A dosimetric analysis of rectal hydrogel spacer use in patients with recurrent prostate cancer undergoing salvage high-dose-rate brachytherapy

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Abstract

Background/objective: We hypothesize rectal hydrogel spacer (RHS) improves rectal dosimetry in patients undergoing salvage high-dose-rate brachytherapy (HDR-BT) for intact, recurrent prostate cancer (PC).

Methods: A prospectively collected institutional database was queried for recurrent PC patients treated with salvage HDR-BT from 09/2015 to 11/2021. Patients were offered RHS beginning 06/2019. Dosimetric variables were compared between RHS and no-RHS groups for the average of two fractions using Wilcoxon rank-sum tests. Primary outcomes were rectal volume receiving 75% of prescription dose (V75%) and prostate volume receiving 100% of prescription dose (V100%). Generalized estimating equation (GEE) model was used to evaluate the association between other planning variables and rectal V75%.

Results: Forty-one PC patients received salvage HDR-BT, of whom 20 had RHS. All patients received 2400cGy in 2 fractions. Median RHS volume was 6.2cm^3 [Standard deviation (SD): ± 3.5cm^3]. Median follow-up was 4 months and 17 months in the RHS and no-RHS groups, respectively. Median rectal V75% with and without RHS were 0.0cm3 (IQR: 0.0–0.0cm3) and 0.06cm3 (IQR: 0.0–0.14cm3), respectively (p<0.001). Median prostate V100% with and without RHS were 98.55% (IQR: 97.86–99.22%) and 97.78% (IQR: 97.50–98.18%), respectively

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(p=0.007). RHS, rectum, and prostate volumes did not significantly affect rectal V75% per GEE modeling. There was 10% G1–2 and 5% G3 rectal toxicity in RHS group. There was 9.5% G1–2 and no G3+ rectal toxicities in the no-RHS group.

Conclusion: Absolute improvement in rectal V75% and prostate V100% was significant with RHS in PC patients undergoing salvage HDR-BT, but clinical benefit is marginal.

Keywords

Rectal hydrogel spacer; high dose-rate brachytherapy; prostate cancer; salvage therapy; re-irradiation; dosimetry

INTRODUCTION

Due to high toxicity rates of salvage therapies, less than 20% of patients with locally recurrent, intact prostate cancer historically underwent salvage therapies and the majority have received androgen deprivation therapy (ADT) alone [1, 2]. The ADT-delaying and potentially curative benefits of radiotherapy salvage options, which have roughly 50% 5-year biochemical control and relapse-free survival rates, must be weighed against their increased risk of toxicities in the reirradiation setting [3, 4]. External beam reirradiation with conventional fractionation results in unacceptably high late toxicity with approximately 30% of patients experiencing grade 4 genitourinary (GU) and gastrointestinal (GI) side effects [5]. Stereotactic body radiotherapy has demonstrated a more favorable late toxicity profile but with short follow-up [6, 7]. High-dose-rate brachytherapy (HDR-BT) has emerged as a favorable modality for reirradiation due to its sharp conformality and steep dose fall-off which limit bladder and rectal dose [8]. Studies with 5 or more years of follow-up have reported rates of G3+ late GU and GI adverse events in the 0–20% range [9–11]. Focal HDR-BT guided by magnetic resonance imaging to target only recurrent lesions instead of whole prostate gland have further improved GU and GI toxicity rates. Grade 3 or higher toxicities with a single 19Gy dose or two 13.5Gy fractions of focal HDR-BT have been reported to be very low with no acute GU and GI G3+ events, no late G3+ GI events, and <5% late G3+ GU toxicity [12, 13]. However, this technique has not been compared to whole-glade HDR-BT and may impose technical and resource limitations. In order to increase the number of patients receiving potentially curative reirradiation, the toxicities of salvage whole-gland HDR-BT should be further diminished.

