

## NRG ONCOLOGY

### RTOG 0712

#### **A Phase II Randomized Study For Patients With Muscle-Invasive Bladder Cancer Evaluating Transurethral Surgery And Concomitant Chemoradiation By Either BID Irradiation Plus 5-Fluorouracil And Cisplatin Or QD Irradiation Plus Gemcitabine Followed By Selective Bladder Preservation And Gemcitabine/Cisplatin Adjuvant Chemotherapy**

#### **Study Chairs**

(12/18/14)

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**SCHEMA (4/14/11)**

**Transurethral Surgery (TUR)**

↓  
**Stratify**

Based on T-Stage: T2 vs. T3/T4

↓  
**Randomize**

Within 6 weeks of TUR

↓  
**Induction Chemoradiotherapy**

Starts within 8 weeks of the TUR

†Arm 1(a): 5FU, Cisplatin and b.i.d. irradiation (2.5 weeks)

†Arm 2 (b): Gemcitabine and q.d. irradiation (4 weeks)

↓  
**Post-Induction Response Evaluation**

3-4 weeks following Induction Chemoradiotherapy



**Tumor Response T0, Ta, Tcis\***

\*At site distant from original tumor



**Consolidation Chemoradiotherapy**

Starts 7-14 days following Post-Induction TUR

†Arm 1(c): 5FU, Cisplatin and b.i.d. irradiation (1.5 weeks)

†Arm 2(d): Gemcitabine and q.d. irradiation (2.5 weeks)



**Post-Consolidation Response Evaluation**

8-10 weeks following Consolidation Chemoradiotherapy



**Adjuvant Therapy**

Starts 4-5 weeks following Post-Consolidation TUR

Gemcitabine on day 1 and day 8, Cisplatin on day 1 (Four 21 day cycles)

**Tumor Response ≥ T1\*\***

\*\*On re-biopsy, the tumor persists and invades into or beyond the lamina propria



**Radical Cystectomy**

3-8 weeks following Post-Induction TUR



**Adjuvant Therapy**

Starts 8-12 weeks following Radical Cystectomy

Gemcitabine on day 1 and day 8, Cisplatin on day 1 (Four 21 day cycles)

†See **a**, **b**, **c**, and **d** in tables below for more details

**Continued on next page**

<b>INDUCTION THERAPY</b>																						
<b>a. ARM 1</b>	<b>Day</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>8</b>	<b>9</b>	<b>10</b>	<b>11</b>	<b>12</b>	<b>15</b>	<b>16</b>	<b>17</b>								
5-FU 400 mg/m <sup>2</sup>		X	X	X								X	X	X								
Cisplatin 15 mg/m <sup>2</sup>		X	X	X			X	X	X			X	X	X								
XRT, bid x 13 days		X	X	X	X	X	X	X	X	X	X	X	X	X								
[1.6 Gy small pelvic fields/ 1.5 Gy boost to whole bladder																						
x 5 (days 1-5) plus 1.5 Gy boost to bladder tumor																						
x 8 (days 8-17) with a minimum 4 hour interval]																						
<b>b. ARM 2</b>	<b>Day</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>8</b>	<b>9</b>	<b>10</b>	<b>11</b>	<b>12</b>	<b>15</b>	<b>16</b>	<b>17</b>	<b>18</b>	<b>19</b>	<b>22</b>	<b>23</b>	<b>24</b>	<b>25</b>	<b>26</b>	
Gemcitabine 27 mg/m <sup>2</sup>		X		X			X		X			X		X			X		X		X	
XRT, qd x 20days		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[2 Gy small pelvic fields x 10 (days 1-12)																						
2 Gy boost to whole bladder x 4 (days 15-18)																						
2 Gy boost to bladder tumor x 6 (days 19-26)]																						

\*Induction therapy should begin within 8 weeks of TUR.

<b>CONSOLIDATION THERAPY</b>															
<b>c. ARM 1</b>	<b>Day</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>8</b>	<b>9</b>	<b>10</b>						
5-FU 400 mg/m <sup>2</sup>		X	X	X						X		X		X	
Cisplatin 15 mg/m <sup>2</sup>		X	X							X		X		X	
Pelvic X RT, bid x 8 days		X	X	X	X	X				X		X		X	
(1.5 Gy small pelvic fields with a minimum 4 hour interval)															
<b>d. ARM 2</b>	<b>Day</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>8</b>	<b>9</b>	<b>10</b>	<b>11</b>	<b>12</b>	<b>15</b>	<b>16</b>		
Gemcitabine 27 mg/m <sup>2</sup>		X		X			X		X			X			
XRT, qd x 12 days		X	X	X	X	X	X	X	X	X	X	X	X	X	
(2 Gy small pelvic fields)															

\*Consolidation therapy should begin 7-14 days following Post-Induction Evaluation

<b>OUTPATIENT ADJUVANT CHEMOTHERAPY</b>														
<b>AGENTS</b>	<b>Day</b>	<b>1</b>	<b>8</b>											
Gemcitabine 1000 mg/m <sup>2</sup>		X		X										
Cisplatin 70 mg/m <sup>2</sup>		X												
(Paclitaxel 150 mg/m <sup>2</sup> if cisplatin not tolerated)														

\*Adjuvant chemotherapy should begin 4-5 weeks following Post-Consolidation Evaluation **OR** 8 -12 weeks following Radical Cystectomy.

\*Repeat every 21 days for 4 cycles.

See pre-registration requirements in Section 5.0.

See details of radiation therapy and chemotherapy in Sections 6.0 and 7.0.

For surgery details and response evaluations see Section 8.0.

**Patient Population:** (See Section 3.0 for Eligibility)

- Operable patients with muscularis propria invasion carcinoma of the bladder, all histologies
- AJCC Stages T2-T4a, NX or N0, M0
- No histologic evidence of tumor invasion into the stroma of the prostate
- No tumor-related hydronephrosis

(2/6/14) **Required Sample Size: 64**

\_\_\_\_\_ (Y) 1. Does the patient have a primary carcinoma of the bladder (transitional cell cancer) with muscularis propria invasion diagnosed within 8 weeks of registration?

\_\_\_\_\_ (Y) 2. Is the clinical stage T2-T4a, Nx or N0, M0 without hydronephrosis?

\_\_\_\_\_ (Y/N) 3. Did the patient have a lymph node interpreted as positive radiographically?

\_\_\_\_\_ (Y) If yes, was it evaluated by lymphadenectomy or percutaneous needle biopsy and confirmed as negative?

\_\_\_\_\_ (Y) 4. Is the patient considered able to tolerate systemic chemotherapy combined with pelvic radiation and a radical cystectomy by joint agreement of the Urologist, Radiation Oncologist and Medical Oncologist?

\_\_\_\_\_ (Y) 5. Is the Zubrod 0 or 1?

\_\_\_\_\_ (Y) 6. Is the age of the patient greater than or equal to 18 years?

\_\_\_\_\_ (Y) 7. Have the following laboratory tests been done within 4 weeks prior to registration on this study?

\_\_\_\_\_ (Y) WBC greater than or equal to 4000?

\_\_\_\_\_ (Y) ANC greater than or equal to 1800?

\_\_\_\_\_ (Y) Hemoglobin greater than or equal to 10.0?

\_\_\_\_\_ (Y) Platelets greater than or equal to 100,000?

\_\_\_\_\_ (Y) Creatinine clearance greater than or equal to 60ml/min?

\_\_\_\_\_ (Y/N) Serum creatinine of 1.5 or less?

\_\_\_\_\_ (Y) If no, is the creatinine clearance greater than 60 ml/min and serum creatinine no more than 1.8?

\_\_\_\_\_ (Y) Serum bilirubin of less than or equal to 2.0mg%?

\_\_\_\_\_ (Y/NA) 8. If the participant is a woman of childbearing potential, has a pregnancy test been done less than or equal to 72 hours prior to study entry and has the participant agreed to practice adequate contraception?

\_\_\_\_\_ (Y/NA) 9. If the participant is male and sexually active, has he agreed to practice adequate contraception?

\_\_\_\_\_ (N) 10. Is there evidence of distant metastases?

\_\_\_\_\_ (N) 11. Has the patient received prior pelvic radiation therapy?

\_\_\_\_\_ (N) 12. Has the patient received prior chemotherapy for any malignancy?

\_\_\_\_\_ (N) 13. Does the patient have a prior or concurrent malignancy of any other site or histology unless the patient has been disease-free for greater than or equal to 5 years (exceptions: non-melanoma skin cancer and /or stage T1a prostate cancer or carcinoma in situ of the uterine cervix)?

\_\_\_\_\_ (N) 14. Is the patient receiving any drugs that have potential nephrotoxicity or ototoxicity (such as an aminoglycoside [i.e., Gentamicin sulfate or Tobramycin sulfate, etc.]?)?

(Continued on the next page)

**ELIGIBILITY CHECKLIST—STEP 1 (12/9/08)**  
(page 2 of 3)

RTOG Institution # \_\_\_\_\_  
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Case # \_\_\_\_\_

\_\_\_\_\_ (N) 15. Does the patient have any of the severe, active co-morbidities 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; acquired immune deficiency syndrome (AIDS) based upon current CDC definition?

\_\_\_\_\_ (N) 16. Has the patient had a prior allergic reaction to the study drugs involved in this protocol?

**The following questions will be asked at Study 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?
- \_\_\_\_\_ (Y) 4. Date the patient provided study-specific informed 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. Patient's Insurance Status
- \_\_\_\_\_ 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)

RTOG Institution # \_\_\_\_\_  
RTOG 0712  
Case # \_\_\_\_\_

**ELIGIBILITY CHECKLIST—STEP 1 (12/9/08)**  
(page 3 of 3)

\_\_\_\_\_ 18. Medical oncologist [for trials that include a drug component]  
\_\_\_\_\_ (Y/N) 19. Tissue/Blood/Urine kept for cancer research?  
\_\_\_\_\_ (Y/N) 20. Tissue/Blood/Urine kept for medical research?  
\_\_\_\_\_ (Y/N) 21. Allow contact for future research?  
\_\_\_\_\_ 22. Specify T stage (T2 or T3/T4)

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 \_\_\_\_\_

**STEP 2 REGISTRATION**

RTOG Institution # \_\_\_\_\_

RTOG 0712

Case # \_\_\_\_\_ (assigned for Step 1)

**ELIGIBILITY CHECKLIST – STEP 2 (Consolidation) (12/9/08)**

\_\_\_\_\_

1. Name of institutional person registering case.

\_\_\_\_\_ (Y/N)

2. Is the patient able to continue protocol treatment, i.e., consolidation treatment or radical cystectomy?

3. If no, call RTOG HQ to "discontinue" the case; specify reason (progression, patient refusal, physician preference, other) \_\_\_\_\_

\_\_\_\_\_

4. Patient Initials

\_\_\_\_\_

5. Verifying Physician

\_\_\_\_\_

6. Patient ID Number

\_\_\_\_\_

7. Treatment Start Date (CONSOLIDATION CHEMORADIATION OR CYSTECTOMY)

\_\_\_\_\_

8. Randomization Date

\_\_\_\_\_

9. Specify the pathologic T stage at post induction evaluation (pT0, pTa, pTci vs.  $\geq$  pT1)

\_\_\_\_\_

10. Specify the urine cytology results (negative, positive, equivocal).

\_\_\_\_\_

11. Specify induction treatment assignment (5 FU, cisplatin + twice daily RT or Gemcitabine + once daily RT)

Completed by \_\_\_\_\_

Date \_\_\_\_\_

## **1.0 INTRODUCTION**

### **1.1 Background**

Selective bladder preservation using trimodality therapy has been established as a safe and effective alternative to radical cystectomy in appropriately selected patients with muscle invasive bladder cancer. Single institution and RTOG prospective studies demonstrate high rates of bladder preservation with no decrement in overall survival or rates of distant metastasis when a prompt cystectomy is performed for incomplete responders or patients with locally recurrent disease. The treatment paradigm that has evolved consists of a thorough transurethral resection followed by induction radiation and sensitizing chemotherapy. Patients with a complete response to induction therapy receive additional consolidation chemoradiation using the same sensitizing drugs. Others undergo a prompt cystectomy.

This randomized phase II study evaluates both the RTOG regimen incorporating BID radiation sensitized with 5-FU and cisplatin into the selective bladder preservation paradigm and the regimen developed at the University of Michigan which incorporates QD radiation sensitized with gemcitabine.<sup>1-3</sup> The RTOG regimen has demonstrated a high response rate and acceptable toxicity in a phase I/II trial (95-06). A subsequent randomized phase II trial (0233) demonstrated the response rate and the rate of distant metastasis equal to a similar radiation schedule combined with cisplatin and paclitaxel with lesser rates of toxicity. A phase I trial performed at the University of Michigan established the safety of a regimen using concurrent twice weekly gemcitabine and QD radiation to a total of 60 Gy. Twenty-four patients were enrolled on this study and 23 were assessable for toxicity and response. All patients were male. All patients had T2 tumors that were amenable to TURBT. Median age was 62 (range 46-83). Median follow-up is 5.6 years. The MTD of gemcitabine was 27 mg/m<sup>2</sup>. The toxicity by dose level can be summarized as follows: At 10 mg/m<sup>2</sup>, 3 patients were treated and none experienced dose limiting toxicity (DLT). At 20 mg/m<sup>2</sup>, 6 patients were treated. There was one DLT (a grade 3 LFT elevation) and one non-DLT (grade 3 neutropenia). At 33 mg/m<sup>2</sup>, DLT occurred in 2 of 3 consisting of grade 4 diarrhea in one patient, who also had a non-DLT of hematochezia and rectal stricture, and grade 3 edema in another patient, who also had a non-DLT of grade 3 hematochezia. At 27 mg/m<sup>2</sup>, 5 patients were treated without the occurrence of a DLT, but one patient had mild radiation cystitis with a stricture that required dilation. At 30 mg/m<sup>2</sup>, there were 3 DLTs in 6 treated patients. There were no life-threatening complications. There was one significant late complication. The patient who had radiation cystitis during treatment had persistent hematuria unresponsive to conservative measures. This patient ultimately was successfully managed with hyperbaric oxygen. No patient has required a cystectomy due to complications of therapy. There was a high rate of bladder preservation with a clinical CR rate of 91 as assessed by cystoscopy, cytology and imaging studies 4 weeks after completion of radiation. At 5 years, the overall survival and disease specific survival rates were 76% and 82%, respectively.

Distant metastases remain the most common mode of treatment failure for patients with muscle invasive bladder cancer. In recognition of this risk, adjuvant chemotherapy has been an integral component of RTOG protocols since 1995. In this study, patients will receive adjuvant chemotherapy with gemcitabine and cisplatin, an effective and well tolerated doublet in the metastatic setting. A multi-institutional randomized phase III trial demonstrated similar survival rates with a better safety profile and tolerability for this regimen as compared to MVAC (methotrexate, vinblastine, doxorubicin and cisplatin).<sup>4,5</sup> It has since been considered standard of care for patients with locally advanced and metastatic bladder cancer. For patients in the concurrent gemcitabine arm, we suspect the addition of adjuvant chemotherapy may result in lower rates of distant metastasis than reported by the University of Michigan where no adjuvant chemotherapy was offered.

