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Impact of Previous Radiation Therapy on Prostate Specific Membrane Antigen (PSMA) - Radioligand Therapy (RLT)

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Abstract:

Following approval by the European Medicines Agency, Prostate-Specific Antigen Radioligand Therapy (PSMA-RLT) using ^{177}Lu is an established part of the treatment of castration-resistant, metastatic prostate cancer. Biochemical response rate was about 46% in the VISION-Trial. Despite these promising data, response to PSMA-RLT remains heterogeneous with a subset of patients failing to achieve adequate PSA reduction. Insufficient response can be caused by multiple factors, one of them might be the presence of radioresistance, induced by prior radiation (RT) exposure in a previous line of therapy. Possible changes include alterations in microenvironment, DNA-repair pathways or the emergence of temporarily oxygen independent cell strains after radiation exposure. These changes can result in inadequate PSA decrease or progression of disease while undergoing PSMA-RLT. Given these considerations, the present study aims to investigate the impact of previous curative or palliative radiation therapy on the effectiveness and prognosis of patients receiving PSMA-RLT. We observed no difference in overall survival (p = 0.84) and progression-free survival (p = 0.334) between the pre-irradiated and non-irradiated cohort. 66.5% of all patients included had a good response with more than 50% PSA decrease. There were no significant differences (p = 0.81) between prior RT (67.8%) and no RT (60.9%) groups. Only a longer radiation free time before undergoing RLT seemed to be a positive prognostic factor (beta = 0.21, p = 0.01).

Keywords: *prostate, prostate cancer, PSMA, RLT, radiotherapy, irradiation, curative, palliative, Lu-177, radioresistance*

1. Introduction

Recently, Lutetium[^{177}Lu]vipivotidtetraxetan (Pluvicto) was approved by the Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) for patients with metastatic, castration-resistant prostate-cancer (mCRPC) following the results of the VISION trial. The prospective trial for this new prostate specific membrane antigen (PSMA) radioligand therapy (RLT) reported favorable progression-free survival and overall survival compared with standard of care only [1, 2]. Almost all prostate patients receiving PSMA-RLT, underwent at least one radiation therapy regime like definitive, salvage or palliative intended irradiation in the course of their disease.

^{177}Lutetium itself is a beta emitter with a medium range in tissue of approximately 2 mm and linear high dose transfer to the targeted tumor cells. Median absorbed tumor dose is reported to be around 3.2 Gy/GBq for the radioligand therapy (RLT) with PSMA. Despite this high target tumor dose, there are patients, without any benefit from PSMA-RLT at all, leading to (biochemical) progression [3]. Possible reasons for these non-responders are primary or acquired resistance, which comprise PSMA-negative tumor lesions in an allover heterogenous tumor cell population, inadequate dose saturation despite sufficient PSMA expression mostly known in micro metastases or molecular mechanisms of acquired radiation resistance [4–6]. For example an upregulation of cellular radioprotective mechanism like DNA repairing components is known after exposure to non-lethal radiation doses [7, 8]. The influence of these mechanisms on therapeutic effects of radioligand therapy remains to be discussed.

It is highly likely that previous exposure to therapeutic irradiation has an effect on the outcome after PSMA-RLT due to the similarity of its therapeutic approach, whereby the differences in local dose application, such as short-range beta or more recently used alpha radiation (^{225}Ac-PSMA) should be taken into account [9, 10]. Tandem therapies are increasingly performed to suite the heterogeneity in prostate cancer patients. Therefore, the current study aimed to evaluate the impact of previous radiation therapy on the efficacy of PSMA-RLT in a large cohort of patients including aspects of tandem therapy in a daily clinical approach.

2. Material and Methods

2.1. Patients

In this retrospective study we enrolled 212 patients, who underwent PSMA-RLT in the department of Nuclear Medicine at the University Hospital Heidelberg between January 2014 and December 2019 (Table 1). The trial was approved by the local ethics committee (S228-2021). Pre-RLT treatments included antihormonal drugs like LHRH- or GnRH-analogues (96.2%), 2nd-Generation hormonal drugs like enzalutamide or abiraterone (83.4%), taxane-based chemotherapy (58,4%) or other treatments like olaparib or not-taxane-based chemotherapies (15.6%). At the time of data collection, we additionally contacted all patients to update our clinical follow-up. We observed a loss of follow-up of 34.4%. All patients were divided into two main cohorts based on their previous irradiation (n = 41 without RT, n=171 with RT including primary RT/Salvage RT and palliative RT).

