Journal of Nuclear Medicine, published on October 10, 2019 as doi:10.2967/jnumed.119.233429

Additional local therapy of liver metastases in mCRPC patients receiving systemic PSMA targeted therapy

Robert Seifert[1], Katharina Kessel[1], Martin Boegemann[3], Michael Köhler[4], Wolfgang Roll[1], Lars Stegger[1], Matthias Weckesser[1] and Kambiz Rahbar[1]

1. Department of Nuclear Medicine, University Hospital Münster, Münster, Germany

3. Department of Urology, University Hospital Münster, Münster, Germany

4. Department of Clinical Radiology, University Hospital Münster, Münster, Germany

Word count: 3300 (Total)

Key words: PSMA, prostate cancer, SIRT

Short title: PSMA Therapy and SIRT in prostate cancer

Corresponding author:
Kambiz Rahbar, MD
Department of Nuclear Medicine
University Hospital Muenster
Albert Schweitzer Campus 1
Gebäude A1
48149 Muenster
Germany
+49-251-8347362
rahbar@uni-muenster.de

Abstract

Aim

The aim of this study was to evaluate the efficacy of ^{177}Lu-PSMA-617 (Lu-PSMA) and Selective Internal Radiation Therapy (SIRT) for the treatment of liver metastases of castration resistant prostate cancer (mCRPC).

Materials and Methods

Safety and survival of patients with mCRPC and liver metastases assigned to Lu-PSMA alone (n=31) or in combination with SIRT (n=5) was retrospectively analyzed. Additionally, a subgroup (n=10) was analyzed using morphological and molecular response criteria.

Results

Median-estimated survival was 5.7 months for Lu-PSMA alone and 8.4 months for combined sequential Lu-PSMA+SIRT. Lu-PSMA achieved discordant therapy responses with both regressive and progressive liver metastases in the same patient (best vs. worst responding metastases per patient: -35%vs.+63% diameter change; $p<0.05$). SIRT was superior for the treatment of liver metastases compared to Lu-PSMA (0%vs.56%progression).

Conclusion

The combination of Lu-PSMA and SIRT is efficient and feasible for the treatment of advanced prostate cancer. Lu-PSMA alone seems to have limited response rates in the treatment of liver metastases.

Introduction

Despite marked progress in recent years, the therapy of metastasized castration-resistant prostate cancer (mCRPC) remains to be a substantial clinical challenge, especially liver metastases are still associated with poor overall survival (*1*,*2*). This is partly caused by a de-differentiation of the prostate cancer cells in liver metastases, which is called neuroendocrine transdifferentiation and associated with poor survival (*3*,*4*). Radioligand therapies targeting the Prostate Specific Membrane Antigen (PSMA) have been applied to patients with advanced mCRPC in multiple studies (*5–8*). Among the variety of available radioligands, ^{177}Lu-PSMA-617 (Lu-PSMA) is most commonly utilized. Preliminary data suggest that Lu-PSMA extends the progression-free and overall survival while exhibiting a favorable toxicity profile (*5*,*9*,*10*). However, Lu-PSMA seems to be less efficacious for the treatment of liver and other visceral metastases (*5*). In contrast, Selective Internal Radiation Therapy (SIRT) specifically targets liver metastases with great efficacy and therefore represents a treatment option for unresectable primary liver cancer or metastases in the liver (*11*). However, there is no systematic evaluation of Lu-PSMA therapy or SIRT as a local liver therapy for liver metastases in advanced prostate cancer to date. Therefore, the aim of the present retrospective single center study was to evaluate the efficacy of Lu-PSMA and SIRT in mCRPC patients with liver metastases and elucidate the implications for overall survival.

Methods

Patients

Figure1 presents the flow chart of patient selection. All patients with mCRPC and liver metastases referred for therapy to the Department of Nuclear Medicine were considered for this case series (n=36). Patients with metastases were treated with PSMA targeted therapy alone (n=31) or in combination with SIRT (n=5) based on individual tumor board decisions and with informed consent (see supplemental table 1). SIRT was pursued if the extrahepatic tumor burden was controlled, but the hepatic metastases were progredient (no overall therapy failure). Therefore, only 5 patients were eligible to be treated with SIRT. Toxicity according liver metastases were evaluated according Common Toxicity Criteria for Adverse Events (CTCAE Version 5.0).

The following inclusion criteria were applied for the subgroup analysis: presence of liver metastases (1), PET imaging before and after radionuclide therapy (2). All ten patients analyzed in detail received Lu-PSMA therapy, 4 patients were additionally treated with SIRT due to hepatic progress despite controlled extrahepatic tumor burden (see supplemental table 2). The retrospective analysis of patients treated with Lu-PSMA was approved by the local ethics committee (No. 2016-585-f-S, Ethikkommission der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität Münster).

PSMA targeted radionuclide therapy

Conjugation of PSMA-617 with ^{177}Lu has been described previously (*12*). The beta-radiation of ^{177}Lu (E_{max}=0.497MeV) has a maximum tissue range of 2 mm (*13*). Details are given in the supplement.

Selective Internal Radiation Therapy

After selective catheterization, ^{90}Y microspheres were directly injected into the hepatic artery or its branches to cause radioembolization of metastases. Microspheres were manufactured by SIRTEX Medical, Sydney, Australia. The beta particles of ^{90}Y (E_{max}=2.27MeV) have a maximum tissue range of 11 mm (*13*). Details are given in the supplement. Macroaggregated albumin (MAA) Single photon emission tomography (SPECT) was used to assess the vascularization of the metastases (see supplemental Figure 1). Toxicity after SIRT and Lu-PSMA therapy was evaluated using Common Terminology Criteria for Adverse Events (CTCAE; Version 5).

