NRG ONCOLOGY
Radiation Therapy Oncology Group

RTOG 0926

(ClinicalTrials.gov NCT #:* 00981656*)

A Phase II Protocol for Patients with Stage T1 Bladder Cancer to Evaluate Selective Bladder Preserving Treatment by Radiation Therapy Concurrent with Radiosensitizing Chemotherapy Following a Thorough Transurethral Surgical Re-Staging

Amendment 5: February 1, 2019

For **Protocol** Amendment 5 to: RTOG 0926, *A Phase II Protocol For Patients With Stage T1 Bladder Cancer To Evaluate Selective Bladder Preserving Treatment By Radiation Therapy Concurrent With Radiosensitizing Chemotherapy Following A Thorough Transurethral Surgical Re-Staging*

NCI/Local Protocol #: RTOG-0926 / RTOG 0926

NCI Protocol Version Date: February 01, 2019

Section	Change
Document Footer	The protocol version date was updated
Document History Table	The amendment was added
CTSU Contact Information table 5.0 5.2 5.3 5.4	Updated per the NCTN/CTSU standard text
7.9	Due to CTEP's migration from CTCAE v 4.0 to CTCAE v 5.0, this section was revised to reflect the following: ○ CTCAE v 4.0 will be utilized for AE reporting until March 31, 2018; ○ Beginning April 1, 2018, CTCAE version 5.0 will be utilized for CTEP-AERS reporting; ○ All study case report forms will continue to use CTCAE version 4.0.
10.3	This section has been deleted as the reimbursement information is posted on the CTSU website.
10.4	Section 10.4 has been renumber to 10.3 and the first sentence was deleted, as the link is no longer valid.
12.0	Updated per the NCTN/CTSU standard text
Informed Consent	No Changes to the text of the sample consent; the version date of the consent was changed to be consistent with the amended protocol

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Study Chairs (3/6/2015)

(3/31/14)

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Protocol Agent

Agent	**Supply**	**NSC #**	**IND #**
Cisplatin	Commercial	N/A	Exempt
5FU			
Mitomycin			

Participating Sites:

☒ U.S. and Canada

☒ Approved International Member Sites

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Document History

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Amendment 5	**February 1, 2019**	**N/A**
Amendment 4	April 20, 2015	April 27, 2015
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CANCER TRIAls SUPPORT UNIT (CTSU) CONTACT INFORMATION (01-Feb-2019)		
To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	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.	NRG Oncology 1818 Market Street Suite 1720 Philadelphia, PA 19103 Submit data electronically via the NRG Oncology/RTOG web site, www.rtog.org Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting 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' web site 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. : Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For patient eligibility or treatment-related questions Contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical 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.		
The CTSU Web site is located at https://www.ctsu.org		

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RTOG 0926

A Phase II Protocol For Patients With Stage T1 Bladder Cancer To Evaluate Selective Bladder Preserving Treatment By Radiation Therapy Concurrent With Radiosensitizing Chemotherapy Following A Thorough Transurethral Surgical Re-Staging

SCHEMA

(3/31/14)

Institutional TURBT for re-staging →	**Full-dose Radiation* and Concurrent Chemotherapy** →**	**Cystoscopic Surveillance 8-10 weeks after treatment; if negative, q 3 months for the 1st year, q 4 months for year 2, q 6 months for years 3, 4, and 5*** and then annually**
Stage T1 (high grade)	*Total dose of 61.2 Gy in 34 daily fractions **Cisplatin 3 days/week during Weeks 1, 3, and 5 **OR** Mitomycin day 1 and 5-fluorouracil Weeks 1 and 4	***For T1 and Tcis tumor recurrence after RTOG 0926 treatment, recommend early salvage cystectomy. For Ta tumor recurrence, recommend either appropriate conservative treatment or cystectomy.

See pre-registration requirements in Section 5.1. See details of radiation therapy and chemotherapy in Sections 6.0 and 7.0.

Patient Population: (See Section 3.0 for Eligibility) (3/31/14)

- Operable patients with non-muscle invading tumors and with at least one being a high grade Stage T1 urothelial carcinoma for whom radical cystectomy is being considered as the next conventional step in therapy by standard urologic guidelines
- AJCC Stages T1, NX or N0, M0, only transitional cell histology
- Restaged by a urologist in the participating institution with an aggressive, visibly complete TURBT with muscularis propria in the specimen but with no evidence of its invasion by tumor
- Failed standard treatment with, or is medically ineligible for, intravesical biological therapy or chemotherapy
- No evidence of prostatic stromal invasion by tumor

Required Sample Size: 37

NRG Oncology Institution #

RTOG 0926 **ELIGIBILITY CHECKLIST** (4/20/15)
Case # **(page 1 of 3)**

1._____(Y) Does the patient have pathologically proven non-muscle invading urothelial carcinoma of the bladder diagnosed within 105 days prior to registration?

2._____(Y) Is the patient's initial non-muscle invading primary tumor or the recurrent non-muscle invading tumor a stage T1 high grade (either grade 2 or 3) urothelial carcinoma of the bladder?

____(Y) If yes, is there evidence in the pathologic specimen of the recurrent tumor that there is no muscularis propria invasion by the tumor (that is, muscularis propria is in the specimen and not involved with tumor)?

3._____(Y) Does the participating urologist judge that radical cystectomy is the next standard therapy for this patient per standard urologic guidelines?

4_____(Y/N) Has this patient either been judged unsuited for BCG therapy by the urologist or the patient, or failed initial treatment with TURBT + intravesical BCG therapy within 540 days (18 months) after this treatment?

_____(Y) If no, has this patient been deemed medically ineligible for standard treatment for T1 bladder cancer (by further intravesical BCG therapy)?
Please specify this reason: _____
(Either the urologist has judged the patient likely intolerant of BCG therapy due to his/her immuno competence, or the patient refuses this therapy.)

5._____(N/Y) Has a radiologic lymph node evaluation been interpreted as positive?

____(Y) If yes, has further evaluation been done by lymphadenectomy or needle biopsy to confirm no histological or cytological nodal metastases?

6._____(Y) Has the patient undergone, a visibly complete transurethral resection of the present bladder tumor leaving an adequately functioning bladder?

7._____(Y) Are the urologist, radiation oncologist and medical oncologist in joint agreement that the patient is able to tolerate systemic chemotherapy combined with radiation therapy and a radical cystectomy (if necessary)?

8._____(Y) Has a history and physical examination been done within 60 days prior to registration?

9._____(Y) Is the Zubrod performance status 0 or 1?

10._____(Y) Is the patient 18 years of age or older?

11._____(Y) Has a CBC with differential been done within 30 days prior to registration meeting the following parameters: WBC $\geq$ 4,000; ANC $\geq$ 1,800; platelets $\geq$ 100,000 and hemoglobin $\geq$ 10.0?

12._____(Y) If the patient will be receiving cisplatin, is the serum creatinine $\leq$ 1.5?

13._____(Y) Is the serum bilirubin $\leq$ 2.0?

14._____(Y) Is the GFR > 25 ml/min?

15._____(Y) If the patient will be receiving cisplatin, is the GFR $\geq$ 60 ml/min?

16._____(N/Y) Is the patient a female of childbearing potential?

17.____(Y) If yes, has a serum pregnancy test been done $\leq$ 72 hours prior to registration?

18._____(N) Is there evidence of tumor-related hydronephrosis?

19._____(N) Is there evidence of distant metastases?

20._____(N) Has the patient received systemic chemotherapy for bladder cancer?

21._____(N) Does the patient have a prior invasive malignancy (except for non-melanomatous skin cancer; T1a prostate cancer or carcinoma of the uterine cervix) that has not been disease free for ≥ 5 year period or a urothelial carcinoma of the upper urinary tract stage pTa, pTis or pT1 that has been free of disease after treatment for more than a 2 year period?

22._____(N) Is the patient currently receiving any drugs that have potential nephrotoxicity or ototoxicity (such as aminoglycoside)?

23._____(N) Has the patient had any previous radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields?

24._____(N) Does the patient have any severe, active co-morbidity such as: 1) unstable angina and /or congestive heart failure that required hospitalization within the last 6 months; 2) transmural myocardial infarction that occurred within the last 6 months; 3) acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration; 4) chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding any study therapy at the time of registration; 5) hepatic insufficiency resulting in clinical jaundice and/or coagulation defects or 6) acquired immune deficiency syndrome (AIDS) based upon the current CDC definition?

25._____(Y;N/A) If the patient is of child-bearing potential (female) or is a sexually active male, are they willing/able to use medically acceptable forms of contraception?
If N/A, please state why:_____

26._____(N) Has the patient had a prior allergic reaction to the study drug (cisplatin, mitomycin, 5FU) used in this protocol?

27._____(N) Does the patient have pathologically positive nodal disease (pN1;pN2; pN3)?

28._____(N) Does the patient have T2, T3 or T4 disease?

The following questions will be asked at Study Registration:

3D CREDENTIALING IS REQUIRED PRIOR TO REGISTRATION

_____ 1. Institutional person registering this case

_____(Y) 2. Has the Eligibility Checklist been completed?

_____(Y) 3. In the opinion of the investigator, is the patient eligible?

_____ 4. Date Informed Consent signed

_____ 5. Participant Initials

_____ 6. Verifying Physician

_____ 7. Patient's ID Number

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnicity

_____ 11. Gender

_____ 12. Country of Residence

_____ 13. Patients' Zip Code

_____ 14. Method of Payment

_____ 15. Any care at VA or military hospital?

_____ 16. Calendar Base Date

_____ 17. Randomization Date

_____ 18. Medical oncologist

_____(N/Y) 19. Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(N/Y) 20. Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(N/Y) 21. Have you obtained the patient's consent for his or her urine to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(N/Y) 22. Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(N/Y) 23. Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

_____(N/Y) 24. Have you obtained the patient's consent for his or her urine to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(N/Y) 25. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/NRG Oncology audit.

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Background for Evaluating Trimodality Therapy in Patients with Aggressive Forms of Non-Muscle Invading Bladder Cancer Who Have Failed Other Conservative Treatments (3/31/14)

Treating patients with muscle-invading bladder cancer (clinical stages T2-T4a, in X-N0, M0) with selective bladder preservation using trimodality therapy (transurethral resection [TURBT] plus concomitant chemotherapy and radiation therapy) with prompt cystectomy for recurrence has been established as a safe and effective alternative to immediate radical cystectomy in several RTOG protocols and in single institution reports.[1] The treatment design that has evolved consists of as thorough a TURBT as is safely possible followed by irradiation to 64–65 Gy with concurrent sensitizing chemotherapy. Patients with a complete response are followed with surveillance cystoscopy; cystectomy is reserved for patients with recurrent disease. Patients without a complete response undergo prompt cystectomy.