Rectal hydrogel spacers (RHS) are injected through the perineum between the prostate and anterior rectal wall. They have been shown to significantly reduce acute and late rectal toxicity in the external beam setting due to increased distance for dose fall-off between the prostate and rectum [14]. Patients with RHS receiving first-line external beam radiotherapy for prostate cancer have demonstrated a 5% absolute risk reduction in late rectal toxicity. Late G3 rectal toxicity with combined modality external beam plus HDR-BT boost, in which higher total doses to prostate are achieved, can be limited to <1% with RHS [15, 16]. Currently, toxicity benefits of RHS in salvage prostate reirradiation with HDR-BT are unknown. Limited series have reported improvements in rectal dosimetry of first-line HDR-BT and salvage low-dose-rate brachytherapy with RHS, but the effects of RHS in salvage HDR-BT have not been demonstrated [17, 18]. Herein, we present the first report on

the dosimetric and toxicity effects of RHS in the setting of salvage whole-gland HDR-BT for locally recurrent, intact prostate cancer.

METHODS

Patients

This is a single-institution retrospective analysis of a prospectively collected database of prostate cancer patients treated at a high-volume tertiary care center of excellence for brachytherapy. Our database was queried for patients 18 years of age who had intact prostate cancer initially treated with radiotherapy and subsequently developed biopsy-proven local recurrence and received salvage whole-gland HDR-BT between September, 2015, to November, 2021. All grade groups and PSA values at the time of recurrence were allowed. Initial radiotherapy could include external beam photon or proton irradiation, as well as permanent low-dose-rate brachytherapy seed implants or HDR-BT. Not all patients necessarily received their first radiotherapy course at our institution. September 2015 was chosen as the cutoff date because that is when we adopted trans-rectal ultrasound-based treatment planning for all of our prostate cancer HDR-BT cases.

Treatment

To evaluate whether prostate size and pelvic anatomy was amenable to HDR-BT, MRI volume study of the pelvis was performed 1–2 weeks prior to the first scheduled HDR-BT fraction. All patients were offered RHS as an elective procedure beginning June, 2019. The main components of RHS were water and polyethylene glycol. Placement of RHS was performed by a urologist. Patients were placed in supine position and external genitalia were retracted out of the operative field. The perineum was prepped with povidone-iodine antiseptic; then local anesthesia was placed superficially to the level of the apex of the prostate. Following mixing of RHS solutions, bi-planar ultrasound guidance was used to inject RHS between the rectum and prostate throughout their cranial-caudal interface. In patients opting for general anesthesia, laryngeal mask airways and operating rooms were used for the procedure. Pelvic MRI was done 1–2 weeks following RHS placement to measure prostate volume, assess pelvic anatomy, and confirm RHS placement position. Patients were given bowel prep instructions to follow prior to each HDR-BT fraction and were started on tamsulosin 0.4 mg twice daily for prophylaxis against bladder outlet obstruction.

All patients received salvage whole-gland HDR-BT to the prostate without simultaneous integrated boost to radiographically identified lesions. All HDR-BT procedures were performed under general anesthesia and in a shielded operating room. Patients were placed in supine position with their lower extremities elevated in stirrups to allow access to their perineum. A trans-rectal ultrasound probe and a needle template were attached to a frame which allowed controlled motion in six axes. This frame was fixed to the operating room table. Ultrasound positioning is adjusted antero-posteriorly to optimize image quality while minimizing pubic arch interference. If needle placement is obstructed by the pubic arch, posterior pressure is applied on the ultrasound probe to bring the prostate posteriorly. Stainless steel interstitial needles (20 cm x 18 G) were guided into each patient's prostate

through the perineum using the needle template which was calibrated to an ultrasound grid. The grid had 169 holes arranged in square 13×13 format with 5mm between each hole. Once an axial slice of the prostate was visualized on ultrasound, needles were placed around the peripheral zone of the prostate with approximately 10 mm between each adjacent needle. Two to four central needles were also placed at least 10 mm from the urethra. The needles were then advanced to the base of the prostate, with the most posterior needles being advanced ~10 mm into the seminal vesicles. Cystoscopy was performed by a urologist to confirm no needles perforated the bladder.

Contouring of the prostate, urethra, rectum, bladder, and RHS (if present) was done on an ultrasound-based treatment planning system. The prostate was contoured directly as a planning target volume. Each patient was prescribed 1200 cGy per fraction to the whole prostate, and two fractions were performed one to two weeks apart. Treatment planning goals included prostate volume receiving 100% of prescription dose (V100%) 95%, rectum volume receiving 75% of prescription dose (V75%) < 1.0 cm^3, bladder V75% < 1.0 cm^3, and urethra V125% < 1.0 cm^3. Prostate V150% $< 35\%$ was a secondary goal. A single iridium-192 source was delivered via an afterloader sequentially through each needle using predetermined dwell times.

