Explorative analysis of a predictive score for patients with metastatic, castration resistant prostate cancer undergoing radioligand therapy with [177Lu]Lu-labeled prostate-specific membrane antigen

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Abstract

Background: Up to 60% of patients with metastatic, castration-resistant prostate cancer (mCRPC) treated with [¹⁷⁷Lu]Lu-labeled prostate-specific membrane antigen (PSMA) radioligand therapy (RLT) achieve partial biochemical response with a decrease of >50% in prostate-specific antigen (PSA) levels. The remaining fraction of patients, however, do not respond to RLT. The aim of this explorative analysis was to identify pretherapeutic factors for the prediction of response.

Methods: 46 patients (age = 68 years [53-87]) with mCRPC who consecutively underwent RLT with [¹⁷⁷Lu]Lu-PSMA (median applied activity = 6 GBq [2.9-6.2]) were included and analysed retrospectively. Association of different clinical and laboratory factors and parameters from pretherapeutic ⁶⁸Gallium-PSMA positron emission tomography (PET) with the outcome of RLT was tested (Fisher's test). Outcome was defined as PSA changes 8 weeks after the second RLT (partial response [PR], PSA decrease >50%; progressive disease [PD], PSA increase ≥25%; stable disease [SD], others). Significant risk factors were combined in a predictive score.

Results: Median pretherapeutic PSA was 79 ng/ml. Thirty percent of the patients showed a post-treatment PR (median: 73% PSA decrease), 35% SD (median: 17% PSA decrease) and 35% PD (median: 42% PSA increase). Significant predictors for PD were alkaline phosphatase (ALP) >135 U/l (p=0.030), PSA >200 ng/ml (p=0.036), and maximum standardized uptake value (SUVmax) of the "hottest lesion" in pretherapeutic PET <45 (p=0.005). The predictive score including PSA, ALP, and SUVmax could separate 2 distinct groups of patients: ≤2 risk factors (81% PR or SD, 19% PD) and 3 risk factors (10% PR or SD, 90% PD).

Conclusion: The presented predictive score allowed a pretherapeutic estimate of the expected response to RLT. This is hypothesis generating. Prospective trials are needed to test these predictive risk factors

Background

Prostate cancer has the highest incidence and the third highest cancer related mortality for men in Europe [1]. In the last decade, several treatment options for patients with metastatic, castration-resistant prostate cancer (mCRPC) were established, including abiraterone, enzalutamide, docetaxel and cabazitaxel [2]. More recently, radioligand therapy (RLT) with (¹⁷⁷Lu)Lu-labeled prostate-specific membrane antigen (PSMA) was developed and has shown promising results with regards to prostate-specific antigen (PSA) response rates and radiographic responses [3]. Retrospective as well as early prospective data confirmed the favourable safety profile of RLT [4, 5].

Although up to 60% of the patients showed some degree of response to RLT, there are patients who do not benefit from this treatment [4, 5]. The presence of visceral metastases, alkaline phosphatase (ALP) ≥ 220 U/L [5], high platelet count, a regular need for analgesics [6] or elevated lactate dehydrogenase [7] have been identified as negative predictors for the outcome, whereas ALP < 220 U/L, a cumulative injected activity ≥ 18.8 GBq [8], albumin ≥ 38.6 g/L, aspartate transaminase (AST) ≤ 24 U/L,

haemoglobin ≥ 10.4 g/dL, absence of liver metastases [9], and higher standardized uptake value (SUV) mean or max in positron emission tomography (PET) with PSMA ligands have been reported to be associated with favourable outcome [10]. However, the predictive value of these factors varies significantly between studies.

The aim of this study was first, to identify predictive factors for the outcome of RLT with [^{177}Lu]Lu-PSMA considering laboratory parameters, medical history and imaging obtained before first RLT and second, to derive a predictive score which can simplify the selection of patients who are or are not likely to benefit from RLT.

Materials And Methods

Patients

Between 06/2015 and 12/2018, 91 patients with mCRPC consecutively underwent RLT with [^{177}Lu]Lu-PSMA in the department of nuclear medicine of our university hospital.

