



Extended therapy with [¹⁷⁷Lu]Lu-PSMA-617 in responding patients with high-volume metastatic castration-resistant prostate cancer

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Abstract

Purpose The currently used scheme for radioligand therapy (RLT) of patients with metastatic castration-resistant prostate cancer (mCRPC) consists of 4–6 cycles of 6.0–7.4 GBq [¹⁷⁷Lu]Lu-PSMA-617 each. This standard treatment scheme has proved safe and effective resulting in objective response in most patients with no significant toxicity. Many patients, however, show high-volume residual tumor burden after the sixth cycle and may benefit from treatment continuation. Extended treatment with additional cycles has been withheld due to concerns on potential increased toxicity.

Methods Twenty-six patients with high-volume residual tumor burden (according to CHARTED) after standard RLT with [¹⁷⁷Lu]Lu-PSMA-617 and no alternative treatment option received additional RLT cycles reaching a median of 10 (range 7–16) cycles with a mean activity of 7.4 ± 0.9 GBq per cycle. Response assessment with [⁶⁸Ga]Ga-PSMA-11 PET/CT was done every 2–3 cycles or if disease progression was clinically suspected or based on change in PSA value (according to the PCWG3 criteria). Toxicity was measured using routine blood work up including blood counts, liver and renal function, and was graded according to CTCAE v5.0 criteria. Survival outcome was calculated based on the Kaplan-Meier method.

Results Further PSA decline of 33 ± 28% during the extended treatment was observed in 21/26 (81%) patients, whereas 5/26 (19%) patients showed a PSA increase; correspondingly in 11/21 patients with an initial response (PR or SD) to extended cycles, treatment was discontinued due to progressive disease, whereas six (23%) patients achieved low-volume residual disease. Two (8%) patients died without showing progression, and two (8%) patients are still under therapy. The median progression-free survival was 19 (95% CI: 15–23) months, and the overall survival was 29 (95% CI: 18–40) months. Grade ≥ 3 hematological toxicities occurred in 4/26 (15%) patients during treatment extension, and nephrotoxicity (grade ≥ 3) was observed in 1/26 (4%) patient during the follow-up.

Conclusion Extended radioligand therapy is a feasible treatment option in patients with high-volume residual tumor after the completion of standard treatment with six cycles of [¹⁷⁷Lu]Lu-PSMA-617. Improved survival and the acceptable safety profile warrant further investigation of the concept of additional cycles in selected patients.

Keywords Prostate-specific membrane antigen (PSMA) · [¹⁷⁷Lu]Lu-PSMA · Radioligand therapy (RLT) · Extended treatment · Metastatic castration-resistant prostate cancer (mCRPC)

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Background

Several systemic treatment options exist for patients with metastatic castration-resistant prostate cancer (mCRPC), predominantly including taxane-based chemotherapies (e.g., docetaxel and cabazitaxel) and new-generation antiandrogen drugs (e.g., enzalutamide and abiraterone). In more recent years, radioligand therapy (RLT) has been introduced for mCRPC patients ineligible for or refractory to other treatment strategies [1]. For this purpose, a selective radiolabeled ligand is used targeting prostate-specific membrane antigen

(PSMA), a transmembrane glycoprotein avidly expressed on the surface of prostate cancer cells [2, 3]. [¹⁷⁷Lu]lutetium is considered the suitable radioisotope for RLT due to its favorable physical characteristics such as its long half-life and short range of emitted medium-energy beta particles. [¹⁷⁷Lu]Lu-PSMA-617 is the most widely used compound for PSMA-targeted RLT with promising antitumor activity and low toxicity.

Initial experiences with 1–3 cycles of 6 GBq [¹⁷⁷Lu]Lu-PSMA-617 ([¹⁷⁷Lu]Lu-PSMA RLT) showed the therapeutic potential of RLT [4, 5]. Subsequent investigations were performed with up to six cycles, demonstrating encouraging results with low toxicity. The current standard treatment scheme consisting of 4–6 cycles of 6–8 GBq [¹⁷⁷Lu]Lu-PSMA-617 per cycle proved safe and very effective in the randomized VISION phase III trial, prolonging imaging-based progression [6, 7]. Responders, however, frequently show relevant remaining tumor burden after completion of standard [¹⁷⁷Lu]Lu-PSMA RLT with six cycles. Exhausting treatment alternatives, these patients may benefit from treatment continuation while being exposed to a tolerable risk of treatment-related hematological or renal adverse events. Few studies included patients receiving more than six cycles [¹⁷⁷Lu]Lu-PSMA RLT in a re-treatment context, but the safety of continued [¹⁷⁷Lu]Lu-PSMA RLT with more than six cycles has been addressed in only one patient group aiming for complete response [8–11].

This retrospective study assesses the feasibility of extended RLT in patients showing high-volume disease after six cycles of [¹⁷⁷Lu]Lu-PSMA-617. Treatment continued until progression, significant impairment of bone marrow or renal function, or achieving low-volume residual disease not necessitating further [¹⁷⁷Lu]Lu-PSMA RLT cycles.

Methods

Patients

We retrospectively analyzed 26 patients with mCRPC who successfully completed standard RLT with six cycles of [¹⁷⁷Lu]Lu-PSMA-617 and received further treatment cycles due to high residual tumor burden. [¹⁷⁷Lu]Lu-PSMA RLT was performed on a compassionate use basis under the German Pharmaceutical Act §13 (2b). Treatment initiation and continuation were decided by a multidisciplinary tumor board. Patient characteristics at baseline are outlined in Table 1. All patients had progressive, high-volume PSMA-expressing disease in [⁶⁸Ga]Ga-PSMA-11 PET/CT imaging before the commencement of [¹⁷⁷Lu]Lu-PSMA RLT and showed objective response to standard [¹⁷⁷Lu]Lu-PSMA RLT with six cycles. High-volume disease was defined according to