### **1.2 Biomarkers in Bladder Cancer (4/14/11)**

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.<sup>6-11</sup> These markers and others are under investigation through the RTOG genitourinary translational research program using patients from prior RTOG bladder preservation trials. Markers which are targets for therapeutics, such as Her2/neu, VEGF and EGFR, will be prioritized. Special efforts will be made

to obtain the tissue from diagnostic/pretreatment TURB and cystectomy specimens, when salvage cystectomy is performed.

Novel biomarker screening technologies are emerging. Mass spectrometry based metabolomics and proteomics approaches and second generation sequencing based whole transcriptome analysis or whole genome sequencing are among them. RTOG 0712 tissue, blood, and urine biospecimens will be used as validation sets for results obtained through profiling of institutional based biosample discovery sets.

## **2.0 OBJECTIVES**

### **2.1 Primary**

To estimate the rate of distant metastasis at 3 years of two induction chemoradiotherapy regimens including 5-Fluorouracil, cisplatin, and BID irradiation (FCI) or gemcitabine and QD irradiation (GI). Induction chemoradiotherapy will be followed by radical cystectomy if the initial tumor response is incomplete or by consolidation chemoradiotherapy if the tumor has cleared, and both will be followed by adjuvant chemotherapy.

### **2.2 Secondary (4/14/11)**

- 2.2.1** To estimate the completion rate of two treatment regimens with either FCI or GI.
- 2.2.2** To estimate acute and late grade 3+ GU, GI, and hematologic toxicities of two treatment regimens with either induction FCI or GI followed by adjuvant chemotherapy.
- 2.2.3** To estimate the efficacy of transurethral surgery with either induction FCI or GI in achieving a complete response of the primary tumor.
- 2.2.4** To estimate the efficacy of transurethral surgery with either FCI or GI in preserving the native, tumor-free bladder five years after therapy.
- 2.2.5** To estimate the value of tumor histopathologic, molecular genetic, DNA content, metabolomic, and proteomic parameters as possible significant prognostic factors for initial tumor response and recurrence-free survival.
- 2.2.6** Explanatory analysis for AUA Symptom scores at baseline and at 3 years from patients on both arms.
- 2.2.7** To find potentially predictive biomarkers for cystectomy-free survival.
- 2.2.8** To find potentially predictive biomarkers for acute and late toxicities.

## **3.0 PATIENT SELECTION**

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

### **3.1 Conditions for Patient Eligibility (2/28/12)**

- 3.1.1** Pathologically (histologically or cytologically) proven diagnosis of primary carcinoma of the bladder (transitional cell cancer) within 8 weeks of registration. Operable patients whose tumors are primary carcinomas of the bladder and exhibit histologic evidence of muscularis propria invasion and are AJCC clinical stages T2-T4a, Nx or N0, M0 (Appendix IV) without hydronephrosis; patients who have involvement of the prostatic urethra with transitional cell cancer (TCC) that was visibly completely resected and no evidence of stromal invasion of the prostate remain eligible. T2a, T2b, T3a, T3b -substages" are not usually able to be determined with clinical (TURBT) staging.
- 3.1.2** If radiologic evaluation of a lymph node is interpreted as "positive", this must be evaluated further either by lymphadenectomy or percutaneous needle biopsy. Patients with histologically or cytologically confirmed node metastases will not be eligible.
- 3.1.3** Patients must have an adequately functioning bladder after thorough evaluation by an urologist and have undergone as thorough a transurethral resection of the bladder tumor as is judged safely possible.
- 3.1.4** Patients must be considered able to tolerate systemic chemotherapy combined with pelvic radiation therapy, and a radical cystectomy by the joint agreement of the participating Urologist, Radiation Oncologist, and Medical Oncologist.
- 3.1.5** History and physical examination including weight, performance status, and body surface area within 8 weeks prior to study registration
- 3.1.6** Zubrod Performance Status ≤ 1;
- 3.1.7** Age ≥ 18;
- 3.1.8** CBC/differential obtained no more than 4 weeks prior to registration on study, with adequate bone marrow function defined as follows:

- 3.1.8.1 WBC  $\geq$  4000/ml
- 3.1.8.2 Absolute neutrophil count (ANC)  $\geq$  1,800 cells/mm<sup>3</sup>;
- 3.1.8.3 Platelets  $\geq$  100,000 cells/mm<sup>3</sup>;
- 3.1.8.4 Hemoglobin  $\geq$  10.0 mg/dl (Note: The use of transfusion or other intervention to achieve Hgb  $\geq$  10.0 g/dl is acceptable.);
- 3.1.9 Serum creatinine of 1.5 mg% or less; serum bilirubin of 2.0 mg% or less; creatinine clearance of 60 ml/min or greater no more than 4 weeks prior to registration; Note: Calculated creatinine clearance is permissible. If the creatinine clearance is  $>$  60 ml/min, then a serum creatinine of up to 1.8 mg% is allowable at the discretion of the study chair;
- 3.1.10 Serum pregnancy test for female patients of childbearing potential,  $\leq$  72 hours prior to study entry; women of childbearing potential and male participants must practice adequate contraception.
- 3.1.11 Patient must be able to provide study-specific informed consent prior to study entry.

### **3.2 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 Previous systemic chemotherapy (for any cancer) or pelvic radiation therapy
- 3.2.4 A prior or concurrent malignancy of any other site or histology unless the patient has been disease-free for  $\geq$  5 years except for non-melanoma skin cancer and/or stage T1a prostate cancer or carcinoma *in situ* of the uterine cervix
- 3.2.5 Patients judged not to be candidates for radical cystectomy; patients with pN+ or T4b disease are considered to have unresectable disease
- 3.2.6 Patients receiving any drugs that have potential nephrotoxicity or ototoxicity (such as an aminoglycoside)
- 3.2.7 Severe, active co-morbidity, defined as follows:
  - 3.2.7.1 Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;
  - 3.2.7.2 Transmural myocardial infarction within the last 6 months;
  - 3.2.7.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
  - 3.2.7.4 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;
  - 3.2.7.5 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.
  - 3.2.7.6 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.
- 3.2.8 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.
- 3.2.9 Prior allergic reaction to the study drug(s) 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.

**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. **Note:** Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

#### **4.1 Required Evaluations/Management** (baseline prior to initiation of any protocol treatment) [4/14/11]

- 4.1.1 Cystoscopic evaluation by the participating urologic surgeon no more than 6 weeks prior to registration will include bimanual examination under anesthesia, as thorough as possible a

transurethral resection of the bladder tumor, and a biopsy of the prostatic urethra including both mucosa and stroma using a resection loop. Patients referred from an outside hospital with a muscularis propria-invading bladder tumor will be re-resected by the participating urologist.

- 4.1.2 Radiologic evaluation including chest CT, abdominal and pelvic CT and bone scan no more than 6 weeks prior to start of treatment.
- 4.1.3 Alkaline phosphatase, SGOT, bilirubin, LDH, BUN, urinalysis, magnesium and calcium levels obtained no more than 4 weeks prior to registration.

- 4.2 **Highly Recommended Evaluations/Management** (baseline prior to initiation of any protocol treatment) [4/14/11]

- 4.2.1 Serum/plasma/whole blood, urine, and tumor tissue for biomarker studies: For patients who consent to this component of the study. (See Section 10.0 for details on submission requirements.)
- 4.2.2 AUA symptom index, a questionnaire routinely administered in clinical practice to assess urinary function.
- 4.2.3 Urodynamic evaluation.

## **5.0 REGISTRATION PROCEDURES**

### **5.1 Pre-Registration Requirements for 3DCRT Treatment Approach** (4/14/11)

- 5.1.1 Only institutions that have met the technology requirements may enter patients to 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 Headquarters 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 3D-CRT trials of this same disease site may enroll patients on this study without further credentialing.

### **5.2 Regulatory Pre-Registration Requirements** (2/28/12)

- 5.2.1 All 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, [https://www.ctsu.org/public/CTSU-IRBcertif\\_Final.pdf](https://www.ctsu.org/public/CTSU-IRBcertif_Final.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/verification of IRB/REB consent translation to RTOG Headquarters (see Section 5.2.1.1 below)
- IRB/REB assurance number.

- 5.2.1.1 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 RTOG 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.

### **5.2.2 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/Researchers/InternationalMembers.aspx> .

**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** (4/14/11)

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 <http://www.rtog.org/LinkClick.aspx?fileticket=-BXerpBu5AQ%3d&tabid=219>, 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 Logon" 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.org](mailto:websupport@acr.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.

**5.4**

**Post-Induction Registration** (4/14/11)

**5.4.1**

Following the completion of induction chemoradiotherapy and the evaluation of response all patients must be re-registered by calling RTOG Headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. At this time, the response results (biopsy results and cytology results) and the second phase of the treatment (radical cystectomy or consolidation chemoradiotherapy) will be recorded and a new data collection calendar generated.

**5.4.2**

The following information will be supplied:

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

**5.4.3** The treatment option registered at RTOG Headquarters and the new data collection calendar will be based on the parameters specified by the protocol. If the investigator or the patient deviates from the protocol specified treatment, documentation of this and data submission as outlined in Section 12.0 is required.

**5.4.4** Patients who have developed distant metastases during the induction phase of treatment and who will not continue therapy will remain on the original calendar schedule for continued follow up only. This information must be relayed to RTOG Data Management, 1-800-227-5463, ext 4189, and through submission of RTOG Form F0 (see Section 12.1).

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

## **6.0 RADIATION THERAPY (4/14/11)**

### **Note: Intensity Modulated RT (IMRT) Is Not Allowed**

**Protocol treatment must begin within 8 weeks following transurethral resection and endoscopic evaluation.**

All patients will receive the induction course of chemoradiation as per the assigned treatment arm, FCI or GI regimen. This regimen will begin within 8 weeks following the TUR and cystoscopic evaluation by the RTOG participating urologic surgeon. Patients with a complete response to the induction regimen will receive consolidation chemoradiation, as per assigned treatment arm, starting 7-14 days after cystoscopic re-evaluation.

Ideally, treatment should begin on a Monday for both Induction and Consolidation chemoradiation. Treatment times must be recorded in the daily treatment record. On the FCI arm, there will be two treatment sessions per day with an inter-session interval of 4-6 hours or more.

**Note:** For questions regarding field design, please contact the Study Chair, Dr. John Coen, (617-726-5866).

### **6.1 Dose Specifications (01/21/10)**

#### **6.1.1 Induction Treatment**

##### **6.1.1.1 *FCI Regimen (Arm 1)***

On the FCI induction regimen, radiation treatment is delivered twice per day (BID). The first daily treatment consists of 1.6 Gy delivered to the CTV<sub>pelvis</sub> followed by an interval of at least 4-6 hours before the second treatment. The second fraction consists of 1.5 Gy to the CTV<sub>bladder</sub> for the first 5 treatment days. Then, 1.5 Gy is delivered to CTV<sub>boost</sub> as the second treatment for the remaining 8 treatment days. This induction course will deliver a total of 40.3 Gy to the CTV<sub>boost</sub> (20.8 Gy from the pelvic fields, 7.5 Gy from the bladder fields and 12 Gy from the tumor boost).

##### **6.1.1.2 *GI Regimen (Arm 2)***

On the GI induction regimen, radiation treatment is delivered one time per day (QD). For the first 10 treatment days, 2 Gy is delivered to the CTV<sub>pelvis</sub>. Then, 2 Gy is delivered to the CTV<sub>bladder</sub> for the next 4 treatment days, followed by 2 Gy to the CTV<sub>boost</sub> for the remaining 6 treatment days. This induction course will deliver a total of 40 Gy to the CTV<sub>boost</sub> (20 Gy from the pelvic fields, 8 Gy from the bladder fields and 12 Gy from the tumor boost).

#### **6.1.2 Consolidation Treatment**

##### **6.1.2.1 *FCI Regimen (Arm 1)***

On the FCI consolidation regimen, radiation treatment is delivered to the CTV<sub>pelvis</sub> at 1.5 Gy per fraction twice per day (BID) over 8 treatment days for a total of 24 Gy. This is the same pelvic field that was treated as a component of induction therapy. For patients completing both induction and consolidation treatment, the resulting total dose to the CTV<sub>boost</sub> will be 64.3 Gy over 9 weeks in 42 fractions. The total dose to the CTV<sub>pelvis</sub> will be 44.8 Gy.

##### **6.1.2.2 *GI Regimen (Arm 2)***

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

#### **6.1.3**

##### Radiation Dose Prescription

The dose should be prescribed at the center of each treatment volume ( $CTV_{pelvis}$ ,  $CTV_{bladder}$ ,  $CTV_{boost}$ ), or the mid-plane of the patient if only AP/PA beams are used. Criteria for dose coverage are specified in Section 6.7.3.

#### **6.2**

##### **Technical Factors [Equipment, energies]**

Linear accelerators with beam energy of  $\geq 6$  MV must be used.

#### **6.3**

##### **Localization, Simulation, and Immobilization**

A planning CT must be obtained with the patient in the supine position. The bladder must be voided prior to simulation. A pelvic immobilization device is recommended. Use of bladder or rectal contrast is optional. Use of a urinary catheter at the time of simulation or cystoscopic placement of bladder fiducials prior to simulation is also optional. If bladder contrast is used, a 40-50 ml air contrast cystogram is recommended.

#### **6.4**

##### **Treatment Planning/Target Volumes**

###### **6.4.1**

###### Small Pelvic Fields (Appendix V)

These fields should encompass the entire bladder ( $CTV_{bladder}$ ), the bladder tumor volume ( $CTV_{boost}$ ), prostate and prostatic urethra (in men), and the regional lymph nodes. These lymph nodes include the internal and external iliacs and the obturator lymph nodes. All of these structures constitute the  $CTV_{pelvis}$ .

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

Field shaping will be used on the anterior-posterior opposed fields to shield the medial border of the femoral heads. Shaping will also be employed on the lateral opposed fields inferiorly to shield soft tissue anterior to the pubic symphysis and to block the anal canal posteriorly. Superiorly, the lateral fields may include shaping anteriorly to exclude small bowel and anterior rectus fascia which lay anterior to the external iliac lymph node chain.

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

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

###### **6.4.2**

###### Whole Bladder Field

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

###### **6.4.3**

###### Tumor Boost Fields (Appendix V)

The gross tumor volume (GTV= $CTV_{boost}$ ) is derived from information available from bimanual examination, cystoscopic bladder mapping, intraoperative reports and radiographic studies. Close cooperation with the treating urologist is essential. Cystoscopically placed fiducial

markers may be employed. A variety of field arrangements may be considered for treating this volume and efforts should be made to spare uninvolved regions of the bladder. Opposed lateral fields are frequently employed for posterior lesions. Well lateralized lesions may be amenable to an anterior-posterior field arrangement or a wedged pair. Regardless of the chosen field arrangement, the field edges should extend 2 cm beyond the defined GTV. The boost field arrangement needs to be determined early in the planning process as it may impact field weighting in the other phases of treatment such that final doses to the femoral heads and posterior rectum are within specified limits.

#### **6.5 Critical Structures (01/21/10) (01/29/10)**

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

Rectum:

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

Femoral heads:

No more than 20% of the volume above 50 Gy

#### **6.6 Documentation Requirements**

Within 7 working days of the initiation of treatment, the following must be submitted to ITC (see Section 12.2): (1) the CT plan, (2) Digitally reconstructed radiographs of all treatment fields and (3) the initial approved small pelvis port films.

