

Original Article

Single-fraction prostate-specific membrane antigen positron emission tomography- and multiparametric magnetic resonance imaging-guided stereotactic body radiotherapy for prostate cancer local recurrences

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Objective

To analyse the efficacy and safety of focal prostate-specific membrane antigen positron emission tomography (PSMA-PET)- and multiparametric magnetic resonance imaging (mpMRI)-guided single-fraction stereotactic body radiotherapy (SBRT) for the treatment of prostate cancer (PCa) local recurrences.

Patients and Methods

Patients with PSMA-PET-positive PCa local recurrences treated with single-fraction SBRT between 2016 and 2020 were included. Identification for subsequent recurrences or metastatic spread based on increasing prostate-specific antigen (PSA) levels were evaluated using PSMA-PET imaging.

Results

A total of 64 patients were identified. Patients received various treatments before SBRT (31 patients with radical prostatectomy [RP], 18 external beam radiotherapy [EBRT] with RP, five EBRT, and the remaining 10 other combinations). The median follow-up was 21.6 months. The median PSA level before SBRT was 1.47 ng/mL. All patients received a single-fraction treatment with a median prescription dose and isodose line of 21 Gy and 65%, respectively. At the time of SBRT, six patients (9%) received an androgen deprivation therapy (ADT). PSA levels decreased after SBRT ($P = 0.03$) and three local recurrences were detected during the follow-up. The progression-free survival after 1-, 2-, and 3-years was 85.3%, 65.9%, and 51.2%, respectively. Six patients (9%) started ADT after SBRT due to disease progression. The rates of newly started ADT after 1-, 2-, and 3-years were 1.8%, 7.3%, and 22.7%, respectively. Grade 1 or 2 toxicities occurred in six patients (9%); no high-grade toxicity was observed.

Conclusion

While the available data for SBRT in the PCa local recurrence setting describe outcomes for fractionated irradiations, the findings of this first analysis of single-fraction, PSMA-PET- and mpMRI-guided focal SBRT are encouraging. Such treatment appears to be a safe, efficient, and time-saving therapy even in intensively pretreated patients. Recurrence-directed treatments can delay the use of ADT and could avoid prostate bed irradiation in selected patients.

Keywords

prostate cancer, local recurrence, PSMA-PET, multiparametric MRI, MRI, salvage therapy, reirradiation

Introduction

Prostate cancer (PCa) is the most frequent malignant tumour in adult men [1]. The treatment of localised and locally advanced PCa usually consists of radical prostatectomy (RP), external beam radiotherapy (EBRT), or a combination of both with the potential use of androgen deprivation therapy (ADT), as well as active surveillance in selected patients [2,3]. However, with the recent advances in the field of stereotactic body radiotherapy (SBRT) and functional imaging with prostate-specific membrane antigen positron emission tomography (PSMA-PET), new therapy and diagnostic options in the recurrence setting arise [4,5]. Overall, up to ~50% of patients with PCa will have biochemical recurrence (BCR) after treatment of localised disease [6].

With more ongoing trials of SBRT for the primary management of PCa, its efficacy and safety for the treatment of local recurrences warrants further investigation [7–9]. Thanks to functional imaging, such as PSMA-PET-CT or -MRI, and the improvements in non-functional imaging in PCa diagnostics utilising high-resolution, multiparametric MRI (mpMRI), small PCa recurrences can be detected earlier, exactly defined and, therefore, precisely targeted with SBRT [4,10–12]. Such treatment approach may help to avoid prostate bed irradiation and associated toxicity, delay ADT, and could help to treat multiple subsequent recurrences, especially in intensively pretreated patients. The era of oligometastases, precision medicine, advanced imaging techniques, and personalised oncology offers the chance for further treatment refinements in the PCa recurrence management [11]. While reports are emerging that describe the outcomes for SBRT in either patients that previously underwent RP or EBRT, evaluation of SBRT treatment in surgically treated and irradiated patients remains scarce [7,8,13,14]. Moreover, and to the best of our knowledge, available evidence and reports are strictly limited to fractionated SBRT, without any dedicated data on single-fraction SBRT in conjunction with PSMA-PET and mpMRI guidance in the depicted patient cohort [7,8,14]. The objective of this analysis was to describe and to assess the efficacy and safety of single-fraction PSMA-PET- and mpMRI-guided focal SBRT for the treatment of localised PCa recurrences in intensively pretreated patients. The main endpoints of interest were the progression-free survival (PFS) and pattern of failure after treatment.

