Improved Quality of Life in Metastatic Castration-Resistant Prostate Cancer Patients Receiving Consecutive Cycles of ^{177}Lu-PSMA I&T

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The aim of this retrospective analysis was to evaluate health-related quality of life (HRQoL) for patients with metastatic castration-resistant prostate cancer (mCRPC) receiving consecutive cycles of ^{177}Lu-prostate-specific membrane antigen (PSMA) radioligand therapy (RLT) using the reliable and validated European Organisation for Research and Treatment of Cancer core quality-of-life (QoL) questionnaire. In addition, differences in HRQoL between patients with early discontinuation of treatment because of disease progression and patients who were defined as eligible for treatment continuation were analyzed. **Methods:** In total, 60 mCRPC patients were included in this analysis. The European Organisation for Research and Treatment of Cancer core QoL questionnaire was completed at baseline, before each treatment cycle up to the sixth treatment cycle, and at the time of PSMA-ligand PET/CT scans after the second and fourth treatment cycles. QoL assessment included global health status, functional scales, and symptom burden during treatment. **Results:** Global health was significantly improved at the second and fourth cycles of ^{177}Lu-PSMA RLT ($P = 0.014$ and $P = 0.039$, respectively). In line with this, role and emotional functioning showed significant improvements at the second and fourth treatment cycles (role functioning, $P = 0.045$ and $P = 0.048$, respectively, and emotional functioning, $P = 0.035$ and $P = 0.007$, respectively). In addition, compared with baseline, fatigue and pain were significantly alleviated at the second and fourth treatment cycles (pain, $P = 0.035$ and $P = 0.034$, respectively, and fatigue, $P = 0.042$ and $P = 0.041$, respectively). Other aspects of HRQoL, even if not significantly improved, remained stable over time, except for deterioration of fatigue at the study's end ($P = 0.014$) and reduction of dyspnea at the second treatment cycle ($P = 0.012$). Patients with early discontinuation of treatment showed a concordant decline in HRQoL. **Conclusion:** mCRPC patients showed significant improvement in HRQoL in the course of treatment with ^{177}Lu-PSMA RLT. Furthermore, patients with early discontinuation of treatment showed an analogous decline in HRQoL.

Key Words: prostate-specific membrane antigen radioligand therapy (PSMA RLT); metastatic castration-resistant prostate cancer (mCRPC); health-related quality of life (HRQoL); EORTC QLQ-C30

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In patients with metastatic castration-resistant prostate cancer (mCRPC), radioligand therapy (RLT) that targets ^{177}Lu-prostate-specific membrane antigen (PSMA) has emerged as a promising treatment option and has recently received approval from the U.S. Food and Drug Administration and European Medicines Agency. Patients with metastatic prostate cancer commonly present with bone metastases that potentially lead to severe pain and impaired mobility, which might cause substantial deterioration in quality of life (QoL) (*1,2*).

Therefore, the assessment of health-related QoL (HRQoL) and its changes during therapy is of major interest when new treatment strategies are evaluated. The recently published prospective phase II and III trials investigated the influence of ^{177}Lu-PSMA-617 RLT on HRQoL for mCRPC patients, reporting improvements in both QoL and symptom control (*3–5*). A potential tool for the evaluation of QoL in cancer patients is the European Organisation for Research and Treatment of Cancer (EORTC) core QoL questionnaire (QLQ-C30) (*4–6*). Since its introduction, the EORTC QLQ-C30 has been evaluated in several field studies and appeared as reliable and valid (*7*). The EORTC QLQ-C30 defines HRQoL as a multidimensional construct consisting of subjectively perceived global health status, different functional scales, and disease-related symptoms. However, despite recent publications investigating the impact of ^{177}Lu-PSMA-617 RLT on HRQoL using small sample sizes over a short treatment period, data on the impact of repeated ($\geq$2) cycles of ^{177}Lu-PSMA I&T RLT on HRQoL using a larger cohort of mCRPC patients are scarce and limited (*8*). Furthermore, on the basis of our clinical experience, we assumed that patients with treatment discontinuation because of disease progression after the first 2 cycles showed a concordant decline in HRQoL during treatment. Thus, the aims of this analysis were to assess changes in HRQoL with mCRPC during treatment with ^{177}Lu-PSMA RLT and to evaluate potential differences in HRQoL between patients who discontinued treatment because of disease progression and patients who responded and could continue treatment.

