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MRI-guided radiotherapy in twenty fractions for localised prostate cancer; results from the MOMENTUM study

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ABSTRACT

Background and purpose: MRI-guided radiotherapy (MRIgRT) offers multiple potential advantages over CT-guidance. This study examines the potential clinical benefits of MRIgRT for men with localised prostate cancer, in the setting of moderately hypofractionated radiotherapy. We evaluate two-year toxicity outcomes, early biochemical response and patient-reported outcomes (PRO), using data obtained from a multicentre international registry study, for the first group of patients with prostate cancer who underwent treatment on a 1.5 T MR-Linac.

Materials and methods: Patients who were enrolled within the MOMENTUM study and received radical treatment with 60 Gy in 20 fractions were identified. PSA levels and CTCAE version 5.0 toxicity data were measured at follow-up visits. Those patients who consented to PRO data collection also completed EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ-PR25 questionnaires.

Results: Between November 2018 and June 2022, 146 patients who had MRIgRT for localised prostate cancer on the 1.5 T MR-Linac were eligible for this study. Grade 2 and worse gastro-intestinal (GI) toxicity was reported in 3 % of patients at three months whilst grade 2 and worse genitourinary (GU) toxicity was 7 % at three months. There was a significant decrease in the median PSA at 12 months. The results from both the EQ-5D-5L data and EORTC global health status scale indicate a decline in the quality of life (QoL) during the first six months. The mean change in score for the EORTC scale showed a decrease of 11.4 points, which is considered clinically important. QoL improved back to baseline by 24 months. Worsening of hormonal symptoms in the first six months was reported with a return to baseline by 24 months and sexual activity in all men worsened in the first three months and returned to baseline at 12 months.

Conclusion: This study establishes the feasibility of online-MRIgRT for localised prostate on a 1.5 T MR-Linac with low rates of toxicity, similar to that published in the literature. However, the clinical benefits of MRIgRT over conventional radiotherapy in the setting of moderate hypofractionation is not evident. Further research will focus on the delivery of ultrahypofractionated regimens, where the potential advantages of MRIgRT for prostate cancer may become more discernible.

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Introduction

Prostate cancer is the most commonly diagnosed non-cutaneous cancer in men in the Western world [1–5]. Multiple treatment strategies exist for localised prostate cancer and many of those with intermediate-risk and high-risk disease receive external beam radiotherapy (EBRT).

Over the last two decades, outcomes of multiple studies have suggested an improvement in cure rates as well as lower toxicity rates associated with EBRT treatment of prostate cancer. Technological advancements have contributed to this [6]. The five-year biochemical failure free survival has increased from 71 % [7] to 88 % [8] and late, grade 2 and above bowel toxicity has fallen from 33 % [7] to 11.9 % [8]. Improvements in genitourinary (GU) toxicity have been less evident (late grade 2 GU toxicity- 11 % (7) to 11.7 % [8]). Toxicity rates are thought to be further reduced with image-guided radiotherapy (IGRT), the use of which is now standard of care in many centres around the world [9].

Some of the factors that limit the accuracy of radiotherapy delivery include variability in contouring, set-up error, inter- and intra-fraction target and organ-at-risk motion, deformation/rotation of the prostate gland, independent movement of the seminal vesicles and volume changes of the prostate [10]. Although current IGRT methods account for some of these discrepancies, there remain limitations, principally due to poor quality imaging.

The advent of hybrid MRI-linear accelerators has transformed the scope of IGRT for pelvic tumours. There are currently two MRIgRT systems clinically treating patients - the Viewray MRIdian system (ViewRay Inc, Oakwood Village, OH) [11] and the Elekta Unity system (AB, Stockholm, Sweden) [12,13]. The Elekta Unity integrates a 1.5 T imaging system with a 7 Megavoltage linear accelerator. Online-MRIgRT provides superior image quality of pelvic anatomy and real-time visualisation of anatomical movement whilst the beam is on, offering the opportunity to pause treatment if the prostate moves outside of the PTV. MRIgRT also enables daily online adaptation whereby the anatomy of the day is recontoured and an individualised plan created [14]. These features further diminish the inaccuracies outlined above and offer the possibility of improved acute and late toxicity rates without compromising tumour control.

Despite these potential advantages, MR-Linacs are more expensive, the daily treatment times are longer and therefore clinical, not just technical, gains need to be demonstrated prior to mainstream adoption [15]. The Multi-OutcoMe EvaluatioN of radiation Therapy Using the MR-Linac (MOMENTUM) study is a multicentre international registry study set up by the MR-Linac Consortium [16,17]. It aims to investigate the effectiveness and safety of MRIgRT with a view to pursuing an evidence-based approach to testing the benefits of this technology.

Prostate cancer was the first tumour site to be treated on the Unity MR-Linac at many centres. Considering the scarcity of available data, this study aims to explore the potential advantages of MRIgRT within the context of moderately hypofractionated radiotherapy for localised prostate cancer. We investigate the 2-year toxicity outcomes, early biochemical response and patient-reported outcome data from patients enrolled in the MOMENTUM study. The results hold the potential to provide valuable insights and contribute to shaping future studies.

