

Teaching Case

Hydrogel Spacer Rectal Wall Infiltration Associated With Severe Rectal Injury and Related Complications After Dose Intensified Prostate Cancer Stereotactic Ablative Radiation Therapy



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Abstract

The risk of rectal toxicity during and after prostate cancer radiation therapy is common to all treatment regimens. Hydrogel rectal spacers are increasingly being used to mitigate this risk and to facilitate dose-escalation, but also may infiltrate the rectal wall, with unclear clinical implication. We present a case of significant infiltration associated with severe late rectal injury (grade 4) and further grade 3 to 4 sequelae (recto-urethral fistula and associated osteomyelitis requiring exenteration) after high-dose stereotactic body radiation therapy for localized prostate cancer. The injury's temporal pattern associated with the expected timing of gel dissolution and displacement of infiltrated rectal layers potentially toward high dose regions together suggest a contributing role of the infiltration to the injury. In light of the rapid increase of hydrogel rectal spacer utilization, we review the case's evolution, concerning imaging findings, and associated literature and make suggestions regarding treatment planning and endoscopic assessment in the setting of infiltration or expected injury.

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Introduction

Radiation therapy (RT) for prostate cancer remains associated with a dose-dependent and dose-limiting risk of rectal toxicity.¹ Contemporary dose-escalated RT regimens,²⁻⁵ have improved biochemical control at the cost of higher rectal toxicity. Temporary hydrogel spacer placement between the prostate and rectum is an increasingly used method to reduce such risk, with a randomized control trial demonstrating decreased grade 1 to 2 rectal

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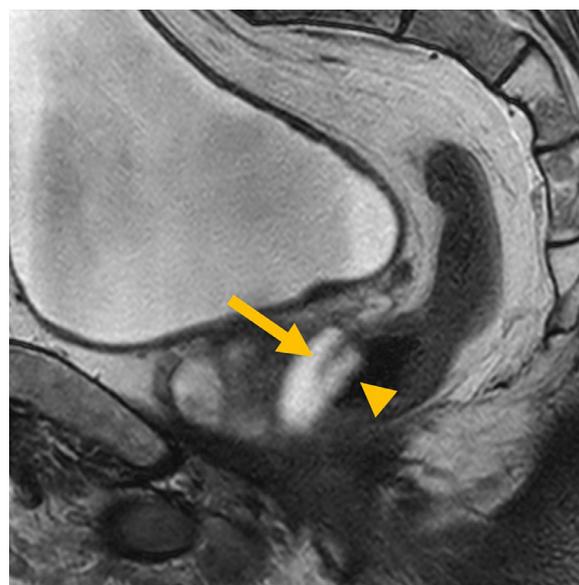
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toxicity and improved bowel domain patient-reported quality of life scores.⁶ Commercially available products are typically absorbed within 3 to 6 months after placement, performed by transrectal ultrasound-guided transperineal approach.⁷ Although placement is generally well tolerated,⁸ postapproval surveillance of unexpected and potentially related injuries remains important to ensuring patient safety. To this end, we present a case of suspected contribution of significant hydrogel spacer gel rectal wall infiltration to a high-grade rectal injury and subsequent grade 3 to 4 urethral/infectious sequelae in a man undergoing high-dose RT for prostate cancer.

