Scientific Article

Radiation Dose to the Rectum With Definitive Radiation Therapy and Hydrogel Spacer Versus Postprostatectomy Radiation Therapy

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Abstract

Purpose: Management options for localized prostate cancer include definitive radiation therapy (RT) or radical prostatectomy, with a subset of surgical patients requiring adjuvant or salvage RT after prostatectomy. The use of a peri-rectal hydrogel spacer in patients receiving definitive RT has been shown to reduce rectal doses and toxicity. However, in the postprostatectomy setting, a hydrogel spacer cannot be routinely placed. Therefore, we sought to compare rectal dosimetry between definitive RT with a hydrogel spacer versus postoperative RT.

Methods and Materials: We identified patients with prostate cancer who underwent conventionally fractionated RT. Rectal dosimetry was evaluated between 2 groups: definitive RT with a hydrogel spacer (79.2 Gy, group 1) and postoperative RT (70.2 Gy, group 2). Rectal dosimetry values were tabulated and compared using Mann-Whitney U test. We implemented a Bonferroni correction to account for multiple comparisons (threshold P < .005). Linear regression analysis evaluated predictors of candidate rectal dose-volume parameters.

Results: We identified 51 patients treated during years 2017 to 2018; 16 (31%) and 35 (69%) patients were included in groups 1 and 2, respectively. The rectal volume receiving ≥65 Gy (V65) was significantly lower in group 1 (median, 2.1%; interquartile range, 0.9%-3.1%) than in group 2 (10.7%, 6.6%-14.5%) (P < .001). Use of a hydrogel spacer in the definitive setting was independently associated with lower V65 (P < .001). Similar results were found for V60, V55, V50, and V45 (P < .005 for all).

Conclusions: Rectal dosimetry is more favorable for definitive RT (79.2 Gy) with a hydrogel spacer compared with postoperative RT (70.2 or 66.6 Gy). This may inform shared decision-making regarding primary management of prostate cancer, especially among patients at high risk of needing postoperative RT after prostatectomy.

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Introduction

Definitive radiation therapy (RT) or radical prostatectomy are the primary curative treatment strategies for localized prostate cancer. Although neither treatment approach has been shown to be superior in terms of oncologic outcomes, their respective toxicity profiles differ. A primary consideration for patients and their physicians is the effect of treatment on health-related quality of life (QOL), in particular in urinary, sexual, and bowel domains. Although urinary and sexual function may be worse with surgery, bowel function is often minimally affected. In contrast, short- and long-term rectal toxicity are major concerns for patients choosing definitive RT.

Further optimization of RT and surgical techniques continues in the contemporary era. The insertion of a hydrogel spacer between the prostate and rectum has been shown to reduce rates of rectal toxicity and improve QOL. Higher rectal radiation doses are associated with increased risk of acute and late rectal toxicity in both the definitive and postprostatectomy setting. The use of a hydrogel spacer reduces radiation dose delivered to the rectum by separating the prostate gland and adjacent rectal tissue, thereby reducing risk of radiation-related rectal toxicity. However, a hydrogel spacer cannot be routinely placed in the postprostatectomy setting, and there are concerns of potential risk of introducing tumor cell dissemination with needle insertion.

Despite higher prescription radiation doses and therefore maximum rectal doses in the definitive setting, we hypothesized that with the use of a hydrogel spacer, smaller volumes of the rectum receiving lower radiation doses could be achieved compared with the postprostatectomy setting. This comparison is important because the decision to perform initial surgery versus RT may be influenced by the desire to reduce rectal toxicity but often fails to account for subsequent therapy that will be delivered in the adjuvant or salvage setting.

To test our hypothesis, we performed a single-institutional analysis of patients treated with postprostatectomy RT versus definitive RT with a hydrogel spacer. Our primary aim was to evaluate the RT dose received by the rectum in both clinical settings.

