A PHASE I/II TRIAL IN PATIENTS WITH MUSCLE-INVADING BLADDER CANCER OF TRANSURETHRAL SURGERY PLUS TAXOL, CISPLATIN AND BID IRRADIATION FOLLOWED BY EITHER SELECTIVE BLADDER PRESERVATION OR RADICAL CYSTECTOMY AND ADJUVANT CHEMOTHERAPY

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SCHEMA

TRANSURETHRAL SURGERY  \rightarrow  INDUCTION TCI a  \rightarrow  POST INDUCTION RESPONSE EVALUATION

WEEKS 1-3  \rightarrow  WEEK 7
(treatment start 4-6 weeks post TUR)

TUMOR RESPONSE:
T0, Ta, Tcis*

\rightarrow  CONSOLIDATION TCI b
WEEKS 8,9  \rightarrow  OUTPATIENT ADJUVANT CHEMOTHERAPY c

\geq T1**

\rightarrow  RADICAL CYSTECTOMY
WEEK 9  \rightarrow  OUTPATIENT ADJUVANT CHEMOTHERAPY c

\rightarrow  WEEKS 8,9  \rightarrow  (4 cycles) Weeks 21-37

\rightarrow  WEEKS 21-37 or weeks 17-33

* At site distant from the original tumor (Section 11.2.1)
** On rebiopsy, the tumor persists and invades into or beyond the lamina propria

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(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 4-6 hour interval)

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(1.5 Gy small pelvic fields with a 4-6 hour interval)

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Begin 12 weeks post consolidation therapy or 8 weeks following cystectomy. Repeat every 28 days for 4 cycles.

Eligible (See Section 3.0 for details)
Patients with muscle invading carcinoma of the bladder, all histologies. AJC Stages cT2-T4a, cNX or pN0, M0, no histologic evidence of tumor invasion into the stroma of the prostate, no tumor-related hydronephrosis; creatinine clearance ≥ 60ml/minute, platelets ≥ 100,000, Zubrod status ≤ 1, ANC ≥ 1800, adequately functioning bladder, no prior chemotherapy or pelvic RT.

Required Sample Size: 81

11/13/00
4/30/01
Institution #  ______________  
RTOG  99-06  
Case #  ______________  

ELIGIBILITY CHECKLIST - STEP 1 (Induction) (11/13/00)  
(page 1 of 2)

1. Is there histological confirmation of muscle-invading carcinoma of bladder?  
   _____(Y)

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

3. Based upon the results of the cystoscopy, TUR, and other clinical radiographic studies, is the AJCC clinical T classification T2-4a?  
   _____(Y)

4. Is there clinical/radiographic evidence of nodal disease?  
   _____(Y/N)  
   _____(Y) If yes, have the clinically positive nodes been biopsied and found to be negative?

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

6. Does the patient have a history of other malignancies except for nonmelanoma skin cancer, T1a prostate, or in situ cervical cancer?  
   _____(Y/N)  
   _____(Y) If yes, has the patient been disease-free for ≥ 5 years?

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?  
   _____(N)

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 a urologist?  
    _____(Y)

12. Will treatment start within 6 weeks post TUR and endoscopic evaluations?  
    _____(Y)

13. Zubrod Performance status ≤ 1?  
    _____(Y)

14. Hemoglobin ≥ 10mg/dl?  
    _____(Y)

15. WBC ≥ 4 ml (per 1000)?  
    _____(Y)

16. Platelet count ≥ 100 mm³ (per 1000)?  
    _____(Y)

17. ANC ≥ 1.8 mm³ (per 1000)?  
    _____(Y)

(continued on page 2)
Institution #  
RTOG  99-06  
ELIGIBILITY CHECKLIST - STEP 1 (Induction) (11/13/00)  
Case #  

______(Y/N)  18.  Serum creatinine ≤ 1.5 mg %?

______(Y) If no, is serum creatinine ≤ 1.8 mg % and creatinine clearance > 60 ml/min?

______(Y)  19.  Creatinine clearance ≥ 60 ml/min (calculated value is acceptable)?

______(Y)  20.  Bilirubin ≤ 2 mg%?

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 Name

6. Verifying Physician

7. Patient’s ID Number

8. Date of Birth

9. Race

10. Social Security Number

11. Gender

12. Patient’s Country of Residence

13. Zip Code

14. Patient’s Insurance Status

15. Will any component of the patient’s care be given at a military or VA facility?

16. Treatment Start Date

17. Treatment Assignment

Completed by  

Date  

______________________________  

______________________________
Institution # __________________
RTOG 99-06 __________________
ELIGIBILITY CHECKLIST – STEP 2 (Consolidation)

Case # __________________
(assigned for Step 1)

1. Name of institutional person registering case.

2. (Y/N) Is the patient able to continue protocol treatment, i.e., consolidation treatment or radical
cystectomy?

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

4. Patient Name

5. Verifying Physician

6. Patient ID Number

7. What was the pathologic T stage at post induction evaluation? (pT0, pTa, pTci vs. ≥ pT1)

8. Results of bimanual exam (negative, positive, equivocal)

9. Treatment Start Date

Treatment Assignment

Completed by ________________________________          Date __________________________
INTRODUCTION

1.1 Background

As the use of combined modality treatment for muscle invasive bladder cancer has matured, the opportunity for bladder preservation has been developed. Preoperative radiation when combined with cisplatin (CDDP) and/or 5-fluorouracil (5-FU) results in the downstaging to pT0 of a significant proportion of patients.1-4 When transurethral resection of a bladder tumor (TURBT), radiation and multi-agent chemotherapy are combined, complete response rates of 70% have been achieved.1,3, 5 Two newer agents, paclitaxel and gemcitabine, have each shown significant single agent activity against urothelial tumors and both have exhibited higher response rates and acceptable toxicity when used in combination with cisplatin and other agents. Both paclitaxel and gemcitabine are potent radiation sensitizers with practical application of this characteristic in the case of paclitaxel but because of extreme sensitization at very low doses, this has not been clinically useful in the case of gemcitabine in studies to date. This Phase I/II trial based on the RTOG experience in bladder preservation,4, 6 trials from the Massachusetts General2 Hospital and from Paris3 combines aggressive TURBT with twice daily irradiation sensitized with CDDP and with the combination of CDDP and Taxol in an effort to preserve the bladder. Eligible patients have muscle invading bladder cancer, which are not associated with ureteral obstruction. Local therapy is followed by six cycles of adjuvant gemcitabine and cisplatin in combination.