Table 1

Characteristics	All Patients (n = 212)
Median age [y]	71 (range, 46-89)
Gleason-Score	
5-6	16
7 (7a/7b)	44 (16/22)
8	42
9+	87
iPSA [ng/ml]	22.4 (range, 1.9 – 10000)
Initial metastasis	70
Current metastasis	
Bone	190
Lymphnodes (LN)	138
Hepatic	33
Pulmonary	20
other	22
Radiotherapy	
1st line	43 (20.3%)
Salvage (prostate fossa and/or pelvic lymphatic pathways)	80
Palliative (bone or LN)	96
PSMA-RLT	
Median number of cycles	3 (range, 2 - 6)
Number of Patients	
Lu-177	165
Ac-225	152
Y-90	54
Median total dose [GBq]	
Lu-177	14.8 (range, 2.0 – 48.7)
Ac-225	14.0 (range, 2.0 – 45.0)
Y-90	3.0 (range, 1.0 – 13.2)

2.2. PSMA-based Imaging and Treatment

All patients underwent PSMA-based imaging, either a PSMA-PET/CT (Siemens, Biograph 6 or Biograph 20) or a PSMA-scintigraphy with planar scanning and at least dual-bed-position SPECT covering thorax/abdomen/pelvis using ^{99m}Tc-MIP1427 or ^{99m}Tc-GCK01. Tumor uptake was assessed visually in comparison to the salivary glands according to PROMISE V2 [11]. Each PSMA-RLT consisted of 2 to 6 cycles. 108 out of 212 patients received at least one cycle combined PSMA-Therapy with ^{177}Lu and ^{225}Ac. This ^{225}Ac/^{177}Lu tandem therapy was used in patients who suffered from diffuse bone metastasis often combined with a pronounced bone marrow infiltration without sufficient uptake for ^{177}Lu only therapy or after insufficient therapy response after one or two cycles of ^{177}Lu therapy. 54 patients with bulky disease were treated using a combination of ^{177}Lu and ^{90}Y. Total median doses were 14.8 GBq, 14.0 GBq and 3.0 GBq, respectively.

2.3. Follow-Up

Blood cell count was done every 2 weeks and creatinine and liver enzymes as well as PSA were tested every 4 weeks after each cycle. Laboratory test were usually performed at least 12 weeks after the last treatment. Image-based restaging was performed 8-12 weeks after the last cycle with a PSMA-PET/CT or a PSMA-scintigraphy matching pretreatment imaging (Figure 1,2).

