 in 13 patients (46.4%). Three patients (10.7%) were reported to be positive for nodal disease (N1) and none of the patients had distant metastases at initial diagnosis. Salvage radiotherapy of the prostatic fossa had been performed in 15 patients (53.6%). Of five patients (17.9%) who had received ADT four had had intermittent ADT several years before the scan, while one patient was receiving ongoing ADT during the study.

Wb-MRI

Wb-MRI examinations were performed on a 1.5 T Magnetom Avanto MRI scanner (Siemens Healthineers, Erlangen, Germany). The longitudinal scan volume included the entire body from the head to the feet with the patient in the supine position, and used a dedicated 16-channel head-and-neck radiofrequency (RF) coil, a 24-channel spine array RF coil and five to seven six-channel flex body coils, depending on the patient's height. The diagnostic MRI protocol included the following sequences (see Table 1 for sequence parameters):

1. A whole-body transverse T2-weighted (T2w) fat-suppressed (fs) half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequence
2. A whole-body coronal diffusion-weighted echo-planar imaging (EPI DWI) sequence (b-values 50, 900)
3. A whole-body T2w coronal turbo inversion recovery magnitude (TIRM) sequence
4. A transverse DWI sequence of the pelvis (b-values 0, 1,000)
5. A high-resolution transverse T2w turbo spin-echo (TSE) of the former prostatic fossa
6. A whole-body transverse T1-weighted (T1w) fs volume-interpolated breath-hold examination (VIBE) sequence after intravenous injection of a gadolinium-based contrast agent (ProHance, Bracco Imaging Deutschland GmbH, Konstanz, Germany).

The standard scan duration for the entire MRI protocol was approximately 55 min.

PET/CT

PET/CT was performed on a Biograph mCT 128 (Siemens Healthineers, Erlangen, Germany) 1 h after intravenous injection of a mean activity of 166 ± 35 MBq ^{68}Ga-PSMA. The

Table 1 Sequence parameters of the MR sequences used in the study

Sequence	Orientation	Contrast agent	Repetition time (ms)	Echo time (ms)	Slice thickness (mm)	Matrix size	Field of view (mm)
T2w HASTE	Transverse	No	1,000	92	5.0	320 × 256	300 × 300
EPI DWI	Coronal	No	5,400	70	6.0	192 × 154	500 × 344
T2w TIRM	Coronal	No	3,000	113	6.0	256 × 205	500 × 500
DWI	Transverse	No	7,400	78	5.0	192 × 192	400 × 300
T2w TSE	Transverse	No	6,254	85	3.0	384 × 384	250 × 250
T1w fs VIBE	Transverse	Yes	4.55	2.01	3.0	256 × 179	400 × 300

T2w HASTE T2-weighted half-Fourier acquisition single-shot turbo spin-echo, *EPI DWI* diffusion-weighted echo-planar imaging, *T2w TIRM* T2-weighted turbo inversion recovery with magnitude, *TSE* turbo spin-echo, *T1w fs VIBE* T1-weighted fat-suppressed volume-interpolated breath-hold examination

longitudinal ^{68}Ga-PSMA PET/CT scan volume included the entire body from the head to the feet with the patient in the supine position (identical to that used in wb-MRI). The CT component was performed after intravenous administration of an iodinated contrast medium and used the manufacturer-supplied automatic tube voltage selection and tube current modulation (CARE kV and CARE Dose 4D; presets 120 kV, 210 reference mAs, collimation 128 × 0.6 mm, pitch 0.8, slice thickness 5 mm). The PET acquisition time was 3 min per bed position (axial field of view 21.8 cm, matrix size 256 × 256). Following the initial whole-body PET/CT scan, each patient was asked to void the bladder for a second PET scan of the pelvis. PET data were corrected for attenuation and reconstructed using an iterative ordered-subsets expectation maximization (OSEM) algorithm (three iterations, 21 subsets, 4 mm gaussian filter). The scan duration for the entire PET/CT protocol was approximately 25 min.

