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Scientific Article

Trimodal Therapy Using an MR–guided Radiation Therapy Partial Bladder Tumor Boost in Muscle Invasive Bladder Cancer

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Purpose: Bladder preservation with trimodal therapy (TMT; maximal tumor resection followed by chemoradiation) is an effective paradigm for select patients with muscle invasive bladder cancer. We report our institutional experience of a TMT protocol using nonadaptive magnetic resonance imaging–guided radiation therapy (MRgRT) for partial bladder boost (PBB).

Methods and Materials: A retrospective analysis was performed on consecutive patients with nonmetastatic muscle invasive bladder cancer who were treated with TMT using MRgRT between 2019 and 2022. Patients underwent intensity modulated RT-based nonadaptive MRgRT PBB contoured on True fast imaging with steady state precession (FISP) images (full bladder) followed sequentially by computed tomography–based RT to the whole empty bladder and pelvic lymph nodes with concurrent chemotherapy. MRgRT treatment time, table shifts, and dosimetric parameters of target coverage and normal tissue exposure were described. Prospectively assessed acute and late genitourinary and gastrointestinal (GI) toxicity were reported. Two-year local control was assessed with Kaplan-Meier methods.

Results: Seventeen patients were identified for analysis. PBB planning target volume margins were ≤8 mm in 94% (n = 16) of cases. Dosimetric target coverage parameters were favorable and all normal tissue dose constraints were met. For MRgRT PBB fractions, median table shifts were 0.4 cm (range, 0-3.15), 0.45 cm (0-2.65), and 0.75 cm (0-4.8) in the X, Y, and Z planes, respectively. Median treatment time for MRgRT PBB fractions was 9 minutes (range, 6.9-17.4). We identified 32 out of 100 total MRgRT fractions that may have benefitted from online adaptation based on changes in organ position relative to planning target volume, predominantly because of small bowel (13/32, 41%) or rectum (8/32, 25%). Two patients discontinued RT prematurely. The incidence of highest-grade acute genitourinary toxicity was 1 to 2 (69%) and 3 (6%), whereas the incidence of acute GI toxicity was 1 to 2 (81%) and 3 (6%). There were no late grade 3 events; 17.6% had late grade 2 cystitis and none had late GI toxicity. With median follow-up of 18.2 months (95% CI, 12.4-22.5), the local control rate was 92%, and no patient has required salvage cystectomy.

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Conclusions: Nonadaptive MRgRT PBB is feasible with favorable dosimetry and low resource utilization. Larger studies are needed to evaluate for potential benefits in toxicity and local control associated with this approach in comparison to standard treatment techniques.

Introduction

Bladder cancer remains among the most common malignancies in the United States, with more than 80,000 new diagnoses estimated in 2022; approximately 25% to 30% of these cases are muscle invasive bladder cancer (MIBC).[1] Although radical cystectomy with or without neoadjuvant chemotherapy is more commonly employed for localized MIBC, bladder preserving trimodal therapy (TMT) has emerged as an effective alternative for selected patients who refuse or are unfit for cystectomy. TMT, consisting of maximal transurethral resection of bladder tumor (TURBT) followed by radical radiation therapy (RT) with concurrent radiosensitizing chemotherapy (chemoRT), results in long-term bladder preservation in more than two-thirds of patients[2-5] and may provide disease-specific survival rates similar to radical cystectomy.[6]

Partial bladder RT boost (PBB) has been used to focally escalate dose to gross tumor and intravesicular regions suspected to harbor microscopic disease while reducing the volume of high dose to the bladder.[7-10] This reduced high-dose volume RT (RHDVRT) technique depends on careful cystoscopic assessment of disease extent and may be limited by suboptimal visualization of gross tumor on computed tomography (CT) imaging after TURBT. Given that accurate target delineation is a key component of RT planning to avoid geographic miss,[11] the limitations of CT-based tumor visualization,[12] even with cystoscopic guidance, might be overcome with the addition of advanced imaging techniques, such as magnetic resonance imaging (MRI), to optimize delivery of RHDVRT with PBB.

