Comparative Analysis of Radiation Therapy Plans Before and After Biodegradable Hydrogel (SpaceOAR) Injection for Reducing Rectal Toxicity in Prostate Cancer Patients Undergoing Carbon Ion Radiotherapy

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ABSTRACT

Comparative Analysis of Radiation Therapy Plans Before and After Biodegradable Hydrogel (SpaceOAR) Injection for Reducing Rectal Toxicity in Prostate Cancer Patients Undergoing Carbon Ion Radiotherapy

Objective: This study aims to evaluate the impact of SpaceOAR insertion on the efficacy and safety of carbon ion radiotherapy (CIRT) plans for prostate cancer patients. The investigation focuses on how SpaceOAR affects dose distribution to the prostate and surrounding organs during CIRT.

Methods: Twenty-five non-metastatic prostate cancer patients were included, with SpaceOAR inserted between the prostate and rectum. Treatment plans were generated using the RayStation treatment planning system, which were compared against conventional, rectum-sparing, and post-SpaceOAR insertion plans in dosimetry aspects including dose-volume histograms (DVHs). Acute toxicity was assessed within 90 days post-initiation of treatment. A robust evaluation was performed to assess plan robustness against patient set-up uncertainties, and ProKnow scoring was used to evaluate treatment plan quality.

Results: Compared to conventional CIRT and rectum-sparing plans without SpaceOAR insertion, plans with SpaceOAR insertion resulted in a substantial reduction in rectal radiation dose for the 25 cases ($p < 0.001$). The SpaceOAR insertion led to superior plan quality, as demonstrated by the mean dose of rectum in DVH analysis and Proknow scoring ($p < 0.001$). The robust evaluation confirmed that SpaceOAR enhances the robustness and safety of the treatment plans.

Conclusion: This work successfully demonstrated that integrating SpaceOAR into CIRT for prostate cancer significantly reduces rectal radiation exposure, thereby reducing radiation toxicity and allowing for dose escalation to the target volume.

Key words: SpaceOAR, Carbon Ion Radiotherapy (CIRT), Prostate Cancer, Rectal Toxicity, Dose-Volume Histograms (DVH), Radiation Therapy Plans, ProKnow Scoring, Robust Evaluation, Acute Toxicity

1. Introduction

Carbon ion radiotherapy (CIRT), characterized by the Bragg Peak, helps spare dose to organs at risk (OARs), offering superior dose distribution compared to photon-based radiotherapy (RT) [1]. Furthermore, CIRT has a higher biological effect, represented by linear energy transfer (LET) and relative biological effectiveness (RBE), compared to proton RT, the most widely used form of particle therapy. These factors are generally incorporated into dose calculation and treatment planning to emphasize the biological effectiveness of CIRT [2-4]. Due to these advantages, CIRT is considered suitable for treating radio-resistant tumors while minimizing the dose to surrounding normal tissues [1, 5].

In prostate cancer radiotherapy, rectal toxicity is a common concern due to the close proximity between the prostate and rectum, especially when escalating the dose to the target volume. This risk compromises the safety of CIRT in prostate cancer treatment. To address this issue, perirectal spacers have been developed to increase the physical distance between the prostate and rectum, thus reducing radiation exposure to the rectum [6, 7]. Several injectable spacer materials, such as hyaluronic acid, collagen, and polyethylene glycol hydrogels, have demonstrated promising outcomes in clinical studies [8, 9]. Among these, the SpaceOAR™ (Boston Scientific, Marlborough, MA, USA) is one of the most well-studied. When injected between the prostate and rectum, SpaceOAR hydrogel expands and solidifies into a soft, absorbable spacer, effectively increasing the separation between the two organs. Clinical studies have shown that SpaceOAR is easy to apply, well-tolerated by patients, and significantly reduces rectal radiation dose, leading to improved clinical outcomes [6].

The clinical and dosimetric advantages of SpaceOAR have contributed to its widespread adoption, particularly in the United States, where it has received FDA approval as a Class II medical device. This approval is based on strong clinical evidence supporting its safety and efficacy in reducing rectal toxicity during prostate cancer radiotherapy. Navigating the regulatory pathway for devices like SpaceOAR involves rigorous evaluation, including extensive clinical trials and long-term safety monitoring. While these stringent requirements are crucial for ensuring patient safety, they also pose challenges for medical devices seeking approval. The success of SpaceOAR reflects the growing trend in medical technology development, where unmet clinical needs—such as minimizing radiation exposure to surrounding tissues—drive innovation. A structured approach to problem-solving, grounded in needs-based clinical innovation, was essential in the development of SpaceOAR[10, 11].

A similar approach is currently being explored in pancreatic cancer radiotherapy, where the close anatomical proximity between the pancreas and duodenum presents significant challenges. Recent studies have demonstrated the potential of using a dissolvable hydrogel spacer to increase the distance between these two organs, thereby reducing duodenal radiation exposure. A patient-specific simulation model, Finite Element Model-Oriented Spacer Simulation Algorithm (FEMOSSA), has been developed to optimize spacer placement and improve clinical outcomes. Although preclinical results have been promising, challenges remain, particularly with procedural complexity, regulatory approval, and commercialization, due to the relatively small patient population compared to prostate cancer [12].

Despite the dosimetric benefits of using perirectal spacers like SpaceOAR, their combination with CIRT has not been extensively investigated [13, 14]. This gap in research highlights the need for further studies to explore the synergistic effects of combining these advanced therapies. This study aims to address this gap by conducting a comparative analysis of CIRT treatment plans for prostate cancer, evaluating plans before and after SpaceOAR injection using computed tomography (CT) images. The primary objective is to assess how SpaceOAR affects dose distribution to the prostate and surrounding organs. By comparing pre- and post-SpaceOAR treatment plans, the study seeks to confirm the safety of using CIRT in combination with SpaceOAR, quantify the reduction in dose, and evaluate the overall impact on treatment plan robustness and efficacy [15-17].

2. Method

2.1 Ethics Approval and Consent

This study was approved by the Institutional Review Board (IRB) of Severance Hospital and conducted in accordance with the Declaration of Helsinki. The need for written informed consent was waived for this retrospective study. The project number is 4-2024-0862.

2.2 SpaceOAR

This study included twenty-five non-metastatic prostate cancer patients who were treated with definitive radiotherapy. Each patient had SpaceOAR inserted percutaneously between the prostate and rectum, positioned Denonvillier's fascia and in front of the rectum. The gel (10 ml) was injected under transrectal ultrasound guidance using an 18-gauge needle, gradually creating a space at the mid-prostate level by separating the prostate and rectum. Within 10 seconds after injection, the hydrogel solidifies without a measurable rise in temperature, effectively creating a perirectal space[14]. The SpaceOAR gel injection was administered prior to the CT and MRI simulation.

2.3 Patient Cohort

From May 2023 to April 2024, we selected 25 prostate cancer patients who consecutively received carbon ion radiotherapy at our institution, considering them a representative patient cohort. All cases involved primary tumors, with the predominant treatment setting being definitive radiotherapy.

All patients underwent computed tomography (CT) and magnetic resonance imaging (MRI) after the injection of SpaceOAR hydrogel for treatment planning. As part of a Phase 2 study, patients received hypofractionated radiotherapy (51.60 Gy in 12 fractions of 4.3 Gy) based on the D'Amico classification, receiving carbon ion therapy for low-, intermediate-, and high-risk prostate cancer.

10 cc of SpaceOAR was systematically injected between the rectum and the prostate under local anesthesia and ultrasound guidance. Since the prostate and SpaceOAR were better visualized on T2-MRI than on CT scans, fusion imaging was subsequently used for target and spaceOAR delineation.

Candidates for the study included patients with T1–T3 stage prostate cancer, Gleason score ≤ 8, prostate-specific antigen (PSA) levels ≤ 20 ng/mL, and an ECOG performance status of 0 to 1, who were scheduled to receive carbon ion radiotherapy.

Exclusion criteria included prostate volume exceeding 80 cm^3, metastatic disease, current or recent androgen deprivation therapy, and previous prostate surgery or radiotherapy. Additionally, cases where the interval between CT scans before and after SpaceOAR insertion exceeded six months or where the difference in prostate volume before and after SpaceOAR insertion exceeded 15% were excluded. This is because if the interval between the CT scans before and after SpaceOAR insertion is longer than six months, the target change between the pre- and post-SpaceOAR plans could be significant, hence the time limit. Even within six months, if the prostate volume difference exceeds 15%, it could lead to significant differences in the impact on surrounding organs during planning.

2.4 Carbon Planning and Details

A retrospective generation of treatment plans was performed using the RayStation treatment planning system (version 11B; RaySearch Laboratories, Sweden) for a cohort of 25 prostate cancer patients (#1–25) undergoing carbon ion radiotherapy. To evaluate the dosimetric impact of carbon ion particle therapy plans, both patients with and without SpaceOAR insertion were included.

For each patient, three distinct treatment plans were developed:

1. A plan prioritizing target coverage using the pre-SpaceOAR CT scan.
2. A plan prioritizing the reduction of rectal dose to predefined thresholds using the pre-SpaceOAR CT scan, with these thresholds corresponding to our institution's rectum clinical goals.
3. A plan utilizing the post-SpaceOAR CT scan to simultaneously optimize target coverage and rectal sparing.

In the fixed-beam treatment room at the carbon ion therapy center, the beam remains stationary while the treatment couch is rotated. For prostate cancer patients, the couch is rotated to 0 and 180 degrees to facilitate treatment delivery from right and left bilateral ports, alternating between RT and LT fields on different days. The total prescribed dose to the PTV was 51.6 Gy, delivered in 12 fractions with each of the RT and LT fields delivering 4.3 Gy across six sessions. In all plans, at least 95% of the PTV had to be covered by the 100% isodose line. The maximum dose point could not exceed 107% of the prescribed dose.

2.5 Evaluations

2.5.1 Acute Toxicity Assessment

All patients undergoing carbon ion radiotherapy were evaluated for treatment-related adverse events (TEAEs) occurring within 90 days of treatment initiation. Adverse events were classified into genitourinary, gastrointestinal, and other categories, and further subdivided into specific terms. Genitourinary adverse events included dysuria, nocturia, urinary retention, urinary tract obstruction, urinary tract pain, urinary urgency, urinary frequency, and urinary incontinence. Gastrointestinal adverse events included rectal incontinence, rectal urgency, diarrhea, and rectal bleeding. Other adverse events included fatigue.

The frequency of adverse events experienced by each patient was recorded to provide an overview of acute toxicity associated with carbon ion radiotherapy. All data were collected through patient medical records and follow-up observations. A radiation oncologist reviewed and assessed the type of adverse events.

2.5.2 Treatment Planning System (TPS)

Plan evaluations were conducted using dose distributions provided by the TPS, clinical goals specified by the user, and DVH values for each organ. Dose-volume histograms (DVHs) for the prostate (PTV), rectum, and penile bulb were calculated for all patients. For the PTV, the minimum dose (Dmin), maximum dose (Dmax), and mean dose (Dmean) were evaluated. However, due to significant volume differences in the bladder before and after SpaceOAR insertion, DVH values for the bladder were not evaluated in the TPS, as the large volume differences could lead to misinterpretations of dose-volume metrics.

To accurately account for the biological effects of the carbon ion treatments, the Relative Biological Effectiveness (RBE) was calculated using the modified Microdosimetric Kinetic Model (mMKM). Local effect model (LEM) and modified MKM are the two primary methods for calculating RBE-weighted dose. LEM focuses on energy deposition in nano-meter level, while it has been adapted to address micro-meter level, like MKM, over time. The mMKM was chosen in this work as its clinical effectiveness has been verified in CIRT clinical sites in Japan without modifications [1, 18-20].