Image analysis

Wb-MRI and ^{68}Ga-PSMA PET/CT images were evaluated in a picture archiving and communication system (IDS7; Sectra, Linköping, Sweden) and on a *syngo*.via workstation (Siemens Healthineers, Erlangen, Germany). Two radiologists with 5 and 4 years of experience in MRI (L.S., J.K.) and two nuclear medicine specialists each with 6 years of experience in PET/CT (H.H., C.A.) independently analysed all images. Discrepant ratings were resolved by discussion in a subsequent consensus reading. The readers were blinded to each patient's identity, history and results of prior and follow-up imaging. Wb-MRI and PET/CT were assessed separately in random order, in different sessions and at least 4 weeks apart to avoid recognition bias. Pca lesion count, localization and diagnostic confidence in identifying Pca lesions (three-point Likert scale: *1* not confident, *2* quite confident, *3* confident) were determined for each wb-MRI and PET/CT image. Lesion shape, local invasiveness, central necrosis and increased contrast enhancement were considered as signs of local recurrence. Lymph nodes with a short axis diameter of >8 mm (pelvic) or >10 mm (inguinal, abdominal, thoracic, neck), spherical configuration, irregular border, inhomogeneity and increased contrast enhancement were categorized as nodal metastases [18]. Lesions that were detectable as locally invasive and showing pathological contrast enhancement or central necrosis were described as distant metastases. Additionally, diffusion restriction was regarded as suspicious for local recurrence and distant metastases on wb-MRI images. On ^{68}Ga-PSMA PET/CT images, visually increased focal radiotracer uptake above that of the surrounding background was considered as a sign of malignancy. The maximum standardized uptake value (SUVmax) was measured in lesions with focal ^{68}Ga-PSMA uptake by manually drawing a region of interest around the lesion.

Reference standard

Seven of 56 lesions were confirmed histopathologically, including local recurrence in one patient and six lymph node metastases in six patients. Because clinical and ethical standards for patient management did not allow surgery or sampling of all detected lesions, a modified reference standard was used for the remaining 49 lesions taking into account follow-up imaging (^{68}Ga-PSMA PET/CT, MRI, CT, scintigraphy; mean interval 7 ± 5 months) and clinical follow-up findings. A decrease in PSA level, lesion size and/or SUVmax under therapy was regarded as a sign of malignancy. Also, lesions with an increase in size and those with constant or increasing PET positivity were considered malignant.

Statistics

SPSS Statistics, version 22 (IBM, Armonk, NY, USA) was used for data analysis. Descriptive data are presented as means ± standard deviation. Pca lesion detection rates with

^{68}Ga-PSMA PET/CT and wb-MRI were calculated on a per-patient basis and on a per-lesion basis. Detection rates with ^{68}Ga-PSMA PET/CT and wb-MRI were compared using the chi-squared test. The Welch test was to used to assess the difference between ^{68}Ga-PSMA PET/CT and wb-MRI regarding diagnostic confidence in identifying Pca lesions. PSA levels at the time of imaging were compared between patients with positive and negative ^{68}Ga-PSMA PET/CT and wb-MRI scans, respectively, using the Mann-Whitney *U* test. A *p* value of <0.05 was considered to indicate statistical significance.

Results

Patient-based analysis

^{68}Ga-PSMA PET/CT detected Pca lesions in 20 of the 28 patients (71.4%) with biochemical Pca recurrence. In contrast, wb-MRI detected Pca lesions in 11 patients (39.3%). The difference between ^{68}Ga-PSMA PET/CT and wb-MRI regarding detection of biochemical recurrence on a per-patient basis was statistically significant ($p = 0.0167$). ^{68}Ga-PSMA PET/CT and wb-MRI detected Pca lesions in the same 11 patients, but PET/CT detected Pca lesions in nine additional patients including five with nodal recurrence, two with nodal and osseous recurrence, one with nodal and pulmonary recurrence, and one with local recurrence in the former prostatic fossa. Both ^{68}Ga-PSMA PET/CT and wb-MRI failed to detect Pca relapse in the same eight patients.

The mean PSA level at the time of imaging was significantly lower in the eight patients with a negative ^{68}Ga-PSMA PET/CT scan than in the 20 patients with a positive ^{68}Ga-PSMA PET/CT scan (0.9 ± 0.8 ng/ml vs. 2.6 ± 2.1 ng/ml, $p = 0.007$). It was also significantly lower in the 17 patients with a negative wb-MRI scan than in the 11 patients with a positive wb-MRI scan (1.4 ± 1.1 ng/ml vs. 3.1 ± 2.6 ng/ml, $p = 0.041$). The mean PSA level at the time of imaging in patients with a positive ^{68}Ga-PSMA PET/CT scan was non-significantly lower than in those with a positive wb-MRI scan (2.6 ± 2.1 ng/ml vs. 3.1 ± 2.6 ng/ml, $p = 0.647$). Table 2 shows the detection rates with ^{68}Ga-PSMA PET/CT and wb-MRI in relation to PSA level.