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%.10, 11 Several randomized trials have demonstrated that combination chemotherapy is more effective than single agent chemotherapy in controlling this disease.12-14 Two of the most effective combinations methotrexate, cisplatin, vinblastine (MCV) and methotrexate, vinblastine, Adriamycin® and cisplatin (MVAC) have shown little difference between the two.15 Systemic therapy also increases the likelihood of control of local disease. The first analysis of the MRC/EORTC Intercontinental trial of adjuvant chemotherapy demonstrated an increase from 12% to 33% in the occurrence of pT0 tumors at cystectomy following MCV therapy.16 Gemcitabine and cisplatin has been selected as the combination given the acceptable toxicity17 associated with it. A phase II trial of gemcitabine and cisplatin in advanced measurable bladder cancer has been completed and the results are awaited. A phase III trial of comparing MVAC with gemcitabine plus cisplatin has also been completed. When these studies have been reported, they should provide the necessary rationale for the selection of gemcitabine and cisplatin.

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 chemotherapy TCI involves accelerated hyperfractionation for the tumor with a standard dose schedule for the pelvis. Weekly CDDP and Taxol are included as radiation sensitizers. This schedule draws from the encouraging results of the Royal Marsden Hospital where local control for muscle invading bladder cancer was enhanced by accelerated hyperfractionation.7,8 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.8 These results are currently being tested in a phase III trial13 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.

Radiosensitization by CDDP and paclitaxel at weekly doses of 40 mg/m² of cisplatin and 50 mg/m² of paclitaxel is used throughout. This will be given as 20 mg/m² of cisplatin on the first two days of each treatment week. A similar CDDP schedule has been combined with pelvic irradiation in two large Phase III trials from the Gynecologic Oncology Group (GOG), which have accrued over seven hundred patients. The dose schedule is based on a successful pilot study of cervical cancer patients by Keys and colleagues of Albany Medical College.9 The adjuvant gemcitabine-cisplatin schedule can be administered entirely on an outpatient basis. There is substantial experience with paclitaxel and simultaneous radiation in the treatment of stage III-A/B non-small cell lung cancer with acceptable toxicity.

OBJECTIVES

2.1 To evaluate the safety and tolerance of induction chemo-radiotherapy by Taxol, Cisplatin, and Irradiation (TCI). To be followed by radical cystectomy if the initial tumor response is incomplete or by consolidation.
TCI if the tumor has cleared. Four cycles of outpatient adjuvant gemcitabine-cisplatin chemotherapy is then given. A protocol completion rate of 90% is sought. (11/13/00)

2.2 To evaluate the efficacy of transurethral surgery plus induction TCI in achieving a complete response of the primary tumor when evaluated after completion of induction TCI.

2.3 To examine the value of tumor histopathologic, molecular genetics and DNA flow cytometric parameters as possible significant prognostic factors for initial tumor response and recurrence-free survival. This will require paraffin blocks of the original tumor or 10 unstained slides of all entered patients to be available for RTOG pathology translational studies.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Operable patients whose tumors are primary carcinomas of the bladder and exhibit histologic evidence of muscle 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 a 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 ≥ 10 mg/dl, WBC ≥ 4000/ml, an absolute neutrophil count of ≥ 1800/ml, a platelet count of ≥ 100,000/mm³, a serum creatinine of 1.5 mg% or less, a serum bilirubin of 2.0 mg% or less and a 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 6 weeks following TUR and endoscopic evaluation.

3.1.7 Signed a study-specific informed consent (Appendix I) prior to study entry.

3.2 Ineligibility Criteria (11/13/00)

3.2.1 Evidence of tumor-related hydronephrosis.

3.2.2 A prior or concurrent malignancy of any other site or histology unless the patient has been disease-free for ≥ 5 years except for non-melanoma skin cancer and/or stage T1a prostate cancer or carcinoma in situ of the uterine cervix.

3.2.3 Previous systemic chemotherapy or pelvic radiation therapy.

3.2.4 Patients with pN+ or T4b disease are considered to have unresectable disease.

3.2.5 Judged not to be a candidate for radical cystectomy at on-study.

3.2.6 Evidence of distant metastases or histologically or cytologically proven lymph node metastases.

3.2.7 Receiving any drugs that have potential nephrotoxicity or ototoxicity (such as an aminoglycoside).

4.0 PRE TREATMENT EVALUATION (11/13/00)

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

4.2 Radiologic evaluation including chest x-ray, bone scan (as applicable), abdominal and pelvic CT scans (no more than 6 weeks before treatment start); 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, and magnesium and calcium levels. Pregnancy test in female patients will be done if applicable.

4.4 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

5.1 Registration for Initial Induction Chemoradiotherapy: (11/13/00)
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 (see Section 5.1). 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 HQ via telephone per Section 5.2.1 and through submission of RTOG Form F0 (see Section 12.1).

5.2.4 After completing either radical cystectomy or consolidation TCI therapy, 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 TCI therapy) in week 17 will be promptly submitted to RTOG Headquarters.

6.0 RADIATION THERAPY

All patients will receive the preliminary course of radiotherapy as part of the induction TCI regimen. This regimen will begin within 6 weeks following the TUR and endoscopic evaluation by the RTOG participating urologic surgeon. Patients who qualify for consolidation TCI will receive treatment as described under consolidation radiotherapy (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. Treatment times must be recorded in the daily treatment record.

6.1 Radiotherapy Given During Induction TCI

6.1.2 Treatment Schedule: External beam irradiation, 1.60 Gy, will be given to the pelvis in the a.m. followed by an interfraction period of at least 4-6 hours. During the p.m., 1.50 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 (12.0 Gy).

