Toxicity and Efficacy of Local Ablative, Image-guided Radiotherapy in Gallium-68 Prostate-specific Membrane Antigen Targeted Positron Emission Tomography–staged, Castration-sensitive Oligometastatic Prostate Cancer: The OLI-P Phase 2 Clinical Trial

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Abstract

Background: Local ablative radiotherapy (aRT) of oligometastatic prostate cancer (PCa) is very promising and has become a focus of current clinical research.

Objective: We hypothesize that aRT is safe and effective in gallium-68 prostate-specific membrane antigen targeted positron emission tomography (PSMA-PET)-staged oligometastatic PCa patients.

Design, setting, and participants: A nonrandomized, prospective, investigator-initiated phase 2 trial recruited patients with oligometastatic PCa (five or fewer lymph node or osseous metastases) after local curative therapy, without significant comorbidity and androgen deprivation therapy (ADT), at two German centers from 2014 to 2018.

Intervention: All PSMA-PET–positive metastases were treated with aRT. No systemic therapy was initiated.

Outcome measurements and statistical analysis: The primary endpoint was treatment-related toxicity (grade ≥2) 24 mo after aRT. A one-sided single-sample test of proportions was planned to test whether the endpoint occurs in <15% of the patients. Key secondary endpoints were time to progression of prostate-specific antigen (PSA) and time to ADT, which were associated with potential prognostic factors by Cox regression.

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1. Introduction

Almost 20 yr ago, Hellman and Weichselbaum postulated a concept of oligometastatic cancer, which can potentially be cured by metastasis (MET)-directed therapy [1,2]. Recently, the concept is gaining increasing acceptance for different entities [3–6].

Stereotactic ablative radiotherapy (aRT) for oligometastatic disease is meanwhile widely available and has shown to be efficient in eradicating metastatic lesions for several tumor locations [7].

For prostate cancer (PCa), prostate-specific antigen (PSA), a specific, sensitive, and easy to evaluate prognostic laboratory marker, is available to assess disease progression after primary treatment. PSA progression after radical treatment of the prostate is associated with the risks of developing distant METs and dying from PCa [8]. The current standard in this situation is shared decision-making for the initiation of androgen deprivation therapy (ADT), recognizing the disease as generalized [9,10]. However, patients with only few METs may be candidates for local ablative therapy aimed at longer-term disease control [11].

Significant advances for selecting patients for such strategies became possible with the advent of molecular imaging to detect metastatic disease in PCa [12,13]. The first randomized trial using choline positron emission tomography (PET) showed promising results in local ablative, MET-directed therapy, and prolongation of the time to PSA progression was described [14].

Meanwhile, gallium-68 prostate-specific membrane antigen targeted positron emission tomography (PSMA-PET) hybrid imaging has largely replaced other molecular imaging approaches and became the gold standard in the detection of METs of PCa. PSMA-PET advanced the selection of patients with oligometastatic status, for whom outcomes might be improved by local ablative therapy of the METs [10,15–18].

Here, we present mid-term follow-up of a gallium-68-PSMA-PET computed tomography (CT)-based clinical trial exploring local aRT of up to five PSMA-PET–avid metachronous METs in castration-sensitive PCa patients after curative primary therapy. This trial addresses toxicity and late adverse events, as well as the clinical endpoints time to PSA progression and time to the start of ADT.

2. Patients and methods

2.1. Study design and participants

The Oligoprogession in androgen sensitive Patients (OLI-P) clinical trial was a nonrandomized, prospective, investigator-initiated phase 2 trial. At two German centers, patients with PSA progression after local curative treatment (surgery and/or radiation therapy) had gallium-68-PSMA-PET–hybrid imaging. Patients with up to five PSMA-PET–positive bone (OSS-MET) or lymph node (LN-MET) metastases without local tumor recurrence or visceral METs were offered participation in the phase 2 clinical trial. Histological confirmation of the METs was not mandatory. All cases were discussed in a multidisciplinary tumor board. At registration, patients had no ongoing ADT, PSA <10 ng/ml, and no severe comorbidity limiting life expectancy to <5 yr. The trial was registered at clinicaltrials.gov (NCT02264379), and positive approvals of the local ethics committees of both centers were obtained (EK 194052014). All included patients gave written informed consent.

