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Fractionated stereotactic body radiotherapy for up to five prostate cancer oligometastases: Interim outcomes of a prospective clinical trial

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Stereotactic body radiotherapy (SBRT) can delay escalation to systemic treatment in men with oligometastatic prostate cancer (PCa). However, large, prospective studies are still required to evaluate the efficacy of this approach in different patient groups. This is the interim analysis of a prospective, single institution study of men relapsing with up to five synchronous lesions following definitive local treatment for primary PCa. Our aim was to determine the proportion of patients not requiring treatment escalation following SBRT. In total, 199 patients were enrolled to receive fractionated SBRT (50 Gray in 10 fractions) to each visible lesion. Fourteen patients were castration resistant at enrolment. The proportion of patients not requiring treatment escalation 2 years following SBRT was 51.7% (95% CI: 44.1–59.3%). The median length of treatment escalation-free survival over the entire follow-up period was 27.1 months (95% CI; 21.8–29.4 months). Prior androgen deprivation therapy (ADT) predicted a significantly lower rate of freedom from treatment escalation at 2 years compared to no prior ADT (odds ratio = 0.21, 95% CI: 0.08–0.54, $p = 0.001$). There was no difference in the efficacy of SBRT when treating 4–5 *vs.* 1–3 initial lesions. A prostate-specific antigen (PSA) decline was induced in 75% of patients, with PSA readings falling to an undetectable level in six patients. No late grade three toxicities were observed. These interim results suggest that SBRT can be used to treat up to five synchronous PCa oligometastases to delay treatment escalation.

Key words: androgen deprivation therapy, oligometastases, prostate cancer, stereotactic body radiotherapy

Abbreviations: ADT: androgen deprivation therapy; ADT-FS: androgen deprivation therapy-free survival; CI: confidence interval; CT: computed tomography; CTCAE: common terminology criteria for adverse events; EBRT: external beam radiotherapy; EQD2: equivalent total dose in 2 Gray fractions; GTV: gross tumour volume; Gy: Gray; HR: hazard ratio; IQR: interquartile range; MDT: metastasis-directed therapy; PCa: prostate cancer; PET: positron emission tomography; PSA: prostate-specific antigen; PSMA: prostate-specific membrane antigen; PTV: planning target volume; RP: radical prostatectomy; RT: radiotherapy; SBRT: stereotactic body radiotherapy; TE-FS: treatment escalation-free survival

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What's new?

Metastasis-directed therapy (MDT), involving surgery or stereotactic ablative radiotherapy, is a promising alternative treatment strategy for prostate cancer patients with metastatic disease. It remains unclear, however, which subsets of patients most benefit from MDT. Here, interim analysis of a large prospective trial involving fractionated stereotactic body radiotherapy (SBRT) for prostate cancer patients with up to five synchronous oligometastases shows that 2 years following SBRT, about half of patients did not require treatment escalation. In addition, nearly one-quarter of patients had prostate-specific antigen levels below baseline. The findings highlight the promise of SBRT for long-term suppression of oligometastatic prostate cancer.

Introduction

Systemic treatment with androgen deprivation therapy (ADT) and/or chemotherapy remains at the core of treating metastatic prostate cancer (PCa).[1] However, metastasis-directed therapy (MDT) has emerged as an alternative approach for a subset of patients with limited metastatic (oligometastatic[2]) disease. In this setting, the rationale for MDT is to (*i*) eradicate the cancerous lesion(s), (*ii*) delay exposure to next-line systemic therapy and (*iii*) delay progression to a castration-resistant state.[3]

Results of the first randomised phase II trial of MDT for oligometastatic PCa were recently published.[4] MDT (surgery or stereotactic ablative radiotherapy) provided ADT-free survival (ADT-FS) of 21 months *vs.* 13 months for surveillance among men with up to three PCa oligometastases. In addition, several relatively small studies demonstrate the efficacy of metastasis-directed radiotherapy to delay the clinical progression of oligometastatic PCa, with minimal adverse effects.[5–8]

Despite these promising results, the subset of patients who will benefit most from MDT has not yet been defined.[3] Studies powered by large sample sizes are still required to assess the influence of factors such as lesion number, lesion location and hormone sensitivity on the efficacy of MDT. In addition, previously published studies limit the number of oligometastases treated to three.

