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Authors

Courtney, Patrick Travis
Dong, Huiming
Lao, Yi
et al.

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BRIEF REPORT

Dosimetric Comparison of Magnetic Resonance Imaging-guided Versus Reduced-margin Computed Tomography-guided Stereotactic Body Radiation Therapy for Localized Prostate Cancer: Post Hoc Analysis of a Phase 3 Trial

Patrick Travis Courtney, MD, MAS,[a] Huiming Dong, PhD,[a] Yi Lao, PhD,[a] Jonathan Pham, PhD,[a] Michael Lauria, PhD,[a] Fang-I Chu, PhD,[a] Andrew J. Krupien, BSc,[a] Luca F. Valle, MD,[a] Daniel A. Low, PhD, DABMP,[a] James Lamb, PhD,[a] Michael L. Steinberg, MD,[a] Xiarong Sharon Qi, PhD,[a] Minsong Cao, PhD, DABR, FAAPM,[b] and Amar U. Kishan, MD[a]

[a]*Department of Radiation Oncology, University of California, Los Angeles, California; and* [b]*Department of Radiation Oncology, University of California, San Francisco, California*

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Purpose: The MIRAGE (Magnetic resonance imaging-guided versus computed tomography-guided stereotactic body radiotherapy for prostate cancer) trial (NCT04384770) showed that aggressive planning target volume (PTV) margin reduction, achieved by leveraging the advanced image-guidance of magnetic resonance imaging guided radiation therapy, led to lower toxicity after stereotactic body radiation therapy (SBRT) to the prostate compared with computed tomography guided SBRT (CTgSBRT) with a standard PTV margin. It is unknown whether the dosimetric benefit of reducing PTV margins alone—independent of the other components of advanced image guided radiation therapy that allowed margin reduction—would be predicted to replicate this decrease in toxicity.

Methods and Materials: We retrospectively replanned 16 CTgSBRT patients with 3- and 2-mm PTV margins from the 4 mm used in MIRAGE to compare with magnetic resonance imaging guided SBRT (MRgSBRT) patients' radiation therapy plans (n = 79), which used a 2-mm PTV margin. We compared target and organs-at-risk dosimetry and performed multivariable linear regression to control for potentially related covariates. We estimated normal tissue complication probability to assess the potential impact of PTV margin reduction on the risks of rectal and bladder toxicity.

Corresponding author: P. Travis Courtney, MD, MAS; E-mail: PCourtney@mednet.ucla.edu

Authors responsible for statistical analysis: Fang-I Chu, PhD; Email: FChu@mednet.ucla.edu, X. Sharon Qi, PhD; Email: XQi@mednet.ucla.edu, and P. Travis Courtney, MD, MAS; Email: PCourtney@mednet.ucla.edu

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X. Sharon Qi, Minsong Cao, and Amar U. Kishan contributed equally to this work.

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Results: Compared with MRgSBRT patients, replanned CTgSBRT patients had similar (3 mm) or statistically significantly improved (2 mm) rectal dosimetry and similar bladder dosimetry (2 mm). These trends persisted on multivariable linear regression. Normal tissue complication probability modeling demonstrated a statistically significant improvement in rectal toxicity whereby margin reduction from 4→3 mm and 4→2 mm resulted in relative reductions in toxicity probabilities of 56% and 78%, respectively. For bladder toxicity, reducing margins from 4 to 3 or 2 mm reduced the probability of bladder toxicity by 96%, although these relative differences were not statistically significantly.
Conclusions: Reducing PTV margins for CTgSBRT plans produced similar to improved organs-at-risk dosimetry compared with the clinical MRgSBRT plans, which in turn would be predicted to reduce toxicity when compared to larger margin CTgSBRT plans. This improvement in dosimetry could explain the reduction in modeled rectal toxicity, but the impact on bladder toxicity is unclear, with large, but nonsignificant relative differences underscoring our incomplete understanding of the drivers of post-SBRT urinary toxicity.

Introduction

The MIRAGE (Magnetic resonance imaging-guided versus computed tomography-guided stereotactic body radiotherapy for prostate cancer) trial (NCT04384770) demonstrated decreased acute and late genitourinary and gastrointestinal toxicities with magnetic resonance imaging (MRI)-guided stereotactic body radiation therapy (MRgSBRT) compared with computed tomography (CT)-guided stereotactic body radiation therapy (CTgSBRT) for localized prostate cancer, attributed to aggressive planning target volume (PTV) margin reduction utilized with MRgSBRT.[1,2] Aggressive PTV margin reduction was enabled through the enhanced image guided radiation therapy (IGRT) features of MRgSBRT, including real-time gating on the prostate itself, improved registration at treatment delivery, and improved contouring with direct MRI-MRI fusions. An unanswered question is whether similar PTV margin reductions with CTgSBRT would lead to similar toxicity reduction. This is important as there are current limitations with MRgSBRT, including potentially longer treatment times[1,3] and dosimetric tradeoffs as a result of the step-and-shoot intensity modulated radiation therapy technique necessitated by MRgSBRT devices[1,4] compared with techniques such as volumetric-modulated arc therapy (VMAT), though the gap is narrowing.[5] Although standard-of-care PTV margins with CTgSBRT remain 4-5 mm,[6] advances in IGRT such as triggered imaging with automatic beam hold[7] and enhanced cone beam CT technologies[8] might allow aggressive margin reduction with CTgSBRT, subsequently enabling improved organ-at-risk (OAR) dosimetry and lower toxicity than seen on the CTgSBRT arm of the MIRAGE trial.