2.2. Procedures

PSMA-PET–hybrid imaging was not part of the clinical trial protocol, but all enrolled patients received diagnostic gallium-68-PSMA-PET–CT or gallium-68-PSMA-PET magnetic resonance imaging as part of clinical routine before inclusion into the trial. The median time from PET to inclusion was 15 d; in ten patients there was a gap of >8 wk.

Local ablative, linear-accelerator–based radiotherapy (aRT) to all PSMA-PET–positive METs was performed. Two different fractionation schedules were defined (30 Gy in three fractions [stereotactic aRT]) or 50 Gy in 25 fractions [conventionally fractionated radiotherapy]). The decision of treatment schedule was left to the treating radiation oncologist. The radiation treatment technique and treatment planning procedures are described in detail in the Supplementary material.

At predefined time points, the clinical status and the PSA value were assessed. Follow-up was scheduled weekly during aRT; at weeks 6 and 12 after treatment; at months 6, 12, 18, and 24 after treatment; and yearly afterward. All events and side effects were prospectively scored at these time points according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE V4.0) scoring system. Radiological examinations were performed only on request or at PSA progression.
In general, the referring physician started ADT in case of further PSA progression. Restaging with PSMA-PET-CT and multidisciplinary tumor board discussion were recommended, but not mandatory.

The study recruited from December 2014 to July 2018. Continuously, risk-based monitoring was performed comparing source data with entered data in electronic case report forms. Based on the primary end-point 24 mo after the start of aRT, a complete source data verification was done after the end of recruitment. All data queries were resolved. The dataset was extracted from the clinical trial database for this analysis on July 19, 2021.

2.3. Outcomes

The primary endpoint was treatment-related toxicity (grade ≥2) at 24 mo after the start of aRT. For this purpose, all toxicities were scored at each study visit and evaluated regarding causality with aRT.

Secondary endpoints included PSA progression–free time (event defined as initial PSA value + 20% or the start of ADT), time to start systemic therapy (ie, time to the start of ADT), progression-free survival (event defined as PSA progression, start of ADT, distant progression, or death), and overall survival. The time was calculated from the start of aRT to the time of the respective event or of censoring. PSA nadir (%) was calculated as a quotient of the lowest PSA value following aRT compared with baseline.

Patterns of progression after aRT and volume of disease at recurrence were evaluated and scored according to Deek et al [19].

2.3. Statistical analysis

For sample size planning, a cumulative rate of treatment-related grade ≥2 late toxicity events of 5% was expected 2 yr after treatment. Type I and II errors were set to 0.05 and 0.2, respectively. The null hypothesis (grade ≥2 toxicity at 24 mo ≥15%) and the alternative hypothesis (grade ≥2 toxicity at 24 mo <15%) were considered clinically meaningful. Under these assumptions, a one-sided single-sample test of proportions revealed a necessary sample size of 60 patients. Considering a dropout rate of 15%, 71 patients were planned to be included (Stata11; StataCorp, College Station, TX, USA).

Descriptive statistics were used to summarize patient- and treatment-related data. PSA nadir (%) was illustrated as a waterfall plot.

The time to secondary endpoints was calculated using the Kaplan-Meier method. Univariate Cox regression was performed to assess the influence of potential prognostic factors; significant factors were included in a multivariate Cox regression analysis.

Two-sided tests were performed, except for the one-sided test of the primary hypothesis, and \( p < 0.05 \) was considered statistically significant. All analyses were performed with SPSS 27 software (IBM Corporation, Armonk, NY, USA).

3. Results

A total of 72 patients were included in this clinical trial. Five patients did not fulfill the inclusion criteria. Another four patients did not receive aRT, as during treatment planning, a very high risk for serious complications was estimated due to the overlap of the target volume for MET with the high dose volume of previous radiotherapy to the primary tumor (Fig. 1). The median follow-up was 37.2 mo (range: 6.6–71.6 mo) for the remaining 63 patients and 40.8 mo for patients without an event. Fifty-one (81%) and 37 (59%) patients had a minimum follow-up of >24 and >36 mo, respectively. Patients' characteristics are shown in Table 1.

![Fig. 1 – CONSORT diagram of the OLI-P phase 2 clinical trial. ADT = androgen deprivation therapy; aRT = ablative radiotherapy; OLI-P = OLigoprogression in androgen sensitive Patients; PET-CT = positron emission tomography computed tomography; PSA = prostate specific antigen.](https://doi.org/10.1016/j.euo.2021.10.002)
A total of 68 LN-METs and 21 OSS-METs were treated. In 46 patients (73%), METs were next to (borderline) or within the previously treated volume. The majority of patients had only one lesion ($n = 45$, 71%). Four patients (6%) had LN-METs and OSS-METs; 16 patients (25%) had OSS-METs only.

