

NRG ONCOLOGY

NRG-GU001

(ClinicalTrials.gov NCT #: NCT02316548)

RANDOMIZED PHASE II TRIAL OF POSTOPERATIVE ADJUVANT IMRT FOLLOWING CYSTECTOMY FOR pT3/pT4 UROTHELIAL BLADDER CANCER

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology, ECOG-ACRIN Cancer Research Group, and SWOG.

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Participating Sites

- ☒ U.S.
☒ Canada
☒ Approved International Member Sites

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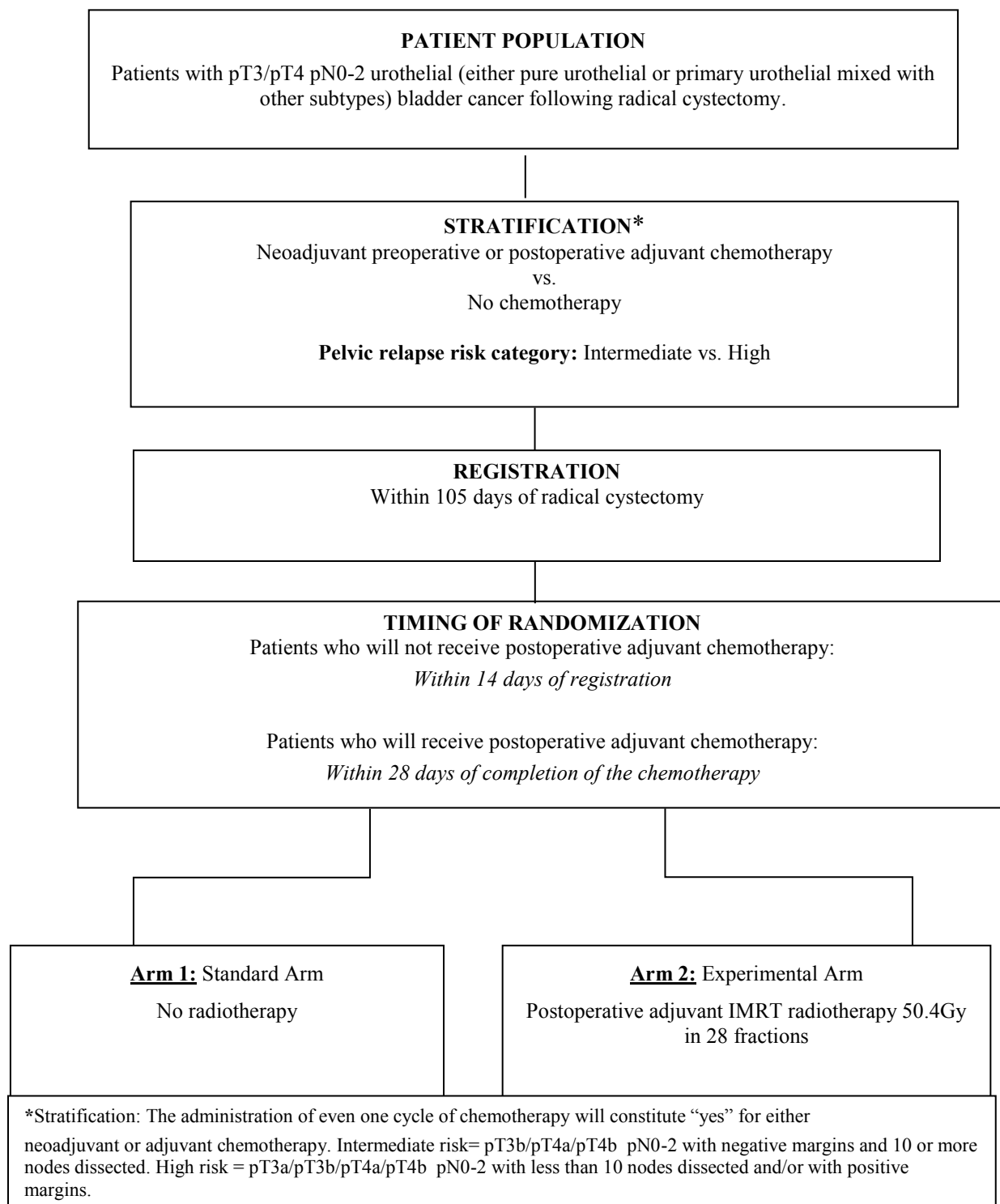
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| NRG ONCOLOGY (8/7/15) | | |
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| NRG-GU001 | | |
| Randomized Phase II Trial of Postoperative Adjuvant IMRT Following Cystectomy for pT3/pT4 Urothelial Bladder Cancer | | |
| CANCER TRIALS SUPPORT UNIT (CTSU) CONTACT INFORMATION | | |
| To submit site registration documents: | For patient enrollments: | Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol: |
| CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone: 1-866-651-CTSU Fax: 215-569-0206 CTSURegulatory@ctsu.cocccg.org (for submitting regulatory documents only) | Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN), which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ -or- https://OPEN.ctsu.org . Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com . | Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. |
| The most current version of the study protocol and all related forms and documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org . Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. | | |
| For patient eligibility: Contact the NRG Oncology Research Associate for Protocol, Data Management section at 215-574-3214. For treatment-related questions: Correspond by e-mail (preferred) or by phone with the study chair designated on the protocol cover page. | | |
| For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com . All calls and correspondence will be triaged to the appropriate CTSU representative. | | |
| For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website https://www.ctsu.org > education and resources tab > CTSU Operations Information > CTSU Regulatory and Monitoring Policy | | |
| The CTSU web site is located at https://www.ctsu.org | | |

NRG-GU001
Randomized Phase II Trial of Postoperative Adjuvant IMRT Following Cystectomy For
pT3/pT4 Urothelial Bladder Cancer

SCHEMA (6/13/16)



1. OBJECTIVES

1.1 Primary Objective

To evaluate the ability of post-cystectomy adjuvant radiotherapy to safely reduce pelvic tumor recurrence, defined as pelvic recurrence-free survival in [Section 16.3.2](#).

1.2 Secondary Objectives

Evaluate increase in disease-free survival

Evaluate toxicity of adjuvant pelvic radiotherapy

2. BACKGROUND (6/13/16)

Pelvic tumor recurrence following contemporary cystectomy has traditionally been considered a relatively infrequent event. Cagiannos and Morash (2009) compiled 8 institutional series between 1977 and 2006 reporting local recurrence rates ranging from 3.9 to 29%. These series have underestimated the true risk of pelvic relapse for a variety of reasons including: exclusion of patients who have also developed distant metastases, using simple numerator/denominator crude risk calculation rather than cumulative incidence rates, not calculating risk according to T stage and excluding pelvic relapses if they have not been biopsied. Herr (2004), reporting the surgical parameters in the neoadjuvant chemotherapy SWOG 8710 trial, demonstrated that despite requiring biopsy confirmation the crude risk of developing local recurrence following cystectomy in pT3/4 disease was 32%.

The 2011 update of the MRC neoadjuvant chemotherapy–cystectomy trial (International Collaboration of Trialists) reported a 48% and 49% rate of pelvic recurrence with and without neoadjuvant chemotherapy, respectively. In a 2011 Canadian survey of contemporary cystectomy, comparably high 48-50% cumulative incidence rates of pelvic failure were found. (Eapen) As neither neoadjuvant nor adjuvant chemotherapy reduce pelvic failure, locoregional control currently is pursued by optimizing nodal dissection. The well-characterized USC experience together with the MSKCC and SWOG 8710 reports emphasize the importance of thorough node dissections defined as a minimum of 10-12 nodes. In a 2012 reanalysis of the USC experience following adequate dissection and counting all pelvic failures except those that occur subsequent to the diagnosis of distant metastases there is a 24% pelvic recurrence rate. (Daneshmand, MD, oral communication) In 2014, Christodouleas reported the U Penn and SWOG 8710 pelvic recurrence experience and identified low, intermediate, and high risk groups according to stage, extent of node dissection and margin status. (Christodouleas 2014) These risk groups experienced 8%, 20% and 41% pelvic recurrence rates, respectively.

