Magnetic Resonance-Guided Adaptive Radiation therapy for Prostate Cancer

The First Results from the MOMENTUM study—An International Registry for the Evidence-Based Introduction of Magnetic Resonance-Guided Adaptive Radiation Therapy

Teunissen, Frederik R.; Willigenburg, Thomas; Tree, Alison C.; Hall, William A.; Choi, Seungtaek L.; Choudhury, Ananya; Christodouleas, John P.; de Boer, Johannes C.J.; de Groot-van Breugel, Eline N.; Kerkmeijer, Linda G.W.; Pos, Floris J.; Schytte, Tine; Vesprini, Danny; Verkooijen, Helena M.; van der Voort van Zyp, Jochem R.N.

Published in:
Practical Radiation Oncology

DOI:
10.1016/j.prro.2022.09.007

Publication date:
2023

Document version:
Final published version

Practical Radiation Oncology® (2023) 13, e261–e269

practical radiation oncology
pro
www.practicalradonc.org

Basic Original Report

Magnetic Resonance-Guided Adaptive Radiation Therapy for Prostate Cancer: The First Results from the MOMENTUM study—An International Registry for the Evidence-Based Introduction of Magnetic Resonance-Guided Adaptive Radiation Therapy

Frederik R. Teunissen, MD,[a] Thomas Willigenburg, MD,[a] Alison C. Tree, MD, FRCR,[b] William A. Hall, MD,[c] Seungtaek L. Choi, MD,[d] Ananya Choudhury, MA, PhD, MRCP, FRCR,[e] John P. Christodouleas, MD, MPH,[f,g] Johannes C.J. de Boer, PhD,[a] Eline N. de Groot-van Breugel, BSc,[a] Linda G.W. Kerkmeijer, MD, PhD,[h] Floris J. Pos, MD, PhD,[i] Tine Schytte, MD, PhD,[j] Danny Vesprini, MD,[k] Helena M. Verkooijen, MD, PhD,[l,m] and Jochem R.N. van der Voort van Zyp, MD, PhD[a,*]

[a]Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, The Netherlands; [b]Department of Urological Oncology, The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London, United Kingdom; [c]Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, Wisconsin; [d]Department of

Sources of support: The MOMENTUM study receives funding from Elekta. Dr Choudhury is supported by the NIHR Manchester Biomedical Research Centre. Dr Tree acknowledges support from the Rosetrees Trust, CRUK grant C33589/A28284 and C7224/A28724, Elekta, and the Medical Research Council. This project represents independent research supported by the National Institute for Health research 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.

Disclosures: Dr Tree reports grants from Elekta during the conduct of the study; grants from Accuray, Varian, Cancer Research UK, Prostate Cancer UK, the JP Moulton Foundation and the Rosetrees Trust; personal fees from Janssen, Elekta, and Accuray, outside the submitted work. Dr Hall reports the project described was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, award number KL2TR001438. The content is solely the responsibility of the author(s) and does not necessarily represent the official views of the National Institutes of Health and that the Medical College of Wisconsin Department of Radiation Oncology receives research and travel support from Elekta. Dr Choudhury reports grants and nonfinancial support from Elekta, during the conduct of the study; grants from National Institute of Health Research Manchester Biomedical Research Centre, Cancer Research, UK, Medical Research Council, UK, Prostate Cancer, UK, and Bayer, UK; personal fees from Janssen Pharmaceutical and BMS; nonfinancial support from ASCO; grants and nonfinancial support from Elekta, outside the submitted work. Dr Christodouleas reports employee status at Elekta. Dr Vesprini reports travel reimbursement from Elekta, outside the submitted work. Dr Kerkmeijer reports grants from the Dutch Cancer Foundation, outside the submitted work. Dr Verkooijen reports grants from Elekta, Dutch Cancer Foundation, National Organisation for Health Research and Development, and the European Commission during the conduct of the study. Dr Voort van Zyp reports grants from ZonMW IMDI-LSH/TKI Foundation (The Netherlands, project number 104006004), outside the submitted work. All other authors have no disclosures to declare.

Research data are not available at this time.

* Corresponding author: Jochem R.N. van der Voort van Zyp, MD, PhD; E-mail: j.r.n.vandervoortvanzyp@umcutrecht.nl

https://doi.org/10.1016/j.prro.2022.09.007

Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; [e]Division of Cancer Sciences, University of Manchester and Department of Clinical Oncology, The Christie NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, United Kingdom; [f]Department of Radiation Oncology, University of Pennsylvania, Philadelphia, Pennsylvania; [g]Elekta AB, Stockholm, Sweden; [h]Department of Radiation Oncology, Radboud University Medical Center, Nijmegen, The Netherlands; [i]Department of Radiation Oncology, The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; [j]Department of Oncology, Odense University Hospital, Odense, Denmark; [k]Department of Radiation Oncology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [l]Imaging and Oncology Division, University Medical Center Utrecht, Utrecht, The Netherlands; and [m]Utrecht University, Utrecht, The Netherlands

Received 27 June 2022; accepted 20 September 2022

Purpose: Magnetic resonance (MR)-guided radiation therapy (MRgRT) is a new technique for treatment of localized prostate cancer (PCa). We report the 12-month outcomes for the first PCa patients treated within an international consortium (the MOMENTUM study) on a 1.5T MR-Linac system with ultrahypofractionated radiation therapy.

Methods and Materials: Patients treated with 5 × 7.25 Gy were identified. Prostate specific antigen-level, physician-reported toxicity (Common Terminology Criteria for Adverse Events [CTCAE]), and patient-reported outcomes (Quality of Life Questionnaire PR25 and Quality of Life Questionnaire C30 questionnaires) were recorded at baseline and at 3, 6, and 12 months of follow-up (FU). Pairwise comparative statistics were conducted to compare outcomes between baseline and FU.