This is the interim analysis of a prospective study evaluating fractionated stereotactic body radiotherapy (SBRT) for patients with up to five synchronous oligometastatic PCa lesions. The primary endpoint was the proportion of patients not requiring treatment escalation 2 years following SBRT. We sought to identify characteristics associated with a better response to SBRT. To the best of our knowledge, this is the largest prospective trial of SBRT for oligometastatic PCa.

Materials and Methods

Study design and setting

This was a single-centre, single-arm, prospective study designed to evaluate the efficacy of SBRT for oligometastatic PCa. The study was approved by the Epworth HealthCare Human Research Ethics Committee, Melbourne, Australia (RT mediated eradication of oligometastatic prostate cancer following prior local treatment (TRANSFORM): a prospective phase II study, Australian New Zealand Clinical Trials Registry number ACTRN12618000566235, retrospectively registered). All patients signed informed consent.

Participants

Eligible patients were men with a histologically confirmed diagnosis of PCa, prior definitive local treatment (external beam radiotherapy [EBRT], brachytherapy or radical prostatectomy [RP]), five or fewer synchronous metastases (N1 and M1 a/b) diagnosed on imaging, and ECOG performance status of 0 or 1. Patients could be ADT-naïve, on a treatment break following prior ADT for metastatic disease, or hormone refractory and taking ADT at the time of enrolment.

Patients who had received prior palliative radiotherapy, or who presented with active local disease in the prostate bed on clinical examination or imaging, were excluded from the study.

Serum PSA and testosterone levels were recorded within 6 weeks prior to enrolment. Staging was performed using a combination of magnetic resonance imaging, whole-body bone scan and choline positron emission tomography–computed tomography (PET–CT) until September 2014, after which prostate-specific membrane antigen (PSMA)-PET-CT became the primary staging modality. Lesions were documented and classified as local recurrence, lymph node metastases (regional or distant) or bony metastases according to the American Joint Committee on Cancer 7th edition guidelines.[9]

Post-SBRT follow-up with PSA testing, clinical evaluation and toxicity assessment was scheduled for 6 weeks following treatment, quarterly for 2 years and then half-yearly thereafter. Patients with a rising PSA were referred for further staging investigations, with the timing of this at clinician discretion.

Intervention

Eligible patients were prescribed a fractionated course of SBRT with the intent to eradicate all visible oligometastatic lesions. The gross tumour volume (GTV) was defined as the tumour visible on the radiotherapy CT planning scan and the available staging scan(s). A planning target volume (PTV) was contoured for each lesion to account for uncertainties in target position due to internal organ motion or patient movement during treatment. The PTV was an isotropic expansion of the GTV of 5 or 1 mm for nodal and bony lesions, respectively. The prescription dose for each lesion was 50 Gray (Gy) in 10 daily fractions, with 90% of the dose (45 Gy) covering the PTV. An altered fractionation regimen was prescribed in cases where there was overlap with previously delivered radiotherapy fields. In these cases, an equivalent total dose in 2 Gy fractions (EQD2) of at least 60 Gy was maintained ($\alpha/\beta = 2$). Patients presenting with new oligometastases following SBRT

were eligible for repeat courses of SBRT given there were no more than five new synchronous lesions and that an EQD2 of at least 60 Gy could be safely delivered to each visible lesion.

SBRT was delivered on the Novalis TX™ (Varian Medical Systems, Palo Alto, CA) or Truebeam™ (Varian Medical Systems, Palo Alto, CA) treatment platforms using either dynamic conformal arcs or intensity modulated radiation therapy. The position of all patients was verified prior to each fraction using cone-beam CT and/or dual orthogonal kV imaging, with corrections made in six degrees using the Exactrac™ (BrainLAB, Munich, Germany) monitoring system and robotic couch.

