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Scientific Article

A Prospective Study of a Resorbable Intravesical Fiducial Marker for Bladder Cancer Radiation Therapy

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Abstract

Purpose: We conducted a prospective pilot study to evaluate safety and feasibility of TraceIT, a resorbable radiopaque hydrogel, to improve image guidance for bladder cancer radiation therapy (RT).

Methods and Materials: Patients with muscle invasive bladder cancer receiving definitive RT were eligible. TraceIT was injected intravesically around the tumor bed during maximal transurethral resection of bladder tumor. The primary endpoint was the difference between radiation treatment planning margin on daily cone beam computed tomography based on alignment to TraceIT versus standard-of-care pelvic bone anatomy. The Van Herk margin formula was used to determine the optimal planning target volume margin. TraceIT visibility, recurrence rates, and survival were estimated by Kaplan-Meier method. Toxicity was measured by Common Terminology Criteria for Adverse Events version 4.03.

Results: The trial was fully accrued and 15 patients were analyzed. TraceIT was injected in 4 sites/patient (range, 4-6). Overall, 94% (95% confidence interval [CI], 90%-98%) of injection sites were radiographically visible at RT initiation versus 71% (95% CI, 62%-81%) at RT completion. The median duration of radiographic visibility for injection sites was 106 days (95% CI, 104-113). Most patients were treated with a standard split-course approach with initial pelvic radiation fields, then midcourse repeat transurethral resection of bladder tumor followed by bladder tumor bed boost fields, and 14/15 received concurrent chemotherapy. Alignment to fiducials could

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allow for reduced planning target volume margins (0.67 vs 1.56 cm) for the initial phase of RT, but not for the boost (1.01 vs 0.96 cm). This allowed for improved target coverage ($D_{95\%}$ 80%-83% to 91%-94%) for 2 patients retrospectively planned with both volumetric-modulated arc therapy and 3-dimensional conformal RT. At median follow-up of 22 months, no acute or late complications attributable to TraceIT placement occurred. No patients required salvage cystectomy.

Conclusions: TraceIT intravesical fiducial placement is safe and feasible and may facilitate tumor bed delineation and targeting in patients undergoing RT for localized muscle invasive bladder cancer. Improved image guided treatment may facilitate strategies to improve local control and minimize toxicity.

Introduction

A treatment option for well-selected patients with muscle-invasive bladder cancer (MIBC) is bladder preservation with chemoradiation following maximal transurethral resection of the bladder tumor (TURBT).[1-4] The ideal patient for bladder preservation has unifocal, T2N0 MIBC, can undergo maximal TURBT with routine surveillance follow-up, is a candidate for chemotherapy, has no evidence of carcinoma in situ or hydronephrosis, and has good baseline urinary function. Although many patients can achieve an excellent outcome with bladder preservation, chemoradiation carries the potential for significant toxicity, typically with grade 3 acute toxicities of 10% to 36%, mostly from gastrointestinal and genitourinary effects.[3,5] There is also a <10% risk of late grade 3+ toxicity[6,7] and a 40% locoregional recurrence risk at 5 years (approximately 15% invasive and 25% noninvasive).[8,9] Strategies are needed to decrease toxicity of treatment and improve local control.

Chemoradiation is given after maximal TURBT over 4 to 8 weeks either as a continuous course or a split-course approach with a planned midcourse treatment break for repeat TURBT to assess treatment response and allow for early salvage cystectomy as needed in nonresponders.[10,11] With either regimen, a standard radiation field often covers an initial "mini pelvis" or whole bladder field to about 45 to 50 Gy followed by a "boost" (shrinking field) to the bladder primary tumor bed to 60 to 66 Gy. The tumor bed location is typically outlined on computed tomography (CT) based on pre- and post-TURBT imaging studies and urology operative reports. However, the tumor bed is often difficult to visualize on radiation therapy (RT) planning CT imaging. After TURBT, small tumors may not demonstrate a defect on CT while the resection bed of larger tumors may demonstrate extensive diffuse bladder wall thickening and edema. As such, there is currently no widely accepted method to delineate the bladder tumor bed on CT scan. Precise alignment for daily radiation treatment is further complicated by daily variation in bladder volume and internal organ motion as well as the inability to clearly visualize the primary tumor bed even with modern image guided platforms using in-room cone beam CT (CBCT). Therefore, standard practice has used relatively large margins for planning target volume (PTV) to account for tumor volume and organ motion uncertainties that typically range between 1 and 2 cm or larger.[3,12] This contrasts with modern dose-escalated image guided techniques for treating prostate cancer, for example, that often use CBCT with or without intraprostatic fiducial markers and often use margins of 5 mm or less.[13] The large PTV margins for bladder cancer RT results in excess radiation dose to surrounding normal tissues including small bowel and rectum. Improved visualization of the bladder tumor location on CT could allow for the use of smaller treatment margins, which can decrease radiation doses delivered to normal tissues and facilitate safe dose escalation to the primary tumor site. This could, in turn, reduce toxicity related to treatment and may have potential to improve tumor local control.

