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THERANOSTICS AND PRECISION MEDICINE SPECIAL FEATURE: REVIEW ARTICLE

Theranostics of prostate cancer: from molecular imaging to precision molecular radiotherapy targeting the prostate specific membrane antigen

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ABSTRACT

Alterations at the molecular level are a hallmark of cancer. Prostate cancer is associated with the overexpression of prostate-specific membrane antigen (PSMA) in a majority of cases, predominantly in advanced tumors, increasing with the grade or Gleason's score. PSMA can be selectively targeted using radiolabeled PSMA ligands. These small molecules binding the PSMA can be radiolabeled with γ-emitters like ^{99m}Tc and ^{111}In or positron emitters like ^{68}Ga and ^{18}F for diagnosis as well as with their theranostic pairs such as ^{177}Lu (β-emitter) or ^{225}Ac (α-emitter) for therapy. This review summarizes the theranostic role of PSMA ligands for molecular imaging and targeted molecular radiotherapy, moving towards precision oncology.

INTRODUCTION

Theranostics in the context of nuclear medicine aims to identify the appropriate molecular targets in neoplasms, so that the optimal ligands and radionuclides with favorable labelling chemistry can be selected for personalized management of disease, taking into consideration the specific patient.[1,2] Personalized medicine improves tailoring and timing of preventive and therapeutic measures by utilizing biological information and biomarkers at the level of molecular disease pathways, genetics, proteomics, and metabolomics.[3] Theranostics using PET/CT (or PET/MRI) as an *in vivo* companion diagnostic for decision-making and monitoring of therapy with radiolabeled ligands, is part and parcel of personalized medicine.[2,4] The successful application of ^{68}Ga for diagnosis, and ^{177}Lu and ^{90}Y for radionuclide therapy using the same peptide for targeting somatostatin receptors in neuroendocrine neoplasms, has paved the way to other indications of theranostics.[1] The recently published results of the randomized controlled NETTER-1 trial revealed a fivefold improvement in response with ^{177}Lu-DOTATATE (Lutathera™) compared with conventional treatment of gastroenteropancreatic neuroendocrine tumors.[4]

Using a ligand targeting, the prostate-specific membrane antigen (PSMA), which is overexpressed in a majority of prostate cancer (PCa) cells, enables effective molecular imaging and targeted radioligand therapy of PCa, with acceptable toxicity. The PSMA ligand labeled with a positron emitter like ^{68}Ga/^{18}F helps not only to select patients who are likely to benefit from the PSMA-radioligand therapy (PRLT) using later on the same ligand labeled with a βbeta emitter like ^{177}Lu or an α-emitter like ^{225}Ac, but also enables detection of recurrent and metastatic disease (staging), assessment of molecular response to therapy, and long-term follow-up after the initial diagnosis. In addition, pre- and/or post-therapeutic dosimetry ensures the optimum balance between risk and therapeutic benefit, and helps to predict toxicity.[1]

PCa is the second most common cancer in males worldwide and causes an estimated 90,000 deaths per year in Europe.[5] The primary treatment for localized PCa is radical prostatectomy, following which salvage radiotherapy and lymphadenectomy are the options with a curative approach in patients with residual or recurrent PCa.[6] However, 20–40% of the clinically localized PCa patients will present with rising prostatic-specific antigen (PSA) after surgery, which is referred to as biochemical recurrence.[7–9] In fact, about 60% of patients with stage pT3 PCa have biochemical recurrence within 5 years of surgery, indicative of local tumor progression and/or metastatic disease. The appropriate time point to initiate a multimodal therapy is vital,

since the course of biochemical recurrence after surgery varies, and does not necessarily correlate with clinical recurrence.[10,11]

The conventional imaging modalities like CT and MRI have a limited role, especially when the PSA levels are low.[12] Indeed, the current guidelines do not recommend additional imaging for staging low-risk PCa due to the poor accuracy of conventional imaging, *e.g.* in detecting small lymph nodes.[13] Pelvic multiparametric MRI and abdominopelvic cross-sectional imaging are recommended in the staging of high-risk localized or locally advanced PCa. Multiparametric MRI has a high accuracy in PCa with higher Gleason score and a larger volume of disease, and is also used to guide biopsy.[14,15] However, its performance is limited in the identification of extraprostatic extension of disease. The guidelines recommend bone scan for the screening of metastases.[13] But this is constrained, especially, by a lack of specificity and the inherent inability to detect extraosseous disease.

Androgen deprivation therapy is an established treatment option after salvage surgery or radiotherapy. However, at some point of time, the disease continues to progress with rise of PSA under hormone therapy, indicating castration resistance. Metastatic castration-resistant prostate cancer (mCRPC) has a poor prognosis and is responsible for nearly all PCa-specific deaths.[16] Abiraterone acetate and enzalutamide, targeting the androgen receptor (AR) signaling, have demonstrated encouraging results in mCRPC.[17–19] Randomized controlled clinical trials in mCRPC have demonstrated a small benefit in the overall survival (OS) with taxane-based chemotherapy and the therapy of skeletal metastases with the α-emitter ^{223}Radium.[20–23]

MOLECULAR IMAGING

The unmet need in PCa has been to identify local recurrence, lymph node, bone and visceral metastases with high sensitivity and specificity in patients with biochemical relapse after initial curative therapy. Molecular imaging with PET/CT or PET/MRI has a great potential to counter the drawbacks of conventional imaging and consequently improve the overall diagnostic accuracy.

^{18}F-FDG PET/CT has limitations in the evaluation of PCa.[24] However, a recent study concluded that assessment of glycolytic activity in addition to the AR expression, had prognostic implications in mCRPC.[25] Most of the mCRPC lesions express ARs, consistent with initial benefit of androgen receptor-signaling inhibitors on a patient basis, 49% had at least one FDG-positive lesion, the imaging phenotype with the most negative effect on survival, possibly due to androgen receptor-signaling inhibitors resistance.[25] ^{11}C-choline PET/CT has demonstrated a potential in the therapy response assessment after chemotherapy in mCRPC.[26] A meta-analysis revealed a pooled detection rate of 62% for biochemical recurrence in PCa, although the detectability was poor when the PSA levels were lower (<2 ng ml^{-1}).[27] Primary staging with choline PET/CT is limited by the non-specific uptake in benign prostatic hyperplasia.[28]

PSMA is a Type II transmembrane glycoprotein with an intracellular, transmembrane, and an extensive extracellular domain, which is overexpressed in PCa, especially in poorly differentiated mCRPC.[29–31] Radiolabeled monoclonal PSMA antibodies such as J591 have been demonstrated to have a role in PCa.[32] However, their long half-life and poor tumor penetration represent a significant limitation of monoclonal antibodies in imaging and therapy. On the other hand, the ^{68}Ga labeled urea-based PSMA inhibitors have nearly ideal pharmacokientics.[30,33] The major uses of PET/CT using PSMA ligands in PCa are: detection of biochemical recurrence, primary staging, radioguided surgery, selection of patients and monitoring the response/follow up after PRLT. Most of the studies reported so far have been using ^{68}Ga-PSMA PET/CT.