MATERIALS AND METHODS

Patient Selection and ^{177}Lu-PSMA I&T RLT

Initially, 92 mCRPC patients with accessible EORTC QLQ-C30 responses who received ^{177}Lu-PSMA I&T RLT in a compassionate-use program between 2014 and 2019 were screened for this retrospective

analysis. Of these, 60 patients fulfilled our study-related inclusion criteria and therefore were identified as eligible for our study. The following criteria were used for inclusion: at least 2 cycles of ^{177}Lu-PSMA I&T; completion of ^{177}Lu-PSMA I&T RLT; Eastern Cooperative Oncology Group (ECOG) 0–2; and completed EORTC QLQ-C30 before treatment initiation and at least 12 ± 4 wk after treatment initiation (at PSMA-ligand PET/CT imaging or before the third treatment cycle). The measured time points (e.g., 12 ± 4 wk) were defined retrospectively by the intervals (4- to 8-wk intervals) in which the patients received their treatment cycles or their interim PSMA-ligand PET/CT imaging.

All patients had previously received second-line hormonal therapy with abiraterone or enzalutamide and chemotherapy or were unfit for chemotherapy. Before treatment, sufficient PSMA expression was confirmed by PSMA-ligand PET imaging. Only patients with PSMA-ligand uptake in tumor lesions at least as high as liver background were treated. Data on treatment response and outcome after ^{177}Lu-PSMA RLT of these patients have been previously reported (*9,10*).

^{177}Lu-PSMA I&T was prepared according to good manufacturing practice and the German Medicinal Products Act (AMG §13 2b). All patients signed informed consent forms and were treated under the conditions of Declaration of Helsinki article 37, "Unproven Interventions in Clinical Practice." The retrospective analysis was approved by the local ethics committee under reference 115/18 S.

In total, 264 cycles of ^{177}Lu-PSMA RLT with a median of 4 cycles per patient (range, 2–20 cycles) were applied. Patients received intravenous treatment with a standard dose of approximately 7.4 GBq of ^{177}Lu-PSMA I&T every 4–10 wk (median, 6 wk). All patients received at least 2 treatment cycles (n = 60), 2 patients received 3 cycles, and 35 patients underwent at least 4 cycles of ^{177}Lu-PSMA RLT (Table 1). Median time on treatment was 4 mo (range, 2–20 mo).

TABLE 1
Baseline Patient Characteristics

Characteristic	Data
Patients receiving ^{177}Lu-PSMA RLT	60
2 cycles	23
3 cycles	2
≥4 cycles	35
ECOG 0	19
ECOG 1	34
ECOG 2	7
Age (y)	72 (67–76)
PSA (ng/mL)	132.3 (29.2–267.6)
LDH (U/L)	252.5 (215.8–316.8)
AP (U/L)	118.5 (78.0–211.8)
Hb (g/dL)	11.5 (10.3–12.6)
Prior systemic therapies for mCRPC, n = 60 (%)	
Docetaxel	44 (73)
Cabazitaxel	12 (20)
Abiraterone	46 (77)
Enzalutamide	40 (67)
^{223}Ra	12 (20)
Previous chemotherapy	44 (73)
Site of metastasis, n = 60	
Lymph node, overall	49
Lymph node, N1+/M1a	5
Bone, overall	54
Bone, M1b, without visceral metastases	38
Visceral, overall, M1c	19
Liver	3
Lung	11
Adrenal	7

PSA = prostate-specific antigen; LDH = lactate dehydrogenase; AP = alkaline phosphatase; Hb = hemoglobin.

Qualitative data are number and percentage; continuous data are median and interquartile range.

QoL Analysis

HRQoL for mCRPC patients was evaluated using the German version of the EORTC QLQ-C30 (version 3.0) (*6*). The questionnaire was filled out before each ^{177}Lu-PSMA I&T cycle and at the time of PSMA-ligand PET/CT scans after 2 and potentially 4 treatment cycles. Specifically developed for cancer patients, the EORTC QLQ-C30 is a reliable and valid 30-item questionnaire of self-assessed HRQoL. It consists of 1 multiitem measured global health status; 5 multiitem measured functional scales, namely, physical functioning, role functioning (i.e., performance in daily activities and free-time activities or work), cognitive functioning, emotional functioning, and social functioning; 3 multiitem measured symptom scales (fatigue, pain, and nausea or vomiting); and 6 single items (constipation, diarrhea, insomnia, dyspnea, appetite loss, and financial difficulties). According to the standardized EORTC scoring procedure, scores for each multi- and single-item measure were linearly transformed to a score value from 0 to 100 (*11*). Although high score values in global health and functional scales represent high levels of health status and functional ability, high scores in symptom scales and single items represent worse symptom status.

