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FULL PAPER

Magnetic resonance image-guided adaptive stereotactic body radiotherapy for prostate cancer: preliminary results of outcome and toxicity

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Objective: Using moderate or ultra-hypofractionation, which is also known as stereotactic body radiotherapy (SBRT) for treatment of localized prostate cancer patients has been increased. We present our preliminary results on the clinical utilization of MRI-guided adaptive radiotherapy (MRgRT) for prostate cancer patients with the workflow, dosimetric parameters, toxicities and prostate-specific antigen (PSA) response.

Methods: 50 prostate cancer patients treated with ultra-hypofractionation were included in the study. Treatment was performed with intensity-modulated radiation therapy (step and shoot) technique and daily plan adaptation using MRgRT. The SBRT consisted of 36.25 Gy in 5 fractions with a 7.25 Gy fraction size. The time for workflow steps was documented. Patients were followed for the acute and late toxicities and PSA response.

Results: The median follow-up for our cohort was 10 months (range between 3 and 29 months). The median age was 73.5 years (range between 50 and 84 years).

MRgRT was well tolerated by all patients. Acute genitourinary (GU) toxicity rate of Grade 1 and Grade 2 was 28 and 36%, respectively. Only 6% of patients had acute Grade 1 gastrointestinal (GI) toxicity and there was no Grade ≥ 2 GI toxicity. To date, late Grade 1 GU toxicity was experienced by 24% of patients, 2% of patients experienced Grade 2 GU toxicity and 6% of patients reported Grade 2 GI toxicity. Due to the short follow-up, PSA nadir has not been reached yet in our cohort.

Conclusion: In conclusion, MRgRT represents a new method for delivering SBRT with markerless soft tissue visualization, online adaptive planning and real-time tracking. Our study suggests that ultra-hypofractionation has an acceptable acute and very low late toxicity profile.

Advances in knowledge: MRgRT represents a new markerless method for delivering SBRT for localized prostate cancer providing online adaptive planning and real-time tracking and acute and late toxicity profile is acceptable.

INTRODUCTION

Prostate cancer is the second most common cancer worldwide in males and it is the fifth leading cause of cancer death.¹ The standard definitive treatment option for patients with localized prostate cancer is external beam radiation therapy (EBRT) combined with androgen deprivation therapy (ADT) and this treatment has similar long-term outcomes identical to radical surgery.^{2,3} Dose escalation resulted in significant improvements for relapse free survival after EBRT for prostate cancer patients in several trials.⁴⁻⁶ The reported α/β ratio for prostate cancer is low and it is suggested that hypofractionation can enhance the biological tumor dose without increasing late toxicity to critical structures.⁷ In relation to that, the

concept of moderate hypofractionation (2.5–4 Gy fraction sizes) or ultra-hypofractionation (>5 Gy fraction size) have been adopted by the most radiation oncology centers for treatment of localized prostate cancer.^{8,9} Ultra-hypofractionation is also known as stereotactic body radiotherapy (SBRT). Additionally, the reduced fractions has economical and logistical advantages as well as increased convenience of patients. Early and late gastrointestinal (GI) and genitourinary (GU) toxicity still remain a concerning issue in patients treated with both moderate as well as ultra-hypofractionated radiation schemes.^{10,11} Over the past decades, there have been many improvements in computing and imaging technologies and these improvements have led

to a number of technical advances in planning and delivery of prostate EBRT. Radiation therapy (RT) techniques have evolved from two dimensional to three-dimensional techniques (namely IMRT, IGRT, more recently SBRT) and localization strategies have evolved from external skin markings to bony localization, implanted fiducial markers, or volumetric imaging and finally, another technological development has fast approached, with MRI-guided RT (MRgRT).¹²

Organ changes during or between fractions of radiation treatment causes major problems for the safe intended dose delivery especially for the abdomen and pelvis located tumors and it is more important with hypofractionation. There is a substantial variability in bladder and rectum filling in prostate cancer patients during radiotherapy.^{13–15} The integration of a MRI system with a megavoltage radiation therapy system in a single unit has given the opportunity to get MR images during the treatment position. The MR images has facilitated the process of online image guidance and this has enabled decision-making if adaptive plans are required during the treatment. The targeted region can be continuously imaged during the dose delivery without increasing the exposed radiation dose.¹⁶

