RADIATION THERAPY ONCOLOGY GROUP

RTOG 0233

A PHASE II RANDOMIZED TRIAL FOR PATIENTS WITH MUSCLE-INVADING BLADDER CANCER EVALUATING TRANSURETHRAL SURGERY AND BID IRRADIATION PLUS EITHER PACLITAXEL AND CISPLATIN OR 5-FUOROURACIL AND CISPLATIN FOLLOWED BY SELECTIVE BLADDER PRESERVATION AND GEMCITABINE/PACLITAXEL/CISPLATIN ADJUVANT CHEMOTHERAPY

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INDEX

Schema
Eligibility Check

1.0 Introduction
2.0 Objectives
3.0 Patient Selection
4.0 Pretreatment Evaluations
5.0 Registration Procedures
6.0 Radiation Therapy
7.0 Drug Therapy
8.0 Surgery
9.0 Other Therapy
10.0 Pathology
11.0 Patient Assessments
12.0 Data Collection
13.0 Statistical Considerations

References

Appendix I - Sample Consent Forms
Appendix II - Performance Status Scoring
Appendix III - Staging System
Appendix IV - Small Pelvic Fields (5/9/08)
Appendix V - Cystoscopy Report Form (5/9/08)
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<table>
<thead>
<tr>
<th>Transurethral Surgery (TUR)</th>
<th>Stratify</th>
<th>R</th>
<th>Induction Chemoradiotherapy</th>
<th>Post-Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>T Stage</td>
<td>A</td>
<td></td>
<td>Treatment starts within 8 weeks of the TUR; Weeks 1-3</td>
<td>Week 7</td>
</tr>
<tr>
<td>1. T2</td>
<td>N</td>
<td></td>
<td>†Arm 1(a): paclitaxel (Taxol®), cisplatin, and b.i.d. irradiation (TCI)</td>
<td></td>
</tr>
<tr>
<td>2. T3/T4</td>
<td>D</td>
<td></td>
<td>†Arm 2(b): 5FU, cisplatin, and b.i.d. irradiation (FCI)</td>
<td></td>
</tr>
</tbody>
</table>

**Tumor Response**  

<table>
<thead>
<tr>
<th>T0, Ta, Tcis*</th>
<th>Consolidation Chemoradiotherapy</th>
<th>Adjuvant Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weeks 8-9</td>
<td>4 cycles, Weeks 21-33</td>
</tr>
<tr>
<td>*At site distant from original tumor (Section 11.2.1)</td>
<td>†Arm 1(c): paclitaxel (Taxol®), cisplatin, and b.i.d. irradiation (TCI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>†Arm 2(d): 5FU, cisplatin, and b.i.d. irradiation (FCI)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>≥ T1**</th>
<th>Radical Cystectomy</th>
<th>Adjuvant Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>On rebiopsy, the tumor persists and invades into or beyond the lamina propria</strong></td>
<td>Week 9</td>
<td>4 cycles, Weeks 17-29</td>
</tr>
</tbody>
</table>

†See a, b, c, and d in tables below for details.
### INDUCTION THERAPY (Weeks 1-3)

<table>
<thead>
<tr>
<th>a. ARM 1</th>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>15</th>
<th>16</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>50 mg/m²</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>15 mg/m²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XRT, bid x 13 days</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[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]

<table>
<thead>
<tr>
<th>b. ARM 2</th>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>15</th>
<th>16</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU 400 mg/m²</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>15 mg/m²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XRT, bid x 13 days</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[1.6 Gy small pelvic fields/1.5 Gy boost to whole bladder x 5 days (days 1-5) plus 1.5 Gy boost to bladder tumor x 8 (days 8-17) with a minimum 4 hour interval]

### CONSOLIDATION THERAPY (Weeks 8,9)

<table>
<thead>
<tr>
<th>c. ARM 1</th>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>50 mg/m²</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>15 mg/m²</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic XRT, bid x 8 days</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(1.5 Gy small pelvic fields with a minimum 4 hour interval)

<table>
<thead>
<tr>
<th>d. ARM 2</th>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU 400 mg/m²</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>15 mg/m²</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic XRT, bid x 8 days</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(1.5 Gy small pelvic fields with a minimum 4 hour interval)

### OUTPATIENT ADJUVANT CHEMOTHERAPY (Weeks 21-33 or Weeks 17-29)

<table>
<thead>
<tr>
<th>AGENTS</th>
<th>Day</th>
<th>1</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine 1000 mg/m²</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>50 mg/m²</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>35 mg/m²</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Begin 12 wks post-consolidation therapy, or 8 wks following cystectomy. Repeat every 21 days for 4 cycles.
ELIGIBILITY (See Section 3.0 for details) June 4, 2004

- 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
- No node metastases
- Adequately functioning bladder
- Patients must have undergone as thorough a transurethral resection of the bladder tumor as is judged safely possible.
- Zubrod performance status of ≤ 1
- Hgb ≥ 10 mg/dl; WBC ≥ 4000/ml; ANC ≥ 1800/ml; platelets ≥ 100,000/mm³; serum creatinine ≤ 1.5 mg%;
  serum bilirubin ≤ 2.0 mg%; creatinine clearance ≥ 60ml/minute
- Treatment must begin within 8 weeks following TUR.
- Patients must be considered able to tolerate systemic chemotherapy, pelvic radiation therapy, and a radical cystectomy.
- No prior systemic chemotherapy or pelvic RT
- No concurrent drugs that have potential nephrotoxicity or otoxicity
- No prior or concurrent malignancy (except stage T1a prostate cancer, carcinoma in situ of the uterine cervix, or non-melanoma skin cancer) unless disease free for ≥ 5 years
- Patients must sign a study-specific informed consent form prior to study entry.

**Required Sample Size: 96**
Institution #  
RTOG 0233  
Case #  

ELIGIBILITY CHECKLIST - STEP 1 (Induction) (4/18/06)  

(Y) 1. Is there histological confirmation of muscle-invading carcinoma of bladder?
(N) 2. Is there evidence of tumor-related hydronephrosis?
(Y) 3. Based upon the results of the cystoscopy, TUR, and other clinical radiographic studies, is the AJCC clinical T classification T2-4a?
(Y/N) 4. Is there clinical/radiographic evidence of nodal disease?

(Y) If yes, have the clinically positive nodes been biopsied and found to be negative?

(N) 5. Does the patient have distant metastasis?

(Y/N) 6. Does the patient have a history of other malignancies except for nonmelanoma skin cancer, T1a prostate, or in situ cervical cancer?

(Y) If yes, has the patient been disease-free for ≥ 5 years?

(N) 7. Has the patient had any prior systemic chemotherapy or pelvic irradiation?

(N) 8. Is the patient receiving any potentially nephrotoxic or ototoxic drugs including aminoglycosides?

(Y) 9. Based on the urologist's, medical oncologist's and radiation therapist's opinions, is the patient medically stable to tolerate chemoradiation and cystectomy, if necessary?

(Y) 10. Has the patient undergone as thorough a transurethral resection of the bladder tumor as is judged safely possible?

(Y) 11. Does the patient have an adequately functioning bladder after evaluation by an urologist?

(Y) 12. Will treatment start within 8 weeks of the TUR and endoscopic evaluations?

(Y) 13. Zubrod Performance status ≤ 1?

(Y) 14. Are laboratory values as specified in Section 3.1.5?

(continued on page 2)
The following questions will be asked at Study Registration:

1. Name of institutional person registering this case?
2. Has the Eligibility Checklist (above) been completed?
3. Is the patient eligible for this study?
4. Date the study-specific Consent Form was signed? (must be prior to study entry)
5. Patient’s Initials (Last, First) [Initials Only effective 2/2/02]
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. Specify T Stage (T2 or T3/4)
17. Medical Oncologist
18. Treatment Start Date

The Eligibility Checklist must be completed in its entirety prior to calling RTOG. 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 ____________________________
Institution # ______________

RTOG 0233

ELIGIBILITY CHECKLIST – STEP 2 (Consolidation)

Case # ______________
(assigned for Step 1)

(assigned for Step 1)

1. Name of institutional person registering case.

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

   If no, call RTOG HQ to “discontinue” the case; specify reason (progression, patient refusal, physician preference, other)

3. Patient Initials

4. Verifying Physician

5. Patient ID Number

6. Specify the pathologic T stage at post induction evaluation (pT0, pTa, pTci vs. ≥ pT1)

7. Specify results of bimanual exam (negative, positive, equivocal)

8. Specify induction treatment assignment (taxol + RT + cisplatin or 5-FU + RT + cisplatin)

9. Treatment Start Date

   Treatment Assignment

   Treatment Assignment

Completed by ________________________________ Date ________________

Completed by ________________________________ Date ________________
1.0 INTRODUCTION

1.1 Background

As the use of combined modality treatment for muscle invasive bladder cancer has matured, the opportunity for bladder preservation has developed. Several previous single institution and RTOG prospective studies have demonstrated high rates of bladder preservation. This has not come at the cost of overall survival and five-year survival rates using combined modality therapy with cystectomy reserved for salvage of those who have an incomplete response or who recur locally are comparable to those obtained in published series employing immediate cystectomy. Preoperative radiation when combined with cisplatin (CDDP) alone, cisplatin and 5-fluorouracil (5-FU) or cisplatin and paclitaxel results in the downstaging to pT0 of a significant proportion of patients. When transurethral resection of a bladder tumor (TURBT), radiation, and multi-agent chemotherapy are combined, complete response rates of 70% or greater have been achieved. The radiation sensitizing effects of cisplatin have been long recognized, and the opportunity to safely enhance this effect by the simultaneous administration of a second radiation sensitizer such as 5-Fluorouracil or paclitaxel has been a goal of RTOG protocols since 1995.

This Phase II randomized trial is based on the RTOG experience in bladder preservation (RTOG 95-06 and 99-06), in which aggressive TURBT has been combined with twice daily irradiation sensitized with cisplatin and either 5-FU or paclitaxel. These two studies have already established dosing schedules of the three drugs. There is substantial experience with cisplatin, 5-FU and simultaneous radiation in bladder cancer from a number of other major centers with very acceptable toxicity. The experience with paclitaxel and simultaneous radiation in bladder cancer is not as widespread, but acceptable toxicity has been shown in the treatment of stage III-A/B non-small cell lung cancer. Two RTOG phase II trials have demonstrated the safety of chemo-radiation employing twice-daily radiation and simultaneous cisplatin/5-FU or cisplatin/paclitaxel. High complete response rates were obtained to the induction regimens. These trials were not, however, designed to compare either the acute morbidity or the efficacy of the alternative protocols. Therefore, it is proposed that this be the thrust of the current randomized trial.

