



Original Research Article

Weekly ultra-hypofractionated radiotherapy in localised prostate cancer

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ABSTRACT

Background: Moderately hypofractionated radiotherapy regimens or stereotactic body radiotherapy (SBRT) are standard of care for localised prostate cancer. However, some patients are unable or unwilling to travel daily to the radiotherapy department and do not have access to, or are not candidates for, SBRT. For many years, The Royal Marsden Hospital NHS Foundation Trust has offered a weekly ultra-hypofractionated radiotherapy regimen to the prostate (36 Gy in 6 weekly fractions) to patients unable/unwilling to travel daily.

Methods: The current study is a retrospective analysis of all patients with non-metastatic localised prostate cancer receiving this treatment schedule from 2010 to 2015.

Results: A total of 140 patients were included in the analysis, of whom 86 % presented with high risk disease, with 31 % having Gleason Grade Group 4 or 5 disease and 48 % T3 disease or higher. All patients received hormone treatment, and there was often a long interval between start of hormone treatment and start of radiotherapy (median of 11 months), with 34 % of all patients having progressed to non-metastatic castrate-resistant disease prior to start of radiotherapy. Median follow-up was 52 months. Median progression-free survival (PFS) and overall survival (OS) for the whole group was 70 months and 72 months, respectively. PFS and OS in patients with hormone-sensitive disease at time of radiotherapy was not reached and 75 months, respectively; and in patients with castrate-resistant disease at time of radiotherapy it was 20 months and 61 months, respectively.

Conclusion: Our data shows that a weekly ultra-hypofractionated radiotherapy regimen for prostate cancer could be an option in those patients for whom daily treatment or SBRT is not an option.

Introduction

Moderately hypofractionated radiotherapy regimens are standard of care for patients with localised prostate cancer and generally involve at least 4 weeks of daily visits to the radiotherapy department. Given the predominance of prostate cancer in the older population, there are some patients who would not like to or are not able to travel daily to the radiotherapy department. For many years, The Royal Marsden Hospital NHS Foundation Trust has used a weekly ultra-hypofractionated regimen of 36 Gy in 6 fractions given once weekly for this patient population. This approach was derived from radiotherapy schedules reported by the group at St Thomas' Hospital [1]. In comparison to the

CHHiP dose regimen (60 Gy in 20 daily fractions), both schedules equal a similar biologically effective dose of around 160 Gy for an alpha/beta of 1.8 Gy [2]. This same weekly fractionation schedule was utilised in the STAMPEDE trial arm H investigating the benefit of local prostate radiotherapy in patients with metastatic hormone sensitive prostate cancer. Within this trial, the toxicity relating to the weekly ultra-hypofractionation schedule has been reported and was well-tolerated [3]. The current study is a retrospective efficacy analysis for patients with non-metastatic localised prostate cancer receiving the ultra-hypofractionated weekly radiotherapy regimen.

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Methods

Patients with non-metastatic prostate cancer treated with weekly ultra-hypofractionated prostate radiotherapy at The Royal Marsden Hospital NHS Foundation Trust between January 2010 and December 2015 were included. Patients with pelvic lymph node disease (N1) were included in the analysis. Patients included were most commonly staged with MR pelvis at diagnosis and as required a CT abdomen and pelvis and bone scan. The majority of patients were elderly and frail and may have not initially been considered for radiotherapy by their oncology teams. Follow-up schedule after radiotherapy would consist minimally with a clinical review and PSA biannually during the first 5 years post-treatment and annually thereafter.

Radiotherapy treatment was delivered as 6 weekly fractions of 6 Gy to the prostate and seminal vesicles using 6-15MV photons with multi-leaf collimators. Pelvic lymph nodes were not included in the target volume as this was not standard of care at the time.[4] Treatment before 2012 was planned using 3D conformal radiotherapy techniques (using a 3 field technique); from 2012 onwards all treatments were planned with intensity modulated radiotherapy.