Table 2 Detection rates with ^{68}Ga-PSMA PET/CT and wb-MRI in relation to PSA level

PSA level (ng/ml)	Percentage of patients with Pca recurrence	
	On ^{68}Ga-PSMA PET/CT	On wb-MRI
0.2 – <1.0	7.1	0
0.2 – <2.0	42.9	21.4
0.2 – <5.0	67.9	35.7
0.2 – ≥5.0	71.4	39.3

Lesion-based analysis

Based on the reference standard, 56 Pca lesions were detected in 20of the 28 patients (Table 3). ^{68}Ga-PSMA PET/CT detected 56 of the 56 lesions (100%), while wb-MRI detected 13 lesions (23.2%). There were no false-positive ratings with either modality. The higher detection rate with ^{68}Ga-PSMA PET/CT was statistically significant ($p < 0.001$). In more detail, PET/CT correctly identified 42 lymph node metastases (24 pelvic, 10 retroperitoneal, 8 thoracic), seven local recurrences, six bone metastases, and one lung metastasis. All these lesions showed pathological ^{68}Ga-PSMA uptake (SUVmax 10.4 ± 6.8). On the other hand, wb-MRI failed to detect 43 Pca lesions: 36 non-enlarged, morphologically nonsuspicious lymph node metastases (18 pelvic, 10 retroperitoneal, 8 thoracic; Fig. 1), three local recurrences (Fig. 2), one lung metastasis, and three bone metastases. All 36 lymph node metastases missed by wb-MRI were associated with focal ^{68}Ga-PSMA uptake and were thus correctly classified as nodal recurrences on hybrid imaging. The three missed local recurrences demonstrated only subtle signal alterations in the former prostatic fossa without marked contrast enhancement on contrast-enhanced T1w fs VIBE MRI and no diffusion restriction, and were consequently rated as posttherapy scar tissue on wb-MRI. Both were classified correctly on PET/CT due to their focal ^{68}Ga-PSMA uptake. The single lung metastasis that was unrecognized on wb-MRI was detectable on ^{68}Ga-PSMA PET/CT as a 5-mm nodule with surrounding ground-glass opacity in the right upper lobe in a patient with a PSA 0.95 ng/ml. Again, PET/CT displayed pathological ^{68}Ga-PSMA uptake in the lung nodule (SUVmax 4.4) as an indication of malignancy. Follow-up PET/CT imaging confirmed the metastasis with local lymphangitis carcinomatosa. Furthermore, on wb-MRI, three costal metastases, which were seen as small ^{68}Ga-PSMA-positive bone lesions on PET/CT (9–10 mm in size, third and fourth laterodorsal ribs), were missed because of their lack of contrast enhancement, diffusion restriction and bone marrow oedema.

Table 3 Types and frequencies of detected Pca lesions in the study population

Type	Number (%) of lesions
Lymph node metastases	42 (75)
Pelvic	24 (42.9)
Retroperitoneal	10 (17.9)
Thoracic	8 (14.3)
Local recurrences	7 (12.5)
Bone metastases	6 (10.7)
Lung metastases	1 (1.8)
Total	56 (100)