The results over the last 3–4 decades using external beam therapy alone for patients with clinical stage T1 bladder cancer have been poor and this approach has been largely abandoned. The Medical Research Council from the United Kingdom reported a multi-institutional randomized trial comparing external beam radiation therapy without concurrent chemotherapy to standard conservative approaches for the treatment of patients presenting with T1G3 tumors and confirmed no benefit from external beam therapy alone.[2] The T1G3 subgroup of non-muscle invading bladder cancer is the most aggressive but makes up only 15% of the total incidence of patients presenting with non-muscle invading cancer.[3] TURBT alone has long been recognized as inadequate treatment with 48% of patients progressing to stage T2 or greater disease in just 3 years.[4] The addition of BCG (bacillus Callamette-Guerin) immunotherapy after TURBT has been shown in a randomized trial to significantly improve the 10-year tumor progression-free rate from 37% to 62% and the 10-year disease-specific survival from 55% to 75%, when compared to TURBT alone.[5] This combination now constitutes the current standard first-line therapy.[3] The standard second-line treatment for patients who fail BCG therapy having had a stage T1 tumor is radical cystectomy.[3,6,7] This is because there is no very effective second-line bladder preserving treatment using additional intravesical agents in patients who develop a recurrence following BCG therapy. Such therapies include BCG + interferon, mitomycin C, gemcitabine, adriamycin, docetaxel, apaziquone, and various combinations of these agents. The results of these intravesical therapies are generally poor and have short follow up.[9-11] Because effective second-line bladder-sparing therapy using these intravesical agents is not well established, the standard treatment in this setting is radical cystectomy, as is recommended in the recent National Comprehensive Cancer Network (NCCN) Guidelines for Bladder Cancer.[12]

However, there are recent indications that concurrent chemotherapy with radiation therapy, unlike radiation alone, may be very effective in eradicating high grade clinical stage T1 tumors. This is based on results from Erlangen, Germany[13] on 84 patients with T1G3 tumors using a trimodality bladder-sparing approach with concurrent chemotherapy and radiation. A 10-year progression-free rate of the bladder tumor of 71% and a 10-year disease-specific survival rate of over 70% was reported. These results in patients with T1G3 tumors are similar to the present standard bladder sparing approach using intravesical BCG in both preventing the progression of the primary tumor and in disease-specific survival (see reference 12, table 4). This favorable result with trimodality therapy in T1G3 tumors makes sense since this approach has been shown to yield good results in patients presenting with muscle invading tumors of clinical stage T2. RTOG protocols and single institution studies[1,14] report a 70+% disease-specific survival rate at 5 years with less than 1/3 of these patients requiring a salvage radical cystectomy. Thus, although there will always be the need in some patients for salvage cystectomy, treatment by this trimodality technique will likely prevent the need for radical cystectomies in many patients with non-muscle invading bladder cancer who have failed BCG intravascular therapy having had high grade T1 disease or high grade Ta disease.

To our knowledge there are no reports as yet of the effectiveness of trimodality therapy as second-line selective bladder preserving treatment in patients with recurrent T1 bladder tumors following BCG treatment. The Massachusetts General Hospital has reported a selective retrospective series of 18 patients who had failed BCG therapy given for T1 bladder cancer who recurred with progression to a clinical stage T2 muscle-invading cancer. The median follow-up was 7.1 years. Ten of 18 patients have had no recurrence of any bladder tumor, muscle-invading or non-muscle invading. The freedom from cystectomy at 3 years was 94%. The actuarial 5-year disease-specific survival rate is 77%.[15] Thus, the present protocol is designed to test the efficacy of chemotherapy-enhanced radiation therapy for the

eradication of bladder cancers with aggressive forms of clinical stage T1 disease in whom radical cystectomy is, by standard urologic guidelines, the next step in therapy.

Based on the above two Phase II reports with concurrent cisplatin and radiation in T1G3 or BCG-failures in bladder cancer, concurrent cisplatin has been selected as the radiation enhancing drug for this protocol. In patients who are not felt to be optimal candidates for cisplatin chemotherapy, mitomycin and 5FU may be substituted as radiation sensitizing chemotherapy. To be eligible for this trial, all patients must be re-staged by a urologist in the participating institution with an aggressive, visibly complete TURBT with muscularis propria in the specimen but with no evidence of its invasion by tumor. Thus, although there will always be the need in some patients for a salvage cystectomy, treatment by this technique will likely prevent the need for radical cystectomy in many patients—probably as many as 3 out of every 4—who have failed BCG therapy having initially had high grade T1 disease or who have failed BCG therapy for an initial high grade stage Ta tumor but who failed BCG with a high grade stage T1 tumor. If cystectomy could be safely avoided in 50–60% of such patients using a trimodality approach, this would be of considerable clinical importance.

1.2 Rationale for Evaluating Patient Tolerance for Whole Bladder Irradiation to 61.2 Gy with Concurrent Chemotherapy (4/6/12)

Efstathiou, Bae, et al recently reported late pelvic toxicity following bladder-sparing therapy in patients with invasive bladder cancer in the analysis of RTOG protocols 8903, 9506, 9706, and 9906.[16] Of 157 patients enrolled in these four prospective RTOG protocols who underwent combined modality therapy and who are surviving two or more years from the start of their treatment with their bladder intact (median follow-up of 5.4 years), 7% experienced late grade 3 pelvic toxicity (5.7% GU and 9.1% GI). Grade 3 GU toxicity persisted in only one of the nine patients with this toxicity. There were no late grade 4 toxicities and no treatment related deaths. Because the rate of significant late pelvic toxicity for patients completing combined modality therapy for invasive bladder cancer is low and likely will be for the proposed trial, the protocol differs slightly from methods used in the previous protocols with patients with usually unifocal but muscle invading transitional cell carcinoma of the bladder. In these prior trials, the whole bladder dose was recommended to be at the 55 Gy level with the final 10-12 Gy boost being, if safely possible, only to the tumor bearing portion of the bladder. Thus the present proposed regimen for the failed T1G3 patients in whom tumors may be multifocal includes radiating the whole bladder to doses of 61.2 Gy. This probably will not result in more acute or late bladder toxicity. The Birmingham Hospital in England led a phase III trial evaluating patients with muscle-invading bladder cancer who received radiation treatment to the whole bladder compared to patients who received partial bladder radiation but with no concurrent chemotherapy. Those patients assigned to partial bladder radiation were given a slightly higher dose.[17] They reported no difference in late bladder toxicity (grade 2 or grade 3 toxicity using the WHO Toxicity Grading System). The University of Michigan recently reported on their phase I trial of combined modality therapy with gemcitabine and radiation as a bladder preserving strategy (with 5.6 years of median follow up) at the 2008 Genitourinary Symposium, sponsored by ASCO, ASTRO, and the SUO.[18] Their treatment approach was similar to this present protocol in that treatment followed a maximum TURBT; the radiation doses and fields were very similar as well. A small pelvic field was treated conformally to 40 Gy and the bladder only boost was treated for an additional 20 Gy—all in 2.0 Gy fractions for a total whole bladder dose of 60 Gy. In this gemcitabine dose-seeking study there were no instances of late grade 3 GI or GU toxicity and the whole bladder radiation dose was certainly the biological equivalent of what we propose in this study (61.2 Gy in thirty-four 1.8 Gy daily fractions). We will monitor late GU toxicity and be able to compare it to the results of our other trials.[19]

1.3 Biomarkers in Bladder Cancer(3/6/2015)

A number of biomarkers have shown promise in predicting the outcome of bladder cancer patients. In particular, her2/neu, EGFR1, p53, p21, pRb, p16 and bcl2. These markers and others are under investigation through the NRG Oncology genitourinary translational research program using patients from an ongoing RTOG selective bladder preservation protocol. These continued efforts are planned for the tissue from diagnostic/pretreatment TURBT and from cystectomy specimens, when salvage cystectomy is performed.

2.0 OBJECTIVES

2.1 Primary Objectives

To evaluate the rate of freedom from radical cystectomy at 3 years.

2.2 Secondary Objectives

2.2.1 To evaluate the rate of freedom from radical cystectomy at 5 years

2.2.2 To evaluate the rate of freedom from the development of distant disease progression at 3 and 5 years

2.2.3 Rate of freedom from progression of bladder tumor to stage T2 or greater at 3 and 5 years

2.2.4 To evaluate disease-specific survival and overall survival

2.2.5 To evaluate the incidence of acute and late pelvic toxicity

2.2.6 To evaluate the efficacy of this treatment approach in preventing the recurrence of any local bladder tumor

2.2.7 To evaluate the potential value of tumor histopathology plus molecular genetic, DNA content, and urine proteomics parameters as possible significant prognostic factors for tumor control with this treatment approach

2.2.8 To collect American Urological Association (AUA) symptom scores at baseline and at 3 years

3.0 PATIENT SELECTION (4/20/15)

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

For questions concerning eligibility, please contact the study data manager.

3.1 Conditions for Patient Eligibility (3/31/14)

3.1.1 Pathologically proven diagnosis of carcinoma of the bladder within 105 days prior to registration.

- Operable patients whose initial tumor is a primary high grade urothelial carcinoma of the bladder exhibiting histologic evidence of invasion into the lamina propria (disease clinical stage T1) or a high grade stage Ta urothelial carcinoma without hydronephrosis; patients who have involvement of the prostatic urethra with urothelial carcinoma and have no evidence of stromal invasion of the prostate remain eligible. If the patient's initial tumor was a high grade stage Ta urothelial carcinoma then his/her recurrent tumor must be a high grade stage T1 urothelial carcinoma to be eligible.

3.1.2 Patients must have a high grade urothelial carcinoma stage Ta or T1 that has recurred within 540 days after completion of the initial treatment (TURBT and intravesical BCG immunotherapy) or on initial presentation with a T1 high grade tumor, the participating urologist judged BCG therapy is contraindicated or unsuitable because the patient is found to be intolerant of BCG therapy or because this patient may be immuno-compromised in ways other than that mentioned in Section 3.2.8 or because the patient refuses BCG therapy.