Distant metastases remain the most common mode of treatment failure for patients with muscle invading carcinoma of the bladder. In the absence of chemotherapy, the incidence of distant metastases at five years is 30-45%. In recognition of this high risk, adjuvant therapy has been an integral part of RTOG protocols since 1995. Several randomized trials have demonstrated that combination chemotherapy is more effective than single agent chemotherapy in controlling this disease. Two of the most effective combinations, methotrexate, cisplatin, vinblastine (MCV) and methotrexate, vinblastine, Adriamycin® and cisplatin (MVAC), have shown little difference between the two. Systemic therapy also increases the likelihood of control of local disease. The first analysis of the MRC/EORTC Intercontinental trial of neoadjuvant chemotherapy demonstrated an increase from 12% to 33% in the occurrence of pT0 tumors at cystectomy following MCV therapy. MCV was originally chosen by the RTOG for adjuvant therapy (95-06) but because of concerns about efficacy, gemcitabine and cisplatin were selected as an alternative adjuvant combination given the acceptable toxicity associated with it when used in metastatic disease. In RTOG 99-05 and a second national multi-group study problems were, however, encountered. The completion rates for all planned cycles of this adjuvant therapy were low because of the induction/consolidation chemotherapy that had preceded it and, in RTOG 99-06, a protocol modification was written to reduce the number of cycles from six to four. Paclitaxel and the newer agent gemcitabine, have each shown significant single agent activity against urothelial tumors and both have exhibited high response rates and acceptable toxicity when used in combination. The Spanish Oncology Group has recently reported the maximum-tolerated doses of paclitaxel and gemcitabine in combination with cisplatin in a dose escalation study on patients with metastatic or locally advanced disease. Others have examined a similar regimen in which cisplatin is replaced by carboplatin. This regimen would appear to be no better tolerated and has a lower response rate (58% vs 77%). Both studies documented the tolerability of these three drug regimens in advanced urothelial cancers. This makes cisplatin, paclitaxel, and gemcitabine an attractive contemporary choice for adjuvant therapy in our own randomized study.

1.2 Schema of Present Protocol

For patients who have T2-T4a muscle invading bladder cancer and who are operable candidates for a radical cystectomy, a concomitant boost schedule will be used. The induction chemoradiotherapy: paclitaxel (Taxol®), cisplatin, and irradiation (TCI) or 5FU, cisplatin, and irradiation (FCI) involves accelerated hyperfractionation for the tumor with a standard dose schedule for the pelvis; cisplatin and either paclitaxel or 5-FU are included as radiation sensitizers. This combination draws from the encouraging experience of the Massachusetts General Hospital with combined cisplatin, 5-FU and twice a day radiation and from the results of the Royal Marsden Hospital where local control for muscle invading bladder cancer was enhanced by accelerated hyperfractionation. In a pilot study involving...
eighty-five patients, twice-daily radiation 1.8 to 2.0 Gy per fraction, five days per week delivered 57.6 Gy to 64 Gy in 32 fractions over twenty-six days, resulted in 80% complete responders. These results are currently being tested in a phase III trial\(^19\) restricting the high dose volume by concomitant boosting. This should preserve the capabilities for ileal neobladder construction while reducing the acute toxicity of the accelerated hyperfractionation regimen. The induction treatment is completed in thirteen treatment days which significantly reduces the delay between the onset of treatment and cystectomy for those patients failing induction. The adjuvant gemcitabine-paclitaxel-cisplatin schedule can be administered entirely on an outpatient basis increasing patient convenience.

**1.3 Biomarkers in Bladder Cancer**

A number of biomarkers have shown promise in predicting the outcome of bladder cancer patients. In particular, p53, p21, pRb, p16, and bcl2.\(^{21-26}\) These markers and others are under investigation through the RTOG genitourinary translational research program using patients from prior RTOG bladder preservation trials. These continued efforts are planned for the tissue from diagnostic/pretreatment TURB and cystectomy specimens, when salvage cystectomy is performed.

**2.0 OBJECTIVES**

2.1 To estimate the safety and tolerance of induction chemoradiotherapy including paclitaxel, cisplatin, and irradiation (TCI) or 5-Fluorouracil, cisplatin, and irradiation (FCI); chemoradiotherapy will be followed by radical cystectomy if the initial tumor response is incomplete or by consolidation chemoradiotherapy if the tumor has cleared. Four cycles of outpatient adjuvant gemcitabine-paclitaxel chemotherapy is then given.

2.2 To estimate the efficacy of transurethral surgery with either induction TCI or FCI in achieving a complete response of the primary tumor

2.3 To estimate the efficacy of transurethral surgery with either TCI or FCI in preserving the native, tumor-free bladder five years after therapy

2.4 To evaluate the function of the preserved bladder after transurethral surgery with either TCI or FCI

2.5 To estimate the value of tumor histopathologic, molecular genetic, and DNA content parameters as possible significant prognostic factors for initial tumor response and recurrence-free survival

**3.0 PATIENT SELECTION**

**3.1 Eligibility Criteria  (June 4, 2004)**

3.1.1 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 III) 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.

3.1.1.1 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.

3.1.2 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.

3.1.3 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.

3.1.4 Zubrod performance status of \(<1\) (Appendix II)

3.1.5 Hemoglobin \(\geq 10\) mg/dl; WBC \(\geq 4000\)/ml; ANC \(\geq 1800\)/ml; platelet count of \(\geq 100,000/mm^3\); serum creatinine of 1.5 mg% or less; serum bilirubin of 2.0 mg% or less; creatinine clearance of 60 ml/min or greater; 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.

3.1.6 Protocol treatment to begin within 8 weeks of the transurethral resection and endoscopic evaluation (4/18/06)

3.1.7 Patients must sign a study-specific informed consent (Appendix I) prior to study entry.

**3.2 Ineligibility Criteria**

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 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)

4.0 PRETREATMENT EVALUATION

4.1 History and physical examination including weight, performance status, and body surface area

4.2 Radiologic evaluation, (no more than 6 weeks before treatment start) including chest x-ray, bone scan (as applicable), abdominal and pelvic CT scans; IVP if indicated

4.3 Laboratory studies, (no more than 4 weeks prior to study entry), to include CBC, platelet count, alkaline phosphatase, SGOT, LDH, bilirubin, BUN, creatinine, urinalysis, 24 hour (or calculated) creatinine clearance, magnesium and calcium levels

4.4 Pregnancy test for female patients of childbearing potential, ≤ 72 hours prior to study entry

4.5 Cystoscopic evaluation by the participating urologic surgeon will include as thorough as possible a transurethral resection of the bladder tumor, bimanual examination under anesthesia, four quadrant bladder and prostatic urethra mucosal biopsies as well as a biopsy of the base of the resected tumor site. Patients referred from outside will be re-resected by the participating urologist.

5.0 REGISTRATION AND RANDOMIZATION

5.1 Registration and Randomization for Induction Chemoradiotherapy:

Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. 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.

5.2 Post-Induction Registration:

Within seven weeks 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 and the second phase of the treatment (radical cystectomy or consolidation chemoradiotherapy) will be recorded and a new data collection calendar generated.

5.2.1 The following information will be supplied:
- original case number
- results of evaluation and pathologic T stage
- treatment start date (radical cystectomy or consolidation chemoradiotherapy)

5.2.2 The treatment option registered at 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.

5.2.3 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).

5.2.4 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) in week 17 will be promptly submitted to RTOG Headquarters.

5.3 Randomization and Registration, ECOG Investigators (June 4, 2004) (4/18/06) (5/9/08)

Submitting Regulatory Documents

Before an ECOG Institution may enter patients, protocol specific regulatory documents must be submitted to the CTSU Regulatory Office at the following address:

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX: (215) 569-0206

Required Protocol Specific Regulatory Documents
1. CTSU Regulatory Transmittal Form.
Note: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3. A. CTSU IRB Certification Form.
   Or
   B. HHS 310 Form.
   Or
   C. IRB Approval Letter

Note: The above submissions must include the following details:
- Indicate all sites approved for the protocol under an assurance number
- OHRP assurance number of reviewing IRB
- Full protocol title and number
- Version Date
- Type of review (full board vs. expedited)
- Date of review
- Signature of IRB official.

The CTSU encourages you to link to the following RSS2.0 web page so that more information on RSS2.0 as well as the submission forms can be accessed [http://www.ctsu.org/rss2.0_page.asp](http://www.ctsu.org/rss2.0_page.asp).

If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or E-mail CTSUContact@westat.com Monday through Friday, 9:00am - 5:30pm.

Patients must not start protocol treatment prior to registration. Treatment should start within three working days after registration.

Note: Patients will be re-registered for Post-Induction Chemoradiotherapy within seven weeks following the completion of induction chemoradiotherapy and the evaluation of response.

Institutions may begin to register eligible patients to this study by completing the checklist via the ECOG web page using the Web-based Patient Registration Program ([http://webreg.ecog.org](http://webreg.ecog.org)). If you need assistance or have questions, please telephone the Central Randomization Desk at the ECOG Coordinating Center at (617) 632-2202. Please note that a password is required to use this program. The following information will be requested: Protocol Number; Investigator Identification (including institution and/or affiliate name and investigator's name); Patient Identification (including patient's initials, chart number, social security number and demographics (sex, birth date, race, nine-digit zip code and method of payment)); Eligibility Verification. Patients must meet all of the eligibility requirements listed in Section 3.0. After completing the checklist on the web, the institution will call the Central Randomization Desk at the ECOG Coordinating Center to provide the Transaction ID # at (617) 632-2022, Monday-Friday, between the hours of 9:00 am and 4:30 pm ET. ECOG members should not call the RTOG directly.

The ECOG Randomization Desk will complete the randomization process and call the institution back to relay the treatment assignment for the patient. The ECOG Coordinating Center will forward a confirmation of treatment assignment to the ECOG participating institution.