Charlson comorbidity index (CCI) was calculated from the available data on patient comorbidities, and included their localised prostate cancer. Eastern Cooperative Oncology Group (ECOG) performance status was either documented in the patient clinical notes, or derived from patient information in the clinician letter at diagnosis if not explicitly documented. Tumours were staged using the 7th edition of the Union for International Cancer Control TNM classification. Presenting PSA was the PSA noted at time of diagnosis, except for patients initially on active surveillance or watchful waiting, where the PSA at the time of initiating active treatment was denoted as the presenting PSA. Risk groups were determined according to the EAU guidelines.[5] Patients were considered STAMPEDE high risk in case of N1 disease or at least 2 of the following: Gleason ≥ 8 , PSA ≥ 40 ng/mL and/or $\geq T3$. [6].

Toxicity data was not analysed due to no standardised toxicity reporting system within the clinical notes and the previously reported prospective toxicity data with this treatment schedule in 979 patients within the STAMPEDE trial. [3].

Progressive disease post-radiotherapy was defined as either biochemical recurrence as per the Radiation Therapy Oncology Group (RTOG) and American Society for Radiation Oncology Phoenix Consensus Conference [7] or as castration-resistant prostate cancer (CRPC) as per the EAU-ESTRO-SIOG guidelines on prostate cancer (i.e. a castrate level of testosterone and radiological progression or three consecutive rises in PSA 1 week apart, resulting in two 50 % increases over the nadir and PSA > 2 ng/ml) [8] or as a consistently rising PSA (≥ 0.3 $\mu\text{g/L}$ difference) whilst on androgen deprivation treatment (ADT). Local progression was defined as progressive local disease on imaging. Follow-up time was defined as the time between start of radiotherapy to last follow-up or death of any cause.

Analysis was performed using descriptive statistics; progression-free survival (PFS) and overall survival (OS) were estimated via Kaplan-Meier methods. Time to progression was calculated from start of radiotherapy to progressive disease or death from prostate cancer, censoring for non-prostate cancer death or at last follow-up if no progression was observed. OS was calculated from start of radiotherapy to death of any cause, censoring at last follow-up if no death had occurred. Analyses were performed using SPSS v27.0.

Results

In total, 140 patients were included in the analysis (Fig. 1). One patient received 30 Gy in 5 fractions, and one patient received only 24 Gy in 4 fractions. All other patients received the planned 36 Gy in 6 fractions. Median age at the time of radiotherapy was 80 (range 50–95) years; with median presenting PSA of 29.55 (range 7.4–853) $\mu\text{g/L}$. Most patients (86 %) presented with EAU high risk disease, with almost a