Imaging

Whole body staging (vertex to proximal tibia) was done using PSMA based PET imaging prior to start of Lu-PSMA therapy (initial staging), after the last cycle of Lu-PSMA (restaging) and after SIRT, so that the therapy effect could be clearly attributed to the precedent therapy. Contrast enhanced MRI or CT were acquired, details are given in the supplement.

Response evaluation

Estimated mean overall survival was used as primary endpoint to compare PSMA targeted therapy alone (n=31) or in combination with SIRT (n=5). Additionally, the response to SIRT and/or Lu-PSMA was assessed using morphological and molecular features in the subgroup analysis (n=10). Morphological response was assessed in analogy to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and only reported for liver metastases: up to four largest hypervascularized hepatic metastases were defined as target lesions (TL) and the sum of their long axis diameter (LAD) was measured (progressive disease (PD)= 20 % increase of LADs or newly formed metastases, partial response (PR)= 30% decrease of LADs, stable disease= neither PD nor PR; completes response= no lesions definable) (*14*). SUV_{max} was measured at baseline in all liver metastases to determine, if Lu-PSMA therapy is feasible. Additionally, the change of PSMA expression caused by SIRT was analyzed as molecular response.

Statistical analysis

IBM SPSS Statistics Version 25 (Armonk, New York, USA) was used for testing and descriptive statistics. Unpaired (Mann-Whitney U) and paired (Wilcoxon) non-parametric statistical tests were performed. Values are presented as median; the range or confidence intervals are additionally specified. A statistically significant difference is assumed if $p<0.05$, otherwise, non-significance is reported (n.s.). The Kaplan Meier method was used to estimate the median survival and Log-Rank method to test for survival differences. The 95% confidence intervals are presented in squared brackets.

Results

Patient characteristics and therapies

All patients were treated with androgen deprivation therapy (table 1). One additional patient was evaluated for SIRT but could not receive treatment. This was due to fast progressing disease compared to the previous imaging. The average interval between Lu-PSMA administrations was 7.5 weeks [95%CI: 6.7-9.3] and three therapy cycles were administered in median, while the average dosage was 6.2 GBq [95%CI: 6.2-6.5]. A mean dosage of 2.2 GBq ^{90}Y was used [range:1.3-2.5] (n=5).

Survival

The median estimated overall survival (n=31) was 5.7 months [95%CI: 2.9-8.5] for patients receiving only Lu-PSMA. For patients receiving Lu-PSMA and SIRT (n=5), the median estimated overall survival was 8.4 months [95%CI: 4.9-11.9]. The estimated overall survival of Lu-PSMA+SIRT was not significantly longer compared to Lu-PSMA therapy alone (Log Rank p=0.227).

Subgroup analysis of the efficacy of PSMA targeted therapy

Treated by Lu-PSMA therapy, liver metastases showed PD compared to the baseline examination in 56% however, 44% displayed stable disease (9 patients, patient 3 was not considered here due to initial SIRT followed by Lu-PSMA therapy). Liver metastases had a discordant response: best and worst responding lesions were significantly different, if multiple liver metastases were present (only patients with multiple liver metastases at baseline were included; n=7; +63% vs. -35% LAD change; $p<0.05$; Figure2+3).

Rating liver metastases of all patients individually, morphologically progressive lesions showed significantly lesser ^{68}Ga-PSMA-11 uptake at baseline compared to stable and regredient ones (only patients with ^{68}Ga-PSMA-11 radionuclide were included; n = 8; PD:6.1SUV_{max}; SD:20.3SUV_{max}; PR:21.5SUV_{max}; $p<0.005$; $p<0.005$; Figure3).

Subgroup analysis of the efficacy of SIRT

Mean follow-up timepoint was 9 weeks after SIRT (range: 3-13, Figure4). Applying morphological criteria, 75% showed a partial response (3 patients) and 25% had a stable disease (1 patient). Best and worst responding lesions did not significantly differ (n=4; -19 % vs. - 44% LAD change; n.s.).

The molecular response evaluation revealed that the PSMA uptake of liver metastases was reduced after SIRT by 39% in median (range: +4% to -83% change).

Toxicity

The hepatic toxicities of Lu-PSMA therapy alone vs. Lu-PSMA therapy in combination with SIRT are presented in supplemental Table 3+4 according to the Common Terminology Criteria for Adverse Events (CTCAE; Version 5). Briefly, there were significant differences comparing alanine aminotransferase (+160.0% vs. +14.6%; p=0.006), aspartate aminotransferase (+130.3% vs. +25.42%; p=0.007), gamma-glutamyltransferase (+652.1% vs. +2.6 %; p=0.0003), but not bilirubin change between Lu-PSMA+SIRT vs. Lu-PSMA alone.

Discussion

The aim of this study was to evaluate the efficacy and safety of Lu-PSMA and SIRT for the treatment of advanced mCRPC with liver metastases, compared to Lu-PSMA alone. Patients treated with Lu-PSMA showed a discordant response to therapy with both regressive and progressing metastases at the same time. The reason for this currently remains unclear. Even initial responses to PSMA therapy may be misleading for a long-term response prediction. Initial responses to Lu-PSMA may not be associated with long term remission, as newly occurring metastases might not respond to additional Lu-PSMA cycles. This might partly be explained by the neuroendocrine transdifferentiation of prostate cancer cells, which is associated with poor overall survival (*3*,*15*). In the transdifferentiation process, neuroendocrine cell markers (like the neuron specific enolase) are expressed, whereas adenocarcinoma markers (like the prostate-specific antigen) are lost (*15*). The neuroendocrine differentiation is frequently present in liver metastases, which might partially explain the occurrence and progression of PSMA negative metastases under Lu-PSMA therapy that was shown in the present study (*3*). However, patients treated with SIRT did not show a discordant hepatic response, which indicates its superiority for the treatment of liver metastases. This might be due to the independence of SIRT from target molecules, therefore, neuroendocrine differentiation should not decrease its efficacy. Moreover, initial treatment of liver metastases with SIRT might prevent the spread of neuroendocrine differentiated tumor cells to other organs.