We evaluated the dosimetric impact of reducing PTV margins in a cohort of patients treated on the CTgSBRT-arm of MIRAGE and compared their updated dosimetry with patients treated on the MRgSBRT-arm, and then used normal tissue complication probability (NTCP) modeling to estimate the predicted impact of any dosimetric improvements on toxicity. We hypothesized that aggressive PTV margin reduction in CTgSBRT would improve dosimetry and reduce the risk of toxicity.

Methods and Materials

Study design

This study is a post hoc analysis of the MIRAGE trial (NCT04384770), in which patients with localized prostate cancer were randomized to either MRgSBRT (n = 79) or CTgSBRT (n = 77) between May 5, 2020 and October 1, 2021. The radiation therapy prescription in both arms was 40 Gy in 5 fractions to the prostate and proximal seminal vesicles. Elective nodal irradiation (ENI) and a simultaneous integrated boost to the dominant intraprostatic lesion (DIL) at doses of 25 and 42 Gy in 5 fractions, respectively, were optional. The MRgSBRT-arm utilized a 2-mm isotropic PTV margin, and treatment was delivered using the MRIdian LINAC (ViewRay Systems) without adaptive radiation therapy utilizing a coplanar, step-and-shoot intensity modulated radiation therapy technique with a median number of beams of 15 (IQR, 15-17). The CTgSBRT-arm utilized a 4-mm isotropic PTV margin, and treatment was delivered using a TrueBeam (Varian Medical Systems) or Novalis Tx (Brainlab AG and Varian Medical Systems) LINAC utilizing a coplanar, VMAT technique with 2-4 arcs.

Retrospective radiation therapy replanning

We selected 16 representative CTgSBRT-arm patients in a semi-random manner to sufficiently incorporate all treatment possibilities (eg, prostate only or with ENI and/or DIL boost). Other factors, such as patient anatomy or dosimetry, were not considered in the selection process. Comparison between the 16 selected CTgSBRT patients and the unselected MIRAGE CTgSBRT patients did not reveal any significant differences in target and OAR dosimetry (Table E1). Each patients' radiation therapy plans were replanned utilizing 3- and 2-mm PTV margins (Fig. 1), following the trial protocol target coverage objectives ,OAR constraints, and optimization priorities (Table 1), for a total of 48 evaluable CTgSBRT plans. The ENI PTV margin was maintained at 4 mm per protocol. All 79 MRgSBRT-arm patients' radiation therapy plans as created on trial were included in the analysis.