2.5.3 Prostate-Rectum Separation and Rectal DVH Analysis

2.5.3.1 Evaluation and Analysis of Prostate-Rectum Separation Distance

To evaluate the prostate-rectum separation distance before and after SpaceOAR insertion in prostate cancer patients, subjects were categorized based on the separation distance between the prostate and rectum. The fusion of CT and MRI images was utilized to enhance accuracy. The separation distance for each patient was determined by averaging the measured distances at the central prostate reference points, designated as 0 cm, +1.5 cm in the superior direction, and -1.5 cm in the inferior direction (Figures 1, 2). Based on these measurements, patients were classified into four groups: 0-5 mm, 5-10 mm, 10-15 mm, and >15 mm. For the 25 patients, the mean and standard deviation of the measurements at each position (0 cm, +1.5 cm, -1.5 cm) were calculated from the images taken before and after SpaceOAR insertion. Figure 3 illustrates the anatomical cross-section and approximate dose distribution during the injection of SpaceOAR between the prostate and rectum under ultrasound guidance.

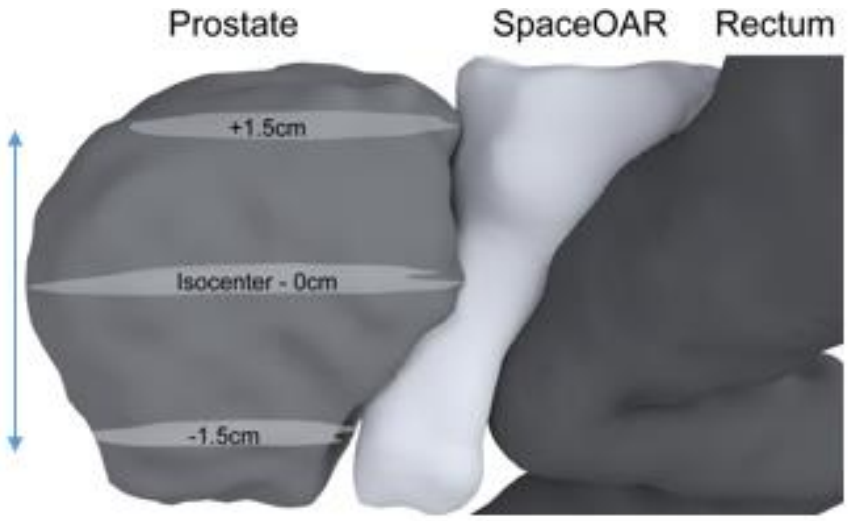


Fig. 1. Illustration of different prostate levels in the sagittal plane. The isocenter at 0 cm represents the center of the prostate. The +1.5 cm point is located 1.5 cm superior to the 0 cm, while the -1.5 cm point is 1.5 cm inferior to the 0 cm.

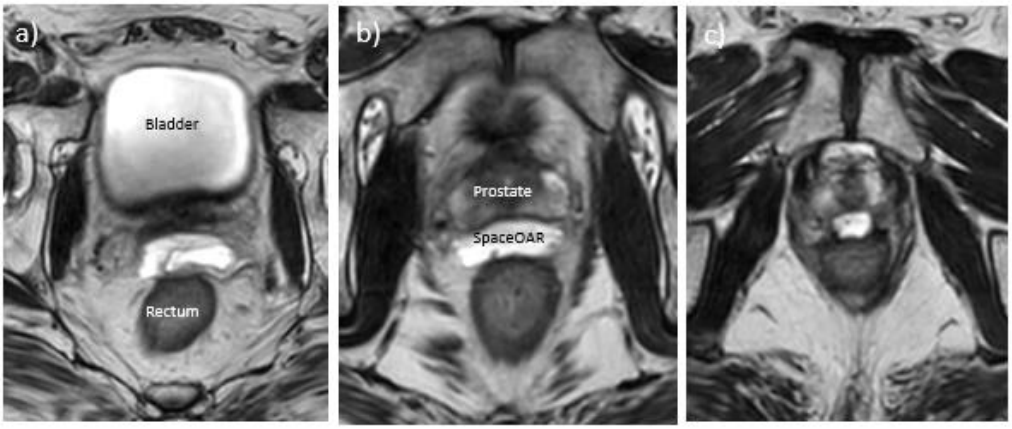


Fig. 2. Transverse view of the T2 magnetic resonance image (T2- MRI). a) +1.5 cm from the center of the prostate, b) Center of the prostate, c) -1.5 cm from the center of the prostate.

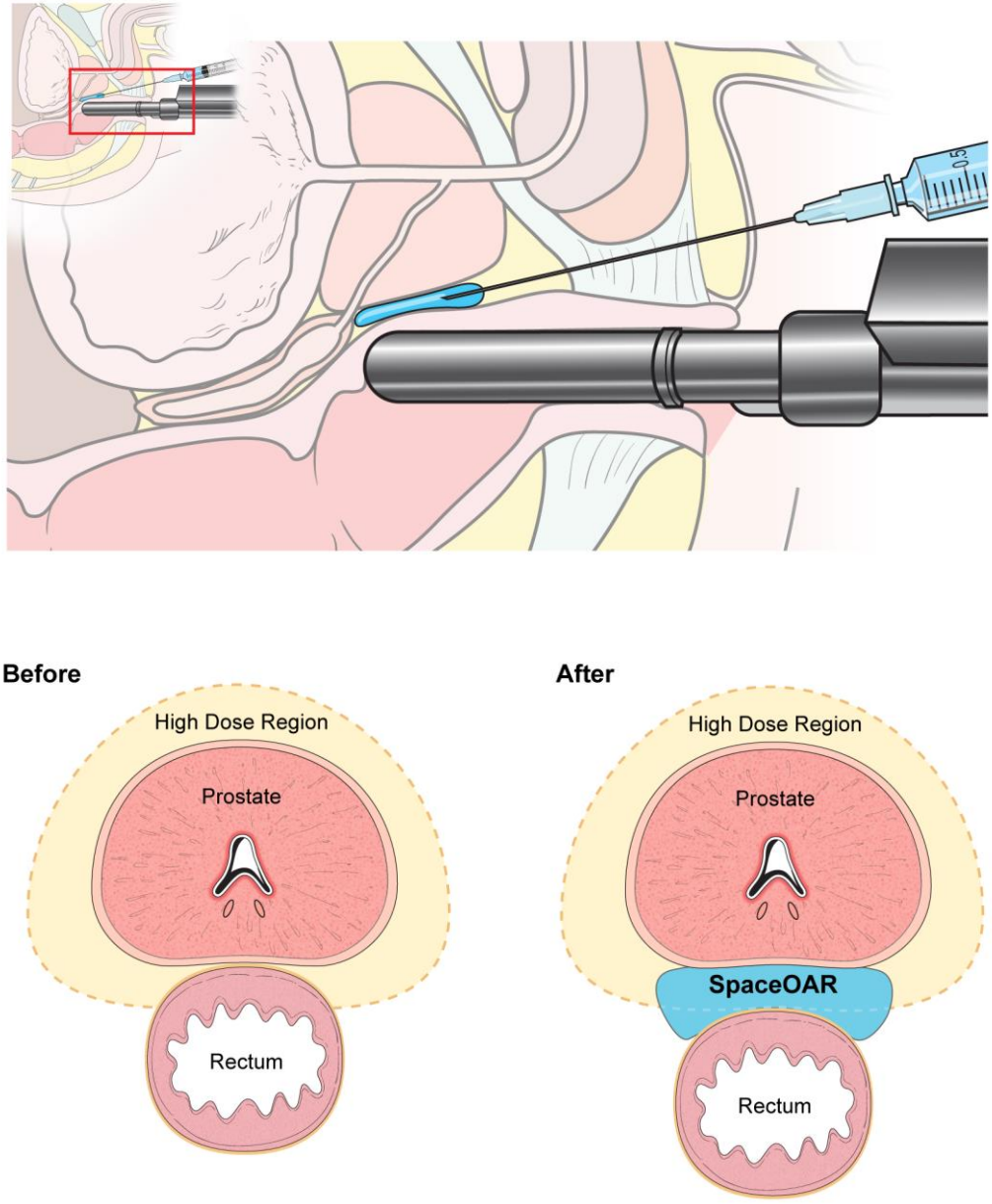


Fig. 3. Sectional view of SpaceOAR injection and dose distribution before and after injection.

2.5.3.2 Analysis of Rectal Dosimetry Parameters

For each patient, dose-volume histogram (DVH) values for the rectum were calculated using the average prostate-rectum separation distance measured at the 0 cm, +1.5 cm, and -1.5 cm positions. This analysis aimed to evaluate the radiation dose distribution to the rectum based on the degree of separation. The analyzed DVH values included Dmin, Dmax, Dmean, V15%, V20%, V30%, V40%, and V50%. These data were utilized to assess changes in rectal radiation dose following SpaceOAR insertion. By employing these methods, the impact of SpaceOAR insertion on rectal sparing during radiation therapy for prostate cancer patients was quantitatively analyzed.

2.5.4 Robust Evaluation of Treatment Plans

The robust evaluation passing rate is a concept in radiation therapy that ensures the effectiveness and safety of treatment plans by considering various uncertainties. It evaluates the robustness of treatment plans against potential errors in patient setup and CT scan density interpretation. RayStation's robust evaluation module allows for the simultaneous assessment of multiple error scenarios, simulating isotropic or anisotropic uncertainties in all directions. By aggregating dose values across all scenarios to find the minimum and maximum dose for each voxel, the passing rate is determined as the percentage of dose points meeting the prescribed dose criteria across different error scenarios. A high passing rate indicates that the treatment plan is robust and can deliver the intended dose despite uncertainties [1].

Patient position uncertainty was modeled with anisotropic uncertainties in six directions, with shifts up to ±0.50 cm in certain directions and ±0.70 cm in others. Specifically, uncertainties in the superior, inferior, and posterior directions were modeled at 0.50 cm, while the anterior direction, where the prostate and rectum are in close proximity, was evaluated more stringently with a 0.70 cm uncertainty. Additionally, density uncertainty was modeled by scaling the mass density of the patient by ±4% using three discretization points. These modeling approaches, combined with the planning criteria detailed in Table 1, ensured the robustness of the treatment plan by accounting for various patient positioning scenarios and density variations [21] (Figure 4).

Table 1. Dosimetric Criteria for Treatment Plans.

Organ	Dosimetric Criteria
Prostate	At least 49.02 Gy (RBE) covering 99.9% of the volume
	At least 49.02 Gy (RBE) covering 100.0% of the volume
Rectum	Maximum 1.00 cm^3 volume at 49.02 Gy (RBE)
	Maximum 5.00 cm^3 volume at 41.28 Gy (RBE)
	Maximum 10.00 cm^3 volume at 25.80 Gy (RBE)
Bladder	Volume receiving 44.89 Gy (RBE) < 25%
	Volume receiving 28.38 Gy (RBE) < 45%
Penile bulb	Dose to a 0.03 cm^3 volume

Anatomical sites such as the prostate, rectum, and bladder were included in the evaluation. The passing rates for these organs were assessed based on their respective evaluation criteria mentioned in Table 1. The mean and standard deviation (SD) of the passing rates were calculated for the three conditions: pre-SpaceOAR, pre-SpaceOAR with rectum protection, and post-SpaceOAR.

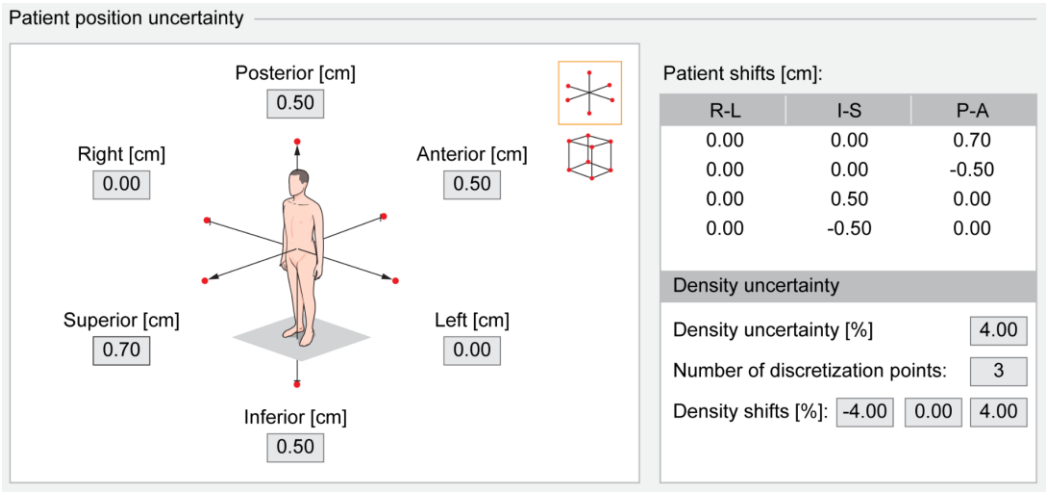


Fig. 4. Robust evaluation of patient position and density uncertainty in RayStation.

