

## RADIATION THERAPY ONCOLOGY GROUP

### RTOG 0529

#### A Phase II Evaluation of Dose-Painted IMRT in Combination with 5-Fluorouracil and Mitomycin-C for Reduction of Acute Morbidity in Carcinoma of the Anal Canal

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**RADIATION THERAPY ONCOLOGY GROUP**

**RTOG 0529**

**A Phase II Evaluation of Dose-Painted IMRT in Combination with 5-Fluorouracil and Mitomycin-C for Reduction of Acute Morbidity in Carcinoma of the Anal Canal**

**SCHEMA (5/31/07)**

<b>5-FU + Mitomycin-C and IMRT</b>		
<b>R</b>	<b>5-FU + Mitomycin-C</b>	<b>IMRT</b>
<b>E</b>		
<b>G</b>	<ul style="list-style-type: none"> <li>Mitomycin-C on days 1 and 29</li> </ul>	The prescription dose scheme will depend on staging as follows: (see Section 6.0 for complete details)
<b>I</b>		
<b>S</b>	<ul style="list-style-type: none"> <li>5-FU by <b>96-hour</b> continuous infusion (M-F)</li> </ul>	<ul style="list-style-type: none"> <li>T2N0: 28 fractions over 5.5 weeks</li> </ul>
<b>T</b>	beginning on day 1 and	<ul style="list-style-type: none"> <li>T3N0 or T4N0: 30 fractions over 6 weeks</li> </ul>
<b>E</b>	again on day 29	<ul style="list-style-type: none"> <li>N+: 30 fractions over 6 weeks</li> </ul>
<b>R</b>	<b>Note:</b> Days 1 and 29 are based on calendar days	

See Section 5.0 for pre-registration requirements.

**Patient Population:** (See Section 3.0 for Eligibility)

Histologically-proven, invasive primary squamous, basaloid, or cloacogenic carcinoma of the anal canal;  
T stage 2-4 and N0-N3 stage

**Required Sample Size: 59**

RTOG Institution # \_\_\_\_\_

RTOG 0529

Case # \_\_\_\_\_

**ELIGIBILITY CHECKLIST (12/21/06, 5/31/07)**

(page 1 of 3)

- \_\_\_\_\_ (Y) 1. Does the patient have histologically-proven, invasive primary squamous, basaloid, or cloacogenic carcinoma of the anal canal?
- \_\_\_\_\_ (Y) 2. Is the T stage 2-4, N stage 0-3, and M0 ?
- \_\_\_\_\_ (Y/N) 3. Does the patient have clinically positive perirectal, pelvic, or inguinal nodes?
- \_\_\_\_\_ (Y/N) If yes, does the patient have inguinal nodes < 1 cm in size that are felt to be clinically positive?
- \_\_\_\_\_ (Y) If yes, did the patient have a fine needle aspiration (FNA) biopsy within 42 days prior to registration?
- \_\_\_\_\_ (Y) 4. Has the patient had an anal examination within 42 days prior to registration, with mandatory biopsy and any of the following: colonoscopy, sigmoidoscopy or rigid proctoscopy, along with a digital rectal examination as described in Section 3.1?
- \_\_\_\_\_ (Y/NA) 5. Has the patient had a groin examination within 42 days prior to registration with documentation of any groin adenopathy and lymphadenopathy?
- \_\_\_\_\_ (Y) 6. Has the patient had an X-ray, CT scan, or PET/CT of the chest within 42 days prior to registration?
- \_\_\_\_\_ (Y) 7. Has the patient had a CT scan, MRI, or PET/CT of the abdomen and pelvis within 42 days prior to registration?
- \_\_\_\_\_ (Y) 8. Is the patient's Zubrod Performance Status 0-1?
- \_\_\_\_\_ (Y) 9. Is the patient  $\geq$  18 years of age?
- \_\_\_\_\_ (Y) 10. Has the patient met all the lab requirements as described in Section 3.1.7?
- \_\_\_\_\_ (Y/NA) 11. If a woman of child bearing potential or a male participant, did the patient agree to practice effective birth control throughout the treatment phase of the study?
- \_\_\_\_\_ (Y/N) 12. Is there clinical suspicion of AIDS?
- \_\_\_\_\_ (Y) If yes, has the patient had an HIV test within 42 days prior to registration?
- \_\_\_\_\_ (Y/N) 13. Did the patient have a prior invasive malignancy (with the exception of non-melanomatous skin cancer)?
- \_\_\_\_\_ (Y) If yes, has the patient been disease free for greater than three years?
- \_\_\_\_\_ (N) 14. Has the patient had prior systemic chemotherapy for anal cancer?

**(Continued on next page)**

RTOG Institution # \_\_\_\_\_

RTOG 0529

Case # \_\_\_\_\_

**ELIGIBILITY CHECKLIST (12/21/06, 5/31/07)**

(page 2 of 3)

- \_\_\_\_\_ (N) 15. Has the patient had prior radiation therapy to the pelvis that would result in overlap of radiation therapy fields?
- \_\_\_\_\_ (Y/N) 16. Has the patient had prior surgery for cancer of the anus?  
\_\_\_\_\_ (N) If yes, was all macroscopic anal cancer removed?
- \_\_\_\_\_ (N) 17. Has the patient had unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months?
- \_\_\_\_\_ (N) 18. Has the patient had a transmural myocardial infarction within the last 6 months?
- \_\_\_\_\_ (N) 19. Does the patient have an acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration?
- \_\_\_\_\_ (N) 20. Does the patient have a Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration?
- \_\_\_\_\_ (N) 21. Does the patient have hepatic insufficiency resulting in clinical jaundice and/or coagulation defects?
- \_\_\_\_\_ (N) 22. Does the patient have uncontrolled diabetes?
- \_\_\_\_\_ (N) 23. Does the patient have uncompensated heart disease or uncontrolled blood pressure per Section 3.2.6.7?
- \_\_\_\_\_ (N) 24. Does the patient have any other immunocompromised status (e.g., organ transplant or chronic glucocorticoid use)?
- \_\_\_\_\_ (N) 25. If female, is the patient pregnant or lactating?
- \_\_\_\_\_ (Y) 26. Did the patient sign a study specific informed consent prior to study entry?

**The following questions will be asked at Study Registration:**

**IMRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION**

- \_\_\_\_\_ 1. Name of institutional person registering the case?
- \_\_\_\_\_ (Y) 2. Has the Eligibility Checklist (above) been completed?

(Continued on next page)

RTOG Institution # \_\_\_\_\_

RTOG 0529

Case # \_\_\_\_\_

**ELIGIBILITY CHECKLIST (12/21/06, 5/31/07, 6/14/07)**

(page 3 of 3)

- \_\_\_\_\_(Y) 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 Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]
- \_\_\_\_\_ 6. Verifying Physician
- \_\_\_\_\_ 7. Patient's ID Number
- \_\_\_\_\_ 8. Date of Birth
- \_\_\_\_\_ 9. Race
- \_\_\_\_\_ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
- \_\_\_\_\_ 11. Gender
- \_\_\_\_\_ 12. Patient's Country of Residence
- \_\_\_\_\_ 13. Zip Code (U.S. Residents)
- \_\_\_\_\_ 14. Patient's Insurance Status
- \_\_\_\_\_ 15. Will any component of the patient's care be given at a military or VA facility?
- \_\_\_\_\_ 16. Calendar Base Date
- \_\_\_\_\_ 17. Registration date: This will be populated automatically
- \_\_\_\_\_(Y/N) 18. Tissue/blood/urine kept for cancer research?
- \_\_\_\_\_(Y/N) 19. Tissue/blood/urine kept for medical research?
- \_\_\_\_\_(Y/N) 20. Allow contact for future research?
- \_\_\_\_\_ 21. Medical Oncologist's Name
- \_\_\_\_\_ 22. Nodal Status (N0, ≤ 3 cm, > 3 cm, unevaluable)

The Eligibility Checklist must be completed in its entirety prior to web registration. 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.

Completed by \_\_\_\_\_ Date \_\_\_\_\_

## **1.0 INTRODUCTION**

### **1.1 Background of Anal Cancer**

Anal cancer accounts for about 4% of all cancers of the lower alimentary tract and 1.6% of all digestive system malignancies. The American Cancer Society estimates that there will be 3,990 new cases of anal margin, anal canal, and anorectal cancer diagnosed in 2005, with 620 deaths from the disease.<sup>1</sup> Greater than 90% of patients present with loco-regional disease and squamous cell carcinoma (SCC) represents over 80% of all cases. Anal canal cancer was once thought to be the result of chronic perianal inflammation, however, studies have since revealed a higher incidence in certain patient populations: those with a history of tobacco use, greater than 10 sexual partners; a history of sexually transmitted diseases to include human papillomavirus virus (HPV serotypes 16, 18, 31 and 33), or human immunodeficiency virus (HIV); and those with a history of vaginal, vulvar, or cervical cancers.<sup>2-4</sup> People with chronic immunosuppression, such as those who have undergone renal transplant and those that require chronic glucocorticoid therapy, are also at increased risk of HPV and anal cancer. Historically, the standard treatment for anal canal cancer was abdominal-perineal resection (APR) resulting in a permanent colostomy, with an estimated 5-year survival of 40 to 70%. However, combined modality therapy with radiation and concurrent chemotherapy, has revolutionized the care of squamous cell carcinoma of the anal canal allowing for organ preservation in approximately 75% of patients, and reserving APR as salvage surgery for patients with persistent or recurrent disease.

### **1.2 Sphincter-preserving Chemoradiation for Anal Canal Cancer**

Nigro et al. and colleagues at Wayne State University first described this chemoradiation approach over three decades ago using a pre-operative regimen of 30 Gy external beam radiation therapy delivered concurrently with two cycles of 5-fluorouracil (5-FU) and one dose of mitomycin-C (MMC). The first three patients demonstrated complete pathologic responses at APR, which led to strategies directed at preservation of the anal sphincter.<sup>5</sup> In a follow-up series, patients with anal canal cancer were initially treated with chemoradiation therapy (same regimen), and subjected to subsequent APR only if there was residual tumor in a post-chemoradiation biopsy.<sup>6</sup> The majority of patients treated with chemoradiation were cured without an APR with 5-year overall survival reported at 67% and colostomy-free survival, 59%.

These findings were subsequently confirmed by multiple investigations using a variety of chemoradiation regimens with radiation therapy (RT) doses of 30-60 Gy. In totality, the data demonstrate that the use of combined chemoradiotherapy results in local failure rates of 14% to 37%, 5-year overall survival rates of 72% to 89%, and 5-year colostomy-free survival rates of 70% to 86%.<sup>7-15</sup> As a result, the use of concurrent radiation and chemotherapy with infusional 5-FU and MMC has become the standard of care for patients with SCC of the anal canal.

### **1.3 Efficacy and Associated Toxicity of RT/5-FU/MMC**

The high colostomy-free survival rate associated with radiation with concurrent 5-FU and MMC has been tempered by significant acute toxicity in the form of painful moist skin desquamation, diarrhea and hematologic decline. Given the toxicity profile of mitomycin-C, a randomized trial was performed by the Radiation Therapy Oncology Group (RTOG)/Eastern Cooperative Oncology Group (ECOG) to determine whether effective organ sparing can be achieved without this agent.<sup>15</sup> A total of 310 patients were accrued to this study. 5-FU was administered at 1000 mg/m<sup>2</sup>/day as a continuous infusion for 4 days beginning days 1 and 28 of radiotherapy. Mitomycin-C was administered at 10mg/m<sup>2</sup> i.v. bolus on day 1 of each 5-FU course. Radiotherapy was given at 1.8 Gy daily, 5 fractions daily per week for 5 weeks, to a total dose of 45 Gy (field reduction at 30.6 Gy and optional boost to 50.4 Gy if palpable residual was found at 45 Gy). Salvage therapy for patients in either arm included 9 Gy/5 fractions radiotherapy boost administered concurrently with 5-FU and cisplatin if a positive biopsy was demonstrated 4-6 weeks after completion of chemoradiotherapy. Toxicities included neutropenia, as well as dermatologic and gastrointestinal. The acute toxicity rates for the two arms are summarized in Table 1. NCI Common Toxicity Criteria was used to score acute chemotherapy toxicity, while the RTOG grading system was used for radiation-associated morbidity. Seventy-nine percent of patients in the 5-FU alone arm received chemotherapy per protocol; 67% of patients in the 5-FU + mitomycin-C arm received chemotherapy per protocol.

<b>Table 1. RTOG 87-04/ECOG1289 Overall Acute Toxicity</b>			
<b>Treatment</b>	<b>Grade 3</b>	<b>Grade 4</b>	<b>Grade 5</b>
RT + 5-FU	54%	7%	0.7%
RT + 5-FU + MMC	55%	23%	3%

Disease free survival (67% vs. 50%,  $p < 0.003$ ), colostomy free survival (64% vs. 58%,  $p = 0.09$ ), and local-regional recurrence (17% vs. 36%,  $p < 0.001$ ) were improved at 5 years with the addition of mitomycin-C. This randomized trial concluded that MMC, despite significantly increasing the rate of grade 4 toxicities, improved local outcome.

The significant toxicity of this combined modality regimen of RT/5-FU/MMC was also demonstrated in the Anal Cancer Trial Working Party of the United Kingdom Coordination Committee on Cancer Research (UKCCCR) trial, which randomly assigned 585 patients with anal SCC to receive either radiotherapy alone (45 Gy external beam in 20 or 25 fractions over four to five weeks plus a 15 Gy external beam or 25 Gy brachytherapy boost), or radiotherapy plus concurrent 5-FU (1000 mg/m<sup>2</sup> for four days or 750 mg/m<sup>2</sup> for five days by continuous infusion during the first and the final weeks of radiotherapy) and MMC (12 mg/m<sup>2</sup> on day one only).<sup>13</sup> The addition of chemotherapy was associated with significant reductions in local failure at 3 years (61 vs. 39%,  $p < 0.0001$ ) and in 3-year cause-related mortality (28 vs. 39%,  $p = 0.02$ ). Three year overall survival was 65% in the chemoradiation arm and 58% in the radiation alone arm, but this difference did not reach statistical significance. More notably, increased acute morbidity, including six deaths, occurred with combined modality therapy. The rates of acute toxicity (reported as number of patients) from the UKCCCR trial are summarized in Table 2.