The pooled detection rates of biochemical recurrence for ^{68}Ga-PSMA-11 PET/CT in a meta-analysis were found to be 58 and 76% for PSA levels of 0.2–1 and 1–2 ng ml^{-1}, respectively.[34] Afshar-Oromieh et al reported a detection rate of 88.1% on a patient basis in a retrospective study of 319 patients, with a sensitivity of 76.6% and a specificity of 100%.[35] In a head-to-head comparison with ^{11}C-/^{18}F-choline, ^{68}Ga-PSMA-11 demonstrated a superiority for the PET/CT detection of biochemical recurrence.[36–38] Many studies have revealed a higher detection rate for ^{68}Ga-PSMA-11 PET/CT than any other imaging modality for PSA levels less than 0.5 ng ml^{-1}.[39] This enables an early and effective salvage treatment modality, *e.g.* lymphadenectomy or radiotherapy.

^{18}F has lower mean positron energy than ^{68}Ga, resulting in a higher intrinsic spatial resolution. In first-in-human studies by the group of Pomper, the two ^{18}F-labeled tracers DCFBC and DCFPyL demonstrated a favorable dosimetry and biodistribution, as well as a superior efficiency for the detection of PCa.[40–43] ^{18}F-DCFPyL PET/CT revealed additional lesions in 3 of 14 patients (21.4%), who had either negative or inconclusive findings on ^{68}Ga-PSMA-11 PET/CT.[44] More recently, Giesel et al published their findings using a ^{18}F-labeled PSMA ligand PSMA-1007, demonstrating a lesion detectability as good as with ^{68}Ga-PSMA PET/CT.[45]

PSMA PET/CT plays an important role in the primary staging, especially the detection of lymph node and distant metastases. ^{68}Ga-PSMA-11 PET was found to be significantly better than cross-sectional imaging for lymph node staging in 130 patients with primary intermediate- to high-risk PCa.[46] The specificity was greater than 95%, which was also confirmed by another study in patients who underwent salvage lymphadenectomy.[47] The intraprostatic tumor could be localized by ^{68}Ga-PSMA-11 PET/CT, and the findings also correlated with histopathology.[48–50] The positive segments demonstrated a significantly higher uptake of ^{68}Ga-PSMA-11 than the negative segments.[48,49] Combination of ^{68}Ga-PSMA-11 PET and mpMRI in 53 intermediate-/high-risk patients revealed a significantly better performance than mpMRI or ^{68}Ga-PSMA-11 PET alone, in terms of sensitivity and specificity for localization of tumor.[51] Therefore, hybrid PET/mpMRI may enable an accurate image-guided biopsy of the most relevant area within the prostate.

^{68}Ga-PSMA PET/CT could have significant impact on the therapy planning, *e.g.* standard or extended lymph node

dissection and change in radiotherapy planning and systemic treatment (Figure 1).[52–54] Radioguided surgery is feasible using pre-operative labeling of lymph node metastases with a γ-emitting PSMA-ligand (*e.g.* ^{111}In-PSMA I&T), allowing detection and resection of very small metastatic lesions.[55,56]

PRECISION MOLECULAR RADIOTHERAPY USING PSMA LIGANDS

PRLT involves selective binding of a radioligand to PSMA, which is overexpressed in mCRPC, in order to increase tumor dose and to spare the normal tissue.[57] Internalization and retention within the tumor cell are essential mechanisms for the cell-killing effect of this molecular radiotherapy (also called endoradiotherapy), which has the advantage of selectively targeting multiple metastases.[58] PRLT is based on the principle of theranostics. The overexpression of PSMA in tumors can be confirmed by pre-therapeutic molecular imaging using ^{68}Ga-PSMA PET/CT (Figure 2). Therefore, we treat what we see. ^{177}Lu, being a γ-emitter, permits post-therapy imaging for the assessment of biodistribution, intensity of uptake as well as dosimetry. Hence, we can see what we treat. ^{68}Ga-PSMA PET/CT can be used as a sensitive and specific imaging modality for patient selection, response assessment and follow up after PRLT.

The patients currently receive PRLT under compassionate basis after treatment failure following chemotherapy and newer anti-hormonal agents, but also possibly after exhaustion of monoclonal antibody therapy or ^{223}Ra-chloride therapy. Distant metastases with high PSMA expression confirmed on pre-therapy ^{68}Ga-PSMA PET/CT, and progressive disease despite extensive previous treatments, are currently the essential inclusion criteria, as stated in the consensus recommendations of the German society of nuclear medicine, which were published in 2016.[59]

Dosimetry

Individualized dosimetry is imperative for precision molecular radiotherapy using ^{177}Lu-PSMA. The kinetics of a certain ligand varies in patients and depends on a number of factors like renal function and tumor load, to name a few. There is additionally a significant intrapatient variability due to tumor responses and varying tumor loads between different therapy cycles.[60] Therefore, for the direct comparison of the different PSMA ligands, patient-specific factors need to be considered. A differential analysis for PSMA I&T and PSMA-617 revealed comparable results for both ligands. In a dosimetry study of 18 patients receiving 1–4 PRLT cycles using ^{177}Lu-PSMA-I&T, Okamoto et al demonstrated organ- and tumor-absorbed doses comparable to ^{177}Lu-PSMA-617.[61] However, they found relatively constant doses among the four different treatment cycles, quite contrary to the results by our group.[61,62] Kabasakal et al also stressed the need for individual dosimetry based on the large inter-individual variation in a study using ^{177}Lu-PSMA-617.[63]

The organs at risk are the salivary glands, lacrimal glands and the kidneys. The highest dose was demonstrated for the lacrimal glands (1–3.8 Gy GBq^{-1}) followed by the salivary glands (0.5–1.4 Gy GBq^{-1}) and then the kidneys (0.53–0.88 Gy GBq^{-1}).[57,61–67] In fact, the dosimetry with the red marrow was the most favorable (0.01–0.04 Gy GBq^{-1}). Therefore, the threshold absorbed dose of 2 Gy to the red marrow for severe hematotoxicity, implies a maximal tolerated cumulative activity of at least 45 GBq.[67,68] Considering the threshold for renal toxicity, a cumulative activity of 40 GBq would be safe.[69,70] Whereas, a maximal dose limit of 45 Gy for salivary dysfunction would allow the administration of a cumulative activity of around 50 GBq of ^{177}Lu-PSMA.[71] However, it must be stressed that no universal dose limits have yet been defined for a molecular radiotherapy, and the ones mentioned above are only extrapolated from the external radiation therapy.