2.5.5 ProKnow Scoring

ProKnow® (ProKnow, LLC) scoring was utilized to evaluate the quality of treatment plans for prostate cancer patients undergoing carbon ion therapy. This method involved analyzing specific metrics for the prostate, rectum, bladder, and penile bulb, with each metric assigned objectives based on clinical goals. Scores were calculated to reflect the compliance of treatment plans with these goals, ranging from 'Ideal' to 'Unacceptable.' The criteria and their respective weights were determined by two radiation oncologists, ensuring a comprehensive evaluation. Composite scores were generated by combining individual metric scores, allowing for comparison across treatment plans [22] (Table 1, 2).

Table 2. Plan metrics collected for each prostate carbon ion therapy radiation treatment plan. (total points 64, 8 plans used to produce per-metric and composite plan scores).

No	Metric description	Minimum requirement	Ideal	Interval	Weight
1	Volume (%) of Bladder covered by 44.89 (Gy)	10	25	5	1
2	Volume (%) of Bladder covered by 28.38 (Gy)	15	45	10	1
3	Dose (Gy) covering 99.90 (%) of the Prostate	49.02	51.6	PTV coverage 1~2% difference	1
4	Dose (Gy) covering 100.00 (%) of the Prostate	49.02	51.6	PTV coverage 1~2% difference	1
5	Volume (cc) of the Rectum covered by 49.02 (Gy)	0.4	1	0.2	2
6	Volume (cc) of the Rectum covered by 41.28 (Gy)	2	5	1	2
7	Volume (cc) of the Rectum covered by 25.80 (Gy)	1	10	3	2
8	Dose (Gy) covering 0.03 (cc) of the Penile bulb	20	50	10	1

2.6 Statistical Analysis

Continuous variables (age, Gleason score and initial PSA levels) were summarized using mean, standard deviation (SD), median, minimum (min), and maximum (max), while categorical variables (ECOG performance status, T stage) were summarized using frequencies and proportions. These descriptive analyses were performed in the entire sample and separately for each risk group (low, intermediate and high). Additionally, dose distribution indices, prostate-rectum distances, DVH values, robustness evaluation pass rates, and total scores for each plan were summarized using mean and standard deviation.

A one-way repeated measures ANOVA was conducted to determine whether the DVH results (Dmin, Dmax, Dmean, V15, V20, V30, V40, V50) for the prostate, rectum, and penile bulb showed significant differences across the three plans (1. Pre-SpaceOAR, 2. Pre-SpaceOAR with rectum protection, 3. Post-SpaceOAR). If significant differences were detected, Bonferroni correction was applied to identify specific plan differences. Additionally, ProKnow scores were compared across the three plans to assess differences in overall plan quality.

A two-way repeated measures ANOVA evaluated the effect of SpaceOAR (first factor) and three anatomical positions from the prostate center (+1.5 cm, 0 cm, -1.5 cm; second factor) on the prostate-rectum distance. Robust evaluation in the rectum was analyzed using three treatment plans (Pre-SpaceOAR, Pre-SpaceOAR with rectum protection, Post-SpaceOAR) and pass rates (%) for three volume thresholds (Max 1cm^3, Max 5cm^3, Max 10cm^3). Bonferroni correction was applied in cases of significant interaction effects.

Finally, regression analyses were performed to assess the relationship between rectum DVH values (Dmin, Dmax, Dmean, V15, V20, V40, V50) and the prostate-rectum separation degree. Beta regression with a logistic link function was used for outcomes expressed as percentages (V15, V20, V40, V50), and ordinary least squares regression was applied for Dmin, Dmax, and Dmean.

All statistical analyses were conducted using R Statistical Software (version 4.1.3; R Foundation for Statistical Computing, Vienna, Austria), with the 'mgcv' package used for beta regression modeling. A *p*-value less than 0.05 was considered statistically significant

3. Result

3.1 Acute Toxicity

A total of 25 patients were included in the acute toxicity assessment, classified into low-risk (N=6), intermediate-risk (N=16), and high-risk (N=3) groups. The demographic characteristics of the patients are as follows: the mean age at the time of radiotherapy was 68.96 years (SD 7.86), with 65.00 years (SD 5.76) for the low-risk group, 67.81 years (SD 6.34) for the intermediate-risk group, and 83.00 years (SD 2.00) for the high-risk group. ECOG performance status PS0 and PS1 were noted for all patients, with no patients classified as PS2 or higher. T stages ranged from T1b to T3a, and Gleason scores of 6, 7, and 8 were represented. Initial PSA (iPSA) levels were higher in the high-risk group, with a median iPSA of 8.93 (range: 7.69–14.00) compared to the low- and intermediate-risk groups, where median values were 5.10 and 5.44, respectively (Table 3).

The primary analysis focused on adverse events associated with the urinary and gastrointestinal tracts, as well as other incidents. The analysis of adverse events (Treatment Emergent Adverse Events, TEAEs) was based on incidents that occurred within 90 days following the start of treatment in clinical trials. In this analysis, potential duplicate subjects were considered, meaning that if a single patient experienced multiple adverse events, each event was counted separately. The results were presented as the number of subjects (N) and percentage (%), with ratios calculated based on each group, and the number of cases (E).

In the urinary tract category, a total of 16 adverse events were recorded. Dysuria was observed in 2 patients (8%) overall, with 1 patient (16.67%) from the low-risk group, 1 patient (6.25%) from the intermediate-risk group, and 1 patient (25%) from the high-risk group. Nocturia was noted in 1 patient (16.67%) from the low-risk group, 3 patients (18.75%) from the intermediate-risk group, and 2 patients (24%) from the high-risk group. Urinary tract obstruction was observed in 1 patient (6.25%) from the intermediate-risk group, with no occurrences in the other risk groups. Urinary urgency affected 2 patients (12.50%), all from the intermediate-risk group. Urinary frequency was reported in 5 patients (20%), including 2 patients (33.33%) from the low-risk group, 2 patients (12.50%) from the intermediate-risk group, and 1 patient (33.33%) from the high-risk group.

In the gastrointestinal tract category, there was 1 recorded event of rectal urgency in a intermediate-risk patient (6.25%). In the category of other adverse events, fatigue was reported in 1 intermediate-risk patient (6.25%) (Table 4).

Table 3. Demographic and baseline characteristics data.

	Low risk group (N=6)	Intermediate risk group (N=16)	High risk group (N=3)	Total (N=25)
Age (years)				
N	6	16	3	25
Mean (SD)	65.00 (5.76)	67.81 (6.34)	83.00 (2.00)	68.96 (7.86)
Median	67	67	83	68
Min, Max	57, 70	58, 78	81, 85	57, 85
ECOG performance status, N (%)				
PS0	2 (33.33)	2 (12.50)	1 (33.33)	5 (20.00)
PS1	4 (66.67)	14 (87.50)	2 (66.67)	20 (80.00)
PS2	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
PS3	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
PS4	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
T stage, N (%)				
T1b	1 (16.67)	0 (0.00)	0 (0.00)	1 (4.00)
T1c	2 (33.33)	0 (0.00)	0 (0.00)	2 (8.00)
T2a	3 (50.00)	7 (43.75)	1 (33.33)	11 (44.00)
T2b	0 (0.00)	3 (18.75)	0 (0.00)	3 (12.00)
T2c	0 (0.00)	6 (37.50)	0 (50.00)	6 (24.00)
T3a	0 (0.00)	0 (0.00)	2 (66.67)	2 (8.00)
T3b	0 (0.00)	0 (0.00)	0 (00.00)	0 (0.00)
Gleason Score (%)				
6	6 (100.00)	3 (13.33)	0 (00.00)	9 (36.00)
7	0 (0.00)	13 (86.67)	1 (33.33)	14 (56.00)
8	0 (0.00)	0 (0.00)	1 (33.33)	1 (4.00)
(-)	0 (0.00)	0 (0.00)	1 (33.33)	1 (4.00)
Initial PSA (iPSA)				
N	6	15	4	25
Mean (SD)	4.95 (0.84)	5.57 (2.07)	10.21 (3.34)	5.98 (2.47)
Median	5.10	5.44	8.93	5.30
Min, Max	3.56, 6.06	2.77, 10.80	7.69, 14.00	2.77, 14.00

Note 1) N(%): The number and ratio of subjects are calculated based on each group.
Note 2) (-): It indicates that the Gleason Score was not assessed.

Table 4. Current status of early adverse events by body organ (Safety set).

System Organ Class Preferred Terms	Low risk group (N=6)		Intermediate risk group (N=16)		High risk group (N=3)		Total (N=25)	
	N (%)	E	N (%)	E	N (%)	E	N (%)	E
Total	2 (33.33)	4	7 (43.75)	11	2 (66.67)	3	11 (44.00)	18
Urinary Tract	**2 (33.33)**	**4**	**6 (37.50)**	**9**	**2 (66.67)**	**3**	**10 (40.00)**	**16**
Dysuria	1 (16.67)	1	1 (6.25)	1	0 (25.00)	0	2 (8.00)	2
Nocturia	1 (16.67)	1	3 (18.75)	3	2 (66.67)	2	6 (24.00)	6
Urinary retention	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
Urinary tract obstruction	0 (0.00)	0	1 (6.25)	1	0 (0.00)	0	1 (4.00)	1
Urinary tract pain	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
Urinary urgency	0 (0.00)	0	2 (12.50)	2	0 (0.00)	0	2 (8.00)	2
Urinary frequency	2 (33.33)	2	2 (12.50)	2	1 (33.33)	1	5 (20.00)	5
Urinary Incontinence	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
Gastrointestinal Tract	**0 (0.00)**	**0**	**1 (6.25)**	**1**	**0 (0.00)**	**0**	**1 (4.00)**	**1**
Rectal incontinence	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
Rectal urgency	0 (0.00)	0	1 (6.25)	1	0 (0.00)	0	1 (4.00)	1
Diarrhea	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
Rectal bleeding	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
Others	**0 (0.00)**	**0**	**1 (6.25)**	**1**	**0 (0.00)**	**0**	**1 (4.00)**	**1**
Fatigue	0 (0.00)	0	1 (6.25)	1	0 (0.00)	0	1 (4.00)	1

Note 1) Analysis of adverse events (Treatment Emergent Adverse Events, TEAEs) occurring within 90 days following the initiation of treatment in clinical trials

Note 2) Duplicate subjects.

Note 3) N (%): Number of subjects (percentage), with ratios calculated based on each group; E: number of cases.

3.2 Comparison of Dosimetry Indices

Contours for the prostate, rectum, bladder, and penile bulb were delineated for all patients. The volumes of the prostate, rectum, bladder, and penile bulb are detailed in Table 5. These contours were used to generate the dose statistics for each patient across the three different treatment plans: pre-SpaceOAR, pre-SpaceOAR with rectal protection, and post-SpaceOAR. The values for Dmin, Dmax, Dmean, and V15 to V50 in Table 6 represent the average values across the 25 patients.

For the prostate, the average Dmin was 51.46 Gy pre-SpaceOAR, 46.54 Gy pre-SpaceOAR with rectal protection, and 51.47 Gy post-SpaceOAR. The average Dmax was 52.30 Gy, 53.86 Gy, and 52.26 Gy, respectively, while the average Dmean was 51.91 Gy, 52.67 Gy, and 51.90 Gy. Significant differences were found in Dmin ($p < 0.001$) and Dmax ($p = 0.025$) between pre-SpaceOAR and pre-SpaceOAR with rectal protection, but no significant difference in Dmean ($p = 0.071$). There were no significant differences between pre-SpaceOAR and post-SpaceOAR for any metric ($p > 0.999$).

