Original article

Response to [177Lu]Lu-PSMA radioligand therapy in metastatic castration-resistant prostate cancer patients presenting with only lymph node metastases

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Objective [177Lu]Lu-PSMA radioligand therapy (PSMA-RLT) is a promising therapy for patients with metastatic castration-resistant prostate cancer (mCRPC) and offers a survival benefit particularly to patients with only lymph node metastases. We therefore sought to evaluate the clinical outcome of this therapy in such a cohort.

Methods Of all prostate cancer patients admitted to our department between September 2015 and March 2019 to receive 1–4 courses of PSMA-RLT (each course consisted of three cycles of highly standardized PSMA-RLT every 4 weeks), only 10 consecutive men were found to have nodal metastases only and were analyzed retrospectively.

Results Nine out of 10 patients responded to their first PSMA-RLT course with a mean prostate-specific antigen (PSA) decline of 71.8 ± 25.2%, seven of them demonstrated a PSA decline of ≥50%. Collectively, seven of eight patients responded to further PSMA-RLT courses with a total PSA reduction of 59.8 ± 30.0%, five of which showed a PSA reduction of ≥50%. One patient experienced complete remission. Median progression-free survival was 85 weeks (range 14–255 weeks) and median overall survival was not reached during the median observation time of 209 weeks (30–298 weeks). Univariate

Cox-regression identified initial PSA decline as the only predictive parameter for progression-free survival (*P* = 0.047).

Conclusion mCRPC patients with only lymph node metastases showed favorable survival and excellent response to PSMA-RLT, leading to transient partial remission of the disease in most of them. *Nucl Med Commun* 43: 1113–1120 Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Prostate cancer is the second most diagnosed type of cancer in men. While the 5-year survival rate of patients with localized or regional prostate cancer approaches 100%, it drops to 30% in case of distant metastases. Consequently, prostate cancer is the second leading cause of cancer deaths in males [1,2]. Currently, established therapies of metastatic castration-resistant prostate cancer (mCRPC) include chemotherapeutics of the taxane class and luteinizing hormone-releasing hormone analogs like abiraterone or enzalutamide. Nevertheless,

treatment success of these therapies is limited [3]. In recent years, [177Lu]Lu-PSMA radioligand therapy (PSMA-RLT) has emerged as a novel treatment modality for end-stage mCRPC. Prostate-specific membrane antigen (PSMA) is a membrane-bound glutamate-preferring carboxypeptidase that is markedly and strongly expressed in cancerous prostatic epithelium. Its inverse correlation with androgen levels promotes its attractiveness as a treatment target for castration-resistant prostate cancer [4]. The effectiveness and safety of PSMA-RLT in patients with mCRPC has already been demonstrated in several studies [5–11]. Moreover, it has been shown to improve patient outcome when added to standard care [12] and its capability to reduce PSA levels was evaluated to be superior to third-line therapies such as cabazitaxel [13,14]. Nevertheless, treatment response varies

and predictive parameters for therapeutic benefit have yet to be fully elicited. Hitherto, prognostic factors for therapy response and longer overall survival (OS) with PSMA-RLT were observed to be chemotherapy naivety, asymptomatic disease, small tumor volume, high PSMA-uptake of the lesions [10,15], low basal prostate-specific antigen (PSA) levels and normal basal hemoglobin levels [16]. Furthermore, previous studies [15,17–19], including our own most recent results [20], suggested a better survival of patients lacking bone or visceral metastases.

Considering these findings, the present study aimed to evaluate the effectiveness of an intensive, standardized PSMA-RLT treatment regime in a prostate cancer patient cohort with exclusively nodal metastasis. We therefore evaluated PSA-based treatment response, OS and progression-free survival (PFS) and its predictive parameters in mCRPC patients who received repeated treatment courses of highly standardized PSMA-RLT, every course consisting of three cycles of therapy at 4 weeks interval.