The TraceIT Tissue Marker (Boston Scientific, Malborough, MA) is an injectable polyethylene glycol-based hydrogel marker visible on CT and CBCT for 3 months after implantation that is absorbed within 6 months. Prior work has shown it is possible to inject the hydrogel safely into patients with bladder cancer undergoing chemoradiation.[14] TraceIT has Food and Drug Administration approval for use as a marker, but its use in RT planning for bladder cancer and reliability for daily radiation treatment alignment have not been well studied.

We conducted a phase 2 prospective clinical trial to test the hypothesis that TraceIT could be used as a temporary bladder tumor fiducial marker placed at the time of TURBT to guide RT treatment planning and daily image guidance for MIBC as part of chemoradiation.

Methods and Materials

Patients

Eligible patients were ≥18 years old with histologically confirmed urothelial carcinoma of the bladder who were indicated for definitive RT. Patients were ineligible if they were unable to have TraceIT hydrogel placed <8 weeks before beginning radiation treatment.

Trial design

This institutional review board approved clinical trial is registered at ClinicalTrials.gov (NCT03125226) and was conducted at the University of Washington Medical Center/Seattle Cancer Care Alliance. TraceIT hydrogel was provided by the manufacturer (Boston Scientific, Malborough, MA). All other imaging, radiation delivery, and drugs administered in this study were performed per standard clinical care. All patients provided written informed consent before study procedures.

Treatment

All patients underwent multidisciplinary evaluation with urology, medical oncology, and radiation oncology to review treatment options and determine candidacy for definitive RT with or without concurrent chemotherapy for MIBC. All patients underwent cystoscopy and repeat TURBT as indicated to achieve maximal tumor resection. TraceIT was injected around the circumference of the tumor bed using a 25G Williams needle (Cook Medical LLC, Bloomington, IN) through the working port of the cystoscope. A minimum of 4 sites were injected circumferentially around the tumor to demarcate the borders of the tumor, injecting 0.3 to 0.9 mL per site per manufacture recommendations. Repeat TraceIT application was optional but was recommended during midcourse TURBT in patients undergoing split-course therapy to ensure that markers would be visible through the entirety of the treatment course.

A minimum of 4 weeks of daily RT was required to allow for longitudinal tracking of fiducial marker location. Radiation treatment prescription was at the discretion of the treating radiation oncologist (Table 1) according to standard of care.[15] All radiation plans underwent peer review as part of standard departmental quality assurance. Daily CBCT localization for image guidance was required during the radiation treatment course. The bladder was emptied before treatment of pelvic lymph nodes or the whole bladder, while partial bladder boosts were performed on a full bladder. In the context of this pilot trial, daily alignment was per standard practice based on pelvic bone match while ensuring the bladder was inside the PTV. Treatment planning margins were per standard practice.

Table 1 Chemoradiation details for all patients

ID	Age (years)	Sex	Stage	Chemotherapy	RT prescription (Gy/fx + boost)	RT technique	Pelvic nodes treated
1	75	Female	II: T2bN0M0	Cisplatin weekly ×7	45/25 + 21.6/12	3D-CRT	Yes
2	68	Male	II: T2aN0M0	Cisplatin weekly ×8	45/25 + 21.6/12	IMRT	Yes
3	78	Male	II: T2aN0M0	Cisplatin weekly ×7	45/25 + 18/10	IMRT	Yes
4	86	Male	II: T2bN0M0	Gemcitabine weekly ×7	45/25 + 21.6/12	IMRT	Yes
5	71	Male	II: T2bN0M0	Cisplatin weekly ×7	40/20 + 24/12	3D-CRT	Yes
6	54	Male	IVa: T2aN0M1a	Gem/Cis q3weeks ×4 -> Gem weekly ×3*	35.75/13 + 24/12†	IMRT	No
7	88	Male	II: T2bN0M0	Gemcitabine weekly ×6	40/20 + 20/10	IMRT	No
8	67	Male	II: T2bN0M0	Cisplatin weekly ×7	45/25 + 21.6/12	IMRT	Yes
9	65	Male	II: T2bN0M0	None (Poor PS)	55/20	3D-CRT	No
10	81	Male	II: T2bN0M0	Gemcitabine weekly ×1	55/20	IMRT	No
11	55	Male	II: T2bN0M0	Cisplatin weekly ×6	45/25 + 19.8/11	IMRT	No
12	73	Female	II: T2bN0M0	Cisplatin weekly ×7	45/25 + 16.2/9	3D-CRT	No
13	86	Male	II: T2aN0M0	Gemcitabine weekly ×6	45/25 + 19.8/11	3D-CRT	No
14	74	Female	II: T2aN0M0	Cisplatin weekly ×1 -> Gemcitabine weekly ×5	45/25 + 21.6/12	3D-CRT	Yes
15	85	Male	II: T2bN0M0	Gemcitabine weekly ×4	55/20	IMRT	No

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy; N/A = not applicable; PS = performance status; PTV = planned target volume; RT = radiation therapy; TURBT = transurethral resection of the bladder tumor.

* Patient presented with abdominal lymphadenopathy with complete radiographic response to 4 cycles of neoadjuvant gem/cis and so proceeded to consolidative bladder RT with concurrent gemcitabine.

† Patient did not complete boost portion of radiation due to radiation proctitis.

