RADIATION THERAPY ONCOLOGY GROUP
RTOG 98-11
A PHASE III RANDOMIZED STUDY OF 5-FUOROURACIL, MITOMYCIN-C, AND RADIOTHERAPY VERSUS 5-FUOROURACIL, CISPLATIN AND RADIOTHERAPY IN CARCINOMA OF THE ANAL CANAL

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Appendix A
Includes the following:

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- NCCTG (R9811)
- SWOG (R9811)
- RTOG (9811)

This study was conducted by the Radiation Therapy Oncology Group (RTOG) and involved a phase III randomized study comparing 5-Fluorouracil, Mitomycin-C, and radiotherapy versus 5-Fluorouracil, Cisplatin, and radiotherapy in carcinoma of the anal canal.
This protocol was designed and developed by the Radiation Therapy Oncology Group (RTOG) of the American College of Radiology (ACR). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by RTOG nor does RTOG assume any responsibility for unauthorized use of this protocol.
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RADIATION THERAPY ONCOLOGY GROUP

RTOG 98-11
(CALGB 89808, ECOG R9811, NCCTG R9811, SWOG R9811)

A Phase III Randomized Study of 5-Fluorouracil, Mitomycin-C, and Radiotherapy Versus 5 Fluorouracil, Cisplatin and Radiotherapy in Carcinoma of the Anal Canal

SCHEMA

<table>
<thead>
<tr>
<th>S</th>
<th>Gender</th>
<th>R</th>
<th>Arm 1: 5-FU + Mitomycin-C and Radiotherapy (Concurrent with EBRT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>1. Male</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>2. Female</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>Clinical</td>
<td>O</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Nodal Status</td>
<td>M</td>
<td>Arm 2: 5-FU + Cisplatin and Radiotherapy (Induction and Concurrent)</td>
</tr>
<tr>
<td>F</td>
<td>1. Positive</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>2. Negative</td>
<td>Z</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>E</td>
</tr>
</tbody>
</table>

Primary Size
1. > 2 cm to 5 cm
2. > 5 cm

- **Chemotherapy** (Note: In Arm 1, both courses of chemotherapy will be administered during radiotherapy. In Arm 2, patients will receive two courses of induction chemotherapy in addition to 2 courses during radiotherapy).

5-FU + Mitomycin-C: Mitomycin-C 10 mg/m² i.v. bolus on days 1 and 29 (not to exceed 20 mg per course)
5-FU 1000 mg/m²/day by continuous infusion on days 1-4 and 29-32

5-FU + Cisplatin: Cisplatin 75 mg/m² i.v. over 60 min. on days 1 and 29, and also repeated on days 57 and 85 (days 57 and 85 should correspond to days 1 and 29 of radiotherapy).
5-FU 1000 mg/m²/day by continuous infusion on days 1-4 and 29-32, and also repeated on days 57-60 and 85-88 (days 57 and 85 should correspond to days 1 and 29 of radiotherapy)

- **External Beam Irradiation (EBRT):** (Note: treatment break of ≤ 10 days will be optional for severe local skin reactions)

Note: Large pelvic field (to 30.6 Gy) and reduced field #1 (to 45 Gy) will be used in all patients; reduced field #2 is to be used for all patients with T3, T4, or N+ lesions and for those patients with T2 lesions that have residual disease after 45 Gy.

1. Initial Field: 30.6 Gy in 17 Fx (1.8 Gy/fx) to large pelvic field with superior border at L5-S1.
2. Field reduction #1: Reduce superior border to inferior level of SI joints
   (a) Deliver 14.4 Gy in 8 Fx (1.8 Gy/fx) for a total of 45 Gy
   (b) For N0 patients, reduce off inguinal nodes after 36 Gy
3. Reduction #2 (for all T3, T4, or N+ lesions and T2 lesions with residual cancer after 45 Gy)
   Deliver 10-14 Gy (2 Gy/fx) to gross primary or nodal disease plus a 2.0 to 2.5 cm margin for a total dose of 55-59 Gy within boost field #2.

- **Surgery:** (a) Biopsy of palpable inguinal lymph nodes prior to treatment.
  (b) (Optional) Full thickness biopsy to be performed 8 weeks after completion of radiation and chemotherapy if any palpable residual abnormality is present.

**Eligibility** (See Section 3.0 for details)

- Primary squamous, basaloid, or cloacogenic carcinoma of the anal canal.
- ≥ 18 years old; KPS ≥ 60; T2-4
- Creatinine ≤ 1.5 mg/dl, bilirubin < 1.4 mg/dl, WBC ≥ 4,000, ANC ≥ 1800, platelets ≥ 100,000
- No prior radiation or chemotherapy; no surgery except for biopsy at study site.

**SWOG Members:** See Section 5.5 for randomization

Required Sample Size: 650 (12/20/99, 2/1/01)
1. Does the patient have a histologically-proven primary squamous, basaloid, or cloacogenic carcinoma of the anal canal other than carcinoma in situ?

2. Is this locally or regionally recurrent disease after local excision or perineal resection?

3. What is the T stage?

4. If the patient has a positive nodal status, is it limited to pelvic or inguinal nodes?

5. Is there evidence of distant metastases?

6. Does the patient currently have another malignancy (excluding non melanomatous skin neoplasm)?

7. If the patient had a prior malignancy, is he/she disease-free for ≥ five years?

8. Does the patient have AIDS?

9. Has the patient had prior radiation or chemotherapy?

10. Has the patient had prior surgery for cancer of the anus, excluding biopsy?

11. Does the patient meet the renal/hematologic requirements specified in Section 3.1.6 of the protocol?

12. Is the patient pregnant or lactating?

13. If the patient is a woman with childbearing potential, has she agreed to practice an effective method of contraception?

14. Does the patient have an active systemic infection, uncontrolled diabetes, uncompensated heart disease, or uncontrolled high blood pressure?

15. What is the Karnofsky Performance score?

16. How old is the patient?

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

1. Name of institutional person registering this case?
2. Has the Eligibility Checklist (above) been completed?
3. Is the patient eligible for this study?
4. Date the study-specific Consent Form was signed? (must be prior to study entry)
5. Patient’s Name
6. Verifying Physician
7. Patient’s ID Number
8. Date of Birth
9. Race
10. Social Security Number
11. Gender
12. Patient’s Country of Residence
13. Zip Code
14. Patient’s Insurance Status
15. Will any component of the patient’s care be given at a military or VA facility?
16. Treatment Start Date
17. Medical Oncologist’s Name
18. Clinical Nodal Status (positive or negative)
19. Primary Tumor Size (> 2cm to 5cm vs. > 5cm)
20. Treatment Assignment

Completed by ________________________________ Date ____________________
1.0 INTRODUCTION
1.1 Background

1.1.1 Biologic Alteration
Carcinoma of the anal canal is an uncommon malignancy and is distinguished from other gastrointestinal malignancies by its biologic behavior and treatment results. Alterations in the expression of wild-type p53 protein appear to be important if not essential to the development of anal canal squamous cell carcinomas (SCCs), as the vast majority of these tumors contain alterations in p53. Anogenital SCCs, those of cervix and anal origin, appear to have a similar etiology. Like cervix cancers, approximately 80% of anal canal SCCs contain one or more subtypes of human papilloma virus (HPV) while most anal canal SCCs that lack HPV have a p53 mutation. Individuals with cervix cancers which contain HPV DNA appear to have a better prognosis, probably due to the degradation of p53 by the HPV E6 protein. In theory, this improved survival may be because tumor DNA damaged by ionizing radiation is left unrepaired due to the absence of wild-type p53. The unrepaired DNA cannot replicate properly and the cell dies.

Given the common etiology of anogenital SCCs, it is possible that anal canal cancers, like cervix cancers, are more susceptible to radiation if functional p53 protein is absent. This is supported by results obtained in pretreatment specimens from subjects enrolled on RTOG 87-04 which suggested that individuals whose tumors overexpressed p53 had a worse outcome that those with normal or absent expression. This hypothesis can be addressed by evaluating the presence of p53 and HPV in the pretreatment tumor specimens from subjects enrolled in RTOG 98-11.

1.1.2 Clinical Aspects
Carcinoma of the anal canal, throughout its natural history, is confined to the pelvis in > 80% of patients and it is a chemotherapy and radiotherapy sensitive tumor. Thus it is a curable cancer with anal preservation in 65% to 75% of patients. Therapeutic developments in the treatment of anal carcinoma have resulted in significant advances. While surgery was the primary therapy 15 years ago, it has now become the method of salvage. The combination of chemotherapy and radiotherapy has now become the standard therapy for local-regional carcinoma of the anal canal. The five-year survival rates of patients with anal epidermoid malignancies managed by radical surgery range from 40-60%. Two hundred and fifty patients treated with combined radiation and chemotherapy employing 5-FU infusion and Mitomycin-C have been reported in seven published series. Completed and sustained tumor eradication has been achieved in 75-85% of patients thus treated. Although organ preservation has become the standard approach for most anal cancers, questions remain regarding approaches which might result in higher rates of local control than those obtained by the use of 5-FU plus mitomycin and radiotherapy. The combined modality program described initially by Nigro, et al. was a preoperative regimen which included 30 Gy in conjunction with two cycles of 5-Fluorouracil infusion and one dose of Mitomycin-C. Subsequent investigators employed a similar regimen with variable dosages of radiation. Nevertheless, all reported regimens employed both 5-FU infusion and Mitomycin chemotherapy as initially described by Nigro. Any significant difference in the percentage of patients with persistent disease on post treatment biopsy would be therefore attributable to the absence or presence of Mitomycin-C in the regimen.

The results of combined modality therapy using 5-FU and Mitomycin plus radiotherapy have been very satisfactory with most series reporting survival and local control at three to five years in the range of 60% to 90% (Table 1). Although acute toxicity in the form of temporarily painful, moist desquamation is frequent, it should be considered acceptable since this therapy offers a high cure rate (Table 2).
**Table 1**

Local Control & Survival After Sphincter-Preserving Therapy in Anal Cancer: Selected Series

<table>
<thead>
<tr>
<th>Authors</th>
<th>Total RT (Gy)</th>
<th>RT Duration (weeks)</th>
<th>Chemotherapy</th>
<th>Pt. #</th>
<th>Primary Tumor Size</th>
<th>Local Control %</th>
<th>Local Control Duration</th>
<th>Survival % Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sischy et al.</td>
<td>41</td>
<td>4.5-5</td>
<td>5-FU, mito-C</td>
<td>79</td>
<td>&lt; 3 cm</td>
<td>84</td>
<td>3 yr.</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 cm</td>
<td>62</td>
<td>3 yr.</td>
<td>68</td>
</tr>
<tr>
<td>Leichman et al.</td>
<td>30</td>
<td>3</td>
<td>5-FU, mito-C</td>
<td>45</td>
<td>2-8 cm</td>
<td>84</td>
<td>50 mos. median</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50 mos. median</td>
<td></td>
</tr>
<tr>
<td>Flam et al.</td>
<td>41-50</td>
<td>4.5-5.5</td>
<td>5-FU, mito-C</td>
<td>30</td>
<td>RNPb</td>
<td>97</td>
<td>6-90 mos.</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6-90 mos.</td>
<td></td>
</tr>
<tr>
<td>Tveit et al.</td>
<td>50</td>
<td>5</td>
<td>5-FU, mito-C</td>
<td>24c</td>
<td>RNPb</td>
<td>83</td>
<td>40-70 mos.</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40-70 mos.</td>
<td></td>
</tr>
<tr>
<td>Cumming et al.</td>
<td>48-50</td>
<td>4-4.8</td>
<td>5-FU, mito-C</td>
<td>66</td>
<td>T1-2e T3-4e</td>
<td>91</td>
<td>2-13 yr.</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>48-60</td>
<td>4-6</td>
<td>5-FU, mito-C</td>
<td>69</td>
<td></td>
<td>86</td>
<td>2-13 yr.</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>45-55d</td>
<td>4</td>
<td>None</td>
<td>33</td>
<td></td>
<td>71</td>
<td>5 yr.</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>31</td>
<td></td>
<td></td>
<td>5 yr.</td>
<td></td>
</tr>
<tr>
<td>Eschwege et al.</td>
<td>60-65</td>
<td>5-6</td>
<td>None</td>
<td>33</td>
<td></td>
<td>71</td>
<td>2-13 yr.</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 yr.</td>
<td>35</td>
</tr>
<tr>
<td>Dogrowsky et al.</td>
<td>45-70</td>
<td>4-7</td>
<td>None</td>
<td>23</td>
<td>RNPb</td>
<td>83</td>
<td>24-125 mos.</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 yr.</td>
<td></td>
</tr>
<tr>
<td>Doggett et al.</td>
<td>45-76</td>
<td>4.5-8</td>
<td>None</td>
<td>35</td>
<td>1.3-4.5 cm</td>
<td>77</td>
<td>1-134 mos.</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 yr.</td>
<td></td>
</tr>
<tr>
<td>Martenson &amp;</td>
<td>47-67</td>
<td>5.5-7</td>
<td>None</td>
<td>18</td>
<td>T1-2f (17 pt)</td>
<td>90</td>
<td>7 yr.</td>
<td>86</td>
</tr>
<tr>
<td>Gunderson</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T3f (1 pt)</td>
<td></td>
<td>5 yr.</td>
<td></td>
</tr>
</tbody>
</table>

FU = follow-up; 5-FU = 5-fluorouracil; mito-C = mitomycin-c; RT = radiation therapy

a. Duration is given exclusive of treatment breaks.
b. Results not presented according to tumor size.
c. Includes 3 patients with distant metastasis before treatment began.
d. The most common regimen was 45 to 55 Gy; 28% of patients were treated by interstitial therapy, either in combination with external radiation therapy (7 patients) or alone.
e. International Union Against Cancer Staging System
f. American Joint Committee Staging System

**Table 2**

Complications Resulting in Colostomy After External Radiation Therapy With or Without Chemotherapy

| Authors               | Total Tumor Dose (Gy) | Daily Fraction Size, Gy | Duration of RT, wk | Chemotherapy          | # Evaluable Patients | Patients with Colostomy from Complications No. (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cummings et al. 10</td>
<td>45-60 50</td>
<td>Usually 2.5 2.5</td>
<td>4-6 4</td>
<td>None 5-FU, mito-C</td>
<td>25 1 4 4 13</td>
<td></td>
</tr>
<tr>
<td>Flam et al. 23</td>
<td>41-50</td>
<td>1.8</td>
<td>4.5-5.5</td>
<td>5-FU, mito-C</td>
<td>30 1c 3c</td>
<td></td>
</tr>
<tr>
<td>Doggett et al. 21</td>
<td>45-76</td>
<td>Usually 1.8-2.0</td>
<td>4.5-8</td>
<td>None 34b</td>
<td>1 3</td>
<td></td>
</tr>
<tr>
<td>Martenson &amp; Gunderson</td>
<td>47-67</td>
<td>1.8-2.0</td>
<td>5.5-7</td>
<td>None 18</td>
<td>2d 11</td>
<td></td>
</tr>
</tbody>
</table>

5-FU = 5-fluorouracil; mito-C = mitomycin-C; RT = radiation therapy
a. Duration is given exclusive of treatment breaks.
b. One patient treated by interstitial implantation is excluded.
c. Personal communication, Marshall Flam.
d. In both patients, restoration of gastrointestinal continuity and sphincter function was possible. Colostomy was temporary.

RTOG and ECOG have compared 5-FU plus radiotherapy (45 Gy) vs 5-FU, mitomycin C plus radiotherapy (45 Gy) in a randomized fashion. The major objective of this study was to evaluate the need for mitomycin C in the combined modality therapy of anal cancers. The results are listed below.

In a clinical correlation study performed on pretreatment biopsies from 64 patients enrolled in the study, tumors with p53 overexpression had decreased local control (52% vs. 78%, p = 0.1), NED survival (52% vs. 68%, p = 0.2), and absolute survival (58% vs. 78%, p = 0.1). A study with increased sample size should clarify the significance of these findings.