MRI allows for precise assessment of disease extent in bladder cancer[13-15] and may improve organ and target delineation.[16] Because of significant inter/intrafractional variation in the position and shape of the bladder,[17] which may be influenced by the variance in daily bladder filling,[18] there has recently been interest in incorporating MRI-equipped linear accelerators (LINACs) as the RT modality in TMT for MIBC. The improved soft-tissue resolution of MRI-based planning may allow for improved delineation of disease extent, which may result in improved local control as well as smaller high-dose target volume and therefore reductions in the excessive normal tissue irradiation associated with CT-based delineation.[19,20] Similarly, the superior soft tissue contrast with MRI guidance may afford improved daily target alignment, facilitating smaller planning target volume (PTV) margins, further contributing to reduced normal tissue irradiation. Additionally, online adaptive optimization capabilities on platforms such as the Elekta Unity (Elekta AB, Stockholm, Sweden) and ViewRay MRIdian (ViewRay Inc, Oakwood Village, OH) could further facilitate target coverage and normal tissue sparing, and early reports have demonstrated the feasibility of this online adaptive RT strategy for MIBC.[21,22]

A drawback to the online adaptive MRI-guided approach is that it is associated with multiple workflow steps, which results in prolonged treatment time and increased resource allocation. An alternative strategy is to leverage the improved soft tissue resolution of MRI-guidance for tumor-focused PBB delineation, daily treatment alignment, and intrafraction motion monitoring, without daily plan adaptation. Here, we aim to describe the feasibility of delivery of a hybrid sequential nonadaptive MRI-guided PBB in our TMT protocol for patients with MIBC.

Methods and Materials

Patients and treatments

Patients were identified from a prospectively maintained database of consecutively treated patients with nonmetastatic MIBC of any histology who underwent TMT with MRI-guided PBB between October 2019 and June 2022. Patients were either medically inoperable or refused to undergo radical cystectomy. TMT included maximal TURBT followed by chemoRT. RT was delivered sequentially via a fixed-field intensity modulated RT-based nonadaptive MR-guided RT (MRgRT) PBB followed by a CT-based minipelvis field and whole empty bladder boost in 1.8 Gy daily fractions. For each patient, the prescribed dose to the tumor bed was 64.8 Gy, if feasible. Chemotherapy choice was delivered concurrently with RT at physician discretion. After TMT, patients were seen in follow-up with surveillance cystoscopy and CT every 3 months for the first 2 years and then 6 months afterward. Patients without complete response (CR) on post-RT cystoscopy or with local recurrences were salvaged with maximal TURBT and intravesical therapy or salvage cystectomy after multidisciplinary discussion.

Radiation treatment planning and delivery

Patients underwent MRI simulation with a full bladder on a ViewRay 0.35 T MRIdian MRI-guided LINAC with

True fast imaging with steady state precession (FISP) images for delineation of PBB volumes. Immediately after MRI simulation, patients underwent CT simulation with a full bladder, followed by an additional CT with an empty bladder with/without intravenous contrast. The full bladder CT image was then fused to the MRI simulation images to allow for dose calculation.

PBB contouring was done in Mirada RTx (Mirada Medical, Oxford, UK) with treatment planning within the MRIdian treatment planning system. The PBB gross tumor volume (GTV) and clinical target volume (CTV) encompassed all visible intra- and extravesicular gross tumor as well as areas considered at clinical risk based upon all available imaging and reports from cystoscopy, respectively. A variable 5- to 12-mm PTV expansion was employed at physician discretion depending on tumor localization and anatomy interfaces (Fig. 1). Daily MRI guidance for PBB fractions was performed with TrueFISP images with manual alignment to the bladder and delineated GTV/CTV without online adaptation. A tracking structure for the partial bladder target volume was drawn in a representative slice in the sagittal plane and expanded by 3 mm to create a tracking boundary structure. A 2-dimensional cine image was acquired during treatment delivery in which the beam was on when at least 95% of the tracking structure was within the boundary structure.