Subjects and methods
Patients
This retrospective study included all prostate cancer patients with lymph node-restricted metastases who received at least one full course consisting of three cycles PSMA-RLT every 4 weeks at the Department of Nuclear Medicine of the Medical University of Vienna, General Hospital of Vienna, between September 2015 and December 2020. Out of a total of 90 patients who received at least one full course of PSMA-RLT during the studied time frame, only 10 patients exhibited only lymph node metastases. This study cohort partially overlaps with our previously published cohorts that had mixed metastases [11,16,20,21]. There was no patient with lymph node-restricted metastasis who did not complete at least one course of PSMA-RLT. The diagnosis and localization of metastases was based on [68Ga]Ga-PSMA-11 PET/MR or PET/CT imaging conducted by two specialists in nuclear medicine and one radiologist (at least 5 years of experience) prior to the start of PSMA-RLT. The imaging protocols have previously been described [21] and patient follow-up was carried out until June 2021. The indication of each PSMA-RLT course was approved by an interdisciplinary tumor board. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Medical University of Vienna (EK: 1143/2019) and all patients gave written informed consent prior each therapy cycle.

[177Lu]Lu-PSMA-RLT regime
PSMA-RLT was conducted in line with §8 of the Austrian pharmaceutical law (AMG). The PSMA-RLT scheme was carried out in courses, each consisting of three cycles of 7450 (range 5760–7920) MBq intravenous [177Lu]Lu-PSMA administration at 4 weeks interval. From September 2015 to March 2019, patients were treated with [177Lu]Lu-PSMA-617 that was acquired from ABX GmbH (Radberg, Germany), and from April 2019 and thereafter with [177Lu]Lu-PSMA I&T, obtained from Scintomics Molecular Applied Theranostics Technologies GmbH (Fürstenfeldbruck, Germany). Patients further received 1L saline infusion (300 ml/h) 30 min before each [177Lu]Lu-PSMA administration. For clinical monitoring and radiation safety reasons, all patients were hospitalized for at least 48 h during each cycle. All patients received at least one full course of the therapy.

During each admission, the general condition of the patients was evaluated by an experienced medical doctor and patient's ECOG (Eastern Cooperative Oncology Group) Status and Karnofsky-Index were accordingly assessed. Furthermore, routine laboratory parameters including complete blood count, biochemistry, and PSA levels were measured. Therapy toxicity was evaluated based on the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Total tumor volume (TTV) before PSMA-RLT-start was calculated for each patient by PET-scan-based delineation of the tumor and metastases using the Hermes Hybrid 3D software (Hermes Medical Solutions, Stockholm, Sweden). In brief and as we published previously [21], significantly elevated PSMA expression was initially identified by using a threshold-based volume of interest (VOI) with 20% higher mean SUV than a cubic $10 \times 10 \times 10$ voxel reference VOI of the liver. The resulting program generated VOIs were then edited manually. The remaining nonspecific and physiological PSMA uptake was cropped and PSMA expressing lymph nodes with SUVs below the specified threshold were added.

Continuation of PSMA-RLT was re-assessed before each course according to the previous response. The time between courses (minimum 3 months) depended on response to the previous PSMA-RLT, disease progression and the general clinical status of the patient.

Definitions of outcome parameters
Therapy response was evaluated by PSA reduction at the time of the nadir after PSMA-RLT relative to PSA before the start of the course. The term "initial PSA reduction" refers to PSA decrease in percentage after the first course of PSMA-RLT, whereas "total PSA reduction" is the PSA decrease in percentage after the last therapy course in relation to PSA levels before the first course. Response to PSMA-RLT was defined as any PSA decrease. Disease progression was noted in case of a PSA increase ≥25% relative to the previous nadir PSA-level. Progression-free survival (PFS) for each course spans from therapy start to following progression of disease. Total PFS refers to the time from the start of the first treatment course to progression after the last PSMA-RLT-related PSA decline during the entire time of follow-up.

Statistical analysis

Statistical analysis was carried out using the software IBM SPSS, version 26.0 (IBM Corp., Armonk, NY, USA). Data were tested for normal distribution by Shapiro-Wilk-test. Accordingly, normally distributed data are presented as mean ± SD and non-normally data are expressed in median and range (minivariate-maximum). Univariate Cox-regression and Mantel-Cox test were used to identify predictive parameters for total PFS. Paired *t*-test was carried out for comparison of biochemical parameters before and after the entire PSMA-RLT and Wilcoxon signed-rank test was used to compare initial and total PSA reduction of patients who responded to consecutive PSMA-RLT. Kendall's tau b was applied to test for an association between the number of conducted PSMA-RLT courses and total PFS. A two-sided *P*-value <0.05 was considered significant. Figures were plotted using R in RStudio (R Foundation for Statistical Computing, Vienna) using the packages ggplot [22], survminer [23] and swimplot [24].