6.0 RADIATION THERAPY (June 4, 2004)(4/18/06)

All patients will receive the preliminary course of radiotherapy as part of the induction TCI or FCI regimen. This regimen will begin within 8 weeks of the TUR and endoscopic evaluation by the RTOG and ECOG participating urologic surgeon. Patients who qualify for consolidation chemoradiotherapy will receive treatment as described in Section 6.2. At least two fields will be treated during each treatment session. There will be two treatment sessions per day with an inter-session interval of 4-6 hours or more. Ideally, treatment should begin on a Monday for both Induction and Consolidation radiotherapy. Treatment times must be recorded in the daily treatment record.

Note: Since the fields are complicated for this study, it is recommended that the principle investigator contact the study chair, Dr. Zietman, (617-724-1158), to discuss fields prior to administration of radiation therapy.
6.1 Radiotherapy Given During Induction TCI or FCI  

6.1.1 Treatment Schedule: External beam irradiation, 1.6 Gy, will be given to the pelvis in the first treatment followed by an interfraction period of at least 4-6 hours. During the second treatment, 1.5 Gy will be delivered to the whole bladder for the first five sessions (7.5 Gy) then to the tumor plus a margin for eight sessions (12. Gy). During the consolidation and whole bladder phases of treatment, patients are instructed to void one hour before treatment. This will ensure that the bladder volume is low but that sufficient urine is present within the bladder for those institutions that wish to use trans-abdominal ultrasound localization (See Section 6.3.4).

6.1.2 Target Volumes (5/9/08)  

6.1.2.1 "Small" Pelvic Fields. (Appendix IV): The field should include all of the bladder, the total bladder tumor volume, the prostate and the prostatic urethra, and the lymph nodes immediately adjacent to the bladder. These lymph nodes regions will include the distal hypogastric and external iliac vessels and those within the obturator space. These fields will be designed on a simulator with the patient having a 40 to 50 ml air contrast cystogram and with contrast material in the rectum. When planning is accomplished via CT-simulation, digitally reconstructed radiographs (DRR) must depict bony anatomy and contrast with quality comparable to fluorographic images. The combination of four shaped anterior, posterior, and lateral fields will be used. In the cranial-caudal dimension, the planning target volume (PTV) will extend from the lower pole of the obturator foramen to the mid-sacrum (approximately the anterior aspect of the S2-S3 junction). In the anterior and posterior pelvic field, PTV widths will extend 1.0 cm lateral to the bony margin of the pelvis at its widest point. The anterior and posterior fields will have shaped inferior corner blocks, which will shield the medial border of the femoral heads. For the two parallel-opposed lateral fields, the anterior boundary of the PTV will be 1.0 cm anterior to the most anterior portion of the bladder mucosa seen on the air contrast cystogram. Posteriorly, the PTV should extend at least 1.5 cm posterior to the most posterior portion of the bladder or 1.5 cm posterior to the bladder tumor mass if it is palpable or identifiable on the pelvic CT scan. Inferiorly, the lateral fields should be shaped with corner blocks to shield tissue outside the symphysis anteriorly and to block the entire anal canal posteriorly. Superiorly, the lateral pelvic fields should be blocked anteriorly to exclude any portions of the bowel and anterior rectus fascia, which lay anterior to the external iliac lymph nodal group. Wedges (usually 15 degree) should be considered for lateral fields as compensators if the transverse contour has a significant slope anteriorly. The small pelvic fields shall be weighted equally from the anterior and posterior directions. AP-PA weighting relative to the paired lateral fields will depend upon the technique chosen for the boost treatment. For example, when paired lateral fields are planned for the boost, Ant: Post: Rt lateral: Lt lateral are weighted 1:1:0.5:0.5 for tumor doses at the point of intersection of central axis of the four fields. Specific weighting will be chosen to limit the dose to the femoral heads to no more than 45 Gy and the posterior rectal wall to no more than 55 Gy. In some women, a bladder cystocele may protrude below the lower border of the obturator foramen, while in other patients a bladder diverticulum may be present and extend outside the usual target volume. In some patients the bladder may herniate through the abdominal wall. In each of these situations appropriate changes in the PTV for these unusual anatomic variations will be required. Finally, if the patient has a significant post-void residual, the size of the PTV at simulation should be appropriately changed to be certain of inclusion of the bladder volume. Typically, the light fields will appear similar to those shown in Appendix IV.

6.1.2.2 Whole Bladder Field: These fields include the whole bladder and are designed during the same simulation with the same air contrast cystogram. The GBV (gross bladder volume) includes the GTV plus the whole bladder volume defined by the cystogram and the bladder wall thickness calculated from the CT scan. The PTV should be 0.5 cm beyond the GBV. This volume is best treated using cerrobend blocks or MLC shaped 4-fields. Typically, the light field encompasses a 2 cm margin on the GBV.

6.1.2.3 Tumor Boost Field (Appendix IV): This field will include the gross bladder tumor volume (GTV) plus margin. These fields will be designed during the same simulation and with the same air contrast cystogram described above. The primary GTV will be derived from the information available from bimanual examination, diagnostic studies and surgical evaluation. This will include the initial cystoscopic report and CT of the pelvis. For the boost volume the clinical tumor volume (CTV) will be equal to the GTV. If the Radiation Oncologist is satisfied that the tumor is limited to one section of the bladder (usually the trigone and posterior bladder), then the CTV should be designed to exclude the uninvolved region. This bladder boost is most likely best achieved by shaped paired lateral fields on high energy linear accelerators or using a 4-field approach, although well-lateralized tumors may be treated with a wedged-pair technique. A 0.5 cm margin beyond the GTV should be used as the Planning Target Volume (PTV). The GTV and PTV both should be clearly indicated on the simulation films or digital reconstructions. Typically, the light field encompasses a 2 cm margin on the GTV.

6.2 Radiation Therapy During Consolidation Chemoradiotherapy  

6.2.1 Consolidation therapy will start 7-14 days following a cystoscopic re-evaluation demonstrating a
complete response to the induction therapy. 1.5 Gy (per fraction) will be given to the pelvis in two
treatment fractions per day, with an interfraction period of at least 4-6 hours. (10/28/04)

6.2.2 The previously simulated small pelvic field will be treated during the consolidation phase.

6.3 Radiation Dose Specifications

6.3.1 The induction radiotherapy course will deliver 20.8 Gy to the small pelvic fields and 40.3 Gy to the
tumor volume (20.8 Gy from the pelvic field, 7.5 Gy from the whole bladder field, and 12.0 Gy from the
tumor boost field).

6.3.2 The radiation given during the consolidation treatment will be 24 Gy to the pelvis and the primary tumor.
This will result in a total dose to the tumor volume of 64.3 Gy over 8 weeks in 42 fractions and a total
dose to the pelvic lymph nodes of 44.8 Gy.

6.3.3 Doses will be specified as follows: (1) on the central ray at mid-separation for two opposed coaxial,
equally weighted beams; (2) at the intersection of the central rays for two or more intersecting beams;
(3) at the center of the PTV for any other field arrangement. The minimum dose within the PTV will be
at least 95% of the protocol dose. The dose maximum will not exceed 107% of the protocol dose.
Linear accelerators with beam energy of $\geq$ 6 MeV must be used. CT based 3-D planning techniques
may also be employed using the same GBV/GTV and PTVs as described in 6.1.

6.3.4 In addition to the standard field set up based on simulated field borders and isocenter, further daily
adjustments may be made using daily target imaging. This may either involve fiducial tumor marking
clips visualized on portal imaging or daily imaging of the bladder and/or tumor by trans-abdominal
ultrasound by participating institutions that have the clinical experience with these techniques. These
daily adjustments would be limited to the bladder-only and tumor-only fields and would not be
necessary for the pelvic field.

6.4 Critical Structure Dose

The maximum dose allowed to the posterior wall of the rectum shall be 55 Gy and to the femoral heads
should be 45 Gy.

6.5 Treatment Interruption

If a grade 3 hematologic toxicity develops, then chemoradiotherapy should be discontinued for one week.
It will be resumed if the ANC returns to 1000/mm$^3$ or above, and the platelet count is 100,000/mm$^3$ or
above. If these laboratory values have not been reached after a one-week delay in chemoradiation
therapy, they should be checked weekly until they recover to these levels. Following recovery of the
blood counts to these levels, radiation therapy can be resumed. If the blood counts fail to recover in three
consecutive weekly measurements, patients should not resume protocol therapy but should be treated off
protocol on an individual basis. For a grade 3 acute colitis or any other grade 3 infiel (radiation-related)
toxicity during any treatment week (such as radiation cystitis), chemotherapy and radiation therapy should
be delayed until resolution of the toxicity is to grade 2 or less. The treatment should be restarted at that
time with a 25% dose reduction of paclitaxel or 50% of 5-FU (see dose modifications). If the delay to
resume treatment is greater than three weeks, then the patient should be considered intolerant of the
protocol therapy and appropriate off-protocol treatment should be administered.

6.6 Compliance Criteria

In keeping with recommendations from the RTOG Quality Control Committee, compliance will be scored
in relation to field borders, radiation dose, fractionation, and elapsed days. Each parameter will be scored
as being per protocol, a variation (acceptable), or a deviation (unacceptable). Isodose distributions
through the central plane of each site will be submitted to RTOG Headquarters.

6.6.1 Field Borders

Per protocol: Actual field borders and/or PTVs either exceed or fall short by 1 cm or less those borders
stated in the protocol.

Variation: Actual field borders and/or PTVs are no more than 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.

6.6.2 Specified Radiation Dose

Per protocol: Actual dose is within 4% of the specified protocol dose.

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

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

6.6.3 Minimum Isodose Coverage

Per protocol: The 95% isodose contour covers target structures.

Variation: Target structures covered with an isodose contour less than 95%, but not less than 90%.

Deviation: Target structures are transected by the 90% isodose contour.