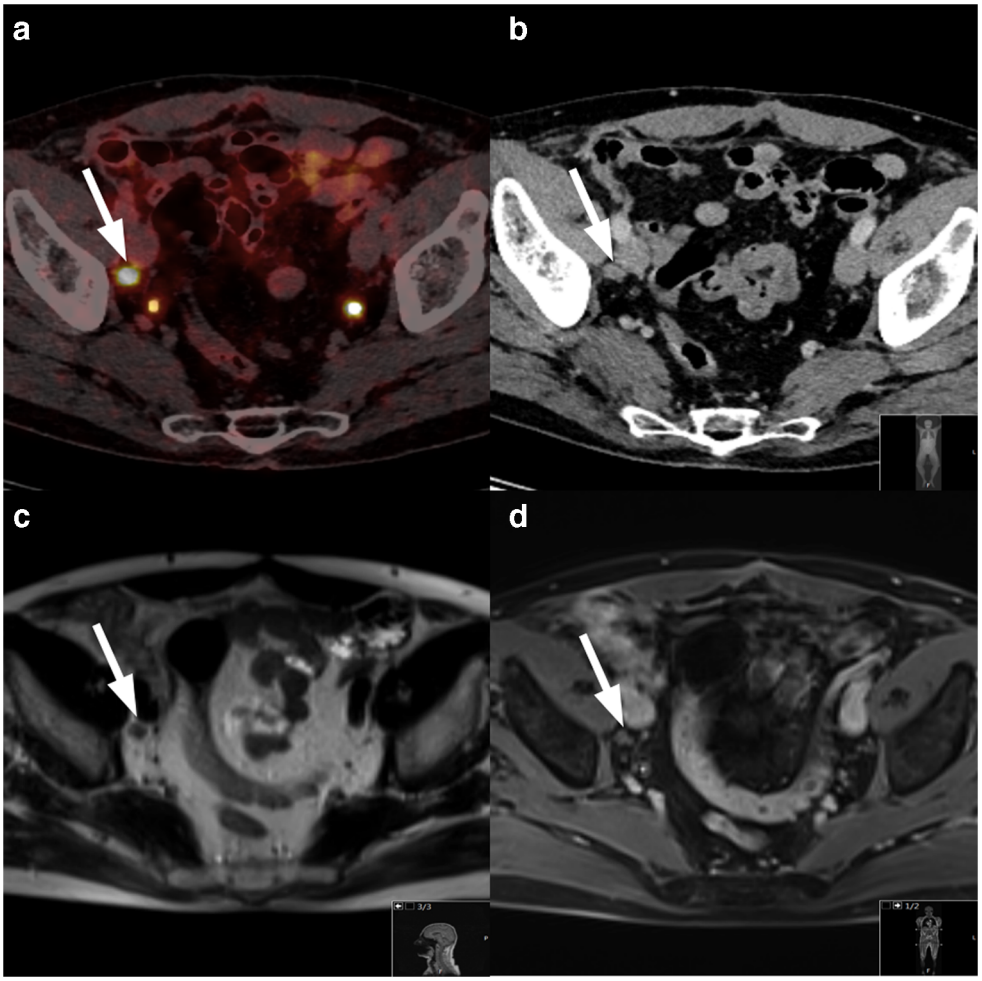

Fig. 1 Example 57-year-old patient with biochemical recurrence of Pca (serum PSA 1.8 ng/ml) after radical prostatectomy and pelvic lymphadenectomy. **a**, **b** ^{68}Ga-PSMA PET/CT: the CT image (**b**) shows a 7-mm right parailiac lymph node (*arrow*) that shows pathological ^{68}Ga-PSMA uptake (SUVmax 14.9, **a** *arrow*) in keeping with a nodal metastasis. **c**, **d** On MRI, the lymph node had an ovoid shape, was not pathologically enlarged and did not show an increased contrast-enhancement, so was not regarded as a lymph node metastasis. Note the radiotracer excretion via the ureter on both sides of the pelvis in **a**

Diagnostic confidence

The overall diagnostic confidence of ^{68}Ga-PSMA PET/CT in categorizing Pca lesions was significantly higher than that of wb-MRI (2.7 ± 0.7 vs. 2.3 ± 0.6, $p = 0.044$). While ^{68}Ga-PSMA PET/CT showed a significantly higher diagnostic confidence in the diagnosis of lymph node metastases ($p = 0.0047$), no significant differences between ^{68}Ga-PSMA PET/CT and wb-MRI were found for local recurrences and bone metastases (Table 4).

Discussion

The results of our study demonstrate a higher tumour detection rate in patients with biochemical recurrence of Pca with ^{68}Ga-PSMA PET/CT than with wb-MRI. ^{68}Ga-PSMA PET/CT was superior on a per-patient basis, allowing localization of relapse in significantly more patients than wb-MRI. Additionally, ^{68}Ga-PSMA PET/CT provided better diagnostic confidence than wb-MRI.

Chronic ADT has long been the standard treatment for patients diagnosed with biochemical recurrence. However, frequent side effects such as osteoporosis, muscle atrophy, gynaecomastia, obesity, erectile dysfunction and depression sparked interest in alternatives to chronic ADT for patients with Pca relapse [19]. Among these, resection and especially targeted salvage radiation with or without short-term ADT have emerged as effective treatment options that lead to long-term freedom from cancer recurrence in patients who present with locally limited recurrence [20–22]. Moreover, the distinction between metastatic and locally recurrent disease is crucial, since survival is significantly worse in patients with systemic disease relapse. Therefore, early and precise image-based assessment is needed to identify the type and site of relapse and to ultimately guide patient management. However, in clinical routine, detection of Pca relapse by conventional imaging modalities such as CT or transrectal ultrasonography is challenging because of limitations in differentiating posttherapy changes from local relapse and visualizing small lymph node metastases.