The MR-Linac (MRIdian, ViewRay Inc. Oakwood Village, OH) consists of a split, 0.35 T super-conductor low-field MRI system. It has a 70 cm bore opening and field of view (FOV) is 50 cm. The linear accelerator (LINAC) system for the radiation delivery consists of a 6 MV ring gantry and a double-focused multileaf collimator (MLC). Image guidance is provided by the volumetric imaging so the target volumes and organs at risk (OARs) changes is assessed. Real-time imaging with soft tissue tracking at single or multislices at 4 frames/second during treatment delivery allows visualizing the target volume(s) and OAR.

Our preliminary results on the clinical utilization of an online daily adaptive MRgRT for prostate cancer have been presented in this study. The workflow of MRgRT, dosimetric parameters, physician-scored toxicities during and after treatment and prostate-specific antigen (PSA) response has also been reported briefly.

METHODS AND MATERIALS

The ethical approval for this study was obtained from our Institutional Review Board (Acibadem MAA University, Medical Research Ethics Committee, Date and protocol number: 09.01.2020 and 2020-01/4). At Acibadem Maslak Hospital, which is the largest and affiliated university hospital of a health-care group, clinical MRgRT has been used for radiotherapy since September 2018 using the MRIdian system. Between September 2018 and March 2020, 60 patients diagnosed with localized prostate cancer were treated using MRgRT, 77 patients were treated using linear accelerators (only 1 SBRT patient) and 5 patients were treated using CyberKnife (3625 cGy in 5 fractions). 50 patients treated with ultra-hypofractionation were included in this retrospective study. The criteria for the inclusion in the study were: age >18 years, Karnofsky score >70%, stage cT1–T3 histologically proven prostate adenocarcinoma, no pathological lymph nodes on imaging studies, GTV <120 cc, no distant metastases, no

previous surgery other than transurethral resection, medically inoperable patients and International Prostate Symptom Score (IPSS) between 0 and 19. Patients with different fractionation schemes, post-operative patients, oligometastatic patients and a patient with an MRgRT boost after external beam radiotherapy were excluded. The patients were grouped according to the D'Amico risk classification and were defined as low-risk if they had Gleason score six and PSA level $\leq 10 \text{ ng ml}^{-1}$ and T1c/T2a disease; intermediate risk if they had Gleason score 7, a PSA level >10 and $\leq 20 \text{ ng ml}^{-1}$, or T2b disease, and high-risk if they had Gleason score ≥ 8 , or PSA $>20 \text{ ng ml}^{-1}$, or $\geq \text{T2c}$ disease.¹⁷ All risk categories were included in the study.

All of the patients treated with MR guidance were checked for contraindications (like claustrophobia, metallic implants, pace-makers etc.). Patients were staged by Gallium PET/CT scan if Gleason score is ≥ 7 . A CT simulation with a slice thickness of 1 mm was obtained for dose calculations. High resolution MR scanning (0.35T) with $1.5 \times 1.5 \times 1.5 \text{ mm}$ resolution was acquired based on a FISP (free precession) technique providing T_2/T_1 weighted image contrast. MR acquisition took 172 s and the field of view was $43 \times 45 \times 50 \text{ cm}$. Headrest, headphones, knee support, soft bed and flexible coils were used in the supine position on an MR compatible board for simulation and also during treatment. Before simulation and each fraction, patients were instructed to empty their bladder, followed by an intake of 500 ml water. Laxatives and low enema if needed were used for rectal preparations. The clinical target volume (CTV) and OAR were delineated by the treating physician according to the international contouring guidelines on the simulation MR-scan with a 3 mm uniform margin was used for PTV in all directions. In patients with low risk CTV consisted of the prostate gland only and for intermediate and high risk patients the base of seminal vesicles was included. The urethra was delineated from the MR images with an appropriate brush and PRV with a 2 mm margin was defined to spare urethra and decrease urinary toxicity in the first four patients. In those four cases, the tumor was not near the urethra and Gallium PET/CT scans and diagnostic MR were used for tumor localization. Doses to target volumes and OAR were evaluated using institutional constraints as shown in Table 1. Doses to OAR met our constraints that were established. Treatment planning was done with step and shoot IMRT technique (with a median number of 23 beams, range 13–23 beams and 60 segments, range 50–176 segments) and daily plan adaptation. A high resolution MR was obtained before each fraction and it was registered with the simulation MR. CTV contours reflecting the treatment day anatomy were manually modified by the attending physician. The baseline plan was recalculated according to the anatomy of day and a reoptimized plan was generated. The reoptimized plan prioritized coverage of the PTV and OAR constraints. The reasons for reoptimized adaptive plans were; inadequate target volume coverage, OAR dose violations, both insufficient coverage and OAR violations, presence of hotspots out of CTV and finally all of the above. After patient-specific quality assurance, positions were checked with a cine MR in the sagittal plane and treatment delivery was started. Sagittal MR images in single plane were used during treatment delivery for real-time gating and intrafractional monitoring. The

