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Dosimetric Features of Ultra-Hypofractionated Intensity Modulated Proton Therapy for Prostate Cancer

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ABSTRACT

Purpose: To report clinical and dosimetric characteristics of 5-fraction stereotactic ablative radiotherapy (SABR) using intensity modulated proton therapy (IMPT) for localized prostate cancer.

Materials and Methods: All patients receiving IMPT SABR from 2017 to 2021 for localized prostate cancer at our institution were included. Five fractions were delivered every other day to the prostate +/− seminal vesicles [clinical target volume (CTV)] with 3 mm/3% robustness. A 4-field arrangement with 2 anterior oblique and 2 opposed lateral beams was used in most patients (97%), and most (99%) had a retroprostatic hydrogel spacer.

Results: A total of 534 patients with low (14%), favorable intermediate (45%), unfavorable intermediate (36%), high (4.0%), or very high-risk (0.6%) disease are evaluated. Prescription dose of 36.25 Gy (31%), 38 Gy (38%), or 40 Gy (31%) was prescribed. Median volume percentage of CTV receiving at least 100% of prescription dose [V100% (%)] was 100% [interquartile range: 99.99–100]. Rectum V50% (%), V80% (%), and V90% (%) were significantly lower in patients who had spacer, with a mean difference of −9.70%, −6.59%, and −4.42%, respectively, compared to those who did not have spacer. Femoral head dose was lower with a 4-field arrangement. Mean differences in left and right femoral head V40% (%) were −6.99% and −10.74%, respectively.

Conclusion: We provide a large, novel report of patients treated with IMPT SABR for localized prostate cancer. Four-field IMPT with hydrogel spacer provides significant sparing of rectum and femoral heads without compromising target coverage.

Introduction

Prostate cancer is the most common noncutaneous cancer diagnosed in American men, with an estimated 268 590 new cases and 34 500 deaths in 2022.[1] Approximately one-third of men with localized prostate cancer receive external beam radiotherapy (EBRT).[2] Conventionally fractionated EBRT delivers 1.8–2.0 Gy fractions to a total dose of 68–80 Gy.[3] Dose response studies demonstrate that prostate cancer may be modeled using an α/β ratio of 1.5–3 Gy, which translates to increased cancer cell killing from high dose per fraction compared to adjacent organs-at-risk (OARs).[4–6] Moderate hypofractionation (2.4–3.4 Gy per fraction)[7–12] and ultra-hypofractionation ($\geq$5 Gy per fraction)[13–18] regimens have comparable tumor control, adverse event (AE) and quality of life profiles relative to conventional fractionation. This has led to adoption of hypofractionation, including stereotactic ablative body radiotherapy (SABR) for localized prostate cancer.[19–21]

Compared to photon therapy, proton therapy can decrease dose to OARs with similar target coverage.[22–24] This stems from the inherent physical properties of protons, which deposit most of their dose over a narrow range with a steep dose falloff beyond the Bragg peak and essentially no meaningful exit dose beyond the target. The resulting dose distribution can potentially reduce genitourinary (GU) and gastrointestinal adverse events AEs[25–29] and mitigate secondary cancer risk.[30,31] Prior studies support conventionally fractionated[32–34] and hypofractionated[35–37] proton therapy for localized prostate cancer.

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The optimal delivery technique for proton-based prostate SABR requires further definition. Previous reports show that passively-scattered proton therapy results in lesser conformality compared to photon intensity modulated radiotherapy (IMRT).[24,38] Intensity modulated proton therapy (IMPT) uses a narrow beam scanned across the target volume. Beam intensity and energy can be adjusted during treatment, resulting in a more conformal dose distribution relative to photon IMRT.[24] This benefit has been associated with reduced GU AEs.[39]

Sharp dose falloff beyond the Bragg peak allows normal tissue sparing but also results in increased sensitivity of protons to tissue inhomogeneities and day-to-day positional variation. Plan robustness is therefore an important consideration when delivering proton SABR. Protons also have higher linear energy transfer at the end-of-range with an estimated relative biological effectiveness (RBE) of approximately 1.1.[40,41] Anteriorly arranged fields may deliver greater rectal dose compared to lateral fields due to range uncertainty and biological enhancement beyond the Bragg peak.[38] In a dosimetric study by Tang et al., anterior combined with lateral fields allowed for reduced AEs with current prescription doses or further dose escalation.[42]

Based on Tang et al. and an internal analysis, we routinely use a 4-field arrangement of 2 anterior oblique and 2 lateral beams to optimize robustness and reduce dose to the femoral heads. We also routinely place a retroprostatic hydrogel spacer[43] to further limit rectal radiation exposure. We now provide a dosimetric analysis of a large, single-institution cohort of patients with localized prostate cancer treated with IMPT SABR using this technique.

