

COVER PAGE FOR PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official Study Title: RADICAL CYSTECTOMY COMPARED WITH
CHEMORADIATION FOR MUSCLE INVASIVE BLADDER CANCER: A PILOT
RANDOMIZED CONTROLLED NON-INFERIORITY TRIAL

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BLADDER CANCER: A PILOT RANDOMIZED CONTROLLED NON-INFERIORITY TRIAL**

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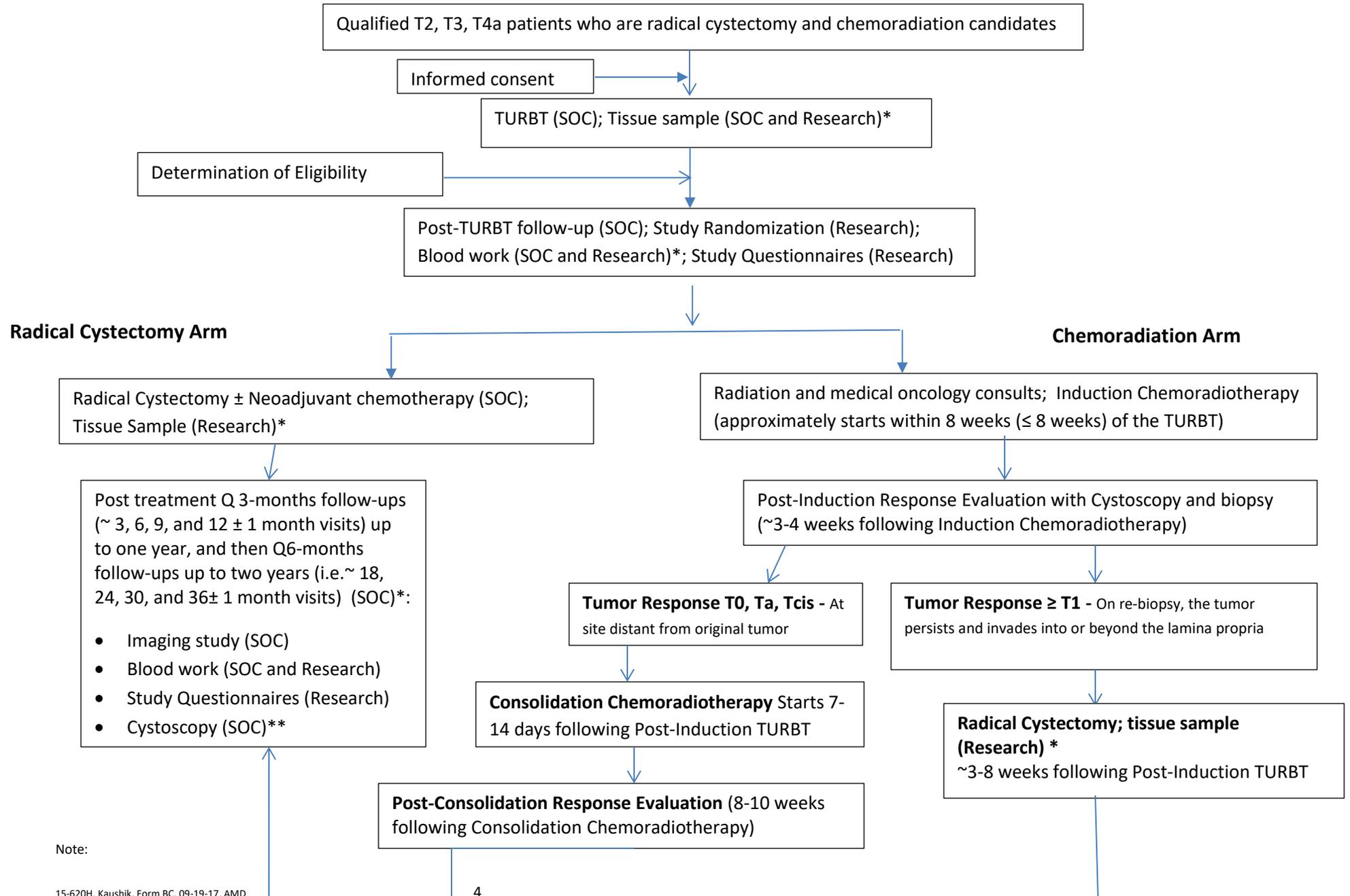
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STUDY SYNOPSIS: Radical cystectomy vs. Chemoradiation Study Chart



Note:

RC=Radical Cystectomy

SOC = Standard of Care

TURBT = Transurethral resection of bladder tumor

*= optional study, "GU Tissue Bank HSC20050234H"

**Post-treatment cystoscopy is SOC for chemoradiation patients

1. BACKGROUND AND SIGNIFICANCE

Radical cystectomy is the gold standard treatment for muscle-invasive bladder cancer. It involves removal of the bladder and prostate for men and anterior exenteration (including the bladder, uterus, ovaries, and part of the vagina) for women. Patients who were treated with the surgical approach report poor overall satisfaction, sexual function, urinary and bowel function, and health-related quality of life. The current NCCN (National Comprehensive Cancer Network) Clinical Practice Guidelines (version 2.2015) indicates bladder-preserving therapy with cystectomy reserved for tumor recurrence represents a safe and effective alternative to immediate radical cystectomy for muscle invasive bladder cancer.

According to the current NCCN guidelines, patients who are not surgical candidates (i.e. those with extensive comorbidities and/or poor performance status), chemoradiation can be used as a curative treatment regimen. This bladder-sparing therapy consist of (1) maximal transurethral resection of bladder tumor (TURBT), (2) induction external-beam radiation therapy with concurrent chemotherapy, (3) cystoscopic assessment of treatment response with prompt cystectomy for non-responders, and (4) active cystoscopic surveillance with salvage cystectomy at the first sign of invasive recurrence.

Retrospective studies have shown that the majority of chemoradiation patients achieves a clinical response and preserves the native bladder in >70% of patients while offering long-term survival rates comparable to contemporary cystectomy series.^{1,2}

We hypothesize that chemoradiation is non-inferior to radical cystectomy with regard to quality of life and progression free and bladder intact survival. Short of a randomized trial, any direct comparison of chemoradiation to radical cystectomy to address our hypothesis is difficult and must account for selection bias and confounding variables resulting from discordance between clinical, pathologic staging, functional status and comorbidities. Our proposed randomized pilot non-inferiority study aims to provide feasibility data for a larger randomized clinical non-inferiority trial comparing the efficacy and safety of chemoradiation and radical cystectomy.

