

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0926

A PHASE II PROTOCOL FOR PATIENTS WITH STAGE T1 BLADDER CANCER TO EVALUATE SELECTIVE BLADDER PRESERVING TREATMENT BY RADIATION THERAPY CONCURRENT WITH CISPLATIN CHEMOTHERAPY FOLLOWING A THOROUGH TRANSURETHRAL SURGICAL RE-STAGING

Study Chairs

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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 Cisplatin Chemotherapy Following A Thorough Transurethral Surgical Re-Staging

SCHEMA

Institutional TURBT for re-staging →	Full-dose Radiation* and Concurrent Cisplatin** 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 (T1G2 or T1G3)	*Total dose of 61.2 Gy in 34 daily fractions **Cisplatin 3 days/week during Weeks 1, 3, and 5	***For T1 and Tcis tumor recurrence, 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)

- Operable patients with Stage T1 disease (T1G2 or T1G3) 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

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ELIGIBILITY CHECKLIST (11/11/09)
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1. _____(Y) Does the patient have pathologically/cytologically proven transitional cell carcinoma of the bladder diagnosed within 10 weeks prior to registration?

2. _____(Y) Is the patient's primary tumor a stage T1 with histopathologic grade 2 or a stage T1 with histopathologic grade 3 transitional cell carcinoma of the bladder?

_____(Y) If yes, is there evidence in the pathologic specimen that there is no muscularis propria invasion?

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 failed initial treatment with TURBT + intravesical therapy within 18 months after this treatment?

_____(Y) If no, has this patient been deemed medically ineligible for standard treatment for T1 bladder cancer (intravesical BCG therapy)?

Please specify this reason: _____

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 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 8 weeks 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 4 weeks 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) Is the serum creatinine \leq 1.5?

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

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

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

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

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

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

18. _____(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 \geq 5 year period?

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

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

21. _____(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?

22. _____(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: _____

23. _____(N) Has the patient had a prior allergic reaction to the study drug (cisplatin) used in this protocol?

The following questions will be asked at Study Registration:

3D CREDENTIALING IS REQUIRED PRIOR TO REGISTRATION

- _____ 1. Name of institutional person registering this case?
- _____(Y) 2. Has the Eligibility Checklist (above) been completed?
- _____(Y) 3. Is the patient eligible for this study?
- _____ 4. Date the patient provided study-specific consent prior to study entry
- _____ 5. Patient's Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
- _____ 11. Gender
- _____ 12. Patient's Country of Residence
- _____ 13. Zip Code (U.S. Residents)
- _____ 14. Method of Payment
- _____ 15. Will any component of the patient's care be given at a military or VA facility?
- _____ 16. Calendar Base Date
- _____ 17. Registration/randomization date: This date will be populated automatically.

(Continued on the next page)

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- _____ 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?
- _____(N/Y) 26. Are you credentialed for 3DCRT?

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/RTOG 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

Treating patients with muscle-involving 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 involving bladder cancer is the most aggressive but makes up only 15% of the total incidence of patients presenting with non-muscle involving 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 with 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.⁸⁻¹¹ 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 irradiating high grade clinical stage T1 tumors. This is based on results from Erlangen, Germany¹³ 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 involving 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 could prevent the need for radical cystectomies in many patients who have failed BCG intravesical therapy with high grade T1 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 just 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-involving cancer. The median follow-up was 7.1 years. Ten of 18 patients have had no recurrence of any bladder tumor, muscle-involving or non-muscle involving. 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. 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 could prevent the need for radical cystectomy in many patients—probably as many as 3 out of every 4—who have failed BCG therapy with high grade T1 disease. 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

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. For this reason, as a secondary objective this trial will have a Phase I component with a stopping rule for acute grade 3 or more pelvic toxicity. The Birmingham Hospital in England led a phase III trial evaluating patients with muscle-invasive 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

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 RTOG genitourinary translational research program using patients from an ongoing RTOG selective bladder preservation protocol. These continued efforts are planned for the tissue from diagnostic/pre-treatment 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