3.1.3 With the presentations as described in Section 3.1.2, the participating urologist judges that the standard next therapy, based on present urologic guidelines for this patient, is radical cystectomy.

3.1.4 If radiologic evaluation of a lymph node is interpreted as "positive", this must be evaluated further either by lymphadenectomy or by percutaneous needle biopsy. Patients with histologically or cytologically confirmed node metastases will not be eligible.

3.1.5 Patients must have an adequately functioning bladder as judged by the participating urologist and radiation oncologist and have undergone a re-staging TURBT by the participating urologist that showed (or was present in the outside pathology specimen) a high grade stage Ta or T1 tumor with uninvolved muscularis propria in the specimen and, if on prostatic urethral biopsy mucosal carcinoma is present, there is no evidence on biopsy in the prostatic stroma of tumor invasion.

3.1.6 Patient must be considered able to tolerate systemic chemotherapy combined with pelvic radiation therapy, and a radical cystectomy (if necessary) by the joint agreement of the participating urologist, radiation oncologist, and medical oncologist.

3.1.7 Appropriate stage for protocol entry, based upon the following minimum diagnostic workup within 60 days prior to registration:

- History/physical examination including weight, performance data, body surface area

3.1.8 Zubrod Performance Status ≤ 1

3.1.9 Age ≥ 18

3.1.10 CBC/differential obtained no more than 30 days prior to registration on study, with adequate bone marrow function defined as follows:

- WBC ≥ 4,000/ml
- Absolute neutrophil count (ANC) ≥ 1,800 cells/mm^3
- Platelets ≥ 100,000 cells/mm^3
- Hemoglobin ≥ 10.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 10.0 g/dl is acceptable.)

3.1.11 *If the patient is to be treated with cisplatin*, the serum creatinine should be ≤ 1.5 mg%; serum bilirubin of ≤ 2.0 mg%
3.1.12 GFR > 25 ml/min *[For patients receiving cisplatin, GFR ≥ 60 ml/min]*
3.1.13 Serum pregnancy test for female patients of childbearing potential, ≤ 72 hours prior to study entry; women of childbearing potential and male participants must practice adequate contraception.
3.1.14 Patient must be able to provide study-specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility (3/31/14)
3.2.1 Evidence of tumor-related hydronephrosis
3.2.2 Evidence of distant metastases or histologically or cytologically proven lymph node metastases
3.2.3 Prior systemic chemotherapy for bladder cancer; prior chemotherapy for a different cancer is allowable
3.2.4 A prior or concurrent malignancy of any other site or histology unless the patient has been disease-free for ≥ 5 years except for non-melanoma skin cancer and/or stage T1a prostate cancer or carcinoma *in situ* of the uterine cervix or a urothelial carcinoma of the upper urinary tract stage pTa, pTis or pT1 that has not been free of disease after treatment for more than a 2 year period
3.2.5 Patients with pN+ or > T1 disease or who have not had a visibly complete TURBT
3.2.6 Patients receiving any drugs that have potential nephrotoxicity or ototoxicity (such as an aminoglycoside)
3.2.7 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields
3.2.8 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 the 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.

3.2.9 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.
3.2.10 Prior allergic reaction to the study drugs (cisplatin, mitomycin, 5FU) involved in this protocol

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

Note: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management (3/31/14)
4.1.1 Cystoscopic evaluation by a participating urologic surgeon will include a visibly complete transurethral resection of the bladder tumor (TURBT), bimanual examination under anesthesia, and prostatic urethra biopsies (see Section 8.1.5), as well as a biopsy of the base of the resected tumor site. Patients referred from an outside hospital will be re-resected by the participating urologist.
4.1.2 Radiologic evaluation, including chest x-ray, bone scan (as applicable), abdominal and pelvic CT scans, and an IVP if indicated, no more than 60 days prior to start of treatment
4.1.3 Alkaline phosphatase, SGOT, LDH, BUN, magnesium and calcium levels

4.2 Highly Recommended Evaluations/Management
4.2.1 AUA Symptom score at baseline before beginning concurrent chemotherapy and radiation

5.0 REGISTRATION PROCEDURES (01-Feb-2019)

Access requirements for OPEN and TRIAD

Site staff will need to be registered with CTEP and have a valid and active CTEP Identity and Access Management (IAM) account. This is the same account (user id and password) used for the CTSU members' web site. To obtain an active CTEP-IAM account, go to https://eapps-ctep.nci.nih.gov/iam.

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov

5.1 Radiation-Specific Pre-Registration Requirements (3/31/14)

Knowledge Assessment

There is a required knowledge assessment for this protocol that is in addition to the Facility Questionnaire and the credentialing requirements. This knowledge assessment must be successfully completed prior to the enrollment of the first patient. Details for the knowledge assessment can be found on the Imaging and Radiation Oncology Core (IROC) Houston QA Center *[formerly the Radiological Physics Center (RPC)]* website at http://irochouston.mdanderson.org .

The RT treatment modality is 3DCRT (see Section 6.0). All sites must be 3DCRT credentialed.

RT Credentialing Requirements	Web Link for Procedures and Instructions: http://irochouston.mdanderson.org	
	Treatment Modality: 3DCRT	Key Information
Facility Questionnaire	X	Update your online electronic Facility Questionnaire via the web address above.
Credentialing Status Inquiry Form	X	Complete this form on the IROC Houston website above to determine if your site has met all of the requirements. This will be completed in place of updating the previous Facility Questionnaire. When the requirements are met the site and NRG Oncology (NRG) will be notified. NRG will then update the RSS database.
Knowledge Assessment	X	The Knowledge Assessment Form will be available on the IROC website at http://irochouston.mdanderson.org

5.2 Digital RT Data Submission to NRG Oncology Using TRIAD (01-Feb-2019)

TRIAD, the American College of Radiology's (ACR) image exchange application, will be used for dosimetry digital treatment data on RTOG 0926. TRIAD provides sites participating in NRG Oncology 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, and be registered as an AP, NPIVR or IVR. Please refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- To submit images, the site physics user must be on the site's affiliated rosters and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role. 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/RTOG 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.

5.3 Regulatory Pre-Registration Requirements (01-Feb-2019)

5.3.1 This study is not on the NCI Cancer Trials Support Unit (CTSU) Menu

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. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the *[NCI RTOG-0926]* protocol page located on the CTSU members' website. *Add if a restricted access protocol:* Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to https://www.ctsu.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
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the *(state organization type e.g. P2C, CITN, NCTN Group name)* link to expand, then select trial protocol #*[RTOG-0926]*
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements For RTOG-0926 Site Registration:

IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

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Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.
)

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- 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
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

5.3.2 **In addition to the requirements noted above, ALL institutions** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206); study-related regulatory documentation also may be e-mailed to the CTSU at CTSURegulatory@ctsu.coccg.org. This must be done prior to registration of the institution's first case:

- IRB/REB approval letter;
- IRB/REB approved consent (English and native language versions*)

***Note**: Institutions must provide certification/verification of consent translation to NRG Oncology (See "Non-English Speaking Canadian and Non-North American Institutions" below)

- IRB/REB assurance number renewal information as appropriate

Non-English Speaking Canadian and Non-North American 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 Oncology 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.

5.3.3 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS
Prior to clinical trial commencement, Canadian institutions must complete and fax (215-569-0206) or e-mail (**CTSURegulatory@ctsu.coccg.org**) the following forms to the CTSU Regulatory Office:

- Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form,
- Qualified Investigator Undertaking Form, and
- Research Ethics Board Attestation Form.

5.3.4 Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS

***For institutions that do not have an approved LOI for this protocol*:**
International sites must submit an LOI to NRG Oncology 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.

5.4 Registration (01-Feb-2019)

5.4.1 OPEN Registration Instructions

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.

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://ctepcore.nci.nih.gov/iam >) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.
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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. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPPA authorization form (if applicable).

Access requirements for OPEN:

- See Section 5.0 for obtaining a CTEP-IAM account.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

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 CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In the event that the OPEN system is not accessible, participating sites can contact NRG Oncology web support for assistance with web registration: websupport@acr.org or call the 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.

6.0 RADIATION THERAPY (4/20/15)

This trial will not utilize the services of the ITC for dosimetry digital treatment data submission.
***PRIOR TO ENROLLING PATIENTS*, please see Section 5.2 for information on installing TRIAD for submission of digital RT data.**

Note: Intensity Modulated RT (IMRT) Is Not Allowed

Protocol treatment must begin within 15 weeks following transurethral resection. Ideally, treatment should begin on a Monday, the chemotherapy to precede the daily radiation therapy during the first three treatments of weeks 1, 3, and 5. Radiation treatment times must be recorded on the daily treatment record.

Note: Because the fields may be complicated for this study, it is recommended that the treating physician contact the Study Co-Principal Investigator, Dr. William Shipley (617-726-8146), to discuss fields prior to designing the CT simulated treatment plan.

6.1 Dose Specifications (4/20/15)

All patients will receive 34 daily fractions (about 7 weeks) of radiation therapy 5 days a week. Radiation therapy will be started within 15 weeks following the TURBT and begin on a Monday, Tuesday, or Wednesday. Radiation therapy will be continuous, without a plan break for tumor assessment during treatment, as has been done in most of the prior RTOG bladder preservation protocols. The overall schema is for small field pelvic irradiation given by 3D conformal irradiation to the entire bladder and prostatic urethra (in men) and the lymph nodal pelvic regions of the internal iliac, the external iliac, and the obturator lymph nodes. All these structures constitute the CTV_{CTV_4140} (see field borders in Appendix IV). The treatment will be given in 23 fractions at 1.8 Gy per daily fraction (5 days per week) to a dose of 41.4 Gy, followed by reduction in field size to include the whole bladder and any possible or suggested areas of tumor extension ($CTV_{\_6120}$) using 1.8 daily fractions for 11 fractions for a total bladder boost dose ($PTV_{\_6120}$) of 19.8 Gy. This will give a total dose to the gross bladder volume of 61.2 Gy over approximately 7 weeks. Heterogeneity corrections must be used.

6.2 Technical Factors [Equipment, energies]

The radiation treatment should be with a high energy linear accelerator with photon energies ≥6 MV, typically using a four field box for the initial small pelvic fields and for the boost for the whole bladder volume, but there may be alternative field arrangements depending on specific characteristics of the individual patient (e.g., a patient with a metal total hip replacement).

