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Intravesical Fiducial Marker Placement to Facilitate Image-Guided Radiation Therapy for Patients With Muscle-Invasive Bladder Cancer

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ABSTRACT

INTRODUCTION: Recent development of image-guided techniques facilitates the monitoring of organ motion during radiation therapy. The purposes of this study were to: (1) describe the technique of intravesical fiducial marker placement using Visicoil linear fiducial markers (Core Oncology; Santa Barbara, CA, USA) for treatment planning and delivery of radiation therapy for invasive bladder cancer, and (2) describe the feasibility of this program and initial results.

METHODS: Participants were 10 male patients with a mean age of 74 years (range, 58-87 years). They underwent placement of Visicoil fiducial markers into the bladder wall under endoscopic guidance for the purpose of facilitating treatment planning and delivery for external beam radiotherapy for bladder cancer. We assessed the feasibility of marker placement and stability of the marker using daily on-board imaging during a standard course of therapy. We assessed acute procedure-related complications and related toxicity using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

RESULTS: All 10 patients had successful implantation of Visicoil fiducial markers without procedure-related acute complications. No patient developed acute toxicity related to the procedure or markers. All markers remained stable during radiation therapy using daily on-board imaging.

CONCLUSION: The use of Visicoil fiducial markers for the guidance of radiation therapy for bladder cancer is safe and feasible. The procedure is associated with minimal toxicity. The use of fiducial markers may enhance the accuracy and efficacy of radiotherapy for bladder cancer.

KEYWORDS: Bladder cancer; Fiducial markers; Image-guided radiotherapy; Radiation therapy

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Abbreviations and Acronyms

2-dimensional, 2D
CT, computed tomography
kV, kilovoltage
TUR, transurethral resection

INTRODUCTION

Radiation therapy in combination with radiosensitizing chemotherapy is often used in the management of muscle-invasive bladder cancer with the goals of organ preservation and disease eradication. One of the major challenges in delivering high radiation doses that are necessary for tumor control is the close proximity of the bladder to healthy, radiosensitive surrounding tissues such as bowel. In addition to the close proximity of dose-limiting organs, the bladder is a hollow organ, and bladder motion during a course of radiation therapy can be substantial and lead to targeting inaccuracies. Typically,

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wide treatment margins have been necessary to account for these uncertainties due to organ motion. Consequently, large volumes of normal tissues have been encompassed in the high-dose regions. Recent development of image-guided techniques has allowed for monitoring and accountability for organ motion. Several studies have demonstrated a significant variability in bladder volume and positioning [1-4]. This variability may contribute to a "geographic miss" of the target with resultant impact on efficacy of therapy. Using imaging throughout radiation therapy may allow for necessary adaptations to account for this motion.

Fiducial markers have been used in many tumor sites to assist in radiation treatment targeting where organ motion is substantial. A recent series by Mangar et al [5] demonstrated the feasibility of this approach using gold seeds. They found that one of the limitations of these markers was a high seed drop-out rate that could be minimized by cystodiathermy at the insertion site. Acute toxicity using this technique was minimal.

As an introductory technique to utilize image-guided radiation therapy for bladder cancer radiotherapy, we initiated a program of cystoscopically placed Visicoil linear fiducial markers (Core Oncology; Santa Barbara, CA, USA) prior to simulation and treatment planning for patients undergoing external beam radiation therapy for bladder cancer. The present study describes the technique and feasibility of this program as well as our early toxicity and outcome experience.

METHODS

Between October 2007 and June 2010, 10 patients were treated with definitive image-guided external beam radiation therapy for T2-T4Nx-N1M0 bladder cancer at Memorial Sloan-Kettering Cancer Center. All patients provided informed consent for fiducial marker placement prior to the procedure.

Participants

The patients underwent a diagnostic and staging workup that included an initial transurethral resection of the bladder tumor, a computed tomography (CT) or magnetic resonance urogram, and chest imaging. Patients were considered either suboptimal surgical candidates due to comorbidities (n=9) or refused cystectomy (n=1). Clinical characteristics of all patients are presented in Table 1. All patients were male and the mean age was 74 years (range, 58-87 years).

Procedures

All patients underwent a restaging transurethral resection (TUR) and examination under anesthesia by a single urologist (BB) prior to simulation for radiation therapy. We developed a technique of fiducial marker insertion using a long, flexible needle applicator that could be inserted through a standard adult rigid cystoscope. At the time of TUR, a minimum of 2 and a maximum of 4 gold Visicoil fiducial markers were placed adjacent to the site of tumor resection.