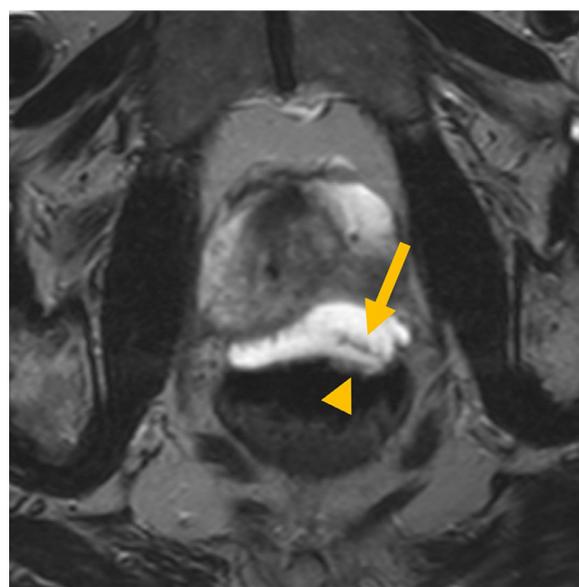
Case Presentation

A 62-year-old man received a diagnosis of intermediate risk prostate cancer (cT1cN0M0, prostate-specific antigen 5.9 ng/mL, ISUP grade group 2). Biopsy was performed of 3 magnetic resonance imaging (MRI)-defined lesions by MRI in-bore transrectal biopsy method (8/9 cores positive from 3 lesions, range 15%-100% positive with maximum pattern 4 of 30%) without complication 3 months before therapy. He had no history of abdominopelvic surgical procedures, repeated prostate biopsies, major comorbidities, ongoing anticoagulant use or inflammatory bowel disease. He elected treatment with ultrahypofractionated RT using high-dose stereotactic ablative radiation therapy (SAbR) without androgen deprivation therapy.

In preparation, he underwent transrectal ultrasound-guided transperineal placement of a commercial hydrogel spacer (SpaceOAR, Boston Scientific) and gold fiducials under moderate sedation, as described.⁹ Both credentialed Urologists and Radiation Oncologists perform this procedure at our institution, and this procedure was performed by the treating radiation oncologist, who at the time had performed >200 such procedures. Visualization of needle placement was performed under both sagittal/axial views in a “dual” view mode. There was no apparent procedural complication or symptoms after the transient discomfort of the actual procedure. Computed tomography (CT)/MRI simulation was used to delineate prostate, standard organs at risk and spacer gel distribution. MRI included T1- and T2-weighted sequences with fast spoiled gradient sequence particularly for fiducial recognition to aid fusion to CT. Simulation procedures included enema for rectal emptying, bladder filling, vacuum mold from arms (up) to mid-thigh, and indexed stereotactic frame. Prostate volume was expanded 3 mm to create the planning target volume. MRI appeared to indicate adequate displacement of rectum from prostate, ranging from 1.2 to 1.5 cm along the craniocaudal axis of the prostate. In retrospect, however, significant anterior rectal wall infiltration was present. In particular, an area of deeper infiltration with “delamination” or



(a)



(b)

Fig. 1 Sagittal (A) and axial (B) T2-weighted treatment planning magnetic resonance imaging show infiltration of hydrogel within the rectal wall with delamination and discontinuity of the muscularis propria (arrows) resulting in accumulation of spacer material in the submucosa (arrowheads).

discontinuity of the muscularis propria was identified (Fig. 1). SAbR was prescribed to an escalated dose of 45 Gy in 5 fractions, delivered on nonconsecutive days over 3 weeks using volumetric modulated arc therapy, after treatment delivery and institutional constraints based upon data from successive phase 2 to 3 trials of SAbR at our institution,^{10,11} including a trial specifically focused

Table 1 Comparison of rectal dose constraints in NRG GU005 to dosimetric values achieved in the presented treatment

Rectal dose volume	NRG GU005 (Gy)	Case (Gy)
Point Dose	<38.06	43.9
D _{3cc}	<34.4	32.2
D _{10%}	<29	21.2
D _{20%}	<29	17.4
D _{50%}	<18.13	2.0

on use of rectal spacer and modified rectal constraints to reduce associated toxicity. Notably, rectal dosimetry (V24 Gy was ~33% of rectal circumference vs 50% limit, V39 Gy was ~10% of rectal circumference vs 35% limit, max dose to 0.035 mL volume was 43.8 Gy) was well within these limits.¹²⁻¹⁵ Moreover, the rectal dosimetry met constraints of an ongoing collaborative group trial of SABR NRG GU005 (NCT03367702) for all but the volumetric maximum constraint, as shown in Table 1. However, doses to the spacer gel in the adjacent area of infiltration ranged 20.7 to 48.6 Gy, creating the potential that poorly visualized layer of muscle wall may yet have received higher doses than anticipated.