According to the current ACR appropriateness criteria, MRI, because of its higher soft-tissue contrast and

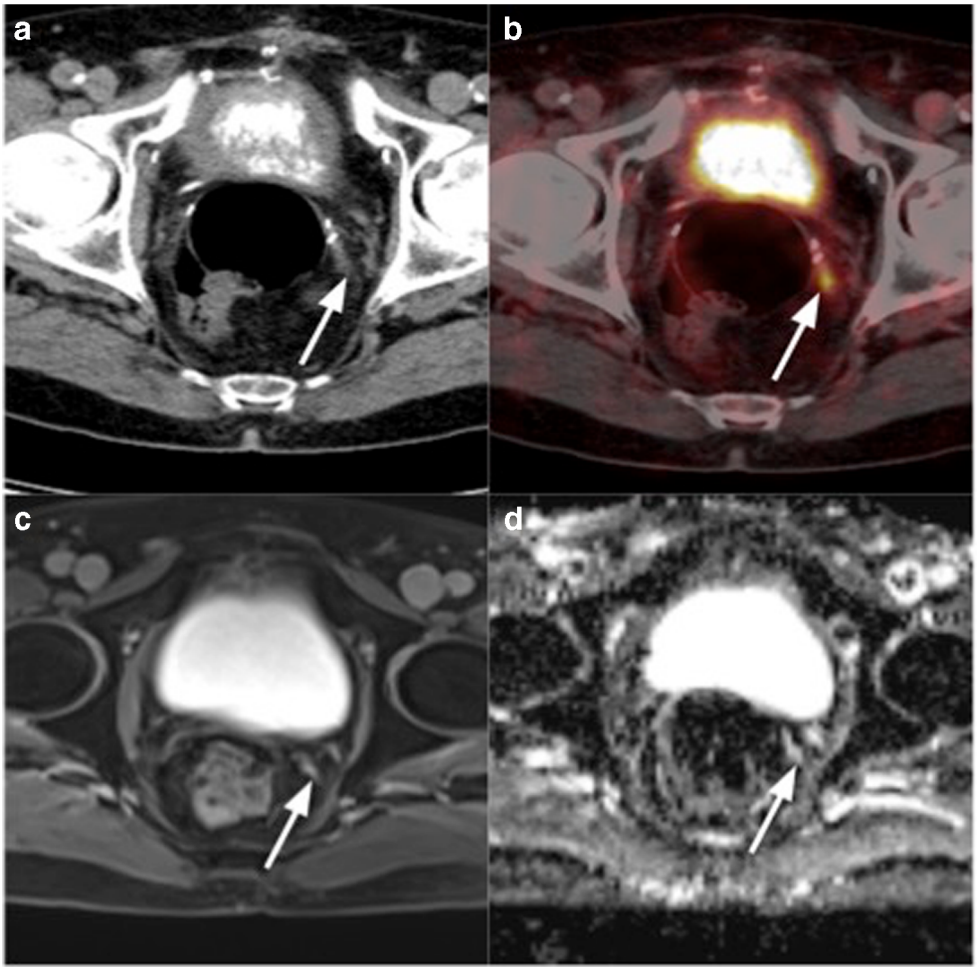

Fig. 2 Example 75-year-old patient with biochemical recurrence of Pca (serum PSA 1.5 ng/ml) after radical prostatectomy and pelvic lymphadenectomy. **a**, **b** ^{68}Ga-PSMA PET/CT: the CT image (**a**) shows a discrete soft-tissue mass adjacent to postprostatectomy clip material in the left pararectal space (*arrow*) that shows pathological ^{68}Ga-PSMA uptake (SUVmax 6.8, **b** *arrow*) in keeping with a local recurrence. **c**, **d** On MRI, the tissue has a streaky appearance with only subtle enhancement (**c**) and without diffusion restriction on DWI (**d**), and was therefore regarded as scar tissue