Results: The study included 425 patients with localized PCa (11.4% low, 82.0% intermediate, and 6.6% high-risk), and 365, 313, and 186 patients reached 3-, 6-, and 12-months FU, respectively. Median prostate specific antigen level declined significantly to 1.2 ng/mL and 0.1 ng/mL at 12 months FU for the nonandrogen deprivation therapy (ADT) and ADT group, respectively. The peak of genitourinary and gastrointestinal CTCAE toxicity was reported at 3 months FU, with 18.7% and 1.7% grade ≥2, respectively. The QLQ-PR25 questionnaire outcomes showed significant deterioration in urinary domain score at all FU moments, from 8.3 (interquartile range [IQR], 4.1-16.6) at baseline to 12.4 (IQR, 8.3-24.8; $P = .005$) at 3 months, 12.4 (IQR, 8.3-20.8; $P = .018$;) at 6 months, and 12.4 (IQR, 8.3-20.8; $P = .001$) at 12 months. For the non-ADT group, physician- and patient-reported erectile function worsened significantly between baseline and 12 months FU.

Conclusions: Ultrahypofractionated MR-guided radiation therapy for localized PCa using a 1.5T MR-Linac is effective and safe. The peak of CTCAE genitourinary and gastrointestinal toxicity was reported at 3 months FU. Furthermore, for patients without ADT, a significant increase in CTCAE erectile dysfunction was reported at 12 months FU. These data are useful for educating patients on expected outcomes and informing study design of future comparative-effectiveness studies.

Introduction

Prostate motion within the pelvis is common because of the presence or absence of gas within the rectum, bowel movement, and filling of the urinary bladder. To account for uncertainties during dose delivery with external beam radiation therapy (EBRT), such as intrafraction motion, the prostate is irradiated with an uncertainty margin, also known as the planning target volume (PTV). This margin is necessary for adequate dose delivery to the prostate. Unfortunately, the PTV margin also overlaps the healthy bladder, rectum, and neurovascular structures, which may lead to posttreatment genitourinary (GU), gastrointestinal (GI), or erectile toxicity.[1]

Magnetic resonance-guided radiation therapy (MRgRT) enables real-time visualization of target volume and organs-at-risk during EBRT.[2] Currently, MRgRT enables correction for interfraction motion and deformation by applying daily contour adaptation and subsequent online replanning before dose delivery without the use of fiducials or beacons. Furthermore, it allows for visualization of intrafraction motion during dose delivery. Such imaging will enable beam pausing or treatment interruption in case there is substantial or unexpected intrafraction motion. This may reduce posttreatment toxicity while maintaining or improving tumor control.[3]

Currently, 2 commercial MRgRT devices are available: the MRidian (ViewRay Inc., Mountain View, CA) and the Unity MR-Linac (Elekta AB, Stockholm, Sweden). The first combines a 0.35T (ie, low-field) MR scanner with a 6MV linear accelerator (a previous version used 3 Co-60 heads)[4] and the latter combines a 1.5T (ie, high-field) MR scanner with a 7MV linear accelerator.[5]

Although several radiation therapy departments have already implemented MRgRT as a standard treatment for low- and intermediate-risk localized prostate cancer (PCa), the theoretical advantages of MRgRT over conventional radiation therapy treatments such as CT-guided EBRT have yet to be proven in clinical practice. Furthermore, clinical outcomes up to 12 months follow-up (FU)

have been reported for low-field MRgRT,[6,7] but not yet for high-field MRgRT. This is essential, as high-field MRgRT may induce different treatment-related challenges.[8] The Multi-OutcoMe EvaluatioN of radiation Therapy Using the MR-linac Study (The MOMENTUM study) was initiated to facilitate evidence-based introduction of 1.5T MRgRT in daily practice.[9]

As a first step, we here report the 12-month toxicity, efficacy, and patient-reported outcomes (PROs) from the first PCa patients enrolled in the MOMENTUM study, who were treated with 5 × 7.25 Gy on the Unity 1.5T MR-Linac system.

Methods and Materials

Patients

This study was conducted within the MOMENTUM study, an international collaboration of early adopters of the 1.5T MR-Linac system, which received approval by local Institutional Review Boards of the participating institutions (Clinicaltrials.gov identifier NCT04075305).[10] In MOMENTUM, all patients treated with radiation therapy on an MR-Linac in one of the participating institutions are eligible for participation. For the current analysis, we included all MOMENTUM participants treated for PCa with 5 × 7.25 Gy on a 1.5T MR-Linac between May 1, 2019 and October 10, 2021. All intermediate-risk PCa patients who are eligible for conventional 5 × 7.25 Gy and have no contraindication for MRI, can receive 5 × 7.25 Gy MRgRT. Low- and high-risk patients can be treated off protocol, in accordance with the physician and patient.

Data acquisition

Within MOMENTUM, patient baseline characteristics, physician-reported toxicity, and PROs were prospectively collected at baseline (before start of radiation therapy treatment) and at 3, 6, 12, and 24 months after the last radiation therapy fraction. Biochemical treatment response was evaluated by prostate specific antigen (PSA) levels at baseline and during FU. Seventeen items of the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0[11] were prospectively obtained from medical records. In case CTCAEs were recorded at multiple time points between the FU moments, at 3 months FU the highest CTCAE grades between the end of the last fraction and 3 months, for the 6 months FU the highest CTCAE grades between 3 and 6 months, and for the 12 months FU the highest CTCAE grades between 6 and 12 months (ie, cumulative incidence). All patients who signed informed consent for completing PRO questionnaires, received the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30[12] and a subset of patients also the EORTC QLQ-PR25.[13] For each FU time point, a separate case report form for PSA level, CTCAE, and PROs was filled out.