6.3 Localization, Simulation, and Immobilization

3D conformal radiotherapy will be used. The patient will be positioned supine. A leg immobilizer or cradle is recommended. A planning CT scan of the pelvis will be obtained. The patient must void to empty the bladder immediately prior to simulation. The bladder is then catheterized to check on the size of a possible post void residual. Twenty to 30 ml of dilute contrast and air may be introduced in the bladder but the bladder should not contain more liquid than that because it is desirable to treat the patient with their bladder empty such that the day-to-day mobility of the bladder will be minimized. Contrast in the rectum usually is not necessary but a rectal tube without contrast may be helpful. The rectum should be as empty as possible for simulation; an enema should be given prior to simulation to accomplish this.

6.4 Treatment Planning/Target Volumes (12/17/13)

6.4.1 Small Pelvic Fields

These fields should encompass the entire bladder, prostate and prostatic urethra (in men), and the regional pelvic lymph nodes (See Appendix IV). All of these structures constitute the $CTV_{\_4140}$. A conformal four field box arrangement should be used (the pelvic lymph nodes do not need to be contoured on the submitted 3D plan). The field margins in the inferior and superior dimensions should extend 1 cm below the lower pole of the obturator foramen to the mid-sacrum (the anterior aspect of the S1-S2 junction). Laterally, the anterior and posterior opposed fields will extend at least 1.5 cm beyond the widest point of the bony margin of the pelvis. For the parallel opposed lateral fields, the field edges will extend 3.0 cm posterior to the $CTV_{\_6120}$ and will extend 1 cm anterior to the most anterior point of the symphysis pubis or 1.5 cm anterior to the anterior tip of the bladder, whichever is the most anterior. Blocking should also be used on the anterio-posterior opposed fields to shield the medial border of the femoral heads. Blocking will also be employed on the lateral opposed fields inferiorly to shield the soft tissue anterior to the pubic symphysis and to block the anal canal posteriorly. Superiorly, the lateral fields may include blocks anteriorly to exclude the small bowel and the anterior rectus fascia which lay anterior to the external iliac lymph node chain.

The field weighting and use of beam modifiers should be chosen to assure that the maximum dose to the femoral heads is no more than 45 Gy.

Anatomic variations in the bladder may necessitate modifications of the CTV_6120 and therefore the $CTV_{\_4140}$, such as a bladder cystocele protruding inferiorly or a bladder diverticulum or, rarely, a very significant post-void residual. Also, variations in the regional pelvic lymph nodes may necessitate modifications of the field borders for the small pelvic fields. For any of these anatomic variations, the variation should be encompassed within the defined $CTV_{\_6120}$ and/or $CTV_{\_4140}$, as required. For such cases, the field edges should be adjusted to extend at least 2 cm beyond the modified $CTV_{\_4140}$.

6.4.2 Whole Bladder Field**(2/25/2014)**

The $CTV_{\_6120}$ includes any gross tumor volume (GTV), the entire bladder volume, and the entire bladder wall thickness. The $PTV_{\_6120}$ consists of a margin 0.5 cm around the $CTV_{\_6120}$ edges except superiorly where the extension is 1.5 cm. The $PTV_{\_6120}$ may be treated by a four field box approach or by only parallel opposed lateral fields. Field corner shaping is employed using MLCs.

The following table summarizes the naming of targets and critical structures for submission of data to RTOG. **Note:** Structures must be labeled as listed in the table below, and digital RT data submission of all of these structures is required. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed.

RTOG 0926	
Standard Name	**Description**
CTV_4140	Pelvic Target
CTV_6120	Whole Bladder Target
PTV_6120	0.5 cm expansion
GTV	Gross Tumor Volume
External	External patient contour
Femur_L	Left Femur
Femur_R	Right Femur
Femurs	Both femurs
Rectum	Rectum

6.5 Critical Structures

Femoral and rectal structure doses must be assessed from DVHs calculated for composite (summed) treatment plans (Pelvis + whole bladder plans). The maximum dose to the femoral heads should be less than 45 Gy. Fifty percent of the rectum volume should receive less than 55 Gy ($V_{55Gy} < 50\%$). 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.

6.6 Documentation Requirements (12/17/13) (3/31/14)

6.6.1 Within 7 working days of the initiation of treatment, the CT treatment plan must be submitted digitally to TRIAD (see Section 12.2).

6.6.2 Within 7 working days of the initiation of treatment, digitally reconstructed radiographs and initial approved small pelvis portal images of each treatment field in JPEG format must be submitted digitally to TRIAD (see Section 12.2).

6.7 Compliance Criteria (12/17/13)

6.7.1 Field Borders/Volumes

Per Protocol: Refer to Section 6.4.

Variation Acceptable: Actual field borders and/or PTVs vary within 1-2 cm from those stated in Section 6.4 and include the target structures described above.

Deviation Unacceptable: Actual field borders and/or PTVs transect a target structure or deviate more than 2 cm beyond the borders stated in Section 6.4.

6.7.2 Specified Radiation Dose (Critical structures)

Per Protocol: Refer to Section 6.5.

Variation Acceptable: Maximum dose to the critical structure is between 0 and 10% higher than the specified protocol dose (See Section 6.5).

Deviation Unacceptable: Maximum dose to the critical structure is greater than 10% higher than the specified protocol dose (See Section 6.5).

6.7.3 Minimum Isodose Coverage (Applies to $CTV_{\_4140}$ and $PTV_{\_6120}$ 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 $D_{99\%}$ is used as the dose specifier.

Per Protocol: $D_{99\%} > 95\%$. Dose covering 99% of the volume of any target volume is no less than 95% of the prescribed dose.

Variation Acceptable: $D_{99\%} < 95\%$ but $D_{99\%} > 90\%$. Dose covering 99% of the volume of any target volume is no less than 90% of the prescribed dose.

Deviation Unacceptable: $D_{99\%} < 90\%$. Target structures coverage falls below 90% of the prescribed dose.

6.7.4 Maximum Dose (Applies to each target independently)

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

Per Protocol: $V_{107\%} < 0.12$ cc. Less than 0.12 cc of the target receives a dose exceeding 107% of the prescribed dose.

Variation Acceptable: $V_{107\%} > 0.12$ cc but this dose does not exceed 110% of this dose.

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

6.7.5 Elapsed Days

Per Protocol: No more than 7 break days

Variation Acceptable: 8-14 break days

Deviation Unacceptable: 15 or more break days

6.8 Treatment Interruption

For a grade 3 acute colitis, cystitis, or any other grade 3 infield (radiation-related) toxicity during any treatment week, treatment (both radiation and chemotherapy) 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.

6.9 R.T. Quality Assurance Reviews (12/17/13)

The Radiation Oncology Co-Chair, William Shipley, MD, will perform RT Quality Assurance Reviews after complete data for the first 20 cases enrolled has been received at IROC Philadelphia. Dr. Shipley will perform the next review after complete data for the next 10 cases enrolled has been received at IROC Philadelphia. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at IROC Philadelphia, whichever occurs first. These reviews will be ongoing.

6.10 Radiation Adverse Events

See Section 7.9 for additional Adverse Events information and Section 7.10 for Adverse Event Reporting Guidelines.

- *Genitourinary:* Frequency of urination, nocturia, acute or chronic bleeding from the bladder mucosal surface and ureteral obstruction

- *Gastrointestinal:* Rectal irritation, bowel obstruction or bleeding, rectal ulcers, hematochezia, fistula formation, nausea and/or vomiting
- *Dermatologic:* Erythema, loss of pubic hair which could be permanent
- *Gynecological:* Vaginal bleeding, fistula formation
- *Other:* Fatigue

7.0 DRUG THERAPY (4/20/15)
Protocol treatment must begin within 15 weeks after transurethral resection.

7.1 Treatment (4/6/12)

7.1.1 Agents

Two radiosensitizing chemotherapy regimens will be permitted for this study: either cisplatin alone OR combination of mitomycin and 5FU. The choice may be made by treating physicians based on their medical discretion for platinum suitability. However, patients with GFR < 60 ml/min MAY NOT be treated with cisplatin.

7.1.2 Dose Definition

Body surface area calculations will be based on actual or ideal body weight as per institutional policy.

7.1.3 Duration of Treatment

Radiation and chemotherapy should both be held together. If any doses of chemotherapy are held or missed, they should not be made up.

7.2 Cisplatin (4/6/12)

Refer to package insert for additional information.

7.2.1 Technique of Administration

Cisplatin (15 mg/m^2) will be administered as a 60-minute infusion on days 1, 2, 3, 15, 16, 17, 29, 30, and 31 over 6 to 8 weeks. Pre-cisplatin hydration: On the days of cisplatin administration patients are instructed to increase their fluid intake to at least six 8-ounce glasses of water (or other fluids) over the 12 hours prior to i.v. hydration preceding chemotherapy. Pre-cisplatin hydration should consist of 500 cc/hr of NS and should continue at that rate until a urinary output of ≥ 100 cc/hr is achieved. Post-cisplatin hydration: The post-cisplatin hydration i.v. hydration should consist of NS 500 cc in one hour.

- Anti-emetic regimens, which may include ondansetron, granisetron, metroclopramide, lorazepam, dexamethasone, diphenhyramine hydrochloride and/or prochlorperazine, are recommended before and after cisplatin administration.

7.2.2 Dose Formulation

Cisplatin is available as 10 mg and 50 mg vials of dry powder which are reconstituted with 10 ml and 50 ml of sterile water for Injection USP, respectively. Cisplatin is also available as a 1 mg/ml solution in 50 and 100 mg vials.

7.2.3 Pharmacology

The dominant mode of action of cisplatin appears to involve the formation of a bifunctional adduct resulting in DNA crosslinks. How this kills the cell remains unclear. There are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents. Plasma levels of cisplatin decay in a biphasic mode with an initial half-life of 18 to 37 minutes and a secondary phase ranging from 44 to 190 hours. This prolonged phase is due to protein binding which exceeds 90%. Urinary excretion is incomplete with only 27 to 45% excreted in the first five days. The initial fractions are largely unchanged drugs.

7.2.4 Administration

Cisplatin should be given immediately after preparation as a slow intravenous infusion.

