Review Article

The Impact of 68Ga-PSMA PET/CT and PET/MRI on the Management of Prostate Cancer

Manuela A. Hoffmann, Helmut J. Wieler, Christian Baues, Nicholas J. Kuntz, Ines Richardsen, and Mathias Schreckenberger

Prostate-specific membrane antigen (PSMA) is a transmembrane protein with significantly increased expression in the cells and metastases of prostate carcinoma (CaP). PSMA-expression correlates with higher serum levels of prostate-specific antigen (PSA) and a higher Gleason score (GS). This finding has led to the development of novel imaging modalities such as 68Ga-/18F-labeled PSMA positron emission tomography/computed tomography (PET/CT) and positron emission tomography/magnetic resonance imaging (PET/MRI). This article reviews the literature pertaining to various new imaging technologies for the management of CaP. PSMA positron emission tomography/computed tomography appears to be an excellent diagnostic tool, that may drastically impact the management of a large number of patients with primary and recurrent CaP.   UROLOGY 130: 1−12, 2019. © 2019 Elsevier Inc.

Prostate carcinoma (CaP) is the most common malignant tumor in men worldwide[1] with annual age-adjusted incidence rates of 85.6 (North America) and 59.3 (Europe) per 100.000, respectively.[2] However, the clinical course among CaP patients is extremely heterogeneous, ranging from indolent and innocuous to aggressive and lethal. Therefore, an accurate assessment of tumor characteristics is crucial for appropriate treatment.

Unfortunately, current method of assessing clinical risk and subsequent management may be outdated or inaccurate in certain situations. Multiple studies have demonstrated shortcomings in the current methods of clinically assessing CaP patients using PSA, clinical stage (cT), and biopsy-Gleason score (bGS), as first described by D'Amico in 1998.[3] For example, upstaging and upgrading occur in more than one-third of cases.[4] The poor relationship between clinical parameters and pathologic findings remains a constant challenge. Therefore, new tools are needed to better define cT and guide treatment options.

OBJECTIVE

To provide an updated review of the literature regarding the role of PSMAPET/CT and PET/MRI for the diagnostic evaluation of primary and recurrent CaP.

MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING (mpMRI)

Despite high false positive and negative rates, the current EAU-ESTRO-SIOG-Guidelines recommend transrectal ultrasound-guided biopsy (TRUS-guided bp) as the standard of care, for the diagnosis of CaP.[5] Furthermore, it is widely accepted that, in very advanced cases, TRUS imaging can only identify actual sites of disease. More recently, MRI has clearly been established as the best available imaging technique for identifying lesions that are likely to be CaP. Although T_2-weighted has been the mainstay of prostate MRI, it is generally nonspecific for malignancy, as the characteristic low signal intensity is also associated with hyperplasia, prostatitis or scarring. As such, mpMRI has become the gold standard for prostate imaging and complements T_2-weighted images with diffusion weighted and dynamic contrast enhanced to improve diagnostic accuracy.

For detecting high-grade lesions the negative predictive value and positive predictive value for mpMRI ranges between 63%-98% and 34%-68%, respectively.[6] With increasing frequency, many centers are performing mpMRI, even prior to an initial prostate biopsy.[7] Additionally, when combining mpMRI with MRI-ultrasound-fusion-guided biopsy (mpMRI-US-guided bp), the accuracy appears to improve further.[7]

Oberlin et al published a study of 231 patients and reported increased cancer detection rates overall, as well

as for high-grade lesions, with mpMRI-US-guided bp compared with both cognitive-registration and conventional TRUS-guided bp.[8]

The updated version of the Prostate Imaging Reporting and Data System (PI-RADSv2)[9] will improve interobserver variability in the definition of positive and negative findings.

PSMA

In recent years there have been several radiopharmaceuticals that have shown promise in CaP imaging. These include for example 18F-/11C-Choline, 11C-Acetate, 18F-Fluciclovine (FACBC) and 18F-16ß-fluoro-5α-dihydrotestosterone (FHDT).

However, none of these appear to hold as much potential, on a worldwide scope, as the introduction of PSMA into the diagnostic repertoire.[10]

PSMA is a membrane-bound surface enzyme, expressed in several tissues including small intestine, proximal renal tubules, and salivary glands. Additionally, due to the neovascularization process, it may be found in the tumor-associated blood vessels of some malignant tissues, including intestinal, renal, lung, and breast cancers.[11]

By comparison, PSMA expression by CaP cells is between 100 and 1000 times higher than these tissues.[12]

Due to these unique characteristics, PSMA represents an excellent target for binding radiolabeled ligands. The spectrum ranges from low molecular weight enzyme inhibitors to macromolecules such as monoclonal antibodies.

PSMA as a cell surface enzyme aids in catalyzing a reaction necessary for folate absorption from the gastrointestinal tract. However, the physiological basis of high PSMA-expression in CaP cells is not fully understood. Some studies suggest that a folate-dependent growth advantage of PSMA expressed cells may play a role in this context.[13] Due to the potential therapeutic relevance of such compounds, in addition to the already mentioned anti-PSMA antibodies, low-molecular weight PSMA inhibitors for PSMA targeting have also been developed and work very successfully.