For the rectum, the average Dmin was 0.08 Gy pre-SpaceOAR, 0.08 Gy pre-SpaceOAR with rectal protection, and 0.09 Gy post-SpaceOAR. The average Dmax was 52.83 Gy, 50.81 Gy, and 50.66 Gy, respectively, with the average Dmean being 9.85 Gy, 8.58 Gy, and 3.32 Gy. Significant differences were observed in Dmin ($p = 0.013$) between pre-SpaceOAR and pre-SpaceOAR with rectal protection, while no significant difference was found between pre-SpaceOAR and post-SpaceOAR ($p = 0.339$). For Dmax, p-values were <0.001 and 0.086, respectively, and all comparisons for Dmean showed p-values <0.001. Additionally, significant reductions in the rectal volume percentages (V15 to V50) were observed, with all p-values <0.05.

For the penile bulb, the average Dmin was 2.88 Gy pre-SpaceOAR, 0.46 Gy pre-SpaceOAR with rectal protection, and 0.41 Gy post-SpaceOAR. The average Dmax was 51.31 Gy, 52.64 Gy, and 53.73 Gy, while the average Dmean was 16.06 Gy, 19.72 Gy, and 16.98 Gy. Significant differences were found in Dmin ($p < 0.001$) and Dmean ($p < 0.001$) between pre-SpaceOAR and pre-SpaceOAR with rectal protection, but no significant difference in Dmax ($p = 0.060$). Comparing pre-SpaceOAR and post-SpaceOAR, there were no significant differences in Dmin ($p = 0.981$) and Dmax ($p = 0.411$), but a significant difference in Dmean ($p = 0.001$). Significant changes in the penile bulb volume percentages (V15 to V50) were also observed, with all p-values <0.001.

Table 5. Volumes of the Target, and surrounding organs (With / Without SpaceOAR).

Patient No.	PTV (Prostate) (cm^3)	Rectum (cm^3)	Bladder (cm^3)	Penile Bulb (cm^3)
	with/without	with/without	with/without	with/without
1	30.88 / 34.30	43.37 / 45.31	343.01/ 109.38	7.25 / 7.15
2	38.08 / 40.83	22.42 / 32.04	340.97 / 198.39	7.89 / 7.88
3	48.54 / 50.91	43.09 / 51.91	265.41 / 221.96	5.81 / 5.53
4	45.63 / 51.20	38.06 / 41.71	323.51 / 45.74	7.48 / 6.56
5	51.91 / 56.47	63.21 / 68.77	196.83 / 372.11	8.22 / 8.67
6	37.00 / 36.64	39.96 / 45.89	143.79 / 238.22	5.55 / 5.80
7	49.15 / 54.55	38.89 / 48.88	417.09 / 120.99	6.49 / 7.25
8	32.30 / 35.50	53.49 / 58.73	407.21 / 176.06	6.52 / 6.21
9	72.14 / 66.50	55.25 / 86.27	269.25 / 161.41	5.64 / 5.54
10	58.98 / 51.54	44.10 / 50.52	273.02 / 148.13	3.89 / 3.79
11	25.43 / 28.80	31.72 / 29.23	493.41 / 113.27	3.26 / 3.30
12	32.79 / 34.62	54.03 / 75.52	363.67 / 853.07	5.64 / 5.50
13	39.16 / 42.42	46.20 / 38.62	249.03 / 93.59	4.98 / 5.19
14	39.43 / 44.93	31.52 / 57.04	309.19 / 86.95	9.38 / 9.16
15	52.63 / 48.07	42.13 / 50.81	255.04 / 40.19	6.86 / 7.10
16	55.14 / 59.64	56.30 / 93.50	261.00 / 120.86	7.74 / 8.10
17	49.19 / 49.38	40.13 / 56.16	186.62 / 64.54	5.35 / 5.64
18	43.83 / 46.34	63.25 / 48.65	381.88 / 145.87	9.10 / 9.48
19	25.61 / 27.04	55.77 / 65.29	121.18 / 136.51	10.01 / 9.86
20	58.89 / 55.40	41.10 / 36.38	179.53 / 100.53	5.32 / 5.54
21	26.81 / 25.97	37.16 / 28.03	196.76 / 78.28	4.09 / 4.27
22	50.74 / 49.26	52.00 / 58.45	218.07 / 293.29	7.96 / 8.00
23	36.66 / 37.34	44.78 / 54.17	184.76 / 96.50	8.52 / 8.26
24	67.37 / 68.39	41.96 / 56.31	205.15 / 419.99	7.58 / 7.87
25	60.98 / 67.70	38.10 / 51.48	223.60 / 124.56	8.16 / 7.77

Note: Volumes are measured in cubic centimeters (cm^3). The data represents the volumes with and without the use of SpaceOAR for each patient.

Table 6. Mean DVH Values Pre-SpaceOAR, Pre-SpaceOAR with Rectum Protection, and Post-SpaceOAR.

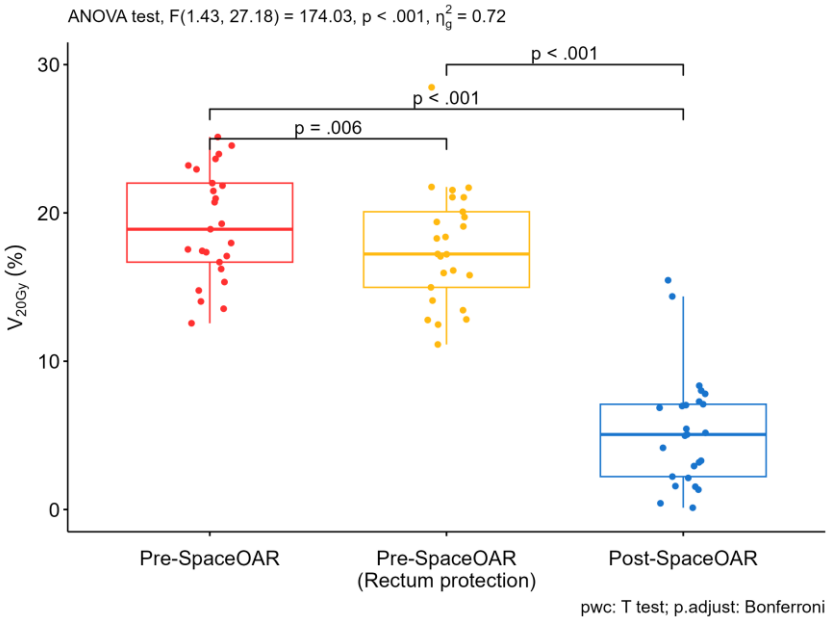
		Prostate			Rectum										Penile bulb								
		Dmin (Gy)	Dmax (Gy)	Dmean (Gy)	Dmin (Gy)	Dmax (Gy)	Dmean (Gy)	V_{15} (%)	V_{20} (%)	V_{25} (%)	V_{30} (%)	V_{35} (%)	V_{40} (%)	V_{45} (%)	V_{50} (%)	Dmin (Gy)	Dmax (Gy)	Dmean (Gy)	V_{15} (%)	V_{20} (%)	V_{25} (%)	V_{30} (%)	V_{35} (%)	V_{40} (%)	V_{45} (%)	V_{50} (%)
Pre-Space OAR	**Mean**	51.46	52.30	51.91	0.08	52.83	9.85	21.60	19.17	17.32	15.67	13.98	12.24	10.61	7.85	2.88	51.31	16.06	37.73	29.93	28.86	27.28	20.46	19.35	18.08	11.12
	SD*	0.12	0.47	0.11	0.03	0.39	1.77	4.09	3.70	3.31	2.95	2.72	2.37	2.03	1.61	11.03	7.08	7.02	16.81	13.93	13.84	13.26	10.91	10.10	9.58	7.08
Pre-Space OAR (Rectum Protection)	**Mean**	46.54	53.86	52.67	0.08	50.81	8.58	20.27	17.66	15.52	13.49	11.35	9.12	6.35	0.06	0.46	52.64	19.72	45.28	37.97	35.84	33.81	28.23	24.97	23.19	15.52
	SD*	3.58	2.70	1.56	0.03	0.82	1.80	4.54	3.92	3.43	3.21	2.68	2.77	2.28	0.06	0.20	1.04	7.32	16.61	15.74	14.28	13.95	13.40	11.75	11.29	9.23
	***p*-value**[1]	<0.001	0.025	0.071	0.013	<0.001	<0.001	0.015	0.006	0.003	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.060	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Post-Space OAR	**Mean**	51.47	52.26	51.90	0.09	50.66	3.32	6.97	5.31	4.34	3.57	2.67	1.97	1.46	0.67	0.41	53.73	16.98	37.38	33.65	29.50	25.41	23.16	20.01	15.93	12.50
	SD*	0.09	0.07	0.02	0.03	4.70	1.88	4.65	3.84	3.50	3.25	2.65	2.22	1.91	1.12	0.18	2.91	6.82	16.26	14.12	13.66	13.11	11.49	10.59	10.27	8.45
	***p*-value**[2]	>0.999	>0.999	>0.999	0.339	0.086	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.981	0.411	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

1 Pre-SpaceOAR VS Pre-SpaceOAR (Rectum Protection)

2 Pre-SpaceOAR VS Post-SpaceOAR

When comparing the *p*-values for the three groups in prostate treatment for the rectum, as seen in Figure 5, significant differences were found across the treatment plans for V20 and V40. For V50, significant differences were observed between pre-SpaceOAR and pre-SpaceOAR with rectal protection, and between pre-SpaceOAR and post-SpaceOAR, but not between pre-SpaceOAR with rectal protection and post-SpaceOAR ($p = 0.071$). Mean dose of the rectum showed significant differences between all pairs of treatment plans. However, Dmax showed significant differences only between pre-SpaceOAR and pre-SpaceOAR with rectal protection ($p < 0.001$), but not between pre-SpaceOAR and post-SpaceOAR ($p = 0.086$) or between pre-SpaceOAR with rectal protection and post-SpaceOAR ($p = 1.000$). Dmin showed significant differences between pre-SpaceOAR and pre-SpaceOAR with rectal protection ($p = 0.013$), but not between pre-SpaceOAR and post-SpaceOAR ($p = 0.339$) or between pre-SpaceOAR with rectal protection and post-SpaceOAR ($p = 0.113$). Box plots show the data distribution, including median, quartiles, and potential outliers, with *p*-values annotated to highlight significant differences (Figure 5).