Statistical Analysis

Demographic variables and gastrointestinal and genitourinary toxicity outcomes were queried from a prospectively collected database and reported descriptively. Volume of RHS and prostate-rectum separation (defined as the shortest distance between prostate and rectum in each patient with RHS on sagittal MRI at mid-gland) were not recorded in the treatment planning documents and were measured directly in the treatment planning software. Dosimetric variables were retrospectively extracted by reviewing treatment plan documents for every fraction. To account for physical changes in prostate, rectal, and RHS volumes, as well as contouring differences between two fractions for the same patient, dosimetric variables for first and second fractions were averaged.

Patient demographic and clinical characteristics were summarized by RHS and no-RHS groups. Comparison of dosimetry between RHS and no-RHS groups for the average of two fractions was done using Wilcoxon rank-sum tests. First and second fraction dosimetry were also compared between RHS and no-RHS groups without averaging for validation. The primary variables of interest were rectal V75% and prostate V100%. In addition, prostate V150% and V200%, dose to 100% (D100%), D75%, D50%, D25%, and D0.1% of the rectum, homogeneity index, and volumes of the prostate and rectum were also analyzed. Homogeneity index of each treatment plan was a ratio calculated by dividing V150% by V100%. Finally, generalized estimating equation (GEE) model was used to evaluate the effect of inter-fraction changes in rectum, prostate, and RHS volumes on rectum V75%. Analyses were done using R version 4.1.2 with 2-sided p < 0.05 to indicate statistical significance.

RESULTS

There were 475 patients in our prospectively collected database of prostate cancer patients undergoing HDR-BT during September, 2015, to November, 2021. Of these, 41 received salvage, whole-gland HDR-BT for intact, recurrent prostate cancer. There were 20 patients in the RHS group and 21 patients in the no-RHS group. Urologists did not report any technical challenges for RHS placement in any of the operative notes. Rectal infiltration was not documented in operative reports either. On post-RHS pelvic MRI, no patient had definitive radiographic evidence of rectal wall infiltration. Trans-rectal ultrasound visibility of the prostate and interstitial needles was excellent in both the RHS and no-RHS groups. There were no cases of iatrogenic bladder perforation in either group. Median follow-up was 4 months in the RHS group and 17 months in the no-RHS group. Median age was 73 years [Interquartile range (IQR): 67 – 76 years)] in the RHS group and 70 years (IQR:67–77) years in the no-RHS group. Conventionally or moderately hypofractionated intensity modulated radiotherapy was the most commonly used initial treatment modality in both groups, followed by proton beam therapy. Additional patient and treatment-related variables are presented in Table 1.

The 41 patients underwent a total of 82 fractions of prostate HDR-BT (2 fractions per patient). Mean RHS volume was 6.2 cm^3 [Standard deviation (SD): $\pm$ 3.5 cm^3] and mean prostate-rectum separation at mid-gland on pre-treatment MRI was 8.0 mm (SD: $\pm$ 2.8 mm). In the no-RHS group, all but 3 patients had direct contact between anterior rectal wall and prostate at mid-gland (2 patients with 1 mm fat plane separation and 1 patient with 2.5 mm separation). Axial and 3-dimensional views of target and avoidance structures on ultrasound imaging with and without RHS are shown in Figure 1. Mean prostate volume was 28.1 cm^3 (SD: $\pm$ 6.4 cm^3) in the RHS group and 27.0 cm^3 (SD: $\pm$ 12.4 cm^3) in the no-RHS group. Mean rectum volume was 22.6 cm^3 (SD: $\pm$ 7.4 cm^3) in the RHS group and 22.0 cm^3 (SD: $\pm$ 7.8 cm^3) in the no-RHS group. There was statistically significant improvement in the primary variables of interest in the RHS group. Median rectal V75% was 0.0 cm^3 (IQR: 0.0 – 0.0 cm^3) in the RHS group and 0.06 cm^3 (IQR: 0.0 – 0.1 cm^3) in the no-RHS group, p < 0.001. Dose-volume histogram of rectum D100%, D75%, D50%, D25%, and D0.01% in RHS and no-RHS groups is presented in Figure 2. Of these variables, D75%, D25%, and D0.1% were significantly lower in the RHS group at 2.3 Gy (IQR: 2.1 – 2.5 Gy) vs 2.7 Gy (IQR: 2.4 – 3.1 Gy), 4.2 Gy (IQR: 3.6 – 4.7 Gy) vs 4.7 Gy (IQR: 4.5 – 5.2 Gy), and 7.6 Gy (IQR 6.8 – 8.2 Gy) vs 9.0 Gy (8.9 – 9.8 Gy), respectively. Median prostate V100% was 98.6% (IQR: 97.9 – 99.2%) in the RHS group and 97.8% (IQR: 97.5 – 98.2%) in the no-RHS group, p = 0.007. Median homogeneity index in the no-RHS group was 0.38 (IQR: 0.36–0.40) and in the RHS group was 0.35 (IQR: 0.34–0.38), p = 0.10. A summary of dosimetric variables for the prostate and rectum is provided in Supplementary Table 1.