Materials and methods

Patients

Following Institutional Review Board approval, a prospectively maintained database was queried to identify all patients receiving IMPT SABR from 2017 through 2021 for histologically confirmed, localized prostate cancer at our institution. Those with node-positive and/or metastatic disease were excluded. This database and the electronic medical record were used to gather clinical characteristics. We risk stratified patients using National Comprehensive Cancer Network (NCCN) guidelines.[44]

Simulation

At least 1 day prior to computed tomography (CT) simulation, all patients underwent placement of 4 intraprostatic carbon fiducial markers using transrectal ultrasound guidance and a transperineal approach. A retroprostatic hydrogel spacer (Figure 1A) was placed in this same setting in 99% of patients. Reasons for spacer omission included significant posterior extraprostatic tumor extension, prior rectal cancer surgery, prior transurethral resection of the prostate, inability to hydrodissect between prostate and rectum, and unexpected delay between spacer placement and start of treatment resulting in spacer biosorption.

Patients underwent a pre-simulation enema and were provided full bladder instructions. A planning CT scan was performed with the patient in supine position, and a knee cushion and custom vacuum-lock bag were used to immobilize the lower extremities. A magnetic resonance imaging (MRI) scan was obtained immediately following CT simulation using the identical patient immobilization and setup. MRI T2 and LAVA-Flex sequences were co-registered to the simulation CT image set in the Eclipse Aria treatment planning system (Varian Medical Systems, Inc., Palo Alto, California) using the fiducials and prostate as reference.

Treatment planning and delivery

The clinical target volume (CTV) included the prostate +/− seminal vesicles. The extent of the seminal vesicles within the CTV was at the discretion of the treating physician and guided by clinical characteristics. Pelvic OARs were contoured and included bladder, rectum, penile bulb, femoral heads, and, when near the treatment field, small and large bowel. The hydrogel spacer was also contoured. MRI images fused to the planning CT were used to aid in contouring the CTV and spacer.

The CTV was prescribed a dose of 36.25–40 Gy in 5 fractions. Prescription dose was guided by physician preference and clinical features. IMPT plans were optimized for robustness to ensure CTV coverage with up to ± 3 mm isocenter shifts in the x, y, or z coordinate axes and ± 3% range uncertainty. OAR priority 1 constraints included: bladder volume (V) receiving at least 50% of prescription dose (V50%) ≤ 40%, V90% ≤ 10%, V100% ≤ 5.5 cc, V107% ≤ 0.3 cc; rectum V50% ≤ 50%, V80% ≤ 20%, V90% ≤ 10%, V100% ≤ 1.5 cc, V107% ≤ 0.3 cc; penile bulb dose (D) to 3 cc (D3cc) ≤ 20 Gy, D0.3 cc ≤ 107%; and femoral head V20Gy ≤ 10cc, V40% ≤ 5%, V107% ≤ 0.3 cc.

All patients were treated with multi-field optimized pencil-beam scanning IMPT on a Hitachi PROBEAT-V proton therapy system (Hitachi, Tokyo, Japan). Most (97%) plans employed a 4-field arrangement of 2 anterior oblique and 2 opposed lateral beams. The anterior oblique beams were delivered from 30° to 50° from the anterior-posterior direction. Weighting factors of 0.15 and 0.35 were used for the anterior oblique and lateral beams, respectively (Figure 1B, C).

Proton plans were verified in an in-house graphics processing unit-based Monte Carlo physical dose simulation (relative biological effectiveness [RBE] 1.1). An in-house Monte Carlo “biologic dose” (MCB) simulation that assumes a linear relationship between linear energy transfer (LET) and RBE, as described previously,[45] was also evaluated on all plans.

Five fractions of SABR were delivered every other weekday over one and a half to 2 weeks. Prior to each fraction, patients received an enema and full bladder instructions to minimize interfraction anatomic variation. Image guidance was performed by online matching of intraprostatic fiducials using onboard orthogonal kilovoltage imaging. Four fields were delivered at each treatment utilizing a gantry with 190° rotational range of motion. The table was rotated 180° between delivery of contralateral sets of fields. Images were taken at this rotation and prior to delivery of these contralateral fields.