(a)



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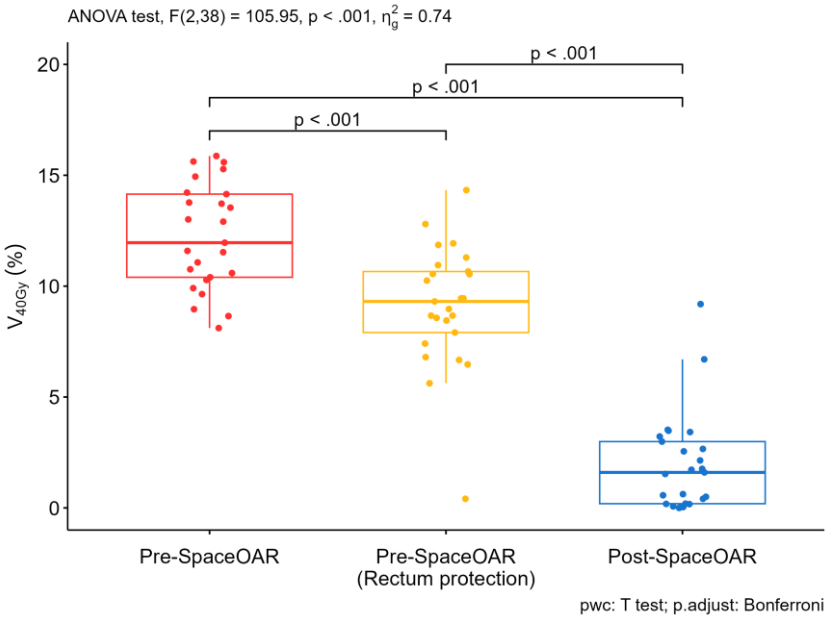
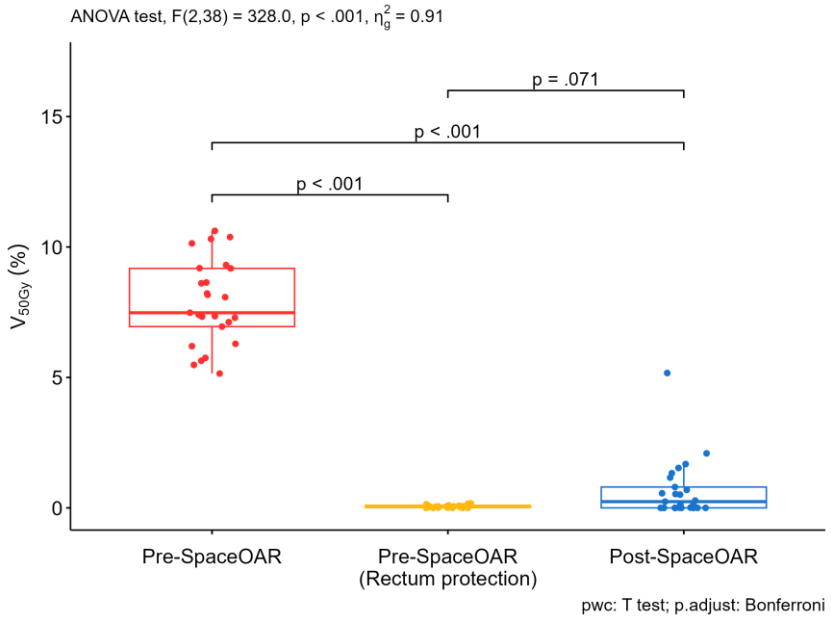
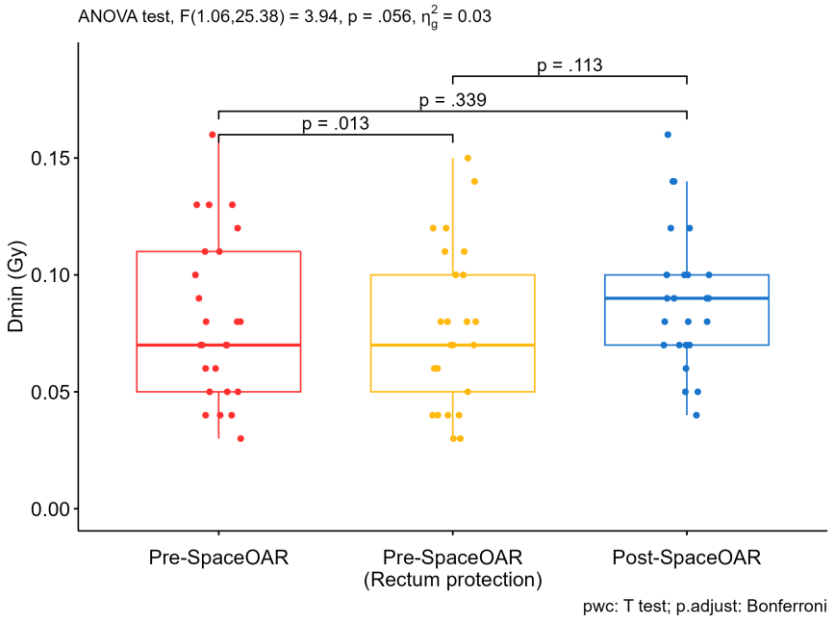


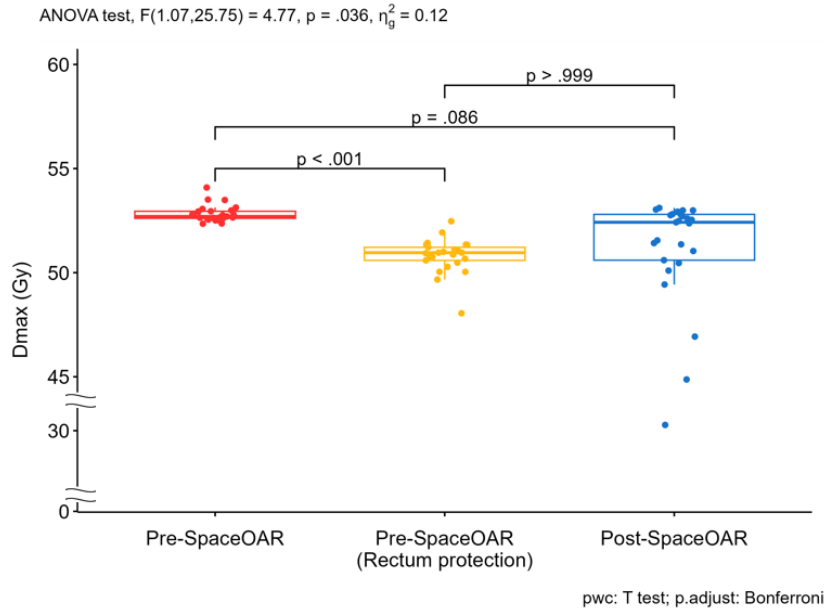
(c)



(d)



(e)



(f)

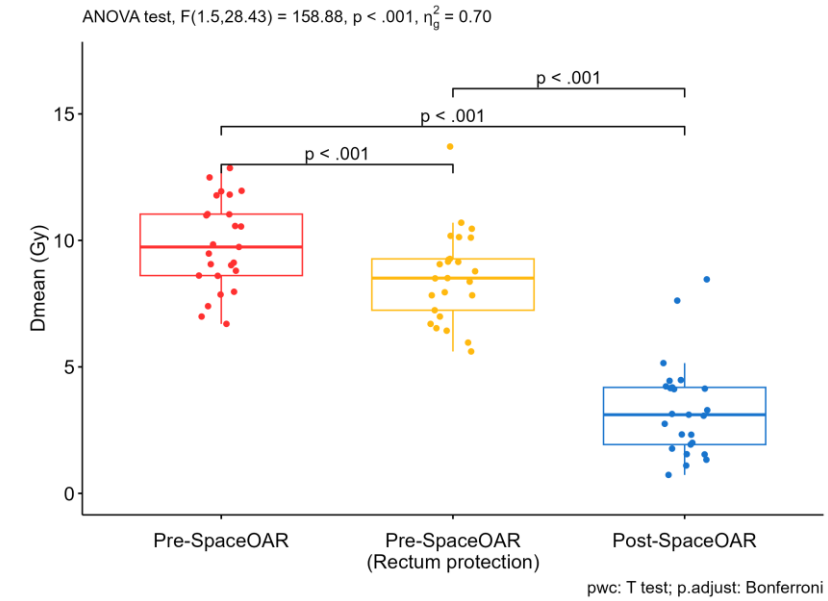


Fig. 5. Rectal dosimetric outcomes for Pre-spaceOAR (Standard Plan), Pre-spaceOAR (Rectum Protection Plan), and Post-spaceOAR. (a) V_{20Gy} (%), (b) V_{40Gy} (%), (c) V_{50Gy} (%), (d) Dmin (Gy), (e) Dmax (Gy) and (f) Dmean (Gy).

3.3. Prostate-Rectum Separation Results

The separation distance between the prostate and rectum for each patient was calculated by averaging the measurements taken at three reference points: 0 cm (central), +1.5 cm (superior), and -1.5 cm (inferior) (Figures 1, 2). Based on these averaged distances, patients were divided into four groups: 0-5 mm (1 patient), 5-10 mm (11 patients), 10-15 mm (11 patients), and >15 mm (2 patients) (Table 7).

Table 7. Patient cases based on Prostate-Rectum separation.

Prostate-Rectum Separation	Patient Cases
0-5 mm	1
5-10 mm	11
10-15 mm	11
>15 mm	2

Note: Patient cases are organized according to the degree of separation between the prostate and the rectum. The degree of separation was determined as the mean of the separation distances measured at the 0 cm, +1.5 cm, and -1.5 cm positions within the prostate.

The introduction of SpaceOAR significantly increased the separation between the prostate and rectum at all measured levels. The mean separation distances and their standard deviations (SD) were recorded for both pre- and post-SpaceOAR conditions. Pre-SpaceOAR measurements showed mean separations of 0.67 cm (SD = 0.62) at +1.5 cm, 0.07 cm (SD = 0.08) at 0 cm, and 0.12 cm (SD = 0.15) at -1.5 cm. Post-SpaceOAR, the separations increased significantly to 1.34 cm (SD = 0.59) at +1.5 cm, 0.98 cm (SD = 0.35) at 0 cm, and 0.84 cm (SD = 0.44) at -1.5 cm. These differences were statistically significant ($p < 0.001$) at all three measurement points, demonstrating the effectiveness of SpaceOAR in increasing the distance between the prostate and rectum across different anatomical levels (Figure 6).

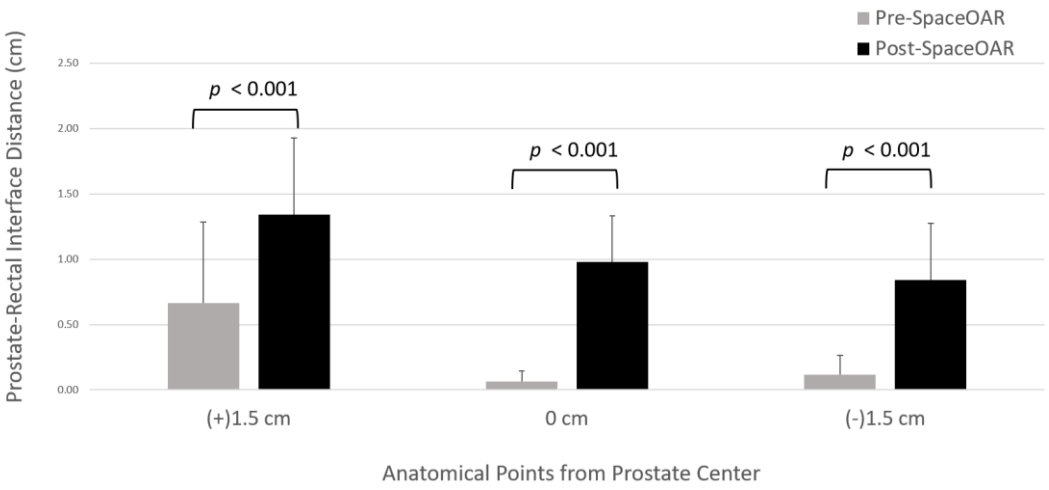


Fig. 6. Prostate-rectum separation before and after injection of SpaceOAR at difference levels of the prostate.

3.4 Rectum DVH Analysis

The analysis of rectum DVH values based on prostate-rectum separation degrees is summarized in Table 8 and Figure 7. Table 8 displays the dose-volume histogram (DVH) values for various separation distances, showing metrics such as Dmin, Dmax, Dmean, V15, V20, V30, V40, and V50. This table indicates that as the separation distance increases, there are observable changes in the percentage of the rectum volume receiving specific doses of radiation.

Figure 7, which visualizes the data from Table 8, provides a graphical representation of the relationship between prostate-rectum separation and rectum DVH values. The slopes for V15, V20, V40, and V50 all show significant negative correlations, with p-values < 0.05. This indicates that as the separation increases, the percentage of rectal volume exposed to radiation doses decreases.