In particular, urea compounds which carry aromatic radicals at a certain distance from the binding motif (interaction with lipophilic binding pocket)[12] show high affinity and specific binding to PSMA.

Currently, the most widely used radiopharmaceutical in PET diagnostic imaging for CaP is 68Ga-PSMA-HBED-CC.[14] Several properties of this compound allow rapid and accurate radiolabeling, a sufficiently long half life (68 minutes), as well as readily available nuclides (68Ge/68Ga-Generator) and synthesis modules. The 68Ga-PSMA-HBED-CC PET/CT has been shown to detect primary tumors as well as lymph nodes (LNs), soft tissue, and bone metastases with high sensitivity and specificity. In fact, we have shown previously that 68Ga-PSMA-11 PET/CT could distinguish between low- and high-grade carcinoma in primary CaP with a sensitivity of 84%, and specificity of 100%.[15]

Increasingly, alternative PSMA targeted tracers, such as the radiofluorinated PSMA-inhibitor (N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-[18F]fluorobenzyl-L-cysteine, [18F]DCFBC have been used clinically.[16] By comparison to 68Ga, 18F has a half life of 110 minutes, making it more favorable for shipping from the production site. In addition, 18F has a lower positron-energy than 68Ga, which results in moderately higher resolution and lower radiation exposure for the patient. Although promising, there is currently very limited data on the efficacy of 18F-labeled PSMA ligands in a clinical setting. Of note, there are 2 other potential ligands in the clinical introduction phase, 2-(3-[1-carboxy-5-[(6-[18F]fluoro-pyridine-3-carbonyl)-amino]-pentyl]-ureido)-pentanedioic acid, [18F]DCFPyL[17] and [18F]PSMA-1007.[18]

PRIMARY CAP—"PRIMARY IMAGING"

MpMRI has made a major impact on CaP management in the last decade. It is hypothesized that mpMRI provides more accurate initial staging, with an upstaging rate of 31% when used in this setting.[19]

In addition, due to more accurate clinical staging, mpMRI has demonstrated usefulness in surgical planning, especially when a nerve-sparing approach is desirable. Routine use of mpMRI, however, is still limited by its poor specificity for the differentiation of "significant" from "indolent" CaP.[20] Furthermore, the sensitivity and specificity of mpMRI can range between 22%-85% and 50%-99% respectively, depending on technical variables and the study population. Therefore, there is clearly still a demand for improved imaging methods to more accurately identify CaP.

As tumor grade and GS also play an important role in treatment decisions, it is important that the new imaging can distinguish aggressive from indolent disease. It is known that when using systematic TRUS-guided bp the GS is underestimated when compared to the "true" GS from prostatectomy in up to 30% of patients.[21] Epstein et al reported that patients with a bGS = 7 showed a higher rate of agreement with final pathology compared with patients with a bGS = 6.[22]

It is hoped that the accuracy of the true GS is improved by performing 68Ga-PSMA PET/CT and/or PET/MRI in primary staging (Table 1). However it is rarely used in the evaluation of patients with localized CaP. Also, other radiotracers like 11C-Acetate or 11C-Choline have not demonstrated sufficiently high specificity to justify routine imaging of organ-confined disease.[23]

However, as PSMA in comparison to Choline-derivates has shown a higher specificity to CaP cells,[15] this combination of functional and anatomic hybrid imaging could be a breakthrough with implications for the diagnosis and treatment of primary, recurrent, and metastatic CaP.

Sathekge et al reported clearly visible primary prostate tumors in 93/95 patients with 68Ga-PSMA PET/CT imaging[24] (Fig. 1) and others have reported a low false

Table 1. Characteristics of selected studies investigating the role of PSMA PET/CT and PET/MRI to detect primary and recurrent CaP and to change management.