Table 1. Target volume and organ at risk dose constraints for treatment plans

Structure	Dosimetric index (Volume)	Acceptance criteria (Gy)
PTV	>95%	36.25
	<2%	38.78
	<Maximum	39.87
Rectum	<0.1 cc	38.06
	<1.0 cc	36.25
	<5.0 cc	34.43
	<10 cc	32.62
	<20 cc	25
	<5%	32
	<10%	28
	<35%	18
	<41%	17.50
Bladder	<0.1cc	38.06
	<1.0 cc	36.25
	<15 cc	32.62
	<40%	18.10
	<43%	17.50
Urethra	>95%	32.50
	Mean	34.50
	<Maximum	36.25
Penile bulb	<3 cc	14
	<Maximum	34

PTV, planning target volume.

SBRT consisted of 36.25 Gy in 5 fractions with a 7.25 Gy fraction size for all patients delivered every other day. The workflow steps were documented in minutes during treatment: set up, low-resolution/high-resolution scanning, recontouring, dose prediction, reoptimization with online QA, real-target cine MR imaging, unexpected disruptions and beam delivery. Our detailed analysis of online MRgRT workflow steps according to anatomical sites has been recently published elsewhere.¹⁸ The setup, low/high-resolution scanning, beam delivery steps were conducted by radiation therapy technologists; the recontouring step was done by treating physicians, reoptimization with online QA steps were conducted by medical physicists.

Patients were followed for the acute side-effects during treatment and late toxicities after treatment and Common Terminology Criteria for Adverse Events (CTCAE) scale v. 5.0 was used to record toxicities. The incidence and grade of GI symptoms (rectal hemorrhage, proctitis, diarrhea, fecal incontinence, pain) and GU symptoms (dysuria, urgency, frequency, cystitis, obstruction, nocturia, incontinence, hematuria) were scored by treating physicians. Patients were followed every 3 months for the outcome and late toxicities. Grading was reported as the

Table 2. The patients' characteristics

Characteristics	Number (%)
Median age (at the time of diagnosis)	73.5 (range, 50–84 years)
PSA levels before RT	7.4 ng ml ⁻¹ (range, 2.7–44.0)
TURP before RT	6 (12%)
Gleason sum	
6	15 (30%)
7	30 (60%)
≥8	5 (10%)
Clinical T stage	
T1	30 (60%)
T2	18 (36%)
T3	2 (4%)
Class of risk	
Low	6 (12%)
Intermediate	30 (60%)
High	14 (28%)
Androgen deprivation therapy	
Yes	14 (28%)
No	36 (72%)
IPSS score before RT	
Mild	46 (92%)
Moderate	4 (8%)
CTV volume (Median-Range)	58.9 (22.4–110.7)
Overall treatment time (minutes)	
Median (range)	45 (29–100)

