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Teaching Case

Use of Stereotactic Magnetic Resonance-Guided Online Adaptive Radiation Therapy for Treatment of a Pelvic Recurrence of Prostate Cancer in a Patient With an Orthotopic Neobladder

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Introduction

Radical cystoprostatectomy is a key component of therapy for many men with bladder cancer. Options for a urinary reservoir include reconstruction of an orthotopic neobladder, typically using a loop of small bowel. This bowel is then anastomosed to the urethra and ureters. For men who require pelvic radiation therapy (RT) after radical cystoprostatectomy and orthotopic neobladder reconstruction, appropriate RT dose constraints for the neobladder and the anastomosis between the neobladder and urethra, a site already at risk for stricture,[1] have not been established. Postoperative RT guidelines for bladder cancer have been published, but explicitly state that no consensus dose limits for these structures exist.[2]

Here, we report on a case of a man with a history of extensive urothelial carcinoma in situ for which he underwent a radical cystoprostatectomy, with a Gleason score 4 + 3 prostate cancer incidentally discovered on the pathology. He developed a gross prostate cancer recurrence adjacent to both the neobladder and the anastomosis of the neobladder to the urethra. He was treated with stereotactic magnetic resonance-guided online adaptive radiation therapy (SMART) as outlined in more detail in the following sections. SMART was used to reduce the risk of a complication in either the neobladder or at the anastomotic site, as these regions are particularly at risk for a significant toxicity (eg, fistula or urethral stricture). We illustrate our overall approach and constraints for this clinical context of using pelvic SMART in a patient with an orthotopic neobladder.

Clinical Case

Patient details

The patient initially presented to our department at age 84. He had a previous diagnosis of extensive urothelial carcinoma in situ for which he underwent a radical cystoprostatectomy 12 years prior with a neobladder reconstruction performed at that time using the terminal ileum and ileocecal valve. A prostate adenocarcinoma was incidentally found within the cystoprostatectomy specimen, Gleason score 4 + 3, pT2 involving 10% of the submitted tissue, negative margins. At the time he presented to our department, his prostate-specific antigen (PSA) was 15.4. A fluciclovine positron emission tomography/computed tomography (CT) scan showed a soft tissue density at the base of the bladder with avid uptake (Fig 1A), as well as a mildly avid lung nodule felt to be inflammatory after further dedicated chest imaging. Magnetic resonance imaging (MRI) of the pelvis

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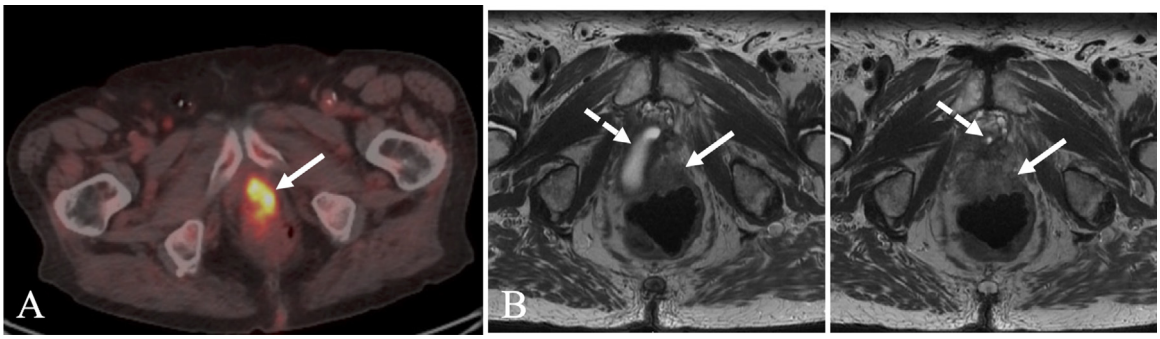

Fig. 1 (A) Fused ^{18}F-fluciclovine positron emission tomography (PET)/computed tomography (CT) scan showing a large PET avid mass in the prostate fossa (white arrow). (B) This mass (solid arrows) sits adjacent to the neobladder and the anastomosis with the urethra (dashed arrows).

demonstrated a 4.8×3.7×3.3-cm tumor in the prostatectomy bed abutting the anterior margin of the rectum and the inferior margin of the neobladder (Fig 1B).

