RADIATION THERAPY ONCOLOGY GROUP
RTOG 95-06

A PHASE I/II TRIAL OF TRANSURETHRAL SURGERY PLUS INDUCTION CHEMORADIOThERAPY FOLLOWED EITHER BY SELECTITIVE BLADDER PRESERVATION OR RADICAL CYSTECTOMY AS DETERMINED BY INITIAL RESPONSE AND OPERABILITY IN PATIENTS WITH MUSCLE-INVADING BLADDER CANCER

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Activation Date:  April 28, 1995

CLOSURE DATE:  December 1, 1996

TERMINATION DATE:  November 5, 2013

Current Edition:  October 1, 1996  Includes Revisions 1-3

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SCHEMA

TRANSURETHRAL SURGERY → INDUCTION CFI \(^a\) → RESPONSE EVALUATION

WEEKS 1 and 3 (out-patient)
WEEK 8

CR or < CR (medically inoperable patients)

CONSOLIDATION CFI \(^b\) (within 7-10 days of evaluation)

< CR (operable)

RADICAL CYSTECTOMY

WEEK 10

INDUCTION CFI

a. AGENT

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CONSOLIDATION CFI

b. AGENT

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TOTAL DOSES

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<th>CISPLATIN</th>
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<th>XRT</th>
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<td>90 mg/m²</td>
<td>2400 mg/m²</td>
<td>24 Gy (pelvis)</td>
</tr>
<tr>
<td>CONSOLIDATION CFI</td>
<td>90 mg/m²</td>
<td>2400 mg/m²</td>
<td>20 Gy (bladder)</td>
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<tr>
<td>TOTAL</td>
<td>180 mg/m²</td>
<td>4800 mg/m²</td>
<td>44 Gy</td>
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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 hydronephrosis; creatinine clearance ≥ 60ml/minute, platelets ≥ 100,000, Karnofsky status ≥ 70, no prior chemotherapy or pelvic RT.

Required Sample Size: 30

10/13/95
1. Has the patient been diagnosed to have carcinoma of the bladder?
2. Is there histologic verification of muscle invasion?
3. Is there evidence of hydronephrosis?
4. What is the AJCC clinical T classification based upon the results of the cystoscopy TURBT, and other clinical radiographic studies?
5. Will treatment start within 4 weeks of endoscopic evaluations and TURBT?
6. Based on the urologist's, medical oncologist's and radiation therapist's opinions, is the patient able to tolerate chemotherapy and pelvic irradiation?
7. Is the patient considered medically operable in the event a cystectomy is necessary?
8. Based on clinical/radiographic assessments, is there evidence of nodal disease?
   - If yes, have the clinically positive nodes been biopsied and found to be negative?
9. Does the patient have distant metastasis?
10. Is the patient receiving any potentially nephrotoxic or ototoxic drugs including aminoglycosides?
11. Has the patient had any prior systemic chemotherapy or pelvic irradiation?
12. Has the patient had any concurrent or second malignancy except for nonmelanoma skin cancer, T1a prostate, or in situ cervical cancer?
   - If yes, has the patient been disease-free for ≥ 5 years?
13. Patient's age?
15. Hemoglobin results.
16. WBC (ml) per 1000.
17. Platelet count (mm$^3$) per 1000.
18. ANC (mm$^3$) per 1000.
Institution # ____________
RTOG 95-06 ELIGIBILITY CHECK - STEP 1 (Induction)
Case # ____________ (page 2 of 2)

19. Serum creatinine (mg %).
   ______(≤ 1.5)
20. Creatinine clearance (ml/min)
   ______(≥ 60)
21. Bilirubin (mg%)
   ______(≤ 2)
22. Has the patient signed a study-specific informed consent?
   ______(Y)

_________________________ Patient's Name
_________________________ Verifying Physician
_________________________ Patient ID #
_________________________ Referring Institution
_________________________ Medical Oncologist
_________________________ Birthdate
_________________________ Sex
_________________________ Race
_________________________ Social Security Number
_________________________ Zip Code (9 digit if available)
_________________________ Method of Payment
_________________________ Treatment Start Date (3-4 weeks post TUR)
_________________________ Treatment Assignment

Completed by ______________________________ Date ____________________________
RTOG 95-06  ELIGIBILITY CHECK - STEP 2

Case # ____________________________
(assigned for Step 1)

_____(Y)  1. At the time of re-evaluation (following induction chemoradiation) has the patient been determined to have a treatment response?

_____(Y)  2. Is the patient able to continue protocol treatment, i.e., consolidation or radical cystectomy?
   (If no, call RTOG HQ to "discontinue the case; provide reason ________________)

_____(Y/N) 3. Was the patient re-biopsied?
            ______ If yes, what was the results of the biopsy? (negative or positive)

____  4. Results of urine cytology?
       (negative, positive, atypical/suspicious, not done)

____(N)  5. Evidence of distant metastasis?

____  6. Results of pelvic CT?
       (negative, positive, equivocal, not done)

____  7. Results of bimanual exam (negative or positive).

____  8. What phase of consolidation treatment are you planning to proceed with?
       (chemoradiation or radical cystectomy)

