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Case reports and case series

Case series illustrating the synergistic use of hydrogel spacer and MR-guidance to increase the radiotherapeutic index for localized prostate cancer

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ABSTRACT

Background: The risk of gastrointestinal (GI) toxicity may limit the use of curative-intent radical radiotherapy (RT) for prostate cancer (PCa) in circumstances where morbidity of treatment may exceed an acceptable threshold. Rectal spacers are used to expand the distance between the anterior rectal wall and the prostate, consequently sparing the rectum from the high-dose region.

Case presentations: We report three clinical scenarios of PCa patients treated at our institution, where risk of RT-associated rectal toxicity may be increased: inflammatory bowel disease (IBD), salvage brachytherapy (BT) after previous external beam RT (EBRT), and tailored dose-escalation with focal BT to the gross tumor volume followed by stereotactic body RT. Prior to RT, a polyethylene glycol (PEG) hydrogel spacer was successfully placed in all cases. Treatment comprised magnetic resonance (MR) guided high dose-rate BT ± EBRT. All patients completed treatment uneventfully, without any significant GI toxicity at last follow-up.

Conclusions: These cases illustrate the utility of PEG hydrogel spacer, where concerns of radiation induced toxicity may have previously limited the application of radiotherapy. The synergistic use of these novel devices together with MR-guided BT may expand the indications and therapeutic index of curative-intent RT-based treatments, while minimizing the risks of GI toxicity.

Introduction

Gastrointestinal (GI) toxicity remains a dose-limiting factor for curative-intent prostate cancer (PCa) radiotherapy (RT) due to the proximity of the anterior rectal wall (RW) that results in its inclusion in the high-dose RT region. Increasing the distance between both organs reduces the dose to the RW, where several methods have been proposed [1,2]. Of these, polyethylene glycol (PEG) hydrogel (SpaceOAR; Augmenix, Inc) is, to date, the only FDA-approved device for use in PCa RT [3].

Recently, a phase III trial randomized 222 men treated with dose-escalated RT to spacer or control group, demonstrated improved late rectal toxicity and patient-reported GI-related quality of life (QoL) in those allocated to the spacer arm [4]. Nevertheless, considering the low 3-years cumulative rate of rectal toxicity in the control arm [grade (G) 2 (6%) and G3 or higher (1.3%)] and associated costs, the unselected use of this device seems challenging to sustain. Therefore, judicious application in clinical scenarios where increased toxicity rates are anticipated is warranted.

The use of a rectal spacer is not constrained by technical challenges in its placement (i.e. successfully achieved in 98% of cases) [5], but certain material properties may limit broader applicability. The spacer has similar density to the prostate on computed tomography (CT), in turn hindering the delineation of the boundary between these structures during RT treatment planning. Additionally, the echogenic characteristics of hydrogel obscure the visualization of underlying structures (i.e. prostate, brachytherapy [BT] catheters) in the traditional transrectal ultrasound (TRUS)-guided BT setting. In contrast, magnetic resonance (MR) imaging provides unparalleled resolution of the prostate, surrounding organs, and BT catheters, even with hydrogel spacer in place.

Herein we report three clinical scenarios in which the benefits of PEG hydrogel are exploited and enabled by MR-guided (MRg)

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RT: inflammatory bowel disease (IBD), salvage BT for local recurrence post RT, and tailored BT dose-escalation for patients with intraprostatic gross tumor. Patients were assessed at baseline (prior to HDR-BT), weekly during treatment, at 6 weeks and every 3 months thereafter post-RT completion. Toxicity and patient reported outcomes were collected prospectively using the Common Terminology Criteria for Adverse Events version 4.0 and Expanded Prostate Cancer Index Composite (EPIC), respectively [6].

Case 1: Ulcerative colitis

Inflammatory bowel disease (IBD) is a chronic GI disorder comprising Crohn's disease and ulcerative colitis (UC). Typically, IBD has a relapsing and remitting clinical course. RT has been identified as a risk factor for disease flare-ups [7], and 8–29% of IBD patients treated with RT experience G3 or higher GI complications [8,9]. Hence, IBD remains a relative contraindication for PCa RT [10].

We present a 79 years old (yo) patient with 20-year history of UC on maintenance mesalamine and intermittent hydrocortisone rectal foam during flare-ups, diagnosed with a favorable intermediate-risk (FIR) PCa [PSA 8.28 ng/mL, cT1-category, Gleason 7 (3 + 4) in 4/12 cores]. To maximize bowel sparing combined MRg HDR-BT boost (15 Gy in 1 fraction) plus external beam RT (EBRT) (37.5 Gy in 15 fractions) to the whole gland (WG) was recommended (Fig. 1). During the treatment, the patient experienced G2 diarrhea at week 2 managed with loperamide. He returned to baseline bowel function within 6 weeks of RT completion, in keeping with commonly observed GI toxicity in patients without IBD treated with HDR + EBRT [11]. One year after RT, he has not reported any flare-up of his UC nor GI toxicity.