Statistics

Treatment planning data including prescription dose, beam arrangement, spacer use, CTV and OAR dosimetric data extracted from the Eclipse Aria treatment planning system. CTV V100% (%) robustness was compared between those receiving a 4- versus non-4-field arrangement. MCB dose to rectum, including V105% and V110%, was compared between patients with and without hydrogel spacer. Unpaired t-tests were used for dosimetric comparisons.

Results

Patients

A total of 534 patients were included (Table 1). NCCN risk group was low (79 patients, 15%), favorable intermediate (238, 45%), unfavorable intermediate (194, 36%), high (20, 4.0%), and very high (3, 0.6%). Among the 22 patients with high or very high risk disease, 7 had T3 tumors. Gleason score was 4 + 4, 4 + 5, and 5 + 4 in 9, 2, and 1

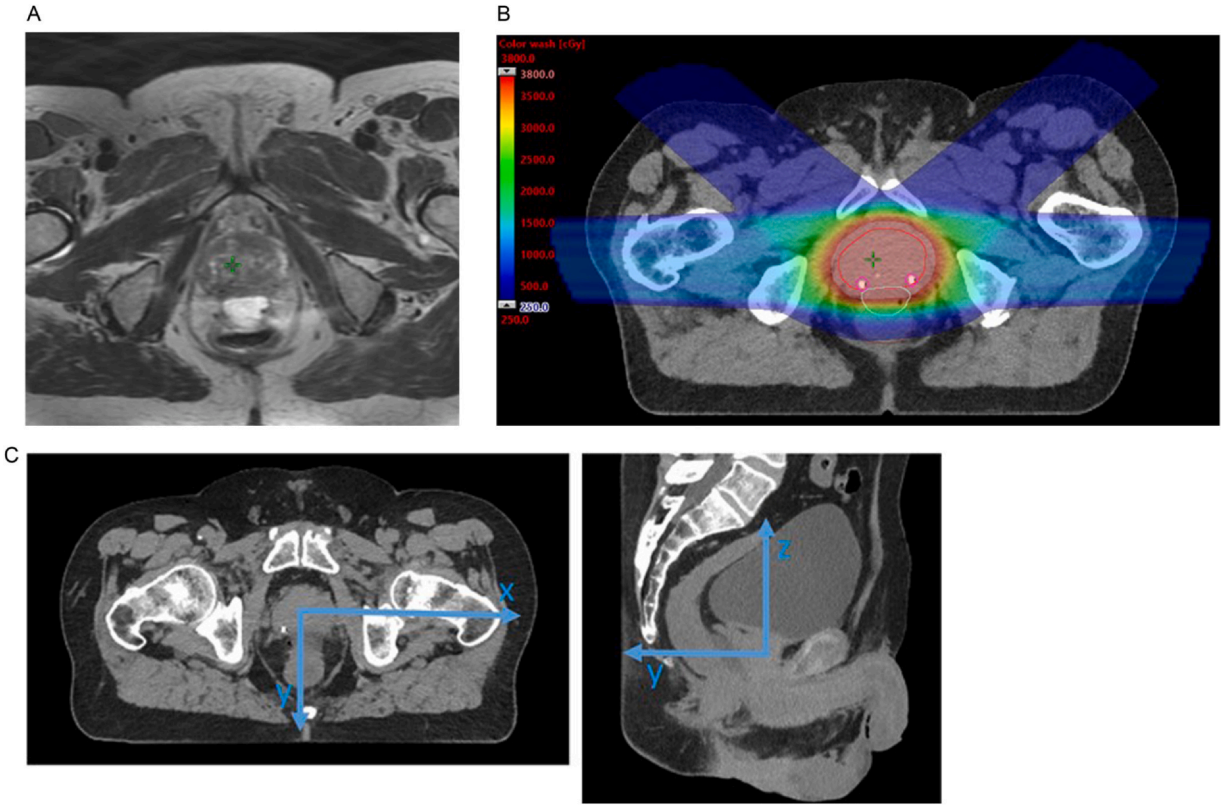

Figure 1. Sample treatment plan of prostate intensity modulated proton therapy stereotactic ablative radiotherapy. A) T2-weighted magnetic resonance imaging, showing placement of hyperintense retroprostatic hydrogel spacer; B) four-field arrangement with color wash range (250 to 3800 cGy) involving two anterior oblique and two opposed lateral beams, with contours of clinical target volume (red), intraprostatic fiducials (pink), hydrogel spacer (blue), and rectum (brown); C) coordinate system used in treatment planning (from isocenter, positive x points to patient left, positive y to posterior, and positive z to superior).

patient, respectively. Median age at the start of RT was 69 years [interquartile range (IQR): 64–74].