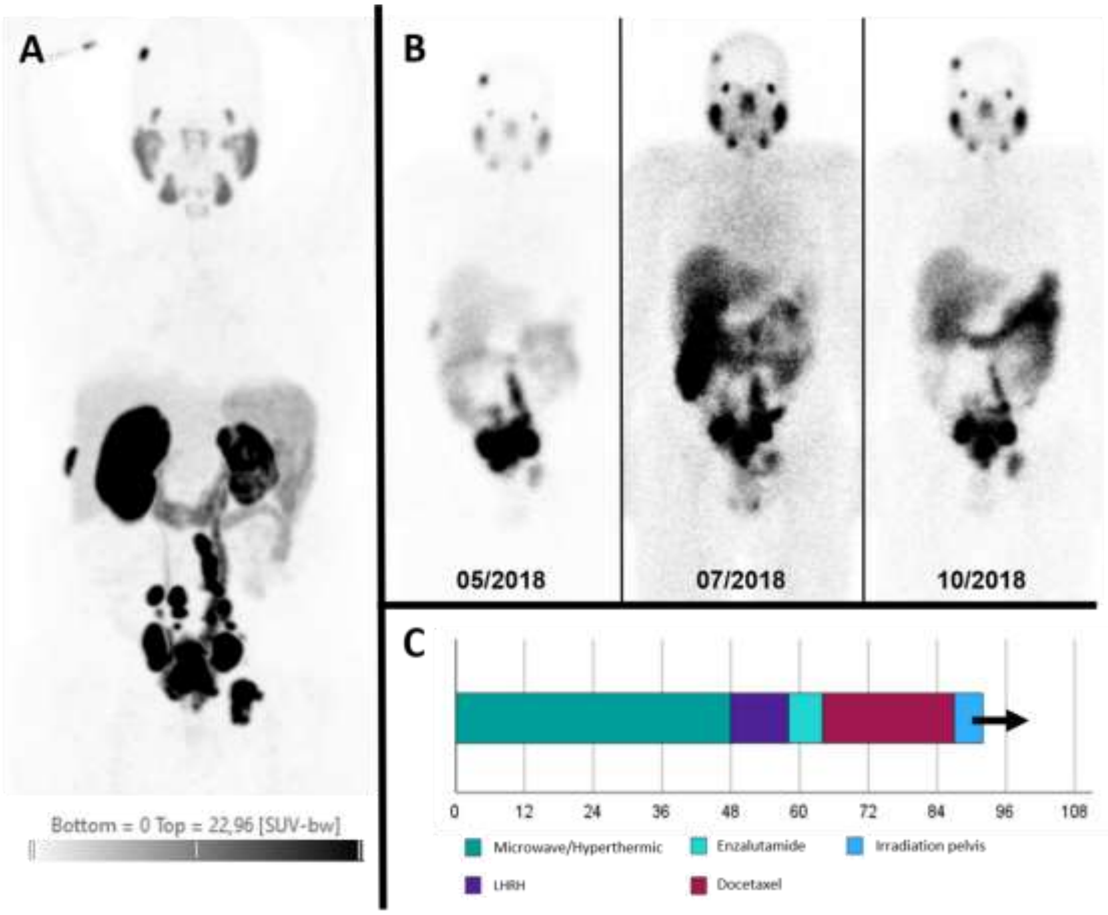

Figure 1. *Patient with prostate cancer undergoing PSMA-RLT.* ***A:*** *Pre-therapeutic ^{18}F-PSMA-1007 PSMA-PET/CT (MIP) showing pelvic and paraaortic lymphnode metastases as well as pelvic bone metastases. High tracer Uptake, PSMA Score 3 according PROMISE V2 criteria.* ***B:*** *Post-therapeutic scintigraphies demonstrating a reduction in tumor burden* ***C*** *Swimmer plot of displaying patient's therapeutic history.*

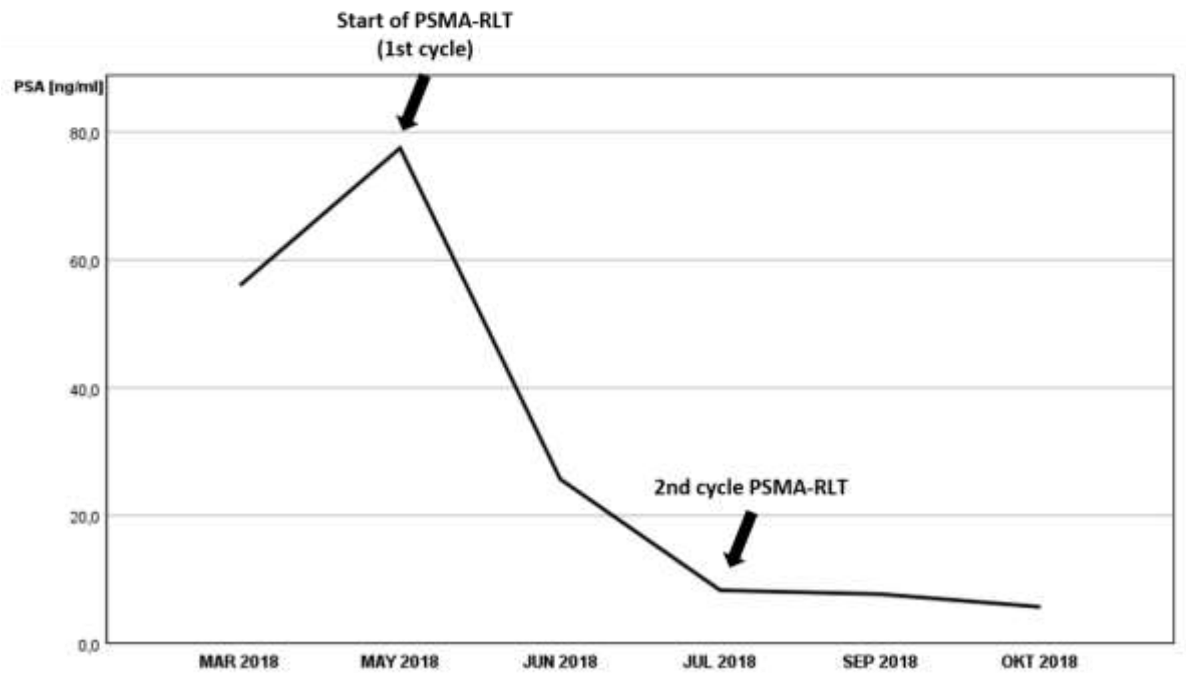

Figure 2. *PSA trend over the course of PSMA-RLT in the example patient shown in Figure 1*

