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EDITORIAL

Rectal Spacer Usage with Proton Radiation Therapy for Prostate Cancer

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First, and perhaps most importantly, Dinh et al are to be applauded for presenting their prospective series of men treated with proton therapy at the University of Washington and their carefully reported rectal toxicity outcomes in the context of dose-volume histogram analysis as well as differing rectal immobilization devices.[1] These results provide strong evidence suggesting that without the use of a rectal spacer, there is increased rectal toxicity with proton therapy compared with intensity modulated radiation therapy (IMRT). These data stand in stark contrast to the popular opinion that protons are inherently "less toxic" than photon-based radiation therapy (RT). Their decision to publish these contradictory results should be commended. We will first discuss the clinical benefit seen from their use of rectal spacers before addressing the larger issue raised by this work: the potential for worse toxicity with proton RT for prostate cancer.

To understand how we got here: Prostate cancer, the most common cancer among men, displays a notable level of heterogeneity in biological behavior and outcomes. However, definitive treatment is warranted for those whose cancers are higher risk, and definitive RT is a well-established treatment. Efforts to improve definitive RT found success with dose-escalation trials in the 1990s to 2000s. These trials decreased the risk of recurrence as measured by a rising prostate-specific antigen level; however, they also failed to demonstrate an improvement in prostate cancer death or overall survival. As a result, the improved biochemical disease control frequently came at the cost of increased acute and late grade gastrointestinal (GI) and urinary toxicity.

Specific efforts to improve rectal toxicity have focused on reducing the radiation dose delivered to the rectum, such as with image guided RT, IMRT, proton therapy, or devices such as rectal balloons or spacers. It has been demonstrated that late rectal toxicity is largely a function of dose, the evidence for which was summarized in the Quantitative Analysis of Normal Tissue Effects in the Clinic.[2] More recently, this dose-response was upheld in the era of IMRT and hypofractionated treatments (Fig. 1).[3]

Mechanical devices can be used to alter rectal dosimetry—most commonly rectal balloons and, more recently, rectal hydrogel spacers. We will not further discuss rectal balloons here because no level 1 evidence has demonstrated their utility in reducing clinical toxicity or high doses to the anterior rectal wall.[4,5] A more recent advancement in this area has been the approval of a rectal hydrogel spacer, which is placed between the anterior wall of the rectum and posterior wall of the prostate, increasing the physical distance and thereby decreasing the amount of high-dose radiation to the rectal wall.

The clinical benefit of this increased separation was demonstrated in a phase 3 clinical trial that showed significantly reduced rates of late rectal toxicity in patients who received a rectal spacer compared with those who did not. In this study, all men were treated with centrally reviewed plans using fiducial marker–based image guided RT with IMRT to deliver 79.2 Gy in 1.8 Gy fractions to the prostate with or without seminal vesicles. Of particular note, there was no grade 2+ physician-reported rectal toxicity for any patient who received a rectal spacer (compared with 5.7% for those who did not). When

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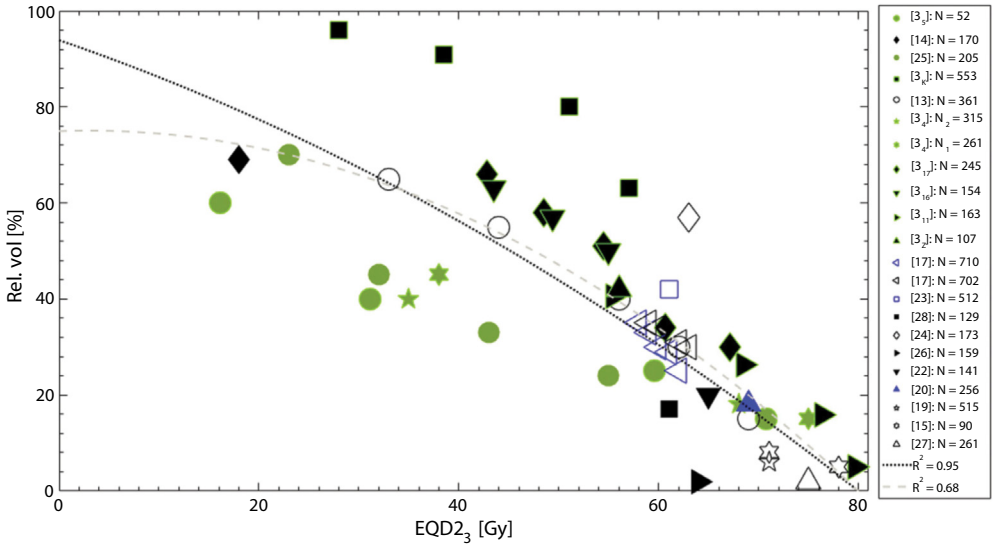