<b>Table 2. UKCCCR Trial</b>	<b>Radiation Alone</b>	<b>RT/5-FU/MMC</b>
<b>Acute Toxicity</b>	110/285 patients	140/292 patients
Hematologic (WBCx10 <sup>9</sup> /L)		
<2.0	0	13
<1.0	0	6
Plateletsx10 <sup>9</sup> /L		
<50	0	7
<25	0	7
Skin		
Overall	76	93
Severe	39	50
Gastrointestinal		
Overall	39	46
Severe	5	14
Genitourinary		
Overall	13	20
Severe	1	3

Subsequently, the RTOG conducted a pilot study (RTOG 92-08) to examine radiation dose escalation with the 5-FU/MMC regimen.<sup>16</sup> Forty-six patients received 5-FU 1000 mg/m<sup>2</sup>/day for 4 days during weeks 1 and 7 of radiation and MMC 10 mg/m<sup>2</sup> iv bolus on day1 of each course of 5-FU. The radiation dose used was 59.4 Gy in 1.8 Gy fractions over 9 weeks with a 2-week mandatory rest. The results were compared to the RTOG 87-04 trial in which patients were treated with 45 Gy in a continuous schedule plus the same chemotherapy regimen.<sup>15</sup> Forty percent of patients suffered Grade 3 toxicity, 23% had Grade 4 toxicity, and one patient died from infection, as shown in Table 3. Although these toxicity profiles were similar to RTOG 87-04, the two-year colostomy rate with 59.4 Gy and a two week break was much higher than expected (30% vs. 9%). Because of this, an additional 20 patients were treated to 59.4 Gy, but without a break. There were no treatment-related deaths, however morbidity was significant. The main Grade 3 and 4 toxicities were dermatologic (78%), hematologic (78%), infectious (17%), and gastrointestinal (28%). The authors concluded that, for higher doses to improve local control, radiation therapy might have to be given in a continuous fashion with 5-FU and MMC, with a resultant further increase in acute toxicity.

<b>Treatment</b>	<b>Grade 3</b>	<b>Grade 4</b>	<b>Grade 5</b>
59.4 Gy RT + 5-FU + MMC	40%	23%	One patient

#### **1.4 Cisplatin-based Chemoradiation Strategies to Reduce Toxicity**

Alternative chemoradiation regimens have been tested in a continuing effort to avoid the significant toxicity associated with mitomycin-C. The combination of 5-FU and cisplatin (CDDP) has been the most promising. The Eastern Cooperative Oncology Group performed a Phase II trial of 19 patients investigating this approach.<sup>17</sup> A split course radiation technique was used; a two-week break was given after delivery of 36 Gy. The total dose to the primary and any involved nodes was 59.4 Gy. The inguinal nodes were treated electively to 30.6 Gy. 5-FU was delivered on days 1-4 by continuous infusion at a dose of 1000mg/m<sup>2</sup>. Cisplatin was administered on day 1 at a dose of 75mg/m<sup>2</sup>. This regimen was repeated starting on day 43 with the resumption of radiation after a scheduled two-week break. Fifteen of 19 patients achieved a complete response. With a maximum follow-up of 33 months, 68% had local disease control. Grade 4 or 5 toxicity remained significant as it was reported in 37% of the patients and was primarily due to neutropenia. One patient died of sepsis.

The most recent intergroup study led by the RTOG for anal cancer, RTOG 98-11, also addressed the use of cisplatin in place of MMC as part of combined modality therapy. This was a two-arm phase III randomized trial comparing external beam radiation (using continuous radiation doses of up to 59 Gy, depending on the burden of primary and nodal disease) plus concurrent standard 5-FU/MMC (5-FU, 1,000 mg/m<sup>2</sup>, days 1-4 and 29-32 and MMC, 10 mg/m<sup>2</sup>, days 1 and 29) vs. two courses of induction 5-FU and cisplatin followed by concurrent RT plus 5-FU + cisplatin (5-FU, 1,000 mg/m<sup>2</sup>, days 1-4, 29-32, 57-60, and 85-88 and cisplatin, 75 mg/m<sup>2</sup>, days 1, 19, 57, and 85). Accrual goals have been met and the trial has closed. Preliminary toxicity and survival results were presented at the American Society of Clinical Oncology 2006 annual meeting.<sup>18</sup> Of the 682 patients accrued, 598 were analyzable. Preliminary five-year estimated disease-free survival (DFS) was 56% for the 5-FU/MMC group and 48% for the 5-FU/cisplatin arm (p=0.28), with five-year estimated overall survival rates of 69% for both arms (p=0.24). Male gender (p=0.04), clinically node positive cancers (p<0.0001), and tumor diameter > 5 cm (p=0.005) were all independent predictors of DFS in a multivariate analysis. The five-year colostomy rate was 10% with 5-FU/MMC and 20% for 5-FU/cisplatin (p=0.12). Acute toxicities were graded using CTC v. 2.0 criteria and are reported in Table 4. Overall, there were no significant differences in the grade 3-4 hematologic acute toxicity profile between the two arms in this preliminary analysis; however, the grade 3-4 non-hematologic toxicity profile favored the 5-FU/cisplatin arm.

<b>Toxicity</b>	<b>RT/5-FU/MMC (n=322) Grade</b>				<b>RT/5-FU/CDDP (n=312) Grade</b>			
	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>
Blood/bone marrow	10%	21%	34%	26%	19%	29%	26%	16%
Dermatologic/skin	9%	34%	43%	5%	10%	39%	38%	2%
Gastrointestinal	17%	38%	31%	3%	12%	37%	41%	3%
Infection/febrile neutropenia	2%	12%	16%	2%	1%	15%	9%	1%
Genitourinary	17%	19%	3%	0.3%	16%	20%	3%	0%
Worst non-hematologic	2%	21%	61%	12%	2%	23%	64%	8%
Worst overall	2%	10%	52%	34%	1%	16%	60%	21%

#### **1.5 Intensity Modulated Radiation Therapy to Reduce Toxicities**

The external beam radiotherapy used in these aforementioned large trials have all been planned and delivered using conventional 2-dimensional (2D) or 3-dimensional (3D) techniques.

Intensity-modulated radiation therapy (IMRT) is an emerging technology that allows delivery of radiation dose in a more conformal manner than conventional 2D or 3D radiation therapy by varying the radiation beams spatially or temporally.<sup>19</sup> The implementation of IMRT or “dose painting” allows the radiation oncologist to effectively target the tumor while sparing normal surrounding structures. IMRT has been extensively investigated and widely practiced in the treatment of head-and-neck cancers<sup>20-23</sup> and prostate cancer.<sup>24</sup>

Anal cancer is well suited for IMRT because avoidance structures such as small bowel, bladder, external genitalia, skin, femoral head and neck, and bone marrow can potentially be spared from the higher radiation doses that are used to treat the primary and gross nodal disease. Normal tissue tolerance doses form the basis for IMRT dose–volume constraints, though concurrent chemotherapy likely lowers the threshold doses. Use of IMRT may also help patients complete their treatment course in a timely fashion, without long treatment breaks that may negatively influence outcome, as demonstrated in RTOG 92-08.

Chen et al. published their dosimetric comparison of IMRT and conventional plans for coverage of the pelvic and inguinal/femoral lymph nodes in two patients with anal cancer.<sup>25</sup> Each patient was immobilized and underwent planning CT scans with 0.5 cm slices (AcQSim CT, Philips Medical Systems, Eindhoven, The Netherlands) in the supine position with a Vac-Lock immobilization bag (Med Tec Inc., Chicago, IL). For dosimetric comparison, a conventional isodose plan to a total dose of 36 Gy in 20 fractions was generated using 6-MV AP, 10-MV PA pelvic fields, and 16-MeV electron boost fields prescribed to isocenter and depth of inguinal nodal region. The treatment plan was designed to deliver a homogeneous dose of 36 Gy to the pelvis. A step-and-shoot inverse IMRT planning was subsequently generated with XiO Radiation Therapy Planning System 4.2.0 by CMS (St. Louis, MO). IMRT dose constraints were defined as: less than half of prescription dose (18 Gy) to femoral head and neck and external genitalia. The primary IMRT beam geometry comprised seven coplanar fields with gantry angles of 0°, 40°, 100°, 170°, 190°, 260°, and 320°, respectively. An isodose plan with prescription dose of 36 Gy in 20 fractions covering at least 95% of target volume was generated. The coverage of the tumor volume was comparable among the conventional and IMRT treatment techniques. The mean doses to the femoral head and neck were 58.3% and 59.5% of the prescription dose by conformal avoidance IMRT for Patients 1 and 2, respectively, which were moderately reduced as compared with the conventional technique using photons with enface electrons (71.2% and 72.6%). The median doses to the external genitalia were 55.9% and 63.6% of the prescription dose with IMRT for Patients 1 and 2, respectively, which also was significantly reduced as compared to conventional planning (78.4% and 97.7%).

Milano et al. published their series of 17 patients with stage II-III squamous cell cancer of the anal canal treated with IMRT in a two phase technique (large field and boost).<sup>26</sup> CT planning was performed in the supine position with 4 mm slices and immobilization. The gross tumor volume (GTV) and clinical target volume (CTV) were contoured on axial CT scan slices. The CTV included clinical and suspected subclinical involvement, and encompassed the perirectal, internal iliac, external iliac, and inguinal lymphatics. For the boost dose, the CTV was defined as the GTV. The radiation dose was prescribed to a planning target volume (PTV), which was generated by expanding the CTV by 1 cm and incorporating set-up uncertainty and organ motion. IMRT plans were generated using commercial inverse planning software (CORVUS, versions 3.0–5.0, NOMOS Corp., Sewickley, PA). Dynamic multileaf collimators were used to shape the fields. Nine-field coplanar plans were used, with fields evenly separated around a 360° arc. The dose–volume constraints of the target and normal tissues were defined as follows: 10–20% of bowel to receive 20–30 Gy with a dose maximum of 50 Gy, 10–20% of bladder to receive 30 Gy with a dose maximum of 45 Gy, and 50–60% of genitalia and perineum to receive 40 Gy with a dose maximum of 50 Gy. The IMRT plans were optimized to minimize the volume of PTV receiving 95% of the prescribed dose and the volume receiving 115% of the prescribed dose. The initial PTV for the AP/PA plan for patients who received concurrent chemotherapy was prescribed 45.0 Gy, followed by a 9.0 Gy boost to the GTV. Toxicity was graded using RTOG morbidity scoring criteria. Seven patients were planned with three-dimensional anteroposterior/posterior-anterior (AP/PA) fields for dosimetric comparison to IMRT. IMRT significantly reduced the mean doses to the bladder and genitalia/perineum. IMRT also significantly reduced the mean dose to the bowel as compared with AP/PA without a field reduction. Thirteen of 17 patients received their planned course of treatment without breaks in

radiation or chemotherapy. No treatment breaks were attributable to gastrointestinal or skin toxicity. Acute toxicity is described in Table 5. No patients experienced acute Grade 3 non-hematologic toxicity. All patients experienced acute Grade 2 dermatitis, namely moist desquamation in the perianal and intergluteal areas. Three of 17 patients, who did not achieve a complete response, proceeded to an abdominoperineal resection and colostomy. At a median follow-up of 20.3 months, there were no other local failures. Two-year overall survival, disease-free survival, and colostomy-free survival were: 91%, 65%, and 82% respectively, comparable to historical controls.

	<b>Grade 0</b>	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
Blood/bone marrow	0%	12%	12%	24%	29%
Dermatologic/skin	0%	100%	0%	0%	0%
Gastrointestinal	12%	35%	53%	0%	0%
Genitourinary	65%	35%	0%	0%	0%

Boston Medical Center and Massachusetts General Hospital developed a method of delivering a single-phase IMRT plan using a dose-painting (DP-IMRT) technique. Six patients with squamous cell carcinoma (stage T2N0 and above) of the anal canal were treated with DP-IMRT and concurrent chemotherapy.<sup>27</sup> The DP-IMRT dose prescriptions were 50.4 Gy at 1.8 Gy/fraction to the primary tumor and 42 Gy at 1.5 Gy/fx to the elective nodes for T2 N0 disease, or 54 Gy at 1.8 Gy/fx to the tumor and 45 Gy at 1.5 Gy/fx to the elective nodes for T3-4/N+ disease. Involved nodes were prescribed 54 Gy at 1.8 Gy/fx if > 3 cm in size or 50.4 Gy at 1.68 Gy/fx if ≤ 3 cm. For the dosimetric analysis, the DP-IMRT plans were compared with optimal, 3-D CT-based conformal therapy (CRT) per RTOG 98-11 design and doses. For the early clinical analysis, acute toxicity was assessed using the RTOG scoring system. The mean percentage of the primary clinical target volume receiving the prescription dose was 97% for both the DP-IMRT and CRT plans. DP-IMRT provided better tissue sparing of most normal structures as shown in Table 6. The acute toxicity experienced by the six patients treated with DP-IMRT was generally well-tolerated. All patients completed therapy as prescribed, and no patient required a treatment break of over one week. Four patients experienced grade ≥ 3 skin toxicity; three had grade ≥ 3 hematologic toxicity, and no patients had grade ≥ 3 GI toxicity. No patient experienced inguinal skin desquamation; however since perianal tissue is target, moist desquamation in the anus was observed. One patient with T2N3 disease did experience unexpected diarrhea and perianal desquamation on day 4 of RT, indicating a possible defect in 5-FU metabolism.<sup>28</sup> All patients achieved a complete tumor response based on clinical and radiographic assessment. Sample TLD (thermoluminescent dosimeters) measurements at the anal canal showed the daily delivered dose to be 190 cGy (range, 179-199 cGy).