2.4. Statistics

Data were analyzed using IBM SPSS Statistics Version 29. Primary endpoints were defined as overall survival (OS), progression-free survival (PFS) including biochemical progression-free survival and treatment efficiency based on PSA-decrease. Progression was defined as (1) two consecutive PSA-increases during PSMA-RLT or (2) progressive post-therapeutic or restaging imaging. Successful treatment expected a PSA-decrease of at least 50% based on pre-PSMA-RLT PSA. Secondary endpoints included the impact of RT-free intervals before PSMA-RLT as additional predicting factor for OS, PFS or PSA-decrease. The Kaplan-Meier method was used for estimations on OS and PFS. Treatment efficiency was evaluated using modified box-plots and scatter plots in combination with the Kruskal Wallis Test.

3. Results

In total 212 patients underwent PSMA-therapy after being tested for sufficient PSMA-expression using PSMA-based imaging between 2014 and 2019.

Median overall survival of all patients enclosed in this study with or without RT was 35.0 months [95%-CI; 28.9 – 41.1] whereby 49 (26.6%) deaths were recorded. Subgroup analysis comparing patients with previous RT or no RT demonstrated no significant differences in median OS with 35.0 months [95%-CI: 22.3 – 47.7] and over 108 months caused by not reaching the 0.5 survival probability at the time of data collection (Figure 3) (p = 0.85). Moreover, the time between RT (curative or palliative) and RLT was no relevant factor in Cox Regression testing (p = 0.36). With regard to treatment intention curative RT resulted in a longer median OS (36.0 months [95%-CI: 28.8 – 43.2]) compared to palliative RT (16.0 months [95%-CI: 9.9 – 22.1]) (p = 0.02).

For median PFS we observed no significant differences between irradiation (7.0 months [95%-CI: 5.5 – 8.5]) and irradiation-naïve (6.0 months [95%-CI: 2.9 – 9.1]). Median PFS in curative and palliative intent (7.0 months [95%-CI: 5.4 – 8.6] vs. 5.0 months [95%-CI: 1.6 – 8.4], p = 0.11) also showed no significant differences. Median PFS of all patients regardless of previous therapies was 7 months [95%-CI: 5.6 – 8.4] and time interval was no relevant factor (p = 0.93).

Therapy response after RLT is usually verified by PSA testing. A good PSA response (> 50% decrease) was present in 66.5% of the entire cohort (67.8% in the radiation or 60.9% in the non-radiation group, respectively). Median PSA decrease was 73.1% and 60.9% (p = 0.85; H = 0.034). There was no statistically significant difference between the subgroup with curative irradiation compared to the cohort with palliative RT (77.6% vs 61.0%, p = 0.14) (Figure 4). ANOVA testing for the time interval between RT and RLT occurred to be a modelling factor on PSA response (p = 0.01, standardized coefficient 0.21). Longer radiation-free-time corresponded with a slightly better PSA response (Figure 5).