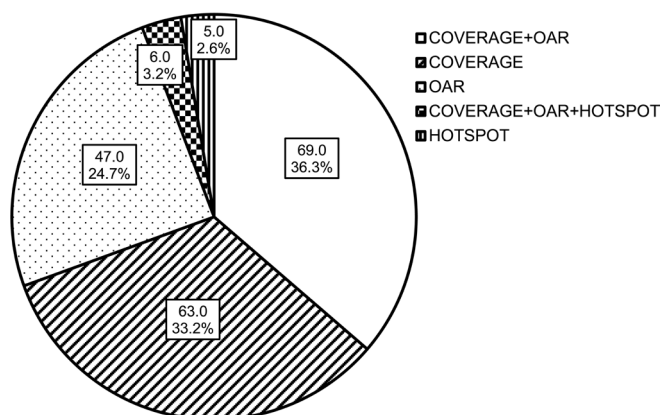
CTV, clinical target volume; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen; RT, radiation therapy; TURP, transurethral resection of the prostate.

maximum of any GU or GI symptom. IPSS and PSA levels were recorded before and after treatment at follow-up visits. IPSS scores were classified into three groups as defined by the American Urological Association (AUA) classification; which was mild if IPSS is between 0 and 7, moderate if IPSS is between 8 and 19 and severe if IPSS is between 20 and 35. No patients were lost to follow-up and all patients were alive at the time of analysis. Statistical analyses were conducted using SPSS software (v. 20.0; IBM, Armonk, NY).

RESULTS

Between September 2018 and March 2020, 50 patients with localized prostate cancer were treated with ultra-hypofractionation and MRgRT in 250 total fractions. The baseline patients' characteristics are summarized in Table 2. The median follow-up time was 10 months (range between 3 and 29 months). The median age was 73.5 years (range between 50 and 84 years). The median PSA before treatment was 7.4 ng ml⁻¹ (range between 2.7 and 44.0 ng ml⁻¹). Regarding IPSS scores, only 8% of our patients had moderate symptoms (IPSS 8–19) at baseline, 92% of patients

Figure 1. Reoptimized adaptive plan reasons. OAR, organ at risk.



had mild symptoms. Thirty percent of patients ($n = 15$) had a Gleason score of 6, 60% ($n = 30$) had a score of 7 and only 10% had Gleason eight or greater ($n = 5$). The clinical T stages were T1 in 30 patients (60%), T2 in 18 patients (36%), and T3 in two patients (4%).

Six patients (12%) were classified as low-risk prostate cancer, 30 patients as intermediate-risk (60%) and 14 patients (28%) as high-risk. 5 out of 30 intermediate-risk and 9 out of 14 high-risk patients received ADT. None of the patients in low risk group received ADT. 30 patients in the intermediate and high risk group refused ADT although it was suggested by physicians. Concomitant antiandrogen and a luteinizing hormone-releasing hormone (LHRH) agonist were used either as neoadjuvant or concomitantly.

MRgRT was well tolerated by all patients. Acute Grade 1 physician scored GU toxicity rate was 28% and acute Grade 2 GU toxicity was 36%. Increased frequency and urge were the most common early GU toxicity symptoms and a patient with acute Grade 2 toxicity needed a catheter insertion for urinary retention. Only 6% (3 out of 50) of patients had acute Grade 1 GI toxicity; and Grade 2 or higher acute GI toxicity was not reported. There were no treatment breaks attributable to acute GI or GU toxicity. To date, 12 patients (24%) experienced late Grade 1 GU toxicity, one patient (2%) experienced Grade 2 GU toxicity and 3 patients (6%) reported Grade 2 GI toxicity. Grade 3 or higher toxicity was not observed so far.