1.2 Results of the Randomized Trial (RTOG 87-04/ECOG 1289)

This protocol was the first randomized study comparing two methods of chemoradiotherapy in patients with anal carcinoma. One arm utilized 5-FU alone with radiotherapy and the other arm utilized 5-FU + mitomycin C. 5-FU was administered at 1000 mg/m²/day as a continuous infusion for 4 days beginning days 1 and 28 of radiotherapy. Mitomycin C was administered at 10mg/m² iv bolus on day 1 of each 5-FU course. Radiotherapy was given at 1.8 Gy daily, 5 x per week for 5 weeks to a total radiotherapy dose of 45 Gy (field reduction at 30.6 Gy and optional boost to 50.4 Gy if with palpable residual after 45 Gy). Salvage therapy for patients in either arm included 9 Gy/5 Fx radiotherapy boost concurrently with 5-FU and cisplatin if with a positive biopsy 4-6 weeks after completion of chemoradiotherapy. A pilot arm was first done to evaluate tolerance of radiotherapy plus 5-FU and mitomycin C and then the randomization portion of the trial was started. The pilot mitomycin C dose of 12 mg/m² was poorly tolerated and thus, it was reduced to 10mg/m².

Patients were accrued between January 15, 1988 and December 1, 1991. A total of 310 patients were randomized with a monthly accrual rate of 7 patients/month between the two cooperative groups.

<table>
<thead>
<tr>
<th>Patients</th>
<th>RT + 5-FU</th>
<th>RT + 5-FU + mito</th>
<th>Pilot</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total entered</td>
<td>154</td>
<td>156</td>
<td>19</td>
<td>329</td>
</tr>
<tr>
<td>Ineligible</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Properly entered and eligible</td>
<td>148</td>
<td>151</td>
<td>19</td>
<td>318</td>
</tr>
<tr>
<td>Analyzed</td>
<td>147</td>
<td>148</td>
<td>19</td>
<td>314</td>
</tr>
</tbody>
</table>

Common toxicity included leukopenia (particularly in patients receiving mitomycin C), dermatologic, and diarrhea. Toxicities reported for initial radiotherapy and chemotherapy are shown below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT + 5-FU</td>
<td>54%</td>
<td>6%</td>
<td>0</td>
</tr>
<tr>
<td>RT + 5-FU + mito</td>
<td>55%</td>
<td>19%</td>
<td>1%</td>
</tr>
<tr>
<td>Pilot (RT + 5-FU + mitomycin C)</td>
<td>63%</td>
<td>32%</td>
<td>0</td>
</tr>
</tbody>
</table>

79% of patients in 5-FU alone arm received chemotherapy per protocol. 67% of patients in 5-FU + mitomycin C arm received chemotherapy per protocol.

Analysis in July 1994 demonstrated that with respect to local regional failure, there was a statistically significant difference in favor of mitomycin C + 5-FU arm (p = 0.002). At two years, almost twice as many failed in the 5-FU alone arm (33% vs 17%). The advantage is also seen for 5-FU + mitomycin C arm with respect to colostomy rate. At two years, the colostomy rate for 5-FU + mitomycin C arm is 7% as compared to 20% for 5-FU arm (p = 0.002). The 5-FU + mitomycin C arm also demonstrated an improved disease-free survival without colostomy at 78% vs 62%. The statistically significant advantage was also seen for “NED” survival (p = 0.02). The differences for the rate of patient with distant metastases and overall survival shows a trend in favor of 5-FU + mitomycin C arm but not statistically significant. A more recent analysis shows that the advantage to RT + 5-FU + mitomycin C persisted, but results in T3, T4, and N+
patients still are not optimal with local failure rates of 27% (T3, T4) and 41% (N+), and colostomy-free survival of 55% (T3, T4) and 37% N+.

The question of EBRT alone versus EBRT plus 5-FU mitomycin-C has been addressed in separate randomized trials performed by EORTC and Great Britain investigators. The EORTC results were reported at ASCO in 1995 and revealed advantages in local control ($p = 0.0008$) and colostomy-free survival ($p = 0.02$) for the radiochemotherapy arm. Only patients with lesion size $4 \text{ cm}$ were included in the EORTC trial. Overall survival was similar in the two treatment arms. In the British trial, the radiochemotherapy arm was also superior to irradiation alone with regard to 3-year local control ($61\% \text{ vs. } 39\%, \ p < 0.0001$) and cause-specific survival ($72\% \text{ vs. } 61\%, \ p = 0.02$). Absolute rates of local failure were $36\% \text{ vs. } 59\%$. Overall survival was not statistically better in the radiotherapy patients, although suggestive trends exist ($3\text{-year survival of } 65\% \text{ vs. } 58\%$).

1.3 5-FU plus Cisplatin

Cisplatin is a radioenhancer in vitro similar to 5-FU. 5-FU plus cisplatin has resulted in significant antitumor activity in patients with metastatic anal carcinoma. The combined therapy with 5-FU+cisplatin+radiotherapy has also demonstrated an advantage over radiotherapy alone in squamous cell carcinoma of the esophagus. Thus 5-FU, cisplatin, plus radiotherapy has generated increasing interest. A number of reports (Table 3) also support this level of enthusiasm. Overall, the results demonstrate a response rate ranging from 55% to 82%.

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Patients</th>
<th>Agents Employed</th>
<th>Number of Patients With Responses</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahjoubi, 1990a</td>
<td>20</td>
<td>CDDP, 5-FU</td>
<td>2, 9, 11 (55%)</td>
<td>Locally recurrent and/or metastatic</td>
</tr>
<tr>
<td>Brunet, 1990</td>
<td>22</td>
<td>CDDP, 5-FU</td>
<td>6, 13, 18 (82%)</td>
<td>Primary tumors; neoadjuvant therapy</td>
</tr>
</tbody>
</table>

Table 3

Anal Cancer: Response Rates to Cisplatin-Containing Chemotherapy

1.4 Results of ECOG Phase II Study (5-FU+Cisplatin + 59.4 Gy Radiotherapy) (12/20/99)

Combined modality treatment for anal cancer using radiotherapy, 5-FU ($1,000\text{mg/m}^2\text{/day on days 1-4}$) and cisplatin ($75\text{mg/m}^2$) has been studied in 33 patients in an ECOG phase II study. There was no apparent increase in the incidence of acute toxicity. Similarly, chronic toxicity was not more than anticipated compared with 5-FU/mitomycin C and radiotherapy studies. Similarly, chronic toxicity was not more than anticipated compared with 5-FU, mitomycin, and radiotherapy studies.

1.4.1 Twenty patients were entered on Step 1 of ECOG 4292 study between 2/1/93 and 7/21/93. One patient never received any treatment and is excluded from further analysis. The median follow-up time in the patients still alive is 10.4 months, with a maximum of 14 months. There are 17 patients evaluable for response, and 12 (71%) had a complete response, three had a partial response (18%), and 2 (12%) had stable disease. Thus, 15 of the 17 patients (88%) responded. A 95% confidence interval for the response rate is (63.6%, 98.5%).

Toxicity information on the 19 eligible patients revealed that it was considered severe in 8 patients, life-threatening in 6, and one patient died of treatment-related complications. These data suggest that this regimen approaches the limits of tolerability for the treatment of anal cancer.

1.4.2 An additional 13 patients were entered on Step 2 of ECOG 4292 but treated without a planned two week interruption in treatment. Thirty-two of the 33 total patients were analyzable. This is a preliminary analysis of that data. It is not intended for distribution or publication outside this intergroup protocol.
Table 4

Best Overall Objective Response

<table>
<thead>
<tr>
<th>Response</th>
<th>Step 1</th>
<th>Step 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>13</td>
<td>11</td>
<td>24</td>
</tr>
<tr>
<td>Partial</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>No Change</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>19</td>
<td>13</td>
<td>32</td>
</tr>
</tbody>
</table>

Fisher's Exact Test for step differences, p = 0.802. Estimates of overall median survival is 48 months, and the over median disease free survival is also 48 months (not enough data to do separately by step).

Table 5

Worst Toxicity

<table>
<thead>
<tr>
<th>Grade</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>4</td>
<td>8</td>
<td>6</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>Step 2</td>
<td>1</td>
<td>8</td>
<td>4</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>5</td>
<td>16</td>
<td>10</td>
<td>1</td>
<td>32</td>
</tr>
</tbody>
</table>

Table 6

Updated Toxicities for Step 1

<table>
<thead>
<tr>
<th>TOXICITY</th>
<th>Mild/Mod (1/2)</th>
<th>SEVERE (3)</th>
<th>LIFE THREAT (4)</th>
<th>LETHAL (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>8</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>16</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Fever (no infection)</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TOXICITY</th>
<th>Mild/Mod (1/2)</th>
<th>SEVERE (3)</th>
<th>LIFE THREAT (4)</th>
<th>LETHAL (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>11</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>8</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Liver</td>
<td>8</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin</td>
<td>12</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Neuro-Clinical</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 7
Updated Toxicities for Step 2

<table>
<thead>
<tr>
<th>TOXICITY</th>
<th>MILD/MOD (1/2)</th>
<th>SEVERE (3)</th>
<th>LIFE THREAT (4)</th>
<th>LETHAL (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>4</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Fever (no infection)</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>9</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Liver</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin</td>
<td>2</td>
<td>10</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Neuro-Clinical</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>7</td>
<td>7</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

1.5 Results of RTOG pilot study (5-FU+mitomycin+ 59.4 Gy of Radiotherapy)

1.5.1 RTOG 92-08 was opened on June 22, 1992 and closed on July 15, 1993. In this pilot study, patients received 5-FU 1000mg/m²/24 hours for 96 hours, during weeks 1 and 7 during radiotherapy and mitomycin C 10mg/ m² iv bolus on days 1 of each 5-FU courses. Radiation therapy consisted of 1.8 Gy fractions 5 x per week to 59.4 Gy (in 33 fractions) over 9 weeks with a 2 week rest during weeks 5 and 6 (after dose of 36 Gy). A total of 46 eligible patients were accrued. Grade 3 toxicity has been observed in 40% of patients. Grade 4 toxicity has been observed in 23% of patients. Grade 5 toxicity due to infection occurred in one (3%) patient. The most common toxic effects included leukopenia, cutaneous toxicity, and thrombocytopenia. Toxicities during the follow up period have been mild. Thirty seven of 40 patients evaluated completed protocol chemotherapy. Further follow-up will be necessary to determine the long-term toxic effects and therapeutic effects. The preliminary information demonstrate the feasibility of testing the higher dose irradiation of 59.4 Gy since acute toxicity levels were the same as in the RTOG 87-04/ECOG 1289 protocol using the same chemotherapy with initial irradiation doses of 45-50 Gy ± salvage dose of 9 Gy with 5-FU + cisplatin.

1.5.2 The initial design of the RTOG 92-08 using 59.6 Gy with concurrent 5-FU and mitomycin C included a planned treatment-break is described above. This approach resulted in an unexpectedly high rate of colostomy (23%) and local failure rate.32 This high rate of local failure was considered to be due to split course chemoradiotherapy, thus a second phase of this study eliminated the planned break in treatment. Twenty patients with > 2 cm anal carcinoma were treated without a mandated treatment break.33 Predominant grade 3 and 4 toxicity in 18 evaluable patients was dermatitis (78%), hematologic (78%), infection (17%), and gastrointestinal (28%). There was no treatment-related death. Nine patients completed therapy without a break and nine required a median treatment break of 11 days (range, 7-19 days) at a median radiotherapy dose of 41.4 Gy (range, 32.4 to 48.6 Gy). This compares favorably to 40 (of 47) patients, in the initial phase of this study, who had a 12-day planned treatment break at 36 Gy. One patient required colostomy because of a persistent disease and the other for an anal fistula, thus the colostomy rate in the second phase of the study is 11% (2/18). These data suggest that 59.6 Gy of radiotherapy given concurrently with 5-FU and mitomycin can be delivered safely without a planned therapy break in patients with localized anal carcinoma. (12/20/99)

1.6 Rationale for the Proposed Study

Both irradiation alone and in combination with chemotherapy have resulted in excellent local control and survival leaving some to ponder whether we can improve upon current standard treatment with irradiation plus 5-FU + Mitomycin-C.

Although organ preservation has become standard treatment for most anal cancers, questions still exist with regard to treatment optimization. Separate analyses from PMH15, University of Kansas,34 M.D. Anderson35 and unpublished data from RTOG 83-14 and RTOG 87-04 31 support both high irradiation dose as well as the type and duration of chemotherapy to improve both local control and systemic control of disease. The pelvic failure rate (anal primary + pelvic and inguinal nodes) in those series ranges from 20 to
Primary tumor control may, plus or minus survival, increase as a function of irradiation dose level. In an M.D. Anderson (MDAH) analysis of T2-T4 lesions, primary control by dose level was as follows for irradiation plus continuous infusion 5-FU: 45-49 Gy-4/13 or 31%, 50-55 Gy-5/7 or 71%, 55 to > 60 Gy - 14/16 or 87%.

When 55 Gy was combined with infusion 5-FU and CDDP at MDACC, local control was achieved in 45 of 62 patients or 73% with chemoradiation alone and 53 of 62 or 85% with surgical salvage. (Note: local control rates with chemoradiation may be falsely low as patients were deemed as local failure as early as 8 weeks from the end of treatment). Pooled data on 57 patients from five Kansas City institutions revealed similar findings; 77% of patients received chemotherapy with irradiation, 5-FU + Mitomycin C or CDDP. Local control (LC) was achieved in 81%; all local failures occurred within 1.5 years of treatment and salvage was achieved in 8 of 11 for an eventual LC of 95%. LC by irradiation dose level was as follows: < 45 Gy-64%, 45 to 55 Gy - 72%, >55 Gy - 92% (p=0.05). On the basis of Cox multivariate analysis, RT dose > 55 Gy was the only variable associated with improved LC. In the recent MGH analysis of 50 patients treated with chemoradiation, both local control and overall survival appeared to improve as a function of the radiation dose ≥ 54.0 Gy vs. < 54.0 Gy (77% vs 61%; P = 0.04 and 84% vs 47%; P = 0.02).

The proposed intergroup study (to be coordinated by RTOG), will address combinations of external beam irradiation (EBRT) plus chemotherapy in a 2-arm phase III randomized trial comparing EBRT plus concurrent 5-FU/mitomycin C (control arm as best arm of RTOG87-04/ECOG 1289) with 2 courses of induction 5-FU + cisplatin followed by concurrent EBRT plus 5-FU + cisplatin. The hypothesis is that induction chemotherapy in the experimental arm may reduce the tumor bulk prior to concurrent chemoradiation and thereby provide better local control and colostomy-free survival. In addition, four cycles of chemotherapy in the experimental arm vs. two cycles in the control arm may reduce the rates of distant metastases. All patients will receive a minimum of 45 Gy with concurrent chemotherapy; those with T3, T4, or N+ lesions or those with T2 lesions with residual disease after 45 Gy will receive additional boost dose irradiation of 10-14 Gy.

2.0 OBJECTIVES (12/20/99)

2.1 To compare the initial and total local and distant failure rates in patients treated with either 5-FU plus mitomycin C concurrently with radiation therapy or induction 5-FU plus cisplatin followed by 5-FU plus cisplatin concurrently with radiation therapy.

2.2 To identify any differences in local control and colostomy rates at 2 years.

2.3 To determine any differences in colostomy-free, disease-free, or overall survival.

2.4 To compare the toxicity profiles between the two treatment arms.

2.5 To evaluate the prognostic effects of tumor markers P53 overexpression, human papilloma virus status and enzyme HAP1.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria (2/1/01)

3.1.1 Histologically proven primary squamous, basaloid, or cloacogenic carcinoma of the anal canal, other than carcinoma in situ (patients with local or regional recurrence after local excision or abdominal perineal resection are not eligible).