7.2.5 Storage

The intact vials should be stored at room temperature. Once reconstituted, the solution should be kept at room temperature to avoid precipitation. Due to a lack of preservatives, the solution should be used within 8 hours of reconstitution.

7.2.6 Supply

Commercially available.

7.2.7 Adverse Events

- *Hematologic:* Myelosuppression
- *Gastrointestinal:* Nausea and vomiting; anorexia
- *Renal:* Elevation of BUN and creatinine, hyperuricemia, renal tubular damage
- *Cardiac:* Rare cardiac abnormalities

- *Neurological:* Sensory (taste), peripheral neuropathy, seizures
- *Allergy:* Anaphylactoid and urticarial reactions (acute); rash
- *Other:* Fatigue, otoxicity including hearing loss or tinnitus, loss of muscle function

7.3 Cisplatin Dose Modifications (4/6/12)

7.3.1 A complete blood count and serum creatinine will be drawn at the start of weeks 1, 3, and 5 or at the end of the week prior. Dose modifications for the drugs given that week will be based upon these results. Dose reductions based upon clinical problems such as neurotoxicity may involve discontinuation of the drug altogether and are specified in the text below.

7.3.2 Modifications for nephrotoxicity during chemoradiotherapy are as listed in the table below. (If serum creatinine is out of range, but CrCl is in range, 100% can be given):

Day 1 Level	Dose
Serum creatinine ≤ 1.5 mg%	100%
Serum creatinine > 1.33 x baseline	75%
Serum creatinine > 1.5 x baseline	Hold cisplatin

7.3.3 Modifications for myelosuppression during chemoradiotherapy are as listed in the table below:

% Calculated Dose

		Platelet Count			
		≥ 150K	100-149K	75-99K	< 75K
ANC (x 1000)	≥ 1.4	100	100	100	75
	1.0 - <1.4	100	75	75	75
	< 1.0	0	0	0	0

7.3.4 Modification for peripheral neurotoxicity grade 3: Omit cisplatin.

7.4 Mitomycin (4/6/12)

7.4.1 For patients treated with mitomycin and 5FU, mitomycin will be given as an intravenous bolus dose of 12 mg/m^2 on day 1 of radiotherapy. No additional mitomycin will be administered.

7.5 5FU (4/6/12)

Refer to package insert for additional information.

7.5.1 Technique of Administration

5FU will be administered as a continuous infusion at 500 mg/m2/24 hrs for 5 consecutive days during weeks 1 and 4 of radiation treatment (corresponding to fractions 1-5 and 16-20). A suitable infusion pump will be used for this purpose.

7.5.2 Any desired antiemetics may be used. Typically, simple antiemetics such as oral prochlorperazine are sufficient for nausea control.

7.5.3 Supply

Commercially available

7.6 5FU Dose Modifications (4/6/12)

7.6.1 The principal toxicities of 5FU are diarrhea and mucositis. Mild diarrhea may be controlled when necessary with loperamide. If palmar desquamation occurs, this may be managed with pyridoxine 50 mg every other day. Grade 4 toxicities are rare at the proposed doses, but any such occurrences should be immediately reported and treatment halted. Dose modifications for diarrhea or mucositis are described in the table below:

Dose Modifications for 5FU-Related Diarrhea or Mucositis

Grade 1	Grade 2	Grade 3	Grade 4
No change	1. Reduce infusion dose by 125 mg/m2/day 2. Continue radiation on schedule	1. Discontinue infusion permanently 2. Consider interruption of radiation until resolution to < grade 1	1. Discontinue all therapy 2. Reassess weekly and consider resumption of radiation after resolution to < grade 1

7.7 Treatment Interruption (4/6/12)

For grade 3 or greater hematologic toxicity (ANC, platelets), both radiation and chemotherapy (i.e., all treatment) should be held until toxicities resolve to grade 1. For radiation on hold (Section 6.8), chemotherapy should be held also. For a grade 3 acute colitis, cystitis, or any other grade 3 infield (radiation-related) toxicity during any treatment week, treatment (both radiation and chemotherapy) 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.

For any grade 4 toxicity, all treatment should be held, and chemotherapy should not be resumed. Patients should be reassessed weekly, and radiation therapy may be restarted after resolution of toxicity to the grade 2 level. If the delay is greater than 3 weeks, the patient should be considered intolerant of protocol therapy and appropriate off-protocol therapy given.

7.8 Modality Review (4/6/12) (3/31/14)

The Medical Oncology Co-Chair, M. Dror Michaelson, MD PhD, will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: **Per Protocol:Acceptable Variation; Unacceptable Deviation; and Not Evaluable**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

Dr. Michaelson will perform a review after complete data for the first 20 cases enrolled has been received at NRG Oncology. Dr. Michaelson will perform the next review after complete data for the next 10 cases enrolled has been received at NRG Oncology. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at NRG Oncology, whichever occurs first.

7.9 Adverse Events (01-Feb-2019)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.)

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).

7.9.1 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. February 29, 2012; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm]

7.9.2 Serious Adverse Events (SAEs) — Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in Section 7.10 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in Section 7.10. **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.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.9.3 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.

7.10 CTEP-AERS Adverse Event Reporting Requirements (3/31/14)**(3/6/2015)**

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 Operations 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 routine 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 12.1).

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies Utilizing a Commercially Available Agent within 30 Days of the Last Administration of the Commercially Available Agents (Cisplatin, Mitomycin, 5FU)/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 ≥ 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.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

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.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational 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

8.0 SURGERY (4/20/15)

8.1 Pre-Chemoradiation Evaluation

We recommend that the endoscopic evaluation include the following:

8.1.1 Cystoscopy with tumor mapping on the initial Cystoscopic Report (Appendix V)

8.1.2 A visibly complete transurethral resection of the tumor (TURBT). Tumor specimens should be sent to the NRG Oncology Biospecimen Bank – San Francisco as described in Section 10.0.

8.1.3 After the TURBT, if possible, take one biopsy of the tumor base and two biopsies of the periphery of the tumor by cold cup for additional analysis of the completeness of the TURBT.

8.1.4 Bimanual examination before and after TURBT to evaluate possible residual tumor bulk using the following criteria: exam not performed, no pelvic mass, mobile pelvic mass, fixed pelvic mass. Bimanual examination may not be possible in some patients, such as those that are very obese.

8.1.5 One biopsy each from the bladder neck and from the prostatic urethra sampling the mucosa and, if the prostatic mucosa has a visible tumor, the stroma beneath the prostatic mucosa should also be biopsied.

8.2 Post-Chemoradiation Endoscopic Response Evaluation

This evaluation will take place 8-10 weeks following completion of the chemoradiation. The evaluation will include: cytology, cystoscopy, tumor site transurethral biopsy, and bimanual examination after biopsy (this latter requirement need not be met in an obese patient). Operative reports and pathology reports from TURBT specimens should be submitted (see Section 12.1). Operative reports should describe the surgeon's assessment of the tumor burden in the bladder and prostatic urethra as well as the overall clinical stage at the conclusion of the resection. Moreover, it should document the findings of the bimanual examination. The pathology report should include the gross and microscopic description of tumor location, tumor grade, and tumor stage using the T-classification of the TNM staging system. Specifically, pathology reports should include a description of the depth of tumor invasion.

8.3 Radical Cystectomy

For most patients who have a persistent tumor on re-evaluation following completion of the protocol, a radical cystectomy is recommended. In the male, radical cystectomy will include a complete en bloc resection of the bladder, prostate, seminal vesicles, and intramural ureters, as well as associated peritoneum and perivesical fat. In the female, radical cystectomy will include resection of the bladder along with the intramural ureters, perivesical fat and peritoneum associated with the bladder. Depending on the local extent of the tumor and urinary diversion choice of the patient, a resection of the urethra anterior and lateral walls of the vagina, uterus, fallopian tubes, and ovaries may also be required.

Orthotopic diversion, continent cutaneous diversion, and incontinent cutaneous diversions are all permissible as jointly determined by the surgeon and patient.

When feasible, total lymphadenectomy should be performed. The dissection should include resection of nodal tissue from the bifurcation of the common iliac vessels to the inguinal ligament and from the genitofemoral nerve to the hypogastric artery. Operative reports and pathology reports from cystectomy specimens should be submitted (see Section 12.1). The pathology report should include the gross and microscopic description of tumor location, tumor grade and tumor stage using the TNM staging system. Specifically, pathology reports should include a description of the depth of tumor invasion, involvement of other organs or pelvic structure, summary of the margin status and the location and total number of lymph nodes resected and involved with carcinoma.

8.4 Surveillance Cystoscopies in Complete Responding Patients

Subsequent cystoscopic evaluations will be every 3 months for the first year, every 4 months for the second year and every 6 months for years 3, 4, and 5, and then annually, provided there has been no recurrence of the tumor. These periodic evaluations will be done in accordance with the schedule in Section 11.0 and Appendix I and will include cytology, biopsy of the original tumor site, and biopsy of any suspicious areas as well as a bimanual examination. If after two re-evaluations in which the tumor site re-biopsies have been negative and the urologist observes nothing suspicious, a cytology without biopsy is permitted. Regular cystoscopic follow-up will allow additional therapy to be initiated at the earliest prompt opportunity if relapse occurs.

8.5 Surgical Quality Assurance Reviews

The Urology Co-Chair, Douglas Dahl, MD, will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at NRG Oncology. Dr. Dahl will perform the next review after complete data for the next 10 cases enrolled has been received at NRG Oncology. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at NRG Oncology, whichever occurs first. Surgical reviews will require detailed operative and pathology notes.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy (4/6/12)

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 within each site's source documents as concomitant medication.

9.1.1 For patients who are treated with attempted bladder preservation, either radical cystectomy or possibly, further intravesical drug therapy will be promptly considered for a local persistence or local re-occurrence. This subsequent therapy will be given at the discretion of the urologist. The rates of local recurrence and/or distant metastases will be reported.

9.1.2 For patients who develop distant metastases, additional therapies will be treated at the discretion of the primary physicians.

9.1.3 Anti-emetic regimens, which may include ondansetron, granisetron, metoclopramide, lorazepam, dexamethasone, diphenhydramine, hydrochloride and/or prochlorperazine, are recommended before and after chemotherapy administration.