PSA response was determined with a median of two post-treatment measurements (range between 1 and 7) and the entire cohort has achieved a median PSA level of 1.6 ng ml^{-1} (range between 0.03 and 5.9 ng ml^{-1}). Due to the short follow-up, PSA nadir has not been reached yet in our cohort. 2 out of 50 patients (4%) developed biochemical relapse, both refused to receive ADT at the time of diagnosis. One patient underwent a Gallium PSMA PET/CT which revealed bone oligometastatic disease with a complete response at the primary 1 year after treatment. ADT and SBRT were suggested as a salvage treatment. The Gallium PSMA PET/CT scan of the other patient who had a pre-radiotherapy PSA level of 3.9 ng ml^{-1} and a Gleason

score of 7 revealed an uptake at the peripheral lobe of the prostate. The patient had a diagnostic MR and PSMA PET/CT that was used for tumor localization and target volume delineation. Recurrent adenocarcinoma of the prostate was proven by biopsy. This patient is among 4 out of 50 patients who were treated with urethral sparing; however, the location of the recurrent foci was far away from the urethra.

Median CTV volume was 58.9 cc (range between 22.4 and 110.7 cc). All patients were treated with an online adaptive approach. The plans of 76% (190/250 fractions) of all fractions have been reoptimized. The reasons for reoptimized adaptive plans were as follows (Figure 1): insufficient target volume coverage (33.2%), OAR dose violations (24.7%), both insufficient coverage and OAR violations (36.3%), presence of hotspots out of CTV (2.6%) and finally all of the above (3.2%). All adapted treatment plans passed the online QA. The duration of an MRgRT fraction for our cohort was median 45 min (range between 29 and 100 min). Median beam-on delivery time was 15 min and was approximately one-third of the total treatment duration. Distribution of workflow steps in detail is shown in Figure 2.

DISCUSSION

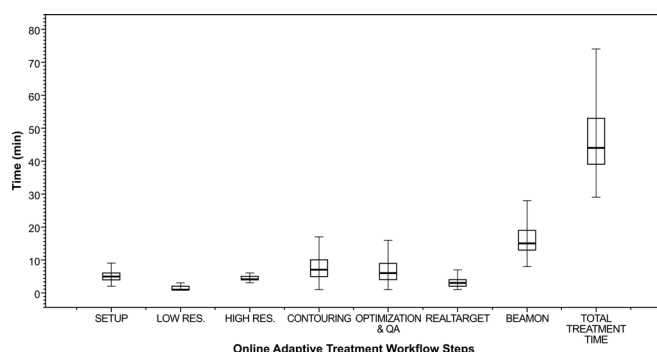
This study reports our experience with preliminary results, early PSA response, and toxicity of prostate SBRT using MRgRT.

SBRT for the treatment of localized prostate cancer has become an promising alternative to conventionally fractionated RT due to the significantly decreased treatment time, potential health-care savings, patient convenience and comparable control rates with acceptable toxicity.^{19,20}

There are published randomized trials comparing conventional and moderate hypofractionation RT for treating prostate cancer. The CHHiP trial suggested that hypofractionated RT (60 Gy in 20 fractions) is non-inferior to conventional fractionation (74 Gy in 37 fractions) and recommended this as a new standard of care for patients.⁸ The HYPRO trial showed that hypofractionated RT with 19 fractions of 3.4 Gy for patients with intermediate and high risk prostate cancer had comparable relapse free survival rates and toxicities.⁹ In a non-inferiority trial from RTOG (NRG Oncology RTOG 0415), the efficacy of 70 Gy in 28 fractions was not inferior to 73.8 Gy in 41 fractions in low-risk prostate cancer.²¹ These moderate hypofractionation regimens had changed clinical practice in European and American centers.

Ultra-hypofractionation (also referred as extreme-hypofractionation) is defined as EBRT with a fraction size $\geq 500 \text{ cGy}$. Two non-randomized studies compared conventional fractionation with ultra-hypofractionation and found that biochemical control rates are high and toxicities are low in low-risk patients.^{22,23} The HYPO-RT-PC compared ultra-hypofractionation with conventional fractionation in intermediate to high-risk prostate cancer patients and as the first randomized trial concluded that ultra-hypofractionation was not inferior with a median follow-up of 5 years.¹¹ Acute side-effects reported by HYPO trial were more pronounced but late toxicity was similar. The American Society for Clinical Oncology

Figure 2. Box plot time distribution of workflow steps.