Table 1 Patient characteristics at initiation of [¹⁷⁷Lu]Lu-PSMA RLT

| | All patients (n = 26) |
|---|-----------------------|
| Age | 72 (68–77) |
| Gleason score | |
| 4–7 | 6 (23) |
| 8–10 | 15 (58) |
| Unknown | 5 (19) |
| VAS | |
| ≥ 4 | 9 (35) |
| < 4 | 17 (65) |
| ECOG | |
| 1 | 13 (50) |
| 2 | 12 (46) |
| 3 | 1 (4) |
| PSA at [¹⁷⁷ Lu]Lu-PSMA RLT initiation (ng/mL) | 108 (54.2–698.0) |
| Alkaline phosphatase (U/L) | 194 ± 257 |
| Lactate dehydrogenase (U/L) | 267 ± 112 |
| Previous treatment | |
| Abiraterone | 22 (85) |
| Enzalutamide | 19 (73) |
| [²²³ Ra]RaCl ₂ | 9 (35) |
| Docetaxel | 16 (62) |
| Cabazitaxel | 8 (31) |
| Sites of involvement | |
| Bone | 26 (100) |
| Oligofocal | 0 (0) |
| Multifocal | 14 (54) |
| Disseminated | 7 (27) |
| Diffuse | 5 (19) |
| Lymph nodes | 17 (65) |
| Visceral | 7 (27) |
| Primary | 6 (23) |

Data are presented as median with interquartile range (IQR), mean ± standard deviation, or n (%)

[¹⁷⁷Lu]Lu-PSMA RLT [¹⁷⁷Lu]Lu-PSMA-617 radioligand therapy, PSA prostate-specific antigen, eGFR estimated glomerular filtration rate, VAS visual analog scale, ECOG Eastern Cooperative Oncology Group

the CHARTED criteria (presence of visceral metastasis or ≥ 4 bone lesions with ≥ 1 beyond the vertebral bodies and pelvis [12]). [¹⁷⁷Lu]Lu-PSMA RLT was continued in responding patients showing high-volume residual disease (multifocal [n = 18] or disseminated/diffuse [n = 8] bone involvement; visceral involvement [n = 5]) in [⁶⁸Ga]Ga-PSMA-11 PET/CT performed after the sixth cycle. Other prerequisites for extended [¹⁷⁷Lu]Lu-PSMA RLT were estimated glomerular filtration rate (eGFR) of > 30 mL/min/1.73 m², white blood cells (WBC) ≥ 2.00 × 10⁹/L, platelets (Plt) ≥ 75 × 10⁹/L, and hemoglobin (Hb) ≥ 8.0 g/dL after the first six cycles.

Extended treatment cycles were intended until achieving a low-volume residual disease state in [^{68}Ga]Ga-PSMA-11 PET/CT. Extended [^{177}Lu]Lu-PSMA RLT was discontinued upon progression in [^{68}Ga]Ga-PSMA-11 PET/CT, significant renal toxicity, irreversible and refractory hematological toxicity, insufficient PSMA expression (\leq liver uptake) in remaining tumor lesions, or clinical deterioration (Eastern Cooperative Oncology Group (ECOG) performance status > 3). All patients gave their written consent after being thoroughly informed about the risks and side effects of this therapy and consented to publication of their data in accordance with the Declaration of Helsinki. The study was approved by the local Institutional Review Board (ethics committee permission number 310/18).

Radioligand therapy with [^{177}Lu]Lu-PSMA-617

[^{177}Lu]Lu-PSMA RLT was performed as inpatient procedure at the nuclear medicine therapy ward every 6–8 weeks with an intended activity of 7.4 GBq per cycle. ABX (Advanced Biochemical Compounds GmbH, Radeberg, Germany) provided the PSMA-617 ligand which was labeled in-house with [^{177}Lu]LuCl₃ (ITM Isotopen Technologien München AG, Garching/Munich, Germany) as described in detail previously [13, 14]. Salivary glands were cooled with ice packages for 2 h beginning 30 min before the administration to support xerostomia limitation. [^{177}Lu]Lu-PSMA-617 was administered intravenously in 30–60 s preceded and followed by the infusion of 1000 mL sodium chloride 0.9% solution. Renal dosimetry was conducted using planar whole-body scintigraphy and single-photon emission computerized tomography (SPECT) performed at 24 h, 48 h, and 72 h p.i. Patients' renal masses were determined using CT images.

Response and toxicity assessment

PSMA-based imaging response was assessed after every 2–3 cycles or if disease progression was suspected using prostate-specific antigen (PSA) as a tumor marker. The international consensus on [^{68}Ga]Ga-PSMA-11 PET/CT imaging response assessment was used for evaluation [15]: partial response (PR, reduction of uptake and tumor PET volume by $> 30\%$), stable disease (SD, uptake and tumor PET volume $\pm \leq 30\%$; no new lesions), and progression (PD, appearance of > 2 new lesions or uptake or tumor PET volume $\geq 30\%$ increased). PSA progression was defined according to the PCWG3 criteria as $\geq 25\%$ increase exceeding 2 ng/mL, confirmed by a second measurement ≥ 3 weeks apart [16].

Hematological (Hb, WBC, and Plt) and renal (eGFR) toxicity evaluation was performed through a blood workup routine at baseline, prior to each therapy cycle, 2–4 weeks

after each cycle, and in 6–12-week intervals throughout follow-up. Severity of adverse events was graded based on Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE v5.0) with grade ≥ 3 toxicities considered significant. Mouth dryness was evaluated at every [^{177}Lu]Lu-PSMA RLT cycle using a modified, self-reported eight-item xerostomia questionnaire [17]. The visual analog scale (VAS; ranging from 0 to 10) was assessed at baseline and at each treatment cycle and used to evaluate the pain level. The ECOG scale was used to assess the patients' performance status.

Statistical analysis

Statistical analyses were performed using the SPSS software (IBM SPSS Statistics 28.0, Armonk, NY, USA). GraphPad Prism version 9.1.1 (GraphPad Software, San Diego, CA, USA) was used to plot graphs. The significance level was set two-sided at $p < 0.05$. The paired sample *t*-test was used to compare intraindividual changes in continuous biochemical parameters. Imaging-based progression-free survival (PFS) was defined as the time interval from [^{177}Lu]Lu-PSMA RLT initiation to the date of the first progression, or death, if no imaging-based progression occurred. Overall survival (OS) was defined as the time from treatment initiation to death from any cause; censoring was done if the patient was alive at the time of analysis. PFS and OS were determined using the Kaplan-Meier method (log-rank testing).

