A PHASE III TRIAL TO STUDY THE ROLE OF NEOADJUVANT MCV* CHEMOTHERAPY COMBINED WITH TRANSURETHRAL SURGERY PLUS CISPLATIN WITH RADIATION THERAPY FOR SELECTIVE BLADDER PRESERVATION IN PATIENTS WITH MUSCLE-INVADING BLADDER CANCER

* MCV: Methotrexate, Cisplatin, Vinblastine

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RTOG 89-03

A Phase III Trial to Study the Role of Chemotherapy Combined with Transurethral Surgery plus Cisplatin with Radiation Therapy for the Selective Bladder Preservation in Patients with Muscle-Invading Bladder Cancer

SCHEMA

STRATIFY: 1. Clinical T stage (T2 vs. T3 or T4)
2. Known bladder tumor remaining after entry TURB (yes or no)

R
A MCV, 2 cycles
N plus
D Cisplatin* and
O 40 Gy
M Arm 2
I Cisplatin** and
Z 40 Gy
E

ARM 1:

E Incomplete Responders IMEDIATE RADICAL CYSTECTOMY
R IMEDIATE RADICAL CYSTECTOMY
V Responders CONsolidation with CT and XRT
P O A Complete Responders
U O A Complete Responders
I N T Responders
S I Cisplatin** and
O 24.80 Gy (total dose of 64.8 Gy)
N

ARM 2:

MCV: Methotrexate*, 30 mg/m²; Cisplatin, 70 mg/m²; Vinblastine, 3 mg/m².
TURB: Transurethral Resection of Bladder tumor by Institutional urologist.
* Methotrexate dose will be 20 mg/m² if creatinine is 1.6-2.0 mg/dL.
** Cisplatin, 100 mg/m².

ELIGIBLE

Patients with muscle-invading carcinoma of the bladder, all histologies, AJC stages c T2-4a, cNX, MO. Patients must have Karnofsky status of at least 70. For additional requirements see Section 3.0.

DEFINITION OF COMPLETE REGRESSION IMMEDIATELY AFTER THE NEOADJUVANT TREATMENT

Examination under anesthesia, cystoscopy and limited TUR (biopsy) of all previously positive tumor sites will be utilized to evaluate the tumor status (response) within two weeks following completion of MCV chemotherapy (Arm 1) as well as after the initial radiotherapy plus cisplatin (Arm 2) and after both (Arm 1). 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 however contain no identifiable tumor cells histologically. Patients will be considered to have a complete regression following 39.6-40 Gy plus cisplatin when the bimanual exam under anesthesia is negative and the biopsies of all previously positive sites are negative for tumor. Only at this time of evaluation will a positive urine cytology not be considered definitive evidence of tumor.

MCV INDUCTION CHEMOTHERAPY (Arm 1 only)

MCV (Methotrexate, Cisplatin and Vinblastine) chemotherapy will begin within 2 to 4 weeks of TURB. Patients will receive two cycles of chemotherapy. The treatment schema is adapted from Yagoda et al.¹,¹⁴ and is shown below.

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Body surface Area (BSA) calculations are based on ideal or actual weight, which is less.

REQUIRED SAMPLE SIZE: 174
RTOG 8903
Eligibility Check - Randomization

Case #

1. Has the patient been diagnosed to have carcinoma of the bladder? (Y)
2. Is there histologic verification of muscle invasion? (Y)
3. Based upon results from cystoscopy TURB an other clinical radiographic evaluation and using the protocol staging, provide the clinical T classification. (T2-4a)
4. Will treatment start within 4 weeks of staging and TURB? (Y)
5. In the opinion of the medical oncologist and radiation therapist is the patient able to tolerate the chemotherapy regimens and pelvic irradiation?
   Name of Medical Oncologist responsible for the patient's chemotherapy (Y)
6. Is the patient considered medically operable in the event cystectomy is necessary? (N/Y)
7. Based on the clinical and required radiographic evaluations is there any evidence of nodal disease? If yes, have clinical positive nodes been evaluated histologically and proven to be negative? (N)
8. Any evidence of distant metastases? (N)
9. Is the patient receiving any potentially nephrotoxic or ototoxic drugs including aminoglycosides? (N)
10. Any prior systemic chemotherapy or pelvic radiotherapy? (N)
11. Any concurrent or prior second malignancy unless disease free for > 5 years? (or are site non-melanoma skin, in-situ cervix or T1(A) prostate?) (N)
12. Patient's age. (218)
13. Karnofsky Performance Status. (270)
14. Hemoglobin results. (210)
15. White Blood Count (per 1000). (24)
16. Platelet Count (per 1000). (2100)
17. Serum Creatinine (mg%). (51.7)
18. Creatinine Clearance results (ml/min). (60)
19. Bilirubin (mg%). (2)
20. Has a study specific informed consent form been signed? (Y/N)
21. Will the patient be entered on the QOL study, RTOG 91-16? If no, why not? __________

STRATIFICATION
1. Clinical T stage (T2 vs. T3 or T4).
2. Known bladder tumor remaining after entry TURB (yes or no).

DEMOGRAPHICS

Patient Name
Verifying Physician
Patient ID #
Referring Institution
Birthdate
Sex
Race
Social Security Number
Zip Code (9 digit if available)

revised: 8/2/91
2/14/92
Eligibility Check - Reregistration

1. Has the patient been evaluated for treatment response following completion of the option?

2. Any evidence of distant metastases or disease progression?

Outcome Questions

1. Results of biopsy.
   1 - negative (Go to question 2)
   2 - positive (Cystectomy)

2. Are there other signs of tumor or progression such as positive findings at bimanual exam or positive CT scan?
   1 - no (Consolidation)
   2 - yes (Cystectomy)

3. Results of urine cytology.
   1 - negative
   2 - positive
   3 - atypical or suspicious
   4 - not done

4. Results of CT
   1 - negative
   2 - positive
   3 - equivocal
   4 - not done
1.0 INTRODUCTION

Combined modality therapy for patients with muscle-invading bladder cancer was introduced when supravoltage radiotherapy was added to cystectomy. While there may be questions as to the value of adjuvant radiation treatment, the patients in each series reported who reached a pT0, pTis, or pT1 experienced a marked improvement in survival when compared to historical or to controlled populations. This may be because small volume tumors responded to radiation therapy or because papillary tumors responded. After Yagoda and colleagues demonstrated good activity with systemic cisplatin against metastatic transitional cell carcinoma others initiated the studies combining cisplatin with radiation therapy in the treatment of patients, without planned cystectomy, who had locally advanced bladder cancer. Indications for increased efficacy of cisplatin plus radiation (relative to radiation alone) is based on reports of higher local complete response rates using cisplatin plus radiation (75-80%) when compared to those using only radiation (40-51%).

Undetectable dissemination of tumor which occurs before the patient ever reaches the physician is the most common cause of treatment failure. Multi-drug chemotherapy is reported to have a higher objective response rate when treating measurable metastatic bladder cancer than is achieved with one drug alone. Cisplatin alone or methotrexate alone each yield approximately a 30% objective response rate while the combination together is reported to yield 40-50%. When vinblastine and or doxorubicin are added to the regimen the objective response rate is reported to increase 55-67%. Because of this apparent improvement, the focus has recently changed to concentrate on the effects of such multi-drug chemotherapy both on the primary bladder tumor and on the possibility that they may sterilize undetected micrometastatic disease. However to date their are no randomized trials that demonstrate or validate any advantage of neoadjuvant chemotherapy regimens and thus such trials must be undertaken before any such treatment approach can be considered of proven benefit.

Recently the RTOG and others have used the response of the primary tumor to single or multiple agent chemotherapy plus radiation therapy (given as neoadjuvant treatment) as a way to select patients for bladder preservation. The goal is to select only those patients who have a very high likelihood of having a permanent local cure of their bladder cancer for bladder preservation. The selection, which is done by the urologists, is as follows: If tumor is found on cystoscopic re-evaluation with biopsy immediately following chemotherapy and 40 Gy, cystectomy is performed; if not, consolidation by a radiation boost to 64.8 Gy plus cisplatin is given. To date this approach has been well tolerated. Recent analysis of 40 evaluable patients on RTOG 85-12 revealed this to be a well tolerated regimen and one which has yielded a complete regression of the tumor (a negative tumor-site biopsy) after cisplatin plus 40 Gy in 65% of patients. The Massachusetts General Hospital has reported a similar approach but with the addition of upfront methotrexate, cisplatin and vinblastine chemotherapy given in two cycles prior to cisplatin plus 40 Gy. In 36 evaluable patients this group reported a complete regression rate of 78%. This additional upfront chemotherapy has been moderately well tolerated with 36 of the first 44 patients completing the planned protocol (i.e., completed either full radiation therapy (64.8 Gy) or radical cystectomy after MCV and 40 Gy plus cisplatin). To date of the 25 patients who have completed the consolidation radiation therapy and cisplatin to 64.8 Gy, 22 or 88% were complete responses at 3 months following completion of the radiation (both tumor site biopsy was negative and urinary cytology was negative) and 19 (or 76%) remain tumor-free in the bladder, i.e., in maintained CR. With 6 to 28 months of follow-up 6 to 25 treated patients have had recurrent or persistent tumor in their bladder to date. Two have had invasive tumors recur and have undergone radical cystectomy without undue difficulty. Four have developed carcinoma in situ and have undergone intravesical therapy. Two of these 4 patients are tumor-free and 2 have a persistently positive urine cytology. Importantly no patient with the combined MCV and full-dose radiation plus cisplatin has any persistent significant bladder or bowel sequelae.

On June 1, 1988 the RTOG opened protocol 88-02 which is Arm I of the present randomized protocol. This protocol has been accruing 3 to 4 patients per month and is generally well accepted by the physicians and the patients. It is anticipated that this phase II/III study of neoadjuvant combined modality treatment with selective bladder preservations for patients with invasive bladder cancer will be completed by April of 1989. Assuming that no toxicity in excess of that seen from Massachusetts General Hospital pilot study is encountered, the present phase III protocol is planned as the next important
RTOG bladder study. The present phase III trial compares the effect of MCV neoadjuvant chemotherapy on the important end points of overall patient survival, disease-free survival, and successful bladder preservation (without a tumor recurrence and good bladder tolerance).

2.0 OBJECTIVES

2.1 To determine in a prospective trial whether neoadjuvant MCV chemotherapy provides patients with muscle-invading bladder cancer a significantly improved rate of successful bladder preservation (tumor-free and with good function) at 3 years.

2.2 To determine, in the context of a potential bladder preserving treatment regimen, whether neoadjuvant MCV chemotherapy provides patient with muscle-invading bladder cancer protection against disease recurrence.

2.3 To assess and compare the duration of tumor response (disease-free survival, and patterns of failure), and patient survival in Arm 1 vs. Arm 2. The parameters evaluated will be the durability of the complete response of the local tumor in those patients with bladder preserved and the frequency of the subsequent development of distant metastases in all patients.

2.4 To evaluate the possible effect of neoadjuvant MCV chemotherapy or treatment-related sequelae from radiation therapy, surgery or intravesical chemotherapy.

2.5 To examine the value of cell DNA analysis by flow cytometry in predicting patients whose tumors will achieve and will maintain a complete response to combined chemotherapy and radiotherapy.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients whose tumors are primary carcinoma of the bladder of any histology and who exhibit histologic evidence of muscle invasion and are clinical stages cT2-4a, cNX and M0. The patient may have urinary diversion prior to the initiation of treatment. Staging procedures and TURB must be done within four weeks of study entry.

3.1.2 Patient must have had as thorough a transurethral resection of the bladder tumor as is judged safely possible.

3.1.3 Patient must be considered able to tolerate systemic chemotherapy and pelvic radiation therapy and possible cystectomy by the joint agreement of participating urologists, radiation therapists, and medical oncologists.

3.1.4 Patient must have signed the informed consent (Appendix I).

3.1.5 Karnofsky performance status of 70 or greater (Appendix III).

3.1.6 WBC ≥ to 4000/mm³, a platelet count ≥ 100,000/mm³, serum creatinine ≤ 1.7 mg% and bilirubin ≤ 2 mg%, and a creatinine clearance ≥ 60 ml/min. (revised 8/2/91)

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

3.1.8 No evidence of distant metastases or histologically or cytologically proven nodal metastases in any lymph nodes (see Appendix II). Clinically positive nodes must be proven negative histologically.

3.1.9 Patient is not receiving any drugs that have potential nephrotoxicity or ototoxicity (aminoglycosides).

3.1.10 Patient must be ≥ 18 years old.

3.2 Ineligibility Criteria

3.2.1 Prior or concurrent malignancy of any other site or histology unless disease-free for greater than 5 years, except for non-melanoma skin cancer and/or stage T1 (A) prostatic cancer and/or in situ cervix carcinoma.