#### **6.7 Compliance Criteria**

##### **6.7.1 Field Borders**

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

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

##### **6.7.2 Specified Radiation Dose (Critical structures)**

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

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

##### **6.7.3 Minimum Isodose Coverage (Applies to each CTV independently)**

Generally the minimum dose to any target should be 95 % of the prescription dose to that target. To address the single pixel calculation anomalies the  $D_{99\%}$  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:**  $D_{99\%} < 95\%$  but  $D_{99\%} > 90\%$ . Dose covering 99% of the volume of any target volume is no less than 90% of the prescribed dose.

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

##### **6.7.4 Maximum Dose (Applies to each CTV independently)**

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

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

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

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

##### **6.7.5 Interfraction Interval – Only applies to FCI Arm**

**Per protocol:** All treatments delivered BID with minimum interfraction interval of 4 hours

**Variation:** No more than one QD treatment delivered during each phase of chemoradiotherapy; interfraction interval between 3.5 hours and less than 4 hours

**Deviation:** More than three QD treatments during either phase of chemoradiotherapy; any interfraction interval less than 3.5 hours

#### **6.7.6 Elapsed Days**

**Per protocol:** No more than 3 break days

**Variation:** 4 to 7 break days

**Deviation:** 8 or more break days

#### **6.8 Treatment Interruption (4/14/11)**

If a grade 3 hematologic toxicity (ANC or platelets) develops during chemoradiotherapy, all treatment (both radiation and chemotherapy) should be discontinued for a minimum of 1 week. Treatment may be resumed when the hematologic toxicity resolves to  $\leq$  grade 2. If these laboratory values have not been reached after a 1-week delay, they should be checked weekly until they become acceptable. If after 3 weeks the blood counts have not recovered, all protocol treatment should be discontinued and the patients should be treated on an individual basis.

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

#### **6.9 R.T. Quality Assurance Reviews**

The Radiation Oncology Co-Chair, John Coen, M.D., will perform remote RT Quality Assurance Reviews after complete data for the first 20 cases enrolled has been received at ITC. Dr. John Coen will perform the next remote review after complete data for the next 20 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 and performed remotely.

#### **6.10 Radiation Adverse Events (4/14/11)**

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

#### **6.11 Radiation Adverse Event Reporting**

See Section 7.14 for Adverse Events and 7.15 for Adverse Event Reporting Guidelines.

### **7.0 DRUG THERAPY (4/14/11)**

**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 8 weeks after transurethral resection and endoscopic evaluation. Ideally, treatment should start on a Monday.**

#### **7.1 Induction Chemoradiotherapy with 5-Fluorouracil and Cisplatin with BID irradiation or Gemcitabine with QD irradiation**

**7.1.1** Body surface area calculations will be based on actual or ideal body weight as per institutional policy. The following premedication is recommended:

**7.1.2** Induction Chemotherapy, Arm 1(**a**): 5-Fluorouracil and Cisplatin plus BID irradiation (FCI) or Arm 2(**b**): Gemcitabine plus QD irradiation (GI) will begin within 8 weeks following the transurethral resection (TUR). On days of chemotherapy administration, patients are instructed to increase their fluid intake to at least six 8-oz. glasses of water (or other fluids) over the 12 hours prior to *i.v.* hydration preceding chemotherapy. The prechemotherapy *i.v.* hydration should be 0.5 NS, or NS at a rate of 500cc/hr for one hour.

**7.1.3** 5-Fluorouracil ( $400\text{mg}/\text{m}^2$ ) is to be administered as a 24-hour infusion on days 1,2,3, and 15,16,17.

- 7.1.4 Cisplatin (15 mg/m<sup>2</sup>) will be administered as a 60-minute infusion on days 1,2,3,8,9,10,15,16,17. The post-cisplatin *i.v.* hydration should consist of NS of 500cc in one hour.
- 7.1.5 Gemcitabine (27 mg/m<sup>2</sup>) will be administered as a 30-minute infusion on days 1, 4, 8, 11, 15, 18, 22, 25. The post-gemcitabine *i.v.* hydration should consist of NS of 500cc in one hour.
- 7.1.6 For the FCI regimen (Arm 1), radiation will be given twice a day with a minimum four-hour interfraction interval. On days when both chemotherapy and two fractions of radiation therapy (XRT) are given, the first XRT fraction may be given before chemotherapy and the second fraction after chemotherapy, while maintaining the minimum four-hour interfraction interval.
- 7.1.7 For the GI regimen (Arm 2), radiation is given once a day. On days when both chemotherapy and radiation therapy (XRT) are given, chemotherapy precedes radiation treatment.
- 7.1.8 Anti-emetic regimens, which may include ondansetron, granisetron, metoclopramide, lorazepam, dexamethasone, diphenhydramine hydrochloride and/or prochlorperazine, are recommended before and after cisplatin and gemcitabine.
- 7.1.9 The patient will have an evaluation of response (as described in Section 8.2) 3-4 weeks following completion of induction chemoradiotherapy
  - 7.1.9.1 (3/26/09) For patients who have a pT0, Ta, or Tcis (at site distant from original tumor) response documented by the first response evaluation, consolidation therapy will begin within 7-14 days.
  - 7.1.9.2 For operable patients who have a pT1 or worse tumor response, radical cystectomy will be performed within 3-8 weeks following their post-induction response evaluation.

- 7.2 Consolidation Chemoradiotherapy for Patients Selected for Bladder Preservation (4/14/11)**
- 7.2.1 Consolidation Chemotherapy, Arm 1(c): 5-Fluorouracil and Cisplatin plus BID irradiation (FCI) or Arm 2(d): Gemcitabine (27 mg/m<sup>2</sup>) plus QD irradiation (GI) will begin within 7-14 days following post-induction response evaluation.
- 7.2.2 On days of chemotherapy administration, patients will be instructed to increase their fluid intake to at least six 8 oz. glasses of water (or other fluids) over the 12 hours prior to *i.v.* hydration preceding chemotherapy. The prechemotherapy *i.v.* hydration should be 0.5 NS or NS at a rate of 500 cc/hr for 1 hour.
- 7.2.3 5-Fluorouracil, (400 mg/m<sup>2</sup>), will be administered as a 24-hour infusion on days 1, 2, 3 and 8, 9, 10.
- 7.2.4 Cisplatin, (15 mg/m<sup>2</sup>), will be administered as a sixty-minute infusion on days 1, 2, 8, 9. The post cisplatin *i.v.* hydration will consist of NS at a rate of 500 cc/hr for 1 hour.
- 7.2.5 Gemcitabine (27 mg/m<sup>2</sup>) will be administered as a 30-minute infusion on days 1, 4, 8, 11, 15. The post-gemcitabine *i.v.* hydration should consist of NS of 500cc in one hour.
- 7.2.6 Anti-emetic regimens, which may include ondansetron, granisetron, metoclopramide, lorazepam, dexamethasone, diphenhydramine hydrochloride and/or prochlorperazine, are recommended before and after cisplatin and gemcitabine.
- 7.2.7 For the FCI regimen (Arm 1), radiation will be given twice a day with a minimum four-hour interfraction interval. On days when both chemotherapy and two fractions of radiation therapy (XRT) are given, the first XRT fraction may be given before chemotherapy and the second fraction after chemotherapy, while maintaining the minimum four-hour interfraction interval.
- 7.2.8 For the GI regimen (Arm 2), radiation is given once a day. On days when both chemotherapy and radiation therapy (XRT) are given, chemotherapy precedes radiation treatment.
- 7.2.9 The patient will have an evaluation of response (as described in Section 8.4) 8-10 weeks following completion of consolidation chemoradiotherapy.

- 7.3 Adjuvant Chemotherapy (4/14/11)**
- 7.3.1 Outpatient adjuvant chemotherapy will begin 4-5 weeks following the post-consolidation endoscopic evaluation or 8-12 weeks following radical cystectomy. Adjuvant chemotherapy consists of gemcitabine and cisplatin given on a 21-day cycle. For patients with inadequate renal function as defined in the dose modification section, paclitaxel will be substituted for cisplatin. A cycle is defined as 2 consecutive weeks of treatment followed by a week of rest. Patients will receive four cycles of adjuvant chemotherapy.
  - 7.3.1.1 Gemcitabine (1000 mg/m<sup>2</sup>) will be administered intravenously over 30-60 minutes (preferably 30 minutes) on Days 1 and 8 of each 21-day cycle. Calculate the body surface area of the patient according to actual height and weight at the beginning of each cycle.

7.3.1.2 (3/26/09) Cisplatin (70 mg/m<sup>2</sup>) will be administered as a sixty-minute infusion on day 1 of each 21-day cycle. Pre and post hydration should consist of 500m/hr x 1 liter of NS.

7.3.1.3 When used, paclitaxel (150 mg/m<sup>2</sup>) will be administered as a sixty-minute infusion on day 1 of each 21-day cycle. The post-paclitaxel *i.v.* hydration should consist of NS of 500cc in one hour.

#### **7.4 5-Fluorouracil (5-FU)**

7.4.1 Dose Formulation: 5-FU is available in 10-ml ampules, as a colorless to faint yellow aqueous solution containing 500 mg 5-FU, with pH adjusted to approximately 9.0 with sodium hydroxide.

7.4.2 Pharmacology: 5-FU is a marketed drug available in 500 mg vials. It is fluorinated pyrimidine belonging to the category of antimetabolites. 5-FU resembles the natural uracil molecule in structure, except that a hydrogen atom has been replaced by a fluorine atom in the 5 position. There is evidence that the metabolism of fluorouracil in the anabolic pathway blocks the methylation reaction of deoxyuridyllic acid to the thymidyllic acid. In this fashion 5-FU interferes with the synthesis of DNA and to a lesser extent inhibits the formation of ribonucleic division and growth, the effect of fluorouracil may be to create a thymidine deficiency which provides unbalanced growth and death of the cell.

7.4.3 Administration: 5-Fluorouracil (400mg/m<sup>2</sup>) is to be administered as a 24-hour infusion. Administration of 5-FU should be only by the intravenous route taking care to avoid extravasation.

7.4.4 Storage: Although 5-FU solution may discolor slightly during storage, the potency and safety are not adversely affected. Store at room temperature (49°-86°F). Protect from light. If a precipitate occurs due to exposure to low temperatures, resolubilize by heating to 140°F with vigorous shaking; allow to cool to body temperature before using.

7.4.5 Adverse Events:

- *Hematologic:* Myelosuppression
- *Gastrointestinal:* Nausea and vomiting; diarrhea, stomatitis, mucositis, pharyngitis, increased liver function tests (SGOT, SGPT, bilirubin, alkaline phosphatase), biliary sclerosis, or acalculous cholecystitis
- *Cardiac:* Myocardial infarction (MI), angina
- *Neurological:* Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy, sensation of flashing lights; blurred vision, scintillating scotoma
- *Allergy:* Anaphylactoid and urticarial reactions (acute); rash, pruritis
- *Other:* Alopecia, fatigue, disorientation, dizziness, lack of coordination, visual changes, photosensitivity (eyes and skin); nail changes including loss of nails, skin thickening, cracking, dryness or sloughing; vein pigmentation

7.4.6 Supply: Commercially available.

#### **7.5 Cisplatin (Platinol®)**

7.5.1 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.

7.5.2 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.

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

7.5.4 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. The solution may be further diluted in a chloride containing vehicle such as D5NS, NS, or D5-1/2NS (ppt. Occurs in

D<sub>5</sub>W). Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes.

**7.5.5 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

**7.5.6 Supply:** Commercially available.

**7.6 Gemcitabine**

**7.6.1 Chemistry:** Gemcitabine (2'-deoxy-2'2'-difluorocytidine monohydrochloride) is a purine analog structurally similar to cytarabine and an analog to deoxycytidine. Gemcitabine has two fluoride atoms in the geminal position of the second carbon of the ribose sugar.

**7.6.2 Dose Formulation:** Gemcitabine is supplied in 200 mg and 1000 mg vials. Two hundred mg vials are reconstituted in 5 cc sodium chloride then diluted to a concentration of as low as 0.1 mg/ml if necessary for infusion. One thousand mg vials are reconstituted with 25 cc sodium chloride.

**7.6.3 Mechanism of Action:** Gemcitabine inhibits DNA synthesis in tumor cells by competing with deoxycytidine triphosphate for incorporation into DNA. Gemcitabine metabolites also inhibit enzymes in DNA synthesis. Finally, gemcitabine is masked from DNA repair enzymes with the addition of one additional nucleotide after gemcitabine is in the DNA chain.

**7.6.4 Pharmacokinetics:** Gemcitabine is metabolized into active metabolites gemcitabine diphosphate and gemcitabine triphosphate. It is also metabolized to inactive compound, gemcitabine difluorouridine. Ninety-nine percent of the dose is excreted in the urine and there is negligible protein binding. The serum half-life is significantly affected by decreases in creatinine clearance. However, there is no schedule for dose reduction in renal dysfunction.

**7.6.5 Administration:** Gemcitabine at the appropriate dose and dilution will be administered over 30 minutes.

**7.7.5 Storage:** Gemcitabine is stored at room temperature until given.

**7.6.7 Adverse Events:**

- *Hematologic:* Myelosuppression, neutropenia, anemia, and thrombocytopenia
- *Gastrointestinal:* Nausea and vomiting; anorexia, stomatitis, diarrhea, constipation, elevation of liver function tests
- *Renal:* Rare decrease in creatinine clearance, edema
- *Allergy:* Anaphylactoid and urticarial reactions (acute); rash
- *Other:* Fatigue, fever, alopecia, pain, dyspnea

**7.6.8 Supply:** Commercially available.

**7.7 Paclitaxel (Taxol®)**

**7.7.1 Formulation:** Paclitaxel is a poorly soluble plant product from the western yew, *Taxus brevifolia*. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water. Vials will be labeled with shelf life. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours.

**7.7.2 Preparation:** A sterile solution concentrate, 6 mg/ml in 5 ml vials (30 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use. Paclitaxel for injection must be diluted before administration with 5% dextrose USP, 0.9% sodium chloride USP, or 5% dextrose in Ringer's injection to a final concentration of 0.3 to 1.2 milligrams/milliliter. This solution is stable for 27 hours under ambient temperature (25 degrees Celsius) and room lighting (Prod Info Taxol®, 1997). Use 5% polyolefin containers due to leaching of diethylhexphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. Each bag/bottle should be

prepared immediately before administration. NOTE: Formation of a small number of fibers in solution has been observed after preparation of paclitaxel (NOTE: acceptable limits established by the USP Particular Matter Test for LVP's). Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: Millex-GV Millipore Products) into the *i.v.* fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

**7.7.3** Administration: Paclitaxel, at the appropriate dose and dilution, will be given as a one-hour infusion. The paclitaxel is mixed in non-PVC containers and infused via polyolefin-lined nitroglycerin tubing or low absorption AVI *i.v.* administration with 0.22 m in-line filter. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as the *i.v.* administration sets (polyethylene or polyolefin) which are used to infuse parenteral Nitroglycerin. Nothing else is to be infused through the line through which paclitaxel is administered.

**7.7.4** Storage: Paclitaxel vials should be stored between 2°-25°C (36°-77°F).

**7.7.5** Adverse Events:

- *Hematologic:* Myelosuppression
- *Gastrointestinal:* Nausea and vomiting; diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis, increased liver function tests (SGOT, SGPT, bilirubin, alkaline phosphatase); hepatic failure, hepatic necrosis
- *Heart:* Arrhythmias, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, atrial arrhythmia, hypotension, hypertension, lightheadedness
- *Neurological:* Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy, sensation of flashing lights; blurred vision, scintillating scotoma
- *Allergy:* Anaphylactoid and urticarial reactions (acute); flushing, rash, pruritis
- *Other:* Alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration (erythema, induration, tenderness, rarely ulceration); radiation recall reaction.