6.1.3 Target Volumes

6.1.3.1 "Small" Pelvic Fields, (Appendix VI): The patient should void prior to treatment. The field should include all 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 VI.

6.1.3.2 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.

6.1.3.3 Tumor Boost Field (*Appendix VI*): 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 probably 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 TCI

6.2.1 Consolidation TCI will start 7-10 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.

6.2.2 The previously simulated small pelvic field will be treated during the consolidation phase. **During consolidation radiotherapy, the patient must void prior to each treatment.**

6.3 Radiation Dose Specifications

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*). 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. 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 ≥ 6 MeV must be used.

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 (11/13/00)

If a grade 3 hematologic toxicity develops, then chemoradiotherapy should be discontinued for one week. It will be resumed if the WBC returns to 3,500/mm³ or above and the platelet count is 100,000/mm³ or above. If these levels have not been reached after a 1-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 infield (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 Taxol. 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 HQ.

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%.

Deviation: greater than 110%.

6.6.5 Interfraction Interval

Per protocol: all treatments delivered BID with interfraction interval of 4-6 hours.

Variation: no more than one QD treatment delivered during each phase of TCI. Interfraction interval between 3.5 hours and less than 4 hours.

Deviation: more than three QD treatments during either phase of TCI. 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

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

7.1 Induction Chemoradiotherapy with Cisplatin and Taxol

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 Chemotherapy (Cisplatin and Taxol) and Irradiation therapy (TCI) will begin within 6 weeks following the TUR. On days of chemotherapy administration, patients are instructed to increase their fluid intake to at least six 8-oz. glasses of water (or other fluids) over the 12 hours prior to i.v. hydration preceding chemotherapy. The prechemotherapy i.v. hydration should be 0.5 NS, or NS at a rate of 500 cc/hr for one hour.

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

7.1.4 Cisplatin (20 mg/m²), will be administered as a 60 minute infusion on days 1, 2, 8, 9, 15 and 16. The post-cisplatin i.v. hydration should consist of NS of 500 cc in one hour.

7.1.5 Radiation will be given twice a day with a 4-6 hour interfraction interval. On days when both chemotherapy and two fractions of radiation therapy (XRT) are given, the first XRT fraction should be one hour after the completion of the chemotherapy.

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

7.1.7 Four weeks following completion of TCI, a patient will have an evaluation of response as described in Section 7.1.7.1 For patients who have a pT0, Ta, or Tcis response documented by the first response re-evaluation, consolidation therapy will begin within 7-10 days.

7.1.7.2 For operable patients who have a pT1 or worse tumor response, radical cystectomy will be performed within two weeks of the first response re-evaluation.

7.2 Consolidation Chemoradiotherapy for Patients Selected for Bladder Preservation

7.2.1 Taxol (50 mg/m²) and Cisplatin (20 mg/m²), consolidation, will begin within 7-14 days following urologic re-evaluation. See Section 7.1 for hydration guidelines. Dose reductions will be based upon the laboratory results obtained during the previous week. Irradiation should be given one hour after the completion of the chemotherapy. Two daily 1.5 Gy fractions are given to the pelvis with a 4-6 hour interfraction interval.

7.3 Adjuvant Chemotherapy

7.3.1 Outpatient adjuvant chemotherapy consists of Cisplatin (70 mg/m²) as a 60 minute infusion on day 1 of each cycle. The prechemotherapy i.v. hydration should be NS at a rate of 500 cc/hr in one hour. The post cisplatin i.v. hydration should also be NS 500 cc in one hour. Prehydrate with 500 ml NS normal saline over one hour followed by gemcitabine (1000 mg/m²) in 250cc normal saline over 30 minutes followed by cisplatin 70 mg/m2 and (at the discretion of the investigator) mannitol 12.5g in 250 cc normal saline over at least two hours on day one. On days 8 and 15, gemcitabine is given without pre or post hydration. Chemotherapy will begin 4 weeks following the post-consolidation endoscopic evaluation, or 8 weeks following radical cystectomy. This schedule is repeated every 28 days. Patients will receive four cycles of adjuvant chemotherapy.

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 (NOTE: acceptable limits established by the USP Particular Matter Test for LVP’s) have been observed after preparation of paclitaxel. 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 μm in-line filter. In order to maximize radiosensitization of paclitaxel, patients will proceed with pelvic radiation 1½ 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, typhlitis, ischemic colitis, neutropenic enterocolitis, increased liver function tests (SGOT, SGPT, bilirubin, alkaline phosphatase) hepatic failure, hepatic necrosis.
- Heart: Arrhythmias, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, atrial arrhythmia, hypotension, hypertension, lightheadedness.
- Neurological: Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy, sensation of flashing lights, blurred vision, scintillating scotoma.
- Allergy: Anaphylactoid and urticarial reactions (acute), flushing, rash, pruritis.
- Other: Alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration (erythema, induration, tenderness, rarely ulceration), radiation recall reaction.

7.4.6 **Supplier:** Commercially available.

7.5 **Cisplatin (CDPP)**

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

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

7.5.3 **Supplier:** Cisplatin is available commercially.

7.5.4 **Storage:** The intact vials should be stored at room temperature. Once reconstituted, the solution should be kept at room temperature to avoid precipitation. Due to a lack of preservatives, the solution should be used within eight 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. Cisplatin should be given immediately after preparation as a slow intravenous infusion.

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

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

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

7.6.4 Known Side Effects and Toxicities - The primary dose limiting toxicity of gemcitabine is hematological including neutropenia, anemia and thrombocytopenia. This is based on 979 patients in 22 clinical trials with various malignancies. The starting dose range was from 800-1250 mg/m² and most patients received an induction course for seven weeks of weekly treatments followed by four week cycles, three weekly treatments and one week rest. This protocol has no induction course and begins with four week cycles. Ten percent of patients discontinued therapy overall due to toxicity. 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.

7.6.5 Pharmaceutical Data - 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. The dose is usually given over 30 minutes. One-thousand mg vials are reconstituted with 25 cc sodium chloride. It is stored at room temperature until given.