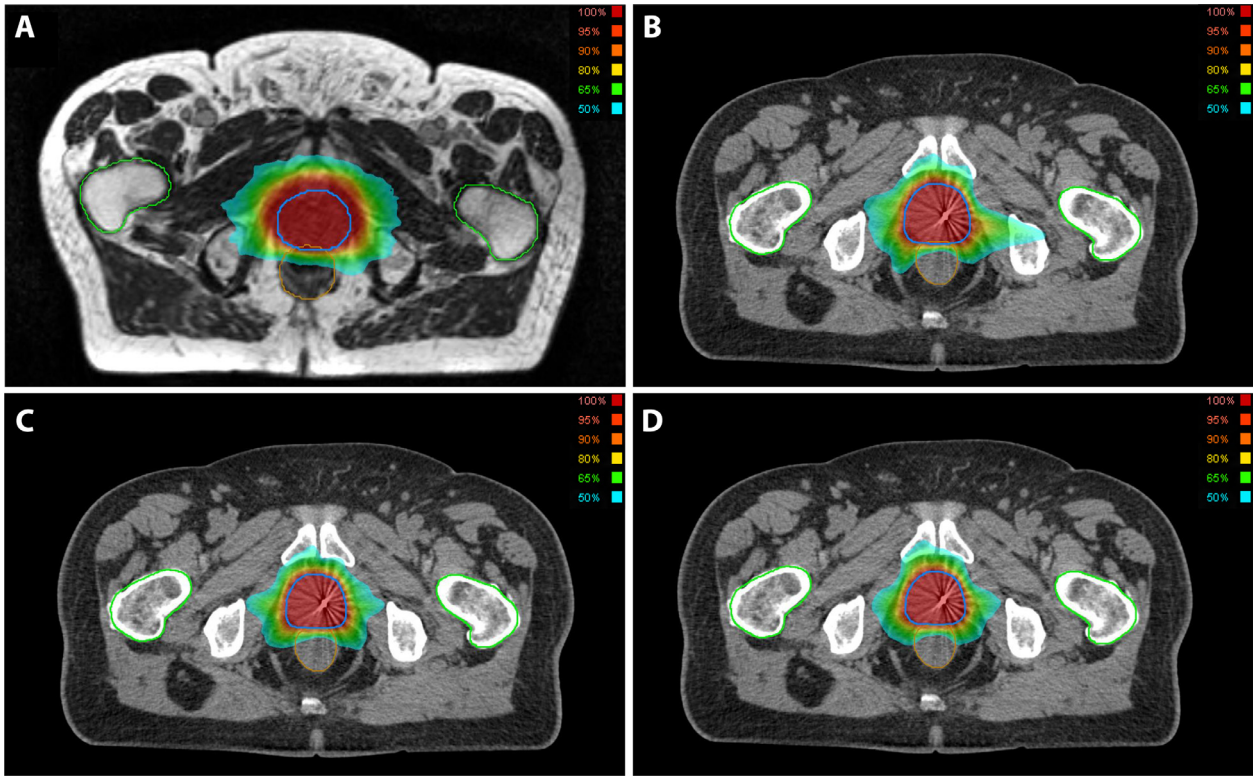

Fig. 1. Example radiation therapy plans for patients treated with MRgSBRT (patient 1) or CTgSBRT (patient 2). The 40 Gy planning target volume (PTV) is outlined in blue, the rectum is outlined in brown, and the femoral heads are outlined in green. (A) Axial view of MRgSBRT utilizing a 2-mm PTV margin per MIRAGE (Magnetic resonance imaging-guided versus computed tomography-guided stereotactic body radiotherapy for prostate cancer) protocol for patient 1. (B) Axial view of CTgSBRT utilizing a 4-mm PTV margin per MIRAGE protocol for patient 2. (C) Axial view of CTgSBRT retrospectively replanned utilizing a 3-mm PTV margin for patient 2. (D) Axial view of CTgSBRT retrospectively replanned utilizing a 2-mm PTV margin for patient 2. *Abbreviations:* CTgSBRT = computed tomography guided stereotactic body radiation therapy; MRgSBRT = magnetic resonance imaging guided stereotactic body radiation therapy.

Table 1 Dosimetric parameters and objectives per MIRAGE (Magnetic resonance imaging-guided versus computed tomography-guided stereotactic body radiotherapy for prostate cancer) trial protocol

Structure	Parameter	Objective
Target	1. Percentage of the 40 Gy volume receiving 40 Gy [$PTV_{40\ Gy}$(%)] 2. Percentage of the 25 Gy volume receiving 25 Gy [$PTV_{25\ Gy}$(%)]* 3. Percentage of the 42 Gy volume receiving 42 Gy [$PTV_{42\ Gy}$(%)]†	1. $PTV_{40\ Gy}$(%) >95% 2. $PTV_{25\ Gy}$(%) >95% 3. $PTV_{42\ Gy}$(%) >95%
Rectum	1. Percentage of rectum receiving 40 Gy [$V_{Rectum40\ Gy}$(%)] 2. Volume (cm^3) of rectum receiving 38 Gy [$V_{Rectum38\ Gy}$(cm^3)] 3. Percentage of rectum receiving 36 Gy [$V_{Rectum36\ Gy}$(%)]	1. $V_{Rectum40\ Gy}$(%) <5% 2. $V_{Rectum38\ Gy}$(cm^3) <2 cm^3 3. $V_{Rectum36\ Gy}$(%) <10%
Bladder	1. Percentage of bladder receiving 40 Gy [$V_{Bladder40\ Gy}$(%)] 2. Volume (cm^3) of bladder receiving 39 Gy [$V_{Bladder39\ Gy}$(cm^3)]	1. $V_{Bladder40\ Gy}$(%) <5% 2. $V_{Bladder39\ Gy}$(cm^3) <2 cm^3
Penile bulb	1. Mean dose (Gy)	1. Mean penile bulb dose <16 Gy
Small bowel	1. Volume (cm^3) of small bowel receiving 20 Gy [$V_{Small\ Bowel20\ Gy}$(cm^3)]*	1. $V_{Small\ Bowel20\ Gy}$(cm^3) <30 cm^3

Abbreviations: CTgSBRT = computed tomography guided stereotactic body radiation therapy; Gy = Gray; MRgSBRT = magnetic resonance imaging guided stereotactic body radiation therapy; PTV = planning target volume.

* In patients who received elective nodal irradiation 25 Gy in 5 fractions [CTgSBRT n = 6 (37.5%); MRgSBRT n = 18 (23.4%)].

† In patients who received a dominant intraprostatic lesion boost to 42 Gy [CTgSBRT n = 9 (56.2%); MRgSBRT n = 19 (24.7%)].

Statistical analysis

Dosimetric endpoints included those related to target coverage as well as rectal, bladder, penile bulb, and in patients receiving ENI [MRgSBRT n = 18 (22.8%); CTgSBRT n = 6 (37.5%)], small bowel dosimetry (Table 1). Since all dosimetric measures were obtained independently, we compared dosimetric parameters between the 3 CTgSBRT margin groups individually and the MRgSBRT group, as well as across CTgSBRT groups. With the assumption of independence on the obtained images to derive dosimetric measures, the comparisons of dosimetric parameters between groups were assessed via Wilcoxon rank-sum tests. On multivariable analysis, the relationship was evaluated via linear regression, controlling other covariates, including contoured prostate volume in cubic centimeters, rectal hydrogel spacer [MRgSBRT n = 32 (40.5%); CTgSBRT n = 8 (50%)], and DIL boost [MRgSBRT n = 19 (24.1%); CTgSBRT n = 9 (56.2%)]. Considering that the potential within-subject correlations among the images retrieved from the same patient in CTgSBRT groups and the limited capability of the small sample to account for such on multivariable analysis, the comparisons between groups were assessed via Wilcoxon signed-rank test, as a sensitivity analysis, to validate the results.