6.6.4 Maximum Dose

Per protocol: 107%

Variation: Greater than 107%, but less than 110%
6.6.5 Interfraction Interval

**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

6.6.6 Elapsed Days

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

**Variation:** 4 to 7 break days

**Deviation:** 8 or more break days

7.0 CHEMOTHERAPY (June 4, 2004)

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual. ECOG participants can access the RTOG Procedures Manual on the RTOG web site at [http://www.rtog.org/frame/frame_manual.html](http://www.rtog.org/frame/frame_manual.html)

7.1 Induction Chemoradiotherapy with Paclitaxel and Cisplatin or 5-Fluorouracil and Cisplatin

7.1.1 Body surface area calculations will be based on actual body weight. The following premedication is recommended:

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Route</th>
<th>Administration Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>20 mg</td>
<td>oral</td>
<td>12 and 6 hours prior to paclitaxel</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>20 mg</td>
<td>intravenous</td>
<td>30 to 60 minutes prior to paclitaxel</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>50 mg</td>
<td>intravenous</td>
<td>30 to 60 minutes prior to paclitaxel</td>
</tr>
<tr>
<td>Cimetidine or</td>
<td>300 mg</td>
<td>intravenous</td>
<td>30 to 60 minutes prior to paclitaxel</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>50 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7.1.2 Induction Chemotherapy, Arm 1(a): Paclitaxel and Cisplatin plus irradiation (TCI) or Arm 2(b): 5-Fluorouracil and Cisplatin plus irradiation (FCI) will begin within 8 weeks of the transurethral resection (TUR). On days of chemotheraphy 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. (10/28/04) (4/18/06)

7.1.3 Paclitaxel (50 mg/m²) is to be administered as a one-hour infusion on days 1, 8, and 15. The post-paclitaxel i.v. hydration should consist of NS at a rate of 500cc/hr for 1 hour. This also serves as pre-cisplatin hydration.

7.1.4 5-Fluorouracil (400mg/m²) is to be administered as a 24-hour infusion on days 1,2,3, and 15,16,17.

7.1.5 Cisplatin (15 mg/m²) 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.

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

7.1.8 In week 7 (four weeks following completion of induction chemoradiotherapy), the patient will have an evaluation of response as described in Section 8.2.

7.1.8.1 For patients who have a T0, Ta, or Tcis response documented by the first response evaluation, consolidation therapy will begin within 7-14 days. (10/28/04)(4/18/06)

7.1.8.2 For operable patients who have a T1 or worse tumor response, radical cystectomy will be performed within two weeks of the first response evaluation.(4/18/06)

7.2 Consolidation Chemoradiotherapy for Patients Selected for Bladder Preservation

7.2.1 Consolidation Chemotherapy, Arm 1(c): Paclitaxel (50 mg/m²) and Cisplatin (15 mg/m²) plus irradiation (TCI) or Arm 2(d): 5-Fluorouracil (400mg/m²) and Cisplatin (15mg/m²) plus irradiation (FCI) 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 Paclitaxel, 50 mg/m², will be administered as a one-hour infusion on days 1 and 8. The post-paclitaxel i.v. hydration will consist of NS at a rate of 500 cc/hr for 1 hour. This also serves as pre-cisplatin hydration.

7.2.4 5-Fluorouracil, 400 mg/m², will be administered as a 24-hour infusion on days 1, 2, 3 and 8, 9, 10.

7.2.5 Cisplatin, 15 mg/m², 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.

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

7.2.7 Radiation will be given twice a day to the pelvis at 1.5 Gy per fraction, with a minimum 4-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 4-hour interfraction interval.

7.3 Adjuvant Chemotherapy

7.3.1 Outpatient adjuvant chemotherapy will begin 4 weeks following the post-consolidation endoscopic evaluation or 8 weeks following radical cystectomy. Adjuvant chemotherapy consists of gemcitabine, paclitaxel, and cisplatin given on a 21-day cycle. 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/m²) 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 at the beginning of each cycle.

7.3.1.2 Paclitaxel (50 mg/m²) will be given on Day 1 and 8 of each 21-day cycle. Paclitaxel will be administered following gemcitabine on the day of therapy and will be administered via a free-flowing intravenous line with an infusion time of 1 hour.

7.3.1.3 Cisplatin (35 mg/m²) will be administered as a sixty-minute infusion on days 1 and 8 of each 21-day cycle. The post-cisplatin i.v. hydration should consist of NS of 500cc in one hour.

Premedications:
- dexamethasone, 20mg oral, 12 and 6 hours prior to paclitaxel
- diphenhydramine, 50mg i.v., 30-60 minutes prior to paclitaxel
- cimetidine, 300mg i.v. or ranitidine, 50mg i.v., prior to paclitaxel

7.4 Paclitaxel (Taxol®)

7.4.1 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.

7.4.2 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 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.

7.4.3 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. In order to maximize radiosensitization of paclitaxel, patients will proceed with pelvic radiation 1 ½ hours after paclitaxel infusion has been completed. 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.
7.4.4 Storage: Paclitaxel vials should be stored between 2°-25°C (36°-77°F).
7.4.5 Adverse Effects:
- Hematologic: Myelosuppression
- Gastrointestinal: Nausea and vomiting; diarrhea, stomatitis, mucositis, pharyngitis, typhilitis, 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, pruritus
- Other: Alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration (erythema, induration, tenderness, rarely ulceration); radiation recall reaction.
7.4.6 Supply: Commercially available.

7.5 5-Fluorouracil (5-FU)
7.5.1 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.
7.5.2 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 deoxyuridylic acid to the thymidylic 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.
7.5.3 Administration: 5-Fluorouracil (400mg/m²) 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.
7.5.4 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.
7.5.5 Side Effects and Toxicities: The spectrum of toxicity includes stomatitis and esophagopharyngitis (which may lead to sloughing and ulceration); diarrhea with cramping and/or bleeding; anorexia, nausea and emesis are commonly seen during therapy. Leukopenia usually follows every course of adequate therapy with fluorouracil. The lowest white blood cell counts are commonly observed between the 9th and 14th days after the first dose, although uncommonly, the maximal depression may be delayed for as long as 20 days. By the 30th day the count has usually returned to the normal range. Alopecia and dermatitis may be seen. The dermatitis most often seen is a pruritic maculopapular rash usually appearing on the extremities and less frequently on the trunk. Other side effects include myocardial ischemia, angina, lethargy, malaise, headache, allergic reactions, disorientation, confusion, euphoria, dizziness, lack of coordination, visual changes, photosensitivity (eyes and skin); nail changes including loss of nails; skin thickening, cracking, dryness or sloughing; vein pigmentation, biliary sclerosis, or acalculous cholecystitis.
7.5.6 Supply: 5-FU is available commercially.

7.6 Cisplatin (Platinol®)
7.6.1 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.
7.6.2 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.
7.6.3 Administration: Cisplatin should be given immediately after preparation as a slow intravenous infusion.
7.6.4 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 D5W). Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes.

7.6.5 **Adverse Effects:** Include anorexia, nausea, vomiting, renal toxicity (with an elevation of BUN, creatinine, and impairment of endogenous creatinine clearance, as well as renal tubular damage which appears to be transient); ototoxicity (with hearing loss which initially is in the high-frequency range, as well as tinnitus); hyperuricemia, seizures, rash, ocular toxicities, rare cardiac abnormalities; or possible acute myeloid leukemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretory tracts. Myelosuppression, often with delayed erythrosuppression, is expected. In the high-dose treatment regimen with osmotic diuresis, the nadir of white cells and platelets occurred regularly at about two weeks with recovery generally at about three weeks after the initiation of therapy. Rare complications are loss of taste, allergic reactions, and loss of muscle or nerve function.

7.6.6 **Supply:** Cisplatin is available commercially.

7.7 **Gemcitabine**

7.7.1 **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.

7.7.2 **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.

7.7.3 **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.

7.7.4 **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.

7.7.5 **Administration:** Gemcitabine (1000mg/m²) in 250cc normal saline over 30 minutes.

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

7.7.7 **Known Side Effects and Toxicities:** The primary dose limiting toxicity of gemcitabine is hematological, including neutropenia, anemia, and thrombocytopenia. Other toxicities include mild elevation in liver function tests; rare decrease in creatinine clearance; edema, nausea, vomiting, rash, constipation, diarrhea, fever, alopecia, pain, dyspnea, and stomatitis.

7.7.8 **Supply:** Commercially available.

7.8 **Dose Modifications for Induction/Consolidation Cisplatin**

7.8.1 A complete blood count and serum creatinine will be drawn at the start of each week of induction or consolidation chemotherapy or at the end of the week prior. Dose modifications for the drugs given that week will be based upon these results. Dose reductions based on CBC and creatinine during induction do not, therefore, carry through to consolidation unless the blood abnormality persists. The same applies for paclitaxel and 5-Fluorouracil. Dose reductions based upon clinical problems such as neurotoxicity may involve discontinuation of the drug altogether and are specified in the text below.

7.8.2 **Modifications of cisplatin for nephrotoxicity** during induction or consolidation chemoradiotherapy are as listed in the table below:

<table>
<thead>
<tr>
<th>CrCl &gt;60 or serum creatinine ≤ 1.5 mg%</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>serum creatinine &gt; 1.33 x baseline</td>
<td>75%</td>
</tr>
<tr>
<td>serum creatinine &gt;1.5 x baseline</td>
<td>Hold cisplatin</td>
</tr>
</tbody>
</table>

7.8.3 **Modifications for myelosuppression** during induction or consolidation chemoradiotherapy are as listed in the table below:

<table>
<thead>
<tr>
<th>ANC (x 1000)</th>
<th>Platelet Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.4</td>
<td>100K</td>
</tr>
<tr>
<td>1.0-&lt; 1.4</td>
<td>100</td>
</tr>
</tbody>
</table>
ANC = Absolute neutrophil count per ml

7.8.4 Modification of cisplatin for peripheral neurotoxicity, grade 3: Omit cisplatin (in both induction and consolidation chemoradiotherapy).

7.9 Dose Modifications for Induction/Consolidation Paclitaxel

7.9.1 Hematologic Toxicity
Granulocytopenia alone will not be considered the only criteria for dose reduction. For patients with grade 3 neutropenia (< 1000/mm³) and/or thrombocytopenia (< 50,000), CBC, differential, and platelets will be repeated weekly until complete recovery. The paclitaxel dose for hematologic toxicity (during induction and consolidation chemoradiotherapy) will be modified as follows:

<table>
<thead>
<tr>
<th>ANC OR Platelet Counts</th>
<th>Paclitaxel Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1000</td>
<td>&gt; 75,000</td>
</tr>
<tr>
<td>500-1000</td>
<td>50,000-75,000</td>
</tr>
<tr>
<td>&lt; 500</td>
<td>&lt; 50,000</td>
</tr>
</tbody>
</table>

7.9.2 Hepatic
Grade 3-4 elevation of SGOT, SGPT, or bilirubin due to paclitaxel will require a dose reduction of 25% after recovery to ≤ grade 2. A second dose reduction will not be allowed for continued toxicity.