_________________________ Patient Name

_________________________ Verifying Physician

_________________________ Patient ID Number

_________________________ Result of Biopsy (negative or positive)

_________________________ Treatment Start Date (consolidation treatment)

_________________________ Treatment Assignment

Completed by ___________________________    Date ________________
1.0 INTRODUCTION

This phase I/II trial is similar to and based on RTOG experience with chemoradiotherapy induction and selective bladder preservation on RTOG protocols 85-12, 88-02, and 89-03, the National Bladder Cancer Group protocol 8, and MGH selective bladder preserving protocols including a recent CFI pilot and especially the pilot institutional study by the University of Paris Group at Hopital de Necter. This regimen, which now combines both Cisplatin and 5-FU in the induction chemoradiotherapy program, is judged to be optimal for our group to evaluate for several reasons:

1.1 5-Fluorouracil has been shown by several phase II studies to be potentially effective in combination with radiotherapy against primary bladder cancer.

1.2 The CFI program is judged to be considerably less myelosuppressive unlike the recently closed RTOG 89-03. The full chemotherapy and radiation therapy compliance was only 40% for the neoadjuvant chemo-radiotherapy Arm I in RTOG 89-03. The chemotherapeutic program from the CFI pilot regimen by University of Paris Group was tolerated satisfactorily on an outpatient basis. This regimen will encourage accrual within the RTOG.

1.3 The complete response rates to the CFI induction program from the University of Paris was 70%, as high as any other phase II study. Their results also included pathological confirmation in all 18 of the clinical complete responding patients who underwent immediate radical cystectomy. The Paris group also reported that urinary diversion by an ileal neo-bladder was satisfactory in 4 of 5 patients undergoing this type of urinary diversion.

1.4 The high dose twice a day pelvic fractions given twice a week has previously been piloted by the RTOG with satisfactory acute and long term tolerance.

1.5 The eligibility criteria will exclude patients with larger bulkier clinical stage T4b tumors and those with hydronephrosis. Those with hydronephrosis are known to have had a low complete response rate to induction chemotherapy.

1.6 Better tolerance should allow for the subsequent administration of systemic multidrug adjuvant chemotherapy of three cycles following completion of the treatment of the primary disease, if this initial RTOG pilot allows adequate accrual and completion rates. We judge that this systemic adjuvant approach of three cycles, if subsequently shown to be feasible, may be the safest and most effective form of systemic chemotherapy to be tested in a subsequent comparative randomized trial.

2.0 OBJECTIVES

2.1 To evaluate the safety and tolerance for induction chemoradiotherapy by CFI to be followed by radical cystectomy if the initial tumor response is incomplete and the patient is suited for cystectomy, or by consolidation CFI if the tumor has cleared and/or if the patient is not suited for cystectomy. A protocol completion rate of 90% is sought.

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

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

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 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 only mucosal involvement of the prostatic urethra with transitional cell cancer that was visibly complete resected and no evidence of stromal invasion.
of the prostate are eligible.

3.1.2 Patients must have a thorough evaluation by a urologist and have undergone as thorough a transurethral resection of the bladder tumor as is judged safely possible. (10/13/95)

3.1.3 Patients must be considered able to tolerate systemic chemotherapy combined with pelvic radiation therapy by the joint agreement of the participating Urologist, Radiation Oncologist and Medical Oncologist.

3.1.4 Patients must have signed a study-specific informed consent (Appendix I).

3.1.5 Patients must have a Karnofsky performance status of $\geq 70$ (Appendix II).

3.1.6 Patients must have a hemoglobin $\geq 10$ mg/dl, WBC $\geq 4000$/ml, an absolute neutrophil count of $\geq 1800$/ml, a platelet count of $\geq 100,000$/mm$^3$, 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.

3.1.7 Patients must have had no prior pelvic radiation therapy or systemic chemotherapy.

3.1.8 Patients must have no evidence of distant metastases and no histologically or cytologically proven lymph node metastases.

3.1.9 Patients must not be receiving any drugs that have potential nephrotoxicity or ototoxicity (such as an aminoglycoside).

3.1.10 Patients must be $\geq 18$ years old.

3.1.11 Protocol treatment to begin 3-4 weeks following TUR and endoscopic evaluation.

3.1.12 Patients who are considered unresectable due to other medical condition (medically inoperable) are eligible.

3.2 Ineligibility Criteria

3.2.1 Evidence of hydronephrosis.

3.2.2 A prior or concurrent malignancy of any other site or histology unless the patient has been disease-free for greater than 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 Karnofsky performance status < 70.

3.2.4 Previous systemic chemotherapy or pelvic radiation therapy.

3.2.5 Hemoglobin of less than 10 mg/Dl, an absolute neutrophil count of less than 1800, WBC < 4000, a platelet count of < 100,000 mm$^3$, a serum creatinine of > 1.5 % mg, or a creatinine clearance of < 60 ml/minute.

3.2.6 Unresectable disease

4.0 PRE TREATMENT EVALUATION

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 scan, and IVP if indicated. 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.

4.3 Laboratory studies to include CBC, platelet count, alkaline phosphatase, SGOT, LDH, bilirubin, BUN, creatinine, urinalysis, 24 hour creatinine clearance, and magnesium and calcium levels. Serum PSA in male patients; pregnancy test in female patients as applicable.