**7.7.6** Supply: Commercially available.

**7.8** Accountability

Drug accountability records must be maintained at all sites according to good clinical practices and NCI guidelines.

**7.9** Dose Modifications for Induction/Consolidation (4/14/11)

**7.9.1** A complete blood count and serum creatinine will be drawn at the start of each week of induction and consolidation chemotherapy. Dose modifications for the drugs given that week will be based upon these results. Dose reductions based on CBC and creatinine during induction do not carry through to consolidation unless the blood abnormality persists. Dose reductions based upon clinical problems, such as neurotoxicity, may involve discontinuation of the drug altogether and are specified in the text below.

If a grade 3 hematologic toxicity (ANC or platelets) develops during chemoradiotherapy, all treatment (both radiation and chemotherapy) should be discontinued for a minimum of 1 week. Treatment may be resumed when the hematologic toxicity resolves to  $\leq$  grade 2. If these laboratory values have not been reached after a 1-week delay, they should be checked weekly until they become acceptable. If the blood counts have not recovered after 3 weeks, all protocol treatment should be discontinued and the patients should be treated on an individual basis.

The guidelines above apply to cisplatin, gemcitabine, and 5-fluorouracil.

**7.9.2 Dose Modifications of Cisplatin during Induction/Consolidation**

**7.9.2.1** *Dose Modifications of Cisplatin for Nephrotoxicity* during induction and consolidation chemoradiotherapy are listed in the table below:

**Please note:** If serum creatinine is out of range, but CrCl is in range, 100% can be given if in the judgment of the treating physician. If cisplatin is held, re-evaluate day 1 each week to restart.

Day 1 Level	Dose
CrCl >60 ml/min or serum creatinine $\leq$ 1.5 mg%	100%
serum creatinine > 1.33 x baseline	75%
serum creatinine >1.5 x baseline	Hold cisplatin

**7.9.2.2** *Dose Modifications of Cisplatin for Myelosuppression* during induction and consolidation chemoradiotherapy are as listed in the table below:

**% Calculated Dose**

ANC (x 10 <sup>9</sup> /L)	Platelet Count			
	$\geq 150K$	100 - 149K	75 - 99K	<75 - 50K
$\geq 1.4$	100% dose	100% dose	HOLD dose	HOLD dose
<b>1.2 - 1.39</b>	100% dose	75% dose	HOLD dose	HOLD dose
$< 1.2$	HOLD dose	HOLD dose	HOLD dose	HOLD dose

ANC = Absolute neutrophil count per ml

**7.9.2.3** *Modification of Cisplatin for Peripheral Neurotoxicity* during induction and consolidation chemoradiotherapy:  $\geq$  Grade 3: Omit cisplatin.

**7.10 Dose Modifications of 5-Fluorouracil (5-FU) during Induction/Consolidation (9/27/11)**

**7.10.1** *Modifications of 5-Fluorouracil for Myelosuppression* during induction and consolidation chemoradiotherapy are as listed in the tables below and should be assessed weekly:

**% Of Initial Calculated Dose**

ANC (x 10 <sup>9</sup> /L)	Platelet Count			
	$\geq 150K$	100 - 149K	75 - 99K	<75 - 50K
$> 1.6$	100% dose	100% dose	75% dose	50% dose
<b>1.4 - 1.6</b>	100% dose	75% dose	50% dose	50% dose
<b>1.0 - 1.3</b>	75% dose	75% dose	50% dose	HOLD dose
$<1.0$	HOLD dose	HOLD dose	HOLD dose	HOLD dose

ANC = Absolute neutrophil count per ml

**7.10.2 Modifications of 5-FU for Gastrointestinal Toxicities** during induction and consolidation

Grade	% Calculated Dose
Grade 1	100% dose
Grade 2	75% dose- for the duration of 72h infusion *
Grade 3	50% dose - for the duration of 72h infusion *

\*only decreased for diarrhea, not stomatitis

**7.11 Dose Modifications for Gemcitabine during Induction/Consolidation (4/14/11)**

**7.11.1 Modifications of Gemcitabine for Myelosuppression** during induction and consolidation chemoradiotherapy are as listed in the table below:

ANC ( $\times 10^9/L$ )	Platelet Count		
	> 75K Grade 1	<75 - 50K Grade 2	< 50K Grade 3
≥ 1.0 Grade 2	100% dose	50% dose	HOLD dose
0.5-0.99 Grade 3	HOLD dose	HOLD dose	HOLD dose
< 0.5 Grade 4	HOLD dose	HOLD dose	HOLD dose

Patients with grade 3 or greater non-hematologic toxicity will have gemcitabine discontinued and not restarted until toxicities have improved to grade 2 or less. Gemcitabine will then be started at a 20% dose reduction. This dose reduction will remain throughout the rest of therapy. If a second grade 3 or greater non-hematologic toxicity occurs, gemcitabine dose will be reduced an additional 20%.

**7.12 Dose Modification for Adjuvant Chemotherapy (gemcitabine, cisplatin, and paclitaxel) (4/14/11)**

**7.12.1 Dose Modification within a Cycle**

If the start of an adjuvant cycle is delayed, re-evaluate weekly to initiate the cycle. If day 8 of the cycle is held, do not make up the gemcitabine dose for day 8. The next adjuvant treatment cycle will start according to schedule after a re-evaluation of patient's toxicities.

**Gemcitabine dose adjustments:** Dose adjustments within a cycle for gemcitabine will be made following the guidelines shown below based on weekly absolute neutrophil count (ANC) and platelet counts taken within 24 hours before infusion and on clinical assessment of non-hematologic toxicities.

**Hematologic Toxicities**

ANC ( $\times 10^9/L$ )	Platelets ( $\times 10^9/L$ )	Percent of Full Dose
≥ 1.0	and ≥ 75	100% dose
0.5 - 0.99	or 50 - 74	50% dose
< 0.5	or < 50	HOLD dose

### Non-hematologic Toxicities

CTCAE Version 3.0	Percent of Full Dose
<b>Gemcitabine</b>	
Grade 1-2	100% dose
Grade 3	50% or Hold dose *
Grade 4	Hold dose *

\*This decision will depend upon the type of non-hematologic toxicity seen and which course is medically most sound in the judgment of the treating physician.

**Cisplatin dose adjustments:** If creatinine clearance is below 60ml/min prior to the start of a cycle, cisplatin should not be administered and the patient should receive paclitaxel as a substitute in all further cycles.

### Hematologic Toxicities

ANC (x 10 <sup>9</sup> /L)	Platelet Count			
	<b>≥ 150K</b>	<b>100 - 149K</b>	<b>75 - 99K</b>	<b>&lt;75 - 50K</b>
<b>≥ 1.4</b>	100% dose	100% dose	HOLD dose	HOLD dose
<b>1.2 - 1.39</b>	100% dose	75% dose	HOLD dose	HOLD dose
<b>&lt; 1.2</b>	HOLD dose	HOLD dose	HOLD dose	HOLD dose

### Non-hematologic Toxicities

CTCAE Version 3.0	Percent of Full Dose
	<b>Cisplatin</b>
Grade 1-2	Physician discretion*
Grade 3 nausea and vomiting	75% of full dose
Grade 3-4 ototoxicity	Physician discretion*
Grade 3-4 neurotoxicity	Physician discretion*
Creatinine clearance < 60ml/min	Give paclitaxel for all future cycles

\*This decision will depend upon the type of non-hematologic toxicity seen and which course is medically most sound in the judgment of the treating physician.

**Paclitaxel dose adjustments:** Dose adjustments within a cycle for paclitaxel will be made following the guidelines shown below based on weekly absolute neutrophil count (ANC) and platelet counts taken within 24 hours before infusion and on clinical assessment of non-hematologic toxicities.

### Hematologic Toxicities

ANC (x 10 <sup>9</sup> /L)	Platelets (x 10 <sup>9</sup> /L)	Percent of Full Dose
		<b>Paclitaxel</b>
<b>≥ 1.0</b>	<b>and</b> <b>&gt; 75</b>	75% dose
<b>0.5 - 0.99</b>	<b>or</b> <b>50 to 74</b>	HOLD dose
<b>&lt; 0.5</b>	<b>or</b> <b>&lt; 50</b>	HOLD dose

### Non-hematologic Toxicities

CTCAE Version 3.0	Percent of Full Dose
	<b>Paclitaxel</b>
Grade 1-2 (and Grade 3 nausea/vomiting)	75% dose
Grade 3 (except nausea/vomiting)	50% or Hold dose *
Grade 4	Hold dose *

\*This decision will depend upon the type of nonhematologic toxicity seen and which course is medically most sound in the judgment of the treating physician.

#### 7.12.2 Dose Modification for Subsequent Cycles

7.12.2.1 The following guidelines should be followed:

- Doses of gemcitabine and paclitaxel cannot be escalated above the starting dose.
- Absolute neutrophil count must be greater than  $1.2 \times 10^9/L$ , and platelet count must be greater than  $100 \times 10^9/L$  to proceed with the next cycle.
- If day 8 is held for a grade 3 or grade 4 hematologic toxicity, subsequent cycles will be dose reduced by 25% and the reduction will be maintained for the duration of treatment.

#### **7.12.2.2 Hematologic Toxicity**

- Patients who sustain either febrile neutropenia or Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia associated with new-onset gross hematuria or other clinical evidence of bleeding should be dosed at 50% of the starting dose of gemcitabine delivered in the previous cycle, the latter to apply to each gemcitabine dose administered during that cycle. Subsequent dose escalation of gemcitabine only by 50% (e.g., from  $500 \text{ mg/m}^2$  to  $750 \text{ mg/m}^2$ ) will be allowed in subsequent cycles provided the patient tolerates the initial dose of adjustment.

#### **7.13 Modality Review**

The Medical Oncology Co-Chair, Donald S. Kaufman, M.D., 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.

The Medical Oncology Co-Chair, Donald S. Kaufman, M.D., will perform a Quality Assurance 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 20 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.

#### **7.14 Adverse Events (2/6/14)**

Beginning October 1, 2010, this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for grading of all adverse events. A copy of the CTCAE version 4.0 can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. **All AE reporting on the study case report forms will continue to use CTCAE version 3.0.**

All adverse events (AEs) as defined in the tables 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>).

Serious adverse events (SAEs) as defined in the tables below will be reported via CTEP-AERS.

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

#### **7.14.1 Adverse Events (AEs)**

**Definition of an AE:** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements; [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/adverse\\_events.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm)]

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 CTEP Adverse Event Reporting Requirements in text and/or table in Section 7.15 also must be reported via CTEP-AERS.**

**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.**

**7.14.2 Serious Adverse Events (SAEs)** — Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in Section 7.15 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in Section 7.15. **Contact the CTEP-AERS Help Desk if assistance is required.**

**Definition of an SAE:** Any adverse drug 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.

**7.14.3 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.

**7.15 CTEP-AERS Adverse Event Reporting Requirements (2/6/14)**

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 RTOG and satisfies RTOG 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 RTOG 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 report 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 an CTEP-AERS report, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation **to the RTOG 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 RTOG 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).

**Phase 2 and 3 Trials Utilizing an Agent Under a Non-CTEP IND: CTEP-AERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days<sup>1</sup> of the Last Dose of the Commercially Available Agents in this Study (Arms 1 & 2)**

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 <sup>2</sup>	Grades 4 & 5 <sup>2</sup>
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	without Hospitalization	Expected with Hospitalization	without Hospitalization	Unexpected	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

<sup>1</sup> 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 under a non-CTEP IND require reporting as follows:

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

- Grade 4 and Grade 5 unexpected events

CTEP-AERS 10 calendar day report:

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

<sup>2</sup> Although an CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

**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 CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - 40 calendar days” - A complete CTEP-AERS 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 CTEP-AERS 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 CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a Non-CTEP IND:**

Not applicable to this study.

**8.0 SURGERY**

**8.1 Pre-Induction Chemoradiotherapy Evaluation:** Endoscopic evaluation must include:

- 8.1.1 Cystoscopy with tumor mapping on the initial Cystoscopic Report (Appendix VI);
- 8.1.2 Transurethral resection (TUR) of the tumor as thoroughly as is judged safely possible. Tumor specimens should be sent to the RTOG Biospecimen Resource as described in Section 10.0;
- 8.1.3 Bimanual examination before and after TUR to evaluate possible residual tumor bulk using the following criteria: exam not performed, no pelvic mass, mobile pelvic mass, fixed pelvic mass;
- 8.1.4 A biopsy of the prostatic urethra sampling mucosa and prostatic stroma using a resection loop.

**8.2 Post-Induction Chemoradiotherapy Endoscopic Response Evaluation (4/14/11)**

This evaluation will take place in 3-4 weeks following the completion of the induction chemoradiotherapy. Evaluation will include: urine cytology, cystoscopy, tumor site transurethral biopsy, and bimanual examination after biopsy.

Operative reports and pathology reports from TUR 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 (4/14/11)**

Operable patients who have a pT1 or worse tumor response on re-evaluation following initial TUR and induction chemoradiotherapy will have a radical cystectomy 3-8 weeks following the post-induction response evaluation. 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 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 after induction chemoradiotherapy, 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 structures, summary of the margin status and the location and total number of lymph nodes resected and involved with carcinoma.

#### **8.4 Post-Consolidation Endoscopic Evaluations (2/28/12)**

The first post-therapeutic evaluation will be in 8-10 weeks following completion of the consolidation chemoradiotherapy, when the initial response was pT0, Ta, or Tis. Subsequent cystoscopic evaluation will be every three months in the first year, every four months in the second year, every six months for three years, then annually, provided there has been no recurrence of tumor. These periodic evaluations will be done according to the schedule in Section 11.0 and will include urine cytology, biopsy of the original tumor site and any suspicious areas, and bimanual examination. If after two re-evaluations in which the tumor site re-biopsies have been negative and the urologist observes nothing suspicious, cystoscopy and cytology without biopsy is permitted. The post-induction evaluation may be considered the first of these two negative re-evaluations. Regular cystoscopic follow up will allow additional therapy such as transurethral surgery, intravesical chemotherapy, or cystectomy to be initiated at the earliest prompt opportunity, if relapse occurs.

#### **8.5 Surgical Quality Assurance Reviews**

The Urology Co-Chair, Cheryl T. Lee, MD, will perform a urologic Quality Assurance Review after complete data for the first 20 cases enrolled has been received at RTOG Headquarters. Dr. Lee will perform the next review after complete data for the next 20 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. Surgical reviews will require detailed operative and pathology notes.

### **9.0 OTHER THERAPY**

#### **9.1 Permitted Supportive Therapy**

- 9.1.1** For patients who are treated with attempted bladder preservation using consolidation FCI or GI, either radical cystectomy or intravesical drug therapy will be promptly considered for a local persistence or local re-occurrence if it occurs in patients without evidence of distant metastases. Intravesical drug therapy should be administered for patients developing carcinoma *in situ* or tumors involving the bladder mucosa or lamina propria, but not for muscle invading tumors. This subsequent therapy will be given at the discretion of the primary physicians. 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 cisplatin and gemcitabine.
- 9.1.4** Growth factors

### **10.0 TISSUE/SPECIMEN SUBMISSION**

The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Biospecimen Resource 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. The RTOG Biospecimen Resource also collects tissue for Central Review of pathology.