Adverse effects

The potential adverse effects to be kept in mind are hematological, renal and salivary gland toxicities. Overall, ^{177}Lu-PRLT is tolerated well by all the patients with no severe acute or long-term adverse events. Short-lasting mild fatigue was the most common immediate side effect.[60] Long-term side effects seem to be relatively mild with transient xerostomia, being a non-hematological side effect in about 5–10% of the patients, and grade 3/4 hematological toxicity being reported in a few cases.[60,72–76]

Docetaxel, the most commonly used chemotherapeutic agent in mCRPC, is associated with different adverse effects impairing also the quality of life.[77] One or more serious adverse events were observed in 26% of the patients receiving docetaxel every 3 weeks including two (0.3 %) treatment-related deaths.[78] The most common severe (grade ≥3) side effects of the second-line chemotherapy with cabazitaxel were neutropenia, leukopenia, anemia, and thrombocytopenia, with neutropenia being the most common, in 82% of the patients. On the other hand, diarrhea was the most common non-hematological adverse event, seen in 47% of the patients. 18 patients (5%) died due to the side-effects.[79] The most common adverse events with abiraterone include fluid retention/ edema, hypokalemia, hypertension, cardiac disorders, atrial fibrillation, and an increase in liver enzymes.[80] On the other hand, fatigue, diarrhea, hot flashes, musculoskeletal pain, headache, cardiac disorder, seizure (<1%), and myocardial infarction (<1%) were associated with enzalutamide.[81]

In a systematic review of third-line treatment and ^{177}Lu-PRLT, G3-4 hematological toxicities were reported in about 2% of the patients undergoing PRLT.[82] On the other hand, the first study of ^{177}Lu-PSMA I&T reported only G1-2 anemia/pancytopenia and no G3-4 hematological toxicity.[57] Indeed, renal insufficiency may also increase the risk due to a higher circulation time and hence dose to the bone marrow. The risk of development of hematotoxicity increases with extensive bone marrow involvement and previous chemotherapy or ^{223}Ra-treatment.[60,65] Long-term low-dose concept, *i.e.* fractionation, may be beneficial to avoid/ minimize bone marrow toxicity.

Since 2013, we have not seen any clinically significant nephrotoxicity in long-term follow-up of over 200 patients treated with up to 12 cycles of PRLT, even in the more than 15 patients with a single functioning kidney.[83] Yordanova et al found elevated cystatin C in 32/55 patients (58%); however, 14 of who already had elevation of cystatin C before treatment. The renal function

Figure 1. A 76-year-old patient with progressive mCRPC s.p. prostatectomy, pelvic lymphadenectomy, ADT as well as enzalutamide and 16 cycles of docetaxel chemotherapy. After 3 cycles of ^{177}Lu-PRLT (cumulative administered activity 21.8 GBq), there was PR of the LNM (*oblique arrows*) as well as of the primary tumor (*horizontal arrow*). (A) ^{68}Ga-PSMA MIP image before PRLT; (B) after two cycles and (C), after three cycles; (D,F) axial PET/CT images; (E,G) contrast-enhanced CT images. There was response to PRLT (PR) according to RECIST 1.1 as well as EORTC criteria (reduction of uptake) of the left iliac LNM (D,E, before PRLT; F, G, after three PRLT cycles) and of the primary tumor. ADT, androgen deprivation therapy; LNM, lymph node metastases; mCRPC, metastatic castration-resistant prostate cancer; PR, partial remission; PRLT, PSMA radioligand therapy; PSMA, prostate-specific membrane antigen.