In aggregate, this clinical data emphasizes the –to date–neglected problem of significant pelvic failure in pT3/4 patients following cystectomy. This pelvic failure can occur alone (15-20%) or as is more often the case, in conjunction with distant metastases. As such, it constitutes an absolute ceiling on the curability of bladder cancer by surgery and chemotherapy, and also can be a source of significant patient morbidity. Thus both the approximately 15% of patients with isolated pelvic recurrence in whom cure rates may be improved as well as the patients in whom symptoms of pelvic recurrence may be prevented (even in the presence of distant metastases) stand to benefit from a reduction in pelvic failure. One randomized and several retrospective series of postoperative radiotherapy in squamous and transitional bladder cancer suggest superior pelvic control and survival. The hypothesis

to be tested is that postoperative IMRT will reduce any pelvic tumor recurrence (occurring either in isolation or together with distant metastases) with acceptable toxicity in patients with pT3/T4 transitional cell bladder cancer following cystectomy. In 1992, Zaghloul et al published the results of a phase III trial of postoperative radiotherapy in squamous cell bladder cancer showing reduced pelvic failure. In 1999, Cozzarini from Milan presented their retrospective review of postcystectomy radiotherapy. They compared partial/total cystectomy alone versus with postoperative radiotherapy of 45-66Gy (median 50.4Gy). Adjuvant RT to doses 50.4 Gy or higher was associated with improved survival and improved pelvic control. There was an attendant 7% risk of bowel obstruction reported. This trial is important as it will be the first prospective randomized trial in Europe and North America to address the significant problem of pelvic failure. In this phase II study, with contemporary IMRT, we aim to demonstrate the reduction of pelvic recurrence with postoperative radiotherapy in the North American context. The IMRT regimen utilized will mirror the radiotherapy delivered postoperatively in uterine cancers in RTOG trials. This contemporary radiotherapy minimizes both gastrointestinal and pelvic marrow toxicity. The latter is particularly relevant in patients who may have received neo or adjuvant chemotherapy and in those patients who might need chemotherapy for the palliation of metastatic disease. Using IMRT we can expect to achieve this improved pelvic control with certainly no more, and likely less toxicity than reported from the Egyptian and European experiences. (Baumann) The Cairo group has in April 2013 published the results of their pre versus postop randomized phase III radiotherapy trial demonstrating very low rates of gastrointestinal and surgical serious toxicity with 50Gy/25 fractions with non IMRT radiotherapy. Stringent collection of all serious bowel toxicity encountered will be buttressed by well-defined stopping rules to ensure that we identify any clinically significant increase in bowel toxicity that requires surgical correction. There is a limited USC experience with pelvic radiotherapy in patients who have neobladders demonstrating its safety in ten patients (Ballas 2015). Three patients had Grade 1 or 2 acute (diarrhea , proctitis, rectal discomfort) and no patients had chronic GI toxicity. No patient had acute, and two patients had grade 1 chronic “GU” toxicity (mild nocturnal incontinence, some diminished pouch capacity). A larger neobladder irradiation experience from France again demonstrating the safety of neobladder irradiation has not yet been published (Sargos, personal communication). Thus we will include patients who, following cystectomy, have non-continent diversions (eg, ileal conduits) or continent non-orthotopic catheterizable diversions (eg, Indiana pouch) or continent orthotopic diversions (eg, Studer pouch or neobladder). Potential neobladder irradiation toxicity will be closely monitored.

To reconcile the concept of studying radiotherapy in only those patients who have had the ideal operation (minimum of ten removed nodes and negative margins) with the reality that for 55% of patients these specifics have not been attained with the surgery performed currently in North America (AUA 2012), we will study all radical cystectomy pT3/T4 patients and stratify according to intermediate and high risk failure grouping. In a similar vein, we will utilize a pragmatic approach to the issue of adjuvant and neoadjuvant chemotherapy balancing the facts that only 8% of patients get neoadjuvant chemotherapy, the strong conviction that patients should be considered for postop adjuvant chemotherapy, the clinical reality that a substantial proportion of patients get neither neoadjuvant nor adjuvant chemotherapy, and finally that when adjuvant chemotherapy is used it is the uniform perspective that it should precede any consideration of adjuvant radiation. The lack of impact of chemotherapy on pelvic recurrence makes the issue more of the impact on patient

selection and radiotherapy efficacy that the administration of adjuvant chemotherapy introduces. Specifically, randomization before chemotherapy will likely result in a proportion of patients not getting the assigned adjuvant radiotherapy because of chemotherapy toxicity, overall treatment, fatigue and early manifestation of some of the 30% of pelvic recurrences that occur within 6 months of cystectomy. Thus we will register trial eligible patients within 105 days post cystectomy and randomize regarding adjuvant radiotherapy at that time for patients not getting chemotherapy, but delay that randomization until after chemotherapy in patients so treated. However, the pelvic relapse data will be collected in all registered patients. This approach to dealing with issues of the surgical quality and chemotherapy grounds the study in the reality of contemporary North American management of locally advanced bladder cancer and allows the asking of whether adjuvant radiotherapy can usefully help the pelvic recurrence problem.

Given that patients with locally advanced cancer have a high rate of systemic metastases, it is important to determine the impact of pelvic radiotherapy not only on pelvic relapse but also on overall disease-free survival. We will thus be powering the study looking for a 10% increase in DFS, the signal that will warrant proceeding to a confirmatory phase III trial. We will proceed to this phase III trial only if our primary pelvic failure and secondary DFS endpoints are met with acceptable toxicity.

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Biostatistical/Data Management Center (via the contact list on the NRG web site). For radiation therapy-related eligibility questions, please contact IROC Philadelphia RT (via the contact list on the NRG web site).

3.1 PATIENT SELECTION GUIDELINES

Although the guidelines provided below are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

- 3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.
- 3.1.2 Women of childbearing potential and men who are sexually active should be willing and able to use medically acceptable forms of contraception during therapy.

3.2 ELIGIBILITY CRITERIA (6/13/16)

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

Prior to Step 1 Registration

- 3.2.1 Initial histological diagnosis of muscle invasive urothelial carcinoma
- 3.2.2 Patients must have undergone a radical cystectomy (reconstructed urinary diversion may be non-continent diversions (eg, ileal conduits) or continent non-orthotopic catheterizable diversions (eg, Indiana pouch) or continent orthotopic diversions (eg, Studer pouch or

neobladder) for urothelial bladder carcinoma within 105 days prior to registration. Final cystectomy pathology must be either pure urothelial carcinoma or dominant urothelial carcinoma with admixture of other histologies excluding small cell variants.

- Neoadjuvant (preoperative) or adjuvant (postoperative) chemotherapy for the bladder cancer is permitted; however, all patients, even those who will receive adjuvant chemotherapy, must be registered within 105 days after completing cystectomy regardless of whether adjuvant chemotherapy has started. Patients who will be receiving adjuvant (postoperative) chemotherapy will be randomized within 28 days of completing that chemotherapy.

3.2.3 Patients with the following pTNM stages per the AJCC 7th ed. are eligible: (8/7/15)

1. pT3apN0;pN1;pN2 provided less than 10 nodes dissected and/or positive surgical margins
2. pT3bpN0;pN1;pN2
3. pT4apN0;pN1;pN2
4. pT4bpN0;pN1;pN2

3.2.4 Appropriate stage for study entry based on the following diagnostic workup:

- History/physical examination ≤ 45 days prior to registration;
- CT or MRI or PET-CT that includes chest, abdomen and pelvis should be performed for initial radiological staging. This may be performed pre- or post-surgery ≤ 90 days prior to registration except in patients getting postoperative adjuvant chemotherapy, who will require CT, MRI or PET-CT including the chest and abdomen and pelvis no more than 30 days prior to registration. Imaging performed postoperatively should show no evidence of residual disease.

3.2.5 Age ≥ 18

3.2.6 Zubrod Performance Status 0-2 ≤ 45 days prior to registration

3.2.7 CBC/differential obtained ≤ 14 days prior to registration with adequate bone marrow function defined as follows:

- Absolute neutrophil count (ANC) $\geq 1,500$ cells/mm³
- Platelets $\geq 100,000$ cells/mm³
- Hemoglobin ≥ 8.0 g/dl (NOTE: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.)

3.2.8 The patient must provide study-specific informed consent prior to study entry.

3.3 INELIGIBILITY CRITERIA (6/13/16)

Patients with any of the following conditions are NOT eligible for this study.

3.3.1 Definitive clinical or radiologic evidence of metastatic disease; pN3 disease is not allowed (positive common iliac node).

3.3.2 Prior invasive solid tumor or hematological malignancy (except non-melanomatous skin cancer and incidentally discovered prostate cancer at time of cystoprostatectomy) unless disease free for a minimum of 3 years

3.3.3 Prior radiotherapy to the pelvis

3.3.4 Patients with a history of inflammatory bowel disease

3.3.5 Patients who have required any treatment (medical or surgical) for bowel obstruction prior to diagnosis of bladder cancer or who have required surgical treatment for bowel obstruction after the cystectomy

3.3.6 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;
- Severe hepatic disease, defined as a diagnosis of Child-Pugh Class B or C hepatic disease;
- HIV positive with CD4 count < 200 cells/microliter. Note that patients who are HIV positive are eligible, provided they are under treatment with highly active antiretroviral therapy (HAART) and have a CD4 count \geq 200 cells/microliter within 30 days prior to registration. Note also that HIV testing is not required for eligibility for this protocol.
- Other major medical illness which requires hospitalization or precludes study therapy at the time of registration.

3.3.7 Women who are breastfeeding

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP
(6/13/16)

| PRE-TREATMENT ASSESSMENTS | | |
|--|---|---|
| Assessments | Prior to Registration STEP 1 (calendar days) | Prior to Randomization STEP 2 (calendar days) |
| Radical cystectomy | ≤105 days | |
| History/physical exam | ≤45 days | |
| CT or MRI or PET-CT chest, abdomen and pelvis | For patients not receiving adjuvant chemotherapy: Pre- or post-surgery ≤ 90 days For patients receiving adjuvant chemotherapy: One of these scans must be done within 30 days prior to registration showing no evidence of residual disease | |
| Zubrod performance status | ≤45 days | In patients getting postoperative chemotherapy ≤28 days* |
| CBC w/ diff | ≤14 days | |
| Informed consent | Prior to registration | |
| *Prior to randomization these patients need to be reassessed to ensure they meet the criteria to proceed to randomization and have recovered from chemotherapy in that their blood work and performance status meet the criteria specified in Sections 3.2.6 and 3.2.7 . | | |

| ASSESSMENTS DURING TREATMENT | |
|--|------------------|
| Assessments | |
| Pertinent history and physical exam | Weekly during RT |
| CBC w/ diff See Section 6 for dose modifications. | |
| CTCAE toxicity evaluation | |
| | |

| ASSESSMENTS IN FOLLOW UP | |
|---|---|
| Assessments | Arm 1: From randomization Arm 2: From end of radiotherapy |
| History and physical* *NOTE: Follow up assessments may be performed by a radiation, urological, or medical oncologist. As possible radiation toxicity is being evaluated the involvement of a radiation oncologist is encouraged. CTCAE toxicity evaluation | 6 weeks after randomization (Arm 1) -OR- 6 weeks after end of RT (Arm 2) Then q3 months x 1 year, q4 months during year 2, then q6 months x 3 years. Then annually for years 5-10; also at progression/relapse (Arms 1 and 2) |
| Abdominal and pelvic CT or MRI or PET-CT | q6 months for 3 years and subsequently at progression/relapse and physician discretion |
| Chest imaging with Chest x-ray, CT or PET-CT | q6 months for 3 years and subsequently at progression/relapse and physician discretion |

4.1 Definition of Disease Assessment

Pelvic recurrence is defined as soft tissue tumor recurrence in the pelvis anywhere between the L5-S1 disc space superiorly and the pelvic floor inferiorly, taking into account distant metastases or death as competing risks.