Methods and Materials

This retrospective analysis was approved by the Yale University Institutional Review Board and Ethics Committee. Consecutively treated (September 2017 to September 2018) men with localized prostate cancer managed with conventionally fractionated definitive or postoperative (adjuvant or salvage) RT were included. All patients who underwent brachytherapy, hypofractionated RT, or stereotactic body RT were excluded in an effort to maintain direct dosimetry comparison between cohorts.

Hydrogel spacer insertion was performed in all definitive RT cases based on the principles and techniques described in a randomized trial and with positioning verified with postprocedure magnetic resonance imaging before RT initiation. No postoperative RT patient received hydrogel spacer insertion. Hydrogel spacers were placed approximately 1 week before simulation, and prostate fiducials (either electromagnetic transponder, gold, or polymer) were placed during the same procedure. Final decisions on simulation, target volume delineation, immobilization, and treatment planning were at the discretion of the treating physician and are further detailed in this article.

Patients were simulated in the supine position with full bladder. The full bladder was achieved by timed emptying of bladder and drinking approximately 16 fluid ounces of water 30 minutes before simulation. Patients were encouraged to follow a low-residual diet and to have an empty rectum at the time of simulation and during daily radiation treatment. Computed tomography (CT) simulation and postprocedure magnetic resonance imaging images were imported into Eclipse software (Varian Medical Systems, Palo Alto, CA) for radiation treatment planning. The prostate, rectum, and prostate bed were contoured following standard guidelines set forth by the Radiation Therapy Oncology Group (RTOG). Additionally, the femoral heads, penile bulb, bladder, and bowel bag (in cases of patients receiving pelvic radiation) were contoured as organs at risk. The most commonly used clinical target volume to planning target volume expansion was 5 mm (range, 4-8 mm) in the intact setting and 6 mm (range, 4-6 mm) in the postoperative setting. The prescription dose was 79.2 Gy in patients with an intact prostate and 70.2 Gy in postoperative cases (all using standard fractionated doses of 1.8 Gy). There was a prostate cone down from the seminal vesicles or elective pelvic lymph nodes at 66.6 Gy in 10 definitive patients. Elective pelvic lymph node fields, if used, were prescribed to 45.0 Gy or 50.4 Gy at the discretion of the treating physician. Volumetric modulated arc therapy was used for all patients with either 6 or 10 MV energy photon beams. Representative radiation treatment plans are shown in Figures E1 for an intact and postoperative patient.

Patients were treated on commercially available high energy linear accelerators including Elekta Synergy (Elekta, Stockholm, Sweden) or Varian TrueBeam, Trilogy, 2300 C/D (Varian Medical Systems) treatment systems. Definitive patients underwent daily target localization using electromagnetic detection of implanted transponders (Calypso 4D Localization System) or daily imaging of implanted fiducials with weekly cone beam CT (CBCT) scan. All postoperative patients underwent image guided RT with daily CBCT scans.
We evaluated rectal dose-volume histograms (DVHs) from both the definitive RT (group 1) and postprostatectomy RT (group 2) cohorts. Because 70.2 Gy is on the higher end of recommended postprostatectomy RT doses, which could pose a bias for rectal dosimetry, we constructed a hypothetical third group (group 3) by reducing group 2 prescription dose from 70.2 Gy to 66.6 Gy.

Statistical analyses were performed with Stata 16 (College Station, TX) and Microsoft Excel 2016 (Redmond, WA). Descriptive statistics between groups 1 and 2 were tabulated and compared using the Fisher’s exact test for categorical independent variables and the Mann-Whitney U test for continuous independent variables. Rectal dosimetric values were tabulated for groups 1 to 3 and compared using the Mann-Whitney U test. A Bonferroni correction was used to denote statistical significance at \( P < .005 \) on account of using multiple comparisons (rectal V70, V65, V60, V55, V50, V45, V40, V35, V30, and mean). \( V_x \) refers to the volume of the rectum receiving at least \( x \) Gy (ie, V70 is the volume of the rectum receiving \( \geq 70 \) Gy). Linear regression analysis was used to determine clinical variables associated with lower rectal V65, which is a standard post RT rectum dose constraint used in the ongoing NRG-GU-003 clinical trial. After univariable analysis, multivariable assessment was carried out using backward stepwise selection with \( P < .2 \) as the selection cutoff.