Representative dosimetry and dose volume histogram are demonstrated in Fig. 2. Standard procedures including

use of rectal enema, bladder filling, and frame-based stereotactic setup using fiducial and soft tissue anatomy guidance by matching on-board cone beam CT to reference CT image were used. No abnormalities were noted during plan quality assurance or intrafraction imaging at the time and in repeated later review. The patient tolerated treatment well without gastrointestinal complaints and return to baseline urinary function by 6 weeks on selective alpha-blocker (tamsulosin).

Starting ~5 months after RT completion, the patient reported worsening urinary symptoms, perineal fullness and occasional blood on wiping after bowel movements attributed initially to hemorrhoids. Cystoscopic examination was negative for signs of urethral or bladder neck injury. During the next month, he subsequently developed anal pain and mucous discharge with some bowel movements, unresponsive to hydrocortisone suppository, and methylprednisolone dose pack for suspected radiation proctitis. Digital rectal examination noted anterior rectal wall tenderness with nodularity in expected area of prostate but without blood. Before endoscopic assessment could be pursued electively, he experienced acute worsening of rectal bleeding, prompting hospital admission outside our institution. Sigmoidoscopy revealed a large anterior wall ulceration (Fig. 3) corresponding with the previously seen area of spacer infiltration, and diverting colostomy was pursued at now 6 months after RT. Biopsies were taken of the ulcerated edge, consistent on

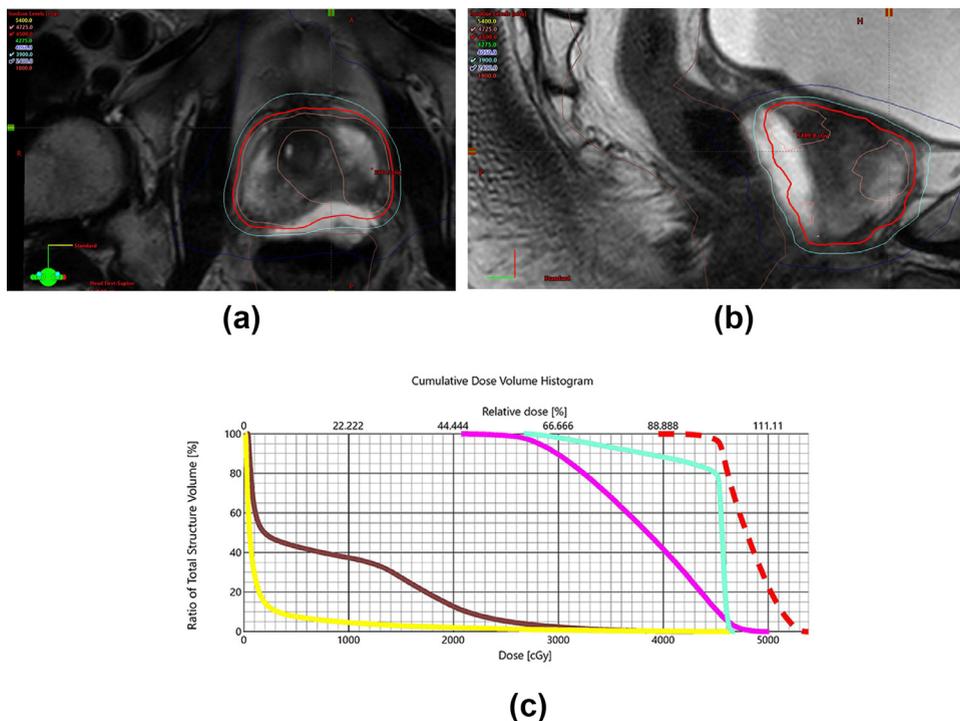
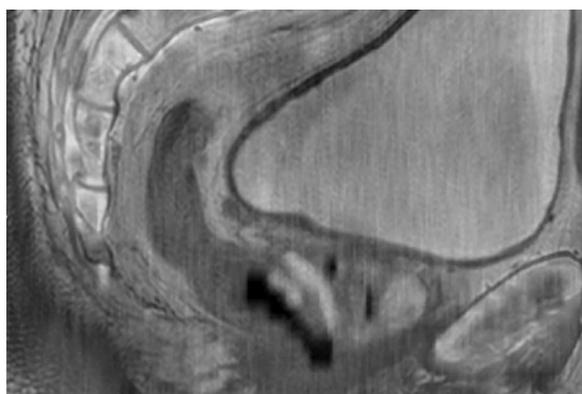
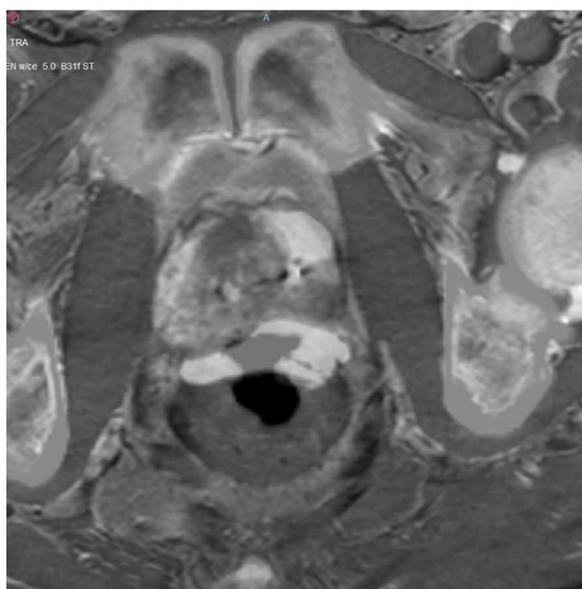