RESULTS

Response and survival

Twenty-six patients who responded to six cycles RLT with [^{177}Lu]Lu-PSMA-617 received a median of 4 (IQR 2–6) cycles during extended [^{177}Lu]Lu-PSMA RLT reaching 10 (range 7–16) cycles and a cumulative activity of 75.0 ± 19.1 GBq. In 5/26 (19%) patients, PSA increased despite 1 to 2 additional cycles and disease progression was confirmed on [^{68}Ga]Ga-PSMA-11 PET/CT imaging, leading to treatment termination. In the remaining 21/26 patients showing objective response in [^{68}Ga]Ga-PSMA-11 PET/CT after six cycles, a further PSA decline of $33 \pm 28\%$ was observed after initiation of extended treatment, corresponding to an imaging-based partial response (PR) in 10 patients and stable disease (SD) in 11 patients. Six (23%) patients continued treatment until achieving low-volume disease ($n = 5$, Fig. 1) or insufficient PSMA expression in remaining tumor lesions ($n = 1$, Fig. 2). In 11 (42%) patients with initial response (PR + SD) to extended [^{177}Lu]Lu-PSMA RLT, progression after subsequent cycles resulted in treatment discontinuation (Fig. 3). Two (8%) patients are still

Fig. 1 From left to right: maximum-intensity projections (MIP) of [⁶⁸Ga]Ga-PSMA-11 PET images of a patient with multifocal bone and lymph node metastases responding to the standard treatment with six cycles and showing further response to the extended RLT with low-volume residual disease after a total of 11 cycles of [¹⁷⁷Lu]Lu-PSMA RLT (PFS: 40 months)

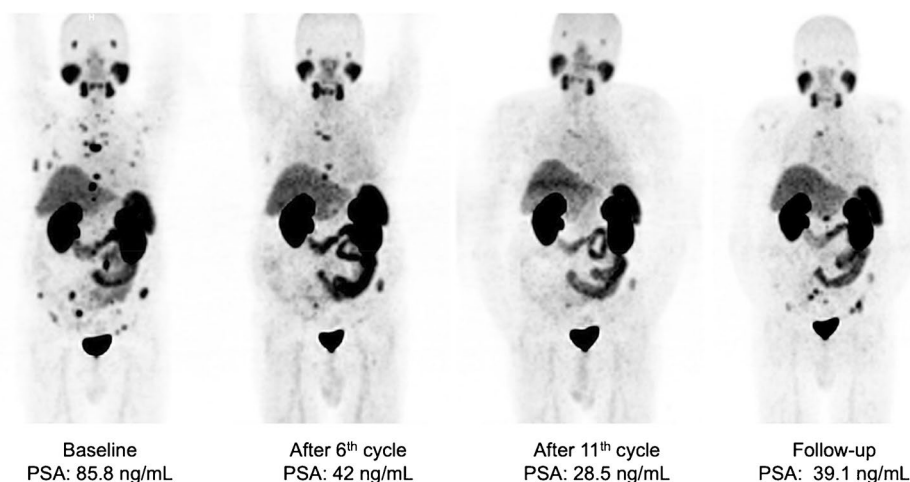
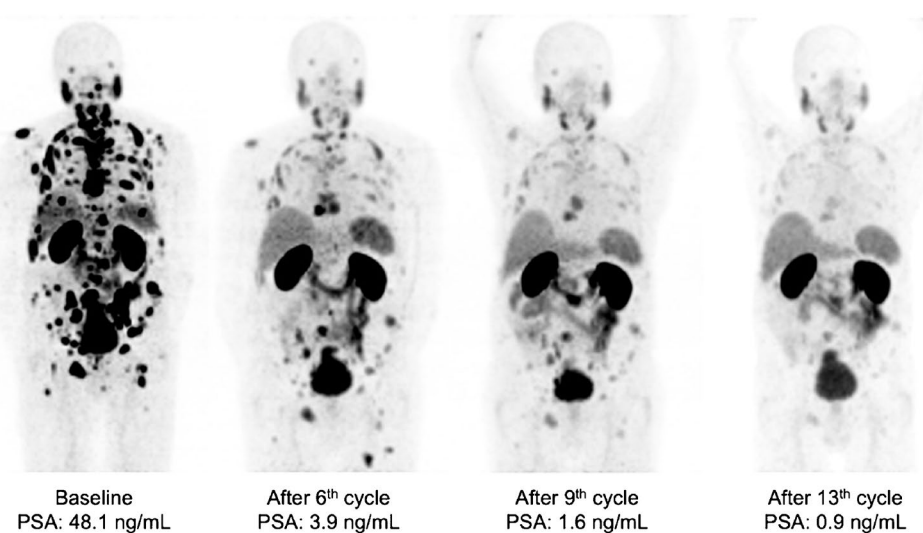


Fig. 2 From left to right: MIP of [⁶⁸Ga]Ga-PSMA-11 PET images of a patient with disseminated bone metastases and local disease responding to the standard treatment with six cycles and showing further response to the extended RLT. Treatment was discontinued due to insufficient PSMA-expressing residual disease after 13 cycles of [¹⁷⁷Lu]Lu-PSMA RLT (PFS: 58 months)



under treatment, and two (8%) patients died without showing disease progression or significant toxicity (Fig. 4). No treatment-induced clinical deterioration or death was recorded. Performance status improved in all nine patients with an uncontrolled pain state (VAS ≥ 4 , ECOG 2; Table 1) at baseline as a result of significant pain reduction (> 2 VAS reduction) during [¹⁷⁷Lu]Lu-PSMA RLT. Altogether, 16/26 (62%) patients died by the time of this analysis. Median PFS was 19 (95% CI: 15–23) months, and median OS was 29 (95% CI: 18–40) months. The Kaplan-Meier survival curves are displayed in Fig. 5.

Safety

Hematological parameters showed a significant decline during the extended [¹⁷⁷Lu]Lu-PSMA RLT (Fig. 6). Mean Hb changed from 11.8 ± 1.7 to 9.7 ± 1.6 g/dL ($p < 0.001$), WBC from 6.5 ± 2.5 to $4.6 \pm 1.5 \times 10^9/L$ ($p < 0.001$), and Plt from 239 ± 82 to $175 \pm 65 \times 10^9/L$ ($p < 0.001$; Table 2). No

significant hematotoxicity was observed during the standard [¹⁷⁷Lu]Lu-PSMA RLT. Four patients (15%), however, developed significant hematological toxicity (grade ≥ 3) in at least one parameter during the extended treatment period: anemia in 4 (15%) patients managed by transfusions and reversible thrombocytopenia in one (4%) patient. Significant leukopenia was not observed.