4.4 Cystoscopic evaluation by a urologic surgeon including 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. (10/13/95)

5.0 REGISTRATION

5.1 Registration for Initial Induction Chemoradiotherapy:

Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG Headquarters at (215) 574-3191, Monday through Friday 8:30 am to 5:00 pm ET. The patient will be registered to treatment and a case number will be assigned and confirmed by mail. The following information must be provided:

- Institution Name & Number
5.2 **Post-Induction Registration:**
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 (215) 574-3191. 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,
- presence/absence of distant metastases,
- results of re-biopsy of the bladder,
- results of bimanual examination,
- results of urine cytology *(negative, atypical, suspicious, or positive)*,
- results of repeat pelvic CT scan,
- date of commencement of the consolidation phase of the treatment.

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 as per Section 5.2.1

6.0 **RADIATION THERAPY**
All patients will receive the preliminary course of radiotherapy as part of the induction CFI regimen. This regimen will begin 3-4 weeks following the TUR and endoscopic evaluation by the RTOG participating urologic surgeon. Patients who qualify for consolidation CFI 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 intersession interval of 4 hours or more. Treatment times must be recorded in the daily treatment record.

6.1 **Radiotherapy Given During Induction CFI**

6.1.2 *Treatment Schedule:* External beam radiation in 3 Gy fractions will be given to the small pelvic fields in two fractions per day *(separated by at least 4 hours)* on days 1,3,15 and 17. Patients will receive 6 Gy per day on days 1 and 3 during the course of infusional cisplatin and 5-FU. The procedure will be repeated on days 15 and 17.

6.1.3 *Target Volumes* (*"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 barium in the rectum. The combination of four shaped anterior, posterior and lateral fields will be used. The pelvic fields will extend 1.0cm inferiorly relative to the lower pole of the obturator foramen and superiorly for distance of 13 to 14cm to just below the sacral promontory or just below the S1-L5 disc on the AP projection. The anterior and posterior pelvic field widths will extend 1.5cm lateral to the bony margin of the pelvis at its widest point and will have shaped inferior corner blocks 3 to 4cm on a side which will shield the medial border of the femoral heads. For the two parallel opposed lateral fields,
the anterior boundary of the field will be 1.5cm anterior to the most anterior portion of the bladder mucosa seen on the air contrast cystogram. Posteriorly, these fields should extend at least 2.5cm posterior to the most posterior portion of the bladder or 2.5cm posterior to the bladder tumor mass if it is palpable or present on the pelvic CT scan. Inferiorly these lateral fields should be shaped with corner blocks to shield tissue outside the symphysis anteriorly and to block the entire anal canal posteriorly. Superiorly these lateral pelvic fields should be blocked anteriorly to exclude any portion of the bowel and anterior rectus fascia not needed to be included because it 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 fields relative to the paired lateral fields (i.e., Ant: Post: Paired lateral is 1:1:1 weighted as equal tumor doses at point of intersection of central axes of the four fields.) In some women, a bladder cystocele may protrude below the lower border of the obturator foramen. In some patients a bladder diverticulum may protrude below the lower border of the obturator foramen. In some patients the bladder may herniate through the abdominal wall. In each of these situations appropriate changes in the fields for these unusual anatomic variations will be required. Finally if the patient has a significant post-void residual the size of the bladder at simulation should be appropriately changed to be certain of its inclusion in the target volume.

6.1.4 Radiation Doses: The induction radiotherapy course will deliver 24 Gy to the small pelvic fields. The radiation given during the consolidation CFI treatment will be 20 Gy to the bladder and the primary tumor. This will result in a total dose to the bladder and tumor volume of 44 Gy over 10-11 weeks in 16 fractions and a total dose to the pelvic lymph nodes 24 Gy in 2.5 weeks in 8 fractions.

6.2 Radiation Therapy During Consolidation CFI

6.2.1 Consolidation CFI will start 7-10 days following a cystoscopic re-evaluation demonstrating a complete response to the induction therapy or less than a complete response in patients unsuitable for a cystectomy. 2.5 Gy (per fraction) will be given to the pelvis in two treatment fractions per day during days 1,3,15 and 17 of the consolidation.

6.2.2 The entire bladder will be treated during the consolidation phase including the bladder and the tumor volume which will be derived from the information available from the bimanual exam and other diagnostic radiographic and surgical information. This will include the information on the initial Cystoscopic Report Form and on the initial pelvic CT scan. This bladder boost is probably best achieved by shaped paired lateral fields on high energy linear accelerators or using a 4-field approach. In either instance this target volume including the bladder and the tumor should be designed using a simulator with 40-50ml of air and dye in the bladder to allow for appropriate quality assurance. Patients should be treated with his or her bladder empty. A 2.0cm margin beyond the tumor volume should be used as the Planning Target Volume (PTV). During consolidation radiotherapy, the patient must void prior to each treatment.

6.3 Critical Structure Dose

The maximum dose allowed to the posterior wall of the rectum shall be 37 Gy and to the femoral heads should be 30 Gy.

6.4 Treatment Interruption

Modifications of the radiation treatment schedule for intestinal toxicity during the consolidation CFI are shown in Section 7.2.4. If a grade 3 hematologic toxicity develops (platelets less than 50,000 cells/mm³ or WBC less than 2,000 cells/mm³), then chemoradiotherapy should be discontinued for one week and 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 do 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. Toxicities related to radiation therapy to the pelvic soft tissue such as urinary frequency, dysuria, hematuria, nausea or diarrhea that do not respond to appropriate medications will be an indication for a delay in the chemoradiation therapy of one or more weeks as is necessary.

