INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY • BIOLOGY • PHYSICS
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BRIEF REPORT

Interim Toxicity Analysis From the Randomized HERMES Trial of 2- and 5-Fraction Magnetic Resonance Imaging–Guided Adaptive Prostate Radiation Therapy

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Received Jul 17, 2023; Accepted for publication Sep 18, 2023

Purpose: Ultrahypofractionated radiation therapy (UHRT) is an effective treatment for localized prostate cancer with an acceptable toxicity profile; boosting the visible intraprostatic tumor has been shown to improve biochemical disease-free survival with no significant effect on genitourinary (GU) and gastrointestinal (GI) toxicity.

Methods and Materials: HERMES is a single-center noncomparative randomized phase 2 trial in men with intermediate or lower high risk prostate cancer. Patients were allocated (1:1) to 36.25 Gy in 5 fractions over 2 weeks or 24 Gy in 2 fractions over 8 days with an integrated boost to the magnetic resonance imaging (MRI) visible tumor of 27 Gy in 2 fractions. A minimization algorithm with a random element with risk group as a balancing factor was used for participant randomization. Treatment was delivered on the Unity MR-Linac (Elekta AB) with daily online adaption. The primary endpoint was acute GU Common Terminology Criteria for Adverse Events version 5.0 toxicity with the aim of excluding a doubling of the rate of acute grade 2+ GU toxicity seen in PACE. Analysis was by treatment received and included all participants who received at least 1 fraction of study treatment. This interim analysis was prespecified (stage 1 of a 2-stage Simon design) for when 10 participants in each treatment group had completed the acute toxicity monitoring period (12 weeks after radiation therapy).

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Disclosures: This research has been supported by the JP Moulton Foundation. We are very grateful for their support. R.W. is funded by The Royal Marsden NHS Foundation Trust with the funding of the research fellow program receiving funds from Elekta.

The Royal Marsden and the Institute of Cancer Research are members of the Elekta MR Linac consortium. E.H. acknowledges support from Cancer Research UK to the ICR-CTSU (C1491/A15955) and support from a Cancer Research UK Network Accelerator Award Grant (A21993) to the ART-NET consortium. A.C.T. receives research funding and has received honoraria and travel grants from Elekta; research funding from Accuray and Varian and honoraria from Accuray and Janssen; and is supported by Cancer Research UK at a Cancer Research UK Radiation Research Centre of Excellence at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust (C33589/A28284 and C7224/A28724). This project represents independent research supported by the National Institute for Health research (NIHR) Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ijrobp.2023.09.032.

Acknowledgments—The authors thank members of the HERMES Independent Data Monitoring Committee who gave permission for release of interim data presented in this report. The authors would also like to express gratitude for support from the MOMENTUM team, particularly Professor Verkooijen and Dr Blezer. A.T. would like to acknowledge informal advice and support from Andrew Loblaw, Gerard Morton, Peter Hoskin, and Himanshu Nagar. This research has been supported by the JP Moulton Foundation

Int J Radiation Oncol Biol Phys, Vol. 118, No. 3, pp. 682–687, 2024
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https://doi.org/10.1016/j.ijrobp.2023.09.032

Results: Acute grade 2 GU toxicity was reported in 1 (10%) patient in the 5-fraction group and 2 (20%) patients in the 2-fraction group. No grade 3+ GU toxicities were reported.
Conclusions: At this interim analysis, the rate of GU toxicity in the 2-fraction and 5-fraction treatment groups was found to be below the prespecified threshold (5/10 grade 2+) and continuation of the study to complete recruitment of 23 participants per group was recommended. © 2023 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Introduction

The treatment of prostate cancer with utltrahypofractionated regimens is logical because of its low α/β ratio and resultant sensitivity to higher doses per fraction, while also minimizing hospital visits for patients and facilitating more cost-effective treatments.[1−3]

