UNIVERSITY OF WASHINTON SCHOOL OF MEDICINE
FRED HUTCHINSON CANCER RESEARCH CENTER
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TraceIT™ Hydrogel Tissue Marker for Patients Receiving Definitive Chemoradiation for Bladder Cancer

Principal Investigator:

Jing Zeng, MD
Assistant Professor
Department of Radiation Oncology
University of Washington Medical Center
1959 NE Pacific Street, Box 356043
Seattle, Washington 98195-6043
Phone: 206-598-4100
Fax: 206-598-6218
Email: jzeng13@uw.edu

Co-Investigators:

Jay Liao, MD
Kenneth Russell, MD
Jonathan Wright, MD
Stephen Bowen, PhD
Daniel Hippe, MS (statistician)
Stephanie Schaub, MD

Research Coordinator:

Phone: 206-598-4100
Fax: 206-598-3786
Email: radoncrc@uw.edu

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Study Summary

Title	*TraceIT™ Hydrogel Tissue Marker for Patients Receiving Definitive Chemoradiation for Bladder Cancer*
Short Title	*TraceIT™ Hydrogel for Bladder Cancer*
Protocol Number	*CCIRB 9798*
Phase	*Pilot Study*
Methodology	*Single Arm Open-Label*
Study Duration	*1 year*
Study Center	*University of Washington Medical Center*
Objectives	*To utilize the TraceIT™ hydrogel tissue marker in localizing bladder tumors during TURBT (transurethral resection of bladder tumors), to improve identification of gross tumor location in patients receiving chemoradiation treatment for bladder cancers. The long-term goal being to reduce radiation field sizes to decrease radiation toxicity and improve tumor control.*
Number of Subjects	*12 evaluable subjects*
Diagnosis and Main Inclusion Criteria	*Patients diagnosed with non-metastatic bladder cancers receiving definitive Chemoradiation.*
Study Product, Dose, Route, Regimen	*TraceIT™ Hydrogel Tissue Marker, FDA approved, will be injected into the bladder wall (at least 3 sites of injection around the peripheral of the tumor location) to mark the location of the bladder tumor during TURBT.*
Duration of Administration	*TraceIT™ Hydrogel Tissue Marker is absorbable and will start to breakdown after 3 months, fully absorbed by 6 months.*
Statistical Methodology	*Radiation treatment will be delivered daily for 4-8 weeks, with daily cone beam CT imaging prior to treatment. Location of the hydrogel will be visible on imaging, and tracked daily to monitor for interfraction variation in tumor bed size, shape, and location. Tumor location will also be compared against bony pelvic anatomy (pelvic brim), which is often used in aligning bladder cancer patients for their daily radiation treatment. Interfraction variation in tumor bed size, shape, and location will be compared for each patient, as well as across patients.*

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1. Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