Inclusion criteria were: 1) at least two cycles of RLT with [^{177}Lu]Lu-PSMA, 2) [^{68}Ga]Ga-PSMA positron emission tomography (PET) / computed tomography (CT) examination in the same department ≤ 8 weeks prior to first cycle of RLT and 3) complete patient records including follow-up for at least 2 months after second cycle RLT. 45 patients were excluded for the following reasons: PSMA-PET prior to RLT in other facilities or non-PET imaging with PSMA-ligands ($n = 43$) and absence of follow-up after RLT ($n = 2$). Thus, the final study population included 46 patients.

Patients records were assessed for the medical history including age at the time point of RLT, time between first diagnosis and RLT, initial Gleason score, initial D'Amico risk classification [11], presence of distant metastases at the time of initial diagnosis, treatment before RLT and type of metastases at time of RLT. Baseline laboratory tests including liver, renal and hematologic function, electrolytes, PSA and testosterone levels were recorded. Imaging parameters from ^{68}Ga -PSMA PET/CT including maximum and mean standard uptake value (SUVmax and SUVmean) of the lesion with the highest tracer uptake and the visual tumor burden were also determined. Visual tumor burden was subdivided into three categories: low (number of focal lesions in PET/CT < 10), medium (number of lesions in PET/CT > 10 and < 30) and high (disseminated metastatic spread).

Treatment, imaging, laboratory and response assessment

RLT with [^{177}Lu]Lu-PSMA and imaging with [^{68}Ga]Ga-PSMA PET/CT were performed according to consensus recommendation or as previously described [12, 13]. Laboratory parameters for liver, renal and hematologic function, electrolytes, PSA and testosterone levels were collected at each RLT cycle. In line with the German multicenter study for RLT with ^{177}Lu -PSMA [5], evaluation of the treatment response was based on the change in PSA levels between baseline at the first RLT cycle and two months after the second RLT cycle. Treatment response was defined according to Prostate Cancer Clinical Trials Working

Group 2 and 3 as follows: partial response (PR): >50% decline; progressive disease (PD): $\geq 25\%$ increase; stable disease (SD): $\leq 50\%$ decline and < 25% increase of PSA level [14, 15].

Statistical Analysis

Statistical analyses were performed using SPSS 25 (IBM Corporation, Armonk, NY, USA). To evaluate the association between single factors and PD under RLT, receiver operating characteristic (ROC) curve analysis was performed for each factor. For factors with an area under the curve (AUC) > 0.65 or < 0.35 and a p-value < 0.05, the optimal cut off value was determined (Youden's index) for binarization, and Fisher's exact test for PD vs. SD/PR was performed. P-values for each factor were corrected for multiple comparisons using the Benjamini-Hochberg procedure [16]. A p-value < 0.05 was considered significant. The combined predictive score included all single factors with equal weighting that had shown significant association with PD in Fisher's exact test.

Results

Patient, Treatment and Response Data

The median patient age was 68 years (range, 53–87). The median PSA value before RLT was 79 ng/ml (range, 4–3133). Patient characteristics including previous treatments and relevant baseline parameters are summarized in Table 1.

Table 1
Patient characteristics.

Characteristic	Number (% or range)
Total patient number	46
Median age [years]	68 (50–87)
Median baseline PSA [ng/mL]	79 (4-3133)
Median Gleason score	9 (6–10)
Initial D'Amico group:	3 (6)
Low-risk	4 (9)
Intermediate-risk	39 (85)
High-risk	
Median time since first diagnosis [months]	60 months (10 to 140)
Extent at first diagnosis	30 (65)
Localized	16 (35)
Distant metastasized	
Previous therapy	24 (52)
RPX	26 (57)
Radiation therapy	46 (100)
Androgen-deprivation therapy	28 (61)
Abiraterone	26 (57)
Enzalutamide	29 (63)
Chemotherapy	14 (30)
²²³ Radium or / and radiotherapy (bone)	8 (17)
Others (including e.g. immunotherapy)	
Site of metastases at first RLT	39 (85)
Lymph nodes	44 (96)
Bone	7 (15)
Liver	14 (30)
Visceral including liver	
Median baseline ALP [U/L]	119 (54-1188)

Characteristic	Number (% or range)
Median baseline SUVmax	47 (5-133)
Median baseline SUVmean	21 (4–49)
Visual tumor burden	18 (39)
Low	10 (22)
Median	18 (39)
High	

Overall, 117 treatment cycles were performed with a median activity of 6 GBq (range, 2.9–6.2) [¹⁷⁷Lu]Lu-PSMA per cycle. 3 patients underwent four, 19 patients three and 24 patients underwent two RLT cycles.

