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Safety and Tolerability of Online Adaptive High-Field Magnetic Resonance–Guided Radiotherapy

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Abstract

IMPORTANCE In 2018, the first online adaptive magnetic resonance (MR)-guided radiotherapy (MRgRT) system using a 1.5-T MR-equipped linear accelerator (1.5-T MR-Linac) was clinically introduced. This system enables online adaptive radiotherapy, in which the radiation plan is adapted to size and shape changes of targets at each treatment session based on daily MR-visualized anatomy.

OBJECTIVE To evaluate safety, tolerability, and technical feasibility of treatment with a 1.5-T MR-Linac, specifically focusing on the subset of patients treated with an online adaptive strategy (ie, the adapt-to-shape [ATS] approach).

DESIGN, SETTING, AND PARTICIPANTS This cohort study included adults with solid tumors treated with a 1.5-T MR-Linac enrolled in Multi Outcome Evaluation for Radiation Therapy Using the MR-Linac (MOMENTUM), a large prospective international study of MRgRT between February 2019 and October 2021. Included were adults with solid tumors treated with a 1.5-T MR-Linac. Data were collected in Canada, Denmark, The Netherlands, United Kingdom, and the US. Data were analyzed in August 2023.

EXPOSURE All patients underwent MRgRT using a 1.5-T MR-Linac. Radiation prescriptions were consistent with institutional standards of care.

MAIN OUTCOMES AND MEASURES Patterns of care, tolerability, and technical feasibility (ie, treatment completed as planned). Acute high-grade radiotherapy-related toxic effects (ie, grade 3 or higher toxic effects according to Common Terminology Criteria for Adverse Events version 5.0) occurring within the first 3 months after treatment delivery.

RESULTS In total, 1793 treatment courses (1772 patients) were included (median patient age, 69 years [range, 22-91 years]; 1384 male [77.2%]). Among 41 different treatment sites, common sites were prostate (745 [41.6%]), metastatic lymph nodes (233 [13.0%]), and brain (189 [10.5%]). ATS was used in 1050 courses (58.6%). MRgRT was completed as planned in 1720 treatment courses (95.9%). Patient withdrawal caused 5 patients (0.3%) to discontinue treatment. The incidence of radiotherapy-related grade 3 toxic effects was 1.4% (95% CI, 0.9%-2.0%) in the entire cohort and 0.4% (95% CI, 0.1%-1.0%) in the subset of patients treated with ATS. There were no radiotherapy-related grade 4 or 5 toxic effects.

(continued)

Key Points

Question What is the risk of high-grade acute radiotherapy-related toxic effects in patients treated with a 1.5-T magnetic resonance (MR)–equipped linear accelerator, specifically in patients treated with online adaptive radiotherapy, in which the radiation plan is adapted to the MR-visualized anatomy at each treatment session?

Findings In this cohort study of 1793 treatment courses (1772 patients) treated using 1.5-T MR-guided radiotherapy, the overall risk of acute high-grade toxic effects was 1.4%. The risk for the subgroup treated with the online adaptive approach was 0.4%.

Meaning The findings of this study suggest that online adaptive MR-guided radiotherapy is associated with a low risk of high-grade acute toxic effects.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

CONCLUSIONS AND RELEVANCE In this cohort study of patients treated on a 1.5-T MR-Linac, radiotherapy was safe and well tolerated. Online adaptation of the radiation plan at each treatment session to account for anatomic variations was associated with a low risk of acute grade 3 toxic effects.

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Introduction

The introduction of magnetic resonance (MR)-guided radiotherapy (MRgRT) has the potential to improve delivery precision of external beam radiotherapy. A hybrid treatment system, in which MR is integrated with a linear accelerator (MR-Linac), enables MR imaging (MRI) while the patient is on the treatment table.[1,2] The recent integration of a high-field (1.5-T) MRI with greater signal-to-noise ratios may improve the quality of the MRI.