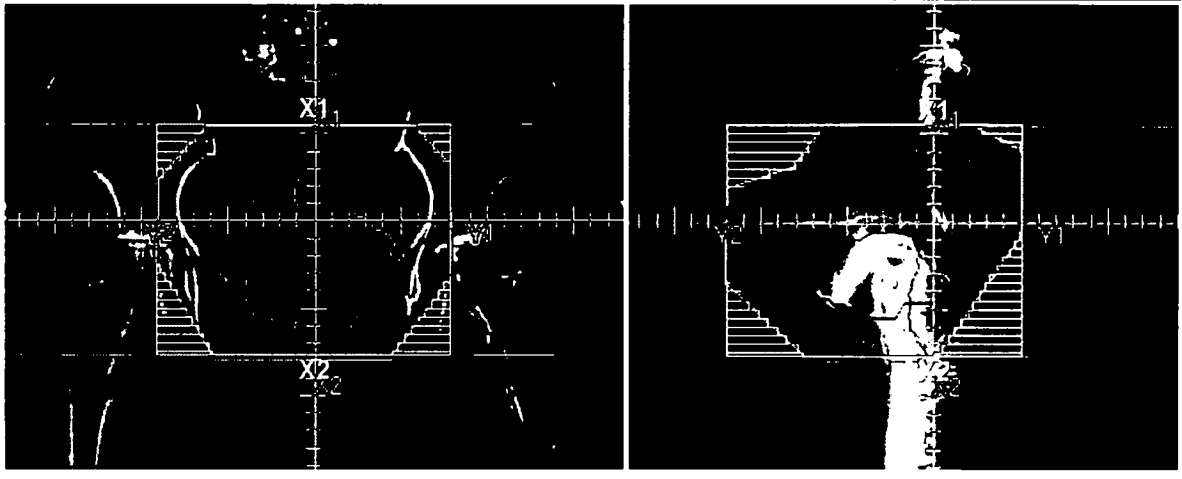
1.1 Background

For patients with muscle invasive bladder cancer, one treatment alternative to a radical cystectomy is bladder preservation with chemoradiation [1-4]. Ideal patients for bladder preservation therapy with chemoradiation should have a single tumor, completely resected by TURBT (transurethral resection of bladder tumor), no CIS (carcinoma-in-situ), T2 tumors, urothelial histology, and no evidence of hydronephrosis [4]. For this ideal patient population, 5-year overall survival is around 60% when treated with bladder preservation therapy, comparable to radical cystectomy results. There are also patients with bladder cancers that are not ideal candidates for bladder preservation therapy with chemoradiation, but elect to undergo chemoradiation due to a variety of reasons, such as patient preference or medically inoperable due to comorbidities.

Bladder preservation with chemoradiation carries the potential for significant toxicity due to the bladder's proximity to adjacent normal tissues. Patient first undergo maximum possible tumor resection with TURBT, and then 4-8 weeks of concurrent chemoradiation. Common chemotherapy regimens used during chemoradiation for bladder cancer treatment include cisplatin based regimen, mitomycin and 5-FU, and gemcitabine. These chemoradiation regimens typically result in grade 3-4 toxicities of 10-36% acutely, with main acute toxicities being hematologic, gastrointestinal (e.g. diarrhea), and genitourinary (e.g. bladder urgency, frequency, discomfort with urination). There is also a <10% risk of late Grade 3+ toxicity. Overall complete tumor response to chemoradiation is around 70%, with 40% locoregional recurrence risk at 5 years (mix of invasive and non-invasive bladder cancer recurrence). Strategies are needed to both improve tumor control and decrease toxicity of treatment.

Radiation is typically given in daily 1.8 Gy fractions to >60 Gy total over 4-8 weeks [5, 6]. Standard radiation field cover a "mini-pelvis" field (Figure 1), typically covering an area

Figure 1. Typical radiation field for bladder cancer treatment. LEFT: anterior radiation field outlined; RIGHT: left lateral radiation field outlined. Black outline is the bladder. Gray outline is the rectum.



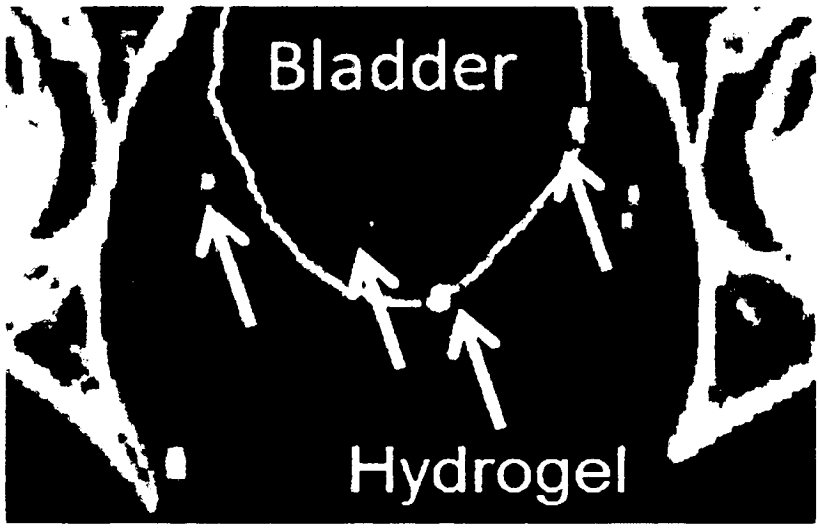
from S3 vertebral body superiorly to below the obturator foramen inferiorly, laterally to provide a 1-2 cm margin around the bony pelvis, anteriorly and posteriorly with 1-2 cm margin around the bladder. After treating this larger field to about 45-50 Gy, there is typically a boost to the bladder tumor bed to >60 Gy, depending on normal tissue tolerance in the region. This boost is typically determined based on a radiation oncologist's estimation of bladder tumor location prior to TURBT, based on scan reports and urology operative reports describing the tumor location.