## Results

In total, 51 patients were included; 16 (31%) patients received definitive RT with a hydrogel spacer in group 1, and 35 (69%) underwent postprostatectomy RT in group 2. Clinical characteristics of the populations are shown in Table 1. With the exception of age, groups were well-balanced in terms of several other parameters, including prostate size, body mass index (BMI), T stage, percent cores positive, and pelvic coverage. Thirteen of the patients receiving definitive RT underwent target localization using electromagnetic detection of implanted transponders with weekly CBCT. The remaining 3 patients had other types of prostate fiducials (gold or polymer) implanted. All postprostatectomy RT patients underwent image-guided RT with daily CBCT scans.

Rectal dosimetry is given in Table 2 and illustrated in Figure 1. The V65 was significantly lower in group 1 (median, 2.1%; interquartile range, 0.9%-3.1%) than in group 2 (10.7%; 6.6%-14.5%) \( (P < .001) \). Similar results were found for V60, V55, V50, and V45 \( (P < .005 \) for all). Given the heterogeneity in radiation plans, we also illustrate in Figure 2 overlapping DVH curves from rectal V30 to V80 for each individual patient receiving definitive RT (group 1) and postoperative RT (group 2) to show the actual differences in total DVH curves as well as variations within each group.

Table 3 displays factors predictive of rectal V65 on linear regression analysis. On univariable analysis, the use of a hydrogel spacer and BMI were correlated with lower rectal V65 \( (P < .001 \) and \( P = .011 \), respectively). When they were included in multivariable analysis to adjust for potential confounders, the use of a hydrogel spacer and BMI were still significantly correlated with lower rectal V65 \( (P < .001 \) and \( P = .016 \), respectively). Of note, we did not find BMI to be a significant predictor of beam energy level \( (P = .622) \) on logistic regression, and there also was no statistically significant association between beam energy level and rectal V65 \( (P = .221) \) on linear regression analysis. Univariable and multivariable linear regression analyses were not performed for rectal V40 because there was not a statistically significant difference found between groups 1 and 2 or group 1 and 3 on rank-sum comparison of rectal V40.

To address the issue that group 2 may have received higher rectal doses owing to a higher prescription dose in the postprostatectomy setting, a comparison was made between group 1 and group 3 (66.6 Gy). The aforementioned findings regarding V65-V45 remained statistically

| Table 1 | Patient and treatment characteristics |
|---------|--------------------------------------|
|         | Definitive RT 79.2 Gy (n = 16) | Postoperative RT 70.2 Gy (n = 35) | \( P \) value |
| Age, median (range) | 69.5 (54-81) | 63 (48-81) | .030 |
| ECOG, No. (%) | 0 | 12 (75) | 26 (74) | .622 |
| 1 | 4 (25) | 9 (26) | |
| BMI (kg/m²), median (range) | 32 (24-42) | 31 (22-43) | .516 |
| Prostate size (mL), median (range) | 36 (22-67) | 36 (21-110) | .967 |
| PSA, median (range) | 9.0 (4.7-21.2) | 7.9 (2.1-218) | .452 |
| Clinical T stage, no. (%) | T1 | 13 (81) | 12 (34) | .128 |
| T2-3 | 3 (19) | 13 (37) | |
| Unknown | 0 (0) | 10 (29) | |
| Gleason score, no. (%) | 6 | 0 (0) | 1 (2.9) | |
| 7 | 11 (69) | 24 (69) | |
| 8-9 | 5 (31) | 10 (29) | |
| % Positive cores, median (range) | 50 (15-100) | 46 (14-92) | .316 |
| Pelvic radiation, no. (%) | 3 (18) | 14 (40) | .119 |
| ADT, no. (%) | 14 (88) | 21 (60) | .136 |