Results

Patient cohort

Collectively, only 10 prostate cancer patients (aged 71 ± 1 years), who received a median of 2 courses (range 1–4), median 6 cycles (range 3–12) of [^{177}Lu]Lu-PSMA therapy, were found to exhibit only lymph node metastasis. Prior to therapy initiation, patients had a median PSA level of 13.6 µg/L (range 2.94–597) and a median TTV of 11.3 ml (range 0.35–361.6). The clinical and biochemical characteristics of the patients prior to PSMA-RLT are summarized in Table 1.

All patients except patient no. 7 had previously undergone radical prostatectomy, and six of them had additionally undergone radiotherapy. Eight patients were castration resistant, four of the patients had a history of chemotherapy (CHT) and new-generation hormone therapy (HT) (Table 1).

Despite a significant decrease of mean hemoglobin (Hb) and platelet count over the entire PSMA-RLT (Hb: 13.4 ± 0.6 vs. 12.7 ± 1.6 g/dl, *P* = 0.027; thrombocytes: 232 ± 27 vs. 180 ± 70 g/L, *P* = 0.004), we observed no emerging hematopoietic or renal toxicity as defined by CTCAE 5.0.

Response and outcome of the patient collective

Nine out of ten studied patients (90%) responded to their first PSMA-RLT course with a mean PSA decrease of 71.8 ± 25.2%, seven (70%) and five (50%) patients experienced a PSA decline of ≥50% and ≥80%, respectively. Two patients received only one course of the treatment, whereas the other eight patients received up to four consecutive PSMA-RLT courses. Of them, seven patients (88%) exhibited any PSA decline and demonstrated a total PSA reduction of 59.8 ± 30.0% at the end of all therapy courses, five patients (63%) revealed a PSA reduction of ≥50% and one patient (13%) had PSA reduction of ≥80% (Table 2 and Fig. 1). Among these patients, the difference between initial PSA reduction and total PSA reduction was NS (*P* = 0.176).

Nine patients (90%) of the entire studied cohort survived until the endpoint of the study with a median observation time of 209 weeks (range 30–298). The median total PFS of the entire patient cohort was 85 weeks. Table 3 depicts the survival outcome in detail and Fig. 2 summarizes the total PFS of the patient cohort. The trend toward shorter PFS with each consecutive course was statistically NS in Log Rank (Mantel-Cox) analysis (Chi-square = 7.08, df3, *P* = 0.06).

Response and outcome of the individual patients

For a better overview, the individual disease burden and outcome of each patient are listed in Table 2 and illustrated in Fig. 3.

Patient no. 1 and no. 2 both received one course of PSMA-RLT. The chemotherapy-naïve patient no. 1 experienced 98% PSA reduction with sustained metastatic remission in PSMA-PET imaging (Fig. 4), whereas patient no. 2 was the only nonresponder who was effectively treated with docetaxel after unsuccessful PSMA-RLT.

Patients no. 3 to no. 7 were treated with two courses of PSMA-RLT. Patient no. 3 and no. 4 both demonstrated continuous excellent therapy response, and the chemotherapeutically pretreated patient no. 3, who received

Table 1 Clinical and biochemical patient characteristics prior to prostate-specific membrane antigen-radioligand therapy