<b>T2N0 (n = 3)</b>		<b>T3-4 / N+ (n = 3)</b>			
<b>Tissue Structure</b>	<b>Dose Level (Gy)</b>	<b>3-D CRT</b>	<b>DP-IMRT</b>	<b>3-D CRT</b>	<b>DP-IMRT</b>
Small Bowel	30	41	25	59	29
	40	25	12	18	11
Femoral Heads	45	3	0	17	4
Genitalia	35	89	56	91	40
	45	78	37	87	23
Bladder	30	100	68	100	85
	40	100	22	100	50
Perianal Skin	50	36	34	23	22

## **1.6 Rationale for the Proposed Study**

Several recent studies, including the closed RTOG 98-11, support the administration of higher radiation doses in the treatment of anal cancer.<sup>13-18,26-27</sup> The current standard dose recommendations range from 45 Gy for early lesions to 59.4 Gy for T2–T4 disease. The combination of these increased radiation doses with 5-FU and MMC therapy have resulted in encouraging local control rates, but have been tempered by significant acute morbidity, most notably grade 2+ hematologic, dermatologic and gastrointestinal, Table 4 RTOG 98-11. IMRT in the treatment of anal canal cancer has tremendous potential for reducing this toxicity, while allowing for these higher radiation doses to the gross tumor volume. Radiation dose to normal structures is reduced compared to conventional 2D and 3D treatment planning.<sup>25-27</sup> IMRT in these three aforementioned pilot studies appear well tolerated, with most patients experiencing only mild to moderate acute symptoms, and few patients experiencing treatment breaks. Locoregional control also appears acceptable, albeit in one small series with limited follow-up.<sup>26</sup>

One of the significant hurdles facing implementation of IMRT for pelvic malignancies, however, involves the complexity of target and elective lymphatic definition, as well as conformal avoidance dose volume constraints for normal organ structures. Precise contouring of primary tumors in the pelvic area is often difficult. Accurate, reproducible, and time-efficient delineation of subclinical volumes, including elective nodal regions at risk, represents an even greater challenge. Methods that simplify and increase uniformity of this process will be valuable to facilitate the implementation of IMRT for pelvic malignancies, and in this case – anal canal cancer - in routine practice. The primary objective of this study, therefore, is to investigate the feasibility of treating patients with anal cancer using IMRT as part of combined modality therapy with standard 5-FU and MMC chemotherapy as per RTOG 98-11 in a multi-institutional setting. The rationale is that with standardized anal IMRT, we may be able to reduce grade 2+ and grade 3+ morbidity, without compromising locoregional control.

## **2.0 OBJECTIVES**

### **2.1 Primary**

**2.1.1** To determine if the combined rate of  $\geq$  grade 2 GI and GU adverse events from IMRT+ 5-FU & Mitomycin-C is decreased by at least 15% in the first 90 days following the start of treatment, as compared to the RT+ 5-FU & Mitomycin-C arm from RTOG 9811

### **2.2 Secondary**

**2.2.1** To determine the feasibility of performing IMRT in a cooperative group setting for the treatment of anal carcinoma;

**2.2.2** To evaluate adverse events associated with this treatment regimen and to decrease the grade 2 and higher and grade 3 and higher overall adverse event rates by 15% or 20% as compared to the RT and Mitomycin-C arm of RTOG 9811;

**2.2.3** To estimate clinical complete response at 8 weeks following treatment completion;

**2.2.4** To evaluate total duration of radiotherapy treatment time;

**2.2.5** To estimate the following efficacy endpoints: local-regional failure, disease-free survival, time to colostomy, colostomy-free survival and overall survival.

## **3.0 PATIENT SELECTION**

### **NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED**

#### **3.1 Conditions for Patient Eligibility (5/31/07)**

**3.1.1** Histologically-proven, invasive primary squamous, basaloid, or cloacogenic carcinoma of the anal canal;

**3.1.2** T stage 2-4 and N0-N3 stage (see Appendix IV), based upon the following minimum diagnostic workup:

**3.1.2.1** History/physical examination within 14 days prior to registration;

**3.1.2.2** Within 42 days prior to registration, the patient must have an anal examination with mandatory biopsy and any of the following: colonoscopy, sigmoidoscopy, or rigid proctoscopy. Digital rectal examination with documentation of primary anal lesion size, distance from anal verge, and anal tone (excellent–fair) is also required.

**3.1.2.3** Groin examination within 42 days prior to registration with documentation of any groin adenopathy and lymphadenopathy (location: right vs. left; medial vs. lateral; mobile vs. fixed; and size);

**3.1.2.4** Clinically positive nodes:

- Small inguinal nodes < 1 cm in size that are felt to be clinically positive must be confirmed by biopsy (fine needle aspirate preferred) within 42 days prior to study registration;
  - A biopsy is not needed for enlarged inguinal, perirectal, or pelvic nodes on exam or CT scan,  $\geq 1.0$  cm, considered to be clinically positive.
- 3.1.3** X-ray (PA and lateral), CT scan, or PET/CT scan of the chest within 42 days prior to registration;
- 3.1.4** CT scan, MRI, or PET/CT of the abdomen and pelvis within 42 days prior to registration;
- 3.1.5** Zubrod Performance Status 0-1;
- 3.1.6** Age  $\geq 18$ ;
- 3.1.7** Laboratory data obtained  $\leq 14$  days prior to registration on study, with adequate bone marrow, hepatic and renal function defined as follows:
- Absolute neutrophil count (ANC)  $\geq 1,800$  cells/mm<sup>3</sup>;
  - Platelets  $\geq 100,000$  cells/mm<sup>3</sup>;
  - Hemoglobin  $\geq 8.0$  g/dl (Note: The use of transfusion or other intervention to achieve Hgb  $\geq 8.0$  g/dl is acceptable.);
  - Serum creatinine  $\leq 1.5$  mg/dl;
  - Bilirubin < 1.4mg/dl;
  - WBC  $\geq 3,000/\mu\text{l}$ ;
  - ALT/AST < 3 x ULN;
  - INR  $\leq 1.5$
  - Negative serum pregnancy test for women of child-bearing potential;
- 3.1.8** Women of childbearing potential and male participants must agree to use a medically effective means of birth control throughout their participation in the treatment phase of the study.
- 3.1.9** If there is clinical suspicion of AIDS, an HIV test must be done within 42 days prior to registration. **Note:** HIV positive patients without AIDS are eligible for this trial.
- 3.1.10** Patients must sign a study-specific informed consent prior to study entry.

### **3.2 Conditions for Patient Ineligibility (5/31/07)**

- 3.2.1** Prior invasive malignancy (except non-melanomatous skin cancer), unless disease free for a minimum of 3 years;
- 3.2.2** Prior systemic chemotherapy for anal cancer;
- 3.2.3** Prior radiotherapy to the pelvis that would result in overlap of radiation therapy fields;
- 3.2.4** T1 tumors (2 cm) or evidence of distant metastases (M1);
- 3.2.5** Prior surgery for cancer of the anus that removed all macroscopic anal cancer;
- 3.2.6** Severe, active co-morbidity, defined as follows:
- 3.2.6.1** Unstable angina and/or congestive heart failure requiring hospitalization within the past 6 months;
- 3.2.6.2** Transmural myocardial infarction within the last 6 months;
- 3.2.6.3** Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
- 3.2.6.4** Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;
- 3.2.6.5** Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects;
- 3.2.6.6** Uncontrolled diabetes, defined as diabetes mellitus, which in the opinion of any of the patient's physicians requires an immediate change in management; a patient may be considered eligible for the study if the physician managing the patient's diabetes considers that the appropriate changes in management have resulted in adequate control.
- 3.2.6.7** Uncompensated heart disease or uncontrolled high blood pressure, which in the opinion of any of patient's physicians, requires immediate change in management; a patient may be considered eligible for the study if the physician managing the patient's heart disease or blood pressure considers that the appropriate changes in management have resulted in adequate control. (also see Appendix II for New York Heart Association Class definitions);
- 3.2.6.8** Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; patients with known AIDS will be ineligible for this protocol because the treatments involved may be significantly immunosuppressive. Patients with clinical suspicion of AIDS and who are unwilling to have an HIV test are not eligible for this trial.
- 3.2.6.9** Other immunocompromised status (e.g., organ transplant or chronic glucocorticoid use).
- 3.2.7** Women who are pregnant or lactating are ineligible because the treatment involved in this study may be significantly teratogenic.

#### **4.0 PRETREATMENT EVALUATIONS/MANAGEMENT**

**Note: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.**

##### **4.1 Additional Mandatory Pre-treatment Evaluations/Interventions**

- 4.1.1 Assessment of weight and general nutritional status within 14 days prior to study entry;
- 4.1.2 Assessment of smoking and alcohol history (past and current) within 14 days prior to study entry.

##### **4.2 Additional Highly Recommended Pre-treatment Evaluations/Interventions**

**Note that these evaluations/interventions are highly recommended as part of good clinical care of patients on this trial but are not mandatory.**

- 4.2.1 Human Papilloma Virus (HPV) determination (specifically sub-types 16, 18, 31 and 33) from anal biopsy

#### **5.0 REGISTRATION PROCEDURES**

##### **5.1 Pre-Registration Requirements**

###### **5.1.1 Pre-Registration Requirements for IMRT Treatment Approach**

In order to use IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements, or determining if they have already been met, are available at the Radiological Physics Center (RPC) web site, <http://rpc.mdanderson.org/rpc/> by selecting "Credentialing" and "RTOG".

- 5.1.2 Each institution must contact the Washington University Image-Guided Center (ITC) at [itc@castor.wustl.edu](mailto:itc@castor.wustl.edu) and request an FTP account for digital data submission.

- 5.1.3 Each institution must submit and successfully complete a protocol-specific Dry-Run Test (the treatment plan for the first patient to be treated at the site on this protocol), and a Rapid Review will be performed **PRIOR TO DELIVERING ANY PROTOCOL TREATMENT**. The Dry-Run Test will be reviewed by the ITC. The Rapid Review will be conducted by the RPC and suggestions regarding protocol compliance will be forwarded to the participating institution.

The treatment plans for subsequent patients enrolled at a site will not be required to be reviewed prior to treatment, but a review will be performed for protocol compliance at a later date. Instructions for submitting the dry run can be found on Advanced Technology Consortium (ATC) web site, <http://atc.wustl.edu>.

##### **5.2 Registration**

###### **5.2.1 Online Registration**

Patients can be registered only after eligibility criteria are met.

Institutions must have an RTOG user name and password to register patients on the RTOG web site. To obtain a user name and password:

- The Investigator must have completed Human Subjects Training and been issued a certificate (See <http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp> for details on training).
- The institution must complete the Password Authorization Form at [www.rtog.org/members/webreg.html](http://www.rtog.org/members/webreg.html) (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site ([www.rtog.org](http://www.rtog.org)), going to "Data Center Login" and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be

printed so that the registering site will have a copy of the registration for the patient's record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study's database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

Institutions can contact RTOG web support for assistance with web registration: [websupport@phila.acr.org](mailto:websupport@phila.acr.org).

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site's user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

## **6.0 RADIATION THERAPY (5/31/07)**

**Note: Intensity Modulated RT (IMRT) Is Mandatory. Tomotherapy Is Allowed.**

(For specific questions or concerns regarding this section please contact Dr. Lisa Kachnic at Boston University Medical Center by email: [lisa.kachnic@bmc.org](mailto:lisa.kachnic@bmc.org) or telephone: 617-638-7070; or contact Dr. Robert Myerson at Washington University School of Medicine by email: [Myerson@radonc.wustl.edu](mailto:Myerson@radonc.wustl.edu) or telephone: 314-747-7236.)

**Protocol treatment must begin within 21 days after protocol registration.**

### **6.1 Dose Specifications (5/31/07)**

**6.1.1** The treatment plan used for each patient will be based on an analysis of the volumetric dose, including dose-volume histogram (DVH) analyses of the PTV and critical normal structures. An "inverse" planning method using dose-objective-based computerized optimization shall be used. The treatment aim will be the delivery of dose to the PTVs and the exclusion of noninvolved tissue.

**6.1.2** Target prescription dose: The prescription dose scheme shall depend on staging as follows:

**6.1.2.1** For T2N0 disease: The primary tumor PTV (PTVA) will receive 50.4 Gy in 28 fractions at 1.8 Gy per fraction. The nodal PTVs will receive 42 Gy in 28 fractions at 1.5 Gy per fraction.

- PTVA will receive 50.4 Gy in 28 fractions at 1.8 Gy per fraction.
- PTV42 will receive 42 Gy in 28 fractions at 1.5 Gy per fraction and will include all nodal regions (see section 6.4.2.3 below).

**6.1.2.2** For T3N0 or T4N0 disease: The primary tumor PTV (PTVA) will receive 54 Gy in 30 fractions at 1.8 Gy per fraction. The nodal PTVs will receive 45 Gy in 30 fractions at 1.5 Gy per fraction.

- PTVA will receive 54 Gy in 30 fractions at 1.80 Gy per fraction.
- PTV45 will receive 45 Gy in 30 fractions electively at 1.5 Gy per fraction and will include all nodal regions (see section 6.4.2.4 below).

**6.1.2.3** For N+ disease: The primary tumor PTV (PTVA) will receive 54 Gy in 30 fractions at 1.8 Gy per fraction. For involved nodes  $\leq 3$  cm in maximum dimension, the involved nodal PTV will receive 50.4 Gy in 30 fractions at 1.68 Gy per fraction. For involved nodes  $> 3$  cm in maximum dimension, the involved nodal PTV will receive 54 Gy in 30 fractions at 1.80 Gy per fraction.

For example, if the right groin nodes are positive and  $> 3$  cm, the left groin nodes are positive but  $\leq 3$  cm, and the pelvic nodes are clinically negative, then the respective PTV doses are 54, 50.4, and 45 Gy in 30 fractions

- PTVA will receive 54 Gy in 30 fractions at 1.8 Gy per fraction.
- PTV45 will receive 45 Gy in 30 fractions electively at 1.5 Gy per fraction and will include all uninvolved nodal regions.

- PTV50 will receive 50.4 Gy in 30 fractions at 1.68 Gy per fraction and will include all nodal regions containing involved nodes < 3cm in greatest dimension.
  - PTV54 will receive 54 Gy in 30 fractions at 1.8 Gy per fraction and will include all nodal regions containing involved nodes > 3cm in greatest dimension.
- 6.1.3** Treatment Schedule: Treatment will be delivered once daily, 5 fractions per week (except for holiday weeks). All targets will be treated simultaneously. Breaks in treatment should be minimized; any interruptions in treatment for longer than 7 days should be reported to Dr. Kachnic or Dr. Myerson.
- 6.1.4** Dose specifications: The prescription isodose surface will encompass at least 90% of the primary and involved nodal PTVs, and at least 85% of the uninvolved nodal PTVs, reflecting the inherent difficulty of covering the shallow portions of these targets.
- No more than 5% of any PTV will receive < 90% of the prescription dose.
  - No more than 2% of any PTV will receive < 80% of the prescription dose.
  - No more than 2% of the primary PTV will receive > 115% of the prescription dose.
- 6.1.5** Planning priorities: Tumor prescription goals followed by critical normal structure constraints are the most important planning goals.
- 1) Dose Specifications (Sections 6.1.1, 6.1.2, 6.1.4)
  - 2) Critical Normal Structure Constraints (Section 6.5.1);

## **6.2 Technical Factors**

Megavoltage equipment capable of delivering static intensity modulation with a multileaf collimator or dynamic intensity modulation (using a multileaf collimator or tomotherapy) is required. Inverse-planned IMRT is required; conventional 3D CRT methods and forward-planned IMRT are excluded.