3.2.2 A Karnofsky performance status of less than 70.

3.2.3 Patients that have received pervious systemic chemotherapy or pelvic radiation therapy.

3.2.4 Patients with a hemoglobin < 10 mg/Dl. A WBC < 4,000 mm³, a platelet count < than 100,000 mm³. 24 hour creatinine clearance < 60 cc per minute, or serum creatinine > 1.7 mg. (revised 8/2/91)

4.0 PRETREATMENT EVALUATIONS

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

4.2 Radiological evaluation including chest x-ray, intravenous pyelogram and CT scan of the pelvis. If radiological evaluation of lymph node is interpreted as "positive", this must be sampled at least by percutaneous needle biopsy. Patients with histologically or cytologically confirmed nodal metastases will not be eligible.
4.3 Bone scan.
4.4 Laboratory studies - CBC, platelets, alkaline phosphatase, SGOT, LDH, bilirubin, BUN, creatinine, urinalysis, and 24 hour creatinine clearance.
4.5 Bimanual examination under anesthesia, cystoscopy, selective mucosal biopsies, tumor(s) biopsy, and urine cytology. As thorough as possible a transurethral resection of the bladder tumor should be done, as judged by the institutional urologist.
4.6 Histological evaluation, including documentation of muscle invasion.
4.7 All diagnostic studies must be done within one month of starting treatment.

5.0 REGISTRATION/RANDOMIZATION

5.1 Randomization for Initial Induction Therapy
5.1.1 Patients will be registered and randomized by telephone call to RTOG Headquarters, 215/574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m., ET.
The following information must be provided: patient’s name, patient’s identification number, institution, physician responsible for eligibility review, medical oncologist’s name, histology, stage, performance status, and all eligibility information required in section 3.0.
5.1.2 Patients will be randomized to receive either:
5.1.2.1 Arm 1: MCV for 2 cycles plus cisplatin and 40 Gy.
5.1.2.2 Arm 2: Cisplatin and 40 Gy.
A case number, and treatment assignment will be assigned and will be confirmed by mail.

5.2 Post Induction (Second Phase) Registration
5.2.1 Within three weeks of completion or discontinuation of the initial radiotherapy and chemotherapy (induction phase) and 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 treatment (cystectomy or consolidation radiation and chemotherapy) will be recorded and a new data collection calendar generated.
5.2.2 The following information will be supplied:
Original Case Number
Presence/Absence of Distant Mets
Results of Biopsy
Results of Bimanual exam
Results of urine cytology (negative, atypical, suspicious or positive)
Results of CT if available
Date of Commencement of the Second Phase of Treatment
5.2.3 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 patient deviates from the protocol specified treatment, documentation of this and data submission as outlined in section 11.2 is to be followed.
5.2.3.1 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.

6.0 RADIATION THERAPY
All patients shall receive the preliminary course of radiotherapy (Sec. 6.3). Treatment for patients randomized to Arm 1 should begin 2-3 weeks after the end of the second cycle of MCV chemotherapy. Patients randomized to Arm 2 should begin their treatment 3 to 4 weeks following the transurethral resection of tumor (TURB). Patients with documented regression of tumor following preliminary radiotherapy-chemotherapy shall also receive the consolidation course of radiotherapy (Sec. 6.4).

6.1 Dose Specification
6.1.1 Standard Specifications
6.1.1.1 For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.
6.1.1.2 For an arrangement of 2 or more intersecting beams: at the intersection of the central ray of the beams.
6.1.1.3 For complete rotation or arc therapy: in the plane of rotation at the center of rotation.
6.1.1.4 For a single beam: on the central ray at the center of the target area.
6.1.1.5 For two opposing coaxial unequally weighted beams: on the central ray at the center of the target area.

6.1.1.6 Other or complex treatment arrangements: at the center of the target area. (Note: there may be several target areas).

6.1.2 The dose is to be calculated and recorded at the following points (see Appendix V, Figures 1): 1) the posterior base of the bladder and tumor in the midsagittal plane; this point (point V) is 1.0 cm posterior to the most posterior portion of the bladder mucosa outlined contrast material in the bladder as seen in the lateral simulator film or further posterior than this measurement as is indicated by pelvic and/or rectal exam or other available diagnostic radiographic information; 2) the pelvic side wall (point W) which is the point 5.0 cm lateral to the isocenter of the anterior and posterior pelvic fields.

6.2 Technical Factors
Beam Energy - Equipment must have effective photon energies of 4 MV or higher. Cobalt teletherapy is not considered acceptable because of its lack of a sharp beam edge.

Treatment Distance - Minimum treatment distance to skin shall be 80 cm for SSD technique and 100 cm to isocenters for SAD technique.

6.3 Preliminary Course of Radiotherapy
6.3.1 Target Volume ("Small" pelvic fields - Figure 1)
Field should include all of the bladder, the total bladder tumor volume, the prostate and the prostatic urethra, and the lymph nodes immediately adjacent to the bladder. This field will extend 1.0 cm inferiorly to the caudal pole of the obturator foramen and superiorly for a distance of 11-13 cm to just below the sacral promontory or just below the S1-L5 disc on the AP projection. These fields will include the nodes proximal to the bladder within the perivesical, obturator, external iliac and internal iliac lymph nodes but clearly not the common iliac lymph nodes. The anterior and posterior fields should be shaped with inferior corner blocks usually 3-4 cm on a side which, when possible, should shield the medial border of the femoral heads. The field widths should extend 1.5 cm lateral to the bony margin of the pelvis at its widest point. (These measurements referred to are demagnified values.) Lymphangiographical delineation of the external iliac nodes may occasionally require wider fields to include these nodes. For lateral fields the anterior boundary of the fields should be 1.0 cm anterior to the most anterior portion of the bladder mucosa seen on air contrast cystogram or 1.0 cm anterior to the anterior tip of the symphysis, whichever is the more anterior. Posteriorly, the fields should extend at least 2.5 cm posterior to the most posterior portion of the bladder (point V, Figure 1) or 2.5 cm posterior to the tumor mass, if it is palpable or present on pelvic CT. This posterior border is usually at or posterior to the S1-S2 junction on their anterior surface. The heights of such lateral fields are likely to be 13-14 cm at isocenter. These lateral fields should be shaped with corner blocks inferiorly to block the tissues outside the symphysis and block the entire anal canal. Superiorly, these lateral fields should be blocked anteriorly to exclude any portion of the bowel and anterior rectus fascia not needed to be included because it lays anterior to the external iliac lymph nodal group. Wedges (usually 15°) should be considered for lateral fields as compensators if the transverse contour has a significant slope anteriorly. The 4-field box technique includes (Appendix V, Figure 2) weighting of the tumor dose from the paired anterior-posterior portion and from the paired lateral ports usually 18:7 but depends on the planned cone-down technique so as to minimize the total dose to the rectum and the femoral heads.

Appropriate radiographic studies (CT scan of the pelvis and cystogram) must be available to identify unusual anatomical variations necessitating alterations in the above described target volume. In some women, a bladder cystocele may protrude below the lower border of the obturator foramen. In some patients the bladder may herniate through the abdominal wall anteriorly or extend posterolaterally. In some patients bladder diverticulum may be present and extend outside the usual target volume.

Radiation fields will be designed on a treatment simulator during which the bladder is to be localized by catheter installation of contrast media-iodinated dye and/or air. Only 50 cc should be introduced into the bladder for simulation purposes because the patient will be
treated immediately following voiding. If, however, the patient has a significant post-void residual, this should be accounted for in the simulation and treatment plan.

6.3.2 Doses
The preliminary radiotherapy course shall consist of 39.60 Gy to the bladder, bladder tumor, and immediately adjacent pelvic lymph nodes in 22 fractions (1.80 Gy per day) in 41/2 - 5 weeks as in section 6.3.1.

6.4 Consolidation Radiotherapy
Consolidation radiotherapy will start within 1-2 weeks after documentation of complete regression following the cisplatin and Initial 39.6 Gy. The initial pelvic fields will be treated with an additional 5.4 Gy for a total of 45.00 Gy before the boost volume is treated with an additional 19.8 Gy for a total of 64.8 Gy.

6.4.1 Boost Target Volume
The primary bladder tumor volume will be entered on the patient transverse contour from the information available from the bimanual exam and other diagnostic radiographic or surgical information. If the radiation therapist is satisfied that all the initial site (s) of tumor is limited to one section of the bladder (usually in trigone and/or posteriorly), then the high dose volume should be designed to exclude the uninvolved areas of the bladder. If this situation occurs, the cone-down boost to the bladder tumor volume will be designed by the participating radiation therapist in his or her judgment what is optimal for their treatment beam characteristics. This will most likely have to be done by a 120° arc rotation for linear accelerators of lower beam energy (4 to 6 MV) but otherwise always by parallel opposed 2 or 4 fixed field plans for institutions having isocentric linear accelerators of 10 MV or greater beam energy. If the tumor volume is located at the trigone and/or in the posterior or posterolateral third of the bladder, this cone-down boost is probably best done by shaped paired lateral fields as shown in Appendix V, Figure 3a. With high energy beams such treatment planning considerations will result in these efforts minimizing the dose to the rectum, indicate the dose to the femoral heads of less that 45 Gy (See Appendix V, Figures 1-4)

6.4.2 Doses
The target volume for the bladder tumor boost shall receive 19.80 Gy in 11 1.8 Gy fractions in 2 1/2 to 3 weeks bringing the total dose to that volume to 64.80 Gy. (The initial pelvic field will have been previously treated to 45.0 Gy is 25 fractions.)

6.4.3 Treatment technique
Multiple field arrangement shall be used. Shaped multiple fields allow for adequate coverage of irregularly shaped bladder tumor volume, while retaining reasonable treatment volumes (Appendix V, Figures 4-6). This cannot be, in most patients, achieved with rotational therapy, although with 4 MV beams arc rotations may be necessary (Appendix V, Figure 5).

During consolidation radiotherapy the patient must void prior to each treatment.

6.4.4 Critical Structure Dose
The maximum dose to the rectum (posterior wall) shall be 55 Gy. The anterior wall of the rectum may receive the same dose as the bladder. The dose to the femoral neck should be ≤ 45 Gy.

6.5 Treatment Interruption
If a treatment interruption is necessary for acute radiation toxicity, the total dose to the initial pelvic field should not exceed 45 Gy and the total dose to the bladder tumor should not exceed 64.80 Gy. If treatment interruption is necessary for reasons other than radiation toxicity, the total dose could be increased, at the discretion of the individual radiation therapist, to achieve the comparable TDF of the small pelvic portion of the therapy (TDF = 70) or the total dose to the cone-down tumor volume (TDF 98-100). This latter increase in dose presumably would be given if the interruption was substantial and if the patient’s acute radiation tolerance was excellent. The total interval to deliver radiation therapy is not planned to exceed 10 weeks.
6.6 Modification of radiation treatment schedule: (revised 8/2/91)

Myelosuppression may occur during concomitant DDP and radiation therapy. If grade III hematologic toxicity (platelet < 50,000 or WBC < 2,000) develops then radiation therapy should be discontinued for one week and resumed if the WBC returns to 3500/mm3 or above and the platelet count is 100,000/mm3 or above. If these levels have not occurred after a one-week delay in radiation therapy they should be checked weekly until they recover to these levels. Following recovery of the blood counts, 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 of the pelvic soft tissues such as urinary frequency, dysuria, hematuria, nausea or diarrhea that do not respond to appropriate medications will be an indication for and interruption in the radiation therapy of one or more weeks as necessary.

6.7 Documentation

Radiation fields will be designed on a treatment simulator during which time the bladder is to be localized by catheter installation of contrast media-iodinated dye and/or air. Only 50 cc should be introduced into the bladder of for simulation purposes because the patient will be treated immediately following voiding. If, however, the patient has a significant post-void residual, this should be accounted for in the simulation and treatment plan.

7.0 DRUG THERAPY

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

Body Surface area calculations will be based upon ideal body weight or actual body weight, whichever is less. A standard nomogram may be used to calculate body surface area. See Appendix VII.

7.1 MCV Induction Therapy (Arm 1 only)

7.1.1 Treatment Schema

MCV chemotherapy will begin within 2 to 4 weeks of TURB. Patients will receive two cycles of MCV chemotherapy. The first day of MCV is day 0. The second cycle starts on day 28. Specific blood counts are required during chemotherapy as listed in section 7.1.2. Appendix IV provides a general outline for the administration of cisplatin. Methotrexate and Vinblastine are always given IV bolus. The treatment schema is shown below.