Abbreviations: ADT = androgen deprivation therapy; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; PSA = prostate-specific antigen; RT = radiation therapy.
significant ($P < .005$ for all). Moreover, to address the potential effect of pelvic RT on rectal doses, we repeated our rectal dose comparisons after excluding patients who received pelvic RT (Fig E3 and Table E1). Differences in rectal V65-V50 remained statistically significant ($P < .005$ for all) between group 1 and group 2 as well as between group 1 and group 3, and rectal V45 was no longer statistically significant ($P = .008$ for group 1 vs group 2, $P = .010$ for group 1 vs group 3).

**Discussion**

In this study, we observed more favorable rectal dosimetry parameters in patients receiving definitive RT (79.2 Gy) with a hydrogel spacer compared with postoperative RT (70.2 or 66.6 Gy), especially regarding the percentage of the rectum receiving higher doses (between 45-65 Gy). Given the higher prescription dose used in the definitive setting, a small volume of the rectum in definitive patients did receive 75 to 80 Gy (V75 0.2% compared with 0% in the postoperative setting), whereas most postoperative patients did not receive doses to 75 Gy. Nevertheless, these lower and higher dose volumes are well within acceptable dose constraints and are less likely to be clinical drivers of rectal toxicity in our patient populations compared with rectal V45 to V65.12-14

Because the choice for definitive treatment modality is influenced by the risk for acute and late toxicities, our findings can inform decision-making regarding primary management of prostate cancer, especially among patients at high risk of needing postoperative RT after prostatectomy.

Clinically significant late rectal toxicity is an uncommon event in the intensity modulated RT era.15 However, a randomized trial was able to detect statistical and

| Table 2  | Radiation dosimetry to the rectum by treatment group |
|---------|-----------------------------------------------------|
| Median percent volume | Definitive RT 79.2 Gy (group 1, n = 16) | Postoperative RT 70.2 Gy (group 2, n = 35) | Postoperative RT 66.6 Gy (group 3, n = 35) |
| V75 (%) | 0.2 | 0.0 | 0.0 | <.001* | <.001* |
| V70 (%) | 0.8 | 1.5 | 1.4 | .277 | .435 |
| V65 (%) | 2.1 | 10.7 | 10.2 | <.001* | <.001* |
| V60 (%) | 3.5 | 14.9 | 14.1 | <.001* | <.001* |
| V55 (%) | 5.3 | 18.1 | 17.2 | <.001* | <.001* |
| V50 (%) | 7.5 | 21.1 | 20.1 | <.001* | <.001* |
| V45 (%) | 9.6 | 24.2 | 22.9 | .002* | .004* |
| V40 (%) | 12.6 | 28.0 | 26.5 | .007 | .014 |
| V35 (%) | 17.2 | 33.0 | 31.3 | .031 | .049 |
| V30 (%) | 25.5 | 39.3 | 37.3 | .084 | .123 |
| Mean dose (Gy) | 20.6 | 28.7 | 27.2 | .065 | .128 |

* Abbreviation: RT = radiation therapy.
* Statistically significant at $P < .005$.  

**Figure 1** Mean rectal volumes receiving at least 30 Gy (V30) to 80 Gy (V80).
clinically meaningful benefits with a hydrogel spacer despite the relatively low event rates. This was primarily because toxicities were evaluated in a more composite manner (eg, measuring grade 1 toxicities rather than grade 2 or 3 events). Additionally, the incorporation of QOL assessments allowed for a more precise metric with which to discern intercohort differences. Although our study did not evaluate toxicities and QOL, the reduction of rectal doses could be associated with differences in toxicity rates and QOL, as illustrated by the aforementioned trials.