Outcome measurements

The primary endpoint of our study was the proportion of men not requiring treatment escalation within 2 years of initial SBRT. Treatment escalation was defined as the commencement of ADT for hormone naïve patients and those who had prior ADT, the commencement of second-line ADT or chemotherapy for patients with concurrent ADT at enrolment, or palliative radiotherapy. Treatment was escalated at the discretion of the treating clinician(s) based on PSA progression, in-field recurrence following SBRT, progression to polymetastatic disease (greater than five new metastases) or clinician concern at the rate of disease progression despite lack of radiologic progression. Secondary endpoints were (*i*) length of treatment escalation-free survival (TE-FS), (*ii*) change in PSA post-SBRT and (*iii*) SBRT-related grade three toxicity. Toxicity was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. At the time of the interim analyses, all patients had gone through at least 2 years of follow-up. Secondary endpoints were assessed using all available data.

Statistical analysis

These are the interim analyses of a 5-year follow-up study. The interim analyses used a conservative alpha set to $p < 0.01$, two-tailed, as utilised by Hsueh *et al.*,[10] for both the primary and secondary endpoints. Ninety-five per cent confidence intervals (CIs) were reported to allow for comparison with other studies.

The number of patients without treatment escalation at 2 years was reported using percentages together with Clopper–Pearson binomial 95% CIs. Time to treatment escalation, including the escalations that occurred after 2 years, was analysed using Kaplan–Meier curves. Association of clinical characteristics with the proportion of men not requiring treatment escalation within 2 years post-SBRT and the length of TE-FS were analysed using logistic regression[11] and Cox proportional hazards regression,[12] respectively. The Cox regression models were checked against the proportional hazards assumption for any significant violations.

Waterfall plots[13] were used to show the maximal per cent change in PSA from baseline following SBRT for each patient. For patients with a PSA drop following treatment, the maximal percentage change was relative to the lowest PSA reading recorded during the total follow-up period, even if the PSA level eventually increased above baseline. For patients who did not record a PSA drop, the maximal PSA change was relative to the highest PSA reading recorded during the total follow-up period. Plots were truncated at a maximum PSA change of +300%.

Waterfall plots were generated using SAS 9.4 (SAS Institute Incorporated, Cary, NC2014), and all other statistical and graphical analyses were performed using Stata 15 (Stata Corporation, College Station, TX, 2017).

Data availability statement

The dataset analysed in our study is not publicly available due to participant confidentiality restrictions. Information will be made available by the corresponding author upon reasonable request.

Results

Participants

Two hundred and eight patients were enrolled between April 2014 and April 2016. Nine patients were subsequently excluded from the study. Staging with PSMA-PET-CT was performed for 152 patients (76.4%). Five patients could not be treated to an EQD2 of 60 Gy due to overlap with previous treatment or PTV size. Two patients did not have all visible oligometastatic lesions treated. One patient did not have metastatic PCa on follow-up restaging scans and one patient had received prior palliative radiotherapy. In total, 199 patients received SBRT. Baseline characteristics for these patients are presented in Table 1. There were no SBRT-related late grade three toxicities. One hundred and nine patients (54.5%) received a single course of SBRT, 63 (31.7%) received two courses, 19 (9.5%) received three courses and 8 (4.0%) received four courses.

The median follow-up time following SBRT was 35.1 months (range: 6.5–51.3 months), including patients lost to follow-up. Thirty-three patients (16.6%) had received prior ADT. Fourteen patients (7.0%) were castration-resistant at enrolment and received concurrent ADT with SBRT. The initial number of lesions treated was 1–3 and 4–5 in 165 (82.9%) and 34 (17.1%) patients, respectively.

One hundred and seventy-six patients were included for analysis of the primary endpoint. Twelve patients were excluded due to local recurrence in the prostate bed. Six patients developed further oligometastases (five or fewer) following the initial treatment but were not eligible for further SBRT on trial due to overlap with previous radiotherapy fields. Two patients were lost to follow-up, two patients withdrew from the trial and one patient died prior to 2 years follow-up.