## **6.3 Localization, Simulation, and Immobilization**

- 6.3.1** A custom immobilization device (such as Alpha Cradle for supine patients and an Alpha Cradle with bowel displacement device for prone patients) is suggested to minimize set-up variability. Simulation will be done with the patient in the supine "arms up" or prone "arms up" position using a CT-simulator with a slice thickness  $\leq 5$  mm. Oral and IV CT contrast is recommended, as is air in the rectum, and an anal marker at the verge or at the inferior extent of the tumor. Of note, daily portal imaging is strongly encouraged for patients being treated in the prone position on a bowel displacement device. Additionally, consideration should be given to using the lightest couch top available to avoid unnecessary bolusing.
- 6.3.2** Treatment planning CT scans will be required to define gross target volume, and clinical target volumes. The treatment planning CT scan should be acquired with the patient in the same position and using the same immobilization device as for treatment. A description of the immobilization system used by each institution, patient position (supine or prone) and data regarding the range of positioning errors (if data exists) should be provided.
- 6.3.3** All tissues to be irradiated must be included in the CT scan. CT scan thickness should be 0.5 cm or smaller slices through the region that contains the primary target volumes. The regions above and below the target volume may be scanned also with slice thickness of 0.5 cm.
- 6.3.4** The GTV and CTV (*see Section 6.4*), and normal tissues must be outlined on all CT slices in which the structures exist.

## **6.4 Treatment Planning/Target Volumes**

The definition of volumes will be in accordance with the 1993 ICRU Report #50: Prescribing, Recording and Reporting Photon Beam Therapy.

- 6.4.1** The Gross Tumor Volume (GTV) is defined as all known gross disease determined from CT (and MRI or PET if performed), clinical information, digital exam, endoscopic findings and biopsy. There will be three GTVs:
- 6.4.1.1** GTV<sub>A</sub> includes the gross primary anal tumor volume (as documented by digital exam, and as seen on CT, and PET or MRI if performed).
- 6.4.1.2** GTVN50, including all involved nodal regions (as documented by biopsy or radiograph) containing macroscopic disease < 3 cm in greatest dimension (which will receive 50.4 Gy).
- 6.4.1.3** GTVN54, including all nodal regions (as documented by biopsy or radiograph) containing macroscopic disease > 3 cm in greatest dimension (which will receive 54 Gy).
- 6.4.2** The Clinical Target Volume (CTV) is defined as the GTV plus areas considered to contain potential microscopic disease. Three different CTVs will be defined, namely CTVA for the primary anal tumor volume; CTV45 or CTV42 for the elective nodal regions (per 6.1 elective

nodal regions will receive 42 Gy for T2N0 cases and 45 Gy for all others); CTV50 for nodal regions containing macroscopic disease < 3cm in greatest dimension; and CTV54 for nodal regions containing macroscopic disease > 3cm in greatest dimension.

- 6.4.2.1** CTV<sub>A</sub> includes the gross primary anal tumor volume, the anal canal, and a 2.5 cm expansion (except into bone or air).
- 6.4.2.2** CTV<sub>45</sub>, CTV<sub>50</sub>, CTV<sub>54</sub> includes the nodal regions (respectively uninvolved, involved with nodes ≤ 3 cm, and involved with nodes > 3 cm) and a 1.0 cm expansion (except into uninvolved bone, genitourinary structures, muscles, or bowel).
- 6.4.2.3** **Nodal regions include:**
- Mesorectal (including peri-rectal and presacral)
  - Right and left inguinal
    - Right and left external iliac
    - Right and left internal iliac
- Examples of the definitions of the appropriate nodal groups can be found on the ATC web site, <http://atc.wustl.edu>.
- 6.4.3** The Planning Target Volume (PTV) will provide a margin around the CTV to compensate for the variables of treatment set-up and internal organ motion. A minimum of 1 cm around the CTV is required in all directions to define each respective PTV. A nodal PTV should not be allowed to overlap with the primary PTVA, provided that their dose objectives are different, so that the maximum dose to the nodal PTV can be controlled in the optimization.
- 6.4.4** Target Volumes: Target tumor volumes are delineated slice by slice on the treatment planning CT images and are defined in Section 6.4.1. The PTVs should spare non-target skin surfaces (manually or automatically trimmed to 3-5 mm within the skin surface).
- 6.4.5** Critical Normal Structures: In addition, surrounding critical normal structures, including the femoral heads (right and left), bladder, external genitalia, iliac crest, small bowel, large bowel outside the CTVs, and perianal skin should be outlined. The normal tissues will be contoured and considered as solid organs. The tissue within the skin surface and outside all other critical normal structures and PTVs is designated as unspecified tissue.
- 6.4.6** Heterogeneity Corrections: All dose distributions shall include corrections for tissue heterogeneities. The method used for heterogeneity calculations shall be reported.
- 6.4.7** TLDs (thermoluminescent dosimeters) or diodes should be placed at the anal verge for at least one full treatment fraction to verify the planned dose to that region within 20% accuracy. If TLDs are used, a set of at least 3 chips should be placed.

## **6.5 Critical Structures (5/31/07)**

- 6.5.1** Critical normal structures: DVHs must be generated for all critical normal structures.  
**NOTE:** Effort should be made to achieve the listed dose constraints to normal tissues below. Failure to meet the 6.5.1.1 and 6.5.1.2 dose constraints will result in minor deviation. The dose constraints are listed in order from most to least important.
- 6.5.1.1** Small bowel:
- No more than 200 cc above 30 Gy
  - No more than 150 cc above 35 Gy
  - No more than 20 cc above 45 Gy
  - None above 50 Gy
- 6.5.1.2** Femoral heads:
- No more than 50% above 30 Gy
  - No more than 35% above 40 Gy
  - No more than 5% above 44 Gy
- 6.5.1.3** Iliac crests:
- No more than 50% above 30 Gy
  - No more than 35% above 40 Gy
  - No more than 5% above 50 Gy
- 6.5.1.4** External genitalia:
- No more than 50% above 20 Gy
  - No more than 35% above 30 Gy
  - No more than 5% above 40 Gy
- 6.5.1.5** Bladder:
- No more than 50% above 35 Gy
  - No more than 35% above 40 Gy

- No more than 5% above 50 Gy
- 6.5.1.6**     Large bowel:
- No more than 200 cc above 30 Gy
  - No more than 150 cc above 35 Gy
  - No more than 20 cc above 45 Gy

**6.6**     **Documentation Requirements (5/31/07)**

**6.6.1**     Imaging is required for set-up verification. This could be in the form of orthogonal images for isocenter verification or treatment machine-generated CT images through at least one plane (the largest) within the PTVA, with the tumor and critical structures turned on for display. It is strongly recommended that the reference simulation images used for set-up verification include target volumes.

For IMRT systems where isocenter is not defined (e.g., tomotherapy), setup verification images may consist of a series of axial CT images (megavoltage or kilovoltage) obtained over at least 5 cm length, to be compared with simulation CT images. It is recommended that there be an option to display target structures on the simulation images. It is also recommended that the setup verification images be obtained at levels where cephalocaudal positioning, as well as transverse positioning, can be verified. Appropriate levels would include either around the mid to upper sacrum or around the upper border of the acetabulae.

- 6.6.2**     The ITC will display, and compare with hard copies, isodose distributions through the planning target volume to verify correct digital submission and conversion.
- 6.6.3**     The ITC will compare the submitted digital dose-volume histograms (DVHs) for the PTVs, the designated critical structures, and unspecified tissues with DVHs calculated by the ITC.

**6.7**     **Compliance Criteria (5/31/07)**

**6.7.1**     Each treatment shall be judged according to the following guidelines:

**6.7.1.1**     PTVs (primary or nodal):

- 1) No deviation: the prescription criteria in Section 6.1.4 are fulfilled.
- 2) Minor deviation: 6-10% of PTV receives < 90% of prescription dose. Or 2-5% of PTV receives < 80% of prescription dose. Or > 2% of PTV receives more than the overdose level of 115% of prescription.
- 3) Major deviation: ≥ 10% of PTV receives < 90% of prescription dose, or ≥ 5% of PTV receives < 80% of prescription dose.

**6.7.1.2**     Small bowel:

- 1) No deviation: the criteria in Section 6.5.1.1 are fulfilled.
- 2) Minor deviation: 150-300 cc above 35 Gy, or 20-30 cc above 45 Gy
- 3) Major deviation: ≥ 300 cc above 35 Gy, or ≥ 30 cc above 45 Gy

**6.7.1.3**     Femoral heads:

- 1) No deviation: the criteria in Section 6.5.1.2 are fulfilled.
- 2) Minor deviation: 5-10% above 44 Gy
- 3) Major deviation: ≥10% above 44 Gy

**6.8**     **R.T. Quality Assurance Reviews**

The Radiation Oncology Co-Chairs, Lisa Kachnic, MD and Robert Myerson, MD, will remotely perform an RT Quality Assurance Review after complete data for the first 19 cases enrolled has been received. The remaining cases will be reviewed within 3 months after this study has reached the target accrual and as soon as complete data for all cases enrolled have been received.

**6.9**     **Radiation Adverse Events**

**6.9.1**     Interruption of radiation during the treatment program is discouraged. However, a rest period of ≤ 7 days will be allowed for grade 4 skin reactions. If radiation is held for > 7 days, the Study Chair, Dr. Kachnic, or designate, must be notified by telephone: 617-638-7070 or email: [lisa.kachnic@bmc.org](mailto:lisa.kachnic@bmc.org) within 24 hours.

**6.9.2**     **Radiation therapy must be held/interrupted for the following indications:**

- ANC < 500/mm<sup>3</sup> and/or platelets < 50,000: Radiation will resume when ANC ≥ 500 and PLT ≥ 50,000.
- ≥ Grade 3 diarrhea (≥ 7 stools/day above baseline): Resume radiation when diarrhea is

≤ grade 2 (< 7 stools/day above baseline). Obtain electrolytes and creatinine for ≥ grade 3 diarrhea.

- Grade 4 dermatitis: Radiation therapy can be resumed when dermatitis is ≤ grade 3. If RT is held for > 7 days, the Study Chair, Dr. Kachnic, or designate, must be notified. Ulceration deemed to be due to tumor regression, rather than radiation dermatitis, is not a mandatory condition for holding treatment.
- Hold radiation therapy for ≥ grade 3 vomiting: Resume radiation therapy at ≤ grade 2
- If localized or generalized infection develops secondary to an area of confluent moist desquamation, radiation therapy will be held. In this setting, radiation therapy will be resumed after there has been complete resolution of infection.

#### **6.10 Radiation Adverse Event Reporting**

For Adverse Events Reporting, see Section 7.6.

### **7.0 DRUG THERAPY (5/31/07)**

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

**Concurrent chemotherapy is to start on day 1 of radiation therapy. The second course of chemotherapy will be given on calendar day 29. If radiation is held for 5 or more days prior to the administration of the second course of chemotherapy, please discuss the timing of the second course of chemotherapy with the study chair.**

#### **7.1 5-Fluorouracil (5-FU)**

**7.1.1 Dose Formulation:** 5-FU is a marketed drug available as 50 mg/ml in 10, 50 or 100 ml vials as a colorless to faint yellow preservative free aqueous solution, with pH adjusted to approximately 9.0 with sodium hydroxide. Compatible with NS, D5W. Administration of 5-FU should be only by the intravenous route taking care to avoid extravasation. Direct administration is over 1-2 minutes, or intermittently in 50-100 ml minibag over 20-30 minutes, or by continuous infusion (in 1 L normal saline or ambulatory infusion pump) which has the best therapeutic index. Vein pigmentation and thrombophlebitis may be seen distal to infusion sites. For continuous infusion a central venous access device is preferred. Compatible with heparin and leucovorin but not with ondansetron.

**7.1.2 Pharmacology:** It is a fluorinated pyrimidine antimetabolite. 5-FU resembles the natural uracil molecule in structure, except that a fluorine atom has been substituted for a hydrogen atom in the 5 position.  $T_{1/2}$  is 8-13 minutes. It is distributed in all body water by passive diffusion and crosses the placenta. There is evidence that the metabolism of fluorouracil in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid. 5-FU generates fluorinated nucleotides (FdUMP, FUTP), which interfere with the synthesis of DNA and to a lesser extent inhibit the formation of ribonucleic division and growth by incorporation into RNA. The effect of fluorouracil may be to create a thymidine deficiency which provides unbalanced growth and death of the cell. Catabolism is via hepatic and extrahepatic routes via DPD to dehydrofluorouracil (DHFU), which is subsequently metabolized to fluoro-β-alanine (FBAL). Excreted as respiratory CO<sub>2</sub>, only 5% being excreted unchanged in the urine. Administration should be avoided in the presence of hepatic dysfunction.

**7.1.3 Supplier:** 5-FU is available commercially. Generic forms are available.

**7.1.4 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) and protect from light. If a precipitate occurs due to exposure to low temperatures, resolubilize by heating to 140°F (60°C) with vigorous shaking; allow to cool to body temperature before using. Discard after 8 hours once vial is opened. Discard if yellow coloration is marked since this indicates decomposition. Stable in D5W for 30 days in plastic syringes at room temperatures. In portable infusion pump reservoirs 5-FU is stable for up to 7 days but precipitation may occur at low temperatures.

**7.1.5 Side Effects and Toxicities:** Immediate side effects include mild nausea and vomiting (common), lacrimation, conjunctivitis, angina, arrhythmia, radiation recall and anaphylaxis (rare).