5. TREATMENT PLAN/REGIMEN DESCRIPTION (6/13/16)

All eligible patients will be registered within 105 days of undergoing cystectomy. Patients not receiving postoperative adjuvant chemotherapy will be randomized within 14 days of

registration to the standard arm of no further treatment (Arm 1) or the investigational arm of pelvic radiotherapy (Arm 2). Patients who do receive postoperative adjuvant chemotherapy will be randomized between these same two arms within 28 days after completion of the chemotherapy.

- 5.1** All patients will undergo a radical cystectomy (reconstructed urinary diversion may be non-continent diversions (eg, ileal conduits) or continent non-orthotopic catheterizable diversions (eg, Indiana pouch) or continent orthotopic diversions (eg, Studer pouch or neobladder) and at least a standard pelvic node dissection as follows: All potential lymph node bearing tissue to include a complete dissection of the external and internal iliac and obturator lymph nodes. All potential node bearing tissue should be removed within the following boundaries: laterally the genitofemoral nerve; distally Cooper's ligament to include the lymph node of Cloquet; proximally the common iliac (CI) bifurcation; medially the bladder to include the tissue medial to the hypogastric artery; and posteriorly the floor of the obturator fossa with circumferential mobilization of the external iliac artery and vein unless contraindicated due to extensive atherosclerotic vascular disease. Of note, a more extensive pelvic lymph node dissection is allowed. A standard pelvic node dissection as described above represents a minimum requirement. (6/13/16)

- 5.1.1** No concurrent chemoradiation: Some patients may get 2-4 cycles of postoperative adjuvant chemotherapy, in which case radiotherapy will start within 49 days after the chemotherapy is completed, patients have recovered, and provided there is no recurrence of the cancer.

5.2 Radiation Therapy (6/13/16)

For patients on Arm 2, radiation therapy must begin within 21 days after randomization.

NOTE 1: IMRT is required for this protocol. In patients not getting postoperative adjuvant chemotherapy the radiation treatment must begin within 140 days after cystectomy. For patients getting adjuvant chemotherapy radiation treatment must start within 49 days of completing chemotherapy.

NOTE 2: Pre-Treatment reviews are required for the first case for an individual site. Based on the results of this case review, the reviewers might request that the second case also be selected for pre-treatment review. Please allow 3 business days for this to be completed. If a resubmission is required the 3 business day timeline will restart. Treatment cannot begin until approval from NRG Oncology has been received at the site.

5.2.1 Treatment Technology (8/7/15)

Photon IMRT with megavoltage equipment capable of delivering static intensity modulation with a multileaf collimator or dynamic intensity modulation using a multileaf collimator or tomotherapy is required. IMRT should utilize six or more fields with a minimum source-axis distance of 100cm except in the case of tomotherapy that uses 85cm or CyberKnife that uses 80 cm. 6-10 MV energy photon beams should be used. VMAT is allowed. Protons are not allowed.

5.2.2 Immobilization and Simulation (8/7/15)

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 torso cradles and/or leg immobilizers.

Simulation Imaging

Patients must be immobilized in the supine position.

To better visualize the pelvic vasculature, IV contrast is recommended but not required since some patients may have renal insufficiency. To better delineate the urinary diversion, oral or rectal contrast may be injected into the diversion, but this is also not required.

CT scan thickness should be $\leq 3\text{mm}$ 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.

5.2.3 Imaging for Structure Definition, Image Registration/Fusion, and Follow-up (8/7/15)

CT simulation scans with or without intravenous or bowel contrast as described above. In the case in which contrast is present in the treatment planning CT, the density of the contrast should be overridden to a representative background electron density.

5.2.4 Definition of Target Volumes and Margins (8/7/15)

NOTE: All structures must be named for digital RT data submission as listed in the table below. The structures marked as “Required” in the table must be contoured and submitted with the treatment plan. Structures marked as “Required when applicable” must be contoured and submitted when applicable. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing, and use of underscores must be applied exactly as indicated.

The target volume in patients with positive surgical margins is the cystectomy bed and the pelvic lymph nodes. In patients with negative surgical margins, the target volume is the pelvic lymph nodes alone. The cystectomy bed is omitted in patients with negative margins because the risk of cystectomy bed failure is significantly reduced.

| Standard Name | Description | Validation |
|---------------|--|---|
| CTV_5040 | CTV_5040 will only include the pelvic lymph nodes in patients with negative surgical margins and will include the pelvic lymph nodes plus the cystectomy bed in patients with positive surgical margins. | Required |
| CTVn_5040 | The Nodal_CTV includes the presacral nodes and the bilateral distal common iliac, external iliac, internal iliac, and obturator nodes and can be created from the union of three sub-structures: sacral_nodes, iliac_nodes, and obturator_nodes. | Required |
| CTVsb_5040 | The cystectomy bed CTV is intended to include tissue in the pelvis that surrounded the intact empty bladder and proximal vagina or prostate preoperatively, and the surgical cystectomy bed including the anterolateral para-rectal tissues. | Required only for patients with positive surgical margins. |
| PTV_5040 | PTV to receive 5040 cGy will be a symmetrical expansion of 7.0 mm beyond the CTV_5040 | Required |

Detailed Specifications

CTV_5040:

The CTV_5040 will only include the pelvic lymph nodes (CTVn_5040) in patients with negative surgical margins and will include the pelvic lymph nodes (CTVn_5040) plus the cystectomy bed (CTVsb_5040) in patients with positive surgical margins.

CTVn_5040:

The CTVn_5040 includes the presacral nodes and the bilateral distal common iliac, external iliac, internal iliac, and obturator nodes and can be created from the union of three sub-structures: sacral_nodes, iliac_nodes, and obturator_nodes. The presacral_nodes will extend from L5-S1 to the top of S3 and will include 1.0 – 1.5 cm of tissue anterior to the sacrum and between the vessel contours. The iliac_nodes will be derived by contouring the common iliac, external and internal iliac vessels starting superiorly at L5-S1. The external iliac vessels will be contoured inferiorly to the top of the femoral heads and the internal iliac vessels will be contoured inferiorly until they are no longer visible on the CT scan or exit through the true pelvis via the greater sciatic notch. The iliac_nodes will be created by expanding the iliac vessels by 7 mm in the anterior, posterior and lateral dimensions, but not the superior and inferior dimensions. The obturator_nodes will encompass 1.0 cm width of tissue medial to the obturator internus muscles extending from the anterior border of the ilium to the posterior border of the ilium. The obturator_nodes will be contoured starting superiorly where the internal and external iliac vessel contours stop and extend inferiorly to the top of the symphysis pubis. The CTVn_5040 should be created from the union of the sacral_nodes, iliac_nodes, and obturator_nodes, but should be trimmed to not extend outside the true pelvis, nor into muscle or bone. See Figures 1 and 2.

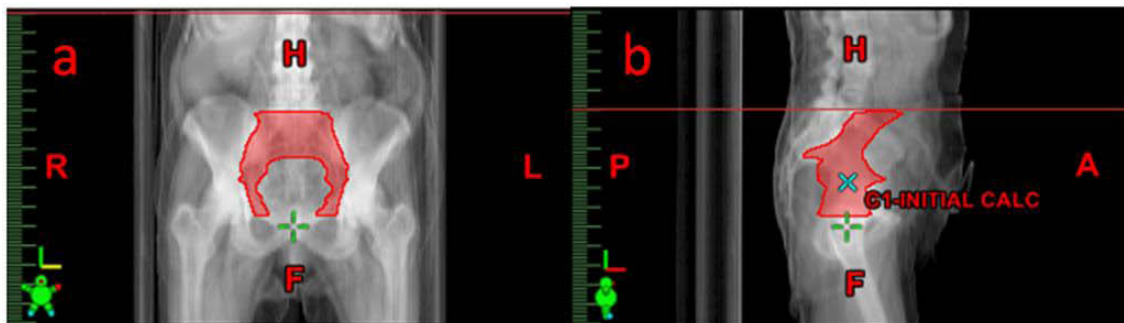


Figure 1. Anterior-posterior (a) and lateral projections of the Nodal_CTV.