Methods and materials

Study design

MOMENTUM (NCT04075305) is an observational cohort study run as an academic-industrial partnership between multiple institutions worldwide and Elekta [18]. Institutional Review Board (IRB) approval was obtained at each centre. Patients were given the option to consent to collection of health-related quality of life (HRQOL) data.

Patients and data acquisition

All patients enrolled within the MOMENTUM study, who received radical radiotherapy for localised prostate cancer in 20 fractions, without limits on National Comprehensive Cancer Network (NCCN) risk group, were eligible for this analysis. The protocol required that patients were reviewed at baseline, 3, 6, 12 and 24 months after treatment.

Clinical data was recorded by the physician or the research team. This included patient and tumour characteristics, technical details of the radiotherapy, CTCAE version 5.0 toxicity data [19] (Supplementary Table 1) and response assessments. Acute toxicity was defined as adverse events occurring at three months and late toxicity as that occurring at six months onwards. Response to treatment was identified by monitoring PSA levels and kinetics. Further detailed description of data collection within MOMENTUM is provided elsewhere [20].

HRQOL data was recorded for a subset of patients, at the same timepoints, using the standardised 5-level EuroQol five dimensions (EQ-5D-5L) [21], EORTC QLQ-C30 [22] and EORTC QLQ-PR25 [23] questionnaires. These were provided to the patients either face to face, by post or online.

Treatment

All patients consented to treatment with 60 Gy in 20 fractions over four weeks. The MRIgRT workflow varied amongst the sites (Supplementary Fig. 1). Patients had a planning CT and a T2-weighted (T2W) large field of view (LFOV) MRI scan. These were fused to aid contouring. During the study period, one site transitioned to using a planning MRI alone. Bladder and rectal preparation adhered to respective local departmental protocols. An experienced radiation oncologist (alongside a radiologist at one site) delineated the target and organ-at-risk structures and an initial plan was created. Whilst some sites used the PRISM clinical trial protocol (NCT 03658525) other sites used a modified version or a local protocol. Further details of the different margin expansions used for treatment can be found in the appendix (Supplementary Table 2).

On each day of treatment, after patient set-up on the MR-Linac, an initial 'session' MRI scan was obtained. Image registration between the reference MRI scan (either the planning MR or fraction 1 session MRI scan) was performed and contours propagated. The decision to adopt an adapt-to-shape (ATS) or adapt-to-position (ATP) workflow was institution dependent. The ATS pathway involved either editing or re-delineating the propagated target contours, or a simplified version where the pre-defined target structure was translated and rotated to fit the daily anatomy. In an ATP workflow, only translational adjustments of the target structure were performed. Propagated organ-at-risk structures were modified if required and where any contour editing took place, an ATS workflow was adopted [25]. A radiotherapy treatment plan was then optimised based on the daily anatomy.

In the ATS pathway, an additional T2W LFOV MRI scan (verification scan) was acquired before beam-on to check significant target motion had not occurred during re-planning. A subsequent ATP shift was applied, if necessary, to account for any positional changes that might have occurred during editing and planning. On average, the MRIgRT workflow lasted 45 min [26] and a breakdown of the mean time for each stage of an ATS pathway can be found in the literature [27]. Additional details of the Unity MR-Linac workflow can be found elsewhere [24,28].

Statistical analysis

All analyses were performed with GraphPad PRISM (v 9.4.1). Descriptive statistics are used for patient characteristics, treatment information and the frequency of acute and late toxicities. Toxicity data was not complete for each patient, therefore missing responses were excluded on a question-by-question basis. Median values with interquartile ranges were used for non-parametric data and mean values and

standard deviations were used to represent normally distributed data.

Median follow-up was calculated using a reverse Kaplan-Meier approach. For PSA comparisons between baseline and 12 months, the Wilcoxon signed-rank test was performed. Comparison of the difference in median value of the paired PSA changes from baseline to 12 months for androgen deprivation therapy (ADT) versus no ADT was performed with the Mann-Whitney *U* test. A p-value of < 0.05 is considered statistically significant.

HRQOL outcomes from the EORTC questionnaires were scored as per the scoring manual [29,30] and paired changes in scores were calculated. The median (IQR) and mean (SD) were analysed for each scale and a difference of ten points or more was considered a minimally important difference (MID) for the EORTC questionnaires [31,32], whilst a five point difference is regarded as a possible direction of change [33,34].

Results

A total of 146 patients were enrolled for radical treatment between November 16, 2018 and June 9, 2022 from six sites; 140 patents are included in the final analysis. Details of patients enrolled and reasons for exclusion are detailed in Fig. 1. This data was entered into the registry prospectively by five sites. One site added most of their data retrospectively, which had previously been collected prospectively in paper form.

At the time of analysis, median follow-up is 24.0 months (IQR 15.6–24). Follow-up was administratively censored on 3rd August 2022 or at 24 months (whichever was earliest). 130 (93 %) patients, 120 (86 %) patients and 79 (56 %) patients had reached 3, 12 and 24 months of follow-up respectively. Six patients died, one patient withdrew from the study, one patient was withdrawn by the physician and eight patients were lost to follow-up.

The median age was 71.5 years (range 47.0–81.0). The patients were treated at six different institutions worldwide. Ninety-seven (69 %) patients had ECOG performance status score of 0 (Table 1). The majority (95 patients; 68 %) had NCCN intermediate risk and 38 (27 %) patients had high risk prostate cancer. Eighty-one (58 %) patients received ADT (Table 1). Intended ADT duration is not documented.