Various treatment options were reviewed at our institutional multidisciplinary conference, including observation, androgen deprivation therapy (ADT), or RT. Given the patient's excellent performance status and few other medical comorbidities, he elected for local therapy with RT, given with a short course (4 months) of neoadjuvant, concurrent, and adjuvant ADT. We considered various RT treatment approaches, including conventionally fractionated external beam RT, brachytherapy, and stereotactic body RT (SBRT). We ultimately settled on treatment with SBRT for a number of factors including: (1) shortening time under treatment during the ongoing COVID-19 pandemic for this patient who lived several hours from our center; and (2) the theoretical advantage of using higher doses per fraction in a prostate adenocarcinoma whose α/β ratio may be lower than that of surrounding critical bowel (neobladder) and rectum.

MRI-guided RT

The patient was treated using MR-guided RT using an integrated MRI-linear accelerator. This approach was chosen to provide better visualization of the tumor and surrounding organs at risk (OARs; particularly the neobladder) during daily setup and to give us the option to adapt treatment daily if needed for changes in neobladder or rectal anatomy.

Treatment planning was performed with a True Fast Imaging with Steady state Precession (TRUFI) imaging sequence acquired at 0.35 T. The TRUFI imaging sequence is used for real time visualization of the treatment site. Planning and treatment were performed using the integrated 6 MV flattening filter free linear accelerator, sandwiched between split bore magnets. The linear accelerator is equipped with a double-focused double-stack multileaf collimator so that the beams have sharp penumbra with minimal leakage through the leaves. Multileaf collimators are designed to project field sizes from 0.2 × 0.4 cm^2 up to 27.4 × 24.1 cm^2.

The patient was simulated using both the MRI outlined previously as well as computed tomography (CT). He was simulated in the MRI with the neobladder full, in headfirst supine position on a mattress with torso coils. CT simulation was performed without torso coils. Field of view for MR scans was 40 × 43 × 40 cm with resolution of 0.15 × 0.15 × 0.3 cm acquired in 128 seconds with the patient breathing freely. All scans were exported for contouring target volumes and OARs. Radiation oncologist approved contours and scans were exported to our treatment planning system for planning and CT was registered to MR for electron density information.

For daily treatment the patient was set up similar to the simulation. A TRUFI MR scan was acquired using the simulation parameters and the scan was registered to the planning MR. All OARs were transferred from planning scan to the daily MR scan deformably using intensity-based registration while planning target volume (PTV), clinical target volume, and gross tumor volume (GTV) were rigidly transferred to the daily MR scan. All contours were reviewed by the physician and necessary edits were done for OARs within a 3-cm uniform ring around the PTV. Subsequently, the original plan dose was predicted on that day's anatomy and the plan was reoptimized if the predicted dose didn't meet the physician-defined treatment planning objective. In this case, particular attention was paid to the dose to the neobladder, the urethra, and the rectum. Once the reoptimized plan was approved by the physician, the patient was treated with the new plan after performing online quality assurance by the physicist.

The prescription to the target was 36.25 Gy in 5 fractions. The target structures included PTV and GTV, and OARs included bladder, bowel, rectum, urethra, right and left femoral head, and penile bulb. Constraints for these OARs are listed in Table 1.

Treatment delivery

GTV, bladder, urethra, and rectum contours were edited on a daily basis. Adaptive plans were evaluated

Table 1 Planning objectives for SBRT

Coverage	
PTV	D95% ≥ 36.25 Gy
	D98% ≥ 34 Gy
	D2% < 40 Gy
Constraints (take precedence over coverage)	
Neobladder	D0.03 cc < 30 Gy
Rectum	D0.03 cc < 30 Gy
Urethra	D0.03 cc < 30 Gy
Objectives (coverage takes precedence)	
Urethra	D0.1 cc < 25 Gy
Anal canal	V15 Gy < 3 cc
Femoral heads	D1 cc < 30 Gy; V20 Gy < 10 cc
Penile bulb	D0.03 cc < 36.25 Gy; V20 Gy < 3 cc

Abbreviations: PTV = planning target volume; SBRT = stereotactic body radiation therapy.

and adopted for all fractions except fraction 5, in which the adaptive plan provided no dosimetric befit compared with the initial plan. Daily changes in neobladder filling and surrounding anatomy are shown in Figure 2A. Median bladder volume was 445.4cc (range, 428.7-459.4 cc) and urethra median volume was 1.19 cc (range, 0.6-2.53 cc). The PTV receiving the prescription dose of 36.25 Gy was higher for the first and fourth fractions in the reoptimized plans compared with the original plan. For the rectum, the volumes receiving 32.6 and 29 Gy were lower in all the reoptimized plans compared with the original plan. A large difference in the dose to the urethra was noted for fraction 4 compared with planned dose (see Fig 2B). Dosimetric parameters for each fraction are summarized in Table 2.