Intra-fraction changes in RHS, rectum, and prostate volumes did not significantly affect rectum V75% on GEE modeling. Variation of intra-fraction RHS volume by 1 cm^3 results in 0.0015 cm^3 change in rectum V75% (95% CI: –0.0018 – 0.0047 cm^3, p = 0.38). Changes in intra-fraction rectum and prostate volumes by 1 cm^3 also had insignificant effects on rectum V75%: –0.0003 cm^3 (95% CI: –0.0011 – 0.0006 cm^3, p = 0.54) and 0.0008 cm^3 (95% CI: –0.0011 – 0.0027 cm^3, p = 0.39), respectively.

Acute and late toxicities were similar between RHS and no-RHS groups. In terms of GI toxicity, there was one grade 1 and one grade 2 acute toxicity, and one grade 3 late toxicity in the RHS group. The single grade 3 late toxicity was in a patient who developed an enterovesicular fistula and required diverting colostomy 4 months following his second salvage HDR-BT fraction. This patient originally received 79.2GyE in 44 fractions via proton beam therapy. In the no-RHS group, there was one grade 1 and one grade 2 acute toxicity, and no patient developed late toxicities. Additionally, there were 7 grade 1–2 acute GU toxicities in the RHS group and 6 grade 1–2 acute GU toxicities in the no-RHS group. One patient in each of the RHS and no-RHS groups developed late GU toxicity. Both late GU toxicities were grade 3 hematuria requiring cystoscopy and fulguration.

DISCUSSION

In our cohort of patients with locally recurrent prostate cancer treated with salvage whole-gland HDR-BT, there was statistically significant improvement in rectal dose constraints in the RHS group. The increased separation between prostate and rectum due to RHS resulted in significant dosimetric improvements including reduction of median rectal V75% from 0.06 cm^3 to 0.00 cm^3 and increase in prostate V100% from 97.8% to 98.6%. The clinical significance of these dosimetric gains, however, is questionable, as the absolute differences in dosimetric variables were small and descriptive toxicity profiles were similar. In both groups, there was one grade 1 and one grade 2 acute rectal toxicity. However, one patient in the RHS group developed a grade 3 late toxicity involving an enterovesicular fistula requiring diverting colostomy whereas none of the patients in the no-RHS group developed any late toxicity. There are two factors which may have precipitated this enterovesicular fistula. The first being occult infiltration of RHS into the rectal wall at the time of insertion. The second being proton beam therapy as the initial treatment eight years prior to salvage HDR-BT as historical studies have demonstrated increased GI toxicities with proton versus photon irradiation [19]. Nevertheless, we believe our results are meaningful for patients with local failure after definitive radiotherapy.

Rectum V75% is closely associated with rectal toxicities following brachytherapy and is used as the standard rectal constraint in both the definitive and salvage setting [20–22]. All patients readily met the goal of rectum V75% < 1.0cm^3 in the absence of RHS. The maximum rectal V75% in the no-RHS group was 0.75 cm^3 in our study, which happens to be the mean reported in a historical cohort [17]. Clinically, this translated to the miniscule frequency and severity of acute GI toxicities observed in both groups, as only 4 out of 41 total patients (10%) developed any acute GI toxicity. Assessment of late rectal sequelae is hindered by short follow-up in the RHS group. Nevertheless, only one patient developed any late GI toxicity in our entire cohort so we anticipate fewer than 20% of patients – which is the rate reported in a historical cohort of patients undergoing salvage HDR-BT – will develop late GI toxicity given longer follow-up [22].