Given the potential non-inferiority of chemoradiation relative to radical cystectomy, clinical prediction of non-response to chemoradiation in terms of biomarkers would be of interest. However, there is paucity of predictive markers that can identify non-responders of chemoradiation. If predictive markers could be identified, patients might then be selected for the treatment most likely to benefit them, which would have the added advantage of maximizing overall cure rates and minimizing poor outcomes. Characterization of the genomic drivers of bladder cancer has been proposed for evaluating progression. Immunohistochemistry has been utilized with limited accuracy. A number of investigators have queried whether comprehensive genomic profiling of cancer-related genes could potentially assist in the selection of targeted therapies for patients with radiation refractory bladder cancer.³ As part of our pilot study, we propose to perform microarray gene expression profiling using Agilent long oligonucleotide (60 mers) technology to search for molecular alterations differing between responders and non-responders of chemoradiation with radical cystectomy as a reference.

1.1. PRELIMINARY DATA

1.1.1. **Data on Chemoradiation:** The Kaplan–Meier plot in Figure 1 (copied from Reference 1) shows 348 patients with muscle invasive bladder cancer who underwent chemoradiation at Massachusetts General Hospital (MGH) by response (incomplete, complete). For clinical stage T2, three-year disease specific survival rates were 74% and 50% for patients who were complete and incomplete responders respectively.¹ The MGH Kaplan Meier curves for disease-specific survival suggest that response to chemoradiation may contribute to the non-inferiority of chemoradiation relative to radical cystectomy with regard to progression free survival in this study [Section 2, Specific Aim 1b].

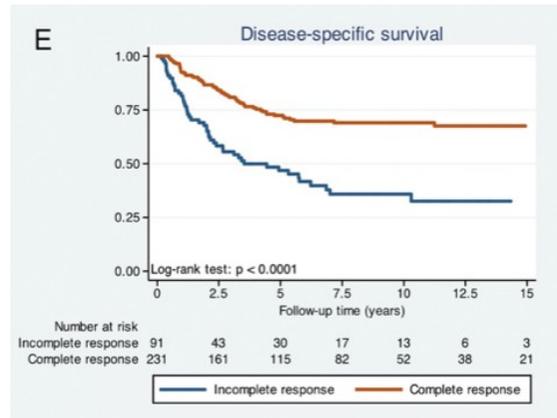


Figure 1: Kaplan Meier plots for disease-specific survival following chemoradiation for all stratified by induction response status in the MGH study¹.

1.1.2. **Role of genome sequencing:** In a radiotherapy test cohort ($n = 201$), high tumor MRE11 expression (one of the candidate genes in our research) in patients receiving radiotherapy (RT) was associated with better cancer-specific survival compared with cystectomy [70% versus 55% 3-year cause-specific survival (CSS), $P = 0.021$]⁴, suggesting that MRE11 expression may play an important role with regard to predicting response to chemoradiation [Section 2, Specific Aim 2a]. Figure 2 shows the relevant plots copied from Reference 4.

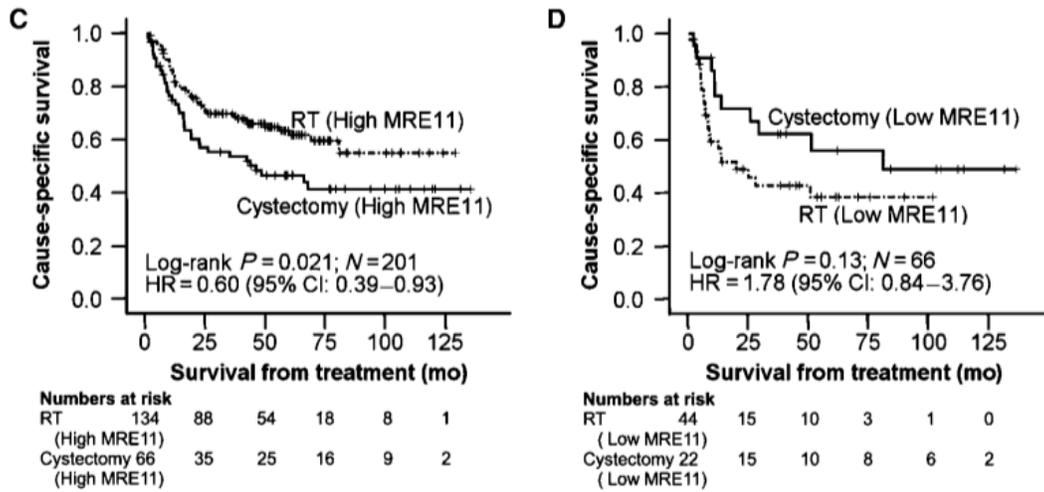


Figure 2: Kaplan-Meier CSS curves for low and high MRE11 Radiation Therapy (RT) compared to cystectomy

2. HYPOTHESIS AND SPECIFIC AIMS

Multiple prospective radiation therapy protocols have evaluated bladder-preserving chemoradiation therapy approach for muscle-invasive bladder cancer (MIBC), with radical cystectomy reserved for radiation failure. Aims of bladder preservation in MIBC are to offer a quality-of-life advantage and avoid potential morbidity or mortality of RC without compromising oncologic outcomes. Because of lack of level-1 evidence, oncologic equivalence of bladder preservation modality treatments compared with RC remains unknown.

2.1 HYPOTHESIS:

We hypothesized that chemoradiation is non-inferior to radical cystectomy for treatment of MIBC.

2.2 SPECIFIC AIMS:

SPECIFIC AIM 1a To determine and quantify quality of life in patients treated with radical cystectomy and chemo radiation therapy

1b To determine and quantify progression free survival and bladder-intact survival in patients treated with radical cystectomy and chemoradiation therapy,

SPECIFIC AIM 2a To evaluate genetic markers predicting response to chemoradiation by performing tissue RNA microarrays.

2b To assess the feasibility of conducting an adequately powered non-inferiority trial of the same design via recruitment rate, patient adherence to both treatment arm, and attrition.

2.3 STUDY DESIGN:

Our study will be a pilot, prospective, single-center, randomized non-inferiority trial comparing chemoradiation therapy to radical cystectomy. Patients diagnosed with muscle invasive bladder cancer after transurethral resection of bladder tumor and are surgical candidates will be randomized to either radical cystectomy (with neoadjuvant chemotherapy if suitable candidate) or chemoradiation.