Statistical Analysis

All analyses were performed using GraphPad Prism version 9.4.1(458) (GraphPad Software) for Mac (Apple). A mixed-effects model that allows missing values was performed to analyze repeated measures data of HRQoL for the total patient cohort and for patients stratified according to their ECOG performance status at baseline (ECOG 0, ECOG 1, or ECOG 2). Questionnaires with a response rate of less than 25% (15%, n = 9) after the sixth treatment cycle were excluded from further analysis. Results were presented as mean changes from baseline scores of HRQoL. A paired t test visualized in Tukey box-and-whisker plots was performed to evaluate differences in HRQoL between patients who were excluded after 2 or 4 treatment cycles (nonresponder) and those who continued treatment beyond 2 or 4 treatment cycles (responder). HRQoL deterioration-free survival was defined as the time between treatment initiation and first HRQoL score deterioration of at least 5 points compared with the baseline score (without subsequent improvement ≥5 points compared with baseline or improvement to ≥90 if the baseline score was ≥90) or death, whichever occurred first (*12*). Deterioration-free survival curves were estimated using the Kaplan–Meier method for estimation of event time distributions, and log-rank tests were used for group comparisons. Patients who were alive were censored at the last HRQoL follow-up (26 ± 4 wk) if deterioration of at least 5 points from baseline was not observed or if a decrease of at least 5 points was present but was followed by improvement of at least 5 points or improvement to at least 90 if the baseline score was at least 90. HRQoL for patients who were

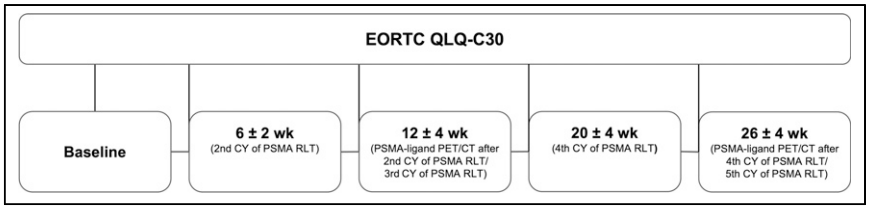

FIGURE 1. Study design. CY = cycle.

excluded from treatment (nonresponder) and in those who were defined as eligible for treatment continuation (responder) was analyzed on the basis of disease progression upon PSMA-ligand PET/CT imaging routinely performed after 2 treatment cycles (at 12 ± 4 wk). The corresponding hazard ratio (HR) and 95% CI are presented. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

QoL in the Entire Patient Cohort

Patient characteristics are shown in Table 1. Before treatment, 32% (n = 19), 57% (n = 34), and 11% (n = 7) of the patients presented with ECOG 0, ECOG 1, and ECOG 2, respectively. At baseline and at 12 ± 4 wk (PSMA-ligand PET/CT imaging after the second treatment cycle or before the third treatment cycle) the questionnaire was available for all 60 (100%) patients (Fig. 1). For 39 (65%), 18 (30%), 16 (27%), and 9 (15%) patients, the questionnaire was available at 6 ± 2 wk (second treatment cycle), 20 ± 4 wk (fourth treatment cycle), 26 ± 4 wk (PSMA-ligand PET/CT imaging after the fourth treatment cycle or before the fifth treatment cycle), and 34 ± 4 wk (sixth treatment cycle) after the first treatment cycle, respectively (Fig. 1).

Compared with baseline, HRQoL improved significantly, revealing elevated global health status at 6 ± 2 wk (P = 0.014) and at 20 ± 4 wk (P = 0.039) after treatment initiation (Fig. 2A; Table 2). In accordance with this, role functioning and emotional functioning demonstrated significant improvements after the first cycle of ^{177}Lu-PSMA RLT and over time (role functioning, 6 ± 2 wk [P = 0.045] and 20 ± 4 wk [P = 0.048]; emotional functioning, 6 ± 2 wk [P = 0.035] and 20 ± 4 wk [P = 0.007]; Figs. 2C and 2D; Table 2). Other aspects of functional ability, namely, physical functioning, cognitive functioning, and social functioning, although not significantly improved, remained constant during treatment (Fig. 2B; Table 2). Moreover, compared with baseline, some symptom scales, such as fatigue and pain, were significantly alleviated at 6 ± 2 and 20 ± 4 wk (fatigue, P = 0.042 and P = 0.041, respectively, and pain, P = 0.035 and P = 0.034, respectively; Figs. 2E and 2F; Table 2). In addition, at 26 ± 4 wk, significant deterioration (P = 0.014) of fatigue was detected (Fig. 2E). Other symptoms, even if not significantly improved (except significant alleviation of dyspnea at 6 ± 2 wk, P = 0.012), showed no deterioration over time (Table 2). Patients with ECOG 0 had higher HRQoL scores and less symptom burden in all domains during the course of treatment, whereas patients within the ECOG 1 and ECOG 2 group had worse HRQoL (Fig. 2; Supplemental Tables 1 and 2 [supplemental materials are available at http://jnm.snmjournals.org]). However, the presented significant effects of ^{177}Lu-PSMA RLT on HRQoL for the total patient cohort were not found within the ECOG-stratified groups (ECOG 0, ECOG 1, or ECOG 2; Fig. 2; Supplemental Tables 1 and 2).