Volume delineation and treatment planning for CT-based pelvic and whole empty bladder fields were planned in a Pinnacle or RayStation treatment planning system. Both plans were exported to Mirada RTx, and images for the CT-based treatments were rigidly registered to the MR images with respect to the organs at risk (OARs). Registration was then applied to the dose volumes from both plans to create an estimated cumulative dose to targets and OARs. Standard dosimetric goals used for MRI-guided PBB plans, whole bladder plans, and the composite plan are detailed in Table E1. Priority was placed on coverage of PBB, where coverage of the pelvic and whole bladder targets could be compromised to meet OAR constraints. Constraints were individualized in some cases dependent on patient and target anatomy. Image guidance was performed with daily cone beam CT. The minipelvis field encompassed the entire bladder, visible perivesicular disease, and the obturator, internal iliac, and external iliac lymph node chains. The whole bladder boost was delivered to the empty bladder with an isotropic 5- to 12-mm PTV expansion depending on surrounding anatomy. Minipelvis and whole bladder fields were delivered with intensity modulated RT.

Study endpoints and statistical methods

The aim of the current report is to describe our current protocol and assess the feasibility of delivering a hybrid sequential PBB with nonadaptive MRgRT followed by CT-based RT to the bladder and pelvic lymph nodes. Endpoints included dosimetric parameters and features of treatment delivery, which included table shifts and treatment time. We also aimed to report changes in position of OARs in relation to the PBB PTV on daily MRgRT fractions in an effort to identify patients who would be most likely to benefit from daily online adaptation. As we did not treat with a daily online adaptive approach, daily acquired MRI was limited field of view, and therefore we were unable to reconstruct the actual dose delivered to target and organs on daily fractions in comparison to the predicted dose. We retrospectively identified fractions that could have been considered for adaptation based upon changes in organ position relative to the PBB PTV. Organs of interest included the rectum, sigmoid colon, and small bowel. We define a trigger for adaptation as an organ (rectum, sigmoid, or small bowel) moving into the PBB PTV when it was not previously within the PTV on initial planning or moving out of the PBB PTV when it was present within the PTV on initial planning. Fractions in which there was no change in this relationship (ie, organ was present within PTV on initial planning and on anatomy of the day) were considered to not be candidates

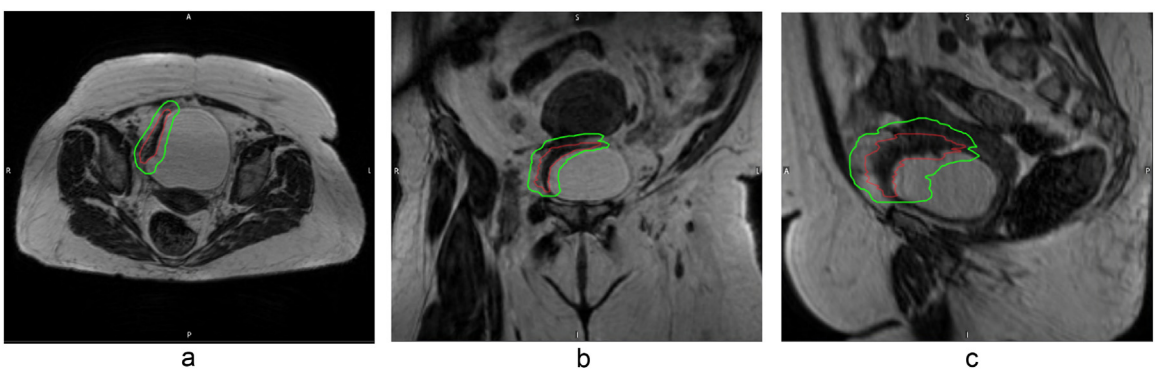

Figure 1 True fast imaging with steady state precession (FISP) magnetic resonance images of gross tumor volume (red) and planning target volume (green) in the axial (A), coronal (B), and sagittal (C) planes.

for online adaptation. We used χ^2 analyses to identify factors associated with the need for adaptation.

Toxicity was attributed prospectively in on-treatment visit documents according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Oncologic outcomes, including clinical response rates determined on post-RT cystoscopy, local control (defined as no persistent disease or in-bladder recurrence), progression-free survival (PFS; defined as any recurrence or death), overall survival (OS), and cystectomy rates were also recorded. Survival endpoints were calculated from the date of MIBC diagnosis and censored at the date of last follow-up. Survival analyses were performed with Kaplan-Meier methods. Comparison of means between groups was performed with analysis of variance tests. Statistical analyses were performed with SPSS version 28 (IBM, Armonk, NY).

