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

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Activation Date: July 1, 1997
Closure Date: June 1, 1999
Termination Date: November 5, 2013
Current Edition: April 1, 1999
Includes Revisions 1-3

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RADIATION THERAPY ONCOLOGY GROUP
RTOG 97-06
A PHASE I/II TRIAL IN OPERABLE PATIENTS WITH MUSCLE-INVADING BLADDER CANCER OF TRANSURETHRAL SURGERY AND CISPLATINUM/BID IRRADIATION FOLLOWED EITHER BY SELECTIVE BLADDER PRESERVATION OR RADICAL CYSTECTOMY AND ADJUVANT CHEMOTHERAPY

SCHEMA

TRANSURETHRAL INDUCTION CI\textsuperscript{a} RESPONSE EVALUATION
SURGERY WEEKS 1-3 WEEK 6
(registration < 6 weeks post TUR) (out-patient)

CR CONSOLIDATION CI\textsuperscript{b} OUTPATIENT MCV\textsuperscript{c} (3 cycles)
WEEKS 7,8

< CR RADICAL CYSTECTOMY OUTPATIENT MCV\textsuperscript{c} (3 cycles)
WEEK 8

<p>| A. INDUCTION THERAPY (Wk 1-3) |</p>
<table>
<thead>
<tr>
<th>Agent</th>
<th>Day</th>
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<th>2</th>
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<th>11</th>
<th>12</th>
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<tr>
<td>Cisplatin 20 mg/m\textsuperscript{2}</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XRT, bid x12</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>(1.80 Gy pelvis/1.60 Gy bladder tumor boost with a minimum 4 hr interval)</td>
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<tr>
<td>INDUCTION Cisplatin 120 mg/m\textsuperscript{2}; XRT 21.60 Gy 40.80 Gy</td>
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<p>| B. CONSOLIDATION THERAPY (Wk 7,8) |</p>
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<td>X</td>
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<td>Pelvic XRT, bid x 8</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>(1.50 Gy with a minimum 4 hr interval)</td>
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</tr>
<tr>
<td>INDUCTION Cisplatin 200mg/m\textsuperscript{2}; plus CONSOLIDATION XRT 45.60 Gy 64.80 Gy</td>
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<p>| C. OUTPATIENT ADJUVANT MCV CHEMOTHERAPY |</p>
<table>
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<tr>
<th>Agent*</th>
<th>Day</th>
<th>1</th>
<th>2</th>
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<th>4...</th>
<th>15</th>
<th>16...</th>
<th>22</th>
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<tbody>
<tr>
<td>Methotrexate (30 mg/m\textsuperscript{2})</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Vinblastine (3 mg/m\textsuperscript{2})</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin (25 mg/m\textsuperscript{2})**</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>* MCV to be repeated every 28 days for 3 cycles ** Cisplatin (70 mg/m\textsuperscript{2}) may be given instead as a single dose on day 2</td>
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</table>

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, adequately functioning bladder, no prior chemotherapy or pelvic RT.