Population	Reference	Study type	Aim	Tracer	N	Results
Primary CaP	Hoffmann et al[15]	Retrospective	Diagnostic performance of PSMA PET/CT to detect significant CaP. Comparison with the histopathologic Gleason score (GS) of biopsies.	68Ga-PSMA -11 + comparison with 18F-Fluoroethyl choline (18FEC)	25	68Ga-PSMA-11 PET/CT was able to distinguish between GS $\leq$7a/$\geq$7b with a sensitivity of 84%, specificity of 100%, NPV 67% + efficiency 88% (P <0.001). + Comparison with 18FEC:sensitivity of 61% , specificity of 92% , NPV 50% + efficiency 70% (P =0.01).
Primary metastatic CaP	Cho et al[16]	Retrospective	Tumor detection of DCFBC PET/CT in patients with metastatic prostate cancer.	18F-DCFBC	5	Thirty-two PET-positive suspected metastatic sites were identified, with 21 concordant on both PET and conventional imaging for abnormal findings compatible with metastatic disease. Of the 11 PET-positive sites not identified on conventional imaging, most were within the bone and could be considered suggestive for the detection of early bone metastases.
Primary + recurrent CaP	Li et al[17]	Retrospective	Semiquantitative parameters in PSMA PET: variability in normal-organ uptake. The coefficient of variation (COV) for each organ was calculated.	18F-DCFPyL	64	The COV of SUV_{mean} and SUL_{mean} was lower in the liver (13.8%,14.5%) than in any other organ and was less than the comparable COV for 18F-FDG PET. The COV of SUV_{mean} and SUL_{mean} in the 3-cm sphere in the liver was also low and similar to the variability in the whole liver (14.2%,14.7%).
Primary CaP	Kesch et al[18]	Retrospective	Comparison of PSMA PET/CT, mpMRI + RP.	18F-PSMA-1007	10	PET/CT: NPV of 68%/91%, accuracy of 75%/93%; mpMRI: NPV of 88%/91%, accuracy of 73%/87% for total/near-total agreement analysis. Retrospective combination of mpMRI + PET/CT: accuracy of 81% for total and 93% for near-total agreement.
Primary CaP	Giesel et al[42]	Retrospective	Comparison of 18F-PSMA-1007 with 68Ga-PSMA-11 PET/CT.	18F-PSMA-1007	10 (patients) + 3 (volunteers)	18F-PSMA-1007 performs comparably to 68Ga-PSMA-11. Advantages of 18F-PSMA-1007: longer half life, superior energy characteristics, nonurinary excretion.
Primary + recurrent CaP	Umbehr et al[23]	Review + meta-analysis	The role of choline PET + PET/ CT in CaP.	11C-Choline + 18F-Fluorocholine	Staging: 10 studies, n = 637. Restaging: 12 studies, n = 1055	Staging: sensitivity, specificity, diagnostic odds ratio (DOR) of 84% (95% CI 68%-93%), 79% (95% CI 53%-93%) + 20.4 (95% CI 9.9-42.0). Restaging: sensitivity, specificity, DOR of 85% (95% CI 79%-89%), 88% (95% CI 73%-95%) + 41.4 (95% CI 19.7-86.8).

Table 1. Continued

Population	Reference	Study type	Aim	Tracer	N	Results
Primary CaP	Sathekge et al[24]	Prospective	Preliminary results on differences in primary staging (PSMA PET/CT) between black (BSAs) and white (WSAs) South Africans.	68Ga-PSMA-11	95	Ninety-three out of 95 patients where readily identified on 68Ga-PSMA-11 PET/CT imaging. SUVmax values proved significantly higher in BSAs compared to WSAs: 11.9 vs 4.38 (P =0 .004). GS normalized median SUVmax values proved 2.5 times higher in BSAs compared to WSAs (P =0.005).
Primary CaP	Uprimny et al[25]	Retrospective	Determination whether a correlation exists between the primary tumor-related PSMA-accumulation + GS or PSA.	68Ga-PSMA-11	90	Eighty-two patients (91.1%) demonstrated pathologic tracer accumulation in primary tumor and physiologic tracer uptake in normal prostate tissue (median SUVmax: 12.5 vs 3.9). Tumors with GS of 6, 7a (3 + 4) and 7b (4 + 3) showed significantly lower PSMA-uptake (median SUVmax: 5.9, 8.3, 8.2) compared to GS >7 (median SUVmax: 21.2; P <0.001). PSA ≥10.0 ng/mL exhibited significantly higher uptake than PSA <10.0 ng/mL (median SUVmax: 17.6 vs 7.7; P <0.001).
Primary CaP	Sachpekidis et al[26]	Retrospective	Evaluation of the pharmacokinetics + biodistribution by means of dynamic PSMA PET/CT.	68Ga-PSMA-11	24	23/24 patients were PSMA positive with a detection rate of 95.8%.
Primary CaP	Maurer et al[29]	Retrospective	Diagnostic efficacy of PSMA PET/MRI or PET/CT compared to conventional imaging (MRI or CT) for LN staging of CaP-patients.	68Ga-PSMA-11	130	PSMA PET: on patient-based analysis sensitivity, specificity + accuracy were 65.9%, 98.9% + 88.5%; MRI/CT: 43.9%, 85.4% + 72.3%. PSMA PET: on LN template-based analysis sensitivity, specificity + accuracy 68.3%, 99.1% + 95.2%; MRI/CT: 27.3%, 97.1% + 87.6%.
Primary CaP	Van Leeuwen et al[30]	Prospective	PSMA PET/CT for preoperative LN staging in CaP.	68Ga-PSMA-11	30	Patient analysis: sensitivity 64% for detection of LN metastases, specificity 95%, PPV 88%, NPV 82%. LN region-based analysis: sensitivity 56%, specificity 98%, PPV 90%, NPV 94%.
Primary + recurrent CaP	Herlemann et al[31]	Retrospective	PSMA PET/CT for preoperative LN staging in CaP.	68Ga-PSMA-11	34	Sensitivity, specificity, PPV, NPV for detection of LN metastases were 84%, 82%, 84%, 82% for PET + 65%, 76%, 75%, 67% for CT. PET was more accurate for LN staging compared with CT both at primary LN dissection (88% vs 75%) + secondary LN dissection (77% vs 65%).