Patients and Methods

Patients who had a localised PCa recurrence were included in this analysis. Patients with previous and current distant metastasis were excluded. Patients with previously treated local recurrences were allowed. All local therapies at first diagnosis and for following recurrences before SBRT were allowed, including RP, EBRT, high-intensity focussed ultrasound (HIFU), photodynamic therapy (PDT), and irreversible electroporation (IRE). Moreover, ADT was also

permitted as a part of the therapy before or at the time of SBRT. All local recurrences before SBRT must have been diagnosed with a respective rise of PSA in two subsequent tests and must have been additionally validated and localised by a PSMA-PET-CT or PSMA-PET-MRI and mpMRI. Only patients with a localised disease in the prostate, prostate bed, or seminal vesicles were analysed in the present study. Recurrences in local lymph nodes were excluded. Grade Groups were classified according to the International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma [15]. Gleason scores <6 were integrated into the ISUP Grade Group 1. The minimum follow-up duration was 6 months. Follow-up was defined as the time from SBRT until the last clinical contact with PSA testing or PSMA-PET-CT/MRI imaging or death. Age was measured at the time of SBRT. In cases where two distinct local recurrences in direct proximity of each other were observed, they were counted as one and included in one treatment field. This was the case for four patients.

Treatments were done in a single session utilising the CyberKnife® robotic radiosurgery system (Accuray Inc., Sunnyvale, CA, USA). All patients underwent percutaneous placement of a fiducial close to or into the PCa recurrence for SBRT tracking. Treatment planning was done with the integrated treatment planning system, using mpMRI, CT, and PSMA-PET-CT/MRI data. The gross tumour volume (GTV) was defined as the visible PCa recurrence, matched, and verified with the functional imaging data from the PSMA-PET-CT/MRI. The exact delineation of the GTV outline was based on the T2 and diffusion MRI sequences. The planning target volume (PTV) was created by adding a single margin of 2 or 3 mm. The shortest distance of the urethra to the PTV was measured in millimetres, with cases with ≥ 10 mm being classified as one group. Dose constraints for organs at risk were applied according to the American Association of Physicists in Medicine Task Group 101 (AAPM TG 101) report but subject to minor deviations in favour of target coverage in selected patients [16]. After SBRT, PSA tests were done every 3 months. If the PSA continued to rise twice or a PSA increase was seen in two repeated tests after an initial decrease, a PSMA-PET-CT/MRI was regularly executed for further investigation of a recurrence or tumour progression.

Tumour local control (LC) was defined as the absence of tumour growth and new PSMA-PET signal within the PTV based on PSMA-PET-CT/MRI imaging. Locoregional control was defined as the absence of new tumour growth outside the PTV but in other prostate or pelvic areas, including all regional lymph nodes but excluding bone structures. Distant control was defined as the absence of any detectable metastases in the bones, parenchymal organs, and lymph nodes outside the pelvis. Treatment failure was defined as tumour growth, i.e., new recurrence or metastases, anywhere on PSMA-PET-CT/MRI during the available follow-up after

SBRT. For the pattern of failure analysis, the treatment failure and its location as defined above were only based on the PET imaging which identified the first disease progression after SBRT, no subsequent imaging information was incorporated. The PFS was measured from the day of SBRT to treatment failure or death. Patients were censored at the last available follow-up if no treatment failure was detectable until then. Descriptive statistics utilised ranges, means, medians, and the interquartile range (IQR) for continuous variables. Categorical variables were shown with their frequencies and percentages. Comparisons of continuous variables with more than three groups (PSA before and after SBRT) were done using an ANOVA. Time-to-event variables (PFS, time to new ADT) were assessed using the Kaplan–Meier estimate. The impact of various patient, tumour, or treatment characteristics on PFS was assessed with a Cox proportional hazards (PH) model. For the PFS Cox PH model, PSA before first SBRT, tumour volume (PTV), prescription dose, ISUP Grade Group, time from first diagnosis to SBRT, and usage of ADT at time of SBRT were taken into account. *P* values were two-sided, and statistical significance was defined as $P \leq 0.05$. All analyses were performed with STATA MP 16.0 (StataCorp, College Station, TX, USA). This work was approved by the local institutional review board.