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<td>Vinblastine</td>
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<td>3mg/M²</td>
<td>3mg/M²</td>
<td>3mg/M²</td>
<td>3mg/M²</td>
<td>3mg/M²</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Within two weeks following the completion of the last dose of MCV (approximately day 49) all patients will have an evaluation of response as described in section 8.1.2. The initiation of cisplatin and radiation therapy will be within 2 1/2 weeks, if possible, following the completion of MCV.

7.1.2 Hematologic Toxicity (revised 8/2/91)

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

<table>
<thead>
<tr>
<th>Platelet Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
</tr>
<tr>
<td>Methotrexate</td>
</tr>
<tr>
<td>Cisplatin</td>
</tr>
<tr>
<td>Vinblastine</td>
</tr>
</tbody>
</table>

(a) This applies only to the course 2, day 1 dose of cisplatin
### White Blood Count

<table>
<thead>
<tr>
<th>WBC</th>
<th>Methotrexate</th>
<th>Cisplatin</th>
<th>Vinblastine</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 3,500</td>
<td>30mg/M²</td>
<td>70mg/M²</td>
<td>3mg/M²</td>
</tr>
<tr>
<td>3,499 to</td>
<td>15mg/M²</td>
<td>70mg/M²</td>
<td>1.5mg/M²</td>
</tr>
<tr>
<td>2,500</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

(a) This only applies to the course 2 day 1 dose of cisplatin.
(b) For patients with WBC < 3,000 on day 14, only patients with WBC ≥ 3500 on day 21 will receive methotrexate or vinblastine. For patients with WBC < 3000 on day 21 of cycle 1 only patients with WBC ≥ 3500 on day 0 of cycle 2 will receive methotrexate, cisplatin and vinblastine. If a patient with a WBC < 3000 on day 14 or day 21 does not recover to 3500 or above in one week, this patient will be declared unsuitable to continue on protocol.

#### 7.1.3 Nephrotoxicity (revised 8/2/91)

**On Day 14 and/or Day 21 of Both Cycles 1 and 2**

<table>
<thead>
<tr>
<th>Creatinine (ml/dl)</th>
<th>Methotrexate</th>
<th>Vinblastine</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.5</td>
<td>30 mg/M²</td>
<td>3 mg/M²</td>
</tr>
<tr>
<td>1.6 or 1.7 and ≤ 1.33 x baseline</td>
<td>20 mg/M²</td>
<td>3 mg/M²</td>
</tr>
<tr>
<td>&gt; 1.7 or &gt; 1.33 x baseline</td>
<td>0</td>
<td>3 mg/M²</td>
</tr>
</tbody>
</table>

**On Days 0 + 1 of second MCV Cycle**

<table>
<thead>
<tr>
<th>Creatinine (ml/dl)</th>
<th>Methotrexate</th>
<th>Cisplatin</th>
<th>Vinblastine</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.5 and ≤ 1.33 x baseline</td>
<td>30 mg/M²</td>
<td>70 mg/M²</td>
<td>3 mg/M²</td>
</tr>
<tr>
<td>≥ 1.6 or &gt; 1.33 x baseline, obtain a 24 hour creatinine clearance:</td>
<td>30mg/M²</td>
<td>70 mg/M²</td>
<td>3mg/M²</td>
</tr>
<tr>
<td>≥ 60 cc/min</td>
<td></td>
<td>20 mg/M²</td>
<td>70 mg/M²</td>
</tr>
<tr>
<td>≥ 50- &lt; 60cc/min</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| < 50 cc/min | | | | The 24 hour creatinine clearance should be repeated in one week. If it is > 50 cc/min, treat as in table above. If it is < 50 cc/min, the patient will be declared unsuitable to continue treatment.

#### 7.1.4 Gastrointestinal Toxicity

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

#### 7.1.5 Hepatic Dysfunction:

<table>
<thead>
<tr>
<th>Bilirubin (mg%)</th>
<th>Methotrexate</th>
<th>Vinblastine</th>
<th>Cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2.0</td>
<td>30 mg/M²</td>
<td>3 mg/M²</td>
<td>70 mg/M²</td>
</tr>
<tr>
<td>2.1 - 4.0</td>
<td>20 mg/M²</td>
<td>0</td>
<td>70 mg/M²</td>
</tr>
<tr>
<td>&gt; 4.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
7.2 Cisplatin Therapy During Radiotherapy (Arms 1 and 2)

7.2.1 Treatment Schema:
Patients assigned Arm 1 will receive cisplatin 100 mg/m² and begin pelvic radiotherapy concurrently, either three weeks after completion of MCV if WBC > 3500 and platelets > 100,000. (this will be considered day 1.) Treatment will be delayed and CBC checked weekly until the above hematologic parameters are satisfied.

Patients assigned to Arm 2 will receive their day 1 cisplatin 100 mg/m² and begin pelvic radiotherapy concurrently 2-4 weeks following their staging cystoscopy.

The second dose of cisplatin 100 mg/m² will be given on 22 for all patients.

Patients who achieve complete regression, will receive a third dose of cisplatin 100 mg/m² on or about day 43, which is the first day of consolidation radiotherapy. Patients receiving consolidation radiotherapy must be registered at RTOG headquarters as soon as their complete regression status has been confirmed.

7.2.2 Hematologic Toxicity
The dose of cisplatin will not be reduced for hematologic toxicity.

7.2.3 Nephrotoxicity during radiotherapy (revised 8/2/91)

For Day 0 of Arm 1 patients

<table>
<thead>
<tr>
<th>creatinine clearance (cc/min)</th>
<th>cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>100 mg/M²</td>
</tr>
<tr>
<td>≥ 50- &lt;60</td>
<td>70 mg/M²</td>
</tr>
<tr>
<td>&lt;50</td>
<td></td>
</tr>
</tbody>
</table>

The 24 hour creatinine clearance should be repeated in one week. If it is ≥ 50 cc/min, treat as in the table above. If it is < 50 cc/min, no further cisplatin should be given and that patient should complete their radiotherapy per protocol.

For Day 21 and consolidation dose (~Day 43), Arms 1 +2

<table>
<thead>
<tr>
<th>Creatinine (mg/dl)</th>
<th>Cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.5</td>
<td>100 mg/M²</td>
</tr>
<tr>
<td>1.6 or 1.7 and ≤ 1.33 x baseline</td>
<td>70 mg/M²</td>
</tr>
<tr>
<td>&gt; 1.7 or &gt; 1.33 x baseline, obtain a</td>
<td></td>
</tr>
<tr>
<td>24 hour creatinine clearance:</td>
<td></td>
</tr>
<tr>
<td>≥ 60 (cc/min)</td>
<td>100 mg/M²</td>
</tr>
<tr>
<td>≥ 50- &lt;60 (cc/min)</td>
<td>70 mg/M²</td>
</tr>
<tr>
<td>&lt;50 (cc/min)</td>
<td>0 (and complete XRT per protocol)</td>
</tr>
</tbody>
</table>
7.3 Chemothapeutic Agent: Formulation and procurement.

7.3.1 Cisplatin (DDP - Bristol Laboratories) Chemical name is cis-diamminedichloroplatinum (II) NSC #119875.

7.3.1.1 Formulation: dry powder with 10 mg in each vial. Ninety mg NaCl and 100 mg mannitol also present in each vial. Dissolve in 10 cc sterile water for use.

7.3.1.2 Anticipated toxicity: nausea and vomiting. Irreversible renal damage and hearing impairment may occur with toxicity being cumulative and more likely to occur in patients with preceding renal or auditory abnormalities. Mild to moderate marrow suppression may occur with nadir WBC and platelet counts at days 14-21 and recovery at days 18-21. Lymphoid tissue depletion has been noted in several animal species. Rarely hypocalcemia, hypomagnesemia and allergic reactions have been associated with DDP administration.

7.3.1.3 Supplier: commercially available.

7.3.1.4 Administration: Refer to Appendix IV for guidelines in administering Cisplatin.

7.3.2 Methotrexate (MTX - Lederle, Bristol) Chemical name is 4-amino-4-deoxy-N10-methyl-pteroylglutamic acid (amethopterin) NSC # 470.

7.3.2.1 Formulation: supplied as sodium salt in vials of 5 mg and 50 mg. With preservatives it is stable for one week at room temperature after reconstitution of dilution. Preservative-free cryodesiccated 20 mg vials are for single use only and must be reconstituted immediately prior to use.

7.3.2.2 Anticipated toxicities: mild to moderate oral mucositis. Mild to moderate anemia, leukopenia and thrombocytopenia with nadir at 8-12 days recovery at 15 to 21 days. Mild nausea and vomiting. Occasional dermatitis and hepatic dysfunction.

7.3.2.3 Supplier: commercially available.

7.3.3 Vinblastine Sulfate (VBL - Lilly) Chemical name is vincleukoblastine sulfate.

7.3.3.1 Formulation: vials contain 10 mg of vinblastine sulfate in the form of lyophilized drug, without excipients. Dissolve in 10 cc of normal saline prior to use.

7.3.3.2 Anticipating toxicities: epilation; mild to severe leukopenia depending upon dosage; mild to severe nausea and vomiting; constipation or paralytic ileus; diarrhea; occasional numbness and paresthesia; peripheral neuropathy; mental depression; cellulitis; and phlebitis. This drug is a vesicant and caution must be used during administration.

7.3.3.3 Supplier: commercially available

7.4 Adverse Drug Reaction Reporting

7.4.1 The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol which uses commercial anticancer agents. The following ADRs experienced by patients accrued to these patients accrued to these protocols and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days:

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

The ADR report should be documented on (Form FDA 1639) (Appendix IX) and mailed to:

Investigational Drug Branch
P.O. Box 30012
Bethesda, MD 20814

7.4.2 Further information on reporting Adverse Drug Reaction is detailed in Appendix IX.

8.0 SURGERY

8.1 Endoscopic Evaluation During Treatment Phase

During the treatment portion of the protocol, there will be two or three cystoscopic evaluations by the participating urologists for patients on Arm 1. If a patient on Arm 1 has a complete
regression following MCV, no evaluative cystoscopy is necessary after cisplatin and 39.6-40.0 Gy. For patients on Arm 2 two cystoscopic evaluations will be made during the protocol.

8.1.1 Before any cytotoxic therapy: evaluation at this time will include; (a) Cystoscopy with tumor mapping; (b) Transurethral resection, (TUR) of the tumor, should be as thorough as is judged safely possible. The specimens should allow determination of grade and depth of penetration (muscle should be in the specimen); (c) Bimanual examination before and after TUR to estimate possible residual tumor bulk; (d) Selected Mucosal Biopsies from the following sites: right wall, left wall, posterior wall, dome trigone, bladder neck, prostatic urethra and adjacent to tumor; (e) Cytology specimens will be measured; (f) bladder capacity. At this evaluation the Cystoscopic Report Form (Appendix V, Figure 3) must be completed.

8.1.2 After MCV chemotherapy: this evaluation will take place 1-2 weeks following chemotherapy and will include: cystoscopy, bimanual examination, tumor site biopsy, barbotage cytology, and bladder capacity.

8.1.3 After cisplatin x 2 and 39.6-40 Gy Radiotherapy: This evaluation will be done within 2 weeks of completing 39.6-40 Gy of radiation therapy. It will include: cystoscopy, bimanual examination, tumor site biopsy, barbotage cytology, and bladder capacity.

8.2 Post Treatment Endoscopic Evaluation
These periodic evaluations will be done according to the schedule in Section 11.0 and will include cytotology, bimanual examination, biopsy of suspect areas, barbotage cytology, and bladder capacity. However, at the endoscopic evaluation after cisplatin and 39.6 Gy the tumor site(s) biopsy is negative but the urine cytology is positive an evaluation for a possible “early” salvage radical cystectomy will be done 4-6 weeks following completion of the additional 19.8 Gy (64.8 Gy total) radiotherapy. In this circumstance the “early” endoscopic re-evaluation may change the recommended treatment from surveillance to salvage cystectomy or intravesical drug therapy if the bladder urine cytology continues to be positive (and the ureter collection cytologies are negative) and/or the tumor-site or selected mucosal biopsies are positive.

8.3 Additional Urologic Procedures
Percutaneous nephrostomy or individually urethral catheter placement may be necessary to assure adequate drainage and function of a kidney affected by urethral obstruction. This should be done prior to determination of the baseline creatinine clearance in order to identify maximal renal function. For some patients who present with very advanced tumors, a pretreatment urinary diversion may be required at the urologist’s discretion before entry into protocol. At the time of urinary diversion, if this is necessary, a biopsy of suspicious or positive lymph nodes should be carried out.