Required Sample Size: 40
4/20/98
9/8/98
<table>
<thead>
<tr>
<th>Case #</th>
<th>Question                                                                }</th>
<th>(Y/N)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Y)</td>
<td>Is there histological confirmation of muscle-invading carcinoma of bladder?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N)</td>
<td>Is there evidence of hydronephrosis?</td>
<td></td>
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<tr>
<td>(Y)</td>
<td>Based upon the results of the cystoscopy, TUR, and other clinical radiographic studies, is the AJCC clinical T classification T2-4a?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Y/N)</td>
<td>Is there clinical/radiographic evidence of nodal disease?</td>
<td></td>
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</tr>
<tr>
<td>(Y)</td>
<td>If yes, have the clinically positive nodes been biopsied and found to be negative?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N)</td>
<td>Does the patient have distant metastasis?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Y/N)</td>
<td>Has the patient been diagnosed with any concurrent or second malignancy except for nonmelanoma skin cancer, T1a prostate, or in situ cervical cancer?</td>
<td></td>
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</tr>
<tr>
<td>(Y)</td>
<td>If yes, has the patient been disease-free for ≥ 5 years?</td>
<td></td>
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<tr>
<td>(N)</td>
<td>Has the patient had any prior systemic chemotherapy or pelvic irradiation?</td>
<td></td>
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</tr>
<tr>
<td>(N)</td>
<td>Is the patient receiving any potentially nephrotoxic or ototoxic drugs including aminoglycosides?</td>
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</tr>
<tr>
<td>(Y)</td>
<td>Based on the urologist's, medical oncologist's and radiation therapist's opinions, is the patient medically operable and medically stable to tolerate cystectomy, if necessary, and chemoradiation?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Y)</td>
<td>Has the patient undergone as thorough a transurethral resection of the bladder tumor as is judged safely possible?</td>
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<tr>
<td>(Y)</td>
<td>Does the patient have an adequately functioning bladder after evaluation by a urologist?</td>
<td></td>
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<tr>
<td>(Y)</td>
<td>Will treatment start within 6 weeks following TUR and endoscopic evaluations?</td>
<td></td>
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<tr>
<td>(Y)</td>
<td>Is the patient's age ≥ 18 years of age?</td>
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<tr>
<td>(Y)</td>
<td>Karnofsky Performance status ≥ 70?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Y)</td>
<td>Hemoglobin ≥ 10mg/dl?</td>
<td></td>
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<tr>
<td>(Y)</td>
<td>WBC ≥ 4 ml (per 1000)?</td>
<td></td>
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<tr>
<td>(Y)</td>
<td>Platelet count ≥ 100 mm$^3$ (per 1000)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Y)</td>
<td>ANC ≥ 1.8 mm$^3$ (per 1000)?</td>
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</tbody>
</table>

*continued on page 2*
Case # ____________________________ (page 2 of 2)

_____ (Y) 19. Serum creatinine ≤ 1.5 mg%?

_____ (Y) 20. Creatinine clearance ≥ 60 ml/min (calculated value is acceptable)?

_____ (Y) 21. Bilirubin ≤ 2 mg%?

_____ (Y) 22. Has the patient signed a study-specific informed consent?

The following question will be asked at Registration:

_____ (Y) 1. Was the eligibility Checklist (above) completed?

_____ (Y) 2. Is the patient eligible for this study?

_________________________ Patient's Name
_________________________ Verifying Physician
_________________________ Patient ID #
_________________________ Referring Institution (if different #)
_________________________ Medical Oncologist
_________________________ Birthdate
_________________________ Sex
_________________________ Race
_________________________ Social Security Number
_________________________ Zip Code (9 digit if available)
_________________________ Method of Payment
_________________________ Treatment Start Date (< 6 weeks post TUR)
_________________________ Will any component of the patient’s care be given at a VA or military facility?
_________________________ Treatment Assignment

Completed by ____________________________ Date ____________________________
Institution #
RTOG 97-06

ELIGIBILITY CHECK - STEP 2

Case #
(assigned for Step 1)

(Y) 1. 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 ________________)

(N) 2. Evidence of distant metastasis? (If yes, call RTOG HQ to "discontinue" the case; provide reason ________________)

(Y/N) 3. At the time of re-evaluation (following induction chemoradiation) has the patient been determined to have a complete response?

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

5. Results of the rebiopsy? (negative, positive, equivocal, not done)

6. Results of bimanual exam (negative, positive, equivocal, not done)

7. What phase of consolidation treatment will the patient proceed with? (chemoradiation or radical cystectomy)

_________________________ Patient Name

_________________________ Verifying Physician

_________________________ Patient ID Number

_________________________ Treatment Start Date (consolidation treatment or radical cystectomy)

_________________________ Treatment Assignment

Completed by ________________________________ Date ____________________
1.0 INTRODUCTION

1.1 Background

As the use of combined modality treatment for muscle invasive bladder cancer has matured the opportunity for bladder preservation has developed. Preoperative irradiation when combined with CDDP and/or 5-fluorouracil results in the downstaging to pT0 of a significant proportion of patients.\textsuperscript{1-4} When TURBT, radiation, and multiagent chemotherapy are combined complete response rates of 70% or greater have been obtained.\textsuperscript{1,3,5} This phase I/II trial, based on the RTOG experience in bladder preservation,\textsuperscript{4,6} trials from the Massachusetts General Hospital,\textsuperscript{2} and Paris\textsuperscript{3} combines aggressive TURBT with twice daily irradiation sensitized with CDDP (CI) in an effort to preserve the bladder. Eligible patients have muscle invading bladder cancer which does not obstruct the ureters. Local therapy is followed by three cycles of adjuvant MCV combination chemotherapy.