Parameters	Values
Age (mean ± SD) years	71 ± 1
Weight (mean ± SD) kilogram	86 ± 3
[^{177}Lu]Lu-PSMA MBq	7450 (5760–7920)
ECOG index < 2	10/10
Karnofsky score ≥ 80	10/10
Previous ADT	8/10
Previous arbiraterone/enzalutamide	[b]4/10
Previous CHT	[b]4/10
TTV[a] ml	11.3 (0.35–361.6)
PSA[a] µg/L	13.6 (2.94–597)
Hemoglobin (mean ± SD) g/dl	13.4 ± 0.6
Thrombocytes (mean ± SD) g/l	232.0 ± 26.7
Leucocytes[a] g/L	6.96 (2.94–22.73)
CRP[a] (g/dl)	0.15 (0.03–14.70)
Creatinine[a] mg/dl	0.92 (0.77–1.45)
AP (mean ± SD) U/L	73.8 ± 13.3
LDH[a] U/L	160 (136–395)
Lymph node metastases ± local recurrence	
Cervical-axillary	4/10
Mediastinal-hilar	4/10
Abdominal	6/10
Regional	5/10

ADT, androgen deprivation therapy; AP, alkaline phosphatase; CHT, chemotherapy; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; MBq, megabecquerel; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RLT, radioligand therapy; TTV, total tumor volume.
[a]Data not normally distributed, presented in median and range.
[b]Same four patients.

Table 2 Tumor burden and outcome of the individual patients

| Pat.	C.	TTV (ml)	Initial PSA (µg/L)	Initial PSA decline (%)	Total PSA decline (%)	End PSA (µg/L)[a]	Total PFS (weeks)	OS (weeks)
1	1	3.7	16.0	98	98	0.38	46	261
2		224.53	90.3	−38	−38	125	14	30
3	2	361.6	597.0	95	100	<0.02	255[b]	278
4		0.35	2.9	52	59	1.21	54	139
5		3.15	9.4	52	7	8.73	73	291
6		0.5	4.3	94	55	1.94	148	156
7		11.46	18.1	40	−10	20.2	42	78[c]
8	3	43.19	11.3	40	68	3.61	96[b]	96
9	4	19.07	32.6	85	50	16.2	142	300
10		11.07	7.0	91	42	4.09	229	265

C., number of courses; (<), less than; OS, overall survival; Pat., patient; PFS, progression-free survival; PSMA, prostate-specific membrane antigen; PSA, prostate-specific antigen; RLT, radioligand therapy; TTV, total tumor volume.
[a]Nadir PSA value after last therapy course.
[b]No progress after the last PSMA-RLT.
[c]Death.

Fig. 1
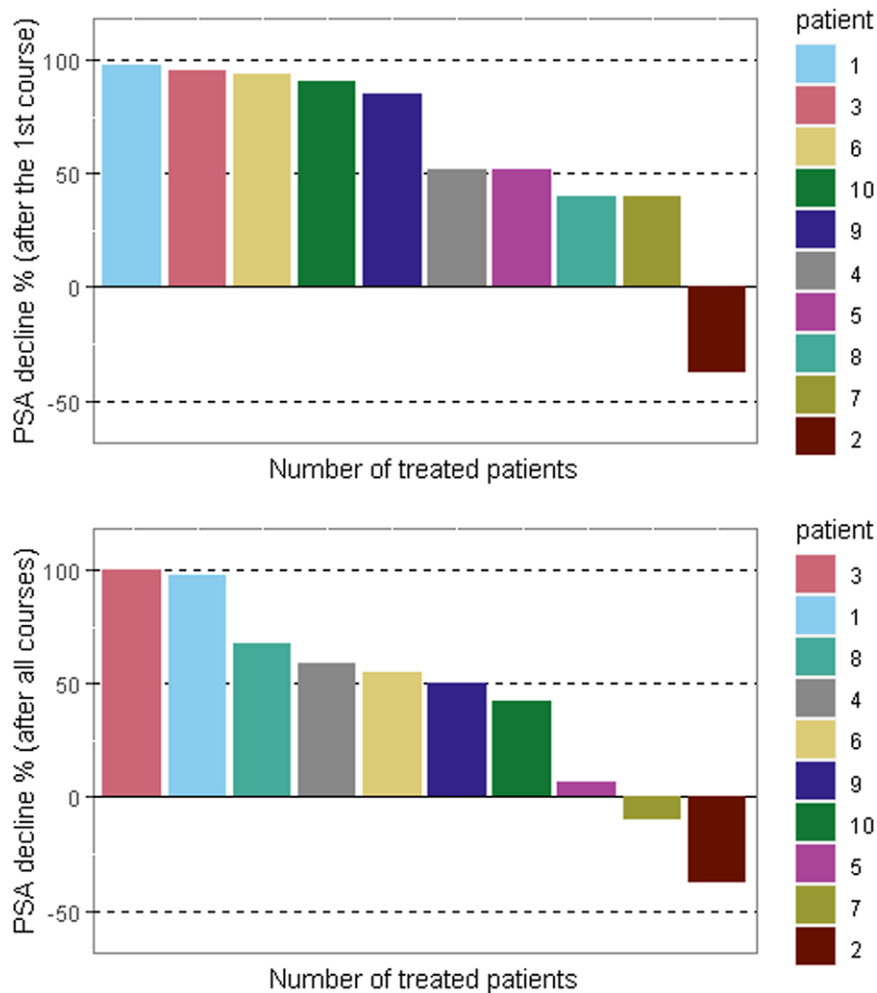
Percentage of PSA decline in the studied patients after the first and all courses of PSMA-RLT, with each course consisting of three cycles at 4 weeks interval. PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RLT, radioligand therapy.