3.1.2 Patients must be ≥ 18 years of age.

3.1.3 Performance status ≥ 60 Karnofsky.

3.1.4 T stage 2-4 (See Appendix III).
3.1.5 Any N stage (eligible only if pelvic or inguinal; see Appendix III).

3.1.6 Adequate hepatic, renal and bone marrow function: Creatinine $\leq$ 1.5 mg/dl (or creatinine clearance 80 ml/min if serum creatinine level is $> 1.5$ mg/dl); bilirubin $< 1.4$ mg/dl; WBC $\geq 4,000$/µl; ANC $\geq 1,800$ µl; platelet count $\geq 100,000$; hemoglobin $\geq 10$g/dL.

3.1.6.1 Creatinine clearance determined by 24 hour collection or nomogram:

$$\text{CrCl} \text{ male} = \frac{(140 - \text{age}) \times (\text{wt. as kg})}{(\text{Serum Cr}) \times 72}$$

$$\text{CrCl} \text{ female} = 0.85 \times (\text{CrCl} \text{ male})$$

3.1.7 Study-specific consent form must be signed prior to randomization.

3.2 Ineligibility Criteria (12/20/99)

3.2.1 Karnofsky Performance status $< 60$.

3.2.2 Patients with histologies other than those listed in Section 3.1.1 are ineligible.

3.2.3 T1 tumors (2 cm) or evidence of distant metastases (M1).

3.2.4 Previous radiation to the pelvis; prior radiation to any site or prior chemotherapy unless completed $> 5$ years ago. Prior surgery for cancer of the anus, except biopsy.

3.2.5 Other malignancies (excluding non-melanomatous skin neoplasms) unless successfully treated and disease-free for at least five years.

3.2.6 Presence of an active systemic infection, uncontrolled diabetes, uncompensated heart disease or uncontrolled high blood pressure.

3.2.7 Patients mental condition and social support is such that he or she can neither understand the nature of the protocol nor can comply with its requirements.

3.2.8 Patients with AIDS.

3.2.9 Pregnant or lactating women; patients of childbearing potential must agree to practice an effective method of contraception since pelvic irradiation and chemotherapy are hazardous to the fetus.

4.0 PRETREATMENT EVALUATION (10/28/03)

All laboratory studies must be performed within 2 weeks prior to randomization. All radiographs must be done within 35 days prior to randomization.

4.1 Complete Physical Examination (3/11/03)

4.1.1 Sigmoidoscopy or proctoscopy, biopsy, and an examination under anesthesia if necessary.

4.1.2 Chest x-ray, PA and lateral and CT or MRI scan of pelvis and abdomen. All radiographs must be obtained within 35 days of registration. Inguinal lymphangiogram is preferred if CT scan is positive for nodes (optional procedure).

4.1.3 CBC, platelet and differential counts, bilirubin, renal function studies, electrolytes, and urinalysis. Creatinine clearance should be calculated according to the Cockcroft and Gault formula (see Section 3.1.6.1) when indicated (for patients with serum creatinine of $> 1.5$ mg/dl). Pregnancy test for women of child-bearing potential. All laboratory investigations should be performed within 14 days of registration.

4.1.4 Tumor size and extent is to be documented.

4.1.5 Biopsy of clinically positive inguinal nodes (see Section 8.2.1).

1) Needle aspiration biopsy
2) Excisional biopsy of one node if needle aspiration is negative
3) Enlarged pelvic nodes seen on CT scan and considered to be clinically positive, need not be biopsied. Patients may be stratified as having positive nodes.

4.1.6 HIV will be checked if patient is in a high risk group.

5.0 REGISTRATION PROCEDURES (12/20/99, 2/1/01)

5.1 Randomization

- It is the responsibility of each participating Cooperative Group to decide which of its member institutions may participate in this protocol. Each participating Cooperative Group must ensure that IRB approval was obtained prior to accession of cases. Member institutions will phone their respective Cooperative Group headquarters Mondays through Fridays. See Section 5.5.

- Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a
case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. For RTOG members, the completed, signed, and dated Checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

5.2 The Cooperative Group will then phone RTOG Headquarters, Monday-Friday, between 8:30 a.m. to 5:00 p.m. ET and RTOG will assign the treatment option and RTOG case number. See Section 5.5.

5.3 After receiving the case number and treatment assignment, the Cooperative Group will phone their registering institution and relay this information.

5.4 The case number and treatment option will be confirmed by mail. RTOG will send a Confirmation of Registration and a Forms Due Calendar to the participating Cooperative Group for each case. The participating Group should then forward a copy of the calendar and the confirmation to the participating institution.

5.5 RTOG (215) 574-3191, 8:30 am - 5:00 pm Eastern Time

SWOG (206) 667-4623, 6:30 am - 1:30 pm, Pacific Time
SWOG Group Member and Affiliates: Patients from Southwest Oncology Group Member and Affiliate institutions must be registered with the Southwest Oncology Group Statistical Center by telephoning 206/667-4623 between the hours of 6:30 a.m. and 1:30 p.m. (PT) Monday through Friday, excluding holidays. The Statistical Center will confirm that the patient is eligible and will request the date informed consent was obtained and the date of IRB approval for each entry. The Statistical Center will then contact the RTOG Headquarters to randomize the patient after which the Statistical Center will contact the institution to confirm registration and relay the treatment assignment for that patient. The RTOG will forward a Confirmation of Randomization to the Statistical Center for routing to the appropriate institution.

SWOG CCOP Institutions: Patients from Southwest Oncology Group CCOP institutions must be registered with the Southwest Oncology Group CCOP Office by telephoning 206/652-CCOP (206/652-2267) between the hours of 7:00 a.m. and 1:30 p.m. (PT), Monday through Fridays, excluding holidays. The CCOP Office will confirm that the patient is eligible and will request the date informed consent was obtained and the date of IRB approval for each entry. The CCOP Office will then contact the RTOG Headquarters to randomize the patient after which the CCOP Office will contact the institution to confirm registration and relay the treatment assignment for that patient. RTOG will forward a Confirmation of Randomization assignment to the Southwest Oncology Group Statistical Center for routing to the CCOP Office and the appropriate institution.

Please note: Southwest Oncology Group institutions will follow their normal procedures for documentation of IRB approval.

CALGB (919) 286-4704, 9:00 am – 4:30 pm, Eastern Time For CALGB institutions, registration will be accepted only through institutions with direct registration privileges. Confirm all eligibility criteria as listed in Section 3.0. Registrations must occur prior to initiation of therapy. Confirm eligibility criteria (Section 3.0). Call the CALGB Registrar (919-286-4704, Monday-Friday, 9:00 a.m.-4:30 p.m. Eastern Time) with the following information:

Your name
Study #
Institution #
Treating Physician
Patient’s Social Security #, or hospital ID#
Patient’s Name, I.D. #
Signed Informed Consent (10/28/03)
Race, Sex, Date of Birth
Zip code of residence
Method of Payment
Diagnosis, Date of Diagnosis
Names of Surgeon and Medical and Radiation Oncologists
Treatment Start Date
Eligibility Criteria met (Section 3.0) (no, yes)
List of prior CALGB protocols
Date of most recent Institutional Review Board approval (<1 year)

The CALGB Registrar will then contact the Radiation Therapy Oncology Group Headquarters for treatment assignment after which the CALGB Registrar will inform the institution of the treatment assignment (see Sections 5.2-5.4).

ECOG (617) 632-2022, 8:30 am - 4:30 pm, Eastern Time (3/11/03)

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

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19102
FAX: (215) 569-0206

Required Protocol Specific Regulatory Documents
1. CTSU Regulatory Transmittal Form.
   **Note:** Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.
3. A. CTSU IRB Certification Form.
   **Or**
   B. HHS 310 Form.
   **Or**
   C. IRB Approval Letter
   **Note:** The above submissions must include the following details:
   - Indicate all sites approved for the protocol under an assurance number.
   - OHRP assurance number of reviewing IRB.
   - Full protocol title and number.
   - Version Date
   - Type of review (full board vs. expedited).
   - Date of review.
   - Signature of IRB official.

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

If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or E-mail CTSUContact@westat.com. Monday through Friday, 9:00am - 6:00pm.

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

Institutions may begin to register eligible patients to this study by completing the checklist via the ECOG webpage 24 hours a day, 7 days a week, using the Web-based Patient Registration Program ([http://webreg.ecog.org](http://webreg.ecog.org)). If you need assistance or have questions, please telephone the Central Randomization Desk at the ECOG Coordinating Center at (617) 632-2202. Please note that a password is required to use this program. The following information will be requested: Protocol Number; Investigator Identification (including institution and/or affiliate name and investigator’s name); Patient Identification (including patient’s name or initials, chart number, social security number and demographics (sex, birth date, race, nine-digit zip code and method of payment)); Eligibility Verification. Patients must meet all of the eligibility requirements listed in Section 3.0. After completing the checklist on the web, the institution
will call the Central Randomization Desk at the ECOG Coordinating Center to provide the Transaction ID # at (617) 632-2022, Monday-Friday, between the hours of 9:00 am and 4:30 pm ET. ECOG members should not call the RTOG directly.

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

If a patient does not receive any protocol therapy, the patient may be canceled. Reasons for cancellation should be noted on the data forms and submitted to the ECOG Coordinating Center (ATTN: DATA) as soon as possible. The On-Study form and Eligibility Checklist should also be submitted.

**Note:** A patient may be canceled only if no protocol treatment is administered. Written notification and an explanation must be received at RTOG as soon as this has been determined. RTOG will notify ECOG if the patient may be canceled. Once a patient has been given any protocol treatment, all forms must be submitted.

**NCCTG**
A signed 310 form must be on file for this study at the NCCTG Randomization Center before a NCCTG institution may enter a patient.

To register a patient, fax a completed eligibility checklist (507-284-0885) to the NCCTG Randomization Center between 8:00 a.m. and 3:00 p.m. central time, Monday through Friday. The NCCTG Randomization Center will obtain and confirm all eligibility criteria. The NCCTG Randomization Center will then contact RTOG Headquarters to register the patient. The treatment assignment and case number from RTOG will be relayed to the registering institution by NCCTG. RTOG will send a Confirmation of Registration and a Forms Due Calendar to NCCTG Operational Support Unit who will forward this information to the participating institution.

### 6.0 RADIATION THERAPY

#### 6.1 Radiation Therapy Doses

6.1.1 a) All patients will be treated with a daily dose of 1.8 Gy, 5 days per week to a dose of 45 Gy in 25 Fx in 5 to 6.5 weeks (*≤10-day break, as indicated, for skin intolerance*).

b) Patients with T3, T4, or N+ lesions or T2 lesions with residual disease after 45 Gy should receive additional 10-14 Gy (2 Gy per Fx) to a reduced field.

6.1.2 **Simulation:** Treatment for patients must be planned on a simulator which exactly reproduces the geometry of the treatment machine and is capable of producing diagnostic quality radiographs. Patients are to be simulated in supine position; however, prone techniques are acceptable. A radio-opaque marker should be placed over the anus or the most caudal extent of the tumor, whichever is most inferior.

6.1.3 **Equipment:** Patients must be treated with radiotherapy equipment with photon energy of 6 MV or greater for pelvic fields with minimum target/axis distance (*TAD of 100 cm*). Supplementary inguinal node irradiation (*see Sections 6.2.5, 6.2.5.1 and 6.3.3*) is to be given preferably by electrons (*low energy photons are allowed at investigator's discretion*).

#### 6.2 Treatment Fields

6.2.1 **Fields** (*see Appendix VI*) The initial pelvic field (*to 30.6 Gy*) and reduced pelvic field #1 (*to 45 Gy*) are the same for all patients.

6.2.2 **Initial Pelvic Fields** (*Figs. 1-2 in Appendix VI*). Treat to 30.6 Gy at 1.8 Gy/day with patient supine and bladder distended (*see Section 6.2.1*).

The pelvis, anus, perineum, and inguinal lymph nodes will be treated with either AP-PA fields or a 4-field technique to include lateral inguinal nodes within AP/lateral field but not PA field (*see Section 6.2.5*). The superior border of this initial pelvic field shall be L5-S1. The inferior border shall include the anus with a minimum margin of 2.5 cm around the anus and tumor. The lateral border of the AP field shall include the lateral inguinal nodes as determined by bony landmarks or lymphangiogram (*see Fig. 1, Appendix VI*). The lateral border of the PA field shall extend 2 cm lateral to the greater sciatic notch (*see Fig. 2, Appendix VI*).
6.2.2.1 Four-field technique: If utilized, the target volume includes all areas at risk (pelvis, anus plus margin, inguinal nodes, external iliac nodes). A CT or lymphangiogram should be used to construct nodal volumes (includes a 1.5 cm margin). Inguinal nodes must not be underdosed (see Section 6.2.5). The AP and lateral fields should be shaped such that the lateral inguinal nodes are included in these fields. The inguinal nodes should not be included in the PA field.

6.2.3 Reduced Pelvic Field #1: Deliver 14.4 Gy/8 Fx for a total of 45 Gy at 1.8 Gy/day (see Figs. 1-3 and Section 6.3.2).

6.2.3.1 After 30.6 Gy has been given to an initial pelvic field, outlined in Section 6.2.2, the superior border shall be dropped to the upper level of the greater sciatic notch (inferior border of SI joints). The reduced pelvic field shall be continued to 45 Gy at 1.8 Gy per day.

6.2.3.2 NOTE THAT A ≤ 10-DAY BREAK IS TO BE GIVEN ONLY AS INDICATED FOR SEVERE SKIN TOXICITY (see Section 6.3.2).

6.2.4 Reduced Pelvic Field #2: (For all T3, T4, and N+ patients or T2 patients with residual disease after 45 Gy)

After 45 Gy, boost fields shall be utilized to encompass the original primary tumor volume plus a 2.0 to 2.5 cm margin. Treatment field options include reduced multiple photon fields with the patient in supine position (i.e., 4-field or PA and laterals with wedges) or a direct photon or electron perineal field with the patient in the lithotomy position. An additional 10-14 Gy (2 Gy per Fx) shall be delivered (total 55-59 Gy). If pelvic nodes are grossly involved, they should be included in the final boost field if small bowel can be avoided.

6.2.5 Inguinal Fields

6.2.5.1 All patients shall receive inguinal node irradiation outlined in Appendix VI. The initial AP pelvic field should be designed to include the entire inguinal region along with the pelvis; the PA field will not include the lateral inguinal region. Patients with N0 disease will receive 36 Gy at a minimum depth of 3 cm from the anterior surface (use CT or lymphangiogram to calculate exact depth, see Section 6.3.3). Since lateral inguinal nodes are not covered by the PA photon field, supplementary RT will be delivered with anterior electron fields to the lateral inguinal region which are matched with the exit PA field; the boost may be given with low energy photons if electron beam is not available (see Appendix VI, Fig. 1 & 2).

6.2.5.2 In patients with involved inguinal nodes not completely included within the idealized pelvic AP photon fields, the treatment volume is to be extended as needed to provide a minimum 2 cm margin around all palpable and radiographic metastatic disease.

6.2.5.3 For patients with inguinal metastases, the entire metastatically involved inguinal region is to be included to 45 Gy and boost irradiation shall be given as outlined in Sections 6.2.5.4.

6.2.5.4 Inguinal Boost Field: (Nodal boost field for patients with N+ disease at diagnosis): Pelvic lymph node metastases will require photon therapy to include the primary tumor along with nodal disease. Inguinal lymph node metastases will require carefully planned electron fields (low energy photons may be used if electrons are not available). In this setting, the original volume of the tumor plus a 2.0 to 2.5 cm margin will receive an additional boost of 10-14 Gy in 5-7 fractions at 2.0 Gy/fx.