Distant metastasis remains 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 metastasis at 5 years 30-45%.\textsuperscript{10,11} Several randomized trials have demonstrated that combination chemotherapy is more effective than single agent therapy in controlling this disease.\textsuperscript{12-14} Comparison of the two most effective combinations, however, MCV and MVAC (methotrexate, vinblastine, adriamycin, and cisplatinum) has shown little difference between the two.\textsuperscript{15} Systemic therapy also increases the likelihood for control of local disease. The first analysis of the MRC/ EORTC intercontinental trial of neo-adjuvant chemotherapy demonstrated an increase from 12% to 33% in the occurrence of pT0 tumors at cystectomy, following MCV therapy.\textsuperscript{16} MCV has been selected for the current trial due to its equivalent effectiveness and ease of administration.

A current phase II trial of adjuvant Paclitaxel and CDDP for advance urothelial cancers has shown a high response rate and acceptable toxicity.\textsuperscript{17} A goal of this series of phase I/II trials of local therapy is to define an optimal treatment schedule which can be combined in a phase III trial with improved systemic therapy.

1.2 Schema of Present Protocol

For patients who have T2-T3 muscle-invading bladder cancer and who are operable candidates for a radical cystectomy, we will use a concomitant boost schedule, the induction CI involves accelerated hyperfractionation for the tumor with a standard dose schedule for the pelvis. Weekly CDDP is included as a radiation sensitizer. This schedule draws from the encouraging results from the Royal Marsden Hospital, where local control for muscle-invading bladder cancer was enhanced by accelerated hyperfractionation.\textsuperscript{7,8} In a pilot study involving 85 patients, twice daily irradiation (1.8-2.0 Gy per fraction, 5 days per week) delivered 57.6 Gy- 64 Gy in 32 fractions over 26 days, resulting in 80% complete responders.\textsuperscript{8} These results are currently being tested in a phase III trial.\textsuperscript{18}

Restricting the high dose volume via concomitant boosting should preserve the capability for ileal neo-bladder construction while reducing the acute toxicity of the accelerated hyperfractionation regimen. The induction treatment is completed in 12 treatment days, which significantly reduces the delay between the onset of treatment and cystectomy for those patients failing induction.

Radiosensitization by CDDP at a weekly total dose of 40 mg/m\textsuperscript{2} is used throughout. This will be given as 20 mg/m\textsuperscript{2} 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 700 patients during the past four years. The dose schedule is based on a successful pilot study of cervical cancer patients by Keys and colleagues at the Albany Medical College.\textsuperscript{9} The adjuvant MCV schedule included here can be administered entirely on an outpatient basis.

2.0 OBJECTIVES

2.1 To evaluate the safety and tolerance for induction chemoradiotherapy by CI to be followed by radical cystectomy if the initial tumor response is incomplete, or by consolidation CI if the tumor has cleared. Three cycles of outpatient adjuvant MCV chemotherapy is then given. A protocol completion rate of 90% is sought.

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

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  (4/20/98)

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 only mucosal 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. Intraductal disease must be limited to CIS or papillary TCC.

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

3.1.5  Patients must have a Karnofsky performance status of ≥ 70 (Appendix II).

3.1.6  Patients must have a 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 60ml/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 ≥ 18 years old.

3.1.11 Protocol treatment to begin within 6 weeks following TUR and endoscopic evaluation.

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 mm³, a serum creatinine of > 1.5 % mg, or a creatinine clearance of < 60 ml/minute, bilirubin > 2.0 mg%.