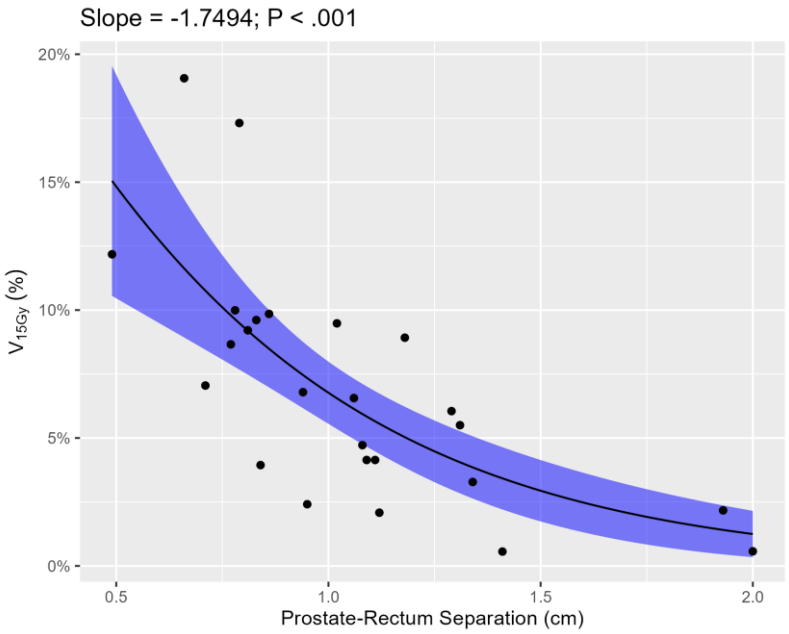
Figure 7 also illustrates the dose metrics in relation to the separation distance. It shows that the minimum, maximum, and mean doses to the rectum tend to decrease with greater prostate-rectum separation. The statistical analysis confirms significant reductions with p-values for Dmin and Dmean being 0.021 and <0.001 respectively. While Dmax showed a decreasing trend with a negative slope, the p-value of 0.140 indicates it is not as statistically significant as the other metrics.

Table 8. Rectum DVH values by Prostate-Rectum separation degree.

Patient No.	Separation Mean (cm)	Dmin (Gy)	Dmax (Gy)	Dmean (Gy)	V15 (%)	V20 (%)	V30 (%)	V40 (%)	V50 (%)
1	0.81	0.08	52.48	4.23	9.21	7.28	5.68	3.48	1.68
2	0.66	0.14	53.03	8.46	19.06	15.46	13.26	9.19	5.17
3	0.77	0.08	52.80	4.12	8.66	7.10	5.20	3.42	1.53
4	0.83	0.09	52.99	4.19	9.61	6.98	5.07	2.66	0.69
5	1.34	0.07	51.55	1.77	3.28	2.13	0.78	0.17	0.00
6	2.00	0.05	50.10	0.73	0.57	0.42	0.15	0.03	0.00
7	1.18	0.08	53.11	4.16	8.92	6.86	4.18	2.14	0.51
8	1.06	0.07	52.81	3.07	6.56	5.06	3.05	1.72	0.56
9	0.79	0.16	52.93	7.62	17.31	14.37	10.59	6.70	2.09
10	1.02	0.10	52.42	4.14	9.48	7.04	3.80	1.60	0.12
11	1.08	0.07	51.04	2.33	4.72	3.29	2.06	0.57	0.11
12	0.95	0.09	46.93	1.55	2.41	1.34	0.45	0.04	0.00
13	0.94	0.05	52.37	3.14	6.79	5.44	3.44	1.76	0.24
14	1.31	0.12	51.36	2.75	5.50	4.16	1.91	0.50	0.01
15	0.71	0.10	52.54	3.29	7.05	5.17	3.28	1.53	0.28
16	0.86	0.07	52.76	4.48	9.85	8.02	5.55	3.52	1.33
17	1.41	0.09	30.22	1.10	0.56	0.12	0.00	0.00	0.00
18	1.93	0.04	49.43	1.33	2.17	1.58	0.66	0.18	0.00
19	1.09	0.06	50.60	2.00	4.14	3.18	1.68	0.62	0.01
20	0.49	0.12	52.99	5.15	12.18	8.35	6.97	3.22	0.53
21	0.78	0.09	52.60	4.45	9.99	7.80	5.28	2.99	0.80
22	0.84	0.09	44.87	1.93	3.94	2.22	0.72	0.07	0.00
23	1.12	0.10	51.42	1.54	2.08	1.54	0.45	0.19	0.00
24	1.29	0.14	52.71	3.11	6.05	4.98	3.79	2.55	1.16
25	1.11	0.10	50.46	2.32	4.14	2.93	1.22	0.41	0.00

Note: *Separation mean value is measured in centimeters (cm). DVH values are represented as percentages (%) and doses in Gray (Gy). Data is rounded to two decimal places.*

(a)



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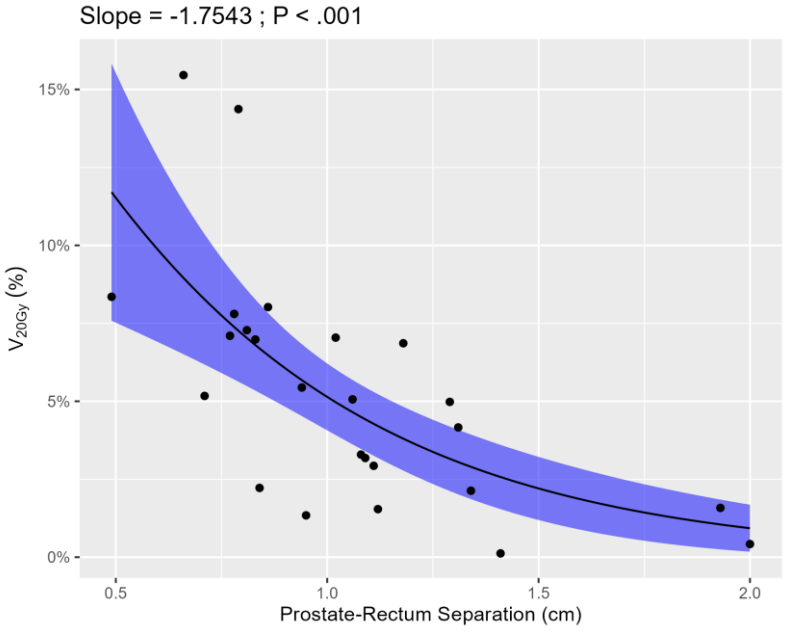

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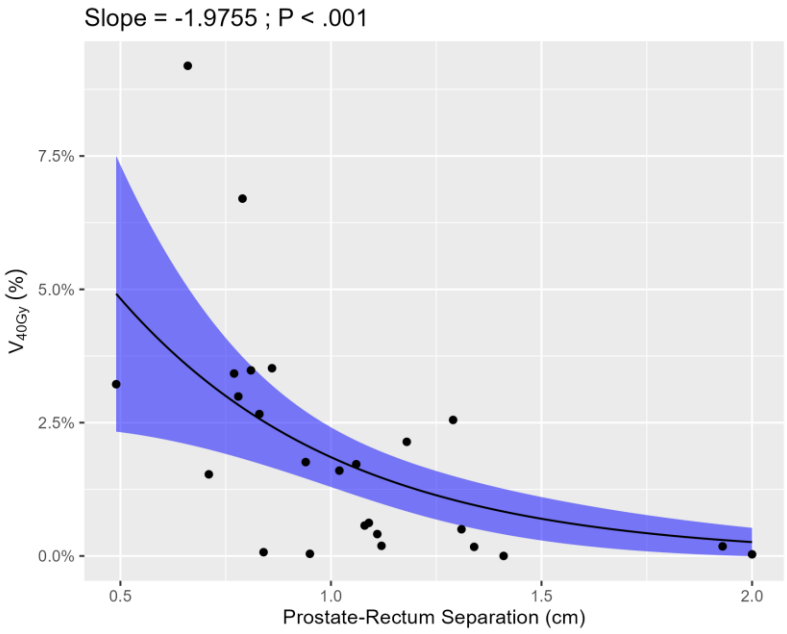

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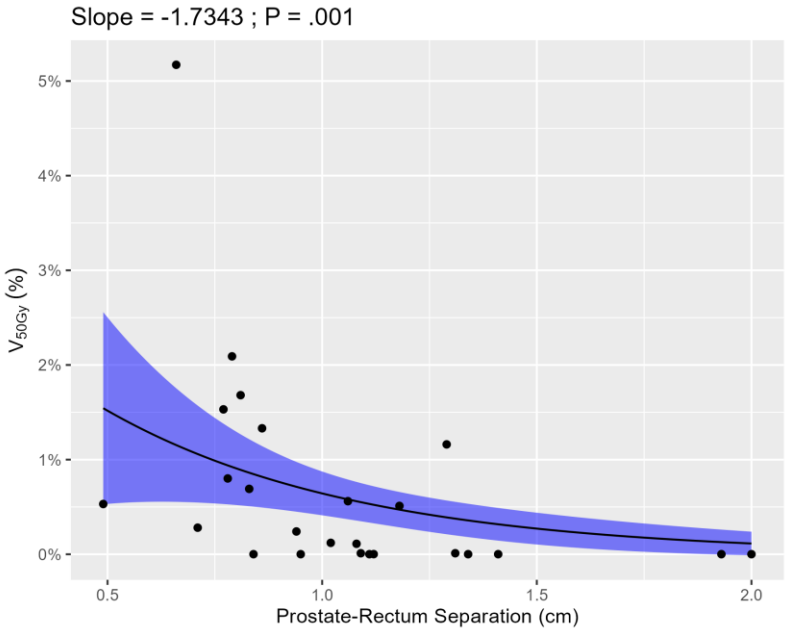

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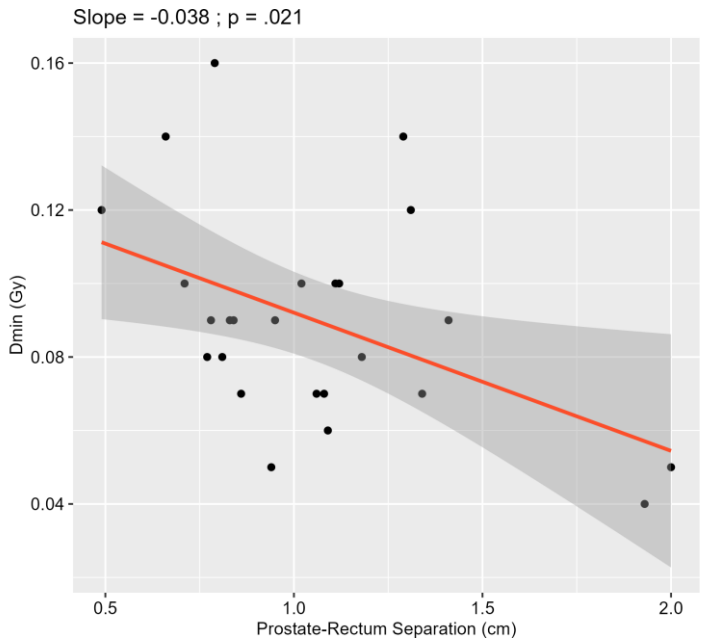

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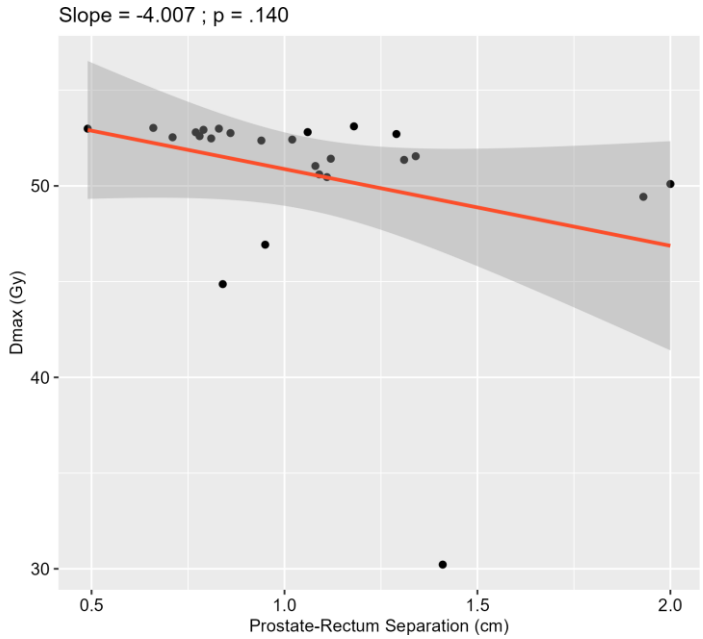

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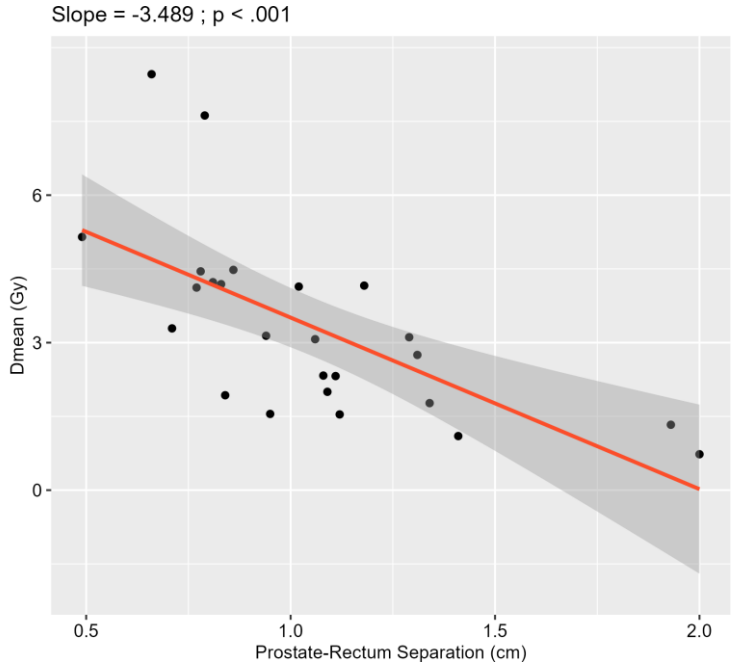

Fig. 7. Rectum DVH values by Prostate-Rectum separation degree. (a) V_{15Gy} (%), (b) V_{20Gy} (%), (c) V_{40Gy} (%), (d) V_{50Gy} (%), (e) Dmin (Gy), (f) Dmax (Gy) and (g) Dmean (Gy).