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

3.1 Conditions for Patient Eligibility

- 3.1.1 Pathologically (histologically or cytologically) proven diagnosis of carcinoma of the bladder within 10 weeks prior to registration.
 - 3.1.1.1 Operable patients whose tumors are primary transitional cell carcinomas of the bladder exhibiting histologic evidence of invasion into the lamina propria (disease clinical stage T1) without evidence of muscularis propria invasion (muscularis propria must be present in the TURBT specimen) and are AJCC clinical stage T1, NX or N0, M0 (see Appendix IV) without hydronephrosis; patients who have involvement of the prostatic urethra with transitional cell carcinoma and have no evidence of stromal invasion of the prostate remain eligible.
- 3.1.2 Patients must have a T1G2 or T1G3 transitional cell carcinoma that has recurred within 18 months after initial treatment for \leq T1 tumors (TURBT and intravesical BCG immunotherapy) or have presented to a participating urologist who judged BCG therapy is contraindicated because this patient may be immuno-compromised in ways other than that mentioned in Section 3.2.8.6.
- 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 T1G2 or T1G3 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 cisplatin 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 8 weeks prior to registration:
 - 3.1.7.1 History/physical examination including weight, performance data, body surface area
- 3.1.8 Zubrod Performance Status \leq 1
- 3.1.9 Age \geq 18
- 3.1.10 CBC/differential obtained no more than 4 weeks prior to registration on study, with adequate bone marrow function defined as follows:
 - 3.1.10.1 WBC \geq 4,000/ml
 - 3.1.10.2 Absolute neutrophil count (ANC) \geq 1,800 cells/mm³
 - 3.1.10.3 Platelets \geq 100,000 cells/mm³

- 3.1.10.4 Hemoglobin \geq 10.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb \geq 10.0 g/dl is acceptable.)
- 3.1.11 Serum creatinine of \leq 1.5 mg%; serum bilirubin of \leq 2.0 mg%
- 3.1.12 Serum pregnancy test for female patients of childbearing potential, \leq 72 hours prior to study entry; women of childbearing potential and male participants must practice adequate contraception.
- 3.1.13 Patient must be able to provide study-specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility

- 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 \geq 5 years except for non-melanoma skin cancer and/or stage T1a prostate cancer or carcinoma *in situ* of the uterine cervix
- 3.2.5 Patients judged not to be candidates for radical cystectomy; patients with pN+ or > 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:
 - 3.2.8.1 Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;
 - 3.2.8.2 Transmural myocardial infarction within the last 6 months;
 - 3.2.8.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
 - 3.2.8.4 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;
 - 3.2.8.5 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.
 - 3.2.8.6 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 drug (cisplatin) 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

- 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 8 weeks 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

5.1 Pre-Registration Requirements for 3DCRT Treatment Approach

- 5.1.1 Only institutions that have met the technology requirements and that have provided the baseline physics information that are described in 3DCRT Quality Assurance Guidelines may enter patients onto this study.
- 5.1.2 The new facility questionnaire (one per institution, available on the ATC website at <http://atc.wustl.edu>) is to be sent to RTOG for review prior to entering any cases. Upon review and successful completion of a “Dry-Run” QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study. Institutions that have previously enrolled patients on 3DCRT trials of this same disease site may enroll patients on this study without further credentialing.

5.2 Regulatory Pre-Registration Requirements

- 5.2.1 **U.S. and Canadian institutions** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, http://www.rtog.org/pdf_file2.html?pdf_document=CTSU-IRBCertiffForm.pdf, 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 of consent translation to RTOG Headquarters
 - IRB/REB assurance number
- 5.2.2 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS
- 5.2.2.1 Prior to clinical trial commencement, Canadian institutions must complete and fax to the CTSU Regulatory Office (215-569-0206) Health Canada’s Therapeutic Products Directorates’ Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form.
- 5.2.3 Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS
- 5.2.3.1 **For institutions that do not have an approved LOI for this protocol:**
International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form.doc
- 5.2.3.2 **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.

5.3 Registration

5.3.1 Online Registration

Patients can be registered only after eligibility criteria are met.