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

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

4.0  PRE TREATMENT EVALUATION  (9/8/98)

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 (no more than 6 weeks before treatment start); IVP if indicated.

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. 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.

4.5  Urine cytology will be repeated immediately prior to the beginning of induction CI.

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. Patients may also be registered via computer modem 24 hours a day, 7 days a week. 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
- Patient’s Name & ID Number
- Verifying Physician’s Name
- Medical Oncologist's Name
- Eligibility Criteria Information
- Demographic Data
- Treatment Start Date

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 (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,
- presence/absence of distant metastases,
- results of evaluation (includes rebiopsy of the bladder, bimanual examination, and urine cytology),
- 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 as per Section 5.2.1 and through submission of RTOG Form F1 (see Section 12.1).

5.2.4 Within 4 weeks of completing either radical cystectomy or consolidation CI therapy, all response results to the second phase of treatment (i.e., either pathologic staging from the radical cystectomy or cystoscopic re-evaluation performed 6 weeks following completion of consolidation CI therapy) 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 CI 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 CI 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 CI**

6.1.2 *Treatment Schedule:* External beam irradiation, 1.80 Gy, will be given to the pelvis in the A.M. followed by an interfraction period of at least 4 hr. During the P.M., 1.60 Gy will be delivered to the tumor plus a margin.

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 vertebrae).*
6.1.3.2 Tumor boost field (Appendix VI): This field will include the bladder gross 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 CI

6.2.1 Consolidation CI 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 Planning target volume. 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 21.6 Gy to the small pelvic fields and 40.8 Gy to the tumor volume (21.6 Gy from the pelvic field and 19.2 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 64.8 Gy over 8 weeks in 40 fractions and a total dose to the pelvic lymph nodes of 45.6 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.

6.4 Critical Structure Dose

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

6.5 Treatment Interruption

If a grade 3 hematologic toxicity develops (platelets less than 50,000 cells/mm³ or WBC less than 2,000
cells/mm$^3$), then chemoradiotherapy should be discontinued for one week and resumed if the WBC returns to 3,500/mm$^3$ or above and the platelet count is 100,000/mm$^3$ 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.

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).

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 Interfracion 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 CI. Interfracion interval between 3.5 hours and less than 4 hours.

Deviation: more than one QD treatment during either phase of CI. 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 CI with Cisplatin

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

7.1.1 Treatment Schema: Cisplatin and Irradiation (CI) 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, 0.5 NS, or NS at a rate of 200cc/hr for 1 hour. Cisplatin (20mg/m$^2$d), is to be administered as a 1 hour infusion on days 1,2,8,9,15 and 16. Post-chemotherapy i.v. hydration should include 5% Dextrose, 0.5 NS, or NS of 150cc in 45 minutes. On days when both chemotherapy and two fractions of radiation therapy (XRT) are given, the first XRT fraction should be 1.5 hours after the completion of the chemotherapy (a 1 to 3 hour interval is permissible). Anti-emetic regimens which may include ondansetron, granisetron, metoclopramide, lorazepam, dexamethasone, diphenhydramine hydrochloride
and/or prochlorperazine are recommended before and after cisplatin. Radiation will be given twice a day with a 4 hour interfraction interval. Within 3 weeks following completion of the last dose of CI all patients will have an evaluation of response as described in Section 8.2.

7.1.2 Cisplatin Dose Modifications for Nephrotoxicity during weeks 2 and 3 are as follows: For a serum creatinine of 1.5 mg/dl or less 20 mg per m² will be given. For a serum creatinine of 1.6 to 1.7 and no more than 1.33 baseline, 15 mg 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 CI 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 planned dose of Cisplatin will be the same as given during induction CI. Dose reductions, following the same schema (Tables 1 and 2), will be based upon the laboratory results obtained during the previous week (Section 11.1).

For patients who have a complete response documented by urologic re-evaluation, consolidation therapy will begin within 7-10 days. Cisplatin will be given on consolidation days 1, 2, 8, and 9. Irradiation should be given 1.5 hours after the completion of the chemotherapy (1 to 3 hours is permissible) with a 4-6 hour interfraction interval. Daily, two 1.5 Gy fractions are given to the pelvis.