6.3 Dose/Fractionation Parameters

Treatment will be given daily Monday through Friday. The only exception to the M-F treatment schedule shall be that, during chemotherapy, RT on Saturday and Sunday shall be allowed, if needed, in order to achieve 4 consecutive days of concurrent chemotherapy and radiation therapy. At least two fields will be treated each day (if using AP-PA treat both fields daily; if using 4-field technique, it is allowed to alternate AP-PA and lateral fields).

6.3.1 Dose to Pelvic Fields (Fields described in Section 6.2.1).

The initial dose to the pelvis shall be 30.6 Gy, at a rate of 1.8 Gy/day, 5 days per week, 17 fractions in 3.5 weeks.

The dose to the second volume (reduced field #1) shall be 14.4 Gy at a rate of 1.8 Gy/day, 5 days per week. The cumulative dose at this juncture will be 45 Gy.

For patients with T3, T4, or N+ lesions or T2 lesions with residual disease after 45 Gy, an additional 10-14 Gy to reduced field #2 may be delivered in one of two ways:

1) Reduced pelvic photon fields with borders 2.0 to 2.5 cm beyond the original primary tumor.

2) Direct en face perineal field. The use of bolused photons or electrons of appropriate energy are acceptable.

6.3.2 Dose Specifications:

6.3.2.1 Photon Beams:

a) For two opposed coaxial equally weighted beams: on the central ray at mid separation of beams.
b) For an arrangement of 2 or more intersecting beams: at the intersection of the central rays of beams.

c) For two opposing coaxial unequally weighted beams: on the central ray at the center of the target area.

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

e) Off axis calculation at the level of the primary tumor is required.

6.3.2.2 Electron Beams:

a) The target dose shall be prescribed at the depth of maximum dose.

b) The energy and field size shall be chosen so that the target volume is encompassed within 90% of the prescribed dose.

c) The maximum or minimum acceptable dose variation across the tumor volume is ± 10% of the maximum dose at central axis.

6.3.3 Dose to Inguinal Node Fields

6.3.3.1 The daily dose, at the appropriate depth specified below, shall be 1.8 Gy. The total dose at this depth shall be 36 Gy for N0 patients or 45 Gy for N+ patients, and 55-59 Gy for patients with inguinal metastases (2 Gy per fx after 45 Gy).

6.3.3.2 In N0 patients, the dose shall be specified at a minimum depth of 3 cm (use CT or lymphangiogram for exact depth). See Appendix VI, Fig. 1. If electrons are used, energy is to be selected so that the dose at d_{max} is no more than 10% greater than the dose at prescription depth.

6.3.3.3 In patients with metastatically involved inguinal lymph nodes, the dose shall be specified on the central axis at the deepest portion of metastatically involved tumor (e.g., as measured by CT scan or lymphangiogram. See Appendix VII, Figs. 1 and 4 and Examples 1 and 2). If electrons are used, energy is to be selected so that the dose at d_{max} is no more than 10% greater than the dose at the specified prescription depth. After a dose of 45 Gy, residual adenopathy is boosted to 55-59 Gy in 2 Gy fractions.

6.4 Monitoring and Supportive Care During RT (12/20/99, 2/1/01)

6.4.1 Patients are to be seen in status check at least once weekly with notation of weight, primary tumor status, skin toxicity, and tolerance to treatment. As noted in Section 11.0, blood counts are to be checked twice weekly during radiation therapy.

6.4.2 General measures to improve patient tolerance, such as nutritional support and provision of antiemetics, should be provided as appropriate.

6.4.3 Side effects expected from the combined modality therapy include tiredness near the end of treatment, diarrhea, rectal irritation, urinary frequency, loss of pubic hair, and drying and reddening around irradiated area. These should disappear soon after treatment is completed. In addition, blood counts may be temporarily suppressed. Long-term side effects, although uncommon may include rectal ulcer, bowel obstruction, ureteral obstruction, and fistula formation between pelvic tissues.

6.4.4 Port films of photon fields should be obtained at least every other week and at field size changes.

6.4.5 Granulocyte macrophage colony stimulating factors (GM-CSF or G-CSF) may not be used during RT or chem/RT except during the recovery phase of induction chemotherapy (Arm 2) in accordance with ASCO guidelines. Erythropoietin may be used in lieu of blood transfusion.

6.5 Treatment Interruptions (12/20/99, 2/1/01)

6.5.1 A rest period of ≤ 10 days will be allowed only for severe skin reactions. Interruption of radiation during the first 28 days of the treatment program without permission of the study chairman is discouraged.

6.5.2 Pelvic irradiation should usually be continued without interruption per Section 6.5.3; transfusion of packed red cells and platelets may be used to support the patient. It is anticipated that nadir blood counts obtained between days 7 and 21 are primarily due to mitomycin C and, therefore, blood count recovery is anticipated despite continued radiation.
6.5.3 Modifications Based on Chemoradiotherapy-Related Toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Condition</th>
<th>Agent</th>
<th>Dosage Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td>ANC &lt;1000 and/or PLT &lt;50,000</td>
<td>RT</td>
<td>Continue with transfusion support, a or temporarily suspend RT b (blood counts twice weekly will continue during Rx suspension; RT will resume when ANC &gt;1000 and PLT &gt;50,000) d</td>
</tr>
<tr>
<td>GI c</td>
<td>Severe diarrhea: &gt;6 Stools/day above baseline  (Grade 3)</td>
<td>RT</td>
<td>Temporarily suspend RT b until ≤6 stools/day above baseline</td>
</tr>
<tr>
<td>GI</td>
<td>Vomiting (Grade 4) Requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse.</td>
<td>RT</td>
<td>Temporarily suspend RT b until vomiting is ≤ Grade 3</td>
</tr>
</tbody>
</table>

a. Since nadir counts obtained between days 7 and 21 are primarily due to chemotherapy, blood count recovery is anticipated despite continued irradiation.
b. If RT is suspended for > 3 weeks, call study chair before proceeding.
c. Obtain electrolytes and creatinine levels for diarrhea ≥ grade 2.
d. Granulocyte macrophage colony stimulating factors (GM-CSF or G-CSF) may not be used during RT or chem/RT except during the recovery phase of induction chemotherapy (Arm 2) in accordance with ASCO guidelines. Erythropoietin may be used in lieu of blood transfusion.

6.5.4 Skin toxicity: If localized or generalized infection develops secondary to an area of desquamation, radiation therapy will be suspended. In this setting, radiation therapy will be resumed after there has been complete resolution of sepsis and re-epithelialization in the area of desquamation. The presence of moist desquamation in the absence of infection shall not constitute grounds for unplanned suspension of radiation therapy.

6.6 Protocol Compliance Criteria

<table>
<thead>
<tr>
<th>FIELD BORDERS</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 5 %</td>
<td>2 cm to ≤ 2.5 cm</td>
</tr>
<tr>
<td>&gt; 5% to ≤ 10%</td>
<td>MIN 1.5 to &lt; 2 cm OR MAX &gt; 2.5 to ≤ 3.5 cm</td>
</tr>
<tr>
<td>&gt; 10%</td>
<td>&lt; 1.5 cm OR &gt; 3.5 cm</td>
</tr>
</tbody>
</table>

7.0 CHEMOTHERAPY

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

7.1 Timing (2/1/01)

7.1.1 Concurrent chemotherapy is to start within 24 hours of commencement of radiation therapy. The second course of chemotherapy will be given beginning day 29th of radiation therapy. Granulocyte macrophage colony stimulating factors may not be used during RT or chem/RT except during the recovery phase of induction chemotherapy (Arm 2) in accordance with ASCO guidelines. Erythropoietin may be used in lieu of blood transfusion.

7.2 5-Fluorouracil (5-FU)

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

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

7.2.3 Supplier 5-FU is available commercially.

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

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

7.3 Cisplatin (CDPP)

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

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

7.3.3 Supplier: Cisplatin is available commercially.

7.3.4 Storage: The intact vials should be stored at room temperature. Once reconstituted, the solution should be kept at room temperature to avoid precipitation. Due to a lack of preservatives, the solution should be used within eight hours of reconstitution. The solution may be further diluted in a chloride containing vehicle such as D5NS, NS, or D5-1/2NS (ppt. occurs in D5W). Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes. Cisplatin should be given immediately after preparation as a slow intravenous infusion.

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

7.4 Mitomycin C

7.4.1 Dose Formulation: Each vial contains either Mitomycin-C 5 mg. and mannitol 10 mg. or mitomycin C 20 mg. and mannitol 40 mg. To administer, add sterile water for injection, 10 ml. or 40 ml. respectively. Shake to dissolve. If product does not dissolve immediately, allow to stand at room temperature until solution is obtained. Mitomycin C should be given intravenously only, using care to avoid extravasation. If extravasation occurs, cellulitis ulceration, and slough may result.
7.4.2 **Pharmacology:** Mitomycin C selectively inhibits the synthesis of deoxyribonucleic acid (DNA). The guanine and cytosine content correlates with the degrees of mitomycin C-induced cross-linking. At high concentrations of the drug, cellular RNA and protein synthesis are also suppressed. In humans, mitomycin is rapidly cleared from the serum after intravenous administration. Time required to reduce the serum concentration by 50% after a 30 mg. bolus injection is 17 minutes. After injection of 30 mg., 20 mg., or 10 mg. i.v., the maximal serum concentrations were 2.4 mcg./ml., 1.7 mcg./ml., and 0.52 mcg./ml., respectively. Clearance effected primarily by metabolism in the liver, but metabolism occurs in other tissues as well. The rate of clearance inversely proportional to the maximal serum concentration because, it is thought, of saturation of the degradative pathways. Approximately 10% of a dose of mitomycin C is excreted unchanged in the urine. Since metabolic pathways are saturated at relatively low doses, the percent of a dose excreted in urine increases with increasing dose.

7.4.3 **Supplier:** Mitomycin C is available commercially.

7.4.4 **Storage:**
1. Unreconstituted: Mitomycin-C is stable for the lot life indicated on the package. Avoid excessive heat (over 40°C).
2. Reconstituted with Sterile Water for Injection to a concentration of 0.5 mg. per ml., Mitomycin-C is stable for 14 days refrigerated or 7 days at room temperature.
3. Diluted in various i.v. fluids at room temperature, to a concentration of 20 to 40 micrograms per ml:

<table>
<thead>
<tr>
<th>IV Fluid</th>
<th>Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% Dextrose Injection</td>
<td>3 hours</td>
</tr>
<tr>
<td>0.9% Sodium Chloride Injection</td>
<td>12 hours</td>
</tr>
<tr>
<td>Sodium Lactate Injection</td>
<td>24 hours</td>
</tr>
</tbody>
</table>

7.4.5 **Side Effects and Toxicity**
Toxicities include thrombocytopenia and leukopenia which are cumulative. Deaths due to septicemia have been reported. Stomatitis and alopecia occur frequently. Rashes are rare however necrosis and consequent sloughing of tissue may result is the drug is extravasted during injection (see Appendix VII). There have been reports of delayed (weeks to months) erythema and/or ulceration occurring either at or distant from the injection site. Mitomycin may also cause a rise in creatinine, dyspnea with cough and radiographic evidence of pulmonary infiltrate. A few cases of adult respiratory distress syndrome have been reported. Microangiopathic hemolytic anemia, renal failure, fever, anorexia, nausea, vomiting, syncope, fatigue, edema, thrombophlebitis, hematemesis, or diarrhea may occur.

7.5 **5-FU plus Mitomycin C Regimen (Arm 1)**
7.5.1 **5-FU:** 1000 mg/m²/day given as continuous infusion in 5% Dextrose or 0.5 NS daily for 96 hours continuously starting day 1. Cycle is to be repeated on day 29.
7.5.2 **Mitomycin C:** 10 mg/m² bolus i.v. on the first day of both 5-FU infusions. **Dose not to exceed a total 20 mg per cycle.** Injections should be via the tubing of a free-flowing infusion.

7.5.3 **Toxicity Modifications (3/11/03)**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Parameters</th>
<th>Agent</th>
<th>Modification **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Grade 3 increase of ≥ 7 stools/day or incontinence; or need for parenteral support for dehydration</td>
<td>5-FU</td>
<td>Decrease dose 50%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Grade 4 Physiologic consequences requiring intensive care; or hemodynamic collapse</td>
<td>5-FU</td>
<td>Decrease dose 50%</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Parameters</td>
<td>Agent</td>
<td>Modification**</td>
</tr>
<tr>
<td>------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>-------</td>
<td>----------------</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>Grade 3 painful erythema edema, or ulcers requiring IV hydration</td>
<td>5-FU</td>
<td>Decrease dose 50%</td>
</tr>
<tr>
<td></td>
<td>Grade 4 severe ulceration or requires parenteral or enteral nutritional support or prophylactic intubation</td>
<td>5-FU</td>
<td>Decrease dose 50%</td>
</tr>
<tr>
<td>Skin (radiation dermatitis)</td>
<td>Grade 3 confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema</td>
<td>5-FU</td>
<td>Decrease dose 50%</td>
</tr>
<tr>
<td>Skin (radiation dermatitis)</td>
<td>Grade 4 skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion</td>
<td>5-FU</td>
<td>Do not give next course</td>
</tr>
</tbody>
</table>

Hematologic* | ANC <500 or PLT <50,000 | 5-FU and mitomycin-C | Decrease dose 50%

* Second cycle of chemotherapy will not be resumed unless ANC is ≥ 1800, platelets are ≥ 100,000, and patients have recovered from above treatment-related toxic effects.

** Once reduced, drug doses must not be reescalated to the original dose.

**NOTE:** Localized perineal and perianal skin reaction (including moist desquamation), by itself, should not form a basis for chemotherapy dose modification in the absence of more generalized skin reaction.

### 7.6 5-FU plus Cisplatin Regimen (Arm 2)

All patients randomized to Arm 2 will first receive 2 courses of induction chemotherapy with 5-FU + cisplatin to be administered on days 1 and 29. Two additional courses of 5-FU + cisplatin will be administered on days 57 and 85 (days 57 and 85 should correspond to days 1 and 29 of radiotherapy).

#### 7.6.1 5-FU

1000 mg/m²/day given as continuous infusion in 5% Dextrose or 0.5% NS daily for 96 hours continuously starting day 1. Cycle is to be repeated on day 29, 57, and 85 (days 57 and 85 should correspond to days 1 and 29 of radiotherapy).

#### 7.6.2 Cisplatin

75 mg/m² in 250 ml NS intravenous infusion over 60 min on the first day of all four 5-FU infusions.

Patients should receive up to 2,000 ml of a physiologic i.v. fluid prior to cisplatin therapy. This may be accomplished in 4-8 hours prior to dose administration or more gradually beginning the previous evening. Post-cisplatin i.v. hydration of at least 1,000 ml of physiologic solution containing potassium and magnesium supplementation may follow. Patients should be recommended to drink excessive amount of liquids orally before and after cisplatin therapy (suggested volume is 2L). Use of furosemide and/or mannitol is discouraged as it is usually not necessary if adequate hydration is provided.
Aggressive anti-emetic regimen is highly recommended (could include ondansetron, granisetron, metoclopramide, lorazepam, dexamethasone, diphenhydramine hydrochloride, and chlorperazine) before and after cisplatin therapy. The following table will be used to modify therapy for the next course of 5-FU plus cisplatin.