SIRT obtained higher response rates and a longer mean overall survival for the treatment of liver metastases compared to Lu-PSMA. The mean SIRT delivered tumor dose for colorectal metastases is 55Gy (*16*). Lu-PSMA therapy delivers mean tumor dosages of 32Gy (for 6GBq of ^{177}Lu) (*17*). For colorectal metastases, a deposition of at least 60Gy is favorable for prolonged overall survival (*16*). Despite the fundamentally different tumor biology of prostate compared to colorectal cancer, the distinct efficacy of Lu-PSMA and SIRT might be partially explained by the delivered dosages.

The increase of aspartate and alanine aminotransferase as well as gamma-glutamyltransferase levels were significantly higher in the SIRT group compared to patients treated with Lu-PSMA alone. However, baseline (prior to Lu-PSMA or/and SIRT) and post therapeutic (after SIRT or/and Lu-PSMA) liver enzymes were compared to evaluate the overall toxicity. Therefore, the increase of liver enzymes is at least partly attributed to the progression of hepatic metastases rather than to hepatotoxicity. Moreover, the increase in Bilirubin levels was not significantly different.

The limitations of the present study comprise the retrospective data analysis, small patient cohort and a potential selection bias. However, liver metastases are an end stage phenomenon of prostate cancer and thus generally rare. Therefore, the presented initial results are valuable and have direct implications for the treatment of prostate cancer and liver metastases, especially in case of castration resistance and Lu-PSMA evaluation. In the present manuscript, SIRT was the only evaluated local treatment for the liver metastases. Therefore, future studies should investigate, if other local therapies of liver metastases like transcatheter arterial chemoembolization or extracranial stereotactic radiotherapy are efficient as well. An additional limitation is the efficacy assessment of Lu-PSMA and SIRT therapy, which was based on morphological features. Future studies should consider additional imaging modalities like FDG-PET or diffusion weighted MRI for the evaluation of treatment response, especially in the context of neuroendocrine transdifferentiation (*18*).

Conclusion

The combination of Lu-PSMA and SIRT is efficacious and feasible for the treatment of liver metastases in advanced mCRPC. Lu-PSMA alone seems inferior to SIRT for the treatment of liver metastases.

Disclosures

K.R. is scientific consultant/advisor of ABX GmbH. The University of Münster received consulting fees from ABX GmbH, Radeberg, Germany for K.R. and M.B. All authors declare that they have no conflict of interest according subject and matter presented here.

KEY POINTS

QUESTION:

Is the combination of a local (SIRT) and systemic (Lu-PSMA) radionuclide therapy feasible tolerable in patients with liver metastases and castration resistant prostate cancer?

PERTINENT FINDINGS:

This retrospectively analysed patient group indicates that the combination of SIRT and Lu-PSMA is feasible and effective. Lu-PSMA alone only yields disconcordant response of liver metastases, whereas SIRT efficiently targets all liver metastases.

IMPLICATIONS FOR PATIENT CARE:

Local therapies targeting liver metastases in addition to systemic Lu-PSMA therapy should be evaluated in further clinical studies.

References

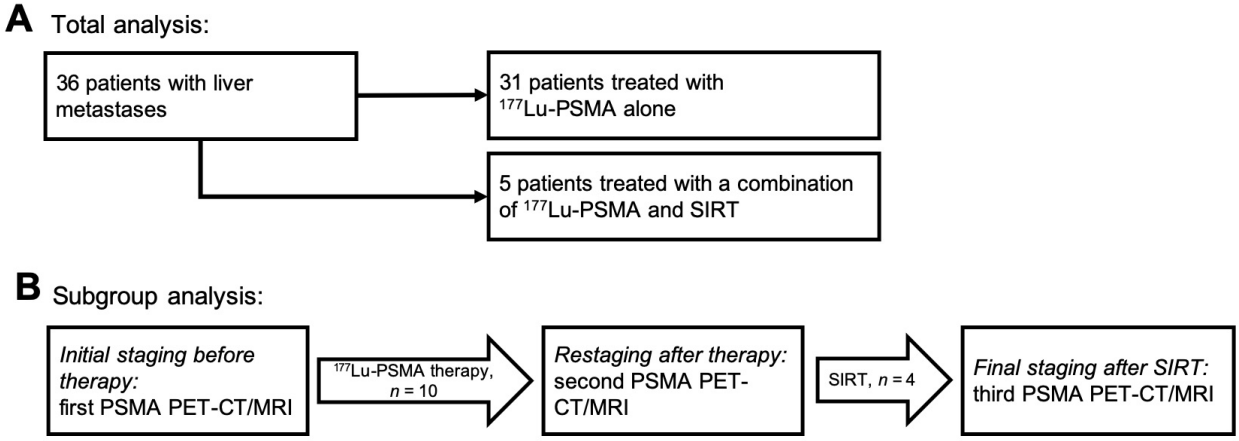
1. Halabi S, Kelly WK, Ma H, et al. Meta-analysis evaluating the impact of site of metastasis on overall survival in men with castration-resistant prostate cancer. *J Clin Oncol*. 2016;34:1652-1659.
2. Kessel K, Seifert R, Schäfers M, et al. Second line chemotherapy and visceral metastases are associated with poor survival in patients with mCRPC receiving 177Lu-PSMA-617. *Theranostics*. 2019.
3. Pouessel D, Gallet B, Bibeau F, et al. Liver metastases in prostate carcinoma: Clinical characteristics and outcome. *BJU Int*. 2007;99:807-811.
4. Wang HT, Yao YH, Li BG, Tang Y, Chang JW, Zhang J. Neuroendocrine Prostate Cancer (NEPC) Progressing from conventional prostatic adenocarcinoma: Factors associated with time to development of nepc and survival from NEPC Diagnosis-A systematic review and pooled analysis. *J Clin Oncol*. 2014;32:3383-3390.
5. Rahbar K, Ahmadzadehfar H, Kratochwil C, et al. German Multicenter Study Investigating 177Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients. *J Nucl Med*. 2017;58:85-90.
6. Hofman MS, Violet J, Hicks RJ, et al. [177 Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. *Lancet Oncol*. 2018.
7. Brauer A, Grubert LS, Roll W, et al. (177)Lu-PSMA-617 radioligand therapy and outcome in patients with metastasized castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging*. 2017;44:1663-1670.
8. Rahbar K, Bögeman M, Yordanova A, et al. Delayed response after repeated177Lu-PSMA-617 radioligand therapy in patients with metastatic castration resistant prostate cancer. *Eur J Nucl Med Mol Imaging*. 2018;45:243-246.
9. Ahmadzadehfar H, Wegen S, Yordanova A, et al. Overall survival and response pattern of castration-resistant metastatic prostate cancer to multiple cycles of radioligand therapy using [(177)Lu]Lu-