abiraterone in parallel to PSMA-RLT, reached persistent complete biochemical remission 59 weeks after the last therapy cycle. Furthermore, consecutive post-therapy PET scans of both patients did not reveal any PSMA-expressing metastases until the end of follow-up. Notably, their tumor burden at the start of therapy differed greatly (Table 2). In

contrast, patient no. 5 and no. 6 experienced PSA rebound after the first course, which was only partly repressed by the second course. Patient no. 7, the only patient who had not undergone prostatectomy, had been treated with trenantone, abiraterone, enzalutamide, docetaxel and cabazitaxel prior to PSMA-RLT and died shortly after not responding to his second treatment course. Another patient with history of new-generation hormone therapy and chemotherapy, patient no. 8, experienced successive moderate PSA decline over his three courses of PSMA-RLT, which was also reflected in PET imaging (Fig. 4). Remarkably, throughout the 11 months between his first and second course, he did not experience any PSA progression.

Patient no. 9 and no. 10 received 4 therapy courses. Both demonstrated intermittent PSA increases, patient no. 9

between his courses and patient no. 10 within his third and fourth course. Their last nadirs of PSA were above previous nadir values but still below PSA before treatment start.

Predictive parameters

The only predictive parameter for total PFS in our study was initial PSA reduction (univariate Cox-regression analysis: $P = 0.047$). Total PSA reduction and following parameters were nonpredictive: age, weight, previous ADT, new-generation HT and CHT, TTV, nonregional lymph node metastases, basal PSA as well as basal hemoglobin, thrombocyte count, leucocyte count, C-reactive protein, creatinine, alkaline phosphatase, lactate dehydrogenase. Furthermore, upon exclusion of the inaccurately high PFS of patient no. 6, even initial PSA reduction was no longer a significant prognosticator for total PFS.

To investigate whether the number of received courses is a mediating variable between initial PSA reduction and total PFS, Kendall's tau b correlation analysis was performed. The number of PSMA-RLT courses was not associated with initial PSA reduction or total PFS.

Discussion

PSMA-RLT is an investigational treatment option for patients with mCRPC that has been available in Europe for less than 8 years. It has not yet been included in guidelines because promising study results have only been published very recently. The Vienna General Hospital in Vienna, Austria, offers this therapy since September 2015 as one of the few clinical centers in central Europe. We follow a highly standardized therapy protocol consisting