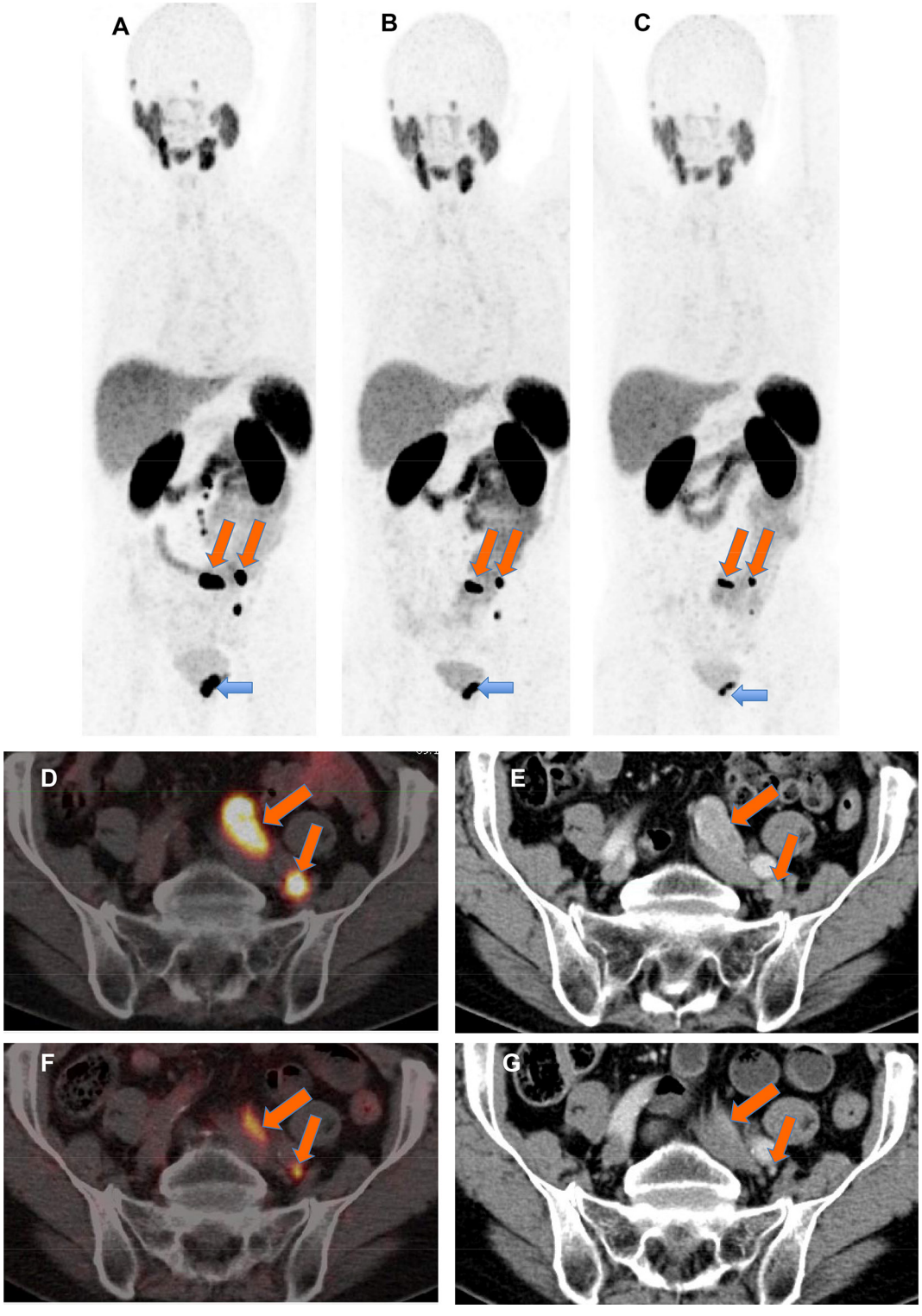
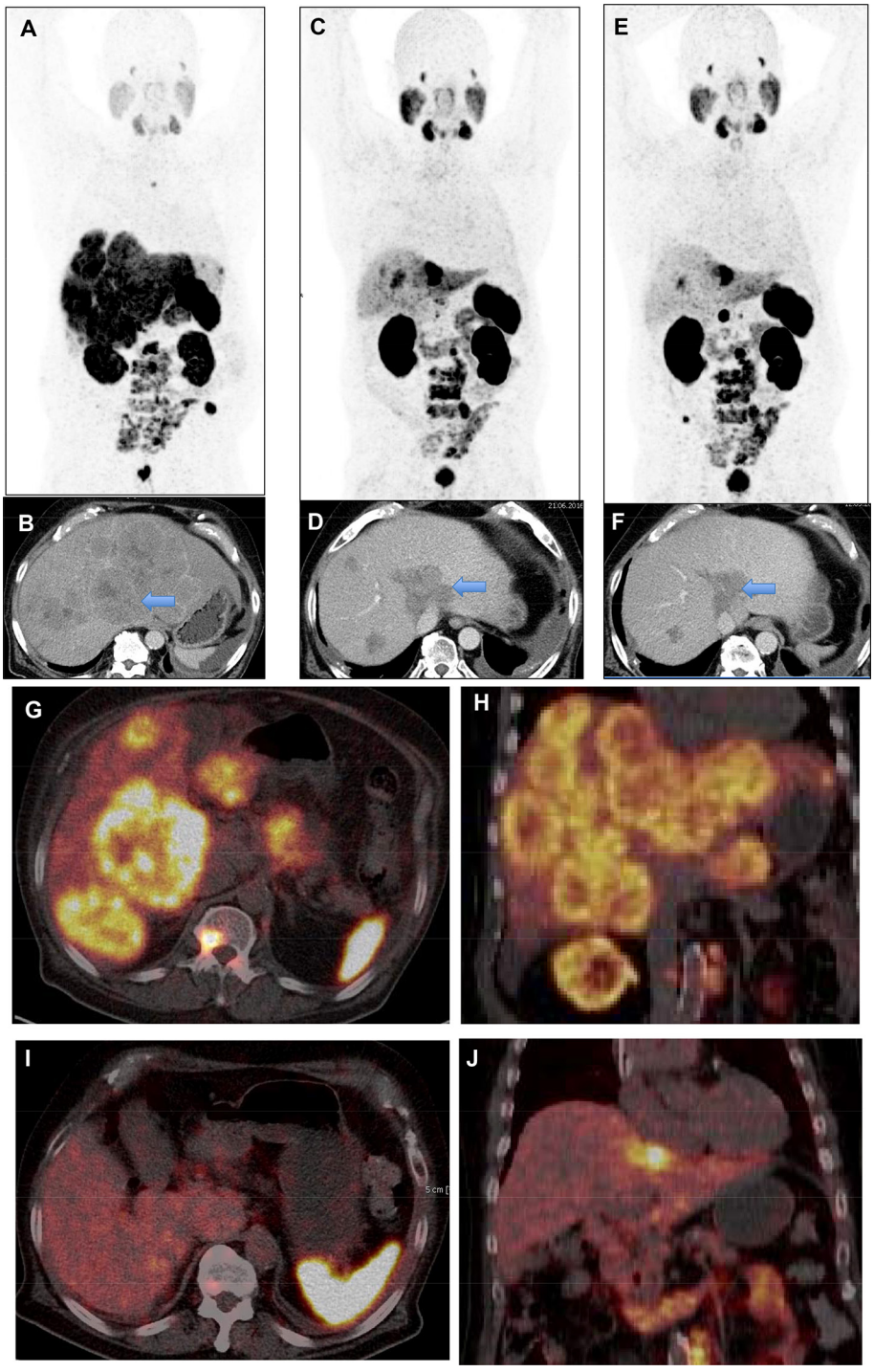


Figure 2. A 75-year-old patient with progressive mCRPC, s.p. prostatectomy, ADT and enzalutamide as well as docetaxel chemotherapy (wheel-chair bound with pain and low Karnofsky performance status) with disseminated osseous as well as extensive liver metastases (hepatomegaly) exhibiting very high PSMA expression. After 3 cycles of ^{177}Lu-PSMA-radioligand therapy (cumulative administered activity 22.7 GBq), excellent response of the multiple liver metastases (PR according to RECIST 1.1 and EORTC criteria) with significant decrease in size of the lesions as well as of the whole liver occurred. The general condition of the patient improved remarkably (coming for follow-up studies driving his own car) and he lived for another 2 years after the last PRLT cycle. (A) ^{68}Ga-PSMA MIP image before PRLT; (C), after two cycles and (E), after three cycles; (B,D,F) contrast-enhanced CT images. (G,I) axial PET/CT images; (H,J) coronal PET/CT images; (G,H) before PRLT; (I,J) after 3 PRLT cycles. ADT, androgen deprivation therapy; LNM, lymph node metastases; mCRPC, metastatic castration-resistant prostate cancer; MIP, maximum intensity protection; PR, partial remission; PRLT, PSMA radioligand therapy.



significantly correlated with age, hypertension and prior renal disease.[84] The renal specific PSMA-binding can be blocked by PMPA (2- (phosphonomethyl)pentanedioic acid), a PSMA-inhibitor, which has been validated in pre-clinical studies.[85] But due to its lack of availability and also the possibility of concurrent blockade within the tumor, this compound is not in routine clinical use.