PSMA-617. *Eur J Nucl Med Mol Imaging*. 2017;44:1448-1454.

10. Rahbar K, Boegemann M, Yordanova A, et al. PSMA targeted radioligandtherapy in metastatic castration resistant prostate cancer after chemotherapy, abiraterone and/or enzalutamide. A retrospective analysis of overall survival. *Eur J Nucl Med Mol Imaging*. 2018;45:12-19.
11. Bastiaannet R, Kappadath SC, Kunnen B, Braat AJAT, Lam MGEH, Jong HWAM De. The physics of radioembolization. 2018.
12. Rahbar K, Bode A, Weckesser M, et al. Radioligand Therapy With 177Lu-PSMA-617 as A Novel Therapeutic Option in Patients With Metastatic Castration Resistant Prostate Cancer. *Clin Nucl Med*. 2016;41:522-528.
13. Seregni E, Maccauro M, Chiesa C, et al. Treatment with tandem [90Y]DOTA-TATE and [177Lu] DOTA-TATE of neuroendocrine tumours refractory to conventional therapy. *Eur J Nucl Med Mol Imaging*. 2014;41:223-230.
14. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228-247.
15. Molenaar JPF, Baten A, Blokx WAM, Hoogendam A. Development of Carcinoid Tumour in Hormonally Treated Adenocarcinoma of the Prostate. *Eur Urol*. 2009;56:874-877.
16. Levillain H, Derijckere ID, Marin G, et al. Y-PET / CT-based dosimetry after selective internal radiation therapy predicts outcome in patients with liver metastases from colorectal cancer. 2018:1-9.
17. Delker A, Fendler WP, Kratochwil C, et al. Dosimetry for 177Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. *Eur J Nucl Med Mol Imaging*. 2015;43:42-51.
18. Barabasch A, Heinzel A, Bruners P, Kraemer NA, Kuhl CK. Diffusion-weighted MRI Is Superior to PET/CT in Predicting Survival of Patients Undergoing ^{90} Y Radioembolization of Hepatic Metastases. *Radiology*. 2018;288:764-773.