Mean administered activity was 7.4 ± 0.9 GBq per cycle, and mean renal absorbed dose was 0.54 ± 0.22 Gy/GBq resulting in a mean cumulative administered activity of 75.0 ± 19.1 GBq and absorbed total renal dose of 39.7 ± 15.3 Gy. Correlation of cumulative administered activity and cumulative absorbed renal dose up to each cycle is shown in Fig. 7 ($r = 0.847$, $p < 0.001$). Mean renal absorbed dose per administered activity increased from 0.47 ± 0.21 GBq/Gy during the first 6 cycles to 0.78 ± 0.13 Gy/GBq after additional cycles ($p = 0.012$) resulting in cumulative renal absorbed dose of 22.3 ± 10.3 Gy during standard treatment and 17.4 ± 11.3 Gy

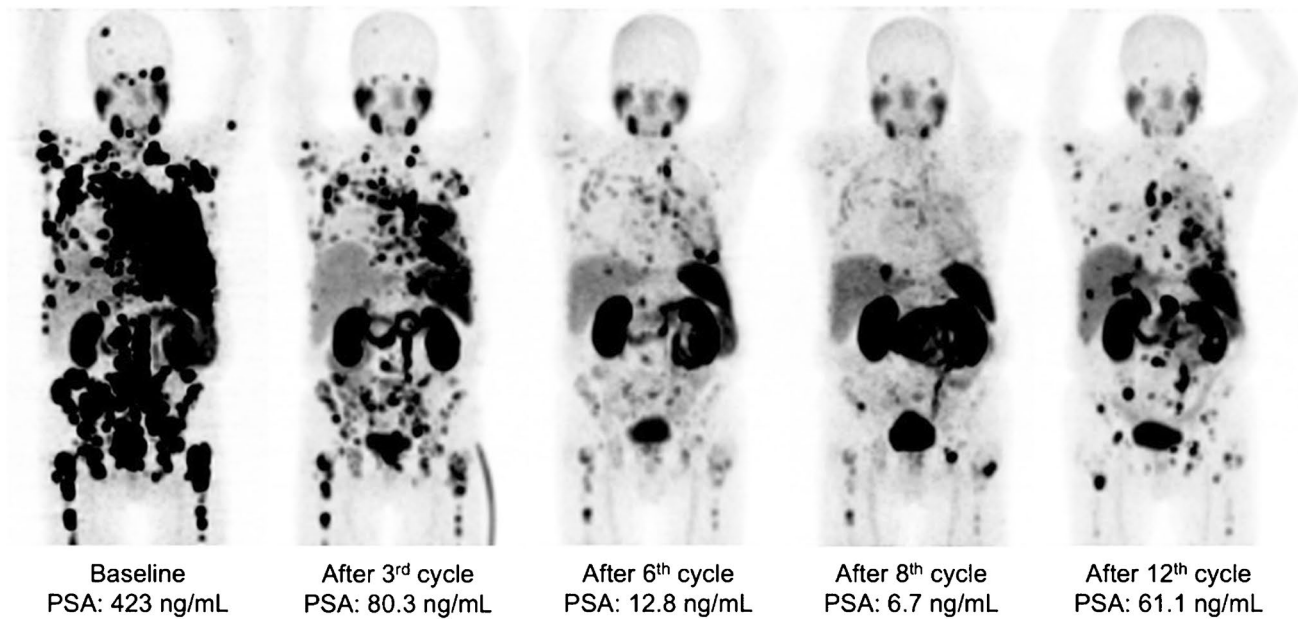
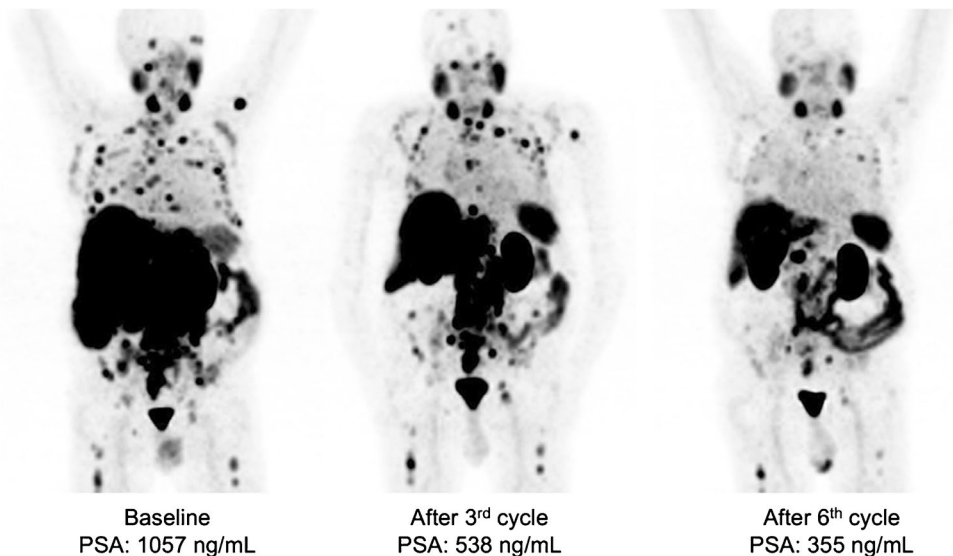


Fig. 3 From left to right: MIP [⁶⁸Ga]Ga-PSMA-11 PET images of a patient with disseminated bone and lymph node metastases, pleural carcinosis along with infiltration of the thoracic wall, lymph

node metastases, and local disease responding to the initial cycles of extended treatment. [¹⁷⁷Lu]Lu-PSMA RLT was discontinued upon progression after 12 cycles (PFS: 21 months)

Fig. 4 From left to right: MIP [⁶⁸Ga]Ga-PSMA-11 PET images of a responding patient with disseminated lymphatic, skeletal, and hepatic metastatic disease who died after the 7th cycle of [¹⁷⁷Lu]Lu-PSMA-617 without showing progressive disease



during additional 4 (IQR 2–6) cycles. A patient example with a cumulative administered activity of 56.4 GBq resulting in a cumulative absorbed renal dose of 14.5 Gy is presented in Fig. 8.