Early onset effects include stomatitis and esophagopharyngitis (which may lead to sloughing and ulceration), diarrhea with cramping and/or bleeding, and anorexia. 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. Megaloblastosis may occur. Alopecia (usually mild) 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, lethargy, malaise, headache, allergic reactions, neurotoxicity (disorientation, confusion, euphoria, dizziness, incoordination-acute cerebellar syndrome, encephalopathy), visual changes, photosensitivity (eyes and skin), nail changes including loss of nails, skin thickening, cracking, dryness or sloughing, biliary sclerosis, or acalculous cholecystitis. Hand foot syndrome (palmar plantar erythrodysesthesia) is more common with continuous infusion. Late effects may include tear duct fibrosis and neurotoxicity.

**7.2 Mitomycin-C (1/25/07, 5/31/07)**

**7.2.1** 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 to a concentration of 0.5 mg per ml. Shake to dissolve. If product does not dissolve immediately, allow to stand at room temperature or shake vial under warm tap water for 2 minutes to assist dissolution. Reconstituted mitomycin is a clear blue or purple solution. If reconstituted to higher concentrations (1-2 mg/ml) avoid low temperatures because crystals may form.

Mitomycin-C should be given intravenously only, using care to avoid extravasation (severe, see Appendix V). Give as slow push through sidearm of free flowing i.v. at 1.5 mg/3 ml per minute. May be mixed in 50-100 ml minibag over 10-30 minutes.

**7.2.2** Pharmacology: Mitomycin-C is an antibiotic with alkylating agent properties cross-linking guanine and cytosine, which selectively inhibits the synthesis of deoxyribonucleic acid (DNA) and degrades preformed DNA. This results in nuclear lysis and formation of giant cells. At high concentrations of the drug, cellular RNA and protein synthesis are also suppressed. Non-phase specific, but has maximum effects in late G1 and S.

In humans, mitomycin, which acts as a pro-drug is rapidly cleared from the serum after intravenous administration. It is distributed in kidneys, muscles, heart, lungs, intestines and ascites; and enters breast milk. 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 is affected primarily by metabolism in the liver, but metabolism occurs in other tissues as well. The rate of clearance is inversely proportional to the maximal serum concentration likely due to 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. Small amounts are also found in the bile and feces.

Administer with caution in the presence of impaired liver or renal function.

**7.2.3** Supplier: Mitomycin-C is available commercially. Generic forms are available.

**7.2.4** Storage:

- 1) Unreconstituted: Mitomycin-C is stable for the lot life indicated on the package. Store at room temperature. Avoid excessive heat (over 40°C) and keep away from light.
- 2) Reconstituted Mitomycin-C is stable for 14 days refrigerated or 7 days at room temperature (up to 30°C). Higher concentrations than 0.5 mg/ml may degrade and precipitate if stored.
- 3) Compatible with D5W, NS and Ringer's lactate Diluted in various i.v. fluids at room temperature, to a concentration of 20 to 40 micrograms per ml:

IV Fluid	Stability
5% Dextrose Injection	3 hours
0.9% Sodium Chloride Injection	12 hours
Sodium Lactate Injection	24 hours

**7.2.5** Side Effects and Toxicity

Immediate effects may include vein irritation, mild nausea and vomiting (1-2 hours) and bronchospasm (4-12 hours).

Early toxicities include thrombocytopenia and leukopenia which are cumulative. Nadir occurs at 24-28 days, with recovery at 42-56 days. Deaths due to septicemia have been reported. Stomatitis is frequent but mild, alopecia is rare. Rashes are rare and blue bands may be seen in the nails. Mitomycin may also cause dyspnea with cough and radiographic evidence of pulmonary infiltrate. A few cases of adult respiratory distress syndrome (interstitial pneumonitis) have been reported; also fever, anorexia, fatigue, blurred vision, amenorrhea, edema, thrombophlebitis, hematemesis, elevated LFTs or diarrhea may occur. CNS effects may include syncope and rarely acute encephalopathy.

Delayed toxicities (weeks to months) include chronic pulmonary fibrosis, erythema and/or ulceration occurring either at or distant from the injection site, rising creatinine, microangiopathic hemolytic anemia, and renal failure.

Note: Mitomycin is a vesicant and cellulitis, necrosis, ulceration and consequent sloughing of tissue may result if the drug is extravasated during injection (see Appendix V).

### **7.3 5-FU plus Mitomycin-C Regimen (5/31/07)**

**7.3.1 Treatment:** Based on actual body weight as follows:

Agent	Dose	Route	Schedule
5-FU	1000 mg/m <sup>2</sup> /day	IV	In 5% Dextrose or 0.5 NS daily for 96 hours (M-F) continuously starting Day 1; cycle is repeated on Day 29.
Mitomycin-C	10 mg/m <sup>2</sup> Do not exceed 20 mg per cycle	IV	On Day 1 and Day 29

### **7.4 Dose Modifications (5/31/07, 10/11/07)**

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

Toxicity	Parameters	Agent	Modification <sup>c,d</sup>
Diarrhea	Grade 3	5-FU	Decrease dose 50% <sup>a</sup>  Hold RT until diarrhea is ≤ grade 2
	Grade 4	5-FU	Decrease dose 50% <sup>a, b</sup>  Hold RT until diarrhea is ≤ grade 2
Mucositis/Stomatitis	Grade 3	5-FU	Decrease dose 50% <sup>a</sup>
	Grade 4	5-FU	Decrease dose 50% <sup>a, b</sup>
Rash: Dermatitis associated with radiation	Grade 3	5-FU	Decrease dose 50%  No interruption
	Grade 4	5-FU	Do not give the next cycle  Hold RT until ≤ grade 3
ANC or Platelets	Grade 3	5-FU and mitomycin-C	Decrease dose 50% <sup>e</sup>

		RT	Hold RT; resume when ANC $\geq$ 500 and PLT $\geq$ 50,000
	Grade 4	5-FU and mitomycin-C	Decrease dose 50% <sup>b</sup>
		RT	Hold RT; resume when ANC $\geq$ 500 and PLT $\geq$ 50,000
<b>NOTE: Second cycle of chemotherapy will not be administered unless ANC is <math>\geq</math> 1,800 and platelets are <math>\geq</math> 100,000</b>			

- Obtain electrolytes and creatinine according to good medical practice, if not performed in previous 24 hours, and correct any electrolytic, renal, or volume abnormalities. These should have returned to baseline prior to any further chemotherapy being administered.
- Obtain CBC for any non-hematologic toxicity (including sepsis, fever, and bleeding) other than rash. In the presence of **any** non-hematologic toxicity, use the most severe hematologic toxicity observed during cycle 1 (including during drug infusion, interval, incidental, or pre-treatment) in considering dosages for the second cycle as follows:  
Responses to modifications of 5-FU dosage are unpredictable due to genetic polymorphism (Dihydropyrimidine dehydrogenase, or DPD). If, in the investigator's opinion it would *not* be in the best interest of the patient to continue with 5-FU after a grade 4 adverse event because of the risk of repeated severe toxicity, further 5-FU should not be administered. Assessment of the patient should be based on the patient's *overall* condition including consideration of each individual toxicity encountered. Consideration must include the duration of the toxicity in addition to its *severity*. In a study of patients experiencing severe toxicity from 5-FU, a correlation was shown between the sum of all the toxicity grades for mucositis, neutropenia, thrombocytopenia, diarrhea, and neurotoxicity (always graded 4 as neurotoxicity is a strong predictor for DPD deficiency) and measured DPD levels.<sup>28</sup> Patients with any neurotoxicity or several concurrent grade 4 toxicities should not receive further 5-FU without a DPD assay. However, there is no absolutely safe level, and all patients require careful individual assessment. Women are more likely to have DPD deficiency than men. A thorough discussion should be conducted with the patient as to the possible risks and benefit of receiving further 5-FU.
- If a grade 4 toxicity occurs during the 96-hour infusion of 5-FU, the 5-FU must immediately and permanently be discontinued for that cycle.
- The second cycle of chemotherapy will not be administered until all toxicities have resolved to  $\leq$  grade 2 **AND** ANC is  $\geq$  1,800 and platelets are  $\geq$  100,000.
- Based on pre-treatment counts, not interval counts.

### **7.5 Modality Review**

The Medical Oncology Co-Chair, Michael Goodyear, M.D., will remotely perform a Quality Assurance Review after complete data for the first 19 cases enrolled has been received. The remaining cases will be reviewed within 3 months after this study has reached the target accrual and as soon as complete data for all cases enrolled has been received.

### **7.6 Adverse Events**

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for grading of all adverse events. **All** adverse events, routine and serious, must be reported on the appropriate case report form (see Section 12.1). A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). The CTEP home page also can be accessed from the RTOG web page at <http://www.rtog.org/regulatory/regs.html>. All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site ([https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers\\_main\\$.startup](https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup)).

In the rare occurrence when Internet connectivity is lost, an AE report may be submitted using CTEP's Adverse Event Expedited Report-Single Agent or Multiple Agent paper template (available at <http://ctep.cancer.gov>) and faxed to 301-230-0159. A 24-hour notification is to be made to CTEP by telephone at 301-897-7497, only when Internet connectivity is disrupted. Once Internet connectivity is restored, an AE report submitted on a paper template or a 24-hour notification phoned in must be entered electronically into AdEERS by the original submitter at the site.

Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site (<http://www.rtog.org/members/toxicity/main.html>) for this information.

**In order to ensure consistent data capture, serious adverse events reported on AdEERS reports also must be reported on an RTOG case report form (CRF).** In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

**7.6.1 Adverse Events (AEs)**

**Definition of an AE:** Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

The following guidelines for reporting adverse events (AEs) apply to **all** NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported via AdEERS. Use the patient's case number as the patient ID when reporting via AdEERS. AEs reported using AdEERS also **must be reported on the AE case report form** (see Section 12.1). **NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting may be required. Reporting AEs only fulfills Data Management reporting requirements.**

**7.6.2 Serious Adverse Events (SAEs) — All SAEs that fit any one of the criteria in the SAE definition below must be reported via AdEERS within 24 hours of discovery of the event. Contact the CTEP Help Desk if assistance is required.**

**Definition of an SAE:** Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE drug experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported via AdEERS within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

**All supporting source documentation, if applicable or if being faxed to NCI, must be properly labeled with the study/case numbers and the date of the adverse event and must be faxed to the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. All forms (and supporting source documentation) submitted to RTOG Headquarters must include the RTOG study/ case numbers; non-RTOG intergroup study and case numbers must be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient's case number as the patient ID when reporting via AdEERS.**

**SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as “expedited reporting NOT required” must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the “NOT Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of**

**the results of the assessment. Note:** Sites must print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

**7.6.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)**

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the **NCI/CTEP Secondary AML/MDS Report Form** available at <http://ctep.cancer.gov/forms/index.html>. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of a report via the AdEERS system and **must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.**

RTOG Headquarters
AML/MDS Report
1818 Market Street, Suite 1600
Philadelphia, PA 19103

**7.7 Phase 2 Trials** Utilizing a Commercially Available Agent: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days<sup>1</sup> of the Last Dose of the Agent

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 <sup>2</sup>	Grades 4 & 5 <sup>2</sup>
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	without Hospitalization	Expected with Hospitalization	without Hospitalization	Unexpected	Expected
<b>Unrelated Unlikely</b>	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
<b>Possible Probable Definite</b>	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

<sup>1</sup> Adverse events with attribution of possible, probable, or definite that occur **greater** than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:

- AdEERS 24-hour notification followed by complete report within 5 calendar days for:
  - Grade 4 and Grade 5 unexpected events
- AdEERS 10 calendar day report:
  - Grade 3 unexpected events with hospitalization or prolongation of hospitalization
  - Grade 5 expected events

<sup>2</sup> Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see exceptions below under section entitled “Additional Instructions or Exceptions.”

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**Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. “On study” is defined as during or within 30 days of completing protocol treatment.**

- Expedited AE reporting timelines defined:
  - “24 hours; 5 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - “10 calendar days” - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

## **8.0 SURGERY**

### **8.1 Primary Tumor Site (5/31/07)**

**8.1.1** Eight weeks following completion of radiation therapy, the patient will be evaluated (see Section 11.2.1) and managed as follows:

- Suspected clinically progressive disease: A biopsy is required.
  - Negative biopsy: Re-evaluate at 12 weeks post completion of radiation therapy.
  - Positive biopsy and no evidence of distant disease: An anterior-posterior resection (APR) is recommended.
- Disease present, not progressive: No biopsy; re-evaluate at 12 weeks post completion of radiation therapy.
- Complete clinical response: No biopsy; No evaluation at 12 weeks post completion of radiation therapy.

**8.1.2** Twelve weeks following completion of radiation therapy, the patient will be evaluated and managed (based on the eight-week evaluation) as follows:

- Disease present, not progressive: A biopsy is required, and an APR is recommended for pathologically confirmed residual disease.

## **9.0 OTHER THERAPY**

### **9.1 Permitted Supportive Therapy**

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol, with the exception of those in Section 9.2, and documented on each site's source documents as concomitant medication.

### **9.2 Non-permitted Supportive Therapy**

**9.2.1** Granulocyte macrophage colony stimulating factors (CSF) may not be used during radiation therapy or chemoradiation. In the event of severe toxicity, CSF may be used to hasten hematological recovery and reduce the risk of severe infection but not to improve hematological parameters in order to administer further chemotherapy. If toxicity is severe enough to warrant CSF, further chemotherapy should be discontinued.

**9.2.2** Concurrent use of amifostine is not permitted.

### **9.3 Permitted Therapy Prior to Study Entry**

**9.3.1** Diverting colostomy without tumor resection is permitted prior to study entry.

## **10.0 TISSUE/SPECIMEN SUBMISSION (5/31/07)(6/2/09)**

### **10.1 General Information**

The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high-quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Biospecimen Resource provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. The RTOG Biospecimen Resource also collects tissue for Central Review of pathology. Central Review of tissue can be for eligibility and/or analysis.

In this study, specimens will be submitted to the RTOG Biospecimen Resource for the purpose of specimen banking as described below.

### **10.2 Specimen Collection for Banking (strongly encouraged)**

**For patients who have consented to participate in the tissue/blood component of the study (See Appendix I).**

Sites may submit the following specimens:

#### **10.2.1 Blocks/slides**

- 10.2.1.1** One H&E stained slide
- 10.2.1.2** A paraffin-embedded tissue block of the tumor or a 2 mm diameter core of tissue, punched from the tissue block containing the tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number. NOTE: A kit with the punch, tube, and instructions can be obtained from the Biospecimen Resource. If both of these tissue types are unavailable, 15 unstained slides may be submitted. Block, core, or slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.
- 10.2.1.3** A Pathology Report documenting that the submitted block, core, or slides contain tumor. The report must include the RTOG protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.
- 10.2.1.4** A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG Biospecimen Resource; if for translational research, this should be stated on the form. The form must include the RTOG protocol number and patient's case number.