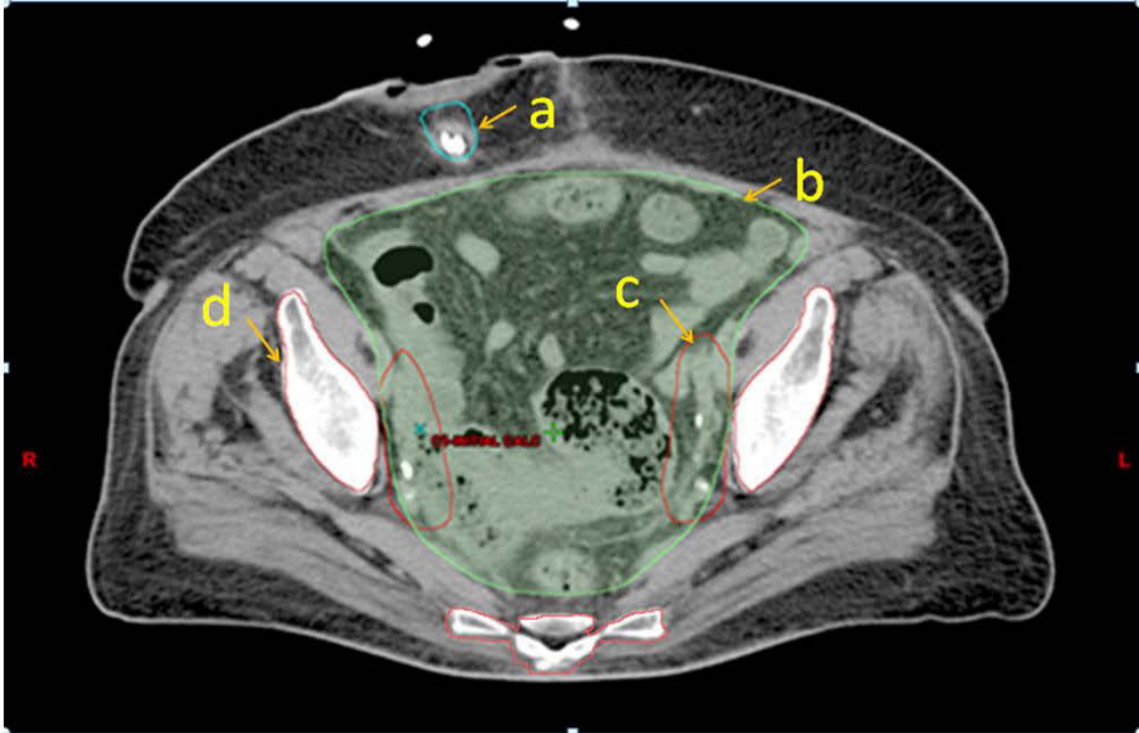


Figure 2. A representative axial CT slice showing the Urinary diversion (a), Bowel space (b), Nodal CTV (c) and Pelvic bones (d) contours.

Cystectomy bed CTV (CTVsb_5040):

The cystectomy bed CTV is intended to include tissue in the pelvis that surrounded the intact empty bladder and proximal vagina or prostate preoperatively, and the surgical cystectomy bed including the anterolateral para-rectal tissues. These contours do not intentionally include or exclude surgical clips. In addition, small bowel should not be carved out of the CTV. See Table below for anatomical borders of the cystectomy bed clinical target volume.

| Table 1. Anatomical borders of the cystectomy bed clinical target volume | |
|---|---|
| Superior | The contour will extend 2 cm superior to the superior aspect of the pubic symphysis. |
| Anterior | The contour will extend to the posterior aspect of the pubic rami/symphysis. Above and below the pubic symphysis, the contour will stop anteriorly at the planes defined by extending lines superiorly (Plane 1 in Figures 3 and 4) and inferiorly (Plane 2 in Figures 3 and 4) from the posterior aspect of the symphysis. |
| Posterior | The contours will about the anterior one-third of the external ano-rectal circumference without extending into the ano-rectum. Above the level of the rectum, the contour will stop posteriorly at the plane defined by extending a line superior from the anterior border of the rectum (Plane 3 in Figures 3 and 4). |
| Lateral | The contour will extend to the medial border of the obturator internus muscles bilaterally. Inferior to the obturator internus muscles, the lateral border of the contour will extend to the vaginal wall or the prostate bed. |
| Inferior | The contour will stop 2-3mm (1 CT slice on axial images) above the penile bulb for males and 1 cm below the lower pole of the obturator foramen for females. |

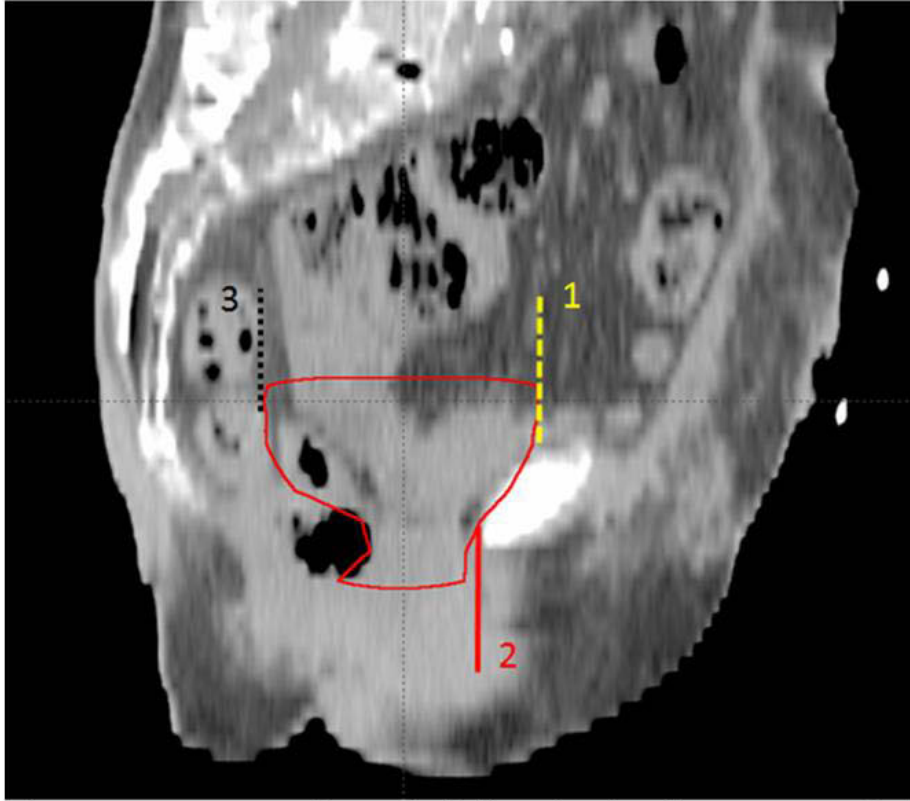


Figure 3. A representative sagittal slice showing the cystectomy bed on a female patient. Above and below the pubic symphysis, the cystectomy bed contour will stop anteriorly at the planes defined by extending lines superior (Plane 1) and inferior from the anterior border (plane 2). Above the level of the rectum, the contour will stop posteriorly at the plane defined by extending a line superior from the anterior border of the rectum (plane 3).

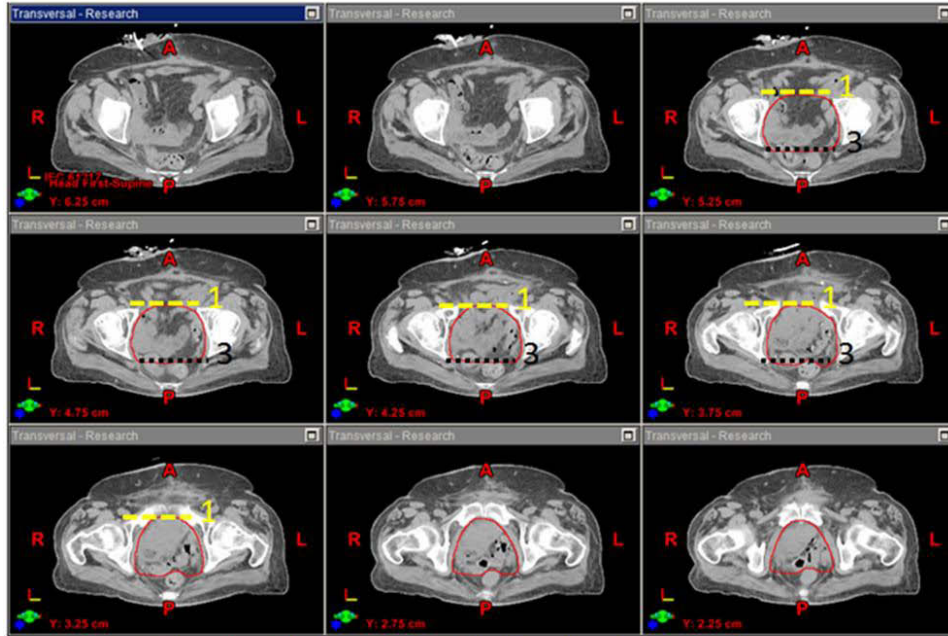


Figure 4a. Representative axial slices showing the cystectomy bed on the upper pelvis of a female patient. Above and below the pubic symphysis, the cystectomy bed contour will stop anteriorly at the planes defined by extending lines superior (Plane 1) and inferior from the anterior border (plane 2). Above the level of the rectum, the contour will stop posteriorly at the plane defined by extending a line superior from the anterior border of the rectum (plane 3).