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 for myelosuppression during consolidation CI are as listed in the table below.

### Table 1

Dose Modification of Cisplatin (C) for Myelosuppression during CONSOLIDATION CI (% of initial calculated dose)

<table>
<thead>
<tr>
<th>ANC (x 1000)</th>
<th>Platelet Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.5</td>
<td>&gt;150K</td>
</tr>
<tr>
<td>1.0-&lt; 1.5</td>
<td>C-100</td>
</tr>
<tr>
<td>&lt; 1.0</td>
<td>C-0</td>
</tr>
</tbody>
</table>

ANC = Absolute neutrophil count per ml

7.2.3 Modifications of cisplatin for nephrotoxicity during induction or consolidation CI are listed in the table below.

### Table 2

Dose Modification of Cisplatin (C) + for Nephrotoxicity during INDUCTION or CONSOLIDATION CI (% of initial calculated dose)

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>% calculated dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl &gt;60 and serum creatinine ≤ 1.5 mg/ml</td>
<td>C-100</td>
</tr>
<tr>
<td>CrCl of 50-60 (or serum creatinine &gt; 1.33 x baseline)</td>
<td>C - 75</td>
</tr>
<tr>
<td>CrCl of &lt;50 (or serum creatinine &gt;1.5 x baseline)</td>
<td>C - 0</td>
</tr>
</tbody>
</table>

7.2.4 Modification of cisplatin for peripheral neurotoxicity (Appendix IV) grade 3, omit cisplatin.
7.3  **Cisplatin (CDPP)**

7.3.1  **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.

7.3.2  **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.

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

7.3.4  **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.

7.3.5  **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 erythrosuppression, is expected. In the high-dose treatment regimen with osmotic diuresis, the nadir of white cells and platelets occurred regularly at about two weeks with recovery generally at about three weeks after the initiation of therapy. Rare complications are loss of taste, allergic reactions, and loss of muscle or nerve function.

7.4  **Adjuvant Systemic Therapy (9/8/98)**

MCV outpatient chemotherapy will begin 2-3 weeks following the post-consolidation endoscopic evaluation, or 8 weeks following radical cystectomy. Patients will receive three cycles of MCV therapy. The first day of therapy is day 1. The second cycle starts on day 29 and the third cycle on day 57. Therapy will be given as an outpatient with the MCV doses as shown on the schema page. These are methotrexate 30 mg/m$^2$ on days 1, 15 and 22, vinblastine 3 mg/m$^2$ on days 2, 15 and 22, and Cisplatin 25 mg/m$^2$ on days 2, 3 and 4. Cisplatin (70 mg/m$^2$) may be given as a single dose on day 2 instead of 25 mg/m$^2$ on days 2, 3 and 4. This schedule is repeated every 28 days for 3 cycles. Dose-reduction schedules are listed below.

### 7.4.1  **Hematologic Toxicity**

The dose of cisplatin during adjuvant therapy will not be reduced for hematologic toxicity. Dose reductions for methotrexate and vinblastine are given below.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Platelet Count</th>
<th>White Blood Count</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>99,999 to 74,999</td>
<td>3,499 to 3,500</td>
</tr>
<tr>
<td></td>
<td>to 100,000</td>
<td>to 2,500</td>
</tr>
<tr>
<td></td>
<td>75,000 to 50,000</td>
<td>&lt; 2,500</td>
</tr>
<tr>
<td></td>
<td>&lt; 50,000</td>
<td></td>
</tr>
</tbody>
</table>

#### Platelet Count

<table>
<thead>
<tr>
<th>Drug</th>
<th>Platelet Count</th>
<th>99,999 to 74,999</th>
<th>75,000 to 50,000</th>
<th>&lt; 50,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>30 mg/m$^2$</td>
<td>22.5 mg/m$^2$</td>
<td>15 mg/m$^2$</td>
<td>0(a)</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>25 mg/m$^2$</td>
<td>25 mg/m$^2$</td>
<td>25 mg/m$^2$</td>
<td>0(a)</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>3 mg/m$^2$2.25 mg/m$^2$</td>
<td>1.5 mg/m$^2$</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

(a)  This applies to courses 2 and 3.