3.5 Robust evaluation

The robust evaluation of anatomical organs was conducted to assess the passing rates across different conditions: pre-SpaceOAR, pre-SpaceOAR with rectum protection, and post-SpaceOAR. These passing rates were evaluated based on the dose criteria outlined in Table 1. Each criterion was analyzed separately for the right (RT) and left (LT) directions, with the mean passing rates and standard deviation (SD) values for the prostate, rectum, and bladder recorded in Table 9.

For the prostate, the evaluation considered two criteria: doses at 99.9% and 100% of the volume, with the mean passing rate recorded as 40.06% (SD = 44.10) pre-SpaceOAR, 0.00% (SD = 0.00) pre-SpaceOAR with rectum protection, and 37.81% (SD = 39.07) post-SpaceOAR. For the rectum, the evaluation used three criteria: at most 1.00 cm^3 volume at 49.02 Gy, 5.00 cm^3 at 41.28 Gy, and 10.00 cm^3 at 25.80 Gy. The mean passing rate increased significantly from 40.77% (SD = 22.58) pre-SpaceOAR to 60.35% (SD = 11.98) with rectum protection, and further to 83.33% (SD = 15.71) post-SpaceOAR. The bladder was evaluated based on two criteria, maintaining a 100% passing rate across all conditions (Table 1, 9).

Since the rectum is the primary organ at risk in prostate cancer treatment, the analysis focused on comparing the rectal passing rates before and after SpaceOAR insertion. Figure 8 provides a detailed analysis of the rectum's robust evaluation passing rates, based on the three criteria outlined in Table 1. The results showed that the passing rates were significantly higher post-SpaceOAR compared to pre-SpaceOAR and pre-SpaceOAR with rectum protection, with p-values <0.05 for all comparisons. Additionally, the passing rates for pre-SpaceOAR with rectum protection were significantly higher than pre-SpaceOAR ($p < 0.05$). Box plots and statistical methods, including ANOVA and post-hoc tests, were used to illustrate and analyze the variations in passing rates, highlighting the effectiveness of SpaceOAR in improving treatment plan robustness (Figure 8).

Table 9. Robust evaluation passing rates for anatomical organs.

Anatomical Sites	Pre-SpaceOAR		Pre-SpaceOAR (Rectum Protection)		Post-SpaceOAR	
	Mean	SD	Mean	SD	Mean	SD
Prostate	40.06	44.10	0.00	0.00	37.81	39.07
Rectum	40.77	22.58	60.35	11.98	83.33	15.71
Bladder	100.00	0.00	100.00	0.00	100.00	0.00

Note: Mean and standard deviation (SD) values are represented as percentages (%).

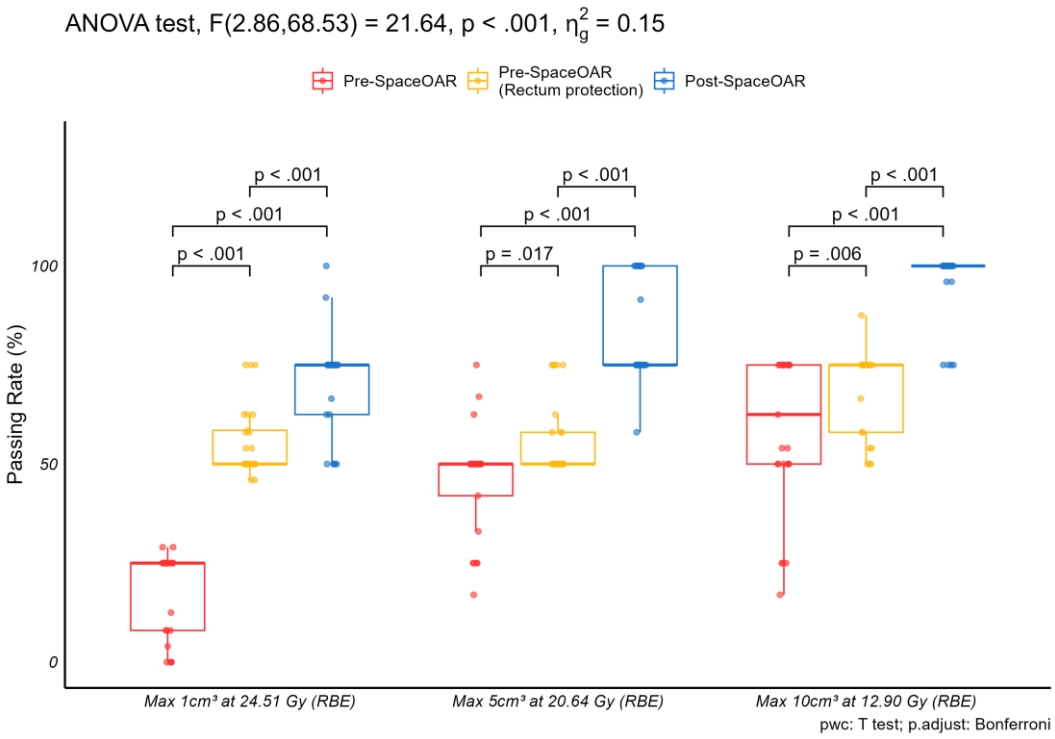

Fig. 8. Rectum: Robust evaluation passing rate results by criteria.

3.6 ProKnow Scoring

The ProKnow scoring analysis was conducted to compare CT plan scores across three different stages: pre-SpaceOAR with standard planning, pre-SpaceOAR with rectum protection planning, and post-SpaceOAR. The ProKnow scoring in this study was based on the aggregate of all evaluation criteria for the prostate, rectum, bladder, and penile bulb, as outlined in Table 1.

Table 10 shows the scores for 25 patients across the three groups with a maximum score of 64 points and the percentage of the maximum score. In cases 6, 7, 18, and 21, the rectum protection score for pre-SpaceOAR was lower than the pre-SpaceOAR score. Notably, in case 9, the post-SpaceOAR score was lower than the rectum protection score. When averaging the scores across all 25 patients, the rectum protection score was higher than the pre-SpaceOAR score, and the post-SpaceOAR score was the highest among the three conditions.

In the standard plan before SpaceOAR insertion, the mean score was 28.19 (44.05%) with an SD of 5.03 (7.86%), while the rectum protection plan before SpaceOAR showed a slightly higher mean score of 33.80 (52.81%) with an SD of 4.89 (7.64%). After SpaceOAR insertion, the mean score significantly increased to 56.98 (89.03%) with an SD of 5.19 (8.11%).

Figure 9 graphically represents these differences, showing the statistical significance of the improvements with p-values all being <0.001.

Table 10. Comparative Analysis of Plan Scores Pre-SpaceOAR, Pre-SpaceOAR (Rectum Protection), and Post-SpaceOAR Injection.

Case	Pre-SpaceOAR	%	Pre-SpaceOAR (Rectum Protection)	%	Post- SpaceOAR	%
1	27.09	42.33%	29.27	45.73%	53.16	83.06%
2	36.17	56.52%	38.10	59.53%	46.82	73.16%
3	25.77	40.27%	31.92	49.88%	54.15	84.61%
4	20.68	32.31%	25.06	39.16%	58.49	91.39%
5	27.42	42.84%	36.08	56.38%	58.91	92.05%
6	37.66	58.84%	35.93	56.14%	60.00	93.75%
7	28.37	44.33%	26.66	41.66%	57.78	90.28%
8	25.10	39.22%	35.27	55.11%	61.51	96.11%
9	22.01	34.39%	43.03	67.23%	37.63	58.80%
10	29.03	45.36%	37.35	58.36%	58.57	91.52%
11	37.77	59.02%	41.26	64.47%	59.65	93.20%
12	28.41	44.39%	34.00	53.13%	59.40	92.81%
13	25.69	40.14%	32.73	51.14%	58.58	91.53%
14	22.13	34.58%	31.15	48.67%	59.52	93.00%
15	34.77	54.33%	45.34	70.84%	60.30	94.22%
16	23.74	37.09%	32.38	50.59%	51.30	80.16%
17	24.10	37.66%	27.31	42.67%	59.27	92.61%
18	31.54	49.28%	29.18	45.59%	59.75	93.36%
19	24.00	37.50%	31.69	49.52%	59.72	93.31%
20	27.53	43.02%	33.14	51.78%	56.78	88.72%
21	36.75	57.42%	35.82	55.97%	58.73	91.77%
22	23.49	36.70%	31.01	48.45%	58.11	90.80%
23	29.06	45.41%	34.19	53.42%	59.96	93.69%
24	27.45	42.89%	36.22	56.59%	56.44	88.19%
25	29.05	45.39%	30.85	48.20%	59.96	93.69%
Mean	**28.19**	**44.05%**	**33.80**	**52.81%**	**56.98**	**89.03%**
SD	**5.03**	**7.86%**	**4.89**	**7.64%**	**5.19**	**8.11%**

Note: A perfect score in this analysis is 64 points.

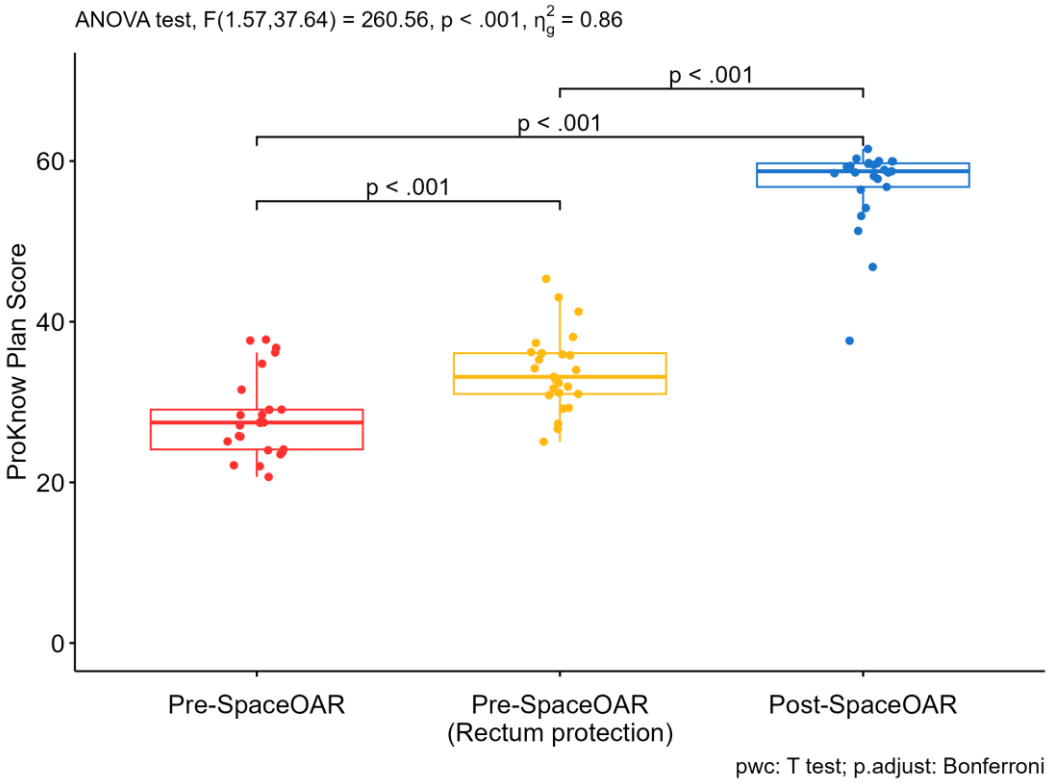

Fig. 9. Comparison of *p*-values from ProKnow plan evaluation.