An ATP-only workflow was adopted for 40 (29 %) patients whilst an ATS pathway was used in 70 (50 %) patients. A combination of both pathways was required in 26 (19 %) patients. 117 (84 %) patients received 60 Gy to the prostate (Table 1).

PSA values are available for all 140 (100 %) patients at baseline, 90 (80 %) patients at 12 months and 54 (68 %) patients at 24-month follow-up.

There was a significant decrease in the median paired PSA from baseline, PSA 7.6 ng/ml (5.7–11.5), to 12 months, PSA 0.38 ng/ml (0.1–1.0), $p < 0.0001$. The decrease in the median PSA remained statistically significant when analysed by ADT use (Table 2). There was also a statistically significant difference in the median decrease in PSA from baseline to 12 months between the hormone group (median decrease of 8.25 ng/ml) and non-hormone group (median decrease of 7.4 ng/ml), $p < 0.0001$.

At baseline, 101 out of 140 patients had CTCAE version 5.0 toxicity data recorded. This fell to 55 patients at 12 months and 34 patients at 24 months (Supplementary Table 3).

Grade ≥ 1 CTCAE GI toxicity fell from approximately a fifth of patients at baseline and three months to 10 % at six months where it remained to 12 months (A, Fig. 2). Three (3 %) patients recorded acute grade 2 GI toxicity at three months and 1 patient reported late grade 2 rectal haemorrhage at 24 months. No other grade 2 GI toxicity was reported.

At baseline, 48 (49 %) and 6 (6 %) of patients reported Grade ≥ 1 and

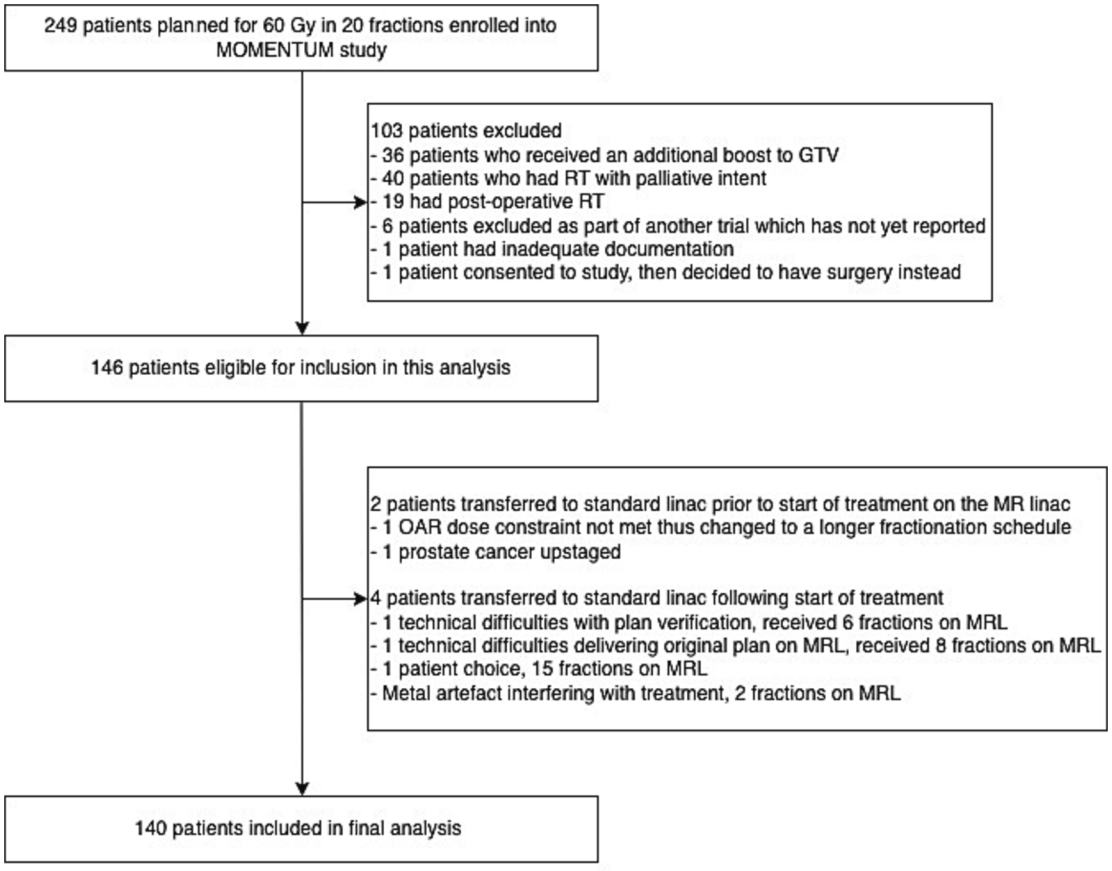

Fig. 1. Study profile. Outlines number of, and reasons for, patient exclusion and number included in final analysis.