Results

Patient and Treatment Characteristics

A total of 64 patients with 64 SBRT treatments, treated between June 2016 and December 2020, met the inclusion criteria. The median age at treatment was 73.6 years, with a median time of 7.9 years from initial PCa diagnosis to SBRT. PCa first diagnoses occurred between 1998 and 2020. Fifty-five patients (86%) underwent surgical treatment, mostly consisting of RP (95%). Most of the RP patients had a Gleason 7 tumour, comprising 20 Gleason 3 + 4 and 12 Gleason 4 + 3 tumours. Patients without RP and PCa diagnosis per biopsy were mostly diagnosed with a Gleason 7 tumour as well. The median and mean PSA level at first diagnosis was 7.4 and 10.4 ng/mL, respectively. Patients had received various treatments before SBRT, 31 patients underwent RP alone, 18 EBRT and RP, five patients EBRT alone, and the remaining 10 patients other treatment combinations (Table 1). The initial mean and median EBRT doses were 65.8 and 66 Gy, respectively, with three patients receiving proton RT. The median PSA before SBRT was 1.47 ng/mL. All SBRT treatments were done with a single-fraction. The median prescription dose and isodose line were 21 Gy and 65%, respectively. The median PTV was 2.8 mL. In patients with previous EBRT, all patients were treated in an area previously irradiated. In 41 of 64 treatments (64%), the shortest distance of the urethra to PTV was <10 mm. In

Table 1 Patient and treatment characteristics of the 64 patients.

Variable	Value
Age at SBRT, years	
Median (IQR)	73.6 (66.7–76.7)
Mean (sd)	71.7 (7.1)
Follow-up, months	
Median (IQR)	21.6 (13.7–38.1)
Mean (sd)	26.6 (15.5)
PSA at first diagnosis*, ng/mL	
Median (IQR)	7.4 (5.5–13.0)
Mean (sd)	10.4 (9.9)
PSA before SBRT, ng/mL	
Median (IQR)	1.47 (0.86–3.23)
Mean (sd)	2.73 (3.14)
Time from first diagnosis to SBRT, years	
Median (IQR)	7.9 (3.4–13.0)
Mean (sd)	8.6 (5.2)
Prescription dose, Gy	
Median (IQR)	21 (21–21)
Mean (sd)	20.9 (0.3)
Prescription isodose line, %	
Median (IQR)	65 (65–70)
Mean (sd)	67.4 (2.5)
Planning target volume, mL	
Median (IQR)	2.8 (2.0–5.3)
Mean (sd)	4.4 (4.4)
Absolute number of treatments before SBRT, <i>n</i>	
RP	52
EBRT	27
TURP	3
Brachytherapy	5
HIFU	1
IRE	1
PDT	1
ADT	17
Treatment groups before SBRT, <i>n</i>	
RP	31
EBRT	5
RP with EBRT	18
Other combinations [‡]	10
ISUP Grade Group [‡] , <i>n</i>	
1	13
2	25
3	15
4	9
5	2
T stage at first diagnosis (RP), <i>n</i>	
pT1c	1
pT2a/b/c	30
pT3a/b	20
N stage at first diagnosis (RP) [‡] , <i>n</i>	
pNx	6
pN0	36
pN1	8
Gleason score at first diagnosis (RP) [‡] , <i>n</i>	
≤3 + 3	2
3 + 3	6
3 + 4	20
4 + 3	12
7	1
4 + 4	6
4 + 5	2
5 + 3	2
Gleason score at first diagnosis (biopsy), <i>n</i>	
3 + 2	1
3 + 3	4
3 + 4	4

Table 1 (continued)

Variable	Value
4 + 3	3
4 + 4	1

*The initial PSA was not available for three patients. [†]These include: two patients with brachytherapy alone, two with TURP and EBRT, one with RP and IRE, one with TURP and brachytherapy, one with HIFU alone, one with brachytherapy and EBRT, one with RP, EBRT and brachytherapy, and one with RP and PDT. [‡]For one patient that underwent RP, a Gleason score of 7 was reported without further grading information. This patient was classified as ISUP Grade Group 2. [§]One patient underwent RP but only had a Gleason score based on a biopsy before RP. [#]One patient had no information regarding the nodal status.