#### White Blood Count

<table>
<thead>
<tr>
<th>White Blood Count</th>
<th>3,499 to 3,500</th>
<th>2,500 to &lt; 2,500</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3,499 to 3,500</td>
<td>2,500 to &lt; 2,500</td>
</tr>
</tbody>
</table>
Methotrexate  30mg/m²  15mg/m²(b)  0
Cisplatin  25mg/m²  25mg/m²  0(a)
Vinblastine  3mg/m²  1.5mg/m²(b)  0

(a) This applies to courses 2 and 3.
(b) For patients with WBC less than 3,000 on day 14, only those patients who increase their WBC to more than 3500 on day 21 will receive methotrexate or vinblastine. For patients with WBC less than 3000 on day 21 of cycle 1, only those patients with WBC more than 3500 on day 0 of cycle 2 will receive methotrexate, cisplatin and vinblastine. For patients whose WBC falls below target values, G-CSF may be used to stimulate recovery. During subsequent cycles of MCV therapy, G-CSF may be used prophylactically to ensure timely dose delivery. Patients whose WBC is < 3000 on day 14 or on day 21, and fail to recover following one week of G-CSF support, will be declared unsuitable to continue on protocol.

7.4.2  Nephrotoxicity
On Day 14 and/or Day 21 of Cycles 1, 2 and 3

<table>
<thead>
<tr>
<th>Creatinine (ml/d)</th>
<th>Methotrexate</th>
<th>Vinblastine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 or less</td>
<td>30 mg/m²</td>
<td>3 mg/m²</td>
</tr>
<tr>
<td>Creatinine clearance of 50-60 cc/min or serum creatinine more than 1.33 x baseline</td>
<td>20 mg/m²</td>
<td>3 mg/m²</td>
</tr>
<tr>
<td>Creatinine clearance less than 50 cc/min or serum creatinine more than 1.5 x baseline</td>
<td>0</td>
<td>3 mg/m²</td>
</tr>
</tbody>
</table>

On Days 1 - 4 of second and third MCV Cycles

<table>
<thead>
<tr>
<th>Creatinine (ml/d)</th>
<th>Methotrexate</th>
<th>Cisplatin</th>
<th>Vinblastine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 or less and less than 1.33 x baseline</td>
<td>30 mg/m²</td>
<td>25 mg/m²</td>
<td>3 mg/m²</td>
</tr>
<tr>
<td>1.6 or more or more than 1.33 x baseline, obtain a 24 hour creatinine clearance:</td>
<td>30 mg/m²</td>
<td>25 mg/m²</td>
<td>3 mg/m²</td>
</tr>
<tr>
<td>more than 60 cc/min</td>
<td>20 mg/m²</td>
<td>15 mg/m²</td>
<td>3 mg/m²</td>
</tr>
<tr>
<td>50-60cc/min</td>
<td>20 mg/m²</td>
<td>15 mg/m²</td>
<td>3 mg/m²</td>
</tr>
<tr>
<td>less than 50 cc/min</td>
<td>20 mg/m²</td>
<td>15 mg/m²</td>
<td>3 mg/m²</td>
</tr>
</tbody>
</table>
|                                                                                  | The 24 hour creatinine clearance should be repeated in one week. If it is more than 50 cc/min, treat as in table above, if it is less than 50 cc/min, the patient will be declared unsuitable to continue treatment.

7.4.3  Gastrointestinal Toxicity
For severe oral ulceration (grade 2 or more) on day of treatment, MTX will be held. If grade 2 or more ulceration resolves prior to the next dose of methotrexate the dose of methotrexate should be reduced by 25%.