Prior to the each daily radiation treatment, images are taken to ensure the patient is set up in the proper location, and then radiation treatment is delivered. Since the bladder tumor bed is not visible on x-rays and CT scans, bony anatomy is often used for patient setup alignment. Daily cone beam CT scans performed on the linear accelerator are typically obtained to ensure that the bladder is inside the radiation treatment volume, and make further adjustments in patient position as needed to target the bladder tumor. However, since there currently exists no standard method to reliably delineate the bladder tumor bed on CT scan, during the radiation treatment planning phase, radiation oncologists typically contour a generous target volume that likely encompasses the tumor bed, and then add an additional 1-2 cm treatment "margin" around the suspected tumor bed to account for expected daily bladder motion, as well as daily changes in bladder filling which can change the bladder size and shape. Better visualization of the bladder tumor location could result in decreasing these added treatment margins needed to ensure the radiation field does not miss the tumor, thereby decreasing the amount of normal tissues that are receiving radiation, and potentially increasing our ability to give more radiation dose to the tumor, without causing excess toxicity.

1.2 Rationale for TraceIT™ Hydrogel Tissue Marker

The TraceIT™ Tissue Marker (Augmenix, Waltham, MA) is an injectable polyethylene glycol based hydrogel marker designed to be visible under CT, cone beam computed tomography (CBCT, commonly used for daily pre-radiation treatment imaging for patient alignment), MR and ultrasound imaging for three months after implantation, and then to absorb within six months. Peer reviewed abstracts by other groups have shown that it is possible to inject the hydrogel safely into patients with bladder cancer, undergoing chemoradiation treatment (Figure 2)[7]. Each injection is about 0.3-0.4 ml in volume.

Figure 2. TraceIT™ hydrogel injected into bladder, and visualized on CT (Ref



This gel technology is in routine clinical use in patients with prostate cancer to create a space between the rectum and prostate so as to protect the rectum in patients receiving radiation to the prostate. The formulation being used in the bladder, TraceIT™, is modified so that it is visible on imaging and is used as a marker rather than a spacer. TraceIT™ has FDA approval for use as a marker, and there have been abstracts with small patient numbers describing its use in bladder cancer, but its reliability for daily radiation treatment alignment has not been studied.

Accurately visualizing the tumor bed can help reduce the volume of tissue that is treated with radiation, which can decrease toxicity, and make it possible to further escalate the radiation dose without causing excess toxicity. However, there is no data on the daily variation in tumor bed size and shape, which occurs naturally with daily changes in bladder filling. We presume that the standard radiation treatment contouring guidelines accurately encompasses the tumor bed, but without a reliable method of marking the tumor bed during cystoscopy, this is actually not known. It is possible that there is greater daily variation in the bladder tumor bed location than routinely accounted for in radiation planning, and this could lead to under dosing of the tumor bed in some patients, contributing to the rate of local failure. There is also no data on the relationship between tumor location marked by hydrogel, and pelvic bony anatomy. Again, a greater than expected discrepancy between the two can lead to tumor under dosing. We propose this study, with the objectives outline below, to explore these questions.