We performed NTCP modeling according to the Lyman−Kutcher−Burman model[9-11] and using the RADBIOMOD program[12] to estimate the impact of CTgSBRT margin reduction on the probability of rectal and bladder toxicity. For rectal toxicity, the outcome was grade ≥2 rectal toxicity or bleeding, and the parameters were n = 0.09, m = .013, and TD_{50} = 76.9 Gy.[12] For bladder toxicity, the outcome was symptomatic bladder contracture and volume loss, and the parameters were n = 0.5, m = 0.11, and TD_{50} = 80 Gy.[12] Complication probabilities were calculated for each CTgSBRT patient within each margin group and were compared between PTV margin groups using paired *t* tests.

We used R V4.4.1[13] for statistical analyses, assuming a 2-sided alpha of 0.05.

Results

Descriptive and regression analyses

Baseline cohort characteristics were overall similar between the selected CTgSBRT, unselected CTgSBRT, and MRgSBRT cohorts (Table 2). $PTV_{40\ Gy}$(%) was

Table 2 Cohort baseline characteristics

Characteristic	Selected CTgSBRT cohort (n = 16, %)	MRgSBRT cohort (n = 79, %)	Unselected MIRAGE CTgSBRT cohort (n = 61, %)
Age, median (IQR)	71 (67-76)	71 (68-75)	70 (67-77)
Self-identified Race/ethnicity			
Asian	1 (6.3)	9 (11.4)	7 (11.5)
Black	0 (0)	5 (6.3)	4 (6.6)
Hispanic	1 (6.3)	2 (2.5)	3 (4.9)
White	14 (87.5)	63 (79.8)	47 (77)
NCCN risk group			
Favorable Intermediate	2 (12.5)	14 (17.7)	13 (21.3)
Unfavorable Intermediate	5 (31.3)	40 (50.6)	20 (32.8)
High/very high	9 (56.2)	20 (25.3)	21 (34.4)
Imaging N+	0 (0)	5 (6.3)	7 (11.5)
Extracapsular extension on MRI[*,†]	9 (56.2)	19 (24.0)	12 (19.7)
Seminal vesicle invasion on MRI	2 (12.5)	11 (13.9)	9 (14.7)
Nodal irradiation	6 (37.5)	18 (22.8)	13 (21.3)
Dominant intraprostatic lesion boost[*,†]	9 (56.2)	19 (24.0)	13 (21.3)
Rectal hydrogel spacer	8 (50.0)	37 (46.8)	24 (39.3)
Prior TURP or HOLEP	2 (12.5)	5 (6.3)	1 (1.6)
Hip replacement	2 (12.5)	6 (7.8)	1 (1.6)

Abbreviations: CTgSBRT = computed tomography guided stereotactic body radiation therapy; HOLEP = holmium laser enucleation of the prostate; MRgSBRT = magnetic resonance imaging guided stereotactic body radiation therapy; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network; TURP = transurethral resection of the prostate.

[*] *P* value < .05 by Fisher Exact test or Wilcoxon rank-sum test (age) between selected CTgSBRT and MRgSBRT cohorts.

[†] *P* value < .05 by Fisher Exact test or Wilcoxon rank-sum test (age) between selected CTgSBRT and unselected MIRAGE (Magnetic resonance imaging-guided versus computed tomography-guided stereotactic body radiotherapy for prostate cancer) CTgSBRT cohorts (under assumption of independent observations).