Both treatment methods are considered “standard of care” recommended by the NCCN Clinical Practice Guidelines (http://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf) in treating muscle invasive bladder cancer.

3. STUDY ENROLLMENT AND WITHDRAWAL

3.1 Inclusion Criteria:

3.1.1 Pathologically (histologically) proven diagnosis of primary carcinoma of the bladder (transitional cell cancer) within 8 weeks of registration. Operable patients whose tumors are primary carcinomas of the bladder and exhibit histologic evidence of muscularis propria invasion and are AJCC clinical stages T2-T4a, Nx or N0, M0

3.1.2 Patients without histologically or cytologically confirmed node metastases or any other metastases

3.1.3 Patients must have an adequately functioning bladder after thorough evaluation by an urologist and have undergone as thorough a transurethral resection of the bladder tumor as is judged safely possible.

3.1.4 Patients must be considered able to tolerate systemic chemotherapy combined with pelvic radiation therapy, and radical cystectomy.

3.1.5 History and physical examination including weight, performance status, and body surface area within 8 weeks prior to study registration

3.1.6 Zubrod (ECOG) Performance Status 0-2

3.1.7 Age \geq 18;

3.1.8 CBC/differential obtained no more than 4 weeks prior to registration on study, with adequate bone marrow function defined as follows:

- a) WBC \geq 4000/ml
- b) Absolute neutrophil count (ANC) \geq 1,800 cells/mm³;
- c) Platelets \geq 100,000 cells/mm³;
- d) Hemoglobin \geq 10.0 mg/dl (Note: The use of transfusion or other intervention to achieve Hgb \geq 10.0 g/dl is acceptable.);

3.1.9 Patient's comprehensive metabolic panel (CMP) must be done no more than 6 weeks prior to informed consent and the CMP levels must be within acceptable institutional limits or to the discretion of the treating physician, which may be the principal investigator of the study.

3.1.10 Serum pregnancy test for female patients of childbearing potential, \leq 72 hours prior to study entry; women of childbearing potential and male participants must practice adequate contraception.

3.1.11 Patient must be able to provide study-specific informed consent prior to study entry

3.2 Exclusion Criteria:

3.2.1 Unable and unwilling to provide informed consent

3.2.2 Evidence of distant metastases or histologically or cytologically proven lymph node metastases

3.2.3 Previous systemic chemotherapy (for any cancer) or pelvic radiation therapy

3.2.4 A prior or concurrent malignancy of any other site or histology unless the patient has been disease-free for \geq 5 years except for non-melanoma skin cancer and/or stage T1a prostate cancer or carcinoma *in situ* of the uterine cervix

3.2.5 Patients judged not to be candidates for radical cystectomy; patients with pN+ or T4b disease are considered to have unresectable disease

3.2.6 Severe, active co-morbidity, defined as follows:

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;
- Transmural myocardial infarction within the last 6 months;

- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
- Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;
- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol.
- Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.

3.2.7 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.2.8 Is pregnant; women of childbearing potential and male participants unwilling to practice adequate contraception.

3.3 Randomization Procedure

A total of 30 patients will be randomized to either chemoradiation group (n=15) or radical cystectomy (with or without neoadjuvant chemotherapy group, n=15). Permuted block randomization process through sequentially numbered, opaque sealed envelopes will be utilized in assigning participants into either radical cystectomy or chemoradiation group. All subjects will be randomized in blocks of size 2. A randomization list containing sequence numbers and treatment assignments will be prepared by the statistician and used as the sole basis for treatment assignments throughout the study.

3.4 Participant Withdrawal

- The PI can withdraw participants if the PI determines the participants have sustained any injury or complication that prevents them from continuing with the study.
- The PI can withdraw participant if the participant is considered not a candidate for chemoradiation treatment after radiation and/or medical oncology consult.
- Participants can voluntarily withdraw from the study at any time.

4. SCHEDULE OF EVENTS

This study requires a minimum of nine study visits to the MARC, CTRC, and/or UHS. The research staff will try to schedule these study visits at the same time as the patient's routine follow-up visits as much as possible to lessen the participant's burden. Since this study is a comparison of two standard of care treatments, participant will not be limited to receiving treatments (i.e. radical cystectomy, radiation, and/or chemotherapy) at UTHSCSA affiliated medical facilities. If participant choose to receive treatment (i.e. radical cystectomy, radiation, and/or chemotherapy) outside of UTHSCA affiliated medical facilities and still would like to remain in the study, we will request for the participant to release his/her medical records and treatment summaries from outside facilities to us after treatment completion. Participant will return to MARC, CTRC, and/or UHS for the routine post-treatment follow-up visits with the treating Urologist. The specific location for the follow-up routine visits will be to the discretion of the treating physician and also the participant's insurance coverage. A summary of study schedule of events is as follows:

4.1 Screening and enrollment

Research staff will review clinic schedules to identify potential participants. Treating Physicians/Physician's Assistant/Nurse Practitioner seeing patients at the MARC Urology Clinics, CTRC will also identify study candidates. Advertising material such as a study flyer will also be placed in the Urology clinics to facilitate with participant recruitment. Potential study candidates identified by the research staff and the information regarding study eligibility will be made available to the treating physician who provides clinical care and sees the patient in clinic. The treating physician, physician assistants (PA), or nurse practitioner (NP) will make initial contact with patients whose pre-screening/chart review indicates they may be eligible for study participation.

Interested participants may also contact the research staff, and if determined possibly eligible for study participation, are scheduled for a research appointment. Screening information collected on ineligible participants will be shredded at the end of study recruitment.

Once the patient has been determined to meet pre-screening criteria, potential participants will first be approached in their private examination room by their treating medical provider, who may also be a research investigator. If the patient indicates an interest in study participation, he will be provided further information about the study, answer questions, and provide a copy of the consent form. The individual will be encouraged to take the consent form home to read and discuss with family, friends, or physicians. If interested, the potential participant will be scheduled to come in and sign consent and undergo study assessments.

The technical aspects of the study will be discussed with potential participants by the Principal Investigator, approved research team members and/or by study co-investigators. Research staff members who are IRB approved and designated for that role will conduct the consent process. The following consent elements will be discussed: voluntary nature of participation, purpose of the study, study procedures, risks and benefits, the collection of protected health information, confidentiality, and participant rights. The participant will be given a copy of the informed consent

to read and consider and ample opportunity will be given to answer any questions. The participant may decline to participate, decide to participate, or take the consent home to think about participating. A copy of the signed consent form will be provided to each participant.