multiparametric information from DWI or dynamic contrast enhancement (DCE), is preferred over CT for Pca follow-up in patients with clinical concern for recurrent disease [23]. For example, Panebianco et al. evaluated 262 patients with a high risk of biochemical recurrence after radical prostatectomy with multiparametric MRI of the pelvis [16]. Using a combination of T2w imaging and DWI with a b-value of 1,000 s/mm^2, they found a sensitivity of 93%, a specificity of 89%, and an accuracy of 88% in the detection of intrapelvic recurrence. Regarding the detection of recurrence following radiation therapy, a meta-analysis by Wu et al. showed a pooled sensitivity and specificity of multiparametric MRI of 82% and 74%, respectively, on a per-patient basis [24]. In spite of the above-mentioned evidence for multiparametric MRI of the pelvis, the data for whole-body staging of biochemical recurrence using wb-MRI are still limited. In a recent study, Barchetti et al. found that wb-MRI including T1w, T2w, short tau inversion recovery (STIR), and DWI provided an accuracy of 98% in the identification of bone metastases and pathological lymph nodes, using ^{18}F-choline PET/CT as the reference standard [25]. In another study, Wieder et al. found that, using histopathology and clinical follow-up as the reference standard, wb-MRI with DWI performed worse than ^{11}C-choline PET/CT in the detection of local recurrence and bone metastasis, while both modalities showed comparable accuracy in the detection of lymph node metastases [26]. Moreover, Giovacchini et al. found that ^{11}C-choline PET/CT was able to predict patient survival in Pca patients with biochemical recurrence after radical prostatectomy and low PSA levels (<1 ng/ml) [27, 28].

Since its introduction into clinical routine in 2013, ^{68}Ga-PSMA PET/CT has rapidly established itself as the new

Table 4 Comparison of the diagnostic confidence between ^{68}Ga-PSMA PET/CT and wb-MRI in relation to lesion type

	PET/CT	Wb-MRI	*p* value
Local recurrence	2.3 ± 1.0 (*n* = 7)	2.3 ± 0.5 (*n* = 4)	>0.05
Nodal metastases	2.8 ± 0.5 (*n* = 42)	2.2 ± 0.8 (*n* = 6)	0.0047*
Bone metastases	2.2 ± 1.0 (*n* = 6)	2.7 ± 0.6 (*n* = 3)	>0.05

Values are mean ± standard deviation three-point Likert scale scores: *1* not confident, *2* quite confident, *3* confident

*$p < 0.05$, Welch test

imaging gold standard for Pca staging and is currently also endorsed for imaging in men with biochemical recurrence after radical prostatectomy. Numerous studies have shown that PET/CT with PSMA-targeting radiotracers such as ^{68}Ga-PSMA has a very high diagnostic value for the restaging of Pca due to its ability to identify increased PSMA expression in cancerous lesions as compared to surrounding tissue. A meta-analysis of 37 studies showed an overall rate of detection of biochemical recurrence of up to 96.6%, depending on serum PSA levels [29]. A major strength of ^{68}Ga-PSMA PET/CT is its ability to detect lesions in patients with low PSA levels (>60% PET-positive scans in patients with PSA <5 ng/ml) [11, 29, 30]. It has also been found to outperform PET/CT with choline-based radiotracers in the detection of Pca metastases and to lead to significant changes in treatment strategy in 62% of patients with biochemical recurrence [31, 32]. However, evidence regarding the use of ^{68}Ga-PSMA PET/CT in direct comparison to wb-MRI for the detection of Pca relapse has so far been lacking; however, the results of our study are partly in line with previously published data.

The data presented confirm the diagnostic value of ^{68}Ga-PSMA PET/CT for whole-body staging in men with biochemical recurrence of Pca, particularly considering that our patient cohort also showed a low average serum PSA level (2.09 ± 1.95 ng/ml). In the lesion-based analysis, ^{68}Ga-PSMA PET/CT identified significantly more Pca recurrences than wb-MRI alone as a result of pathological radiotracer uptake in cancerous lesions with a nonsuspicious or uncertain morphology. In particular, ^{68}Ga-PSMA PET/CT identified a large number of subcentimetre nodal metastases with increased ^{68}Ga-PSMA uptake that were considered benign on wb-MRI based on region-specific size criteria for lymph node metastases on cross-sectional imaging [18]. The value of the information provided by ^{68}Ga-PSMA PET is further underlined by the finding that ^{68}Ga-PSMA PET/CT detected three more local recurrences in the former prostatic fossa than wb-MRI. These three local recurrences showed no pathological signal alteration, contrast enhancement or diffusion restriction, and thus were not considered suspicious on wb-MRI. Despite the superior diagnostic performance of ^{68}Ga-PSMA PET/CT, its availability is partly limited by logistical, financial or approval issues. Hence, some university or peripheral centres are still using PET/CT with choline-based radiotracers in patients with biochemical recurrence and PSA ≥1 ng/ml, while multiparametric MRI of the pelvis is used in those with PSA 0.2–1 ng/ml to detect small local recurrences, as recommended by Mapelli et al. [33].