7.4.4  Hepatic dysfunction
<table>
<thead>
<tr>
<th>Billirubin (mg%)</th>
<th>Methotrexate</th>
<th>Vinblastine</th>
<th>Cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0 or less</td>
<td>30 mg/m²</td>
<td>3 mg/m²</td>
<td>25 mg/m²</td>
</tr>
<tr>
<td>2.1 - 4.0</td>
<td>20 mg/m²</td>
<td>0</td>
<td>25 mg/m²</td>
</tr>
<tr>
<td>4.0 or more</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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
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 (II).
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 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;
8.1.6 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 CI Endoscopic Re-evaluation:** This evaluation will take place 3 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 CI. 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. Neobladder conduits are acceptable after induction CI, when the surgeon judges them to be safe.

8.4 **Post-consolidation CI 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 6 weeks after completion of the consolidation CI, when the initial response was a complete response.

9.0 **ADDITIONAL TREATMENT**

9.1 For patients who are treated with attempted bladder preservation using consolidation CI 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
10.0 PATHOLOGY

10.1 Central Review

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 the RTOG Tissue Bank:

LDS Hospital
Department of Pathology
E.M. Laboratory
8th Avenue & C Street
Salt Lake City, UT 84143

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 CI</th>
<th>At initial cystoscopic re-evaluation</th>
<th>During Consolidation CI</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>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>x</td>
<td>weekly</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Karnofsky Status</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine Clearance</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystoscopy</td>
<td>x</td>
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<tr>
<td>Urine Cytology</td>
<td>x</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Bimanual exam under anesthesia</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bladder Biopsy</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CBC, Platelets, diff</td>
<td>x</td>
<td>weekly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Creatinine, BUN</td>
<td>x</td>
<td>weekly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT Scan</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVP</td>
<td>x a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Scan</td>
<td>x a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, Alk Phos.</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>(prior to)</td>
</tr>
<tr>
<td>SGOT, LDH</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>(prior to)</td>
</tr>
<tr>
<td>Magnesium, Calcium</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bladder Volume</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test a</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

**11.2 Definition of Complete Response Immediately after Neoadjuvant Treatment (4/1/99)**

**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 three 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. Superficial bladder cancer (Tis or Ta) found after induction therapy in a site remote from the primary tumor does not constitute failed induction. These patients will be scored as having had a complete response.

**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 CI 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 CI 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 CI 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 (4/20/98)**

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

**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>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>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>
</tr>
<tr>
<td>Isodose Distribution (T6)</td>
<td></td>
</tr>
<tr>
<td>Boost Films for consolidation phase (simulation and portal) (T8)</td>
<td></td>
</tr>
<tr>
<td>Post Induction Evaluation Form (F0)</td>
<td>Within 8 weeks from start of induction; and</td>
</tr>
</tbody>
</table>
within 12 weeks after completion of consolidation chemoradiation.

Post Operative Form (S6)  
Operative Report (S2)  
Pathology Report (S5)

Consolidation Treatment Form (F4)  
*(Option 2)*

Chemotherapy Flowsheets (M1)  
Following each cycle of chemotherapy, at

termination of treatment and upon
observation of ≥ grade 4 toxicity

Follow-up Form (F1)  
consolidation treatment or cystectomy, then

Every 3 months for 1 year; upon completion of
q 4 months x 1 year, q 6 months x 3
annually. Also at progression/relapse and at
death.

Autopsy Report (D3)  
As applicable

**13.0 STATISTICAL CONSIDERATIONS**

**13.1 Study Endpoints**

**13.1.1 Primary Endpoint**  
Completion of CI induction followed by definitive local therapy of either radical cystectomy or consolidation CI with three cycles of outpatient adjuvant MCV chemotherapy.

**13.1.2 Secondary Endpoints**

- Treatment toxicity
- Complete response after CI induction
- Invasive local treatment failure *(including failure to achieve complete response with CI induction and invasive local relapse after consolidation)*
- Distant metastasis

**13.2 Sample Size**

Treatment completion is the major question of the trial. The study is designed to detect 90% completion rate against a 70% completion rate suggested from early RTOG studies. Yet, there are some concerns about the possibility of a completion rate of lower than 70% due to the toxicity of MCV regimen. In RTOG 89-03, the completion rate is 62% (38/62) for the MCV arm. Therefore, a two-sided test with null hypothesis of 70% completion rate against the alternative 90% completion should be used for the study. Based on binomial distribution, 36 patients are required to test the hypothesis with a significance level of 0.05 and a power of 85%. Considering the possible 10% unevaluable cases, the total sample size is 40. 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 CI induction is (39%, 71%). Similarly, based on invasive local treatment failure rate (48%) and 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 (32%, 64%) and (15%, 43%) respectively.