Results

Patients

Seventeen patients were identified for analysis. The median follow-up time from diagnosis was 18.2 months (95% CI, 12.4-22.5). Patient characteristics are summarized in Table 1. The median age was 71 years (range, 57-81). At initiation of treatment, the median Karnofsky performance status was 90 (range, 60-90). Five patients had an in situ disease component, and 3 patients had clinical nodal involvement (cN1). Four patients received neoadjuvant chemotherapy consisting of gemcitabine plus cisplatin. All patients received concurrent chemotherapy with either gemcitabine (41%), cisplatin (53%), or 5-fluorouracil plus mitomycin C (6%).

Table 1 Patient characteristics (N = 17)

Characteristic	Value
	Median (range)
Age (y)	71 (57-81)
Karnofsky performance status	90 (60-90)
	No. (%)
Sex	
Male	10 (59%)
Female	7 (41%)
Neoadjuvant chemotherapy	
Yes	4 (24%)
No	13 (76%)
Concurrent chemotherapy	
Cisplatin	9 (53%)
Gemcitabine	7 (41%)
5FU + mitomycin C	1 (6%)

Abbreviation: 5FU = fluorouracil.

RT dosimetry

Prescription doses to the PBB, whole bladder, and minipelvis are summarized in Table 2. The majority of patients were prescribed 64.8 Gy to the PBB (range, 59.4-64.8 Gy), 54 Gy to the whole bladder (range, 50.4-54 Gy), and 41.4 Gy to the minipelvis (range, 0-41.4 Gy). One patient with an involved pelvic lymph node received a lymph node boost to 52.9 Gy (2.3 Gy/fraction), another patient with 2 involved lymph nodes received 57.5 Gy (2.5 Gy/fraction) to 1 lymph node and 56.35 Gy (2.45 Gy/fraction) to another lymph node, and the other patient with cN1 disease received 57.5 Gy (2.5 Gy/fraction) to an involved pelvic lymph node; pelvic lymph node boosts were delivered via simultaneous integrated boost over 23 fractions with the minipelvis fields. Sixteen cases (94%) used a PBB PTV expansion of ≤8 mm, including 8 cases (47%) with a margin of 5 mm. The median PBB PTV was 95.7 cc (range, 34.8-201). Five patients had rectum within the PBB PTV, 11 had sigmoid colon within the PBB PTV, and 7 had small bowel within the PBB PTV. Dosimetric parameters of target volume coverage and normal tissue dose are summarized in Table 3. The median prescription dose coverage of the PBB PTV was 95% (range, 94.7-97.2). On MRgRT PBB plans, the median maximum dose (D_{max}) to the rectum, sigmoid, and small bowel were 7.8 Gy (range, 1.9-11.6 Gy), 10.8 Gy (0.82-11.8 Gy), and 6.19 Gy (0.45-11.6 Gy), respectively. The median composite plan D_{max} to the rectum, sigmoid, and small bowel was

Table 2 RT prescription doses

Target-related prescription dose	No. (%)
Partial bladder tumor total prescription dose	
64.8 Gy	14 (82%)
61.2 Gy	2 (12%)
59.4 Gy	1 (6%)
Whole bladder total prescription dose	
54 Gy	12 (75%)
52.2 Gy	2 (12%)
50.4 Gy	2 (12%)
41.4 Gy	1 (6%)
Pelvis prescription dose	
41.1 Gy	16 (94%)
0 Gy	1 (6%)

Abbreviation: RT = radiation therapy.

Table 3 Dosimetric parameters

Target/OAR	MRgRT PBB plan median (range)	Composite plan median (range)
Partial bladder Rx (Gy)	-	64.8 (59.4-64.8)
Whole bladder Rx (Gy)	-	54 (50.4-54)
Pelvis Rx (Gy)	-	41.4 (0-41.4)
Rectal D_{max} (Gy)	7.8 (1.9-11.6)	51.7 (30.6-66.8)
Sigmoid D_{max} (Gy)	10.8 (0.8-11.8)	58.8 (52.7-67.3)
Small bowel D_{max} (Gy)	6.2 (11.6)	56.8 (23.8-64.8)
PTV D100% coverage (%)	95 (94.7-97.2)	-

Abbreviations: D_{max} = maximum dose; MRgRT = magnetic resonance imaging–guided radiation therapy; PBB = partial bladder boost; PTV = planning target volume; Rx = prescription; OAR = organ at risk.

