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Brief Correspondence

Can Local Ablative Radiotherapy Revert Castration-resistant Prostate Cancer to an Earlier Stage of Disease?

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Abstract

In prostate cancer, disease progression after primary treatment and subsequent androgen deprivation therapy is common. Intensification of systemic treatment is the standard of care. Recently, ^{68}Ga prostate-specific membrane antigen positron emission tomography (PSMA-PET) imaging was introduced to identify oligometastatic prostate cancer patients. In this retrospective, exploratory study, we report on the efficacy of PSMA-PET-guided local ablative radiotherapy (aRT) in 15 oligometastatic castration-resistant prostate cancer (CRPC) patients, selected from our prospective institutional database and treated between 2013 and 2016. After multidisciplinary discussion, aRT was delivered with two different schedules. Androgen deprivation therapy remained unchanged. Prostate-specific antigen (PSA) response and time to PSA progression were analysed. For comparison, individual time to PSA progression without aRT was estimated by individual PSA doubling time (PSADT). PSA response was observed in 11 patients (73%). Mean time to PSA progression or last follow-up was 17.9 mo, as opposed to 2.9 mo estimated from the PSADT without aRT ($p < 0.001$). A relevant subset of CRPC patients had a PSA response with aRT to PET-positive lead metastases. A prospective trial is in preparation.

Patient summary: In selected patients with prostate-specific antigen (PSA) increase during androgen deprivation, metastases were detected with prostate-specific membrane antigen positron emission tomography imaging. Fifteen patients with three or fewer metastases were treated with high-dose radiotherapy. Subsequently, PSA values dropped in 11 patients and in six patients no PSA progression was detected for >12 mo.

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In prostate cancer, disease progression after primary treatment and subsequent androgen deprivation therapy (ADT) is common. Castration-resistant prostate cancer (CRPC), defined as rising levels of prostate-specific antigen (PSA) under suppressed testosterone, develops in a considerable number of patients within 2–3 yr after the start of ADT. Intensification of systemic treatment is the standard of care in this situation. Under the assumption that the disease has spread systemically, several systemic treatment options are established in CRPC, for example, chemotherapy, next-generation hormonal treatment, or alpha-emitter therapy. In the past, radiotherapy was applied with palliative intention only, alleviating or preventing symptoms [1].

Recently, ^{68}Ga prostate-specific membrane antigen positron emission tomography (PSMA-PET) imaging was introduced to identify oligometastatic prostate cancer patients. To date, however, the specific impact of PSMA-PET imaging on treatment decision and radiotherapy planning remains unclear, as no prospective interventional trials have been published so far [2,3].

Stereotactic ablative body radiotherapy (SABR) is a well-established form of locally ablative treatment in patients with a limited number of distant metastases (generally less than five metastases in less than three organs, ie, oligometastatic). Since local control is high and toxicity low, SABR has been shown to improve progression-free survival in, for example, lung, breast, and hormone-naive prostate cancer metastases [4–6].

At our centre, patients with early CRPC are being offered ^{68}Ga-PSMA-PET/computed tomography or ^{68}Ga-PSMA-PET/magnetic resonance. In a multidisciplinary tumour board, either systemic therapy or, in case of oligometastatic disease, local fractionated ablative radiotherapy (aRT) to all PSMA-positive metastases is advised.

For this retrospective study, 15 patients were identified from our prospective institutional database, fulfilling the following inclusion criteria: aRT for asymptomatic oligometastatic CRPC between 2013 and 2016, availability of at least two pre- and two post-therapeutic PSA values, and prior definitive local therapy of prostate cancer (surgery or radiotherapy).

This retrospective study was approved by the local Ethics Committee (EK3012017), and all patients had given informed consent. Details on aRT (30 Gy in three fractions [N = 6 patients] or 50 Gy in 25 fractions [N = 9 patients]) can be found in the Supplementary material. All patients continued ADT. In general, patients were followed up every 3 mo; data on PSA values and information on subsequent therapies were collected.

We report the outcome on PSA progression (PSA nadir + 2 ng/ml [PSA + 2]) as recommended by the Prostate Cancer Clinical Trials Working Group [7] (Fig. 1). Additionally, the individual time to PSA + 2 without aRT was estimated for all patients by their individually calculated PSA doubling time (PSADT) before aRT [8]. For both groups, survival curves were calculated by the Kaplan-Meier method and compared by log rank test (SPSS 23; IBM Corporation, Armonk, NY, USA). Relative changes of PSA values were reported as waterfall plots (Supplementary Fig. 1) showing the difference between last pretherapeutic PSA value and PSA nadir after intervention [7]. Since post-radiotherapy imaging was not performed routinely, data on radiological progression cannot be provided. Patient and tumour characteristics are shown in Table 1. Mean time to PSA + 2 or last follow-up was 17.9 mo (95% confidence interval [CI]: 9.7–21.4 mo) compared with 2.9 mo (95% CI: 1.4–4.5 mo) estimated from the pretreatment PSADT without local ablative therapy ($p < 0.001$; Fig. 1). In the 11 responding patients (73%), the mean PSA decrease was 86% (range 72–100%) from baseline (Supplementary Fig. 1). Mean time to PSA nadir was 7.2 mo (range 4.3–10.1 mo).