QoL for Patients with Early Exclusion from Treatment

Following PSMA-ligand PET/CT imaging after 2 treatment cycles (at 12 ± 4 wk; Fig. 1), 23 patients discontinued treatment because of disease progression and were stratified as nonresponders, whereas 37 patients were defined as eligible for treatment continuation and were stratified as responders (Table 1).

The nonresponder group presented with a lower baseline HRQoL than did the responder group in most assessed domains (Table 3). In addition, significantly worse physical functioning (P = 0.0495) and role functioning (P = 0.011), deterioration of fatigue (P = 0.046), and increased nausea and vomiting (P = 0.008) were detectable at 12 ± 4 wk in the nonresponder group (Figs. 3B, 3C, and 3E; Table 3). In contrast, patients in the responder group showed significantly improved global health status (P = 0.002), alleviation of pain (P = 0.011), and reduced dyspnea (P = 0.047; Figs. 3A and 3F; Table 3). Other aspects of HRQoL, although not significantly improved, remained stable over time (Table 3).

In line with this, the nonresponder group had a significantly higher risk of HRQoL deterioration in global health status (HR,

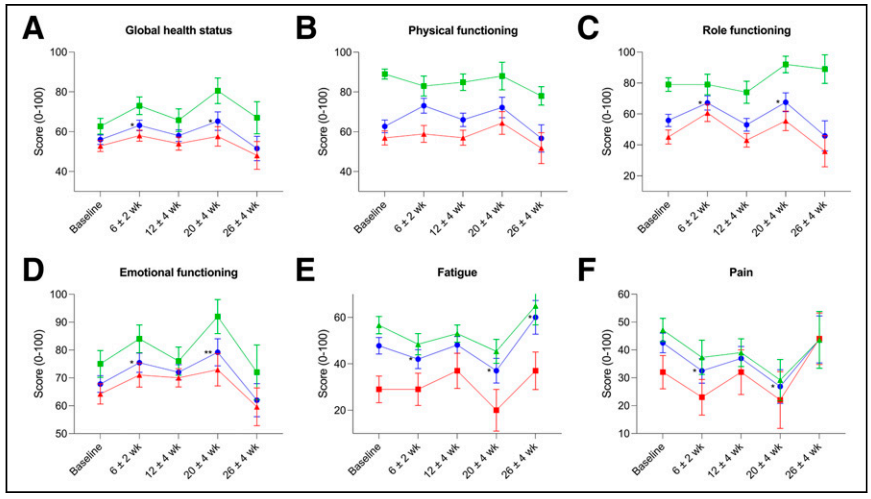

FIGURE 2. Changes in global health status, selected functional scales (physical functioning, role functioning, and emotional functioning), and selected symptom scales (fatigue and pain) for total patient cohort (blue) and for patients with ECOG 0 (green) and ECOG 1 or ECOG 2 (red) performance status during treatment with ^{177}Lu-PSMA RLT, according to EORTC QLQ-C30. Results are presented as mean changes from baseline and SEM. (A) In total patient cohort, global health status was significantly improved at 6 ± 2 wk (P = 0.014) and 20 ± 4 wk (P = 0.039). (B–D) In total patient cohort, role functioning and emotional functioning were significantly improved at 6 ± 2 wk (P = 0.045 and P = 0.035) and at 20 ± 4 wk (P = 0.048 and P = 0.007), while physical functioning, although not significantly improved, remained constant during treatment. (E and F) In total patient cohort, fatigue and pain were significantly alleviated at 6 ± 2 wk (P = 0.042 and P = 0.035) and at 20 ± 4 wk (P = 0.041 and P = 0.034), whereas fatigue was significantly deteriorated at 26 ± 2 wk (P = 0.014). *P < 0.05. **P < 0.01.