In this study, primary tumor tissue from the pretreatment TUR as well as two biopsies obtained from the tumor periphery will be submitted to the RTOG Biospecimen Resource for the purpose of central review (required) and tissue banking for biomarker studies (highly recommended but not required).

#### **10.1 Central Review: Required**

H&E slides from the pre-treatment tumor TUR, and a biopsy sampling the mucosa and prostatic stroma should be sent. Also, the cystoscopy report, and the pathology report will be reviewed by a central pathologist to determine if there is unequivocal proof of invasion of the *muscular propria* plus other possible histopathologic factors including tumor grade, the presence or absence of tumor-associated carcinoma *in situ*, the presence or absence of vascular space invasion, and the tumor configuration (papillary, solid or mixed). There will be no restaging of the patient's clinical stage based only on the apparent depth of invasion of the *muscularis propria* from the tumor TUR specimen. However if there is no tumor invasion of the *muscularis propria* documented in the specimens resected by the participating urologist, slides from the original tumor TUR from the outside hospital that reported the presence of invasion of the *muscularis propria* should be requested and sent to RTOG for central review.

See Section 10.3.1 for shipping information.

#### **10.2 Specimen Collection for Tissue Banking for Biomarker Studies: Strongly recommended**

(4/14/11)

**NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission.**

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 of the protocol. **Note:** Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

**For patients who have consented to participate in the tissue/blood/urine component of the study (See Appendix I).** The following must be provided in order for the case to be evaluable by the Biospecimen Resource:

**10.2.1** One H&E stained slide

**10.2.2** A 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 punch tool 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 Biospecimen Resource. Block or core must be clearly labeled with the pathology identification number that corresponds to the Pathology Report. See Appendix VII.

**10.2.3** A Pathology Report documenting that the submitted block or core contains tumor. The report must include the RTOG 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 RTOG Biospecimen Resource; if for translational research, this should be stated on the form. The form must include the RTOG protocol number and patient's case number.

**10.2.5** Serum, plasma, whole blood, and urine

See Appendix VII for the blood and urine collection kits and instructions. The following must be provided in order for the case to be evaluable by the Biospecimen Resource: A Specimen Transmittal Form documenting the date of collection of the serum, plasma, and urine; the RTOG protocol number, the patient's case number, time point of study, and method of storage, for example, stored at -80° C, must be included.

**10.2.6** Storage Conditions

Store frozen specimens 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).

**OR:**

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

**OR:**

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

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

**10.3 Specimen Collection Summary (2/28/12)**

Specimens for Central Review (Required)		
Specimens taken from patient:	Submitted as:	Shipped:
H&E stained slides from pre-treatment tumor TUR	H&E stained slide	Slides shipped ambient
1 biopsy sampling mucosa and prostatic stroma	H&E stained slide	Slides shipped ambient

Specimens for Tissue Banking (Strongly recommended)			
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 diameter core of tissue, punched from the tissue block with a punch tool	Pre-treatment	Paraffin-embedded tissue block or punch biopsy	Block or punch shipped ambient
SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge	1) Pre-treatment During Treatment: 2) During chemoradiation: 20 Gy into induction therapy regimen ( <i>for bid XRT patients: day 10, take BEFORE treatment that day; for qd XRT patients: day 15, take BEFORE treatment that day</i> ) 3) At the time of post-induction response evaluation (Week 7) 4) At the time of post consolidation evaluation (Week 17) Post-treatment: 5) At 1 year follow up 6) At the time of relapse	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 tube #1 (purple/lavender top) and centrifuge	1) Pre-treatment 2) During chemoradiation: 20 Gy into induction	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

	<p>therapy (<i>for bid XRT patients: day 10, take BEFORE treatment that day; for qd XRT patients: day 15, take BEFORE treatment that day</i>)</p> <p>3) At the time of post-induction response evaluation (<i>Week 7</i>)</p> <p>4) At the time of post consolidation evaluation (<i>Week 17</i>)</p> <p>Post-treatment:</p> <p>5) At 1 year follow up</p> <p>6) At the time of relapse</p>		
DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix	Pre-treatment (if this collection time point is missed, the whole blood may be collected at any other time point, but this must be noted on the STF)	Frozen whole blood samples containing 1ml per aliquot in 1 ml cryovials (three to five)	Whole blood sent frozen on dry ice via overnight carrier
10-20 mL clean-catch urine	<p>1) Pre-treatment</p> <p>During Treatment:</p> <p>2) During chemoradiation: 20 Gy to induction therapy regimen (<i>for bid XRT patients: day 10, take BEFORE treatment that day; for qd XRT patients: day 15, take BEFORE treatment that day</i>)</p> <p>3) At the time of post-induction response evaluation (<i>Week 7</i>)</p> <p>4) At the time of post consolidation evaluation (<i>Week 17</i>)</p> <p>Post-treatment:</p> <p>5) At 1 year follow up</p> <p>6) At the time of relapse</p>	Two 5-10 mL urine aliquots in 2 sterile 15 ml polypropylene centrifuge tubes. Store frozen at -20° C or -80° C	Urine sent frozen on dry ice via overnight carrier

#### 10.3.1 Submit materials to:

##### U. S. Postal Service mailing address: For Non-frozen Specimens Only

RTOG Biospecimen Resource  
 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 Specimens**

RTOG Biospecimen Resource  
University of California San Francisco  
2340 Sutter Street, Room S341  
San Francisco, CA 94115

**Telephone:** 415-476-RTOG (7864)

**Fax:** 415-476-5271

[RTOG@ucsf.edu](mailto:RTOG@ucsf.edu)

**10.4 Reimbursement** (4/14/11)

RTOG will reimburse institutions for submission of protocol specified biospecimen materials sent to the Biospecimen Resource at the University of California San Francisco and other protocol-specified collection repositories/laboratories. After confirmation from the RTOG Biospecimen Resource or other designated repository/laboratory that appropriate materials have been received, RTOG Clinical Trials Administration will authorize payment according to the schedule posted with the Reimbursement and Case Credit Schedule found on the RTOG web site (<http://www.rtog.org/LinkClick.aspx?fileticket=Csxzt1v1hEk%3d&tabid=323>). Biospecimen payments will be processed quarterly and will appear on the institution's summary report with the institution's regular case reimbursement.

**10.5 Confidentiality/Storage** (01/21/10)

(See the RTOG Patient Tissue Consent Frequently Asked Questions, <http://www.rtog.org/Researchers/BiospecimenResource/BiospecimenResourceFAQs.aspx> for further details.)

**10.5.1** Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The RTOG Biospecimen Resource 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.

**10.5.2** Specimens for tissue banking will be stored for an indefinite period of time. 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** (4/14/11)

See Appendix II for a summary of assessments and time frames. See Sections 11.2 and 11.3 for details and/or exceptions to Appendix II.

**11.2 Evaluations during Chemoradiotherapy** (4/14/11)

**Induction chemoradiotherapy for Arms 1a and 2b begins within 8 weeks following transurethral resection. Consolidation chemoradiotherapy for Arms 1c and 2d begins within 7-14 days following post-induction response evaluation.**

**11.2.1 Weekly during Induction Chemoradiotherapy (FCI or GI)**

On day 1 of each week, the patient's weight will be assessed for BSA, Zubrod performance status will be obtained, and the following lab evaluations will be conducted: CBC/differential, platelets, serum creatinine, and BUN. Creatinine clearance also should be assessed.

At the beginning of week 3 as part of the blood draw for required lab evaluation, plasma, serum, and urine will be collected for biomarker studies (highly recommended but not required; for patients that have given consent for this component of the study).

**11.2.2 Post-Induction Evaluation**

The following assessments should be conducted within 3-4 weeks of the completion of the induction chemoradiotherapy: cystoscopy; urine cytology; bimanual exam under anesthesia; and a bladder biopsy. A physical examination should be performed and the following lab evaluations should be conducted: CBC/differential, platelets, serum creatinine and BUN.

During the time of assessment, plasma, serum, and urine will be collected for biomarker studies (highly recommended but not required; for patients that have given consent for this component of the study).

**11.2.3 Weekly during Consolidation Chemoradiotherapy (FCI or GI)**

The following should be assessed on day 1 of consolidation chemoradiotherapy prior to the start of treatment: Creatinine clearance, bilirubin, alkaline phosphatase, SGOT, and LDH.

On day 1 of each week, the patient's weight will be assessed for BSA, Zubrod performance status will be obtained, and the following lab evaluations will be conducted: CBC/differential, platelets, serum creatinine and BUN. Creatinine clearance should also be assessed.

**11.2.4 Post-Consolidation Evaluation**

The following assessments should be conducted within 8-10 weeks of the completion of the consolidation chemoradiotherapy: cystoscopy, urine cytology, bimanual exam under anesthesia and bladder biopsy. The following radiologic assessments should be evaluated: CT scan (abdominal/pelvic and chest) and bone scan. A history/physical examination should be performed and the following lab evaluations should be conducted: CBC/differential, platelets, serum creatinine, and BUN.

**11.3 Evaluation Following Chemoradiotherapy (2/28/12)**

**11.3.1 Post Cystectomy prior to Starting Adjuvant Treatment**

A physical examination should be performed and the following lab evaluations should be assessed: CBC/differential, platelets, serum creatinine, and BUN. The following radiologic assessments should be evaluated: CT scan (abdominal/pelvic and chest) and bone scan.

**11.3.2 During Adjuvant Chemotherapy**

Prior to Day 1 of each cycle, the following should be assessed: Zubrod performance status and creatinine clearance. Prior to Day 1 and Day 8 of each cycle, the patient's weight will be assessed for BSA. Laboratory evaluations should also be conducted: CBC/differential, platelets; serum creatinine; BUN; bilirubin, alkaline phosphatase, SGOT, LDH.

**11.3.3 During Post-Treatment Follow-Up**

The following should be assessed q 3 months during the first year, q 4 months during the second year, q 6 months for years 3, 4, and 5, then annually until year 10 of follow-up: history/physical examination, weight, and Zubrod performance status; CBC/differential, platelets; serum creatinine; BUN. The following radiological evaluations should be done q 6 months: abdominal/pelvic CT and chest CT.

The following will also be assessed q 3 months during the first year after completion of consolidation treatment, q 4 months during the second year, q 6 months for years 3, 4, and 5, then annually until year 10 of follow-up: cystoscopy, urine cytology, bladder biopsy. If after two re-evaluations, where the post-induction re-evaluation may be considered the first of the two, in which the tumor site re-biopsies have been negative and the urologist observes nothing suspicious, cystoscopy and cytology without biopsy is permitted.

Note: Only if cystectomy is not done within the first 6 weeks after consolidation chemoradiotherapy. Please read Section 8.4 which allows biopsies to be omitted after the second follow-up evaluation under the described circumstances.

An urodynamic evaluation (cystometrogram + uroflow, pressure flow study, or fluorouro-dynamics study) and AUA symptom score are recommended in the third post-treatment year for patients who still have a native bladder. This will incorporate measures of average and peak urinary flow rate, bladder functional capacity, compliance, and leak pressures (continence).

After completion of 10 years of post-treatment follow-up, required assessments and schedule are at the discretion of the treating physician.

If patient was discontinued due to progressive disease, required assessments and schedule are at the discretion of the treating physician.

**11.4 Measurement of Response (4/14/11)**

**11.4.1 Definition of Complete Response Immediately after Induction Treatment**

Examination under anesthesia, cystoscopy, and biopsy of all previously positive tumor sites will be utilized to evaluate the tumor status (response) 3-4 weeks following completion of induction chemoradiotherapy. In some patients, radiographic or cystoscopic evaluation will reveal abnormalities at the bladder tumor-site (such as thickening of the wall, ulcerations, or possible nodularities) which contain no identifiable tumor cells histologically. Patients will be considered as having a clinical complete response when all biopsies are negative for any tumor at the site(s) of the pretreatment tumor(s). If, at a site distant from the original tumor, severe dysplasia, a Ta tumor or carcinoma *in situ* is documented by selective mucosal biopsy, this will not prevent the patient from being declared a complete response at the tumor site. The protocol guideline will be for that patient to undergo consolidation TCI or FCI according to original randomization.

**11.4.2 Distant metastasis:** 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.

**11.4.3** 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 biopsy. For a primary tumor response following consolidation, a urine cytology specimen that is not positive is also required.
- **Partial Response (PR)** requires that all response criteria of a CR except that the urine cytology remains positive or CIS is seen in the biopsy.
- **No Response (NR)** requires the continued presence of the tumor (T $\geq$ 1) in the tumor-site biopsy specimen.
- **Progression** requires the increase of 50% or more in the largest diameter of the endoscopically appreciable tumor in the tumor-site biopsy specimen, the development of new bladder tumors, or the development of metastatic disease.

#### **11.5 Criteria for Discontinuation of Protocol Treatment (4/14/11)**

- Progression of disease;
- Intolerance of therapy as judged by the treating physicians;
- Patient-initiated discontinuation or refusal to follow protocol-specified treatment;
- A delay in protocol treatment, as specified in Sections 6.0 and/or 7.0;
- Delay of more than 3 weeks due to an adverse event.

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

### **12.0 DATA COLLECTION**

Data should be submitted to:

**RTOG Headquarters\***  
1818 Market Street, Suite 1600  
Philadelphia, PA 19103

**\*If a data form is available for web entry, it must be submitted electronically.**

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 (4/14/11)**

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 2 weeks of study entry
Initial Evaluation Form (I1)	
Pathology Report (P1)	
Slides/Blocks (P2)	

Surgical Report (from cystoscopy) (S2)

Treatment Form (TF)

Within 2 weeks after completing induction therapy

**Post induction Evaluation (F0)**

**Surgical Path Report (S5)**

**Cystoscopy Report (S2)**

Within 2 weeks after undergoing post induction evaluation; within 2 weeks after undergoing evaluation after consolidation chemoradiation

**Surgical Form (S1)**

**Surgical Path Report (S5)**

Within 2 weeks of cystectomy (if applicable)

**Surgical Operative Report (S2)**

Treatment Form (SF)

Within 2 weeks of completing consolidation therapy

Treatment Form (AF)

After each course of adjuvant therapy (4 cycles)

Follow-up Form (F1)

**Cystoscopy Report (if applicable) (S2)**

**Surgical Path Report (if applicable) (S5)**

Starting 6 months after study entry (3 months post- consolidation therapy or cystectomy) and q 3 months for year 1; q 4 months for year 2; q 6 months for years 3, 4 and 5; then annually until year 10

**AUA Symptom Index (PQ)**

At baseline (prior to any treatment) and during year 3 post treatment

Urodynamics Form (cystometrogram) (UR)

At baseline (prior to any treatment) and during year 3 post treatment.