Table 1. Clinical Characteristics of All Patients (N = 10).
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Characteristic	n	% n
Age, years		
< 65	2	20
≥ 65	8	80
Gender		
Male	10	100
Female	0	0
Tobacco history		
Yes	10	100
No	0	0
Stage		
T2N0	9	90
T3-T4N0	1	10
Tumor location		
Posterolateral	7	70
Dome	0	0
Bladder neck	3	30
Hydronephrosis		
Yes	1	10
No	9	90

Fiducial Marker and Applicator Preparation

We selected Visicoil fiducial markers with a diameter of 0.35 mm and length of 1.0 cm. The markers are supplied preloaded on a needle carrier device (Figure 1). For the insertion, a 22-gauge applicator needle (Echotip; Cook Medical, Winston-Salem, NC, USA) (Figure 2) was selected, which is backloaded with 1 fiducial marker. The stylet of the applicator needle is withdrawn approximately 1.5 to 2 cm and the fiducial marker needle carrier device is inserted into the applicator needle tip. The needle extension guide is set at 1 cm, allowing the needle tip to protrude into but not through the detrusor wall to allow for an intramuscular insertion. The fiducial marker is then deployed into the applicator and the needle tip is withdrawn into the sheath.

Fiducial Marker Placement

All patients were placed under laryngeal mask anesthesia per institutional standard for TUR. A maximal resection was performed using standard transurethral techniques. Following

Figure 1. Visicoil Linear Fiducial Marker (Core Oncology; Santa Barbara, CA, USA) on Carrier Needle.
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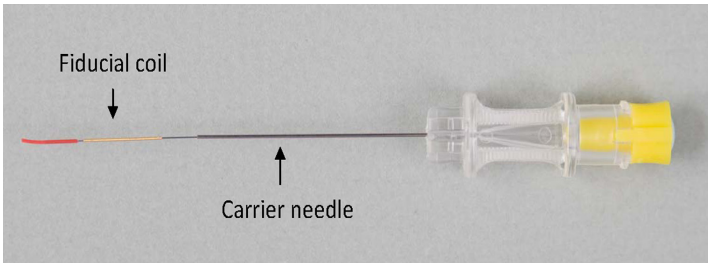

resection, the adult rigid cystoscope was inserted transurethrally. The loaded applicator needle (Figure 2) was then advanced out of the working channel sheath of the cystoscope and the tip of the applicator was applied to the mucosal surface. The needle tip was then advanced out of the sheath while applying pressure on the catheter so that the needle tip was allowed to penetrate into the detrusor muscle. Once the needle tip was in position within the bladder wall, the stylet was advanced slowly and completely, thus moving the fiducial marker out of the applicator needle. The needle and sheath were then retracted and the insertion site visually inspected to confirm marker deployment. Every attempt was made to avoid visualization of the marker in the bladder lumen. Following adequate delivery, the applicator was withdrawn and the procedure repeated for each fiducial marker.

Figure 2. Applicator Needle.
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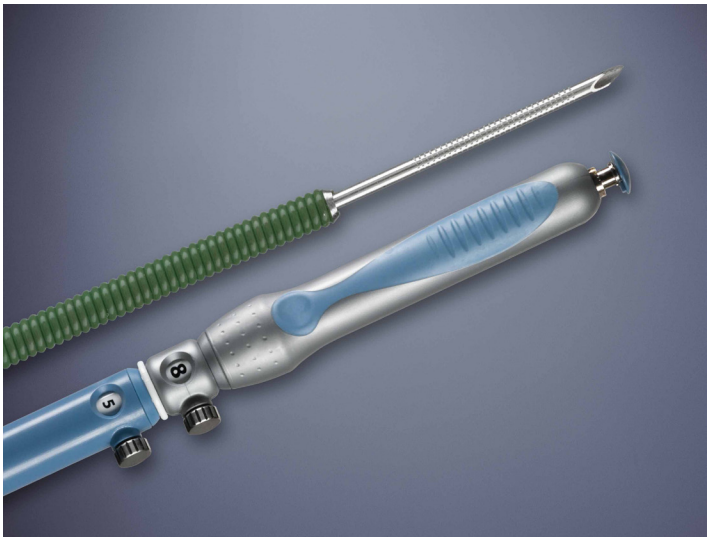

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A single intravenous dose of antibiotic was administered at the time of marker placement and 3 doses of oral antibiotics were prescribed following the procedure.

Radiation Treatment Planning and Delivery

Approximately 1 week following placement of the fiducial markers, a CT simulation was performed with the patient in the supine position with an empty bladder. Aquaplast (WFR/Aquaplast Corp; Avondale, PA, USA) immobilization was used for all patients. Normal tissue and target contours were delineated on an in-house treatment planning system. The planning target volume for the initial plan included the bilateral pelvic lymphatics as defined by a 1 cm circumferential margin around the bilateral iliac vessels from the aortic bifurcation to the obturator nodes. In addition, the whole bladder and prostate were defined with a 1.5 cm margin. 15 MV photons were used for all patients. A total dose of 4500 cGy was delivered in 180 cGy daily fractions for 25 days. An additional 2160 cGy was delivered in 180 cGy daily fractions to a boost volume defined using the fiducial markers and imaging/cystoscopy information obtained prior to TUR. Concurrent gemcitabine (n=8) or cisplatin (n=2) chemotherapy was used in all patients.