Table 1. Continued

Population	Reference	Study type	Aim	Tracer	N	Results
Primary + recurrent CaP	Roach et al[32]	Prospective	Impact of PSMA PET/CT on Management Intent in CaP.	68Ga-PSMA-11	431	PSMA PET/CT led to change in planned management in 51%. Impact was greater in group of recurrent patients (62%) than primary staging (21%). PSMA PET/CT revealed unsuspected disease in the prostate bed in 27% of patients, locoregional LNs in 39%, and distant metastatic disease in 16%.
Recurrent CaP	Van Leeuwen et al[34]	Retrospective	Examination of the detection rates of PSMA PET/CT + impact on management.	68Ga-PSMA-11	70	Detection rate: 54% (38/70 patients). Major management change in 20 patients (28.6%).
Recurrent CaP	Ceci et al[35]	Retrospective	Examination of the detection rates of PSMA PET/CT + association with PSA levels + PSA kinetics.	68Ga-PSMA-11	70	Detection rate: 74.2% (52/70 patients). Detection rate of pelvis lesions: 42.8%. Detection rate of distant lesions: 11.4%. PSA level ($P =0.017$) + PSA doubling time ($P =0.0001$) were significantly different between PET-positive + PET-negative patients.
Recurrent CaP	Afshar-Oromieh et al[14]	Retrospective	Diagnostic value of PSMA PET/CT in the diagnosis of recurrent CaP with histopathologic verification on a lesion-based + patient-based analysis.	68Ga-PSMA-11	42	Detection rate: 82.8%. Lesion-based analysis of sensitivity, specificity, NPV + PPV of 76.6%, 100%, 91.4% + 100%. Sensitivity on patient-based analysis: 88.1%.
Recurrent CaP	Verburg et al[36]	Retrospective	Examination of the relationship between extent of CaP + PSA, PSA doubling time, GS.	68Ga-PSMA-11	155	Detection rate: 44%,79%,89% (PSA $\leq$1, 1-2, $\geq$2 ng/mL). High PSA was associated with high rates of local CaP ($P <0.001$). Short PSA doubling time was associated with pelvic LN metastases ($P =0.026$). High GS was associated with more frequent pelvic LN metastases ($P =0.039$).
Recurrent CaP	Hope et al[37]	Prospective	Effect of PSMA PET/MRI or PET/CT on the intended management of CaP patients.	68Ga-PSMA-11	126	Detection rate: 82% (103/126 patients). Major management change in 67 patients (53.2%). Minor management change in 8 patients (6.4%).
Recurrent CaP	Grubmüller et al[39]	Retrospective	Diagnostic performance of PSMA PET/MRI or PET/CT + impact on therapeutic decision-making.	68Ga-PSMA-11	117	Detection rate: 65%, 85.7%, 85.7%, 100% (PSA 0.2- <0.5, 0.5- <1, 1- <2, $\geq$2 ng/mL). Management change in 74.6% of 67 patients with no suspicious correlates on MRI or CT; $P <0.001$: 86% of them considered for metastases-directed therapies.
Recurrent CaP	Afaq et al[40]	Retrospective	Impact of PSMA PET/CT on CaP management.	68Ga-PSMA-11	100	Management change in 39% (39/100 patients). Positive scan results ($P <0.001$) + higher PSA ($P =0.024$) were associated with management changes.

Table 1. Continued

Population	Reference	Study type	Aim	Tracer	N	Results
Recurrent CaP	Afshar-Oromieh et al[41]	Retrospective	Comparison of PSMA PET/CT and PET/MRI for the diagnosis of CaP.	68Ga-PSMA-11	20	PET/MRI advantages: different diagnostic sequences, higher contrast of lesions, higher resolution of MRI, lower radiation exposure. PET/MRI disadvantages: scatter correction was challenging; reduced PET-signal at the level of kidneys and around the urinary bladder in 15/20 patients, reduced SUV.
Recurrent CaP	Calais et al[44]	Retrospective	Impact of PSMA PET/CT on salvage radiotherapy.	68Ga-PSMA-11	270	Major impact in 52/270 patients (19%) of PSMA PET/CT on salvage radiotherapy planning (patients with PSA <1.0 ng/mL).
Recurrent CaP	Zschaeck et al[45]	Retrospective	Evaluation of intermediate-term outcome after PSMA PET/CT guided radiotherapy of CaP.	68Ga-PSMA-11	22	Management change in 77% of salvage radiotherapy patients after PSMA PET. Twenty-nine months median follow-up time: prolonged PSA responses below baseline in 14 of remaining 20 patients.
Recurrent CaP	Henkenberens et al[46]	Retrospective	Evaluation of PSMA PET/CT-based radiotherapy for LN metastases of CaP.	68Ga-PSMA-I&T	23	PSA level decreased in 22/23 patients (95.6%). Biochemical failure-free survival + time to initiation of systemic therapy at median follow-up (12.4 months): 95.6% + overall survival 100%.
Recurrent CaP	Emmett et al[47]	Retrospective	Treatment outcome from PSMA PET/CT-informed salvage radiotherapy of CaP. Prognostic value of negative PSMA PET/CT.	68Ga-PSMA-11	164	Overall treatment response in 71/99 patients (72%). Treatment response in 23/27 patients (85%) after negative PSMA PET/CT + salvage radiotherapy.
Primary + recurrent CaP	Han et al[48]	Review + meta-analysis	Impact of PSMA PET on the management of CaP.	68Ga-PSMA-11 + -I&T	15 studies, n = 1163	Management change in 54% (95% CI 47%-60%).
Recurrent CaP	Habl et al[49]	Retrospective	Evaluation of oligometastasized CaP treated with local stereotactic body radiotherapy of bone metastases after PET/CT.	68Ga-PSMA + 11C-Choline	15	22.5 months median follow-up time after radiotherapy. Median PSA-progression-free survival (PFS) 6-9 months. In 6/15 patients with PSA-decrease of at least factor 10: PSA-PFS >12 months + median PSA-PFS of 23.1 months.
Recurrent CaP	Calais et al[50]	Randomized prospective phase III trial	Evaluation of success rate/outcome of salvage radiotherapy of CaP with + + without planning based on PSMA PET/CT.	68Ga-PSMA-11	193	Results still pending. Primary endpoint: success rate of salvage radiotherapy measured as PSA-PFS after initiation of therapy. Patients will be followed until: 5 years after initiation, biochemical progression, metastases, additional salvage therapy, or death.