Factors explaining our favorable dosimetry include use of real-time, trans-rectal, 3-dimensional ultrasound-based treatment planning and vast HDR-BT case volume at our institution. Accuracy of interstitial needle positioning at the base of the prostate along the bladder interface and in the peripheral zone adjacent to the rectum is challenging without

real-time visualization. The prostate-bladder and prostate-rectum interfaces are readily identified on trans-rectal ultrasound which allows accurate placement of interstitial needles close to organs-at-risk but without iatrogenic injury. It has been demonstrated that utilizing 3-dimensional ultrasound guidance for needle placement and planning enhances treatment plan quality by providing sub-millimeter needle precision. This translates to improved dose conformality and rectum and bladder sparing [23]. The trans-rectal ultrasound probe also allows for manipulation of prostate and rectal positioning. Certain cases call for posterior pressure to be applied to the probe to reduce needle placement interference from the pubic arch. In patients receiving de-novo prostate radiotherapy with HDR-BT, the separation between the prostate and rectum may be artificially increased by this technique, thereby reducing dose to the anterior rectal wall in the absence of RHS. In patients undergoing prostate re-irradiation, this separation potential is still possible without RHS, but is greatly reduced by fibrosis of the prostate-rectum interface. Furthermore, in addition to the 41 patients treated with salvage HDR-BT during the time period of this study, 434 patients received either definitive prostate HDR-BT or prostate boost with HDR-BT following external beam irradiation to the pelvis. This accounts for nearly 1000 fractions in a 6-year interval, and the benefits of clinician experience may be intangible. The vast experience with whole-gland prostate HDR-BT aided by 3-dimensional ultrasound guidance at our institution allows our treatment planners to prioritize rectum sparing without sacrificing prostate coverage in patients without RHS. This may account for the low rectum V75% with or without RHS.

The ease of achieving the standardized treatment planning goals in our patients shows that there is room for dose intensification in salvage HDR-BT for improving biochemical control. Focal HDR-BT boost using MRI-guidance has been a recent area of investigation in the upfront prostate cancer setting and may improve efficacy of salvage treatment from historical 5-year biochemical control rates of 50–60% [24, 25]. Further, more stringent constraints may be implemented in addition to the existing rectum V75%. Low-dose to large-volume constraints such as rectum V100% have been associated with grade ≥ 2 proctitis and rectal bleeding [26]. Additionally, high-dose to small-volume constraints are also important to consider, as rectum V25% > 25% and V10% > 40% are significantly associated with late diarrhea [27]. Implementing additional dose constraints and intensifying treatment via focal boost to gross disease may yield improved safety and efficacy of salvage HDR-BT.

There are limitations to our study. Median follow-up was 17 months in the no-RHS group and 4 months in the RHS group. This short follow-up duration, in addition to small cohort size, results in inadequate evaluation of late toxicities. Additionally, the retrospective study design predisposes our patients to selection bias. Patients who received RHS may have had unfavorable anatomy such as large prostate volume or a history of GI comorbidities or toxicities owing to their first course of radiotherapy. All patients were treated with a regimen of 24Gy in 2 fractions which may not be generalizable to the entire population of patients receiving salvage HDR-BT. Other popular prescriptions include 36 Gy in 6 fractions and 32 Gy in 4 fractions [8, 22]. Our dose prescription of 24 Gy in 2 fractions may have played a role in our low rate of rectal toxicities as this two-fraction course can be more sparing for normal tissues while delivering equivalent BED_{2Gy} to the prostate. Prostate-rectum

separation was also measured on pre-treatment MRI, and may not accurately represent prostate-rectum separation intraoperatively. It is possible that prostate-rectum separation was artificially increased on a case-by-case basis in the no-RHS group by applying posterior pressure on the ultrasound probe. Lastly, patients with RHS had marginal improvement in dosimetry compared to historical patient cohorts. Relative decreases in rectum V75% have been reported as high as 70% with use of RHS in the external beam setting [28]. In such reports, 10cm^3 is a standard RHS volume achieved compared to our cohort in which the median RHS volume was 6.2cm^3 [29]. The reduced volume of injected RHS highlights the difficulty of dissecting the prostate-rectum plane in previously radiated fields. To reduce the impact of this obstacle, future studies in salvage HDR-BT may select patients for RHS implantation who had lower rectal doses from initial courses of radiotherapy and avoided treatments with high relative biologic effectiveness.