Assessments

Patients underwent baseline examination and staging per standard of care. Patients were evaluated weekly during radiation by the treating radiation oncologist. Follow-up and subsequent imaging included cystoscopy, urine cytology, and CT imaging every 3 to 6 months in the first 2 years posttreatment, and every 6 to 12 months thereafter.[16]

Endpoints

The primary endpoint was the difference between radiation treatment planning margin on daily CBCT based on alignment to TraceIT versus standard-of-care pelvic bone anatomy. Secondary endpoints included adverse events related to TraceIT, visibility of TraceIT during the RT course, 2-year progression-free survival, and overall survival. Survival was calculated from the first date of treatment. A radiation oncologist qualitatively assessed visibility of fiducial markers on CT simulation planning scan and daily localization CBCTs. Toxicity was graded based according to the Common Terminology Criteria for Adverse Events 4.03. Dosimetric analysis was performed on 2 randomly selected patients to illustrate dosimetric differences between alignment to TraceIT and pelvic bones. Treatment was planned as per the current Southwest Oncology Group (SWOG) 1806 bladder chemoradiation trial with intensity modulated RT delivered to the bladder to 64 Gy in 32 fractions, as well as an alternative commonly used 3-dimensional conformal RT (3D-CRT) hypofractionated approach of 55 Gy in 20 fractions.[3]

Image-guided radiation therapy (IGRT) analysis

Each visible hydrogel marker was delineated as an independent structure using the initial CT simulation scan as the reference and was subsequently tracked on each daily CBCT until either the end of treatment or when it was no longer visible. Analysis was performed first with alignment to the pelvic bone match, then realignment was performed to match to the hydrogel markers using a manual technique involving translations only to mirror our clinical alignment practice with the goal of minimizing the vector displacement of all the visible fiducials seen on the daily CBCT compared with the reference CT. Given that the bladder deforms daily, priority was placed on minimizing displacement from the reference scan for all visible fiducials rather than tracking a single fiducial in an effort to best align the tumor bed. For patients who had a midtreatment TURBT, the repeat CT simulation scan for the boost served as the new reference scan for the CBCTs associated with the boost portion of the treatment regimen. Coordinates in x/y/z planes were assigned to each hydrogel marker on the planning CT and daily CBCT to calculate interfraction motion. Shifts in marker contour centroid position relative to the reference planning CT were recorded for each patient and each fraction as the median shift across all visible fiducials on daily CBCT. Systematic IGRT error in each patient was defined as the average marker contour centroid shift across fractions for each treatment phase (initial, boost). Random IGRT error in each patient was defined as the standard deviation in marker contour centroid shifts across fractions for each treatment phase (initial, boost). Systematic errors estimated the accuracy in patient setup based on pelvic bony alignment or hydrogel marker alignment, while random errors estimated the precision in patient setup. The cohort systematic IGRT error was computed as the standard deviation of the individual patient systematic errors. The cohort random IGRT error was computed as the root-mean-square of the individual patient random errors. The Van Herk (VH) margin formula for the PTV margin was calculated as a function of cohort systematic and random IGRT errors such that the clinical target volume received at least 95%-prescription dose in 90% of patients[17]:

$$VH = 2.5\sum + 0.7\sigma \quad (1)$$

Differences in individual patient systematic and random error distributions between bony alignment and fiducial alignment were evaluated via nonparametric pairwise Wilcoxon signed-rank testing. Time to loss of visibility on radiographic imaging and survival was estimated by the Kaplan-Meier method. All 2-sided P values were considered significant with $\alpha = 0.05$.

Results

Patients

Fifteen patients were eligible for analysis between April 2017 and January 2020. Patient and treatment characteristics are shown in Table 2 and individual patient radiation course in Table 1. Most (14/15) patients had stage II MIBC, with 1 patient with M1a disease also undergoing definitive radiation to the bladder. The patient with M1a disease had limited metastases on presentation that completely responded to gemcitabine/cisplatin and so proceeded to consolidative chemoradiation therapy. Eight (8/15) patients were potential cystectomy candidates and had a midradiation TURBT to assess treatment response, whereas 7 (7/15) patients were deemed surgically inoperable due to medical comorbidities and did not have a midradiation TURBT.

Table 2 Patients and tumor baseline characteristics

Characteristic	n = 15
Age, year	
Median	73
Range	53-88
Sex	
Female	3 (20%)
Male	12 (80%)
Race: white	15 (100%)
ECOG performance status	
0	8 (53%)
1	5 (33%)
2	1 (7%)
3	1 (7%)
Histology: Urothelial carcinoma	15 (100%)
Clinical stage of primary tumor	
T2	15 (100%)
Clinical nodal stage	
N0	15 (100%)
Visibly complete resection on TURBT	14 (93%)
TraceIT fiducial sites	
Median	4
Range	4-6
TraceIT volume injected per site, mL	
Median	0.5
Range	0.3-0.9
Radiation modality	
IMRT	9 (60%)
3D conformal	6 (40%)
Bladder tumor bed PTV expansion	
5 mm	1 (7%)
10 mm	3 (20%)
15 mm	10 (67%)
20 mm	1 (7%)
Hypofractionated radiation (>200 cGy/fx)	4 (27%)
Sequential radiation boost (Y)	11 (73%)
Median total dose ($EQD2_{10}$)	
Median (cGy)	6372
Range (cGy)	3798-6549
Concurrent chemotherapy	
Cisplatin (weekly)	7 (47%)
Gemcitabine (weekly)	6 (40%)
Other	1 (7%)
None	1 (7%)
Midtreatment TURBT (Y)	8 (53%)

(*continued on next page*)

Table 2 (*Continued*)

Abbreviations: 3D = 3-dimensional; ECOG = Eastern Cooperative Oncology Group; EQD2 = equivalent dose in 2 Gy fractions; IMRT = intensity modulated radiation therapy; PTV = planned target volume; TURBT = transurethral resection of the bladder tumor.