## **FOR PROTOCOLS INVOLVING SUBMISSION TO ITC:**

### **12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1) (4/14/11)**

<u>Item</u>	<u>Due</u>
<b>Preliminary Dosimetry Information (DD)</b> Digital Data Submission – <u>Treatment Plan</u> submitted to ITC via SFTP account exported from treatment planning machine by Physicist Digital data submission includes the following: <ul style="list-style-type: none"><li>• CT data, critical normal structures, all GTV, CTV, and PTV contours (<b>C1, C3</b>)</li><li>• Digital beam geometry for initial and boost beam sets</li><li>• Doses for initial and boost sets of concurrently treated beams</li><li>• Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan (<b>DV</b>)</li></ul>	Within 1 week of start of RT

Digital Data Submission Information Form (**DDSI**) – Submitted online (Form located on ATC web site, <http://atc.wustl.edu/forms/DDSI/ddsi.html>)

Hard copy isodose distributions for total dose plan  
**(T6)**

**NOTE: Sites must notify ITC via e-mail ([itc@wustl.edu](mailto:itc@wustl.edu)) after digital data is submitted. The e-mail must include study and case numbers or, if the data is phantom, –dry run” or –benchmark”.**

**Final Dosimetry Information**

Within 1 week of RT end

**Induction Radiotherapy Form (T1) [copy to HQ and ITC]**

**Daily Treatment Record (T5) [copy to HQ and ITC]**

**Consolidation Radiotherapy Form (F4) [copy to HQ and ITC]**

Modified digital patient data as required through consultation with Image-Guided Therapy QA Center

**NOTE:** All simulation and portal films and/or digital film images will be kept by the institution and only submitted if requested.

**12.2.1 *Digital Data Submission to ITC***

Digital data submission may be accomplished using media or the Internet.

**For network submission:** The SFTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to:

[itc@wustl.edu](mailto:itc@wustl.edu)

**For media submission:** Please contact the ITC about acceptable media types and formats.

**Hardcopies** accompanying digital data should be sent by mail or Federal Express and should be addressed to:

**Image-Guided Therapy Center (ITC)**  
**ATTN: Roxana Haynes**  
**4511 Forest Park, Suite 200**  
**St. Louis, MO 63108**  
**314-747-5415**  
**FAX 314-747-5423**

**13.0 STATISTICAL CONSIDERATIONS**

**13.1 Study Endpoints (4/14/11)**

**13.1.1 Primary Endpoint**

The rate of distant metastasis at 3 years of induction chemoradiotherapy regimens including 5-Fluorouracil, cisplatin, and BID irradiation (FCI) or gemcitabine and QD irradiation (GI), followed by consolidation chemotherapy or cystectomy (depending on response) with adjuvant chemotherapy.

**13.1.2 Secondary Endpoints**

- Completion rate of induction and consolidation chemoradiotherapy regimens including 5-Fluorouracil, cisplatin, and BID irradiation (FCI) or gemcitabine and QD irradiation (GI) plus adjuvant chemotherapy.
- Grade 3 or more GU, GI, and hematologic toxicity of two treatment regimens using CTCAE v. 3.0.
- The efficacy of transurethral surgery with either induction FCI or GI in achieving a complete response of the primary tumor.
- The efficacy of transurethral surgery with either FCI or GI in preserving the native tumor-free bladder five years after therapy.
- To estimate the value of tumor histopathologic, molecular genetic, DNA content, metabolomic, and proteomic parameters as possible significant prognostic factors for initial tumor response and recurrence-free survival.
- To find potentially predictive biomarkers for cystectomy-free survival.

- To find potentially predictive biomarkers for acute and late toxicities.
- Descriptive analysis for AUA Symptom score.

### **13.2 Sample Size (2/6/14)**

The primary goal of this study is to determine if either of the two treatment arms under consideration is promising enough to be pursued in a subsequent phase III study with respect to the rate of distant metastasis free at 3 years. The sample size is calculated with Clopper-Pearson's exact binomial confidence intervals methods<sup>12</sup> with type I error of 0.1. If either of the two arms has at least 75% of distant metastasis free rate at 3 years, then we conclude that the treatment is promising enough for a phase III study with or without the adjuvant chemotherapy. We hypothesize that the lower boundary of one-sided 90% confidence interval of the rate of distant metastasis free at 3 years is 0.75. Due to the well-known non-monotonic ("sawtooth"-type) boundary of Clopper-Pearson confidence interval, the study now requires 32 analyzable patients in each arm, which also warrants a 10% chance of observing a 3-year distant metastasis free rate of less than 75% if the true rate is 86%. Therefore, 32 analyzable patients for each arm, or 64 analyzable patients in total, are needed for this study to retain the original study design objective.

### **13.3 Accrual and Duration (2/6/14)**

Based on patient accrual in previous RTOG studies, the initial 6 months accrual will be negligible while institutions are obtaining IRB approval. Accrual rates in previous RTOG selective bladder sparing protocols have been between 1.5 and 2 patients per month. The analysis for the February 2014 NRG Oncology semi-annual meeting showed that the average accrual rate is lower than expected. The modified sample size calculation may ensure the study is completed within the projected time frame without compromising statistical integrity.

### **13.4 Randomization**

Patients will be randomized to one of two treatment arms in order to avoid any patient selection bias. The treatment allocation scheme described by Zelen<sup>13</sup> will be used because it balances patient factors other than institution. Additionally, patients will be stratified by T-stage (T2 vs. T3-T4a)

### **13.5 Analysis Plan (2/6/14)**

#### **13.5.1 Primary Analysis**

The primary analysis will be performed when all eligible patients have at least 3 year follow-up. The distant metastasis free rate at 3 years is defined as the proportion of patients who do not have distant metastasis failure by 3 years among all eligible patients in each arm. If the rate for either arm is greater than or equal to 75%, then it will be strongly considered as a potential arm in a subsequent phase III study, assuming treatment delivery and adverse events are acceptable. If both arms meet the criteria, then the treatment arm that has less toxicity will be chosen. The confidence interval of the rate will be calculated by Clopper-Pearson's exact binomial confidence intervals methods<sup>12</sup> with one-sided type I error of 0.1.

#### **13.5.2 To estimate the completion rate**

The treatment completion rate is defined as the proportion of patients who complete the protocol treatment among all eligible patients in each arm. The following descriptive statistics are reported: the number of patients who complete induction chemotherapy, the number of patients who complete consolidation chemotherapy or have a cystectomy, with four cycles of gemcitabine and cisplatin.

#### **13.5.3 To estimate the grade 3+ adverse event**

Tabulation of acute and late GU, GI, and hematologic adverse events and the number of patients who complete adjuvant chemotherapy will be reported by type, grade, and attribution of adverse event based on the CTCAE v3.0. in each arm. Acute adverse events are defined as toxicities that occur from the start of treatment to the end of treatment. Late adverse events are defined as toxicities that occur from the end of treatment to 180 days. Late adverse events will be evaluated at 180 days from the end of treatment. The grade 3+ adverse event rate is calculated as the proportion of patients who have acute or late adverse events among all eligible patients.

Logistic regression will be used to model the distribution of grade 3+ acute adverse events. Both unadjusted and adjusted odd ratios and the respective 95% confidence interval will be computed.

The time to late grade 3+ adverse events will be estimated using the cumulative incidence method. Death without a grade 3+ adverse event will be considered as a competing risk. Alive patients without late grade 3+ adverse events will be censored at the time of the analysis.

**13.5.4** To estimate the efficacy of transurethral surgery with either FCI or GI in achieving a complete response of primary tumor (See Section 11.4.3). Logistic regression will be used to model the distribution of the complete response of the primary tumor. Both unadjusted and adjusted odd ratios and the respective 95% confidence interval will be computed.

**13.5.5** To estimate the efficacy of transurethral surgery with either FCI or GI in preserving the native tumor-free bladder five years after surgery. Logistic regression will be used to model the distribution of preserving the native tumor-free bladder five years after surgery. The multivariate logistic regression model will be adjusted for covariates, at least gender, age. Both unadjusted and adjusted odd ratios and the respective 95% confidence interval will be computed.

**13.5.6** To find potential biomarkers predicting which patients require cystectomy.

At the time of data maturity of this study, we will propose specific details of the markers to be investigated. We will address the assays that will be used and a list of specific correlative aims with appropriate statistical considerations. At minimum, her2/neu, EGFR1, p53, p21, pRb, p16, and bcl2 will be explored since these markers have shown promise in predicting the outcome of bladder cancer patients.<sup>6-11</sup>

The following is a general guideline for the statistical consideration for this analysis. This analysis will be done in each arm separately to test the prognostic values of biomarkers. A genomic, proteomic, or metabolomic biomarker will be categorized into two subgroups (not receiving cystectomy vs. receiving cystectomy) based upon previously defined (or hypothesized) cut-off points and these two groups will be referred to as favorable and unfavorable risk groups. The patients with genomic, proteomic, and metabolomic biomarkers will be compared with the patients without a value for that biomarker to determine if there are any differences with respect to distribution of baseline. We also want to know if there is a difference in time to distant metastasis and time to death due to any cause between these two groups. The null ( $H_0$ ) and alternative ( $H_A$ ) hypotheses for survival distribution (S) are

$$H_0: S_0(t) \geq S_1(t) \text{ vs. } H_A: S_0(t) < S_1(t), \text{ where } t \text{ is time}$$

Tests will be performed to see if one group is statistically significantly better than the other in the absence of distant metastasis and overall survival. However, the selection of the cut-off point for each biomarker is not established. If the hypothesized cut-off points do not yield statistical significance, other cut-off points may be evaluated. Therefore, various cut-off points are evaluated for their statistical significance. To correct the problem from the multiple testing, the Bonferroni correction will be used. The overall survival functions will be estimated by the Kaplan-Meier method<sup>14</sup> and will be tested for the overall survival difference between the favorable and unfavorable groups using the log-rank test<sup>15,16</sup>. We will use the cause-specific hazard rate approach<sup>17,18</sup> to estimate distant metastasis failure distributions and test the failure difference between the two groups using the cause-specific log-rank test. A stepwise procedure will be used to develop the base model for each outcome endpoint prior to evaluating the prognostic impact of the biomarkers. This approach will be employed to account for as much variation as possible for each outcome before it is tested. It is entirely possible that factors shown to be prognostic in other published series may not be found prognostic here.

**13.5.7** Descriptive analysis for AUA Symptom score

It will be collected at baseline and at 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, standard deviation) will be computed.

**13.5.8** Early stopping due to Adverse Events

Interim reports (see Section 13.5.9) will be prepared every 6 months until the final analysis. The frequency and grade of adverse events due to protocol treatment are presented to the Data Safety Monitoring Board (DSMB) for their review every 6 months, and they will make a

recommendation regarding continuation of this study. Also, this 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 RTOG GU Cancer Committee chair, and the RTOG Executive Committee. CRFs, source documentation, and a statistical report summarizing the study data 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 RTOG GU Cancer Committee chair, and the RTOG Executive Committee will discuss the findings and make a decision about amending the protocol and/or continuing the study.

**13.5.9 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;
- the frequencies and severity of adverse events due to chemotherapy and radiation therapy.

**13.5.10 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 31, and October 31.

**13.6 Gender and Minorities (2/6/14)**

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 7% non-white patients and 19% women. With the proposed 32 evaluable patients per arm, 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**

<b>Ethnic Category</b>	<b>Gender</b>		
	<b>Females</b>	<b>Males</b>	<b>Total</b>
Hispanic or Latino	0	1	1
Not Hispanic or Latino	12	41	63
<b>Ethnic Category: Total of all subjects</b>	<b>12</b>	<b>42</b>	<b>64</b>
<b>Gender</b>			
<b>Racial Category</b>	<b>Females</b>	<b>Males</b>	<b>Total</b>
	0	0	0
American Indian or Alaskan Native	0	1	1
Asian	2	3	5
Native Hawaiian or other Pacific Islander	0	0	0
White	14	44	58
More than one race	0	0	0
<b>Racial Category: Total of all subjects</b>	<b>16</b>	<b>48</b>	<b>64</b>

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## APPENDIX I

### RTOG 0712

#### **Informed Consent Template for Cancer Treatment Trials** (English Language)

#### **A Phase II Randomized Study For Patients With Muscle-Invasive Bladder Cancer Evaluating Transurethral Surgery And Concomitant Chemoradiation By Either BID Irradiation Plus 5-Fluorouracil And Cisplatin Or QD Irradiation Plus Gemcitabine Followed By Selective Bladder Preservation And Gemcitabine/Cisplatin Adjuvant Chemotherapy**

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have bladder cancer.

#### **Why is this study being done?**

The purpose of this study is to find out what effects (good and/or bad) chemotherapy combined with external radiation therapy and possible removal of your bladder has on you and your cancer. The chemotherapy drugs (cisplatin, 5-Fluorouracil [5-FU], and gemcitabine) used in this study are not experimental drugs. These drugs have been used in the treatment of many patients with tumors such as yours. This research is being done because we do not know whether one combination of drugs with radiation is superior to another in the treatment of your disease.

The usual treatment for your type of bladder cancer is surgical removal of the bladder and the surgical construction of an alternative bladder that usually requires a permanent opening (stoma) in your abdomen for urine drainage. Also, with the standard treatment, chemotherapy and radiation therapy may be recommended following surgical removal of the bladder.

This study uses similar therapies to the standard treatment, but chemotherapy and radiation therapy are given before removal of the bladder is considered. In this study, bladder removal is advised if, after chemotherapy and radiation, your tumor has not completely disappeared, if your tumor comes back, or if it gets larger.

There are 2 treatment groups in this study:

- 1) Patients who receive cisplatin and 5-FU chemotherapy and radiation twice per day.
- 2) Patients who receive gemcitabine chemotherapy and radiation once per day.

If you agree to participate in this study, you will receive one of these 2 treatments.

#### **How many people will take part in the study? (2/6/14)**

About 64 people will take part in this study.

#### **What will happen if I take part in this research study? (4/14/11)**

If you take part in this study, you will have a surgical procedure called a transurethral bladder resection. Under sedation (anesthesia), a lighted tube is inserted through the urethra (the small tube-like structure that allows urine to empty from the bladder) into the bladder. The surgeon examines your bladder tumor through this fiberoptic scope. The surgeon then will remove your tumor as thoroughly as is safely possible using an electric current. Some of your tissue around the tumor also will be removed for biopsy.

## **Before you begin the study ...**

You will need to have the following exams, tests or procedures. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- History and physical exam
- Cystoscopy, which is a bladder exam through a fiberoptic scope (a short procedure done in your doctor's office)
- Bladder biopsy (a small outpatient surgery requiring anesthesia)
- Blood tests
- For women who are able to have children, a test prior to study entry to see if you are pregnant
- Urinalysis, which involves the collection and examination of your urine. It involves a number of tests to detect and measure various compounds that pass through the urine.
- Transurethral bladder tumor resection (TURBT): Some patients will require more than one TURBT surgery if the TURBT surgery that is performed prior to study entry does not remove the entire tumor. (If the tumor was removed completely at that time, no further surgery will be required).
- Bone scan
- CT scan of your pelvic and abdominal area: A CT scan is a study using x-rays to look at one part of your body.
- Chest CT scan
- Your bladder function may be tested
- You may be asked to fill out a questionnaire on urinary symptoms and function (AUA), which will take approximately 10 minutes to complete.

## **During the study ...**

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. Neither you nor your study doctor can choose the group you will be in. You will have approximately an equal chance of being placed in one of the two groups below, and your treatment will begin within 8 weeks after the transurethral bladder resection (removal of your tumor).