7.6.3 *Toxicity Modification* (based on maximum interval toxicity) (3/11/03)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Parameters</th>
<th>Agent</th>
<th>Modification ** **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic*</td>
<td>ANC &lt;500 or PLT &lt;50,000</td>
<td>5-FU and cisplatin</td>
<td>Decrease dose 50%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Grade 3 increase of ≥7 stools/day or incontinence; or need for parenteral support for dehydration</td>
<td>5-FU</td>
<td>Decrease dose 50%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Grade 4 Physiologic consequences requiring intensive care; or hemodynamic collapse</td>
<td>5-FU</td>
<td>Decrease dose 50%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>Grade 3 Painful erythema edema, or ulcers requiring IV hydration</td>
<td>5-FU</td>
<td>Decrease dose 50%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>Grade 4 severe ulceration or requires parenteral or enteral nutritional support or prophylactic intubation</td>
<td>5-FU</td>
<td>Decrease dose 50%</td>
</tr>
<tr>
<td>Skin (radiation dermatitis)</td>
<td>Grade 3 confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema</td>
<td>5-FU</td>
<td>Decrease dose by 50%</td>
</tr>
<tr>
<td>Skin (radiation dermatitis)</td>
<td>Grade 4 skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion</td>
<td>5-FU</td>
<td>Do not give next course</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Between 1.5 and 2.0</td>
<td>Cisplatin</td>
<td>Decrease dose 50%</td>
</tr>
<tr>
<td>Creatinine</td>
<td>&gt;2.0</td>
<td>Cisplatin</td>
<td>Do not give next course</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Parameters</td>
<td>Agent</td>
<td>Modification**</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>---------</td>
<td>----------------</td>
</tr>
<tr>
<td>Neuro: Peripheral neuropathy <em>(Sensory)</em></td>
<td>Grade 2 objective sensory loss or paresthesia <em>(including tingling)</em>, interfering with function, but not interfering with activities of daily living</td>
<td>Cisplatin</td>
<td>Decrease dose 50%</td>
</tr>
<tr>
<td>Neuro: Peripheral neuropathy <em>(Sensory)</em></td>
<td>Grade 3 sensory loss or paresthesia interfering with activities of daily living</td>
<td>Cisplatin</td>
<td>Do not give next course</td>
</tr>
<tr>
<td>Otoxicity <em>(inner ear/hearing)</em></td>
<td>Grade 2 tinnitus or hearing loss, not requiring hearing aid or treatment</td>
<td>Cisplatin</td>
<td>Decrease dose 50%</td>
</tr>
<tr>
<td>Otoxicity <em>(inner ear/hearing)</em></td>
<td>Grade 3 tinnitus or hearing loss, correctable with hearing aid or treatment</td>
<td>Cisplatin</td>
<td>Do not give next course</td>
</tr>
<tr>
<td>Nausea</td>
<td>Grade 3 no significant intake, requiring IV fluids</td>
<td>Cisplatin</td>
<td>Decrease dose 50%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Grade 3 ≥6 episodes in 24 hours over pretreatment; or need for IV fluids</td>
<td>Cisplatin</td>
<td>Decrease dose 50%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Grade 4 Requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse</td>
<td>Cisplatin</td>
<td>Decrease dose 50%</td>
</tr>
</tbody>
</table>

* Subsequent cycles of chemotherapy will not be resumed unless ANC is ≥ 1800, platelets are ≥ 100,000, and patients have recovered from above treatment related toxic effects.

** Once reduced, drug doses must not be re-escalated to the original doses.

7.7 Adverse Reaction Reporting/RTOG Members (2/1/01)

7.7.1 The revised NCI Common Toxicity Criteria Version 2.X will be used to score chemotherapy and acute radiation (≤ 90 days) toxicities. The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol that uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days.

7.7.1.1 Any ADR which is both serious *(life threatening, fatal)* and unexpected.

7.7.1.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.

7.7.1.3 Any death on study if clearly related to the commercial agent(s).

7.7.1.4 Acute myeloid leukemia *(AML)*. The report must include the time from original diagnosis to development of AML, characterization such as FAB subtype, cytogenetics, etc. and protocol identification.

7.7.2 The ADR report should be documented on Form FDA 3500 and mailed to:

**Investigational Drug Branch**
**P.O. Box 30012**
**Bethesda, Maryland 20824**
*(301) 230-2330*
*available 24 hours*
7.7.3 Special Reporting for this Study (telephone (215) 574-3150)
7.7.3.1 All grade ≥ 4 nonhematologic toxicities must be reported to RTOG within 24 hours.
7.7.3.2 All grade ≥ 4 hematologic toxicities must be reported to RTOG within 24 hours.
7.7.3.3 Data submission must adhere to the timetable specified by the patient calendar and Section 12.0.

7.8 Adverse Event Reporting for ECOG Investigators (3/11/03)
7.8.1 All ECOG Investigators are responsible for reporting adverse events according to the NCI guidelines. ECOG participants should employ definitions of adverse events as provided by the RTOG reporting guidelines in section 7.7. Both 24 hour and written/electronic adverse reports should be made directly to the RTOG according to the instructions in that section.

Reporting of AML/MDS

<table>
<thead>
<tr>
<th>AML/MDS</th>
<th>NCI/CTEP Secondary AML/MDS Report Form¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

¹To be completed within 30 days of diagnosis of AML/MDS that has occurred during or after protocol treatment. A copy is to be sent to ECOG and RTOG accompanied by copies of the pathology report (and when available, a copy of the cytogenetic report). ECOG will forward copies to the NCI.

ECOG Telephone Number: (617) 632-3610
ECOG Fax Number: (617) 632-2990
ECOG Mailing Address:
ECOG Coordinating Center
FSTRF
ATTN: Adverse Event
900 Commonwealth Avenue
Boston, MA 02215

NCI Fax Number: (301) 230-0159
NCI Mailing Address:
Investigational Drug Branch
P.O. Box 30012
Bethesda, MD 20824

FDA Fax Number 1-800-332-0178
FDA Mailing Address:
Medwatch
5600 Fishers Lane
Rockville, MD 20852-9787

7.9 Adverse Reaction Reporting Requirements/CALGB Members (12/20/99)

CALGB Investigators: Adverse Drug Reactions (ADRs) for CALGB patients will be routed through the CALGB Central Office. The CALGB Central Office (773-702-9860) must be called within 24 hours for all toxicities that need to be reported by telephone (See Section 7.7.3). All written reports must be submitted within five working days to the CALGB Central Office (c/o the Regulatory Affairs Coordinator), 208 South LaSalle Street, Suite 2000, Chicago, IL, 60604-1104, for tracking purposes. The CALGB Central Office will forward these reports to the RTOG Headquarters.

7.10 Adverse Reaction Reporting Requirements/NCCTG Members (12/20/99, 2/1/01)

7.10.1 This study will utilize the CTC version 2.0 for toxicity and Adverse Event reporting. A copy of the CTC version can be downloaded from the CTEP home page (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTC version 2.0.

7.10.2 This study will be monitored by the Clinical Data Update System (CDUS) version 1.X. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.
7.10.3 AE reporting is based on the Common Toxicity Criteria (CTC) Version 2.0. Adverse events that require the submission of an FDA Form 3500 to the NCCTG Operations Office must also be reported to the local IRB.

<table>
<thead>
<tr>
<th>FDA Form 3500 to NCCTG within 5 days</th>
<th>Unexpected grade 4 – 5</th>
<th>Increased incidence of a known AE</th>
<th>Secondary AML/MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC/CTEP Secondary AML/MDS Report Form to NCCTG within 15 working days</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

1. Any increased incidence of a known AE that has been reported in the package insert or the literature, including adverse event resulting from a drug overdose.
2. Reporting for this toxicity required during or after treatment.
3. Fax or mail:

   **NCCTG Operations Office**
   200 First Street, SW
   Rochester, MN 55905
   Fax: (507) 284-1902

The NCCTG Coordinating Center will call the RTOG Office for reportable ADRs. A copy of the ADR report will also be forwarded to RTOG.

7.11 Reporting for Commercial Drugs, SWOG Institutions: (2/1/01)

7.11.1 Guidelines for Reporting of Adverse Events (AE)/Adverse Drug Reactions (ADR) Occurring With Commercial Agents

1. **WITHIN 24 HOURS OF THE EVENT CALL THE OPERATIONS OFFICE AT 210-677-8808.**

2. **WITHIN 10 DAYS, SEND TO THE OPERATIONS OFFICE**
   a) A COPY OF THE FDA FORM 3500, including Investigator’s attribution of the event in item 5 (or the NC/CTEP Secondary AML/MDS Report Form for cases of secondary AML or MDS).
   b) COPIES OF PRESTUDY FORM(S), AND FLOW SHEETS FROM PRESTUDY THROUGH THE EVENT
   c) IRB NOTIFICATION DOCUMENTATION
   d) OTHER DATA AS REQUESTED DURING TELEPHONIC REPORT.

3. **IN ADDITION, FOLLOW THE GUIDELINES BELOW**

These guidelines apply to patients accrued to NCI research protocols which use commercial anticancer agents. The following events, when attributed as possibly, probably, or definitely related to the commercial agent(s), must be reported:

(a) Any AE/ADR which is life threatening (Grade 4) or fatal (Grade 5) and unexpected (is not listed as a known toxicity, or is of greater severity or specificity than listed toxicity). Any occurrence of secondary AML or MDS must also be reported.

(b) Any AE/ADR which is fatal (Grade 5), even if an expected toxicity.

The AE report, documented on FDA Form 3500 (or NC/CTEP Secondary AML/MDS Report Form) should be sent within 10 days to FDA, with a copy to NCI, as indicated below:
8.0 SURGERY

8.1 Primary Tumor Site

8.1.1 Eight weeks following completion of RT, the patient shall be evaluated. If the patient has had a complete response (disappearance of all palpable tumor), biopsy need not be done. If the patient has had a partial response, continued shrinkage, or stable disease, a full-thickness biopsy is preferably performed but it will be optional. If the patient has evidence of disease progression, increase in size of primary tumor or regional nodes or appearance of metastatic disease, biopsy need not be performed. Patients found to have persistent disease on biopsy or disease progression will be off-study and may receive salvage therapy (see Section 8.3 regarding surgical salvage) or other appropriate treatment at their physician's discretion.

8.1.2 The intent of a full-thickness biopsy when indicated (entire depth of the residual thickened tissue where the primary tumor was situated) is to provide adequate material for the determination of whether or not any malignant cells persist following combined modality therapy. However, with anterior lesions in women and in lesions which were initially greater than 4 cm and have left an area of thickening which is more than 25% of the anal circumference, significant morbidity (retrovaginal fistula, long-standing fissures or incontinence) might follow an extensive biopsy of such residual. If the surgeon feels that the removal of all thickened tissue would leave either exposure of a large area of vaginal submucosa or would require too extensive a defect in the anal ring, a biopsy of the central portion of the thickening which would include the deepest of the scar is acceptable and advised. If there appears to be clearly malignant tumor remaining, a portion of this cancer is all one needs to biopsy in order to document its persistence and allow the patient to go on to off-study salvage therapy.

8.2 Inguinal Lymph Nodes

8.2.1 If inguinal lymph node(s) are palpably enlarged at presentation, a biopsy should be performed to determine if nodal enlargement is due to metastasis or nodes are reactive. This can be accomplished with needle aspiration with cytologic examination. If negative, an excisional biopsy of one node should be obtained. Only those patients with pathologically confirmed positive nodes will receive a radiation boost.
8.3 Post Treatment Biopsy
8.3.1 If post treatment biopsies are positive for tumor the patient may undergo salvage therapy off-study. Surgical options include wide local excision only if margins of 1cm can be achieved or abdomino-perineal resection. Non-surgical options are also available.
8.3.2 Any complications resulting from post treatment biopsy should be reported on data forms.

9.0 OTHER THERAPY
Not applicable to this protocol.

10.0 PATHOLOGY (3/11/03)
10.1 Central Review
10.1.1 Central pathology review is planned for this study. In previous anal canal protocols, the uniformity of histological classification of tumors has been a significant problem.
10.1.2 H & E stained slide(s) from the pre-treatment biopsy must be submitted for central review.
10.1.3 H & E stained slide(s) from the post-treatment biopsy also must also be submitted for central review.
10.1.4 For patients having salvage surgery, the pathologic materials must also be submitted for central review.
10.2 Tumor Marker Evaluation (6/2/09)
10.2.1 p53: Tumors will be evaluated for nuclear p53 staining. At least 100 cells from three separate areas of the tumor will be counted. A score will be assigned for each area (score = positive cells/total cells x 100), with the median of the three used for statistical purposes. This median score will be categorized as “bad” if it is > 5, and “good” if it is ≤ 5.
10.2.2 HPV: Both PCR and in situ hybridization techniques will be performed on the tumor specimens. If either PCR or in situ hybridization demonstrates HPV subtypes 16, 18, 31 or 33, the specimen will be categorized as “bad” for statistical purposes. If both procedures fail to find HPV, or if the only subtype(s) identified is/are 6 and/or 11, the specimen will be categorized as “good”.
10.2.3 At least one formalin-fixed, paraffin-embedded block for tumor marker evaluation/banking from a representative area of the primary tumor and one formalin-fixed paraffin embedded block from normal mucosa will be submitted along with a copy of the surgical pathology report and the RTOG Pathology Submission Form to the address below:

U. S. Postal Service Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu

10.2.3.1 If blocks are not available, a representative H&E stained section and 20 unstained slides (cut at 5 microns, at least 2 sections per slide, on silane coated slides) should be submitted.
10.2.3.2 Block submission is highly desirable for this study. If slides are submitted instead, the flexibility of study technique is compromised. It is planned that the cases will be evaluated for p53 tumor suppressor gene expression using immunocytochemical evaluation for the p53 protein (DO7 antibody). HPV expression will be evaluated by PCR and in situ hybridization, looking for sub types 6/11, 16, 18, 31, and 33. To perform this procedure, silane coated slides are necessary and multiple tissue sections must be placed on each slide along with positive and negative controls. Having blocks rather than slides available will facilitate this procedure. The RTOG Biospecimen Resource has histotechnologist staffing to enable the proper preparation of slides for this procedure. Thus, the work...
of the submitting institution is diminished. The evaluation of inherent radiosensitivity will be done using immunocytochemical detection of the enzyme HAP1.

10.2.3.3 Blocks and original sections will be returned on completion of the trial if specifically requested at completion. Otherwise, they will be stored permanently at the RTOG Biospecimen Resource.

10.2.3.4 Unstained slides and slides prepared from the blocks will be permanently retained.

10.2.3.5 RTOG will reimburse submitting institutions $300 per case for fresh or flash frozen tissue, $200 per case for a block or core of material, or $100 per case for slides submitted for tumor marker evaluation/banking. After confirmation from the RTOG Biospecimen Resource that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution’s summary report with the institution’s regular case reimbursement.

10.3 Intergroup Pathology Submission (3/11/03)(6/2/09)

10.3.1 SWOG Institutions

All RTOG guidelines listed in Section 10.1 apply to SWOG Institutions. All specimens and original forms must be submitted DIRECTLY to the RTOG Biospecimen Resource at the address below RTOG will reimburse the submitting institutions as detailed in Section 10.1.5.5.

U. S. Postal Service Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu

10.3.2 (3/11/03) ECOG institutions should submit a representative H&E stained section and 20 unstained slides (cut at 5 microns at least 2 sections per slide, on silane coated slide) along with a copy of the surgical pathology report. If ECOG institutions submit paraffin blocks, they will be returned to the contributing institution and slides will be requested. ECOG members will send pathology material to the ECOG Pathology Coordinating Office:

ECOG Pathology Coordinating Office
Robert H. Lurie Comprehensive Cancer Center
Northwestern University Medical School
Olson Pavilion - Room 8501
710 North Fairbanks Court
Chicago, IL 60611

Note: A copy of the completed ECOG Pathology Material Submission Form No. 638 will be sent to the ECOG Study Chair and to the ECOG Coordinating Center by the Pathology Coordinating Center. The ECOG PCO will log the materials and route them to the RTOG Tissue Bank at LDS Hospital using an RTOG Pathology Transmittal Form.

10.3.3 CALGB Institutions should submit the following to:

CALGB Central Pathology Office
The Ohio State University
B054 Graves Hall
333 West 10th Ave.
Columbus, OH 43210-1239
Telephone (614) 688-3495
1. The required materials listed in Section 10.1 properly identifying:
   a. patient’s name
   b. CALGB patient number and RTOG patient number
   c. CALGB study number and RTOG study number
2. **Original** completed RTOG Pathology Submission Form
3. **Original** completed CALGB Form C-350
4. A copy of the responsible pathologist’s surgical pathology report from the TREATING institution, and, if applicable, from the REFERRING institution.