This study also serves as proof of concept in the use of TraceIT™ as a fiducial marker in a thin walled organ that has not be able to reliably undergo markings with traditional solid fiducial markers (as these other markers are not reliably retained in the bladder wall). Other similar organs that might benefit in the future from better delineating of tumor locations and where traditional fiducials are not well anchored include small and large bowel, esophagus, and the mucosal lining of the upper aero digestive tract.

2. Study Objectives

Primary Objective:

To utilize the TraceIT™ hydrogel tissue marker in localizing bladder tumors during TURBT (transurethral resection of bladder tumors), to improve identification of gross tumor or tumor bed location in patients receiving chemoradiation treatment for bladder cancers. There is currently no standard method of marking tumor location in bladder cancer patients undergoing chemoradiation, and the daily tumor bed motion is unknown. Radiation treatment will be delivered daily for 4-8 weeks with daily cone beam CT imaging per current standard of care. Location of the hydrogel will be visible on imaging, and daily interfraction variation in tumor bed size, shape, and location will be tracked.

Hypothesis:
The hydrogel will show the bladder tumor bed motion on a daily basis, with changes in size, shape, and location due to daily variation in bladder filling. We plan to characterize the changes in size, location, and deformability to inform the design of future radiation fields. Field design for this protocol will use the standard treatment margins in current clinical use. We expect that the tumor bed location will remain inside the planning target volume (PTV), predefined by the

radiation oncologist prior to starting radiation treatment. We have the means to replan the radiation fields if this is not the case and deemed medically necessary.

Secondary Objective

a) To report adverse events surrounding the placement of the TraceIT™ Tissue Marker.

Hypothesis:

We predict placement of the TraceIT™ Tissue Marker will be a well-tolerated procedure without any significant adverse events within the time after placement to the initiation of radiation therapy.

b) To calculate the actual dose received by the bladder tumor bed, as delineated by the hydrogel. Since daily CBCTs will be obtained, actual daily dose to bladder tumor bed can be calculated daily.

Hypothesis:

There will be adequate coverage of the tumor bed in most patients, due to large margins used in current standard radiation treatment planning, although the margins can likely be reduced if markers are used to delineate the tumor bed.

c) To compare the dosimetric impact to the tumor bed of daily patient alignment to the pelvic bones, versus alignment to the whole bladder, versus alignment to the hydrogel markers. Standard of care for radiation treatment is daily alignment to pelvic bony anatomy or whole bladder, since there is currently no standard way to delineate the tumor bed.

Hypothesis:

Using hydrogel to localize bladder tumor location will lead to more accurate targeting of the bladder tumor with radiation.

d) To calculate the amount of normal tissue radiation dose decrease achievable without losing tumor coverage, with better tumor targeting with hydrogel placement.

Hypothesis:

Using hydrogel to better localize the bladder tumor can lead to smaller margins being used in radiation planning, which can make it possible to increase radiation dose to the tumor without excess radiation to surround normal tissues. We hypothesize that a 5 mm margin around the hydrogel markers will encompass >95% of daily motion, which is significantly smaller than the 2 cm margin commonly used in current radiation treatment planning.

3. Study Design

3.1 General Design

This is a pilot study to utilize the TraceIT™ hydrogel tissue marker in localizing bladder tumors during TURBT (transurethral resection of bladder tumors), to improve identification of gross tumor location in patients receiving chemoradiation treatment for bladder cancers. The long-term goal being to reduce radiation field sizes to decrease radiation toxicity and improve tumor control. All patients will undergo hydrogel injection during TURBT. All patients will receive standard of care chemoradiation for bladder cancer. As part of this standard chemoradiation, patients undergo daily imaging prior to radiation treatment for alignment. Patients are aligned per pelvic bony anatomy per standard of care, but the hydrogel will also be visible on imaging, and its location relative

to the pelvic bony anatomy will be analyzed. See Table 1 below for summary of study assessments.