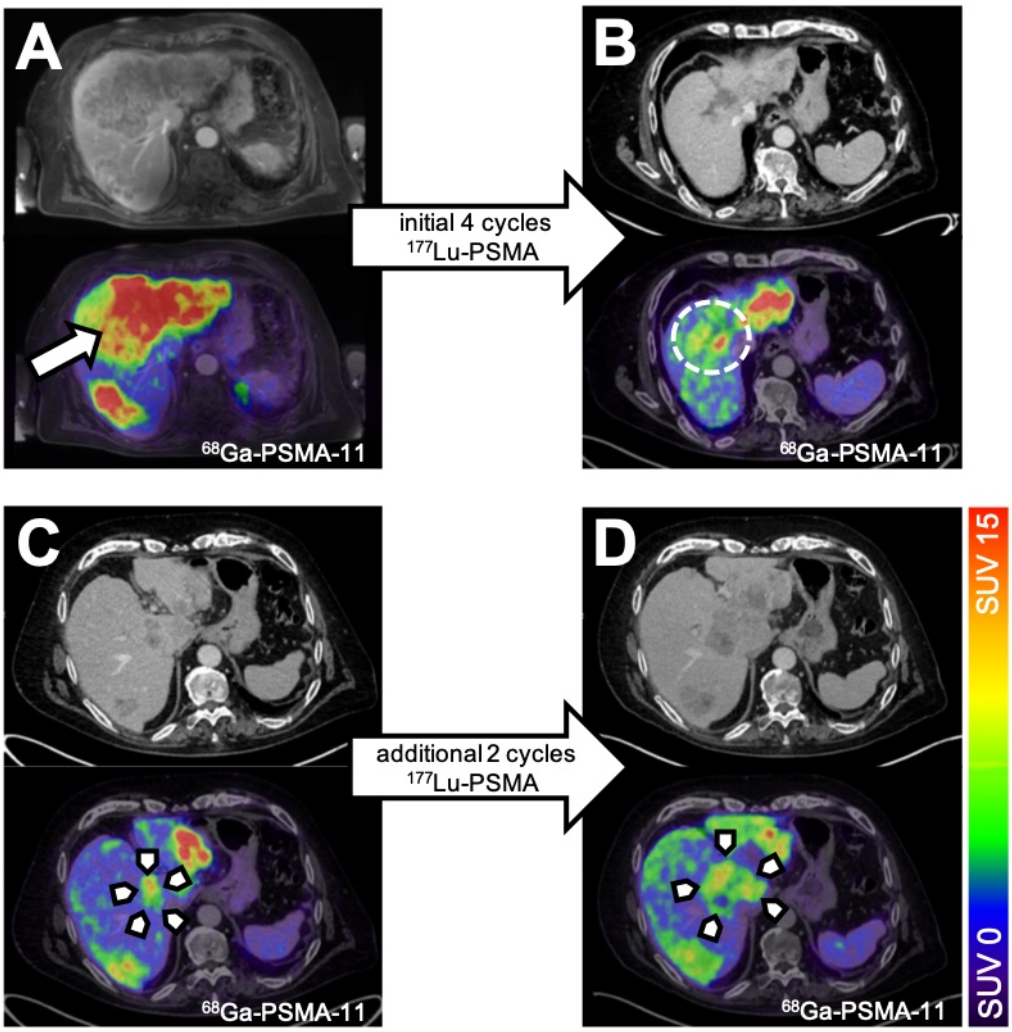
Figure legends

Figure 1 Patients



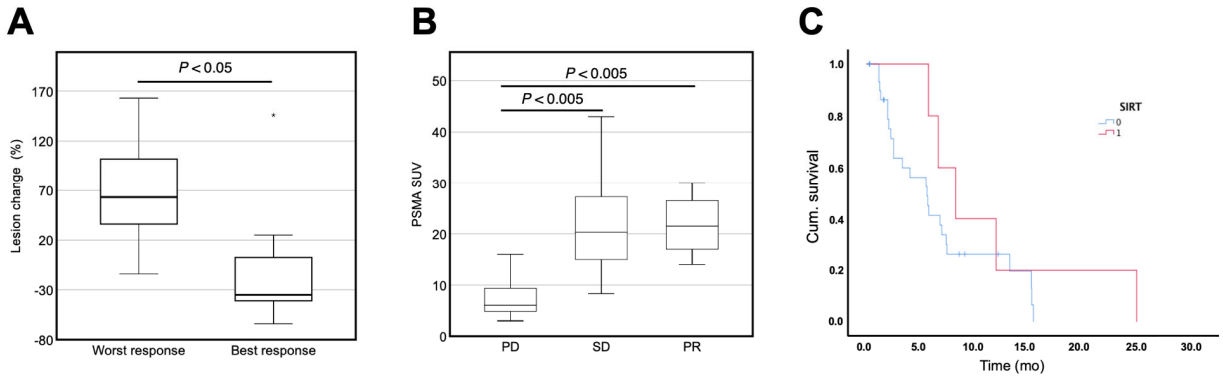
Flowchart of patient selection for the overall survival analysis (A). Details on the subgroup analysis (B) examination sequence (PSMA-PET/CT or MRI before radionuclide treatment = baseline, after Lu-PSMA =restaging, and after SIRT =final staging).

Figure 2 Discordant response of liver metastases to Lu-PSMA



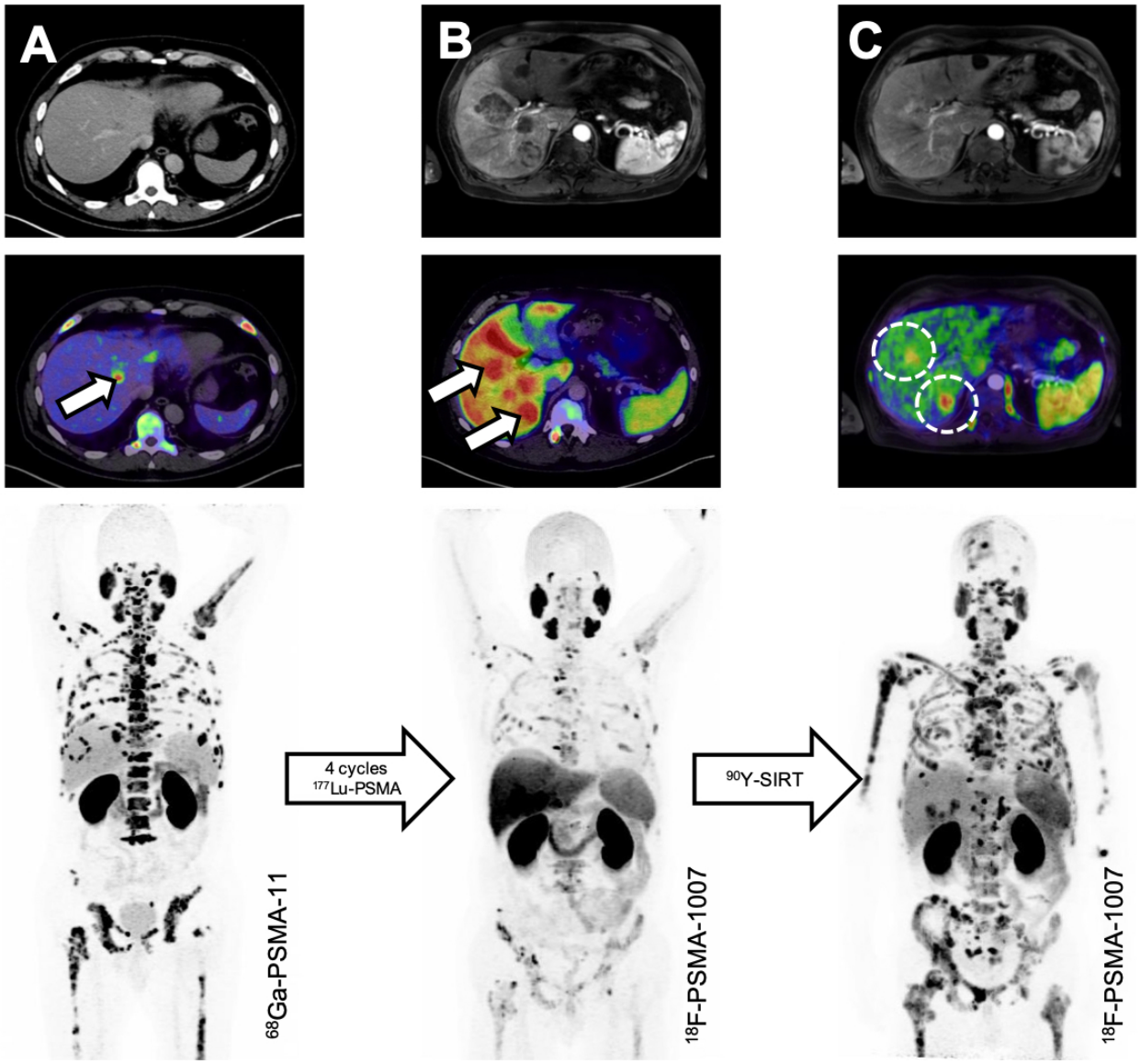
Patient 6 was treated with 6 cycles of Lu-PSMA. Prior to Lu-PSMA therapy start, PET-MRI reveals major liver metastases in both lobes (A, arrow). After the treatment with four cycles of Lu-PSMA, metastases were decreasing (B+C, dashed cycle). However, past two additional cycles, metastases were progredient and showed only modest PSMA uptake caused by dedifferentiation (C+D, arrowheads).