7.7 Dose Modifications for Cisplatin

7.7.1 Modifications of cisplatin for nephrotoxicity during INDUCTION or CONSOLIDATION TCI are listed in the table below:

<table>
<thead>
<tr>
<th>Day 1 Level</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl &gt;60 or serum creatinine ≤ 1.5 mg%</td>
<td>100%</td>
</tr>
<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</td>
</tr>
</tbody>
</table>

7.7.2 Modifications for myelosuppression during CONSOLIDATION TCI are as listed in the table below.

<table>
<thead>
<tr>
<th>ANC (x 1000)</th>
<th>Platelet Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;150K</td>
<td>100</td>
</tr>
<tr>
<td>100-149K</td>
<td>100</td>
</tr>
<tr>
<td>75-99K</td>
<td>75</td>
</tr>
<tr>
<td>&lt;75K</td>
<td>75</td>
</tr>
</tbody>
</table>

ANC = Absolute neutrophil count per ml

7.7.3 Modification of cisplatin for peripheral neurotoxicity grade 3, omit cisplatin (both induction and consolidation).

7.8 Dose Modifications for Taxol

7.8.1 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 (induction and consolidation) will be modified as follows:
<table>
<thead>
<tr>
<th>ANC OR</th>
<th>Platelet Counts</th>
<th>Paclitaxel Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1000</td>
<td>&gt; 75,000</td>
<td>Full Dose</td>
</tr>
<tr>
<td>500-1000</td>
<td>50,000-75,000</td>
<td>50% Reduction</td>
</tr>
<tr>
<td>&lt; 500</td>
<td>&lt; 50,000</td>
<td>Hold Dose</td>
</tr>
</tbody>
</table>

7.8.2 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.

7.8.3 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.

7.8.4 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.

7.8.5 Gastrointestinal Toxicity
If grade 3 or 4 nausea/vomiting or ileus toxicity occur, 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, patient will be removed from protocol therapy. Toxicity must resolve before treatment.

7.8.6 Neurologic Toxicity
In the event of grade 4 neurologic toxicity, paclitaxel will be discontinued. A dose reduction of 25% 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. Patients must return to a toxicity of grade 1 or less before retreatment.

7.8.7 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 administered 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.

7.8.8 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.

7.8.9 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.

7.9 Dose Modification for Adjuvant Gemcitabine and Cisplatin (11/13/00)
7.9.1 Gemcitabine will be given on Days 1,8, and 15 of each 28-day cycle. A cycle is defined as 3 consecutive weeks of treatment followed by a week of rest. A dose of 1000 mg/m² of gemcitabine will
be administered intravenously over 30-60 minutes (preferably 30 min.) on the day of therapy. Calculate the body surface area of the patient according to actual height and weight at the beginning of each cycle.

7.9.2 Cisplatin 70 mg/m² will be given on Day 1 of each 28-day cycle. Cisplatin will be administered following gemcitabine on the day of therapy.

7.9.3 Cisplatin will be administered via a free-flowing intravenous line with an infusion time of at least one hour on Day 1 of each 28 day cycle. Patients will require pretreatment intravenous hydration. The following administration schedule is recommended:

- Prehydrate with 500mL NS normal saline over 1 hour followed by gemcitabine 1000 mg/m² in 250 cc normal saline over 30 minutes followed by cisplatin 70 mg/m² and (at the discretion of the investigator) mannitol 12.5 g i.v. push.
- Post chemotherapy, hydrate with at least 500 mL NS over one hour.

7.9.4 **Dose Adjustments within a Cycle for Gemcitabine (11/13/00)**

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 for Gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.0</td>
<td>≥ 75</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

**CTC Version 2.0**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Percent of Full Dose for Gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 (and Grade 3 nausea/vomiting)</td>
<td>100</td>
</tr>
<tr>
<td>3 (except nausea/vomiting)</td>
<td>50 or Holda</td>
</tr>
<tr>
<td>4</td>
<td>Holda</td>
</tr>
</tbody>
</table>

*aThis decision will depend upon the type of nonhematologic toxicity seen and which course is medically most sound in the judgement of the physician-investigator.

7.9.5 **Dose Adjustments for Subsequent Cycles**

7.9.5.1 The following guidelines should be followed:

- Doses of gemcitabine plus cisplatin cannot be escalated above the starting dose.
- Absolute granulocyte count must be greater than 1.2 x 10⁹/L and platelet count must be greater than 100x10⁹/L to proceed with the next cycle.

7.9.5.2 **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 cisplatin 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/m² to 750 mg/m²) will be allowed in subsequent cycles provided the patient tolerates the initial dose of adjustment.

7.9.5.3 See Tables in Section 7.9.4 for further dosing guidelines.

7.9.5.4 The serum creatinine will be drawn within 24 hours of chemo administration to calculate creatinine clearance. Doses of cisplatin will be adjusted based on Day 1 calculated creatinine clearance according to the following table:

### Renal Toxicity

<table>
<thead>
<tr>
<th>Calculated Creatinine Clearance</th>
<th>% Cisplatin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60 mL/min</td>
<td>100</td>
</tr>
<tr>
<td>≥ 50 to 59 mL/min</td>
<td>50</td>
</tr>
</tbody>
</table>
< 50 mL/min Hold (repeat weekly)

Renal: Dose modifications based on Day 1 of each chemotherapy cycle

Patients who have sustained reduced creatinine clearance of 50 to 59 mL/min and hematologic toxicity sufficient to require a 25% dose reduction of cisplatin should receive a 50% dose reduction of cisplatin.

If criteria for retreatment are not met on Day 1 of the treatment cycle, the creatinine should be repeated weekly. If by 6 weeks from the first infusion of the previous cycle the criteria for retreatment are not met, the patient should be discontinued from the study. If cisplatin is held for any length of time, retreatment should be at 50% dose reduction regardless of the creatinine value.

7.9.5.5 Dose adjustments will be based on signs and symptoms on the day of treatment. If Grade 3 or 4 neurotoxicity occurs, the treatment cycle will be delayed for a maximum of 2 weeks.