If the radiation dose fraction size has to be reduced for diarrhea, additional radiation therapy
will be given on days 21 and 23 without chemotherapy but using the b.i.d. schedule to make up the total dose that the bladder receives to 44 Gy.

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 CFI with Cisplatin and 5-Fluorouracil**

Body surface area calculations will be based on ideal body weight or actual body weight, whichever is less.

7.1.1 **Treatment Schema:** Cisplatin, 5-Fluorouracil, and Irradiation (CFI) therapy will begin 3-4 weeks following the completion of the TUR. On days of chemotherapy administration patients are instructed to increase their p.o. 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 pre-chemotherapy i.v. hydration should be 5% Dextrose or 0.5 NS at a rate of 200cc/hr for 1 hour. 5-FU (400 mg/m²/d) is administered by direct i.v. push followed by cisplatin (15 mg/m²/d), as a 1 hour infusion on days 1,2,3,15,16 and 17. Post-chemotherapy i.v. hydration should include 5% Dextrose or 0.5 NS of 150cc in 45 minutes. On days when both chemotherapy and two fractions of radiation therapy (XRT) are given (days 1,3,15 and 17), the first XRT fraction should be 1.5 hours after the completion of the chemotherapy (a 1 to 3 hour interval is permissible). Before and after cisplatin anti-emetic regimens are recommended which may include ondansetron, granisetron, metoclopramide, lorazepam, dexamethasone, diphenhydramine hydrochloride and/or prochlorperazine. Radiation will be given twice a day with a 4 hour interfraction interval on days 1,3,15 and 17 in two 3 Gy doses to small pelvic fields. (10/13/95)

Within 4-5 weeks following completion of the last dose of CFI all patients will have an evaluation of response as described in Section 6.2.1.

7.1.2 **Cisplatin Dose Modifications for Nephrotoxicity** during the second course beginning day 15 are as follows: For a serum creatinine of 1.5 mg/dl or less 15mg per m² will be given. For a serum creatinine of 1.6 to 1.7 and no more than 1.33 of baseline, 10mg per m² will be given. For a serum creatinine of 1.8 or more or more than 1.5 times base line, cisplatin will be omitted.

7.2 **Consolidation CFI for patients selected for bladder preservation**

7.2.1 **Treatment Schema:** This treatment should be planned to begin in 7-10 days following cystoscopic re-evaluation. The doses of Cisplatin and 5-FU will be the same as given during induction CFI. Thus, this will be on consolidation days 1,2,3,15,16 and 17. Laboratory parameters as outlined in Section 11.1 will be done the preceding week.

For patients who have a complete response documented by urologic re-evaluation or for patients who are unsuited for cystectomy who have less than a complete response consolidation CFI therapy will begin within 7-10 days. Using the same guidelines, Cisplatin (15mg/m²/d) and 5-Fluorouracil (400mg/m²/d) will be administered by short infusion. This will be given on consolidation days 1,2,3,15,16 and 17. Irradiation should be given 1.5 hours after the completion of the chemotherapy (1 to 3 hours is permissible) with a 4 hour interfraction interval beginning in two 2.5 Gy fractions to the tumor volume and the urinary bladder on days 1,3,15 and 17.

For operable patients who have less than a complete response, radical cystectomy will be performed within two weeks of the urologic re-evaluation.

7.2.2 **Modifications of cisplatin and 5-fluorouracil for myelosuppression** during consolidation CFI are as listed in the table below.

**Table 1**

Dose Modification of Cisplatin (C) and 5-Fluorouracil (5-FU) for Myelosuppression during CONSOLIDATION CFI (% of initial calculated dose)

<table>
<thead>
<tr>
<th>ANC (x 1000)</th>
<th>Platelet Count</th>
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</thead>
<tbody>
<tr>
<td>&gt;150K</td>
<td>100-149K</td>
</tr>
<tr>
<td>&gt; 1.6</td>
<td>C-100</td>
</tr>
<tr>
<td>5FU-100</td>
<td>5FU-100</td>
</tr>
<tr>
<td>ANC (x 1000)</td>
<td>Platelet Count</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------</td>
</tr>
<tr>
<td>1.4-1.6</td>
<td>C-100 5FU-100</td>
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<tr>
<td></td>
<td>C-100 5FU-75</td>
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<tr>
<td></td>
<td>C-100 5FU-50</td>
</tr>
<tr>
<td>&lt; 1.0</td>
<td>C-75 5FU-75</td>
</tr>
<tr>
<td></td>
<td>C-75 5FU-50</td>
</tr>
<tr>
<td></td>
<td>C-75 5FU-0</td>
</tr>
</tbody>
</table>

ANC = Absolute neutrophil count per ml

7.2.3 Modifications of cisplatin and 5-FU for nephrotoxicity during consolidation CFI are listed in the table below.

**Table 2**
Dose Modification of Cisplatin (C) + 5-Fluorouracil (5-FU) for Nephrotoxicity during CONSOLIDATION CFI (% of initial calculated dose)