9.1.4 The use of growth factors is permitted.

10.0 TISSUE/SPECIMEN SUBMISSION (4/20/15)

NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission or quality of life assessment. If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient's specimens as specified in Section 10.0 of the protocol. Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 Tissue/Specimen Submission

The NRG Oncology Biospecimen Bank at the University of California San Francisco acquires and maintains high quality specimens from NRG Oncology trials. Tissue from each block is preserved through careful block storage and processing. NRG Oncology encourages participants in protocol studies to consent to the banking of their tissue. The NRG Oncology Biospecimen Bank provides tissue specimens

to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions.

In this study, primary tumor tissue from the pretreatment TURBT as well as two biopsies obtained from the tumor periphery will be submitted to the NRG Oncology Biospecimen Bank for the purpose of tissue banking for biomarker studies (strongly recommended but not required). Blood and urine specimens will be collected for banking for future research (strongly recommended but not required).

10.2 Specimen Collection: Strongly Recommended (12/17/13)
For patients who have consented to participate in the tissue/blood/urine component of the study (See sample consent).
The following must be provided in order for the case to be evaluable by the NRG Oncology Biospecimen Bank:

10.2.1 One H&E stained slide (slide can be a duplicate cut stained H&E of the diagnostic slide [block]; it does not have to be the diagnostic slide itself)

10.2.2 A corresponding paraffin-embedded tissue block of the tumor or a 2 mm diameter core of tissue, punched from the tissue block containing the tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number. NOTE: A kit with the punch, tube, and instructions can be obtained free of charge from the NRG Oncology Biospecimen Bank. Block or core must be clearly labeled with the pathology identification number and block number that corresponds to the Pathology Report.

- The submitted material must be from malignant tumor, not necrotic or fibrotic tissue. If the submitted material is reviewed and is not tumor, the site may be assessed a protocol violation.

10.2.3 A Pathology Report documenting that the submitted block or core contains tumor. The report must include the RTOG (NRG) protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

10.2.4 A Specimen Transmittal Form clearly stating that tissue is being submitted for the NRG Oncology Biospecimen Bank; if for translational research, this should be stated on the form. The form must include the RTOG (NRG) protocol number and patient's case number.

10.2.5 Serum, plasma, whole blood, and urine
See Appendix VI for the blood and urine collection kits and instructions.
The following materials must be provided to the NRG Oncology Biospecimen Bank: A Specimen Transmittal Form documenting the date of collection of the serum, plasma, whole blood, and urine; the RTOG (NRG) protocol number, the patient's case number, and method of storage, for example, stored at -20° C, must be included.

10.2.6 Storage Conditions
Store at -80°C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only).
  OR:
- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only).
  OR:
- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only).

Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

10.2.7 Specimen Collection Summary

Specimen Collection			
Specimens taken from patient:	**Collected when:**	**Submitted as:**	**Shipped:**
Representative H&E stained slides of the primary tumor	Pre-treatment	H&E stained slide	Slide shipped ambient
A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or a 2 mm	Pre-treatment	Paraffin-embedded tissue block or punch biopsy (must match the H&E slide being submitted)	Block or punch shipped ambient

diameter core of tissue, punched from the tissue block with a skin punch			
SERUM: 5-10 mL of whole blood in each of 2 red-top tubes and centrifuge	Pre-treatment	Frozen serum samples containing **0.5 mL** per aliquot in 1 mL cryovials (five to ten)	Serum sent frozen on dry ice via overnight carrier
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tubes (purple/lavender top) and centrifuge	Pre-treatment	Frozen plasma samples containing **0.5 mL** per aliquot in 1 mL cryovials (five to ten)	Plasma sent frozen on dry ice via overnight carrier
DNA: 5-10 mL of anticoagulated whole blood in EDTA tubes (purple/lavender top) and mix	Pre-treatment	Frozen whole blood samples containing **1 mL** per aliquot in 1ml cryovials (three to five)	Whole blood sent frozen on dry ice via overnight carrier
10-20 mL clean-catch urine	Pre-treatment	Two **5-10 mL** urine aliquots in 2 sterile 15 ml polypropylene centrifuge tubes. Store frozen at -20° or 80° C	Urine sent frozen on dry ice via overnight carrier

10.2.8 Submit materials as follows:

U. S. Postal Service Mailing Address: <u>For Non-Frozen Specimens Only</u>
NRG Oncology Biospecimen Bank
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): <u>For Trackable FFPE and ALL Frozen Specimens</u>
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

Questions: 415-476-7864/FAX 415-476-5271; NRGBB@ucsf.edu

10.3Confidentiality/Storage (01-Feb-2019)
(

10.3.1 Upon receipt, the specimen is labeled with the RTOG (NRG) protocol number and the patient's case number only. The NRG Oncology Biospecimen Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.3.2 Specimens for banking will be stored for an indefinite period of time. Specimens for the biomarker component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

11.1 **Study Parameters**: See Appendix I for a summary of assessments and time frames. See Section 11.2 below for details and/or exceptions to Appendix I.

11.2 Evaluation Following Chemoradiotherapy

11.2.1 After the first year of post-treatment follow-up, the bimanual exam under anesthesia with bladder biopsy may be omitted if the office cystoscopy and urine cytology are not positive.

11.2.2 During the 3rd post-treatment year, the AUA symptom score will be obtained for patients who still have a native bladder.

11.3 Measurement of Response

11.3.1 The objective response of the local bladder tumor will be described as follows:

- Complete Response (a CR or a pT0 response) requires the absence of any tumor in the tumor site re-biopsy specimen or elsewhere in the bladder and a urine cytology specimen that is not positive.
- Partial Response (PR) requires that all response criteria of a CR except the urine cytology remain positive.
- No Response (NR) requires the continued presence of a tumor in the tumor site biopsy specimen or elsewhere. The depth of invasion of the persistent or recurrent tumor will be noted (i.e., Ta, Tis, T, or ≥ T2).
- Progression requires an increase of 50% or more in the largest diameter of the endoscopically appreciable tumor or the progression from stage T1 to stage T2 or beyond.

11.3.2 Distant disease progression: The first appearance of disease in a non-regional lymph node, solid organ or bone. This may be identified on a routine follow-up CT scan or bone scan or a study performed to work up a specific patient complaint. Additional radiographic studies or biopsies may be performed at the discretion of the treating physician in equivocal cases but are not required. Radiographic evidence of metastasis is sufficient for evaluation of this endpoint. Time to development of distant metastasis will be defined as the time to the first appearance of distant metastasis.

11.4 Criteria for Discontinuation of Protocol Treatment

- Progression of disease;
- A delay in protocol treatment, as specified in Sections 6.0 and/or 7.0

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

12.0 DATA COLLECTION (01-Feb-2019)

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster 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. 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 can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also 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 members’ 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 ctsucontact@westat.com.

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission (12/17/13)

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** Pathology Report [from TURBT] **(P1)** Operative Report [from TURBT] **(S2)**	**Within 2 weeks of study entry.**
American Urological Association (AUA) Symptom scores **(PQ)**	**Within 2 weeks of study entry and then in year 3 post treatment for patients with a native bladder**
Treatment Form **(TF)**	**Within 2 weeks after chemoradiation therapy is completed**
Post-treatment Evaluation Form **(F0)**	**Within 8-10 weeks following completion of chemoradiation**
Follow-up Form **(F1)**	**Post chemoradiation: every 3 months for (1) year; every 4 months for (1) year; every 6 months for (3) years; then annually**
Surgical Form (for cystectomy) **(S1)**	**Within 2 weeks after surgery (if cystectomy done)**
Surgical Operative Note (from cystectomy) **(S2)** Surgical Pathology Report (from cystectomy) **(S5)**	

Item	Due
Digitally reconstructed radiographs and initial approved small pelvis portal images of each treatment field **(TP)**	**Within 1 week of RT start** Must be digitally submitted in Dicom or JPEG format to TRIAD. See Section 12.2.
Final Dosimetry Information:	
Radiotherapy Form **(T1) web entry**	**Within 1 week of RT end**
Complete Daily Treatment Record **(T5) [Copy to HQs]**	**Within 1 week of RT end**
NOTE: ADDITIONAL SIMULATION AND PORTAL FILMS AND/OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.	

12.2 Summary of Dosimetry Digital Data Submission (Submit to TRIAD; see Section 5.0 for account access and installation instructions) (12/17/13)

Preliminary Dosimetry Information **Digital data submission includes the following:** • CT dataset with contours for all critical normal structures, CTV, and PTVs • Digital beam geometry for initial and boost beam sets • Doses for initial, boost and composite sets of concurrently treated beams • Digital DVH data for all required critical normal structures, CTV, and PTVs for total dose plan • All required structures **MUST** be labeled per the table in Section 6.4. • Digitally reconstructed radiographs and initial approved small pelvis portal	Within 1 week of start of RT

images of each treatment field in JPEG format **(TP)** • Digital Data Submission Information (DDSI) Form **Upon submission of the digital data via TRIAD, complete an online Digital Data Submission Information (DDSI) Form** **http://www.rtog.org/CoreLab/RTQASubmissionInformation.aspx**	

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint

The rate of freedom from radical cystectomy at 3 years

13.1.2 Secondary Endpoints

- To assess the following clinical outcomes:
  - Rate of freedom from radical cystectomy at 5 years
  - Rate of freedom from the development of distant disease progression at 3 and 5 years
  - Rate of freedom from progression of bladder tumor to stage T2 or greater at 3 and 5 years
  - Disease-specific survival at 5 years
  - Overall survival
- Incidence of adverse events (based on the CTEP Active Version of the CTCAE)
- Recurrence rate of any local bladder tumor
- Collection of pretreatment and post-treatment tissue, blood, and urine specimens for translational studies and for correlation with response and clinical outcome
- Descriptive analysis for AUA symptom score at baseline and 3 years

13.2 Sample Size

It is hypothesized that this treatment will result in a 3-year freedom from radical cystectomy rate of 75%. A lower bound of 60% on the confidence interval for the 3-year freedom from radical cystectomy rate will be promising enough to pursue this regimen further. A sample size of 33 analyzable patients will provide a one-sided 97.5% confidence interval around the hypothesized 75% three-year freedom from radical cystectomy rate with a lower-bound of 60%. In terms of type I error, this design provides a 2.5% chance of observing a 3-year freedom from radical cystectomy rate of less than 60% if the true rate is 75%. Adjusting the sample size for ineligible or dropout cases by 10%, a **total of 37 patients** are needed for this study.