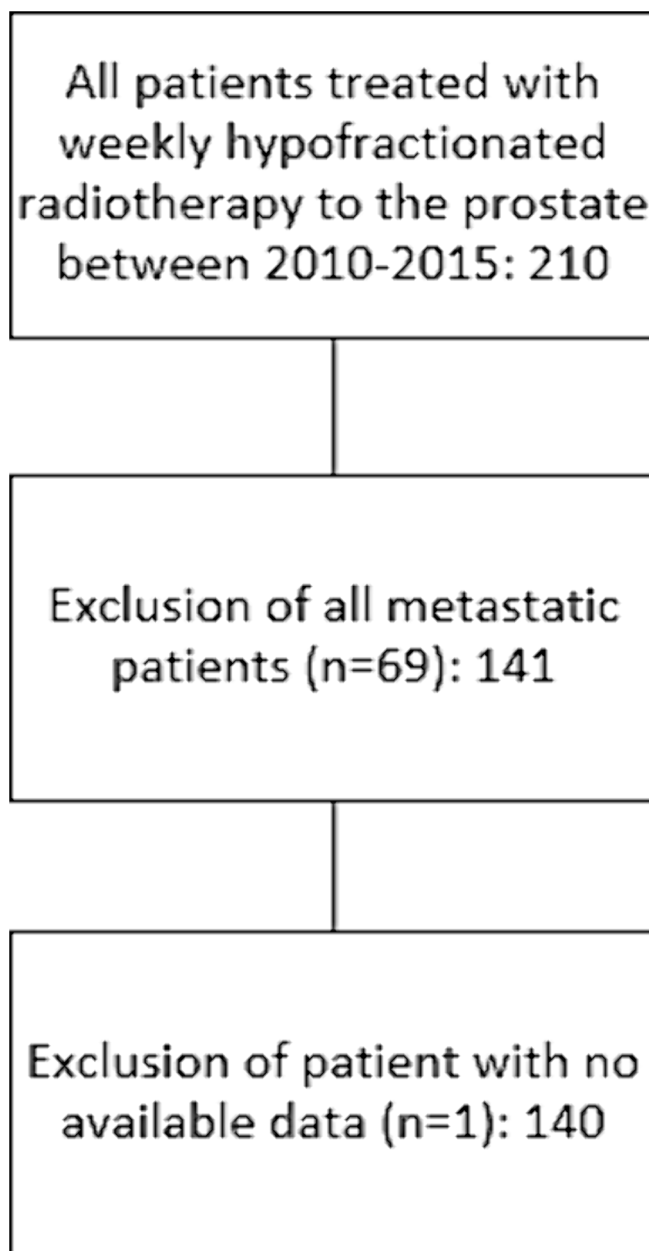


Fig. 1. CONSORT diagram of patients included in the analysis.

third of patients (31 %) having Gleason Grade Group 4 and 5 disease and almost half of all patients (48 %) having MR defined T3 disease or higher. Nodal disease was observed in 6 patients. A third of all patients were STAMPEDE high risk at diagnosis (34 %). A CCI of 5 points or more – indicating a ≤ 50 % estimated 3-year survival – was noted in 91 % of patients.[9] Seventy-one percent of patients had an ECOG performance status of 0–1. Median follow-up was 52 (range 1–122) months. Baseline patient characteristics are presented in Table 1.

All patients received hormone treatment, consisting of either luteinizing hormone-releasing hormone (LHRH) agonist/antagonists, orchidectomy or bicalutamide monotherapy. The majority of patients (57 %) received hormone treatment for 18 months or longer. Time between start of hormone treatment and radiotherapy differed substantially between patients, with often a long interval between both; with a median of 11 months and a maximum of up to almost 14 years (interquartile range: 5–39 months). A third of all patients (34 %) had progressed to CRPC prior to starting radiotherapy and a fifth (20 %) of all patients had a rising PSA at time of radiotherapy. Of the group with 11

Table 1
Baseline characteristics for patient cohort.

		All patients		HSPC at time RT		CRPC at time RT	
		N	%	N	%	N	%
Total group		140		90		47	
Age at radiotherapy (years)	median	80		80		81	
	range	50–95		50–90		62–95	
Presenting PSA (ng/ml)	median	29.6		20.8		60	
	range	7.4–853		7.4–576		7.4–853	
EAU risk group	low	1	1	1	1	0	0
	intermediate	18	13	17	19	0	0
	high	121	86	72	80	47	100
STAMPEDE high risk	no	77	55	64	71	13	28
	yes	48	34	23	26	25	53
	unknown	12	9	3	3	9	19
Gleason score	≤6	16	11	11	12	5	11
	3 + 4	43	31	31	34	11	23
	4 + 3	33	24	22	24	9	19
	8	15	11	8	9	7	15
	≥9	28	20	16	18	12	26
	unknown	5	4	2	2	3	6
T stage	1	7	5	4	4	3	6
	2 (unspecified)	24	17	22	24	1	2
	2a	5	4	2	2	3	6
	2b	9	6	6	7	2	4
	2c	14	10	13	14	1	2
	3 (unspecified)	20	14	12	13	8	17
	3a	14	10	12	13	2	4
	3b	22	16	11	12	10	21
	4	11	8	5	6	6	13
	unknown	14	10	3	3	11	23
N stage	0	133	95	88	98	42	89
	1	6	4	2	2	4	9
	unknown	1	1	0	0	1	2
ECOG Performance Status	0	52	37	33	37	19	40
	1	47	34	26	29	19	40
	2	10	7	9	10	1	2
	3	2	1	2	2	0	0
	4	0	0	0	0	0	0
	unknown	29	21	20	22	8	17
Charlson Comorbidity Index at time of RT	0	0	0	0	0	0	0
	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	1	1	1	1	0	0
	4	2	1	0	0	2	4
	5	21	15	14	16	7	15
	6	67	48	42	47	23	49
	≥7	40	29	29	32	11	23
	unknown	9	6	4	4	4	9