Radiotherapy

RT details are shown in Table 1. Patients received 5 fractions every other day over a median of 10 days (IQR: 9–14). Prescription dose was 36.25 Gy (166, 31%), 38 Gy (201, 38%), or 40 Gy (167, 31%). Among patients treated with a non-4-field arrangement, 13 (77%) received parallel opposed beams and the remaining 4 (23%) received parallel opposed beams with a single anterior oblique beam. All 3 patients who did not have spacer placed had a parallel opposed beam arrangement.

Dosimetric data

Dosimetric data in the overall cohort and dosimetric comparisons between groups are detailed in Tables 2 and 3, respectively. Median CTV V100% (%) was 100% (IQR: 99.99–100). There was no difference in CTV coverage based on spacer use or number of treatment fields.

Rectum dose was significantly lower in patients who underwent spacer placement compared to those who did not. The mean difference in rectum V50% (%) was −9.70% [95% confidence interval (CI): −18.14 to 1.25, $P = .02$), V80% (%) −6.59% (95% CI: −10.37 to 2.82, $P < .001$), and V90% (%) −4.42% (95% CI: −6.64 to 2.20, $P < .001$).

Femoral head dose was less with a 4-field arrangement. Mean differences in left and right femoral head V40% (%) were −6.99% (95% CI: −7.74 to 6.23, $P < .001$) and −10.74% (95% CI: −12.04 to 9.43, $P < .001$), respectively. Patients with spacer also had less femoral head dose, although it is noted that all 3 patients without spacer placed had a 2-field arrangement.

Robustness of CTV V100% (%) was compared between those receiving a 4- versus non-4-field arrangement (Table 4). Coverage with a +3 mm isocenter shift in the y axis was significantly improved with 4 fields [mean difference: 0.60% (95% CI: 0.02–1.17), $P = .04$]. MCB dose to the rectum was not significantly different with spacer, although it was numerically lower with a spacer for all 4 metrics evaluated (Table 5).

Discussion

Proton therapy has the potential to reduce toxicity for patients with localized prostate cancer while achieving equivalent oncologic outcomes compared to photon therapy.[22–24,30–37] Ultra-hypofractionation has shown efficacy in multiple randomized trials[13,15,18] and is being increasingly adopted. Proton SABR leverages the benefits of both approaches, however the optimal delivery method requires further study. We report on a large cohort of patients with localized prostate cancer treated with 5 fraction IMPT SABR. We use a 4-field arrangement of 2 anterior oblique and 2 lateral beams, along with routine placement of retroprostatic hydrogel spacer. Our dosimetric analysis demonstrates that this technique enables significant sparing of the rectum and femoral heads while maintaining excellent CTV coverage.

Table 1
Clinical and radiotherapy characteristics of 534 patients.

Characteristic	Number (%)
T stage	
T1a	1 (0.2%)
T1c	372 (69.7%)
T2a	106 (19.9%)
T2b	27 (5.1%)
T2c	21 (3.9%)
T3a	5 (0.9%)
T3b	2 (0.4%)
Gleason score	
3 + 3	76 (14.2%)
3 + 4	309 (57.9%)
4 + 3	137 (25.7%)
4 + 4	9 (1.7%)
4 + 5	2 (0.4%)
5 + 4	1 (0.2%)
PSA, ng/mL	
< 10	435 (81.5%)
10-20	94 (17.6%)
≥ 20	5 (0.9%)
NCCN risk group	
Low	79 (14.8%)
Favorable intermediate	238 (44.6%)
Unfavorable intermediate	194 (36.3%)
High	20 (3.7%)
Very high	3 (0.6%)
Age at RT start (years), median (IQR)	69 (64–74)
Year of RT start	
2017	39 (7.3%)
2018	71 (13.3%)
2019	104 (19.5%)
2020	153 (28.7%)
2021	167 (31.3%)
RT duration (days), median (IQR)	10 (9–14)
Prescription dose (Gy)	
36.25	166 (31.1%)
38	201 (37.6%)
40	167 (31.3%)
Fields, number	
2	13 (2.4%)
3	4 (7.5%)
4	517 (96.8%)
Hydrogel spacer	
Yes	531 (99.4%)
No	3 (0.6%)
Hydrogel spacer (cc), median (IQR)	10.1 (8.8–11.5)

Abbreviations: IQR, interquartile range; NCCN, National Comprehensive Care Network; PSA, prostate specific antigen; RT, radiotherapy.