Table 3 Progression-free survival (in weeks) after each course of prostate-specific membrane antigen-radioligand therapy
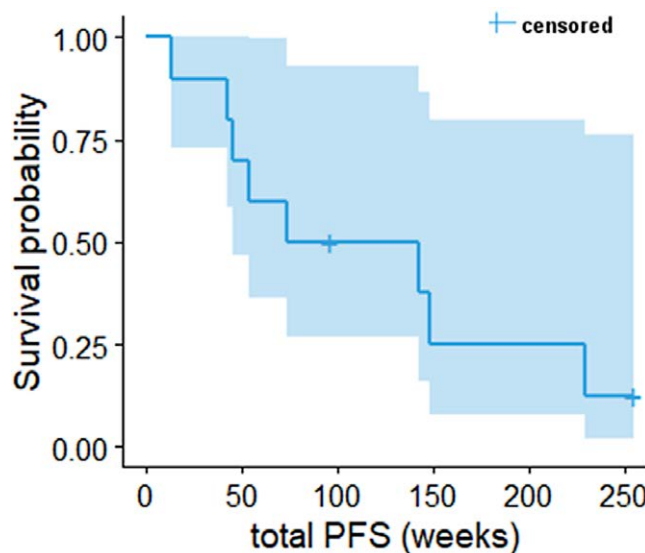
Patient	Course 1 PFS	Course 2 PFS	Course 3 PFS	Course 4 PFS	Total PFS (weeks)
1	46				46
2	14				14
3	22	219[b]			255
4	54[a]	32			54
5	41	26			73
6	50	98			148
7	42[a]	20			42
8	79[a]	23	17[b]		96
9	21	23	26	22	142
10	61	31	31	17	229
M	44	29	26	20	85

M, median; PFS, progression-free survival; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RLT, radioligand therapy.
[a]No further PSA progression until the next course of PSMA-RLT.
[b]No PSA progression until the end of observation.

Fig. 2

Kaplan–Meier curve of total progression-free survival of the entire patient cohort.

Fig. 3
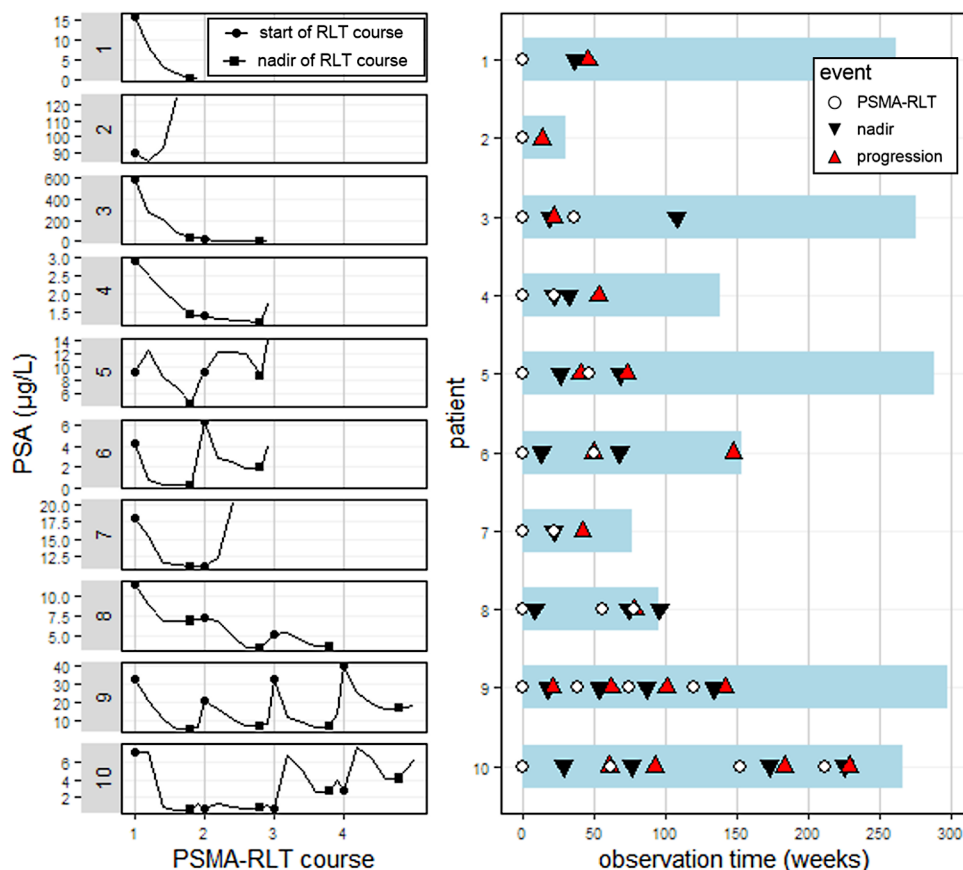
PSA development during the time of PSMA-RLT (left) and swimmer plot of the time between events during the observation period (right) of each patient. PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RLT, radioligand therapy.