51.7 Gy (range, 30.6-66.8 Gy), 58.8 Gy (52.7-67.3 Gy), and 56.8 Gy (23.8-64.8 Gy), respectively.

RT delivery

A total of 100 MRgRT PBB fractions were delivered. For MRgRT PBB, the median table shifts from initial patient setup imaging to treatment position were 0.4 cm (range, 0-3.15), 0.45 cm (0-2.65), and 0.75 cm (0-4.8) in the X, Y, and Z planes, respectively. Median total treatment delivery time (time from beam on until beam off) for PBB fractions was 9 minutes (range, 6.9-17.4).

Evaluating the change in organ position relative to the PBB PTV on MRgRT fractions, 2 fractions had the rectum move into the PTV, 10 had it move out of the PTV, and 89 fractions resulted in no change. For the sigmoid colon, 2 fractions had the sigmoid move into the PTV, 7 had it move out, and 91 resulted in no change. For the small bowel, 5 fractions had the small bowel move into the PTV, 12 had it move out of the PTV, and 83 resulted in no change. In total, 10 of 17 patients had a change in organ position relative to the PBB PTV on at least 1 MRgRT fraction (eg, organ moved into or out of the PTV) that could trigger adaptation; all 10 of these patients had more than 1 fraction with changes that could have triggered adaptation (median, 2; range, 0-6). Thirty-two of the total 100 MRgRT fractions could be considered for adaptation, including 8 (25%) for changes in the rectum, 4 (12.5%) for changes in the sigmoid, 13 (41%) for changes in the small bowel, and 7 (22%) for changes in the position of multiple organs relative to the PTV.

There was no association between boost delivery at posterior wall ($P = .26$), bladder dome ($P = .91$), or multiple sites ($P = .91$) and likelihood of requiring adaptation of at least 1 MRgRT fraction. Similarly, there was no association between the presence of the rectum ($P = .95$) or sigmoid colon ($P = .13$) within the PBB PTV on initial treatment planning and likelihood of requiring adaptation of at least 1 MRgRT fraction. However, patients with the small bowel present within the PBB PTV on initial planning imaging were significantly more likely to require any adapted fractions (6 out of 7) compared with patients who did not have the small bowel present in the PTV at baseline (4 out of 10; $P = .06$). Patients who required adaptation of the first MRgRT fraction were significantly more likely to require adaptation of at least 1 additional fraction (6 out of 6) than patients who did not require adaptation of the first MRgRT fraction (4 out of 11).

RT tolerability and toxicity

Two patients discontinued RT prematurely (PBB dose delivered for each patient was 52.2 and 59.4 Gy, respectively). One patient with a history of colectomy for diverticulitis was planned to receive a composite 64.8 Gy PBB, 54 Gy to the whole bladder, and 41.4 Gy to the minipelvis, but only completed 4 of 6 of the PBB fractions before requiring a treatment break for *Clostridioides difficile* infectious colitis, after which the last 2 fractions of the PBB were not completed. The patient was able to resume the course of RT 13 days later with the minipelvis field to 41.4 Gy, followed by whole bladder boost to 52.2 Gy to achieve a composite PBB dose of 59.4 Gy in 33 fractions. Another patient was planned for a composite PBB to 64.8 Gy, whole bladder to 54 Gy, and minipelvis to 41.4 Gy; however, the patient requested discontinuation after delivery of the PBB and minipelvic field because of fatigue and diarrhea. In effect, this patient received a composite 52.2 Gy PBB and 41.4 Gy to the whole bladder and minipelvis.