The potential participant will then be scheduled for a TURBT (transurethral resection of bladder tumor) with the treating urologist, which may also be the study's principal investigator or co-investigator. TURBT is the standard of care which allows the treating urologist to formally assess the extent of disease progression and also to evaluate whether the candidate can be treated with both radical cystectomy and chemoradiation treatment. Potential participant will be approached to store any leftover tissue specimens, not needed for diagnosis, into the "GU Tissue Bank" (IRB HSC20050234H). The tissue collected will be processed per standard of care, and slides or tissue blocks may be accessed later for future use in correlative studies. The leftover specimens may be used for future research studies that may include genetic testing related to bladder cancer. This banking portion is optional and not required to be in the main study. If the participant declines to participate in the optional study, any leftover specimens will be permanently de-identified through the GUTB (05-234H).

The potential participant will then return to the clinic for a routine follow-up visit to review the TURBT results and discuss treatment options with the treating Urologist within 4 weeks post-TURBT. Final eligibility will be determined during the TURBT follow-up visit. If potential participant is eligible for the study, randomization will occur. The following section outlines study procedure during the visit.

4.2 Baseline Visit

The potential participant will return to the urology clinic to review pathology results and treatment options within 4 weeks of TURBT. This is a routine post-TURBT follow-up visit (i.e. baseline visit). If the potential participant is deemed eligible for both radical cystectomy and chemoradiation by the treating urologist, the potential participant will then be randomized either to radical cystectomy arm or chemoradiation arm.

Each participant will be assigned a unique subject identifier (subject ID) that has no meaning external to the study database. The participant identifiers will be further masked and password protected, and stored only on a secure server behind a "firewall". Only authorized research study members will have access to these identifiers. A research study file will be kept for each participant accrued. This file will include the participant's consent, the assigned unique subject identifier, and copies of relevant source documents. All participant records will be securely stored in the Urology research offices at the MARC. A data entry system will be prepared in RedCap for the study. Both the subject identifier, sequence number, and the treatment assignment for each patient will be entered into the database together with clinical outcome data collected across visits.

During this visit, the participant will complete a study questionnaire packet, which may include and not limited to demographics, medical history; and study questionnaires *such as* EORTC QLQ C30 and FACT-BI. In the interest of time, the study questionnaire packet may also be completed at participant's home and return to the study team via mail or email (per participant preference). Study team member will strongly encourage participant to complete the study questionnaire at

the time of baseline visit. If the participant completes the questionnaires from home, a study team member may follow-up with the participant over the phone, if the completed questionnaires are not received within a week of the visit. Two tubes (~ 10 mL or 2 teaspoons each) of research blood will also be drawn. Study team member or clinic staff will record participant's height, weight, and vital signs. At the completion of the baseline measurements, each participant will be randomized to either "Radical Cystectomy" or "Chemoradiation" following a process through sequentially numbered, opaque sealed envelopes by an authorized research study member.

4.3. Required Evaluations/Management (baseline prior to initiation of any protocol treatment)

- a) Cystoscopic evaluation by the participating urologic surgeon no more than 6 weeks prior to registration will include bimanual examination under anesthesia, as thorough as possible, a transurethral resection of the bladder tumor. Patients referred from an outside hospital with a muscularis propria-invading bladder tumor will be re-resected by the participating urologist.
- b) Radiologic evaluation including chest CT, abdominal and pelvic CT and bone scan no more than 6 weeks prior to start of treatment.
- c) Comprehensive metabolic panel (CMP) obtained no more than 4-6 weeks prior to registration

5. Randomization

5.1 Radical Cystectomy Arm- Those randomized to “Radical Cystectomy” will be scheduled for surgery. In brief, radical cystectomy is the removal of the entire bladder, nearby lymph nodes (lymphadenectomy), part of the urethra, and nearby organs that may contain cancer cells. In men the prostate, the seminal vesicles, and part of the vas deferens are also removed. In women the cervix, the uterus, the ovaries, the fallopian tubes, and part of the vagina are also removed. Participants in this group may also undergo neoadjuvant chemotherapy prior to the surgery as is the current standard of care. The decision for specific chemotherapy regimen is based on medical oncologist’s evaluation. All AE occurring during the study period will be assessed and attribution assigned.

The surgical approach, robotic versus open, is determined by patient and surgeon mutual preference. All urinary diversions will be done via an open incision and the mode of diversion, whether intracorporeal or extracorporeal (orthotopic neobladder, continent cutaneous diversion or ileal conduit) will be selected by mutual agreement of the surgeon and patient, as is customarily done. The extent of the lymph node dissection will be determined by the surgeon but at minimum will include the external iliac, obturator, and hypogastric regions.

Lymph node dissection: Minimum lymph node (men and women) – all potential lymph node bearing tissue with the lateral limit the genitofemoral nerve, distally Cooper’s ligament to include the lymph node of Cloquet, proximally the crossing of the ureter over the common iliac vessels, medially the bladder to include the tissue medial to the hypogastric artery, posteriorly the floor of the obturator fossa with circumferential mobilization of the external iliac artery and vein.

5.2 Chemoradiation Arm - Those randomized to chemoradiation will undergo radiation therapy concurrently with chemotherapy which serves as radiosensitizer. The following is a brief outline of the radiation therapy. Specific treatment frequency and dosage will be at the discretion of the treating physician/center.

Radiation Therapy (Protocol treatment must begin within 8 weeks following transurethral resection and endoscopic evaluation)

All patients who are randomized to bladder preservation arm will receive the induction course of chemoradiation first. This regimen will begin within 8 weeks following the TUR and cystoscopic evaluation by the participating urologic surgeon. Patients with a complete response to the induction regimen will receive consolidation chemoradiation, starting 7-14 days after cystoscopic re-evaluation. Ideally, treatment should begin on a Monday for both Induction and Consolidation chemoradiation.

5.2.1 Dose Specifications

a) Induction Treatment

On the induction regimen, radiation treatment is delivered one time per day (QD). For the first 10 treatment days, 2 Gy is delivered to the CTVpelvis. Then, 2 Gy is delivered to the CTVbladder for the next 4 treatment days, followed by 2 Gy to the CTVboost for the remaining 6 treatment days. This induction course will deliver a total of 40 Gy to the

CTVboost (20 Gy from the pelvic fields, 8 Gy from the bladder fields and 12 Gy from the tumor boost).

b) Consolidation Treatment

On the consolidation regimen, radiation treatment is delivered to the CTVpelvis at 2 Gy per fraction one time per day (QD) over 12 treatment days for a total of 24Gy. This is the same pelvic field that was treated as a component of induction therapy. For patients completing both induction and consolidation treatment, the resulting total dose to the CTVboost will be 64 Gy over 10 weeks in 32 fractions. The total dose to the CTVpelvis will be 44 Gy.

c) Radiation Dose Prescription

The dose should be prescribed at the center of each treatment volume (CTVpelvis, CTVbladder, CTVboost), or the mid-plane of the patient if only AP/PA beams are used. Criteria for dose coverage are specified in Section 4.6.3.