Mean eGFR levels changed from 85.3 ± 18.9 mL/min/1.73 m² to 80.6 ± 16.7 mL/min/1.73m² after the 6th cycle ($p=0.025$) and to 65.8 ± 19 mL/min/1.73 m² after extended [¹⁷⁷Lu]Lu-PSMA RLT at the last follow-up ($p=0.002$; Fig. 9). Mean yearly change of eGFR in all patients was -10.3 ± 8.5 mL/min/1.73m²/year. Cumulative absorbed

renal dose of > 40 Gy was not significantly associated with a more prominent eGFR reduction per year (-9 ± 9.5 vs. -11.5 ± 7.5 ; $p=0.462$) as shown in Fig. 10. Significant nephrotoxicity (grade ≥ 3) was observed in 1/26 (4%) patient 2 months after discontinuation of the extended [¹⁷⁷Lu]Lu-PSMA RLT after having received 12 cycles (Fig. 11). No significant xerostomia was reported, but 6/26 (23%) patients developed xerostomia of grades 1 and 2 during the extended treatment and after a median of 10 (IQR 7–12) cycles. A summary of the adverse events is shown in Table 3.

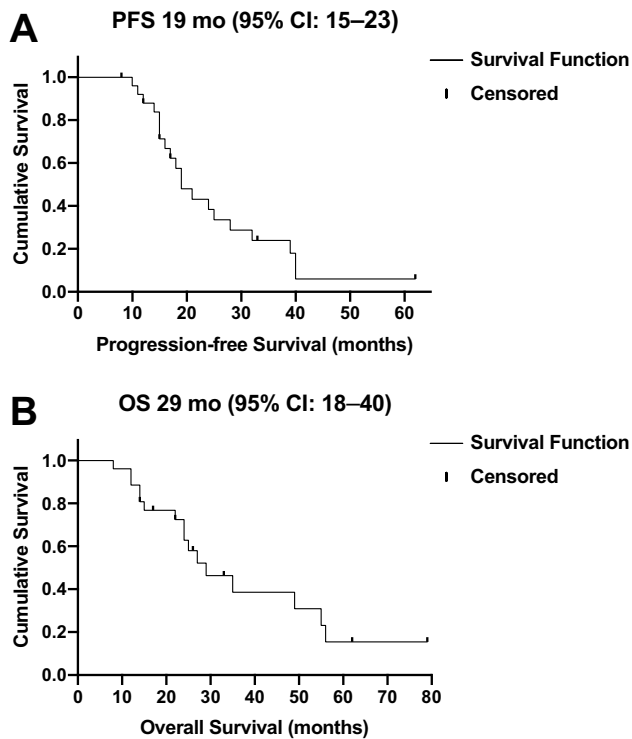


Fig. 5 **A** Progression-free survival and **B** overall survival of the patients ($n = 26$) in months

Fig. 6 Violin plots for hemoglobin, white blood cells (WBC), and platelets at baseline and upon maximum deterioration during the first six and extended cycles

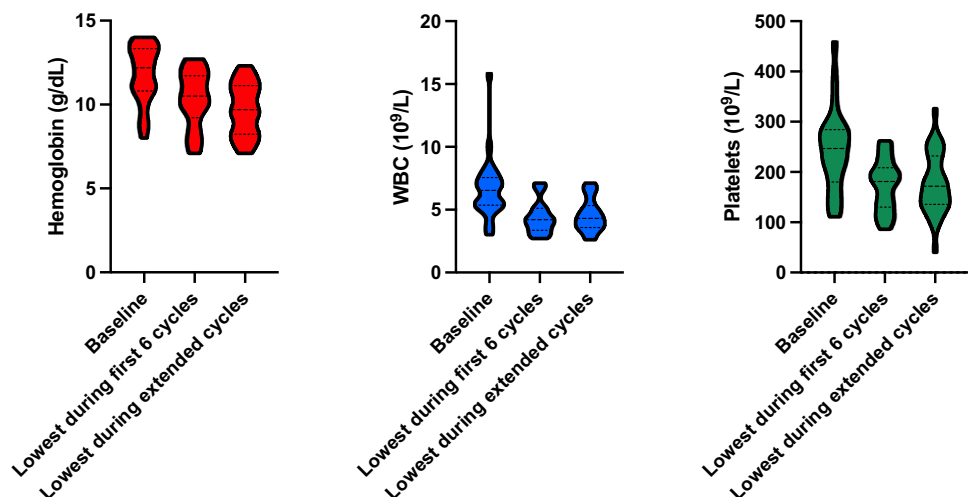


Table 2 Hematological and renal parameters: prior to [^{177}Lu]Lu-PSMA RLT, during the standard and extended cycles, and at the last follow-up

| Blood parameter | Baseline | Nadir standard | After six cycles | Nadir extended | Last follow-up |
|--|-----------------|-----------------|------------------|-----------------|----------------|
| Hb (g/dL) | 11.8 ± 1.7 | 10.3 ± 1.7 | 11.1 ± 1.7 | 9.7 ± 1.6 | 9.9 ± 1.7 |
| WBC ($10^9/\text{L}$) | 6.5 ± 2.5 | 4.4 ± 1.3 | 5.3 ± 1.6 | 4.6 ± 1.5 | 5.1 ± 1.4 |
| Plt ($10^9/\text{L}$) | 239 ± 82 | 175 ± 52 | 203 ± 68 | 175 ± 65 | 191 ± 75 |
| eGFR ($\text{mL}/\text{min}/1.73\text{m}^2$) | 85.3 ± 18.9 | 73.7 ± 18.7 | 80.6 ± 16.7 | 67.9 ± 18.1 | 65.8 ± 19 |

Discussion

This retrospective study introduces the concept of extended [^{177}Lu]Lu-PSMA RLT in mCRPC patients responding to [^{177}Lu]Lu-PSMA RLT but completing standard treatment of six cycles with high residual tumor load. Patients received additional treatment cycles until disease progression, occurrence of significant toxicity, or achieving low PSMA-expressing tumor burden. Further tumor reduction in 38% ($n = 10$) of patients and a relatively long PFS of 19 months in our patients with high-volume disease and poor prognosis [12] indicate the clinical benefit of additional treatment cycles. Furthermore, the toxicity rate remained low in our patient group despite a cumulative administered activity of 75.0 ± 19.1 GBq, underlining the safety of [^{177}Lu]Lu-PSMA RLT. These findings encourage extended treatment in selected patients with no other promising therapeutic options.