Treatment

All patients were treated in 5 fractions of 7.25 Gy with a 2-day interval between fractions. Before the first fraction, a pretreatment planning MR scan was acquired on which the target volume and organs-at-risk were delineated. There is no need for a CT scan. Gross tumor volume, clinical target volume (CTV), and PTV delineations were at the discretion of the treating physician and varied across institutions (Table E1). The Elekta Monaco treatment planning system (version 50.40.01, Elekta Inc., Stockholm, Sweden) was used to create intensity modulated radiation therapy treatment plans, prescribing a dose of 36.25 Gy to the PTV. During each fraction, after positioning the patient on the treatment table, a daily online T2-weighted MR scan was acquired in treatment position. Bladder and rectal preparation before MRgRT varied between the different institutes. In case a so-called "adapt-to-shape" (ATS) workflow was applied, the contours from the pretreatment planning MR or online MR from the first fraction (for fraction 2-5) were propagated onto the daily online MR.[14] Afterward, contours were manually adjusted if necessary.[15] After approval of the daily contours, the treatment plan was recalculated and simultaneously a position verification MR scan was obtained. Adapt-to-position (ATP) was applied in case of a substantial CTV shift, or regardless of the CTV shift (ie, always ATP). Androgen deprivation therapy (ADT) prescription was at the discretion of the treating physician and ADT protocols varied across institutions.

Statistical analysis

Outcomes included PSA kinetics during FU, physician-reported toxicity (CTCAE) and PROs at baseline, 3-, 6-, and 12-months FU. Descriptive statistics were provided for patient characteristics. Normally distributed data was presented as mean with 95% confidence intervals (CI). Skewed data was presented as median with range or interquartile range (IQR). For PSA level, CTCAE grades, and PRO scores, paired comparisons between baseline and 3-, 6-, and 12-months FU were performed using the Wilcoxon signed-rank test. Minimal clinical important difference values are not yet available in literature or the PR25. Therefore, for each PRO score comparison, the effect size (ES) was calculated. The ES is calculated by dividing the standard

score (z score) by the square root of the sample size (N). Analyses were performed for the total population and after stratification for ADT. A P value < .05 was considered statistically significant. An ES of <0.30 was considered small, 0.30 to 0.49 moderate, and ≥0.50 large.[16] All analyses were performed using R version 4.1.2.

Results

The study included 425 patients with PCa patients within MOMENTUM who had completed radiation therapy treatment. An ATS workflow was adopted in 310 (72.9%) patients and an ATP-only workflow in the remaining 115 (27.1%) patients. Three months FU was reached by 365 patients, 6 months FU by 313 patients, and 12 months FU by 186 patients. PSA values were available for 423 (99.5%) patients at baseline, 271 (74.2%) patients at 3 months FU, 223 (71.2%) patients at 6 months FU, and 117 (62.9%) at 12 months FU. Prospective CTCAE data was available for 227 (53.4%) patients at baseline, 177 (48.5%) patients at 3 months FU, 120 (38.3%) patients at 6 months FU, and 62 (33.3%) at 12 months FU. In total, 362 (85.2%) patients consented to fill out PRO questionnaires. The response rate of the PRO questionnaires was 85.4% at baseline, 80.2% at 3 months, 78.6% at 6 months, and 72.6% at 12 months FU.

The median (range) age was 70 (51-85) years. Most patients had intermediate risk PCa (n = 337, 82,0%) followed by low-risk (n = 47, 11.4%) and high-risk (n = 27, 6.6%) according to the National Comprehensive Cancer Network risk groups (Table 1). Seventy-eight (18.4 %) patients received ADT.

A significant decline in was observed in median (IQR) PSA level from baseline to 12 months FU of 7.8 (5.6-10.6) ng/mL to 1.2 (0.7- 2.0) ng/mL in the non-ADT group and from 8.7 (5.9-13.0) ng/mL to 0.1 (0.1-0.4) ng/mL in the ADT group (Fig. 1 and Table E2).

Table 1 Baseline characteristics of patients with localized prostate cancer treated with 5 × 7.25 Gy on a 1.5T MR-Linac

Characteristic	No.
Age, median (range, y	70 (51-85)
cT-stage, n (%)	
cT1	162 (39.2)
cT2	230 (55.7)
cT3	21 (5.1)
Missing, n	12
ISUP grade, n (%)	
1	90 (21.2)
2	261 (61.6)
3	69 (16.3)
4	4 (0.9)
Missing, n	14
PSA, n (%)	
<10 ng/mL	291 (68.8)
10-20 ng/mL	120 (28.4)
>20 ng/mL	12 (2.8)
Missing, n	2
Risk group (NCCN), n (%)	
Low	47 (11.4)
Intermediate	337 (82.0)
High	27 (6.6)
Missing, n	14
ADT, n (%)	
No	347 (81.6)
Yes	78 (18.4)
Missing, n	0

Abbreviations: ADT = androgen deprivation therapy; cT-stage = clinical tumor stage; IQR = interquartile range; ISUP = International Society of Urologic Pathology; NCCN = National Comprehensive Cancer Network; PSA = prostate specific antigen.