Case 2: Salvage HDR BT post-EBRT

Despite improvements in RT for PCa, local recurrence (LR) can still occur in 20–30% of PCa patients treated with EBRT [12]. Local salvage curative-intent treatments may achieve cure in up to 30–50% of cases, but are limited by the risk of toxicity [13,14]. Salvage BT focused to the MR-identified intraprostatic LR has been suggested to provide similar oncologic outcomes with lower toxicity rates compared to WG approaches [15].

A 72 yo patient treated with curative-intent EBRT (78 Gy in 39 fractions) for a FIR PCa [PSA 7.8 ng/mL, cT1c-category, Gleason 7 (3

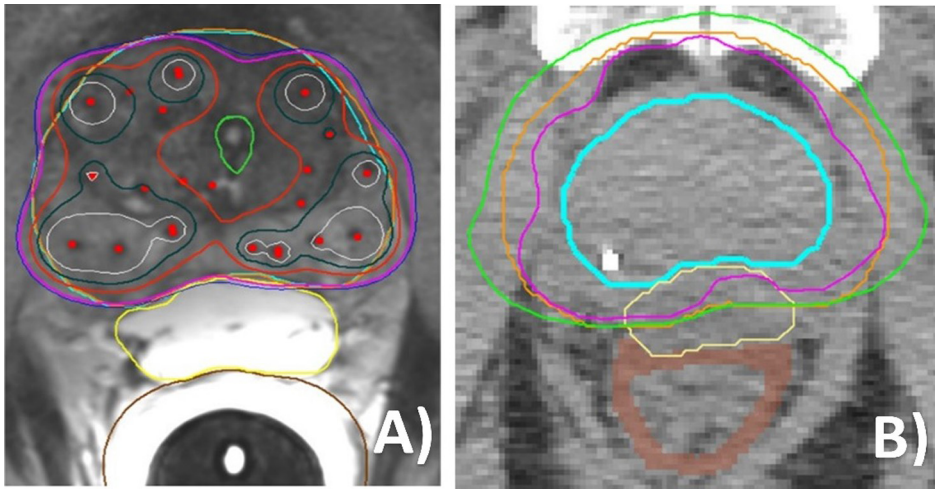

Fig. 1. SpaceOAR (yellow contour), hyperintense structure between prostate and rectum on T2-weighted (T2-w) MR images for HDR-BT planning (A), and isodense on CT simulation for VMAT planning (B). Organs: Prostate gland [clinical target volume (CTV)] light blue, planning target volume (PTV) orange, rectum brown and urethra green. Isodose lines in relation to the prescription dose: (A) (15 Gy) White 200%, dark green 150%, red 125%, purple 100 %,and dark blue 75%. (B) (37.5 Gy): Purple 100 % and light green 95%. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

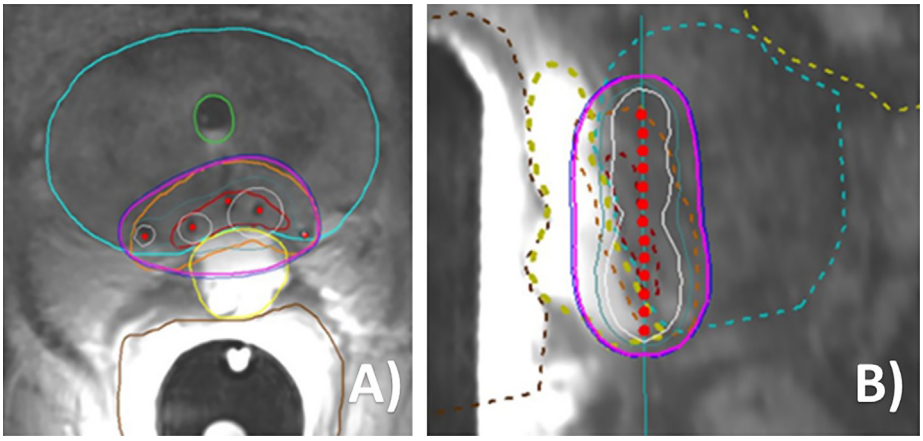

Fig. 2. T2-w MR images used for focal salvage HDR-BT planning. SpaceOAR is visualized (contoured in yellow) in axial (A) and sagittal (B) reconstructions. Structures: gross tumor volume (GTV) red, PTV (GTV + isotropic expansion of 5 mm + additional 2 mm S/I) orange, prostate light blue, rectum brown and urethra green. The use of SpaceOAR in this case allowed to exclude the rectum from the prescription dose (13 Gy). Isodose lines: White 200%, dark green 150%, purple 100 % and dark blue 75%. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