## **10.2.2** Serum

- 10.2.2.1** Collection Schedule: Specimens will be collected at baseline and 8-12 weeks post-treatment.
- 10.2.2.2** Collection Instructions: For detailed instructions, see Appendix VI. Specimens will be collected in red-top tubes (5-10 mL tubes)
  - After allowing the serum to clot, keep serum tubes refrigerated (4°-8° C) until processing (tubes may be on ice up to 2 hrs). Centrifuge specimens at approximately 2500 RPM in a standard clinical centrifuge at for 10 minutes.
  - Using sterile techniques to avoid contamination, aliquot 0.5-1 mL serum into cryovials and freeze. Take great care to collect only serum and avoid collecting any solid particulate matter before transferring serum into the cryovials.
  - Label each aliquot with study protocol and case numbers, the date and time of collection, specimen type (i.e., serum) and the time point taken.
  - The following materials must be provided to the RTOG Biospecimen Resource: A Specimen Transmittal Form documenting the date and time of collection of the specimen; the RTOG protocol number, the patient's case number, and method of storage, for example, stored at -20° C, must be included.

## **10.2.3** Plasma

- 10.2.3.1** Collection Schedule: Specimens will be collected at baseline and 8-12 weeks post-treatment.
- 10.2.3.2** Collection Instructions: For detailed instructions, see Appendix VI. Specimens will be collected in tubes containing EDTA (purple/lavender-top tubes)
  - After collecting the specimens, invert the tubes multiple times to mix the blood thoroughly with the EDTA anticoagulant.
  - After thoroughly mixing, centrifuge specimens at approximately 2500 RPM in a standard clinical centrifuge for 10 minutes.
  - Using sterile techniques to avoid contamination, aliquot 0.5-1 mL plasma into cryovials and freeze. Take great care to collect only plasma and avoid collecting any solid particulate matter before transferring plasma into the cryovials.
  - Label each aliquot with study protocol and case numbers, the date and time of collection, specimen type (i.e., plasma) and the time point taken
  - The following materials must be provided to the RTOG Biospecimen Resource: A Specimen Transmittal Form documenting the date and time of collection of the specimen; the RTOG protocol number, the patient's case number, and method of storage, for example, stored at -20° C, must be included.

## **10.2.4** Buffy Coat

- 10.2.4.1** Collection Schedule: Specimens will be collected at baseline and 8-12 weeks post-treatment.
- 10.2.4.2** Collection Instructions: For detailed instructions, see Appendix VI. Specimens will be collected in tubes containing EDTA (purple/lavender-top tubes)
  - Carefully remove plasma from the collection tubes (see above instructions)
  - Using a pipette, remove the buffy coat layer and place into cryovials and freeze
  - Label each aliquot with study protocol and case numbers, the date and time of collection, specimen type (i.e., buffy coat) and the time point taken
  - Place specimens in freezer or ship immediately on dry ice.
  - The following materials must be provided to the RTOG Biospecimen Resource: A Specimen Transmittal Form documenting the date and time of collection of the specimen; the RTOG protocol number, the patient's case number, and method of storage, for example, stored at -20° C, must be included.

### **10.2.5** Urine

**10.2.5.1** Collection Schedule: Specimens will be collected at baseline and 8-12 weeks post-treatment.

**10.2.5.2** Collection Instructions: For detailed instructions, see Appendix VI. A minimum of 10 mL urine should be collected in a sterile collection cup labeled with patient ID, date and time of collection, and placed into a freezer for storage.

### **10.2.6** Specimen Collection Summary

<b>Specimens taken from patient:</b>	<b>Collection schedule:</b>	<b>Submitted as:</b>	<b>Shipped:</b>
One H&E stained slide of the primary tumor	Pre-treatment biopsy	H&E stained slide	Slide shipped ambient
A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or a 2 mm diameter core of tissue, punched from the tissue block with a skin punch	Pre-treatment biopsy	Paraffin-embedded tissue block or punch biopsy	Block or punch shipped ambient
5-10 mL of whole blood in red-top tube and centrifuge for serum	Baseline and 8-12 weeks post-treatment	Frozen serum samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials	Serum sent frozen on dry ice via overnight carrier
5-10 mL of anticoagulated whole blood in EDTA tubes (purple/lavender top) and centrifuge for plasma	Baseline and 8-12 weeks post-treatment	Frozen plasma samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials	Plasma sent frozen on dry ice via overnight carrier
5-10 mL of anticoagulated whole blood in EDTA tubes (purple/lavender top) and centrifuge for buffy coat	Baseline and 8-12 weeks post-treatment	Frozen buffy coat samples in 1 mL cryovials	Buffy coat sent frozen on dry ice via overnight carrier
10-25 mL clean-catch urine	Baseline and 8-12 weeks post-treatment	Frozen urine samples containing a minimum of 5 mL unpreserved urine in a sterile collection container	Urine sent frozen on dry ice via overnight carrier

**10.2.7** Submit materials for Tissue Banking to:  
**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** Reimbursement

RTOG will reimburse submitting institutions \$300 per case for fresh or flash frozen tissue, blood, serum, and buffy coat cells; \$200 per case for a block or core of material; and \$50 for urine. 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.

### **10.4** Confidentiality/Storage

(See the RTOG Patient Tissue Consent Frequently Asked Questions, <http://www.rtog.org/tissuebank/tissuefaq.html> for further details.)

- 10.4.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The RTOG Biospecimen Resource database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.
- 10.4.2 Specimens for tissue banking will be stored for an indefinite period of time. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

## **11.0 PATIENT ASSESSMENTS**

**11.1 Study Parameters:** See Appendix II.

### **11.2 Criteria For Evaluation And Endpoint Definitions**

#### **11.2.1 Measurement of Local Tumor**

- 11.2.1.1 Patients should be evaluated (per Section 11.2.1.2) for response at 8 weeks after completing treatment. If the patient is not a complete responder at 8 weeks, they must be evaluated (per Section 11.2.1.2) again at 12 weeks to determine if the patient has persistent/progressive disease.
- 11.2.1.2 Complete response will be determined by digital rectal exam and proctosigmoidoscopy supplemented with pelvic axial imaging. Complete response will be the absence of all disease based on these evaluations.
- 11.2.1.3 Any measurable disease after 12 weeks from the completion of chemoradiation therapy will be considered a treatment failure (local persistence).

#### **11.2.2 Other Response Parameters**

11.2.2.1 **Progressive Disease:** Local or regional progression per RECIST (see criteria below) or appearance of any distant metastases

*RECIST criteria for progressive disease:* At least a 20% increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more lesions

- 11.2.2.2 **Regional Failure:** Regional failure is defined as follows: a) For patients with no disease in pelvic and/or groin nodes, the appearance of disease in pelvic or groin nodes; b) For patients with disease in pelvic and/or groin nodes at study entry, nodal recurrence following clearance or persistent nodal disease for more than 12 weeks after completion of treatment.
- 11.2.2.3 **Local-Regional Failure (LRF):** LRF is defined as a local (per Section 11.2.1) or regional (per Section 11.2.2.2) failure.
- 11.2.2.4 **Distant Metastases Failure:** The appearance of distant metastases
- 11.2.2.5 **Second Primary Failure:** The appearance of second primary tumor
- 11.2.2.6 **Disease-Free Survival (DFS):** Local-regional failure, appearance of distant metastases, appearance of a second primary and death due to any cause
- 11.2.2.7 **Colostomy Failure:** For patients entering the study without a diverting colostomy, failure is a colostomy for any reason. For patients entering the study with a diverting colostomy, failure is defined as one of the following: a) If the colostomy is reversed within 1 year from study entry, failure is a subsequent colostomy for any reason; b) If the colostomy is not reversed within 1 year, then it will be considered a colostomy failure at that time.
- 11.2.2.8 **Colostomy-Free Survival:** Failure is a colostomy (defined in Section 11.2.2.7) or death due to any cause.
- 11.2.2.9 **Overall Survival:** Failure is death due to any cause.

### **11.3 Criteria For Discontinuing Protocol Treatment**

- 11.3.1 Progressive disease;
- 11.3.2 Treatment-related delay of chemotherapy or radiation therapy > 14 days.

## **12.0 DATA COLLECTION**

Data should be submitted to:

**RTOG Headquarters\***  
**1818 Market Street, Suite 1600**

**\*If a data form is available for web entry, it should be submitted electronically.**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

**12.1 Summary of Data Submission (12/21/06)**

<b><u>Item</u></b>	<b><u>Due</u></b>
Demographic Form (A5)	Within 2 weeks of registration
Initial Evaluation Form (I1)	
Pathology Report (P1)	
Slides/Blocks (P2)	
<b>Radiotherapy Form (T1) (Copy to ITC)</b>	Within 1 week of the end of RT
Treatment Form (TF)	Within 1 week of the end of chemo/RT
Follow-up Form (F1)	Every 3 months from the start of RT for year 1; every 6 months for year 2; then annually
Post treatment Response Form (F2)	Within 1 week of 8 and 12 week post-RT completion evaluations

## **12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1)**

<b><u>Item</u></b>	<b><u>Due</u></b>
<b>Preliminary Dosimetry Information</b>	
Digital Data Submission Form ( <b>DDSI</b> )	Within 1 week of start of RT
CT data, critical normal structures, all GTV, CTV, and PTV contours ( <b>C1, C3</b> )	
Simulation films and/or digital film images for all initial treatment fields and orthogonal set up pair	
First day port films (or digital images) of all initial treatment fields and orthogonal set up pair	
Digital beam geometry for initial and boost beam sets	
Doses for initial and boost sets of concurrent treated beams	
Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan ( <b>DV</b> )	
Hard copy isodose distributions for total dose plan as described in QA guidelines( <b>T6</b> )	
<b>Final Dosimetry Information</b>	Within 1 week of RT end
Radiotherapy Form ( <b>T1</b> ) [ <b>copy to HQ and ITC</b> ]	
Daily Treatment Record ( <b>T5</b> )	
Simulation films and/or digital film images (or digital images) of all boost treatment fields and orthogonal set up pair ( <b>T8</b> )	
First day port films of all boost treatment fields and orthogonal set up pair ( <b>T8</b> )	
Modified digital patient data as required through consultation with Image Guided Therapy QA Center	

### **12.2.1 Digital Data Submission to ITC**

Digital data submission may be accomplished using media or the Internet.

For network submission: The FTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to:

[itc@castor.wustl.edu](mailto:itc@castor.wustl.edu)

For media submission: Please contact the ITC about acceptable media types and formats.

Hardcopies accompanying digital data should be sent by mail or Federal Express and should be addressed to:

**Image-Guided Therapy Center (ITC)**  
**ATTN: Roxana Haynes**  
**4511 Forest Park, Suite 200**  
**St. Louis, MO 63108**  
**314-747-5415**  
**FAX 314-747-5423**

## **13.0 STATISTICAL CONSIDERATIONS**

### **13.1 Primary Endpoint**

#### **13.1.1 GI and GU Adverse Events (per CTCAE, v. 3.0):**

To decrease the combined rate of  $\geq$  grade 2 GI & GU adverse events from IMRT + 5-FU & Mitomycin-C by at least 15% in the first 90 days following the start of treatment, as compared to the RT+ 5-FU & Mitomycin-C arm from RTOG 9811

### **13.2 Secondary Endpoints (5/31/07)**

#### **13.2.1 Reproducibility of Radiation Technique:**

The ability of various clinical sites to perform IMRT within the guidelines delineated in Section 6.0 of this protocol

#### **13.2.2 Adverse Events (AEs) [Per CTCAE, v. 3.0]**

**13.2.2.1** To evaluate the adverse event rates occurring in the first 90 days following the start of treatment, as specified in Section 13.3.3

**13.2.2.2** Evaluate adverse events associated with this treatment regimen after 90 days from the start of treatment

#### **13.2.3 Clinical Complete Response**

Estimate the clinical complete response (defined in Section 11.2.1) rate at 8 weeks after completion of treatment.

#### **13.2.4 Radiotherapy Treatment Time**

Evaluate elapsed time from radiotherapy treatment start to radiotherapy treatment end.

#### **13.2.5 Efficacy Endpoints**

##### **13.2.5.1 Local-Regional Failure**

Estimate the rate of local-regional failure (defined in Section 11.2.2.3); local-regional failure will be measured from study entry to date of first local or regional failure.

##### **13.2.5.2 Colostomy Failure**

Estimate the rate of colostomy failure (defined in Section 11.2.2.7); colostomy failure will be measured from study entry to date of colostomy failure.

##### **13.2.5.3 Colostomy-Free Survival**

Estimate the rate of colostomy-free survival (defined in Section 11.2.2.8); colostomy-free survival will be measured from study entry to date of colostomy failure or date of death.

##### **13.2.5.4 Disease-Free Survival**

Estimate the rate of disease-free survival (defined in Section 11.2.2.6); disease-free survival will be measured from study entry to date of first local, regional, distant or second primary failure or date of death.

##### **13.2.5.5 Overall Survival**

Estimate the rate of overall survival (defined in Section 11.2.2.9); overall survival will be measured from study entry to date death.

### **13.3 Study Design**

#### **13.3.1 Sample Size for Primary Endpoint**

The sample size will be determined by the primary endpoint of the combined rate of  $\geq$  grade 2 GI & GU adverse events (AEs) [per CTCAE, v. 3.0] in the first 90 days following the start of treatment. Based on the RT + 5-FU & Mitomycin-C arm of RTOG 9811, we are assuming a 77% grade 2 or higher combined GI & GU adverse event rate. The primary hypothesis is that using IMRT in combination with 5-FU & Mitomycin-C will reduce this rate by at least 15%. Fifty-four evaluable patients will provide 80% power to detect a 15% reduction in the combined rate of  $\geq$  grade 2 GI & GU AEs, using a one-sided chi-squared test with a type I error rate of 0.05. If the true reduction is 17.5% or 20%, then the power to detect these reductions, with 54 evaluable patients, will be 88% and 94% respectively. To allow for an 8% ineligibility/lost rate, **the total sample size will be 59 patients.**

#### **13.3.2 Sample Size Derivation for Feasibility Endpoint**

There will be a central, final RT review by the radiation oncologist study chairs for each case after the treatment delivery is completed. The radiation therapy, for each case, will be scored by the study chair as acceptable, marginally acceptable, or unacceptable, using the criteria in Section 6.7. The sample size for this endpoint is based on Simon's two-stage design.<sup>29</sup> Let  $p$  be the true probability that the final review is acceptable or marginally acceptable. A  $p$  close to 1 implies that the radiation therapy is reproducible in a multi-center setting. If  $p$  is less than or equal to 80%, the goal is to have at most a 5% probability of concluding that the technique is reproducible. On the other hand, if  $p$  is greater than or equal to 95%, the desired level, the goal is have at most a 10% probability of concluding that the technique is not reproducible. With these specifications, 42 evaluable patients are required. Out of the first 42 evaluable patients on the study, if 5 or more are scored unacceptable upon final RT review, the technique will be considered not reproducible; otherwise, it will be concluded that this technique is reproducible.