Treatment escalation

The proportion of patients not requiring treatment escalation 2 years following SBRT was 51.7% (95% CI: 44.1–59.3%). Table 2 lists the indications for commencing escalated treatment alongside the treatment type. Rising PSA ($n = 43$) and progression to polymetastatic disease (greater than five

Table 1. Patient characteristics

Characteristics	All patients (n = 199)
Age at baseline	
Mean (SD)	67.4 (6.5)
Gleason score	
6	4 (2.0)
7	111 (55.8)
8	15 (7.5)
9 and 10	62 (31.2)
Missing	7 (3.5)
PSA at baseline (ng/ml)	
Median (IQR)	1.8 (0.8–4.6)
Missing	6 (3.0)
Type of primary therapy	
Radical prostatectomy	185 (93.0)
External beam radiotherapy	9 (4.5)
Brachytherapy	3 (1.5)
Not stated	2 (1.0)
Prior ADT	
No	152 (76.4)
Yes	33 (16.6)
Concurrent	14 (7.0)
Castration sensitivity	
Resistant	14 (7.0)
Sensitive	185 (93.0)
Number of initial oligometastatic lesions	
1	81 (40.7)
2	50 (25.1)
3	34 (17.1)
4	24 (12.1)
5	10 (5.0)
Site of initial oligometastatic lesions	
Bone only	45 (22.6)
Node only	126 (63.3)
Bone and node	24 (12.1)
Other	4 (2.0)
Time between primary therapy and SBRT (years)	
Median (IQR)	3.8 (1.3–7.2)

Data are presented as n (%) unless otherwise indicated.
Abbreviations: ADT, androgen deprivation therapy; IQR, inter quartile range; PSA, prostate-specific antigen; SBRT, stereotactic body radiotherapy; SD, standard deviation.

synchronous metastases; n = 35) were the predominant reasons for treatment escalation.

Subgroup analyses for treatment-escalation at 2 years following SBRT are presented in Table 3. Of the patients who had received prior ADT, 6 (22.2%) were free from treatment escalation at 2 years post-SBRT compared to 79 (58.1%) patients with no prior history of ADT, this difference being statistically significant (p = 0.001). There was no statistically significant difference between patients treated for 1–3 *vs.* 4–5 lesions.

At the time of last follow-up, 105 patients had treatment escalation. The median TE-FS for the cohort was 27.1 months (95% CI: 21.8–29.4 months). Increasing age (hazard ratio [HR] = 1.39, 95% CI: 1.30–1.48, $p < 0.001$) was a statistically significant predictor for treatment escalation. Prior ADT (HR = 1.97, 95% CI: 1.22–3.18, p = 0.005) but not concurrent ADT (HR = 1.43, 95% CI 0.72–2.84, p = 0.30) was also associated with poorer TE-FS compared to hormone naïve patients (Fig. 1*a*). Patients with both bone and nodal lesions were at increased risk of treatment escalation compared to bone only (HR = 2.12, 95% CI: 1.12–4.02, p = 0.022) (Fig. 1*b*), however, the association was not statistically significant at the $p < 0.01$ level. There was no significant difference in TE-FS when comparing the node only and bone only groups (HR = 0.82, 95% CI: 0.51–1.31, p = 0.404) or when comparing patients with 4–5 *vs.* 1–3 initial lesions (HR = 1.07, 95% CI: 0.68–1.67, p = 0.78) (Fig. 1*c*).

PSA response

A total of 144 patients (75.0%) had at least one PSA reading lower than baseline following SBRT, with six patients recording an undetectable PSA level. There were n = 7 patients with a missing baseline PSA. The maximal PSA change from baseline following treatment is depicted by a waterfall plot in Figure 2.

At the time of last follow-up, 41 (23.3%) of 176 patients were free from treatment escalation and had a PSA reading which continued to be below their baseline PSA level. For these 41 patients, the median (interquartile range [IQR]) baseline PSA was 1.7 (0.9–2.9) ng/ml, 33 were initially staged with PSMA-PET-CT, 33 had 1–3 lesions initially treated, 30 received SBRT to nodes only and 36 patients had no prior ADT.

Discussion

To the best of our knowledge, this is the largest prospective trial of SBRT in the setting of oligometastatic PCa and the first to include patients with up to five initial lesions. Our study showed that over 50% of patients were free from treatment escalation 2 years following SBRT with no late grade three toxicities reported. The median TE-FS was 27.1 months. Forty-one patients (23.3%) had a PSA level lower than baseline in addition to being free from treatment escalation at the time of last follow-up.