On the 1.5-T MR-Linac, each treatment can be performed using 1 of 2 workflows: adapt-to-position (ATP) or adapt-to-shape (ATS)[3] (eFigure 1 in Supplement 1). With ATP, the planned dose distribution is shifted based on the daily anatomy, assuming that shape, volume, and relative position of the tumor and organs at risk (OAR) remain the same. This approach resembles conventional radiation, but uses MR instead of computed tomography to provide better soft tissue contrast. ATS, an online adaptive workflow, represents a more radical advancement. ATS treatment plans are optimized to real-time anatomy, including changes in shape, volume, and position of the tumor and OAR as seen on the MRI right before treatment (eFigure 1, eFigure 2 in Supplement 1). Theoretically, this increases the precision by which radiotherapy can be delivered and enables higher dose delivery to the target lesion while simultaneously sparing surrounding OARs. This might lead to improved local tumor control without increasing, and potentially reducing, the risk of radiotherapy-related toxic effects.

The introduction of MR-Linac has raised new patient and treatment complexities. For example, the magnetic field influences the trajectory of the charged electrons, which may affect the estimated dose distribution, known as the electron return effect.[4] MRI also has the potential for spatial distortions which could affect the accuracy of target identification and radiotherapy dose deposition. Finally, with ATS, the plan is adapted while the patient is on the treatment table, creating increased time pressure on the clinical team. Hypothetically, such pressure could impede the quality of treatment delivery. Therefore, the risk of high-grade acute radiotherapy-related toxic effects after MRgRT, in particular with daily online adaptation of the treatment plan using ATS, must be evaluated in large patient populations.

Novel radiotherapy technology has historically been introduced with minimal confirmatory evidence of safety. The Multi-Outcome Evaluation of Radiation Therapy Using the MR-Linac (MOMENTUM) study was initiated in 2019 to serve as a platform for evidence-based implementation of the MRgRT following R-IDEAL.[5] Initial patterns of care, tolerability, and safety of the 1.5-T MR-Linac have been reported previously.[6,7] Herein we report updated safety outcomes of the 1.5-T MR-Linac with a focus on patients treated with online adaptation (ie, ATS).

Methods

Study Design

The MOMENTUM study design (NCT04075305) has been published previously.[6,8] In brief, MOMENTUM is an ongoing prospective international observational cohort study for which participating centers received ethical approval by local or national ethical committees. Eligible

participants were aged 18 years or older and treated on the Unity MR-Linac (Elekta AB) at participating institutions. Written informed consent was obtained from all participants.

Radiotherapy plans were in accordance with standard practice. Follow-up was performed in routine care following local or national guidelines. The current study included all participants who were enrolled between February 2019 and October 2021. All patients had at least 3 months of follow-up. This report followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Data Collection

Data was collected by trained clinical research coordinators. At baseline, demographics and tumor characteristics were collected. Tumor sites were defined according to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* and represent the anatomical location of the target area. Targeted lymph nodes were considered as a separate group, independent of their anatomical location. Postradiotherapy, delivered treatment characteristics were collected and 3 months postradiotherapy, disease status, and information on toxic effects were collected.

Outcomes

Outcomes of interest included treatment patterns, tolerability and technical feasibility, acute high-grade toxic effects, and oncologic outcomes. Treatment patterns comprised radiotherapy modalities, fractionation, and dose. Each treatment course was classified as ATS, ATP, or mixed ATP-ATS. Differences between these treatment strategies were described above and were published previously.[3] If unexpected anatomic changes resulted in an alteration from the intended ATP to the ATS workflow, the session was classified as ATS.

Tolerability and technical feasibility were defined as patients being able to finish treatment as originally planned. Reasons to discontinue treatment on the MR-Linac were technical issues (including machine downtime or scheduling), physician choice (cancer progression or decline in performance status), or withdrawal by patient (patient intolerability or patient choice).