(ASCO), the American Society for Radiation Oncology (ASTRO) and the AUA published an evidence based guideline in 2018 and recommended that moderate hypofractionation should be offered to all patients with localized prostate cancer choosing EBRT for treatment, independent of risk group since it confers similar outcomes and similar late toxicity rates. However, this recommendation is graded as “conditional” until randomized studies are done and provides evidence.²⁴ In a prospective clinical trial by King et al,²⁵ 1100 patients were included and 58% of patients were classified as low-risk, 30% as intermediate-risk, and 11% as high-risk. Kishan et al²⁶ evaluated the long-term outcomes associated with SBRT in a large cohort of 2142 males with low and intermediate risk prostate cancer across multiple institutions between 2000 and 2012. They have presented that SBRT is safe and disease control profile is favorable and there was not an increase in late toxicity.²⁶

In a large series by Katz et al,²⁰ biochemical control rates were excellent and toxicity was low and acceptable, the outcomes of long-term follow-up was similar with high dose rate brachytherapy reports and the 7.4% of patients were high-risk. A multicenter patient registry compared results of SBRT for the treatment of localized prostate cancer with single institutions’ results and found comparable early outcomes and the 7.6% of patients were in high-risk group.²⁷ The Multi-institutional Registry for Prostate Cancer Radiosurgery (RPCR, Inc.) has reported that SBRT is an alternative option to conventional radiotherapy for the treatment of localized prostate cancer with a series of 2000 patients and the 11% of patients were in high-risk group.²⁸ Based on these favorable outcomes, the NCCN guidelines have stated that SBRT “can be considered as an alternative to conventionally fractionated regimens at clinics with appropriate technology, physics, and clinical expertise” and can be considered for high and very high-risk patients if delivering longer courses would present a medical or social difficulty, although, the NCCN guidelines still states that “longer follow-up and prospective multi-institutional data are required to evaluate longer-term results”.²⁹ A number of randomized trials are underway and more information will be available, they are all comparing ultra-hypofractionation with conventional or moderate hypofractionation. Linear-quadratic model is valid at ultra-hypofractionation and HYPO-RT-PC study outcomes demonstrates an α/β ratio close to 3 Gy for both tumor and normal tissue.¹¹ When results from ongoing randomized studies like the HEAT (NCT01794403), the PACE

(ISRCTN17627211) and NRG GU005 trial (NCT03367702) comparing 7.25 Gy x 5 fractions (36.25 Gy) are reported, more information about the α/β ratio will be available.¹¹

Hypofractionation creates concerns about increased toxicity but with modern techniques, it is possible to ensure high-quality treatment. Motion during and between fractions are important factors during the definitive treatment of prostate cancer. Hypofractionated regimens necessitate a high level of accuracy and precision because errors in delivering dose may lead to problems in target coverage and the OAR dose. Daily IGRT improves the accuracy and precision of radiation treatment.³⁰ The most common imaging techniques used for IGRT during the treatment of prostate cancer include ultrasonography, portal imaging with fiducial markers, and fan-beam or cone-beam CT.³¹ Imaging the patient before treatment may not be adequate because of the intrafraction variations in rectal and/or bladder filling. MRgRT with improved soft-tissue contrast allows for superior visualization during treatment delivery itself. MRgRT also protects patients from undesirable radiation exposure during IGRT and with markerless visualization and tracking; it is non-invasive and has a potential of assessing treatment response. Real-time IGRT using cine-mode tracking, fast-planning that enables recontouring when the patient is lying on the table and replanning makes online adaptive RT easier. ViewRay MRIdian is the first clinical MRgRT LINAC system with 0.35 T magnetic field at the treatment isocenter and has been implemented in the routine clinical use at Acibadem Maslak Hospital as the first system in Turkey.