CaP, prostate carcinoma; CI, confidence interval; NPV, negative predictive value; PET/CT, positron emission tomography/computed tomography; PET/MRI, positron emission tomography/magnetic resonance imaging; PPV, positive predictive value; PSMA, prostate-specific membrane antigen.

Figure 1. 68Ga-PSMA PET/CT with evidence of a left-sided lesion with significantly increased PSMA-avidity (primary staging). The histopathologic findings confirmed a prostate carcinoma. PET/CT, positron emission tomography/computed tomography; PSMA, prostate-specific membrane antigen.

negative rate for primary tumor detection, ranging between 7% and 9%.[25]

As demonstrated previously, there appears to be a clear, and statistically significant correlation between 68Ga-PSMA uptake of primary CaP tumors and serum PSA.[26] This finding is further supported by earlier literature demonstrating elevated immunohistochemical expression and enzymatic activity of PSMA in advanced CaP.[27] The underlying reason for this finding is unclear and it is a topic for future investigation.

The diagnostic accuracy of 68Ga-PSMA PET/CT and/or 68Ga-PSMA PET/MRI remains to be seen, as only a limited number of studies have been published to date.

Addressing this issue is a much anticipated, prospective, multicenter trial comparing preoperative 68Ga-PSMA-11 PET/CT to histopathology following prostatectomy in high-risk patients currently underway.[28]

Uprimny et al[25] retrospectively evaluated the diagnostic efficacy of 68Ga-PSMA PET/CT imaging for primary staging in 90 patients with TRUS-guided bp-proven CaP and reported pathologic tracer accumulation in the primary tumor in 91% of their cohort. Additionally, there was a significant difference in the maximum standardized uptake value (SUVmax) of low- and intermediate-risk lesions (GS 6, 7a, 7b) compared to high-risk (GS>7) lesions (P <0.001), as well as for patients with higher PSA (≥10.0 ng/mL).[25]

Another major area where 68Ga-PSMA PET/CT has made a clinical impact is in the staging of LNs, especially of pelvic LNs. In a series of 130 consecutive patients with intermediate- to high-risk CaP, 68Ga-PSMA PET/CT or 68Ga-PSMA PET/MRI was performed prior to radical prostatectomy (RP) and pelvic LN dissection. The

sensitivity, specificity, and accuracy of 68Ga-PSMA PET were 65.9, 98.9, and 88.5% respectively compared to 43.9, 85.4 and 72.3% for CT or MRI alone in a patient-based analysis. The dissected LN template-based analysis showed a great advantage for 68Ga-PSMA PET compared to morphological imaging alone, especially in sensitivity (68.3 vs 27.3%).[29]

Additionally, a prospective study by Van Leeuwen et al showed that the size of the involved LNs correlated with detection on 68Ga-PSMA PET/CT imaging.[30]

In a study of 34 patients, Herlemann et al evaluated the accuracy of 68Ga-PSMA PET/CT for LN staging prior to LN dissection in intermediate- and high-risk CaP patients and also compared PET alone to CT alone. Detection rates, confirmed histologically, showed that 68Ga-PSMA PET was superior to CT for both primary LN metastases, (sensitivity 88% vs 75%) and recurrent LN metastases (sensitivity of 77% vs 65%).[31]

With improved staging accuracy, implementation of 68Ga-PSMA PET/CT has the potential to alter management significantly. In a prospective, multicenter study of 431 intermediate-/high-risk CaP patients undergoing primary staging, a change in management occurred in 21%, as a direct result of the findings on 68Ga-PSMA PET/CT and a 27% increase in the operative plan to include a LN dissection.[32] Furthermore, in this series, the ability of the imaging to alter management remained high even at low PSA values (<0.2 ng/mL), and was independent of both PSA and tumor grade.

To summarize, it appears that for the preoperative staging of CaP, 68Ga-PSMA PET/CT or 68Ga-PSMA PET/MRI is superior to standard imaging with CT or MRI alone, and has the potential to replace these modalities in future guidelines.

68GA-PSMA PET IMAGING IN PATIENTS WITH BIOCHEMICAL RECURRENCE

Following primary treatment of CaP, a rise in PSA may occur due to local, regional, or systemic recurrence, often several years prior to the development of clinical symptoms. Biochemical recurrence (BCR) following RP is defined as a PSA value of ≥0.2 ng/mL on 2 separate occasions.[33] Unfortunately, in this setting, it is well known that the diagnostic sensitivity of conventional imaging is quite poor, especially for low PSA values (<10 ng/mL).