During radiation therapy, 2-dimensional (2D) kilovoltage (kV) imaging was obtained daily in all patients. In addition, cone-beam CT scans were performed weekly in 5 of 10 patients. The marker drop-out rate was assessed using 2D and 3D imaging obtained during radiation therapy.

Acute genitourinary toxicity was assessed at simulation and weekly during radiation therapy using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 grading system [6].

RESULTS

A total of 10 male patients successfully underwent fiducial marker placement. The first 3 patients had 2 markers placed, 1 patient had 3 markers placed, and the remaining 6 patients had 4 markers placed. Initially, we had technical difficulty loading the applicator needle due to removing coils from the carrying device. The 0.35 mm Visicoil markers are fragile and subject to uncoiling if manipulated by hand. However, once we implemented loading into the applicator needle using the backloading technique as described above, this problem was overcome.

No intraprocedural or delayed complications were encountered. No patient had febrile complications following the procedure.

On treatment-planning CT scans, all implanted fiducial markers

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Figure 3. Treatment-Planning Computed Tomography Scan Images With Fiducial Markers in Place. doi: 10.3834/uij.1944-5784.2011.02.16f3

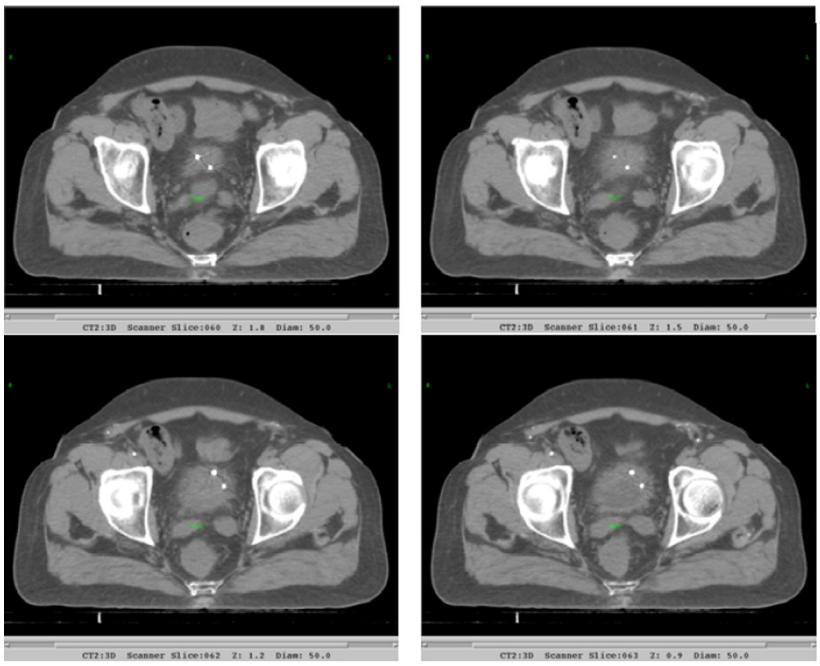

Figure 4a. Digitally Reconstructed Radiograph With 4 Fiducial Markers Shown.
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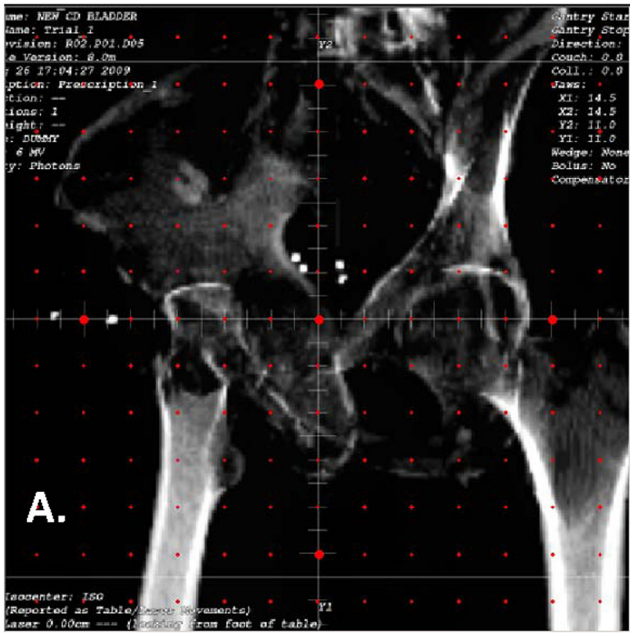
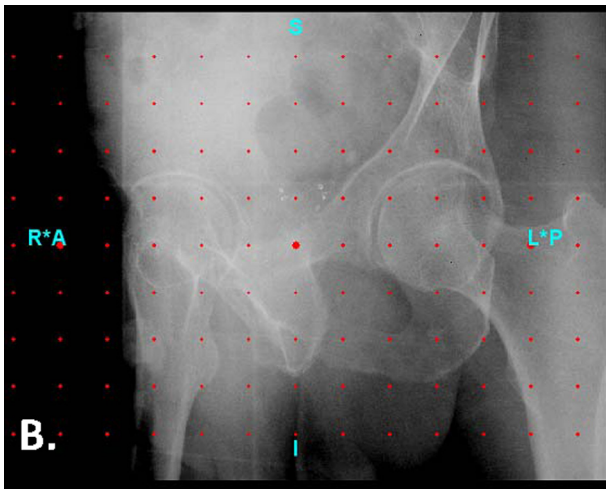