8.4 Radical Cystectomy: in the male radical cystectomy will include the peritoneum, fat and lymph nodes of an area defined by the medial border of the psoas muscle to a point level with the midpoint 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 of the associated peritoneum and perivesical fat will be removed en bloc. Lymphadenectomy should include at least the obturator space and the nodes of the hypogastric vessels. The external iliac nodes will be removed if clinically suspicious at the time of surgery. In the female, in addition to the peritoneum, fat and lymph nodes mentioned above, the bladder, anterior and lateral walls of the vagina, uterus, tubes and ovaries will be included in the radical cystectomy specimen.

9.0 OTHER THERAPY
Not applicable to this study.

10.0 PATHOLOGY
All of the slides from the initial TURB as well as the cystoscopy note and pathology report will be reviewed by a central pathologist to determine if invasion is present, depth of invasion, grade and histology. Paraffin block will be submitted to Headquarters for FCM to determine if FCM can predict tumor recurrence better than histology by analysis for aneuploid cells. Smear or cytopsin in
preparations of any urinary cytology specimens should also be sent to headquarters.

For cases that undergo cystectomy, the bladder specimen will be examined for evidence of tumor downstaging. The pathologic stage will be determined by the deepest level of invasion by visible tumor. The following guidelines for pathologic examination must be followed:

10.1 Radical Cystectomy
Operative reports and pathology reports from cystectomy specimens should be submitted. The pathology report should include gross and microscopic descriptions of tumor location depth of invasion and descriptions of involvement of lymph nodes, margins of resection and invasion of other structures.

11.0 PATIENT ASSESSMENTS

11.1 Endpoints (Arm 1 patients compared with Arm 2 patients)
11.1.1 Primary tumor response during treatment: Endoscopic evaluation as in 8.1.2 and 8.1.3. Complete Regression during treatment requires that bimanual exam under anesthesia is negative and that biopsies of all previous positive sites for tumor are negative for tumor. The urine cytology need not be negative.

11.1.2 Primary tumor response after consolidation with cisplatin and radiation (64.8 Gy): A Complete Response (CR) requires the absence of any endoscopically visible tumor, the absence of any tumor in the tumor-site(s) biopsy specimen(s), urine cytology that is not positive and a pelvic CT scan (done 3 months post treatment these q 6 months x 3) that does not show persistence of a tumor mass.

11.1.2 Degree of pathologic downstaging seen in patients who undergo cystectomy.
11.1.3 Toxicity of combined chemotherapy-radiotherapy.
11.1.4 The maintenance of bladder function and local control in patients who are treated by definitive cisplatin-radiotherapy.
11.1.5 The effectiveness of salvage cystectomy or intravesical drug therapy for chemo-radiotherapy failures.
11.1.6 Sites of recurrence and the rate of distant metastasis-free survival. Patients whose pathologic stage at cystectomy is pN+ or pT3b-4 with a positive margin will be considered not disease-free and may be offered additional treatment as an investigator's option.

11.1.7 Survival
11.1.8 Quality of Life assessment

11.2 Study Parameters (revised 8/2/91)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prestudy</th>
<th>During MCV</th>
<th>At each Cystoscopy</th>
<th>Prior to each DDP</th>
<th>During XRT</th>
<th>During 1st and 2nd yr every 3 months</th>
<th>During 3rd, 4th and 5th yr every 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Surface Area</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>H &amp; P</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Weight</td>
<td>x</td>
<td>weekly</td>
<td>x</td>
<td>x</td>
<td>weekly</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Karnofsky Status</td>
<td>x</td>
<td>weekly</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Creatinine Clear.</td>
<td>x(repeat in 1 wk)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Cystoscopy</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Urine Cytology</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Bimanual Exam under</td>
<td>Anesthesia</td>
<td>x</td>
<td>.x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Bladder Biopsy</td>
<td>CBC, Platelets</td>
<td>x</td>
<td>weekly</td>
<td>x</td>
<td>weekly</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>HCT/HGB</td>
<td>x</td>
<td>weekly</td>
<td>x</td>
<td>weekly</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>x</td>
<td>days 0 + 28</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Alk Phos</td>
<td>x</td>
<td>days 0 + 28</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>x</td>
<td>weekly</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>CT Scan++</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Scan</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CXR</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>Days</td>
<td>0 + 28</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>--------</td>
<td>--------</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td></td>
</tr>
<tr>
<td>SGOT</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>LDH, BUN, UA</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Bladder Volume</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

+ Only if cystectomy is not done.
++ Repeat after cisplatin and 39.6 - 40 Gy and then 3 months after all treatment (consolidations or cystectomy) and thereafter every 6 months x 3 and as otherwise indicated.

12.0 DATA COLLECTION (6/3/96)

12.1 Forms

<table>
<thead>
<tr>
<th>Data Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical oncology treatment Planning Form (M2)</td>
<td>Within one week of randomization</td>
</tr>
<tr>
<td>On-study form (F1)</td>
<td>Within 2 weeks of randomization</td>
</tr>
<tr>
<td>Diagnostic Pathology report (P1)</td>
<td></td>
</tr>
<tr>
<td>Pathology slides/blocks (P2)</td>
<td></td>
</tr>
<tr>
<td>Staging Cystoscopy note (S2)</td>
<td></td>
</tr>
<tr>
<td>Post-Induction Evaluation Form (F0)</td>
<td>Upon completion MCV and platinum + XRT; following completion of consolidation in patients with positive urine cytology; following post platinum + XRT evaluation.</td>
</tr>
<tr>
<td></td>
<td>An additional F0 is required on MCV arm following cycle 1 and before cycle 2.</td>
</tr>
<tr>
<td>Chemotherapy flowsheets (M1)</td>
<td>Following each cycle of chemotherapy; at termination of treatment and upon observation of significant toxicity.</td>
</tr>
<tr>
<td>Initial dosimetry:</td>
<td>Within 1 week of start of RT</td>
</tr>
<tr>
<td>RT Prescription (T2)</td>
<td>On completion of induction RT and induction chemotherapy</td>
</tr>
<tr>
<td>Initial simulation &amp; port films (T3)</td>
<td></td>
</tr>
<tr>
<td>Calculations (T4)</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy form (T1)</td>
<td>+ Two weeks following assigned or salvage surgery</td>
</tr>
<tr>
<td>+ Post-operative form (S6)</td>
<td></td>
</tr>
<tr>
<td>+ Operative (cystectomy) note (S2)</td>
<td></td>
</tr>
<tr>
<td>+ Pathology (cystectomy) note (S5)</td>
<td></td>
</tr>
<tr>
<td>Additional treatment form (F4)</td>
<td>On completion of consolidation radiotherapy and consolidation chemotherapy (if applicable)</td>
</tr>
<tr>
<td>Final Dosimetry:</td>
<td>At completion of radiation therapy</td>
</tr>
<tr>
<td>Treatment record (T5), Isodose (T6)</td>
<td></td>
</tr>
<tr>
<td>Additional calculations, Boost field simulation &amp; port films (T8)</td>
<td></td>
</tr>
</tbody>
</table>

11
13.0 STATISTICAL CONSIDERATIONS

13.1 Randomization

Treatment allocation will be done by a randomized permuted block within strata to balance for patient factors other than institution. The strata are clinical T stage (T_{2} vs. T_{3} or T_{4}), and known bladder tumor remaining after entry TURB (yes or no).

13.2 Endpoint

The primary endpoint is successful bladder preservation (functional and tumor free). This will be in the form of a maintained complete response rate in the primary bladder tumor evaluated at 3 years after initial treatment. Other endpoints will be duration of response (local control and freedom from distant metastases), overall patient survival and disease free survival. The tumor complete regression rate when re-evaluated immediately following the 40 Gy plus cisplatin will also be an endpoint.

13.3 Sample Size

Reasonable estimates regarding study endpoints and sample size can be made based on previous experience of the National Bladder Cancer Group and the recent early analysis of RTOG protocol 8512 and the Massachusetts General Hospital protocol 180 with regard to local complete tumor regression rates, overall survival and disease-free survival at 4 years. The accuracy of these estimates depends on the percentage of patients accrued to this protocol who are clinical T_{2} vs. clinical T_{3} or T_{4}. The ratio of 1 to 2 is projected. Another important estimate is the percentage of patients who will be entered into the protocol who are cystectomy candidates should the disease remain after the treatment up to and including cisplatin plus 40 Gy vs. those patients who are not cystectomy candidates at entry or only candidates for salvage cystectomy; this ratio is projected at 4 to 1. Further, these estimates include the following assumptions: 1) that immediate cystectomy will be only offered for patients having residual histologic tumor at the tumor site biopsy following 40 Gy and cisplatin, 2) 8% of the patients in Arm I will be protocol non-completers while 4% of patients in Arm II will be protocol non-completers, 3) all protocol non-completers will ultimately be non-survivors and not free of local or distant disease, 4) 1/2 of the patients who are less than complete regressors at the 40 Gy plus cisplatin point who are continued with bladder preserving treatment to 64.8 Gy and cisplatin will become complete responders when re-evaluated 3 months following treatment – in both Arm I and Arm II patients, 5) for patients treated with 64.8 Gy plus cisplatin for bladder preservation 15% of the Arm I patients who were complete responders 3 months after treatment will ultimately develop a local recurrence while 25% of those in Arm II who are complete responders at 3 months will develop a local recurrence, 6) with a clinical stage at entry ratio (cT2 vs. cT3-4) of 1 to 2, 40% of the patients in Arm II will develop distant metastases.

From these assumptions, we project that treatment in Arm I (in relation to Arm II) will provide a 20% increase (75% vs. 55%) in the bladder tumor-free rate at 3 years, and if so this would be clinically significant. It therefore is desirable that the protocol design provide sufficient power to detect a difference of 20% or more if, in fact, such a difference exists. A reasonable confidence level of 95% is recommended, i.e. a statistical significance level of 5%. With \( \alpha = .05 \) (one sided), and \( 1-\beta = .80 \), and a difference \( \delta = .20 \), 79 patients are required on each arm. Allowing for 10% of the patients to be either lost to follow-up or with invaluable data, the total accrual requirement for this study would be 79 + 79 + 16 = 174.

We further estimate, based on the above considerations, that treatment on Arm I relative to Arm II will provide a 15% increase (55% vs. 40%) in overall patient survival and will also provide a 20% decrease (20% vs. 40%) in distant metastases and that, if so, this would be clinically
significant. Also based on above assumptions we estimate that treatment on Arm I (relative to Arm II) will provide a 15% increase in the tumor complete regression rate when re-evaluated immediately following the 40 Gy plus cisplatin (75% vs. 60%).

13.4 Expected Accrual

We estimate that combining with patients in MGH protocol 8802, eight patients/month would be entered. Required patient accrual should be complete within 2 years.

13.5 Frequency of Reports

Interim accrual and morbidity reports will be prepared on at least a semi-annual basis prior to each RTOG meeting and will contain the following items:

13.5.1 Projections for completion of accrual phase, based on patient accrual rates observed d'uring the last year and/or for the whole study.

13.5.2 Patient accrual by institution.

13.5.3 Disposition of all cases entered into the study will respect to analysis. Analyzable cases are those eligible as confirmed by the submitted on-study pretreatment data with submitted treatment data. Cancelled and ineligible patients excluded from analysis are identified by their unique case number and reasons for their exclusions are generally provided.

13.5.4 Distribution of stratifying variables used in randomization and of other important prognostic variables for each assigned treatment regimen.

Interim response and survival analyses including endpoints such as complete response rate, local control, freedom from distant metastases, disease free survival and survival, will be performed as soon as 50% and 75% of the required sample size has been obtained.

13.6 Monitoring Committee

In order to effectively monitor the study, a committee is created consisting of the principal study chairman, the responsible statistician, the GU Site Committee Chairman, the Group Chairman of the RTOG and the Group Statistician of the RTOG. This Committee will receive the accrual and toxicity results unblinded, and the response and survival data blinded. Based on the results, the Committee can make one of the three decisions: 1) continue the study as it is; 2) revise the study because (Amended 5/21/90) of toxicity or execution problems; 3) close the study before it has realized its accrual objectives because of insufficient patient accrual, or a highly significant advantage observed on the experimental arm, or because of the extremely low probability of observing the lack of difference for an experimental arm if the hypothesized difference is, in fact, true. See early stopping rules below.