CONCLUSION

Salvage HDR-BT is an underutilized modality for treatment of locally recurrent, intact prostate cancer but is safe and yields low rates of acute and late GI toxicities when performed at high volume centers. Rectal hydrogel spacer marginally improves rectal sparing and prostate dose coverage in the setting of readily achievable constraints. Larger cohorts with longer follow-up are needed to further elucidate the benefit of RHS for patients undergoing salvage HDR-BT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

Data Availability:

All relevant data generated and analyzed during this study are included in this article. Access to data with patient identifiers is prohibited.

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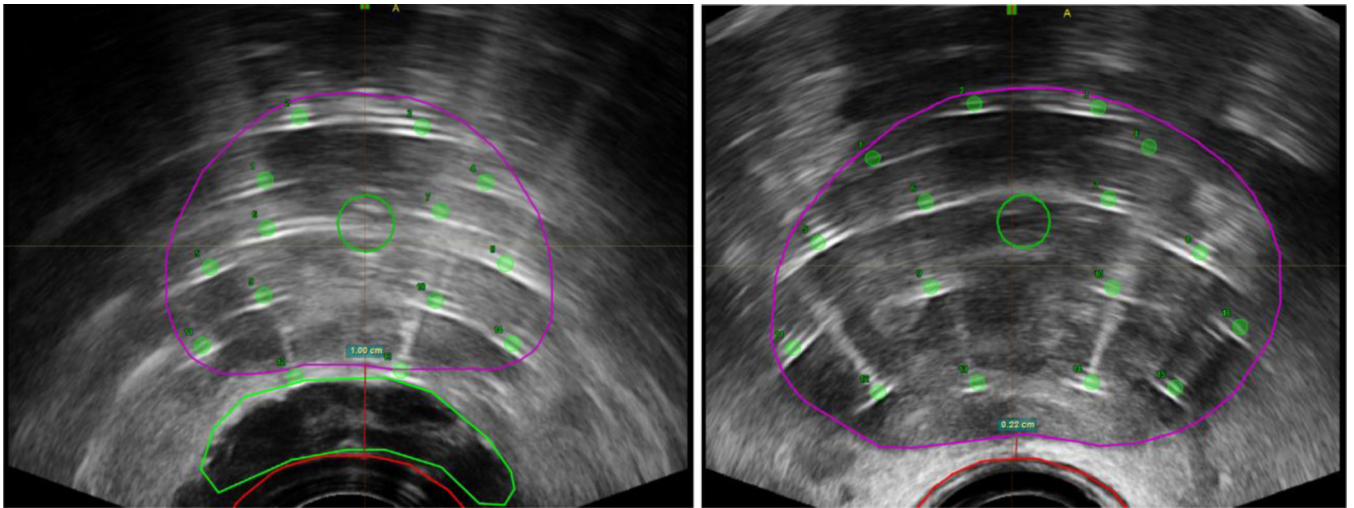
Figure 1.
Axial views of prostate (purple), rectum (red), and urethra and RHS (green) of salvage, whole-gland HDR-BT planned on ultrasound imaging with RHS (left) and without RHS (right). Images are captured at the time of treatment delivery. Prostate-rectum separation at mid-gland was 1.00cm with RHS, versus 0.22cm without RHS, in these cases.