The results of our study are comparable to other prospective studies of MDT for up to three oligometastatic PCa lesions. With single fraction stereotactic ablative radiotherapy, Siva *et al.*[5] reported that 48% of patients with no prior history of ADT remained ADT-free at 2 years. In a study of repeated fractionated SBRT, Decaeststecker *et al.*[8] reported a median ADT-FS of 25 months. Ost *et al.*[4] found a slightly shorter median ADT-free survival of 21 months, however included both surgery and SBRT as the MDT intervention. It should also be noted that our definition of treatment escalation included chemotherapy and palliative radiotherapy in addition to ADT. However, ADT was still the predominant

Table 2. Indications for escalating treatment within 2 years of SBRT

Type of treatment	*n* (%)	Reason	*n* (%)	Median (IQR) PSA level at time of TE[1] (ng/ml)
ADT	75 (88.2)	Rising PSA	43 (57.3)	8.0 (3.8–4.5)
		Polymetastatic disease	25 (33.3)	4.2 (2.0–8.5)
		Oligometastatic disease—overlap with previous RT fields	7 (9.4)	3.6 (2.7–5.4)
Chemotherapy	5 (5.9)	Polymetastatic disease	5 (100.0)	11.6 (5.8–12.0)
Palliative RT	5 (5.9)	Polymetastatic disease	5 (100.0)	8.1 (7.4–9.7)
Total	85 (100.0)			6.5 (3.1–12.8)

[1]The median (IQR) time between last recorded PSA and treatment escalation was 22 (10–40) days.
Abbreviations: ADT, androgen deprivation therapy; PSA, prostate-specific antigen; RT, radiotherapy; TE, treatment escalation.

Table 3. Subgroup analyses for treatment-escalation status 2 years post-SBRT

	Treatment escalation free	Relationship with patient characteristic		
Characteristics	*n* (%)	OR	95% CI	*p*-value
Age at baseline	–	0.99	0.94–1.03	0.574
Gleason score				
6 or 7 (*n* = 106)	57 (53.8)	Ref		
8 (*n* = 13)	7 (53.9)	1.003	0.32–3.18	0.996
9 and 10 (*n* = 52)	23 (44.2)	0.68	0.35–1.33	0.261
PSA at baseline	–	0.94	0.88–1.003	0.063
Type of primary therapy				
RP (*n* = 166)	84 (50.6)	Ref		
EBRT (*n* = 6)	5 (83.3)	4.88	0.56–42.68	0.152
Initial staging with PSMA-PET-CT				
No (*n* = 38)	17 (44.7)	Ref		
Yes (*n* = 138)	74 (53.6)	1.43	0.69–2.95	0.334
Prior ADT				
No (*n* = 136)	79 (58.1)	Ref		
Yes (*n* = 27)	6 (22.2)	0.21	0.08–0.54	0.001
Concurrent (*n* = 13)	6 (46.1)	0.62	0.20–1.94	0.173
Castration sensitivity				
Resistant (*n* = 13)	5 (38.5)	Ref		
Sensitive (*n* = 163)	86 (52.8)	1.78	0.56–5.69	0.326
Number of initial oligometastatic lesions				
1–3 (*n* = 145)	75 (51.7)	Ref		
4–5 (*n* = 31)	16 (51.6)	0.996	0.46–2.16	0.991
Site of initial oligometastatic lesions				
Bone only (*n* = 36)	17 (47.2)	Ref		
Node only (*n* = 113)	66 (58.4)	1.57	0.74–3.33	0.241
Bone and node (*n* = 23)	5 (21.7)	0.31	0.09–1.02	0.054
Time between primary therapy and SBRT (years)	–	1.0	1.0–1.0002	0.905

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; EBRT, external beam radiotherapy; OR, odds ratio; PSA, prostate-specific antigen; Ref, reference category; RP, radical prostatectomy; SBRT, stereotactic body radiotherapy.

next-line therapy, used in 92 (87.6%) of the 105 patients receiving escalated treatment by the time of most recent follow-up.