months or more between start of hormone treatment and radiotherapy (n = 68), 35 % (n = 24) had a rising PSA at time of radiotherapy. Median PFS for all patients was 70 months (95 % confidence interval [CI] 64.2–75.8); for those who had already progressed to CRPC prior to radiotherapy median PFS was 20 months (95 % CI 1.2–38.8), and in those without CRPC prior to treatment median PFS was not reached. Median OS for the whole group was 72 months (95 % CI 61.8–82.2), for those with CRPC prior to radiotherapy it was 61 months (95 % CI 43.2–78.8), and for those without CRPC prior to radiotherapy median OS was 75 months (95 % CI 57.8–92.2) (Fig. 2).

During follow up, 70 patients died, with the cause of death being

prostate cancer in 13 patients (12 of these patients had CRPC at time of radiotherapy), 23 due to other causes and in 34 patients the cause of death was unknown. Fourteen patients from the 140 patients experienced local progression, of whom nine had CRPC at time of radiotherapy and four had HSPC at time of radiotherapy (for one patient it was unknown whether he was HSPC or CRPC at time of radiotherapy). Progression occurred in 49 patients after radiotherapy.

Use of systemic treatments in the whole patient population consisted predominantly of additional second line hormone treatments, with 57 patients receiving bicalutamide, 28 receiving dexamethasone, 15 receiving abiraterone/prednisolone, 4 receiving enzalutamide and 4