The CALGB Pathology Office will forward a copy of the RTOG Pathology Submission Form to RTOG Headquarters.
10.3.4 NCCTG Institutions

Pathologic materials from the pre-treatment, post-treatment and salvage surgery are required for central review. NCCTG members will forward one formalin-fixed, paraffin-embedded block from a representative area of the primary tumor, and one formalin-fixed paraffin embedded block from normal mucosa to the NCCTG bank at the Research Base along with a copy of the surgical pathology report. The NCCTG Operations Office Pathology Coordinator will forward the materials to the Mayo Clinic Histology Core Laboratory where an H&E stained section and 20 unstained sections will be obtained. These slides will be forwarded to RTOG and the tissue blocks will be returned to the NCCTG Tissue Resource Repository for storage. These blocks will be accessible by NCCTG members upon request. The appropriate NCCTG institutional pathologist will be notified if a block has been depleted.
## 11.0 PATIENT ASSESSMENTS
### 11.1 Study Parameters (12/20/99) (10/28/03)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prior to randomization&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Weekly during therapy</th>
<th>Every 4 weeks during therapy</th>
<th>8 wks after therapy</th>
<th>At followup per Sec. 12.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical exam/KPS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tumor measurement</td>
<td>X</td>
<td>X</td>
<td>As indicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC, diff, platelets, ANC</td>
<td>X</td>
<td>(twice weekly during RT)</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Creatinine ± BUN, (creatinine clearance for creatinine &gt;1.5), bilirubin</td>
<td>X</td>
<td>X&lt;sup&gt;d,e&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Urinalysis, HIV&lt;sup&gt;b&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrolytes</td>
<td>X</td>
<td></td>
<td>X</td>
<td>8 weeks following completion of therapy, then annually</td>
<td></td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sigmoidoscopy or Proctoscopy</td>
<td>X</td>
<td></td>
<td>X</td>
<td>q 6 months x 4 then PRN</td>
<td></td>
</tr>
<tr>
<td>MRI or CT scan Abdomen and Pelvis</td>
<td>X</td>
<td></td>
<td>Yearly x 2 then PRN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Pregnancy test</td>
<td>X&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>As needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphangiogram (if CT positive)</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td>(optional)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Tumor Biopsy</td>
<td>X&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td>full thickness biopsy (optional)</td>
<td>As needed</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> All lab studies to be done within 2 weeks prior to randomization; radiographs must be done within 35 days.
<sup>b</sup> As required.
<sup>c</sup> Not required for postmenopausal or surgically sterilized women.
<sup>d</sup> Magnesium levels will be evaluated prior to each course of chemotherapy.
<sup>e</sup> Electrolytes and creatinine will also be assessed if the patient develops ≥ grade 2 diarrhea.
<sup>f</sup> And clinically positive nodes.

### 11.2 Definition of Tumor Response or Progression:

#### 11.2.1 Complete Response
Complete disappearance of all clinically detectable disease. Response must last at least 4 weeks.

#### 11.2.2 Partial Response
Greater than or equal to 50% decrease in the sum of the product of the longest perpendicular diameter of the measurable tumor. No new lesion may appear. Response must last at least 4 weeks.

#### 11.2.3 Minor Response
Less than 50% decrease in the sum of the product of the longest perpendicular diameter of the measurable tumor. No new lesion may appear.

#### 11.2.4 No Response
No change in the sum of the product of the longest perpendicular diameter of the measurable tumor.

#### 11.2.5 Tumor Progression
Greater than 25% increase in the sum of the product of the longest perpendicular diameter of the measurable tumor or appearance of a new lesion.

#### 11.2.6 Tumor Relapse or Metastases
Suspected local-regional recurrence within the irradiation field must be documented histologically or cytologically. Similarly, pathological documentation of suspected metastatic lesion is recommended.

**11.3 Function Assessment**

**11.3.1 Continence**

0 = Normal continence; able to control stool movements at all times
1 = Gas incontinence only; able to control stool movements but not gas
2 = Minor spotting or leakage of stool (up to coin size) about once per week
3 = Minor spotting or leakage of stool (up to coin size) more than once per week
4 = Significant leakage of stool (larger than coin size) about once per week
5 = Significant leakage of stool (larger than coin size) more than once per week

**11.3.2** In addition, presence of fistula, persistent cramps, intermittent SBO, and any GYN dysfunction will be recorded.

**12.0 DATA SUBMISSION (6/2/09)**

**12.1 Summary of Data Submission (3/11/03)**

All material (with the exception of Dosimetry) will be sent to the appropriate Cooperative Group office according to the following schedule and then forwarded to RTOG Headquarters. **CALGB, ECOG, NCCTG, and SWOG will send all Dosimetry material (T2, T3, T4) directly to RTOG Headquarters, 1818 Market Street, Suite 1600, Philadelphia, PA 19103; Fax# 215/928-0153.** All dosimetry material (films, etc.) must be identified with labels available from RTOG. **All data items must be identified with both RTOG and other Group's study and case number. Unidentified data/films will be returned.**

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Demographic Form (A5)</td>
<td>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Tumor Diagram (I2)</td>
<td></td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Blocks/Slides (P2)</td>
<td></td>
</tr>
<tr>
<td>Preliminary Dosimetry Information:</td>
<td></td>
</tr>
<tr>
<td>RT Prescription (Protocol Treatment Form) (T2)</td>
<td>Within 1 week of start of RT</td>
</tr>
<tr>
<td>Films (simulation and portal) (T3)</td>
<td></td>
</tr>
<tr>
<td>Calculations (T4)</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy Form (T1)</td>
<td>Within 1 week of RT end.</td>
</tr>
<tr>
<td>Final Dosimetry Information:</td>
<td></td>
</tr>
<tr>
<td>Daily Treatment Record (T5)</td>
<td></td>
</tr>
<tr>
<td>Isodose Distribution (T6)</td>
<td></td>
</tr>
<tr>
<td>Boost Films (simulation and portal) (T8)</td>
<td></td>
</tr>
<tr>
<td>Biopsy Evaluation Form (F2)</td>
<td>Within 8 weeks of RT end</td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td>As applicable for post-treatment biopsy and salvage surgery</td>
</tr>
<tr>
<td>Pathology Blocks/Slides (P2)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy Flow Sheets (M1)</td>
<td>After each cycle</td>
</tr>
<tr>
<td>Surgical Form (S1)</td>
<td>As applicable for salvage surgery</td>
</tr>
<tr>
<td>Surgical Pathology Report (S5)</td>
<td></td>
</tr>
<tr>
<td>Surgical Operative Report (S2)</td>
<td></td>
</tr>
<tr>
<td>Initial Follow-up Form (FS)</td>
<td>90 days from start of RT</td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>Every 3 months from initial followup assessment (FS) for 1 year; q 6 months x 1 year, then annually. Also at progression/relapse and at death.</td>
</tr>
</tbody>
</table>
12.2 Data Forms (12/20/99, 2/1/01)(6/2/09)

12.2.1 RTOG will send a forms package to RTOG members for each case registered. Other Groups will attach a forms appendix to their members’ version. It will be the responsibility of the other Groups’ members to copy the attached forms and to maintain a supply of available forms for data submission. The RTOG and cooperative groups’ assigned case and study numbers must be recorded on all data items submitted. Except for material which requires rapid review (see Section 12.3), data should be routed according to the mechanism set up by each participating Group. Generally the participating Group will require data to be routed through their offices and they will send the forms to:

RTOG Headquarters -
1818 Market Street, Suite 1600
Philadelphia, PA 19103

12.2.2 (3/11/03) ECOG institutions will send originals of completed forms to:

ECOG Coordinating Center
Frontier Science
ATTN: Data
900 Commonwealth Avenue
Boston, MA 02215

The RTOG case number as well as the ECOG case number should appear on every form. Investigators should retain a copy for their records. The ECOG Coordinating Center will forward date-stamped originals to the RTOG Headquarters. ECOG members should NOT send forms directly to RTOG. RTOG forms should be used. DO NOT use ECOG data forms except for the ECOG Pathology Material Submission Form No 638.

12.2.3 CALGB Institutions should submit data forms (excluding dosimetry) as listed in this section at the required intervals to:

CALGB Data Management Center
First Union Plaza, Suite 340
2200 West Main Street
Durham, NC 27705
(919) 286-0045
Fax (919) 826-1142

12.2.4 NCCTG: All forms listed in Section 12.1 are to be submitted to:

NCCTG Operations Office
200 First Street SW
Rochester, MN 55905

NCCTG will forward to RTOG. Include the RTOG protocol and patient case numbers as well as the local ID number and the NCCTG protocol number, R9811.

12.2.5 SWOG Institutions

The Pathology Report P1 and blocks/slides and the RTOG Pathology Submission Form must be submitted DIRECTLY to the RTOG as listed in Section 12.1. All original pathology submission forms, samples, and supporting paperwork must be submitted DIRECTLY to the RTOG Headquarters as listed in Sections 10.3.1 and 12.2.

12.2.5.1 Group Members and Affiliates: The RTOG required numbers of copies of forms for submission plus one additional copy of the data forms as listed in Section 12.1 must be submitted at the required intervals to the Southwest Oncology Group Statistical Center, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, MP-557, P.O. Box 19024, Seattle, WA 98109-1024 for forwarding to the RTOG Statistical Center. Include the RTOG and SWOG protocol numbers and patient numbers on each page of data.
12.2.5.2  **CCOP Institutions**: The RTOG required numbers of copies of forms for submission plus one additional copy of the data forms as listed in Section 12.1 must be submitted at the required intervals to:

**Cancer Research and Biostatistics (CRAB)**

ATTN: SWOG CCOP Office

1100 Olive Way, Suite 1150
Seattle, WA 98101-1892

Include the RTOG and SWOG protocol numbers and patient numbers on each page of data. The Southwest Oncology Group CCOP Office will forward the required copies to RTOG.

12.3  **Rapid Review Items**

Time critical data which requires rapid submission must be sent directly to RTOG (fax #215/928-0153):

- T2 - Protocol Treatment Form
- T3 - Photon localization film (*for all fields treated initially*)
- T4 - Photon dose calculations (*for all fields treated initially*)

12.4  **Request for Study Information and Forms Request**

Requests for additional information or clarification of data will be routed through the participating Cooperative Group for distribution to the individual institution. The RTOG memo requesting the additional information must be returned with the response. Responses should be returned according to the procedure used to submit data forms. You may receive reminders prompting response. Periodically (*generally three times per year*), computer generated lists identifying delinquent material are prepared and are routed through the participating Cooperative Group for distribution.

13.0  **STATISTICAL CONSIDERATIONS**

13.1  **Endpoints (12/20/99)**

13.1.1 Disease Free Survival (*Failure: disease relapse or second primary or death without progression*);

13.1.2 Overall Survival (*Failure: Death from any cause*);

13.1.3 Cumulative Incidence of Colostomy;

13.1.4 Cumulative Incidence of Local Regional Failure and Distant Metastases;

13.1.5 Toxicity.

13.1.6 Hazard ratios for tumor markers P53 overexpression, human pilloma virus status and enzyme marker HAP1.

13.2  **Accrual for the Study**

13.2.1 **Intergroup Accrual**

RTOG completed RTOG 87-04 with ECOG participating (*ECOG 1289*). The average annual accrual rate was 100-110 patients after ECOG joined in October 1989. If T1 patients are excluded, the average accrual rate is reduced to evaluable 80 patients. At the December 1997 GI intergroup meeting, all groups indicated that they would participate in this trial. The accrual of 130 evaluable patients per year is projected for this study.

13.2.2 **Sample Size**

The study will investigate a comparison of the experimental treatment of two courses of 5FU + Cisplatin followed by 5FU + Cisplatin given concurrently with radiotherapy with the standard treatment of 5FU + Mitomycin-C given concurrently with radiotherapy. Patients on both treatment arms will receive XRT boost as indicated for residual disease. The primary object of the study will be to determine if the 5FU + Cisplatin regimen can result in longer disease-free survival than the 5FU + Mitomycin-C regimen. Although there are several endpoints of interest, the sample size calculation will be based on disease-free survival. The results with Mitomycin-C from the intergroup study RTOG 87-04/ECOG 1289 were updated for the 1998 ASCO meeting and will be utilized here. Its estimated yearly hazard rates for disease-free survival were 0.2165 for the first year, 0.0485 for the second year, 0.0658 for the third year, 0.0584 for the fourth year, 0.0684 for the fifth year, and 0.1190 for the sixth year. For planning purposes, we will assume a constant hazard rate of 0.0917 for the Mitomycin-C arm which will give us the same 5 year NED rate (63%) as that in RTOG 87-04/ECOG 1289. Using that we will underestimate the number of failures occurring during the patient's first year. We hypothesize a 33% reduction in hazard for the Cisplatin regimen, i.e. a 5-year disease free survival rate of 73%. We use a statistical power of 0.80, alpha level of 0.05 (*two sided*) and exponential distribution for survival rates. Adapting the group sequential design with planned two interim and a final analyses, 215 events (*failures*) are needed to show the hypothesized difference in disease-free survival rates. O'Brien-Fleming boundary shape is used for the
early stopping rules. We further assume five-year accrual with a constant rate of patient entering and three-year follow up period. The total sample size needed for this study is 650.

13.4 Randomization Schema

The treatment allocation will be used in a randomized permuted block within strata to balance the patient factors other than institutions, as Zelen has described. Patients will be stratified by gender (male vs. female), clinical nodal stage (positive vs. negative), and size of primary (> 2 cm to ≤5 cm vs. > 5 cm) prior to randomization.

13.5 Analysis Plan for Treatment Test

13.5.1 Interim Analyses to Monitor the Study Progress:
Interim reports with statistical analyses will be prepared twice a year until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase, the data quality, the compliance rate of the treatment delivery, the distributions of the important prognostic baseline variables, and the frequencies and severity of the toxicity by treatment arms. They will not contain the results from the treatment comparisons with respect to the efficacy endpoints. (Disease free survival, overall survival, patterns of failure)

13.5.2 Significance Testing for Early Termination (12/20/99)

We plan two interim analyses to test early termination. These two interim analyses will be performed when 50% and 75% of total required events (failures) occur, i.e. at about the end of 4th and 6th year of the study.

- The stopping rules for the first interim analysis are:
  i. If the outcome shows highly significant difference in favoring either arm
     (i.e. |z| > 2.753, O’Brien-Fleming approach), or
  ii. If the outcome is lack of evidence to show the difference at the end of the study
     (i.e. |z| < 0.656, O’Brien-Fleming approach).

- The stopping rules for the second interim analysis are:
  i. If the outcome shows highly significant difference in favoring either arm
     (i.e. |z| > 2.217, O’Brien-Fleming approach), or
  ii. If the outcome is lack of evidence to show the difference at the end of the study
     (i.e. |z| < 1.401, O’Brien-Fleming approach).

If an early stopping rule is met, the study statistician would recommend to the DMC that the randomization be discontinued and the study be immediately written up for publication. In the case when the study is stopped due to the first (i) stopping rule and Cisplatin or Mitomycin-C shows the positive effect, the study statistician would recommend it as the treatment of the choice. In the case when the study is stopped due to the second (ii) stopping rule in either interim analysis, the study statistician will further evaluate the treatment toxicities. If the toxicity from Cisplatin regimen is significantly less than Mitomycin-C regimen, the study statistician would also recommend the choice of the treatment being Cisplatin regimen.

It is estimated there will be 520 patients already entered study if study is terminated at the first interim analysis. All patients (650) are accrued at the time of second interim analysis. Assuming these patients are available for toxicity assessment at the time, the various differences of two toxicity proportions that can be detected with statistical power of 0.80 and alpha of 0.05 (two sided) are listed in the table below.