<table>
<thead>
<tr>
<th>Serum Creatinine (mg/dl)</th>
<th>% calculated dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.5</td>
<td>C-100 5-FU - 100%</td>
</tr>
<tr>
<td>1.6 or 1.7</td>
<td>C - 75 5-FU - 100%</td>
</tr>
<tr>
<td>(or &gt; 1.33 x baseline)</td>
<td></td>
</tr>
<tr>
<td>&gt; 1.7</td>
<td>C - 0 5-FU - 100%</td>
</tr>
<tr>
<td>(or 1.5 x baseline)</td>
<td></td>
</tr>
</tbody>
</table>

7.2.4 Modifications of cisplatin 5-FU and radiation therapy for gastrointestinal toxicity (see page 21) experienced during CFI are listed in the table below.

**Table 3**
Dose Modification of C, 5-FU and XRT for Gastrointestinal Toxicity during CONSOLIDATION CFI (% of initial calculated dose)

<table>
<thead>
<tr>
<th>Grade</th>
<th>% calculated dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>C-100% 5-FU -100%</td>
</tr>
<tr>
<td></td>
<td>XRT - 100%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>C - 75% 5-FU - 75% - 3 days</td>
</tr>
<tr>
<td></td>
<td>XRT - 1.5 Gy b.i.d*</td>
</tr>
<tr>
<td>Grade 3</td>
<td>C - 75% 5-FU - 50% - 3 days</td>
</tr>
<tr>
<td></td>
<td>XRT - 1.5 Gy b.i.d*</td>
</tr>
</tbody>
</table>

* only decreased for diarrhea, not stomatitis

If the radiation dose fraction size has to be reduced for diarrhea, additional radiation therapy will be given on days 21 and 23 without chemotherapy but using the b.i.d. schedule to make up the total dose that the bladder receives to 44 Gy.

7.2.5 Modification of cisplatin for peripheral neurotoxicity (see page 22): grade 3, omit cisplatin.
5-Fluorouracil (5-FU)

7.3.1 **Dose Formulation:** 5-FU is available in 10-ml ampules, as a colorless to faint yellow aqueous solution containing 500 mg 5-FU, with pH adjusted to approximately 9.0 with sodium hydroxide. Administration of 5-FU should be only by the intravenous route taking care to avoid extravasation.

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

7.3.3 **Supplier:** 5-FU is available commercially.

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

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

Cisplatin (CDPP)

7.4.1 **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.

7.4.2 **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.

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

7.4.4 **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 reconstituenton. 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.

7.4.5 **Side Effects and Toxicity:** Includes 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.

7.5 Adverse Reaction Reporting

7.5.1 The following ADR’s attributed to commerical agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, and to the Study Chairman within 10 working days:

7.5.1.1 Any ADR which is both serious (life threatening, fatal) and unexpected.
7.5.1.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.
7.5.1.3 Any death on study of clearly related to the commercial agent(s).
7.5.1.4 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.

7.5.2 The ADR Report should be documented on Form FDA 3500 and mailed to the address on the form and to:

Investigational Drug Branch (IDB)
Box 30012
Bethesda, MD 20824
(301) 230-2330 (24 hours)
fax # (301/230-0159)

8.0 SURGERY

8.1 Pre-chemoradiotherapy evaluation: Endoscopic evaluation should include:

8.1.1 Cystoscopy with tumor mapping on the Initial Evaluation Form (I1).
8.1.2 Transurethral resection (TUR) of the tumor as thoroughly as is judged safely possible. Tumor specimens should be sent to pathology and to the urologic research lab for genetic evaluation;
8.1.3 Tumor base and 4 quadrant 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 Four quadrant bladder mucosal biopsies from the right wall, left wall, posterior wall and dome as well as from the bladder neck and prostatic urethra;
8.1.6 Cytology specimens from bladder washings;
8.1.7 Measurement of bladder capacity under anesthesia. The urologic surgeon should schedule the patient for endoscopic reevaluation in 8 weeks and, if he or she judges that less than a visibly complete TUR of the tumor was accomplished, the patient should be tentatively scheduled for a radical cystectomy in 10 weeks time.

8.2 Post-induction CFI Endoscopic Re-evaluation: This evaluation will take place 4 to 5 weeks following the completion of the induction chemoradiotherapy. Evaluation will include: barbotage cytology, cystoscopy, tumor site TUR biopsy, and bimanual examination after TUR, and bladder capacity.

8.3 Radical Cystectomy: For operable patients with less than a complete response on re-evaluation following initial TUR and induction CFI. 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 hypo gastric 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.

8.4 Post-consolidation CFI Endoscopic Evaluations: 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, bimanual examination and bladder capacity. 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. The first post-therapeutic evaluation will be 12 weeks after completion of the consolidation CFI if the initial response was a complete response: if the response was less than a complete response this re-evaluation should be in 6 weeks. This would allow the option for additional therapies if the primary bladder tumors still persists.

9.0 ADDITIONAL TREATMENT
9.1 For patients who are treated with attempted bladder preservation using consolidation CFI 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 in 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. This likely will be in the form of adjunctive systemic chemotherapy. This will be administered at the discretion of the primary physicians and may include patients who do not have such grave pathologic tumor findings at the time of immediate cystectomy. Adjuvant chemotherapy is not categorically discouraged for patients who have completed favorably consolidation CFI and whom are at high risk of distant failure.