**If you are in group 1 (often called "Arm 1")** you will receive the drugs cisplatin and 5-Fluorouracil (5-FU). You will receive cisplatin three days a week by injection over one hour into a vein (intravenously) along with special fluid treatment. You will also receive 5-Fluorouracil three days a week by injection over 24 hours into a vein (intravenously) during the first and last week of your radiation treatment. You will receive two radiation treatments each day, Monday through Friday, at least 4 hours apart. Each radiation treatment will be approximately 20 minutes in duration. The drugs will be given starting approximately one hour before the first daily radiation treatment. The chemotherapy and radiation therapy will take about 2 ½ weeks to complete. Chemotherapy will be delivered on an outpatient basis. There will be 26 radiation treatments delivered over this period of time.

**If you are in group 2 (often called "Arm 2")** you will receive the drug gemcitabine. You will receive gemcitabine two days a week by injection over 30 minutes into a vein (intravenously) along with special fluid treatment. You will receive one radiation treatment each day, Monday through Friday. Each radiation treatment will be approximately 20 minutes in duration. The drug will be given starting approximately one hour before the daily radiation treatment. The chemotherapy and radiation therapy will take about 4 weeks to complete. Chemotherapy will be delivered on an outpatient basis. There will be 20 radiation treatments delivered over this period of time.

### **Groups 1 and 2**

Three to four weeks after the completion of the chemotherapy and radiation, the surgeon will re-examine your bladder through the fiberoptic scope, a biopsy, and a pelvic CT scan. Depending on the results of these examinations, you will have one of the following treatments:

- If your tumor has completely disappeared, you will receive the chemotherapy and radiation therapy you received before the re-examination of your tumor for an additional 2-3 weeks. Again, all chemotherapy will be delivered on an outpatient basis. On arm 1, patients will receive an

additional 16 radiation treatments. On arm 2, patients will receive an additional 12 treatments. Also, you then will have 4 months of additional chemotherapy (with cisplatin and gemcitabine) to reduce the chance of cancer spreading to other parts of your body.

- If your tumor has not completely disappeared, and you are medically fit for surgery, surgical removal of your bladder within 3-8 weeks will be recommended. After surgery, you then will have 4 months of additional chemotherapy (with cisplatin and gemcitabine) to reduce the chance of cancer spreading to other parts of your body.

**If your bladder is not removed**, you will undergo careful and frequent evaluations of the bladder through a fiberoptic scope (cystoscopy), a test that allows your doctor to look at the inner lining of the bladder and the urethra (a small tube-like structure that allows urine to empty from the bladder). Should the bladder tumor come back or get bigger, then surgical removal of your bladder may be recommended.

#### **During chemoradiotherapy:**

- Weekly measurement of your weight
- Weekly blood tests
- Fiberoptic scope evaluation
- Urine cytology (a series of tests that are done to identify all the different types of cells and other substances in your urine)

#### **When you are finished receiving chemoradiotherapy (consolidation) and before additional chemoradiotherapy:**

You will need these tests and procedures 8-10 weeks after the completion of chemoradiotherapy:

- History and physical exam
- Bladder exam through a fiberoptic scope
- Urine cytology (a series of tests that are done to identify all the different types of cells and other substances in your urine)
- Bladder biopsy
- Blood tests
- CT scan of your abdominal and pelvic area and your chest
- Bone scan

#### **During additional chemotherapy:**

You will need these tests during additional chemotherapy. They are part of regular cancer care. They are being done more often because you are in this study:

- Weekly measurements of your weight
- Weekly blood tests
- Assessment of your ability to carry out activities of daily living

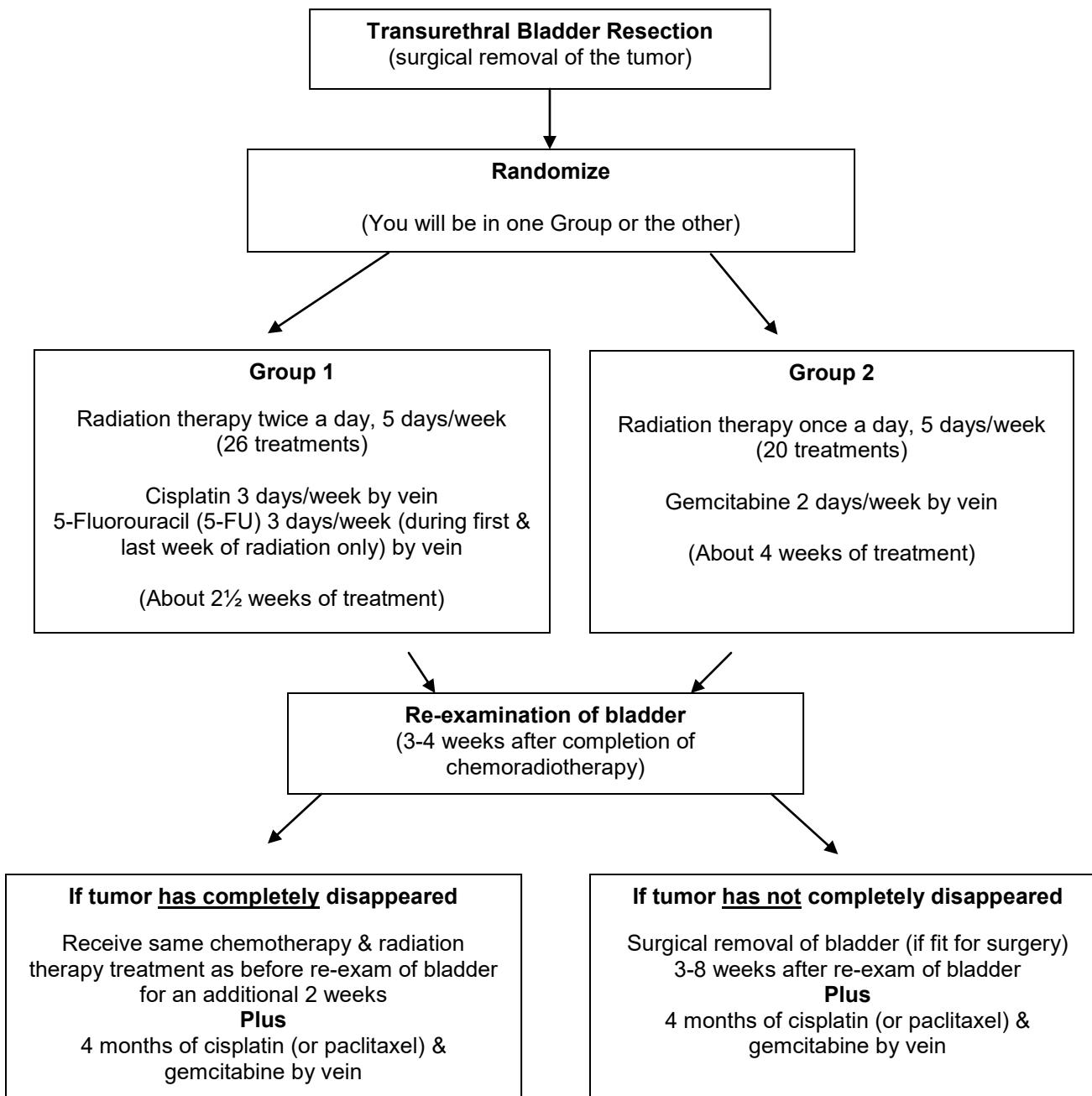
#### **When you are finished with protocol treatment:**

You will need these tests and procedures during follow-up visits after the completion of chemoradiotherapy:

- History and physical exam, blood tests, a bladder exam through fiberoptic scope, cystoscopy, urine cytology, and bladder biopsy of the original area every 3 months after all treatment for the first year, every 4 months during the 2nd year, every 6 months during years 3, 4, and 5, then annually thereafter until year 10. A CT scan of your pelvic and abdominal area and a chest CT scan will be performed every 6 months after completion of treatment.
- If two tumor site biopsies are negative, repeat biopsies are not needed.
- For patients who still have their bladder, your bladder function may be tested in the third year after completion of treatment
- You may be asked to fill out a questionnaire on urinary symptoms and function (AUA) in the third year after completion of treatment

## Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.



## How long will I be in the study?

Treatment will begin within 8 weeks after the transurethral bladder resection. You will be in the study for 8 months of treatment. Follow-up visits will take place every 3 months after all treatment for the first year, every 4 months during the 2nd year, every 6 months for years 3, 4, and 5, then annually until year 10.

## Can I stop being in the study?

Yes. You can decide to stop at any time. Tell your study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell your study doctor if you are thinking about stopping so any risks from the chemoradiation can be evaluated by him/her. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

Your doctor may decide to take you off this study at any time if your doctor believes it is in your medical best interest, if funding for this study is stopped, if your condition worsens, if you do not follow the study rules, or if the study is stopped. You may also be taken off this study if new information becomes available about how to better prevent growth of bladder cancer.

## What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop chemotherapy or radiation. In some cases, side effects can be serious, long lasting, or may never go away.

In general, there is a higher risk of complications for you when surgery follows radiation and chemotherapy. Surgery and bladder reconstruction can be more difficult and the choices for bladder reconstruction are limited.

- In addition, if chemotherapy fails to decrease the size of the tumor, your cancer can be more advanced at the time of surgery.

You should talk to your study doctor about any side effects that you have while taking part in the study.

### **Risks and side effects related to radiation therapy to the pelvis include those which are:**

#### **Likely**

- Loss of pubic hair
- Reddening and irritation of the skin in the treatment area
- Diarrhea
- Urinary frequency, possibly with pain and/or blood
- Tiredness near the end of treatment
- Nausea and/or vomiting
- Poor digestion of food
- Rectal irritation
- Pain with sexual intercourse
- Shortening and narrowing of the vagina
- Low blood counts causing easy bruising
- Mucous-like stools

#### **Rare but serious**

- Weight loss; if this is severe, you may need a tube placed into your stomach to provide nutrition
- Rectal ulcer
- Bleeding or narrowing of the rectum
- Bleeding, and/or blockage of the bowel, which may require surgery
- Bladder shrinkage, discomfort or bleeding which may require aggressive medical or surgical management including removal of the bladder.
- Ureteral (tube connecting kidneys to the bladder) obstruction
- Fistula (opening) forming between pelvic tissues, which could result in a communication between the bladder and rectum or small bowel.
- Inflammation of the colon

- Inflammation or infection of the bladder

Radiation to the pelvis will cause sterility (inability to father children or become pregnant). Women of childbearing potential will go through menopause and may require the use of hormones given orally to replace the hormones normally produced by the ovaries.

**Risks and side effects related to cisplatin include those which are:**

**Likely**

- Nausea and/or vomiting
- Tiredness, weakness
- Hearing loss or ringing in the ears
- Loss of appetite and/or taste; metallic taste in your mouth
- Numbness or tingling in the hands or feet
- Decrease in blood counts which can lead to a risk of infection and bleeding.

**Less Likely**

- Restlessness
- Muscle cramps or spasm
- Loss of coordination
- Involuntary movements or shaking
- Loss of muscle or nerve function which may cause weakness or numbness in your hands & feet
- Facial swelling

**Rare but serious**

- A decrease in the kidneys' ability to handle the body's waste, which may be permanent.
- Allergic reactions which can cause difficulty breathing, fast heartbeat, and sweating
- Decrease in liver function resulting in abnormal blood tests or jaundice(a yellowish color of the skin, tissues, and certain body fluids)
- Development of another cancer called Acute Leukemia

**Risks and side effects related to 5-FU (5-Fluorouracil) include those which are:**

**Likely**

- Loss of appetite
- Nausea and/or vomiting
- Diarrhea with cramping or bleeding
- Skin rash
- Fatigue
- Headaches
- Hair loss, which is temporary
- Mouth sores and/or sore throat, which may require medication to decrease discomfort
- Decrease in blood counts which can lead to a risk of infection and bleeding

**Less Likely**

- Confusion
- Inflammation of the fingers and toes
- Increased sensitivity to sunlight
- Darkening of the skin, nails, or veins
- Loss of coordination or balance

**Rare but serious**

- Chest pain
- Infection at the puncture site

**Risks and side effects related to gemcitabine include those which are:**

**Likely**

- Lower blood counts, which can lead to a risk of infection and bleeding
- Nausea and/or vomiting
- Fatigue

**Less Likely**

- Skin rash
- Constipation
- Diarrhea
- Fever
- Hair loss
- Pain
- Swelling
- Shortness of breath
- Sores in the mouth

**Rare but serious**

- Decrease in liver function resulting in abnormal blood tests or jaundice (a yellowish color of the skin, tissues, and certain body fluids)
- Decrease in the kidneys' ability to handle the body's waste, which may be permanent
- Pneumonia

**Risks and side effects related to paclitaxel include those which are:**

**Likely**

- Skin redness or rash
- Fatigue
- Hair loss, which is temporary
- Mouth sores and/or sore throat, which may require medication to decrease discomfort
- Decrease in blood counts which can lead to a risk of infection and bleeding
- Numbness, tingling or burning of the hands and/or feet.

**Less Likely**

- Muscle aches and/or joint pain
- Nausea and/or vomiting
- Headaches
- Skin or nail darkening
- Skin ulcers

**Rare but serious**

- Changes in vision
- Decrease in blood pressure.
- Allergic reaction, which can cause difficulty breathing, irregular heartbeat, low blood pressure and even be life threatening
- Continuing, long-lasting numbness, tingling or burning in the hands and feet.
- Severe rash called Stevens-Johnson syndrome which can cause fever and red sores in your mouth and eyes.

## Risks of Surgery

### **If removal of your bladder is necessary:**

In men, after radiation, the operation generally includes removal of the bladder, the pelvic lymph nodes, the seminal vesicles, and the prostate. As a result, there is likely to be loss of erections. In women, the operation may include removal of the bladder, vagina, uterus, tubes, and ovaries. As a result, women will not be able to have children and may find intercourse difficult due to vaginal dryness, shortening or narrowing. Also during surgery, a urinary diversion procedure is necessary; this probably will include placement of a permanent opening (stoma) created in the abdomen and a bag placed over it to collect the urine. In some circumstances other types of urinary diversion may be possible, based on the judgment of your surgeon.

After bladder removal, the major complications that can occur include infection, heart attack, stroke, severe bleeding, blood clots in the legs or the lung and injury to the rectum or other areas of the intestine. This type of injury may require a second temporary stoma to allow the intestine to heal. Injury to the intestine may also lead to abnormal connections (fistulas) between the intestines and other organs. Minor complications include wound infection and delayed hospital stay due to intestinal inactivity (ileus).

**Reproductive risks:** You should not become pregnant or father a baby while on this study because the radiation and drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

As described above, radiation therapy to the pelvis will result in sterility. Surgery to remove the bladder and other organs also will result in loss of erections, and women will not be able to bear children.

For more information about risks and side effects, ask your study doctor.

## Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While researchers hope chemotherapy plus radiation and removal of the bladder (for some patients) will be more useful against bladder cancer compared to the usual treatment (surgical removal of the bladder with or without chemotherapy and radiation after tumor removal), there is no proof of this yet. It is also not clear what constitutes the ideal regimen of chemotherapy and radiation. We hope that concurrent gemcitabine with once a day radiation will be more effective than cisplatin and 5-fluorouracil with twice a day radiation, but there is no proof of this. We do know that the information from this study will help researchers learn more about the use of chemotherapy plus radiation and possible removal of the bladder as a treatment for bladder cancer. This information could help future cancer patients.