Hybrid PET (PET/CT, PET/MRI) has improved diagnostic accuracy in this setting, as it facilitates anatomic localization of PET-positive findings, and provides additional morphologic information (Table 1). In a prospective study of 300 patients, Van Leeuwen et al performed 68Ga-PSMA PET/CT imaging on patients with BCR following RP, who were considered for salvage radiotherapy (RT). Seventy patients were included with a PSA <1.0 ng/mL, and a normal CT scan. They demonstrated pathologic 68Ga-PSMA uptake in 54% of their cohort, which resulted in a major management change in 28.6%. This includes enlarging the volume of the radiation template to include pelvic nodes, shrinking the radiation field to exclude the prostate fossa, adding adjuvant androgen deprivation therapy, or converting to a salvage LN dissection. In a well-defined cohort, this study demonstrates the robust ability of 68Ga-PSMA PET/CT to correctly stage, and alter management, even at low PSA levels <0.5 ng/mL.[34]

In a retrospective study published by Ceci et al 68Ga-PSMA PET/CT was positive in 52/70 (74.2%) of patients with BCR. The lesions were confined to the pelvis in 42.8% compared to distant metastases in 11.4%, and both local and systemic lesions in 20%. Not surprisingly, the significant predictors of a PET-positive lesion included the PSA-level and PSA-doubling time.[35]

In a similar, retrospective analysis of 319 BCR-patients (42 with histologic verification), Afshar et al reported at least one PET-positive lesion in 82.8%.[14] They also found PSA to be a predictor of test positivity, however, this was not the case for GS and PSA-doubling time. A lesion-based analysis of sensitivity, specificity, negative predictive value and positive predictive value revealed values of 76.6%, 100%, 91%, and 100%. A patient-based analysis revealed a sensitivity of 88.1%. Although follow-up data was limited (116/319 patients), 50 patients went on to have local salvage therapy, suggesting a potential benefit of 68Ga-PSMA PET/CT in delaying systemic treatments, and this improving quality of life in patients without evidence of systemic disease. Another interesting finding of this study was the significant number of PET-positive lesions in patients with very low PSA levels, including 8/17 patients with PSA ≤0.2 ng/mL, 5/10 patients with PSA 0.21-0.5 ng/mL and 14/24 patients with PSA 0.51-1.0 ng/mL. In the most challenging group, with PSA <0.2 ng/mL, GS was significantly higher in patients with pathologic 68Ga-PSMA PET/CT-results compared to patients without pathologic 68Ga-PSMA PET/CT-results.[14]

Other retrospective studies have demonstrated similar results with low PSA values. In a study of 155 patients, Verburg et al reported 68Ga-PSMA PET/CT PSMA-avid lesions in 44%, 79%, and 89% of BCR-patients with PSA values of ≤1, 1-2 and ≥2 ng/mL, respectively.[36] Patients with high PSA levels showed significantly higher rates of local recurrences, extrapelvic LN and bone metastases. As in the Ceci et al publication, a shorter PSA-doubling time was significantly associated with pelvic LNs, extrapelvic LNs, bone and visceral metastases.[35] A high GS was associated with more frequent pelvic LN metastases (Figs. 2 and 3), whereas the PSA-doubling time was the only independent marker of bone metastases. In the group with PSA levels >1 ng/mL, they found pelvic LN metastases (cN1) in 10/27 patients (37%). Hope et al reported positive 68Ga-PSMA PET/CT imaging in 82% of their cohort of 126 BCR-patients, including 58%, 64%, and 65% of patients with a PSA <0.2, 0.2-0.5 and 0.5-1.0 ng/mL, respectively.[37]

While the current EAU guidelines recommend against imaging with Choline-based PET and other imaging modalities such as MRI or CT in patients with PSA levels <1-2 ng/mL, both of these studies demonstrated that a considerable proportion of patients with PSA levels <1 ng/mL yielded clinically useful diagnostic results. Such findings could have significant clinical implications on treatment decisions, for example switching to pelvic lymphadenectomy instead of salvage RT, for BCR-patients with PSA ≤0.5 ng/mL.[38] In the latter study, a major change in management was reported in 53% of patients, most commonly changing from systemic therapy to focal targeted therapy such as RT.[37] The results also showed that there was less change in management of patients after RP than in those treated with RT previously. It is unknown, however, if this change in management resulted in improved outcomes, which is the major limitation in many retrospective studies.