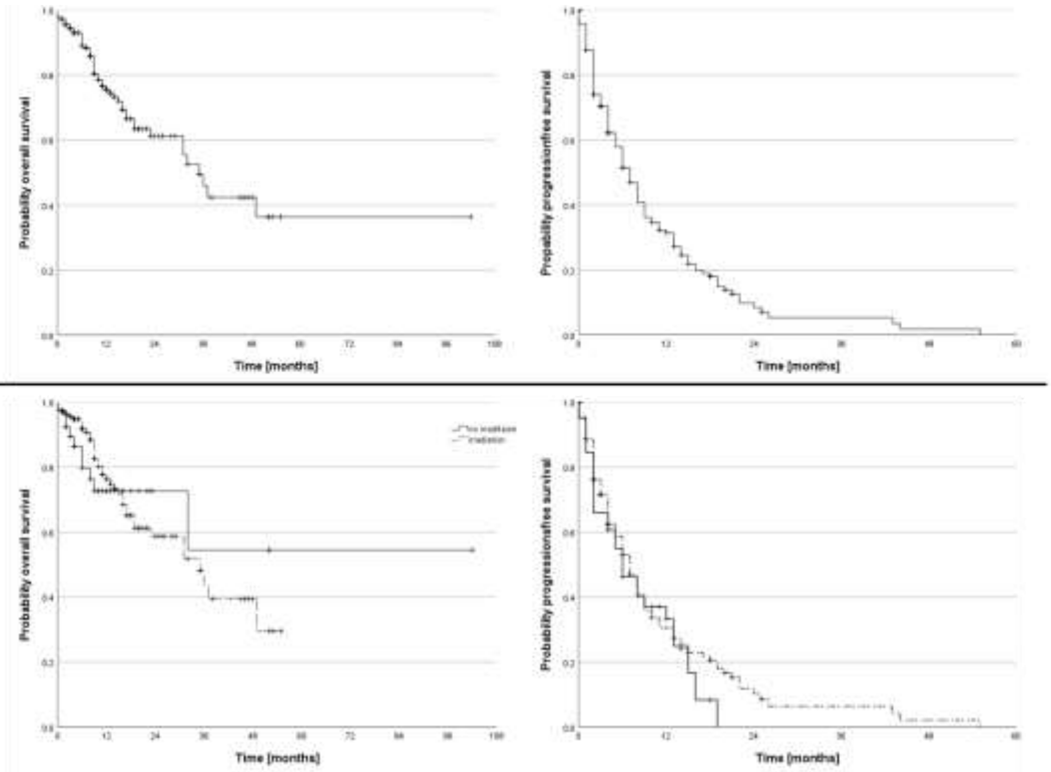

Figure 3. *Kaplan–Meier curves of overall survival and progression-free survival for the entire cohort (n = 212), as well as stratified by subgroup: radiotherapy (n = 171) versus no radiotherapy (n = 41).*

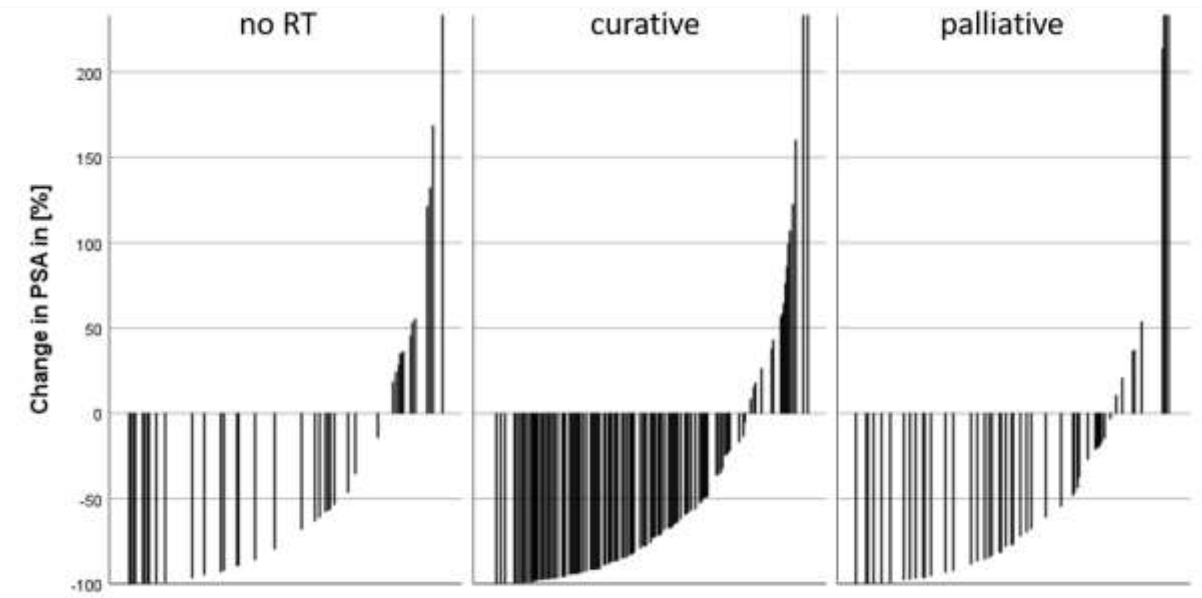

Figure 4. *Waterfall plot illustrating PSA changes under radioligand therapy (RLT) in the individual subgroups.*