Figure 4b. Two-Dimensional Kilovolt Imaging Obtained During Radiation Therapy With 4 Fiducial Markers Shown.
doi: 10.3834/uij.1944-5784.2011.02.16f4b



were identified (Figure 3). Two patients had 3 markers in the perivesical fat. All remaining markers were identified within the bladder wall. All 10 patients completed the entire course of radiation therapy without requiring a treatment interruption. During radiation therapy, all markers were clearly visualized on kV imaging (Figure 4a; Figure 4b). Throughout radiation therapy, 2D kV imaging revealed that no patient had loss of fiducial markers due to drop-out. The fiducial markers remained stable in position for all patients throughout treatment.

During radiation therapy, 9 of 10 patients developed grade 1-2 urinary toxicity including frequency, nocturia, dysuria, and/or urgency. No patient developed grade 3-4 urinary toxicity. All patients completed the prescribed course of therapy without interruption.

DISCUSSION

Bladder organ motion is a major obstacle to the accurate delivery of radiation therapy for bladder cancer. As a thin-walled hollow organ, the bladder is subject to inflation and deflation related to urine filling and emptying. In addition, bladder wall motion can be significant and difficult to predict, particularly in diseased bladders. Muren et al [2] reported significant bladder displacements in a series of 20 patients who had serial CT imaging during radiotherapy such that 89% of serial scans had bladder target volumes outside of the planned volumes. In addition, 40% of patients had at least 1 scan with bladder displacements > 15 mm. In a similar study by Pos et al [3], 65% of patients had bladder displacements outside of planning volumes at least once during radiotherapy. To account for these volume changes, treatment margins > 1.5-2 cm would be needed.

A fiducial marker is an ideal maneuver to track and account for such motion during a course of radiation therapy. In a prior report, the placement of gold fiducial seeds was feasible and well-tolerated; however, the seeds were subject to dropout, probably related to the expansion and contraction of the bladder muscle [5]. We selected the flexible gold fiducial marker, which may have better stability. The stability may be due to the way that the marker grasps the bladder muscle and expands and contracts in concert with the bladder wall. In our series, the fiducial markers placed in all patients remained stable throughout a 7-8 week course of radiotherapy with no fiducial marker drop-out. In addition, toxicity related to fiducial marker placement was negligible.

Although not a selection criteria for inclusion, our study is limited in that only male patients were included. Therefore, these results may not be applicable to female patients who may have thinner bladder walls. Future experience using this technique in women is necessary to evaluate the optimal marker length for patients with thin bladder walls.

In addition to organ motion, the identification of the tumor bed when planning radiation therapy has been problematic. Radiation oncologists often use information obtained from imaging prior to TUR, operative notes, or 2D bladder maps to correctly identify the tumor bed. Embedded fiducial markers placed at the time of TUR may eliminate the uncertainty of tumor location and improve the accuracy of targeted radiotherapy. Inaccuracies in target identification may contribute to the local failure rate following a standard course of radiation therapy. Minimizing this uncertainty may help improve outcomes and optimize bladder-preservation therapy using combined modality therapy. In addition, improving the accuracy of radiation therapy in terms of organ motion and targeting allows the possibility of dose escalation and perhaps better local control over historical experience. Further studies are ongoing to assess the use of fiducial markers and image-guided radiation therapy and how these technical advances may impact outcomes using multimodality bladder-preservation therapy.

CONCLUSION

Our technique of the cystoscopic placement of flexible gold fiducial markers in the bladder wall provides a simple and stable method of tracking bladder-wall motion during radiation therapy. The procedure has minimal toxicity. The use of fiducial markers may improve the accuracy of radiation therapy for bladder cancer.

Conflict of Interest: none declared

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