5.2.2 Technical Factors

The radiation treatment should be with a high energy linear accelerator with photon energies ≥ 6 MV.

5.2.3 Localization, Immobilization and Simulation

a) Immobilization

Proper immobilization is required for this protocol but the specific method of immobilization is up to the discretion of the treating institution. Patient setup reproducibility must be achieved using appropriate clinical devices that might include customized body fix and/or leg immobilizers.

b) Simulation

A planning CT must be obtained with the patient in the supine position. CT scan thickness should be ≤ 3 mm through the region that contains the target volumes and the critical structures requiring Dose-Volume histogram analysis. CT scan should extend at least 4cm above and below the target volumes. The superior limit of the scan will be at least at the L1/2 interspace and the inferior limit will be below the perineum.

The bladder must be voided prior to simulation. Use of IV, bladder or oral contrast is optional. Use of a urinary catheter at the time of simulation or cystoscopic placement of bladder fiducials prior to simulation is also optional. If bladder contrast is used, a 40-50 ml air contrast cystogram is recommended.

5.2.4 Treatment Planning/Target Volumes

a) Small Pelvic Fields

These fields should encompass the entire bladder (CTVbladder), the bladder tumor volume (CTVboost), prostate and prostatic urethra (in men), and the regional lymph nodes. These lymph nodes include the internal and external iliacs and the obturator lymph nodes. All of these structures constitute the CTVpelvis.

Four shaped anterior, posterior and lateral fields will be used. In the cranio-caudal dimension, these fields will extend from the lower pole of the obturator foramen to the mid-sacrum (the anterior aspect of S2-S3 junction). Laterally, the anterior-posterior opposed fields will extend 1.5 cm beyond the widest point of the bony margin of the pelvis. For the parallel opposed lateral fields, the anterior and posterior field edges will extend 2 cm beyond the CTVpelvis.

Field shaping will be used on the anterior-posterior opposed fields to shield the medial border of the femoral heads. Shaping will also be employed on the lateral opposed fields

inferiorly to shield soft tissue anterior to the pubic symphysis and to block the anal canal posteriorly. Superiorly, the lateral fields may include shaping anteriorly to exclude small bowel and anterior rectus fascia which lay anterior to the external iliac lymph node chain.

Wedges should be considered in the lateral fields as tissue compensators if there is a significant anterior slope. Weighting of the four field arrangement should be considered in light of the tumor boost planned such that the final dose to the femoral heads is no more than 45 Gy and the final dose to the posterior rectum is no more than 55 Gy.

Anatomic variations in the bladder may necessitate CTV pelvis modifications and deviation from the standard protocol defined field borders. Examples include a bladder cystocele protruding below the obturator foramen, a bladder diverticulum, bladder herniation through the abdominal wall, or a significant post-void residual. For any of these anatomic variations, the variation should be encompassed within the defined CTV bladder which in turn is used to define the CTV pelvis, and the field edge adjusted to extend 2 cm beyond the modified CTV pelvis.

b) Whole Bladder Fields

The CTVbladder includes the gross tumor volume (GTV) plus the whole bladder volume including the bladder wall thickness. This volume is covered using a four-field arrangement. Field edges extend 2 cm beyond the CTVbladder. Likewise, field shaping is employed to cover the CTVbladder with a 2 cm margin.

c) Tumor Boost Fields

The gross tumor volume (GTV=CTVboost) is derived from information available from bimanual examination, cystoscopic bladder mapping, intraoperative reports and radiographic studies. Close cooperation with the treating urologist is essential. Cystoscopically placed fiducial markers may be employed. A variety of field arrangements may be considered for treating this volume and efforts should be made to spare uninvolved regions of the bladder. Opposed lateral fields are frequently employed for posterior lesions. Well lateralized lesions may be amenable to an anterior-posterior field arrangement or a wedged pair. Regardless of the chosen field arrangement, the field edges should extend 2 cm beyond the defined GTV. The boost field arrangement needs to be determined early in the planning process as it may impact field weighting in the other phases of treatment such that final doses to the femoral heads and posterior rectum are within specified limits.

5.2.5 Critical Structures

The rectum volume is defined on CT from the anus (at the level of the ischial tuberosities) for a length of 15 cm or to the rectosigmoid flexure. A DVH for the rectum, bladder, and both femoral heads should be submitted. The following DVH criteria should be achieved.

Rectum:

No more than 50% of the volume above 30 Gy
No more than 10% of the volume above 55 Gy

Femoral heads:

No more than 20% of the volume above 50 Gy

5.2.6 Compliance Criteria

a) Field Borders

Variation: Actual field borders and/or PTVs are within 2 cm beyond those stated in the protocol and include the target structures described above.

Deviation: Actual field borders and/or PTVs transect a target structure or are greater than 2 cm beyond the borders stated in the protocol.

b) Specified Radiation Dose (Critical structures)

Variation: Planned dose is within 10% of the specified protocol dose.

Deviation: Planned dose deviates by more than 10% from the specified protocol dose.

c) Minimum Isodose Coverage (Applies to each CTV independently)

Generally the minimum dose to any target should be 95 % of the prescription dose to that target. To address the single pixel calculation anomalies the D99% is used as the dose specifier.

Per protocol: D99% > 95%. Dose covering 99% of the volume of any target volume is no less than 95% of the prescribed dose.

Variation: D99% < 95% but D99% > 90%. Dose covering 99% of the volume of any target

volume is no less than 90% of the prescribed dose.

Deviation: D99% < 90%. Target structures coverage falls below 90% of the prescribed dose.

d) Maximum Dose (Applies to each CTV independently)

Generally the maximum dose to any target should be less than 107% of that target's prescribed dose.

Per protocol: V107% < 0.12 cc. Less than 0.12 cc of the CTV receives a dose exceeding 107% of the prescribed dose.

Variation: V107% > 0.12 cc but this dose does not exceed 110% of this dose.