13.7 Early Stopping Rules

Two interim reports are to be prepared when 50% and 75% of the required sample size is met (section 13.5.4). The variable to be utilized for analysis is complete response at the completion of cisplatin and 40 Gy. If an experimental arm shows a highly significant improvement over the standard arm (p < .003 at the first interim response report and p < .004 at the second interim response report), recommendation will be made to drop the standard arm. These p-levels are selected in order to preserve an overall significance level of .05. If an experimental arm fails to show any improvement over the standard arm, recommendation will be made to drop the experimental arm. Judgement will be based on rules similar to the methods of Wieand19.

In addition, very early stopping will be considered after 40 evaluable patients, 20 in each arm, if there is a complete response rate of 80% (16 of 20) in Arm 1 vs. 20% (4 of 20) in Arm II. This would be statistically significant at p < .001.

14.0 ADDITIONAL TREATMENT

14.1 For patients who are treated with definitive chemotheraphy-radiotherapy, cystectomy or intravesicle drug therapy will be promptly considered for local recurrences without evidence of distant metastases. Any subsequent therapy may be given at the discretion of the primary physicians. The dates of local recurrence and distant metastases will be reported.

14.2 For patients treated with immediate cystectomy, and where pathologic tumor stage is pN+ or pT3B-4 with a positive margins will be considered not disease free and additional therapy may be offered at the description of the investigators.

14.3 For patients who develop distant metastases additional therapy may be given.
REFERENCES


Appendix I

RTOG 89-03

A PHASE III TRIAL OF WITH AND WITHOUT NEOADJUVANT MCV CHEMOTHERAPY COMBINED WITH TRANSURETHRAL SURGERY PLUS CISPLATIN WITH RADIATION THERAPY FOR SELECTIVE BLADDER PRESERVATION IN PATIENTS WITH MUSCLE-INVADING CANCER

Suggested Patient Consent Form

RESEARCH STUDY

I, ____________________________, willingly agree to participate in this study which has been explained to me by Dr. ________________. This research study is being conducted by the Radiation Therapy Oncology Group and by ______________________.

PURPOSE OF THE STUDY

It has been explained to me that I have an advanced form of cancer of the bladder. I understand that, despite conventional treatment with transurethral surgery, cisplatin (an anti-cancer drug) and radiation, and possibly cystectomy (surgical removal of my bladder), there may be subsequent recurrence of my tumor either in the pelvic tissues or in some other of my organs. This study involves the evaluation of the use of three anti-cancer drugs (MCV chemotherapy—methotrexate, cisplatin, and vinblastine) for seven weeks used before a course of one anti-cancer drug (cisplatin) and radiation for five weeks. The purpose of this study is to determine whether these drugs may improve the chance of tumor control when used in addition to transurethral surgery, cisplatin with radiation therapy, and possible removal of my bladder (cystectomy). I realize that None of the anti-cancer drugs used in themselves are experimental drugs—they all have been used in the treatment of many patients with tumors such as mine.

It is not clear at the present time which of the two regimen is better. For this reason, the therapy which is to be offered to me will be based upon chance using the method of random selection called "randomization". Randomization means that my physician will call a statistical office which will assign one of the two treatment regimen to me, and the chance of my receiving either one of the two therapies will be approximately equal.

This study involves random (by chance) assignment to one of the two arms. If I agree to participate in this program I would be assigned to receive either the MCV chemotherapy in conjunction with cisplatin chemotherapy with radiation therapy, or cisplatin chemotherapy and radiation therapy only.

PROCEDURES

If I am assigned to receive the initial MCV chemotherapy, this will be done following the transurethral surgery and will take approximately seven weeks. These drugs will be given intravenously either weekly or every other week by injection into my vein. These drug injections, which will usually take from 1 to 30 minutes, can usually be done in the clinic although two will require that I be in the hospital two nights for a special intravenous fluid treatment as well. I will have blood tests and possibly other laboratory evaluations during my drug and radiation treatments to check if my body is tolerating the therapy satisfactorily. One to two weeks following MCV chemotherapy, the urologic surgeon will evaluate the response of the tumor in my bladder by cystoscopy and tumor biopsy.

If I am assigned to not receive the MCV chemotherapy I will begin treatment with cisplatin and radiation therapy about three weeks following my initial transurethral surgery.

If I have been assigned to receive the MCV chemotherapy, cisplatin and radiation treatment will begin about a week following the evaluation by the urologic surgeon of the response of my tumor to MCV treatment. This phase of treatment will include a 5-week course of external beam radiation treatments to my urinary bladder.
and surrounding pelvic tissues given five days a week and will be accompanied by two doses of cisplatin chemotherapy. Cisplatin chemotherapy will require a 2-night hospitalization for special fluid therapy. The radiation therapy can be given to me as an out-patient on a daily basis. Following completion of this phase of the treatment, the urologic surgeon will evaluate the response of my bladder tumor by cystoscopy and biopsy with a repeat of the pelvic CT scan.

If after chemotherapy and the 5-week course of radiation 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 three to four weeks.

If, however, the tumor has completely disappeared or I am judged medically unfit for surgery, or if I refuse the recommendation to have surgical removal of my bladder, I will be advised to have one addition intravenous treatment with cisplatin chemotherapy and two and a half more weeks or radiation therapy.

If I do not undergo removal of my bladder, then after completion of the chemotherapy and radiation treatment, I will have to undergo careful and frequent cystoscopic evaluation by my urologic surgeon. Should my bladder tumor subsequently recur, then surgical removal of my bladder, if possible, may be recommended. All tests and necessary hospitalizations proposed are often recommended treatment for patients with bladder cancer.

**BENEFITS**

It is not possible to predict whether or not any personal benefit will result from the use of MCV chemotherapy as a supplement to cisplatin with radiation therapy, transurethral surgery and possibly removal of my bladder. Possible benefits include an decreased probability of this tumor spreading to some of my other organs or increase the chance of my tumor completely disappearing following transurethral surgery, cisplatin chemotherapy, and radiation, and thus prevent the need for surgical removal my bladder.

**RISKS AND DISCOMFORTS**

The potential side effects of any or all of the MCV chemotherapy drugs are bone marrow suppression, which could lead to bleeding, anemia, and the inability to fight infection. The drug cisplatin has been associated with the production of renal failure, hearing loss, nausea, and vomiting. It can also potentially produce numbness and tingling in the hands and feet and other forms of nerve damage. Vinblastine may produce constipation, hair loss, and ulcer at the site of the injection are also possible side effects of this drug. Methotrexate can produce sores in my mouth, diarrhea, kidney failure and, rarely liver dysfunction.

I understand that the external beam radiation treatments are given as standard treatment for bladder tumors—five sessions per week for either five or seven and a half weeks on an out-patient basis. I understand there are often side effects from the radiation therapy that may include fatigue, diarrhea, increased frequency of urination, pain on urination, or blood in my urine. Following completion of radiation therapy, the possible late effects of radiation include injury to my bladder or intestine, and the possible loss of sexual function.

I understand that there is a low risk of tumor progression during either the MCV chemotherapy or the course of cisplatin and radiation therapy as compared to immediate surgical excision of my bladder.

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 vesicals, 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, severely bleeding, and blood clots.
I understand that if, after the full course of the one or three anti-cancer drug chemotherapy, and the seven and a half weeks of radiation therapy, 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. However, I understand that after the chemotherapy treatment and the full 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 complication following surgery.

**ALTERNATIVES TO PARTICIPATION**

I understand that participation in this protocol is voluntary and that I will be given the opportunity to have usual conventional treatment or no treatment if I so desire. Conventional treatment for my type of bladder cancer would either be removal of my bladder and the construction of a substitute bladder and stoma, and/or external beam radiation therapy, usually with cisplatin and radiation therapy.

**CONTACT PERSONS**

In the event that injury occurs as a result of this research, treatment for injury will be available. I understand, however, I will not automatically be provided with reimbursement for medical care or receive other compensation. For more information concerning the research and research related risks or injuries, I can notify __________, the investigator in charge at, __________, in addition, I may contact ______________________ at (telephone) for information regarding patients' rights in research studies.

**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 research-related injury, I understand my participation has been voluntary.

**CONFIDENTIALITY**

I understand that record of my progress while on the study will be kept in a confidential form at (Institution) and also in a computer file at Headquarters of the Radiation Therapy Oncology Group. The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug administration (FDA) and the National Cancer Institute (NCI) 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 slides, may be sent to a central office for review.

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)                                                

__________________________________________________________
(Date)
APPENDIX II
1983 AJC Staging For Bladder Carcinoma\(^1\)

Clinical staging prior to entering into study will be accomplished by the following:

a) excretory urogram
b) bimanual examination under anesthesia other than local according to the AJC criteria for staging
c) cystourethrocscopy and as thorough a transurethral resection of the bladder tumor as possible with sufficient material to demonstrate presence or absence of muscle invasion by the tumor.
d) pelvic CT scan and/or lymphangiogram
e) observations and tests as outlined in section 11.0.

**Primary Tumor (T)-Clinical Staging**

The suffix "m" should be added to the appropriate "T" category to indicate multiple lesions.

\*TX Minimum requirements to assess the primary tumor cannot be met.

\*T0 No evidence of primary tumor. In a patient with a treated tumor, thorough re-evaluation reveals no endoscopically viable tumor, all biopsy specimens of the original tumor site are negative and the urine cytology is not positive.

\*Tis Carcinoma in situ (if used without subscript. T is indicates bladder alone.)*

b: bladder p.r.u.: prostatic urethra
u: ureter p.d.: prostatic ducts

\*Ta Papillary noninvasive carcinoma.

\*T1 Carcinoma without microscopic invasion beyond the lamina propria. On bimanual examination a freely mobile mass may be felt; this should not be felt after complete transurethral resection of the lesion.

T2 Microscopic invasion of superficial muscle of the bladder. On bimanual examination there may be induration of the bladder wall, which is mobile. There is no residual induration after transurethral resection of the lesion.

T3 On bimanual examination there may be induration or a nodular mobile mass palpable in the bladder wall that persists after transurethral resection (T3 may not be used alone).

T3a Microscopic invasion of muscle; this is defined as histologic evidence of tumor clearly extending among muscle bundles.

T3b Invasion into perivesical fat.

T4 Microscopic evidence of muscle invasion, tumor is fixed or invades neighboring structures. The subclassifications below should be used when conditions are met.

T4a Tumor invades substance of prostate (microscopically proven), uterus, or vagina.

\*T4b Tumor is fixed to the pelvic wall or infiltrates the abdominal wall.

**Nodal Involvement (N)**

The retroperitoneal lymph nodes will be evaluated radiographically by lymphanglogram and/or computed tomography for the presence of detectable nodal involvement outside the planned fields or irradiation (see Figures 1 and 2). If these studies are interpreted as "positive" for metastases in or above the common iliac regions, confirmation by "skinny" needle biopsy should be done. Patients must have histologic or cytologic proof of a radiographically positive lymph m - node for cancer at or above the bifurcation of the common iliac to be eligible for this protocol. In patients undergoing a urinary diversion prior to protocol treatment, radiographically "positive" lymph nodes can be assessed by surgical sampling

NX Minimum requirements to assess the regional nodes cannot be met.

NO No involvement of regional lymph nodes.

N1 Involvement of a single homolateral regional lymph node.

N2 Involvement of contralateral, bilateral, or multiple regional lymph nodes.

N3 There is a fixed mass on the pelvic wall with a free space between the wall and the tumor.

\*N4 Involvement of juxta-regional lymph nodes (M1).

**Distant Metastasis (M)**

MX Minimum requirements to assess the presence of distant metastasis cannot be met.

M0 No (known) distant metastasis.

\*M1 Distant metastasis present

Specify _____________________________

\* Patients not eligible for this study.

APPENDIX III

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.

APPENDIX IV

GUIDELINES FOR THE ADMINISTRATION OF CISPLATIN

Daily: Creatinine, BUN and Electrolytes.

EVENING PRIOR TO CISPLATIN:

Normal saline + 20 mEq KCl/1000 cc @ 150 cc/hr; minimum total 2000 cc in 12-18 hours. STRICT INTAKE AND OUTPUT

DAY OF CISPLATIN:

Antiemetic order as per M.D. Chemotherapy nurse will give Cisplatin mixed in 250 cc normal saline, preceded by 12.5 grams of Mannitol IV push.

FIRST 4 HOURS AFTER CISPLATIN

D5W 1/2 N.S. + 20 mEq KCl/1000 cc @ 250 cc/hr
Check hourly intake and output.
Replace output (urine, emesis and diarrhea) above 200 cc/hr.
cc/cc above the hourly maintenance IV ordered. Use same IV solution for replacement.

FROM 4 TO 24 HOURS AFTER CISPLATIN

D5W 1/2 N.S. + 20 mEq KCl/1000 cc @ cc/hr
Check hourly intake and output 125 cc/hr.
Replace output (urine, emesis and diarrhea) above 150 cc/hr.
cc/cc above the hourly maintenance IV ordered. Use the same IV solution for replacement.