Physician-reported toxicity

Grades 1 and 2 GI toxicity was significantly higher at 3 months (17.5% and 1.7%, respectively) compared with baseline (6.2% and 0.9%, respectively; P <.001; Table 2). At 6- and 12-months FU, no significant difference with baseline GI toxicity was observed. GU toxicity increased significantly from 32.2% for grade 1 and 4.8% for grade 2 at baseline, to a rate of 38.6% grade 1, 18.7% grade 2 and 0.6% grade 3 toxicity at 3 months (P <.001). No statistically significant difference in GU toxicity at 6 and 12 months compared with baseline was observed (Table 2). For the non-ADT patients, a significant increase of ED toxicity from 24.3% grade 1, 13.5% grade 2, and 2.2% grade 3 ED at baseline to 28.8% grade 1, 21.2% grade 2, and 3.8% grade 3 ED at 12 months FU (P = .034) was observed.

Patient-reported outcomes

For the QLQ-PR25 urinary symptoms domain score, a significant increase in median score from 8.3 (IQR, 4.1-16.6) at baseline to 12.4 (IQR, 8.3-24.8; P = .005; ES = 0.28) at 3 months, 12.4 (IQR, 8.3-20.8; P = .018; ES = 0.28) at 6 months, and 12.4 (IQR, 8.3-20.8; P = .001; ES = 0.43) at 12 months FU was observed (Fig. 2 and Table E3.5). Median bowel symptom domain scores did not change between baseline and all FU moments. After

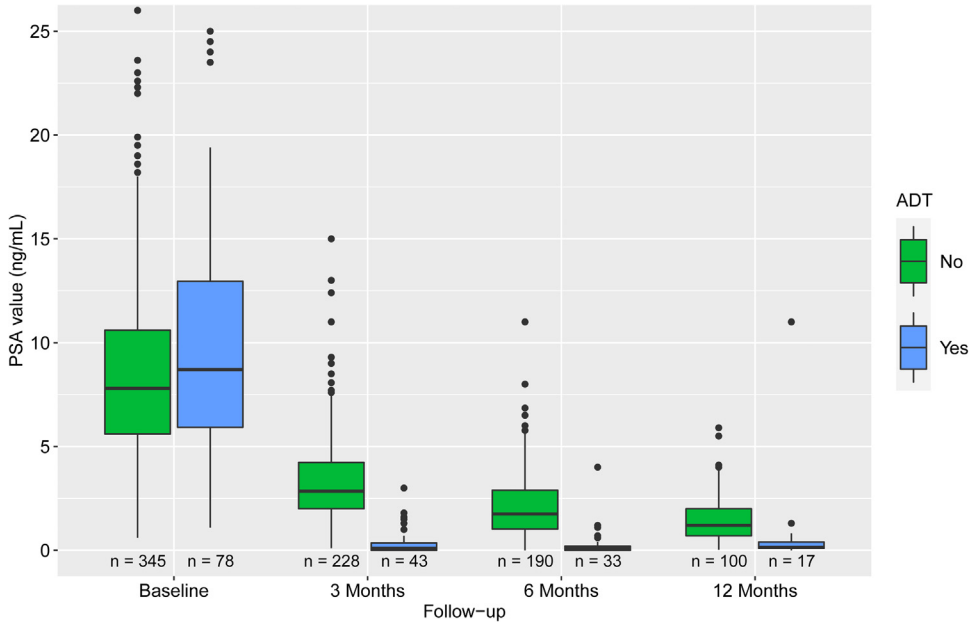

Figure 1 Boxplots of prostate specific antigen level (PSA) level stratified by androgen deprivation therapy (ADT) treatment at baseline and follow-up.

stratifying for ADT, no change was observed in the median sexual active domain score in the non-ADT group, but a significant decline in the median sexual function domain score from 83.5 (IQR, 64.7-91.8) at baseline to 75.3 (IQR, 58.5-83.5; P = .002; ES = 0.53) at 3 months FU and 75.0 (IQR, 58.3-83.4; P = .015; ES = 0.49) at 12 months FU.

The percentage of non-ADT patients who reported to be sexually active during the 4 weeks before filling out the

Table 2 Physician-reported toxicity using the CTCAE specified (summary of 17 items)

	CTCAE grade				*P* value*
	0	1	2	3	
GI toxicity					
Baseline n = 227	211 (93.0%)	14 (6.2%)	2 (0.9%)	-	
3 mo FU n = 177	143 (80.8%)	31 (17.5%)	3 (1.7%)	-	< .001
6 mo FU n = 120	105 (87.5%)	13 (10.8%)	2 (1.7%)	-	.178
12 mo FU n = 62	53 (85.5%)	8 (12.9%)	1 (1.6%)	-	.072
GU toxicity					
Baseline n = 227	143 (63.0%)	73 (32.2%)	11 (4.8%)	-	
3 mo FU n = 177	78 (44.1%)	66 (37.3%)	32 (18.1%)	1 (0.6%)	< .001
6 mo FU n = 120	77 (64.2%)	34 (28.3%)	9 (7.5%)	-	.503
12 mo FU n = 62	38 (61.3%)	16 (25.8%)	8 (12.9%)	-	.803
ED non-ADT patients					
Baseline n = 185	111 (60.0%)	45 (24.3%)	25 (13.5%)	4 (2.2%)	
3 mo FU n = 145	98 (67.6%)	34 (23.4%)	11 (7.6%)	2 (1.4%)	.118
6 mo FU n = 102	56 (54.9%)	31 (30.4%)	13 (12.7%)	2 (2.0%)	.052
12 mo FU n = 52	24 (46.2%)	15 (28.8%)	11 (21.2%)	2 (3.8%)	.034

Abbreviations: ADT = androgen deprivation therapy; CTCAE = Common Terminology Criteria for Adverse Events; ED = erectile dysfunction; FU = follow-up; GI = gastrointestinal; GU = genitourinary.