TraceIT injection and chemoradiation

No complications beyond the expected mild and transient post-TURBT voiding symptoms were reported from TURBT with TraceIT injection. In 13/15 patients, 4 sites were injected at the periphery of the TURBT site to delineate the 4 quadrants of the tumor bed. In 2/15, 6 sites were injected due to the size and complex shape of the tumor bed site. Figure 1 shows a patient illustrating the typical cystoscopic appearance after placement of TraceIT and the corresponding radiographic appearance of TraceIT on CT simulation scan and daily localization CBCT, which demonstrated excellent visualization. Presence of TraceIT on CT simulation scan was useful in delineating the TURBT primary tumor site for RT planning. For instance, the primary tumor site in the patient shown in Figure 1 would not have been clearly visible on CT after TURBT without TraceIT.

Radiation was initiated a median of 20 days (interquartile range, 17-27) after placement of TraceIT. Four of 15 patients were treated with a hypofractionated regimen of 55 Gy in 20 fractions to the whole bladder without a midtreatment break, while 11/15 patients were treated with an initial pelvic field followed by a bladder tumor bed boost. For the 11 patients treated with a sequential boost, 8/11 had midtreatment TURBT and 4/8 underwent additional TraceIT injection at that time. The trial protocol initially did not call for additional TraceIT injections during the midtreatment TURBT, but after the initial 4 patients, it was noted that TraceIT visibility declined after the midtreatment TURBT with tumor bed biopsies, and the latter 4 patients undergoing midtreatment TURBT had additional TraceIT injections at the time of the procedure.

The median duration of RT was 69 days (interquartile range, 33-70). PTV expansions from the bladder tumor bed were typically 15 mm or greater. Median cumulative dose to the bladder primary site was 63.7 Gy in equivalent dose in 2 Gy fractions (Table 2). Pelvic lymph nodes were targeted in radiation field in 8/15 patients to a median dose of 45 Gy. One patient did not complete radiation after developing abdominal pain and radiation proctitis after 13 fractions to 35.75 Gy. All but 1 patient received concurrent chemotherapy (14/15). This patient did not