13.3 Accrual and Duration(3/6/2015)

At the time of trial design the legacy cooperative group of RTOG (now NRG Oncology) had no prior experience with accrual of patients with non-muscle invading bladder cancer. Thus it seems wise to state that the accrual rate will be likely at the level of one patient per month. However, a questionnaire returned by the principal investigators of our full membership institutions and our affiliate membership institutions who have accrued previously to bladder studies indicate accrual will be twice this estimate. Assuming the accrual to this study will be 37 patients, this trial should complete accrual within 3 years.

13.4 Analysis Plan

13.4.1 Primary Analysis

The primary analysis will be performed when all eligible patients have at least 3 years of follow-up. The rate of freedom from radical cystectomy at 3 years is defined as the proportion of patients who have not had a radical cystectomy by 3 years among all eligible patients.

This rate will be evaluated based on a 1-sided 97.5% confidence interval. If the bottom of the confidence interval is at least 0.60, then the regimen will be considered promising enough to warrant further investigation. If the bottom of the confidence interval is less than 0.25, then the regimen will not be considered any further. If the bottom of the confidence interval is anywhere between 0.25 and 0.59, the investigators will consider the possibility of further investigations of this regimen.

13.4.2 Secondary Analysis

- Analysis Plan for Clinical Outcomes

All eligible patients who received protocol treatment will be included in the outcome analyses. The rates of freedom from radical cystectomy at 5 years will be estimated by a proportion; logistic regression will be used to model the distribution of freedom from radical cystectomy at both 3 and 5 years; both unadjusted and adjusted odds ratios and respective 95% confidence interval will be computed. All other secondary clinical outcome endpoints will be estimated as time-to-event endpoints. The time to failure will be measured from the date of registration to the date of the event of interest. Z-statistics will be used for the rate of freedom from radical cystectomy at 5 years. The rates of freedom from distant metastasis and disease-specific survival will be estimated by using cumulative incidence[20] of the event of interest, taking into account the informative nature of censoring due to competing risks. Overall survival will be estimated using the Kaplan-Meier method.[21] All time-to-event endpoints will be modeled by Cox proportional hazard regression[22] with appropriate clinical and demographic variables.

- Evaluation of Grade 3+ Adverse Events

  Tabulation of adverse events will be reported by type, grade, and attribution of adverse event based on the CTEP Active Version of the CTCAE. The grade 3+ adverse event rate is defined as the proportion of patients who have adverse events among all eligible patients.

  Logistic regression will be used to model the distribution of grade 3+ adverse events. Both unadjusted and adjusted odd ratios and the respective 95% confidence interval will be computed. The time to grade 3+ adverse events will be estimated using the cumulative incidence method.[20] Death without a grade 3+ adverse event will be considered as a competing risk. Alive patients without acute grade 3+ adverse events will be censored at the time of analysis.
- Evaluation of Recurrence Rate of Any Local Bladder Tumor

  The recurrence rate of any local bladder tumor is defined as the proportion of patients who have local bladder tumor recurrence. This proportion will be estimated. Logistic regression will be used to model the distribution. Both unadjusted and adjusted odds ratios and respective 95% confidence interval will be computed.
- Analysis Plan for AUA Symptom Score

  AUA symptom score will be collected at baseline and 3 years for information regarding bladder capacity, compliance, detrusor instability and leak pressures, and a partial assessment of "bother factor" from the symptom score. The change from baseline to 3 years for each patient will be calculated and descriptive statistics (mean, median, and standard deviation) will be calculated.
- Early Stopping Due to Adverse Events

  The study will be monitored by the CDUS version 3.0. If at any time a grade 5 adverse event definitely, probably, or possibly related to treatment is reported, it will be reviewed by the study chairs, the study statistician, the NRG Oncology GU cancer committee chair, or other appropriate NRG Oncology Leadership as needed. Case report forms, source documentation, and a statistical report summarizing the study will be reviewed as soon as possible. During this review, accrual will be suspended if necessary. Following this review, the study chairs, the study statistician, the NRG GU cancer committee chair, and the NRG executive committee will discuss the findings and make a decision about amending the protocol and/or continuing the study.
- Interim Reports

  Interim reports will be prepared every six months until the final analysis. In general, the interim reports will include information about:
  - Patient accrual rate with projected completion rate;
  - Pretreatment characteristics of patients accrued;
  - Compliance rate of treatment per protocol; and
  - Frequency and severity of adverse events due to radiation therapy and chemotherapy.
- CDUS Reporting

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

13.5 Gender and Minorities

In conformance with the National Institutes of Health Revitalization Act of 1993 with regard to the inclusion of women and minorities in clinical research, the possible difference in any of the above

endpoints between men and women, or whites and non-whites, will be investigated. The prior RTOG bladder cancer trial, 0233, accrued about 1% Hispanic, 7% non-white patients and 16% women. With the proposed 37 evaluable patients, there will not be enough statistical power to detect the difference in the primary endpoint between race groups and/or gender groups. Nonetheless, the descriptive statistics for each of these groups will be reported.

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	**0**	**1**	**1**
Not Hispanic or Latino	**7**	**29**	**36**
Ethnic Category: Total of all subjects	**7**	**30**	**37**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	**0**	**1**	**1**
Asian	**0**	**0**	**0**
Black or African American	**1**	**2**	**3**
Native Hawaiian or other Pacific Islander	**0**	**0**	**0**
White	**6**	**27**	**33**
Racial Category: Total of all subjects	**7**	**30**	**37**

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APPENDIX I: STUDY PARAMETER TABLE: Pre-Study Assessments (3/31/14)

Pre-Study Assessments (may be required for eligibility)	
"Outside" pathology/cytology evaluation	See Section 4.1.1
Body Surface Area	x
History/Physical	x
Weight	x
Zubrod Status	x
TURBT	x
Cystoscopy	x
Bimanual exam under anesthesia	x
Bladder Biopsy	x
CBC w/diff, Platelets	x
Serum Creatinine	x
Bilirubin, Alk Phos.	x
GFR	x
SGOT, LDH, BUN	x
Magnesium, Calcium	x
Pregnancy Test	x
CT Scan	x
IVP	Optional
Bone Scan	Optional
Chest X-ray	x
AUA SI	x
-Continued on next page-	

APPENDIX I, STUDY PARAMETER TABLE: Assessments During ChemoRT			
	Before each chemotherapy cycle	**Weekly**	**Final treatment day**
Weight		x	
Zubrod Status			x
CBC w/diff, Platelets		x	
Serum Creatinine	x		
Adverse event evaluation	x		
-Continued on next page-			

APPENDIX I, STUDY PARAMETER TABLE: Assessments in Follow Up **See Section 11.2 for details.*		
	8-10 weeks Post-ChemoRT	**Post-treatment Follow-Up** q 3 mos in 1st yr; q 4 mos in 2nd yr; q 6 mos for yrs 3, 4, and 5; then annually
History/Physical		x
Weight		x
Zubrod Status		x
Cystoscopy	x	x
Urine Cytology	x	x
Bimanual exam under anesthesia	x	x*
Bladder Biopsy	x	x*
CBC w/diff, Platelets		x
Serum Creatinine		x
CT Scan		Yearly for the first 3 years
Chest X-ray		Yearly for the first 3 years
AUA SI		3rd post-treatment yr*
Adverse event evaluation	x	x

APPENDIX II

ZUBROD PERFORMANCE SCALE

0	**Fully active, able to carry on all predisease activities without restriction**
1	**Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work**
2	**Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours**
3	**Capable of only limited self-care, confined to bed or chair 50% or more of waking hours**
4	**Completely disabled. Cannot carry on self-care. Totally confined to bed**
5	**Death**

APPENDIX III(3/6/2015)
AJCC Staging System, 6th Edition
Bladder

DEFINITION OF TNM

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Ta Noninvasive papillary carcinoma
Tis Carcinoma *in situ*: "flat tumor"
T1 Tumor invades subepithelial connective tissue
T2 Tumor invades muscle
  T2a Tumor invades superficial muscle *(inner half)**
  T2b Tumor invades deep muscle *(outer half)**
T3 Tumor invades perivesical tissue
  T3a microscopically
  T3b macroscopically *(extravesical mass)*
T4 Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
  T4a Tumor invades the prostate, uterus, vagina
  T4b Tumor invades the pelvic wall, abdominal wall

*For clinical staging based on the TURBT tissue it is commonly not possible for the pathologist to distinguish between cT2a and cT2b, so the protocol plan will be to group cT2a and cT2b together as all cT2

Regional Lymph Nodes (N)

Regional lymph nodes are those within the true pelvis; all others are distant nodes.

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single lymph node, 2 cm or less in greatest dimension
N2 Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension
N3 Metastasis in a lymph node more than 5 cm in greatest dimension

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

STAGE GROUPING

Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0

AJCC Staging System, 6th Edition
Bladder

Stage IV	T4b	N0	M0
	Any T	N1	M0
	Any T	N2	M0
	Any T	N3	M0
	Any T	Any N	M1

HISTOPATHOLOGIC TYPE

The histologic types are:

Transitional cell carcinoma *(urothelial)*
- *In situ*
  - Papillary
  - Flat
- With squamous metaplasia
- With glandular metaplasia
- With squamous and glandular metaplasia

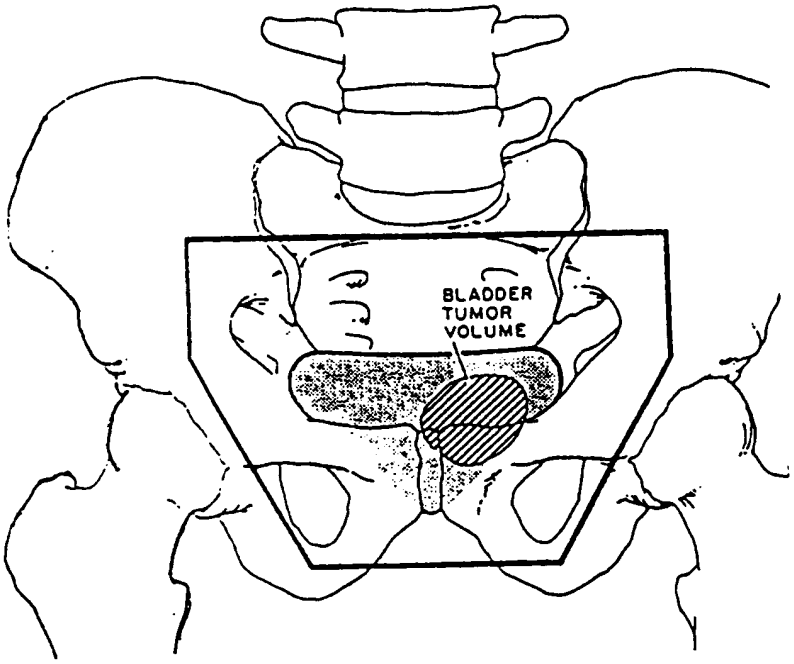
Squamous cell carcinoma
Adenocarcinoma
Undifferentiated carcinoma