Reversible xerostomia has been reported in about 5–10% of patients treated with ^{177}Lu-PRLT, and is likely to be caused by high PSMA-specific binding of the tracer in the salivary glands.[60,72–76] This was objectively assessed by Scarpa et al, who found a significant reduction in the SUV_{max} on ^{68}Ga-PSMA PET/CT as well as a decrease in the volume of the salivary glands after PRLT.[67] The SUV_{max} on ^{68}Ga-PSMA PET/CT decreased on cooling of the glands.[86] A possible significant breakthrough for salivary gland protection, especially crucial in the context of targeted α therapy using ^{225}Ac-PSMA, was the demonstration of reduced ligand uptake 45 days after injection of botulinum toxin into the salivary gland unilaterally.[87] The SUVmean on Ga-68 PSMA PET/CT in the injected parotid gland showed a highly significant decrease of up to 64% compared with the other side. The vascularization of the salivary glands on Doppler was demonstrated to remained unchanged after botulinum use by Coskun et al.[88] This implies that additional mechanisms might be playing part in the action of Botulinim toxin, probably a post-denervation atrophy, causing a decrease in PSMA expression.[89]

Efficacy

The excellent tumor response is attributable to the high doses delivered to metastases based on the specific ^{177}Lu-PSMA tumor uptake. High uptake can be demonstrated pre-therapy on ^{68}Ga-PSMA PET/CT, which is an important pre-requisite for PRLT. PSMA PET/CT, therefore, plays an important role in the selection of patients for PRLT. Tumor doses exceeding 50 Gy and ranging up to 500 Gy have been reported.[60,67] Significant PSA decline (by ≥50%) was observed in 30–60% of the patients.[57,60,72–76] von Eyben et al noted that^{177}Lu-PSMA RLT caused a best decline of PSA ≥50% twice as often as the third-line treatment with a higher frequency of objective remission as well as fewer side effects than third-line treatment.[82] Patients undergoing PRLT tended to live longer than patients given third-line treatment (median of 14 months *vs* 11 months), but the difference was not statistically significant. Third-line treatment was stopped more often due to adverse effects.

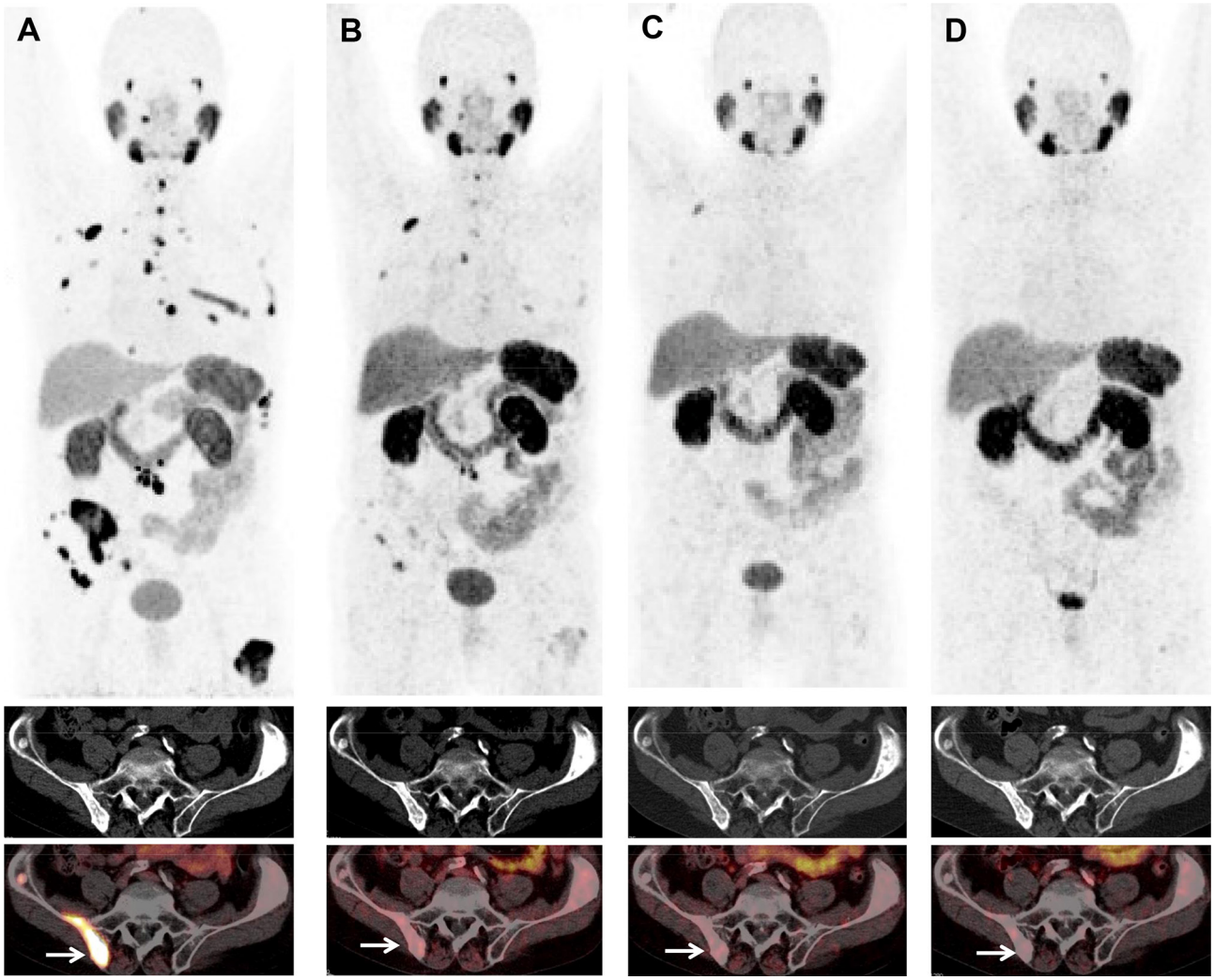
^{68}Ga-PSMA PET/CT is a very sensitive and specific modality for the early assessment of response in comparison with the morphological imaging like CT, since molecular response precedes morphological changes (Figure 3). Lymph node metastases of mCRPC responded better to PRLT than bone metastases.[60] This may be explained by a higher and more uniform absorbed radiation dose by lymph node metastases, which—in general—exhibit a higher uptake (SUV) on ^{68}Ga-PSMA PET/CT as compared to bone lesions. In addition, the biological differences in radiation sensitivity might be an influencing factor. ^{68}Ga-PSMA PET/CT is also superior in response assessment of skeletal metastases compared to CT alone, in which the actual size of the osteoblastic metastases is difficult to measure and change in size is difficult to appreciate.