Most studies of proton therapy for prostate cancer used opposed lateral beams.[22–24,32–37] This technique results in femoral head dose that approaches tolerance and exceeds that of IMRT.[22,24,46] By adding anterior oblique beams, we reduce bilateral femoral head dose by 7%–11%. Sparing the femoral heads and minimizing the associated risk of hip fracture and osteoarthritis[47] is of particular importance in patients receiving primary EBRT for prostate cancer, a population that tends to be older.[48]

Anterior oblique beams can potentially increase rectal dose due to proton range uncertainty. The range uncertainty with prostate treatment is estimated at approximately 3% of the path length.[49] With the reduced path length afforded by anterior oblique beams, the net range uncertainty is diminished, resulting in improved treatment robustness. We found that CTV coverage robustness with a +3 mm y axis shift was improved with use of 4 fields. Biologic enhancement at the end-of-range can also contribute to higher rectal dose.[38,40,41] We routinely place a spacer to mitigate this risk. In our analysis, use of a spacer was associated with reduced rectal dose. While MCB dose was not significantly different, all 4 metrics assessed were numerically lower in the spacer cohort. While the use of spacer for rectal sparing during photon therapy is well established, our data lend support to its use with proton therapy.

Although considerable research has been published on ultra-hypofractionation and proton therapy, evidence supporting the use of proton SABR is limited. A prospective trial of proton SABR for localized prostate cancer is ongoing (NCT03159676). This trial is being undertaken at Mayo Clinic and utilizes the same method described in the current report. Results from this study will help inform the safety, patient-reported outcomes, and oncologic efficacy associated with 4-field proton SABR.

We acknowledge the study limitations of this retrospective, non-randomized analysis. The number of patients with omission of spacer and/or a non-4-field arrangement were small, and our findings require validation from a larger comparative cohort.

Proton SABR is an accepted standard treatment for localized prostate cancer,[44] and its use continues to evolve. Multiple delivery approaches have been reported in the literature.[22–24,32–37] Our unique 4-field arrangement with hydrogel spacer results in significant sparing of the rectum and femoral heads without compromising target coverage. To our knowledge, this represents the largest series to date of patients with localized prostate cancer treated with IMPT SABR. These findings will help inform the optimal delivery strategy for these patients.

Table 2
Dosimetric data.

	Overall	4-field	Non-4-field	Spacer	No spacer
N (%)	534	517 (96.8%)	17 (3.2%)	531 (99.4%)	3 (0.6%)
	Median (IQR)				
CTV V100% (%)	100 (99.99–100)	100 (99.99–100)	100 (99.96–100)	100 (99.99–100)	100 (99.89–100)
Bladder V50% (%)	12.90 (7.34–18.78)	13.05 (7.46–18.90)	8.67 (5.47–13.35)	12.77 (7.38–19.06)	9.53 (8.67–15.53)
Bladder V100% (%)	1.21 (0.58–2.12)	1.22 (0.58–2.13)	0.98 (0.60–1.99)	1.24 (0.58–2.17)	1.15 (0.90–1.62)
Rectum V50% (%)	7.46 (3.27–13.22)	7.43 (3.27–13.22)	8.02 (4.04–12.03)	7.77 (3.53–13.37)	22.03 (16.58–23.00)
Rectum V80% (%)	1.71 (0.31–4.37)	1.66 (0.31–4.35)	2.45 (0.55–5.25)	1.83 (0.39–4.46)	9.54 (7.36–11.80)
Rectum V90% (%)	0.57 (0.03–2.27)	0.55 (0.03–2.24)	0.98 (0.04–3.31)	0.66 (0.04–2.27)	4.49 (3.89–2.27)
Penile bulb V50% (%)	0 (0–4.75)	0 (0–4.89)	0 (0–0.32)	0 (0–5.15)	0 (0–0.24)
Fem. head L V40% (%)	0 (0–0.16)	0 (0–0.12)	3.10 (1.44–11.27)	0 (0–0.19)	9.41 (6.11–14.79)
Fem. head R V40% (%)	0 (0–0.23)	0 (0–0.15)	6.41 (2.93–16.09)	0 (0–0.23)	6.46 (4.05–11.43)

Abbreviations: CTV, clinical target volume; IQR, interquartile range; L, left; R, right; V100% (%), % of volume receiving at least 100% of prescription dose.