Acute high-grade toxic effects were defined as grade 3 or higher according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, occurring during or within the first 3 months after start of treatment.[9] The highest-graded toxic effect within each domain was recorded. Toxic effects included symptoms of any cause. The treating physician scored grade 3 or higher toxic effects as radiotherapy-related, possibly radiotherapy-related, or unrelated to radiotherapy. For calculation of radiotherapy-related toxicity rates, events classified as radiotherapy-related or possibly radiotherapy-related were included.

In some institutions, all patients had systematic, explicit graded toxic effects. In other centers, some patients had explicit graded toxic effects, while for others, occurrence of toxic effects was captured from free text. For the primary analysis on toxic effects, treatment courses without explicit grading of toxic effects in records were scored as no grade 3 or higher toxic effect. Considering its severity, we presumed that if a grade 3 or higher toxic effect was not explicitly reported, it had not occurred. As this might underestimate the true rate of toxic effects, we recalculated the acute grade 3 or higher toxic effect rate in patients with explicit grading of toxic effects. This analysis was considered to represent the upper bound of the true high-grade toxic effect rate.

Oncologic outcomes were overall survival (OS), progression-free survival (PFS), disease-free survival (DFS), clinical tumor control, and pathological tumor response, which was collected until August 2023. These were defined and assessed for clinically coherent subgroups; patients with primary prostate cancer, lymph node oligometastasis following prostate cancer, glioblastoma, primary rectal cancer, and pancreatic adenocarcinoma (eTable 1 in Supplement 1). OS, PFS, and cumulative incidence were measured from date of start of radiotherapy, and DFS was measured from date of surgery. For patients with multiple radiotherapy courses, OS and PFS were estimated from first course of radiotherapy. Patients were censored when they were alive at their last moment of

follow-up. Pathological tumor response and DFS were not determined for prostate cancer, lymph node metastasis, and glioblastoma as there was no surgical resection after radiotherapy.

Statistical Analysis

Descriptive statistics were used to describe patient, tumor, and treatment characteristics and presented as mean with SD, median with IQR, or frequency with percentage, depending on their distribution. Observed toxic effects rates were summarized as proportions with 95% CIs calculated using the Clopper-Pearson (exact) method in SPSS version 25 (IBM Inc). These descriptive results were presented for the complete study population, and for subgroups of patients treated with ATS and ATP. All time-to-event analyses were estimated using Kaplan-Meier in R version 4.2.2 (R Project for Statistical Computing).

Results

Study Population

A total of 1826 patients with 1847 MR-Linac treatment courses were included between February 2019 and October 2021. Of those, 54 participants (3.0%) were enrolled but did not receive any treatment on the MR-Linac. This was due to technical problems (3 [0.2%]), violation of radiotherapy constraints (5 [0.3%]), patient intolerance (2 [0.1%]), logistical problems (4 [0.2%]), changed tumor characteristics observed during planning (6 [0.3%]), patient frailty (2 [0.1%]), patient withdrawal prior to first day of treatment (18 [1.0%]), and unknown reasons (14 [0.8%]). A patient was considered to have had more than 1 treatment course if there was at least 6 months interval between treatment sessions. Overall, 1772 patients with 1793 treatment courses were included. Twenty patients (1.1%) underwent a second treatment course, and 1 patient (0.1%) underwent a third treatment course on the MR-Linac over the study period.

The median age of participants was 69 years (range, 22-94 years) and most patients were male (1384 patients [77.2%]) (eTable 2 in Supplement 1). Treatment was administered to a primary tumor in 1239 courses (69.1%), and 1299 courses (72.4%) were performed with curative intent. In total, 41 different tumor sites were treated (eTable 3 in Supplement 1). Tumor sites that were most frequently treated included prostate (745 [41.6%]), lymph node metastasis (233 [13.0%]), and brain (189 [10.5%]). In 1575 courses (87.9%), the entire treatment course was delivered on the MR-Linac. MRgRT was combined with other radiotherapy modalities in 180 courses (10.0%), including combinations with computed tomography–guided radiotherapy (CTgRT) or brachytherapy. In 20 of these courses (1.1%), changing to an alternative treatment was unplanned.