An important difference between our study and those previously published is our use of PSMA-PET for disease staging. Three quarters of patients in our study were initially staged using PSMA-PET. These patients had a lower rate of treatment escalation at 2 years following initial SBRT and slightly longer TE-FS compared to patients who were not initially staged with PSMA-PET, however, these differences were not statistically significant. PSMA-PET has excellent sensitivity and specificity[14] and is a superior modality for detecting PCa

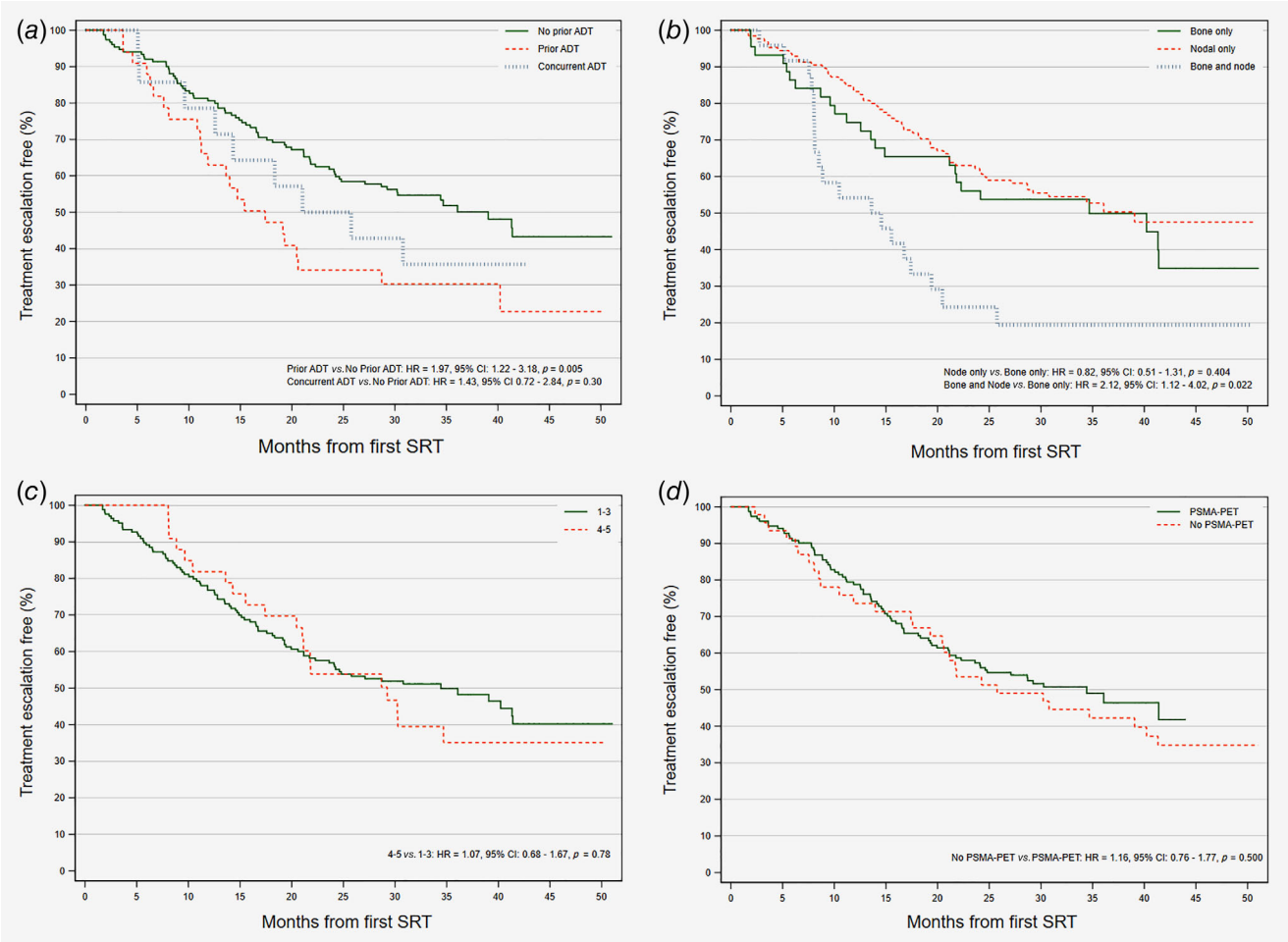

Figure 1. (*a*) Time to treatment escalation stratified by prior ADT status. (*b*) Time to treatment escalation stratified by lesion type. (*c*) Time to treatment escalation stratified by number of lesions treated. (*d*) Time to treatment escalation stratified by if a patient received PSMA-PET-CT at baseline. [Color figure can be viewed at wileyonlinelibrary.com]