Table 1
Baseline and clinical characteristics outlined. Numbers (percentage) given except where indicated by an asterix.

		n (%)
Age in years	Median (IQR)*	71.5 (67–75)
	Range*	47–81
WHO performance status	PS 0	97 (69 %)
	PS 1	19 (14 %)
	PS 2	1 (1 %)
	Missing	23 (16 %)
NCCN risk group	Low risk	6 (4.3 %)
	Intermediate risk	95 (67.9 %)
	High risk	38 (27.1 %)
	Not assessed	1 (0.7 %)
Clinical tumour stage	T1a-T1b-T1c-T1x	35 (25 %)
	T2a-T2b-T2c-T2x	80 (57 %)
	T3a-T3b-T3x	24 (17 %)
	Missing	1 (1 %)
Gleason total score	≤6	13 (9 %)
	7	112 (80 %)
	≥8	15 (11 %)
Baseline PSA in ng/ml*	<10	96 (69 %)
	10–20	35 (25 %)
	>20	9 (6 %)
	Median (IQR)*	7.9 (5.7–12.3)
ADT	No	57 (41 %)
	Yes	81 (58 %)
	Missing	2 (1 %)
Workflow	ATP only	40 (29 %)
	ATS only	70 (50 %)
	Combination of ATP + ATS	26 (19 %)
	Missing	4 (3 %)
Dose delivered	60 Gy	117 (84 %)
	>60 Gy, ≤62 Gy	23 (16 %)
QoL data collected	Yes	85 (61 %)
	No	55 (39 %)

Grade ≥ 2 CTCAE GU toxicity respectively (B, Fig. 2). Grade ≥ 1 toxicity peaked at three months (68 %), fell to 38 % at six months where it remained to 12 months. Grade ≥ 2 toxicity remained between 6 and 7 % until six months and resolved by 12 months (Fig. 2).

Skin toxicity was low, as expected, throughout (C, Fig. 2). The number of patients reporting grade ≥ 1 fatigue peaked at three months (43 %) and decreased to better than baseline levels at 12 months (D, Fig. 2). Grade 2 fatigue rose from 0 at baseline to approximately 4 % at three months, where it remained until 24 months.

In patients receiving ADT (n = 52), the incidence of erectile dysfunction (ED) peaked at three months after which, an improvement is seen in all grades at six months (E, Fig. 2). In patients not receiving ADT (n = 36) grade ≥ 1 ED peaked at six months (53 %) and remained unchanged at 12 months whilst grade ≥ 2 ED peaked at three months (16 %), after which it demonstrated an improvement to 12 months (F, Fig. 2).

Eighty-five patients (61 %) gave informed consent for additional collection of HRQOL data. Compliance with questionnaire completion decreased with time (Supplementary Table 5). Of those patients who gave consent, 53 % (n = 45) completed the EORTC questionnaires and 40 % (n = 34) the EQ-5D-5L questionnaire at baseline. By 24 months data completeness had fallen to 32 % (n = 15) and 21 % (n = 21) respectively.

The mean change in EORTC global health status/QoL scale score fell in the first six months following radiotherapy to a clinically relevant threshold by 11.4 (Fig. 3, Supplementary Table 6). This returned to baseline levels by 24 months. Physical, role, emotional and social functioning scales (Supplementary Fig. 2) all demonstrated a similar pattern whereby the mean scores appeared to decline in the first six months.

EORTC OLQ-C30 and PR25 bowel and urinary symptoms did not show any clinical important changes in scores when compared to baseline (Supplementary Fig. 2 & Table 5). Hormonal symptoms demonstrated a rise at three months which persisted to six months, both clinically important changes, and returned to baseline by 24 months. The results for sexual activity are shown for all men and those who were not on ADT (Fig. 3, Supplementary Table 6). A clinically important decrease of sexual activity was seen in all men including those not on ADT at three months, after which an improvement to baseline levels is seen by 12 months (Fig. 3).

The EQ-5D-5L questionnaire data (Fig. 4, Supplementary Table 7) demonstrates that in all but one health dimension, the number of patients experiencing problems increased to a peak at six months and then improved by 12 months. For anxiety/depression this peak was at three months. The proportion of patients reporting being in 'full health' declined to a nadir at six months (F, Fig. 4). There was an improvement until 24 months, to levels higher than at baseline.

Discussion

This study presents the first reported data on toxicity rates in those patients receiving moderately hypofractionated radiotherapy for prostate cancer on a 1.5 T MR-Linac within the context of an international study. The analysis conducted demonstrates outcomes comparable to those published in the literature. However, the results do not provide compelling evidence to support the potential advantages of MRIgRT over standard CT-guidance in this setting.

Grade ≥ 2 CTCAE GI toxicity was low (3.3 % at three months). The CHHiP study reported 3.3 % grade ≥ 2 RTOG toxicity at 18 weeks (8) in those receiving 60 Gy in 20 fractions and the conventional arm of the PACE B trial (62 Gy in 20 fractions or 78 Gy in 39 fractions) reported 0.5 % grade 2 GI RTOG toxicity at 12 weeks post-treatment [35]. Late toxicity at two years is also similar; 3.7 % (n = 1) of patients in this study reported grade 2 toxicity compared to 3 % in the 60 Gy group in the CHHiP study and 2 % in the conventional arm of PACE-B [36]. Our data should be cautiously interpreted due to small numbers of patients followed up at 24 months.