Deviation: The maximum dose to the 0.12 cc volume does exceed 110% of the prescribed dose.

e) Elapsed Days

Per protocol: No more than 3 break days

Variation: 4 to 7 break days

Deviation: 8 or more break days

5.2.7 Treatment Interruption (12/6/15)

If a grade 3 hematologic toxicity (ANC or platelets) develops during chemoradiotherapy, all treatment (both radiation and chemotherapy) should be discontinued for a minimum of 1 week.

Treatment may be resumed when the hematologic toxicity resolves to \leq grade 2. If these laboratory values have not been reached after a 1-week delay, they should be checked weekly until they become acceptable. If after 3 weeks the blood counts have not recovered, all protocol treatment should be discontinued and the patients should be treated on an individual basis.

For a grade 3 acute colitis, cystitis, or any other grade 3 infield (radiation-related) toxicity during any treatment week, treatment should be delayed until the toxicity subsides to the grade 2 level. If the delay is greater than 3 weeks, then the patient should be considered intolerant of protocol therapy and appropriate off-protocol therapy given.

5.2.8 Radiation Adverse Events

- *Genitourinary*: Frequency, nocturia, acute or chronic bleeding from the bladder mucosal surface, cystitis, ureteral obstruction, erectile dysfunction in men, sterility
- *Gastrointestinal*: Rectal irritation, bowel obstruction or bleeding, rectal ulcers, hematochezia, fistula formation, colitis, mucous-like stools
- *Dermatologic*: Erythema, loss of pubic hair which could be permanent
- *Gynecological*: Dyspareunia, ovarian failure and sterility
- *General*: Weight loss, fatigue

5.3 DRUG THERAPY

Medical Oncologist will determine the chemotherapy regimen concurrently used with radiation as a radiation sensitizer. The following is a list of chemotherapeutic drugs that could be used per NCCN guideline:

Cisplatin

Cisplatin and 5-FU

5-FU and Mitomycin

Cisplatin and Paclitaxel

Low dose gemcitabine

All AE occur during the study period will be assessed and attribution assigned.

6. Post-Induction Response Evaluation (for Chemoradiation Arm only)

Following the completion of induction chemoradiotherapy and the evaluation of response all patients must be re-registered via cystoscopy and biopsy. At this time, the response results (biopsy results and cytology results) and the second phase of the treatment (i.e. radical cystectomy for tumor response $T \geq 1$ or consolidation chemoradiotherapy for tumor response T0, Ta, and Tcis) will be recorded and a new data collection calendar generated. Details regarding “Radical Cystectomy” can be found at Section 5.1. Details regarding “Consolidation Chemoradiotherapy” can be found at Section 5.2.2.

The following information will be supplied:

- original case number
- results of evaluation and pathologic T stage
- treatment start date (radical cystectomy or consolidation chemoradiotherapy)

The treatment option registered and the new data collection calendar will be based on the parameters specified by the protocol. If the investigator or the patient deviates from the protocol specified treatment, documentation of this and data submission as outlined in our study Standard operating procedure.

Patients who have developed distant metastases during the induction phase of treatment and who will not continue therapy will remain on the original calendar schedule for continued follow up only.

After completing either radical cystectomy or consolidation chemoradiotherapy, all response results to the second phase of treatment (i.e., either pathologic staging from the radical cystectomy or cystoscopic re-evaluation performed following completion of consolidation chemoradiotherapy) will be promptly submitted to Data Management.

7. 1 Post-Treatment Study Visits at 3, 6, 9, 12, 18, 24, 30, and 36 month \pm 1 month

Post-treatment study visits will occur every three months (\pm 1 month) up to one year and every six months (\pm 1 month) thereafter up to two years (i.e. Months 18, 24, 30, and 36). These study visits will be scheduled during the same time as the participant's routine visit (i.e. standard of care) whenever possible. If not, study team member will work with participant on a time that is convenient. An imaging study either a CT abdomen and pelvis or MRI of abdomen and pelvis will be done as standard of care prior to the routine clinic visit. The treating physician will assess AE and assign attribution. Research study team member will coordinate with the participant to meet either before or after the routine clinic visit. Participants will be asked to complete study questionnaires. The questionnaires may also be mailed and/or emailed back to the study team if they cannot be completed within the allotted study time. And those randomized to "chemoradiation Group" will also undergo routine cystoscopy during these follow-up visits (SOC).

7.2 Withdraw Visit

Whenever possible, participant will be scheduled for a withdraw visit if she/he chooses to withdraw from the study early or if the PI needs to withdraw the participant from the study. This is an optional visit. During this visit, participant will be asked to have research blood draw and complete study questionnaires. Reasons for withdraw will also be asked and recorded. Participant will have the choice to partake any or all of the activities during withdraw visit.

7.3 Unscheduled Visit

Date and reason for any study-related unscheduled visit will be recorded. Any medical notes, radiographic, and/or lab results related to this study-related unscheduled visit will also be obtained and recorded.

8. STUDY CALENDAR

8.1 RADICAL CYSTECTOMY ARM

	Initial visit	Pre-Treatment (tx) TURBT	Baseline	Treatment Period: Radical Cystectomy	Post-tx 3 mon f/u ± 1 mon	Post-tx 6 mon f/u ± 1 mon	Post-tx 9 mon f/u ± 1 mon	Post-tx 12 mon f/u ± 1 mon	Post-tx 18 mon f/u ± 1 mon	Post-tx 24 mon f/u ± 1 mon	Post-tx 30 mon f/u ± 1 mon	Post-tx 36 mon f/u ± 1 mon (end of study visit)		
Study eligibility	X		X											
Informed consent	X													
Assessment of AE						X	X	X	X	X	X	X	X	X
SOC Image studies (X-Ray, CT, and/or MRI)			X			X	X	X	X	X	X	X	X	X
Research blood sample			X			X	X	X	X	X	X	X	X	X
Ht, Wt, and Vitals [#]			X			X	X	X	X	X	X	X	X	X
Research Study Questionnaires			X			X	X	X	X	X*	X*	X*	X*	X*

Note:

SOC = Standard of Care

[#] information may be extracted from EMR

*Research study questionnaire may be emailed or mailed per patient's stated preference