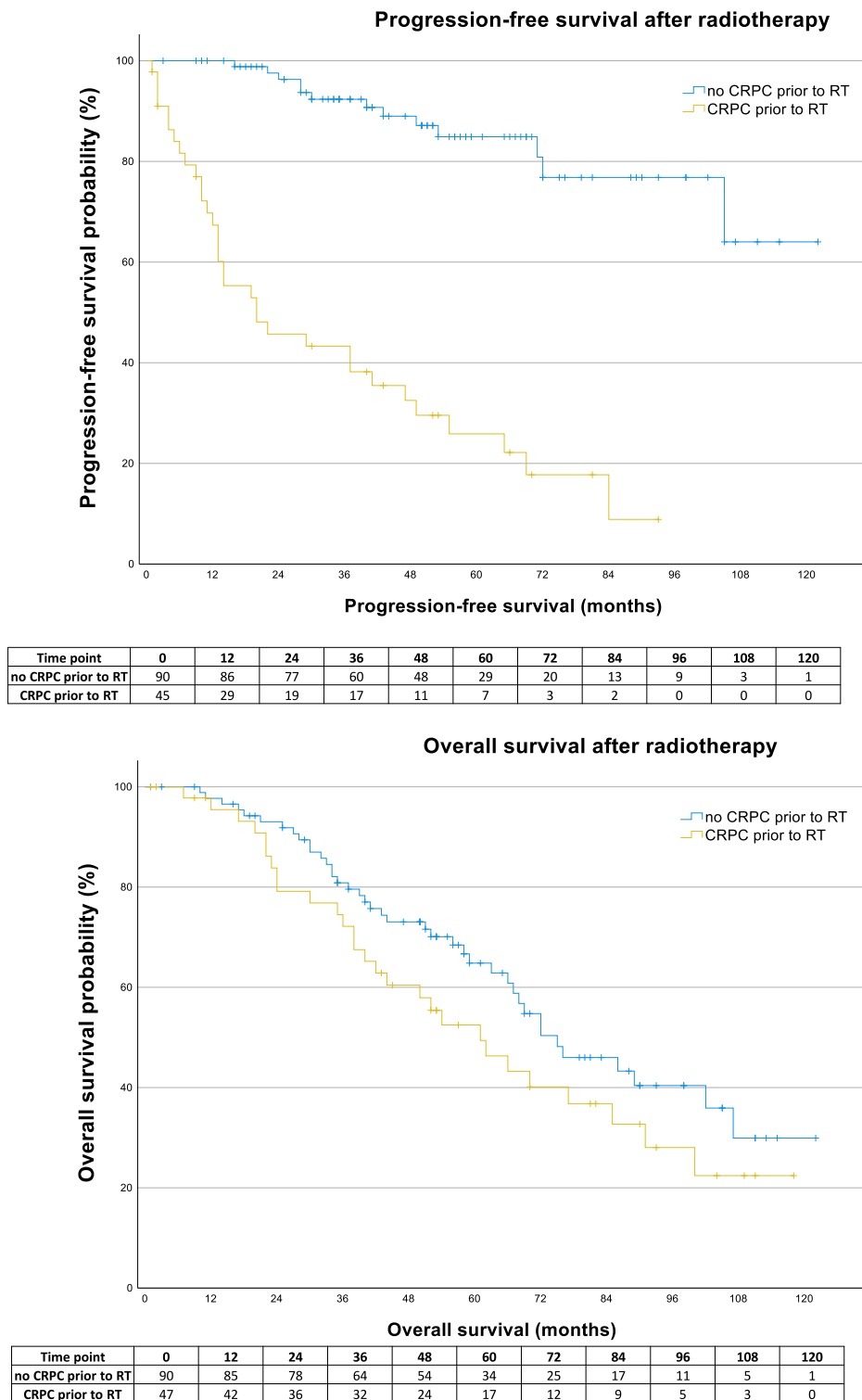


Fig. 2. Progression-free survival (top chart) and overall survival (bottom chart) Kaplan-Meier curves. The patients are split into two groups: those with hormone sensitive prostate cancer at time of radiotherapy (blue) and those with castration-resistant prostate cancer at time of radiotherapy (yellow). Numbers at risk are presented below each chart. Abbreviations: CRPC: castration-resistant prostate cancer; RT: radiotherapy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

receiving stilboestrol. Four and two patients were treated with docetaxel and cabazitaxel, respectively. Important to note, these patients were treated in a different time period when stilboestrol was a standard of care treatment option [10], which is not the case anymore. Results are summarized in Table 2.

Discussion

The current data illustrates that a weekly ultra-hypofractionated radiotherapy schedule is a feasible alternative for patients whose management plan includes prostate radiotherapy, yet are unwilling or unable to undergo daily radiotherapy sessions for many consecutive days

Table 2
Treatment and outcome characteristics for patient cohort.

		All patients (n=140)		HSPC at time of RT (n=90)		CRPC at time of RT (n=47)	
		N	%	N	%	N	%
Time between start hormone treatment and radiotherapy (months)	median	11		7		59	
	range	-1—165		-0.5 – 69		8	
	IQR	5–39		5–14		165	
Duration of hormone treatment	short (<6 months)	15	11	15	17	0	0
	intermediate (6–18 months)	17	12	17	19	0	0
	long (18–36 months)	23	16	19	21	4	4
	very long (>36 months)	58	41	17	19	39	43
	unknown	27	19	22	24	4	4
Rising PSA at time of radiotherapy	yes	28	20	1	1	27	57
	no	106	76	88	98	15	32
	unknown	6	4	1	1	5	11
CRPC	Prior to radiotherapy	47	34	NA	NA	47	100
	Progression to CRPC post-radiotherapy	5	4	5*	6	NA	NA
	Never CRPC	85	61	85	94	NA	NA
	Unknown	3	2	0	0	NA	NA
Further systemic treatments	Docetaxel	4	3	0	0	4	9
	Cabazitaxel	2	1	0	0	2	4
	Bicalutamide	57	41	13	14	44	94
	Dexamethasone	28	20	3	3	24	51
	Abiraterone	15	11	0	0	15	32
	Enzalutamide	4	3	0	0	4	9
	Stilboestrol	4	3	0	0	4	9
	Prostvac	2	1	0	0	2	4
	Radium-223	1	1	0	0	1	2
	Ketoconazole	1	1	0	0	1	2
Progression after radiotherapy	yes	49	35	13	14	34	72
	no	89	64	77	86	12	26
	unknown	2	1	0	0	1	2
Type of progression (during entire follow-up)	biochemical only	12	9	5	6	6	13
	distant progression, no local progression	23	16	4	4	19	40
	local progression, no distant progression	7	5	3	3	4	9
	local and distant progression	7	5	1	1	5	11
Cause of death	prostate	13	9	1	1	12	26
	other	23	16	22	24	1	2
	unknown	34	24	17	19	15	32
Follow up between start of radiotherapy and last follow-up or death (months)	median	52		53		50	
	range	1–122		1–122		1–118	
	IQR	34–75		34–74		24–74	