Only a few studies have reported response as assessed according to morphological (RECIST) or molecular imaging criteria.[57,60,67,74,90,91] Often, there is a discordance between the PSA levels and the PET/CT imaging findings implying that PSA alone is definitely not a reliable parameter for the assessment of therapy response.[57,60,65,67] Yadav et al demonstrated according to molecular imaging criteria, a complete remission (CR) in 2/6 patients, PR in 3/6 patients and stable disease (SD) in 1/6 patients.[90] An overall assessment of bone and soft tissue metastases by Heck et al revealed a CR in 5% of patients, SD in 63% and PD in 32%.[91] On the other hand, Fendler et al used RECIST to define response and found PR in 4/15, SD in 6/15, and PD 5/15 patients after two PRLT-cycles with^{177}Lu- PSMA-617.[74] Scarpa et. al showed an objective molecular and radiological response in half of the patients (5/10), wherein in addition to PR and SD, they also defined a mixed response as patients responding remarkably to PRLT at one metastatic lesion site, but developing new lesions at another site.[67]

In an analysis of 224 patients with metastatic PCa treated at our center since April 2013, we observed any PSA reduction in 157/224 (70 %) patients; 121/224 patients (54%) demonstrated a PSA decline by >50% and the best response was CR with undetectable PSA. The response according to RECIST was as follows: CR in 9 patients (4%), PR in 53 patients (23.7%), SD in 91 patients (40.6%), and PD in 71 patients (31.6%). According to the molecular imaging criteria, CR was noted in 10 patients (4.5%), PR in 78 (34.8 %), SD in 61 (27.2 %) and PD in 75 patients (33.5%). The median OS in all patients was 27 months and the median progression-free survival (PFS) was 11.5 months. First-line PRLT (with no previous hormone therapy) was associated with the longest OS (median not reached at 55 months, all 18 patients are alive). Chemotherapy-pre-treated patients lived significantly shorter (median OS 19 months) as compared to chemotherapy naive patients (38 months, $p < 0.05$). OS was also shorter in patients with previous ^{223}Ra treatment (17 months). Addition of abiraterone or enzalutamide provided a significant prolongation of survival (40 months, $p < 0.05$). On the other hand, prior surgical or radiation treatment of primary tumor had no significant effect on the OS (30 months, $p > 0.05$). In patients demonstrating a PSA decline of >50% after at least two PRLT cycles, the OS was significantly longer (38 months). The significantly shorter OS reported by other groups might be due to use of PRLT as last line after exhaustion of other therapy options (newer antiandrogen agents, chemotherapy).[72,76] On the other hand, patients treated at an earlier stage of the disease had a favorable outcome in our study, leading to a significantly longer median OS.

Prognostic factors influencing the outcome of PRLT have been studied. In the retrospective multicenter German study, negative predictors were elevated alkaline phosphatase and the presence of visceral metastases, whereas the total number of therapy cycles were associated with a favorable outcome.[75] Ahmadzadehfar et al found that patients with any PSA decline had a significantly

Figure 3. A 77-year-old patient (first diagnosis in 1998) with progressive mCRPC and initial osseous metastases, s.p. orchiectomy, ADT and abiraterone, repeated external beam radiotherapy and chemotherapy with docetaxel and cabazitaxel. After 3 cycles of ^{177}Lu-PSMA PRLT (cumulative administered radioactivity 12.9 GBq) between October 2015 and March 2016, the patient experienced nearly complete remission (with no toxicity), persisting for 2 years after the last cycle. This patient presented with chronic renal insufficiency and G2 anemia before PRLT, which did improve (!) after PRLT. ^{68}Ga-PSMA PET/CT images: (A), October 2015; (B) March 2016; (C), July 2016 and (*D*) December 2017; *upper* panel, MIP images; *middle panel*, CT images revealing no significant change over time in the osteosclerotic iliac bone lesions; *lower panel,* fused ^{68}Ga-PSMA PET/CT images after PRLT exhibiting a significant decrease in PSMA expression of the metastases (*arrow* showing metastasis in the right iliac bone), related to treatment response according to molecular imaging criteria. ADT, androgen deprivation therapy; mCRPC, metastatic castration-resistant prostate cancer; MIP, maximum intensity protection; PRLT, prostate-specific membrane antigen; PSMA, prostate-specific membrane antigen.

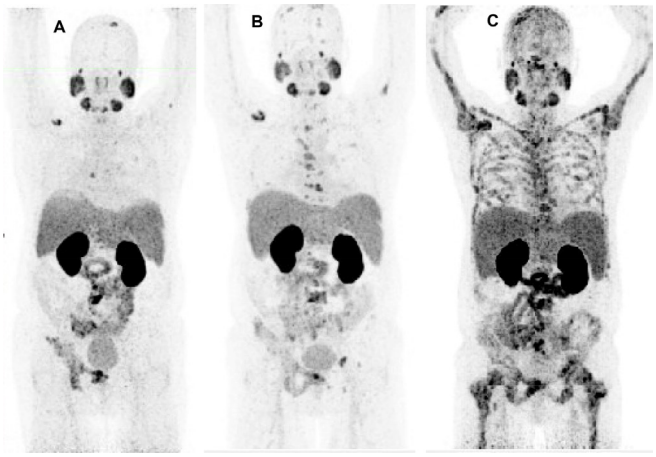


longer OS than patients without PSA decline (68 *vs* 33 weeks).[72] The median OS is significantly longer in patients without hepatic involvement, with high levels of albumin and Hb and low levels of aspartate aminotransferase and a decline in PSA levels of more than 14% was the most important response parameter with regard to OS.[92] Bräuer et al noted that PSA decline after the first therapy cycle was associated with a longer OS and only alkaline phosphatase <220 U l^{-1} lended a longer PFS (median PSA-PFS 18 weeks).[73] On the other hand, a lack of PSA response after the first therapy cycle should not preclude further treatments, since these patients did respond after the second or third therapy cycle.[93]