Outcome

The patient tolerated therapy very well. He had minor hot flashes and fatigue associated with ADT. He had no acute gastrointestinal or genitourinary toxicities during treatment. He had baseline incontinence to urine that was unchanged during or after treatment. Likewise, he had no evidence of toxicity at follow-up visits 3 and 9 months after completion of RT.

His PSA declined from a pretreatment level of 15.46 to undetectable (<0.01) at 3 months post-RT (6 months after a single 30-mg leuprolide injection). His PSA remained undetectable 9 months after completion of RT (and 12 months after the single leuprolide injection).

The patient developed an infection of his knee 15 months after completing RT, complicated by bacteremia, sepsis, and then a fall resulting in a catastrophic subarachnoid hemorrhage and the patient's death. He was without any clinical evidence of recurrent prostate cancer at that time.

Discussion

Radiation dosimetry constraints for an orthotopic neobladder remain undefined in the literature. Guidelines that have been published for adjuvant RT after radical cystoprostatectomy for bladder cancer recommend contouring the urinary diversion and limiting beams being directed through it so long as this does not compromise coverage of the target(s). However, no specific constraints are given.[2] Trials have examined adjuvant RT for bladder and have demonstrated reasonable toxicity, with a suggestion of some increased grade 3 late adverse effects in patients who receive adjuvant chemotherapy plus radiation versus radiation alone.[3] Likewise, use of adjuvant RT in patients specifically with an orthotopic neobladder has been reported with good tolerance of this therapy and few toxicities.[4] However, this was done with conventional fractionation. We are aware of no published data on the tolerance of an orthotopic neobladder to radiation using high doses per fraction (ultrahypofractionation or SBRT).

One potential approach, and the one we used here, is to treat the neobladder like bowel for the purposes of radiation dose constraints. Suggested constraints for bowel when using SBRT have been published,[5] and several series and trials have been published using SBRT to treat intra-abdominal and pelvic tumors using MRI-guided RT, with suggested constraints for bowel structures.[6-9] Overall, these trials have shown good tolerance, with acceptable toxicity. There are fewer data on the use of SBRT or SMART in patients who have had prior abdominal or pelvic surgeries that involve significant reconstructions using bowel. Several retrospective case series have investigated the use of SBRT in patients with pancreatic and rectal cancer who have had prior surgery, many of whom have also had prior RT. These have shown good tolerance overall, though with some acute and late ≥ grade 3 toxicities