HISTOPATHOLOGIC GRADE (G)

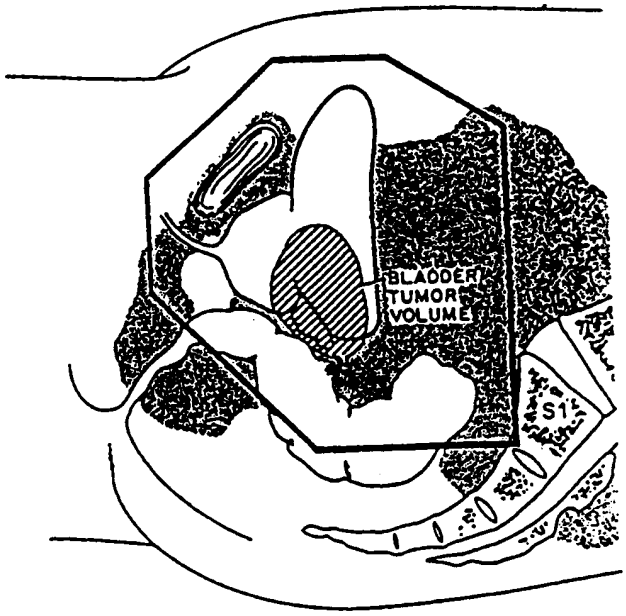
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3-4	Poorly differentiated or undifferentiated

APPENDIX IV
SMALL PELVIC FIELDS

Anterior View



Lateral View



APPENDIX V(3/6/2015)
CYSTOSCOPY REPORT FORM

PDF form (attached) to be incorporated into PDF version of protocol that will be posted on RTOG legacy website.

APPENDIX VI (4/20/15)

Appendices for NRG Oncology Biospecimen Collection
FFPE Specimen Plug Kit Collection
Blood Collection Kit Instructions
Urine Collection Kit Instructions

Shipping Instructions:

U.S. Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen or Trackable Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

- ❑ Include all NRG Oncology paperwork in pocket of biohazard bag.
- ❑ Check that the Specimen Transmittal Form (STF) has the consent boxes checked off.
- ❑ Check that all samples are labeled with the RTOG (NRG) study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

- ❑ **FFPE Specimens:**
  - ○ Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
  - ○ FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear the slides shaking it is likely that they will break during shipping.
  - ○ Slides, Blocks, or Plugs can be shipped ambient or with a cold pack either by United States Postal Service (USPS) to the USPS address (94143) or by Courier to the Street Address (94115). **Do NOT ship on Dry Ice**.

- ❑ **Frozen Specimens:**
  - ○ Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
  - ○ Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  - ○ Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - ○ Send frozen specimens via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80° C until ready to ship.

- ❑ **For Questions regarding collection/shipping please contact the NRG Oncology Biospecimen Bank – San Francisco by e-mail: NRGBB@ucsf.edu or phone: 415-476-7864 or Fax: 415-476-5271.**

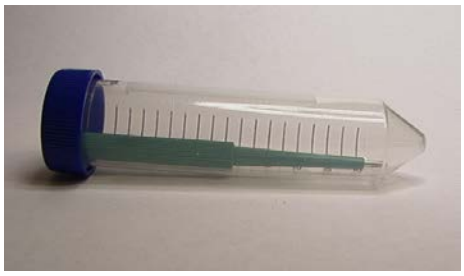
NRG ONCOLOGY FFPE SPECIMEN PLUG KIT INSTRUCTIONS

This Kit allows sub-sampling of an FFPE block for submission to the NRG Oncology Biospecimen Bank – San Francisco. The plug kit contains a shipping tube and a punch tool.

Step 1
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.

Step 2
Label the punch tool with the proper specimen ID. DON'T remove specimen from the punch.

Use a separate punch tool for every specimen. Call or e-mail us if you have any questions or need additional specimen plug kits.



Step 3
Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID.

***NOTE:** If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the NRG Oncology Biospecimen Bank – San Francisco and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.

Ship specimen plug kit, specimen in punch tool, and all paperwork to the address below. For Questions regarding collection/shipping or to order an FFPE Specimen Plug Kit, please contact the NRG Oncology Biospecimen Bank – San Francisco by e-mail: NRGBB@ucsf.edu or call 415-476-7864/Fax 415-476-5271.

U.S. Postal Service Mailing Address: For Non-frozen Specimens Only
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NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

NRG ONCOLOGY BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of serum, plasma, or whole blood *(as specified by the protocol)*:

Kit contents:

- One Red Top tube for serum (A)
- One Purple Top EDTA tube for plasma (B)
- One Purple Top EDTA tube for Whole Blood (C)
- Twenty-five (25) 1 ml cryovials
- Biohazard bags (3) and Absorbent shipping material (3)
- Styrofoam container (inner) and Cardboard shipping (outer) box
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form (STF) and Kit Instructions

PREPARATION AND PROCESSING OF SERUM, PLASMA AND WHOLE BLOOD:

(A) Serum (if requested): Red Top Tube

- ❑ Label as many 1ml cryovials (5 to 10) as necessary for the serum collected. Label them with the RTOG (NRG) study and case number, collection date, time, and time point, and clearly mark cryovials “serum”.

Process:

1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the STF.
3. Aliquot 0.5 ml serum into as many cryovials as are necessary for the serum collected (5 to 10) labeled with RTOG (NRG) study and case numbers, collection date/time, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as “serum”.
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90° C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90° C until ready to ship on dry ice. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the STF.

(B) Plasma (If requested): Purple Top EDTA tube #1

- ❑ Label as many 1ml cryovials (5 to 10) as necessary for the plasma collected. Label them with the RTOG (NRG) study and case number, collection date, time, and time point, and clearly mark cryovials “plasma”.

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the STF..
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot 0.5 ml plasma into as many cryovials as are necessary for the plasma collected (5 to 10) labeled with RTOG (NRG) study and case numbers, collection date/time, time point collected and clearly mark specimen as “plasma”. Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C.
6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the STF.

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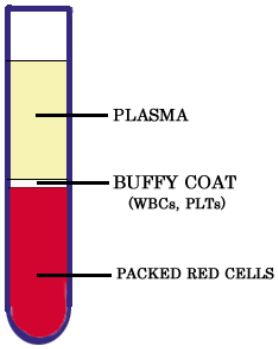

(C) Whole Blood for DNA (if requested): Purple Top EDTA tube #2

- ❑ Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected..Label them with the RTOG (NRG) study and case number, collection date/time, and time point, and clearly mark cryovials "blood".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0 ml blood into as many cryovials as are necessary for the blood collected (3 to 5) labeled with RTOG (NRG) study and case numbers, collection date/time, time point collected and clearly mark specimen as "blood".
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80° Celsius.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on STF.

Freezing and Storage:

- ☐ Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- ❑ Store at –80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- ❑ Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all NRG Oncology paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- ❑ Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
  (continued on next page)

- Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- **For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail NRGBB@ucsf.edu or call (415)476-7864.**

Shipping Address:

Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
For questions, call 415-476-7864 or e-mail: NRGBB@ucsf.edu

APPENDIX VI (continued)
NRG ONCOLOGY URINE COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of urine specimens.

Kit Contents:

- One (1) Sterile Urine collection cup
- Two 7 ml disposable pipettes
- Absorbent paper towel
- Two 15 ml polypropylene centrifuge tubes
- Biohazard bags
- Parafilm for sealing outside of tubes

Preparation and Processing of Urine Specimens:

Process:

- A clean catch urine specimen will be collected. To collect the specimen, use the following instructions:
  - Males should wipe clean the head of the penis and females need to wipe between the labia with soapy water/cleansing wipes to remove any contaminants.
  - After urinating a small amount into the toilet bowl to clear the urethra of contaminants, collect a sample of urine in the collection cup.
  - After 10-25 mL urine has been collected, remove the container from the urine stream without stopping the flow of urine.
  - Finish voiding the bladder into the toilet bowl.
- Aliquot 5-10 mls of Urine into each of two 15 ml polypropylene centrifuge tubes (disposable pipets are provided in the kit). Do not fill with more than 10 mls to avoid cracking of tubes due to expansion during freezing. Replace the cap and tighten on the tubes. Make sure the cap is not cross-threaded or placed on incorrectly or leaking will occur.
- Use parafilm to seal the cap around the outside rim of the urine tube to prevent leakage.
- Discard remaining Urine and collection cup.
- Label the specimen with the RTOG (NRG) study and case number, collection date and time, time point of collection, and clearly mark specimens as “urine”.
- Wrap Urine Tubes with absorbent material (paper towels) and place into biohazard bag and seal the bag. Freeze and store Urine samples in a -20°C or -80°C freezer until ready to ship.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED with RTOG (NRG) study and case numbers, collection date/time, and time point collected (e.g. pretreatment, post-treatment).

Storage and Shipping:

Freezing and Storage:

- ❑ Urine specimens may be sent in batches or with other frozen biospecimens, if within 30-60 days of collection. Store at -20°C or -80°C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:
  - Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
  - Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all NRG Oncology paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- ❑ Place sealed specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Samples received thawed will be discarded, and a notification will be sent immediately to the Principal Investigator and Clinical Research Assistant of the submitting institution. The institution should send a subsequent sample, collected as close as possible to the original planned collection date.
- ❑ **For questions regarding ordering, collection, or shipping of a Urine Collection Kit, please e-mail NRGBB@ucsf.edu or call (415)476-7864 or fax (415) 476-5271.**

APPENDIX VI (continued)
NRG ONCOLOGY URINE COLLECTION KIT INSTRUCTIONS

Shipping Address: FedEx/UPS/Courier address (For all frozen samples)
NRG Oncology Biospecimen Bank – San Francisco
2340 Sutter Street, Room S341, San Francisco, CA 94115 Contact Phone: (415) 476-7864