Fig. 1. The 29 identified dose-volume histogram thresholds for rectal bleeding after external beam radiation therapy alone (excluding the 4 anal canal thresholds) and the 25 dose-volume histogram thresholds for grade 2 or higher rectal bleeding that were identified by Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC)[3] are shown. QUANTEC studies are marked with a bright green border, with different symbols for different sub-QUANTEC studies. All 54 thresholds were stratified with respect to organs at risk (blue, anorectum; black, rectum; green, rectal wall; black dotted line, final fit for rectal bleeding; gray dashed line, fit including 25 QUANTEC thresholds). Reproduced from Olsson et al.[3] (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2020.05.034.)

evaluating patient reported outcomes, 41% of control patients at 3 years had a change in bowel function meeting a clinically significant difference (with 21% having a large difference); in those treated with rectal spacer, a detectable difference in bowel summary score was only noted in 14% of men ($P = .002$; odds ratio, 0.28; 95% confidence interval [CI], 0.13-0.63) with a large difference limited to 5% ($P = .02$; odds ratio, 0.30; 95% CI, 0.11-0.83). Of note, patient-reported clinically meaningful rectal bleeding was uncommon in each group and was not statistically different (4.2% vs 2.7% at 6 months), with the largest differences noted in the frequency of bowel movements and painful stools.[6]

The results of that trial should be emphasized at this point because they represent the state of the art in rectal toxicity minimization for photon-based dose-escalated definitive prostate RT. This represents a significantly better result than seen with another "rectal-sparing" approach that has been the subject of much debate in the prostate radiation oncology community: proton-based radiation. The unique physical properties of proton RT, specifically the Bragg peak, allow for potentially tighter control of high-dose radiation delivery with sharper fall-off compared with 3D conformal x-ray therapy, potentially reducing radiation dose to nearby structures. However, dosimetric studies have shown that while proton-based plans decrease the mid and low doses to the rectum, high doses are often similar or occasionally worse with protons. A recent dosimetric analysis comparing volumetric arc therapy, pencil-beam scanning intensity modulated proton therapy, and 4-π RT similarly showed worse intermediate- and high-dose delivery to the rectal wall.[7] Proponents of proton therapy have argued that this low- and midrange dosimetric benefit is likely to reduce toxicity, but high-quality evidence to support this argument does not exist.[8] There is significant concern, however, that because of the potentially worse high-dose delivery, protons may worsen late rectal toxicity rather than improve it.

Adding insult to possible injury, protons may be more biologically damaging than is currently accounted for with modern planning. Proton planning is done with an assumed constant relative biological effectiveness (RBE) of 1.1. However, there is a significant amount of data to suggest this may not be an entirely valid assumption. In vitro and in vivo data have demonstrated that the RBE of protons depends on several factors, including dose per fraction, the cell type irradiated (and its corresponding α/β ratio), and the linear energy transfer, which varies along a proton beam's path.[9] These factors may mean that proton RBE increases throughout the Bragg peak. Inside the spread-out Bragg peak for a prostate cancer treatment plan, this increase may cause significant underestimation of the highest doses delivered to the rectum. A recent dosimetric study of 6 patients demonstrated that when using any of 3 different variable-RBE models, the maximum dose to the rectum (as measured by the D1cc) exceeded the maximum rectal dose constraint in all 6 patients analyzed, along with a corresponding increase in the normal-tissue complication probability of grade 2+ late rectal toxicity.[10] To date, no randomized trials comparing photons with protons have been published, although some are ongoing. Given the higher cost of proton RT, uncertain clinical benefit, and

legitimate concern for worse toxicity, the role of proton therapy in prostate cancer is not currently clear; however, many patients still strongly believe that proton RT is better, which in part drives its continued use.

In this context, Dinh et al evaluated 313 men treated with definitive proton RT (267 included in the final analysis) for prostate cancer in a single-institutional prospective registry between 2013 and 2018. All patients received intraprostatic placement of fiducial markers; in a nonrandomized fashion, 192 (72%) were treated with a rectal balloon and 75 (28%) had hydrogel spacer. Additionally, patients with T3 or T4 disease were ineligible for spacer placement. As a result, more patients treated with rectal balloon had high-risk disease (26%) than those treated with spacer (13%).

Nearly all patients received a dose of 79.2 cobalt Gray equivalents in 44 fractions. Patients treated before 2015 were mostly treated with passive scatter protons, and those after 2015 were treated mainly with pencil beam scanning protons. As previously seen in the IMRT reports, the use of rectal spacer even with protons significantly reduced the volume of rectum irradiated across all reported volumes from V50 to V70. The mean rectal V70 and V75 and their interquartile ranges were 11.7% (5.8%) and 8.5% (4.6%) for the nonspacer group, respectively. For the spacer group, these were 3.8% (5.9%) and 1.7% (3.3%), respectively (personal communication with authors D.K. and J.J.L.). Of particular note, proton therapy did not appear to provide an improvement in any of these dose-volume histogram metrics compared with similar values for V70 and V75 on the randomized trial of hydrogel spacer using IMRT.