The high rate of GU reported symptoms seen at baseline (Fig. 2) is comparable to published rates (PACE B study, 50.2 % had grade ≥ 1 CTCAE symptoms and 4.4 % reported grade ≥ 2 symptoms at baseline). We report 7 % Grade ≥ 2 CTCAE GU toxicity at three months. This again appears similar to the literature; in the CHHiP study, 4.9 % of patients

Table 2
PSA response for all patients in ng/ml. The results demonstrate the median and IQR range at each follow up timepoint for all patients, as well as in the ADT and non-ADT groups. The p-values demonstrate a significant decrease in the median PSA from baseline to 12 months in paired data.

PSA values	Baseline	3 months	6 months	12 months	24 months
All patients	n = 140 7.6 (5.7–11.5)	n = 105 0.26 (0.1–1.6)	n = 105 0.36 (0.1–1.3)	n = 90 0.38 (0.1–1.1) p < 0.0001	n = 54 0.3 (0.1–0.6)
ADT	n = 81 8 (6.3–12.7)	n = 61 0.1 (0–0.2)	n = 55 0.1 (0.1–0.2)	n = 49 0.2 (0.1–0.3) p < 0.0001	n = 33 0.2 (0.1–0.4)
No ADT	n = 57 7.9 (5.6–11)	n = 43 2.3 (1.1–3.35)	n = 48 1.3 (0.7–2.2)	n = 39 1 (0.6–1.75) p < 0.0001	n = 20 0.8 (0.4–1.8)

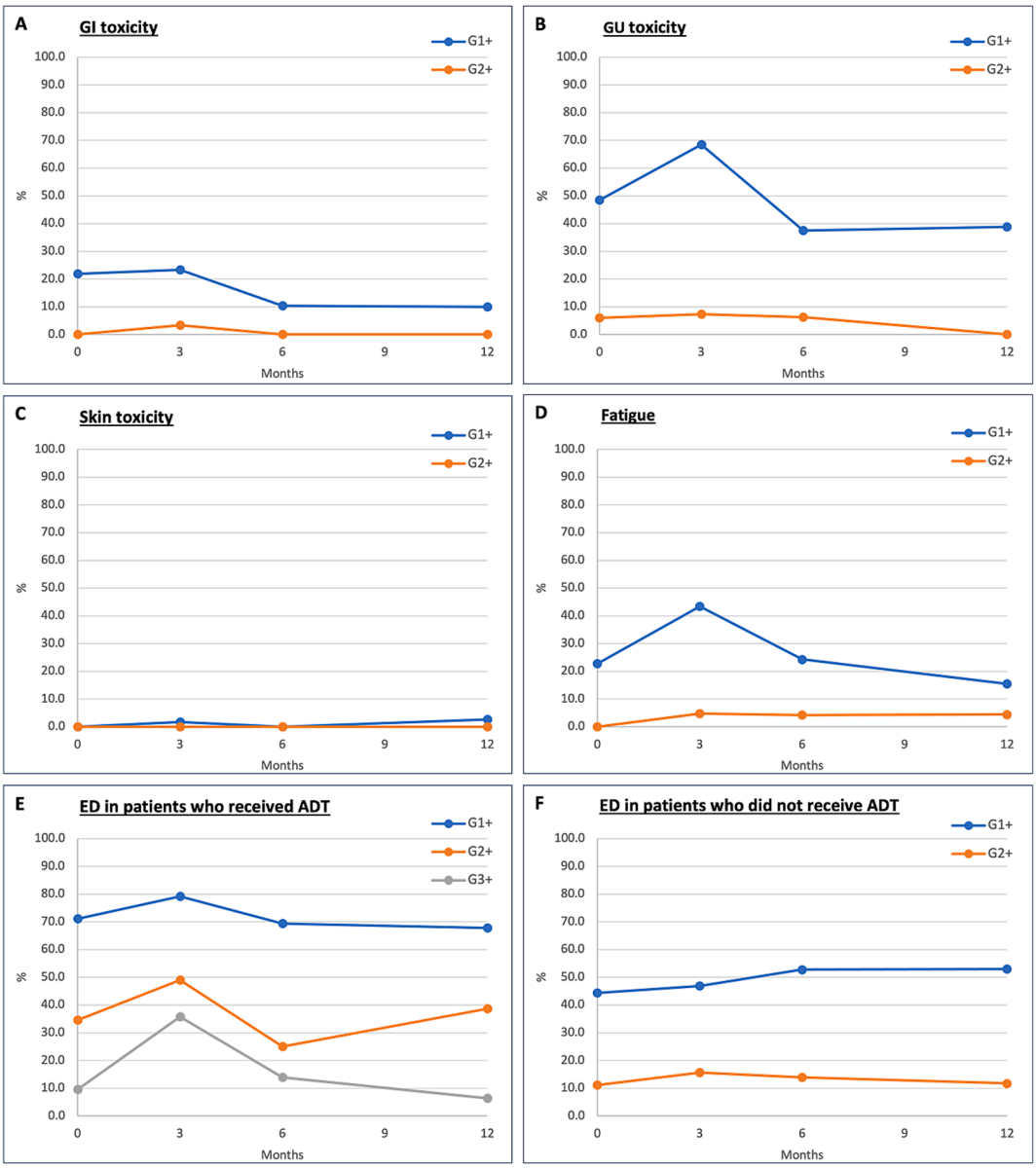

Fig. 2. CTCAE toxicity. The graphs demonstrate proportion of patients (y axis) against time since radiotherapy in months, up to 12 months (x axis). Baseline scores are demonstrated at 0. G1 + signifies a CTCAE score of grade 1 or worse and G2+, a grade 2 score or worse. There were no grade 3 or 4 toxicities reported for the predefined CTCAE toxicity criteria (except in patients with ED who received ADT). The corresponding data tables can be found in the Supplementary Appendix, Table 4.