Adaptation Workflows

The majority of courses used the ATS workflow (1050 [58.6%]), followed by ATP (571 [31.8%]) and mixed ATP-ATS (101 [5.6%]) (**Table 1**). Workflow type was not captured in 71 courses (4.0%). Distribution of tumor sites and other characteristics varied between the workflows. The most frequently treated tumor sites were prostate (474 [45.1%]), lymph nodes (194 [18.5%]), and pancreas (97 [9.2%]) for ATS courses; prostate (219 [38.4%]), brain (150 [26.3%]), and liver (73 [12.8%]) for ATP courses; and prostate (33 [32.7%]), brain (26 [25.7%]), and oropharynx (15 [14.9%]) for mixed ATP-ATS courses. Furthermore, the use of concurrent chemotherapy, which can affect overall acute toxic effects rates, differed between the workflow types. Concurrent chemotherapy was used in 32 ATS treatment courses (3.0%), 107 ATP courses (18.7%), and 44 mixed ATP-ATS courses (43.6%).

Dose-Fractionation Schemes

The median (IQR) delivered dose to prostate targets was 36 Gray (Gy) (36-60 Gy) with a median number of fractions of 5 (5-20). The median (IQR) delivered dose to brain targets was 54 Gy (40-60 Gy) with a median number of fractions of 30 (15-30). For rectum targets, the median (IQR) delivered

Table 1. Baseline Characteristics of Patients Treated on the MR-Linac Stratified by Workflow

Characteristic	Treatment courses, No. (%) (N = 1793)			
	ATS (n = 1050)	ATP (n = 571)	Mixed ATP-ATS (n = 101)	Unknown workflow (n = 71)
Age, median (range), y	70 (25-91)	67 (22-94)	69 (32-91)	65 (22-86)
Sex				
Female	205 (19.5)	153 (26.8)	21 (20.8)	24 (33.8)
Male	845 (80.5)	418 (73.2)	80 (79.2)	41 (57.7)
Unknown/missing	0	0	0	6 (8.5)
Performance score (ECOG/KPSS)[a]				
0 / 90-100	587 (55.9)	276 (48.3)	46 (45.5)	34 (47.9)
1 / 70-80	187 (17.8)	137 (24.0)	25 (24.8)	14 (19.7)
2 / 50-60	45 (4.3)	20 (3.5)	8 (7.9)	7 (9.9)
3 / 30-40	1 (0.1)	3 (0.5)	2 (2.0)	0
4 / 10-20	0	0	0	0
Unknown/missing	230 (21.9)	135 (23.6)	20 (19.8)	16 (22.5)
Tumor type, No. (%)				
Distant metastasis	126 (12.0)	108 (18.9)	1 (1.0)	8 (11.3)
Lymph node metastasis	179 (17.0)	28 (4.9)	9 (8.9)	5 (7.0)
Primary tumor	688 (65.5)	418 (73.0)	89 (88.1)	44 (62.0)
Recurrence at primary site	49 (4.7)	16 (2.8)	2 (2.0)	5 (7.0)
Unknown/missing	8 (0.8)	1 (0.2)	0	9 (12.7)
Treatment intention				
Curative	751 (71.5)	407 (71.3)	89 (88.1)	52 (73.2)
Palliative	290 (27.6)	156 (27.3)	12 (11.9)	6 (8.5)
Missing	9 (0.9)	8 (1.4)	0	12 (16.9)
Tumor site				
Bladder	22 (2.1)	0	0	1 (1.4)
Brain	3 (0.3)	150 (26.3)	26 (25.7)	10 (14.1)
Breast	0	17 (3.0)	0	2 (2.8)
Esophagus	8 (0.8)	1 (0.2)	1 (1.0)	1 (1.4)
Gynecological[b]	20 (1.9)	5 (0.9)	3 (3.0)	7 (9.9)
Liver and intrahepatic bile ducts	32 (3.0)	73 (12.8)	1 (1.0)	2 (2.8)
Lung	16 (1.5)	7 (1.2)	0	1 (1.4)
Lymph nodes	194 (18.5)	28 (4.9)	7 (6.9)	4 (5.6)
Oropharynx	3 (0.3)	9 (1.6)	15 (14.9)	4 (5.6)
Pancreas	97 (9.2)	13 (2.3)	1 (1.0)	2 (2.8)
Prostate	474 (45.1)	219 (38.4)	33 (32.7)	19 (26.8)
Rectum	95 (9.0)	16 (2.8)	6 (5.9)	2 (2.8)
Other[c]	86 (8.2)	33 (5.8)	8 (7.9)	10 (14.1)
Unknown/missing	0	0	0	0
Treatment modality				
MR-Linac only	1013 (96.5)	453 (79.3)	81 (80.2)	28 (39.4)
Multimodal radiotherapy treatment as planned	28 (2.7)	109 (19.1)	13 (12.9)	10 (14.1)
Multimodal radiotherapy not as planned	6 (0.6)	6 (1.1)	7 (6.9)	1 (1.4)
Unknown/missing	3 (0.3)	3 (0.5)	0	32 (45.1)
Concurrent systemic treatment[d]				
Chemotherapy	32 (3.0)	107 (18.7)	44 (43.6)	6 (8.5)
Hormone treatment	95 (9.0)	100 (17.5)	22 (21.8)	7 (9.9)
Immunotherapy	14 (1.3)	10 (1.8)	2 (2.0)	0
No concurrent treatment	855 (81.4)	356 (62.3)	32 (31.7)	30 (42.3)
Unknown/missing	55 (5.2)	0	1 (1.0)	28 (39.4)