A study by Grubmüller et al helps to highlight the enhanced ability for 68Ga-PSMA PET to detect distant sites of disease compared to standard imaging with just CT or MRI.[39] This retrospective series evaluated 117 BCR-patients following RP who had a 68Ga-PSMA PET/CT (n = 46) or PET/MRI (n = 71). The detection rates were similar to other studies at 85.5% (100/117) with a median PSA of 1.04 ng/mL. Interestingly, PSMA PET imaging (either PET/CT or PET/MRI) identified PSMA-positive lesions in 67 patients that were otherwise negative on CT or MRI alone. This reportedly resulted in a statistically significant change in the therapeutic strategy, in nearly 75% of patients (P <0.001).[39] This includes changing to metastases-directed therapy in some cases, such as salvage lymphadenectomy in 13 patients (26%) and PSMA PET-directed RT in 30 patients (60%). In other cases, it prevented focal therapy when the patient was unlikely to benefit, such as using combined chemohormonal therapy due to multiple tumor sites in 5 patients, and watchful waiting in 2 patients, that would have otherwise been treated with androgen deprivation therapy and RT.
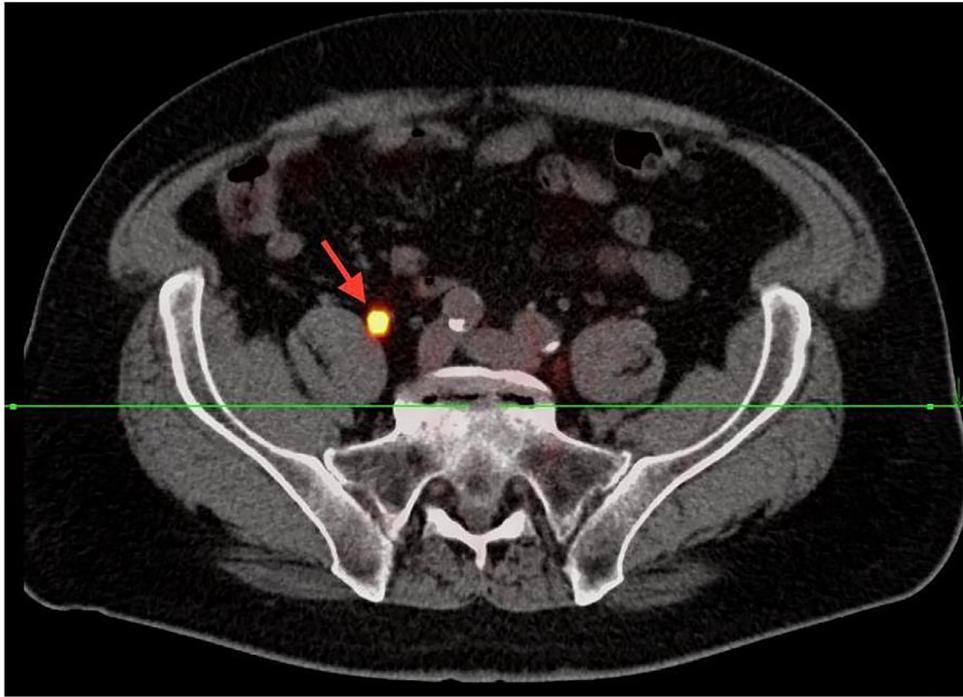
Figure 2. 68Ga-PSMA PET/CT with markedly increased PSMA-avidity (SUVmax = 6.8) in the right parailiacal region.

In general, the detection of the actual sites of disease has important implications for patient management, allows for a more direct treatment approach, and avoids treatment of sites with no disease.

Other studies have also demonstrated that management is altered in a significant number of patients in the BCR setting due to PSMA PET/CT imaging. A large, multicenter trial of 431 patients resulted in a management change in 62% of their cohort, due to identification of PSMA-positive lesions, previously undetected by conventional imaging.[32] Similarly, Afaq et al[40] reported a management change in 39% of BCR patients, most of which (50%)

Figure 3. CT native detects a right parailiacal lymph node (4 mm), which was assessed as unremarkable. For comparison with the corresponding PET/CT: see Figure 2.

were following RT, as opposed to RP (33.8%). Higher PSA levels were associated with management changes (P =0.024), while Gleason grade and tumor stage were not. The proportion of PET/CT scans with positive results in this study (47%) was significantly lower than the proportion described by Afshar-Oromieh et al (83%)[14] and Ceci et al (74%).[35] There was a large variety of changes from the initial to the revised management strategy in 39 patients. The largest subgroup was the patient group where PSA surveillance was originally intended (n = 18). In 2 patients, the initial plan was high intensity focused US, which was changed to RP.

In general, the detection of additional sites of disease has important implications for patient management as recurrence localized to the tumor bed can potentially be treated with curative and directed stereotactic radiation therapy, while oligometastatic cancer can be treated with targeted therapies such as stereotactic body radiation therapy or LN dissection. On the other hand, patients with diffuse metastatic disease should start systemic treatment and be spared RT to the prostatic fossa.

One of the major drawbacks of 68Ga-PSMA, and other PSMA-targeting PET-tracers is the accumulation in the urinary tract and bladder, which in effect, reduces the diagnostic confidence in the surrounding tissue to the halo artifact effect,[41] a common problem in PET/MRI-devices. However, the introduction of future tracers such as 18F-PSMA-1007 due to its substantially reduced urinary clearance, should minimize this, especially with PET/MRI devices.[42]

Additionally, its superior energy characteristics, 18F reduces blurring effects leading to a higher spatial resolution, and the longer half life (110 minutes in comparison to 68Ga with 68 minutes) makes it easier to distribute from a central processing facility.[42]

Currently there is very limited data on the clinical efficacy of 18F-PSMA PET imaging, or its comparison to 68Ga-PSMA, however the preliminary results appear promising.[42] Further prospective trials, evaluating 18F-labeled PSMA tracers are needed prior to widespread clinical implementation.