The current standard treatment scheme for [^{177}Lu]Lu-PSMA RLT is based on previous experiences with peptide receptor radionuclide therapy (PRRT) for neuroendocrine tumors (NET) consisting of four cycles of 7.4 GBq [^{177}Lu]Lu-DOTA-TATE per cycle [18]. This scheme was successfully adapted in the phase III VISION trial with a slight modification, and responders with residual tumor burden after the fourth cycle of [^{177}Lu]Lu-PSMA-617 could be offered up to two extra

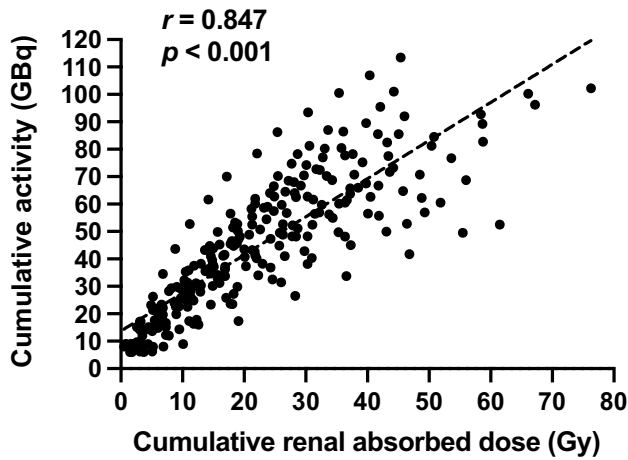


Fig. 7 Cumulative renal-absorbed dose (Gy) after each cycle in relation to the cumulative activity after each cycle (GBq)

cycles (i.e., six cycles) [6]. [¹⁷⁷Lu]Lu-PSMA RLT with 1–6 cycles of [¹⁷⁷Lu]Lu-PSMA-617 improved the survival of mCRPC patients as compared to standard of care, resulting in a PFS of 8.7 and an OS of 15.3 months [6]. No information was available regarding the number and outcome of the subgroup of responding patients receiving a total of six cycles. In our study, patients showed an OS of 29 months receiving extended [¹⁷⁷Lu]Lu-PSMA RLT with a median of 10 cycles (range 7–16). This comparatively long overall survival may be partly due to the composition of our patient group consisting solely of responders with an expectedly more favorable outcome [9, 19]. The observed PFS of 19 months in our study is in line with the results of the only study addressing the outcome of patients receiving additional [¹⁷⁷Lu]Lu-PSMA RLT cycles. In a study by Derlin et al. in 26 patients including 19 (73%) patients with a PSA

Fig. 8 From left to right: MIP [⁶⁸Ga]Ga-PSMA-11 PET images of a patient with high-volume disease receiving a low renal dose after initial cycles of [¹⁷⁷Lu]Lu-PSMA RLT. Mean cumulative renal-absorbed dose was 14.5 Gy after a cumulative administered activity of 56.4 GBq, and Δ eGFR per year was –13.8%. RLT was discontinued due to a cerebrovascular insult after 8 cycles

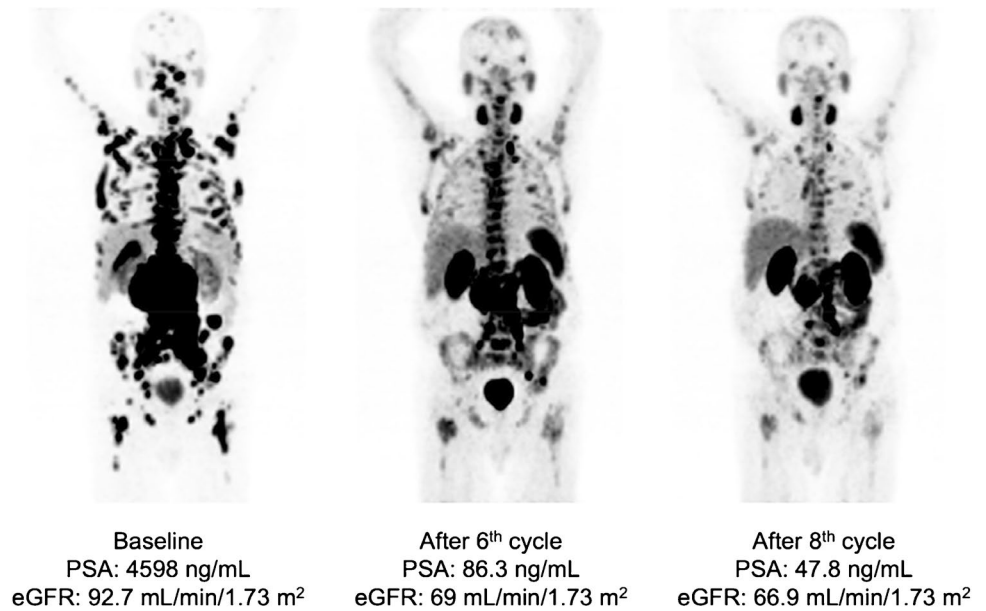
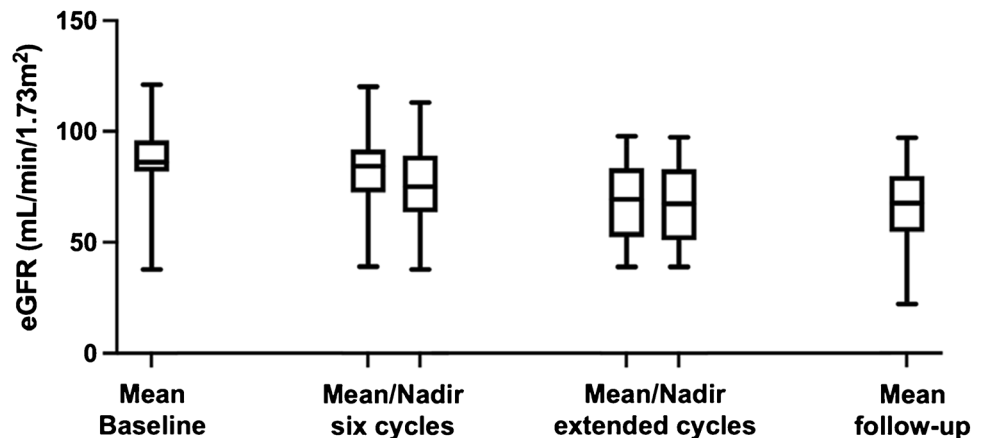


Fig. 9 Mean eGFR at baseline, during the standard and extended [¹⁷⁷Lu]Lu-PSMA RLT, and at the last follow-up