Abbreviations: ATS, adapt-to-shape; ATP, adapt-to-position; ECOG, Eastern Cooperative Oncology Group; KPSS, Karnofsky Performance Status Score; MR-Linac, magnetic resonance–equipped linear accelerator.

[a] Performance score was scored according to local practices which was either ECOG or KPSS.

[b] Combination of vagina, cervix, corpus uteri.

[c] A complete overview of all tumor sites including the other category can be found in eTable 3 in Supplement 1.

[d] Because patients can receive multiple concurrent systemic treatments, percentages do not add up to 100%.

dose was 25 Gy (25-25 Gy) with a median number of fractions of 5 (5-5). The median (IQR) delivered dose to lymph node targets was 35 Gy (35-45 Gy) with a median number of fractions of 5 (5-5). And for pancreatic targets, the median (IQR) delivered dose was 40 Gy (40-50 Gy) with a median fractionation of 5 (5-5). In total, 1215 courses (67.8%) were delivered with hypofractionation (more than 4 Gy per fraction), 356 courses (19.9%) with moderate hypofractionation (2 to 4 Gy per fraction), 175 courses (9.8%) with conventional fractionation (1.8 to 2 Gy per fraction), and 16 courses (0.9%) with hyperfractionation (less than 1.8 Gy per fraction). For 31 patients (1.7%), the dose-fractionation scheme was unavailable. No pattern in dose or fractionation between workflows was observed (eFigure 3 in Supplement 1).

Tolerability and Technical Feasibility

Treatment courses were not completed as initially planned in 44 of 1793 courses (2.5%). Patient intolerability was the cause of a discontinued MR-Linac course in 5 of 1793 total courses (0.3%), and in 1 of 1050 ATS courses (0.1%) (**Table 2**).