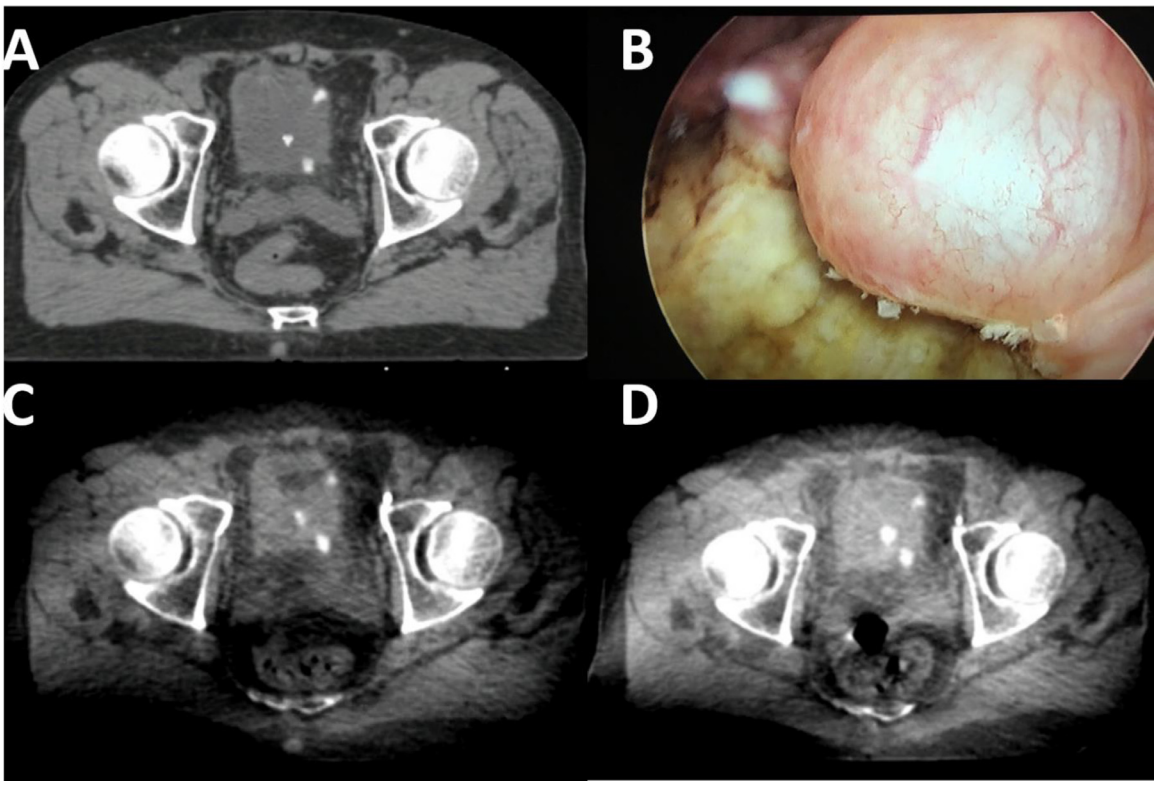

Fig. 1 **(A)** Radiation therapy planning CT scan with TURBT resection bed outlined by TraceIT fiducial sites in left lateral bladder. **(B)** Typical appearance of TraceIT on cystoscopy view using a standard cystoscope using a 25G Williams needle (Cook Medical) through the working port of the cystoscope outlining the resected tumor bed. **(C)** TraceIT visibility on day 1 of treatment CBCT and **(D)** end of treatment CBCT (88 days after TURBT). *Abbreviations:* CBCT = cone beam computed tomography; CT = computed tomography; TURBT = transurethral resection of the bladder tumor.

receive chemotherapy due to poor performance status (detailed in Table 1).

Primary outcome-setup margins

Alignment to TraceIT fiducials versus bone anatomy allowed for reduced VH margins (0.67 vs 1.56 cm) for the initial radiation portion. This was associated with a decrease in the systematic error distribution (median 0.62 vs 0.21 cm, $P = .003$), but not random error distribution (median 0.54 vs 0.48 cm, $P = .29$). For the boost phase, the VH margin was similar between fiducial and bone alignment (1.01 vs 0.96 cm) with no significant differences in systematic or random error. Figure 2 shows the degree and direction of systemic error when initial fields were aligned to the bony pelvis versus TraceIT fiducials alone. Of note, bladder volume changed by an average of 49.6 mL (95% confidence interval [CI], 23.8-75.5) from the sim volume for each fraction of the initial course and varied by an average of 22.0 mL (95% CI, 13.9-30.2) for the boost course. This highlights the challenges of aligning to a reproducible setup to allow conformal RT in the absence of fiducial markers.

Visibility of TraceIT during radiation

All injection sites were visible on simulation CT for radiation planning, and all patients had at least 1 visible TraceIT site on CBCT at the conclusion of the initial RT course (4-5 weeks into treatment). A total of 12/15 patients had all injection sites visible and 3/15 patients had some injection sites disappear. For the first 4 patients who underwent a midradiation TURBT with tumor bed biopsies, 2/4 patients did not have fiducial sites visible at the end of the boost portion of radiation. After that discovery, the last 4 patients undergoing a midradiation TURBT had additional TraceIT injected at midtreatment TURBT, and 4/4 had fiducial sites visible at the end of radiation.

On a per-injection site analysis, there were a total of 76 sites injected across 15 patients for initial and repeat TURBT. By time-to-event analysis, 94.1% (95% CI, 89.8%-98.4%) of sites were visible at 20 days (median start of RT from TURBT), 71.2% (62.0%-80.5%) were visible at 50 days (median time from TURBT to end of initial portion of RT), and 65.0% (51.6%-76.3%) were visible at 95 days (median time from TURBT to end of RT). The median length of time over which injection sites