SALVAGE RADIOTHERAPY

PSMA PET/CT has the potential to significantly change the therapy of prostate carcinoma in a meaningful way, perhaps no more evident than in the setting of biochemical relapse.

After RP, salvage RT of the prostate fossa is the most common salvage therapy following biochemical recurrence and nearly 50% achieve complete remission. Despite salvage RT of the prostate fossa being the standard approach, the supporting evidence for its use is surprisingly limited to few, nonrandomized, retrospective studies from more than a decade ago.[43] In most cases, salvage RT is indicated following a sustained PSA rise following RP, assuming staging imaging remains negative for systemic metastases. In the absence of sufficient imaging

options, and a high probability of local recurrences, Radiation Oncologists often defined their target volume as the prostate fossa. However, this entire treatment paradigm come into question, given the promising data of PSMA PET imaging, and its ability to detect and localize the areas of relapses, which may or may not be a local recurrence, as well as regional and/or distant metastases. In this setting Calais et al demonstrated that with BCR and PSA <1.0 ng/mL, nearly 20% of suspicious lesions on 68Ga-PSMA PET/CT would not have been integrated into the target volume of a standard salvage radiation template.[44] These missed areas would likely have resulted in treatment failures. With new, innovative radio-oncological equipment, it becomes possible to treat the now localized recurrences with precision. In this context, an important question is: If a local recurrence in a LN metastasis can be detected, should the entire lymphatic bed be irradiated or just the (presumed) local recurrence? Only a few studies have evaluated RT of localized PSMA PET positive recurrences and there have been no reports about stereotactic RT. However, some authors have used the information from PSMA PET/CT in the context of salvage RT, although these studies are retrospective, monocentric and include a small number of patients. Nevertheless some studies have at least partly answered important questions even if long-term follow-up data are lacking. Zschaeck et al reported one possible method of modification of the RT field by administering a simultaneous integrated boost of the PET-positive lesions, in addition to the prostate fossa,[45] or in a sense, a type of dose escalation in the RT plan. This modification was implemented in 77% of their cohort of BCR-patients following RP.[45] Conversely, Henkenberens et al irradiated only the PSMA-positive LN metastases with standard fractionated RT up to 50.4-54 Gy.[46] They reported low toxicities, good local control and a PSA decrease in almost every patient.[46] However both studies, reported low toxicities with durable PSA responses.

A prospective randomized study is necessary to answer the question of whether local RT with a corresponding reduction of the treatment toxicity should be preferred to radiation of the entire prostatic fossa and possibly the lymphatic bed.

There also appears to be a benefit to the patient when the PSMA PET is negative, as the most likely site of recurrence, by default, is in the prostatic fossa. In this setting, Emmet et al demonstrated an 85% increase in the effectiveness of salvage RT when the pretreatment PSMA PET was negative.[47]

A current meta-analysis evaluated the impact of PSMA PET in the management of CaP.[48] The authors focused primarily on BCR, and the proportional changes among treatment options and concluded that there was a shift toward local treatment.

The current body of literature pertaining to PSMA PET/CT or PET/MRI is primarily focused on the efficacy in various clinical settings, and its impact on treatment decisions. However, there is very little data pertaining to the outcomes of the subsequent treatment decisions that

result from such imaging. It remains to be seen how RT protocols will change with the development of localization studies, and if local RT will take the place of prostatic fossa and lymphatic chains, in the salvage setting.

It could be argued that focal treatment of PSMA PET positive lesions, although less morbid, may not treat the occult, microscopic foci of disease that would have been managed with a larger RT field. But in theory, local radiation should at least reduce the PSA level and delay the onset of androgen deprivation therapy. As demonstrated in other oligo-metastatic diseases, patients seem to benefit from local treatment of metastases, even if they are not universally cured.[49]

Clearly more research is needed on the topic of image-guided, individually tailored treatment, and this data will certainly be of significant importance moving forward.

With all positive new developments, and growing options in the treatment of localized recurrence of CaP, the importance of irradiation of the prostatic fossa should not be forgotten or underestimated. And here too, PSMA PET/CT and PSMA PET/MRI can make a very positive contribution.

68Ga-PSMA PET/CT and PET/MRI are likely to become the standard imaging modalities in the staging of intermediate-to-high-risk primary CaP. Both methods have become, in a relatively short period of time, the gold standard for restaging recurrent CaP in those countries and clinical centers where these imaging modalities are available. Their potential to facilitate more accurate prostatic biopsy, to guide therapy and to monitor the therapeutic response to all treatment modalities is currently under intense investigation (Table 1).

The long-term outcome of altering treatment planning based on 68Ga-PSMA PET/CT or PET/MRI has not yet been addressed in any longitudinal studies. Further studies, that for example, assess the long-term outcomes of patients with negative PSMA-PET studies, on which clinicians elect not to treat, and the possibility of randomized trials of observation vs salvage RT in this setting, are desperately needed. The first randomized prospective phase 3 trial to prove outcome after salvage RT is being carried out by the UCLA Nuclear Medicine research team at this time.[50]

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