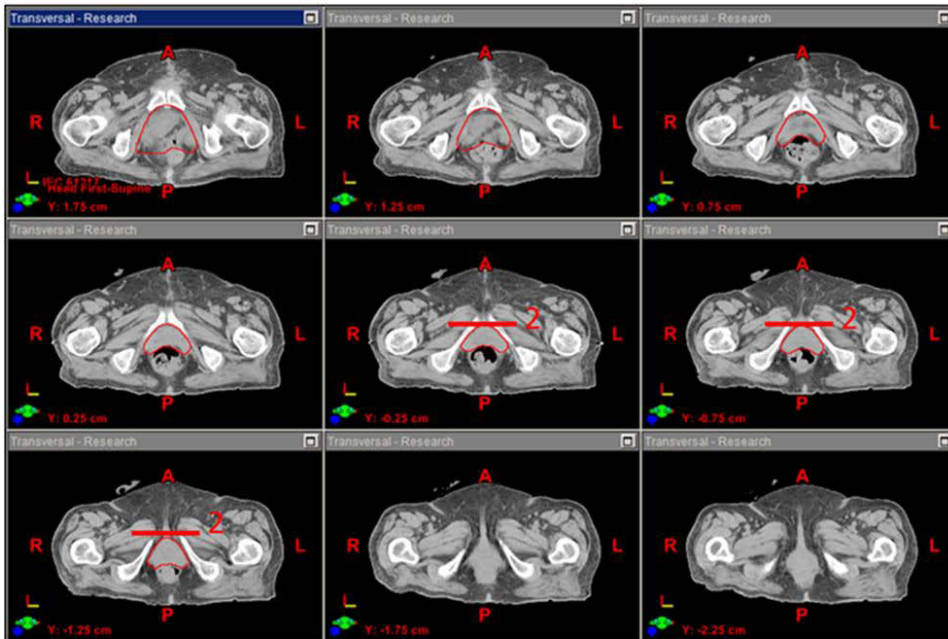


Figure 4b. Representative axial slices showing the cystectomy bed on the lower pelvis of a female patient. Above and below the pubic symphysis, the cystectomy bed contour will stop anteriorly at the planes defined by extending lines superior (Plane 1) and inferior from the anterior border (plane 2). Above the level of the rectum, the contour will stop posteriorly at the plane defined by extending a line superior from the anterior border of the rectum (plane 3).

PTV_5040: The PTV will be a direct expansion of 7.0 mm beyond the CTV_5040.

5.2.5 Definition of Critical Structures and Margins (6/13/16)

NOTE: All structures must be named for digital RT data submission as listed in the table below. The structures marked as “Required” in the table must be contoured and submitted with the treatment plan. Structures marked as “Required when applicable” must be contoured and submitted when applicable. Resubmission of data will be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing, and use of underscores must be applied exactly as indicated.

| Standard Name | Description | Validation |
|----------------------|---|-------------------|
| BowelSpace | Bowel space will include the small bowel, cecum, ascending colon, transverse colon and sigmoid colon in one bowel bag contour | Required |
| Rectum | Rectum | Required |
| Bone_Pelvic | Pelvic bones near PTV | Required |
| UreterDivert | See description below | Required |
| Bag_Ostomy | External ostomy bag | Optional |

Detailed Specifications

BowelSpace:

Superiorly, the Bowel_space contour will start 3 cm above the superior extent of the CTVn_5040. Inferiorly, the contour will be discontinued on the CT slice where no portion of small bowel or colon is visible. The contours will include the volume

surrounding loops of bowel out to the edge of the peritoneum as bowel may occupy this space at any time during the course of treatment. BowelSpace will include the entire small bowel, cecum, ascending colon, transverse colon and sigmoid colon in one bowel bag contour. See Figure 2.

Rectum:

The Rectum contour will include the rectum and anal canal and will be contoured on every slice from the rectosigmoid junction superiorly to the level of the ischial tuberosities inferiorly.

Bone_Pelvic:

A structure named Bone_Pelvic will be created to track radiation plan parameters that may be associated with changes in bone marrow reserve or insufficiency fractions. It is recommended that hot spots be avoided in the Bone_Pelvic when possible. Contour the pelvic bones starting superiorly 1 cm above the superior extent of the CTVn_5040 extending inferiorly to 1 cm inferior to the inferior limit of the CTVsb_5040. The pelvic bones can be auto-contoured using a CT density-based algorithm. See Figure 2.

UreterDivert:

It is recommended that the urinary diversion be contoured so treatment planners can avoid bringing beams directly through this structure when possible. Determining which tissues are included in the UreterDivert contour depends on the type of diversion that the patient has had. If the patient has had a non-continent diversion with a bowel conduit (e.g. ileal conduit), the contour will include the stoma and the visible portion of the bowel conduit. If the patient has had a continent non-orthotopic catheterizable diversion (e.g. Indiana pouch), the contour will include the stoma, bowel conduit and internal urine reservoir. If the patient has had a continent orthotopic diversion (e.g. Studer pouch or neobladder), the contour will include the bowel reservoir. For some patients, some of the tissues of the urinary diversion may not be fully captured in the CT simulation so only a portion will be contoured.

Bag_Ostomy:

For patients who have had a non-continent urinary diversion, it is recommended that the external ostomy bag be contoured so treatment planners can avoid bringing beams directly through this structure when possible. Bag_Ostomy structure should be created by contouring the entire external urine reservoir that is visible on the CT simulation.

5.2.6 Dose Prescription

NOTE: The information provided in this section can be used for adjusting the dose constraints for treatment planning purposes. This table together with the planning priority table should be used during dose optimization. It is important to remember that ideal plans might not be achievable in all cases. Thus, the Compliance Criteria table could be different than the information given here. Cases will be scored using the Compliance Criteria table.

| Target Standard Name | Dose (Gy) | Fraction Size (Gy) | # of fractions | Dose Specification |
|----------------------|-----------|--------------------|----------------|--------------------|
|----------------------|-----------|--------------------|----------------|--------------------|

| | | | | Technique |
|----------|------|-----|----|--|
| PTV_5040 | 50.4 | 1.8 | 28 | 97% of the PTV will receive 50.4Gy in 28 fractions |

5.2.7 Compliance Criteria (6/13/16)

The compliance criteria listed here will be used to score each case. Given the limitations inherent in the treatment planning process, the numbers given in this section can be different than the prescription table. The *Per Protocol* and *Variation Acceptable* categories are both considered to be acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results. A final category, called *Deviation Unacceptable*, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal and additional treatment planning optimization is recommended.

Normalization of Dose: The plan is normalized such that 97% of the PTV_5040 volume receives prescription dose of 50.4 Gy.

NOTE: Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met.

Target Volume Constraints and Compliance Criteria

| Name of Structure | Dosimetric Parameter | Per Protocol | Variation Acceptable |
|-------------------|-----------------------|--------------|----------------------|
| PTV_5040 | D _{97%} (Gy) | 50.4 | 49 to 52 |
| | D _{min} (Gy) | >48 | 46 to 48 |
| | D _{max} (Gy) | <56 | 56 to 58 |

Per protocol range is excluded from that of variation acceptable

Normal Structure Constraints and Compliance Criteria

| Name of Structure | Dosimetric Parameter | Per Protocol | Variation Acceptable |
|-------------------|-----------------------|--------------|----------------------|
| BowelSpace | V _{40Gy} (%) | <30 | 30 to 50 |
| Rectum | V _{45Gy} (%) | <70 | 70 to 80 |

Recommended dose acceptance criteria for other normal tissue, but not to be used for plan score.

| Structure | Recommended dose acceptance criteria |
|-------------|--------------------------------------|
| Bone_Pelvic | Per protocol: V15Gy < 90% |

Delivery Compliance Criteria

| | Per Protocol | Variation Acceptable |
|------------------------|---------------------|-----------------------------------|
| Overall Treatment Time | 44 days | ≥ 45 days and ≤ 58 days |
| Interruptions | 1 to 7 days | ≥ 8 days and ≤ 14 days |

5.2.8 Treatment Planning Priorities and Instructions (8/7/15)

Critical Structure and Target priorities must be listed in order of decreasing importance.

1. BowelSpace
2. PTV_5040
3. Rectum
4. Bone_Pelvic

5.2.9 Dose Calculations (8/7/15)

Required Algorithms

Acceptable choices of algorithm are listed at:

[http://irochouston.mdanderson.org/rpc/Services/Anthropomorphic %20Phantoms/TPS%20-%20algorithm%20list%20updated.pdf](http://irochouston.mdanderson.org/rpc/Services/Anthropomorphic_%20Phantoms/TPS%20-%20algorithm%20list%20updated.pdf). Any dose calculation algorithm used for this study must be listed as one of the acceptable algorithms by IROC Houston.

Primary Dataset for Dose Calculation

The primary dataset for dose calculation must be a free breathing CT without contrast. In the case in which contrast is present in the treatment planning CT, the density of the contrast should be overridden to a representative background electron density.

Dose Matrix Resolution

Dose grid size should be ≤ 3 mm in all directions.

5.2.10 Daily Treatment Localization/IGRT

Daily IGRT images should be obtained to ensure proper alignment of the isocenter of the simulated fields. These IGRT images may include 1) CBCT with Megavoltage (MV) or kilovoltage (kV) x-ray; or 2) paired kV 2D images.

5.3 **General Concomitant Medication and Supportive Care Guidelines**

The two likely side effects during radiotherapy are radiation enteritis (small bowel/rectum) and perineal skin reaction. Enteritis manifesting as diarrhea may be treated with antidiarrheals such as Imodium and Lomotil. Enteritis manifesting as ileus or bowel obstruction will require strong consideration of radiotherapy interruption and/or stoppage with other supportive measures as required. Skin toxicity can be managed with topical application of barrier or steroid creams.