34 plans (53%), the urethra had contact with the PTV. Twenty-three PTVs (36%) had a distance of ≥ 10 mm. At the time of SBRT, six patients received ADT (9%). Patient and treatment characteristics are summarised in Table 1.

Treatment Outcomes and Toxicity

The median follow-up was 21.6 months for all patients. For patients with and without any treatment failure, the median follow-up durations were 29.6 and 21.0 months, respectively. In six patients (9%), a local recurrence was observed after the first SBRT at our institution, verified by PSMA-PET-CT/MRI. Three recurrences were inside the PTV and, therefore, classified as local failures after SBRT. Three had local recurrences outside the PTV inside the prostate who, together with the three local failures, underwent a second course of SBRT at our institution. The three patients with local failures underwent their second SBRT after 23, 24, and 27 months, respectively. Two had a RP and two had received EBRT before (68 and 50.4 Gy, the latter having received an additional brachytherapy boost with 24 Gy). Dose constraints were waived in these special cases and with respect of the patients' treatment preferences. During the available follow-up, the majority of treatment failures occurred locoregionally, with a total number of 23 (Fig. 1). Distant and local failures accounted for the second and third most frequent remaining recurrences (six and three, respectively, Fig. 1). The PFS rates after 12, 24, and 36 months were 85.3%, 65.9%, and 51.2%, respectively (Fig. 2). There were no deaths during the available follow-up. Six patients started ADT after SBRT due to new recurrences or distant progression. The mean and median times to starting a new ADT were 21.3 and 23.3 months, respectively (Fig. S1). Four of six patients with ADT at the time of SBRT stopped ADT during the available follow-up. One of them showed signs of tumour recurrence at the last available follow-up.

In the multivariable Cox PH model for PFS, no variable was significantly associated with disease progression (Table 2). PSA values significantly decreased after SBRT ($P = 0.03$, Fig. 3). The median pretreatment PSA of 1.47 ng/mL

Fig. 1 Pattern of failure after SBRT. The majority of new tumour growth or metastasis occurred locoregionally, indicating a proficient SBRT target selection.

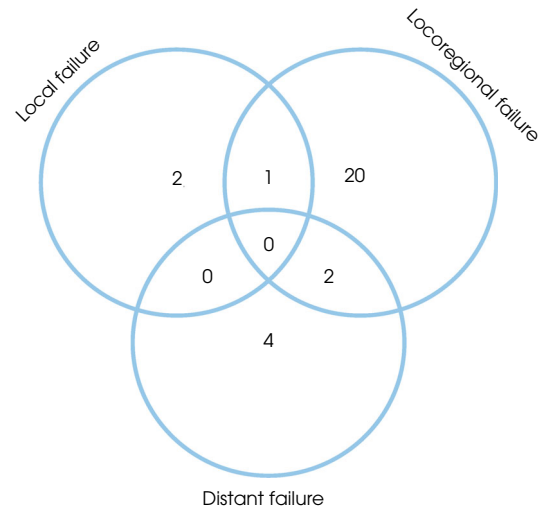
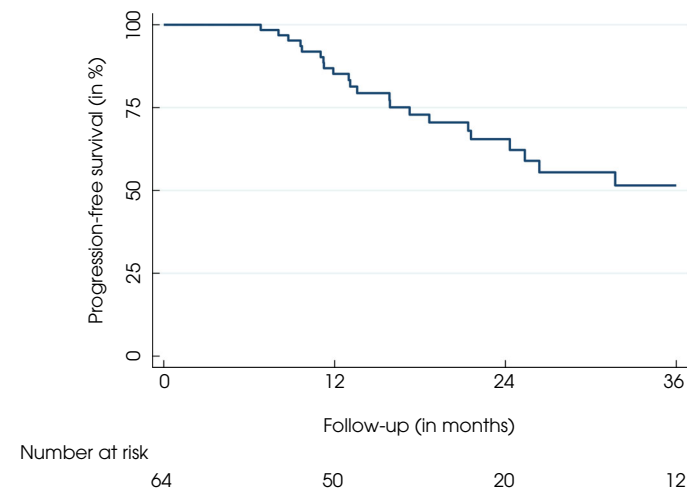