Safety

Medical files of 1697 courses (94.7%) were evaluated for toxic effects. No patients with multiple treatment courses experienced grade 3 or higher toxic effects. Therefore, in the following results sections, *patient* refers to individual treatment course. A total of 201 individual grade 3 or higher toxic effects were reported. Of these, 15 were deemed possibly radiotherapy-related, and 34 toxic effects radiotherapy-related (**Table 3**). The most common radiotherapy-related grade 3 events were dysphagia (9 events), esophagitis (7 events), and dry mouth (6 events). A detailed description of

Table 2. MR-Linac Treatment Tolerability and Technical Feasibility in Courses Stratified by Workflow[a]

Treatment plan delivery	Treatment courses, No. (%)[b] (N = 1793)				
	Total (n = 1793)	ATS (n = 1050)	ATP (n = 571)	Mixed ATP-ATS (n = 101)	Unknown workflow (n = 71)
As planned	1720 (95.9)	1034 (98.5)	554 (97.0)	93 (92.1)	39 (54.9)
Not as planned	44 (2.5)	15 (1.4)	17 (3.0)	8 (7.9)	4 (5.6)
Physician choice	11 (0.6)	5 (0.5)	3 (0.5)	1 (1.0)	2 (2.8)
Technical issues	9 (0.5)	4 (0.4)	2 (0.4)	3 (3.0)	0
Withdrawal by patient	5 (0.3)	1 (0.1)	3 (0.5)	0	1 (1.4)
Other	19 (1.1)	5 (0.5)	9 (1.6)	4 (4.0)	1 (1.4)
Unknown/missing	29 (1.6)	1 (0.1)	0	0	28 (39.4)

Abbreviations: ATS, adapt-to-shape; ATP, adapt-to-position; MR-Linac, magnetic resonance–equipped linear accelerator.

[a] Treatment tolerability and technical feasibility was defined being able to finish treatment as initially planned.

[b] As a result of rounding, percentages might not add up to 100%.

Table 3. Prevalence of High-Grade Toxic Effects According to Grade and Likelihood of Relatedness to Radiotherapy Treatment

Characteristic	Toxic effects, No. (n = 201)	Courses with toxicity reported, No.[a]	Toxic effect rate in all reviewed courses, % (95% CI) (n = 1697)[b]
Grade 3			
Unrelated to RT	138	88	5.2 (4.2-6.3)
Possibly related to RT	15	9	0.5 (0.2-1.0)
Related to RT	34	15	0.9 (0.5-1.5)
Unknown	8	6	0.4 (0.1-0.8)
Grade 4			
Unrelated to RT	3	2	0.1 (0.0-0.4)
Possibly related to RT	0	0	0
Related to RT	0	0	0
Grade 5			
Unrelated to RT	3	3	0.2 (0.0-0.5)
Possibly related to RT	0	0	0
Related to RT	0	0	0

Abbreviation: RT, radiotherapy.

[a] Numbers may exceed the total because some patients experienced multiple grades of toxic effects. A total of 109 patients experienced high-grade toxic effects.

[b] Toxicity rates were calculated by dividing the number of patients with toxic effects by the total number of patients of whom health files were reviewed.

patients with high-grade radiotherapy-related toxic effects can be found in eTable 4 in Supplement 1. Grade 4 events were reported 3 times in 2 patients, and grade 5 events were reported in 3 patients, but none were classified as radiotherapy-related or possibly radiotherapy-related.

On a patient level, at least 1 acute radiotherapy-related grade 3 toxic effect was observed in 23 of 1697 patients (1.4%; 95% CI, 0.9-2.0). In the subset of 1044 patients with explicit toxic effects grading (58.2%), acute radiotherapy-related grade 3 toxic effects were observed in 23 patients (2.2%; 95% CI, 1.4-3.3) (eTable 5 in Supplement 1).

At least 1 acute radiotherapy-related grade 3 toxic effects occurred in 4 of 1005 ATS treatment courses (0.4%; 95% CI, 0.1-1.0), in 13 of 562 ATP courses (2.3%; 95% CI, 1.2-3.9), and in 6 of 94 mixed ATP-ATS courses (6.4%; 95% CI, 2.4-13.4) (**Table 4**). In the sensitivity analysis, radiotherapy-related grade 3 toxic effects occurred in 4 of 500 ATS treatment courses (0.8%; 95% CI, 0.2-2.0), in 13 of 447 ATP courses (2.9%; 95% CI, 1.6-4.9), and in 6 of 71 mixed ATP-ATS courses (8.5%; 95% CI, 3.2-17.5) (eTable 6 in Supplement 1).