5.3.1 Permitted Supportive/Ancillary Care and Concomitant Medications

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

- Antiemetics
- Anticoagulants
- Antidiarrheals

- Analgesics
- Hematopoietic Growth Factors
- Nutritional supplementation

5.4 Duration of Therapy (6/13/16)

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression;
- Intercurrent illness that prevents further administration of treatment;
- Unacceptable adverse event(s), including the following:
 - CTCAE Grade 2-4 bowel obstruction during the course of radiation treatment
 - CTCAE Grade 2-4 neutropenia, thrombocytopenia, or anemia during the course of radiation treatment that involves more than a 3-week interruption of radiotherapy;
 - Any grade AE that requires surgical intervention or revision of the neobladder
- Patient declines further treatment as per study protocol; or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6. TREATMENT MODIFICATIONS/MANAGEMENT

Patients who develop CTCAE Grade 2-4 small and/or large bowel obstruction during the course of radiation treatments must have the radiotherapy stopped and NOT resumed. Patients who develop CTCAE Grade 2-4 neutrophil and/or platelet hematological toxicity should have the radiotherapy held till parameters recover to the following values:

- Absolute neutrophil count (ANC) $\geq 1,500$ cells/mm³
- Platelets $\geq 100,000$ cells/mm³

If this involves more than a 3-week interruption radiotherapy should be stopped.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Adverse Events

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 for adverse event (AE) reporting. The CTCAE version 4 is identified and located on the CTEP web site at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.

Adverse events (AEs) that meet expedited reporting criteria defined in the table(s) below will be reported via the CTEP Adverse Event Reporting System (CTEP-AERS) application accessed via the CTEP web site (<https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1389817585865>).

7.1.1 Adverse Events (AEs)

Definition of an AE: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal

(investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements.; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm]

7.1.2 Serious Adverse Events (SAEs) — Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in [Section 7.2](#) will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in [Section 7.2](#). **Contact the CTEP-AERS Help Desk if assistance is required.**

Definition of an SAE: Any adverse drug event (experience) occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- Important medical events (IME) that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

7.1.3 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

AML or MDS that is diagnosed as a secondary malignancy during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system within 30 days of AML/MDS diagnosis.

Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

7.2 CTEP-AERS Adverse Event Reporting Requirements

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the CTEP Adverse Event Reporting System, accessed via the CTEP web site, <https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1389817585865>.

Submitting a report via CTEP-AERS serves as notification to NRG Oncology and satisfies NRG requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Oncology Office at 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

- CTEP-AERS-24 Hour Notification requires that a CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a CTEP-AERS 5 Calendar Day Report. Serious adverse events that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below.
- Supporting source document is not mandatory. However, if the CTEP-AERS report indicates in the *Additional Information* section that source documentation will be provided, then it is expected. If supporting source documentation accompanies a CTEP-AERS report, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation **to the NRG Oncology dedicated SAE FAX, 215-717-0990**.
- A serious adverse event that meets expedited reporting criteria outlined in the following table but is assessed by the CTEP-AERS System as “expedited reporting NOT required” must still be reported to fulfill NRG Oncology safety reporting obligations. Sites must bypass the “NOT Required” assessment; the CTEP-AERS System allows submission of all reports regardless of the results of the assessment.

CTEP defines expedited AE reporting requirements for phase 2 and 3 trials as described in the table below. **Important:** All AEs reported via CTEP-AERS also must be reported on the AE section of the appropriate case report form (see [Section 15.2](#)).

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur within 30 Days of the Last Administration of the Intervention^{1, 2}

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

- 1) Death
- 2) A life-threatening adverse event
- 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for \geq 24 hours
- 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- 5) A congenital anomaly/birth defect.
- 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

| Hospitalization | Grade 1 Timeframes | Grade 2 Timeframes | Grade 3 Timeframes | Grade 4 & 5 Timeframes |
|--|--------------------|--------------------|--------------------|-------------------------|
| Resulting in Hospitalization \geq 24 hrs | 10 Calendar Days | | | 24-Hour 5 Calendar Days |
| Not resulting in Hospitalization \geq 24 hrs | Not required | | 10 Calendar Days | |

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- “24-Hour; 5 Calendar Days” - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- “10 Calendar Days” - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

¹Serious adverse events that occur more than 30 days after the last administration of commercially available agent /intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

² For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.

Effective Date: May 5, 2011

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials

For Arm 1, expedited adverse event reporting is not applicable; routine adverse event reporting on the case report form fulfills safety reporting requirements for all adverse events.

8. REGISTRATION, STUDY ENTRY, AND WITHDRAWAL PROCEDURES

Access requirements for OPEN, Medidata Rave, and TRIAD

Site staff will need to be registered with CTEP and have a valid and active CTEP Identity and Access Management (IAM) account.

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials). Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures below for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at http://ctep.cancer.gov/branches/pmb/associate_registration.htm. For questions, please contact the CTEP Associate Registration Help Desk by email at ctepreghelp@ctep.nci.nih.gov.

8.1 Investigator Registration Requirements

8.1.1 Prior to the recruitment of a patient for this study, investigators must be registered members of a Lead Protocol Organization. Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually. Registration requires the submission of:

- a completed **Statement of Investigator Form** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed **Supplemental Investigator Data Form** (IDF)
- a completed **Financial Disclosure Form** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at http://ctep.cancer.gov/investigatorResources/investigator_registration.htm. For questions, please contact the CTEP Investigator Registration Help Desk by email at pmbregpend@ctep.nci.nih.gov.

8.2 Site Registration Requirements

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering credentials at <https://www.ctsuo.org>. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Sites participating in the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing, or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

Downloading Site Registration Documents

Site registration forms may be downloaded from the NRG-GU001 protocol page located on the CTSU members' website.

- Go to <https://www.ctsuo.org> and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the NRG Oncology link to expand, then select trial protocol NRG-GU001
- Click on the Site Registration Documents link

Requirements for NRG-GU001 Site Registration

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)
- IRB Approval Letter (for sites not participating via the NCI CIRB)
- IRB/REB Approved Informed Consent (English and native language versions*)
***NOTE:** Institutions must provide certification/verification of IRB/REB consent translation to NRG Headquarters (described below).
- IRB/REB registration number renewal information as appropriate.
- CTSU RT Facilities Inventory Form
NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Imaging and Radiation Oncology Core (IROC) Houston QA program. If this form has been previously

submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

Submitting Regulatory Documents

Submit completed forms along with a copy of your IRB Approval and Informed Consent to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

Checking Your Site's Registration Status

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (NOTE: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to <https://www.ctsu.org> and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Non-English Speaking Canadian and International Institutions:

Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

8.2.1 Pre-Registration Requirements FOR INTERNATIONAL INSTITUTIONS (8/7/15)

*For institutions that **do not have an approved LOI** for this protocol:*

International sites must submit an LOI to NRG Headquarters to receive approval to participate in this trial. For more details see link below:
<http://www.rtog.org/Researchers/InternationalMembers/LetterofIntent.aspx>.

*For institutions that **have an approved LOI** for this protocol:*

All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

8.3 RT-Specific Pre-Registration Requirements

For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. Specific credentialing components may require you to work with various QA centers; however, the Imaging and Radiation Oncology Core (IROC) Houston will notify your institution when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study.

| RT Credentialing Requirements | Web Link for Procedures and Instructions: http://irochouston.mdanderson.org | |
|---|---|--|
| | Treatment Modality | Key Information |
| | IMRT | |
| Facility Questionnaire | X | The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ go to http://irochouston.mdanderson.org/questionnaires |
| Credentialing Status Inquiry Form | X | To determine whether your institution needs to complete any further credentialing requirements, please complete the “Credentialing Status Inquiry Form” found under credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org) |
| Phantom Irradiation | X | An IROC Houston anthropomorphic phantom must be successfully completed (if the institution has not previously met this credentialing requirement). Instructions for requesting and irradiating the phantom are available on the IROC Houston website (http://irochouston.mdanderson.org) |
| Pre-Treatment Review | X | For the first case for an individual site. Based on the results of this case review, the reviewers might request that the second case also be selected for pre-treatment review. Patient cases must be submitted through TRIAD and a DDSI form must be completed. Please allow 3 business days for this to be completed. If a resubmission is required the 3 business day timeline will restart. Treatment cannot begin until approval from NRG Oncology has been issued to the institution. |
| Credentialing Issued to: | | |
| Institution | X | IROC Houston QA Center will notify the institution and NRG Headquarters that all desired credentialing requirements have been met. |

8.3.1 Digital RT Data Submission to NRG Oncology Using TRIAD

TRIAD is the image exchange application used by NRG Oncology. TRIAD provides sites participating in NRG clinical trials a secure method to transmit

DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements

- Site physics staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to the beginning of Section 8 for instructions on how to request a CTEP-IAM account.
- To submit images, the site physics user must have been assigned the 'TRIAD site user' role on the relevant Group or CTSU roster. NRG users should contact your site Lead RA to be added to your site roster. Users from other cooperative groups should follow their procedures for assignment of roster roles.
- RAs are able to submit standard of care imaging through the same method.

TRIAD Installations

When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found on the NRG Oncology website Core Lab tab.