After the 2nd RLT cycle, fourteen patients (30%) demonstrated PR with median PSA decrease of 73%, sixteen patients (35%) showed SD with median PSA decrease of 17%, and sixteen patients (35%) developed PD with median PSA increase of 42%. The median overall survival was 19.4 months (range, 5.0-42.5) from 1st RLT cycle.

Predictors of Treatment Response

According to the predefined selection criteria, among all the analysed parameters only PSA, ALP, SUVmax and SUVmean were evaluated further for their suitability as predictive factors. Results of the ROC analysis are summarized in Table 2.

Table 2
ROC curve analysis for PD after RLT.

Parameter	AUC (95% confidence interval)	p-value
Age	0.59 (0.43–0.76)	0.299
Time since first diagnosis	0.58 (0.41–0.75)	0.393
Gleason score	0.41 (0.23–0.59)	0.299
D'Amico risk	0.42 (0.24–0.60)	0.393
Extent at first diagnosis	0.47 (0.30–0.65)	0.764
Abiraterone	0.66 (0.49–0.82)	0.080
Enzalutamide	0.52 (0.34–0.69)	0.854
Chemotherapy	0.58 (0.41–0.76)	0.356
Lymph node metastases	0.43 (0.25–0.61)	0.406
Bone metastases	0.53 (0.36–0.71)	0.712
Liver metastases	0.62 (0.44–0.80)	0.174
Visceral metastases (including liver)	0.60 (0.43–0.78)	0.258
PSA	0.84 (0.69–0.99)	0.003
Serum creatinine	0.56 (0.39–0.73)	0.518
Aspartate transaminase	0.63 (0.45–0.80)	0.159
Alanine transaminase	0.53 (0.33–0.73)	0.747
ALP	0.73 (0.54–0.93)	0.041
Gamma-glutamyltransferase	0.67 (0.46–0.89)	0.130
Blood urea nitrogen	0.45 (0.28–0.63)	0.612
Uric acid	0.57 (0.29–0.85)	0.611
Leucocytes	0.42 (0.24–0.59)	0.344
Erythrocytes	0.41 (0.23–0.59)	0.310
Thrombocytes	0.37 (0.20–0.54)	0.153
Hemoglobin	0.42 (0.24–0.59)	0.356
SUVmax	0.29 (0.13–0.46)	0.022
SUVmean	0.30 (0.14–0.47)	0.029
Statistically significant results are printed in bold.		

Parameter	AUC (95% confidence interval)	p-value
Visual tumor burden	0.47 (0.29–0.65)	0.747
Statistically significant results are printed in bold.		

Table 3 shows the results of the Fisher's exact test for the aforementioned parameters with their corresponding optimal cut-off values. All factors remained statistically significant after Benjamini-Hochberg adjustment. SUVmean was not considered in the predictive score because it did not show superior predictive value compared to the SUVmax while demonstrating lower inter-rater reliability due to the non-standardized measurement. Thus, the predictive score included baseline PSA > 200 ng/ml, AP > 135 U/l, and SUVmax < 45, equally weighted.

Table 3
Fisher's exact test for association of single variables with PD after RLT.

Parameter	Patients (SD + PR)	Patients (PD)	2-sided p-value
PSA	5 (11%)	8 (18%)	0.036
> 200 ng/mL	25 (54%)	8 (17%)	
≤ 200 ng/mL			
ALP	4 (9%)	10 (22%)	0.030
> 135 ng/mL	26 (56%)	6 (13%)	
≤ 135 ng/mL			
SUVmax	10 (22%)	13 (28%)	0.005
< 45	20 (43%)	3 (7%)	
≥ 45			
SUVmean	4 (9%)	8 (18%)	0.013
< 13	26 (56%)	8 (17%)	
≥ 13			

Among 46 patients, 36 showed ≤ 2 risk factors and 10 showed 3 risk factors. Among the 36 patients with ≤ 2 risk factors, 29 patients (81%) had SD or PR compared to 7 patients (19%) with PD. In 10 patients with 3 risk factors, 1 patient (10%) showed SD or PR while 9 patients (90%) developed PD (Fisher's exact test, p = 0.009).

Discussion

To the best of our knowledge, this is the first simple clinical score to predict the outcome after the first two cycles of [¹⁷⁷Lu]Lu-PSMA in patients with mCRPC. The score combines laboratory (PSA, ALP) and

imaging (SUVmax) parameters and can identify patients likely to benefit from RLT and potential non-responders to RLT.