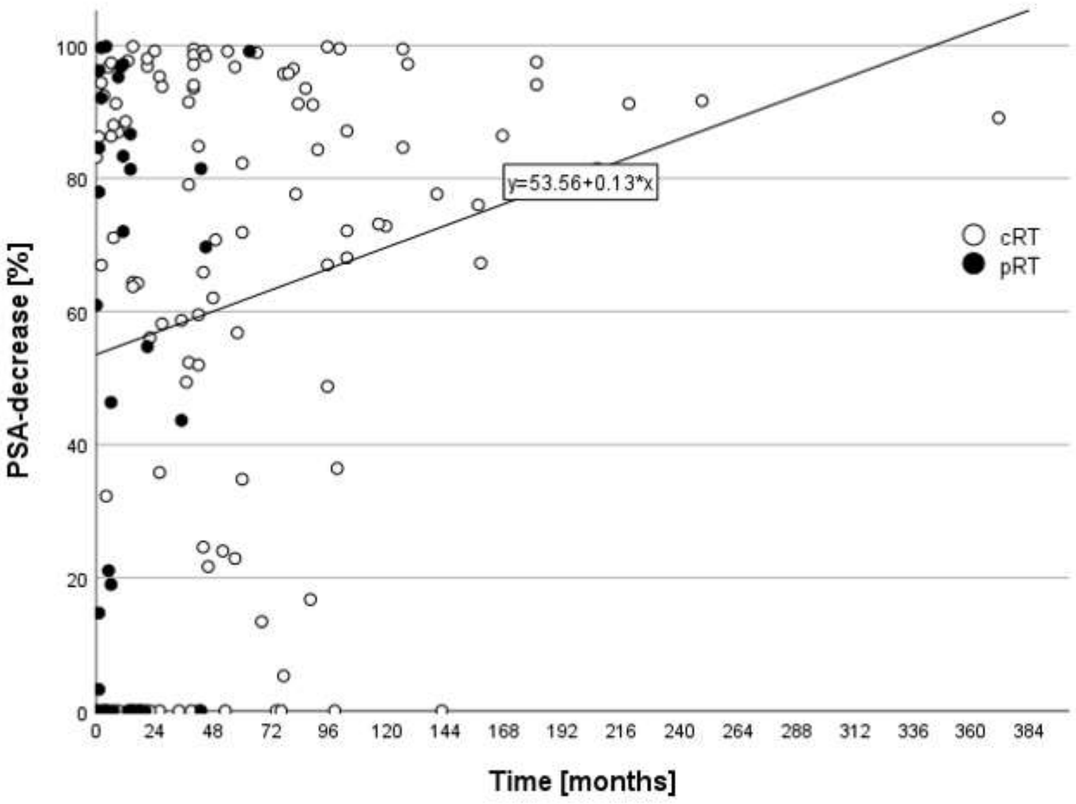

Figure 5. *Correlation between time and PSA decline within the individual subgroups curative (cRT) and only palliative (pRT) irradiation.*

4. Discussion

The results of the Vision Trial highlighted, that PSMA radioligand therapy with ^{177}Lu is an adequate treatment option for patients with metastatic, castration-resistant prostate cancer at the end of the guideline-based treatment options. PSMA-negative tumor lesions at the time of the PET scan or low PSMA uptake caused in ineligibility for treatment. In addition, patients with a superscan in the baseline bone scan and transfusion within 30 days both possible signs of a spread bone marrow carcinomatosis were also excluded. Possible prognostic factors were not assessed separately. The Vision trial reported a PSA decrease in 71.5% of the patients [2]. We have to assume at least 28.5% non-responders according to PSA-level. Predictors for the identification of these non-responders, although high PSMA uptake is present, are still topic of intense study and discussion [4, 12]. Previously induced radioresistance might be one of them. The exact mechanisms of radioresistance in RLT patients are still the subject of research. One approach at the molecular level describes the activation of genotoxic stress pathways [13]. In addition, stimulated mutations such as those resulting in acquired TP53 negativity appear to play a significant role [8]. Accordingly, our study was designed to investigate the effect of primary or palliative pre-irradiation as possible reason for these changes on the efficacy and life expectancy or PFS of patients undergoing PSMA therapy.