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

8.4 Patient Enrollment

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

8.4.1 Oncology Patient Enrollment Network (OPEN)

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at [< https://eapps-ctep.nci.nih.gov/iam/index.jsp >](https://eapps-ctep.nci.nih.gov/iam/index.jsp)) and a 'Registrar' role on either the LPO or participating organization roster. All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at <https://open.ctsu.org> or from the OPEN tab on the CTSU members' web site <https://www.ctsu.org>.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at <https://www.ctsuo.org> or at <https://open.ctsuo.org>. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsuocontact@westat.com.

In the event that the OPEN system is not accessible, participating sites can contact NRG web support for assistance with web registration: websupport@acr.org or call the NRG Registration Desk at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

9. DRUG INFORMATION

Not applicable for this study.

10. PATHOLOGY/BIOSPECIMEN

Not applicable for this study.

11. SPECIAL STUDIES (NON-TISSUE)

Not applicable for this study.

12. MODALITY REVIEWS

Radiation Therapy Quality Assurance Reviews

One of a 5 person team of radiation oncologists led by the Principal Investigator, Libni Eapen, MD, will perform RT Quality Assurance Reviews after cases enrolled have been received at IROC Philadelphia RT. The first case from each site will have a pre-treatment review and treatment cannot be started until the case is approved. Based on the results of this case review, the reviewers might request that the second case also be selected for pre-treatment review. Three business days are required for this review to be completed once complete data is received. Resubmissions will restart the 3 business day clock. The site will be notified by the Imaging and Radiation Oncology Core (IROC) Philadelphia RT on the status of the review. The RTQA reviews will be ongoing, and will be facilitated by IROC Philadelphia RT.

The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of radiotherapy treatment data as specified in [Section 15.2](#). The scoring mechanism is: Per Protocol, Variation Acceptable, and Deviation Unacceptable.

13. ASSESSMENT OF EFFECT DURING TREATMENT

- 13.1** The assessment of treatment effect is solely related to the documentation of radiation associated toxicity. At each visit the history and physical examination and blood test will document any hematological, GI, GU (genital/urethral), or pelvic soft tissue toxicity.
- 13.2** The following lab tests will be done at each visit: CBC and platelet count.

14. DOCUMENTATION OF CANCER RECURRENCE AND OTHER CANCER EVENTS

- 14.1** At each follow up visit the patient will have a history and physical examination and recent imaging reports will be reviewed to determine the presence of pelvic tumor recurrence, distant metastases, or both.
- 14.2** The following assessments will be done: CT and/or MRI scan of the pelvis will be performed every 6 months after treatment. Additional imaging will be performed as the clinical situation warrants.
- 14.3** Criteria for pelvic recurrence: The primary endpoint is pelvic recurrence, which is defined as any pelvic soft tissue and/or nodal recurrence (measuring at least 1cm in linear dimension) between the L5-S1 interspace and the pelvic floor and/or tumor documented at urethroscopy. Ninety-five percent of the pelvic failures will be demonstrated on pelvic imaging. Biopsy confirmation is NOT required.
- 14.4** Criteria for distant metastases: Distant metastases will be any hematogenous metastases and/or lymph node metastases above the L5-S1 interspace, documented by imaging (CT and/or MRI and/or bone scans).

15. DATA AND RECORDS

15.1 Data Management/Collection

Data collection for this study will be done exclusively through Medidata Rave®. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS (Regulatory Support System). To access iMedidata/Rave, the site user must have an active CTEP-IAM account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization rosters at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata (iMedidata-Notification@mdsol.com) to activate their account. To accept the invitation, site users must log into the Select Login (<https://login.imedidata.com/selectlogin>) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts also will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information

on iMedidata/Rave is available on the CTSU website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctscontact@westat.com.

15.2 Summary of Data Submission (8/7/15)

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See [Section 7](#) for information about expedited and routine reporting.

Summary of Data Submission: Refer to the CTSU members website.

Digital Data Submission Requirements

Summary of Dosimetry Digital Data Submission

Submit Digital RT Data via TRIAD; see [Section 8.3.1](#) for TRIAD account access and installation instructions.

15.3 Global Reporting/Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

16. STATISTICAL CONSIDERATIONS

16.1 Study Design

16.1.1 Stratification

Patients will be stratified before randomization with respect to neoadjuvant/adjuvant chemotherapy (yes vs. no) and pelvic relapse risk category (intermediate vs. high). The administration of even one cycle of chemotherapy will constitute “yes” for either neoadjuvant or adjuvant chemotherapy. The treatment allocation scheme described by Zelen (1974) will be used because it balances patient factors other than institution.

16.1.2 Randomization (8/7/15)

Patients will be randomized in a 1:1 allocation scheme to the standard arm (ARM 1, No RT) or to the experimental arm (ARM 2, Post-op adjuvant IMRT of 50.4 Gy in 28 fractions) after surgery and completion of adjuvant chemotherapy (if given). In patients getting postoperative adjuvant chemotherapy, randomization will occur following completion of the chemotherapy.

16.1.3 Total Accrual

185 patients

16.1.4 Justification of Design

A randomized phase II design is used to isolate the effect of radiation therapy.

16.2 Study Endpoints

16.2.1 Primary Endpoint

Pelvic recurrence-free survival

16.2.2 Secondary Endpoints

Disease-free survival, toxicity

16.3 Primary Objectives Study Design

16.3.1 Primary Hypothesis and Endpoints

Hypothesis: Postoperative adjuvant radiotherapy following radical cystectomy will reduce pelvic recurrence.

Endpoint: Pelvic recurrence-free survival

16.3.2 Definitions of Primary Endpoint and How This Will Be Analyzed

The primary endpoint is pelvic recurrence-free survival (PRFS), defined as time free of pelvic recurrence or death, with patients who experience distant metastasis censored at the time of occurrence. Pelvic recurrence is specifically defined as soft tissue and /or lymph node tumor recurrence in the pelvis anywhere between the L5-S1 disc space superiorly and the pelvic floor inferiorly. This will be determined on the basis of pelvic imaging (CT or MRI scan demonstrating soft tissue or nodal recurrence at least 1cm in linear dimension) or urethroscopy. Biopsy is not required.

For the definitive analysis at the specified event information, IMRT will be tested in terms of a difference in cause-specific-hazards (Kalbfleisch & Prentice 1980; Gaynor et al. 1993) for PRFS using the log-rank test. The cumulative incidence of PRFS in the presence of competing risks will be computed via cumulative incidence curves (Gaynor). We also may test for differences in cumulative incidence of PRFS using Gray's test (Gray 1988), as comparison of both the cause-specific hazards and cumulative incidence is relevant to fully interpreting the potential benefit of the intervention (Freidlin & Korn 2005, Dignam & Kocherginsky 2008). The Cox (1972) proportional hazards model also may be used for multivariable analysis of the PRFS cause-specific hazard including additional covariates such as stratification factors and any other relevant covariates. We may similarly explore the treatment effect on the subdistribution hazard scale (Fine & Gray 1999).

16.3.3 Reporting the Initial Treatment Analysis

The analysis reporting the treatment results will be carried out after the criteria for early stopping/reporting are met. Three interim analyses and one final analysis will be performed for efficacy and futility of the experimental treatment and will be carried out as described in [Section 16.4.1](#). It will include tabulation of all cases entered and those excluded from the analyses; the distribution of the important prognostic baseline variables; safety treatments; treatment compliance; and observed results with respect to the primary and secondary endpoints will be shown. All eligible patients randomized will be included in the comparison and will be grouped by assigned treatment in the analysis (intent-to-treat analysis). In addition, exploratory analyses of treatment comparisons of the primary and secondary survival endpoints will be tested using the Cox and/or Fine and Gray's proportional hazard model that includes treatment arms, the stratification factors, and any other appropriate covariates.

16.3.4 Sample Size and Power Calculations

The sample size calculation addresses the specific primary hypothesis that the PRFS failure rate at 2 years in Arm 2 (postoperative IMRT) will be better than in Arm 1. Assume an exponential survival distribution for each arm and define λ_1 is the hazard rate

for Arm 1 and λ_2 is the hazard rate for Arm 2. (HA: $\lambda_1 > \lambda_2$).

$$H_0: \lambda_1 \leq \lambda_2 \quad \text{vs.} \quad H_A: \lambda_1 > \lambda_2$$

We project that the proportion failing for the PRFS endpoint in Arm 1 at 2 years is 30% (a 70% PRFS percentage with a yearly hazard rate of 0.178). The study is designed to show an absolute reduction of 15% in the 2-year PR proportion to 15%, which translates to 85% PRFS and a yearly hazard rate of 0.081 in Arm 2. Forty-seven pelvic recurrences and/or deaths are required to detect this 54% relative reduction in the yearly death rate with 90% statistical power using a one-sided log-rank test (Mantel 1966) at the 0.10 significance level. At the planned accrual rate and additional follow-up time of 12 months, 176 eligible patients would be required. Guarding against an ineligibility or loss of patients due to pre-randomization failures of up to 5%, **the final targeted accrual for this study will be 185 patients.**

To assess whether this intervention should advance to phase III evaluation, we also will evaluate the effect of radiation therapy on the totality of potential failure events among these patients via the disease-free survival (DFS) endpoint, defined as the first occurrence of either: pelvic failure, distant metastasis, or death. The disease-free survival proportion in the control group is assumed to be 40% (annual failure rate 0.458). With the patient sample size fixed at 176 eligible patients, the experimental treatment can be tested for a reduction in DFS events by approximately 30% (hazard ratio 0.7025), for a two-year DFS proportion of 52.5% (annual failure rate 0.322) with 83% power and one-sided alpha 0.20. A larger DFS event reduction of 33% could be detected with power 88% (or equivalently, 80% power with one-sided alpha 0.12) and for a smaller DFS event reduction of 25%, power would approach 75% at alpha 0.20. Thus, this trial will provide a reasonably reliable but not definitive test (as appropriate in phase II) for a DFS event reduction with the addition of radiation therapy.