demonstrated grade $\geq$ 2 RTOG GU toxicity at 18 weeks and 7 % of patients reported grade 2 GU CTCAE toxicity at 12 weeks post-treatment in the conventional arm of the PACE B trial [8,35]. At 24 months, we report 7 % grade $\geq$ 2 toxicity. In the CHHIP study, 2 % of patients had grade $\geq$ 2 toxicity at two years (moderate hypofractionation arm) and in the PACE B trial, 7 % of men had grade $\geq$ 2 toxicity at this timepoint [36].

We acknowledge that cross-trial comparisons of toxicity data may potentially suggest misleading similarities or difference. Different toxicity scales may pick up varying rates of toxicity [37] and what constitutes GI or GU toxicity may include a different combination of adverse events.

As the duration of ADT delivered is not known this confounds the interpretation of the ED data. Baseline levels of ED are significant and there is evidence of worsening ED during ADT, as expected. The EORTC HRQOL data suggests that quality of life deteriorates in the first six months, with multiple domains demonstrating clinically important changes from baseline at this timepoint. This is also reflected in the EQ-5D-5L data. Hormonal symptoms and sexual activity demonstrated clinically important worsening at three months. A MID of ten points, which we have used, for assessing the EORTC HRQOL may be conservative. Gamper et al. suggests that the true MID lies between five and ten points and may vary for each scale, and that it could be less than four on occasion [32]. Thus, the changes we have seen in the HRQOL data may be more clinically meaningful than is highlighted.

Radiotherapy symptoms and outcomes are related to multiple factors [38,39]. In this study, margin prescriptions, volume of SV included in target volumes, use of ADT, doses, workflow modality (ATP versus ATS) as well as plan adaptation strategies varied between the six institutions. Thirty percent of patients in this study were treated on an ATP workflow, which involves a positional shift similar to that performed during conventional CT-guided radiotherapy. These factors can all introduce bias and impact on the outcome and toxicity. By controlling for these variables, the strength of the data could be significantly improved.