Level 1 evidence has shown that ultrahypofractionated schedules are as good as moderately fractionated regimens in the treatment of prostate cancer.[4] Furthermore, toxicity data has been promising, with comparable toxicity profiles to moderate hypofractionation.[2,4]

Intraprostatic relapse after external beam radiation therapy (EBRT) usually occurs at the site of the primary tumor, with focal dose boosting of the magnetic resonance imaging (MRI)-defined gross tumor volume (GTV) showing a significant improvement in biochemical disease-free survival (bDFS) in conventionally fractionated radiation therapy.[1,5]

The Unity MR-Linac (Elekta AB) combines MRI with daily online adaptive radiation therapy.[6] Such a platform allows for a safe reduction in clinical target volume (CTV) to planning target volume (PTV) margins while maintaining target coverage.[7,8]

HERMES is the first study to investigate 2-fraction ultrahypofractionated MRI-guided adaptive radiation therapy (MRIgART) with a focal GTV boost in the treatment of intermediate to high-risk prostate cancer.[9] This prespecified interim analysis assesses acute Common Terminology Criteria for Adverse Events version 5.0 (CTCAE) genitourinary (GU) toxicity.

Materials and Methods

Study design and patient population

HERMES is a single-center, noncomparative randomized phase 2 trial examining the feasibility of ultrahypofractionated radiation therapy (UHRT) in men with localized prostate cancer focusing on acute GU toxicity as its primary outcome.

Patients with a histologic diagnosis of intermediate- to lower-high-risk prostate adenocarcinoma (MRI stage T2-T3a, Gleason 4+3 or less, maximum prostate-specific antigen 25), with a dominant lesion visible on multiparametric magnetic resonance imaging (mpMRI) were eligible. Six months of concurrent androgen deprivation therapy (ADT) with bicalutamide or luteinizing hormone-releasing hormone agonists (LHRHa) was mandatory. ADT was started before radiation therapy with the aim of continuing until at least 2 months after UHRT was delivered. A maximum of 12 months was permitted as prescribed at the doctor's discretion.

Consenting participants were allocated centrally by the Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU) on a 1:1 basis to either 5-fraction or 2-fraction stereotactic body radiation (SBRT) using a minimization algorithm balanced for National Comprehensive Cancer Network (NCCN) risk group (intermediate or lower-high) and incorporating a random element. Treatment allocation was not masked. All participants were co-enrolled into the MOMENTUM observational registry.[10]

HERMES recruited patients at The Royal Marsden NHS Foundation Trust and is sponsored by the ICR. The trial was approved by the local institutional review board and regional ethics committee (20/LO/1162). HERMES is conducted in accordance with the principles of Good Clinical Practice. All participants provided voluntary written informed consent. The trial is registered on ClinicalTrials.gov (NCT04595019) and participants continue to be followed up.

Staging and radiation therapy planning

Participants underwent standard staging investigations before recruitment. To be suitable for HERMES a PI-RADS 3 to 5 mpMRI definable dominant intraprostatic lesion and concordant biopsy confirming prostate adenocarcinoma (usually MRI-targeted) was required.

No participant had a spacer device placed for treatment. Before radiation therapy planning, a pretreatment CT and MRI were used to aid treatment planning, with the contours and resultant reference plan generated on a planning MRI acquired on the MR-Linac (T2 3D Tra). Patients were scanned with a moderately full bladder and microenemas were used before scanning.

The prostate plus 1 cm of seminal vesicles (SV) was defined as CTV1. In the upper- intermediate participants (Gleason 4+3) and high-risk participants, a further CTV was defined as the prostate plus 2 cm of SVs (CTV2).

The target volumes for each group and the dose they were prescribed are outlined in Table 1 and displayed in Figure E1. The GTV did not receive a boost in the 5-fraction group. Participants in the 2-fraction group were prescribed 27 Gy to the GTV.