Figure 3 Evaluation of Lu-PSMA and SIRT efficacy



Lu-PSMA achieved only discordant responses of liver metastases; therefore, the size changes of best and worst responding lesions were compared (A, only patients with multiple liver metastases at baseline were included, n=7). Overall, liver metastases were responding significantly different to Lu-PSMA therapy (B). Treatment with Lu-PSMA therapy is only efficient in patients with strong ^{68}Ga-PSMA-11 uptake of liver metastases (B); the mean SUV of lesions was reported separately for progressive disease (PD), stable disease (SD) and partially responding (PR) liver metastases (only patients with ^{68}Ga-PSMA-11 radionuclide were included, n=8). The overall survival of patients treated with Lu-PSMA alone (C, 5.7 months in median, blue color) did not significantly differ from patients treated with a combination of Lu-PSMA and SIRT (C, 8.4 months in median, red color).

Figure 4 Response of liver metastases to Lu-PSMA and SIRT



Patient 1was initially treated with 4 cycles of Lu-PSMA, followed by SIRT. Compared to the pretherapy scan (A), liver metastases were progredient after Lu-PSMA treatment, whereas extrahepatic metastases were regredient (D, arrows). After SIRT, liver metastases had responded and had no relevant PSMA expression (C, center image, dashed cycles). However, extrahepatic metastases are severely progressive (C, bottom image). The lookup table is depicted in Figure2.

Tables

Table 1 Patient characteristics

Parameters	**$LM_{PSMA\ alone}$**	**CI (95%)**	**$LM_{PSMA+SIRT}$**	**CI (95%)**	**All patients**	**CI (95%)**
Patient count	31		5		36	
Age	71.9	66.9-73.7	73.8	64.8-78.7	72.4	67.6-73.5
Gleason score	8	N/A	8	N/A	8	N/A
PSA baseline (ng/ml)	363	501.6-1776	49.5	-262.1-1096	355.5	484.2-1593
ALP (U/l)	229.0	214.9-369.1	81.0	-15.91-288.7	223.5	200.6-340.2
LDH (U/l)	448.0	398.9-1425	389.0	214.3-468.7	435.0	389.3-1276
PSMA-RLT						
Av. no. of cycles	2	2.0-3.6	3	2.7-4.0	2.5	2.2-3.6
Cycles total	89	N/A	17	N/A	106	N/A
Av. Duration interval	7.7	6.5-8.5	7.5	2.9-16.9	7.5	6.7-9.3
Av. Activity (GBq)	6.2	6.1-6.4	6.4	5.7-7.5	6.2	6.2-6.5
ECOG PS	**Individuals**	**%**	**Individuals**	**%**	**Individuals**	**%**
0-1	21	67.8	4	80	25	69.4
2	8	25.8	1	20	9	25.0
3	2	6.4	0	0	2	5.0
Site of metastases	**Individuals**	**%**	**Individuals**	**%**	**Individuals**	**%**
Bone	31	100	3	60	34	94.4
Lymph node	24	77.4	4	80	28	77.7
Lung	8	25.8	0	0	8	22.2
Other	1	3.2	0	0	1	2.7
Previous therapy of mCRPC	**Individuals**	**%**	**Individuals**	**%**	**Individuals**	**%**
Docetaxel	29	93.5	3	60	32	88.8
Cabazitaxel	14	45.2	2	40	16	44.4
Abiraterone	26	83.8	4	80	30	83.3
Enzalutamide	25	80.6	4	80	29	80.5
Both (ABI+ENZA)	22	70.1	3	60	25	69.4
^{223}Radium	6	19.3	1	20	7	19.4
EBRT-Bone	17	54.8	2	40	19	52.8

N/A = not applicable; $LM_{PSMA\ alone}$: Liver metastases only PSMA therapy; $LM_{PSMA+SIRT}$: Liver metastases PSMA therapy + SIRT; CI: confidence interval; PSA: prostate specific antigen, ALP: alkaline phosphatase; LDH, lactate dehydrogenase, PSMA RLT, prostate specific membrane antigen radioligand therapy; ECOG: eastern co-operative oncology group; EBRT: external beam radiation therapy.