7.10 Toxicity Reporting

7.10.1 The revised NCI Common Toxicity Criteria Version 2.0 (3/98) will be used to score chemotherapy and acute radiation (≤ 90 days) toxicities. The RTOG Late Radiation Morbidity Schema (Appendix IV) will be used to score radiation toxicities appearing or persisting beyond 90 days from start of RT. The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol, which uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days.

7.10.1.1 Any ADR which is both serious (life threatening, fatal) and unexpected.
7.10.1.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.
7.10.1.3 Any death on study if clearly related to the commercial agent(s).
7.10.1.4 Acute myeloid leukemia (AML). The report must include the time from original diagnosis to development of AML, characterization such as FAB subtype, cytogenetics, etc. and protocol identification.

7.10.2 The ADR report should be documented on Form FDA 3500 (Appendix V) and mailed to:

Investigational Drug Branch
P.O. Box 30012
Bethesda, Maryland 20824
Telephone (301) 230-2330
available 24 hours
fax (301) 230-0159

8.0 SURGERY

8.1 Pre-Induction Chemoradiotherapy Evaluation: Endoscopic evaluation should include:
8.1.1 Cystoscopy with tumor mapping on the initial Cystoscopic Report (Appendix VII);
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 The First Post-Induction TCI Endoscopic Re-evaluation: This evaluation will take place in week seven following the completion of the induction chemoradiotherapy. Evaluation will include: barbotage cytology, cystoscopy, tumor site TUR biopsy, and bimanual examination after TUR.

8.3 Radical Cystectomy: Operable patients who have a pT1 or worse tumor response on re-evaluation following initial TUR and induction TCI 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 perivesical 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 TCI, 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 TCI, 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 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

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 muscle from the TUR specimen.

10.1.2 Paraffin blocks of the original tumor or 10 unstained slides should be submitted for appropriate pathologic translational studies. The pathology materials, relevant pathology reports, and a completed Pathology Submission Form will be mailed to the RTOG Tissue Bank:

LDS Hospital
Department of Pathology
E.M. Laboratory
8th Avenue & C Street
Salt Lake City, UT 84143
(801) 321-1314
FAX (801) 321-5020
11.0 PATIENT ASSESSMENT

11.1 Study Parameters (11/13/00)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-Study</th>
<th>During Induction TCI</th>
<th>At initial Cystoscopic re-evaluation</th>
<th>During Consolidation TCI</th>
<th>Follow-up evaluation 1st &amp; 2nd year</th>
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<tbody>
<tr>
<td>Body Surface Area</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>H&amp;P</td>
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<td>Zubrod Status</td>
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<tr>
<td>Creatinine Clearance</td>
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<td>Day 1 of each cycle</td>
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<td>Cystoscopy</td>
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<td>Urine Cytology</td>
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<td>Bimanual exam under Anesthesia</td>
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<tr>
<td>Bladder Biopsy</td>
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<tr>
<td>CBC, Platelets, diff</td>
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<td>X</td>
<td>weekly</td>
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<tr>
<td>Serum Creatinine, BUN</td>
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<td>Weekly</td>
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<tr>
<td>CT Scan</td>
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<tr>
<td>IVP</td>
<td>X</td>
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<tr>
<td>Bone Scan</td>
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<td>Chest X-ray</td>
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<td>Bilirubin, Alk Phos.</td>
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<td>(prior to)</td>
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<td>SGOT, LDH</td>
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<td>(prior to)</td>
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<tr>
<td>Magnesium, Calcium</td>
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<td>Pregnancy Test(^a)</td>
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</table>

a. As applicable.
b. Only if cystectomy is not done within the first 6 weeks after consolidation TCI. 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.

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.

11.3 Endpoints

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

- **Complete Response (a CR or a pT0 response)** requires the absence of any tumor in the tumor-site 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.

- **No Response (NR)** requires the continued presence of the tumor 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. Following consolidation TCI, the patient’s bladder will be evaluated by serial cystoscopic re-evaluation as per the schedule in Section 8.4 and Section 11.1.

11.3.2 Patient tolerance and completion of the protocol. The portion of patients completing the planned protocol with no or minor treatment variations will be analyzed with the anticipation that a 90% or greater protocol completion rate will be achieved.

11.3.3 The late or delayed safety or possible toxicity of this combined modality regimen will be evaluated with TCI program and on the absence of treatment-related sequelae in patients treated with either the cystectomy or consolidation programs regarding the pelvis and GI as well as GU function.
### 12.0 DATA COLLECTION

(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)

#### 12.1 Summary of Data Submission

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<tr>
<td>Demographic Form <em>(A5)</em></td>
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<td>Initial Evaluation Form <em>(II)</em></td>
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<td>Diagnostic Pathology Report <em>(P1)</em></td>
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<tr>
<td>Pathology slides/blocks <em>(P2)</em></td>
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<td>Surgical Report <em>(S2)</em></td>
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<td>Preliminary Dosimetry Information:</td>
<td>Within 1 week of start of RT</td>
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<td>RT Prescription <em>(Protocol Treatment Form)</em> <em>(T2)</em></td>
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<tr>
<td>Films <em>(simulation and portal)</em> <em>(T3)</em></td>
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<td>Calculations <em>(T4)</em></td>
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<td>Induction Radiotherapy Form <em>(T1)</em></td>
<td>Within 1 week of RT end</td>
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<td>Final Dosimetry Information:</td>
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<td>Daily Treatment Record <em>(T5)</em></td>
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<td>Isodose Distribution <em>(T6)</em></td>
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<td>Boost Films for consolidation phase <em>(simulation and portal)</em> <em>(T8)</em></td>
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<td>Post Treatment Evaluation Form <em>(F0)</em></td>
<td>Within 8 weeks from start of induction; and within 12 weeks after completion of consolidation chemoradiation.</td>
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<tr>
<td>Post Operative Form <em>(S1)</em></td>
<td>Within 4 weeks of cystectomy <em>(Option 3)</em></td>
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<td>Operative Report <em>(S2)</em></td>
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<td>Pathology Report <em>(S5)</em></td>
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<td>Consolidation Radiotherapy Treatment Form <em>(F4)</em></td>
<td>Within 1 week of end of consolidation RT <em>(Option 2)</em></td>
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<tr>
<td>Study-Specific Flowsheets <em>(SF)</em></td>
<td>Following each cycle of chemotherapy, at termination of treatment and upon observation of ≥ grade 4 toxicity</td>
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<tr>
<td>Initial Follow-up Form <em>(FS)</em></td>
<td>At 13 weeks</td>
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<tr>
<td>Follow-up Form <em>(F1)</em></td>
<td>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.</td>
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<tr>
<td>Autopsy Report <em>(D3)</em></td>
<td>As applicable</td>
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13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint (11/13/00)
Completion and safety of induction chemo-radiotherapy (cisplatin, paclitaxel and irradiation [TCI]) followed by definitive local therapy of either radical cystectomy (for patients for whom the initial tumor is not a complete response) or consolidation TCI (for patients for whom the initial tumor has cleared), followed by four cycles of outpatient adjuvant gemcitabine-cisplatin chemotherapy.