Our data observed that prior radiotherapy does not appear to have any major influence on overall survival and recurrence-free survival in our patients. We detected a slight difference in OS for our curative vs. palliative radiation subgroups. Possible explanations might be the dose and time the radiation was done. High initial tumor doses and extensive radiation fields, which are used for curative therapies, are discussed to have a lower chance of producing resistant cell lines due to its lower tumor survival rate than lower doses, used for palliative radiation, which aim for symptom control and low rates of side effects. Surviving tumor cells at the margin of the field of radiation with maybe inducted mechanisms for radioresistance might be the starting point for prognostic dominant radioresistant tumor phenotypes resulting in worse survival data [14]. Moreover, patients in need for palliative radiation usually have an advanced metastatic tumor stage and are in worse overall condition due to their symptoms mainly including pain and restricted mobility or obstructive urinary flow, which need additional therapy causing a decrease in quality of live and lifetime itself. Palliative irradiation aims for better symptom control and usually has none or low impact of survival data at all [15].

In addition, our data provide notes that time gone by between external radiotherapy and the start of PSMA therapy has a prognostic value itself. Significant differences in effectiveness, measured by the PSA decrease, were shown. One explanation for this observation might be previously done irradiation as possible evolutionary pressure. Temporal clonogenic survival of certain resistant cell strains can be the result. During RLT already existing radioresistant cell strains then might have an advantage over other PSMA-positive tumor cells. Due to other evolutionary factors these cell strains can vanish again if non-advantageous characteristics in the absence of radiation are present [16]. Possible characteristics include DNA repair pathways, situational gene expression or changes in tumor microenvironment [17].

Induction of radioresistance is also described as Warburg Effect. While undergoing radiotherapy tumor cells are able to primarily use glycolysis, which result in oxygen independent survival and therefore faster tumor recurrence or missing therapy effect at all. In the case of radiation, an important survival factor. On the other hand, without radiation the Warburg Effect can result in lower metabolic activity caused by the limited ATP regeneration [18, 19]. Longer radiation-free intervals might lead to vanishing resistant cell strains due to evolutionary pressure as explained above. Reduced time between external beam radiation and PSMA RLT might increase the risk of a radioresistant phenotype being present, thus reducing the response from the outset.

At the same time, it must be noted that the long intervals between radiation therapy and RLT only occurred in patients who had received curative radiation therapy alone. It is conceivable that these patients with a long interval have a less aggressive tumor phenotype, making dedifferentiation with the development of a possible PSMA-negative variant less likely. This circumstance, in addition to possible induced resistance, could be a reason for the better response. With regard to patients who received at least one palliative radiotherapy, the typical distribution between non-responders, intermediate, and good responders is observed, comparable to the data from the VISION trial [2].

However, our data from a monocentric, not controlled study must be interpreted carefully. We did not exclusively use ^{177}Lu as investigated in the Vision trial. In our everyday clinical practice, tandem therapy with ^{225}Ac is used more and more frequently used. It is known that alpha ligand therapy can break through radioresistance to a small extent and may have a positive influence on the results (no signs of negative prediction caused by previous radiation). Characteristics favorable for alpha therapy are short path lengths with high kill rates for tumor cells, high linear energy transfer (LET) with more double-strand breaks in the tumor DNA, overcoming hypoxia induced resistance or the “Nanogenerator Effect” which refer to the alpha emitting daughter nuclides like ^{213}Bi or ^{221}Fr [20].

Pronounced bone marrow carcinomatosis often results in a life expectancy less than 6 months. In addition, it shows a diffuse and mild distribution pattern. We utilize the properties of alpha radiation to achieve adequate dose saturation nevertheless. The Influence of the use of alpha emitters on the results remains unclear but represents daily clinical life in our hospital. It can be the reason, why no major negative effects on overall survival and PFS are discovered in our monocentric study.

5. Conclusion

Prior radiotherapy in general does not appear to have a major impact on patient survival or PFS at first hand. Only palliative intended irradiation was observed to be a negative prognostic factor according to survival data considering advanced tumor stage or worse overall condition. The time interval from the last irradiation to the start of PSMA therapy shows only a slightly negative impact on the effectiveness of PSMA therapy.

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