Table 1 The target structures and dose prescribed in the 5-fraction and 2-fraction groups

Structure	Description	Name and dose for 5-fraction group (structure_dose in Gy)	Name and dose for 2-fraction regimen (structure_dose in Gy)
GTV	DIL	n/a	GTV_27
CTV1	Prostate + 1 cm of SVs	CTV_40	n/a
CTV2*	Prostate + 2 cm of SVs	n/a	n/a
PTV1 (grown from CTV1)	CTV1 + 3 mm	PTV_36.25	PTV_24
PTV2 (grown from CTV2)*	CTV2 + 3 mm	PTV_30	PTV_20

Abbreviations: CTV = clinical target volume; DIL = dominant intraprostatic lesion; GTV = gross tumor volume; n/a = no dose prescribed to this structure; PTV = planning target volume; SV= seminal vesicle.
* Only for upper-intermediate and high-risk patients.

Radiation delivery

All participants received 11-field intensity modulated radiation therapy on the MR-Linac using the Adapt-to-Shape workflow.[11] Five-fraction treatment was delivered on alternate days, excluding weekends. Fractions were given 7 days apart in the 2-fraction regimen, with each fraction delivered in 2 sequential subfractions. This was to reduce the intrafraction motion that might occur during the lengthy beam-on time, with readjustments of the plan for the second subfraction each day. Patients partially emptied their bladder after getting off the couch and then waited 20 minutes before receiving the second subfraction.

All targets and organs at risk (OARs) were propagated from the reference planning MRI to the daily session MRI (T2 3D Tra) via deformable image registration, except GTV and urethra which were rigidly propagated. The target and OARs were edited daily, and a new plan created. Target objectives and OAR constraints are shown in Tables E1 and E2.

Imaging was repeated immediately before beam-on and any nonnegligible displacements in target anatomy corrected for using Adapt-to-Position workflow.[11]

Assessments

During the acute toxicity period, GU and gastrointestinal (GI) toxicities were reported using CTCAE v5.0 with scoring at baseline, end of treatment, and at 2, 4, 8, and 12 weeks after radiation therapy. Patients on alpha blockers or antimuscarinics were scored as having grade 1 GU toxicity, provided they stayed on the same dose. Patient-reported outcomes measures were also collected.

Statistical analysis

The primary endpoint was cumulative incidence of acute CTCAE grade 2+ GU toxicity from the start of radiation therapy to 12 weeks posttreatment.

For each treatment group, a sample size of 23 patients was determined using a Simon 2-stage optimal design. This sample size allows the exclusion of a doubling in the toxicity rate compared with that seen in the PACE trial (31% grade 2+ cumulative GU CTCAE toxicity by 12 weeks post treatment)[12] with one-sided 5% significance level and 90% power. Each group is therefore individually powered to exclude a GU 2+ toxicity rate of 62%.

Under the 2-stage design, the interim (stage 1) toxicity assessment was carried out once 10 participants had completed 12 weeks of post-SBRT follow-up in both treatment groups. If 5 or fewer (≤50%) participants reported a grade 2 + genitourinary toxicity by 12 weeks, recruitment to that treatment group would continue. Analyses were conducted at ICR-CTSU using Stata version 16.1. This interim analysis focuses on the primary outcome, as specified previously.

Results

Between September 2021 and February 2023, 20 patients (10 5-fraction, 10 2-fraction) had received UHRT and completed 12 weeks of follow-up. The characteristics of the 20 stage 1 participants are shown in Table 2.

A fraction of radiation therapy in the 2-fraction regimen took, including the resting time between the 2 subfractions, on average 140 minutes to complete. The average time for a 5-fraction treatment was 59 minutes.

A grade 2 or higher (grade 2+) acute GU toxicity was reported by a total of 1/10 (10%) participants treated with 5 fractions and 2/10 (20%) participants treated with 2 fractions of UHRT (Table 3). The 5-fraction participant reporting grade 2+ toxicity experienced grade 2 urinary frequency and grade 2 urinary urgency at 2, 4, and 8 weeks after radiation therapy. In the 2-fraction group, 1 participant reported grade 2 urinary frequency at the end of treatment and a further participant reported grade 2 urinary frequency at week 2 and week 8. No grade 3 or 4 GU toxicities were reported.