7.9.3 Renal
Grade 3-4 elevation of serum creatinine due to paclitaxel will require one dose reduction of 25% after recovery to ≤ grade 2. A second dose reduction will not be allowed for continued toxicity.

7.9.4 Mucositis
Grade 2 or greater will require a first dose reduction of 25% after recovery to ≤ grade 1. Recurrence after one dose reduction will require that the patient will receive no further paclitaxel.

7.9.5 Gastrointestinal Toxicity
If grade 3 or 4 nausea/vomiting or ileus toxicity occurs, in spite of administration of prophylactic antiemetic regimen, the subsequent cycle should be reduced by 25%. In the event of grade 3 or 4 nausea/vomiting or ileus toxicity in spite of the dose reduction, patients will be removed from protocol therapy. Toxicity must resolve before treatment.

7.9.6 Neurologic Toxicity
In the event of grade 4 neurologic toxicity, paclitaxel will be discontinued. A dose reduction of 25% in paclitaxel will be required in the event of grade 3 neurotoxicity (neurosensory, neuromotor). If, in a subsequent cycle, despite the dose reduction, grade 3 neurotoxicity is observed, no further paclitaxel therapy should be given. Patients must return to a toxicity of grade 1 or less before retreatment.

7.9.7 Hypersensitivity Reactions
An infusion will be discontinued if a patient develops any signs of severe hypersensitivity reaction (dyspnea, symptomatic hypotension, angioedema, generalized urticaria, or chest pain). Patients should be treated with the necessary support measures and removed from protocol therapy. The following management of hypersensitivity reactions is recommended:

- Administration of diphenhydramine 50 mg i.v. (or its equivalent);
- Administration of adrenalin (or its equivalent) every 15-20 minutes until the reaction subsides or a total of six doses are given;
- If hypotension is present that does not respond to adrenalin, administration of i.v. fluids is recommended;
- If wheezing is not responsive to adrenalin, administration of nebulized albuterol (or its equivalent) is recommended;
- Although corticosteroids have no effect in the initial reaction, they have been shown to block “late” allergic reactions. Thus, methylprednisolone 125 mg i.v. (or its equivalent) may be given to prevent recurrent or ongoing allergic manifestations.

In the event of grade ≤ 2 hypersensitivity reactions (flushing, skin rash), the infusion may be continued with further support as necessary (steroids, antihistamines, etc.). There will be no dose modifications for hypersensitivity reactions, but extreme caution with subsequent cycles should be employed.

7.9.8 Cardiac Toxicity
There will be no dose modifications for asymptomatic (grade 1 or 2) cardiac toxicity or asymptomatic hypotension. In the event of first degree AV block, paclitaxel therapy will be continued at full dose under continuous cardiac monitoring. In the event of grade 3 or 4 cardiac toxicity, i.e., CHF, no further paclitaxel will be given.

7.9.9 Myalgia/Arthralgia
Myalgia/arthralgia will be classified as mild (grade 1): muscle and joint aches; moderate (grade 2): decreased function, decreased ability to perform daily tasks, but still functioning; or severe (grade 3):
unable to function, confined to bed. Treatment for myalgia and arthralgias may include terfenadine (Seldane®) 60 mg every 12 hours for pain and, if ineffective, nonsteroidal anti-inflammatory medication (Toradol®, ibuprofen, etc.). If there is still no relief, narcotic pain medications may be used. Grade 3 toxicity, reasonably attributable to paclitaxel, will require a dose reduction of 25% following resolution to grade ≤ 1. No further dose reduction will be permitted, and no further paclitaxel will be given.

### 7.10 Dose Modifications for Induction/Consolidation 5-Fluorouracil (5-FU)

Modifications of 5-fluorouracil for myelosuppression during induction or consolidation chemoradiotherapy are as listed in the tables below:

#### 7.10.1 Myelosuppression (% of initial calculated dose)

<table>
<thead>
<tr>
<th>ANC (x 1000)</th>
<th>Platelet Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;150K</td>
<td>100-149K</td>
</tr>
<tr>
<td>&gt; 1.6</td>
<td>5FU - 100</td>
</tr>
<tr>
<td>1.4-1.6</td>
<td>5FU-100, 5FU-75</td>
</tr>
<tr>
<td>1.0-&lt; 1.4</td>
<td>5FU-75</td>
</tr>
<tr>
<td>&lt;1.0</td>
<td>5FU-0</td>
</tr>
</tbody>
</table>

ANC = Absolute neutrophil count per ml

#### 7.10.2 Gastrointestinal toxicity

<table>
<thead>
<tr>
<th>Grade</th>
<th>% calculated dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>5-FU -100%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>5-FU - 75% - 3 days*</td>
</tr>
<tr>
<td>Grade 3</td>
<td>5-FU - 50% - 3 days*</td>
</tr>
</tbody>
</table>

* only decreased for diarrhea, not stomatitis

### 7.11 Dose Modification for Adjuvant Chemotherapy (gemcitabine, cisplatin, paclitaxel)

#### 7.11.1 Dose Modification Within a Cycle (June 4, 2004; October 28, 2004)

Dose adjustments within a cycle for gemcitabine will be made following the guidelines shown below based on weekly absolute granulocyte count (AGC) and platelet counts, taken within 24 hours before infusion, and on clinical assessment of nonhematologic toxicities. There is no dose adjustment for cisplatin.

#### Hematologic Toxicities

<table>
<thead>
<tr>
<th>AGC (x 10⁹/L)</th>
<th>Platelets (x 10⁹/L)</th>
<th>Percent of Full Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.2</td>
<td>&gt; 100</td>
<td>100</td>
</tr>
<tr>
<td>1.0 to 1.19</td>
<td>75 to 99</td>
<td>100</td>
</tr>
<tr>
<td>0.5 to 0.99</td>
<td>50 to 74</td>
<td>50</td>
</tr>
<tr>
<td>&lt; 0.5</td>
<td>&lt; 50</td>
<td>Hold</td>
</tr>
</tbody>
</table>
Nonhematologic Toxicities

<table>
<thead>
<tr>
<th>CTC Version 2.0</th>
<th>Gemcitabine</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 (and Grade 3 nausea/vomiting)</td>
<td>100</td>
<td>75</td>
</tr>
<tr>
<td>3 (except nausea/vomiting)</td>
<td>50 or Hold(^a)</td>
<td>50 or Hold(^a)</td>
</tr>
<tr>
<td>4</td>
<td>Hold(^a)</td>
<td>Hold(^a)</td>
</tr>
</tbody>
</table>

\(^a\)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.

Cisplatin Dose Adjustments

<table>
<thead>
<tr>
<th>Dose Adjustments</th>
<th>Cisplatin Dose Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-2 (and grade 3 nausea and vomiting)</td>
<td>75% of full dose</td>
</tr>
<tr>
<td>Grade 3-4 neurotoxicity or ototoxicity</td>
<td>Hold drug</td>
</tr>
<tr>
<td>Creatinine clearance falls between 50 and 59ml/min</td>
<td>50% dose reduction</td>
</tr>
<tr>
<td>Creatinine clearance falls below 50ml/min</td>
<td>Hold drug</td>
</tr>
</tbody>
</table>

7.11.2 Dose Modification for Subsequent Cycles

7.11.2.1 The following guidelines should be followed:
- Doses of gemcitabine, cisplatin, and paclitaxel cannot be escalated above the starting dose.
- Absolute granulocyte 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.

7.11.2.2 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 75\% of the dose of paclitaxel and 50\% of the starting dose of gemcitabine delivered in the previous cycle, the latter to apply to all three gemcitabine doses administered during that cycle. Subsequent dose escalation of gemcitabine only by 50\% (e.g., from 500 mg/m\(^2\) to 750 mg/m\(^2\)) will be allowed in subsequent cycles provided the patient tolerates the initial dose of adjustment.

7.11.2.3 Nephrotoxicity (June 4, 2004)
- Patients whose creatinine clearance falls below 50ml/min will receive no further drug.
- Patients whose creatinine clearance falls to between 50 and 59ml/min will only receive 50\% dose in future cycles.

7.12 Adverse Events (5/9/08) (3/29/10)

Beginning April 1, 2010, the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

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

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

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

7.12.1 Adverse Events (AEs)

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

The following guidelines for reporting adverse events (AEs) apply to all NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1). Note: AEs indicated in the AdEERS
**Expedited Reporting Requirements in text and/or table in Section 7.13 also must be reported via AdEERS.**

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

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

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

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

**Definition of an SAE:** Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy occurring on study must be reported via AdEERS as a medically significant event.

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

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

All supporting source documentation indicated as being provided in the Additional Information Section of the AdEERS Report must be properly labeled with the study/case numbers and the date of the event and must be faxed to both the NCI at 301-230-0159 and the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. The RTOG Case Number without any leading zeros should be used as the Patient ID when reporting via AdEERS. Non-RTOG intergroup study and case numbers must also be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient’s case number as the patient ID when reporting via AdEERS.

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

### 7.12.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)

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

**RTOG Headquarters**

**AML/MDS Report**

**1818 Market Street, Suite 1600**
### 7.13 AdEERS Expedited Reporting Requirements

CTEP defines routine AE reporting requirements for phase 2 and 3 trials as described in the table below.