MRI is widely regarded as one of the most sensitive imaging techniques for the detection of bone metastases; however, MRI missed three osseous recurrences in our study cohort that were detected by ^{68}Ga-PSMA-PET/CT. These three metastases were small osteoblastic lesions (two 10 mm, one 9 mm) of the third and fourth laterodorsal ribs, and as such had lower MR signal than osteolytic lesions, in which MRI reveals the metastatic tissue inside the bone marrow with high lesion-to-background contrast. This relatively limited specificity for osteoblastic bone metastases has been found in previous studies [34, 35]. A further disadvantage of MRI is its limited ability to detect small pulmonary lesions owing to motion artefacts and the small number of protons in the lungs [36, 37]. This is supported by the results of our lesion-based analysis, in which one lung metastasis (5 mm) was missed by wb-MRI. The superior diagnostic confidence of ^{68}Ga-PSMA PET/CT reflects another beneficial feature of hybrid imaging: it reduces ambiguity in lesion assessment in comparison with conventional imaging.

Our analysis of PSA levels showed that the detectability of Pca recurrences on ^{68}Ga-PSMA PET/CT and wb-MRI depends on the actual PSA level at the time of imaging. These results are in line with those of previous studies investigating the connection between PSA levels and lesion detection [38]. Interestingly, despite the higher rate of detection of Pca recurrences on ^{68}Ga-PSMA PET/CT than on wb-MRI, there was no significant difference between the PSA levels of patients with positive ^{68}Ga-PSMA PET/CT and MRI scans, which might have been a consequence of the sample size and due to outliers in our study cohort.

This study had some limitations. Our wb-MRI protocol included a contrast-enhanced T1w fs VIBE sequence but no pelvic DCE imaging. Even though the study by Panebianco et al. indicated that the combination of high-resolution pelvic T2w and DWI offers high accuracy comparable to that of T2w and DCE in the detection of local recurrences [16], detectability might have been improved by adding a DCE sequence to the MRI protocol. Another limitation was the relatively small patient cohort included. Nevertheless, as the first prospective study to compare wb-MRI and ^{68}Ga-PSMA PET/CT for the detection of biochemical recurrence of Pca, the data presented should encourage further studies including larger patient cohorts. Furthermore, we used a composite reference standard based on histopathological sampling, follow-up imaging, changes in PSA levels after salvage irradiation, and clinical information to define the nature of lesions. While this composite reference standard might be considered slightly inferior to histopathological sampling alone, it is in line with previous studies, ethical principles, and cancer management guidelines, which do not permit the sampling of all detected lesions [39]. Also, some authors have suggested that DWI b-values higher than b-1,000, as used in this study, should be used for prostate imaging. However, while studies have shown that higher b-values can increase Pca visibility in local staging of the primary tumour, there is no clear evidence providing guidance for the imaging of recurrent disease following radical prostatectomy [40]. However, it cannot be excluded that the detectability of local recurrences might have been improved if higher b-values of >1,500 had been used.

In conclusion, our results underscore the excellent performance of ^{68}Ga-PSMA PET/CT for whole-body staging of Pca patients with biochemical recurrence after radical prostatectomy. Wb-MRI provides a significantly lower lesion detection rate and inferior diagnostic confidence compared with ^{68}Ga-PSMA PET/CT. ^{68}Ga-PSMA PET/CT was superior on a per-patient basis, enabling the localization of disease recurrence in significantly more patients than wb-MRI. In patients with biochemical recurrence and low PSA levels, wb-MRI carries a considerable risk of missing small lymph node metastases.

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Compliance with ethical standards

Ethical approval All procedures performed were in accordance with the ethical standards of the institutional research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments.

Conflicts of interest None.

Informed consent Informed consent was obtained from all individual participants included in the study.

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