Maintain urine output > 100 cc/hr.

BEYOND 24 HOURS:

Fluid orders as per investigator.

NOTE:

1) Avoid use of aminoglycoside antibiotics.
2) Replace low K+ and low Mg++
3) The use of dexamethasone and high dose metoclopramide to prevent nausea is encouraged.
APPENDIX V

Figure 1

LATERAL

ANTERIOR and POSTERIOR
APPENDIX V

Figure 2

ISOCENTRIC FOUR-FIELD PELVIC XRT PLANS

10 MV X-RAYS

4 MV X-RAYS
APPENDIX V

Figure 3

Cystoscopy Report Form

PT NAME _________________________ UNIT NUMBER ________

DATE OF CYSTOSCOPY ___/___/___ Surgeon ______________________

A VISIBLY COMPLETE TURB OF TUMOR WAS DONE?

YES ___ NO ___

A PALPABLE MASS OR INDURATION WAS PERSISTENT AFTER THE TURB?

YES ___ NO ___

SIZE (Diameter) OF LARGEST TUMOR?

1 cm ___ 1-2.9 cm ___ 3-4.9 cm ___ >= 5 cm ___

TUMOR INVADING PROSTATE OR VAGINA? YES ___ NO ___

TUMOR FIXED TO PELVIC/ABD. WALL? YES ___ NO ___

PLEASE COMPLETE DIAGRAM: DRAW LOCATION OF TUMOR(S). IF TUMOR REMAINS AT THE END OF THE PROCEDURE, PLEASE INDICATE ITS LOCATION ON DIAGRAM.
LATERAL TUMOR BOOST FIELDS
APPENDIX V

Figure 4

XRT PLANS FOR BOOST DOSE TO BLADDER CARCINOMA

10 MV X-RAYS

25 MV X-RAYS

MINIMUM TUMOR DOSE - 1980
7 cm LATERAL FIELDS
APPENDIX V

Figure 5

DEFINITIVE XRT PLANS FOR T2-T3 BLADDER CARCINOMA

10 MV X-RAYS
7 cm LATERAL BOOST

4 MV X-RAYS
6 cm 120° ARC BOOST

WHOLE PELVIS - 4500
AP-PA + LATERAL
17 X 8
TUMOR BOOST - 1980

4300
6700
6480
5040
6000
4000

26
DEFINITIVE XRT PLAN FOR T2-T3 BLADDER CARCINOMA

10 MV X-RAYS

WHOLE PELVIS - 4500
AP-PA + LATERAL
17:3
LAT. TUMOR BOOST - 1980
Cooperative Group Common Toxicity Criteria

INSTRUCTIONS
1. Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.
2. When two criteria are available for similar toxicities, the one resulting in the more severe grade should be used.
3. Toxicity grade = 5 if that toxicity caused the death of the patient.
4. Refer to detailed toxicity guidelines in the protocol, or to RTG Headquarters for toxicity not covered on this table.
5. The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.
6. An accurate baseline prior to start of therapy is necessary.

<table>
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<th>TOXICITY</th>
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<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
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<td>WBC</td>
<td>&lt;= 4.0</td>
<td>3.0 - 3.9</td>
<td>2.0 - 2.9</td>
<td>1.0 - 1.9</td>
<td>&lt; 1.0</td>
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<tr>
<td>Platelets</td>
<td>WNL</td>
<td>75.0 - normal</td>
<td>50.0 - 74.9</td>
<td>25.0 - 49.9</td>
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<td>Hemoglobin</td>
<td>WNL</td>
<td>10.0 - normal</td>
<td>6.5 - 7.9</td>
<td>&lt; 6.5</td>
<td></td>
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<tr>
<td>Granulocytes/Bands</td>
<td>=&gt; 2.0</td>
<td>1.5 - 1.9</td>
<td>1.0 - 1.4</td>
<td>0.5 - 0.9</td>
<td>&lt; 0.5</td>
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<tr>
<td>Lymphocytes</td>
<td>=&gt; 2.0</td>
<td>1.5 - 1.9</td>
<td>1.0 - 1.4</td>
<td>0.5 - 0.9</td>
<td>&lt; 0.5</td>
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<tr>
<td>Hemorrhage (Clinical)</td>
<td>None</td>
<td>Mild, no transfusion</td>
<td>Gross, 1-2 units transfusion per episode</td>
<td>Gross, 3-4 units transfusion per episode</td>
<td>Massive &gt; 4 units transfusion per episode</td>
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<td>Infection</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Life-threatening</td>
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<tr>
<td>Nausea</td>
<td>None</td>
<td>Able to eat/reasonable intake</td>
<td>Intake significantly decreased but can eat</td>
<td>No significant intake</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>None</td>
<td>1 episode in 24 hours</td>
<td>2-5 episodes in 24 hours</td>
<td>6-10 episodes in 24 hours</td>
<td>&gt; 10 episodes in 24 hours or requiring parenteral support</td>
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<tr>
<td>Diarrhea</td>
<td>None</td>
<td>Increase of 2-3 stools per day over pre-Rx</td>
<td>Increase of 4-6 stools/day, or nocturnal stools, or moderate cramping</td>
<td>Increase of 7-9 stools/day or grossly bloody diarrhea, or need for parenteral support</td>
<td>Increase of &gt; 10 stools/day or grossly bloody diarrhea, or need for parenteral support</td>
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<td>Stomatitis</td>
<td>None</td>
<td>Painless ulcers, erythema or mild soreness</td>
<td>Painful erythema, edema or ulcers but can eat</td>
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<td>Requires parenteral or enteral support</td>
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<td>Bilirubin</td>
<td>WNL</td>
<td>&lt;= 1.5 X N</td>
<td>1.5 - 3.0 X N</td>
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<td>&gt; 5.0 X N</td>
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<td>Transaminase (SGOT, SGPT)</td>
<td>WNL</td>
<td>&lt;= 2.5 X N</td>
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<td>5.1 - 20.0 X N</td>
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<td>WNL</td>
<td>&lt;= 2.5 X N</td>
<td>2.6 - 5.0 X N</td>
<td>5.1 - 20.0 X N</td>
<td>&gt; 20.0 X N</td>
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<td>Liver/clinical</td>
<td>No change from baseline</td>
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<td></td>
<td>Precoma</td>
<td></td>
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<td>Creatinine</td>
<td>WNL</td>
<td>&lt;= 1.5 X N</td>
<td>1.5 - 3.0 X N</td>
<td>3.1 - 6.0 X N</td>
<td>&gt; 6.0 X N</td>
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<td>Proteinuria</td>
<td>No change</td>
<td>1+ or 0.3 g% or &lt; 3 g/l</td>
<td>2+ or 0.3 - 1.0 g% or 3 - 10 g/l</td>
<td>4+ or &gt;1.0 g% or &gt;10 g/l</td>
<td>Nephrotic syndrome</td>
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<td>Hematuria</td>
<td>Negative</td>
<td>Micro only</td>
<td>Gross/no clots</td>
<td>Gross + clots</td>
<td>Requires transfusion</td>
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</tbody>
</table>

APPENDIX VI

Liver function tests:
- Bilirubin
- Transaminases:
- Alkaline Phosphatase
- GGT
- Other enzymes: LDH, AST

Gastrointestinal:
- Changes in bowel habits
- Nausea
- Vomiting
- Diarrhea
- Stomatitis

Renal:
- Creatinine
- Proteinuria
- Hematuria

Kidney/Bladder:
- Changes in urinary habits
- Hematuria
- Proteinuria
- Creatinine

28
<table>
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<th>- 2 -</th>
<th>- 3 -</th>
<th>- 4 -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>No loss</td>
<td>Mild hair loss</td>
<td>Pronounced or total hair loss</td>
<td>Dyspnea at rest</td>
<td>Dyspnea at rest</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>None or no change</td>
<td>Asymptomatic with abnormality in PFT's</td>
<td>Dyspnea on significant exertion</td>
<td>Requires monitoring or hypotension or ventricular tachycardia or fibrillation</td>
<td></td>
</tr>
<tr>
<td>Cardiac dysrhythmias</td>
<td>None</td>
<td>Asymptomatic/transient/requiring no therapy</td>
<td>Recurrent or persistent/no therapy required</td>
<td>Requires treatment</td>
<td></td>
</tr>
<tr>
<td>Cardiac function</td>
<td>None</td>
<td>Asymptomatic/decline of resting ejection fraction by &lt;20% of baseline value</td>
<td>Asymptomatic/decline of resting ejection fraction by &gt;20% of baseline value</td>
<td>Requires treatment</td>
<td></td>
</tr>
<tr>
<td>Cardiac/ischemia</td>
<td>None</td>
<td>Non-specific T-wave flattening</td>
<td>Asymptomatic/ST and T wave changes suggesting ischemia</td>
<td>Requires treatment</td>
<td></td>
</tr>
<tr>
<td>Cardiac/pericardial</td>
<td>None</td>
<td>Asymptomatic effusion/no intervention required</td>
<td>Pericarditis (rub, chest pain, ECG changes)</td>
<td>Requires therapy</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>None or no change</td>
<td>Asymptomatic/transient increase by &gt;20mm Hg (D) or to &gt;150/100 if previously WNL/No treatment required</td>
<td>Recurrent or persistent increase by &gt;20mm Hg (D) or to &gt;150/100 if previously WNL/No treatment required</td>
<td>Requires therapy</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>None or no change</td>
<td>Changes requiring no therapy/including transient orthostatic hypotension</td>
<td>Requires fluid replacement or other therapy but not hospitalization</td>
<td>Requires therapy and hospitalization/resolves within 48 hours of stopping the agent</td>
<td></td>
</tr>
<tr>
<td>Neurological/sensory</td>
<td>None or no change</td>
<td>Mild paresthesias/loss of deep tendon reflexes</td>
<td>Mild or moderate objective sensory loss/mild paresthesias</td>
<td>Severe objective sensory loss or paresthesias that interfere with function</td>
<td></td>
</tr>
<tr>
<td>Neurological/motor</td>
<td>None or no change</td>
<td>Subjective weakness/no objective findings</td>
<td>Mild objective weakness without significant impairment of function</td>
<td>Objective weakness with impairment of function</td>
<td></td>
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<tr>
<td>Neurological/cortical</td>
<td>None</td>
<td>Mild somnolence or agitation</td>
<td>Moderate somnolence or agitation</td>
<td>Severe somnolence, agitation, confusion, disorientation or hallucinations</td>
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<tr>
<td>Neurological/cerebellar</td>
<td>None</td>
<td>Slight incoordination/ dysdiadochokinesis</td>
<td>Intention tremor, dysmetria, slurred speech, nystagmus</td>
<td>Locomotor ataxia</td>
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<tr>
<td>Neurological/mood</td>
<td>No change</td>
<td>Mild anxiety or depression</td>
<td>Moderate anxiety or depression</td>
<td>Cerebellar necrosis</td>
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<tr>
<td>Neurological/headache</td>
<td>None</td>
<td>Mild</td>
<td>Moderate or severe but transient</td>
<td>Suicidal ideation</td>
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1/89 2 of 3
<table>
<thead>
<tr>
<th>TOXICITY</th>
<th>- 0 -</th>
<th>- 1 -</th>
<th>- 2 -</th>
<th>- 3 -</th>
<th>- 4 -</th>
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<tr>
<td>Neurologic</td>
<td>None or no change</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Ileus &gt; 96 hours</td>
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<tr>
<td>Neurological/constipation</td>
<td>None or no change</td>
<td>Asymptomatic/hearing loss on audiometry only</td>
<td>Tinnitus</td>
<td>Hearing loss interfering with function but correctable with hearing aid</td>
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<tr>
<td>Neurological/hearing</td>
<td>None or no change</td>
<td>Scattered macular or papular eruption or erythema that is asymptomatic</td>
<td>Urticaria, drug fever = 38°C, 100.4°F/mild bronchospasm</td>
<td>Symptomatic subtotal loss of vision</td>
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<tr>
<td>Neurological/vision</td>
<td>None or no change</td>
<td></td>
<td>Generalized symptomatic macular, papular, or vesicular eruption</td>
<td>Blindness</td>
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<tr>
<td>Skin</td>
<td>None or no change</td>
<td>Transient rash/drug fever &lt; 38°C, 100.4°F</td>
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<td>Exfoliative dermatitis or ulcerating dermatitis</td>
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<tr>
<td>Allergy</td>
<td>None</td>
<td>37.1 - 38.0°C</td>
<td>38.1 - 40.0°C</td>
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<td>Anaphylaxis</td>
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<tr>
<td>Fever in absence of infection</td>
<td>None</td>
<td>98.7 - 100.4°F</td>
<td>100.5 - 104.0°F</td>
<td>&gt; 40.0°C/104.0°F for more than 24 hrs or fever accompanied by hypotension</td>
<td>Plastig surgery indicated</td>
</tr>
<tr>
<td>Local</td>
<td>None</td>
<td>Pain</td>
<td>Pain and swelling with inflammation or phlebitis</td>
<td>ulceration</td>
<td></td>
</tr>
<tr>
<td>Weight gain/loss</td>
<td>&lt; 5.0%</td>
<td>5.0 - 9.9%</td>
<td>10.0 - 19.9%</td>
<td>=&gt; 20.0 %</td>
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<tr>
<td>Hyperglycemia</td>
<td>&lt; 116</td>
<td>116 - 164</td>
<td>161 - 250</td>
<td>251 - 500</td>
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<tr>
<td>Hypoglycemia</td>
<td>&gt; 64</td>
<td>55 - 64</td>
<td>40 - 54</td>
<td>30 - 39</td>
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<tr>
<td>Amylase</td>
<td>WNL</td>
<td>&lt; 1.5 X N</td>
<td>1.5 - 2.0 X N</td>
<td>2.1 - 5.0 X N</td>
<td></td>
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<tr>
<td>Hypercalcemia</td>
<td>&lt; 10.6</td>
<td>10.6 - 11.5</td>
<td>11.6 - 12.5</td>
<td>12.6 - 13.5</td>
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<tr>
<td>Hypocalcemia</td>
<td>&gt; 8.4</td>
<td>8.4 - 7.8</td>
<td>7.7 - 7.0</td>
<td>6.9 - 6.1</td>
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<tr>
<td>Hypomagnesemia</td>
<td>&gt; 1.4</td>
<td>1.4 - 1.2</td>
<td>1.1 - 0.9</td>
<td>0.8 - 0.6</td>
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<tr>
<td>Fibrinogen</td>
<td>WNL</td>
<td>0.99 - 0.75 X N</td>
<td>0.74 - 0.50 X N</td>
<td>0.49 - 0.25 X N</td>
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<tr>
<td>Prothrombin time</td>
<td>WNL</td>
<td>1.01 - 1.25 X N</td>
<td>1.26 - 1.50 X N</td>
<td>1.51 - 2.00 X N</td>
<td></td>
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<tr>
<td>Partial thromboplastin time</td>
<td>WNL</td>
<td>1.01 - 1.66 X N</td>
<td>1.67 - 2.33 X N</td>
<td>2.34 - 3.00 X N</td>
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1/89 3 of 3
<table>
<thead>
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<th>Acute Radiation Morbidity Scoring Criteria</th>
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<tr>
<td><strong>[0]</strong></td>
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<tr>
<td><strong>SKIN</strong></td>
</tr>
<tr>
<td><strong>MUCOUS MEMBRANE</strong></td>
</tr>
<tr>
<td><strong>EYE</strong></td>
</tr>
<tr>
<td><strong>EAR</strong></td>
</tr>
<tr>
<td><strong>SALIVARY GLAND</strong></td>
</tr>
<tr>
<td><strong>PHARYNX &amp; ESOPHAGUS</strong></td>
</tr>
<tr>
<td><strong>LARYNX</strong></td>
</tr>
<tr>
<td><strong>UPPER G.I.</strong></td>
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### Acute Radiation Morbidity Scoring Criteria (continued)