#### **13.3.3 Power for Secondary Endpoint of Reduction in Adverse Events**

Based on 54 evaluable patients, the following table shows the power to detect 15% and 20% absolute reductions in the specified adverse events (per CTCAE, v. 3.0):

	Control*	15% Absolute Reduction			20% Absolute Reduction		
		Rate	Relative Reduction	Power	Rate	Relative Reduction	Power
≥ grade 2 all	96%	81%	16%	<b>95%</b>	76%	21%	<b>99%</b>
≥ grade 3 all	86%	71%	17%	<b>82%</b>	66%	23%	<b>95%</b>
≥ grade 2 GI	72%	57%	21%	<b>67%</b>	52%	28%	<b>88%</b>
≥ grade 2 hematologic	81%	66%	19%	<b>79%</b>	61%	25%	<b>94%</b>
≥ grade 2 skin	82%	67%	18%	<b>74%</b>	62%	24%	<b>92%</b>
≥ grade 2 GU	22%	7%	68%	<b>91%</b>	2%	91%	<b>99%</b>

\*RT + 5-FU & Mitomycin-C arm from RTOG 9811

### **13.4 Patient Accrual**

#### **13.4.1 Accrual for Feasibility Endpoint**

Based on RTOG 9811, the projected monthly accrual is eight patients. It will take approximately 12 months to complete the accrual, assuming there will be very little accrual during the first 6 months after activation while institutions become credentialed and obtain IRB approval.

### **13.5 Schedule of Analyses**

#### **13.5.1 Interim Reports**

Interim reports will be prepared every six months until the primary endpoint has been presented. In general, these reports include:

- the patient accrual rate with projected completion date
- institutional accrual
- pretreatment characteristics
- compliance rates of treatment delivery with respect to the protocol prescription
- the frequency and severity of adverse events due to protocol therapy

#### **13.5.2 Analyses for Reporting Treatment Results**

##### **13.5.2.1 Initial Analysis**

The first analysis will take place after each patient has been followed for a minimum of 8 weeks from the end of treatment. This analysis will focus on the primary endpoint (GI & GU adverse events: Section 13.1.1), as well as the following secondary endpoints: feasibility (Section 13.2.1), adverse events as described in Section 13.2.2.1, clinical complete response (Section 13.2.3), and radiotherapy treatment time (Section 13.2.4).

##### **13.5.2.2 Efficacy Analyses and Adverse Events**

Adverse events more than 90 days from the start of treatment and efficacy analyses per the endpoints listed in Section 13.5 will be analyzed two years after completion of accrual.

##### **13.5.2.3 Analysis Components**

The usual components of the above mentioned analyses are:

- tabulation of all cases entered and reasons for any patients excluded from the analysis
- institutional accrual
- patient accrual rate
- distribution of important pretreatment characteristics
- observed results with respect to the appropriate endpoints

**13.5.2.4** Time from radiotherapy treatment start to radiotherapy treatment end will be reported by skin adverse event grade (< grade 3 vs. ≥ grade 3) and (< grade 2 vs. ≥ grade 2) for the following treatment times: ≤ 35 days, 35- ≤ 42 days, 42- ≤ 49 days and > 49 days.

**13.5.2.5** Estimation of secondary endpoints related to efficacy:

The cumulative incidence approach<sup>30</sup> will be used to estimate the failure rates for local-regional and colostomy failures. The Kaplan-Meier method<sup>31</sup> will be used to estimate overall survival, disease-free survival and colostomy-free survival.

### **13.6 Inclusion of Minorities**

In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, the possible difference in any of the above endpoints among the racial groups will be investigated. Summary statistics such as percentage of minorities entered, estimates of the endpoints by the racial groups will be reported. Based on RTOG study

9811 it is projected that 4% of the patients will be Hispanic or Latino and 96% will not. It is also projected that 90% of patients in the study will be white, 8% will be black or African American, < 1% will be Asian and < 1% will be American Indian or Alaskan Native. With the proposed 42 evaluable patients within each primary disease site, there will not be enough statistical power to detect the difference in the primary endpoint between gender, race or ethnicity groups. Nonetheless, the descriptive statistics for each of these groups will be reported.

**Projected Distribution of Gender and Minorities**

	<b>Gender</b>		
<b>Ethnic Category</b>	<b>Females</b>	<b>Males</b>	<b>Total</b>
Hispanic or Latino	1	1	2
Not Hispanic or Latino	40	17	57
<b>Ethnic Category: Total of all subjects</b>	<b>41</b>	<b>18</b>	<b>59</b>
	<b>Gender</b>		
<b>Racial Category</b>	<b>Females</b>	<b>Males</b>	<b>Total</b>
American Indian or Alaskan Native	1	0	1
Asian	0	1	1
Black or African American	3	2	5
Native Hawaiian or other Pacific Islander	0	0	0
White	37	15	52
<b>Racial Category: Total of all subjects</b>	<b>41</b>	<b>18</b>	<b>59</b>

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## **APPENDIX I (5/31/07, 10/11/07)**

### **RTOG 0529**

#### **Sample Informed Consent Form**

##### **A Phase II Evaluation of Dose-Painted IMRT in Combination with 5-Fluorouracil and Mitomycin-C for Reduction of Acute Morbidity in Carcinoma of the Anal Canal**

This is a clinical trial, a type of research study. The study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask the study doctor for more explanation.

You are being asked to take part in this study because you have a cancer in your anus (anal cancer).

#### **WHY IS THIS STUDY BEING DONE?**

Until recently, surgery that removed the anus and rectum was considered standard therapy for treating anal cancer. In this type of surgery, the bowel is attached to a permanent opening in the skin of the stomach (colostomy). Waste products from the bowel leave the body through this opening and are collected in a bag, which is changed when necessary.

Radiation therapy and chemotherapy (drugs that fight cancer) when given together have been shown to reduce the need for surgery while preserving the anus and rectum. You will only need surgery if radiation and chemotherapy do not get rid of the cancer or if it grows back at a later time.

Standard radiation therapy, although effective in killing cancer cells, has many side effects that may be unpleasant and sometimes may cause long-term complications. This is because the radiation can harm normal parts of the body while killing cancer tissue.

#### **What is IMRT?**

Standard radiation techniques cannot avoid delivering radiation to normal tissues (such as bone, bladder, bowel, genitalia, and skin) that are very close to the cancer and to places to which cancer can spread. Normal tissues do not need to get radiation. New ways of giving radiation such as IMRT (Intensity Modulated Radiation Therapy) spare some of these normal tissues and may reduce unwanted side effects. IMRT is an advanced radiation therapy delivery technique. IMRT tries to lower the amount of radiation that normal tissues receive, while still delivering the desired amount of radiation to your cancer and to the areas that your doctor thinks may have cancer cells, such as lymph nodes. IMRT does this by using multiple, computer-controlled radiation beams aimed at your cancer, while still delivering a radiation dose comparable to standard radiation

#### **Purpose of this Study**

This research is being done to see if it is possible to reduce the amount of radiation given to the normal areas around anal cancers by using IMRT and to reduce the side effects that are seen with standard radiation methods. It is not known whether IMRT, which is being used to

reduce side effects, will result in the control of cancer or the decreased need for surgery as is seen with standard radiation.

### **HOW MANY PEOPLE WILL TAKE PART IN THE STUDY**

About 59 people will take part in this study.

### **WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY? (5/31/07)**

**Before you begin the study**, you will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests, or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to the study doctor.

- A physical examination and an examination of the anus and groin
- Examination and measurement of the cancer using a tube with a light on it (a “scope”) in order to see the cancer better; sometimes you will be given a short general anesthetic for this examination.
- A specimen of the cancer (biopsy) will be removed to examine. If the study doctor suspects cancer in the lymph nodes in the groin, a biopsy may be taken from there too.
- An x-ray or a CT scan or a PET/CT scan of your chest to make sure your lungs are clear  
[A CT (Computed Tomography) scan is a study using x-rays to look at one part of your body. A PET (Positron Emission Tomography) is a computerized image that looks at the activity of tumor cells in your entire body and that requires injection of a special marker into your vein, such as sugar (glucose) combined with a low-dose radioactive substance (a tracer). A camera records the tracer’s signal as it travels through your body.]
- A CT scan or an MRI or a PET/CT scan of your abdomen and pelvis to check for any spread of the cancer.  
[An MRI (Magnetic Resonance Imaging) is imaging using a strong magnetic field to look at one part of your body]
- Blood tests to check your bone marrow, kidneys, and liver
- For women able to have children, a pregnancy test because the treatments in this study could harm an unborn baby
- If the study doctor suspects that you might have Acquired Immunodeficiency Syndrome (AIDS), you will be asked to have an AIDS test. HIV positive patients who do not have AIDS can take part in this study.  
[The treatment of anal cancer for individuals with AIDS and high viral loads may be associated with increased side effects; therefore, patients with uncontrolled AIDS are not eligible for this protocol. If your AIDS test comes back positive (showing that you have AIDS), then you will be referred to a specialist for treatment for AIDS. You still may be able to get treatment for anal cancer similar to the treatment being studied in this trial without being on a study.]

### **During the study:**

If the exams, tests, and procedures show that you can be in the study and you choose to take part, then you will need the following tests and treatments. They are part of regular cancer care:

- Weekly physical examination to check for side effects
- Weekly examination of the anus, groin, and skin
- Weekly blood tests to check for side effects

### **Treatments:**

#### **Radiation:**

You will receive IMRT (radiation) once a day, five days a week, for 28 or 30 treatments (5.5 to 6 weeks) depending on your cancer.

Sometimes you may need a break (usually a week or less) in the radiation treatment due to the side effects from the radiation, such as vomiting, diarrhea, skin rash, or lowered blood counts. The study doctor will be checking your side effects throughout treatment.

#### **Chemotherapy:**

You will receive two drugs: mitomycin-c and 5-fluorouracil (5-FU) in two treatments. The first chemotherapy treatment starts on the same day as your first radiation treatment (day 1). The second treatment is given at the start of the fifth week of radiation (day 29).

The mitomycin-c is given through your vein. The 5-FU also is given through your vein, but it has to be given continuously over 96 hours (starting on day 1 and again on day 29). You may be admitted into the hospital to receive the 5-FU. Typically, if you start radiation on a Monday, your 5-FU will be started that day and be stopped on Friday. This means that although the 5-FU is given for 96 hours, you will receive some 5-FU on each of 5 days (Monday to Friday).

#### **Follow up:**

You will be seen 8 weeks after the completion of radiation to see if the IMRT and chemotherapy are working. You will need the following tests and examinations:

- A physical examination
- An examination of the anus and groin
- Blood tests
- A CT scan or an MRI or a PET/CT scan of your abdomen and pelvis
- A chest x-ray
- An examination of the area of the cancer using a tube with a light on it (a “scope”)

If the IMRT and chemotherapy make the cancer get smaller, and no cancer can be found at the 8 week evaluation, you will continue to have regular check ups at 6, 9, 12, 18 and 24 months after the end of radiation therapy, then yearly.

If cancer is still present at the 8 week evaluation and your doctor suspects it is growing, you will have a biopsy. If the biopsy shows that the cancer is growing despite the treatment, your doctor may recommend surgery to remove the anus and rectum.

If cancer is still present in the treated area but it is not growing, you will be evaluated again at 12 weeks after the completion of radiation. If the cancer is still present, but it is not spreading, you will have a biopsy, and your doctor may recommend surgery to remove the anus and rectum.

Another way to find out what will happen to you during the study is to read the chart below. The left-hand column shows the time, and the right-hand column tells you what will happen on that visit.