TABLE 2
EORTC QLQ-C30 Scores for Total Patient Cohort

Parameter	Category	EORTC QLQ-C30 score (0–100)				
		Baseline	6 ± 2 wk	12 ± 4 wk	20 ± 4 wk	26 ± 4 wk
Global health status		56.0 (51.3–60.6)	63.2* (58.0–68.3)	57.8 (52.0–63.5)	65.3* (56.2–74.4)	51.6 (39.6–63.6)
Functional scale	Physical functioning	67.1 (60.9–73.3)	67.2 (59.8–74.5)	65.8 (59.2–72.3)	72.2 (62.2–82.3)	56.7 (43.3–70.1)
	Role functioning	55.8 (48.1–63.6)	67.1* (58.2–76.0)	52.8 (44.7–60.9)	67.6* (55.7–79.5)	45.8 (26.6–65.1)
	Emotional functioning	67.8 (62.0–73.6)	75.4* (68.7–82.2)	71.8 (66.4–77.2)	79.2† (69.6–88.7)	62.0 (50.3–73.6)
	Cognitive functioning	84.7 (79.6–89.9)	84.2 (77.9–90.5)	84.0 (78.7–89.1)	85.2 (76.0–94.4)	87.5 (80.1–94.9)
	Social functioning	65.3 (58.8–71.7)	70.6 (62.4–78.8)	61.9 (54.8–69.1)	75.0 (63.7–86.3)	56.3 (40.5–72.0)
Symptom scale	Fatigue	47.8 (40.8–54.7)	41.8* (33.8–49.9)	48.2 (41.0–55.3)	37.0* (26.6–47.4)	59.7* (45.3–74.1)
	Nausea and vomiting	6.7 (2.7–10.7)	11.8 (5.7–18.0)	9.2 (4.5–13.8)	3.7 (0.0–7.8)	8.3 (0.2–16.5)
	Pain	42.5 (23.6–43.1)	32.5* (23.6–43.1)	36.9 (26.7–43.4)	26.9* (15.8–39.8)	43.8 (25.4–59.1)
Single item	Dyspnea	40.0 (31.5–48.6)	28.1* (18.5–37.7)	30.6 (23.0–38.2)	25.9 (12.8–39.1)	35.4 (20.7–50.1)
	Insomnia	30.6 (21.4–39.7)	29.8 (19.0–40.6)	29.4 (20.5–38.4)	29.6 (17.2–42.1)	25.0 (11.5–38.5)
	Appetite loss	29.4 (17.1–31.8)	28.1 (17.6–38.5)	26.1 (17.8–34.4)	11.1 (2.2–20.0)	33.3 (15.1–51.6)
	Constipation	16.1 (9.7–22.6)	16.7 (8.3–25.0)	18.9 (12.1–25.7)	13.0 (2.5–23.4)	12.5 (0.0–25.3)
	Diarrhea	12.2 (6.3–18.2)	11.4 (3.6–19.2)	11.1 (5.4–16.8)	7.4 (0.0–15.6)	10.4 (2.9–18.0)
	Financial difficulties	10.0 (4.2–15.8)	13.2 (5.3–21.1)	13.3 (7.1–19.5)	18.5 (5.7–31.3)	20.8 (5.7–36.0)

*$P < 0.05$.
†$P < 0.01$.
Data are baseline mean scores and 95% CIs before first ^{177}Lu-PSMA RLT cycle and for 6 ± 2 wk during second ^{177}Lu-PSMA RLT cycle, 12 ± 4 wk during PSMA-ligand PET/CT scan after second ^{177}Lu-PSMA RLT cycle or third ^{177}Lu-PSMA RLT cycle, and 20 ± 4 wk during fourth ^{177}Lu-PSMA RLT cycle after first cycle of ^{177}Lu-PSMA RLT for patients with mCRPC treated with ^{177}Lu-PSMA RLT.

2.9; 95% CI, 1.3–6.6; $P = 0.002$), physical functioning (HR, 2.2; 95% CI, 1.1–4.8; $P = 0.013$), role functioning (HR, 2.2; 95% CI, 1.0–5.2; $P = 0.035$), cognitive functioning (HR, 2.4; 95% CI, 1.0–6.0; $P = 0.035$), fatigue (HR, 2.7; 95% CI, 1.3–5.6; $P = 0.001$), nausea and vomiting (HR, 4.5; 95% CI, 1.6–12.8; $P = 0.001$), appetite loss (HR, 3.5; 95% CI, 1.3–9.7; $P = 0.005$), and diarrhea (HR, 3.4; 95% CI, 1.1–10.1; $P = 0.017$; Figs. 4A–4C and 4E; Supplemental Table 3). Similar trends were observed for most remaining aspects of HRQoL (Figs. 4D and 4F; Supplemental Table 3).

Differences in HRQoL between patients who discontinued treatment (nonresponder, $n = 7$) because of relevant disease progression in PSMA-ligand PET/CT imaging after 4 treatment cycles (at 26 ± 4 wk; Fig. 1) and those who continued treatment (responder, $n = 9$) are given in Supplemental Table 4.

DISCUSSION

The results of our retrospective analysis indicate significant improvements in various aspects of HRQoL (e.g., global health status) during treatment with ^{177}Lu-PSMA I&T RLT in mCRPC. In contrast, patients who discontinued treatment after 2 treatment cycles because of disease progression had a concordant decline in HRQoL and a higher risk of deterioration in QoL than did patients who responded after the initial 2 cycles.

The most affected dimensions of HRQoL were global health status, role functioning, emotional functioning, fatigue, and pain. In these domains, significant improvements were detectable at the second (at 6 ± 2 wk) and fourth (at 20 ± 4 wk) treatment cycles. Our analysis might underline the beneficial impact of ^{177}Lu-PSMA I&T RLT on HRQoL—in contrast to a recently published analysis of mCRPC patients treated with new hormonal agents or first-line chemotherapy, which reported continuous and significant deterioration in, for example, physical functioning, fatigue, and pain (*13*). However, because our analysis evaluates the impact of ^{177}Lu-PSMA I&T RLT on HRQoL over only a short treatment period, further studies analyzing the long-term impact on HRQoL are warranted.