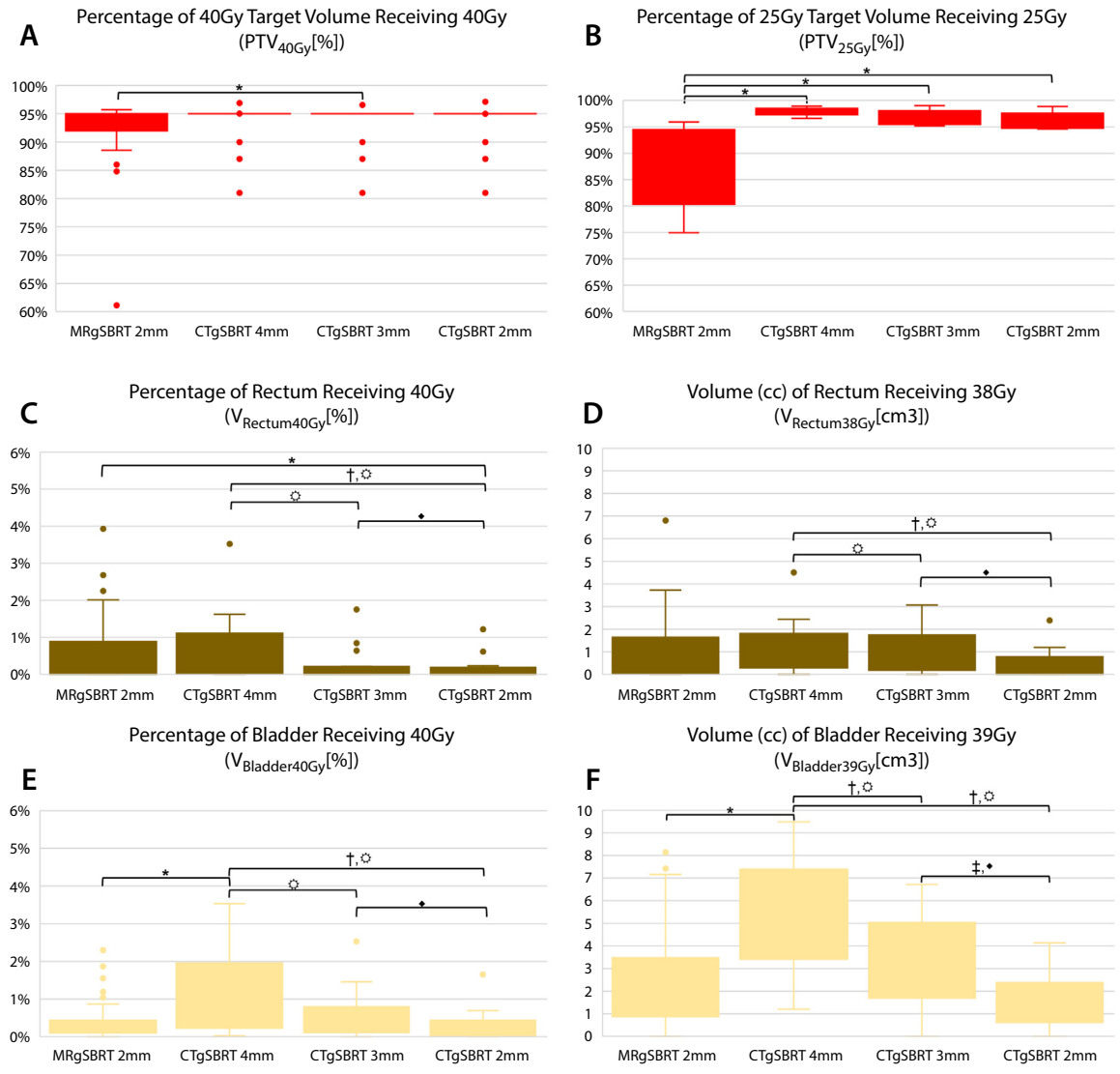

Fig. 2. Box-and-whisker plots of selected dosimetric parameters by planning target volume (PTV) margin group. **A.** Percentage of the 40Gy Target Volume Receiving 40Gy (PTV_{40Gy}[%]). **B.** Percentage of the 25Gy Target Volume Receiving 25Gy (PTV_{25Gy}[%]). **C.** Percentage of Rectum Receiving 40Gy ($V_{Rectum40Gy}$[%]). **D.** Volume (cc) of Rectum Receiving 38Gy ($V_{Rectum38Gy}$[cc]). **E.** Percentage of Bladder Receiving 40Gy ($V_{Bladder40Gy}$[%]). **F.** Volume (cc) of Bladder Receiving 39Gy ($V_{Bladder39Gy}$[cc]). *Abbreviations:*CTgSBRT = computed tomography guided stereotactic body radiation therapy; Gy = Gray; MRgSBRT = magnetic resonance imaging guided stereotactic body radiation therapy. [a]Among patients who received elective nodal irradiation 25 Gy in 5 fractions [CTgSBRT n = 6 (37.5%); MRgSBRT n = 18 (22.8%)]. *P value < .05 by Wilcoxon rank-sum test compared with MRgSBRT group. †P value < .05 by Wilcoxon rank-sum test (under assumption of independent observations) compared with 4-mm PTV margin CTgSBRT cohort (comparisons of 3- and 2-mm PTV margin CTgSBRT groups with 4-mm PTV margin CTgSBRT group only). ☼P value < .05 by Wilcoxon signed-rank test (under assumption of paired observations) compared with 4-mm PTV margin CTgSBRT cohort (comparisons of 3- and 2-mm PTV margin CTgSBRT groups with 4-mm PTV margin CTgSBRT group only). ‡P value < .05 by Wilcoxon rank-sum test (under assumption of independent observations) between 3- and 2-mm PTV margin CTgSBRT groups only. ⍰P value < .05 by Wilcoxon signed-rank test (under assumption of paired observations) between 3- and 2-mm PTV margin CTgSBRT groups only.

maintained compared with both the MRgSBRT group and across the CTgSBRT groups (Fig. 2A; Table 3). The 2 mm CTgSBRT group had a significantly lower $V_{Rectum40\ Gy}$(%) compared with the MRgSBRT group, and the remainder of the rectal dosimetric parameters were not significantly different between the 3 CTgSBRT groups and the MRgSBRT group (Fig. 2C,D). As previously reported,[1] the 4 mm CTgSBRT group had significantly worse bladder dosimetry compared with the MRgSBRT group; however, the 3- and 2-mm CTgSBRT