## What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study. This could include the following options, either alone or in combination with each other:
  - Radiation therapy
  - Chemotherapy
  - Bladder removal
- Taking part in another study
- Getting no treatment. (With this choice, your tumor could continue to grow and your disease could spread.)

**Talk to your study doctor about your choices before you decide if you will take part in this study.**

## Will my medical information be kept private? (2/28/12)

Data are housed at RTOG Headquarters in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total

privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

**Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:**

- The Radiation Therapy Oncology Group (RTOG)
- The National Cancer Institute (NCI) and other government agencies involved in keeping research safe for people, like the Central Institutional Review Board (CIRB) and the Food and Drug Administration (FDA)

**A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.**

*[Note to Informed Consent Authors: the above paragraph complies with the new FDA regulation found at 21 CFR 50.25(c) and must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]*

**What are the costs of taking part in this study?**

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will not be paid for taking part in this study.

**For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.**

**Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.**

**What happens if I am injured because I took part in this study?**

It is important that you tell your study doctor, \_\_\_\_\_ [*investigator's name(s)*], if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at \_\_\_\_\_ [*telephone number*].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

**What are my rights if I take part in this study?**

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

A Data Safety Monitoring Board will be regularly meeting to monitor safety and other data related to phase I, I/II, and II RTOG clinical trials. The Board members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

## Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor \_\_\_\_\_ [name(s)] at \_\_\_\_\_ [telephone number].

For questions about your rights while taking part in this study, call the \_\_\_\_\_ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at \_\_\_\_\_ (telephone number). *[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

**Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say no to taking part in this additional research.**

**You can say yes or no to [each of] the following study[ies]. Below, please circle your choice [for each study].**

### Consent Form for Use of Tissue, Blood, and Urine for Research

#### **About Using Tissue, Blood, and Urine for Research (4/14/11)**

You have had or you will have a biopsy (or surgery) to see if you have cancer. Your doctor has removed or will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research. This information sheet is available to all at the following web site: [http://cdp.cancer.gov/humanSpecimens/ethical\\_collection/patient.htm](http://cdp.cancer.gov/humanSpecimens/ethical_collection/patient.htm) .

In addition, if you agree to participate in this part of the study, you will have blood drawn and urine collected before you start chemoradiation, three times during your treatment, at your 1-year follow-up visit, and in case your tumor comes back when this is detected. We would like to keep about 2 tablespoons of blood and 5 tablespoons of urine at each of these times for future research. If you agree, this blood and urine will be kept to be used in research to learn more about cancer and other diseases.

Your tissue, blood, and urine may be helpful for research whether you do or do not have cancer. The research that may be done with your tissue, blood, and urine is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue, blood, and urine will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

#### **Things to Think About**

The choice to let us keep the left over tissue, blood, and urine for future research is up to you. No matter what you decide to do, it will not affect your care or your participation in the main part of the study.

If you decide now that your tissue, blood, and urine can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue, blood, and urine. Then any tissue, blood, and urine that remain will no longer be used for research and the tissue will be returned to the institution that submitted it. Blood and urine would be destroyed.

In the future, people who do research may need to know more about your health. While the study doctor/institution may give them reports about your health, they will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue, blood, and urine are used for this kind of research, the results will not be put in your health records. Your tissue, blood, and urine will be used only for research and will not be sold. The research done with your tissue, blood, and urine may help to develop new treatments for cancer in the future.

## **Benefits**

The benefits of research using tissue, blood, and urine include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

## **Risks**

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

## **Making Your Choice (4/14/11)**

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at \_\_\_\_\_ (*IRB's phone number*).

No matter what you decide to do, it will not affect your care or your participation in the main part of the study.

1. My specimens may be kept for use in research to learn about, prevent, or treat cancer, as follows:

- Tissue  Yes  No
- Blood  Yes  No
- Urine  Yes  No

2. My specimens may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease), as follows:

- Tissue  Yes  No
- Blood  Yes  No
- Urine  Yes  No

3. Someone may contact me in the future to ask me to take part in more research.

Yes  No

## **Where can I get more information? (2/28/12)**

**You may call the National Cancer Institute's Cancer Information Service at:**

**1-800-4-CANCER (1-800-422-6237)**

**You may also visit the NCI Web site at <http://cancer.gov/>**

- **For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>**
- **For NCI's general information about cancer, go to <http://www.cancer.gov/cancertopics/> <http://cancer.gov/cancerinfo/>**

**You will get a copy of this form. If you want more information about this study, ask your study doctor.**

**Signature**

I have been given a copy of all \_\_\_\_\_ [*insert total of number of pages*] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant \_\_\_\_\_

Date \_\_\_\_\_

**APPENDIX II: STUDY PARAMETER TABLE (Refer to Sections 3.1, 4.1, 4.2, 8.4, 11.2, and 11.3 for details) [2/28/12]**

Parameter	Pre-Study (may be required for eligibility)	During Induction (FCI or GI)	†Post-Induction Evaluation (3-4 weeks after completion of induction)	During Consolidation (FCI or GI)	†Post-Consolidation Evaluation (8-10 weeks after completion of consolidation)	Post-Cystectomy (Prior to initiation of Adjuvant)	During Adjuvant Chemotherapy	Post-treatment Follow-Up (q 3 mos in 1 <sup>st</sup> yr; q 4 mos in 2 <sup>nd</sup> yr; q 6 mos for 3 more yrs, then annually until year 10)
Body Surface Area	X	X		X			X	
H&P	X		X		X	X		X
Weight	X	Weekly		Weekly			Weekly	X
Zubrod Status	X	Weekly		Weekly			Prior to day 1 of each cycle	X
TUR	X		X		X			X
Cystoscopy	X		X		X			
Urine Cytology			X		X			See 11.3.3
Bimanual exam under anesthesia	X		X		X			
Bladder Biopsy	X		X		X			
CBC, Platelets, Diff	X	Weekly	X	Weekly	X	X	Prior to day 1 and day 8 of each cycle	X
Serum Creatinine, BUN	X	Weekly	X	Weekly	X	X	Prior to day 1 and day 8 of each cycle	X
Creatinine Clearance	X	Weekly		Weekly			Prior to day 1 of each cycle	
Bilirubin, Alk Phos.	X			Day 1 prior to start			Prior to day 1 and day 8 of each cycle	
SGOT, LDH	X			Day 1 prior to start			Prior to day 1 and day 8 of each cycle	
Magnesium, Calcium	X							
Urinalysis	X							
Pregnancy Test	≤ 72 hrs prior to regist.							
CT Scan Abd/Pel	X				X	X		q 6 months
Bone Scan	X				X	X		
Chest CT	X				X	X		q 6 months
Urodynamic eval	X							3 <sup>rd</sup> post-treatment yr*
AUA	X							3 <sup>rd</sup> post-treatment yr*
Adverse event evaluation**		X	X	X	X	X	X	X

\*See Section 11.3.3   \*\*And as needed based on reporting requirements.   †See Sections 8.4 and 11.3.3 for additional details regarding negative evaluations.

**(Refer to Sections 3.1, 4.1, 4.2, 8.4, 11.2, and 11.3 for details)**

**APPENDIX III** (01/21/10)

**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 IV

### **AJCC Staging System, 6<sup>th</sup> 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 <i>in situ</i> : "flat tumor"
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscle
	T2a Tumor invades superficial muscle ( <i>inner half</i> )
	T2b Tumor invades deep muscle ( <i>outer half</i> )
T3	Tumor invades perivesical tissue
	T3a microscopically
	T3b macroscopically ( <i>extravesical mass</i> )
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

##### **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

#### APPENDIX IV (continued)

#### **AJCC Staging System, 6<sup>th</sup> 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)**

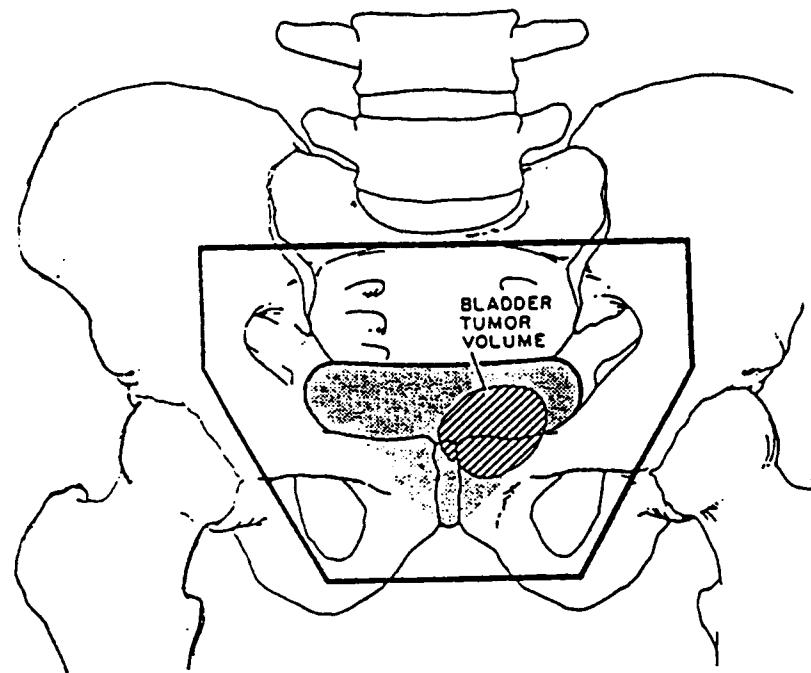
GX Grade cannot be assessed

G1 Well differentiated

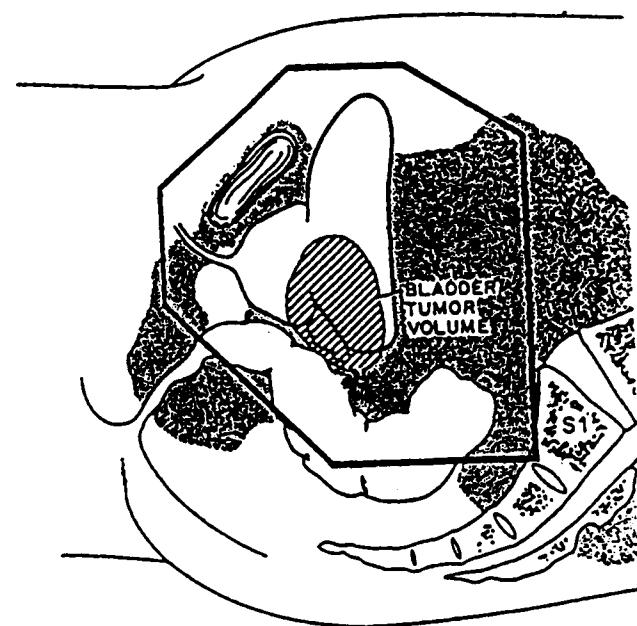
G2 Moderately differentiated

G3-4 Poorly differentiated or undifferentiated

APPENDIX V  
**SMALL PELVIC FIELDS**  
**Anterior View**



**Lateral View**



**APPENDIX VI**  
**(Cystoscopy Report included in PDF version of protocol)**

**APPENDIX VII (2/28/12)**  
**Appendices for RTOG Biospecimen Collection**

RTOG FFPE Specimen Plug Kit Collection  
RTOG Blood Collection Kit Instructions  
RTOG Urine Collection Kit Instructions

**Shipping Instructions:**

**U.S. Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only**  
RTOG Biospecimen Resource  
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**  
RTOG Biospecimen Resource  
University of California San Francisco  
2340 Sutter Street, Room S341  
San Francisco, CA 94115

- Include all RTOG 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 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 RTOG Biospecimen Resource by e-mail: [RTOG@ucsf.edu](mailto:RTOG@ucsf.edu) or phone: 415-476-RTOG(7864) or Fax: 415-476-5271.**

## APPENDIX VII

### RTOG FFPE SPECIMEN PLUG KIT INSTRUCTIONS

This Kit allows sub-sampling of an FFPE block for submission to the RTOG Biospecimen Resource. The plug kit contains a shipping tube and a punch tool.



#### **Step 1**

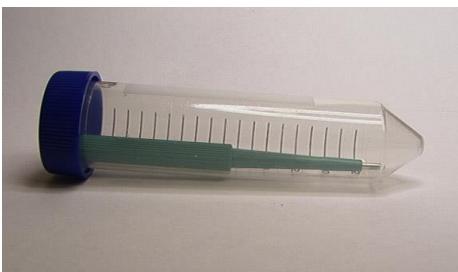
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug 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 RTOG Biospecimen Resource 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 RTOG Biospecimen Resource by e-mail: [RTOG@ucsf.edu](mailto:RTOG@ucsf.edu) or call 415-476-RTOG(7864)/Fax 415-476-5271.**

**U.S. Postal Service Mailing Address: For Non-frozen Specimens Only**  
RTOG Biospecimen Resource  
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 Specimens or Trackable shipments**  
RTOG Biospecimen Resource  
University of California San Francisco  
2340 Sutter Street, Room S341  
San Francisco, CA 94115

## APPENDIX VII

### RTOG 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 (up to 10) as necessary for the serum collected. Label them with the RTOG study and case number, collection date, time, and time point, and clearly mark cryovials as "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 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 (up to 10) as necessary for the plasma collected. Label them with the RTOG study and case number, collection date, time, and time point, and clearly mark cryovials as "plasma".

**Process:**

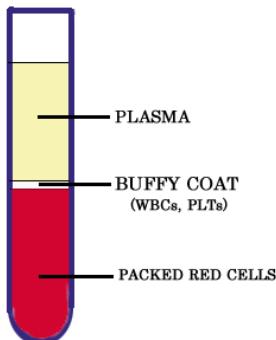
1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature 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 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.**

**(continued on next page)**

## APPENDIX VII

### RTOG BLOOD COLLECTION KIT INSTRUCTIONS (continued)



#### **(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 study and case number, collection date/time, and time point, and clearly mark cryovials as "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 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 RTOG 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.***

- Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.

**(continued on next page)**

## APPENDIX VII

### RTOG BLOOD COLLECTION KIT INSTRUCTIONS (continued)

- *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 [RTOG@ucsf.edu](mailto:RTOG@ucsf.edu) or call (415)476-7864.**

#### Shipping Address:

Courier Address (FedEx, UPS, etc.): **For all Frozen Specimens**  
RTOG Biospecimen Resource  
University of California San Francisco  
2340 Sutter Street, Room S341  
San Francisco, CA 94115  
For questions, call 415-476-RTOG (7864) or e-mail: [RTOG@ucsf.edu](mailto:RTOG@ucsf.edu)

**APPENDIX VII**  
**RTOG URINE COLLECTION KIT INSTRUCTIONS**  
**This Kit is for collection, processing, storage, and shipping of urine specimens.**

**Kit Contents:**

<ul style="list-style-type: none"><li>• One (1) Sterile Urine collection cup</li><li>• Two 7 ml disposable pipettes</li><li>• Absorbent paper towel</li></ul>	<ul style="list-style-type: none"><li>• Two 15 ml polypropylene centrifuge tubes</li><li>• Biohazard bags</li><li>• Parafilm for sealing outside of tubes</li></ul>
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**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 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 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 RTOG 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 [RTOG@ucsf.edu](mailto:RTOG@ucsf.edu) or call (415)476-7864 or fax (415) 476-5271.**

**Shipping Address: FedEx/UPS/Courier address (For all frozen samples)**

**RTOG Biospecimen Resource at UCSF**  
**2340 Sutter Street, Room S341, San Francisco, CA 94115**  
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