There are several limitations to our work. Whilst our study provides

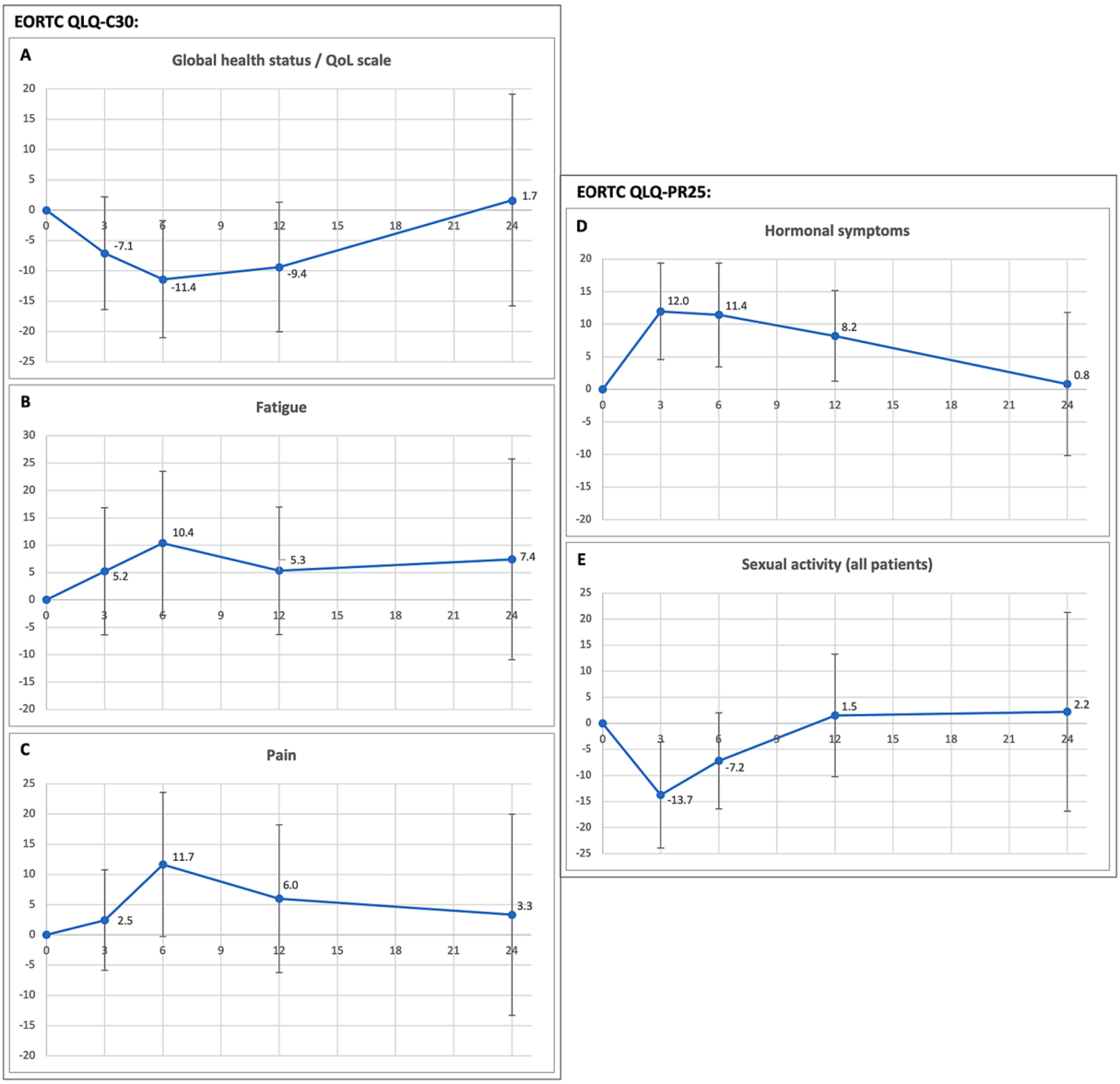

Fig. 3. Key EORTC questionnaire outcomes demonstrated graphically. The remaining results can be found in Supplementary Appendix Fig. 2. The EORTC QLQ-C30 (A–C) assesses multiple facets of well-being whilst the EORTC QLQ-PR25 (D–E) assesses specific symptoms. Graphs below demonstrate the mean change in paired scores (y axis) from baseline to each follow-up timepoint for each scale, with 0 representing no change. Month 0 is the baseline score taken at the start of radiotherapy, with months since radiotherapy shown on the x axis. Error bars show 95 % CI for estimates of mean subdomain scores. At baseline n = 45, 3 months n = 34, 6 months n = 30, 12 months n = 25 and 24 months n = 15.

insight into the toxicity, biochemical response and patient reported outcomes for the treatment of localised prostate cancer with moderately fractionated MRIgRT, it is important to acknowledge a key limitation regarding the collection and representation of data at 24 months. At this specific timepoint, data collection was only partially completed, resulting in a limited number of observations. The reduced number of observations at 24 months may accurately represent the initial cohort, therefore potentially compromising the robustness of the data. Therefore, this data should be cautiously interpreted. In addition, there is a risk of attrition bias due to possible participant dropouts. Two years of follow-up would also be considered short, especially in the context of prostate cancer where extended follow-up periods are typically undertaken in trials, and is likely to only capture the initial response to treatment rather than long-term outcomes, disease progression or potential side-effects. Obtaining comprehensive long-term data is important to establish a complete understanding of the toxicity profile and biochemical response.

The toxicity data timepoints in this study are fewer compared to larger trials. The CHHiP and PACE trials would suggest that acute toxicity peaks at around four to five weeks after commencement of radiotherapy, meaning the maximal acute toxicity rates will have been missed in this dataset, where the first post-baseline assessment is conducted at three months. The PROFIT trial reports 16.7 % worst Grade $\geq$ 2 acute GI RTOG toxicity and 30.9 % worst Grade $\geq$ 2 acute GU RTOG toxicity, which is higher than our data. However, patients were followed up at multiple timepoints during the first 14 weeks thus capturing earlier-occurring toxicity, which we are likely to have missed. There are other studies, such as the Prostate Radiotherapy Integrated with Simultaneous MRI (PRISM) study (NCT03658525), which will address this and provide more details about the time course and incidence of acute toxicity after MRIgRT. The data gathered at three months for acute toxicity will be affected by recall bias as some patients may describe their maximal toxicity during this period whilst other patients would describe their toxicity at the time of their visit only.

Fig. 4. EQ-5D-5L data graphically represented. Patients were asked to rate between levels 1 and 5, whether they have having problems in five separate dimensions (A-E). Each dimension has five levels of perceived problems: Level 1 indicating no problems to level 5 indicating unable to or extreme problems. Those who reported having no problems (level 1) and those reported having any severity of problems (level 2 and above) are demonstrated. Full health represents those patients who scored level 1 in each of the 5 dimensions, i.e. those who reported no problems for each health dimension. The last graph demonstrates those patients in full health at each timepoint. There is a fall in those patients who reported being in full health in the first 6 months, after which there is an improvement back to baseline by 24 months. Supplementary Table 7 provides the raw data.

Although the MOMENTUM registry aimed to collect data prospectively, this was not universally the case. Retrospective entry of data may affect reliability of toxicity data as clinical notes may not record data in sufficient detail to grade side effects, particularly minor ones. This dataset has a large proportion of missing data across domains, which is a significant limitation, but particularly in those domains felt to be "less relevant" such as skin toxicity. Data cannot be assumed to be missing at random and it is impossible to know whether there is bias in the data recorded versus data missing. This is a limitation of the study. Much of this data was collected during the COVID-19 pandemic, which will have affected data completeness and patient follow-up schedules. More patients had telephone follow up during this period, which may have affected data reporting. This will also have impeded PRO completion, which is largely still conducted with paper-based systems.