13.1.2 SecondaryEndpoints (11/13/00)
- Complete response after TCI induction
- Completion and safety of the four cycles of gemcitabine-cisplatin chemotherapy
- Invasive local treatment failure (including failure to achieve complete response with induction TCI and including an invasive local relapse after consolidation)
- Distant metastasis
- To examine 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

13.2 Sample Size (11/13/00, 4/30/01)

13.2.1 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. 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 total sample size 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 87% power to detect an increase in the four cycle adjuvant chemotherapy completion rate from 70% to 90% with a significance level of 0.05.

If the treatment sequence is well tolerated, we hypothesize that it will achieve better outcome than the control arm (Arm 2) of RTOG 89-03: With respect to the endpoints in Section 13.1.2. The following 95% confidence intervals are derived from the proposed sample size and the estimates in Arm 2 (cisplatin and RT) of RTOG 89-03. With the complete response rate of 55%, the 95% confidence interval for complete response rate after TCI induction is (40%, 70%). Similarly, based on the invasive local treatment failure rate (48%) and the distant metastasis rate (29%) at 2 years in Arm 2 of RTOG 89-03, the 95% confidence intervals for the invasive local treatment failure rate and distant metastasis rate at 2 years in this study are (33%, 63%) and (15%, 43%) respectively.

13.2.2 Sample Size Amendment
The primary endpoint of this Phase I/II bladder study is protocol completion and safety. On November 13, 2000, the number of cycles of adjuvant chemotherapy was decreased from six to four. This decision was based on a recent study where the patients had difficulty tolerating a six-cycle regimen of gemcitabine and cisplatinum as evidenced by an unacceptable high incidence of grade 3 and 4 hematological toxicities (neutropenia and thrombocytopenia) and renal toxicities (elevated creatinine and BUN levels and edema). This study was originally designed to accrue 48 patients. To clearly answer the completion and safety question for 4 cycles of adjuvant chemotherapy, we increased the sample size to 81 thereby ensuring 48 patients to be accrued after the November 13, 2000 amendment.

13.3 Early Stopping Rules for Severe Toxicity
The 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. We will reject the null hypothesis if 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%.

13.4 Accrual and Duration
Based upon RTOG 97-06, monthly accrual will be approximately two patients so the trial should be completed in two years. For the efficacy of the treatment, 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 2-year rates for the secondary endpoints.

13.5 Analysis Plan
13.5.1 Interim Reports
Interim reports will be prepared every six months until the final analysis. In general, the interim reports will include information about
- Patient accrual rate with projected completion date,
- Pretreatment characteristics of patients accrued,
- Compliance rate of treatment per protocol,
- The frequencies and severity of toxicity due to chemotherapy and radiation therapy.

13.5.2 Final Analysis (11/13/00)
The final analysis will be performed upon the completion of evaluations of patients on protocol. The number of patients who completed TCI induction will be reported as well as the number of patients who completed consolidation TCI or had a cystectomy with four cycles of gemcitabine and cisplatin. The complete response rate will be reported for each treatment phase.
Study primary outcome will be tested using the binomial distribution. If more than 35 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, 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 any, is associated with very large confidence intervals, and thus the interpretation should be very limited. The probabilities of invasive local treatment failure and distant metastasis will be estimated using the cumulative incidence method to provide the efficacy measurement.

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, 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.
REFERENCES


17. Murphy BA, Johnson DR, Smith J, Koch M, DeVore R, Blanke C, Johnson DH: Phase II Trial of Paclitaxel (P) and Cisplatin (C) for Metastatic or Locally Unresectable Urothelial Cancer. Proc ASCO 15:245, 1996


29. Stadler WM, Kuzel TM, Roth B, Raghavan D, Dorr FA. Phase 2 study of single agent gemcitabine in previously untreated patients with metastatic urothelial cancer.


* Added 4/30/01
APPENDIX I

RTOG 99-06

A PHASE I/II TRIAL IN PATIENTS WITH MUSCLE-INVADING BLADDER CANCER OF TRANSURETHRAL SURGERY PLUS TAXOL, CISPLATIN AND BID IRRADIATION FOLLOWED EITHER BY SELECTIVE BLADDER PRESERVATION OR RADICAL CYSTECTOMY AND ADJUVANT CHEMOTHERAPY

SAMPLE CONSENT FOR RESEARCH STUDY

THERE IS A RESEARCH STUDY ABOUT YOUR CONDITION AND ITS TREATMENT. THIS CONSENT FORM WILL TELL YOU ABOUT THIS STUDY AND HOW THE TREATMENT MAY OR MAY NOT HELP YOU.

IT IS IMPORTANT THAT YOU READ AND UNDERSTAND THIS FORM, THE STUDY AND THE TREATMENT BEFORE YOU DECIDE TO BE PART OF THIS STUDY. IF YOU HAVE ANY QUESTIONS ABOUT THIS STUDY, THE TREATMENT OR HOW IT WILL AFFECT YOU, PLEASE ASK YOUR DOCTOR.

RESEARCH STUDY

You have the right to know about the procedures used in this research study and the risks, benefits and alternatives to the treatment in this study. You should know and understand the treatment proposed in this study, how it will be given, how the treatment may help you, how the treatment may harm you, and the choices available to you. This form will tell you about the study, the benefits, the risks and the alternatives so you can decide whether to be a part of this research study.