Fig. 2 PFS after SBRT. The PFS is mainly driven by locoregional failures.



declined to 0.66, 0.57, 0.47, 0.42, and 0.43 ng/mL after the first five follow-ups (Fig. 3). The treatment potentially caused toxicity in six patients (9%). The observed toxicities comprised an elevated urinary frequency (four patients), haematuria (one), diarrhoea (two), worsening urinary incontinence (one), and constipation (one). All except the worsening incontinence were of grade 1 toxicity. The incontinence was classified as grade 2. There were no grade ≥ 3 toxicities.

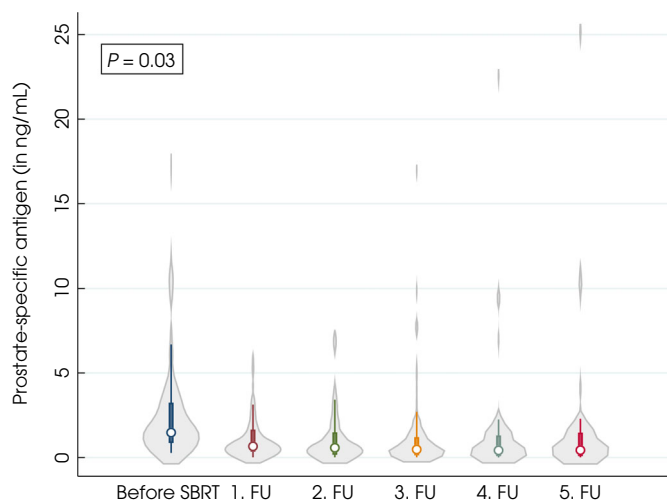
Discussion

Herein, we present our single-centre experience using single-fraction focal SBRT with PSMA-PET and mpMRI guidance

Table 2 Multivariable Cox proportional hazards model for PFS after SBRT. No variable was significantly associated with PFS.

Variable	Hazard ratio	95% CI	P
Prescription dose (Gy)			
20	Reference	–	0.60
21	0.61	0.09–3.91	
22	0.76	0.05–10.51	
PTV (mL)	0.89	0.72–1.10	0.30
PSA at time of SBRT (ng/mL)	1.09	0.93–1.27	0.25
ISUP Grade Group			
1	Reference	–	0.61
2	0.89	0.23–3.35	
3	0.79	0.18–3.37	
4 and 5	1.52	0.30–7.72	
Treatment groups			
RP	Reference	–	0.057
EBRT	0.18	0.01–1.89	
RP and EBRT	0.26	0.06–1.04	
Other combinations	1.28	0.34–4.74	
ADT at time of SBRT	0.34	0.02–4.17	0.40
Time from first diagnosis to SBRT (months)	0.98	0.97–1.00	0.07

Fig. 3 Violin plot of PSA values before and after SBRT. PSA significantly decreases after SBRT treatment. FU, follow-up.



for the management of PCa local recurrences. Throughout a short to intermediate follow-up, we observed a favourable LC and safety profile, which is in agreement with previous reports of SBRT in the management of primary and oligometastatic PCa [7,8,17–19]. PSA levels successfully declined after SBRT, indicating that the reason of rising PSA levels before SBRT was successfully targeted.

Several aspects of this work need to be discussed. While reports on the use of SBRT with PSMA-PET and mpMRI guidance for focal treatment of PCa local recurrences are emerging, the use of single-fraction treatments and the inclusion of patients with multiple previous therapies, including RP, EBRT, and others, are two unique