α-emitter labeled PSMA ligands

Despite the high doses delivered to tumors, approximately a fourth to a third of the patients are refractory to treatment with ^{177}Lu-PSMA, presenting with primary progression under PRLT (Figure 4). Hematological toxicity tends to be frequent after ^{177}Lu-PSMA in patients having disseminated bone and bone marrow involvement. The application of α-emitters with a short range and high linear energy transfer is a very promising option to overcome this limitation, as has been demonstrated by an excellent therapy response using ^{225}Ac-PSMA in the above-mentioned two scenarios.[94,95]

Figure 4. A 56-year-old patient with mCRPC, s.p. orchiectomy and 20 cycles of docetaxel/cabazitaxel chemotherapy (stopped due to severe anemia, neutropenia and fatigue). The patient underwent ^{177}Lu-PSMA RLT as a last line therapy option, however, experiencing progression under PRLT, with disseminated bone and bone marrow involvement (which could be an indication for therapy with the α-emitter ^{225}Ac-PSMA). (A)^{68}Ga-PSMA PET/CT MIP image before PRLT; (B) after two cycles and (C) after four cycles of PRLT. mCRP-C,metastatic castration-resistant prostate cancer; MIP, maximum intensity protection; PRLT, PSMA radioligand; PSMA, prostate-specific membrane antigen.



A first-in-human study reported by Sathekge et al demonstrated a marked response in one patient after two cycles of ^{213}Bi-PSMA-617 using a cumulative activity of 592 MBq.[96] In our experience using ^{213}Bi-PSMA with the administered radioactivities per cycle [median 390 MBq (155–623 MBq)], no significant acute/subacute toxicity was noted and minor responses could be demonstrated. However, higher activities or more frequent cycles of Bi-213 PSMA might be required due to very short half-life of ^{213}Bi (46 min) to achieve the desired response to therapy, which was constrained in our study due to the limited available activity and very high cost of the generator. ^{225}Ac must be considered the first-choice isotope for PSMA-TAT in the setting of PCa.[97]

The efficacy and toxicity of salvage therapy using four different administered radioactivities of ^{225}Ac- PSMA-617 was compared, namely 50 kBq kg^{-1} (n = 4), 100 kBqkg^{-1} (n = 4), 150 kBq kg^{-1} (n = 2), 200 kBq kg^{-1} (n = 4). Severe xerostomia was the dose-limiting toxicity for activities exceeding 100 kBq kg^{-1} per cycle. Therefore, an administered activity of 100 kBqkg^{-1} ^{225}Ac-PSMA-617 per cycle every 8 weeks was concluded to be a reasonable trade-off between toxicity and biochemical response.[94]

Kratochwil et al further retrospectively analyzed the remarkable antitumor activity of ^{225}Ac-PSMA-617 therapy in 40 patients, demonstrating a promising duration of tumor control (median 9 months).[95] A significant PSA response (>50%) was noted in 24/38 (63 %) of the patients. Five patients presented with enduring responses of >2 years. Xerostomia was the main reason to discontinue therapy (in 4/38 patients) as in the case of non-responders (in 5/38 patients). Hence, they concluded that further modifications of the treatment regimen regarding the adverse events were necessary to yield maximal response.

PERSONALIZED PRLT—ON THE WAY TO PRECISION MEDICINE

A growing literature supports the use of PRLT in advanced PCa with potential benefit in OS and acceptable side-effects, when compared with the competing modalities. In clinical practice, we frequently observe good responses despite progression under extensive pre-treatments like newer antihormonal agents, ^{223}Ra and chemotherapy, and poor performance status. The currently unmet need in metastatic PCa is to determine the optimal choice and sequencing of therapy. An ideal patient for PRLT could possibly be one receiving PRLT before chemotherapy with good baseline bone marrow function and a good baseline performance status.[60]

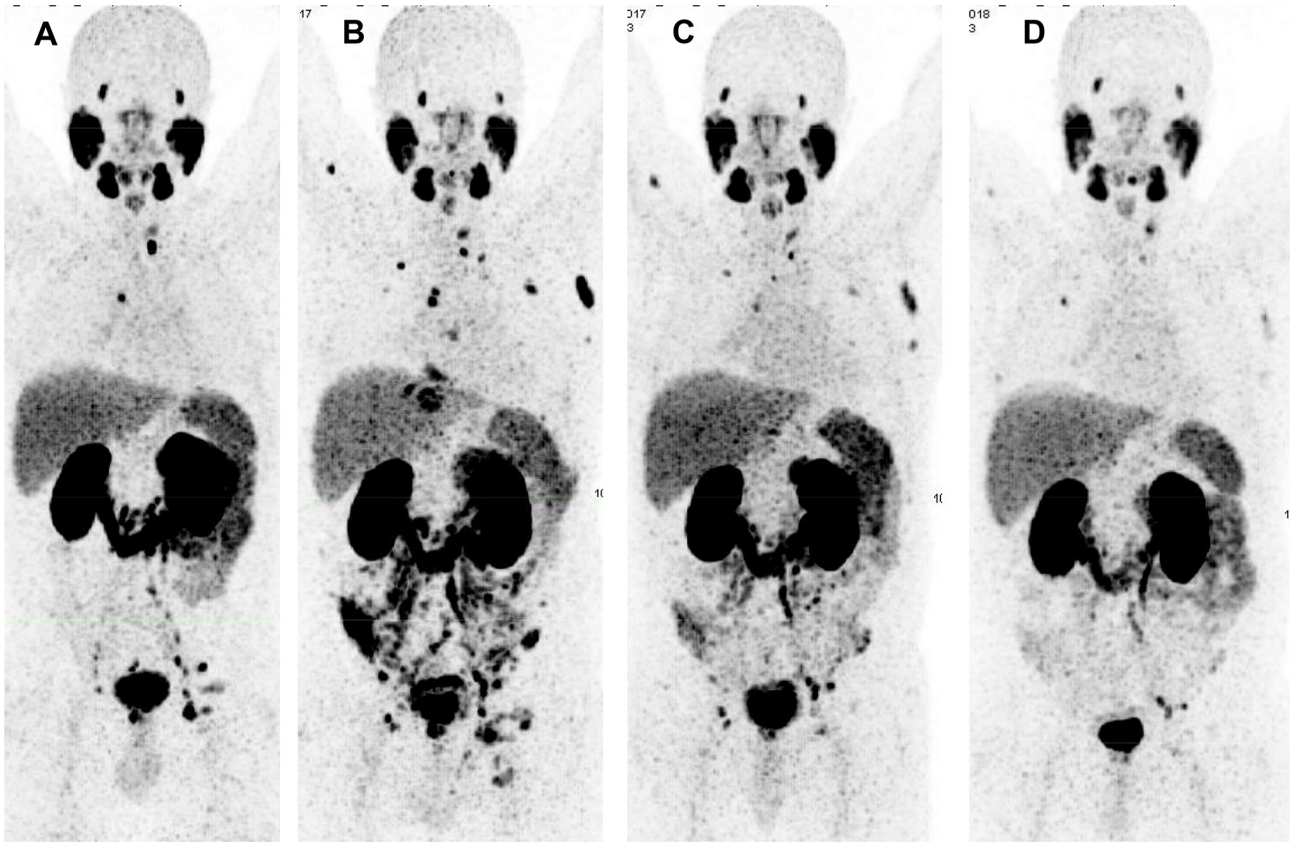
Patients can be effectively selected and the likely response to therapy predicted as well as assessed with molecular imaging (PET/CT or PET/MRI), making use of the same PSMA ligand. In contrast to this theranostic approach, a conventional chemotherapy regimen, *e.g.* is standardized not personalized and pre-defined by a previous randomized controlled clinical trial in a typical patient cohort. A personalized approach using the theranostic concept can be tailored towards an individual patient rather than the concept of "one size fits all".