Table 3 Descriptive comparison of target and OAR dosimetry between prostate CT guided and MRI guided stereotactic body radiation therapy cohorts

Parameter*	MIRAGE trial-specified MRgSBRT 2-mm PTV Margin (n = 79)	MIRAGE trial-specified CTgSBRT 4-mm PTV Margin (n = 16)	Replanned CTgSBRT 3-mm PTV Margin (n = 16)	Replanned CTgSBRT 2-mm PTV Margin (n = 16)
Target volume				
Contoured prostate volume (cm^3)	43.8 (31.7-56.8)	50.0 (35.3-66.0)	50.0 (35.3-66.0)	50.0 (35.3-66.0)
40 Gy Volume (cm^3)	70.5 (52.6-87.3)	99.1 (81.6-120.9)†	91.5 (73.8-106.0)†,‡	73.3 (63.8-96.9)‡,§,‖
$V_{40\ Gy}$ (%)	95.0 (94.1-95.0)	95.0 (95.0-95.0)	95.0 (95.0-95.0)†	95.0 (95.0-95.0)
25 Gy Volume (cm^3)¶	609.7 (538.5-720.2)	632.0 (539.7-678.3)	632.0 (539.7-678.3)	632.0 (539.7-678.3)
$V_{25\ Gy}$ (%)¶	91.2 (81.3-94.4)	97.9 (97.6-98.3)†	96.9 (95.5-97.7)†	96.1 (94.8-97.1)†
Contoured DIL volume (cm^3)#	1.1 (0.6-3.3)	1.3 (0.4-1.9)	1.3 (0.4-1.9)	1.3 (0.4-1.9)
$V_{42\ Gy}$(%)#	97.8 (94.9-100)	100 (99.0-100)	100 (99.0-100)	99.9 (99.0-100)
Rectum				
$V_{40\ Gy}$ (%)	0.2 (0-0.9)	0.1 (0.01-1.1)	0.04 (0-0.2)‡	0 (0-0.2)†,‡,§,‖
$V_{38\ Gy}$ (cm^3)	0.8 (0.01-1.6)	1.2 (0.3-1.8)	0.7 (0.2-1.7)‡	0.2 (0.01-0.8)‡,§,‖
$V_{36\ Gy}$ (%)	2.5 (0.03-4.4)	3.0 (0.9-4.6)	1.9 (0.5-3.0)‡	0.7 (0.1-1.8)‡,§,‖
Bladder				
$V_{40\ Gy}$ (%)	0.3 (0.1-0.4)	0.9 (0.3-1.9)†	0.5 (0.1-0.8)‡	0.2 (0.02-0.4)‡,§,‖
$V_{39\ Gy}$ (cm^3)	1.9 (0.9-3.6)	4.9 (3.4-7.4)†	2.9 (1.8-4.9)‡,§	1.5 (0.6-2.4)‡,§,‖,**
Small bowel V_{20cm3} (cm^3)¶	24.0 (17.4-29.3)	24.7 (20.9-28.6)	20.8 (19.0-27.0)	18.1 (14.9-25.8)
Penile bulb mean dose (Gy)	2.7 (2.3-4.5)	4.6 (2.3-6.6)‡	4.7 (2.4-6.0)‡	4.3 (2.3-5.0)‡,‖

Abbreviations: CT = computed tomography; CTgSBRT = computed tomography guided stereotactic body radiation therapy; DIL = dominant intraprostatic lesion; MRgSBRT = magnetic resonance imaging guided stereotactic body radiation therapy; MRI = magnetic resonance imaging; OAR = organ-at-risk; PTV = planning target volume.

* Median (IQR).

† *P* value < .05 by Wilcoxon rank-sum test compared with MRgSBRT group.

‡ *P* value < .05 by Wilcoxon signed-rank test (under assumption of paired observations) compared with 4-mm PTV margin CTgSBRT cohort (comparisons of 3- and 2-mm PTV margin CTgSBRT groups with 4-mm PTV margin CTgSBRT group only).

§ *P* value < .05 by Wilcoxon rank-sum test (under assumption of independent observations) compared with 4-mm PTV margin CTgSBRT cohort (comparisons of 3- and 2-mm PTV margin CTgSBRT groups with 4-mm PTV margin CTgSBRT group only).

‖ *P* value < .05 by Wilcoxon signed-rank test (under assumption of paired observations) between 3- and 2-mm PTV margin CTgSBRT groups only.

¶ Among patients who received elective nodal irradiation 25 Gy in 5 fractions [CTgSBRT n = 6 (37.5%); MRgSBRT n = 18 (22.8%)].

Among patients who received a dominant intraprostatic lesion boost to 42 Gy [CTgSBRT n = 9 (56.2%); MRgSBRT n = 19 (24.1%)]. Refers to the percentage of the contoured 42 Gy volume receiving 42 Gy.