* For comparison with baseline. The highest grade of a given toxicity that occurred in a timeframe (3 months FU = 0-3 months after treatment; 6 months FU = 3-6 months after treatment; 12 months FU = 6-12 months after treatment).

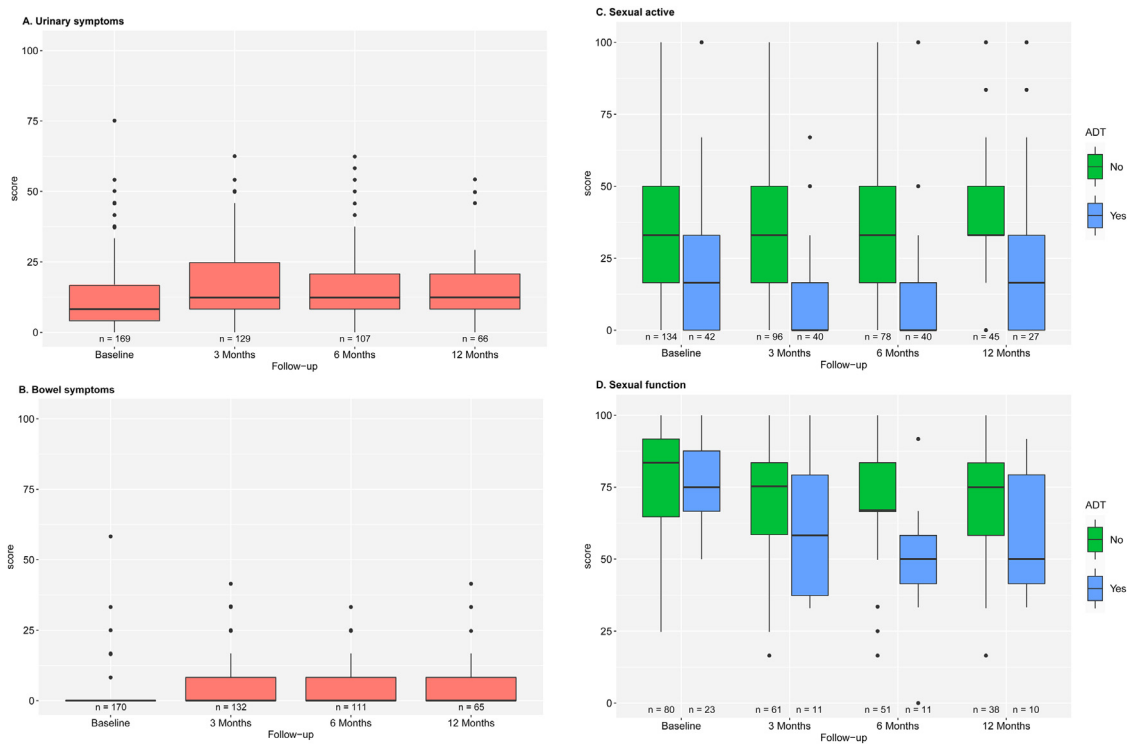

Figure 2 Boxplots of Quality of Life Questionnaire PR25 domain scores at baseline and follow-up. A, Urinary symptoms, B, bowel symptoms, C, sexual activity, and D, sexual function. Sexual activity and function domain are stratified for androgen deprivation therapy treatment. Sexual function domain conditional on being sexually active.

QLQ-PR25 questionnaire was 70.4% at baseline, 67.7% at 3 months, 69.2% at 6 months, and 84.4% at 12 months. The percentage of patients reporting "quite a bit" to "very much" difficulty in getting or maintaining an erection (if sexually active) increased from 21.7% at baseline to 24.6% at 3 months, 25.5% at 6 months, and 31.6% at 12 months (Fig. 3).

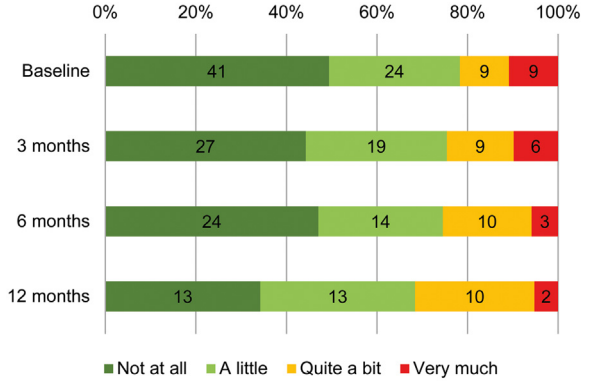

Figure 3 Distribution of answers to Quality of Life Questionnaire PR25 question: "Did you have difficulty getting or maintaining an Erection?" Nonandrogen deprivation therapy patients only. Question should only be answered if recipient has been sexually active during the past 4 weeks (at moment of filling out the Quality of Life Questionnaire PR25 questionnaire).

The QLQ-C30 function and symptom scales showed no significant deterioration between baseline and 3-, 6-, and 12-months FU. There was, however, a decline (improvement) in the fatigue domain score from 11.1 (IQR, 0.0-22.2) at baseline to 0.0 (IQR, 0.0-22.2; $P = .025$; ES = 0.20) at 12 months FU (Table E3.5).

Discussion

In this article, we have reported the first 3-, 6-, and 12-months FU results of 425 PCa patients treated with 5 × 7.25 Gy on 1.5T MR-Linac within the international, multicenter MOMENTUM study. These first results showed that treatment was effective and safe, with a significant and steep decline in PSA level up to 12 months FU and only one case of grade 3 GU toxicity and no grade ≥3 GI toxicity.