PURPOSE OF THIS STUDY

This study involves the evaluation of a chemotherapy (anti-cancer drugs: cisplatin and paclitaxel), combined with twice-a-day external radiation therapy and possible removal of your bladder. This treatment is followed by additional chemotherapy (cisplatin and gemcitabine). The drugs are not experimental drugs. They have all been used in the treatment of many patients with tumors such as yours. This study will test whether or not this treatment approach is feasible.

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 usual treatment, chemotherapy and radiation therapy is often advised following surgical removal of the bladder. The study treatment and usual treatment use similar therapies but differ in the sequence of the therapies. They also differ in that bladder removal is advised only if chemoradiotherapy has not resulted in a complete response of your tumor or if the tumor should come back.

DESCRIPTION OF PROCEDURES (11/13/00)

Following the scraping of the surface of your bladder, you will begin treatment with chemoradiotherapy. You will receive the drug (cisplatin) twice each week by injection over one hour into a vein along with special intravenous fluid treatment. You will also receive paclitaxel once a week on the same day as your first cisplatin injection. Each drug will be given over one hour before the first daily radiation treatment. You will receive two radiation treatments each day about 4-6 hours apart. The chemoradiotherapy will take for about 2 ½ weeks to finish (Monday – Friday).

Three weeks after the completion of this first part of your treatment, the urologic surgeon will evaluate your bladder tumor through a fiberoptic scope (a special examining instrument), biopsy, and a repeat of the pelvic CT scan. The results will offer one of the following:

- If the tumor has completely disappeared, you will receive chemotherapy and radiation therapy as before for an additional 10 days. Also, you will then have four months of additional chemotherapy to reduce the chance of cancer spreading to other parts of your body.
If the tumor has not completely disappeared, and you are medically fit for surgery, surgical removal of your bladder within two weeks will be recommended. Also, you will then have four months of additional chemotherapy 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.

Also, at the time of your diagnosis by biopsy, all or some of your tumor was removed. As is usually done, this tissue went to the hospital’s pathology department for routine testing and diagnosis. After that process was complete, the remaining tumor samples were stored in the pathology department. You are being asked for permission to use the remainder of the tumor samples for additional tests. Since this tissue was removed at the time of surgery or biopsy, your permission to use this tissue will not lead to any additional procedures or expense. This tissue will be sent to a central office for review and research investigation associated with this protocol.

RISKS AND DISCOMFORTS

Cancer treatments, whether given in a research study or in the ordinary practice of medicine, may often hurt or harm you (side effects). The treatment used in this study may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

Radiation Therapy may cause loss of pubic hair, skin irritation, diarrhea, frequency of urination possibly with pain or blood, tiredness and nausea. These side effects usually resolve shortly after the treatment has been completed. More serious complications, which rarely occur, may also develop later on. These include intestinal obstruction and/or intestinal bleeding which may require surgery. If surgery is required later, the risks involved may be slightly increased due to the radiation therapy. Radiation therapy to the pelvis will also cause sterility in fertile females and may require the use of hormones given orally (by mouth) to replace the hormones normally produced by the ovaries. Radiation therapy to the pelvis, combined with this chemotherapy will likely cause you to become sterile. In pregnant females, administration of radiation therapy to the pelvis will cause damage to the fetus (unborn child).

Cisplatin (Platinol) may cause nausea, vomiting, weakness, hearing loss or ringing of the ears. It can also cause damage to the kidneys; you will be given extra amounts of fluids and other medications to lessen the risk of kidney injury. It can lower the blood counts and the levels of calcium and magnesium in your blood. It is possible that you may become anemic and require transfusion. Other less common side effects include allergic reactions (sweating, difficulty breathing, and rapid heart beat), and numbness and tingling in fingers and toes. Rarely the drug causes restlessness, facial swelling, loss of coordination, involuntary movement, liver damage, loss of taste, spasm, muscle cramps or acute leukemia.

Paclitaxel (Taxol) commonly causes a lowering of blood counts, which could lead to an increased risk of infection, weakness and fatigue, or bleeding complications. You might need treatment with antibiotics, require hospitalization, and need transfusions if these problems are severe. Other possible side effects include nausea, mouth sores, hair loss, muscle aches, joint pains, visual loss, and fatigue. There is the possibility of skin irritation should paclitaxel leak from your vein into the surrounding skin. Paclitaxel can rarely cause a severe allergic reaction resulting in the development of a rash, difficulty breathing, and low blood pressure. Medication will be given prior to treatment in an effort to prevent this type of reaction. If you are treated with a high dosage or for a prolonged period, you may experience numbness of the hands and feet. Taxol can occasionally cause a slowing of the heart rhythm, or an irregular heart rhythm, but only rarely does it cause symptoms that you would notice. In addition, paclitaxel may increase the risks of radiation as listed above.

Gemcitabine The most common side effect of gemcitabine is decreased blood counts, usually white blood cells but also red blood cells and platelets. This can lead to an increased risk for infection, fatigue, and bleeding. Other toxicities include mild liver irritation, rare decrease in kidney function, swelling, nausea, vomiting, skin rash, constipation, diarrhea, fever, hair loss, pain, shortness of breath and sores in the mouth. While the decrease in blood cells can occur in up to one in four people, the other side effects may occur in less than one in twenty people.

If, after the full chemoradiotherapy treatment, the tumor recurs or reappears locally in the bladder, surgical removal of your bladder may be recommended, provided that there is no evidence of cancer spreading to any of your other organs. There is a low risk of tumor progression during either the initial or second course of chemoradiotherapy as compared to immediate surgical excision of your bladder.
**Risks of Surgery:** If surgical excision is necessary, this results in the removal of your bladder and other organs. In the male, 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. Also during surgery, a permanent opening (stoma) is created in the abdomen and a bag placed over it to collect the urine. The major complications which can occur are those of any other major surgery including 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.

Your physician will be checking you closely for these side effects. Side effects usually disappear after the treatment is stopped. In the meantime, your doctor may prescribe medication to keep these side effects under control.