* In the group of HSPC at time of radiotherapy, 13 patients progressed after radiotherapy of whom 5 progressed to CRPC. Four other patients progressed with non-castrate testosterone levels, and another 4 patients progressed without measurement of testosterone, though hormone treatment had been stopped at least 3 years earlier, so these patients were not automatically considered CRPC.

and weeks. With the advent of prostate stereotactic body radiotherapy (SBRT) and the available prospective evidence on its safety and efficacy [11], this should be the preferred option in patients with intermediate risk prostate cancer. However, not all patients are candidates for SBRT given many patients require fiducial markers or have significant urinary symptoms at baseline [12]; and not all centres are able to offer SBRT to their patients due to physics resource for planning. Furthermore, even though some will consider SBRT for high risk prostate cancer, large phase 3 trials proving the efficacy and tolerability of SBRT in this setting are unfortunately still lacking. Hence the standard radiotherapy regimen in patients with high risk prostate cancer typically entails a moderately hypofractionated regimen of approximately 20 daily visits. Therefore, if standard-of-care prostate radiotherapy is not possible, the ultra-hypofractionated regimen of 36 Gy in 6 weekly fractions could be

considered a reasonable alternative.

We did not routinely collect side-effect data in a systematic manner in this retrospective evaluation. However, this fractionation schedule has been extensively used in bladder cancer with an acceptable side-effect profile [13,14] and in particular was widely adopted in the STAMPEDE trial in metastatic prostate cancer patients, where treatment was noted to be well-tolerated with only limited toxicity.[3].

The majority of our patient population exhibited high risk prostate cancer at diagnosis. Moreover, a third had progressed to CRPC prior to radiotherapy, a few patients had local nodal disease, and the interval between start of hormone treatment and radiotherapy was 11 months or more in half of all patients, potentially allowing progression to micro-metastatic disease, not visible on conventional imaging. This suggests that the current population had a worse prognosis than a general high

risk population receiving upfront radiotherapy treatment.

Patients without CRPC at the time of radiotherapy had a similar PFS as that expected for a high risk population receiving prostate only radiotherapy, [15,16] and the local progression rate was low at <5 %. [15] The modest OS across all groups is likely to be due to high risk of competing causes of death in this group of patients selected because of underlying frailty. The documented deaths from prostate cancer are low in the HSPC group but somewhat higher in the CRPC group as might be anticipated, but a weakness of this data is the number of patients where the cause of death could not be verified.

The relatively high number of competing causes of death is in line with a large SEER analysis of patients with localised prostate cancer and comorbidities receiving no prostate radiotherapy or surgery. [17] However, our survival data seems somewhat better than the survival data in the SEER analysis of patients with multiple comorbidities. This could be due to the different time period (1992–2005) and lack of local prostate cancer treatment in the SEER analysis; however, it should also be noted that more than half of the patients in the SEER analysis received hormone treatment, which over time might have worsened their pre-existing comorbidities. Immediate lifelong ADT is sometimes started in patients with comorbidities diagnosed with high risk prostate cancer who are unable or unwilling to receive standard-of-care local treatments. [18,19] However, our weekly ultra-hypofractionated prostate radiotherapy schedule could perhaps be an alternative, diminishing the need for lifelong ADT, benefiting their comorbidities.

As it is known that treating localised prostate cancer in patients with a life expectancy of less than 10 years is of little added value, [17] the high CCI noted in our population might suggest that some of these patients should not have received treatment. However, the main driver for the high CCI in this population was a high age combined with the presence of a solid tumour. As an illustration, a fit patient of 70 years old with localised prostate cancer and no comorbidities leads to a CCI of 5, with an estimated 10-year survival rate of only 21 %. However, radical treatment would generally be deemed necessary in such a patient. General performance status in our population was good with 71 % of all patients having an ECOG performance status of 0–1 (although unknown in 21 % of patients), suggesting that these patients were fit at time of treatment. Based on the previously mentioned SEER analysis, [17] the EAU guidelines state that in localized prostate cancer patients with a CCI ≥ 2 most men will die from competing causes. [18] However, the CCI gives 2 points to the presence of a non-metastatic solid tumour. This would imply that all prostate cancer patients will likely die from competing causes, which is obviously not the case. The CCI therefore does not seem a good tool to differentiate between those who will benefit from active prostate cancer treatment and those who will not. It could therefore be useful to assess other tools in this situation, e.g. the modified frailty index, which could potentially aid patient selection in the future.