Each individual user must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via <http://phrp.nihtraining.com/users/login.php>).
- A representative from the institution must complete the Password Authorization Form at www.rtog.org/members/webreg.html (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (<http://www.rtog.org>), going to “Data Center Login” and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient's record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study's database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

Institutions can contact RTOG web support for assistance with web registration: websupport@acr-arrs.org or 800-227-5463 ext. 4189 or 215-574-3189.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site's user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY

Note: Intensity Modulated RT (IMRT) Is Not Allowed

Protocol treatment must begin within 10 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

All patients will receive 34 daily fractions (about 7 weeks) of radiation therapy 5 days a week concurrently with cisplatin on the first 3 days of weeks 1, 3, and 5. Radiation therapy will be started within 10 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_{pelvis} (see field borders in Appendix V). 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_{bladder}) using 1.8 daily fractions for 11 fractions for a total bladder boost dose (PTV_{bladder}) 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 may be used.

6.2 Technical Factors [Equipment, energies]

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

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 V). All of these structures constitute the CTV_{pelvis}. 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_{bladder} 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 antero-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_{bladder} and therefore the CTV_{pelvis}, 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_{bladder} and/or CTV_{pelvis}, as required. For such cases, the field edges should be adjusted to extend at least 2 cm beyond the modified CTV_{pelvis}.

6.4.2 Whole Bladder Field

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

6.5 Critical Structures

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

6.6 Documentation Requirements

6.6.1 Within 7 working days of the initiation of treatment, the CT treatment plan must be submitted digitally to ITC (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 must be submitted digitally to RTOG (see Section 12.1).

6.7 Compliance Criteria

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_{pelvis} and PTV_{bladder} 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

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 ITC. Dr. Shipley will perform the next review after complete data for the next 10 cases enrolled has been received at ITC. 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 ITC, whichever occurs first. These reviews will be ongoing.

6.10 Radiation Adverse Events

See Section 7.6 for additional Adverse Events information and 7.7 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

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

Protocol treatment must begin within 10 weeks after transurethral resection.

7.1 Treatment

7.1.1 Dose Definition

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

7.1.2 Technique of Administration

Cisplatin (15 mg/m²) 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.

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

7.1.3 Duration of treatment

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

7.2 Cisplatin

Refer to package insert for additional information.

7.2.1 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.

7.2.2 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.

7.2.3 Administration

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

7.2.4 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.

7.2.5 Supply

Commercially available.

7.2.6 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, ototoxicity including hearing loss or tinnitus, loss of muscle function

7.3 Dose Modifications

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 \leq 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			
		\geq 150K	100-149K	75-99K	$<$ 75K
ANC (x 1000)	\geq 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 Treatment Interruption

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.

7.5 Modality Review

The Medical Oncology Co-Chair, Donald S. Kaufman, MD, 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, Not Per Protocol, 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. Kaufman will perform a review after complete data for the first 20 cases enrolled has been received at RTOG Headquarters. Dr. Kaufman will perform the next review after complete data for the next 10 cases enrolled has been received at RTOG Headquarters. 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 RTOG Headquarters, whichever occurs first.

7.6 Adverse Events

The CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for adverse event (AE) reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP web site at:

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

All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site ([https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main\\$.startup](https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup)).

Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site (<http://www.rtog.org/members/toxicity/main.html>) for this information.

In order to ensure consistent data capture, serious adverse events reported on AdEERS reports also must be reported on an RTOG case report form (CRF). In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

7.6.1 **Adverse Events (AEs)**

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. January 2005; <http://ctep.cancer.gov/reporting/adeers.html>]

The following guidelines for reporting adverse events (AEs) apply to **all** NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1). **Note: AEs indicated in the AdEERS Expedited Reporting Requirements in text and/or table in Section 7.8 also must be reported via AdEERS.**

NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.

7.6.2 **Serious Adverse Events (SAEs)** — All SAEs that fit any one of the criteria in the SAE definition below must be reported via AdEERS. Contact the AdEERS Help Desk if assistance is required.

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS Notification:

- **Phase II & III Studies: All unexpected potentially related SAEs**
- **Phase I Studies: All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship**

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after 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 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. Any pregnancy occurring on study must be reported via AdEERS as a medically significant event.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported via AdEERS.