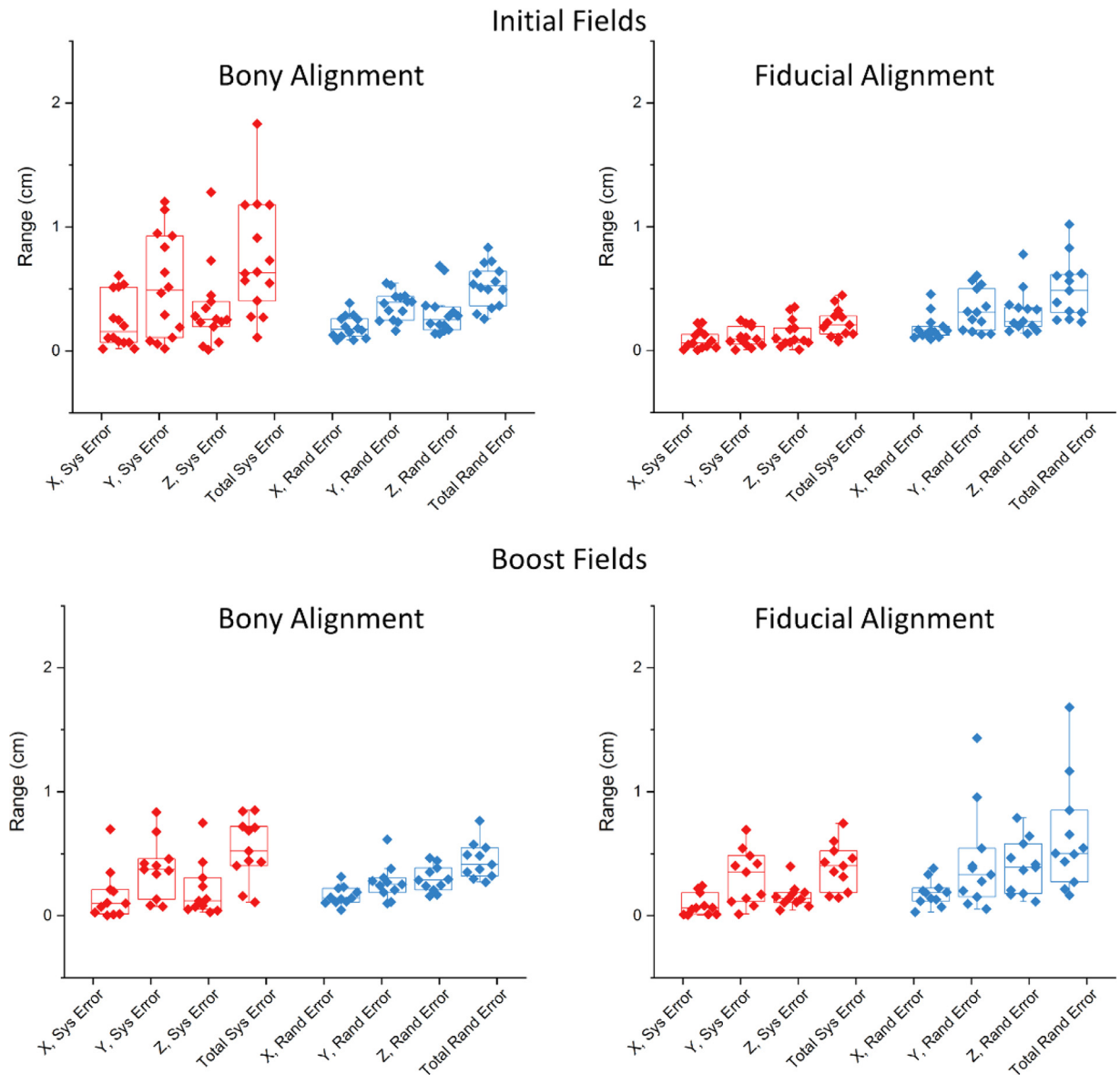

Fig. 2 Systematic and random error of alignment to initial fields and boost fields for bony and fiducial alignment. Reductions in systematic error were seen in all x/y/z coordinate directions.

maintained visibility was 106 days (95% CI, 104-113). Some injection sites remained visible on follow-up surveillance imaging. Notably, these sites appeared similar to tumor-related enhancement with the potential for misclassification if those evaluating the CT scan were not informed of the prior hydrogel injection procedure.

Adverse events

There were no grade 4/5 toxicities; 3 patients had acute grade 3 events (radiation proctitis with discontinuation of RT, hematuria requiring hospitalization in patient on anticoagulation, and dizziness requiring emergency room visit). However, no acute toxicities were attributed to TraceIT placement. Three patients experienced late grade 3 toxicity: 2 related to hematuria and 1 from ureteral stenosis. All other patients had acute grade $\leq$2 genitourinary toxicity, the majority grade 1 (Table 3). All but 1 patient underwent at least 1 repeat cystoscopy after completion of radiation. To date there have been no visual abnormalities noted on repeat cystoscopy in the areas where TraceIT was previously injected.

Dosimetric analysis

To provide a detailed illustration of the dosimetric benefits of using smaller PTV margins, which is possible with fiducial alignment, dosimetric plans for 2 randomly

Table 3 Acute and late toxicities after TraceIT injection and chemoRT

Toxicity	Grade 1	Grade 2	Grade 3
Acute GU	8 (53%)	6 (40%)	1 (7%)
Acute GI	7 (47%)	4 (27%)	1 (7%)
Acute fatigue	12 (80%)	1 (7%)	0 (0%)
Late GU	3 (20%)	3 (20%)	3 (20%)
Late GI	3 (20%)	0 (0%)	0 (0%)
Late fatigue	2 (13%)	0 (0%)	0 (0%)

Abbreviations: GI = gastrointestinal; GU = genitourinary.

selected patients were generated per protocol guidelines. One patient was treated per the SWOG 1806 protocol[18] for 64 Gy in 32 fractions with volumetric-modulated arc therapy (plan 1, see Fig 3) and the other was treated with hypofractionation 55 Gy in 22 fractions with 3D-CRT per BC2001[3] (plan 2), both covering the bladder without boost. It is frequently challenging to provide an adequate radiation dose to the bladder and tumor while limiting dose to the adjacent bowel. The PTV margin is key in this balance as the PTV often encompasses adjacent normal tissues during the expansion from clinical target volume to PTV. To meet the bowel dose constraints per the S1806 protocol for 64 Gy in 32 fractions to the bladder, PTV coverage was 83% at 95% of the prescription dose without using TraceIT but improved to 94% with the smaller margins enabled using TraceIT. Similarly, with hypofractionation and 3D-CRT, an improvement from 80% to 91% at 95% prescription dose was possible using smaller margins enabled with TraceIT. Standard-of-care alignment to pelvic bone required a PTV of 1.5 cm, but alignment to fiducial markers resulted in a PTV margin of 0.7 cm. Both plans met all bowel constraints per respective protocols; however, the maximum dose to the rectum was lower with hydrogel alignment (4466 vs 4166 cGy in plan 1; 5645 vs 5375 cGy in plan 2), rectal volume at >4500 cGy was lower (0.2 vs 1.5 cm^3 in plan 1; 5.3 vs 14.7 cm^3), max bowel dose was similar (5464 vs 5424 cGy in plan 1; 5126 vs 4933 cGy in plan 2), and bowel at >4500 cGy was similar (6.8 vs 5.0 cm^3 in plan 1; 6.5 vs 10.1 cm^3 in plan 2).