However, of substantial concern, the rate of physician-reported grade 2+ late rectal bleeding in the first 2 years was 19% versus 3% for rectal balloon versus hydrogel, respectively ($P = .003$). Similar results were seen with grade 1+ late rectal bleeding (35% vs 13%, respectively; $P < .001$). Fitting these data to a logistic model showed that the most significant predictor of rectal bleeding was V75CGE. Given potential differences in treatment era and patient characteristics, a multivariable analysis was performed demonstrating that receipt of rectal spacer was protective against late rectal bleeding even after adjusting for such potential differences as T stage, Gleason score, risk group, or the use of intensity modulated proton therapy, with an adjusted hazard ratio for grade 2+ bleeding of 0.145 (95% CI, 0.034-0.641). The only other prognostic factor for bleeding was the increased rate observed in patients on anticoagulants (hazard ratio, 5.0; 95% CI, 1.9-13.0).

It is notable that the rates of GI bleeding from this analysis do appear worryingly high compared with contemporary clinical trials using x-ray–based treatments. This is difficult to say with certainty, however, given differences in use of image guidance, IMRT, rectal balloons, passive scatter or pencil beam proton therapy, and rectal spacers. For instance, on a randomized trial of prostate dose escalation (which used 3D conformal x-rays followed by a proton boost and a rectal immobilization device similar to a balloon), grade 2+ rectal toxicity was observed in 8% at 70.2 Gy and 17% at 79.2 Gy ($P = .005$).[11] When looking at proton therapy alone, investigators from MD Anderson reported on clinical outcomes for 423 men treated with proton therapy (with the vast majority using a rectal balloon and 81% with passive scatter treatment) where the rate of late grade 2+ GI toxicity was 9.7%, with the majority of late toxicities being bleeding and coagulation for persistent bleeding used in 5.6%.

Figure 2 gives a visual summary of the rates of either grade 2 rectal bleeding or grade 2 GI toxicity as reported by major trials respecting these variables. From this figure, it is clear that although some retrospective series have shown extremely low rates of grade 2 rectal toxicity, most prospective series of dose-escalated RT have not. These trials, regardless of delivery technique or particle/photon, have consistently reported rates of grade 2+ GI toxicity or rectal bleeding ranging from around 10% to 30%.

Many of these used a rectal balloon (particularly those involving proton therapy), although not all. Across these

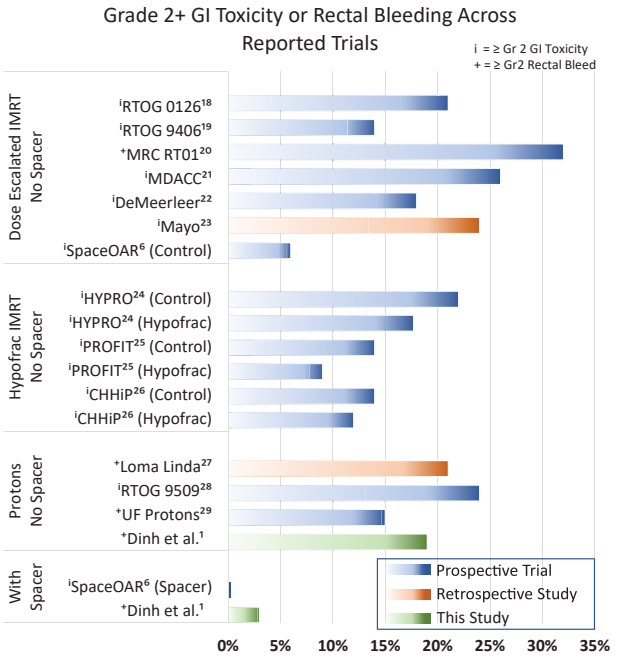

Fig. 2. Late grade 2+ gastrointestinal (GI) toxicity or rectal bleeding reported by relevant prostate cancer radiation therapy trials covering various radiation modalities and treatment techniques. Not all trials specified rectal bleeding rates separately from GI toxicity, but they did specify that the majority of GI toxicities were rectal bleeding. Thus, these results were combined. Studies included RTOG 0126,[18] RTOG 9406,[19] MRC RT01,[20] MDACC Dose Escalation,[21] Belgium Dose Escalation,[22] Mayo Dose Escalation,[23] HYPRO,[24] PROFIT,[25] CHHiP,[26] Loma Linda Experience,[27] RTOG 9509,[28] UF Proton Experience,[29] SpaceOAR Trial,[6] and this trial.[1]

studies, the presence or absence of balloon usage has not appeared to markedly affect results. The most significant factor to date has been the application of a rectal spacer. Although it should be noted that the phase 3 trial comparing hydrogel spacer versus no spacer was supported financially by the hydrogel producer, the trial showed a 0% rate of grade 2 rectal bleeding in the treatment arm and 6% grade 2+ toxicity in the control arm. Dinh el at using proton therapy similarly demonstrated a 3% rate of grade 2+ rectal bleeding with protons and spacer, but 19% without spacer. Based on these data, it is difficult to make claims for a superiority of protons over x-ray−based treatment.