Oncologic Outcomes

For all patients, median (IQR) follow-up was 14 months (8-24 months). In total, 264 deaths were observed. OS varied across different tumor site groups (eTable 7, eFigure 4, and eFigure 5 in Supplement 1). One-year OS probability ranged from 44.0% (95% CI, 29.4%-65.7%) for patients with a pancreatic adenocarcinoma treated with definitive radiotherapy (without surgery) to 100% for patients with lymph node metastases following primary prostate cancer. Baseline of these subgroups can be found in the eTable 8 in Supplement 1. PFS varied between tumor site groups, with 1-year PFS probability of 23.3% (95% CI, 13.1%-41.4%) for patients with a pancreatic adenocarcinoma treated with definitive radiotherapy (without surgery) and 98.0% (95% CI, 96.9%-99.0%) for patients with prostate cancer (eTable 9, eFigure 6 in Supplement 1). Two-year cumulative incidence of biochemical progression was 0.3% (95% CI, 0.0%-0.7%) for patients with primary prostate cancer, and 32.6% (95% CI, 22.0%-41.8%) for patients with lymph node metastasis following prostate cancer (eTable 10, eFigure 7 in Supplement 1). The 1-year cumulative incidence of locoregional progression was 1.1% (95% CI, 0.0%-3.3%) for patients with rectal cancer and 12.8% (95% CI, 2.0%-22.4%) for patients with a pancreatic adenocarcinoma (eTable 10, eFigure 8 in Supplement 1). DFS and pathological tumor response of the neoadjuvant treatment courses can be found in eTable 11 in Supplement 1. Prostate specific antigen values following treatment can be found in eTable 12 in Supplement 1.

Discussion

In this large prospective international cohort of patients, our results showed 1.5-T MRgRT to be safe and well-tolerated for a broad variety of tumor sites. Overall, 1.4% of patients experienced at least 1 acute grade 3 radiotherapy-related toxic effect, and no grade 4 or 5 radiotherapy-related toxic effects were observed. Treatment with the novel ATS workflow accounting for anatomical variation was associated with a very low rate of acute grade 3 radiotherapy-related toxic effects (0.4%). High-field MRgRT is technically robust and well-tolerated by patients, considering that treatment was discontinued or not started due to patient-related causes in 0.3% and 0.1% of courses respectively.

Table 4. Prevalence of Radiotherapy-Related Toxic Effects Rate Stratified by Workflow

	Toxic effects rate in all reviewed patients (n = 1697)[a]	
Workflow	No./Total No.	% (95% CI)
ATP	13/562	2.3 (1.2-3.9)
ATS	4/1005	0.4 (0.1-1.0)
Mixed ATP-ATS	6/94	6.4 (2.4-13.4)

Abbreviations: ATS, adapt-to-shape; ATP, adapt-to-position.

[a] Toxic effects rates were calculated by dividing the number of patients with possibly radiotherapy-related and radiotherapy-related toxic effects by the total number of patients of whom health files were reviewed for toxic effects.

Analyses were conducted within the MOMENTUM study, an ongoing prospective cohort study used as an infrastructure for technical development studies, hypothesis testing, and comparative studies, following the R-IDEAL framework.[5] The current study provides early clinical outcomes in the first 1793 treatment courses of the MR-Linac within the first 4 years of clinical implementation. Such early and high-volume reporting, to our knowledge, is unprecedented within radiation oncology technological introduction. Within this first phase of the ongoing MOMENTUM study, we showed that treatment of patients on a 1.5-T MR-Linac is safe for various tumor sites. Treatment was well-tolerated across multiple global institutions despite concerns expressed with the introduction of this technology.[10,11] As experience and evidence grows, the technological potentials of the MR-Linac (eg, application of quantitative imaging, real-time motion monitoring, dose-escalation) will be further leveraged to potentially improve patient outcomes.