Our study suggests that the use of MRIgRT yields toxicity profiles and biochemical responses comparable to CT-guided radiotherapy. While MRIgRT offers technological advantages over CT-guided radiotherapy, we have not been able to demonstrate a clear benefit. Current radiotherapy techniques already achieve high rates of efficacy and low levels of toxicity for prostate cancer. Thus, showing incremental benefit of MRIgRT in the context of conventional or moderate hypofractionation will be challenging. Additionally, adopting MRIgRT presents several challenges. These include increased costs, heightened complexity, greater workforce demands and extended duration of each treatment [40,41]. Thus, we would argue that the potential advantages offered by this new technology may not justify the additional costs and time investment associated with delivering moderate hypofractionation, particularly as prostate radiotherapy accounts for a sizeable volume of a radiotherapy centre's workload.

However, MRIgRT may provide an advantage for patients where dose constraints are unachievable on a standard linac due to bladder or rectal anatomy, or small bowel close to the target [26,42]. MRIgRT may also give us the opportunity to test new hypotheses which are difficult to test on other machines.

The potential benefits of MRIgRT may be more pronounced in ultrahypofractionated treatments, where accurate delivery of a higher dose per fraction is paramount. The superior soft tissue contrast on MRI could prove beneficial in facilitating delivery of dose accurately to the tumour whilst reducing dose to the surrounding prostate. Studies investigating ultrahypofractionated radiotherapy regimens for prostate cancer on the MR-Linac are more prevalent than those investigating moderate hypofractionation, yet remain in their infancy.

Studies have shown safe delivery of ultrahypofractionated treatments with toxicity rates that are low [43–45] on the MRIdian and Elekta Unity MR-Linacs. Teunissen et al. reported the first outcomes from five fraction stereotactic radiotherapy (SBRT) to the prostate on the 1.5 T MR-Linac [43] to 12 months. The paper demonstrated that MRIgRT for localised prostate cancer was effective and safe. A temporary increase in acute grade 2 GI toxicity at three months was reported (0.9 % at baseline to 1.7 % at three months) as well as in grade 2 GU toxicity (4.8 % at baseline to 18.7 % at three months, which is concordant with published randomised evidence [36,46]. Bruyzneel et al. reported cumulative grade 2 or worse acute GU and GI toxicity as 23.8 % and 5 % respectively on the MRIdian MR-Linac.

The MIRAGE trial (NCT04384770) randomised 156 men to CT-guided SBRT (4 mm margins) vs MRI-guided SBRT (2 mm margins). This trial showed a clear reduction in both cumulative acute CTCAE GU Grade 2 toxicity (from 42.1 % to 24.4 %, $p = 0.01$) and cumulative acute CTCAE GI toxicity (from 10.5 % to 0.0 %, $p = 0.003$) with MRI guidance suggesting a meaningful improvement in patient experience [47]. The 90-day GU Grade 2 acute toxicity of 24.4 % after MR-guided therapy in the MIRAGE trial is comparable to that reported by Teunissen et al. (19 % at three months).

Building on this work we have embarked on a suite of clinical trials exploring ultra-hypofractionated MR-guided radiotherapy in two to five fractions, including the HERMES (NCT04595019) trial [48]. Validation of its benefit, including a cost-effectiveness analysis, through prospective randomised controlled clinical trials is important before adoption can take place. Further work will also test whether leveraging the direct visualisation of the tumour during treatment we can de-escalate the radiation dose to the non-tumour containing prostate.

Conclusion

To our knowledge, this is the first paper which assesses the outcomes of moderately hypofractionated radiotherapy on a 1.5 T MR-Linac for prostate cancer. Online-MRIgRT for prostate cancer is feasible in a multicentre setting. Toxicity is low and comparable with larger published clinical trials. Although our study contributes to the growing body of evidence supporting the feasibility and safety of MRIgRT for prostate cancer, it does not demonstrate that MRIgRT confers a substantial advantage over the current established standard of care, CT-guided radiotherapy, in the context of moderately hypofractionated treatment. Ongoing work seeks to evaluate the potential benefits of reducing prostate radiotherapy to two to five fractions, where the advantages of MRIgRT might become more apparent.

CRediT authorship contribution statement

Kobika Sritharan: Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization. **Lois Daamen:** Formal analysis, Data curation, Writing – review & editing. **Angela Pathmanathan:** Investigation, Writing – review & editing. **Tine Schytte:** Investigation, Writing – review & editing. **Floris Pos:** Investigation, Writing – review & editing. **Ananya Choudhury:** Investigation, Writing – review & editing. **Jochem R.N. van der Voort van Zyp:** Investigation, Writing – review & editing. **Linda G.W. Kerkmeijer:** Investigation, Writing – review & editing. **William Hall:** Investigation, Writing – review & editing. **Emma Hall:** Formal analysis, Writing – review & editing. **Helena M. Verkooijen:** Investigation, Writing – review & editing. **Trina Herbert:** Investigation, Writing – review & editing. **Shaista Hafeez:** Investigation, Writing – review & editing. **Adam Mitchell:** Investigation, Writing – review & editing. **Alison C. Tree:** Investigation, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Conflicts of Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2024.100742.

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