**Important:** All AEs reported via AdEERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

**Phase 2 and 3 Trials Utilizing a Commercially Available Agent:** AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days of the Last Dose of the Investigational Agents in this Study (Arms 1 & 2)

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grades 4 &amp; 5&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Grades 4 &amp; 5&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexpected and Expected</td>
<td>Unexpected</td>
<td>Expected</td>
<td>Unexpected with Hospitalization</td>
<td>Expected without Hospitalization</td>
<td>Unexpected</td>
</tr>
<tr>
<td>Unrelated</td>
<td>Unrelated</td>
<td>Not Required</td>
<td>10 Calendar Days; Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Not Required</td>
<td>Not Required</td>
<td>10 Calendar Days; Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Possible</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days; Not Required</td>
<td>10 Calendar Days</td>
<td>24-Hour; 5 Calendar Days</td>
</tr>
<tr>
<td>Probable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<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 require reporting as follows:
- AdEERS 24-hour notification followed by complete report within 5 calendar days for:
  - Grade 4 and Grade 5 unexpected events
  - AdEERS 10 calendar day report:
    - Grade 3 unexpected events with hospitalization or prolongation of hospitalization
    - Grade 5 expected events

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

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

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

- Expedited AE reporting timelines defined:
  - “24 hours; 5 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - “10 calendar days” - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

#### 7.13.1 Adverse Event Reporting for ECOG Investigators (June 4, 2004; October 28, 2004) (5/9/08)

All ECOG Investigators are responsible for reporting adverse events according to the NCI guidelines. ECOG participants should employ definitions of adverse events as provided by the RTOG reporting guidelines in section 7.12. Both 24 hour and written/electronic adverse reports should be made directly to the RTOG according to the instructions in that section.

RTOG Telephone Number: (215) 574-3214
RTOG Fax Number: (215) 923-1737
RTOG Mailing Address:
8.0 SURGERY (5/9/08)

8.1 Pre-Induction Chemoradiotherapy Evaluation: Endoscopic evaluation should include:
8.1.1 Cystoscopy with tumor mapping on the initial Cystoscopic Report (Appendix V);
8.1.2 Transurethral resection (TUR) of the tumor as thoroughly as is judged safely possible. Tumor specimens should be sent to the RTOG Tissue Bank as described in Section 10.0;
8.1.3 Tumor base and 2 biopsies at the periphery of the tumor by cold cup following TUR of the tumor for additional analysis of the completeness of the TUR;
8.1.4 Bimanual examination before and after TUR to evaluate possible residual tumor bulk;
8.1.5 Two mucosal biopsies from the bladder neck and prostatic urethra.

8.2 Post-Induction Chemoradiotherapy Endoscopic Response Evaluation
This evaluation will take place in week 7 following the completion of the induction chemoradiotherapy. Evaluation will include: barbotage cytology, cystoscopy, tumor site transurethral biopsy, and bimanual examination after biopsy.

8.3 Radical Cystectomy
Operable patients who have a pT1 or worse tumor response on re-evaluation following initial TUR and induction chemoradiotherapy will have a radical cystectomy. In the male, radical cystectomy will include the peritoneum, fat and lymph nodes of an area defined by the medial border of the psoas muscle to a point level with the mid point of the common iliac artery on either side of the pelvis and extending down into the cul-de-sac so that the bladder, seminal vesicles, prostate and ends of the ureter as well as all the associated peritoneum and pelvesical fat will be removed en bloc. Lymphadenectomy should include at least the obturator space and the nodes of the hypogastric vessels. The external iliac nodes will be removed if clinically suspicious at the time of surgery. In the female, in addition to the peritoneum, fat and lymph node mentioned above, the bladder, the urethra, anterior and lateral walls of the proximal vagina, uterus, fallopian tubes and ovaries will be included in the radical cystectomy specimen. Neobladder conduits are acceptable after induction chemoradiotherapy, when the surgeon judges them to be safe.

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, depth invasion, and description of involvement of lymph nodes, margins of resection and invasion of other structures. The pathologic stage will be determined by the deepest level of invasion microscopically by the tumor.

8.4 Post-Consolidation Endoscopic Evaluations
The first post-therapeutic evaluation will be in week 17 after completion of the consolidation chemoradiotherapy, when the initial response was pT0, Ta, or Tcis. 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. These periodic evaluations will be done according to the schedule in Section 11.1 and will include barbotage cytology, biopsy of 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, cytology without biopsy is permitted. 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.

9.0 ADDITIONAL TREATMENT
9.1 For patients who are treated with attempted bladder preservation using consolidation TCI or FCI, 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 superficial tumors 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.

9.2 For patients treated with immediate cystectomy and where the pathologic tumor stage is pN+ or pT3b-T4 with positive margins, these patients will be considered not disease free and additional therapy may be offered at the discretion of the investigators.

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

10.0 PATHOLOGY
(For Patients Who Have Consented to Participate in the Tissue Component of the Study; see Appendix IB)
10.1 Central Review
10.1.1 Slides/blocks from the pre-treatment TUR, 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 on the apparent depth of invasion of the muscularis propria from the TUR specimen.

10.2 Collection Of Tissue For Translational Research
The RTOG has been collecting pretreatment diagnostic tissue from all of the bladder cancer protocols over the last ten years. A number of histologic, cell kinetic/proliferation, and molecular markers are under investigation, with several showing promise for the stratification of patients in future trials. As stated in Section 1.3, a number of biomarkers are under investigation by the RTOG GU TRP group. The results of these ongoing studies will lead to the investigation of promising similar or new biomarkers with the goals of 1) identifying factors predictive of outcome such that patients may be better stratified in future trials, and 2) developing novel treatment strategies which target the molecular abnormalities identified. A final decision on which markers will be studied awaits the results of completed RTOG bladder cancer trials that have reached maturity. The trial described here will not be ready for biomarker analysis for several years. The goal is to measure approximately ten biomarkers using the archived pathologic material.

10.3 RTOG Biospecimen Resource (5/9/08)
10.3.1 The following must be provided in order for the case to be evaluurable for the Biospecimen Resource:
10.3.1.1 One H&E stained slide
10.3.1.2 A paraffin-embedded tissue block of the tumor or a 2 mm diameter core of tissue, punched from the tissue block containing tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number. If available, tumor from the cystectomy specimen of those patients who are incomplete responders also should be included. NOTE: A kit with the punch, tube, and instructions can be obtained from the Biospecimen Resource. If both of these tissue types are unavailable, 15 unstained slides may be submitted. Block, core, or slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.
10.3.1.3 A Pathology Report documenting that the submitted block, core, or slides contain 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.
10.3.1.4 A Pathology Submission Form clearly stating that tissue is being submitted for the RTOG Biospecimen Resource; the form must include the RTOG protocol number and patient's case number.
10.3.1.5 A copy of the patient tissue consent form
10.3.2 Submit materials to: (12/1/04) (5/11/06) (5/9/08)

Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
10.4 Reimbursement (5/9/08)
10.4.1 RTOG will reimburse pathologists from submitting institutions $200 per case if a block or core of material is submitted and $100 per case if unstained slides are submitted. After confirmation from the Biospecimen Resource that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution.

10.5 Confidentiality/Storage (5/9/08)

10.5.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient’s case number only. The 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 The specimens 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.

10.6 Pathology, ECOG Investigators (June 4, 2004)
Materials for diagnostic review and for use in translational research are requested. Materials for diagnostic review are mandatory. Submission of materials for use in the translational study are to be submitted only from those patients who have given written consent for use of their samples in the translational studies.

Submit within 28 days of registration:
1. One copy of corresponding surgical pathology report.
2. RTOG Pathology Submission Form
3. ECOG Pathology Material submission Form (#638)
4. Biological materials
   ▪ One H&E Slide
   ▪ 15 unstained slides from tumor block (5 for diagnostic review, 10 for translational study use).
   ▪ Skin punch (submitted in a tube)
   ▪ Slides from a cystectomy block, if available.

NOTE: If submission of a 2mm core rather than slides is preferred, please contact the ECOG PCO to discuss.

Materials are to be submitted to: ECOG Pathology Coordinating Office, Robert H. Lurie Comprehensive Cancer Center, Northwestern University Medical School, Olson Pavilion - Room 8501, 710 North Fairbanks Court, Chicago, IL 60611, Tel (312) 503-3384, FAX (312) 503-3385.

The ECOG PCO will process and route the appropriate materials to the LDS Hospital.

ECOG INSTITUTIONS: Do not send pathology materials directly to RTOG.

Note: A kit for the punch, with tube, and instructions, can be obtained from the RTOG Biospecimen Resource as indicated in section 10.3.
### 11.1 Study Parameters

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<th>Parameter</th>
<th>Pre-Study</th>
<th>During Induction TCI or FCI</th>
<th>At Post-Induction Evaluation</th>
<th>During Consolidation TCI or FCI</th>
<th>Post-Cystectomy or Post Consolidation Chemo</th>
<th>During Adjuvant Chemotherapy</th>
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</table>

a. As applicable
b. Only if cystectomy is not done within the first 6 weeks after consolidation chemoradiotherapy. These will be done q 3 months the first year after completion of consolidation treatment; q 4 months the second year; q 6 months x 3 years; then annually. Please read Section 8.4 which allows biopsies to be omitted after the second follow-up evaluation under the described circumstances.
c. No more than 6 weeks prior to treatment.
d. In third post-treatment year for patients who still have native bladder. This will incorporate measures of average and peak urinary flow rate, bladder functional capacity, compliance, and leak pressures (continence).
e. For women of childbearing potential

### 11.2 Definition of Complete Response Immediately after Induction Treatment

**11.2.1** Examination under anesthesia, cystoscopy, and biopsy of all previously positive tumor sites will be utilized to evaluate the tumor status (response) following completion of induction chemoradiotherapy in
week 7. 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 complete response, or pT0 response, when the bi-manual examination under anesthesia is negative, when all the 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 or even 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.

11.2.2 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 specimen or elsewhere and a bimanual exam that does not indicate the presence of a tumor mass. 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>1) in the tumor-site biopsy specimen, or elsewhere.

- **Progression** requires the increase of 50% or more in the largest diameter of the endoscopically appreciable tumor and the continued presence of tumor in the tumor-site biopsy specimen.