Various factors like adjusting the administered activity, number of cycles and interval between the cycles are important for obtaining favorable therapeutic responses, *e.g.* a large volume of disease necessitates administering higher radioactivities and *vice versa*. We define herewith, the imaging phenotypes α or β for choosing the isotope. An α imaging phenotype would be extensive bone and bone marrow involvement or superscan and/or status post-chemotherapy, where a PSMA-targeted α radioligand therapy may be more suitable in terms of efficacy and toxicity, than the β phenotype with strongly PSMA-positive, relatively limited disease amenable to PRLT using βbeta emitters like ^{177}Lu.

At our center, restaging is performed using ^{68}Ga-PSMA PET/CT 3–4 months after PRLT. In case of a stable disease or remission (complete or partial), the patient is restaged with PET/CT every 6 months until disease progression is evident on imaging. PRLT can be resumed after detection of progression after a therapy interruption, what we refer to as the next phase of PRLT (Figure 5). Additionally, laboratory parameters (erythrocytes, hemoglobin, platelets, leucocytes, creatinine, BUN, SGOT, SGPT, bilirubin, SAP, TSH, γ-GT and PSA) are evaluated prior to each cycle and at restaging. Renal function is monitored by tubular extraction rate using ^{99m}Tc-MAG3 renography. We also assess the function of the parotid and submandibular salivary glands by dynamic salivary gland scintigraphy, which is a very useful and easy to perform imaging modality for the objective evaluation of xerostomia following ^{177}Lu-PRLT.[98]

It must be emphasized that PRLT of metastatic PCa involves a multidisciplinary management with close collaboration with the referring urologists/oncologists as well as palliative medicine

Figure 5. A 60-year-old patient with mCRPC, s.p. brachytherapy, ADT and enzalutamide, experiencing partial remission of the extensive lymph node and bone metastases after 3 cycles (21.2 GBq) of PRLT (A, ^{68}Ga-PSMA PET/CT MIP image after the third cycle). The disease progressed 6 months later (B) and he underwent a second phase (fourth and fifth PRLT) of treatment (salvage PRLT) with 7.9 and 8 GBq, respectively and concurrent treatment with abiraterone. The combination therapy had an effect/PR (C, ^{68}Ga-PSMA PET/CT MIP image after the fourth cycle and D, after the fifth cycle) without any toxicity after a cumulative administered activity of 37.1 GBq. G1 anemia (present before PRLT) improved over time. ADT, androgen deprivation therapy; mCRPC, metastatic castration-resistant prostate cancer; MIP, maximum intensity protection; PRLT, PSMA radioligand therapy; PSMA, prostate-specific membrane antigen.



physicians. Treatment as a last line option implies that many patients present in a relatively poor general condition, which necessitates also the treatment of accompanying symptoms, commonly pain and anemia (administration of packed red blood cells).

FUTURE PERSPECTIVES

Early initiation of ^{177}Lu-PRLT may be effective in metastatic PCa and may offer a significant survival benefit. Randomized controlled studies are required to best determine the place of this agent (*e.g.* before chemotherapy) in the management of mPC. Administration of higher activities or hyperfractionation may be considered for a better efficacy. A total activity of 30 GBq given 6–10 weeks apart was proved to be safe, considering dose limit to the kidney and bone marrow.[67] Adjusting the amount of ^{177}Lu administered during each cycle is important in contrast to a standardized approach of a fixed activity for each cycle.[99] We analyzed the intrapatient variability in the absorbed doses during different therapy cycles and noted that the mean absorbed tumor dose demonstrated a significant reduction during subsequent cycles. Hence, applying a higher radioactivity in the first cycle seems to be logical in order to obtain the maximal antitumor effect.[99]

Future clinical studies should address the enhancement of the efficacy of PRLT by the combination with radiosensitizers, PARP inhibitors, immune-checkpoint inhibitors etc. Targeted multimodality options like combination with external beam radiation therapy (a concept which we refer to as COMBIERT, combined internal–external radiation therapy) or with bone-targeting agents like ^{177}Lu labeled bisphosphonates (in case of a discordance between PSMA expression and the osteoblastic activity) must be considered for the maximal therapeutic effect. Treatment with newer agents like abiraterone or enzalutamide, which inhibit the AR signaling, leads to the upregulation of PSMA (Figure 5).[100] Therefore, ^{177}Lu-PSMA-RLT may produce a synergistic effect in combination with these agents.[101]

The preliminary results with ^{225}Ac-PSMA-PRLT are definitely highly encouraging. Further studies to overcome the potential side effects, predominantly xerostomia, are urgently warranted.

The demonstration of a proof-of-principle by the intraparencymal injection of botulinum toxin is a step forward in this direction.[87]

Newer radionuclides with favorable kinetics have been studied, permitting pre-therapeutic dosimetry.[102–105] ^{44}Sc has a half-life of 4 h and can be made available using a cyclotron production route in substantial quantities as a highly pure product.[102] It can be effectively labeled with PSMA ligands with *in vitro* and *in vivo* characteristics similar to ^{177}Lu-PSMA-617. This permits delayed imaging after 24 h or later.[103,104] Another attractive radionuclide for PET/CT imaging with its 17.5 h half-life is ^{152}Tb, particularly for predictive dosimetry before PRLT.[105]

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