16.4 Study Monitoring of Primary Objectives

16.4.1 Interim Feasibility/Futility Analysis Plan

We will estimate the cumulative incidence of pelvic only or the concurrent pelvic and systemic recurrences (PR, for this analysis, deaths and distant metastasis are competing risks) for the first 43 patients on the control arm with one year follow up. If the cumulative incidence is <14%, the DMC will consider stopping the trial as such a rate would generally be inconsistent with the risk-to-benefit ratio needed to justify proceeding to a phase III evaluation. Depending on the accrual rate this strategy will result in a variable number of patients avoiding being entered on a potentially futile study; for example, if the accrual rate is 5 patients per month, about 40 patients would not be entered into the study. If the accrual rate is 2.5 patients per month, about 70 patients will avoid accrual to the trial.

16.4.2 Interim Futility Analysis Plan

An interim analysis for the futility hypothesis that the experimental arm is not as effective as or unlikely to be more effective than the standard arm will be performed after observation of one-half of the required events (24 for PRFS) has occurred. At the futility analysis, we will evaluate PRFS of the experimental (radiation) arm relative to the control arm via a hazard ratio. If the observed hazard ratio (experimental/control) is greater than or equal to 1.0, then consideration will be given to stopping for futility (i.e., the experimental arm will be considered ineffective in this disease population) (see below). If the observed hazard ratio of the experimental arm relative to the control arm is less than 1.0, then the trial will continue to the full target accrual. Under reasonable assumptions, termination for futility at the interim analysis using this rule is found to result in minimal loss of power (less than 2%) for the primary hypothesis test (Wieand 1994). This same evaluation will take place for DFS, and the futility analyses should be able to be performed relatively concurrent in calendar time.

If the observed hazard ratio (experimental/control) is ≥ 1.0 , a decision about whether to terminate accrual will be made after consideration of additional information including treatment compliance, follow-up reporting timeliness, and the safety profile of the experimental treatment. The independent DMC will review the decision and then make a recommendation concerning early stopping to the Group Chair.

16.4.2 Interim Report to Monitor the Study Progress

Interim reports with descriptive statistics will be prepared twice per year until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase, compliance rate of treatment delivery with the distributions of important prognostic baseline variables, and the frequencies and severity of the adverse event by treatment arm. The interim reports will not contain the results of the treatment comparisons with respect to the primary endpoint and secondary endpoints.

16.5 Accrual Considerations

16.5.1 Accrual Rate

Based on typically low accrual for bladder studies, but projecting slightly higher because this is a randomized phase II trial, the projected accrual for this trial will be 5 cases per month. Based on this assumption, the study is projected to close to accrual approximately

36 months from the end period of negligible accrual (first 6 months), with a projection of reporting approximately 12-15 months from the end of accrual.

16.5.2 Accrual Goal

The final targeted accrual for this study will be 185 patients.

16.5.3 Study Duration

54 to 57 months

16.5.4 Estimated Duration for Completion of Primary Endpoint

36 months from trial activation

16.6 Secondary Elements (6/13/16)

16.6.1 Secondary Hypotheses and Endpoints

Hypothesis: Reducing pelvic recurrence will result in improved survival with acceptable treatment toxicity.

Endpoint: Disease-free survival (DFS), toxicity

16.6.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

Analysis of Secondary Endpoints

DFS, defined as the first occurrence of either: pelvic failure, distant metastasis, or death, will be estimated by Kaplan-Meier (Kaplan & Meier 1958) and arms compared using the log-rank test (Mantel 1966). Multivariable analysis of DFS including other covariates may follow. Cumulative incidence curves for the additional event types other than PRFS comprising DFS also may be examined including PR, distant metastasis, etc., with interest in whether deaths or distant metastasis failures differ between arms.

Treatment Toxicity

Acute (within 90 days of the first day of radiotherapy) and late (any time beyond the 90 days) radiation bowel toxicity will be scored using CTCAE v4.0 and limited to those AEs listed in [Section 16.6.3](#). Very careful attention will be paid to neobladder and bowel complications that require surgical intervention and/or stoppage of radiotherapy. Specifically, urinary tract obstruction, urinary retention, urinary fistula, hematuria, cystitis noninfective, bladder perforation, and urinary incontinence will be monitored as neobladder complications and gastrointestinal adverse events will be assessed for bowel complications.

16.6.3 Interim Safety Monitoring for Bowel Toxicity Requiring Surgery in Arm 2

We anticipate that 3-5 % of patients without RT and 5-8% of RT patients will require surgery for bowel toxicity and propose close toxicity monitoring with a stopping rule calculated to ensure we do not double this risk. Bowel toxicity is defined as the following subset of CTCAE v4.0 within 90 days of the first radiotherapy treatment regardless of grade and which required surgical intervention:

- System Organ Class: Gastrointestinal Disorders
 - Abdominal distension, abdominal pain
 - Colitis
 - Colonic fistula, colonic hemorrhage, colonic obstruction, colonic perforation, colonic stenosis, colonic ulcer
 - Diarrhea
 - Enterocolitis

- Fecal incontinence
- Gastrointestinal fistula
- Gastrointestinal pain
- Ileal fistula, ileal hemorrhage, ileal obstruction, ileal perforation, ileal stenosis, ileal ulcer
- Ileus
- Jejunal fistula, jejunal hemorrhage, jejunal obstruction jejunal perforation, jejunal stenosis, jejunal ulcer
- Lower gastrointestinal hemorrhage
- Rectal fistula, rectal hemorrhage, rectal mucositis, rectal necrosis, rectal obstruction, rectal pain, rectal perforation, rectal stenosis, rectal ulcer
- Small intestinal mucositis, small intestinal obstruction, small intestinal perforation, small intestinal stenosis, small intestinal ulcer
- Vomiting

Arm 1 (observation only), will be monitored for bowel toxicity requiring surgery to ensure that the anticipated rates are within the expected range. However, for Arm 2, a safety rule will be employed. A bowel toxicity rate of $\leq 5\%$ of patients requiring surgery is considered acceptable and a rate of 15% is considered unacceptable. The null hypothesis is that IMRT post-cystectomy is not tolerable versus the alternative hypothesis that IMRT post-cystectomy is tolerable. The following hypothesis will be tested using Fleming's Multiple Testing Procedure (1982) with a significance level of 0.10 and 80% statistical power.

$$H_0: p_{\text{bts}} \geq 0.15 \text{ vs. } H_A: p_{\text{bts}} \leq 0.05$$

Active decisions regarding safety of continued accrual will be made sequentially when 19, 38, and 57 eligible patients have received radiotherapy in Arm 2. We are more concerned with a false negative decision (i.e., failing to detect the increase in toxicity if it exists) than we are with a false positive decision (i.e., deciding the new regimen is more toxic, when in fact it is not). The stopping and continuation rules in Table 14.1 below will be applied in three stages to the 57 eligible cases randomized to Arm 2 who received at least some RT. If at any stage, we stop and reject the alternative hypothesis and claim that the bowel toxicity requiring surgery (any) rate may be greater than or equal to 15%, we will temporarily close the study to accrual, gather the relevant source data on the cases with bowel toxicity (any), prepare a statistical report summarizing the adverse event findings, and present the report to the radiation and medical oncology study chairs for review.

Following the study chairs' review of data, a conference call will be scheduled with the study chairs, statistician, and other appropriate NRG Oncology leadership as needed to discuss the findings and make a recommendation about the study. Once a recommendation is made, the responsible statistician will present the statistical report along with the recommendation to the NRG Oncology Data Monitoring Committee (DMC) for the Committee's consideration. The DMC will then make a recommendation

about the course of action and future of the study. If at the first or second stage either of the stopping rules is not met, we will continue accrual and monitoring for bowel toxicity requiring surgery. If we continue until the last stage, we will conclude “tolerability” or not.

Table 16.1 Stopping and Continuation Rules for Bowel Complications

| #analyzable* | Continue | Stop and reject $H_A: p \leq 0.05$ |
|--------------|----------|------------------------------------|
| 19 | <3 | ≥ 3 |
| 38 | <4 | ≥ 4 |
| 57 | <5 | ≥ 5 |

* “Analyzable patients” is defined as eligible patients who received IMRT.

16.7 Gender/Ethnicity/Race Distribution

| | Gender | | |
|---|----------------|--------------|--------------|
| Ethnic Category | Females | Males | Total |
| Hispanic or Latino | 4 | 6 | 10 |
| Not Hispanic or Latino | 28 | 147 | 175 |
| Ethnic Category: Total of all subjects | 32 | 153 | 185 |
| | Gender | | |
| Racial Category | Females | Males | Total |
| American Indian or Alaskan Native | 0 | 2 | 2 |
| Asian | 1 | 0 | 1 |
| Black or African American | 4 | 4 | 8 |
| Native Hawaiian or other Pacific Islander | 1 | 0 | 1 |
| White | 26 | 147 | 173 |
| Racial Category: Total of all subjects | 32 | 153 | 185 |

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