All supporting source documentation indicated as being provided in the Additional Information Section of the AdEERS Report must be properly labeled with the study/case numbers and the date of the event and must be faxed to the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. The RTOG Case Number without any leading zeros should be used as the Patient ID when reporting via AdEERS. Non-RTOG intergroup study and case numbers must also be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient's case number as the patient ID when reporting via AdEERS.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as “expedited reporting NOT required” must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the “NOT Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. Note: Sites must select the option in AdEERS to send a copy of the report to the FDA or print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

7.6.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form available at <http://ctep.cancer.gov/forms/index.html>. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of a report via the AdEERS system and must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.

RTOG Headquarters
AML/MDS Report
1818 Market Street, Suite 1600
Philadelphia, PA 19103

7.7 AdEERS Expedited Reporting Requirements

CTEP defines routine AE reporting requirements for **phase 2 and 3 trials** as described in the table below. **Important:** All AEs reported via AdEERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

Phase 2 and 3 Trials Utilizing a Commercially Available Agent: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days¹ of the Last Dose of the Investigational Agent [Cisplatin] in this Study

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 ²	Grades 4 & 5 ²
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	without Hospitalization	Expected with Hospitalization	without Hospitalization	Unex-pected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

¹ Adverse events with attribution of possible, probable, or definite that occur **greater** than 30 days after the last dose of treatment with a commercially available agent require reporting as follows:

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

- Grade 4 and Grade 5 unexpected events

AdEERS 10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

² Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see exceptions below under section entitled “Additional Instructions or Exceptions.”

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Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. “On study” is defined as during or within 30 days of completing protocol treatment.

- Expedited AE reporting timelines defined:
 - “24 hours; 5 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
 - “10 calendar days” - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercially Available Agent

None

8.0 SURGERY

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 VI)
- 8.1.2 A visibly complete transurethral resection of the tumor (TURBT). Tumor specimens should be sent to the RTOG Biospecimen Resource 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

APPENDIX VII
RTOG FFPE SPECIMEN PLUG KIT INSTRUCTIONS

The specimen plug kit contains a shipping tube and a punch tool.



Step 1

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 try to remove the specimen from the punch.

Use a separate punch tool for every specimen. Please do not mix specimens. Call or email us if you have any questions or need additional specimen plug kits.



Step 3

Once the punch tool is labeled, place it in the shipping tube and mail to the address below.

We will remove the specimen from the punch, embed it in a cassette, and label it with the specimen ID.

***NOTE:** If your facility is uncomfortable with obtaining the plug but wants to retain the tissue block, please send the entire block to the RTOG Biospecimen Resource and we will sample a plug from the block and return the remaining block to your facility. Please indicate this request (to perform the plug procedure and return of the block) on the submission form.

Ship specimen plug kit, specimen in punch tool, and all paperwork to the address below:

U.S. Postal Service Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen Specimens or Trackable shipments
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu

APPENDIX VIII
RTOG BLOOD COLLECTION KIT INSTRUCTIONS

Instructions for use of serum, plasma, or buffy coat collection kit (collected as required by protocol):

This kit includes:

- Twelve (12) 1 ml cryovials
- Biohazard bags
- Absorbent shipping material
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Pre-paid shipping label(s)
- UN 3373 Sticker
- UN 1895 Dry Ice Sticker

Serum (if requested):

- Using four (4) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, 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 3000g at 4° Celsius for 30 minutes.
3. Aliquot 0.5-1 ml serum into each cryovial labeled with RTOG study and case numbers, collection date/time, time point collected, and clearly mark specimen as “serum”.
4. Place cryovials into biohazard bag and store serum frozen until ready to ship. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Plasma (If requested):

- Using four (4) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, 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 3000g at 4° Celsius for 30 minutes.
3. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
4. Carefully pipette and aliquot 0.5-1 ml plasma into each cryovial labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as “plasma”.
5. Place cryovials into biohazard bag and store plasma frozen until ready to ship. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Buffy coat (if requested):

For a visual explanation of Buffy coat, please refer to the diagram below.