At PSMA-ligand PET/CT imaging after the second treatment cycle or before the third treatment cycle (12 ± 4 wk) and at PSMA-ligand PET/CT imaging after the fourth treatment cycle or before the fifth treatment cycle (26 ± 4 wk) a slight shift toward HRQoL deterioration was detectable. Similar trends were reported in a previously published prospective phase II trial (*4,14*). A potential hypothesis for this could be a concordant decline of QoL for patients with relevant disease progression, leading to negative affection of HRQoL at the measured time points. This is supported by our results, which revealed significant deterioration of HRQoL

TABLE 3
EORTC QLQ-C30 Scores at Baseline and 12 ± 4 Weeks After Treatment Initiation in Nonresponder Patients Receiving 2 Cycles and Responder Patients Receiving More Than 2 Cycles of ^{177}Lu-PSMA RLT

		EORTC QLQ-C30 score (0–100)				
		Total patient cohort	Nonresponder		Responder	
Parameter	Category	Baseline	Baseline	12 ± 4 wk	Baseline	12 ± 4 wk
Global health status		56.0 (51.3–60.6)	51.8 (44.4–59.3)	44.2 (35.3–53.1)	58.6 (52.1–65.1)	66.2† (60.0–72.5)
Functional scale	Physical functioning	67.1 (60.9–73.3)	61.7 (51.5–72.0)	53.9* (43.7–64.1)	70.5 (62.8–78.1)	73.2 (65.2–81.1)
	Role functioning	55.8 (48.1–63.6)	50.7 (39.5–62.0)	37.0* (24.1–49.8)	59.0 (49.7–68.3)	62.6 (53.0–72.2)
	Emotional functioning	67.8 (62.0–73.6)	59.4 (49.7–69.2)	63.0 (55.7–70.4)	73.0 (65.8–80.1)	77.3 (70.1–84.4)
	Cognitive functioning	84.7 (79.6–89.9)	81.2 (72.1–90.2)	77.5 (68.6–86.4)	86.9 (80.7–93.1)	87.8 (81.3–94.4)
	Social functioning	65.3 (58.8–71.7)	54.4 (43.9–64.8)	48.6 (37.6–59.5)	72.1 (64.9–79.3)	70.3 (62.6–77.9)
Symptom scale	Fatigue	47.8 (40.8–54.7)	49.8 (39.1–60.5)	59.9* (48.8–71.0)	46.6 (37.7–55.4)	40.8 (33.3–48.4)
	Nausea and vomiting	6.7 (2.7–10.7)	7.3 (1.6–12.9)	19.6† (9.6–29.5)	6.3 (0.0–12.8)	2.7 (0.0–6.0)
	Pain	42.5 (23.6–43.1)	51.5 (40.7–62.3)	54.4 (39.3–69.4)	36.9 (28.8–45.1)	26.1* (18.1–34.1)
Single item	Dyspnea	40.0 (31.5–48.6)	50.7 (35.2–66.2)	42.0 (28.6–55.5)	33.3 (24.4–42.4)	23.4* (15.1–31.8)
	Insomnia	30.6 (21.4–39.7)	46.4 (29.9–62.8)	44.9 (28.1–61.8)	20.7 (11.4–30.1)	19.8 (10.7–28.9)
	Appetite loss	29.4 (17.1–31.8)	21.7 (9.3–34.2)	36.2 (21.3–51.2)	26.1 (17.2–35.1)	19.8 (9.6–30.1)
	Constipation	16.1 (9.7–22.6)	18.8 (7.6–30.1)	23.2 (11.5–34.9)	14.4 (8.3–20.5)	16.2 (7.9–24.5)
	Diarrhea	12.2 (6.3–18.2)	11.6 (3.0–20.2)	13.0 (2.6–23.5)	12.6 (5.0–20.3)	9.9 (3.2–16.6)
	Financial difficulties	10.0 (4.2–15.8)	15.9 (4.7–27.2)	15.9 (6.2–25.7)	6.3 (0.0–13.5)	11.7 (2.3–21.1)

*$P < 0.05$.
†$P < 0.01$.
Data are baseline mean scores and 95% CIs before first ^{177}Lu-PSMA RLT cycle in total patient cohort and in nonresponder and responder patients, dichotomized according to number of received treatment cycles of ^{177}Lu-PSMA RLT at 12 ± 4 wk and at 12 ± 4 wk during PSMA-ligand PET/CT scan after second ^{177}Lu-PSMA RLT cycle or third ^{177}Lu-PSMA RLT cycle after first cycle of ^{177}Lu-PSMA RLT in nonresponder and responder patients with mCRPC treated with ^{177}Lu-PSMA RLT.