The median gross and planning (PTV) target volumes were 0.9 and 10.2 ml, respectively. The 50 Gy schedule was used in 34 METs, and 55 METs were treated with stereotactic ablative body radiotherapy; the PTV of the conventionally fractionated METs was significantly larger than the volumes of the hypofractionated METs (median 18.6 vs 9.5 cm$^3$, $p = 0.004$).

No treatment-related grade $\geq 2$ toxicity was observed 2 yr after local aRT (primary endpoint). Thereby, treatment-related grade $\geq 2$ toxicity was significantly lower than 15% ($p < 0.001$), which was the primary hypothesis of the trial.

During follow-up, 36 of 63 patients (57%) had a report of one or more late adverse events (grade $\geq 1$, excluding patients with pre-existing erectile dysfunction, $n = 7$). In total, 70 events occurred after a median time of 10.1 mo. The majority of events were grade 1 (78%); 58 events could not be attributed to aRT. A mild fatigue (grade 1) was described by six patients. After aRT of a MET in the cervical spine (C7), a mild partial radicular paresthesia of the right forearm and right hand (grade 1) was present in one patient from month 6 to 22 after conventionally fractionated aRT. Five events of pain (grade 1) were documented; among these were three patients with OSS-METs (shoulder, lumbar spine, and os ilium). No grade 2 or 3 event was considered related to aRT: 14 grade 2 events (most often incontinence, $n = 9$) and one grade 3 event (bacterial cystitis) were documented.

In 11 patients, 15 severe adverse events occurred during follow-up (Supplementary Table 1). This included six secondary malignancies and two distal ureteral strictures. None of these events were considered to be related to aRT.

A PSA-progression event (initial PSA value + 20% or the start of ADT) occurred in 47 patients after a median of 13.2 mo (95% confidence interval [CI]: 10.6–15.8). In 13 patients, ADT was triggering the PSA-progression endpoint, that is, ADT was initiated before the PSA recurrence definition was reached. After 2 and 3 yr, freedom from PSA progression was 32.7% and 21.4%, respectively (Fig. 2A). Kaplan-Meier estimators of the time to PSA nadir + 2 ng/ml, time to systemic progression (censored at the time of ADT or last follow-up), and overall survival are presented in Supplementary Figure 1. After 36 mo, no further event occurred. The median time to nadir of PSA was 5.2 mo; the median reduction of PSA after aRT was 56.3%. Of the patients, 24.6% had no PSA response or immediate progression of PSA in spite of aRT (waterfall plot, Supplementary Fig. 2). Univariate Cox regression showed that a higher PSA reduction was significantly related to longer time to PSA progression ($p < 0.001$; Table 2). As this was the only statistically significant factor, no multivariate analysis was performed.
ADT was initiated in 40 patients after a median of 20.6 mo (95% CI: 13.1–28.0); 49.2% of the patients (n = 31 of 63) did not start ADT within 2 yr after aRT. ADT = androgen deprivation therapy; aRT = ablative radiotherapy; PSA = prostate-specific antigen.

Progression of LN-METs after aRT was predominately located in lymph nodes, again (n = 12 of 28, 43%). Patients with OSS-METs at inclusion had progression of their METs except for three cases. Thirty-five patients had no failure within 18 mo (class I, long-term control). In case of progression, patients with LN-METs had primarily oligoprogression (class II) and a majority of patients with OSS-METs had polyprogression (class III; Table 4).

4. Discussion

We present the final results of a prospective trial showing that PSMA-PET-hybrid imaging–identified oligometastatic disease in metachronous progressing PCa can safely be targeted by local aRT. This led to mid-term PSA progression–free and ADT-free time in one of five patients.