Table 1. Study Calendar

	Screening	Prior to Start of Radiation Treatment *(<8 weeks prior to RT)*	During Radiation Treatment (weekly) *(4-8 weeks, >60 Gy)*
Informed Consent	X*[a]		
Medical History	X		X
Physical Exam	X[b]		X
Toxicity Evaluation			X
TURBT		X	
TraceIT™ Hydrogel injection during TURBT (at least 3 sites, around tumor periphery)		X*	
CT Simulation for Radiation Planning		X	
Daily Imaging for Radiation Treatment			X

* Denotes a research procedure, all others are standard of care
[a] Indicates the day of study entry
[b] Within 60 days of study entry

3.2 Eligibility Criteria

Conditions for patient eligibility:

- Histologically confirmed malignancy of the bladder
- No prior cystectomy
- Treatment plan for bladder must include at least 4 weeks of daily radiation treatment (most patients will receive chemotherapy concurrent with radiation, but this is not required for trial enrollment)
- Patient must undergo TraceIT™ hydrogel placement within 8 weeks prior to starting radiation therapy for bladder cancer
- Age ≥ 18 years
- Participants must have a complete history and physical examination within 60 days of study entry
- Participants must be able to provide informed consent for treatment and trial participation
- No restrictions on prior treatment to be eligible

3.3 Ineligibility Criteria

Conditions for patient ineligibility:

- Prior cystectomy
- Unable to have TraceIT™ hydrogel placement <8 weeks prior to beginning radiation treatment
- Treatment for metastatic bladder cancer

- Women of child-bearing age unwilling to use acceptable forms of contraception.

3.4 Primary Study Endpoints

In this study, patients with bladder cancers receiving chemoradiation as definitive treatment will undergo injection of the TraceIT™ hydrogel during TURBT. During daily radiation treatment, a cone beam CT will be captured and x/y/z coordinates will be assigned to each hydrogel marker, which allows for calculation of interfraction motion (day to day) of the markers, as well as size and deformation of the tumor bed due to bladder filling changes. These changes will be tracked during the entire radiation course (typically 4-8 weeks), and compared across different patients.

3.5 Secondary Study Endpoints

For secondary objective (a), toxicity data will be collected from routine clinical follow up visits.

For secondary objective (b), daily pre-radiation imaging will be used to run the radiation treatment plan, to calculate the daily dose to the PTV (planning tumor volume) based on hydrogel location. Total radiation dose to the PTV can then be calculated as the sum of the daily dose.

For secondary objective (c), daily pre-radiation imaging will be used to run the radiation treatment plan, to calculate the daily dose to the PTV (planning tumor volume) based on alignment to the hydrogel location, versus alignment to whole bladder location, versus alignment to bony anatomy.

For secondary objective (d), daily pre-radiation imaging will be used to identify the smallest setup margin required for consistent coverage of the gross tumor volume (GTV), which is likely smaller than the current standard of care setup margin of at least 2 cm around the GTV. A smaller margin around the GTV will mean that dose to the normal tissues can be decreased, without decreasing the tumor coverage compared with standard of care radiation therapy.

4. Study Registration

Subjects will be registered by the FHCRC/UW Study Coordinator and entered into the Protocol Accrual Tracking System (PATS). Information regarding the PATS system is available at http://cancerconsortium.org/en/support/resources/systems/pats.html. A complete, signed, study consent, and HIPAA consent are required for registration. Registration will occur after study participant signs consent.

5. Radiation Therapy

5.1. Dose Specifications

This protocol does not specific radiation dose, which will be per standard of care at the discretion of the treating radiation oncologist. This protocol does require that the patient is receiving at least 4 weeks of daily radiation treatment, to allow for longitudinal tracking of marker location. Standard of care radiation treatment for curative treatment of bladder cancer is typically 4-8 weeks of daily radiation, with chemotherapy.

5.2. Localization, simulation, and immobilization
Patients should undergo simulation and immobilization per standard of care at the discretion of the treating radiation oncologist. Daily cone beam CT (CBCT) will be required prior to daily radiation treatment, which is currently standard of care.

5.3. Target Volumes
Target volumes will be contoured per standard of care at the discretion of the treating radiation oncologist. Bladder must be contoured as one of the target volumes, which is part of routine standard radiation treatment planning.