Fig. 2 Clockwise from top left: (A) shows axial dose distribution on fused magnetic resonance imaging with sparing of rectal wall, <35% of circumference receiving 39 Gy (cyan) and <50% of circumference receiving 24 Gy (blue). (B) Shows similar rectal wall sparing in sagittal view. (C) Shows dose volume histogram with doses to the planning target volume (red), urethra (green), spacer infiltration (magenta), rectum (brown), and bladder (yellow).



(a)



(b)

Fig. 3 Sagittal (A) and axial (B) follow-up contrast-enhanced computed tomography images at 7 months posttreatment blended with pretreatment magnetic resonance imaging depict a large defect in the lower anterior rectal wall corresponding to the abnormal area shown in Fig. 1A. This results in free communication between the rectal lumen and the air-filled rectoprostatic space, in keeping with the wall defect identified on sigmoidoscopy (C).

pathology with colitis without malignancy. Notably the endoscopy did not show diffuse radiation changes of the adjacent rectum. Thereafter, he underwent hyperbaric oxygen treatments (50 dives) during the next 2 months, with resolution of rectal bleeding and pain.

At 9 months after RT completion, the patient developed urine per rectum, related to a large recto-urethral fistula, as shown on retrograde urethrogram (Fig. 4). Despite receiving suprapubic tube in attempt to temporize for flap repair, he developed osteomyelitis and soft tissue abscess, eventually requiring abdomino-perineal resection, cystoprostatectomy, and ileal conduit urinary diversion, now

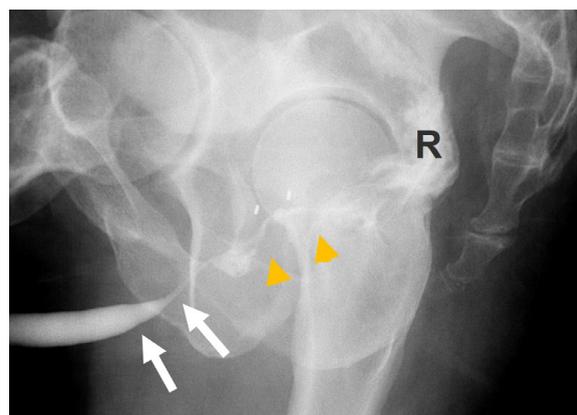


Fig. 4 Oblique lateral radiograph obtained during retrograde urethrogram reveals normal penile and bulbar segments of the anterior urethra (white arrows) but fistulous communication (yellow arrowheads) between the membranous urethra and the rectum (R). Abbreviations: P = prostate; R = rectal wall.

at 15 months from RT. Pathology demonstrated prostate adenocarcinoma with marked radiation therapy changes confined to the prostate and at the prostatic urethra margin, rectourethral fistula tract, and unremarkable rectal mucosa. Due to these complications and corrective procedures, the patient has required routine physical therapy and had to take leave from work for several months, with associated substantial effects on his quality of life. Despite this, he has made remarkable progress. As of last follow-up, he has undetectable prostate-specific antigen, is without evidence of infection or further sequelae, and has even returned to work full time.