8.2 CHEMORADIATION ARM

	Initial Visit	Pre-Treatment (tx) TURBT	Baseline	Treatment Period: Chemoradiation	Post-Induction Response Evaluation with Cystoscopy and biopsy (3-4 weeks following Induction Chemoradiotherapy) and second phase of treatment**	Post-tx 3 mon f/u ± 1 mon	Post-tx 6 mon f/u ± 1 mon	Post-tx 9 mon f/u ± 1 mon	Post-tx 12 mon f/u ± 1 mon	Post-tx 18 mon f/u ± 1 mon	Post-tx 24 mon f/u ± 1 mon	Post-tx 30 mon f/u ± 1 mon	Post-tx 36 mon f/u ± 1 mon (end of study visit??)			
Study eligibility	X		X													
Informed consent	X															
Assessment of AE								X	X	X	X	X	X	X	X	X
SOC Image studies (X-Ray, CT, and/or MRI)			X					X	X	X	X	X	X	X	X	X
Radiation & Medical Oncology Consults (SOC)			X													
Research blood sample			X					X	X	X	X	X	X	X	X	X
Ht, Wt, and Vitals [#]			X					X	X	X	X	X	X	X	X	X
Research Study Questionnaires			X					X	X	X	X	X*	X*	X*	X*	X*

Note:

SOC = Standard of Care

information may be extracted from EMR

*Research study questionnaire may be emailed or mailed per patient's stated preference

** Post-treatment cystoscopy is SOC for chemoradiation patients ONLY

**Pending on the results of post-induction TURBT and response evaluation, participant may receive further treatments. Details on the second phase of treatment are listed in Section 6 and Study Synopsis.

9. DATA COLLECTION & STUDY EVALUATIONS

Medical records will be reviewed prior to “Baseline Study Visit” to confirm study eligibility. After obtaining consent, socio-demographic data will be collected through chart review and interviews. Clinical data that will be collected include but not limited to bladder cancer treatment history, tumor characteristics, stage, laboratory results, medications and co-morbidity.

Study team member or clinic staff will measure height, weight, and vital signs at each specific study time point. Research blood will be drawn at each study time point. Blood and tissue samples may be banked under the optional study (HSC20050234H GU Tissue Bank). For those participants who declined to participate in the optional study, any leftover samples will be permanently de-identified through the GU Tissue Bank (HSC20050234H) honest broker system. At the close of this study, all biological materials collected will be rolled into HSC20050234 GU Tissue Bank.

9.1 Feasibility: We will report recruitment, visit dates, adherence, attrition rates and compliance with randomization for each arm of the study

9.2 Bladder-intact survival: We will report proportion of patients who failed chemoradiation and required salvage cystectomy

9.3 Quality of life: A self-assessment questionnaire using the European Organization for Research and Treatment of Cancer (EORTC) QLQ- C30 and FACT-Bladder will be used for QOL assessment at baseline, 3, 6, 9 and 12 months.⁸

9.4 Progression free survival: This will be measured from the date of finishing chemoradiation or radical cystectomy to the date of first documentation of progression. Progression will be determined using RECIST 1.1 criteria by the treating physician based on radiographic or pathologic evidence of disease progression, or death from disease. Any documented recurrence will be considered progression.⁹ The date of progression will be recorded.

9.5 Candidate gene expression analysis: For the participants who have consented to be part of the optional study (“GU Tissue Bank HSC20050234H), a microarray analysis will be performed on all bladder tumor specimens using Agilent Technologies (Agilent SurePrint G3 Human Gene Expression 8x60K v2) Microarray. Goal is to study the landscape of 50 important candidate genes, which are involved in bladder cancer (for example-BRAF, KRAS, EGFR, FGFR).

9.6 Activities of Daily Living (ADL) scores: This will be measured at baseline, and during all subsequent follow-up visit (i.e. 3, 6, 9 And 12 months) using Activities of Daily Living QOL Questionnaire using Katz Index of Independence in Activities of Daily Living (ADL).¹⁰

9.7 Retrospective screening & chart review: We will screen and review charts of “potential participant” retrospectively using the latest approved eligibility criteria and study schema to determine:

1. the number of “would-be potential participants”
2. the number of those who were initially deemed eligible and was truly eligible after TURBT
3. the number of those who were initially deemed eligible but was ultimately ineligible after TURBT

4. rationale for ineligibility

The retrospective screen & chart review will start from the date when the study was first approved by the IRB (i.e. April 15, 2016) until present time. Data including but not limited to medical record number, initials of name, gender, race, ethnicity, TURBT result, age at time of treatment, treatment received, date of treatment, eligibility status for the study, and rationale if deemed ineligible, will be captured. We do not intend to contact these patients for study enrollment since they would've received treatments for their diagnosis already. Our intention for this retrospective data collection is that it will provide further insight and information on the potentiality of chemoradiation as treatment modality for patients with specific bladder cancer diagnosis. We need to capture this data in order to represent total population of patients screened, thereby determining the denominator of the study population.

9. 8 Outline of Captured Data

Outcome of Interest	Measure	Method of Assessment
Demographics		Self-report questionnaire
Health History including height, weight, and vital signs		Physical exam, review of EPIC
Study Processes		
recruitment rate adherence attrition feasibility bladder intact survival safety		
Outcomes of interest		
Quality of Life	EORTC	Self-report questionnaire
	FACT-BI	Self-report questionnaire
ADL	Katz ADL	Self-report questionnaire
Progression free survival	RECIST 1.1	Physician assessment
Candidate gene expression	Candidate genes	Laboratory analysis of blood and tissue

10. DATA AND SAFETY MONITORING OVERSIGHT

A Data and Safety Monitoring Plan (DSMP) is required for all an individual protocols conducted at CTRC. All protocols conducted at CTRC are covered under the auspices of the CTRC Institutional Data Safety Monitoring Plan. The scoring algorithm for each questionnaire will be included in the data entry system.

The CTRC Institutional DSMP global policies provide individual trials with:

- institutional policies and procedures for institutional data safety and monitoring,
- an institutional guide to follow,
- monitoring of protocol accrual by the CTRC Protocol Review Committee,
- review of study forms and orders by the Forms Committee,
- tools for monitoring safety events,
- monitoring of UPIRSO's by the Director of Quality Assurance and DSMC,
- determining level of risk (Priority of Audit Level Score – PALS) ,
- oversight by the Data Safety Monitoring Committee (DSMC), and
- verification of protocol adherence via annual audit for all Investigator Initiated Studies by the CTRC Quality Assurance Division.

10.1 Monitoring Safety:

The Principal Investigator will perform primary assessment of adverse events, adverse event trends and treatment effects on this study. The PI will conduct independent quarterly review and report findings to the CTRC Data Safety Monitoring Committee (DSMC) and the UTHSCSA IRB.