In both groups the number of participants experiencing a grade 1+ GU toxicity was highest at 2 weeks; 10 (100%) in the 5-fraction arm and 7 (70%) in the 2-fractions arm. There was no distinct peak of grade 2+ toxicity, with all grade 2+ toxicity resolving by 3 months. Toxicity at each time point is shown in Figure 1.

Table 2 Characteristics of the first 20 patients treated within HERMES

		5-fraction SBRT N = 10	2-fraction SBRT N = 10	Overall N = 20
Age (y)	Median	74	73	74
	(range)	(60-80)	(60-82)	(60-82)
NCCN risk group		No. (%)	No. (%)	No. (%)
	Intermediate	8 (80)	7 (70)	15 (75)
	high	2 (20)	3 (30)	5 (25)
PSA (ng/mL)	Median	7.5	7.2	7.5
	(range)	(5.3-13)	(1.6-21)	(1.6-21)
T-stage		No. (%)	No. (%)	No. (%)
	T2	8 (80)	7 (70)	15 (75)
	T3a	2 (20)	3 (30)	5 (25)
Gleason score		No. (%)	No. (%)	No. (%)
	3+3	1 (10)	1 (10)	2 (10)
	3+4	6 (60)	6 (60)	12 (60)
	4+3	3 (30)	3 (30)	6 (30)
Race/ethnicity		No. (%)	No. (%)	No. (%)
	White*	9 (90)	7 (70)	16 (80)
	Black†	1 (10)	2 (20)	3 (15)
	Other	0 (0)	1 (10)	1 (5)

Abbreviations: NCCN = National Comprehensive Cancer Network; PSA = prostate specific antigen; SBRT = stereotactic body radiation therapy.
* Denotes White English, Scottish, Welsh, Northern Irish, or British.
† Denotes Black British, Caribbean, or African.

CTCAE GI toxicity was also recorded and found to be acceptable across the 2 groups. Eight of 10 (80%) 5-fraction participants and 6/10 (60%) of 2-fraction patients reported grade 1 GI toxicity. No grade 2+ GI toxicities were reported.

Discussion

This interim analysis has shown acceptable toxicity rates and recruitment will now continue to completion.

The pattern of toxicity mirrors that of PACE B, with higher rates of GU compared with GI toxicity.[2,12] At present there is no evidence of increased rates of grade 2+ GU toxicity with 2-fraction MRIgART (20%) compared with that seen in PACE B 5-fraction treatment (31%)[12]; however, HERMES is not powered to detect a difference in toxicity between 2-fraction and 5-fraction MRIgART SBRT.

Toxicity rates in HERMES compare favorably to the hypoFLAME trial, in which men received an integrated boost (on average) of 44.7 Gy in 5 fractions to the tumor with cumulative GU acute grade 2 toxicity of 34% at 90 days.[13]

There are 2 published trials of 2-fraction external beam radiation therapy using a nonadaptive platform: 2STAR and 2SMART.[14,15] In 2STAR, 30 men received 26 Gy in 2 fractions with gold seeds and daily CBCT for set up on a c-arm Linac. Cumulative acute GU and GI grade 2 CTCAE toxicities were 40% and 3.3% respectively.[14] The same 30-patient design was used in 2SMART; men with low- to intermediate-risk prostate cancer received 26 Gy in 2 fractions to the CTV with a simultaneous integrated GTV boost of up to 32 Gy.

Table 3 Maximum grade of CTCAE GU toxicity experienced per patient between end of radiation therapy and 3 months post-radiation therapy

	5-fraction SBRT				2-fraction SBRT			
Genitourinary CTCAE	Grade 0	Grade 1	Grade 2	Grade 3	Grade 0	Grade 1	Grade 2	Grade 3
No.	0	9	1	0	1	7	2	0
%	0%	90%	10%	0%	10%	70%	20%	0%

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; GU = genitourinary; SBRT = stereotactic body radiation therapy.