The highest-grade acute toxicity was grade 1 (n = 3, 17.6%), grade 2 (n = 12, 70.6%), and grade 3 (n = 2, 11.8%). The highest-grade acute genitourinary (GU) toxicity was grade 1 (n = 4, 23.5%), grade 2 (n = 8, 47.1%), and grade 3 (n = 1, 5.9%), most commonly acute dysuria or urinary frequency. The highest-grade acute gastrointestinal (GI) toxicity was grade 1 (n = 9, 52.9%), grade 2 (n = 5, 29.4%), and grade 3 (n = 1, 5.9%) respectively, most commonly diarrhea. The patient with acute grade 3 GI toxicity had grade 3 diarrhea; this patient had a history

of pelvic radiation for endometrial cancer approximately 25 years before her bladder cancer was diagnosed, and for this reason she received 50.4 Gy to the whole bladder with a boost of 10.8 Gy to the tumor for a total dose of 61.2 Gy over 34 fractions without treatment of the pelvic lymph nodes. Her estimated small bowel D_{max} was 64.6 Gy. Three patients (17.6%) developed late grade 2 cystitis, with median time to onset 11 months after completion of RT (range, 3-13 months). One patient had late grade 2 urinary frequency at 3 months post-RT. One patient had late grade 1 urethral stricture, and 1 patient had late grade 1 urinary frequency. No late GI toxicity was observed, and no patient developed late grade 3 toxicity. There was no association between PBB PTV size and highest-grade acute GU ($P = .66$) or GI ($P = .74$) toxicity on analysis of variance.

Oncologic outcomes

Sixteen patients (94%) had complete clinical response on cystoscopy after chemoRT. One patient had residual non-muscle invasive bladder cancer (NMIBC) on post-RT cystoscopy; this patient completed the whole course of TMT with radiation to 64.8 Gy using a PBB PTV margin of 5 mm. The case with persistent NMIBC was managed with 6 cycles of intravesical therapy followed by CR without need for cystectomy. The actuarial 2-year local control was 92.2%, the 2-year PFS was 75.5%, and the 2-year OS was 83.3%. Notably, the PFS events included the patient with persistent NMIBC on post-RT cystoscopy 3 months after completion of TMT and 2 deaths unrelated to bladder cancer: 1 patient developed multiple myeloma shortly after chemoRT and later had complications of *C. difficile* colitis and pneumonia with hypoxic respiratory failure, and a second patient developed transfusion-dependent myelofibrosis after TMT with subsequent declining performance status complicated by a fall and development of a lethal subdural hematoma. No patient required cystectomy for disease salvage or palliation of symptoms.

Discussion

We present the first report of a nonadaptive MRI-guided PBB followed by CT-based RT to the minipelvis and whole empty bladder in TMT for MIBC. The regimen was well-tolerated by patients with acceptable toxicity, as less than 12% of patients experienced any grade 3 acute toxicities, and no late grade 3 toxicities were seen. Importantly, MRI-guided PBB fractions were delivered efficiently (median total treatment delivery time of 9 minutes) without compromise of target coverage. Ninety-four percent of patients achieved CR, and despite the study being limited by the cohort size and follow-up, it resulted in favorable oncologic outcomes, with 92% local control at 2 years and no patient requiring salvage cystectomy. These results demonstrate the feasibility of this treatment approach using nonadaptive MRI-guided PBB.

There has been considerable interest in using online adaptive workflows for bladder RT.[23] The bladder is a mobile target with known inter- and intrafractional variation in position and filling that is not easily predictable[18]; in turn, this has resulted in utilization of large target volume expansions with resultant increases in normal tissue irradiation. Prior work has evaluated the efficacy of online adaptive RT based on daily cone beam CT imaging with reduction in high-dose irradiated volume translating into improved normal tissue dosimetry.[23] However, the limitations in soft tissue visualization and inefficiencies in available CT-based adaptive workflow have limited widespread implementation of such techniques. Therefore, it is in this context that MRgRT, with available online adaptive platforms such as the Elekta Unity and ViewRay MRIdian, has been proposed in the management of MIBC.