This study may be harmful to an unborn child. Sufficient medical information is not available to determine whether the study treatment administered to a pregnant woman causes significant risks to the fetus. If you are a woman of childbearing age and have not been surgically sterilized (tubal ligation or hysterectomy), you should have a pregnancy test before enrolling in this study. You must use adequate birth control measures to prevent pregnancy while participating 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 this study, you must tell your doctor immediately.

**COSTS**

Routine blood tests and scans will be done to evaluate the effects of treatment. There may also be laboratory testing and procedures required by this study for research purposes. These additional tests may increase your medical bills although the impact will be dependent on your insurance company. If injury occurs as a result of this research, treatment will be available. The use of medication to help control side effects could result in added costs. This institution is not financially responsible for the treatment of side effects caused by the study treatment. You will not be reimbursed for medical care other than what your insurance carrier may provide. You will not be paid for your participation in this research study.

**CONTACT PERSONS**

(This section must be completed)

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

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<tr>
<th>Name</th>
<th>Telephone Number</th>
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For information about this study, you may contact:

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

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

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</tr>
</tbody>
</table>

**ALTERNATIVES**

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. You should discuss your condition and the expected outcome with your doctor. Your doctor will be available to answer any questions. You are encouraged to ask your doctor any questions you have about this research study and the choices of treatment available to you. If you have any questions at all, please ask your doctor.

If your disease becomes worse, if side effects become very severe, or if developments occur that indicate the research study is not in your best interest, the treatment would be stopped. Further treatment would be discussed at that time.

**BENEFITS**

It is not known whether the treatment you will be given in this research study will help your condition more than the standard treatment for this disease would. The information from this study may also help others by providing information about your type of cancer and its response to treatment. The information will be used scientifically. A possible personal benefit of this research study may be a decrease in the size of your tumor and a longer survival. None of these possible benefits is certain or guaranteed.

**VOLUNTARY PARTICIPATION**

You do not have to take part in this research study. You are free to withdraw or withhold your consent from taking part in this research study at any time. If you refuse to participate, there will be no penalty or loss of benefits. You may seek care from a doctor of your choice at any time. If you do not take part in this study or if you withdraw from the study, you will continue to receive care.

**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). The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (FDA), the National Cancer Institute (NCI), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study may have access to medical records that contain your identity. However, no information by which you can be identified will be released or published.

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.

Patient Signature (or legal Representative)  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).
APPENDIX III

AJCC Staging System, 5th Edition
Bladder

DEFINITION OF TNM

Primary Tumor (T)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Ta</td>
<td>Noninvasive papillary carcinoma</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ: &quot;flat tumor&quot;</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades subepithelial connective tissue</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscle</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumor invades superficial muscle (inner half)</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumor invades deep muscle (outer half)</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades perivesical tissue</td>
</tr>
<tr>
<td>T3a</td>
<td>microscopically</td>
</tr>
<tr>
<td>T3b</td>
<td>macroscopically (extravesical mass)</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor invades the prostate, uterus, vagina</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor invades the pelvic wall, abdominal wall</td>
</tr>
</tbody>
</table>

Regional Lymph Nodes (N)

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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single lymph node, 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>N2</td>
<td>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</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node more than 5 cm in greatest dimension</td>
</tr>
</tbody>
</table>

Distant Metastasis (M)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

STAGE GROUPING

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0a</td>
<td>Ta</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>0is</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>III</td>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
</tr>
</tbody>
</table>
APPENDIX III

AJCC Staging System, 5th Edition
Bladder
(continued)

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
   *The predominant cancer is a transitional cell carcinoma*

HISTOPATHOLOGIC GRADE (G)

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

ADVERSE REACTION REPORTING GUIDELINES

A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. When a protocol toxicity requires special handling, study-specific reporting procedures supercede the General Guidelines.

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman. In the absence of the Group Chairman, the report should be made to the Headquarters Data Management Staff (215/574-3214). When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.

2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.

3. A written report containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).

4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures.

5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

A copy of all correspondence submitted to NCI, or to another Cooperative Group (in the case of RTOG-coordinated intergroup studies) must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.

7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.

8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

2. All life-threatening (grade 4) toxicities resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS
An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

**Known** toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert. **Unknown** toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

### Commercial and Non-Investigational Agents

i. Any fatal (grade 5) or life threatening (grade 4) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. **Known** grade 4 hematologic toxicities need not be reported by telephone.

ii. Unknown adverse reactions (> grade 2) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.

iii. All neurotoxicities (> grade 3) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.

iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is a reasonable suspicion that the effect is due to protocol treatment.

### Investigational Agents

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

Investigational Drug Branch (IDB)
P. O. Box 30012
Bethesda, MD 20824
Telephone number available 24 hours
(301) 230-2330 FAX # 301-230-0159

i. **Phase I Studies Utilizing Investigational Agents**

- All deaths during therapy with the agent. Report by phone within 24 hours to IDB and RTOG Headquarters. **A written report to follow within 10 working days.**

- All deaths within 30 days of termination of the agent. As above

- All life threatening (grade 4) events which may be due to agent. As above
- First occurrence of any toxicity (regardless of grade). Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters.
  **A written report may be required.**

ii. **Phase II, III Studies Utilizing Investigational Agents**

  - All fatal (grade 5) and life threatening (grade 4) **known** adverse reactions due to investigational agent.
  - All fatal (grade 5) and life threatening (grade 4) **unknown** adverse reactions resulting from or suspected to be related to investigational agent.
  - All grade 2, 3 **unknown** adverse reactions resulting from or suspected to be related to investigational agent.

**A written report must be sent to RTOG within 10 working days with a copy to IDB. (Grade 4 myelosuppression not reported to IDB)**

- All fatal (grade 5) and life threatening (grade 4) unknown adverse reactions resulting from or suspected to be related to investigational agent.

- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent.

**Report by **phone** to RTOG Headquarters and the Study Chairman within 24 hours

**A written report must be sent to RTOG within 10 working days with a copy to IDB.**

**See attached (if applicable to this study) NCI Adverse Drug Reaction Reporting Form**