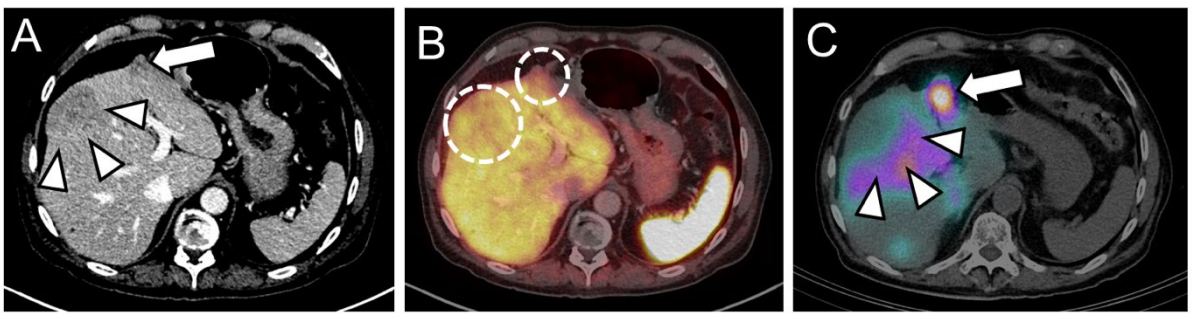
Supplement:

177-Lu-PSMA-617

PSMA-617 was manufactured by ABX GmbH, Radeberg, Germany. Whole-body scintigraphy was performed after 48 hours to monitor the retention of Lu-PSMA in prostate cancer metastases. An administered target activity of 6-7.5 MBq was used per cycle, and the cycles were repeated after 7-8 weeks. Exclusion criteria for Lu-PSMA were: Leucocytes<2000/µl, platelets<75.000/µl, haemoglobin<8g/dl, Creatinine>2mg/dl and aspartate and alanine transaminase >5x of upper limit (*1*).

SIRT

The calculation of administered SIRT activity were performed according to EANM guidelines (body surface area and relative tumour volume dependent) (*2*). Exclusion criteria for radioembolization were: the presence of ascites, elevated levels of bilirubin (cut off:2.0mg/dl), a hepato-pulmonary shunt of more than 20% (assessed by macroaggregated albumin scintigraphy (MAA)) or persisting blood flow from hepatic arteries to the gastrointestinal tract (evaluated by MAA scintigraphy and angiography) (*3*,*4*). Patients were evaluated by angiography and injection of MAA intro hepatic arteries two weeks prior to SIR treatment. Single photon emission tomography (SPECT) and scintigraphy of MAA were used to estimate the relative hepatic tumour volume and to determine, if the metastases were hypervascularized. All lesions showed at least accumulation of MAA at the margin and also within the target lesions. An example is given in Supplemental Figure 1.



Supplemental Figure 1: hypervascularisation of liver metastases.
The large liver metastasis presents a central necrosis (A, arrow heads), low PSMA expression (B, dashed circle) and rim shaped MAA accumulation (C, arrow heads), which represents the hypervascularisation in

the vital margin of the metastasis. The small liver metastasis (A, arrow) exhibits no central necrosis and shows a string MAA accumulation in the entire lesion (C, arrow).

Imaging

The Department of Nuclear Medicine switched from ^{68}Ga-PSMA-11 to ^{18}F-PSMA-1007 usage due to logistic reasons during the interval of this study. Therefore, whole-body staging was done using either tracer if no external acquisition was present. For ^{68}Ga-PSMA-11-PET, 2MBq/kg body weight was injected, and PET acquisition was acquired 60 minutes after tracer administration (Ga-68 generator was manufactured by GalliaPharm, Eckert & Ziegler, Berlin, Germany; PSMA-11 precursor was manufactured by: ABX GmbH, Radeberg, Germany). For ^{18}F-PSMA-1007, 4MBq/kg body weight was injected, scans were acquired 120 minutes after tracer administration (tracer synthesis was performed using the GE TracerLab MX synthesizer, GE Healthcare, Chalfont St Giles, United Kingdom; PSMA-1007 precursor was provided by ABX GmbH, Radeberg, Germany).

A Biograph mMR PET/MR or Biograph mCT PET/CT system was used to sequentially acquire MRI/CT and PET images (Siemens Healthcare, Erlangen, Germany). Whole Body MRI comprised an axial T2 haste, axial and coronal T1 VIBE with fat suppression (post injection of a Gadolinium containing contrast agent) as well as axial T2 TSE of the liver. Contrast enhanced abdominal CT or MRI was performed using standard parameters.

Patients

Supplemental Table 1.