lesions compared to choline-based PET imaging.[15] Based on the responses of a multidisciplinary panel of international experts, PSMA-PET has become the preferred modality for staging biochemically recurrent and advanced PCa.[16] With PSMA-PET, the risk of untreated occult metastatic PCa lesions is lowered. This could explain the slightly higher TE-FS in our study compared to ADT-FS in previous studies, even though we adopted a broad definition of treatment escalation and included patients with up to five initial lesions. Counterbalancing that was the use of PSMA-PET for restaging in our cohort. This would result in the earlier diagnosis of polymetastatic disease compared to conventional imaging. As polymetastatic disease was an indication for treatment escalation, this could potentially result in a relative reduction in TE-FS compared to other studies.

In our study, the only statistically significant predictor for treatment escalation within 2 years of initial SBRT was prior ADT. Only 6 of 27 patients who had received prior ADT remained free of treatment escalation at 12 years. It is likely that a considerable proportion of these patients had polymetastatic disease at the time they originally commenced ADT, although this cannot be proven as PSMA-PET was not available at that time. We would expect this group to commence ADT sooner after SBRT than the ADT naïve cohort, which is consistent with our results.

Franzese *et al.*[7] report worse progression-free survival following SBRT for castration-resistant patients compared to castration-sensitive patients, however, no statistically significant difference was observed between these groups in our study in terms of treatment escalation. This may be because the number of castration-resistant men in our study was too low to detect a difference. Nevertheless, 5 of the 13 patients in this group in our study remained free from treatment escalation at 2 years, suggesting that SBRT can be a worthwhile treatment in this setting.

The number of oligometastatic PCa lesions considered amenable to MDT remains contentious and this is an important aspect of our study. Most previous studies limit the scope of MDT to three synchronous lesions, given that the likelihood of occult metastases increases as the number of detectable lesions increases.[17] However, our data shows that treating 4–5 synchronous PCa lesions with SBRT is just as effective as treating 1–3 lesions in terms of

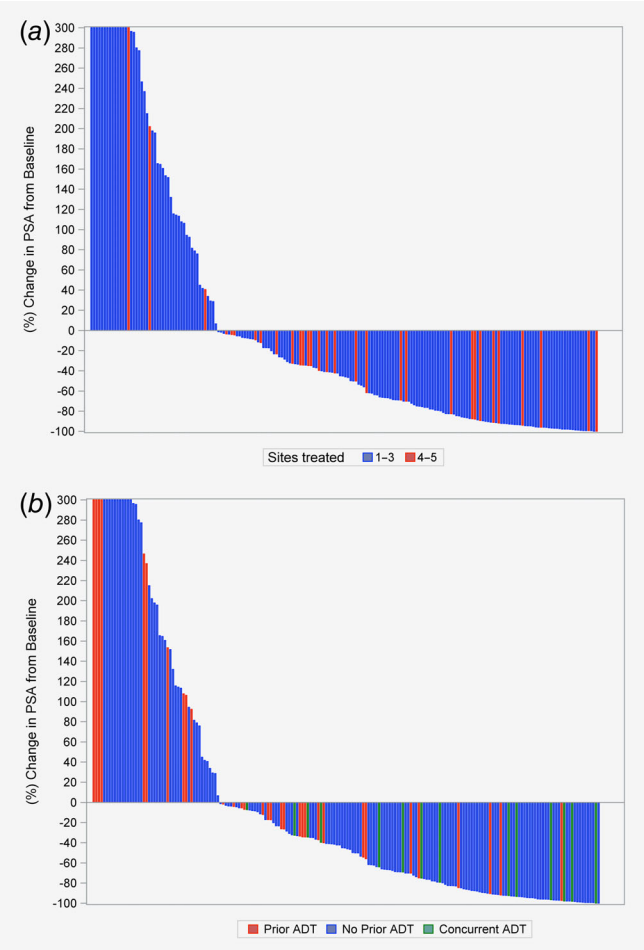

Figure 2. Maximal PSA change from baseline following SBRT stratified by (*a*) lesion number and (*b*) prior ADT status. A PSA decline was recorded for 75% of patients. The PSA level of six patients fell to an undetectable level following SBRT. Fifteen patients had a maximal PSA change of greater than +300% (truncated on plots).

treatment escalation status at 2 years and TE-FS. This approach is likely to be most effective when PSMA-PET is used for staging. It should be acknowledged that PSMA-PET is not yet widely available, although its utilisation is rapidly increasing.