Baseline events and adverse events will be captured using the CTRC Master Adverse Events Document for each patient using CTCAE V.4.03 for the grading and attribution of adverse events. Usage of the CTRC Master Adverse Events Document centrally documents:

- the event and grades, severity, and the seriousness of it,
- if the event was a change from baseline,
- the relationship between the event and study intervention
- if the event was part of the normal disease process, and
- what actions were taken as a result of the event.

10.2 Safety Definitions:

For this study, the following safety definitions will be applicable:

Adverse Event Definition: An adverse event (AE) is defined as any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. For this study, all adverse events will be documented starting with the date of study enrollment and ending 30 days after the "12 months post-treatment study visit".

Serious Adverse Event Definition: is any adverse event that:

1. results in death;

2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);
3. results in inpatient hospitalization or prolongation of existing hospitalization;
4. results in a persistent or significant disability/incapacity;
5. results in a congenital anomaly/birth defect; or
6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

Unanticipated Problems Involving Risks to Subjects or Others Definition: Unanticipated problem involving risk to subjects or others includes any incident, experience or outcome that meets all of the following criteria:

- A. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied (note: the unfounded classification of a serious adverse event as "anticipated" constitutes serious non-compliance);
- B. definitely related or probably related to participation in the research; and
- C. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

10.3 Reporting Requirements

For this study, all Master Adverse Events Documents collected on patients for this protocol will be reviewed by the Principal Investigator on a monthly basis to determine if a serious safety problem has emerged that result in a change or early termination of a protocol such as:

- dose modification,
- suspending enrollment due to safety or efficacy, or
- termination of the study due to a significant change in risks or benefits.

Treatment options in this study are standard of care per NCCN guidelines. Therefore there are no specific end points.

As per the CTSC DSMP, any protocol modifications, problematic safety reports, unanticipated problems, and suspension or early termination of a trial must be reported to all members of the research team. Suspension and early termination of a trial must also be reported immediately to the Director of Quality Assurance (DQA) who will promptly notify the sponsor and the UTHSCSA IRB.

The PI will review the Master Adverse Events documents to determine the significance of the reported events and will file the Investigator Initiated Study Quarterly DSMC Report Form on a quarterly basis with the CTSC DSMC. The Investigator Initiated Study Quarterly DSMC Report Form includes information on adverse events, current dose levels, number of patients enrolled, significant toxicities per the protocol, patient status (morbidity and mortality), dose adjustments with observed response, and any interim findings. Any trend consisting of three or more occurrences of the same event will be reported to the CTSC DSMP for independent review outside of the quarterly reporting cycle, which begins three months following

protocol start up. Conflict of interest is avoided by the independent review of the CTRC DSMC and by ongoing independent review of adverse events trends by the Director of Quality Assurance.

All SAE and UPRISO's will be reported following CTRC and UTHSCSA institutional guidelines.

UTHSCSA SAE/UPRISO REPORTING REQUIREMENTS		
Type Event	Report to	Timeframe
All AE, SAE and UPIRSO	Regulatory Affairs and DQA	Same as other notification timeframes except for SAE/AE which should be reported on Monday for the prior week
SAE	Clinical Trial Sponsor	within 24 hours
AE/SAE	UTHSCSA IRB	Annually
UPIRSO - all	Clinical Trial Sponsor	within 24 hours of the PI determining a UPIRSO exists
UPIRSO - life threatening	UTHSCSA IRB	within 48 hours of the PI determining a UPIRSO exists
UPIRSO - non-life threatening	UTHSCSA IRB	within 7 days of the PI determining a UPIRSO exists

AE's and SAE events that occur during clinical trials with or without an Investigational New Drug (IND) application are mandatory reports submitted to FDA via Medwatch FDA F3500A *within 15 days for events that have at least a possible relationship with the drug.*

10.4 Assuring Compliance with Protocol and Data Accuracy

As with all studies conducted at CTRC, the PI has ultimate responsibility for ensuring protocol compliance, data accuracy/integrity and responding to recommendations that emanate from monitoring activities. Source verification of data will be performed every twelve week. Protocol compliance, data accuracy and reporting of events is further ensured by an annual audit conducted by the Data Safety Officer, whose audit report is shared with the PI, the research team, and will be reviewed by the CTRC DSMC.

11. STATISTICAL CONSIDERATIONS:

For this pilot non-inferiority study, we aim to randomize **30** evaluable patients (**radical cystectomy: n=15, chemoradiation: n=15**).

Categorical outcomes will be summarized with frequencies and percentages. Continuously distributed outcomes will be summarized with the sample size, mean, standard deviation, median, minimum and maximum. A consort diagram giving the number patients screened, the number of screen failures, the number randomized, the number lost to follow-up by reason, and the number completing the study by treatment arm will be created. In Aim 1a we will test the hypothesis that chemoradiation therapy is non-inferior to radical cystectomy with regard to change in quality of life at 36 months relative to baseline. In Aim 1b, we will test the hypothesis that chemoradiation is non-inferior to radical cystectomy with regard progression free survival and bladder intact survival. With regard to Aim 1a, assuming the 50% (p_2) of patients randomized to radical cystectomy and 60% (p_1) of patients randomized to chemoradiation will experience improvement in quality of life at 3 years relative to baseline and a 5% margin (Δ) of non-inferiority, this study would require $n=171$ subjects per group to attain 80% power for testing $H_0: p_1 - p_2 \leq \Delta$ versus $H_1: p_1 - p_2 > \Delta$ with $\alpha=5\%$. The non-inferiority of chemoradiation compared with radical cystectomy with regard to changes in quality of life (Aim 1a) will be assessed with Fisher's exact test. Progression free and bladder-intact survival (Aim 1b) will be summarized by treatment arm with Kaplan-Meier curves and supporting tabulations and non-inferiority will be assessed with a logrank test. The significance of treatment arm differences with regard to biomarkers (Aim 2a) will be assessed with t-tests or Wilcoxon tests. Pairwise correlations between biomarkers will be displayed overall and by treatment arm. Logistic regression will be used to find a best linear predictor of treatment arm in terms of multiple biomarkers. Biomarkers may be log transformed prior to analysis. Feasibility (Aim 2b) will be assessed with a new power and sample size calculation. If the logistic regression model fails in Aim 2a, random forests will be attempted. If the logrank test fails in Aim 1b, Fisher's exact test will be used. R (v3+, Vienna, Austria) or SAS (SAS Institute, Cary, North Carolina) software will be used throughout.

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