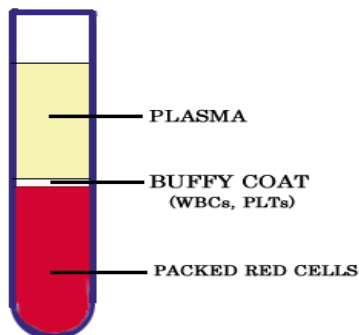
- Using one (1) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovial(s) “buffy coat”.

Process:

1. Centrifuge EDTA (purple top) tube within one hour of collection in a standard clinical centrifuge at 3000g at 4° Celsius for 30 minutes.
2. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
3. Carefully remove plasma close to the buffy coat and set plasma aside (*can be used to send plasma samples – see above instructions*).
(continued on next page)

APPENDIX VIII
RTOG BLOOD COLLECTION KIT INSTRUCTIONS (continued)

4. Remove the buffy coat cells carefully and place into cryovials labeled "buffy coat" (*it is okay if a few packed red cells are inadvertently collected in the process*). Clearly mark the tubes with date/time of collection and time point collected.
5. Place cryovials into biohazard bag and store buffy coat frozen until ready to ship. See below for storage conditions.



PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Storage:

- 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 (please ship out on 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.

*RTOG labels are obtained at the time of patient registration. **PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.**

Shipping/Mailing:

- Include all RTOG paperwork in pocket of biohazard bag.
- Ship specimens overnight Monday-Wednesday. (Monday-Tuesday for Canada). Avoid shipping on a weekend or around a holiday.
- Place frozen specimens and the absorbent shipping material in the Styrofoam cooler and fill with dry ice (if appropriate; double-check temperature sample shipping temperature). Ship ambient specimens in a separate envelope/cooler. Place Styrofoam coolers into outer cardboard box, and attach shipping label 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 still plenty of space for 10 lbs of dry ice.*

Ship: Specimens and all paper work as follows:

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

For questions, call 415-476-RTOG (7864) or e-mail: RTOG@ucsf.edu

APPENDIX IX
RTOG URINE COLLECTION KIT INSTRUCTIONS

This Kit contains:

- One (1) Sterile Urine collection cup
- Biohazard bags

Urine Specimens:

Preparation for collecting **Urine**:

- A clean catch urine specimen will be collected.

Process:

- 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
 - Place the cap on the collection cup and tighten the container. Make sure the cap is not cross-threaded or placed on incorrectly or leaking will occur.
- Label the specimen with the RTOG study and case number, collection date and time, time point of collection, and clearly mark specimen as “urine”.
- If available, use parafilm to seal the cap of the urine cup and to prevent leakage.
- Place urine cup into biohazard bag and seal the bag
- Store specimens frozen at -20°C or -80°C until ready to ship.

Shipping Instructions for all specimens:

Urine Specimens: Urine cups must be wrapped in an absorbent material (e.g., paper towels) and placed in an airtight plastic freezer bag (i.e., re-sealable bag). Urine specimens may be sent in batches, if within 30 days of collection. Pack the frozen specimens in a heavy grade Styrofoam box with dry ice (4-5 lbs. minimum). Seal the box with plastic tape. All paperwork should be placed in a plastic bag, sealed, and taped to the outside of the Styrofoam box. Pack the Styrofoam box in a cardboard box. **Note:** Specimens requiring specific infectious precautions should be clearly labeled, with specific sources of infectious concerns listed, if known. Mark the outer cardboard box “biohazard”.

Send specimens by overnight express to the address below. Specimens should be shipped Monday through Wednesday only to prevent thawing due to delivery delays. Saturday or holiday deliveries will not be accepted. Samples received thawed will be discarded, and a notification will be sent immediately to the Principal Investigator and Clinic Research Assistant of the submitting institution. The institution should send another sample, collected as close as possible to the original planned collection date.

Notes:

- Include all RTOG paperwork in pocket of biohazard bag.
- Place frozen specimens and the absorbent shipping material in the Styrofoam cooler and fill with dry ice (if appropriate; double-check temperature sample shipping temperature).
- *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag.*

Ship specimens and all paper work as follows:

Courier Address (FedEx, UPS, etc.): For Frozen Specimens

**RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115**

For questions, call 415-476-RTOG (7864) or e-mail: RTOG@ucsf.edu