Patient ID	Age	Gleason Score	Diagnosis of Liver metastases prior to Lu-PSMA start	Taxane chemotherapy prior to Lu-PSMA	Enzalutamide or Abiraterone treatment	Lu-PSMA therapy alone	Lu-PSMA and SIRT
1	65.2	4 + 5 = 9	Yes	Yes	Yes	No	Yes
2	73.8	4 + 4 = 8	Yes	Yes	Yes	No	Yes
3	66.3	4 + 5 = 9	Yes	No	Yes	No	Yes
4	77.0	3 + 4 = 7	Yes	No	Yes	No	Yes
5	71.9	4 + 5 = 9	No	Yes	Yes	Yes	No
6	82.9	5 + 5 = 10	Yes	Yes	Yes	Yes	No
7	47.2	N/A	Yes	Yes	Yes	Yes	No
8	82.0	N/A	Yes	No	Yes	Yes	No
9	81.0	3 + 3 = 6	Yes	No	Yes	Yes	No
10	60.4	N/A	Yes	Yes	Yes	Yes	No
11	76.3	4 + 3 = 7	Yes	Yes	Yes	No	Yes
12	77.1	9	No	Yes	Yes	Yes	No
13	69.6	5 + 4 = 9	Yes	Yes	Yes	Yes	No
14	59.3	5 + 4 = 9	Yes	Yes	No	Yes	No
15	68.4	4 + 3 = 7	Yes	Yes	Yes	Yes	No
16	77.2	N/A	Yes	Yes	Yes	Yes	No
17	71.5	4 + 3 = 7	Yes	Yes	Yes	Yes	No
18	76.7	4 + 5 = 9	Yes	Yes	Yes	Yes	No
19	79.3	4 + 4 = 8	Yes	Yes	Yes	Yes	No
20	80.6	3 + 3 = 6	Yes	Yes	Yes	Yes	No
21	76.3	3 + 4 =7	Yes	Yes	Yes	Yes	No
22	67.6	4 + 3 = 7	Yes	Yes	Yes	Yes	No
23	79.4	3 + 3 = 6	Yes	Yes	Yes	Yes	No
24	57.3	4 + 4 = 8	Yes	Yes	Yes	Yes	No
25	76.9	5 + 4 =9	Yes	Yes	No	Yes	No
26	62.7	4 + 4 = 8	Yes	Yes	Yes	Yes	No
27	61.5	4 + 5 = 9	Yes	Yes	Yes	Yes	No
28	69.3	5 + 4 = 9	Yes	Yes	Yes	Yes	No
29	72.9	4 + 4 = 8	Yes	Yes	Yes	Yes	No
30	75.9	4 + 5 = 9	Yes	Yes	Yes	Yes	No
31	70.0	5 + 5 = 10	Yes	Yes	Yes	Yes	No
32	74.7	N/A	Yes	Yes	Yes	Yes	No
33	60.7	4 + 4 = 8	Yes	Yes	Yes	Yes	No
34	73.4	4 + 4 = 8	Yes	Yes	Yes	Yes	No
35	50.8	4 + 4 = 8	Yes	Yes	Yes	Yes	No
36	65.4	4 + 5 = 9	Yes	Yes	Yes	Yes	No

N/A = not available.

Supplemental Table 2.

Subgroup characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age at initial PET	65	74	66	77	72	83	47	82	81	60
baseline PSA [ng/ml]	50	786	N/A	41	6.5	150	4.9	88	858	221
hepatic metastases	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Extrahepatic metastases										
Lymph nodes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Osseous	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Visceral (other than liver)	No	No	No	No	No	Lung	No	Adrenal gland	No	No
(Pre-) Treatment										
ADT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Enzalutamide	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Abiraterone	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Chemotherapy (Docetaxel or Cabazitaxel)	both	Docetaxel	No	No	Docetaxel	Docetaxel	both	No	No	both
Prostate tumour										
Gleason Score	4 + 5	4 + 4	4 + 5	3 + 4	5 + 4	5 + 5	N/A	N/A	3 + 3	N/A
Pathological stage	pT3b, pN1	cT4, cN1	pT3b, pN0	pT3a, pN0	cT4 cN1	N/A	N/A	N/A	pT1c	N/A
Clinical condition										
Karnofsky Performance Status	100	90	100	90	60	80	100	60	90	70
ECOG Performance Status	0	0	0	0	2	1	0	2	0	1
Radionuclide therapies										
Lu-PSMA therapy without SIRT	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Lu-PSMA therapy and SIRT	Yes	Yes	Yes	Yes	No	No	No	No	No	No

N/A = not available; PSA = Prostate Specific Antigen; Lu-PSMA = ^{177}Lu-PSMA-617; SIRT = Selective Internal Radiation Therapy; baseline = start of Lu-PSMA; ADT = Androgen Deprivation Therapy.

Supplemental Table 3.

	Percentual change* SIRT + Lu-PSMA Mean (95% CI)	Percentual change* Lu-PSMA alone Mean (95% CI)	*Passed D'Agostino & Pearson Normaility test*	*P***
Alanine aminotransferase	+160.0% (-46.5-366.5)	+14.6% (-16.1-45.4)	no	**0.006
Aspartate aminotransferase	+130.3% (28.1-232.1)	+25.42% (2.1-48.6)	yes	**0.007
Gamma-glutamyltransferase	+652.1% (3.1-1301)	+14.9% (-22.35-52.11)	yes	***0.0003
Bilirubin	+92.5% (-273-422)	+2.6% (-11.79-17.06)	yes	n.s.

* = Blood parameter prior to therapy (Lu-PSMA or SIRT) compared to the corresponding parameter after therapy.

** = unpaired parametric t-test was used in case of Gaussian distribution, non-parametric Mann-Whitney test was used when data did not pass D'Agostino & Pearson normality test. Outliers have been removed prior to analysis; n.s. = not significant.

Supplemental Table 4.

	CTCAE SIRT + Lu-PSMA					CTCAE Lu-PSMA alone				
	0	1	2	3	4	0	1	2	3	4
Alanine aminotransferase	3	1	0	0	0	20	0	0	0	0
Aspartate aminotransferase	1	2	1	0	0	16	3	1	0	0
Gamma-glutamyltransferase	0	1	1	2	0	8	5	3	4	0
Bilirubin	3	1	0	0	0	20	0	0	0	0

References

1. Rahbar K, Afshar-Oromieh A, Jadvar H, Ahmadzadehfar H. PSMA Theranostics: Current Status and Future Directions. *Mol Imaging*. 2018;17:1536012118776068.

2. Giammarile F, Bodei L, Chiesa C, et al. EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds. *Eur J Nucl Med Mol Imaging*. 2011;38:1393-1406.

3. Fendler WP, Philippe Tiega DB, Ilhan H, et al. Validation of Several SUV-Based Parameters Derived from 18F-FDG PET for Prediction of Survival After SIRT of Hepatic Metastases from Colorectal Cancer. *J Nucl Med*. 2013;54:1202-1208.

4. Kennedy A, Coldwell D, Sangro B, Wasan H, Salem R. Radioembolization for the treatment of liver tumors: General principles. *Am J Clin Oncol Cancer Clin Trials*. 2012;35:91-99.