of three cycles of PSMA-RLT every 4 weeks per therapy course. Based on the evidence of numerous studies, PSMA-RLT is an effective and safe treatment option for patients with mCRPC [5–10,20]. Earlier results indicated that especially patients with exclusively nodal metastasis significantly benefit from PSMA-RLT [15,17–20]. Nevertheless, in most of these studies, this evidence was provided in the context of a large analysis with heterogeneous treatment protocols that included prostate cancer patients with all types of metastases treated with PSMA-RLT. To our knowledge, no study is published reporting results of standardized Lu-PSMA RLT in patients with lymph node metastases only. The present study assessed the PSMA-RLT response, PFS and OS of patients adhering to this criterion (n = 10) and found that 90% of the patients responded to their first course of PSMA-RLT (70% showed reduction ≥50%), resulting in a total progression-free survival of median 85 weeks (range 14–255) and the survival of 9 of the 10 (90%) patients during observation time. There were no severe adverse events related to PSMA-RLT. Moreover, even though this was not the

main objective of this analysis, the results revealed no new-onset hematopoietic or renal toxicity according to CTCAE 5.0, despite a significant decrease in mean Hb and platelet count throughout PSMA-RLT.

Studies on the effect of PSMA-RLT in mCRPC patients with lymph node-restricted metastases are very limited. Previous meta-analyses such as one by Yadav *et al.* [9], including 17 studies with a total of 744 patients without stratification regarding the site of metastases, calculated a response to PSMA-RLT of approximately 75% of the patient collective. Another recent systematic review of 36 studies with a total of 2346 patients has further demonstrated a ≥50% PSA reduction for 50% of the mCRPC patients treated with PSMA-RLT [10]. In addition, the results of this review indicated a longer life for patients treated with an intensified PSMS-RLT regimen than for patients treated with a conventional regimen. The current study cohort has a higher response rate not only compared with these nonstratified patient collectives but also compared with the overlapping cohort of 54 patients

Fig. 4
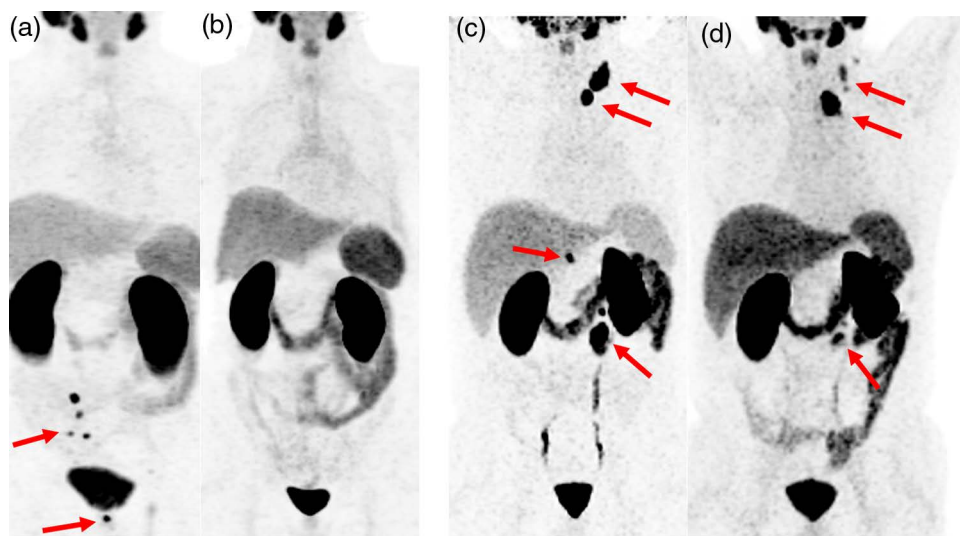
[^{68}Ga]Ga-PSMA PET imaging before and after PSMA-RLT of patient No. 1 (left) and patient No. 8 (right). Patient No. 1 exhibited pelvine lymph node metastases and a local recurrence (arrows) before PSMA-RLT (a), which were not visible anymore after PSMA-RLT (b). Patient No. 8 presented with cervical, mediastinal and abdominal lymph node metastases (c) that showed mixed response to PSMA-RLT therapy (d). PSMA, prostate-specific membrane antigen; RLT, radioligand therapy.