characteristics of this analysis [7,8,14]. We hypothesised that a deviation from the commonly applied four–six fraction regimens with total doses of 34–40 Gy is feasible and safe for patients with confined, small- to medium-sized recurrences. Given the findings and homogeneous dose prescription in the present study (84% of patients received 21 Gy, prescribed to the 65% or 70% isodose line, all patients received one fraction), we appraise the further evaluation of this fractionation scheme and the associated dose escalation in terms of the biologically effective dose (BED) in this distinct patient cohort (BED >240 Gy, assuming an α/β ratio of 2 Gy) [8]. A radiosurgical approach, i.e., utilisation of a single-fraction with an ablative dose, has only been scarcely described to date, especially concerning local recurrences. To the best of our knowledge, this is the first report investigating such a fractionation for PCa local recurrences, whereas first reports of single-fraction SBRT are emerging in the primary PCa therapy setting [20]. Moreover, patient selection for focal SBRT is still a matter of ongoing debates. Most previous analyses in the field focussed on patients that either underwent RP or EBRT before SBRT, with comparable outcomes [7,8,14,21]. However, one has to note that our patient cohort is heterogeneous and received more treatments before SBRT. Patients with localised recurrences and multiple previous therapies are frequently referred to our centre, often with the sole recommendation of starting ADT given their past medical history. To offer them another focal, individualised, and effective treatment, a careful and reasonable patient selection is pivotal.

Subsequently, the treatment indication and planning, as well as the follow-up, was heavily based on PSMA-PET data in conjunction with PSA testing and mpMRI. Regarding the first two points, we had a favourable experience in terms of patient selection and treatment efficacy. The latter aspect may be of specific relevance for the evaluation of our treatment approach. As the PSA testing, with all its advantages and disadvantages, is a generally accepted tool for evaluating the treatment success, rising PSA values up to ~1 ng/mL may represent an unsolved challenge in the setting of PCa recurrences or metastatic spread. Such PSA values may trigger clinicians to perform a PSMA-PET-CT/MRI. However, chances are broadly ranging between 11% and 87% to actually detect the reason for the PSA rise, highlighting a grey zone for affected patients [4,22–24]. Often, no clear origin of the PSA rise, local recurrence or metastatic spread, can be identified based on the functional imaging. This circumstance may influence the further management of the patient. We strongly recommend adding mpMRI for further radiographic evaluation when suspicion of a local recurrence is high [10]. Based on other reports and our institutional experience, this approach greatly helps to identify small local recurrences or locoregional spread to lymph nodes and enables proficient patient selection for the depicted treatment method [14]. On

the other hand, a repeated, delayed imaging or ADT may be viable options in this situation and for pretreated patients but with the recent paradigm shift towards oligometastatic states of disease, the possibility of localised treatments should be carefully considered as well once metastases are detectable [25]. These aspects were also apparent in this study. We observed a high LC in heavily pretreated patients, with most treatment failures being of locoregional nature and identified by PSMA-PET-CT/MRI. Still, a total of 25 patients showed disease progression. In terms of risk factors for PFS, patient, tumour, and treatment characteristics that may affect the treatment outcomes of this specific patient group are largely unknown and further clarification is required.

Besides the value of PSMA-PET imaging, a biopsy could provide additional benefit when suspicion for local recurrence is high. However, as depicted in the present study, our treated cases were mostly of small volume (median PTV 2.8 mL). In addition, nearly 50% of all patients underwent any type of RT before SBRT. Both circumstances make it exceptionally challenging to perform a successful biopsy for histopathological confirmation, as such recurrences may not be efficiently identified and targeted on ultrasound [11]. Thus, we regularly forego biopsy in this patient cohort in favour of PSMA-PET and mpMRI staging, leveraging the sensitivity and specificity of both functional and non-functional imaging techniques [4,26].

The next major aspect that should be addressed is the potential of delaying or avoiding ADT. Despite the fact that a considerable number of patients progressed with the disease after SBRT, as expected in this high-risk, heavily pretreated cohort, some patients were able to stop their ADT or delay its start during the further course of disease. The possibility and concept of this had been previously proposed but mostly in the oligometastatic setting [17,27]. Yet, our data shed further light on the potential of ADT delay in the setting of localised PCa recurrences. Nevertheless, we must note that a handful of patients willingly declined to start ADT after SBRT even in the presence of newly diagnosed metastases or further recurrences, fearing adverse effects of the systemic therapy. This aspect must be considered when interpreting our reported results. Moreover, the sample size and retrospective, single-centre study design certainly represent additional significant limitations concerning this matter. However, there could be a subgroup of patients that profit from PSMA-PET- and mpMRI-guided focal SBRT for local recurrences in the light of ADT avoidance or delay. This may be especially relevant for patients with comorbidities or a limited life expectancy. Despite its significant role in PCa management, ADT is associated with considerable adverse effects and in the era of oligometastases and metastasis-directed treatments, further research must investigate options to delay or avoid it if medically feasible and justifiable [25,28].