Table 2 – Univariate Cox regression analysis for time to PSA progression and time to ADT

<table>
<thead>
<tr>
<th>Variables</th>
<th>Time to PSA progression (47 events)</th>
<th>HR (95% CI)</th>
<th>Time to ADT (40 events)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>p value</td>
<td>p value</td>
<td></td>
<td>p value</td>
<td></td>
</tr>
<tr>
<td>PSA at initial diagnosis (ng/ml)</td>
<td>0.83</td>
<td>1.00 (0.99–1.01)</td>
<td>0.59</td>
<td>1.00 (0.98–1.01)</td>
</tr>
<tr>
<td>Risk NCCN (intermediate/high/very high/local/regional)</td>
<td>0.66</td>
<td>0.80</td>
<td>0.35</td>
<td>0.06</td>
</tr>
<tr>
<td>ISUP grade (1/2/3/4/5)</td>
<td>0.35</td>
<td>0.09</td>
<td>0.09</td>
<td>0.98–1.00</td>
</tr>
<tr>
<td>Time from initial treatment to aRT (mo)</td>
<td>0.06</td>
<td>0.99 (0.98–1.00)</td>
<td>0.019</td>
<td>0.99 (0.98–1.00)</td>
</tr>
<tr>
<td>PSA at inclusion (ng/ml)</td>
<td>0.20</td>
<td>0.91 (0.79–1.05)</td>
<td>0.77</td>
<td>1.02 (0.89–1.17)</td>
</tr>
<tr>
<td>Time from inclusion to aRT (d)</td>
<td>0.09</td>
<td>1.02 (1.00–1.05)</td>
<td>0.14</td>
<td>1.02 (0.99–1.05)</td>
</tr>
<tr>
<td>Age at aRT (yr)</td>
<td>0.08</td>
<td>0.97 (0.93–1.00)</td>
<td>0.10</td>
<td>0.97 (0.93–1.01)</td>
</tr>
<tr>
<td>PSA before aRT (ng/ml)</td>
<td>0.60</td>
<td>0.97 (0.86–1.09)</td>
<td>0.25</td>
<td>1.07 (0.96–1.20)</td>
</tr>
<tr>
<td>Number of treated metastases (per patient)</td>
<td>0.47</td>
<td>1.17 (0.77–1.77)</td>
<td>0.11</td>
<td>1.41 (0.93–2.14)</td>
</tr>
<tr>
<td>Type of metastases (LN-MET/OSS-MET/both)</td>
<td>0.64</td>
<td>0.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractionation schedule (30 Gy/50 Gy/both)</td>
<td>0.71</td>
<td>0.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overlap with previous radiotherapy (no/marginal/high dose volume)</td>
<td>0.92</td>
<td>0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ln(GTV_sum [cm³])</td>
<td>0.68</td>
<td>1.05 (0.83–1.34)</td>
<td>0.17</td>
<td>1.21 (0.92–1.60)</td>
</tr>
<tr>
<td>Ln(PTV_Vol_sum [cm³])</td>
<td>0.83</td>
<td>1.04 (0.73–1.49)</td>
<td>0.047</td>
<td>1.49 (1.01–2.20)</td>
</tr>
<tr>
<td>Nadir (%)</td>
<td>&lt;0.001</td>
<td>1.03 (1.03–1.04)</td>
<td>&lt;0.001</td>
<td>1.01 (1.01–1.02)</td>
</tr>
</tbody>
</table>

ADT = androgen deprivation therapy; aRT = ablative radiotherapy; CI = confidence interval; GTV_sum = sum of volume of all treated gross target volumes; HR = hazard ratio; ISUP = International Society of Urological Pathology; LN-MET = lymph node metastasis; NCCN = National Comprehensive Cancer Network; OSS-MET = osseous metastasis; PSA = prostate-specific antigen; PTV_sum = sum of volume of all planning target volumes of aRT.

Table 3 – Multivariate Cox regression analysis for time to ADT

<table>
<thead>
<tr>
<th>Variables</th>
<th>p value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from initial treatment to aRT (mo)</td>
<td>0.006</td>
<td>0.99 (0.98–1.00)</td>
</tr>
<tr>
<td>Ln(PTV_Vol_sum [cm³])</td>
<td>0.072</td>
<td>1.44 (0.97–2.15)</td>
</tr>
<tr>
<td>Nadir (%)</td>
<td>&lt;0.001</td>
<td>1.02 (1.01–1.02)</td>
</tr>
</tbody>
</table>

ADT = androgen deprivation therapy; aRT = ablative radiotherapy; CI = confidence interval; HR = hazard ratio; PTV_sum = sum of volume of all planning target volumes of aRT.

The strengths of this prospective study include consistent and predefined patient selection, use of the state-of-the-art gallium-68-PSMA-PET hybrid imaging as an initial was not significantly associated with time to PSA progression or time to ADT.