### 12.0 DATA COLLECTION (10/28/04)

RTOG, 1818 Market Street, Philadelphia, PA 19103, FAX#215/928-0153

#### 12.1 Summary of Data Submission

<table>
<thead>
<tr>
<th>Item</th>
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<tbody>
<tr>
<td>Demographic Form (A5)</td>
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<td>Initial Evaluation Form (I1)</td>
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<td>Diagnostic Pathology Report (P1)</td>
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<tr>
<td>Pathology slides/blocks (P2)</td>
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<td>Surgical Report (S2)</td>
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<td>RT Prescription (Protocol Treatment Form) (T2)</td>
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<td>Films (simulation and portal) [CT SIM/DRR] (T3)</td>
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<td>*Boost Films for consolidation phase (simulation and portal) (T8)</td>
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<tr>
<td>Initial Follow-up Form (FS)</td>
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</table>
Follow-up Form (F1) At 6, 9, and 12 months; upon completion of consolidation treatment or cystectomy, then q 4 months x 1 year, q 6 months x 3 years, then annually. Also at progression/relapse and at death

Adjuvant Treatment Summary Form (AF) Within 1 week after cycle 2; within 1 week after cycle 4

Autopsy Report (D3) As applicable

*If applicable

12.2 Data Submission Schedule, ECOG Institutions (June 4, 2004)

12.2.1 Forms submission
The original data forms as listed in Section 12.0 should be submitted at the required intervals to the ECOG Coordinating Center. Include the RTOG and ECOG study number and patient ID number. The ECOG Coordinating Center will forward the forms to the RTOG.

Do not use ECOG Forms for this study, with the exception of the ECOG Pathology Materials Submission Form (#638).

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint
Completion and safety for each of 2 induction chemoradiotherapy regimens: Arm 1(a) – paclitaxel, cisplatin and irradiation (TCI); Arm 2(b) – 5-FU, cisplatin and irradiation (FCI); followed by definitive local therapy of either radical cystectomy (patients for whom the initial tumor is not a complete response) or consolidation chemoradiotherapy (patients for whom the initial tumor has cleared); both followed by four cycles of outpatient adjuvant gemcitabine, paclitaxel and cisplatin chemotherapy.

13.1.2 Secondary Endpoints
- Complete response after induction;
- Bladder-intact survival;
- Bladder function;
- To estimate the value of tumor histopathology, molecular genetics and DNA flow cytometric parameters as possible significant prognostic factors for initial tumor response and recurrence-free survival in combination with previous RTOG studies.

13.2 Sample Size
Treatment completion is the major question of this trial. The study is designed to detect a 90% against a 70% protocol completion rate suggested from earlier RTOG studies for each chemotherapy regimen. A two-sided binomial test with a null hypothesis of 70% completion rate against the alternative 90% completion will be used for the study. Based on the binomial distribution, 39 patients are required to test the hypothesis with a significance level of 0.05 and a power of 87%. In addition, being able to complete the four cycles of adjuvant chemotherapy itself is of interest. Based on RTOG 95-06 we expect approximately 10% of eligible cases not to make it to the adjuvant chemotherapy phase. To allow for this and another 10% for ineligible cases, the sample size for each chemotherapy regimen will be 48. Given 43 evaluable patients, we will have 90% power to detect an increase in the total protocol completion rate from 70% to 90% with a significance level of 0.05 and a power of 87% power to detect an increase in the 4-cycle adjuvant chemotherapy completion rate from 70% to 90% with a significance level of 0.05. The total sample size for the study will be 96; 48 for each chemotherapy regimen.

13.3 Accrual and Duration
Based upon RTOG 97-06 and 99-06, monthly accrual will be approximately 3 patients. Allowing time for IRB approval and other logistical issues at the institutional level, accrual is projected to be completed in 36 months. For the efficacy of the treatments, additional follow ups after the closure of the accrual are needed. With a additional one year of follow up, we will have better estimates of two- and three-year outcome rates.

13.4 Randomization Scheme
Patients will be randomized to one of two combined modality schedules in order to avoid any patient selection bias. The treatment allocation scheme described by Zelen45 will be used because it balances patient factors other than institution. Patients will be stratified by T-stage (T2 vs. T3/T4).

13.5 Analysis Plan

13.5.1 Interim Reports (5/9/08)
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 date;
- pretreatment characteristics of patients accrued;
- the frequencies and severity of toxicity due to chemotherapy and radiation therapy.

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

13.5.2 Early Stopping Rules for Severe Toxicity
Severe toxicity is defined as grade 4 or 5 toxicity due to chemotherapy and radiation therapy. The following early stopping rules are proposed to test the null hypothesis that the proportion of severe toxicity is less than or equal to 5% with significance level 0.05, within each chemotherapy regimen. We will reject the null hypothesis if within a chemotherapy regimen we observe more than
- 2 severe toxicities out of the first 14 evaluable patients, or
- 4 severe toxicities out of the first 29 evaluable patients, or
- 5 severe toxicities out of the first 43 evaluable patients.

If we observe the specified number or fewer of toxicities at the designated time, the trial shall proceed as planned. On the other hand, if we observe more toxicities than that specified, we shall conclude that the proportion of severe toxicity is greater than 5%. After reviewing toxicity data, appropriate actions shall be recommended by study chair, disease chair and statisticians to RTOG Research Strategy Committee for their approval.

Note that the boundary above is set in such a way that the probability that the observed number of severe toxicity exceeds the boundary is 0.05 if the true toxicity rate is 5%; the probability is 0.33 if the true toxicity rate is 10%; the probability is 0.91 if the true toxicity rate is 20%.

13.5.3 Analysis for Reporting Initial Treatment Results
The final analysis will be performed upon the completion of evaluations of patients on protocol. The number of patients who completed each induction regimen will be reported as well as the number of patients for each regimen who completed consolidation or had a cystectomy, with four cycles of gemcitabine, paclitaxel and cisplatin. The complete response rate will be reported for each treatment phase.

Study primary outcome will be tested using the binomial distribution. For each arm, if more than 34 out of 43 evaluable patients complete the treatment, we will reject the null hypothesis of 70% completion rate and conclude with a better treatment completion rate. If fewer than 24 out 43 evaluable patients complete the treatment, we will reject the null hypothesis and conclude with a worse treatment completion rate. Otherwise, we will conclude that there is not enough evidence to reject the null hypothesis of a 70% completion rate. Furthermore, should both arms prove to be tolerable and efficacious, the RTOG will use statistical selection theory to choose which arm should be considered for further testing in the follow-up trial. Briefly, its criterion is to select the treatment arm with the highest response regardless of how small or “non-significant” the advantage is over the other treatment arm.

Furthermore, tabulations of acute and late toxicity will be reported. We acknowledge that with the proposed sample size and duration of the trial, the observed late toxicity, if there is any, is associated with very large confidence intervals, and thus, the interpretation should be very limited. The outcome probabilities will be estimated using the appropriate method, either Kaplan-Meier or cumulative incidence.

13.6 Race and Gender Considerations
In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, the possible difference in any of the above endpoints between men and women, or whites and non-whites, will be investigated. Prior RTOG bladder cancer trials, 89-03, 95-06 and 97-06, accrued about 6% non-whites and 21% women. With proposed 43 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.
## GENDER AND MINORITY ACCRUAL ESTIMATES

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<td><strong>76</strong></td>
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<td><strong>96</strong></td>
</tr>
</tbody>
</table>

*Total of all subjects includes all subjects, including those with unknown ethnicity and race.

---

23
REFERENCES


38. Stadler WM, Murphy B, Kaufman D, Raghavan D, Voi M. Phase II trial of gemcitabine (GEM) and cisplatin


APPENDIX IA (5/9/08)
RTOG 0233
SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE
A PHASE II RANDOMIZED TRIAL FOR PATIENTS WITH MUSCLE-INVADING BLADDER CANCER EVALUATING TRANSCUTERAL SURGERY AND BID IRRADIATION PLUS EITHER PACLITAXEL AND CISPLATIN OR 5-FLUOROURACIL AND CISPLATIN FOLLOWED BY SELECTIVE BLADDER PRESERVATION AND GEMCITABINE/PACLITAXEL/CISPLATIN ADJUVANT CHEMOTHERAPY

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, “Taking Part in Clinical Trials: What Cancer Patients Need To Know,” is available from your doctor.

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 bad) chemotherapy combined with twice-daily external radiation therapy and possible removal of your bladder has on you and your cancer. The chemotherapy drugs (paclitaxel, cisplatin, 5-Fluorouracil, 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.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 96 people will take part in this study.
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.

After this resection, you will be “randomized” into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. A computer will determine into which group you are placed. Neither you nor the researcher will choose what 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 of the resection.

**Treatment 1**
If you are randomized to this group, you will receive the drugs cisplatin and paclitaxel. 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 paclitaxel once a week on the same day as your first cisplatin injection. You will receive two radiation treatments each day, Monday through Friday, at least 4 hours apart. The drugs will be given either starting approximately one hour before the first daily radiation treatment or between the first and second treatment. The chemotherapy and radiation therapy will take about 2 ½ weeks to complete. *(5/9/08)*

**Treatment 2**
If you are randomized to this group, you will receive the drugs cisplatin and 5-Fluorouracil. 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. The drugs will be given either starting approximately one hour before the first daily radiation treatment or between the first and second treatment. The chemotherapy and radiation therapy will take about 2 ½ weeks to complete. *(5/9/08)*

**Treatments 1 and 2**

Three weeks after the completion of the chemotherapy and radiation, the surgeon will re-examine your bladder through the fiberoptic scope and a biopsy will be done. 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 10 days. Also, you then will have four months of additional chemotherapy (with cisplatin, paclitaxel, 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 two weeks will be recommended. After surgery, you then will have four months of additional chemotherapy (with cisplatin, paclitaxel, 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. Should the bladder tumor come back or get bigger, then surgical removal of your bladder may be recommended.

If you take part in this study, you also will have the following tests and procedures:

- A physical exam, a bladder exam through a fiberoptic scope, and bladder biopsy prior to study entry, 3 weeks after chemoradiotherapy, and at follow-up visits if you have not had your bladder removed: every 3 months after all treatment for the first year, every 4 months for the 2nd year, every 6 months for three years, then annually thereafter
- Measurement of your weight weekly during chemoradiotherapy
- Blood tests prior to study entry, weekly during chemoradiotherapy, 3 weeks after chemoradiotherapy, then weekly during additional chemoradiotherapy if you have not had your bladder removed
- Prior to study entry, if recommended by your doctor: a bone scan and an intravenous pyelogram (IVP); the IVP is an x-ray in which dye, which is put into your vein, is used to outline the kidneys, the tubes that carry urine from the kidneys to the bladder, and the bladder on an x-ray.
- CT scan of your pelvic area prior to study entry and at follow-up visits for the first and second year after treatment
- A chest x-ray prior to study entry and at follow-up visits for the first and second year after treatment
- For patients who still have their bladder, a test of bladder function in the third post-treatment year
- For women who are able to have children, a test prior to study entry to see if you are pregnant

**HOW LONG WILL I BE IN THE STUDY? (6/4/04) (4/18/06)**

You will be in the study for 8 months of treatment. Treatment will begin within 8 weeks of the transurethral bladder resection and will take about 2 ½ weeks to complete. Three weeks after the completion of the chemotherapy and radiation, the surgeon will re-examine your bladder. If your tumor has completely disappeared, you will receive chemotherapy and radiation therapy for an additional 10 days. Or, if your tumor has not completely disappeared and you are medically fit for surgery, surgical removal of your bladder within two weeks will be recommended. You will then have four months of additional chemotherapy.