Unsurprisingly, our data did also show that patients who had progressed to CRPC prior to radiotherapy – albeit with localised disease only – had a significantly shorter PFS as compared to those patients who had not progressed to CRPC prior to treatment. Previous large randomised trials showed an OS and PFS benefit of the addition of radiotherapy to ADT at diagnosis [20] which suggests this would be the preferred strategy, instead of waiting until progression to administer radiotherapy. As administering radiotherapy upfront is now standard-of-care, the type of patient observed in our CRPC cohort should not be seen anymore. Furthermore, it is now known that patients with non-metastatic CRPC and a short PSA doubling time have a survival benefit from the addition of darolutamide, enzalutamide or apalutamide. [21–23] Unfortunately, PSA doubling time was not available for our cohort, so it is unknown how many patients would have met this criterion. Given the high risk of developing metastases within 2 years, it is presumably unlikely that non-metastatic CRPC patients with a rapid PSA doubling time benefit from local prostate radiotherapy. Nevertheless, the median PFS in our CRPC group was over a year, suggesting that

local prostate radiotherapy might be considered an additional treatment line, presumably entailing benefit to those with a slower PSA doubling time.

Conclusion

Moderately hypofractionated, daily radiotherapy regimens or SBRT are currently the preferred fractionation schedules in patients with localised prostate cancer. However, in patients in whom these treatments are not an option, the ultra-hypofractionated schedule of 36 Gy in 6 weekly fractions can pose an alternative.

CRedit authorship contribution statement

Nora Sundahl: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Douglas Brand:** Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Chris Parker:** Resources, Investigation, Supervision, Writing – review & editing. **David Dearnaley:** Resources, Investigation, Supervision, Writing – review & editing. **Alison Tree:** Resources, Investigation, Supervision, Writing – review & editing. **Angela Pathmanathan:** Resources, Investigation, Supervision, Writing – review & editing. **Yae-eun Suh:** Resources, Investigation, Supervision, Writing – review & editing. **Nicholas Van As:** Resources, Investigation, Supervision, Writing – review & editing. **Rosalind Eeles:** Resources, Investigation, Supervision, Writing – review & editing. **Vincent Khoo:** Resources, Investigation, Supervision, Writing – review & editing. **Robert Huddart:** Resources, Investigation, Supervision, Writing – review & editing. **Julia Murray:** Conceptualization, Data curation, Formal analysis, Resources, Investigation, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: NS reports speaker fees from Janssen-Cilag. CP reports fees from ITM Radiopharma and institutional fees from Bayer, AAA. DD reports personal fees through the Rewards to Discoverer's Scheme from The Institute of Cancer Research which receives royalty income from abiraterone, support from Cancer Research UK Program Grants C33589/A19727 "Advances in Physics for Precision Radiotherapy", honoraria for advisory boards from Janssen and additionally has a patent EP1933709B1 issued for a localisation and stabilization device. AT reports research funding from Elekta, Varian and Accuray and travel grants/honoraria from Elekta, Accuray and Janssen. YS reports travel grants/honoraria from Janssen, Astellas, Bayer, AstraZeneca. RE reports income as a sole trader (variable and declared to HRMC) from private practices, as well as fees from Janssen, Bayer, Ipsen, AstraZeneca, University of Chicago and is a member of external Expert Committee for AstraZeneca UK. VK reports honoraria for speakers bureaus, personal fees and non-financial support from Accuray, Astellas, Bayer, Boston Scientific, Bristol Myers Squibb, Janssen and Merck Sharp Dohme. RH reports fees from Roche, Merck Sharp Dohme, BMS, Gilead, Astellas, Janssen, Nektar, and Merck/Pfizer, and research funding from Merck Sharp Dohme, Roche, and Elekta. The other authors have no conflicts of interest to declare.

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