To our knowledge, this is the first report showing a statistically and potentially clinically significant impact of local aRT on PSA response in oligometastatic CRPC. We were able to show that in a subset of CRPC patients presenting with rapidly rising PSA values, PSMA-PET hybrid imaging can identify patients who have a meaningful PSA response after aRT and continuation of ADT.

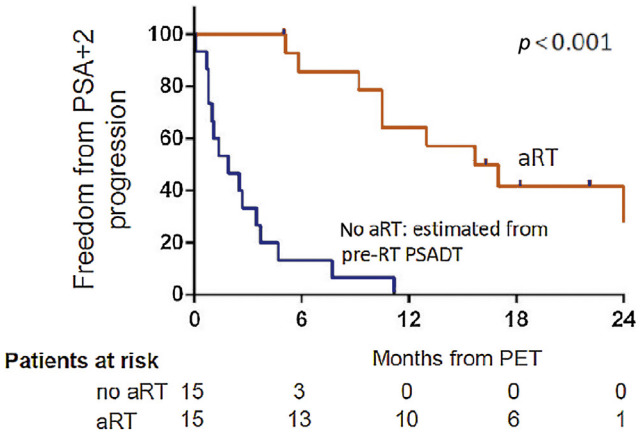

Fig. 1 – Kaplan-Meier estimation of freedom from PSA + 2 progression for patients treated with aRT (red curve). For comparison, time to PSA + 2 progression without irradiation (blue curve) was estimated for the same group of patients based on the PSA doubling time before intervention. The aRT resulted in a significant delay of PSA progression ($p < 0.001$). aRT = ablative radiotherapy; PET = positron emission tomography; PSA = prostate-specific antigen; PSADT = PSA doubling time; PSA + 2 = PSA nadir + 2 ng/ml.

Table 1 – Patient and treatment characteristics

Patient and treatment characteristics (n = 15)	
Follow-up (mo), median (range)	26.4 (12.2–39.9)
Age at PET (yr), median (range)	73.2 (56.3–86.5)
Fractionation schedule, n (%)	
50 Gy (ICRU)	9 (60)
30 Gy (SABR)	6 (40)
Number of treated metastases (per patient), n (%)	
N = 1	9 (30)
N = 2	4 (13)
N = 3	2 (7)
Location of metastases (per patient)	
Bone	12
Lymph nodes	2
Bone + lymph nodes	1
Gleason score at initial biopsy, n (%)	
7	6 (40)
8	5 (33)
9	4 (27)
Initial NCCN risk, n (%)	
Very high	8 (53)
High	6 (40)
Intermediate	1 (7)
Initial local treatment	
Radical prostatectomy, n (%)	13 (87)
+RT to the former prostate	
At biochemical recurrence	6
Immediately after surgery	2
Primary radiotherapy, n (%)	2 (13)
PSA at first diagnosis (ng/ml), median (range)	27 (4.9–400)
PSA at PSMA-PET staging (ng/ml), median (range)	3.4 (1.3–14.5)
PSADT before PSMA-PET (mo), median (range)	3.16 (0.6–8.7)
Duration of any ADT before PSMA-PET (mo), median (range)	38.5 (13.7–215.2)
Duration of complete ADT before PSMA-PET (mo), median (range)	33.3 (3.6–91.3)

ADT = androgen deprivation therapy; ICRU = International commission on Radiation Unit and Measurements; NCCN = National Comprehensive Cancer Network; PET = positron emission tomography; PSA = prostate-specific antigen; PSADT = PSA doubling time; PSMA = prostate-specific membrane antigen; SABR = stereotactic ablative body radiotherapy; RT = radiotherapy.

Our findings support the concept that PSA progression under ADT may be caused by evolution of few ADT-resistant metastases (lead metastases) and does not necessarily reflect the CRPC status of all disease sites.

We postulate that molecular imaging (eg, PSMA-PET based) is able to identify relevant metastases that are no longer controlled by ADT, and that aRT to the lead metastases achieves a PSA response in the majority of patients and may delay intensification of systemic therapy.

Owing to the more advanced disease (a higher number of metastases and higher PSA) of patients included, a comparison with results of phase 3 trials on systemic agents is not possible [9,10]. PSA response is not as relevant as clinical progression-free survival or overall survival, and those endpoints need to be included in future analyses. Furthermore, a predictive biomarker should be incorporated into further clinical trials [6].

Although the number of patients was low, the design of the study was retrospective, and the follow-up was somewhat short, the stringent selection of patients (only one to three metastatic sites, PSMA-PET hybrid imaging) and homogeneous local aRT are the strengths of this study. Nonetheless, the results should be carefully interpreted and prospectively confirmed.

In conclusion, a relevant subset of patients with ^{68}Ga-PSMA-PET–detected oligometastatic low-volume CRPC had a meaningful PSA response to local aRT. The patients were reverted into an earlier stage of their disease again. A prospective randomised trial is in preparation.

Author contributions: Tobias Hölscher had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Lohaus, Hölscher, Baumann.
Acquisition of data: Lohaus, Hölscher.
Analysis and interpretation of data: Lohaus, Hölscher, Löck, Baumann.
Drafting of the manuscript: Lohaus, Hölscher, Troost, Baumann.
Critical revision of the manuscript for important intellectual content: Zöphel, Wirth, Kotzerke, Krause, Baumann, Troost.
Statistical analysis: Löck.
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Supervision: Krause, Troost, Baumann.
Other: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.11.050.

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