MCRPC patients with higher PSA levels have a higher likelihood to develop PD under treatment than patients with lower PSA levels. Especially, a high baseline serum PSA level of > 200 ng/ml seems to be a significant predictor for unfavorable outcome. This is consistent with the results of former studies showing that serum high PSA levels correlate strongly with the risk of prostate cancer progression, not only in the initial stage of disease, but also in advanced disease [17].

In the present study, a high ALP of > 135 U/l was also defined as a significant predictive factor for unfavorable outcome after RLT. This is in line with previous studies showing a poor outcome after RLT with [^{177}Lu]Lu-PSMA in patients with elevated ALP [5, 8, 18]. Similar outcome has been also reported for patients treated with chemotherapy [19]. ALP is a marker for bone turnover [19], which has led to the hypothesis that a high ALP correlates with progressive bone metastases.

Low baseline SUVmax (< 45) in [^{68}Ga]Ga-PSMA PET also suggested an unfavorable outcome after RLT in the current study. The SUVmax/mean denotes the maximum/mean uptake in a specified region of interest (e.g., a lesion) and is the most commonly used semiquantitative parameter in PET. This may be explained by the requirement for a targeted therapy of a minimum level of PSMA expression on the cell surface to achieve adequate lutetium internalization into the cell. The SUVmax of a radiotracer has a significant role in the diagnosis and treatment selection for different types of tumors, e.g. lymphoma [20], head and neck squamous cell carcinoma [21], pancreatic tumor [22], neuroendocrine tumors [23] or even prostate cancer [24]. A recent pilot study on 14 prostate cancer patients showed that patients with a PSA response $\geq 50\%$ after treatment with [^{177}Lu]PSMA had a significantly higher baseline SUVmax in a pre-therapeutic scan with [^{68}Ga]PSMA-PET (44 vs. 17) [10]. This study also reported significantly higher SUVmean in patients with PSA response $\geq 50\%$ (10 vs. 6) [9]. Likewise, SUVmean in [^{68}Ga]Ga-PSMA-PET was a significant predictive factor of response in the present analysis. However, it was not included in the combined predictive score because of its high interrater variability and limited reproducibility [25, 26].

Not all potential imaging parameters were examined in our study, e.g. textural heterogeneity was recently postulated as a predictive factor in [^{177}Lu]Lu-PSMA treatment [27]. Our goal was however, to derive a predictive score that is simple and intuitive for clinical use. Hence, only parameters which are determined routinely and quickly before treatment were analyzed and included.

Clear limitations of this study are the small sample size and the retrospective design. Our results are hypothesis generating and need to be confirmed in further studies.

Conclusion

In this study, a score for easy clinical use to predict the treatment response to [^{177}Lu]Lu-PSMA based on pretreatment PSA, ALP, and SUVmax of the “hottest lesion” in [^{68}Ga]Ga-PSMA-PET is presented, so that

response rates of RLT can be increased and the rate of unnecessary adverse events can be reduced. This is a hypothesis generating study, further trials in independent cohorts are needed to test and validate this predictive score.

Abbreviations

ALP: alkaline phosphatase, AUC: area under the curve, CT: computed tomography, mCRPC: metastatic castrations-resistant prostate cancer, PD: progressive disease, PET: positron emission tomography, PR: partial remission, PSA: prostate specific antigen, PSMA: prostate specific membrane antigen, RLT radioligand therapy, ROC: receiver operating characteristics, SD: stable disease, SUVmax: maximum standardized uptake value, SUVmean: mean standardized uptake value

Declarations

Ethical approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This single-institution retrospective study was approved by the institutional ethics review board (EA2/177/17). All patients signed a written informed consent form for the study.

Consent for publication

Consent for publication was obtained from all individual participants included in the study.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contributions

KH, IS, WB and HA were responsible for the study concept and design. KH, HA, MDS and BE carried out the data acquisition and were responsible for the organisational procedures between the Departments of Urology and Nuclear Medicine. JMMR supervised the statistical analyses. KH + HA prepared the

manuscript. KH wrote the manuscript. KH, IS, JMMR, RLL, MDS, BE, PR, WB, HA edited and revised the manuscript. All authors read and approved the final manuscript.

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