Follow-up visits will take place every 3 months after all treatment for the first 
year, every 4 months for the 2\textsuperscript{nd} year, every 6 months for three years, then annually thereafter.

Your doctor may decide to take you off this study if your doctor believes it is in your medical best interest, if funding for this study is stopped, or if your condition worsens. You may also be taken off this study if new information becomes available about how to better prevent growth of bladder cancer.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

**WHAT ARE THE RISKS OF THE STUDY?**

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the chemotherapy drugs and radiation therapy are stopped, but in some cases side effects can be serious or long lasting or permanent.

**Risks associated with Radiation Therapy to the Pelvis**

**Very 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

**Less Likely 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
- Ureteral (tube connecting kidneys to the bladder) obstruction
- Fistula (opening) forming between pelvic tissues

Radiation to the pelvis will cause sterility. 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 Associated with Cisplatin

**Very 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 and feet
- Facial swelling

**Less Likely, 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
- Another cancer called Acute Leukemia

Risks Associated with Paclitaxel

**Very Likely**
- Decrease in blood counts which can lead to a risk of infection and bleeding
- Hair loss
- Fatigue
- Mouth sores
- Numbness, tingling, or burning in the hands or feet
- Skin redness or rash

**Less Likely**
- Muscle aches and/or joint pains
- Nausea and/or vomiting
- Headaches
- Skin or nail darkening
- Skin ulcers

**Less Likely, 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 or feet
- Severe rash called Stevens-Johnson syndrome, which can cause fever and red sores in your mouth and eyes
Risks Associated with 5-FU (5-Fluorouracil)

**Very 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

**Less Likely, But Serious**
- Chest pain
- Infection at the puncture site

Risks Associated with Gemcitabine

**Very 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

**Less Likely, But Serious**
- Change in liver function
- Decrease in kidney function
- Pneumonia
Risks of Surgery

If removal of your bladder is necessary:
In men, the operation includes removal of the bladder, the pelvic lymph nodes, the seminal vesicles, and the prostate. As a result, there is loss of sexual function. In women, the operation includes removal of the bladder, vagina, uterus, tubes, and ovaries. As a result, women cannot have children and may find intercourse difficult. 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.

The major complications that can occur include infection, heart attack, severe bleeding, and blood clots. After the chemotherapy and radiation therapy treatment, surgery is likely to be more difficult for the urologic surgeon.

Also, there is a somewhat higher risk of complications for you when surgery follows radiation and chemotherapy. Surgery and bladder reconstruction can be more difficult after receiving radiation therapy. If chemotherapy fails to decrease the size of the tumor, your cancer can be more advanced at the time of surgery.

Reproductive Risks

The chemotherapy drugs and radiation in this study may be harmful to a nursing infant or an unborn child. If you are a woman able to have children and have not been surgically sterilized (tubal ligation or hysterectomy), you should have a pregnancy test before enrolling in this study. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you should become pregnant while on study, you must tell your doctor immediately.

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 sexual function for men, and women will not be able to bear children.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with ___bladder cancer in the future. A possible personal benefit of this research study may be a decrease in the size of your tumor and a longer survival, but these benefits are not certain or guaranteed.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be
considered for your condition may include the following: (1) radiation therapy; (2) chemotherapy; (3) surgery; or (4) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread. These treatments could be given either alone or in combination with each other.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY? (June 4, 2004)

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). Your personal information may be disclosed if required by law.

ECOG Patients
Records of patient progress while on the study will be kept in a confidential file at both the Eastern Cooperative Oncology Group (ECOG) and the Radiation Therapy Oncology Group (RTOG).

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (FDA), the National Cancer Institute (NCI) or its authorized representatives, and other groups or organizations that have a role in this study.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization. Medicare should be considered a health insurance provider.

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. If you choose to stop participating in the study,
you should first discuss this with your doctor. In order to provide important information that may add to the analysis of the study, he/she may ask your permission to submit follow-up data as it relates to the study. You may accept or refuse this request. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. (4/18/06)

A group of experts in bladder cancer from the RTOG Genitourinary Committee, the study chairs, and the statistician will be reviewing the data periodically from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

**WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?**

*(This section must be completed)*

For information about your disease and research-related injury, you may contact:

_________________________  __________________________
Name                               Telephone Number

For information about this study, you may contact:

_________________________  __________________________
Name                               Telephone Number

For information about your rights as a research subject, you may contact:

*(OHRP) suggests that this person not be the investigator or anyone else directly involved with the research)*

_________________________  __________________________
Name                               Telephone Number

**WHERE CAN I GET MORE INFORMATION?**

You may call the NCI’s Cancer Information Service at 1–800–4–CANCER (1–800–422–6237) or TTY: 1–800–332–8615.

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (full study plan).

<table>
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<tr>
<th>Patient’s Name</th>
<th>Signature</th>
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<th>Name of Person Obtaining Consent</th>
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ABOUT USING TISSUE FOR RESEARCH

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 remains 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. Your tissue may be helpful for research whether you do or do not have cancer.

The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

All possible methods will be used to ensure your privacy and confidentiality. Identifying information will be taken off anything associated with your tissue/blood before it is given to a researcher. Reports about research done with your tissue/blood 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 for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your tissue 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 and then any tissue that remains will no longer be used for research; or, you may request that your tissue, if any remains, be returned to you or your designee.

In the future, people who do research may need to know more about your health. While___________(doctor/institution) may give researchers reports about your health, your doctor/institution will not give researchers 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 is used for this kind of research, the results will not be put in your health records.

Your tissue will be used only for research. However, the research done with your tissue may help to develop new products in the future. If this occurs, you will not be financially compensated.
**BENEFITS**

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

**RISKS**

**Physical Risks**
Most patients will heal satisfactorily after having surgery or a needle biopsy to remove tissue. Risks and side effects of a biopsy/surgery can include bleeding, pain, delayed healing, possible infection, and rarely, creation of an abnormal opening or passage.

**Social-Economic risks**
There is a very small chance that information from your health records could be incorrectly released. All possible methods will be used to protect your privacy and ensure confidentiality. Unless you have given your specific permission, your ______ (doctor/institution) will not release your personal results or information to third parties such as employers or insurers.

In the case of injury or illness resulting from participating in this research, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

**MAKING YOUR CHOICE**

If you have any questions about the research involving your tissue/blood or about this form, please talk to your doctor or nurse, or call the institution’s research review board at _________ (IRB’s phone number).

Please read each sentence below and think about your choice. After reading each sentence, circle “Yes” or “No”. **No matter what you decide to do, it will not affect your care.**

1. My tissue may be used for the research in the current study.
   - Yes
   - No

2. My tissue may be kept for use in research to learn about, prevent, or treat cancer.
   - Yes
   - No

3. My tissue 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).
   - Yes
   - No

4. Someone from ______ (doctor’s office/institution) may contact me in the future to ask me to take part in more research.
   - Yes
   - No
Participant statement:

I have read and received a copy of this consent form. I have been given an opportunity discuss the information with my doctor/nurse, and all of my questions/concerns have been answered to my satisfaction. My answers above and my signature below indicate my voluntary participation in this research.

_________________________  _______________  _______
Patient's Name                 Signature           Date

Witness statement:

I have explained the information in this consent form to the patient and have answered any questions raised. I have witnessed the patient's signature.

_________________________  _______________  _______
Name of Person Obtaining Consent     Signature           Date
APPENDIX II

KARNOFSKY PERFORMANCE SCALE

100 Normal; no complaints; no evidence of disease
90 Able to carry on normal activity; minor signs or symptoms of disease
80 Normal activity with effort; some sign or symptoms of disease
70 Cares for self; unable to carry on normal activity or do active work
60 Requires occasional assistance, but is able to care for most personal needs
50 Requires considerable assistance and frequent medical care
40 Disabled; requires special care and assistance
30 Severely disabled; hospitalization is indicated, although death not imminent
20 Very sick; hospitalization necessary; active support treatment is necessary
10 Moribund; fatal processes progressing rapidly
0 Dead

ZUBROD PERFORMANCE SCALE

0 Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).
1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).
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 (Karnofsky 50-60).
3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).
4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).
DEFINITION OF TNM

Primary Tumor (T)

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

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 III (continued)
AJCC Staging System, 5th Edition
Bladder

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

HISTOPATHOLOGIC TYPE

The histologic types are:

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

Squamous cell carcinoma

Adenocarcinoma

Undifferentiated carcinoma

HISTOPATHOLOGIC GRADE (G)

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3-4 Poorly differentiated or undifferentiated
APPENDIX IV (5/9/08)

SMALL PELVIC FIELDS

Anterior View

Lateral View
APPENDIX V (5/9/08)

CYSTOSCOPY REPORT FORM

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<tr>
<th>PATIENT NAME</th>
<th>UNIT #</th>
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<th>CYSTOSCOPY DATE</th>
<th>SURGEON</th>
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Specify location/origin of primary (at cyst or TURB)

Visibly complete TURB?  Yes  No

Palpable mass or induration persists after TURB?  Yes  No

Initial largest tumor (diameter):  ≤1 cm  1.1-2.9 cm  3-4.9 cm  ≥5 cm

Does tumor invade prostate or vagina?  Yes  No

Is tumor fixed to pelvic/abdominal wall?  Yes  No

PLEASE COMPLETE THE FOLLOWING TWO DIAGRAMS:

A. TUMOR LOCATION BEFORE TURB

B. POST-TURB: IF MACROSCOPIC TUMOR REMAINS AT END OF PROCEDURE, INDICATE ITS LOCATION. IF NOT, CHECK "NONE."

Diagram of tumor location before and after TURB.