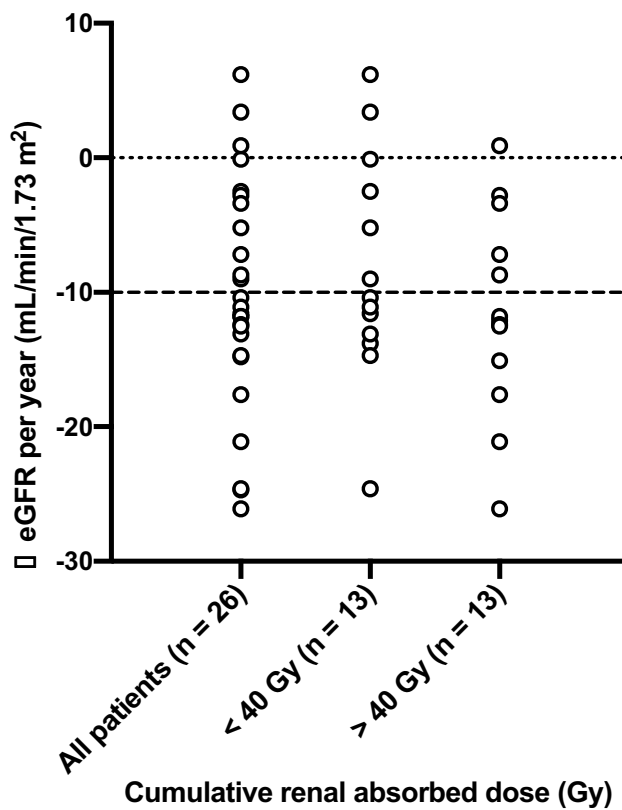


Fig. 10 Yearly change in eGFR of all patients and separately in patients receiving cumulative absorbed renal doses <40 Gy vs. >40 Gy. The dashed line indicates a yearly change in eGFR of $-10 \text{ mL/min/1.73 m}^2$

decline $\geq 90\%$ after six cycles, a median of 9 ± 2 cycles of [¹⁷⁷Lu]Lu-PSMA-617, [¹⁷⁷Lu]Lu-PSMA-I&T, or both was applied, aiming for a complete response (CR). Further PSA decline was seen in 13/26 (50%) patients. Two patients with biochemical CR showed imaging-based CR with no more PSMA-expressing lesions during the additional treatment period. A PFS of 15 months could be reached, but OS was not reported [8].

In patients with metastatic prostate cancer, high-volume disease according to CHARTED (i.e., hepatic or multifocal bone involvement) is associated with poor prognosis [12]. This negative impact on survival has also been observed in the context of [¹⁷⁷Lu]Lu-PSMA RLT. Ahmadzadehfar et al. observed a significantly shorter survival in patients with bone metastases (OS 10.8 months) undergoing [¹⁷⁷Lu]Lu-PSMA RLT, and Khreish et al. reported an impaired outcome in the presence of hepatic metastases, even in the subgroup of patients responding to [¹⁷⁷Lu]Lu-PSMA RLT with an OS of 14.5 months [20, 21]. Considerably longer overall survival of our patients despite high residual tumor load

after six cycles indicates the beneficial effect of extended [¹⁷⁷Lu]Lu-PSMA RLT.

[¹⁷⁷Lu]Lu-PSMA RLT using the standard scheme has been proved safe with a low toxicity profile [6]. An increase in cumulative administered activity raises concerns regarding the safety of the treatment. Kidneys along with bone marrow are considered the main dose-limiting organs in patients undergoing [¹⁷⁷Lu]Lu-PSMA RLT. In contrast to bone marrow suppression, treatment-induced renal function impairment may become clinically evident months after [¹⁷⁷Lu]Lu-PSMA RLT initiation [22–26]. As a result, in patients with a life expectancy of more than 1 year, the cumulative kidney-absorbed dose may only exceed 40 Gy after careful individual benefit-to-risk evaluation [1]. Therefore, in our study, only patients with high total tumor volume and no other promising therapeutic option were selected for extended [¹⁷⁷Lu]Lu-PSMA RLT. The mean cumulative kidney-absorbed dose was $39.7 \pm 15.3 \text{ Gy}$, and 13/26 (50%) patients received >40 Gy. Renal-absorbed dose per administered activity ($0.54 \pm 0.22 \text{ Gy/GBq}$) in our study is in line with the reported values in the literature, most probably due to the high tumor burden and evident tumor sink effect at baseline in our patients (Fig. 9) [1, 27]. Only 1/26 (3.8%) patient treated with a cumulated administered activity of 100.4 GBq resulting in a cumulative kidney-absorbed dose of 63.3 Gy developed significant kidney toxicity (grade 3) 18 months after the treatment initiation (Fig. 8). In the phase III VISION trial, grade 3 to 5 renal effects were observed in 3.4% after a median cumulative dose of 37.5 GBq (range, 7–48.3) and a follow-up of 20.9 months [6]. In the study by Derlin et al., no patient showed significant hematological or kidney toxicity (\geq grade 3) and only one patient discontinued [¹⁷⁷Lu]Lu-PSMA RLT because of aggravating grade 2 nephrotoxicity; the cumulative kidney-absorbed dose was not reported [8]. In the phase III VISION trial, hematological adverse events (grade ≥ 3) including anemia, leukopenia, and thrombocytopenia occurred in 12.9%, 2.5%, and 7.9%, respectively [6]. In a retrospective study on 140 patients analyzing a total of 497 cycles of [¹⁷⁷Lu]Lu-PSMA-617, significant (grade ≥ 3) hematologic adverse events occurred in 13 (9.3%) patients, with anemia in 10 (7.1%), leukopenia in 5 (3.6%), and thrombocytopenia in 6 (4.3%) [28]. Observation of significant hematological toxicity in 4/26 (15%) patients in our study supports the established favorable hematological safety profile of [¹⁷⁷Lu]Lu-PSMA RLT even after high cumulative activities. Furthermore, the presence of progressive disease in 3 of these 4 patients suggested that significant toxicity may be at least partly attributed to tumor-induced bone marrow impairment [29].