5.4. Critical Structures
This protocol does not require any specific normal structure to be contoured as a critical structure. Radiation treatment planning will be per standard of care at the discretion of the treating radiation oncologist. Typically, rectum, bowel, and femoral heads are contoured as critical structures in treatment planning.

5.5. Treatment Planning
This protocol does not specific target or normal tissue dose constraints. Radiation treatment planning will be per standard of care at the discretion of the treating radiation oncologist.

5.6. Radiation Quality Assurance Reviews
All patients treated on this protocol will undergo standard review in the Department of Radiation Oncology. At least two physicians will review the patient history, imaging findings, tumor contours, and radiation plan.

5.7. Radiation Toxicity
Toxicity will be graded based on CTCAE 4.0. Grade 3 and higher adverse events (AEs) will be recorded as well as adverse events that require a treatment interruption. In accordance with institutional policy, all adverse events which in the opinion of the principal investigator are unexpected **and** related or possibly related to the research **and** serious or suggest that the research places research participants or others at greater risk of physical or psychological harm than was previously known or recognized will be reported to the IRB within 10 calendar days of learning of the problem.

5.8. Criteria for Removal/Withdrawal from Treatment
Patients will be withdrawn from treatment if their clinical conditions decline so they are no longer able to tolerate radiation, or are unlikely to clinically benefit from further therapy. Patients will still receive follow up care per standard of care even if they withdraw from the study.

6. Statistical Plan

A total of 12 evaluable patients will be enrolled onto this study at an accrual rate of 12 patients per year. We expect to consent approximately 15 patients to obtain 12 evaluable patients. We will calculate the daily changes in individual hydrogel marker positions, and daily changes in tumor bed size and shape as delineated by the hydrogel. We will compare daily changes

across the patient group as well as within each subjects' treatment course. During daily radiation treatment, a cone beam CT will be captured and x/y/z coordinates will be assigned to each hydrogel marker, which allows for calculation of interfraction motion (day to day) of the markers, as well as size and deformation of the tumor bed due to bladder filling changes. These changes will be tracked during the entire radiation course (typically 4-8 weeks), yielded a distribution of x/y/z positions for each patient. Independent non-parametric testing of systematic (mean) errors in hydrogel marker position and tumor bed size variation between patients, as well as testing of random (root-mean-square error, pooled deviation) residual errors in hydrogel marker position between patients, will be conducted using Kruskal-Wallis ANOVA (k patient samples). While non-parametric testing sacrifices statistical power, it relaxes the criteria for normality in the presence of small sample size. For completeness, we will also perform parametric ANOVA testing in the 12 patient sample size, in order to detect differences in hydrogel positioning error in the range of 5-10 mm at 80% power and 5% Type I error rate.

7. Data and Safety Monitoring Plan

Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human under the provisions of the DSMB, the Cancer Consortium Clinical Trial Support Office subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

7.1 Early Stopping Rules

Early stopping of this trial will be any grade 4 or 5 adverse events (AEs) occurring within ≤ 30 days after the end of treatment defined as possibly, probably, or definitely related to treatment (per CTCAE, v.4.0). All AEs will be immediately monitored and reviewed by PI.

7.2 Interim Data Review

Interim reports with statistical analyses will be prepared twice per year until the initial treatment results have been presented or published. In general, the interim reports will contain the following information:

- Patient accrual rate with a projected completion date (while the study is still accruing)

- Total patients accrued
- Frequencies and severity of adverse events

8. Data Management/Confidentiality

The investigator will ensure that data collected conform to all established guidelines. Each subject is assigned a unique patient number to assure subject confidentiality. Subjects will not be referred to by this number, by name, or by any other individual identifier in any publication or external presentation. The licensed medical records department, affiliated with the institution where the subject receives medical care, maintains all original inpatient and outpatient chart documents.
Subject research files are stored in a secure place (or database). Access is restricted to authorized personnel.

9. References

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