Another potential use of the depicted treatment approach should be discussed as well: for the group of patients after RP and with subsequent PSA rises, the BCR remains a challenge for clinicians as further treatment options become more limited [3,6]. Salvage RT of the prostate bed helps to reduce the risk for systemic progression [3,29]. This approach has recently been investigated by the means of SBRT after initial EBRT as well and may be of further interest in comparison to conventional salvage EBRT given its faster delivery and outcomes [7,8,30]. However, irradiation of a suspected area of tumour recurrence without identification of its exact location opens the door for treatment refinements as re-irradiations in this setting regularly target the whole prostate bed. In cases as depicted in the present study, where functional and non-functional imaging with PSMA-PET and mpMRI reliably identified the morphological reason and origin of BCR, highly conformal, targeted SBRT of local recurrences could be utilised [11,14]. With such an approach, prostate bed irradiation could be delayed in favour of potentially repeatable SBRT treatments for subsequent recurrences. As discussed, being able to offer patients the possibility of a single-session treatment is another noteworthy advantage of the depicted treatment approach. Nevertheless, data on this matter remain scarce and patients undergoing such treatment must be carefully selected and counselled.

Finally, our experience regarding the treatment safety was favourable. No significant toxicity grade ≥ 3 was observed even though a considerable number of targets were treated in direct proximity of the urethra. SBRT for PCa and metastases has shown comparable results with low rates of grade ≥ 3 gastrointestinal or genitourinary toxicity [8,18,25]. However, given our patient cohort with sometimes multiple previous treatments before SBRT, the toxicity rates were not taken for granted when we started to investigate our treatment approach. Yet, the treated recurrences were mostly small and led to a consecutively low PTV, which may explain our present findings. In addition, the follow-up is still insufficient to detect late toxicities. We still must highlight the retrospective nature of our analysis, sample size, patient heterogeneity, and all apparent study limitations. Nevertheless, we appraise the further evaluation of the depicted treatment approach, hope for more reports on this matter, and, ideally, prospective work to address the unanswered questions of ADT delay and potential avoidance of prostate bed irradiation in heavily pretreated patients with PCa local recurrences.

Conclusion

While the available data for SBRT in the recurrent PCa setting describe outcomes for fractionated therapies, this first analysis of single-fraction PSMA-PET- and mpMRI-guided focal SBRT for local PCa recurrences demonstrates encouraging results. Such treatment appears to be a safe,

efficient, and time-saving therapy option even in intensively pretreated patients. Utilising both imaging modalities, PSMA-PET and mpMRI, for patient selection and target delineation is required. Recurrence-directed SBRT treatments can delay the use of subsequent ADT and could avoid prostate bed irradiation in selected patients. Prospective investigations are necessary to confirm the actual effectiveness of this single-fraction treatment approach.

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Disclosure of Interest

Felix Ehret reports honoraria from Accuray Inc. outside the submitted work. All other authors declare no conflict of interest.

Institutional Review Board/Ethical Approval

This work was approved by the institutional review board of the Ludwig-Maximilians-University Munich (internal number 21-0687, date of approval: 21/07/2021).

Data Availability Statement

Research data are not available at this time.

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Abbreviations: ADT, androgen deprivation therapy; BCR, biochemical recurrence; BED, biologically effective dose; (EB) (SB)RT, (external beam) (stereotactic body) radiotherapy; (G) (P)TV, (planning) (gross) tumour volume; HIFU, high-intensity focussed ultrasound; IQR, interquartile range; IRE, irreversible electroporation; ISUP, International Society of Urological Pathology; LC, local control; mpMRI, multiparametric MRI; PCa, prostate cancer; PDT, photodynamic therapy; PET, positron emission tomography; PFS, progression-free survival; PH, proportional hazards; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Time to new androgen deprivation therapy (ADT) after stereotactic body radiotherapy (SBRT).