Discussion

The rapid adoption of rectal hydrogel spacer placement ahead of RT for prostate cancer reflects increasing focus on quality of life in localized prostate cancer RT. Nonetheless, as with any device, postapproval experience may reveal rare complications that inform practice. In our case, we observed a proctitis event whose unusual severity, timing and context are concerning for an injury contributed to if not partially precipitated by the substantial rectal infiltration of the hydrogel spacer itself.

Several factors suggest this contribution rather than typical RT related injury mechanisms alone. First, the timing of rapid and new symptom onset at ~5 months after spacer gel insertion approximates the expected time of its resorption, whereas severe late radiation proctitis typically occurs later and is often preceded by acute/subacute symptoms,¹⁶ particularly in the setting of high dose SBRT related injuries in our prior trial experience.^{11,17} Classically, acute proctitis develops within 3 months of treatment, although late proctitis typically develops >9 months after treatment and is commonly associated with

prior acute symptoms.^{16,17} Second, while infrequent but severe rectal toxicity has been observed with high dose SABR in early studies without spacer gel, as reported by our group,^{10,15} the patient's rectal dosimetry fell well within institutional constraints developed based on those experiences¹⁵ and largely met constraints of lower SABR dose regimens (Table 1). Notably, in our own institution's prospective¹³ and retrospective¹¹ experiences because initiation of rectal hydrogel spacer placement with high dose SABR across all risk groups (n = 250), no other single case of grade >2 rectal toxicity has been noted.¹¹ Third, rectal wall infiltration in retrospect was of substantial depth and resulted in an area of delamination of deep rectal wall muscle layers, best approximated on sagittal sequences.

Infiltration of the rectal wall without apparent consequence was noted in 6% of cases in the randomized prospective study of conventionally fractionated RT leading to rectal hydrogel spacer approval.¹⁸ However, the effect of more severe infiltration and related ischemic stress on the rectal wall in the setting of increasingly used intensified and hypofractionated regimens remains unassessed by such data. Indeed, our elected institutional SABR dose (45 Gy in 5 fractions) exceeds that endorsed by other practitioners (36.25-40 Gy in 5 fractions)¹⁹ and relies upon the demonstrated ability of rectal hydrogel spacer to facilitate rectal doses normally achieved by those latter regimens.¹¹ However, in the setting of delamination of muscle layers, we speculate that portions of vascular supply containing rectal wall may be displaced toward the high dose regions, creating the potential for an occult ischemic injury revealed upon dissolution of the

hydrogel. This possibility would argue for conservative organ-at-risk delineation of rectum to include gel in areas of infiltration. Lastly, although we have predicated our dosing upon the argument that lower SABR doses approximate contemporary conventionally fractionated RT disease control in randomized comparison,²⁰ which are inferior to the outcomes of RT combined with brachytherapy boost,²¹ the recently published Focal Lesion Ablative Microboost in Prostate Cancer (FLAME) trial²² suggests that selective dose-escalation to MRI-defined lesions may offer flexibility for reducing dose along suspected rectal infiltration areas when concern arises.