** *P* value < .05 by Wilcoxon rank-sum test (under assumption of independent observations) between 3- and 2-mm PTV margin CTgSBRT groups only.

bladder dosimetric parameters were not significantly different from the MRgSBRT group (Fig. 2E,F). In patients who received ENI, all CTgSBRT margin groups had significantly improved $PTV_{25\ Gy}$(%) (Fig. 2B) and not significantly different $V_{Small\ Bowel20\ Gy}$(cm^3) compared with MRgSBRT patients, and $PTV_{25\ Gy}$(%) was similar across the CTgSBRT. In patients receiving a DIL boost, there were no significant differences in DIL volume or coverage between the CTgSBRT groups and the MRgSBRT group, nor across the CTgSBRT groups. In the sensitivity analysis utilizing Wilcoxon signed-rank testing, all rectal and bladder dosimetric parameters were significantly lower across decreasing PTV margin group. These trends persisted on multivariable linear regression (Table E2).

NTCP modeling

Compared with the mean rectal toxicity probability of the 4-mm margin group, the 3-and 2-mm groups had 56% and 78% relative reductions in toxicity probability, respectively, and these differences were significant ($P = .004$ and $P = .043$, respectively) (Fig. 3). Compared with the mean bladder toxicity probability of the 4-mm margin group, both the 3- and 2-mm groups had a 96% relative reduction in toxicity probability, though these were not statistically significant ($P = .33$ and $P = .12$, respectively). To further assess the NTCP model result and its sensitivity, we evaluated NTCP over a range of parameters derived from published literature.[12,14,15] Consistent trends were observed across all margin groups.

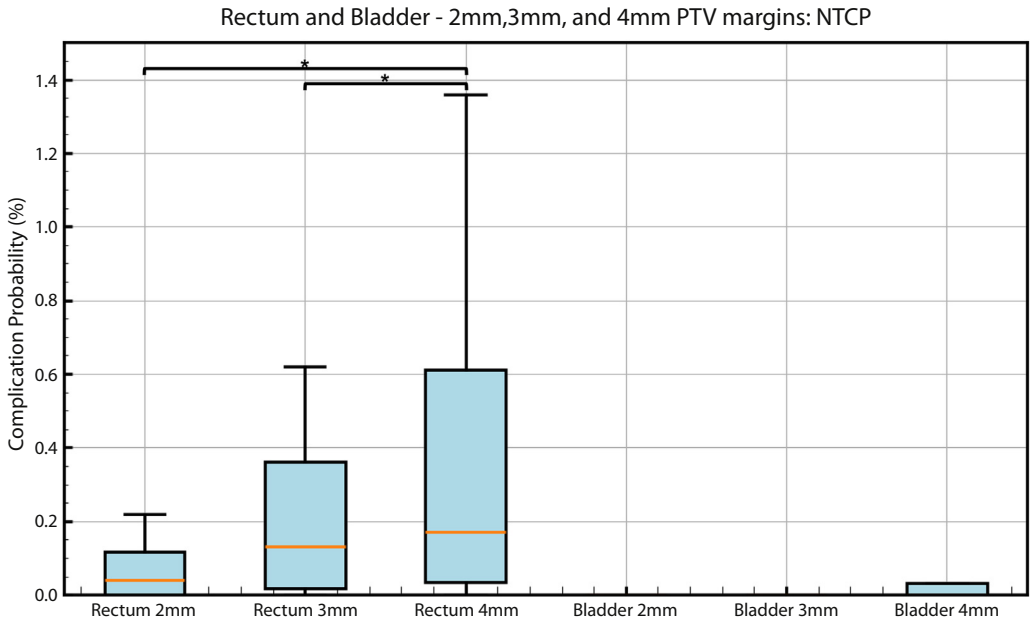

Fig. 3. Box-and-whisker plots of rectum and bladder complication probabilities by each CTgSBRT planning target volume (PTV) margin group according to normal tissue complication probability (NTCP) modeling. *P value < .05 by paired t test. *Abbreviation:* CTgSBRT = computed tomography guided stereotactic body radiation therapy.

Discussion

In this post hoc analysis of the MIRAGE trial, we found that reducing CTgSBRT PTV margins not only rectified the inferior bladder dosimetry seen in the MIRAGE trial CTgSBRT-arm, but more broadly resulted in equivalent to superior OAR dosimetry compared with MIRAGE MRgSBRT-arm patients while maintaining or improving prostate and nodal target coverage. Additionally, target coverage was similar across all CTgSBRT margin groups, which is an integral component toward maintaining oncologic efficacy while aggressively reducing PTV margins in prostate CTgSBRT. Furthermore, we demonstrated with NTCP modeling that CTgSBRT PTV margin reduction significantly reduces the probability of rectal toxicity. There was an effect bladder toxicity probability as well; however, these were not statistically significant differences because of large variance, and likely overestimate the effect size based on the observed urinary toxicity on the MRgSBRT-arm of the MIRAGE trial. Together, this suggests that bladder dosimetry alone likely does not reliably predict post-SBRT urinary toxicity, and reductions in bladder dose do not completely explain the results of the MIRAGE trial.