There are limited published data on the utility of MRgRT for MIBC, and the data available focus on utilization of a daily online adaptive approach. Vestergaard et al[19] initially demonstrated potential dosimetric advantages using online adaptive MRgRT. Hunt et al[21] at the Institute of Cancer Research in London reported their initial clinical experience of 5 patients with MIBC treated with definitive hypofractionated RT using online "adapt-to-shape" MRgRT on a 1.5 T MR-LINAC. Their CTV encompassed the whole bladder plus extravesicular tumor extent with a uniform margin and anisotropic PTV margins (1.5 cm anteriorly and superiorly, 1 cm posteriorly, and 0.5 cm laterally and inferiorly) with a prescription of 36 Gy in 6 fractions to the PTV. Later, authors from the London Institute of Cancer Research developed and reported results of the PERMIT study, which prospectively evaluated the feasibility of online adaptive MRgRT in 5 patients using a hypofractionated simultaneous integrated boost technique treating the partial bladder to 55 Gy and the whole bladder to 46 Gy in 20 fractions on the Elekta Unity platform using PTV margins of 0.5 cm laterally and inferiorly, 1 cm posteriorly, and 1.5 cm anteriorly and superiorly.[22] Both of these studies confirm the feasibility of the adaptive MRgRT approach and report favorable target coverage and normal tissue dosimetry, though neither provided detailed information on toxicity outcomes. Importantly, although the authors appear to have improved the efficiency of the online adaptive reoptimization workflow from their initial cohort, the median total treatment time remained over 30 minutes per fraction.[21,22] A disadvantage of the online adaptive approach is the increased resource utilization of physician, physicist, and therapist time as well as prolonged time on the treatment couch for patients. Although Hunt et al[21] reported favorable patient tolerability surveys, the large number of fractions required for definitive RT of

MIBC render this prolonged treatment time cumbersome. Comparatively, we describe a nonadaptive MRgRT approach with a median treatment time of only 9 minutes, requiring significantly less resource utilization and sufficient target coverage.

We evaluated anatomy on daily images from each MRI-guided PBB fraction to ascertain changes in OAR position relative to the PTV as potential opportunities for online adaptation. These daily images were acquired with limited field of view, preventing offline analysis of the delivered dose in comparison to the predicted dose. However, we defined fractions that could be considered for adaptation if the rectum, sigmoid, or small bowel moved into the PTV when they were initially not within the PTV on treatment planning images or vice versa. Based on this approach, 32% of the MRgRT PBB fractions in our study could be considered for adaptation, predominantly because of changes in small bowel position. Although boost location (eg, posterior wall, dome) was not associated with the likelihood of adaption, we identified that patients who had the small bowel present within the PBB PTV at treatment planning were more likely to have at least 1 fraction adapted (6 out of 7) compared with those without the small bowel within the PTV (4 out of 10; $P = .06$). Similarly, all 6 patients who had an opportunity for adaptation on their first fraction would have adaptation on at least 1 subsequent fraction, versus only 4 out of 11 patients who did not require adaptation at the first fraction ($P = .01$). Although we are unable to characterize the potential dosimetric advantages from daily online adaptation based on this evaluation, these results suggest that a blanket policy of adaptation may not be necessary using an MRI-guided PBB in this context. Both of the series from London Cancer Research Institute used adapt-to-shape for all fractions on the Elekta Unity platform, where adapt-to-position was used only for changes in target position on a final verification scan before treatment delivery.[21,22] Neither Hunt et al[21] nor Mitchell et al[22] reported an offline analysis comparing predicted dose delivered (ie, base plan delivered on session anatomy) to actual dose delivered.

National guidelines support use of a PBB technique, although RHDVRT was not associated with reduced toxicity or improved quality of life compared with standard whole bladder RT in the BC2001 trial.[5] Coupled with the recent meta-analysis of BC2001 and BCON (using whole bladder RT only), which demonstrated improved local control using a hypofractionated schedule of 55 Gy in 20 fractions to the whole bladder,[5] the utility of RHDVRT may be limited. However, these trials used traditional CT-based target delineation techniques requiring large target volume expansions of 1.5 to 2 cm.[3,9] Improved MRI-based target-volume delineation may reduce geographic miss while simultaneously reducing the irradiated volume of normal tissue compared with CT-based planning.[20] In our study, MRI-based planning facilitated reduction of PTV expansions to ≤8 mm in 94% of cases, which is substantially smaller than those traditionally used for CT-based delivery. These smaller PTVs can be justified by potential improvements in alignment related to superior soft tissue visualization offered by MRI and real-time tracking techniques using a tracking boundary structure in which the beam is delivered only when 95% of the target tracking structure is within the boundary structure. Although we are not able to report daily variation in bladder volume or intrafractional bladder filling to support the PTV margins used, Hunt et al[21] reported minimal intrafractional changes in CTV in their series of 5 patients including 29 total fractions of MRgRT. Similarly, although we are unable to report differences in CT- versus MRI-based delineation of target volumes, Chan et al[20] reported that the mean volume of GTVs delineated on MRI were more than 50% smaller than targets delineated on CT. Though limited by retrospective analysis, we report a 2-year locoregional control rate of 92% with an MRgRT PBB, which compares favorably to the 3-year local control of 77.5% and 63.5% in the BC2001 and BCON prospective studies, respectively.[24] Notably, neither Hunt et al[21] nor Mitchell et al[22] reported local control rates with their MRgRT experiences.