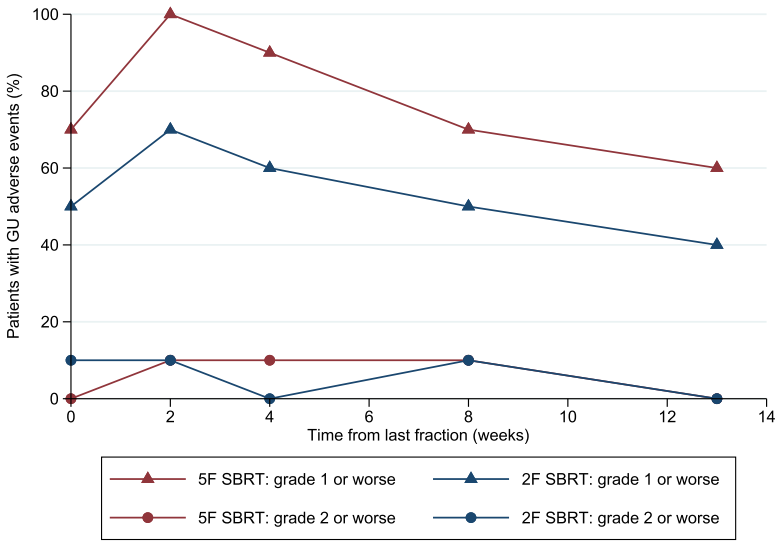

Fig. 1. Graph showing the percentage of patients experiencing grade 1+ and grade 2+ GU toxicity at each time point in each group. There were no grade 3 or 4 GU toxicities.

Cumulative acute grade 2 GU and GI toxicities were reported at 56.7% and 3.3%, respectively.[15] Although this interim analysis is not powered to allow for comparison, the results of HERMES suggest favorable toxicity outcomes compared with 2STAR and 2SMART. This difference may be accounted for by the adaptive nature of the MR-Linac, therefore improving accuracy of dose delivery and reducing the dose received by the OARs in HERMES. In addition, centers may have variable thresholds for prescribing medication for urinary symptoms, thus changing the number of grade 2+ events recorded, which are largely driven by prescription of alpha-blockers. The higher toxicity recorded in 2SMART may be a result of the increased dose to the GTV (EQD2 of 156.4 Gy in 2SMART compared with 113.25 Gy in HERMES)

PSA kinetics will be followed up for 2 years after treatment. It is hoped that the results will echo the 5-year efficacy results of 2-fraction high dose brachytherapy in low- and intermediate-risk prostate cancer, where patients receiving 2 fractions of 13.5 Gy had a 5-year biochemical disease-free survival of 93%.[16]

Two further trials will contribute to the testing of 2-fraction SBRT versus 5-fraction UHRT. FORT (NCT04984343) randomizes to 25 Gy in 2 fractions versus 37.5 Gy in 5 fractions. Participants are being treated on the MR-Linac with the prescription of a boost to the dominant intraprostatic lesion left to the treating physicians' discretion. iSMART (NCT05600400) is also recruiting, randomizing between 40 Gy in 5 fractions and 27 Gy in 2 fractions, both prescribed to CTV.

As an interim analysis this is only a small cohort and therefore robust conclusions cannot be drawn. However, if on completion HERMES shows tolerable levels of toxicity at completion, we will move to a multicenter trial optimizing 2-fraction SBRT on the MRI with an integrated boost to the GTV. Thereafter a randomized noninferiority trial comparing 2 fractions with 5 fractions is warranted.

Conclusion

Both 5-fraction and 2-fraction MRI-guided adaptive SBRT show low levels of acute toxicity. Further analysis will confirm longer-term toxicity and pave the way for further study.

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