There are only a few studies in the literature regarding MRgRT for prostate cancer. Tetar et al³² from VU Amsterdam, reported their results with 140 patients treated with MRgRT and concluded that this innovative approach appeared to be feasible, but it necessitates extended time and has some logistical challenges. 10 patients were treated with the MR-Linac and 130 patients with tri-60Co system. The average duration of an MRgRT fraction was 45 min similar to our findings. Patient reported outcomes were assessed by a questionnaire after the last treatment and MRgRT was well-tolerated generally, patients mostly reported the noise sensations as disturbing.³² Alongi et al³³ reported feasibility, clinician- and patient-reported outcomes of 25 prostate cancer patients for MR-guided SBRT. Their preliminary data showed that MRgRT is safe and tolerable but more mature data are warranted. There was not any Grade ≥ 3 toxicity, 12% of patients reported Grade 2 acute GU toxicity, and only one patient had mild rectal pain. There were no Grade 3 toxicities in our cohort similar to their findings. In a prospective Phase 2 study, Bruynzeel et al³⁴ reported their early GI and GU toxicity after SBRT (36.25 Gy in five fractions) using MRgRT in patients with localized prostate cancer. 101 patients (only 4 patients with low-risk) were enrolled in the study and the maximum cumulative Grade ≥ 2 early GU toxicity was 23.8% and Grade ≥ 2 early GI toxicity was 5.0%. There was not any Grade 3 GI toxicity. The patient accrual of Phase 3 PACE B trial has been completed and included patients were mostly intermediate-risk patients, conventional or moderate hypofractionation and SBRT (5 fraction of 6.25 Gy) was compared and has recently reported GI and GU toxicity between two groups.³⁵

Table 3. Physician-reported early toxicities in ultra-hypofractionation studies

Study	IGRT	Genitourinary toxicity (%)			Gastrointestinal toxicity (%)		
		Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Widmark et al ¹¹	Fiducial-based	29	18	5	41	8	1
Alongi et al ³³	MRgRT	24	12	0	8	4	0
Bruynzeel et al ³⁴	MRgRT	77	20	0	53	3	0
Brand et al ³⁵	Fiducial-based	57	21	2	53	10	1
Current study	MRgRT	28	36	0	6	0	0

IGRT, image-guided radiation therapy; MRgRT, MR-guided radiotherapy.

In the SBRT group, 10 and 23% of patients experienced Grade ≥ 2 GU and GI toxicities, and 12 and 27% of the other group had Grade ≥ 2 toxicities. In contrast to HYPO-RT-PC trial, their results suggested that SBRT does not increase acute GI or GU toxicity. Comparison of above-mentioned studies in terms of acute toxicities are summarized in Table 3.

As ultra-hypofractionation studies report moderate toxicity, dose to the OAR should be reduced. Urethra-sparing techniques might minimize urinary symptoms, as reported from brachytherapy and standard-fractionated studies.^{36,37} There are reports underlining the value of delineating urethra as an OAR, but there are large variations regarding the use in practice and there is no reliable contouring guideline.³⁸ There are some limitations of urethral delineation; such as contouring from the sagittal sections, interobserver variability, dose heterogeneity in PTV due to optimization and being time-consuming. Thus, we discontinued delineating urethra after the fourth patient due to the aforementioned limitations.

PSA nadir as a determinant of outcomes like metastasis free and overall survival in prostate cancer patients treated by definitive RT has been studied in several trials.^{39,40} PSA nadir cut-off values in the literature varied between 0.1 and 0.7 ngml⁻¹.⁴⁰ PSA nadir

was not reached in our MRgRT cohort, and longer follow-up is necessary for adequate evaluation of this outcome.

Also, the analysis of our data coincided with the outbreak of Covid-19 pandemic, time in which hypofractionation was advocated, when feasible, by all guidelines as a measure to reduce overcrowding and spreading of the disease in radiation oncology departments, which made us appreciate the importance of non-invasive, short and safe treatments.

The limitations of our study are a small number of patients with a relatively short follow-up time for prostate cancer. However, this is one of the first studies reporting early outcome and toxicity results with ultra-hypofractionated MRgRT.

CONCLUSION

In conclusion, MRgRT represents a new method for delivering SBRT for localized prostate cancer. This technology has some advantages with better markerless soft-tissue visualization, online adaptive planning and real-time tracking. Although our study suggests that ultra-hypofractionation for prostate cancer has an acceptable acute and very low late toxicity profile, longer follow-up and prospective randomized studies are still warranted. Longer follow-up is also required to evaluate biochemical control rates.

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