Oncologic outcomes

At a median follow-up of 22 months (range, 7-42), 2-year overall survival was 79% and 2-year progression-free survival was 75%. No bladder recurrences were seen and no patients have undergone salvage cystectomy. Regional pelvic recurrence occurred in 1/15 patients and 3/15 developed distant metastases to the lungs.

Discussion

This prospective phase 2 clinical trial demonstrated that the absorbable, radiopaque hydrogel TraceIT is safe as an intravesical fiducial marker to demarcate the borders of bladder tumors after complete resection and can enable reduced planning margins for definitive RT. We

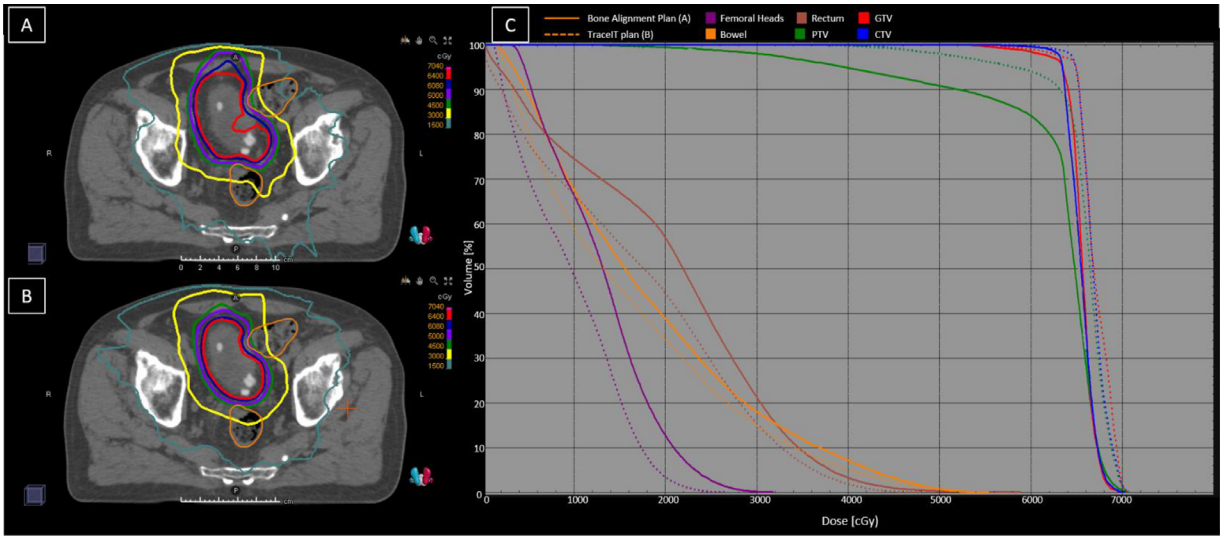

Fig. 3 Example of dosimetric benefit of reduced planning margins made possible with TraceIT fiducials. Panel **(A)** shows the radiation plan of a patient enrolled in this trial, retrospectively planned to 64 Gy/32 fx to the bladder (CTV in green) per SWOG 1802 clinical trial guidelines using a PTV of 1.5 cm per bone alignment versus **(B)** a radiation plan with a smaller PTV by aligning to fiducials. Panel **(C)** shows the dose advantage in a comparative dose-volume histogram with better target coverage and dose to normal tissues. *Abbreviations:* CTV = clinical target volume; GTV = gross tumor volume; PTV = planning target volume; SWOG = Southwest Oncology Group.

observed no adverse events related to TraceIT injection after 2 years of follow-up. TraceIT for daily alignment allows decreased planning margins (PTV) from 15 mm from bone alignment to 7 mm with TraceIT alignment with good visibility during RT course. This can facilitate precise IGRT for dose reduction to adjacent organs and dose escalation to the tumor.

TraceIT injection sites were visible in the bladder for a median of 106 days. However, visualization did decrease over the course of a 6 to 8 week radiation regimen and highlights the challenges in implantation and retention of a fiducial in the bladder. Increasing time intervals between pretreatment TURBT and end of radiation were associated with increased risk of loss of visibility of TraceIT by the last day of radiation. Additionally, the midtreatment TURBT was noted to induce an inflammatory response impairing fiducial visualization for the boost phase if injection was not reperformed at that time.

During the initial phase of treatment, the reduced VH margins were primarily driven by the reduction in systematic error upon alignment to the hydrogel markers, which suggests that this approach may optimally capture systematic changes during the RT treatment course such as bladder filling trends rather than positional setup changes that would have been reflected more in the random error calculations. It is important to highlight the fact that, during the initial phase of treatment, if treating pelvic nodal volumes in addition to the primary bladder tumor, one must account for both structures in image guidance. During the boost phase of treatment, potential reasons for an absence of a meaningful difference could be due to (1) a small number of fractions, decreased visualization of the fiducials when present (especially before reinjection at midtreatment TURBT), and a lower number of patients receiving a boost; and (2) full bladder instructions for treatment in the setting of radiation-induced cystitis resulting in more daily variations. However, given that the boost phase of treatment requires a shrinking radiation field to provide additional radiation dose directed to the tumor bed, adequate visualization for targeting is important.