**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 12 evaluable patients, or
- 3 severe toxicities out of the first 22 evaluable patients, or
- 4 severe toxicities out of the first 36 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 0.89 if the true toxicity rate is 20%.

13.4 Accrual and Duration
Based upon closed RTOG 95-06, yearly accrual will be 24 patients after the first 6 months, the trial should be completed in about 2 years. For the efficacy of the treatment, additional follow-ups after the closure of the accrual are needed. With the additional one year of follow-up, we may have a 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 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
The final analysis will be performed upon the completion of evaluations of patients on protocol. The number of patients who completed CI induction will be reported as well as the number of patients who completed consolidation CI or had a cystectomy with three cycles of MCV. The complete response rate will be reported for each treatment phase.

Study primary outcome will be tested using the binomial distribution. If more than 30 out of 36 evaluable patients complete the treatment, we will reject the null hypothesis of 70% completion rate and conclude with a better treatment completion rate. If less than 20 out 36 evaluable patients complete the treatment, we will reject the null hypothesis and conclude with a worse treatment completion rate. Otherwise, we will tend to accept the null hypothesis.

Furthermore, tabulations of acute and late toxicity will be reported. We acknowledge that with the proposed sample size and duration of the trial, the observed late toxicity, if there is any, is associated with very large confidence intervals, and thus the interpretation should be very limited. The 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. The prior RTOG bladder cancer trials, 8903 and 9506 had accrued about 5% non-whites and 20% women. With proposed 36 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 Unrespectable Urothelial Cancer. Proc ASCO 15:245, 1996
APPENDIX I

RTOG 97-06

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

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, benefits, and alternatives. This disclosure is 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 an anti-cancer drug (cisplatin), combined with twice-a-day external beam radiation therapy and possible removal of my bladder. This treatment is followed by further treatment with additional anti-cancer drugs (methotrexate, cisplatin, and vinblastine). 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. This study will test whether or not this treatment approach is feasible.

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 only if chemo-radiotherapy has not resulted in a complete response of my tumor or if the tumor should subsequently recur.

DESCRIPTION OF PROCEDURES

Following the surgery of my bladder tumor by scraping the surface of my bladder, I understand that I will begin chemoradiotherapy for 16 days receiving the drug (cisplatin) twice each week by injection into my vein, along with special intravenous fluid treatment. I will receive two radiation treatments each day.

Three 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, I will receive chemotherapy and radiation therapy for an additional 10 days.

Following treatment of my bladder, I will undergo three months of additional chemotherapy to reduce the chance of my bladder cancer spreading to other parts of my body.

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.

RISKS AND DISCOMFORTS
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, combined with this chemotherapy will likely cause me to become sterile. 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.

Cisplatin (Platinol) may cause nausea, vomiting, weakness, hearing loss or ringing of the ears. It can also cause damage to the kidneys; I 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 my blood. It is possible that I 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.

Vinblastine (Velban) can lower blood counts which could lead to an increased risk of infection, weakness and fatigue, or bleeding complications. I might need antibiotics, hospitalization, and transfusions if these problems are severe. It can also cause hair loss, constipation, and numbness and tingling of the fingers and toes. There is the possibility of skin irritation should the drug leak from my vein into the surrounding skin.

Methotrexate can cause hair loss, ulcers of the mouth, liver abnormalities, and kidney dysfunction which can be prevented by taking extra fluids. It also can lower blood counts which could lead to an increased risk of infection, weakness and fatigue, or bleeding complications. I might need treatment with antibiotics, need hospitalization, and transfusions if these problems are severe.

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 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 inve: __________________________. In addition, I may contact _________
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

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
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
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

SMALL PELVIC FIELDS

Anterior View

Lateral View