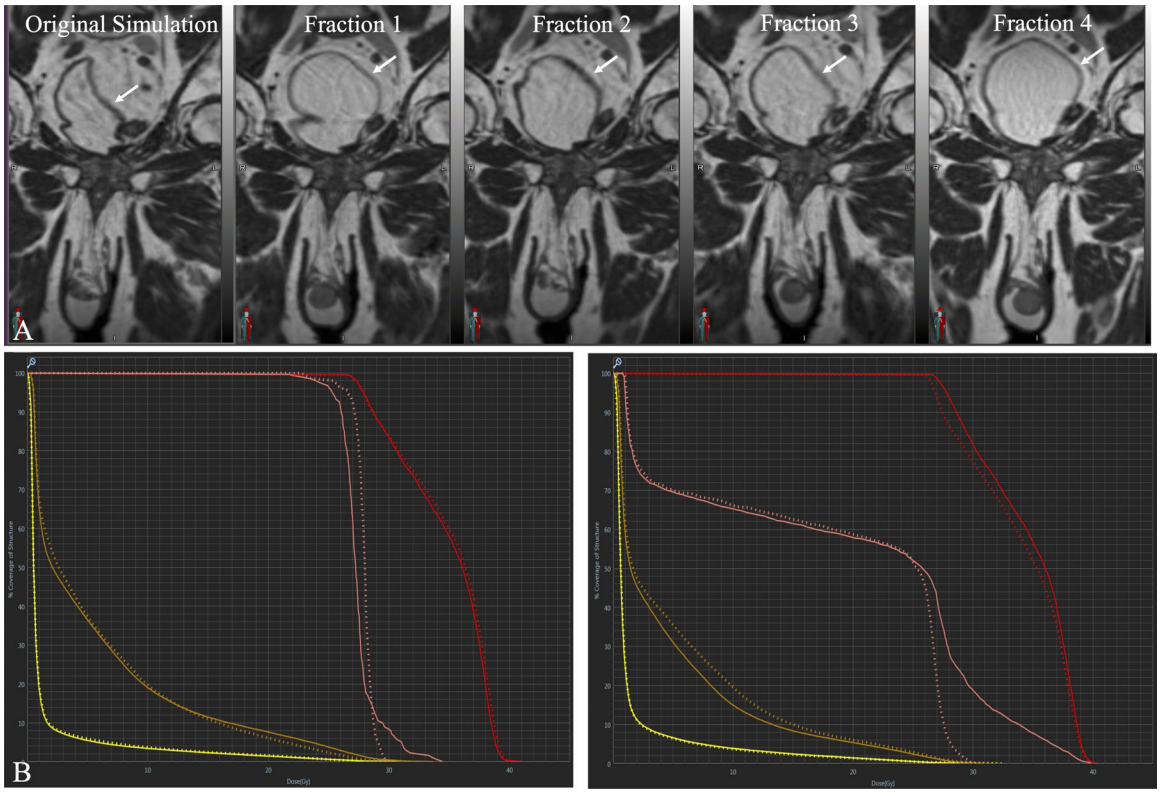

Fig. 2 (A) Variation of neobladder filling (white arrows) for original simulation and 4 adapted fractions. (B) Dose volume histograms of predicted (solid) versus reoptimized (dashed) dose for planning target volume (PTV) (red), rectum (brown), bladder (yellow), and urethra (salmon) for fraction 2 (left) and fraction 3 (right). For both fractions the adaptive plans decreased maximum dose to the urethra.

reported, illustrating that SBRT in the context should be approached with caution.[10-15]

There are some important limitations to the data presented with this case. Although the patient's PSA remained undetectable out to 9 months postradiation (and 12 months after a single 30 mg leuprolide injection), a testosterone level was not obtained at that time, so it is unclear if a low testosterone level was also influencing the PSA value. In addition, there was limited follow-up of this patient (15 months). Although no toxicities from his RT were apparent within this follow-up period, late toxicities can appear years after the completion of radiation.

This case demonstrates that pelvic SBRT using MR-guided RT in the context of prior radical cystectomy and orthotopic neobladder reconstruction is feasible. No acute toxicity was seen in this patient, and no late toxicity was seen from the time he completed RT until he died of an unrelated illness 15 months later. Constraining the

Table 2 Dosimetric parameters for the original plan and each adapted fraction

	Rx		Original	Fx1	Fx2	Fx3	Fx4	Fx5
PTV prostate	**≥95%**	**36.25 Gy**	**46.15%**	**50.86%**	**41.84%**	**42.88%**	**51.67%**	**Not adapted**
Rectum	≤10%	32.6 Gy	0.4%	0%	0.08%	0%	0%	
	≤20%	29 Gy	7.42%	0.24%	0.52%	0.45%	0.31%	
	≤50%	18 Gy	7.84%	7.84%	10.79%	7.31%	9.09%	
Urethra	≤0.03 cc	30 Gy	0.01 cc	0 cc	0 cc	0 cc	0 cc	
	≤0.1 cc	25 Gy	1.6 cc	1.04 cc	0.16 cc	1.99 cc	1.02 cc	
Neobladder	≤0.03 cc	39 Gy	0	0	0	0	0	
	≤10%	33 Gy	7.25%	6.07%	6.33%	10%	5.8%	
	≤50%	18 Gy	29.01%	22.57%	22.68%	34.96%	32.53%	

Abbreviation: Fx = fraction; PTV = planning target volume; Rx = prescription.

orthotopic neobladder to doses typically used for small bowel in abdominal/pelvic SBRT may be a reasonable starting point. The use of MR guidance in this case allowed us to adapt the plan online (ie, immediately before the delivery of each treatment) to account for changes in the shape and position of the neobladder relative to the target.

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