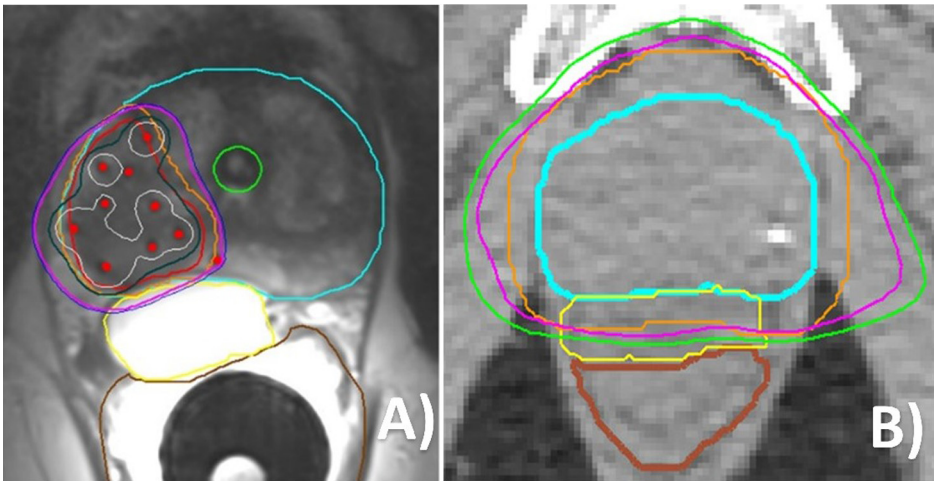

Fig. 3. The prostate (light blue) and the GTV demonstrated as an area of hypointensity (red contour) in the T2-w MR images used to plan the HDR-BT focal boost (A). The spacer is visualized as a hyperintense structure (yellow contour) and allows complete sparring of the rectum from the high-dose region. CT axial slice of the VMAT SBRT plan (B). Organs: Prostate gland [clinical target volume (CTV)] light blue, planning target volume (PTV) orange, rectum brown and urethra green. Isodose lines in relation to the prescription dose: (A) (15 Gy) White 200%, dark green 150%, purple 100 % and dark blue 75%. (B) (30 Gy): Purple 100 % and light green 95%. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

+ 4) in 5/14 cores]. Two years after treatment, he developed biochemical recurrence (PSA 3.0 ng/mL, nadir 0.9 ng/mL, doubling time 10.6 months). MR revealed a 1.6 cm posterior-mid peripheral zone (PZ) lesion (PIRADS-5) [16]. Biopsy confirmed presence of Gleason 7 (3 + 4) adenocarcinoma. Although there was concern with possible technical difficulties related to fibrosis that might have been encountered due to previous RT, PEG hydrogel insertion was attempted and achieved uneventfully. A total dose of 26 Gy to the tumor region was delivered in two separate implants 1 week apart (Fig. 2). At the time of this report (6-months post treatment) the patient has not experienced any GI toxicity. Consistently, patient-reported bowel domain QoL summary score only exhibited minor fluctuations (declined 1.8 points and increased 7.1 points compared to baseline at 1 and 6 months post-treatment, respectively).

Case 3: Focal HDR-BT boost + stereotactic body radiation (SBRT)

Whole-gland dose-escalation strategies have successfully improved biochemical outcomes, but also significantly increase treatment-related toxicity [17,18,19]. Presence of intraprostatic gross tumor predicts worse relapse-free survival, and is the most frequent site of LR after RT [20,21]. Hence, targeted dose-intensification to subprostatic regions with high tumor burden may improve the therapeutic index by allowing better sparing of surrounding normal tissues.

A 69 yo patient with an unfavorable IR PCa [PSA 5.6 ng/mL, cT1c-category, Gleason 7 (3 + 4) in 8/13 cores]. Four of the involved cores (all Gleason 7) disease corresponded to a right PZ PIRADS-5 lesion, while the remainder systematic biopsies harbored Gleason 6 (3 + 3) disease. The patient was treated with focal MRg HDR-BT 15 Gy in 1 fraction followed by WG SBRT (30 Gy in 5 fractions) (Fig. 3). To the time of this report, 6-months after treatment, the patient has not experienced any GI toxicity, and patient-reported bowel domain QoL summary score mildly declined at 1 month (5.3 points), recovering baseline levels at 3-month follow-up.

Discusion

In this case series, we illustrate the use of PEG hydrogel spacer in particularly challenging scenarios with high-risk of GI complications, where the clinical utility of this device may be maximized by MRg therapeutic methods. Despite a limited follow-up, none of our patients reported grade $\geq$ 3 GI toxicity, and only one experienced transient grade 2 toxicity resolving within 6 weeks after RT completion. Also, bowel domain-related QoL marginally declined after treatment, recovering baseline levels at 3 months.

Although previous data supports an overall decrease GI toxicity with the use of rectal spacer, a significant proportion (>90%) of patients may not derive an actual clinical benefit given the low rates of toxicity with modern RT techniques [22]. On the other hand, in clinical scenarios where BT dose-escalation is being considered, the spacer's benefits could be maximized, but are restrained by its physical characteristics interfering with visualization of structures in the conventional BT settings. These limitations associated with the presence of the hydrogel in the CT and TRUS planning settings are circumvented with the use of MRg workflows.

In conclusion, we provide clinical examples in which MRg-BT enabled the use of PEG hydrogel spacer in cases where higher rates of GI toxicity were expected, thereby broadening the application of these advanced technologies towards increasing the therapeutic index of RT-based treatments for localized PCa.

Disclosure

There are no conflicts of interest.

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