A transient but significant increase in cumulative GU and GI toxicity was reported at 3 months FU and a significant increase in ED toxicity for non-ADT patients was reported at 12 months FU to. Compared with baseline, no significant change in the QLQ-PR25 bowel and sexually active domains were observed at 3, 6, and 12 months FU. For the QLQ-PR25 urinary domain, a significant deterioration with a small ES was reported from baseline to 3, 6, and 12 months and a significant decline in the sexual function domain score at 6- and 12-

months FU was observed, with a large and moderate ES, respectively.

Our findings are in line with the results of Bruynzeel et al, who reported the first early results in 101 PCa patients who received 5 × 7.25 Gy on a low-field (0.35T) MR-linac.[6] Their patient group consisted of a higher risk population (4.0% low, 36.6% intermediate, and 59.4% high-risk) and they used a urethra-sparing technique. The QLQ-PR25 urinary and bowel domain scores were comparable to those observed in our study. Also, the cumulative incidence of grade ≥2 GU and GI toxicity were 23.8% and 5.0% at 3 months FU, respectively, and were in the same range as the grade ≥2 GU toxicity of 18.7% and GI toxicity of 1.7% in our study. In a subsequent article by the same research group, the PROs in the same patient cohort up to 1 year of FU were reported.[7] Similar to the QLQ-PR25 results in our study, the effect sizes for the difference in PROs between baseline and 3-, 6-, and 12-months FU for both the urinary and bowel domain were small. The high rate of ADT use (83.2%), as a result of the predominantly high-risk patients included, caused a significant and clinically relevant negative effect on sexual activity. Because only 33% of patients completed the questions on sexual function, this domain was not analyzed in their article.

In a meta-analysis by Jackson et al, in which the results of 32 stereotactic body radiation therapy (SBRT) studies (median dose per fraction: 7.25 [range, 5-10] Gy and median fraction number: 5 [range, 4-9]) were summarized, a cumulative incidence of early grade ≥2 GU toxicity of 16.0% and GI toxicity of 6.2% were observed. Additionally, the cumulative incidence of late grade ≥2 GU and GI toxicity were 13.0% and 5.4%.[17] However, the results are not directly comparable to our results, as the timeframe of acute toxicity was not always ≤3 months in the studies included in the meta-analysis. Furthermore, late toxicity went beyond 12 months FU and toxicity was graded using both the CTCAE (19 studies) and Radiation Therapy Oncology Group (RTOG)/EORTC grading (13 studies) systems.

More detailed information on acute toxicity after SBRT on a CT-guided linac is available from the PACE B trial.[18] In the PACE B trial, the intervention arm consisted of patients with localized low- and intermediate-risk (National Comprehensive Cancer Network) PCa, who received 5 × 7.25 Gy with an additional secondary CTV dose target of 40 Gy on a CT-guided linac (245 [59.0%] on a conventional linac and 170 [41.0%] on a CyberKnife system). Recommended CTV to PTV margins were 4 to 5 mm nonposterior and 3 to 5 mm posterior. None of the patients received ADT. The cumulative incidence of CTCAE grade ≥2 GU and GI toxicity was 30.8% and 15.7% at 3 months FU, respectively, which is higher compared with our results. The lower toxicity that is reported in our study may be a result of more accurate dose delivery due to the ability to perform online MR-guided ATP and ATS.

Because ADT has a detrimental effect on sexual activity and function, we have limited our analysis of sexual activity and function to non-ADT patients only.[19] We observed a significant decline in sexual function from baseline to 3 and 12 months. The effect sizes indicated a large and moderate effect, respectively, which emphasizes the clinical relevance of the domain score decline. The significant increase in CTCAE erectile toxicity at 12 months FU supports this finding. To get a more detailed picture of sexual function of these patients, we looked at the individual questions of the QLQ-PR25. Of the non-ADT patients who reported to have been sexually active over the last 4 weeks at the time of filling out the QLQ-PR25 questionnaire, the percentage of patients who reported to have "quite a bit" to "very much" difficulty in getting or maintaining an erection increased significantly from 21.7% at baseline to 31.6% at 12 months. Previous reports on ED after SBRT treatment for PCa showed a gradual decline in erectile function beyond 12 months FU up to 5 years after treatment. Therefore, longer FU and larger patient numbers are warranted to draw definitive conclusions regarding ED after MRgRT.[20]

Theoretical advantages of MRgRT include intrafraction motion monitoring and correction for interfraction prostate motion (translation and rotation) in case of applying an ATS procedure,[21] more accurate visualization of the dominant intraprostatic lesion for focal boosting,[22] visualization of neurovascular structures to allow sparing,[23] and the potential for MR biomarker-based adaptive treatment.[24] However, for MRgRT to become a cost-effective alternative to conventional CT-based EBRT, brachytherapy, or prostatectomy, a substantial reduction in toxicity is needed.[25] For this, comparative studies, preferably randomized controlled trials, are needed. The MIRAGE-trial is the first RCT comparing (low-field) MRgRT with conventional CT-guided radiation therapy and is currently ongoing.[26] An interim analysis showed promising results, including a significantly lower acute grade ≥2 GU and GI toxicity in patients who received 5 × 8 Gy on an MR-Linac with 2 mm PTV margins compared with patients treated on a CT-guided linac with 4 mm PTV margins (incidence of grade 2 GU toxicity: 11 [22.4%] vs 24 [47.1%], $P = .01$; incidence of grade ≥2 GI toxicity: 0 [0%], vs 7 [13.7%], $P = .01$.).[27] Furthermore, multiple prospective long-term registries are ongoing to collect FU data on toxicity and PROs in patients treated with MRgRT as well as conventional EBRT, brachytherapy, prostatectomy, and active surveillance, which allow for comparison between the various treatments.[9,28] Also, fast intrafraction MR scan acquisition, improved automatic contouring, and fast online and real-time adaptive replanning during beam-on need to be implemented to enable further margin reduction to reduce toxicity and to open up possibilities for extreme hypofractionation in 2 fractions feasible.[24,29-31]