Regardless of mechanism, a recent report from the Food and Drug Administration manufacturer and user facility device experience (MAUDE) database and other available case reports describe a low number of severe injuries associated with use of spacer gel, as summarized in Table 2,²³⁻²⁶ suggesting a rare injury potential exists. Notably, many of the reported injuries occurred as a result of direct perforation of the rectal mucosa with symptoms presenting earlier than in our case; thus, and direct rectal mucosa disruption was possible as a direct injury mechanism, we do not have the support of symptom timing or direct endoscopy to confirm this is what occurred here. Similar injury risk at low rates has also been observed for analogous rectal spacer balloons, whose rigidity was hypothesized to be more commonly associated with acute injuries.²⁷ The present case thus was accordingly reported as another potentially associated event in MAUDE.²³

In regard to the ensuing recto-urethral fistula, its occurrence by timing and location is best ascribed to a

Table 2 Summary of high-grade complications associated with hydrogel spacer in the treatment of prostate cancer

Date of report	Grade	Description	Notes
12/5/14 ²²	3	Ulceration treated conservatively	Received LDR brachytherapy, symptoms began 1 month after placement
1/19/16 ²⁰	3	Proctitis requiring colostomy	Symptoms started 6 months after placement
10/24/17 ²⁰	3	Rectourethral fistula requiring colostomy	High-risk posterior cancer with extraprostatic extension, stepper not used
4/1/18 ²⁰	3	Rectourethral fistula requiring colostomy	Two patients with HDR treatment, fistula "several months" after placement
6/4/18 ²⁰	3	Perirectal fistula requiring surgery	Spacer eroded through rectal wall before radiation, poor rectal preparation
9/29/18 ²⁰	3	Ulceration after rectal wall injection	Radiation not given
1/2/19 ²⁰	3	Rectourethral fistula requiring colostomy	Rectal wall infiltration was present
2/21/19 ²⁰	3	Rectourethral fistula requiring colostomy	Rectal muscle infiltration seen
4/8/19 ²³	3	Rectal ulcer resolved with HBO therapy	High dose IMRT, acute ulceration associated with pseudolumen abutting rectal wall
Present report	4	Rectourethral fistula and associated osteomyelitis ultimately requiring exenteration	Anterior rectal wall infiltration was present, high dose SABR delivered, symptoms began 5 months after treatment, rectal ulcer was instrumented, symptoms initially improved with HBO but later developed fistula, abscess, and osteomyelitis

Abbreviations: HDR = high dose rate; IMRT = intensity-modulated radiation therapy; LDR = low dose rate; SabR = stereotactic ablative radiation therapy.

mechanism of direct exposure of recently irradiated prostate and adjacent membranous urethra to a major rectal ulcer. Moreover, it must be noted that the biopsy at time of sigmoidoscopy evaluation of the rectal injury may have contributed, as suggested in prior experiences.²⁸

In summary, we believe this case reflects an extremely rare potential for rectal hydrogel spacer itself to contribute to major rectal injury, when observed to deeply infiltrate the rectal wall ahead of dose-escalated prostate RT. We report this case to raise awareness of this complication and provide suggested guidance on steps to recognize and intervene upon such infiltration. First, we highlight the importance of careful hydrodissection technique, with care to avoid insertion of the needle into the peri-rectal fat and to abort cases where confident placement is not assured. Second, infiltration of the anterior rectal wall at simulation imaging, particularly with MRI, should be evaluated ideally in collaboration with a MRI radiologist in cases of concern, specifically as regards the presence of deep muscle layer delamination. In such cases, we would propose endoscopic evaluation for evidence of submucosal injury that may argue for delay of RT until the gel dissolves or confirmation after RT that gel dissolution has occurred without later injury. We have instituted this approach because this case without any subsequent rectal injuries observed. Third, we propose to delineate the area of spacer infiltration as part of the rectal wall organ at risk for treatment planning to avoid the potential for treating separated outer layers of rectal wall unintentionally. Finally, given the low incidence of rectal toxicity in those with hydrogel spacer, the occurrence of unusual rectal symptoms or at unusual timing should trigger direct endoscopic evaluation to rule out this rare event.

Conclusions

We describe a case of high-grade toxicity potentially contributed to by deep hydrogel spacer rectal wall infiltration in the context of dose-escalated RT. We suggest concrete steps for its early identification and monitoring, particularly when rectal wall infiltration is associated with delamination of muscle layers. Although the occurrence of this toxicity appears very low, attention to these details may further improve confidence in improving the therapeutic ratio of prostate RT in the long term.

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