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 (10/1/96)
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). The slides should be hematoxylin and eosin stained and the blocks would correspond to these slides. 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. The paraffin blocks should be submitted for appropriate pathologic translational studies. The pathology materials, relevant pathology reports, and a completed Pathology Submission Form will be mailed to:

Pathology Coordinator
RTOG Headquarters
1101 Market Street
Philadelphia, PA 19107
215/574-3192

10.2 Radical Cystectomy
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.
11.0 PATIENT ASSESSMENT

11.1 Study Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-Study</th>
<th>During Induction CFI</th>
<th>At initial cytoscopic re-evaluation</th>
<th>During Consolidation CFI</th>
<th>Follow-up evaluation 1st &amp; 2nd year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Surface Area</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H&amp;P</td>
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<td></td>
<td>X</td>
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<tr>
<td>Weight</td>
<td>X</td>
<td>weekly</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karnofsky Status</td>
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<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine Clearance</td>
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<td></td>
<td></td>
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<tr>
<td>Cystoscopy</td>
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<td>X (prior to)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine Cytology</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bimanual exam under anesthesia</td>
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<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder Biopsy</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC, Platelets, diff</td>
<td>X</td>
<td>weekly</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Serum Creatinine, BUN</td>
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<td>weekly</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT Scan</td>
<td>X</td>
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<td></td>
</tr>
<tr>
<td>IVPb</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Scan</td>
<td>X</td>
<td></td>
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<td></td>
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<tr>
<td>Chest X-ray</td>
<td>X</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, Alk Phos.</td>
<td>X</td>
<td></td>
<td>(prior to)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGOT, LDH</td>
<td>X</td>
<td></td>
<td>(prior to)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium, Calcium</td>
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</tr>
<tr>
<td>Bladder Volume</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Testb, PSAb</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. Only if cystectomy is not done. These will be q 3 months the 1st year, then q 6 months.

b. As applicable.

11.2 Definition of Complete Response Immediately after Neoadjuvant Treatment

11.2.1 Examination under anesthesia, cystoscopy and limited TUR (biopsy) of all previously positive tumor sites as well as bladder washings for cytologic examination will be utilized to evaluate the tumor status (response) in 4 to 5 weeks following completion of induction chemoradiotherapy. In some patients radiographic or cystoscopic evaluation will reveal abnormalities at the bladder tumor-site (such as thickening of the wall, ulcerations, or possible nodularities) which contain no identifiable tumor cells histologically. Patients will be considered as having a complete response when the bi-manual examination under anesthesia is negative, when all the biopsies are negative for tumor and the urine cytologic evaluation of bladder washings is not positive.

11.3 Endpoints

11.3.1 The objective regression of the primary bladder tumor will be described as follows:

- **Complete Response (CR)** requires the absence of any tumor in the tumor-site biopsy specimen or elsewhere, a urine cytology specimen that is not positive, and a bimanual exam that does not indicate the presence of a tumor mass.
- **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.
The maintenance of a CR of the primary tumor following consolidation CFI will be carried out by serial cystoscopic re-evaluation as per the schedule in Section 8.4.

11.3.2 The primary tumor response after consolidation CFI will be the same as above.

11.3.3 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.

11.3.4 The late or delayed safety or possible toxicity of this combined modality regimen will be evaluated with special attention on bladder function and capacity in patients treated on the consolidation CFI 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

12.1 Summary of Data Submission

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 1 week of study entry</td>
</tr>
<tr>
<td>Medical Oncology Treatment Planning Form (M2)</td>
<td></td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td>Within 2 wks of study entry</td>
</tr>
<tr>
<td>Diagnostic Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Pathology slides/blocks (P2)</td>
<td></td>
</tr>
<tr>
<td>Surgical Report (S2)</td>
<td></td>
</tr>
<tr>
<td>Preliminary Dosimetry Information:</td>
<td>Within 1 wk of start of RT</td>
</tr>
<tr>
<td>RT Prescription (Protocol Treatment Form) (T2)</td>
<td></td>
</tr>
<tr>
<td>Films (simulation and portal) (T3)</td>
<td></td>
</tr>
<tr>
<td>Calculations (T4)</td>
<td></td>
</tr>
<tr>
<td>Post Induction Evaluation Form (F0)</td>
<td>Within 8 weeks from start of induction treatment; and within 12 weeks after completion of consolidation chemoradiation</td>
</tr>
<tr>
<td>Radiotherapy Form (T1)</td>
<td>Within 1 week of RT end</td>
</tr>
<tr>
<td>Final Dosimetry Information:</td>
<td></td>
</tr>
<tr>
<td>Daily Treatment Record (T5)</td>
<td></td>
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<tr>
<td>Isodose Distribution (T6)</td>
<td></td>
</tr>
<tr>
<td>Boost Films (simulation and portal) (T8)</td>
<td></td>
</tr>
<tr>
<td>Post Operative Form (S6)</td>
<td>Within 4 weeks of cystectomy (Option 3)</td>
</tr>
<tr>
<td>Operative Report (S2)</td>
<td></td>
</tr>
<tr>
<td>Pathology Report (S5)</td>
<td></td>
</tr>
<tr>
<td>Consolidation Treatment Form (F4)</td>
<td>Within 1 week of end of consolidation chemoRT (Option 2)</td>
</tr>
<tr>
<td>Chemotherapy Flowsheets (M1)</td>
<td>Following each cycle of chemotherapy, at termination of treatment and upon observation of ≥ grade 4 toxicity</td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>Upon completion of consolidation treatment or cystectomy, every 3 months from treatment start* for 1 year; q 4 months x 1 year, q 6 months x 3 years, then annually. Also at</td>
</tr>
</tbody>
</table>
Autopsy Report (D3)