There are some limitations in our study. The small sample size, hampering in-depth statistical analyses, and the retrospective nature, limiting the comparability with

Fig. 11 **A** From left to right: MIP [⁶⁸Ga]Ga-PSMA-11 PET images of a patient with extensive disseminated bone metastasis and extradural infiltration. Extended RLT was discontinued upon progression after 12 cycles and a cumulative renal-absorbed dose of 63.3 Gy. **B** Course of eGFR from baseline to the last follow-up of the same patient, developing nephrotoxicity of grade 3

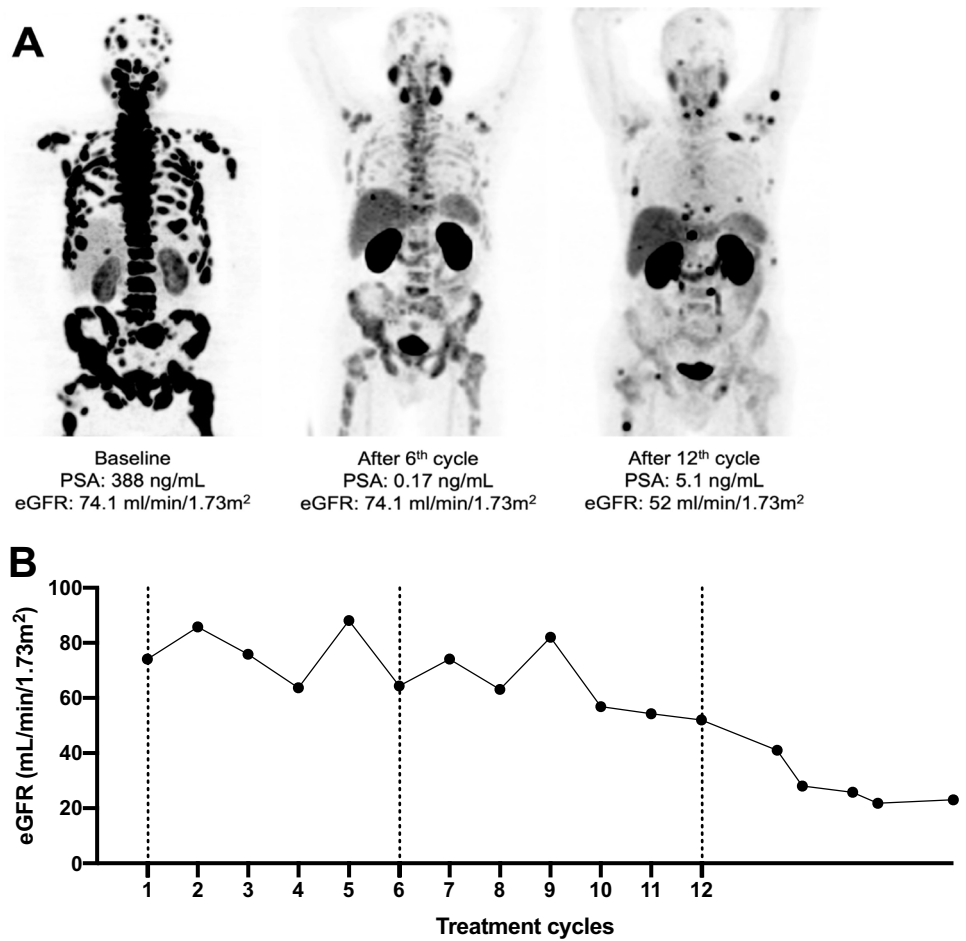


Table 3 Hematologic, renal, and salivary gland toxicity grades based on CTCAE v5.0 at baseline, after 6 cycles, during added cycles, and at follow-up

| Toxicity (grade) | Baseline (%) | | After 6 cycles (%) | | Added cycles (%) | | Follow-up (%) | |
|------------------|--------------|-------|--------------------|-------|------------------|--------|---------------|--------|
| | 1/2 | 3/4 | 1/2 | 3/4 | 1/2 | 3/4 | 1/2 | 3/4 |
| Anemia | 15 (58) | 0 (0) | 26 (100) | 0 (0) | 23 (88) | 3 (12) | 22 (85) | 4 (15) |
| Leukopenia | 2 (8) | 0 (0) | 4 (15) | 0 (0) | 11 (42) | 0 (0) | 7 (27) | 0 (0) |
| Thrombocytopenia | 3 (12) | 0 (0) | 7 (27) | 0 (0) | 12 (46) | 1 (4) | 10 (38) | 0 (0) |
| eGFR* | 3 (12) | 0 (0) | 3 (12) | 0 (0) | 6 (23) | 0 (0) | 8 (31) | 1 (4) |
| Xerostomia | 0 (0) | 0 (0) | 9 (35) | 0 (0) | 15 (58) | 0 (0) | 15 (58) | 0 (0) |

*Estimated glomerular filtration rate

the prospective trials, need to be considered. However, improved survival outcome and low-toxicity rates in our patients justify a serious consideration of extended [¹⁷⁷Lu]Lu-PSMA RLT in selected patients who respond to standard treatment but show high residual tumor load after the sixth cycle.

Conclusions

Extended [¹⁷⁷Lu]Lu-PSMA RLT may improve the survival outcome of mCRPC patients with high-volume residual tumor after the completion of standard treatment with six cycles of [¹⁷⁷Lu]Lu-PSMA-617. Despite high cumulative

activities, the safety profile may remain acceptable, warranting further investigation of the concept of extended treatment with additional cycles in selected patients.

Abbreviations ALP: Alkaline phosphatase; CI: Confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; eGFR: Estimated glomerular filtration rate; GBq: Gigabecquerel; Hb: Hemoglobin; IQR: Interquartile range; LDH: Lactate dehydrogenase; [¹⁷⁷Lu]Lu-PSMA RLT: [¹⁷⁷Lu]Lu-PSMA-617 radioligand therapy; mCRPC: Metastatic castration-resistant prostate cancer; NET: Neuroendocrine tumor; Plt: Platelets; PRRT: Peptide receptor radionuclide therapy; PSA: Prostate-specific antigen; PSMA: Prostate-specific membrane antigen; RLT: Radioligand therapy; VAS: Visual analog scale; WBC: White blood cells

Author contribution N. M. and A. S. designed the study, analyzed and interpreted the data, and drafted the manuscript.

N.M., B.K., C.T.N., J. B., and K. K. acquired data and revised the manuscript.

D.G. and C. H. interpreted the data and substantively revised the manuscript.

F.G., N. T., and F. K. H. C. substantively revised the manuscript and approved its final content.

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Data Availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval All procedures performed were in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All patients gave written informed consent prior to each therapy cycle, and retrospective data analysis was approved by the ethics committee of Goethe University Frankfurt (approval number: 310/18).

Consent for publication All patients gave written informed consent to participation and publication.

Competing interests The authors declare no competing interests.

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