About 12% difference in toxicity rates is able to be detected with designed statistical power.

<table>
<thead>
<tr>
<th>Baseline prop.</th>
<th>80%</th>
<th>70%</th>
<th>60%</th>
<th>50%</th>
<th>40%</th>
<th>30%</th>
<th>20%</th>
<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diff (size = 260/arm)</td>
<td>8.8%</td>
<td>10.5%</td>
<td>11.6%</td>
<td>12.2%</td>
<td>12.2%</td>
<td>11.7%</td>
<td>10.6%</td>
<td>8.5%</td>
</tr>
<tr>
<td>Diff (size = 325/arm)</td>
<td>8.0%</td>
<td>9.5%</td>
<td>10.4%</td>
<td>10.9%</td>
<td>10.9%</td>
<td>10.5%</td>
<td>9.4%</td>
<td>7.5%</td>
</tr>
</tbody>
</table>

The toxicity endpoint in this study will be grade 5 (fatal), grade 3 or 4 non-hematologic which also includes infection and bleeding. WBC, neutrophils and platelets are excluded.

In the Mitomycin-C arm of RTOG 87-04/ECOG 1289, the colostomy free rate was 93.9% at two years. Assuming an alpha level of 0.05 (two sided) and with all 650 patients accrued, this study can detect the colostomy free rate differences at two years for as small as 5% between two the arms with a statistical power of 80%.
13.5.3  

**Analysis for Reporting of the Initial Treatment Results**

This major analysis will take place after a positive significance test in either of the first two time points specified in section 13.5.2 or after all the patients have been entered the study and potentially followed for at least 3 years. If the two early significance tests do not satisfy the early termination criteria, the critical value for “final” analysis will be $|z| = 1.977$ to preserve an overall alpha level of .05 for the study. It will include a tabulation of all cases entered, and those excluded from the analyses with the reasons, the distribution of the important prognostic baseline variables, and observed results with respect to the endpoints mentioned in Section 13.1. All eligible patients randomized will be included in the comparison by assigned treatment arm in the analysis. The primary hypothesis of treatment benefit will be tested using the Cox proportional hazard model with the stratification factor of gender (male vs. female), clinical nodal stage (positive vs. negative), and primary (< 5cm vs. > 5cm) prior to randomization. Additional analyses of treatment effect will include modifying factors such as age, race, and other patient characteristics. These analyses will also use the Cox proportional hazard model. The treatment comparison on overall survival will be analyzed in a similar fashion. The treatment comparisons on the patterns of treatment failures and the toxicity will use the z-statistic for testing binomial proportions.

13.5.4  

**Inclusion of Women and Minorities**

In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regarding to inclusion of women and minorities in clinical research, we have considered the two possible interactions (treatment by race and treatment by gender). In the closed intergroup study RTOG 87-04, there are 34% males and 66% females. Gender turned out to be a significant prognostic factor even after the effects of treatment, tumor size and N stage are adjusted for. Woman did better in terms of disease-free survival in both treatment arms, no treatment by gender interaction was found. Race information was not collected in RTOG 87-04 but was available in a subsequent phase I/II study, RTOG 92-08. Of the 66 patients with information, 51 (77%) were white; 8 (12%), African Americans; 6 (9%), Hispanic Americans; 1 (2%), Filipino. The sample size is too small to test for treatment by race interaction. This phase III study is designed to test the efficacy under the assumption of the similar efficacy rate across the genders and the across the races. A statistical analysis will be performed to examine the possible treatment difference between the genders and among the races. The projected distributions of genders and races are as follows.

<table>
<thead>
<tr>
<th></th>
<th>American Indian or Alaskan Native</th>
<th>Asian or Pacific Islander</th>
<th>Black, not of Hispanic Origin</th>
<th>Hispanic</th>
<th>White, not of Hispanic Origin</th>
<th>Other or Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>4</td>
<td>4</td>
<td>51</td>
<td>39</td>
<td>331</td>
<td></td>
<td>429</td>
</tr>
<tr>
<td>Male</td>
<td>2</td>
<td>2</td>
<td>27</td>
<td>20</td>
<td>170</td>
<td></td>
<td>221</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>6</td>
<td>78</td>
<td>59</td>
<td>501</td>
<td></td>
<td>650</td>
</tr>
</tbody>
</table>

13.6  

**Tumor Marker Evaluation**

An analysis of RTOG 87-04 suggested that the patients with P53 overpression had poorer outcome. This study seeks to confirm the observation that was made in 64 patients. It will also evaluate two other tumor markers, human papilloma virus status and enzyme marker HAP1. Several published papers have reported that they may also impact outcome. It seeks to determine if any of them have prognostic value independent of the other known factors such as tumor size. For planning purpose, each marker is considered as a dichotomous variable and is subdivided into a “good” and a “poor” risk subgroup. Disease free will be the primary endpoint for this analysis. The number of events required for the evaluation of tumor markers are calculated using the equation described by Schoenfeld in various hypothesized scenarios.

Number of deaths = $(Z_{1-\alpha/2} + Z_{1-\beta})^2 / [(\ln HR)^2 w(1-w)]$, where:

$Z_{1-\alpha/2}$th percentile of Standard Normal Distribution

$Z_{1-\beta}$th percentile of Standard Normal Distribution

$HR$ - hazard ratio expressing the increased risk of failing for the “poor” risk subgroup as compared to “good” risk subgroup.

$w$ - prevalence rate for patients in a subgroup
The statistical significance level (\(\alpha\)) is set at \(.05\) (two-sided). The statistical power is set \((1-\beta)\) at \(.90\) and \(.80\) and hazard ratio at \(2.5\) and \(2.0\). The table below gives the number of events in each scenario.

Number of events (failures) required for various hazard ratios and statistical powers:

<table>
<thead>
<tr>
<th>Prevalence rate</th>
<th>Hazard ratio = 2.5</th>
<th>Hazard ratio = 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statistical Power</td>
<td>Statistical Power</td>
</tr>
<tr>
<td>.10</td>
<td>139</td>
<td>243</td>
</tr>
<tr>
<td></td>
<td>.80</td>
<td>104</td>
</tr>
<tr>
<td>.20</td>
<td>78</td>
<td>137</td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>102</td>
</tr>
<tr>
<td>.30</td>
<td>60</td>
<td>104</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>78</td>
</tr>
<tr>
<td>.40</td>
<td>52</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>68</td>
</tr>
<tr>
<td>.50</td>
<td>50</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>65</td>
</tr>
</tbody>
</table>

The study is designed to perform the final treatment analysis when total 215 events (failures) are observed at the end of the study. It is assumed that the tumor marker will be available for 80% of the patients and there is a random pattern with the missing 20%. Therefore there will be about 172 failures \((=.80*215)\) with available tumor markers at the time of the final treatment analysis. With prevalence rates for the subgroups varying between 10 to 90%, a prognostic effect for HR > 2.5 will be detected 9 out of 10 times.

The assumption will be changed when only 50% of patients have the tumor marker available and there is a random pattern with the other missing 50%. There will be about 108 failures \((=.50*215)\) with available tumor markers at the time of the final treatment analysis. With prevalence rates for the subgroups varying between 13 to 87%, a prognostic effect for HR > 2.5 will be detected 9 out of 10 times.

The prognostic value of each tumor marker will be tested using the Cox proportional hazard model with the other study stratification factors and assigned treatment as fixed covariates.
REFERENCES


33. John et al. Dose escalation without split-course chemoradiation for anal cancer: Results of a phase II RTOG study proceedings ASTRO 97.


APPENDIX IA (2/1/01) (10/28/03)

RTOG 98-11
(ECOG R9811, CALGB 89808, NCCTG R9811, SWOG R9811)
A Phase III Randomized Study Of 5-Fluorouracil, Cisplatin, and Radiotherapy Vs. 5 Fluorouracil, Mitomycin-C and Radiotherapy in Carcinoma of the Anal Canal

Sample Patient Consent Form
RESEARCH STUDY

I have the right to know about the procedures that are used if I participate in clinical research so I have the opportunity to make the decision whether or not to undergo the procedure after knowing the risks, benefits, and alternatives. This disclosure is not meant to frighten or alarm me. It is simply an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

It has been explained to me that I have cancer of the anus. Until recently, surgery which removed the anus and rectum or a combination of chemotherapy and radiation were considered standard therapy for my disease. Radiation therapy and chemotherapy given together may eliminate the need for surgery with improved long-term survival. This is because the chemotherapy improves the effectiveness of radiation. This study will attempt to show which of two types of chemotherapy when given with radiation are more effective.

DESCRIPTION OF PROCEDURES (12/20/99)

This study involves at random (by chance) assignment to one of two treatments. It is not clear at the present time which of the two treatments is better. For this reason the therapy which is to be offered to me will be based upon a method of selection called randomization. Randomization means that my physician will call a statistical office which will assign me one of the two treatments by computer. The chance of my receiving one of the two treatments is approximately equal. I will be assigned to one of the following two treatments:

Treatment 1: Chemotherapy (5 FU and Mitomycin-C) and radiation over 5 to 6.5 weeks. Mitomycin-C and 5-FU will be given by i.v. (in my vein) on days 1 and 29. The 5-FU will be given over 4 days in my vein each time. Radiation will be given once a day, five days a week, for 25 treatments. My blood counts will be monitored weekly during chemotherapy and twice weekly during radiation therapy. I may have an additional 5-7 radiation treatments if my tumor is large or the surrounding lymph nodes (glands) contain tumor.

Treatment 2: Patients will first receive 2 cycles of chemotherapy (5FU and Cisplatin) to be completed in approximately 8 weeks prior to radiation therapy, and then receive the same chemotherapy and radiation over 5 to 6 weeks. 5-FU will be given over 4 days in my vein beginning on the first and 29th days of the program without radiation and on the 57th and 85th days of the program with radiation. Cisplatin will be given by i.v. (in my vein) over one hour on the first and 29th days without radiation and on 57th and 85th days with radiation. Radiation will be given once a day, five days a week, for 25 treatments. My blood counts will be monitored weekly during chemotherapy twice weekly during radiation therapy. I may have an additional 5-7 radiation treatments if my tumor is large or the surrounding lymph nodes (glands) contain tumor.

If the glands in the groin are enlarged and thought to have cancer, a biopsy under local anesthesia is recommended before I start my treatment. Also, if I am in a high risk group for AIDS, I will have an HIV test.

Eight weeks after I finish radiation therapy, I may have to have a biopsy of the area of the original tumor to see if there is any remaining cancer. A piece of tissue will be removed by my surgeon for examination. If there is no cancer in the tissue, I will receive no further therapy. If there is cancer present in the tissue, I may have additional therapy. Also at eight weeks, I will have routine blood tests, a chest x-ray, and x-ray examination of my colon and rectum. My doctor will keep me informed of my progress and will continue to monitor me regularly.
Cancer treatments often have side effects. The treatment used in this program may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring. **Risks:**

**Radiation Therapy** may cause loss of pubic hair, skin irritation, diarrhea, tiredness and nausea. These side effects usually go away shortly after the treatment has been completed. If I have a severe skin reaction to the radiation, I will have an up to 10-day break from radiation to recover. Later on, some more serious complications, which rarely occur, may also develop. These include intestinal blockage and/or intestinal bleeding which may require surgery. If surgery is required later on, the risks involved may be slightly increased due to the radiation therapy. Rarely, radiation therapy to the pelvis in males may result in sterility *(incapable of reproduction).*

Radiation therapy to the pelvis will cause fertile females to lose the ability to bear children since radiation causes loss of ovary function. Hormones may be needed to relieve the symptoms such as hot flashes or vaginal dryness caused by the loss of ovary function. In pregnant females, radiation therapy to the pelvis will cause damage to the unborn child if I am pregnant. If I am female, I must have a negative pregnancy test before I join the study. If I am not currently pregnant, I must avoid pregnancy. If I am unwilling to use adequate birth control measures to prevent pregnancy, I should not participate in this study. If I should become pregnant while on this study, I must tell my doctor immediately.

**5-Fluorouracil (5-FU)** can cause diarrhea, a metal taste in the mouth, dry skin, dry nose, and watery eyes. The drug can cause soreness or painful ulcers of the mouth and throat or severe diarrhea. **Loss of hair** may result. The drug may cause thinning of the skin, nail changes, redness or darkening of the skin, rash, and increased sensitivity to the sun. 5-FU can also cause blood counts to drop causing increased bruising or risk of infection. 5-FU may cause headaches which continue after treatment is stopped. Rarely, the drug can cause reversible unsteadiness upon walking, dizziness, and slurred speech. It has also rarely been associated with heart attack.

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

**Mitomycin-C** may cause kidney damage but this is unlikely with short term use. If Mitomycin-C leaks from my vein during administration, severe tissue damage can result. All efforts will be made to prevent this from happening. Other risks include skin rash, dry cough, shortness of breath, loss of appetite, nausea, vomiting, light-headedness, hair loss or thinning, puffiness of the hands and feet, or diarrhea. My blood counts may be lowered leading to an increased risk of severe bruising or infection.

**Surgery:** Risks of biopsy include infection, bleeding and minor pain.

In addition to the above risks, combining chemotherapy and radiation therapy may also cause rectal sores, blockage of urinary tubes, fistula *(openings between organs)* and in females, dryness in the genital region and painful intercourse. A small risk of death may be possible with these treatments.

My physician will be checking me closely to see if any of these side effects are occurring. Routine blood tests will be done twice weekly during the radiation to monitor the effects of treatment. Side effects usually disappear after the treatment is stopped. In the meantime, my doctor may prescribe medication to keep these side effects under control. I understand that the use of medication to help control side effects could result in added costs. This institution is not financially responsible for treatments of side effects caused by the study treatment.

**CONTACT PERSONS**

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

**BENEFITS**

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

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

**ALTERNATIVES**

Alternatives which could be considered in my case include surgery or radiation therapy alone or in combination with chemotherapy or treatments to make me feel better, but not necessarily cure me or make my disease less. An additional alternative is no further therapy, which would probably result in continued growth of my tumor. My doctor can provide detailed information about my disease and the benefits of the various treatments available. I have been told that I should feel free to discuss my disease and my prognosis with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I am free to ask my physician any questions concerning this program that I wish in the future.

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

**VOLUNTARY PARTICIPATION**

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

**CONFIDENTIALITY (12/20/99)**

Records of my progress while on the study will be kept in a confidential form at this institution and also in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). If my doctor is a member of the Eastern Cooperative Oncology Group (ECOG), the Southwest Oncology Group (SWOG), the CALGB Group, or the North Central Group (NCCTG), my records will also be stored with them. The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (FDA), the National Cancer Institute (NCI), and other groups or organizations that have a role this study may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including tissue and/or slides, will be sent to a central office for review of the tumor characteristics and for specific research studies. These may include the evaluation of p53 tumor suppression gene status, evaluation of human papilloma virus status, and evaluation of the tumor's sensitivity to radiation. This last test will use the enzyme HAP1. The results of these evaluations will be kept confidential.

I have read all of the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

________________________________________  __________________________
Patient Signature (or Legal Representative)  Date
ABOUT USING TISSUE FOR RESEARCH

You have had or you will have a biopsy (or surgery) to see if you have cancer. Your doctor has removed or will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that remains for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Your tissue may be helpful for research whether you do or do not have cancer.

THINGS TO THINK ABOUT

The choice to let us keep the left over tissue for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue and then any tissue that remains will no longer be used for research; or, you may request that your tissue, if any remains, be returned to you or your designee.

In the future, people who do research may need to know more about your health. While (doctor/institution) may give researchers reports about your health, your doctor/institution will not give researchers your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your tissue will be used only for research. However, the research done with your tissue may help to develop new products in the future, or your tissue may be used to establish a cell line that could be patented and licensed. If this occurs, you will not be financially compensated.