We acknowledge that our study suffers from some limitations. First, the rate of missing CTCAE data was

substantial, which should be considered when comparing our results to literature. CTCAE data was prospectively registered, but not all radiation oncologists systematically documented the toxicity using the 17 predefined CTCAE items. Furthermore, not all patients had an in-person appointment with their radiation oncologist at all FU moments and the COVID-19 pandemic even further reduced the number of in person appointments. Currently, efforts are being made to increase the CTCAE reporting rate, such as CTCAE registration using paper forms handed out to the physician as well as real-time remote symptom monitoring by a dedicated app.[32] We expect that this will improve CTCAE registration. The gradual decline of data availability rate toward later FU moments, which is also present for PSA values and PROs, may be caused by a delay in data registration in the study database.

Second, although the highest grade of CTCAE toxicity between 0 and 3 months was recorded for the 3 months FU time point, CTCAE registration was only standardized at 3 months FU. Therefore, toxicity which settles before 3 months, may have been missed if not documented in the medical records. This should be considered when comparing our toxicity outcomes at 3 months FU with other studies, such as the series reported by Bruynzeel et al (standardized CTCAE registration at last fraction, 6-, and 12-weeks FU)[6] and the PACE B trial (standardized CTCAE registration at 2-, 4-, 8-, and 12-weeks FU).[18] Both studies report a peak in toxicity between 0- and 3-months FU, which substantially decreased at 3 months FU. In our current report it remains unknown to what extent toxicity occurred and resolved between 0- and 3-months FU and whether this was reported at 3-months FU, but the cumulative incidence is likely an underestimation.

Third, the response rates for the PRO questionnaires were high during follow-up. However, a group of patients did not receive the QLQ-PR25 questionnaire, because they were simultaneously enrolled in another prostate-specific prospective registry (Clinicaltrials.gov identifier NCT04228211) for which the QLQ-PR25 was replaced with the Expanded Prostate Cancer Index Composite (EPIC)-26.[28,33] The QLQ-PR25 and EPIC-26 are similar in terms of questions and domains, but not directly comparable. So, for these patients, PRO data was not lost, but they were not eligible for the QLQ-PR25 analyses. Finally, no PRO data are available on FU moments between baseline and 3 months FU (eg, directly after the final treatment fraction or at 1 month posttreatment). A transient deterioration of PRO scores during and shortly after radiation therapy may therefore have been missed.

Conclusions

The results presented in the current study show that the treatment of localized PCa with SBRT on a 1.5T MR-Linac is effective and safe. A transient but significant increase in the cumulative incidence of physician-reported GU and GI toxicity was reported at 3 months FU and a significant increase in physician-reported ED rates was reported at 12 months FU. Compared with baseline, no relevant deterioration in patient-reported bowel and sexual active domains was observed at 3-, 6-, and 12-months FU, however there was a significant decline in urinary domain scores at 3-, 6-, and 12-months and sexual function domain scores at 6- and 12-months FU. These data are useful for counseling patients on expected outcomes after MRgRT and can be used to inform study designs of future comparative-effectiveness studies.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.prro.2022.09.007.

References

1. de Muinck Keizer DM, Kerkmeijer LGW, Willigenburg T, et al. Prostate intrafraction motion during the preparation and delivery of MR-guided radiotherapy sessions on a 1.5T MR-Linac. *Radiother Oncol*. 2020;151:88-94.
2. Chin S, Eccles CL, McWilliam A, et al. Magnetic resonance-guided radiation therapy: A review. *J Med Imaging Radiat Oncol*. 2020;64:163-177.
3. Zachiu C, Denis De Senneville B, Willigenburg T, et al. Anatomically-adaptive multi-modal image registration for image-guided external-beam radiotherapy. *Phys Med Biol*. 2020:65.
4. Klüter S. Technical design and concept of a 0.35 T MR-Linac. *Clin Transl Radiat Oncol*. 2019;18:98-101.
5. Lagendijk JJW, Raaymakers BW, van Vulpen M. The Magnetic Resonance Imaging-Linac System. *Semin Radiat Oncol*. 2014;24:207-209.
6. Bruynzeel AME, Tetar SU, Oei SS, et al. A prospective single-arm phase 2 study of stereotactic magnetic resonance guided adaptive radiation therapy for prostate cancer: Early toxicity results. *Int J Radiat Oncol Biol Phys*. 2019;105:1086-1094.
7. Tetar SU, Bruynzeel AME, Oei SS, et al. Magnetic resonance-guided stereotactic radiotherapy for localized prostate cancer: Final results on patient-reported outcomes of a prospective phase 2 study. *Eur Urol Oncol*. 2021;4:628-634.
8. de Mol van Otterloo SR, Christodouleas JP, Blezer ELA, Akhiat H, Brown K, Choudhury A, et al. Patterns of Care, Tolerability, and Safety of the First Cohort of Patients Treated on a Novel High-Field MR-Linac Within the MOMENTUM Study: Initial Results From a Prospective Multi-Institutional Registry. *Int J Radiat Oncol Biol Phys*. 2021;111:867-875.
9. de Mol van Otterloo SR, Christodouleas JP, Blezer ELA, Akhiat H, Brown K, Choudhury A, et al. The MOMENTUM Study: An International Registry for the Evidence-Based Introduction of MR-Guided Adaptive Therapy [e-pub ahead of print]. *Front Oncol*. 2020:10. https://doi.org/10.3389/fonc.2020.01328, accessed January 11, 2023.
10. Identifier: NCT04075305, The MOMENTUM Study: The Multiple Outcome Evaluation of Radiation Therapy Using the MR-Linac Study, August 30, 2019. Clin Bethesda Natl Libr Med (US) n.d.