TraceIT compares favorably to previously evaluated injected bladder fiducials for radiation planning. Lipiodol[19-21] is radiopaque, like TraceIT, with the potential loss of visibility with up to 24% volume loss during the course of radiation,[19,22] which was consistent with the loss of visibility rate of TraceIT. However, a limitation of Lipiodol is the potential for extravasation of the implant from the instillation site over the course of RT making, which reduces the utility for image guidance over time.[23] Gold seeds[24,25] can be difficult to implant due to the caliber of needle required and similarly have reduced visibility in up to 40% of implants.[26] A permanent metal marker could also be associated with long term irritation, granuloma formation, and other complications.[26]

A recent retrospective analysis of 32 patients with bladder cancer by Wortel et al[23] reported a similar approach of cystoscopic injection of TraceIT before definitive RT. They evaluated 32 patients treated typically with intensity modulated RT with a simultaneous integrated boost to 75 Gy to the bladder tumor over 20 fractions without treatment breaks. They found 76% of sites were adequately visible at start of RT with diminished visibility on CBCT by end of treatment, with 46.7% of fiducials visible and only 31% of patients with ≥3 spots visible through the whole course of RT. Our results show 71% visibility of all injection sites by 50 days and at least ≥3 sites visible in 67% of patients by end of treatment. The differing visibility estimates may be due to the small numbers in both studies or a difference in injection techniques (ie, volume of hydrogel injected per site, repeat injection during midtreatment TURBT). The current work advances the prior findings by demonstrating that decreased margins are possible by using TraceIT in a prospective cohort of patients and the utility of TraceIT with a midtreatment break and repeat TURBT, a more typical North American regimen (as opposed to 20 fractions over 4 weeks).

The choice of margin is equally important as choice of dose for limiting probability of bowel toxicity in bladder cancer.[27] However, bladder tumors demonstrate extreme variability in interfraction motion and poor visualization so a PTV margin of 1.5 to 2 cm is traditionally used.[19] Even in the setting of modern daily imaging with CBCT, current protocols recommend PTV margins up to 1.5 cm to account for daily variability in the bladder.[18,28] We confirmed a wide margin is appropriate in pelvic bone alignment, and PTV margins can be significantly reduced by aligning to TraceIT. As demonstrated, a reduced PTV margin can allow for reduction in bowel dose while maintaining prescription dose to the bladder tumor.[29-31] TraceIT also provides better radiographic definition of bladder tumor location by in vivo marking of bladder tumor borders for treatment planning compared with CT alone. In addition, this may improve interprovider standardization of target volume delineation of the bladder tumor bed among treating radiation oncologists. Use of a hydrogel marker would enable a clinical trial that uses smaller treatment margins to enable dose escalation to the tumor bed.

Increased interest in dose escalation to bladder tumors undergoing definitive chemoRT has led to attempts to decrease margins with daily adaptive RT or with on-board magnetic resonance imaging daily planning.[28,32] Fiducials, such as with TraceIT, may have particular interest for daily adaptive RT. The tumor-focused dose-escalated adaptive radiotherapy for the radical treatment of bladder cancer (RAIDER) trial, which is investigating dose escalation with adaptive tumor focused RT, includes fiducials as an option.[28] Our results add merit to that concept to allow safe dose escalation with daily adaptation and smaller planning margins. Additionally, as the TraceIT marker

has a limited half-life, dose escalation may be achieved by delivering the boost portion of a dose escalated regimen before whole bladder/pelvis, with alignment to the tumor bed facilitated by TraceIT. Of note, the diminished visualization of TraceIT over time is less of a concern for hypofractionated regimens, which may already be preferable from an oncologic standpoint compared with standard fractionation with a boost.[33,34]

Our study has several limitations that warrant mention. First, we report on a small number of patients with potential implications for generalizability. Additionally, patients were treated with heterogeneity with respect to RT approach, concurrent chemotherapy regimens, as well as subsequent therapies, which may potentially bias oncologic outcome findings. Treatment regimens differed for patients between single courses of hypofractionated RT versus inclusion of midtreatment TURBT and/or sequential boosts. We have accounted for the variability in visibility of TraceIT due to this with time-to-event analysis, and this provides experience with this approach in the context of several standardly used chemoradiation regimens. There is also the potential of selection and confounding biases in a single arm, not randomized, trial conducted in a single tertiary cancer center.

Conclusion

Our early experience supports the safety and feasibility of TraceIT as an intravesical fiducial marker. Visibility of TraceIT was excellent in the majority of patients through the RT treatment course. TraceIT can aid in target delineation of the bladder tumor bed for RT planning and allows for accurate daily image guidance. This can facilitate novel strategies including RT plans with reduced margins, which may reduce treatment toxicity and facilitate dose escalation to the primary tumor bed and improve local control.

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