4. Discussion

This study evaluated the impact of SpaceOAR insertion on the efficacy and safety of CIRT treatment plans for prostate cancer patients. The results showed that SpaceOAR insertion significantly reduced radiation exposure to the rectum while maintaining the therapeutic efficacy for the prostate, thus improving overall treatment outcomes [1, 7, 8].

Despite the reduction in rectal dose following SpaceOAR insertion, the therapeutic efficacy for the prostate remained unchanged. There were no significant differences in the prostate's Dmin, Dmax, and Dmean values before and after SpaceOAR insertion, indicating that SpaceOAR effectively protected the rectum without compromising the prostate treatment. Analysis of the rectum showed that the Dmean significantly decreased after SpaceOAR insertion, while there were no significant changes in the Dmin and Dmax [7, 23]. This suggests that SpaceOAR effectively reduced the mean dose to the rectum without requiring modifications to the treatment plan, thus improving the efficiency of rectal protection [8]. For the penile bulb, there were no significant changes in the Dmin and Dmax values before and after SpaceOAR insertion, but the Dmean significantly increased. Additionally, V15 to V50 values showed significant changes in both pre- and post-SpaceOAR phases, suggesting that the small volume of the penile bulb and positional changes caused by SpaceOAR affected the dose distribution [24] (Table 6).

The pre-SpaceOAR rectum protection plan focused on protecting the rectum, but in some cases, it compromised PTV coverage and negatively impacted the quality of the treatment plan. This was attributed to a reduction in the dose delivered to the prostate, resulting in lower prostate scores. These findings suggest that rectum protection plans negatively affected the uniformity of prostate treatment. Additionally, in one case, the rectum protection score was higher than the post-SpaceOAR score due to the higher weighting of the rectum compared to other organs (Table 1, 2, 10). Overall, these results demonstrate that the rectum protection plan in the pre-SpaceOAR phase affected PTV coverage, while SpaceOAR insertion successfully reduced rectal toxicity, maintained prostate treatment efficacy, and improved the overall quality of the treatment plan (Figure 9).

Unlike previous studies, this research is one of the first to specifically evaluate the combined effect of SpaceOAR and carbon ion radiotherapy (CIRT) in treating prostate cancer. While prior studies have focused primarily on photon-based radiotherapy, this study analyzed the effectiveness of SpaceOAR in CIRT, demonstrating its potential [7, 8, 25].

Additionally, various plan quality metrics were utilized to evaluate the quality of the treatment plans. The increase in physical distance between the prostate and rectum was

measured in the anterior-posterior direction, allowing for a quantitative analysis of the tissue separation after SpaceOAR insertion (Table 7, Figure 6). Through robust evaluation passing rate analysis, we assessed the robustness of the treatment plans before and after SpaceOAR insertion, ensuring the safety and reliability of the plans. Notably, the success rate of rectal protection significantly improved following the insertion of SpaceOAR (Table 9, Figure 4, 8). Using the ProKnow scoring system, treatment plans for 25 patients were compared, and the results showed a significant improvement in overall plan quality after SpaceOAR insertion, positively impacting clinical goal achievement [26] (Table 2, 10, Figure 9). Lastly, the findings support the safety and effectiveness of SpaceOAR insertion, indicating that the combination of SpaceOAR and CIRT is a promising treatment strategy for prostate cancer [1] (Table 5). Although this study is based on simraystatiulations, it is important to note that in clinical practice, the accuracy of treatment plans can be verified through radiation delivery to phantoms or ion chambers, allowing for validation of the simulation results. This process ensures that the planned and delivered dose distributions align, verifying the reliability of the treatment planning system (TPS) [27, 28].

This study provides significant evidence that the combination of SpaceOAR and CIRT has a positive impact on prostate cancer treatment. Future research should further explore and deepen these findings to enhance clinical applications [1].

As previously mentioned regarding the patient cohort, the recruitment of patients for this study posed several challenges due to strict exclusion criteria. Although this was a retrospective study based on patient data, it took a full year to recruit the necessary number of patients for this research. This study, being the first in Korea to combine CIRT and SpaceOAR insertion, could not rely on external data from other institutions, necessitating the use of retrospective patient data for treatment planning. Each patient required the creation and analysis of three different treatment plans, which demanded considerable time and effort. Due to the limitations of treatment planning systems (TPS) in quantitatively comparing the quality of the three treatment plans, the ProKnow evaluation tool was employed. ProKnow allowed for quantitative comparisons across plans, and the analysis adhered to the institution’s dose evaluation criteria. Additionally, since the study was conducted using retrospective patient data, it required approval from the Institutional Review Board (IRB).

5. Limitations

The results of this study provide strong evidence supporting the use of the SpaceOAR system in carbon ion therapy for prostate cancer, but several limitations must be acknowledged.

One limitation is the relatively small sample size, which, while informative, reduces the statistical power of the study's outcomes. A larger cohort would enhance statistical validity and enable more granular analyses, including subgroup assessments based on patient demographics, tumor characteristics, and treatment histories. Future studies should seek to include a more diverse and expansive patient population to improve the external validity of these findings [7, 29] (Table 3). Additionally, this study primarily focuses on the immediate and short-term outcomes following SpaceOAR insertion (Table 5). To comprehensively assess the long-term benefits and potential late toxicities associated with SpaceOAR in CIRT, extended follow-up is necessary. Long-term data are critical for fully evaluating the impact of delayed adverse effects on patient quality of life and overall treatment success [30].

Furthermore, incorporating a patient-reported outcomes questionnaire from the point of SpaceOAR insertion until the commencement of treatment could have provided insights into the side effects experienced by patients during their daily lives after receiving SpaceOAR. This would allow for an evaluation of the adverse effects related solely to the insertion of the SpaceOAR device, independent of the CIRT process. Separately assessing these effects before the initiation of CIRT would have enhanced the clarity regarding the device’s safety profile and its role in patient discomfort. Moreover, the evaluation of toxicity related to invasive procedures, such as the insertion of SpaceOAR, represents an important aspect that could have been further investigated. Assessing procedural complications and adverse effects would provide a more comprehensive understanding of SpaceOAR's safety, especially in the context of its use alongside carbon ion therapy [31, 32].

Collectively, these findings highlight the significant potential of integrating advanced spacer technologies such as SpaceOAR into carbon ion therapy. Ongoing research and clinical trials are imperative to optimize these technologies and ensure they deliver maximum therapeutic benefits to patients.

6. Conclusions

Integrating SpaceOAR into carbon ion radiotherapy (CIRT) for prostate cancer represents a significant advancement in radiation therapy techniques. This study demonstrates that SpaceOAR effectively increases the separation between the prostate and rectum, resulting in more favorable dose distribution and enhanced protection of critical organs at risk (OAR), particularly the rectum. The significant reduction in high-dose radiation exposure plays a crucial role in minimizing rectal toxicity and improving patient outcomes [1, 7, 29].

The ProKnow scoring analysis further highlights the improvement in treatment plan quality following SpaceOAR insertion. The substantial increase in plan scores underscores the efficacy of SpaceOAR in enhancing the precision and effectiveness of CIRT. This improvement is likely to lead to better clinical outcomes, including higher tumor control rates and reduced side effects [30].

As a medical device, the absorbable hydrogel composition of SpaceOAR offers both flexibility and precision, effectively minimizing interactions with surrounding tissues and reducing long-term complications. Its utility extends beyond rectal protection, facilitating more aggressive therapeutic approaches, such as higher radiation doses, which ultimately enhance tumor control. Consequently, SpaceOAR is an indispensable tool for optimizing patient safety while maximizing treatment efficacy. The clinical success of SpaceOAR underscores its potential for broader application across various radiation therapy modalities, including more advanced techniques such as carbon ion radiotherapy (CIRT). This potential is likely to promote its further adoption in clinical settings globally, establishing SpaceOAR as a standard component in prostate cancer radiotherapy [7, 33, 34].

In conclusion, the findings of this study provide compelling evidence for the routine integration of SpaceOAR in CIRT for prostate cancer. The marked improvements in dose distribution, organ-at-risk (OAR) protection, and overall plan quality underscore the clinical efficacy and safety of SpaceOAR. Its seamless integration into existing radiotherapy workflows, alongside its substantial clinical validation, positions SpaceOAR as a crucial instrument in advancing both patient safety and treatment outcomes. Future research should aim to validate these findings in larger, long-term studies and further explore the sustained benefits of this intervention. With ongoing research and validation, SpaceOAR holds the potential to become a standard element in prostate cancer radiotherapy, contributing to improved treatment outcomes and enhanced quality of life for patients.

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Abstract in Korean

전립선암으로 탄소 중입자치료를 시행 받는 환자에서 직장 독성 감소를 위해 생분해성 하이드로겔(SpaceOAR) 주입 전과 후의 방사선 치료 계획의 비교 분석

목적: 본 연구는 전립선암 환자를 위한 탄소이온 방사선 치료(CIRT) 계획에서 SpaceOAR 삽입이 효능과 안전성에 미치는 영향을 평가하는 것을 목적으로 하였다. 특히, SpaceOAR가 CIRT 중 전립선 및 주변 장기, 특히 직장에 대한 선량 분포에 미치는 영향을 중점적으로 분석하였다.

방법: 전이성 전립선암이 없는 25명의 환자를 대상으로 전립선과 직장 사이에 SpaceOAR을 삽입하였다. RayStation 치료 계획 시스템을 이용하여 치료 계획을 생성하였고, 이를 기존 치료 계획, 직장 보호 계획, SpaceOAR 삽입 후 계획과 선량–부피 히스토그램(DVH) 등의 선량학적 지표를 비교하였다. 급성 독성은 치료 시작 후 90일 이내에 평가하였다. 또한, 환자의 위치 설정 불확실성에 대한 치료 계획의 강건성 평가를 수행하였고 ProKnow 스코어링을 통해 치료 계획의 품질을 평가하였다.

결과: SpaceOAR 삽입이 없는 기존 CIRT 및 직장 보호 계획과 비교했을 때, SpaceOAR 삽입 후 계획에서는 25명의 사례 모두에서 직장에 대한 방사선량이 유의하게 감소한 것으로 나타났다($p < 0.001$). SpaceOAR 삽입은 DVH 분석 및 ProKnow 스코어링을 통해 직장의 평균 선량 감소 및 우수한 계획 품질을 입증하였다($p < 0.001$). 강건성 평가 결과, SpaceOAR 삽입이 치료 계획의 강건성과 안전성을 향상시키는 것으로 확인되었다.

결론: 본 연구는 전립선암에 대한 CIRT에 SpaceOAR을 통합함으로써 직장 방사선 노출을 크게 줄이고 방사선 독성을 감소시키며, 표적 부위에 대한 선량 증가가 가능하다는 점을 성공적으로 입증하였다.

핵심되는 말: SpaceOAR, 탄소이온 방사선치료 (CIRT), 전립선암, 직장 독성, 선량–부피 히스토그램 (DVH), 방사선 치료 계획, ProKnow 스코어링, 강건성 평가, 급성 독성