(e.g., physical functioning) for patients who discontinued ^{177}Lu-PSMA RLT after the second treatment cycle because of disease progression (at 12 ± 4 wk), whereas patients who continued treatment showed stabilization or improvement of HRQoL (e.g., global health status). In accordance with this, we could also demonstrate a significantly higher risk of HRQoL deterioration for patients with early treatment discontinuation. This is in line with results from van der Doelen et al., who reported stabilization of HRQoL for patients who completed ^{223}Ra treatment but observed decline in HRQoL for patients who discontinued treatment (*15*). The same was true for most assessed HRQoL domains for patients who discontinued treatment after 4 treatment cycles compared with those who received more than 4 treatment cycles. However, in this patient cohort, none of the detected differences were statistically significant, which is most likely because of the small sample size.

Two previously published prospective phase II trials analyzed HRQoL using the EORTC QLQ-C30 for mCRPC patients undergoing ^{177}Lu-PSMA-617 RLT (*4,5,14*). These trials reported higher HRQoL scores and lower symptom burden at baseline in most domains than found in our results (*5*). The worse HRQoL scores at baseline reported in our analysis might be explained by the more advanced disease stage in our patient cohort, including visceral metastases in 32% of our patients ($n = 19$) versus, for example, 7% of TheraP patients ($n = 7$), given the known negative association of visceral metastases with outcome (*5,16*). In addition, 20% ($n = 12$) of our patients received pretreatment with cabazitaxel versus none of the TheraP patients, also illustrating their more advanced stage regularly associated with decreased QoL (*17*). Differences in administered therapies and disease stages should be considered when comparing HRQoL between studies. Furthermore, a recently published prospective phase III trial investigating the impact of ^{177}Lu-PSMA-617 RLT plus standard of care versus standard of care alone reported a beneficial HRQoL for the ^{177}Lu-PSMA-617 RLT group (*18*). However, because it used "Functional Assessment of Cancer Therapy: Prostate and the Brief Pain Inventory—Short Form" for the assessment of HRQoL and different outcome parameters, a direct comparison with the results of our analysis is not possible (*3*).

Patients with either slight impairment in physically demanding activities (ECOG 1) or total inability in work activities (ECOG 2) had concordantly lower HRQoL than did patients with fully active