Available at: https://clinicaltrials.gov/ct2/show/NCT04075305. Accessed April 27, 2021.
11. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti−PD-1 antibody in cancer. *N Engl J Med*. 2012;366:2443-2254.
12. Aaronson NK, Ahmedzai S, Bergman B, et al. The European organization for research and treatment of cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85:365-376.
13. van Andel G, Bottomley A, Fosså SD, et al. An international field study of the EORTC QLQ-PR25: A questionnaire for assessing the health-related quality of life of patients with prostate cancer. *Eur J Cancer*. 2008;44:2418-2424.
14. Winkel D, Bol GH, Kroon PS, van Asselen B, Hackett SS, Werensteijn-Honingh AM, et al. Adaptive radiotherapy: The Elekta Unity MR-linac concept. *Clin Transl Radiat Oncol*. 2019;18:54-59.
15. Willigenburg T, de Muinck Keizer DM, Peters M, Claes A, et al. Evaluation of daily online contour adaptation by radiation therapists for prostate cancer treatment on an MRI-guided linear accelerator. *Clin Transl Radiat Oncol*. 2021;27:50-56.
16. Fritz CO, Morris PE, Richler JJ. Effect size estimates: Current use, calculations, and interpretation. *J Exp Psychol Gen*. 2012;141:2-18.
17. Jackson WC, Silva J, Hartman HE, et al. Stereotactic body radiation therapy for localized prostate cancer: A systematic review and meta-analysis of over 6,000 patients treated on prospective studies. *Int J Radiat Oncol Biol Phys*. 2019;104:778-789.
18. Brand DH, Tree AC, Ostler P, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): Acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. *Lancet Oncol*. 2019;20:1531-1543.
19. Sharifi N, Gulley JL, Dahut WL. Androgen deprivation therapy for prostate cancer. *J Am Med Assoc*. 2005;294:238-244.
20. Loi M, Wortel RC, Francolini G, Incrocci L. Sexual function in patients treated with stereotactic radiotherapy for prostate cancer: A systematic review of the current evidence. *J Sex Med*. 2019;16:1409-1420.
21. De Muinck Keizer DM, Kerkmeijer LGW, Maspero M, et al. Soft-tissue prostate intrafraction motion tracking in 3D cine-MR for MR-guided radiotherapy. *Phys Med Biol*. 2019;64:235008.
22. Kerkmeijer LGW, Groen VH, Pos FJ, Haustermans K, et al. Focal boost to the intraprostatic tumor in external beam radiotherapy for patients with localized prostate cancer: results from the FLAME randomized phase III trial. *J Clin Oncol*. 2021;39:787-796.
23. Teunissen FR, Wortel RC, Hes J, et al. Adaptive magnetic resonance-guided neurovascular-sparing radiotherapy for preservation of erectile function in prostate cancer patients. *Phys Imaging Radiat Oncol*. 2021;20:5-10.
24. Pathmanathan AU, van As NJ, Kerkmeijer LGW, et al. Magnetic resonance imaging-guided adaptive radiation therapy: A "game changer" for prostate treatment? *Int J Radiat Oncol Biol Phys*. 2018;100:361-373.
25. Hehakaya C, Van der Voort van Zyp JR, Lagendijk JJW, et al. Problems and promises of introducing the magnetic resonance imaging linear accelerator into routine care: The case of prostate cancer. *Front Oncol*. 2020;10:1741.
26. Ma TM, Lamb JM, Casado M, et al. Magnetic resonance imaging-guided stereotactic body radiotherapy for prostate cancer (mirage): A phase III randomized trial. *BMC Cancer*. 2021;21:1-13.
27. Kishan AU, Lamb J, Casado M, et al. Magnetic resonance imaging-guided versus computed tomography-guided stereotactic body radiotherapy for prostate cancer (MIRAGE): Interim analysis of a phase III randomized trial. *J Clin Oncol*. 2022;40(Suppl 6):255-255.
28. Identifier: NCT04228211, Utrecht Prostate Cohort for Cancer Treatment Intervention Studies and Long-term Evaluation (UPC), January 14, 2020. Clin Bethesda Natl Libr Med (US) n.d. Available at: https://clinicaltrials.gov/ct2/show/NCT04228211. Accessed December 21, 2020.
29. Kontaxis C, Bol GH, Kerkmeijer LGW, Lagendijk JJW, Raaymakers BW. Fast online replanning for interfraction rotation correction in prostate radiotherapy. *Med Phys*. 2017;44:5034-5042.
30. Kontaxis C, de Muinck Keizer DM, Kerkmeijer LGW, et al. Delivered dose quantification in prostate radiotherapy using online 3D cine imaging and treatment log files on a combined 1.5T magnetic resonance imaging and linear accelerator system. *Phys Imaging Radiat Oncol*. 2020;15:23-29.
31. Westley R, Hall E, Tree A. HERMES: Delivery of a speedy prostate cancer treatment. *Clin Oncol (R Coll Radiol)*. 2022;34:426-429.
32. Maguire R, McCann L, Kotronoulas G, et al. Real time remote symptom monitoring during chemotherapy for cancer: European multicentre randomised controlled trial (eSMART). *BMJ*. 2021;374:n1647.
33. Szymanski KM, Wei JT, Dunn RL, Sanda MG. Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. *Urology*. 2010;76:1245-1250.