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<tr>
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</thead>
<tbody>
<tr>
<td><strong>LOWER G.I.</strong></td>
<td>Increased frequency or change in quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics</td>
<td>Diarrhea requiring parasympatholytic drugs (e.g., Lomotil)/mucous discharge necessitating sanitary pads/rectal or abdominal pain requiring analgesics</td>
<td>Diarrhea requiring parenteral support/severe mucous or blood discharge necessitating sanitary pads/abdominal distention (flat plate radiograph demonstrates distended bowel loops)</td>
<td>Acute or subacute obstruction, fistula or perforation GI bleeding requiring transfusion abdominal pain or tenesmus requiring tube decompression or bowel diversion</td>
</tr>
<tr>
<td><strong>INCLUDING</strong></td>
<td>No change</td>
<td>Persistent cough requiring narcotic, antussive agents/dyspnea at rest/clinical or radiologic evidence of acute pneumonitis/intermittent U2 or steroids may be required</td>
<td>Severe cough unresponsive to narcotic antussive agent or dyspnea at rest/clinical or radiologic evidence of acute pneumonitis/intermittent U2 or steroids may be required</td>
<td>Severe respiratory insufficiency/continuous oxygen or assisted ventilation</td>
</tr>
<tr>
<td><strong>PELVIS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LUNG</strong></td>
<td>Mild symptoms of dry cough or dyspnea on exertion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GENITOURINARY</strong></td>
<td>No change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HEART</strong></td>
<td>Frequency of urination or nocturia twice pretreatment habit/dysuria, urgency not requiring medication</td>
<td>Frequency of urination or nocturia which is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (e.g., Pyridium)</td>
<td>Frequency with urgency and nocturia hourly or more frequently/dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/ gross hematuria with/without clot passage</td>
<td>Hematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration or necrosis</td>
</tr>
<tr>
<td><strong>HEART</strong></td>
<td>No change over baseline</td>
<td>Symptomatic with EKG changes and radiologic findings of congestive heart failure or pericardial disease, no specific treatment required</td>
<td>Congestive heart failure, angina pectoris, pericardial disease responding to therapy</td>
<td>Congestive heart failure, angina pectoris, pericardial disease, arrhythmias not responsive to nonsurgical measures</td>
</tr>
<tr>
<td><strong>CNS</strong></td>
<td>Fully functional status (i.e., able to work) with minor neurologic findings, no medication needed</td>
<td>Neurologic findings present sufficient to require home care/nursing assistance may be required/meds. including steroids/anti-seizure agents may be required.</td>
<td>Neurologic findings requiring hospitalization for initial management</td>
<td>Serious neurologic impairment which includes paralysis, coma or seizures &gt;3 per week despite medication/hospitalization required</td>
</tr>
<tr>
<td><strong>HEMATOLOGIC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MCV (X 1000)</strong></td>
<td>2.0 – &lt;3.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PLATELETS</strong></td>
<td>&gt;40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(X 1000)</strong></td>
<td>3.0 – &lt;4.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NEUTROPHILS</strong></td>
<td>&gt;100</td>
<td>50 – &lt;75</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(X 1000)</strong></td>
<td>75 – &lt;100</td>
<td>25 – &lt;50</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HEMOGLOBIN</strong></td>
<td>1.0 – &lt;1.5</td>
<td>0.5 – &lt;1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(GM %)</strong></td>
<td>1.5 – &lt;1.9</td>
<td>&lt;0.5 or sepsis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HEMATOCRIT (%)</strong></td>
<td>11 – 9.5</td>
<td>&lt;7.5 – 5.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**GUIDELINES**

The acute morbidity criteria are used to score/grade toxicity from radiation therapy. The criteria are relevant from day 1, the commencement of therapy, through day 90. Thereafter, the EORTC/ROG Criteria for Late Effects are to be utilized.

The evaluator must attempt to discriminate between disease and treatment related signs and symptoms.

All toxicities Grade 3, 4 or 5 must be verified by the Principal Investigator.

*ANY TOXICITY WHICH CAUSED DEATH IS GRADED 5.*
<table>
<thead>
<tr>
<th>ORGAN/TISSUE</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SKIN</strong></td>
<td>None</td>
<td>Pigmentation change</td>
<td>Some loss</td>
<td>Patchy atrophy</td>
<td>Marked atrophy</td>
<td>Ulceration</td>
</tr>
<tr>
<td><strong>SUBCUTANEOUS TISSUE</strong></td>
<td>None</td>
<td>Slight induration (fibrosis) &amp; loss of subcutaneous fat</td>
<td>Moderate fibrosis but asymmetrical/Small field contraction/ &lt; 10% linear reduction</td>
<td>Severe atrophy/Total loss of subcutaneous fat</td>
<td>Necrosis/Contraction &amp; Infarction</td>
<td></td>
</tr>
<tr>
<td><strong>MUCOUS MEMBRANE</strong></td>
<td>None</td>
<td>Slight atrophy and dryness</td>
<td>Moderate atrophy and telangiectasia/ Little mucosa</td>
<td>Marked atrophy with complete dryness/Severe telangiectasia</td>
<td>Ulceration</td>
<td></td>
</tr>
<tr>
<td><strong>SALIVARY GLANDS</strong></td>
<td>None</td>
<td>Slight dryness of mouth/Poor response on stimulation</td>
<td>Moderate atrophy and telangiectasia/ Little mucosa</td>
<td>Complete dryness</td>
<td>Fibrillation</td>
<td></td>
</tr>
<tr>
<td><strong>SPINAL CORD</strong></td>
<td>None</td>
<td>Mild L'Hermitte’s syndrome</td>
<td>Severe L'Hermitte’s syndrome</td>
<td>Objective neurological findings at or below cord level treated</td>
<td>Nociception/Perspiration/Fistula</td>
<td></td>
</tr>
<tr>
<td><strong>BRAIN</strong></td>
<td>None</td>
<td>Mild headache/Slight lethargy</td>
<td>Moderate headache/Great lethargy</td>
<td>Severe headache/Severe CNS dysfunction (partial loss of power or dyskinesia)</td>
<td>Nociception/Perspiration/Fistula</td>
<td></td>
</tr>
<tr>
<td><strong>EYE</strong></td>
<td>None</td>
<td>Asymptomatic cataract</td>
<td>Symptomatic cataract</td>
<td>Severe keratitis</td>
<td>Panophthalmitis</td>
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</tr>
<tr>
<td><strong>LARYNX</strong></td>
<td>None</td>
<td>Hoarseness/Slight atrophy of vocal cords</td>
<td>Moderate arytenoid edema/Chondritis</td>
<td>Severe edema/Severe chondritis</td>
<td>Nociception/Perspiration/Fistula</td>
<td></td>
</tr>
<tr>
<td><strong>LUNG</strong></td>
<td>None</td>
<td>Asymptomatic or mild symptoms (dry cough)</td>
<td>Moderate angina of effort/Mild pericarditis/ Normal heart size/Persistent abnormality T wave and ST changes</td>
<td>Severe angina/Pericardial effusion/Constrictive pericarditis/Moderate heart failure/Cardiac enlargement/Kidney abnormalities</td>
<td>Nociception/Perspiration/Fistula</td>
<td></td>
</tr>
<tr>
<td><strong>HEART</strong></td>
<td>None</td>
<td>Mild fibrosis/Slight diffusely involve lung solids/No pain on swallowing</td>
<td>Unable to take solid food normally/Severe oedema/Swelling semi-solid food/Dilatation may be indicated</td>
<td>Severe fibrosis/Able to swallow only liquids/ May have pain on swallowing/ Dilatation required</td>
<td>Nociception/Perspiration/Fistula</td>
<td></td>
</tr>
<tr>
<td><strong>ESOPHAGUS</strong></td>
<td>None</td>
<td>Mild diarrhea/Mild cramping/Excessive movement 1-5 times daily/ Slight rectal discharge or bleeding</td>
<td>Moderate diarrhea and colicky/bowel movements &gt; 5 times daily/Excessive rectal mucosa or intermittent bleeding</td>
<td>Rectal prolapse/Obstruction or bleeding requiring surgery</td>
<td>Nociception/Perspiration/Fistula</td>
<td></td>
</tr>
<tr>
<td><strong>SMALL/LARGE INTESTINE</strong></td>
<td>None</td>
<td>Mild constipation/Mild cramping/Excessive movement 1-5 times daily/ Slight rectal discharge or bleeding</td>
<td>Moderate diarrhea and colicky/bowel movements &gt; 5 times daily/Excessive rectal mucosa or intermittent bleeding</td>
<td>Rectal prolapse/Obstruction or bleeding requiring surgery</td>
<td>Nociception/Perspiration/Fistula</td>
<td></td>
</tr>
<tr>
<td><strong>LIVER</strong></td>
<td>None</td>
<td>Mild jaundice</td>
<td>Moderate jaundice</td>
<td>Severe jaundice</td>
<td>Nociception/Perspiration/Fistula</td>
<td></td>
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<tr>
<td><strong>KIDNEY</strong></td>
<td>None</td>
<td>Transient albuminuria</td>
<td>Persistent moderate albuminuria (2+)/Mild hypertension/Mild hypertension/No related anemia/Moderate impairment renal function Urea 25-35 mg% Creatinine 1.5-2.0 mg%</td>
<td>Chronic irreversible renal failure Urea &gt; 60 mg% Creatinine &gt; 5.0 mg%</td>
<td>Nociception/Contracture bladder (capacity &lt; 100 cc)</td>
<td></td>
</tr>
<tr>
<td><strong>BLADDER</strong></td>
<td>None</td>
<td>Slight epithelial atrophy/Minor telangiectasia (microscopic hematuria)</td>
<td>Moderate frequency/Generalized telangiectasia/ Intermittent macroscopic hematuria</td>
<td>Severe frequency &amp; dysuria</td>
<td>Nociception/Contracture bladder (capacity &lt; 100 cc)</td>
<td></td>
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<tr>
<td><strong>BONE</strong></td>
<td>None</td>
<td>Asymptomatic/No growth retardation/Reduced bone density</td>
<td>Moderate pain or tenderness/Growth retardation/ Irregular bone sclerosis</td>
<td>Severe pain or tenderness</td>
<td>Nociception/Spontaneous fracture</td>
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<tr>
<td><strong>JOINT</strong></td>
<td>None</td>
<td>Mild joint stiffness/Slip joint limitation of movement</td>
<td>Moderate stiffness or intermittent or moderate joint pain/Moderate limitation of movement</td>
<td>Severe joint stiffness/ Pain on movement/Severe limitation of movement</td>
<td>Nociception/Complete fixation</td>
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</tbody>
</table>
APPENDIX VII