As applicable

*Arm 1: treatment start date is start of induction treatment
Arms 2 & 3: treatment start date is start of consolidation treatment or date of cystectomy, as applicable.

13.0 STATISTICAL CONSIDERATIONS

13.1 Endpoints

13.1.1 Completion of induction CFI followed by definitive local therapy of either radical cystectomy or consolidation CFI.

13.1.2 Safety

13.1.3 Complete response

13.2 Sample Size

Data from a total sample size of N=30 cases will provide sufficient information to distinguish a 90% completion rate from a 70% completion rate using a one-sided 0.05 test of proportions with 80% statistical power. The estimate of the probability of complete response will have a relatively wide 95% confidence interval of approximately plus or minus 20%.

13.3 Accrual

It is expected that accrual to the trial will be three per month, so that accrual should be completed within 12 months.

13.4 Analysis Plans

Tabulation of toxicity and pretreatment characterisitics will reported at the RTOG semi-annual group meetings. Analysis for publication will be undertaken when all patients have had an opportunity to complete the treatment and be evaluated for response.
REFERENCES


APPENDIX I

RTOG 95-06

A PHASE I/II TRIAL OF TRANSURETHRAL SURGERY PLUS INDUCTION CHEMORADIOThERAPY FOLLOWED EITHER BY SELECTIVE BLADDER PRESERVATION OR RADICAL CYSTECTOMY AS DETERMINED BY INITIAL RESPONSE AND OPERABILITY IN PATIENTS WITH MUSCLE-INVADING BLADDER CANCER

Sample Patient Consent Form

RESEARCH STUDY

I have the right to know about the procedures that are used in my participation in clinical research so I have an opportunity to decide whether or not to undergo the procedure after knowing the risks and hazards involved. This disclosure is not meant to frighten or alarm me; it is simply an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

I understand that this study involves the evaluation of anti-cancer drugs (cisplatin, and 5-fluorouracil) combined with twice-a-day external beam radiation therapy and possible removal of my bladder. None of the anti-cancer drugs used in themselves are experimental drugs. They have all been used in the treatment of many patients with tumors such as mine.

I realize that the usual treatment for my type of bladder cancer is surgical removal of my bladder and the surgical construction of an alternative bladder that usually requires a permanent opening (stoma) in my abdomen for urine drainage. Also, with the usual treatment, chemotherapy and radiation therapy is often advised following surgical removal of my bladder. The study treatment and usual treatment use similar therapies but differ in the sequence of the therapies and differ in that bladder removal is advised if chemo-radiotherapy has not resulted in a complete response of my tumor or if the tumor should subsequently recur.

DESCRIPTION OF PROCEDURES (6/3/96)

Following the surgery of my bladder tumor by scraping the surface of my bladder, I understand that I will begin chemoradiotherapy for three days receiving two drugs (cisplatin and 5-fluorouracil) by injection into my vein along with special intravenous fluid treatment. I will also receive two radiation treatments a day on the first and third days of my chemotherapy. Two weeks later I will repeat this schedule.

Four to five weeks after the completion of this first phase of my treatment, the urologic surgeon will evaluate the response of my bladder tumor by the visual examination of my bladder through a fiberoptic scope (a special examining instrument), biopsy, and a repeat of the pelvic CT scan. The results will offer the following:

If after the initial chemo-radiotherapy the tumor has not completely disappeared, and I am judged medically fit for surgery, I will be recommended to have surgical removal of my bladder within two weeks.

If the tumor has completely disappeared, or I am judged medically unfit for surgery, or if I refuse to have surgical removal of my bladder, I will receive chemotherapy and radiation therapy as I did before.

If I do not undergo removal of my bladder, I will undergo careful and frequent evaluation of my bladder through a fiberoptic scope. Should my bladder tumor come back or get bigger, then surgical removal of my bladder may be recommended. All tests and necessary hospitalizations proposed are often recommended for patients with bladder cancer and can be charged to my insurance company, as applicable.
Cancer treatments often have side effects. The treatment used in this program 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. Later on some more serious complications, which rarely occur, may also develop. 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 may rarely result in permanent sterility in males. In pregnant females, administration of radiation therapy to the pelvis will cause damage to the fetus (unborn child). If I am female, I must have a negative pregnancy test before participation in the study. If I am not currently pregnant, I must avoid pregnancy.