MRgRT has been previously evaluated using a 0.35T MR-Linac system. A phase III randomized clinical trial comparing MRgRT vs CTgRT in 156 patients with prostate cancer showed significantly reduced grade 2 or higher toxic effects compared with CTgRT.[12,13] However, for this analysis an online adaptive workflow, ie, ATS, was not used. ATS increases treatment time significantly.[14,15] The question still stands whether the additional use of time and resources for ATS is translated into clinical benefit, and more comparative studies need to be conducted.

Radiotherapy with conventional computed tomography–guided devices has shown varying rates of acute toxic effects in patients treated for various tumor types, from less than 1% gastrointestinal and genitourinary grade 3 or higher toxic effects in patients with prostate cancer to 3% grade 3 or higher toxic effects in patients treated for isolated local pancreatic cancer recurrence.[16-18] A large registry study including 1422 patients with extracranial oligometastases treated with CTgRT showed less than 1% grade 4 radiotherapy-related toxic effects and 5% grade 3 toxic effects.[19] In this registry, oligometastasis located in lymph nodes and lungs were most frequently treated. Considering that prostate and lymph nodes were the most frequently treated tumor sites in MOMENTUM, a proper comparison of toxic effect rates cannot be made. Although we hypothesize that toxic effects in general will decrease when using the MR-Linac with smaller margins, it is expected that differences in toxic effect rates for various tumor sites will remain. These toxic effects results should be interpreted as broadly overarching toxicity results, where only an overall conclusion of safety on a high field MR-Linac can be drawn. With 1.4% of patients with radiotherapy-related grade 3 toxic effects, and no grade 4 or 5 radiotherapy-related toxic effects, we suggest that toxicity seems at least comparable after treatment on the MR-Linac.

Overall survival and oncologic outcomes were consistent with research reporting on comparable subgroups treated with MRgRT[20] or CTgRT,[17,21-24] which further supports the safety of this treatment approach. It should be acknowledged that MOMENTUM has broad inclusion criteria and therefore reports an unselected population of patients.

The MOMENTUM study is an ongoing project. In future phases of the project, we will assess cohort- and treatment-specific toxic effects. Moreover, the platform will be used for hypothesis-testing studies (NCT04595019) and cohort-based trials according to the Trials Within Cohorts[25] design.

Limitations

A few limitations of this study should be acknowledged. First, MOMENTUM has more missing data than is typically seen in hypothesis-testing trials. This is a result of the study design of MOMENTUM, in which data are collected from clinical files. The use of clinical data has notable advantages, particularly less bias related to patient selection, and the results are more likely to be applicable to the routine care setting. The primary end point, data on toxic effects, was missing in 5.3% of patients. Because this rate is relatively low, we expect the potential effect of selection bias to be limited. Second, clinicians estimated the likelihood to which toxic effects were related to radiotherapy. This was not always straightforward, especially in the case of concurrent therapy or disease progression. Finally, because the study was observational, baseline characteristics and therapies differed between the cohorts treated using ATS, ATP, or mixed workflows. Given substantial confounding by indication,

we did decide not to formally test between these groups and only report on the toxic effects associated with the various workflows used.

Conclusions

MR-Linac treatment of a large population treated for various tumor sites is associated with low acute grade 3 radiotherapy-related toxic effects. The innovative ATS workflow is associated with a very low rate of acute high-grade radiotherapy-related toxic effects, indicating the safe utilization for clinical practice. Comparative (randomized) studies are needed to confirm whether innovative applications of MR-Linac technology will lead to improved patient outcomes.

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SUPPLEMENT 1.

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SUPPLEMENT 2.

Data Sharing Statement