Our study does not intend to imply that definitive RT should be pursued over resection in all patients. Approximately half of patients with high-risk pathologic features after prostatectomy may not require postoperative RT. Moreover, with early results from RADICALS-RT trial showing equivalent biochemical progression-free survival between adjuvant RT and early salvage RT, fewer patients may receive postprostatectomy RT as practice patterns change. Because patients who do not receive postoperative RT avoid risk for radiation-related rectal toxicity, we cannot generalize that more favorable rectal dosimetry alone justifies definitive RT over prostatectomy. Rather, while considering the decision between primary surgery or RT, we may not need to be concerned about a potentially higher rectal dose for definitive RT compared with postoperative RT if a hydrogel spacer can be injected. As a result, multidisciplinary teams are encouraged to continue exercising careful patient selection for either surgical- or RT-based options.

Besides the hydrogel spacer, the only other factor that was significantly associated with higher rectal V65 was lower BMI. This finding is similar to other retrospective reports in the brachytherapy and hypofractionation settings, and has been postulated to be associated with differential patterns of abdominopelvic fat distribution in obese patients. Although larger body habitus may prompt use of higher photon beam energy levels, in our study cohort we did not find BMI to be a statistically significant predictor of beam energy levels, nor was there a statistically significant association between beam energy level and rectal V65.

When group 3 was factored into the dosimetric results, there was a very minor numerical difference in the DVH parameters. This is likely because a 3.6 Gy prescription dose reduction cannot compensate for the lack of anatomic space between the target volume and the rectum for postprostatectomy cases (as the RTOG guidelines state that the posterior border of the target should be the anterior rectal wall). Because hydrogel spacers have never been prospectively tested in the postprostatectomy setting, this advantage may only apply to patients with an intact prostate.
There are several limitations of this investigation worth mentioning, in addition to its retrospective nature. First, with any prostate cancer dosimetric study, it is readily acknowledged that daily rectal distention is never perfectly reproduced over the RT course; as a result, the actual delivered doses to the rectum may be different from what was dosimetrically planned. Second, dosimetric results also heavily depend on the nature of target volume delineation. For instance, the degree of seminal vesicle coverage (and dose thereof) for intact cases likely affects rectal doses (especially in cases with close anatomic apposition between the length of the seminal vesicles and the rectum). Additionally, it is acknowledged that there always remains some individual variation for prostate bed contouring, namely the extent of posterolateral coverage. A greater degree of posterolateral contouring may make for more difficult optimization during RT planning such that the rectum cannot be spared as easily. The RTOG guidelines make a mention of this, stating that the posterior border of the target may require more concavity around the lateral aspects. Third, it is also noted that anatomic orientation of hydrogel spacers may distort dosimetry, which could also affect results. Fourth, although not statistically significant in our cohort, there were more patients who received pelvic RT in the postoperative group, which increases the rectum volume exposed to lower doses such as V45 to V30. Although V65 to V50 remains significantly improved in the intact setting after excluding patients who received pelvic RT, the dosimetry advantage at lower doses is likely not due to hydrogel spacer alone, and the use of pelvic RT may be a significant confounder. Lastly, although there are case reports and a small retrospective series evaluating hydrogel spacers in the postprostatectomy setting, there remain unanswered clinical questions, including concern about potential tumor cell dissemination (possibly with disruption of Denonvilliers’ fascia), which warrant further prospective investigation. Postprostatectomy placement is not currently a widely accepted indication.

In conclusion, this study observed more favorable rectal dosimetry in patients receiving definitive RT (79.2 Gy) with a hydrogel spacer compared with postoperative RT (70.20 or 66.6 Gy). Although rectal point maximum dose may be higher in the definitive setting given the increased prescription dose, rectal dosimetry parameters below V70 are significantly reduced with a hydrogel spacer compared with the postoperative setting. Because primary management choice for prostate cancer is influenced by the risk of acute and late rectal toxicities, our data may better inform shared decision-making between multidisciplinary providers and patients.

Supplementary Materials

Supplementary material for this article can be found at https://doi.org/10.1016/j.adro.2020.08.015.

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