that we previously analyzed (about 80% of any decline, 60% with ≥50%) [11]. PSA reduction ≥50% was associated with longer overall survival in previous other studies [10,25]. In our study, 70% of the patients surpassed this threshold, whereas in Eyben *et al.* [19], 90% of patients with only nodal metastasis surpassed it (n = 35, median therapy cycle n = 3). In this regard, it should be considered that in our study a higher proportion of included patients were pretreated with chemotherapy compared to Eyben *et al.* study (40% vs. 20%).

Importantly, the survival rate of 90% in patients studied over an observation time of 209 weeks (30–298) was strikingly longer than the median OS of 70 weeks calculated in the aforementioned recent meta-analysis [10]. Moreover, it exceeded the median OS of 108 weeks in the lymph node subcohort of Ahmadzadehfar *et al.* [15] and the OS of 89% of patients over approximately 130 weeks demonstrated by Eyben *et al.* [19]. Our latest analysis of 43 men with metastases in various organs reported a similarly long median overall survival of 188 weeks [20]. It has been shown that an intensive PSMA-RLT regimen, in terms of a higher applied activity and shorter intervals between the cycles, is associated with longer overall survival [10]. Our treatment strategy ranks among the most intensive PSMA-RLT protocols and might therefore contribute to the better OS of our patients. Nevertheless, the impact of visceral metastasis on OS was apparent in the homogenously treated patient cohort of our earlier study [20]. Factors previously identified as prognostic for OS in patients treated with PSMA-RLT, such as prior chemotherapy, concurrent enzalutamide treatment, total tumor

volume, asymptomatic disease, basal levels of PSA, hemoglobin or alkaline phosphatase [10,15–17], were not associated with the total PFS in our current patient cohort. Interestingly, in this small cohort, lymph node metastasis site (regional or nonregional) was also irrelevant for total PFS during the given observation time. The only significant predictor was the magnitude of PSA reduction after the first course of PSMA-RLT.

Violet *et al.* [26] previously described a reduced time to progress after a re-challenge of PSMA-RLT, where a series of initially four cycles was followed by 1–5 cycles [26]. Although the results were not statistically significant, our current outcomes also point to a diminishing response to successive treatment courses, which is reflected by the lower total PSA response rate as compared to the initial response rate, and the tendency toward shorter PFS after each consecutive RLT course (Table 3). Nevertheless, the continuation of PSMA-RLT proved to be more beneficial than other systemic therapies, and the effectiveness and safety of two courses PSMA-RLT, each consisting of (median) 3 cycles, has further been demonstrated by two other independent studies [20,27].

This study primarily aimed to display the clinical impact of PSMA-RLT on the disease course of mCRPC patients presenting with lymph node-restricted metastasis, who received homogeneous PSMA-RLT treatment courses consisting of three cycles at 4 weeks interval. A main limitation is the small sample size that is easily influenced by outliers and provides low power for statistical analysis, especially regression analysis. A valuable aspect of this

subgroup of patients, however, is the opportunity to provide detailed data on each individual patient. Nevertheless, the retrospective character and heterogeneity in terms of therapies prior to PSMA-RLT as well as inconsistency in follow-up intervals might distort the results of the study.

Conclusion

Based on the clinical outcomes of this study, we conclude that mCRPC patients with exclusively nodal metastasis reveal a particularly favorable response to PSMA-RLT regarding PSA reduction and total PFS, especially in the magnitude and persistence of the initial therapy effect. Even though the overall response ultimately still remains variable, the outstanding OS of the patient cohort is consistent and evident. At the same time, significant severe hematopoietic or renal toxicity did not occur even following multiple cycles of treatment. We encourage future prospective studies to assess these results in a larger patient collective and to further investigate outcome predictors.

Acknowledgements

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