Table 3
Dosimetric comparisons.

	Spacer vs. no spacer	4-field vs. non-4-field
	Mean difference (95% CI), *P*-value	
CTV V100% (%)	−0.12 (−0.76 to 1.00), .79	0.22 (−0.15 to 0.59), .25
Bladder V50% (%)	1.12 (−8.58 to 10.82), .82	1.52 (−2.61 to 5.65), .47
Bladder V100% (%)	0.24 (−1.26 to 1.74), .75	−0.18 (−0.82 to 0.46), .59
Rectum V50% (%)	**−9.70 (−18.14 to 1.25), .02**	0.04 (−3.57 to 3.65), .98
Rectum V80% (%)	**−6.59 (−10.37 to 2.82), < .001**	−0.60 (−2.23 to 1.02), .47
Rectum V90% (%)	**−4.42 (−6.64 to 2.20), < .001**	−0.54 (−1.49 to 0.42), .27
Penile bulb V50% (%)	6.26 (−9.87 to 22.40), .44	1.34 (−5.53 to 8.21), .70
Fem. head L V40% (%)	**−10.31 (−12.39 to 8.24), < .001**	**−6.99 (−7.74 to 6.23), < .001**
Fem. head R V40% (%)	**−7.57 (−11.26 to 3.88), < .001**	**−10.74 (−12.04 to 9.43), < .001**

Abbreviations: CI, confidence interval; CTV, clinical target volume; L, left; R, right; V100% (%), % of volume receiving at least 100% of prescription dose.
Statistically significant comparisons are bolded.

Table 4
CTV coverage robustness comparison with and without use of a 4-field arrangement.

CTV V100% (%) robustness calculation	4-field vs. non-4-field
	Mean difference (95% CI), *P*-value
+3% range uncertainty	1.59 (−1.07 to 4.25), .24
−3% range uncertainty	−0.41 (−1.95 to 1.12), .60
+3 mm isocenter shift, x axis	−0.12 (−0.43 to 0.19), .44
−3 mm isocenter shift, x axis	−0.13 (−0.46 to 0.20), .45
+3 mm isocenter shift, y axis	**0.60 (0.02–1.17), .04**
−3 mm isocenter shift, y axis	−0.15 (−0.94 to 0.64), .71
+3 mm isocenter shift, z axis	−0.10 (−0.68 to 0.48), .74
−3 mm isocenter shift, z axis	−0.65 (−1.72 to 0.42), .23

Abbreviations: CI, confidence interval; CTV, clinical target volume; V100% (%), % of volume receiving at least 100% of prescription dose.
Statistically significant comparisons are bolded.

Table 5
Rectum MCB dose comparison with and without use of a retroprostatic spacer.

Rectum MCB	Spacer vs. no spacer
	Mean difference (95% CI), *P*-value
V105% (%)	–0.80 (−2.15 to 0.55), .24
V105% (cc)	–0.36 (−1.19 to 0.48), .40
V110% (%)	–0.16 (−0.67 to 0.34), .53
V110% (cc)	–0.03 (−0.34 to 0.29), .87

Abbreviations: CI, confidence interval; MCB, Monte Carlo biologic; V105% (%), % of volume receiving at least 105% of prescription dose.

Author Contributions

Robert W. Gao, MD: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review and editing.Jiasen Ma, PhD: Coneptualization, Data curation, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Software, Validation, Visualization, Writing – review and editing. Thomas M. Pisansky, MD: Data curation, Methodology, Project Administration, Writing – review and editing. Jon J. Kruse, MD: Data curation, Resources, Supervision, Writing – review and editing. Bradley J. Stish, MD: Data curation, Resources, Supervision, Writing – review and editing. Roman O. Kowalchuk, MD: Data curation, Investigation, Writing – review and editing. Brendan P. McMenomy, MD: Data curation, Methodology. Mark R. Waddle, MD: Data curation, Writing – review and editing. Ryan M. Phillips, MD, PhD: Data curation, Writing – review and editing. Richard Choo, MD: Conceptualization, Investigation, Supervision, Project Administration, Writing – review and editing. Brian J. Davis, MD, PhD: Conceptualization, Investigation, Methodology, Supervision, Visualization, Writing – review and editing.

Data availability

Individual deidentified patient data that underlie the results reported in this article are available upon request.

Declaration of Conflicts of Interest

The authors have no conflicts to disclose.

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