Ideal Body Weight Charts

Ideal Body Weight for Height

MALES

<table>
<thead>
<tr>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
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<td>145</td>
<td>51.9</td>
<td>159</td>
<td>59.9</td>
<td>173</td>
<td>68.7</td>
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<tr>
<td>146</td>
<td>52.4</td>
<td>160</td>
<td>60.5</td>
<td>174</td>
<td>68.7</td>
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<tr>
<td>147</td>
<td>52.9</td>
<td>161</td>
<td>61.1</td>
<td>175</td>
<td>70.1</td>
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<tr>
<td>148</td>
<td>53.5</td>
<td>162</td>
<td>61.7</td>
<td>176</td>
<td>70.8</td>
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<tr>
<td>149</td>
<td>54.0</td>
<td>163</td>
<td>62.3</td>
<td>177</td>
<td>71.6</td>
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<tr>
<td>150</td>
<td>54.5</td>
<td>164</td>
<td>62.9</td>
<td>178</td>
<td>72.4</td>
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<tr>
<td>151</td>
<td>55.0</td>
<td>165</td>
<td>63.5</td>
<td>179</td>
<td>73.3</td>
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<tr>
<td>152</td>
<td>55.6</td>
<td>166</td>
<td>64.0</td>
<td>180</td>
<td>74.2</td>
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<tr>
<td>153</td>
<td>56.1</td>
<td>167</td>
<td>64.6</td>
<td>181</td>
<td>75.0</td>
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<tr>
<td>154</td>
<td>56.6</td>
<td>168</td>
<td>65.2</td>
<td>182</td>
<td>75.8</td>
</tr>
<tr>
<td>155</td>
<td>57.2</td>
<td>169</td>
<td>65.9</td>
<td>183</td>
<td>76.5</td>
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<tr>
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<td>57.9</td>
<td>170</td>
<td>66.6</td>
<td>184</td>
<td>77.3</td>
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<tr>
<td>157</td>
<td>58.6</td>
<td>171</td>
<td>67.3</td>
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APPENDIX VIII

ADVERSE DRUG REACTION REPORTING GUIDELINES

General Toxicity Reporting 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.

1. The Principal Investigator will report to the RTOG Group Chairman, the details of any unusual, significant, fatal or life-threatening protocol treatment reaction. In the absence of the Group Chairman, the report should be made to the Headquarters Data Management Staff (215/574-3150).

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

3. When directed, a written report containing all relevant clinical information concerning the reported event will be sent by the Principal Investigator to RTOG Headquarters. This must be mailed within 10 working days of the discovery of the toxicity unless specified sooner by the protocol.

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), when feasible, 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 (Adverse Reaction Reports or Drug Experience Reports) submitted to NCI, IDB, FDA, or to another Cooperative Group (in the case of RTOG sponsored Intergroup studies) must also be submitted to RTOG Headquarters when written documentation is required.

6. When telephone reporting is required, the Principal Investigator should have all relevant material available. See attached reporting form for the information that may be requested.

7. See the specific protocol for criteria utilized to grade the severity of the reaction.

8. The Principal Investigator when participating in RTOG sponsored Intergroup studies is obligated to comply with all additional reporting specifications required by the individual study.

9. Institutions must also meet their individual Institutional Review Board (IRB) policy with regard to their toxicity reporting procedure.

10. Failure to comply with reporting requirements in a timely manner may result in suspension of participation, of application for investigational drugs or both.

B. Modality Toxicity Guidelines

1. Radiation Therapy and Hyperthermia Toxicity Reporting

a. All fatal toxicities resulting from protocol radiotherapy or hyperthermia must be reported by telephone to the Group Chairman or to RTOG Headquarters Data Management and to the Study Chairman within 24 hours of discovery.
b. All life-threatening or grade 4 toxicities from altered fractionation protocol therapy or particle radiotherapy must be reported by telephone to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman within 24 hours of discovery.

c. Appropriate data forms and if requested, a special written report, must be submitted to Headquarters within 10 working days of the reported incident.

2. **Adverse Drug Reactions and Toxicities - Drugs 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.

An unknown adverse reaction is a toxicity thought to have resulted from the agent but had not previously been identified as a known side effect.

a. **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. Form 1839 is to be used in reporting details. See Appendix VIII. All relevant data forms must accompany the RTOG copy of Form 1839.

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 and a special written report may be required. See Appendix VIII.

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

b. **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  
P. O. Box 30012  
Bethesda, MD 20814  
Telephone number available 24 hours  
(301) 496-7957
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.**

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 10 working days with a copy to IDB (Grade 4 myelosuppression not reported to IDB)**

- **All fatal (grade 5) and life threatening (grade 4) unknown adverse reactions** resulting from or suspected to be related to investigational agent.
  
  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.
## ADVERSE REACTION REPORT
(Drugs and Biologics)

### I. REACTION INFORMATION

<table>
<thead>
<tr>
<th>1. PATIENT ID/INITIALS (In Confidence)</th>
<th>2. AGE YRS.</th>
<th>3. SEX</th>
<th>4.-6. REACTION ONSET</th>
<th>8.-12. CHECK ALL APPROPRIATE:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>MO. DA. YA.</td>
<td>PATIENT DIED</td>
</tr>
</tbody>
</table>

- Reaction treated with Rx drug
- Resulted in, or prolonged, inpatient hospitalization
- Resulted in permanent disability
- None of the above

### 7. DESCRIBE REACTION(S)

### 13. RELEVANT TESTS/LABORATORY DATA

### II. SUSPECT DRUG(S) INFORMATION

| 14. SUSPECT DRUG(S) (Give manufacturer and lot no. for vaccines/biologics) |
| 20. DID REACTION ABATE AFTER STOPPING DRUG? |
| 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? |

<table>
<thead>
<tr>
<th>15. DAILY DOSE</th>
<th>16. ROUTE OF ADMINISTRATION</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
</tr>
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</table>

<table>
<thead>
<tr>
<th>17. INDICATION(S) FOR USE</th>
<th>18. DATES OF ADMINISTRATION (From/To)</th>
<th>19. DURATION OF ADMINISTRATION</th>
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<tbody>
<tr>
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### III. CONCOMITANT DRUGS AND HISTORY

| 22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (Exclude those used to treat reaction) |
| 23. OTHER RELEVANT HISTORY (e.g. diagnoses, allergies, pregnancy with LMP, etc.) |

### IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

<table>
<thead>
<tr>
<th>24. NAME AND ADDRESS OF MANUFACTURER (Include Zip Code)</th>
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<tr>
<th>24a. IND/VIDA. NO. FOR SUSPECT DRUG</th>
<th>24b. MFR. CONTROL NO.</th>
<th>24d. REPORT SOURCE (Check all that apply)</th>
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<td>LITERATURE</td>
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### V. INITIAL REPORTER (In confidence)

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<th>26. TELEPHONE NO. (Include area code)</th>
<th>26a. NAME AND ADDRESS OF REPORTER (Include Zip Code)</th>
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<table>
<thead>
<tr>
<th>26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?</th>
<th>26d. ARE YOU A HEALTH PROFESSIONAL?</th>
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<tbody>
<tr>
<td>YES</td>
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### Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

**NOTE:** Required of manufacturers by 21 CFR 314.80
INSTRUCTIONS FOR COMPLETING FORM FDA 1639

Use a separate report form for each case. If more space is needed, additional pages may be attached.

I. Patient/Reaction Information (Items 1-12)

1. Patient ID/Initials: Record patient's identification (i.e. medical record number, initials, etc). (This information is kept in confidence by the FDA.)

2. Age: Record the age of the patient. When reporting a congenital malformation, record the age of the mother.

3. Sex: Record the sex of the patient. When reporting a congenital malformation, record the sex of the baby.

4. Weight: Record the weight of the patient in pounds. When reporting a congenital malformation, record the weight of the mother.

5. Height: Record the height of the patient in inches. When reporting a congenital malformation, record the height of the mother.

6. Reporting Date: Record the date when the report was initially communicated to the manufacturer.

7. Reaction Onset Date: Record the date on which the reaction was first observed or detected.

8. Suspected Reaction(s): Describe the signs, symptoms and course of the drug related event in the terminology used by the original observer of the reaction. (Coding terms e.g. COSTART, SNOMED, etc. may also be noted, but only in addition to original description.)

9. Outcome of Reaction: Indicate the status of the patient as of date indicated in Item 23. If the patient died, give the cause and date of death. Include discharge summary and/or autopsy findings, if available.

10. Tests/Laboratory Data: Describe the results of all diagnostic tests and exams (e.g. biochemical tests, x-rays, endoscopy, biopsy, etc.) which were done as a result of the event described in Item 8. Pertinent base line values and laboratory normals should be included with each test or exam reported. If this information is not available at the time of the initial report, a follow up report should be submitted.

11. Treatment Required: If "yes", a short description of treatment should be included in Item 8.

12. Hospitalization Required: If "yes", a short description of the treatment should be included in Item 8.

II. Suspect Drug Information (Items 13-20)

13. Suspect Drug(s): Record the trade name. The generic name should be used only when the trade name is not known. Include IND/NDA number of the drug as well as the lot number, when available.

14. Total Daily Dose: Record the total daily dose as of the date recorded in Item 7. If drug(s) was given in a different dose or form on a previous occasion, include dates and total daily dose for each drug exposure.

15. Route of Administration: Record the route of administration (i.e. po, IM, IV) as of the date recorded in Item 7.

16. Indication(s) for use: Record intended use in accepted medical terminology.

17. Therapy Dates: Give starting and stopping dates of administration for each drug listed in Item 13.

18. Therapy Duration: Give duration of therapy in days.

19. Dechallenge:
   (a) Applicable if the suspect drug was either reduced in dosage or discontinued.
   (b) If 19(a) is checked, indicate whether the reaction subsided upon reduced dosage or discontinuation of the drug.

20. Rechallenge:
   (a) Applicable if the suspect drug was reintroduced to the patient's therapy after dechallenge.
   (b) If 20(a) is "yes", indicate whether or not the reaction reappeared upon rechallenge with the drug.

III. Recent/Concomitant Drugs and Medical Problems (Items 21-22)

21. List all recent or concomitant drugs. Include the total daily dose(s), indication(s) for use, route(s) of administration and dates of administration and/or duration of therapy for each drug.

22. Describe other relevant medical conditions or problems which could have contributed to the reaction. Include pertinent medical history such as allergies, occupation, industrial hazards, diet, smoking, climate, ethnic origin, cosmetics and biologicals. When reporting a congenital malformation, include the date of the last menstrual period of the mother, gravidity, parity and previous abortions.

IV. Other Information (Items 23-26)

23. Manufacturer's Information: Include manufacturer's name, address, control number and date report is sent to FDA. This control number is the identifying number assigned by the manufacturer to the report for internal record control.

24. Indicate if this is an initial submission to FDA or a follow-up of a previously submitted Form FDA 1639. If this is a follow-up attach copy of initial report.

25. Record the name, title and address of the practitioner originating the report. (This information is kept in confidence by the FDA.)

26. Check "yes" or "no", if the source of this report may or may not be released to the Armed Forces Institute of Pathology for further study and follow-up. This is encouraged whenever possible.