Our toxicity outcomes compare favorably with published prospective data evaluating chemoRT for MIBC. With median follow-up, we report 17.2% late grade 2 cystitis, with no late grade GI toxicity or any late grade 3+ adverse events. The authors of BC2001 reported 3.3% and 4.6% late grade 3 to 4 adverse events in patients receiving chemoradiation at 1 and 2 years, respectively, without further detail regarding breakdown of GI versus GU toxicity.[3] Hafeez et al[10] reported no late grade 3 GI and 2 late grade 3 GU events in 18 patients receiving RHDVRT to 70 Gy to the partial bladder and 52 Gy to the whole bladder in 32 fractions. With toxicity assessment limited by the retrospective nature of this study, it is possible that with longer follow-up more late events could be observed in our cohort.

Given that the utility of MRgRT fundamentally alters the treatment planning and delivery of definitive RT for MIBC, the efficacy of RHDVRT techniques in comparison to whole-bladder-only coverage remains to be elucidated. The RAIDER study is an international, phase 2 protocol that randomizes patients to either standard whole bladder single plan RT, standard dose adaptive tumor-focused RT, or dose-escalated adaptive tumor-focused RT in a 1:1:2 fashion, with the primary endpoint being the proportion of patients in the dose-escalated adaptive treatment arm meeting normal tissue dose constraints and a comparison of toxicity between treatment arms. Secondary endpoints of this trial include locoregional control, PFS, and OS.[25] The results of this trial should provide insight into the benefit of selective tumor-focused dose escalation and inform further clinical trial design.

The limitations of our study include the retrospective nature and small sample size. Retrospective evaluation of

toxicity is subject to potential biases related to availability of clinical documentation. Similarly, the short follow-up and small sample size do not allow for comparison of oncologic outcomes to larger published series. Although we are able to report changes in OAR position with respect to their presence inside or outside of the PBB PTV, we are unable to perform an offline analysis of estimated versus delivered dose, limiting our ability to assess the potential dosimetric advantage of daily online adaptation in this context. Similarly, platform limitations prevent retrospective assessment of both inter- and intrafraction changes in bladder filling and position. All PBB volumes were delineated based on MRI, and therefore we are unable to report differences comparing MRI-based against CT-based target delineation. Lastly, we are unable to evaluate whether there may be dosimetric advantages in delivery of PBB with bladder empty compared with bladder full as all patients were treated with full bladder in our study.

Conclusion

To our knowledge, we report results of the first study describing the feasibility of a PBB technique using a non-adaptive, MRI-guided LINAC platform. We report favorable local control with low rates of severe acute and late toxicity, although conclusions are limited because of small sample size and short follow-up. Such an approach results in shorter treatment times, which may result in decreased resource utilization compared with online adaptive reoptimization MRgRT techniques, while still retaining advantages associated with MRI-based delineation. In light of recent prospective data supporting hypofractionated over conventionally fractionated regimens delivered on CT-based platforms, the efficacy of reduced high-dose volume irradiation techniques using advanced image guidance (eg, MRgRT) needs to be prospectively compared against whole bladder irradiation strategies.

Declaration of Competing Interest

Kujtim Latifi reports consulting fees with ViewRay Inc. Stephen A. Rosenberg reports research funding from ViewRay Inc and serves on the ViewRay Lung Research Consortium. G. Daniel Grass reports consulting fees for MyCareGorithm.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101268.

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