Also noteworthy in the analysis by Dinh et al is their use of patient-reported outcomes. They used a validated patient-reported outcomes tool—the Expanded Prostate Cancer Index Composite (EPIC) questionnaire. In the study, authors report a greater decrease in the EPIC bowel summary score for patients who did not receive a rectal spacer (with an absolute difference of 5.5 between the groups; $P = .046$). This result remained significant even after excluding patients with rectal bleeding. The greater decline in EPIC summary score noted in those with rectal balloon also met the threshold for a minimally important difference (which has previously been established at 4-6 points). Investigators from MD Anderson reported a decline in EPIC summary score in those treated with proton therapy of 3.9 points; for UF, this was 4.0 points; and in comparison, a large prospective community-based cohort noted declines of 4.0 points after IMRT.[12]

A number of lessons can potentially be taken from this study. First, it is important to prospectively evaluate new technologies in the treatment of prostate cancer because conflicting results from nonrandomized studies can lead to erroneous conclusions. Is proton therapy really better than photon-based treatments, as is often argued? Perhaps it leads to greater interventions[13] and financial toxicity[14] with little clinical difference.[8] Second, many of the technologies that are routinely used for prostate cancer radiation treatment have not been evaluated in phase 3 trials. The ongoing randomized trial of IMRT versus proton therapy as well as the Patient Centered Outcomes Research Initiative study will provide substantial clarity to this issue. Third, if proton therapy, the most expensive type of external beam RT, can only be delivered safely by adding another expensive technology to its use with hydrogel spacer, this calls into question the role of proton therapy in treating prostate cancer. As it stands, these data, if believed at face value, would demonstrate that proton RT is more likely worse than current IMRT and not better, as is strongly advocated by many within our field and by eager patients.

This publication also adds to the growing body of literature supporting the conclusion that rectal spacers meaningfully and significantly reduce both the dose of radiation to the rectum and the long-term rectal toxicity associated with RT for prostate cancer. Importantly, although the prior phase 3 study demonstrated this with photon-based RT, this study recapitulates those findings with proton RT (both passive scatter and pencil beam scanning). Given the minimal toxicity associated with the placement of the hydrogel itself, it is becoming easier to recommend rectal spacing for patients eligible to receive it. Although use of a rectal spacer appears to have been reasonably shown to significantly reduce rates of late rectal bleeding regardless of proton versus photon treatment modality, many high-risk patients will not be eligible for rectal spacer placement owing to having T3 or T4 disease. For those patients unable to receive a rectal spacer, proton RT should be viewed with increasing suspicion; the results by Dinh et al likely suggest worse outcomes compared with those treated with x-ray−based treatments. Importantly, these patients were treated on a prospective registry trial at a large academic center with ample experience, meticulous planning, and deep physicist expertise. That alone should give pause to patients and physicians alike at newer or smaller proton centers, which may not have the institutional resources used in this study. Furthermore, modern dose-escalated IMRT−based RT using fiducial markers has shown an impressively low rate of late grade 2 rectal toxicity (5.7%) even for patients who do not receive a rectal spacer. This suggests that modern IMRT-based treatment may actually have fewer side effects than proton therapy and should be seriously discussed with patients seeking proton therapy who may mistakenly believe it to be "safer" than x-rays.

Further trials will help refine the role of rectal spacers in reducing rectal toxicity, but at present there are no validated models to clearly identify who benefits most from rectal spacers.[15-17] Nevertheless, their benefit at this time is clear and impressive, with the current study suggesting that even in patients treated with proton therapy, hydrogel spacer appears to provide a substantial reduction in the risk of rectal bleeding and toxicity. For those patients who cannot receive a rectal spacer, however, concern of worse late rectal toxicity for proton-based treatments should not be casually dismissed, and further research is needed to clarify this issue. Although this excellent publication provides support for the increased use of rectal spacers to reduce rectal toxicity, it does not provide convincing evidence to justify the use of proton therapy for prostate cancer. It instead raises additional questions as to the appropriateness of its use given less expensive, and possibly less toxic, IMRT-based treatment. For that we must commend Dinh et al for being willing to present clinical data that fly in the face of the popular belief in the superiority of proton therapy. We hope that this and similar studies will lead to more prospective trials to evaluate the utility of this highly used but costly treatment.

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