**5-Fluorouracil** (5-FU) may cause nausea, loss of appetite, vomiting, diarrhea with cramping or bleeding, skin rash, tiredness, headache, confusion, inflammation of the fingers and toes, mouth sores, sore throat, reversible hair loss, chest pain, increased sensitivity to sunlight, skin, nail or vein darkening or thickening, and a depression of the bone marrow (the blood forming organ) which increase the risk of anemia, infection, or bleeding. If the bone marrow is depressed extensively, transfusions may be required to correct the problem. Escape of drug from the injection site may cause chronic ulceration of the skin or severe local reaction. It is also possible that changes may occur in the sperm of males which might produce birth defects in future children. Additional, more serious side effects which rarely occur include chest pain with some damage to the heart, loss of coordination or balance, or other manifestations of brain or nerve damage.

**Cisplatin** frequently causes loss of appetite, nausea, vomiting, hearing loss, loss of taste, damage to kidneys, and bone marrow suppression (which can lead to anemia, infections, bruising or bleeding ). Other less common but serious side effects include numbness and tingling of fingers and toes and other neurological side effects, allergic reactions, chemical abnormalities of the blood (high uric acid or low magnesium), facial swelling, involuntary shaking, decreased vision and/or hearing, muscle cramps or spasms, rash, seizures, or cardiac abnormalities. There is a risk of leukemia when cisplatin is given with other anticancer drugs.

I understand that if, after the full chemo-radiotherapy treatment, the tumor recurs or reappears locally in the bladder, surgical removal of my bladder may be recommended provided that there is no evidence of spread of the cancer to any of my other organs. I understand that there is a low risk of tumor progression during either the initial or second course of chemo-radiotherapy as compared to immediate surgical excision of my bladder.

**Risks of Surgery:** I understand that if surgical excision is necessary, this results in the removal of my bladder and possibly 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, I understand 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 heart attack, severe bleeding, and blood clots. After the chemotherapy and radiation therapy treatment, this surgery is likely to be more difficult for the urologic surgeon and also more risky to me that is, a probable somewhat higher risk of complications following surgery.

My physician will be checking me closely to see if any of these side effects are occurring. Routine blood and urine tests will be done to monitor the effects of treatment. Side effects usually disappear after the treatment is stopped. In the meantime, my doctor may prescribe medication to keep these side effects under control. I understand that the use of medication to help control side effects could result in added costs. This institution is not financially responsible for treatments of side effects caused by the study treatment. There may be laboratory
testing and procedures required by this study for research purposes. These additional tests may increase my medical bills although the impact will be dependent on my insurance company.

CONTACT PERSONS

In the event that injury occurs as a result of this research, treatment will be available. I understand, however, I will not be provided with reimbursement for medical care other than what my insurance carrier may provide nor will I receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr. __________________________ the investigator in charge at ____________ __________________________. In addition, I may contact ____________ __________________________ at ____________ for information regarding patients' rights in research studies.

BENEFITS

It is not possible to predict whether or not any personal benefit will result from the treatment program. I understand that the information which is obtained from this study may be used scientifically and possibly be helpful to others. The possible benefits of this treatment program are greater shrinkage and control of my tumor and prolongation of my life but I understand this is not guaranteed.

I have been told that should my disease become worse, should side effects become very severe, should new scientific developments occur that indicate the treatment is not in my best interest, or should my physician feel that this treatment is no longer in my best interest, the treatment would be stopped. Further treatment would be discussed.

ALTERNATIVES

Alternatives which could be considered in my case include surgery performed off-study with or without radiation therapy either alone or with chemotherapy or treatments to make me feel better, but not necessarily cure me or make my disease less. An additional alternative is no further therapy, which would probably result in continued growth of my tumor. I understand that my doctor can provide detailed information about my disease and the benefits of the various treatments available. I have been told that I should feel free to discuss my disease and my prognosis with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand that I am free to ask my physician any questions concerning this program that I wish in the future.

My physician will explain any procedures related solely to research. Some of these procedures may result in added costs but may be covered by insurance. My doctor will discuss these with me.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. No compensation for participation will be given. I understand that I am free to withdraw my consent to participate in this treatment program at any time without prejudice to my subsequent care. Refusal to participate will involve no penalty, or loss of benefits. I am free to seek care from a physician of my choice at any time. If I do not take part in or withdraw from the study, I will continue to receive care. In the event of a research-related injury, I understand my participation has been voluntary.

CONFIDENTIALITY

I understand that records of my progress while on the study will be kept in a confidential form at this institution and also 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 the conduct of this study may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including tissue and/or slides, may be sent to a central office for review and research investigation associated with this protocol.

I have read all of the above, asked questions, received answers concerning areas I did not understand, and 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

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

AJCC Staging System, Bladder 1992

DEFINITION OF TNM

Primary Tumor (T)

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

Regional Lymph Nodes (N)

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

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

Distant Metastasis (M)

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

STAGE GROUPING

Stage 0a Ta N0 M0
Stage 0is Tis N0 M0
Stage I T1 N0 M0
Stage II T2 N0 M0
  T3a N0 M0
Stage III T3b N0 M0
  T4a N0 M0
APPENDIX III

AJCC Staging System, Bladder 1992
(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 (*urothelia*)

*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 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. Report by **phone** to RTOG Headquarters and the Study Chairman within 24 hours **A written report must be sent to RTOG within 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. Report by **phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours.** **A written report to follow within 10 working days.**

- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent. **Report in writing** to RTOG Headquarters and IDB within 10 working days.

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

FIELD DIAGRAMS