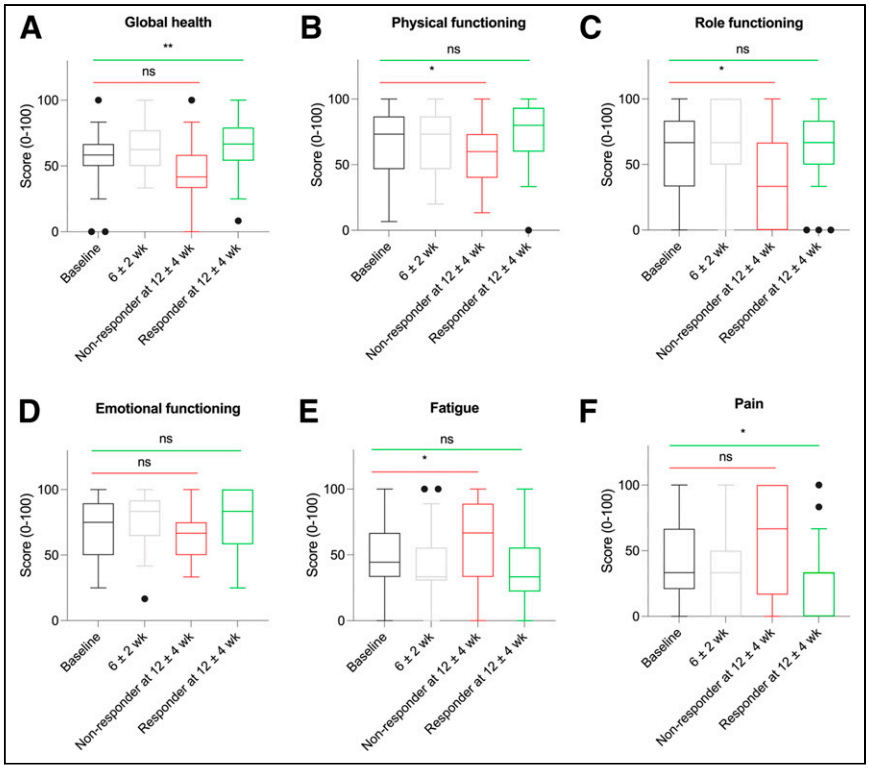

FIGURE 3. Tukey box plot display of global health status, selected functional scales (physical functioning, role functioning, and emotional functioning), and selected symptom scales (fatigue and pain) for total patient cohort at baseline (black) and at 6 ± 2 wk (light gray) and for patients dichotomized according to number of received treatment cycles of ^{177}Lu-PSMA RLT at 12 ± 4 wk (nonresponder, red; responder, green). (A) Compared with baseline, global health status was significantly improved at 12 ± 4 wk in responder group ($P = 0.002$). (B–D) Compared with baseline, physical functioning and role functioning were significantly worse in nonresponder group ($P = 0.0495$ and $P = 0.011$), while no significant differences were detectable for emotional functioning. (E and F) Compared with baseline, fatigue was significantly deteriorated in nonresponder group ($P = 0.046$) and pain was significantly alleviated in responder group ($P = 0.011$). Outliers that differ significantly from rest of dataset were plotted as individual points beyond whiskers on box plot. *$P < 0.05$. **$P < 0.01$. ns = not significant.

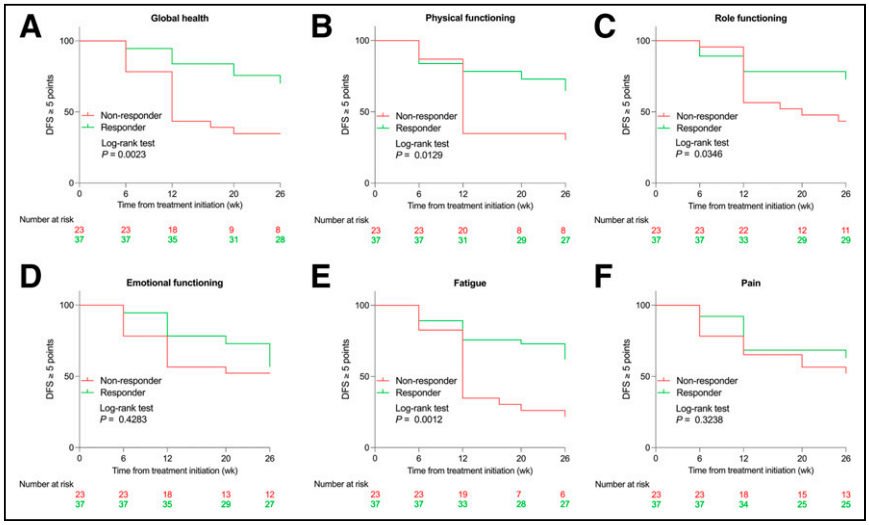

FIGURE 4. Kaplan–Meier survival curves for HRQoL deterioration-free survival for global health status (A), selected functioning scales (physical functioning, role functioning, and emotional functioning) (B–D), and selected symptom scales (fatigue and pain) (E and F) for patients dichotomized according to number of received treatment cycles of ^{177}Lu-PSMA RLT at 12 ± 4 wk (nonresponder, red; responder, green). DFS = deterioration-free survival.

performance status (ECOG 0) at all measuring points. This is in line with results from Marinova et al., who investigated HRQoL for patients with midgut neuroendocrine tumors after peptide receptor radionuclide therapy (*19*). However, the significant impact of ^{177}Lu-PSMA RLT on HRQoL for our total patient cohort was not found within ECOG-divided groups (ECOG 0 vs. ECOG 1 or ECOG 2), although there was a similar tendency detectable (e.g., global health status). This might be explained by the relatively small sample size in each of the analyzed subgroups, which resulted in decreased power of the statistical test. Further studies are warranted to validate our results in larger patient cohorts.

Our study has several limitations, including the single-center retrospective nature of this analysis, which may limit the validity of our results. The small sample size may prevent our findings from being extrapolated and impede the visibility of small effects of ^{177}Lu-PSMA RLT on HRQoL.

CONCLUSION

The results of our analysis indicate a beneficial impact of ^{177}Lu-PSMA RLT on QoL for mCRPC patients. Patients showed improvement in HRQoL and alleviation in relevant disease-related symptoms. In addition, we could demonstrate a significant decline in HRQoL for patients with unfavorable disease progression that resulted in early discontinuation of treatment.

DISCLOSURE

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KEY POINTS

QUESTION: Does ^{177}Lu-PSMA I&T RLT have a beneficial impact on HRQoL for mCRPC patients?

PERTINENT FINDINGS: In our analysis, we could demonstrate that ^{177}Lu-PSMA I&T RLT is associated with a beneficial impact on HRQoL. Moreover, we could detect a significant decline in HRQoL for patients who discontinued treatment because of disease progression.

IMPLICATIONS FOR PATIENT CARE: HRQoL is important when it comes to the evaluation of new treatment strategies such as ^{177}Lu-PSMA RLT. ^{177}Lu-PSMA RLT demonstrates a beneficial impact on patients' HRQoL. However, for patients with early disease progression, the positive impact of ^{177}Lu-PSMA RLT on QoL is limited.

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