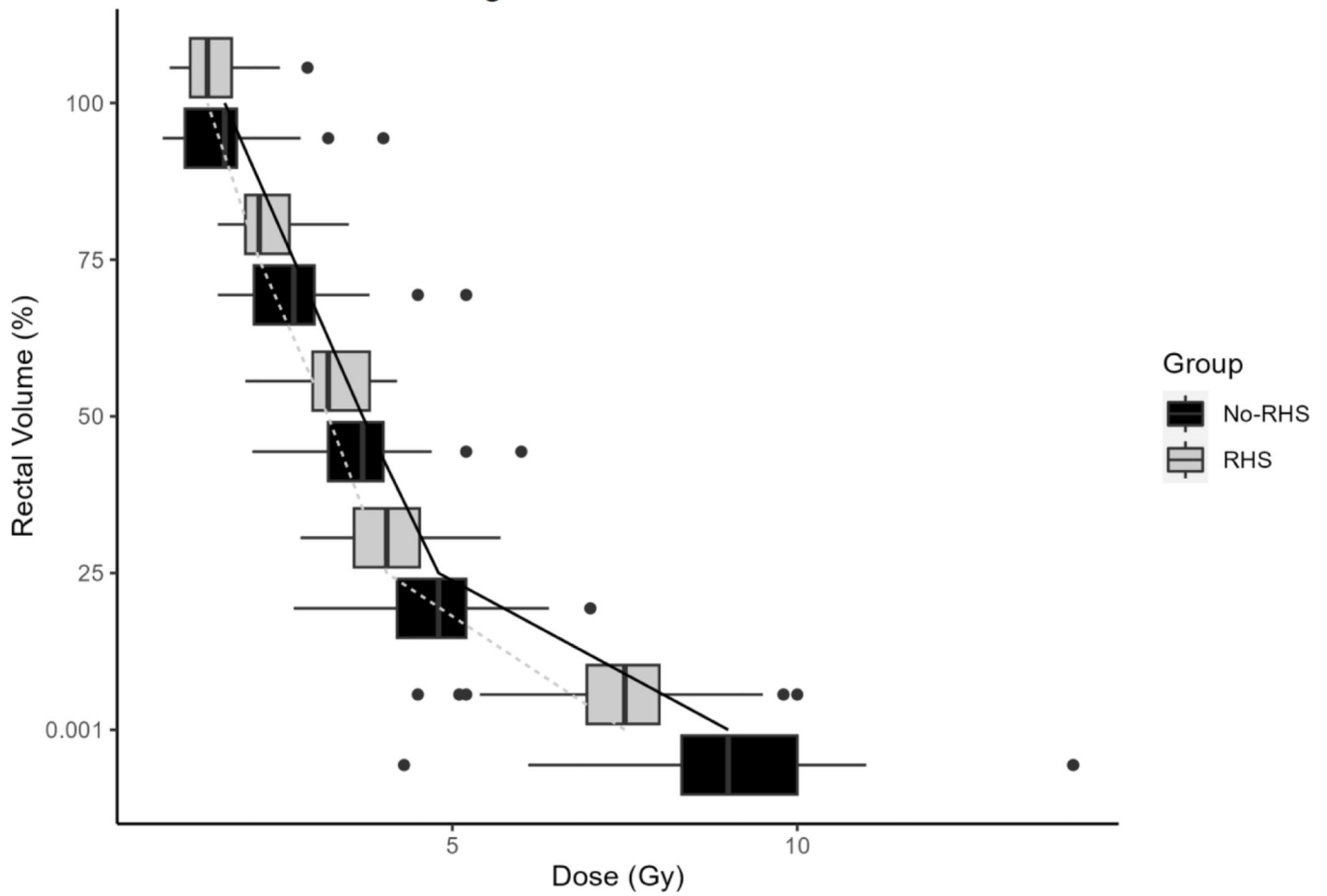
Figure 2.
Dose volume histogram of rectum with and without RHS using D100%, D75%, D50%, D25%, and D0.1% datapoints. Median and interquartile range are demonstrated with box plots. Outliers are represented by bullet points.

Table 1.

Baseline patient characteristics

	RHS Group (n=20)	No-RHS Group (N=21)
Median age	73	70
IQR	67–76	67–77
Median follow-up (months)	4	17
IQR	4–10	15–30
T-Stage at recurrence		
T1	16 (80%)	18 (86%)
T2	3 (15%)	2 (9.5%)
T3	1 (5)	1 (4.8%)
Modality of first treatment		
Conventional EBRT	9 (45%)	16 (76%)
SBRT	2 (10%)	1 (5%)
PBT	6 (30%)	4 (19%)
LDR-BT	3 (15%)	0
Median duration between first RT course and salvage HDR-BT (months)	93	116
IQR	84–162	108–142
Median PSA at recurrence *(ng/mL)	5.1	4.5
IQR	2.6–6.6	2.9–8.8

*PSA values excluded patients who were on androgen deprivation therapy Abbreviations: EBRT = external beam radiotherapy; HDR-BT = high dose-rate brachytherapy; IQR = interquartile range; LDR-BT = low dose-rate brachytherapy; PBT = proton beam therapy; PSA = prostate specific antigen; RHS = rectal hydrogel spacer; SBRT = stereotactic body radiotherapy