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staging procedure, consistent use of two predefined treatment schedules, and relatively long follow-up.

Meanwhile, several clinical trials have been able to show safety and low risk for late complications of high-dose local aRT; nevertheless, there are also reports of serious side effects leading to death after aRT in oligometastatic patients [5,20,21]. Although the majority of patients in our trial had previously been irradiated, and some METs in 73% of patients were marginally or completely overlapping with the initial radiotherapy treatment volume, observed long-term toxicity was mild. A careful planning and evaluation process of previous and current irradiation volumes and cumulative dose distributions was performed to estimate the excess risk of morbidity. In four cases, aRT was considered to bear a too high risk for serious side effects; therefore, these patients were not irradiated.

In this clinical trial, exclusively gallium-68-PSMA-PET scans were used. Other clinical trials applied conventional imaging or choline-PET to identify oligometastatic disease [5,14,22]. PSMA-PET imaging can be considered as gold standard, and is becoming widely available [18,23,24].

Approximately 50% of patients with PSA progression after primary local therapy were in an oligometastatic status appropriate for aRT of the PSMA-PET–positive METs [25]. Despite the high sensitivity of PET-CT in detecting oligometastatic disease, several patients progressed early after aRT. Comparable with 15% in the study of Glicksman et al [25], we observed 25% immediate PSA progression despite MET-directed therapy. This may be explained by the limited resolution of PSMA-PET-hybrid imaging despite the state-of-the-art technology. Only lesions >3–4 mm can be detected with sufficient sensitivity. In addition, there are prostate cancers that do not significantly accumulate PSMA [26]. Future improvement of diagnostic and molecular imaging may potentially allow more accurate selection of patients who profit from local ablative therapy in this situation. The findings of our study regarding the pattern and mode of progression are consistent with other studies [19]. In general, patients with OSS-METs will develop new OSS-METs, and patients with LN-METs are at a high risk to progress in lymph nodes again. This might reflect different types of metastatic spreading behavior of PCa [27].

There are several limitations to our study: the lack of randomization and the selected primary endpoint (toxicity) do not allow for any clinical decisions on the use of aRT in this population. The PET-identified METs were not histologically confirmed. PSA doubling time, as a potentially relevant parameter in this clinical situation, was not calculated at inclusion. Radiological examinations during follow-up were not scheduled on a regular basis, but rather performed on specific clinical request or at PSA progression. The study protocol did not provide a clear-cut definition on the start of ADT, resulting in 13 cases in which ADT was initiated before the predefined PSA endpoint (initial PSA + 20%) was reached. This may negatively influence the time to ADT and even time to PSA progression (as for this endpoint, start of ADT was considered an event).

Our results highlight that well-tolerated, local aRT allows a subset of patients a therapy-free time of years avoiding side effects of androgen deprivation, which can impair quality of life in the usually elderly and sometimes comorbid patients [28].

Further prognostic factors might improve the selection of patients for aRT [29]. In our study, PSA response after aRT and time from initial treatment, potential surrogates for disease dynamics, had significant impact on times to PSA progression and ADT. These results need external validation. Blood- or tissue-based biomarkers are a promising avenue of research to select patients who benefit from aRT, early onset of systemic therapy, or both [22,27,30].

5. Conclusions

Local aRT in selected patients with PSMA-PET-staged oligometastatic PCa is well tolerated, and may delay disease progression and onset of systemic therapy. One in five patients has no progression at 3 yr. Initiation of randomized trials with clinically relevant endpoints appears promising.

In selected patients with prostate-specific membrane antigen targeted positron emission tomography (PSMA-PET)-staged oligometastatic prostate cancer, local ablative radiotherapy is well tolerated, may improve midterm outcome, and may delay the onset of systemic therapy. One in five patients has no progression at 3 yr.
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: Hölscher, Lohaus, Krause, Baumann, Zöphel, Wirth.

Acquisition of data: Hölscher, Lohaus, Koi, Paulsen.

Analysis and interpretation of data: Hölscher, Löck, Lohaus.

Drafting of the manuscript: Hölscher, Lohaus.

Critical revision of the manuscript for important intellectual content: Baumann, Kotzerke, Zöphel, Müller, Zips, Koi, Thomas, Löck, Krause, Wirth.

Statistical analysis: Hölscher, Löck.

Obtaining funding: None.

Administrative, technical, or material support: Baumann, Krause.

Supervision: Baumann, Krause.

Other: None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2021.10.002.

References