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

**RISKS**

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

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

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

**MAKING YOUR CHOICE**

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

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

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

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

3. My tissue may be kept for use in research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer’s disease, or heart disease).
   Yes                No
4. Someone from _____ (doctor’s office/institution) may contact me in the future to ask me to take part in more research.

   Yes          No

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

Patient’s Name ____________________________ Signature ____________________________ Date ________________

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

Name of Person Obtaining Consent ____________________________ Signature ____________________________ Date ________________
APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

## STAGING FOR ANAL CANAL CANCER

*(AJCC, 1997)*

### Primary Tumor (*T*)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma <em>in situ</em></td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor more than 2 cm but not more than 5 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor more than 5 cm in greatest dimension</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size invades adjacent organ(s), e.g., vagina, urethra, bladder (<em>involvement of sphincter muscle[s] alone is not classified as T4</em>)</td>
</tr>
</tbody>
</table>

### Regional Lymph Node (*N*)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in perirectal lymph node(s)</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in unilateral internal iliac and/or inguinal lymph node(s)</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes.</td>
</tr>
</tbody>
</table>

### Distant Metastasis (*M*)

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

### Stage Grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>Primary Tumor</th>
<th>Regional Lymph Node</th>
<th>Distant Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
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<td>N1</td>
<td>M0</td>
</tr>
<tr>
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<td>Any T</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
<tr>
<td>ORGAN TISSUE</td>
<td>GRADE 1</td>
<td>GRADE 2</td>
<td>GRADE 3</td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>SKIN</td>
<td>None</td>
<td>Slight atrophy; Pigmentation change; Some hair loss</td>
<td>Patch atrophy; Moderate telangiectasia; Total hair loss</td>
</tr>
<tr>
<td>SUBCUTANEOUS TISSUE</td>
<td>None</td>
<td>Slight induration (fibrosis) and loss of subcutaneous fat</td>
<td>Moderate fibrosis but asymptomatic; Slight field contracture; &lt;10% linear reduction</td>
</tr>
<tr>
<td>MUCOUS MEMBRANE</td>
<td>None</td>
<td>Slight atrophy and dryness</td>
<td>Moderate atrophy and telangiectasia; Little mucous telangiectasia</td>
</tr>
<tr>
<td>SALIVARY GLANDS</td>
<td>None</td>
<td>Slight dryness of mouth; Good response on stimulation</td>
<td>Moderate dryness of mouth; Poor response on stimulation</td>
</tr>
<tr>
<td>SPINAL CORD</td>
<td>None</td>
<td>Mild L’Hermitte’s syndrome</td>
<td>Severe L’Hermitte’s syndrome</td>
</tr>
<tr>
<td>BRAIN</td>
<td>None</td>
<td>Mild headache; Slight lethargy</td>
<td>Symptomatic cataract; Moderate corneal ulceration; Minor retinopathy or keratitis</td>
</tr>
<tr>
<td>EYE</td>
<td>None</td>
<td>Asymptomatic cataract; Minor corneal ulceration or keratitis</td>
<td>Asymptomatic or mild symptoms (dry cough); Slight radiographic appearances</td>
</tr>
<tr>
<td>LARYNX</td>
<td>None</td>
<td>Hoarseness; Slight arytenoid edema</td>
<td>Moderate arytenoid edema; Chondritis</td>
</tr>
<tr>
<td>LUNG</td>
<td>None</td>
<td>Asymptomatic or mild symptoms (dry cough); Slight radiographic appearances</td>
<td>Moderate symptomatic fibrosis or pneumonitis (severe cough); Low grade fever; Patchy radiographic appearances</td>
</tr>
<tr>
<td>HEART</td>
<td>None</td>
<td>Asymptomatic or mild symptoms; Transient T wave inversion &amp; ST Changes; Sinus tachycardia &gt;110 (at rest)</td>
<td>Severe angina; Pericardial effusion; Constrictive pericarditis; Moderate heart failure; Cardiac enlargement; EKG abnormalities</td>
</tr>
<tr>
<td>ESOPHAGUS</td>
<td>None</td>
<td>Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing</td>
<td>Unable to take solid food normally; Swallowing semi-solid food; Dilation may be indicated</td>
</tr>
<tr>
<td>SMALL/LARGE INTESTINE</td>
<td>None</td>
<td>Mild diarrhea; Mild cramping; Bowel movement 5 times daily Slight rectal discharge or bleeding</td>
<td>Moderate diarrhea and colic; Bowel movement &gt;5 times daily; Excessive rectal mucus or intermittent bleeding</td>
</tr>
<tr>
<td>LIVER</td>
<td>None</td>
<td>Mild lassitude; Nausea, dyspepsia; Slightly abnormal liver function</td>
<td>Moderate symptoms; Some abnormal liver function; tests abnormal; Serum albumin normal</td>
</tr>
<tr>
<td>KIDNEY</td>
<td>None</td>
<td>Transient albuminuria; No hypertension; Mild impairment of renal function; Urea 25-35 mg%;Creatinine 1.5-2.0 mg%; Creatinine clearance &gt; 75%</td>
<td>Persistent moderate albuminuria (2+); Mild hypertension; No related anemia; Moderate impairment of renal function; Urea &gt;36-60mg% Creatinine clearance (50-74%)</td>
</tr>
<tr>
<td>BLADDER</td>
<td>None</td>
<td>Slight epithelial atrophy; Minor telangiectasia (microscopic hematuria)</td>
<td>Moderate frequency; Generalized telangiectasia; Intermittent macroscopic hematuria</td>
</tr>
<tr>
<td>BONE</td>
<td>None</td>
<td>Asymptomatic; No growth retardation; Reduced bone Density</td>
<td>Moderate pain or tenderness; Growth retardation; Irregular bone sclerosis</td>
</tr>
<tr>
<td>JOINT</td>
<td>None</td>
<td>Mild joint stiffness; Slight limitation of movement</td>
<td>Moderate stiffness; Intermittent or moderate joint pain; Moderate limitation of movement</td>
</tr>
</tbody>
</table>
APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

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

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.

   a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.

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

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

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

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

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

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

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

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

B. RADIATION TOXICITY GUIDELINES

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

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

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

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

Known toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

**Commercial and Non-Investigational Agents**

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

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

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

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

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

**Investigational Agents**

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

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

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

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

- All deaths within 30 days of termination of the agent. As above
- All life threatening (grade 4) events which may be due to agent.
  As above

- First occurrence of any toxicity (regardless of grade).
  Report by phone within 24 hours to IDB drug monitor and RTOG Headquarters.
  **A written report may be required.

ii.  Phase II, III Studies Utilizing Investigational Agents

- All fatal (grade 5) and life threatening (grade 4) known adverse reactions due to investigational agent.
  Report by phone to RTOG Headquarters and the Study Chairman within 24 hours.
  **A written report must be sent to RTOG within working days with a copy to IDB.
  (Grade 4 myelosuppression not reported to IDB)

- All fatal (grade 5) and life threatening (grade 4) unknown adverse reactions resulting from or suspected to be related to investigational agent.
  Report by phone to RTOG Headquarters, the Study Chairman and IDB within 24 hours.
  **A written report to follow within 10 working days.

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

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

Figure 1

Figure 2

Figure 3

Figure 4

Figures 3 & 4: When a 4-field technique is used, shaped lateral fields are required and may vary according to individual anatomy. Inguinal nodes must not be undertreated and may require electron boost to required dose level. Lymphangiogram or CT to define volume with 1.5 cm margin beyond nodal volume.

Note: Boost treatment (59.4 Gy arms) is not demonstrated but will require a target volume to include the tumor plus a 2-2.5 cm margin individualized to the patient. Nodal disease (45-59.4 Gy arms) will also require a boost target volume to include nodal metastases plus a 2-2.5 cm margin.
APPENDIX VII

EXTRAVASATION PROCEDURE FOR MITOMYCIN-C

If extravasation occurs, immediate action is required to prevent severe tissue damage. The nurse or physician should proceed immediately with management of extravasation and document same in orders and progress notes.

A. **Purpose:**
   Infiltration of vesicant drug into tissue will cause tissue necrosis and sloughing. Healing may be slow or not occur at all with resulting scarring and contracture.
   The local management of tissue infiltration by a vesicant drug can prevent necrosis and sloughing.

B. **Symptoms of Extravasation:**
   The following characteristics of extravasation will require immediate action:
   1. Local, immediate pain
   2. Local immediate stinging sensation
   3. Local, immediate burning sensation
   4. Redness and/or swelling at the injection site
   5. Lack of blood flashback

C. **Materials:**
   1. Hydrocortisone, 100 mg per 2 ml
   2. 1% Hydrocortisone Cream
   3. Americaine Spray
   4. Several TB Syringes
   5. Sterile Dressing
   6. Paper Tape
   7. Ice Pack

D. **Procedure:**
   1. Remove needle from vein
   2. Apply ice pack
   3. From the 10 mg vial of Hydrocortisone, draw up 0.2 ml in each of several syringes
   4. Americaine spray or other topical anesthetic can be used to ease the discomfort of the injections
   5. Inject the cortisone intradermally and subcutaneously completely surrounding the area of extravasation
   6. Seven to eight (7-8) injections may be required, depending on the size and location of extravasation
   7. After injections, apply 1% Hydrocortisone Cream
   8. Place a sterile 3" x 4" dressing over the area
   9. Reapply ice pack for 24 hours
   10. Continue use of Hydrocortisone Cream twice a day until erythema subsides
   11. Exercise affected arm to maintain motion and stimulate circulation.
APPENDIX VIII

INTERGROUP PARTICIPATION IN RTOG STUDIES

GENERAL GUIDELINES (3/11/03)(6/2/09)

I. **REGISTRATION:** RTOG will be responsible for all registration/randomizations. The procedure is:
   - Each institution affiliated with a Cooperative Group will phone their group and supply the eligibility check information.
   - The participating Cooperative Group will then telephone RTOG 215/574-3191 between 8:30 a.m. and 5:00 p.m. ET and supply the necessary eligibility and stratification information. RTOG will then assign a case number and treatment assignment. The participating Cooperative Group will then inform its member institution.
   - RTOG will send a Confirmation of Registration and a Forms Due Calendar to the participating Cooperative Group for each case registered. The participating Group forwards a copy of the calendar to the participating institution.

II. **PROTOCOL DISTRIBUTION:** Each participating cooperative group is responsible for distribution of the protocol to its members. All protocol amendments will be sent by RTOG to each participating Group office for distribution to member institutions. All communication with NCI regarding this protocol will be routed through the RTOG.

III. **INSTITUTIONAL PARTICIPATION:** It is the responsibility of each participating Cooperative Group to decide which of its member institutions may participate in this protocol. Each participating Cooperative Group must ensure that IRB approval was obtained prior to accession of cases.

IV. **CONFIRMATION/CALENDARS:** A Confirmation of Registration notice and a Data Collection Calendar is produced for each case registered and/or randomized. These will be distributed by RTOG to the appropriate cooperative group office for distribution to their members, if appropriate.

   The form identification code, which appears on the Calendars in the “key” columns, is found on the form in the lower right corner.

   You are expected to respond to each of the items listed either by submitting the item, by notifying us in writing that the item is not available or that the assessment was not done. The calendar may also list items that are not forms (CT or MRI scan reports, pathology reports) but are specific source documents. These items will be noted in the data collection section of the protocol but will not be listed on the Forms Package Index.

   Additional items/forms may be required depending on events that occur e.g. if surgery was done a surgical report may be required. See the protocol for conditional requirements.

   Unless specified otherwise, all patients are followed until death or termination of the study.

V. **FORMS:** Other groups will attach a forms appendix to their members’ version. It will be the responsibility of the other group’s member to copy the attached forms and to maintain a supply of available forms for data submission.

   The Demographic Data Form (A5) is required on all RTOG enrollments. Southwest Oncology Group institutions should submit the Demographic Data Form (A5), answering question 10 with “4”: “Not applicable/no items completed”; SWOG institutions will then receive credit for this form.

   This form is ideally completed by the patient. Instructions are found on the form.

   The RTOG assigned case and study number must be recorded on all data items submitted. Except for material which requires rapid review (see below), data should be routed according to the mechanism set up by the participating Group. Generally the participating group will require forms to be routed through their office and they will send the forms to:
VI. LABELS: Patient specific labels will be supplied to the participating Group for distribution to the individual institutions as patients are registered at RTOG.

When completing the labels, be specific when describing films, e.g.: "Pre op CT Brain Scan," "Large Photon Localization Film," "Follow-up Bone Scan," etc.

Research associates are advised to consult technical staff for assistance when labeling radiotherapy films. Correct film identification is the responsibility of the institutions and is essential to maintain efficient data flow.

VII. CANCELLATION/INELIGIBILITY: Patients who are found to be ineligible subsequent to registration are to be followed according to plan unless you receive written instructions to the contrary.

Patients who receive no treatment whatsoever may be canceled, however, written notification and an explanation must be received at RTOG Headquarters as soon as this has been determined. We must receive this notification not later than two weeks after registration. We will notify you of the determination made regarding the status of the case and instructions regarding subsequent data submission. RTOG requires all patients in randomized trials to be followed with data submission according to protocol schedule.

VI. RAPID REVIEW ITEMS: Time critical data which require rapid submission must be sent directly to RTOG. These items are:

- T2 - Protocol Treatment Form
- T3 - Photon Localization film (for all fields treated initially)
- T4 - Photon dose calculations (for all fields treated initially)

IX. REQUEST FOR STUDY INFORMATION AND FORMS REQUEST: Requests for additional information or clarification of data will be routed through the participating Cooperative Group office for distribution to the individual institution.

The memo requesting the additional information must be returned with the response. Responses should be returned according to the procedure used to submit data forms. You may receive reminders prompting response.

Periodically (generally three times per year) computer-generated lists identifying delinquent material are prepared. These are routed by RTOG through the participating group for distribution.

X. QUESTIONS REGARDING:

<table>
<thead>
<tr>
<th>Data/Eligibility/Treatment/ Adverse Events/Data Management Procedures</th>
<th>RTOG Research Associate (215) 574-3214</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forms Packets (RTOG Members)</td>
<td>Registration Secretary (215) 574-3191</td>
</tr>
<tr>
<td>Pathology</td>
<td>Pathology Clerk (801) 321-1929 (unless specified otherwise in Section 10.0)</td>
</tr>
<tr>
<td>Protocols/Amendments</td>
<td>Director, Protocol Development (215) 574-3195</td>
</tr>
</tbody>
</table>
Radiotherapy data items (*films, radiographs, isodose summations, treatment records, scans, reports and calculations*)

Dosimetry Clerk (215) 574-3219

Randomization/Registration

Registration Secretary (215) 574-3191

If you are unable to reach the person noted, and your call is urgent, ask to speak to any HQ Research Associate.

**XI. ADVERSE EVENTS AND TOXICITY**

**From Radiotherapy:** Unusual toxicities, all grade 5 toxicities, and grade 4 toxicities in altered fractionation studies are reported by telephone within 24 hours of discovery to RTOG Headquarters, to the Group Chairman Dr. Walter Curran, to the Study Chair(s), and to the RTOG Research Associate for this study.

**From Investigational Agents:** Are to be reported according to NCI guidelines. In addition, RTOG Headquarters, RTOG Data Management and the Study Chair(s) are to receive notification as outlined by the NCI procedures. If telephone notification is necessary, RTOG and the Study Chair(s) must also be called.

Copies of all toxicity reports and forms submitted to NCI must be sent to RTOG Headquarters also.

**From Commercial Drugs:** Are to be reported according to NCI/FDA guidelines. A copy of the reports and forms submitted to FDA must be sent to RTOG.

**Data Submission:** Events that require telephone reporting will require current updating of data forms through the date of the event. Submit within 10 working days of the telephone call.

**Second Malignancy:** All second primary tumors that are diagnosed during or following protocol treatment must be reported on the study data collection forms. AML/MDS must be reported on the NCI/CTEP Secondary Reporting Form. Instructions for submission are on the data form.