The PTV margin accounts for various components of radiation therapy delivery, including motion management, setup uncertainty, and contouring uncertainty. Advances in IGRT, such as MRgSBRT, can improve some, or all, aspects of these components, which in turn can allow for PTV margin reduction. These improvements do not just enable PTV margin reduction in silico, but should also improve actual dose delivery, for example, through improved setup, more accurate contouring, and gating. For instance, prior analysis of MIRAGE MRgSBRT-arm patients suggested that motion management remains key in mitigating toxicity even among patients treated with MRgSBRT.[16] However, the improved dosimetry afforded by PTV margin reduction—independent of other components that allow this margin reduction—is likely a key mediator of the reduced toxicity seen with aggressive margin reduction. This study supports this hypothesis, particularly with rectal toxicity, given the results of NTCP modeling. Interestingly, the effect on urinary toxicity is likely an overestimate, and was not statistically significant because of large variations. This uncertainty around urinary toxicity may be the result of clinical factors such as contouring inconsistencies or limitations of the NTCP model itself. It is also possible that other genitourinary OARs, such as the urethra or genitourinary diaphragm, may be affected by PTV margin reduction and subsequently impact the NTCP results. In the case of the former, MIRAGE mandated contouring of the prostatic urethra, which we assume would not be significantly impacted by PTV margin reduction. Furthermore, the trial-specified constraint for the urethra was a maximum point dose, and the ability to meet this constraint is not anticipated to be impacted by PTV margin reduction. For the latter, genitourinary diaphragm dosimetry was not specifically measured, as this was not a planning parameter nor OAR tracked in MIRAGE, and to our knowledge, there are no data clearly demonstrating an association between genitourinary diaphragm dosimetry and genitourinary toxicity[17] nor existing NTCP models for this structure.[15]

Altogether, these data suggest that improvements in plan dosimetry, mediated by aggressive PTV margin reduction, would likely lead to reduced urinary and rectal toxicity after prostate SBRT. A caveat is that the choice of PTV margin is not arbitrary and relies on uncertainties discussed above. The 2-mm CTgSBRT PTV margin used in this in silico study are considerably narrower than what is used in broad practice, whereas the 2-mm MRgSBRT PTV margin used in MIRAGE is now standard practice. Prospective data from ongoing clinical trials evaluating margin reduction enabled by advanced IGRT for CTgSBRT delivery are eagerly anticipated.

Despite notable drawbacks to MRI guided compared with CT guided radiation therapy, the reverse is also true. First and foremost is the superior real-time gating with MRgSBRT,[16] with a frequency of imaging for motion management that significantly exceeds what is typically available with CTgSBRT and allows direct tracking of the prostate itself, rather than proxies of prostate position. CTgSBRT requires fiducial marker placement, which is not without financial cost and risks,[3,18] and may only provide an indirect surrogate of prostate position, which is less accurate when tracking compared with real-time gating on the prostate itself enabled with MRgSBRT. Additionally, VMAT technology may eventually be introduced onto MRgSBRT devices, which may equalize some of the treatment technique-related differences between CT- and MRgSBRT.[19] Finally, although outside the scope of this study, the improved soft tissue visualization with MRgSBRT may be advantageous in the context of online adaptive therapy as well.

This study has limitations. Owing to the resources required to retrospectively replan radiation therapy plans, the CTgSBRT sample size was limited to 16 patients who were selected in a semi-random manner to include all radiation therapy regimens used in MIRAGE. Reassuringly, their dosimetric parameter values are similar to those reported for the entire CTgSBRT-arm cohort in MIRAGE[1] (Table E1), and their baseline characteristics were similar to the MRgSBRT cohort (Table 2). Additionally, MIRAGE stratified patients by baselines International Prostate Symptom Score and prostate gland volume, and thus matching this study cohorts on additional covariates may not be successful. Finally, the linear regression analyses seek to address this limitation by controlling for additional covariates on which we would attempt to match patients. Although CTgSBRT retrospective replanning was performed using MIRAGE-specified constraints and optimization priorities, slight differences in the optimization process may introduce variations in the plan quality and add uncertainties to dosimetric comparison. This study used patient data from a single clinical trial that used 1 MRI guided radiation therapy machine. Finally, there are known limitations with analytical models such as NTCP, including the model's underlying assumptions and parameters. Although the absolute values of the predicted NTCP may not yet be fully reliable, they provide useful insights for the comparative analyses in this study.[20,21] Our findings remained consistent across a range of NTCP parameters. Furthermore, since the comparison is between the CTgSBRT cohorts, the absolute values of the parameters are likely less important relative to the actual differences seen between the CTgSBRT cohorts.

In conclusion, this post hoc analysis of the MIRAGE trial of prostate CTgSBRT versus MRgSBRT demonstrated that reducing CTgSBRT PTV margins to 3 or 2 mm from 4 mm results in equivalent to superior dosimetry compared with MRgSBRT utilizing a 2-mm PTV margin and may reduce the risk of toxicity. These data support efforts to prospectively evaluate triggered imaging with automatic beam hold to reduce toxicity by allowing aggressive reduction of CTgSBRT PTV margins to 2 mm in a forthcoming clinical trial.

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