While lesion number was not predictive of outcomes following SBRT, our results suggest lesion location to be an important factor. PCa patients with bone metastases typically have a worse prognosis compared to those with locoregional nodal metastases only.[18] In our study, the rate of freedom from treatment escalation at 2 years was slightly higher in the node-only group (58.4%) compared to the bone only (47.2%) groups. For the group receiving SBRT to both bony and nodal sites, the rate of freedom from treatment escalation was notably lower (21.7%) and the length of TE-FS was shorter (Fig. 1c). However, the statistical significance of the association between lesion location and treatment-escalation status remains to be confirmed at the final 5-year analysis of these data. Ost *et al.*[4] also showed comparable benefits following MDT for patients with nodal *vs.* nonnodal metastases, however a group with both nodal and nonnodal lesions was not available for comparison.

Importantly, late toxicity was negligible in our study population. Some of our patients have reached 4 years follow-up posttreatment and there remains no evidence of grade three toxicity. This compares favourably to other systemic treatments for metastatic PCa. Rates of grade three or higher toxicity are reported to be in the order of 30–45% for ADT alone and this is augmented when adding abiraterone acetate,[19] docetaxel[20] or enzalutamide.[21] For radiotherapy-based MDT, rates of grade three toxicity are typically low. The POPSTAR study reported one (3%) grade three event (vertebral fracture) using a single 20 Gy fraction.[5] No grade three or higher toxicities were reported by Decaestecker *et al.*[8] (50 Gy in 10 fractions, 30 Gy in 3 fractions), Fanetti *et al.*[6] (4–15 Gy in 1–5 fractions) or Ost *et al.*[4] (30 Gy in 3 fractions).

While it is true that late radiation toxicity can develop with even longer follow-up, the absence of grade three toxicity up to 4 years following SBRT in our study suggests that rates of very delayed toxicity will be low, at worst. One contributing factor may have been our relatively hyperfractionated SBRT schedule of 50 Gy in 10 fractions. We found this regimen particularly advantageous for treating pelvic lymph node metastases where PTVs were often adjacent to small bowel at the time of simulation and planning. Cone-beam CT verification, which was used for pretreatment verification for all lymph node metastases, also revealed that the small bowel migrated daily. The chosen fractionation therefore minimised the total dose received by individual anatomical segments of small bowel to a greater degree than would be seen with a more hypofractionated or single fraction schedule. Potential differences in safety profile between fractionation schemes may become apparent with longer term follow-up.

There are limitations to our study that should be noted. First, several of the subgroups in our study, including the prior ADT and concurrent ADT subgroups, were relatively small and the associated analyses should be interpreted with caution. There was a limited group of patients with castration-resistant disease at enrolment, which could have masked a statistically significant interaction between hormone sensitivity and the efficacy of SBRT. Our study did not assess the role of concurrent SBRT and systemic therapy. Future investigation is required to determine whether this will lead to superior outcomes when compared to single modality approaches. Other limitations of our study include the lack of a control arm and the commencement of next-line therapy at the discretion of the treating clinician(s) rather than according to strict criteria. However, using the objective measure of PSA as a surrogate for total cancer burden, we have shown that nearly 25% of our patients had a lesser cancer burden almost 3 years after treatment. This demonstrates that despite SBRT being a local treatment, it can have a durable systemic impact.

Conclusions

SBRT delays treatment escalation in men with oligometastatic PCa with no associated grade three toxicity. Outcomes for patients with 4–5 initial lesions were not inferior to patients with 1–3 lesions. While these analyses represent only interim outcomes, a significant proportion of patients had long-term disease suppression, suggesting the therapeutic index of fractionated SBRT for oligometastatic PCa may be high. Long-term outcomes will be reported after 5 years post-SBRT follow-up. Further studies are needed to better quantify the benefits of this approach, the subgroups who will benefit most and the optimal combination and timing with other systemic treatments.

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