<u>Day</u>	<u>What Happens</u>
Within 42 days before starting study	<ul style="list-style-type: none"> <li>• Biopsy of tumor</li> <li>• Possible biopsy of lymph nodes</li> <li>• X-ray or CT scan or PET/CT scan of chest</li> <li>• CT scan or MRI or PET/CT scan of abdomen and pelvis</li> <li>• Anal and groin examination</li> <li>• An examination of the area of the cancer using a tube with a light on it (a “scope”)</li> <li>• The study doctor may ask you to have an AIDS test</li> </ul>
At least 14 days before starting study	<ul style="list-style-type: none"> <li>• A physical examination with assessment of weight and nutrition and history of smoking and alcohol use</li> <li>• Blood tests</li> <li>• Women able to have children will have a pregnancy test</li> </ul>
Week 1 (Days 1-7) Day 1	<ul style="list-style-type: none"> <li>• A physical examination</li> <li>• Peri-anal and groin examination</li> <li>• Blood tests</li> <li>• Start radiation</li> <li>• Start chemotherapy with mitomycin-C and 5-FU</li> </ul>
Days 2, 3, 4, 5	<ul style="list-style-type: none"> <li>• Radiation</li> <li>• Chemotherapy with 5-FU</li> </ul>
Week 2 (Days 8-14)	<ul style="list-style-type: none"> <li>• A physical examination</li> <li>• Peri-anal and groin examination</li> <li>• 5 days of radiation (no radiation at weekends)</li> <li>• Blood tests</li> </ul>
Week 3 (Days 15-21)	<ul style="list-style-type: none"> <li>• A physical examination</li> <li>• Peri-anal and groin examination</li> <li>• 5 days of radiation</li> <li>• Blood tests</li> </ul>
Week 4 (Days 22-28)	<ul style="list-style-type: none"> <li>• A physical examination</li> <li>• Peri-anal and groin examination</li> <li>• 5 days of radiation</li> <li>• Blood tests</li> </ul>

Week 5 (Days 29-35)	<ul style="list-style-type: none"> <li>• A physical examination</li> <li>• Peri-anal and groin examination</li> <li>• 5 days of radiation</li> <li>• Chemotherapy with mitomycin Day 29</li> <li>• 5 days of chemotherapy with 5FU</li> <li>• Blood test</li> </ul>
Week 6 (Days 36-42)	<ul style="list-style-type: none"> <li>• 3-5 days of radiation</li> </ul>

<b><u>During follow-up:</u></b>	
8 weeks after the end of radiation therapy	<ul style="list-style-type: none"> <li>• A physical examination</li> <li>• Skin, anal, and groin examination</li> <li>• Scope (tube with a light)</li> <li>• CT scan or MRI or PET/CT of abdomen &amp; pelvis</li> <li>• Chest x-ray</li> <li>• Blood tests</li> <li>• Biopsy, if cancer is worse in the treated area</li> </ul>
12 weeks after the end of radiation therapy	<p>Evaluation only if cancer is present at 8 week evaluation</p> <ul style="list-style-type: none"> <li>• A physical examination</li> <li>• Skin, anal, and groin examination</li> <li>• Scope (tube with a light), if recommended by your study doctor</li> <li>• Blood tests</li> <li>• Biopsy, if cancer is present</li> </ul>
6, 9, 12, 18 and 24 months after the end of radiation therapy	<ul style="list-style-type: none"> <li>• A physical examination</li> <li>• Skin, anal, and groin examination</li> <li>• Scope (tube with a light) if recommended by your study doctor</li> <li>• Blood tests</li> </ul>
12 and 24 months, then annually	<ul style="list-style-type: none"> <li>• X-ray or CT scan or PET/CT scan of chest</li> <li>• CT scan or MRI or PET/CT scan of abdomen and pelvis</li> </ul>
Annual Check ups	<ul style="list-style-type: none"> <li>• A physical examination</li> <li>• Anal and groin examination</li> <li>• Scope (tube with a light), if recommended by your study doctor</li> <li>• Blood tests</li> <li>• X-ray or CT scan or PET/CT scan of chest</li> <li>• CT scan or MRI or PET/CT scan of abdomen and pelvis</li> </ul>

**HOW LONG WILL I BE IN THE STUDY?**

The actual treatment will last 5-6 weeks. You will be followed carefully after completing the treatment to make sure there is no evidence of the cancer returning. By following up, we will

make sure that there are no delayed side effects and that any side effects that did happen during the study have improved.

It is important that we know what happens to you over a long-term period of time, so after the first two years, you will get a check up once a year.

### **CAN I STOP BEING IN THE STUDY?**

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping the study so that any problems you may have been having are carefully recorded.

Another reason to tell the study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

Also the study doctor may stop you from taking part in this study at any time if your condition changes; if there is new information and they believe it is in your best interest; if you do not follow the study rules; or if the study is stopped for any reason. Further care and treatment would be discussed with you.

### **WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY?** **(10/11/07)**

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. Routine tests will be done regularly to check for possible side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you complete your treatments. In some cases, side effects can be serious, long lasting, or may never go away. There is also a remote possibility of death from complications.

You should talk to the study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the **Radiation Therapy** include those which are:

#### **Likely (more than 10%)**

- Redness and skin irritation in the treatment area that may result in bleeding and/or infection, which may require hospitalization
- Loss of pubic hair in the treated area, usually temporary
- Tiredness
- Nausea and/or vomiting
- Sterility (inability to bear children) in fertile women
- Sterility (inability to produce children) in men

#### **Less Likely (3-9%)**

- Diarrhea

- Sores and bleeding from the bowel (these side effects may occur well after treatment and be serious enough to require surgery)
- Narrowing and dryness of the vagina (birth canal) and genital area with painful or difficult intercourse and possibly bleeding
- Development of extra tissue (fibrosis) in the anal canal, which may result in decreased function
- Long-term dryness of the skin
- Inability to have or keep an erection (impotency)
- Hip fracture
- Build up of fluid in ankles, feet, and/or legs

#### **Rare, but serious (less than 2%)**

- Narrowing or blockage of the bowel (these side effects may occur well after treatment and be serious enough to require surgery)
- Blockage of the urinary tubes
- Development of an abnormal path or connection between organs (fistulae)
- Skin damage (tissue death), which may result in surgery
- Narrowing of or persistent bleeding in the vagina (birth canal), which may result in surgery

Risks and side effects related to the **Chemotherapy** (5-FU and Mitomycin) include those which are:

#### **Likely (more than 10%)**

- Diarrhea with cramping or bleeding
- Nausea and or vomiting
- Change in taste, particularly a metallic taste
- Loss of appetite
- Dry skin with rash, cracking, and/or peeling
- Mouth sores and sore throat
- Temporary thinning or loss of hair
- Low white blood cell count, which may increase the risk of infection
- Low red blood cell count, which may result in anemia, tiredness, and/or shortness of breath
- Low platelet count, which may result in increased bruising and bleeding

#### **Less Likely (3-9%)**

- Eye irritation, watery eyes, and/or runny nose
- A blocked tear duct, which may require treatment
- Blurred vision
- Darkening and thinning of the skin
- Darkening, dryness, and marking of the nails
- Increased sensitivity to sunlight
- Headaches, which may continue
- Light-headedness
- Fever

- Puffiness of the hands and feet
- For women, missed menstrual periods
- Redness, tenderness, peeling, and/or tingling of the palms and soles of the feet

**Rare, but serious (less than 2%)**

- Confusion
- Unsteadiness, loss of coordination
- Temporary loss of consciousness
- Slurred speech
- Dry cough and shortness of breath
- Tissue damage from leakage of mitomycin from a vein, which may require surgery
- Vomiting blood from the digestive tract
- Serious infection, which may be life threatening
- Irritation of a vein due to a blood clot, which may result in tenderness over the vein and pain in the part of the body affected and which may require treatment
- Allergic reactions, which can involve flushing, difficulty breathing, and low blood pressure and which can be life threatening
- Change in heart rhythm
- Damage to the heart or spasm of the heart's blood vessels that can cause chest pain
- Heart attack
- Kidney damage
- Inflammation of the liver, which may result in yellowing of the skin and eyes, tiredness, and/or pain on the upper right of the stomach area

Risks and side effects related to **biopsies** include infection, bleeding, and/or pain.

Risks associated with **blood drawing**

You may experience some discomfort, bruising, and/or bleeding at the site of the needle insertion. Occasionally, some people experience dizziness or feel faint. In rare instances, infection may develop at the site of the needle insertion.

**Reproductive risks:**

You should not become pregnant or father a baby while on this study because the drugs and the radiation in this study can affect an unborn baby. Women should not breast feed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with the study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

Radiation therapy to the pelvis will cause fertile women to lose the ability to bear children since radiation causes loss of ovary function and will cause men to lose the ability to produce children. Women may need hormones to relieve symptoms such as hot flashes or vaginal dryness caused by the loss of ovary function.

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.

For more information about risks and side effects, ask the study doctor.

### **ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

Taking part in this study may or may not make your health better. While doctors hope that IMRT will be more useful against cancer compared to the standard radiation method, there is no proof of this yet. The possible benefits of this treatment are reduced side effects, including less need for surgery, but this is not guaranteed.

We do know that the information from this study will help doctors learn more about intensity modulated radiation therapy (IMRT) as a treatment for anal cancer. This information could help future cancer patients.

### **WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?**

Your other choices may include:

- Getting treatment or care for your cancer without being in a study, such as standard radiation and chemotherapy; radiation alone; or surgery in which the anus and rectum are removed and the bowel is attached to a permanent opening in the skin of the stomach (colostomy).
- Taking part in another study, if available
- Getting no treatment or comfort care, also called palliative care. In this case the cancer will likely continue to grow and spread to other parts of the body. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

### **WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?**

Data are housed at RTOG Headquarters in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Your hospital or university Institutional Review Board (IRB), which supervises research projects to make sure that they are carried out correctly.

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people.
- The Radiation Therapy Oncology Group (RTOG), which is carrying out this study.

### **WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?**

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study, including prescriptions to control side effects. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The study doctor will explain any procedures related solely to research. Some of these procedures may result in added costs that may be covered by insurance. The study doctor will discuss these with you.

#### **You will not be paid for taking part in this study.**

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

### **WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?**

It is important that you tell the study doctor, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call them.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for any additional medical treatment.

### **WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?**

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of any injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

## **WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?**

You can talk to the study doctor about any questions or concerns you have about this study. Contact the study doctor \_\_\_\_\_ [name(s)] at \_\_\_\_\_ [telephone number].

For questions about your rights while taking part in this study, call the \_\_\_\_\_ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at \_\_\_\_\_ (telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

\*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only).

(5/31/07)

**Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in this additional research.**

You can say “yes” or “no” to the following studies. Below, please mark your choice for each question.

### **Use of Tissue for Research (5/31/07)**

#### **About Using Tissue for Research**

You are going to have or have had a biopsy (or surgery) to see if you have cancer. Your doctor will remove or has removed 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 is left over 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. Please read the information sheet called "How Is Tissue Used for Research" to learn more about tissue research. This information sheet is available to all at the following web site:

<http://www.cancerdiagnosis.nci.nih.gov/specimens/patient.pdf>

As a result of your participation in the main part of this trial, you will have blood tests performed before you before your start treatment and 8-12 weeks after you have finished treatment. We would like to keep for future research about three tablespoons of the blood taken at each of these times. If you agree, this blood will be kept and may be used in research to learn more about cancer and other diseases.

In addition, we would like to keep some of your urine for future research. We would collect your urine before you start treatment and 8-12 weeks after you have finished treatment. If you agree, the urine will be kept and may be used in research to learn more about cancer and other diseases.

Your tissue, blood, and urine may be helpful for research whether you do or do not have cancer. The research that may be done with your tissue, blood, and urine is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue, blood, and urine will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

## Things to Think About

The choice to let us keep the leftover tissue, blood, and urine for future research is up to you. No matter what you decide to do, it will not affect your care or your participation in the main part of the study.

If you decide now that your tissue, blood, and urine 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, blood, and urine. Then any material that remains will no longer be used for research., Any tissue that remains will be returned to the institution that submitted it, and any blood or urine that remains will be destroyed.

In the future, people who do research may need to know more about your health. While reports may be given about your health, your name, address, phone number, or any other personal information will not be given, so the researchers will not know who you are.

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

Your tissue, blood, and urine will be used only for research and will not be sold. The research done with your tissue, blood, and urine may help to develop new products in the future.

## Benefits

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

## Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

## Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at \_\_\_\_\_ [IRB's phone number].

No matter what you decide to do, it will not affect your care.

**1. My tissue, blood, and urine may be kept for use in research to learn about, prevent, or treat cancer.**

**Yes      No**

**2. My tissue, blood, and urine 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

3. Someone may contact me in the future to ask me to take part in more research.

Yes      No

**WHERE CAN I GET MORE INFORMATION?**

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at <http://cancer.gov/>

- For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>
- For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

You will get a copy of this form. If you want more information about this study, ask your study doctor.

**SIGNATURE**

I have been given a copy of all \_\_\_\_\_ [*insert total of number of pages*] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant \_\_\_\_\_

Date \_\_\_\_\_

**APPENDIX II (5/31/07)**  
**STUDY PARAMETER TABLE**

	Pre-Treatment		During Treatment	Follow-Up Post Completion of Radiation Therapy		
	≤ 42 days prior to study entry	≤ 14 days prior to entry	weekly	At 8 weeks	At 12 weeks <sup>e</sup>	At months 6, 9, 12, 18, and 24; then annually
History/physical		<b>X</b>		<b>X</b>	<b>X</b>	<b>X</b>
Assessment of smoking/alcohol history		<b>X</b>				
Assessment of weight and nutrition		<b>X</b>				
Diagnostic Biopsy	<b>X</b>					
Anal/Groin Exam	<b>X</b>			<b>X</b>	<b>X</b>	<b>X</b>
Skin (inguinal and peri-anal) Exam	<b>X</b>		<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>
Colonoscopy, sigmoidoscopy and/or rigid proctoscopy w/DRE	<b>X</b>			<b>X</b>	<b>X</b>	<b>X<sup>h</sup></b>
Nodal FNA, if necessary	<b>X</b>					
X-ray or CT or PET/CT of Chest	<b>X</b>			<b>X</b>		<b>X<sup>i</sup></b>
CT or MRI or PET/CT of Abdomen & Pelvis	<b>X</b>			<b>X</b>		<b>X<sup>i</sup></b>
Zubrod performance status		<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>
CBC w/ diff, Platelets and ANC		<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>
Serum creatinine and bilirubin		<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>
Electrolytes			<b>X<sup>d</sup></b>	<b>X</b>	<b>X</b>	<b>X</b>
ALT/AST		<b>X</b>		<b>X</b>	<b>X</b>	<b>X</b>
Serum pregnancy test (if applicable)		<b>X</b>				
INR		<b>X</b>				
HIV test <sup>a</sup>	<b>X</b>					
HPV determination from anal biopsy <sup>b</sup>	<b>X</b>					
Adverse event evaluation <sup>c</sup>		<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>
Post-treatment biopsy				<b>X<sup>f</sup></b>	<b>X<sup>g</sup></b>	

- a. If clinical suspicion of AIDS;
- b. Highly recommended, but not required;
- c. And as needed based on reporting requirements;
- d. See diarrhea in Section 7.4;
- e. Only for patients with disease at 8 weeks;
- g. Biopsy, if disease present; not progressive;
- h. At months 6, 9, 12, 18, 24, 36, and then at physician's discretion;
- i. At months 12 and 24, then annually.

### APPENDIX III

#### ZUBROD PERFORMANCE SCALE

<b>0</b>	Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100)
<b>1</b>	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80)
<b>2</b>	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60)
<b>3</b>	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40)
<b>4</b>	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20)
<b>5</b>	Death

#### KARNOFSKY PERFORMANCE SCALE

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

#### NEW YORK HEART ASSOCIATION CLASS DEFINITIONS

<b>Cardiac</b>	<b>Cardiac Symptoms</b>	<b>Limitations</b>	<b>Need for Additional Rest*</b>	<b>Physical Ability to Work**</b>
I	None	None	None	Full Time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, & any activity increases discomfort	Extreme	Marked	Unable to work

\*To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.  
 \*\* At accustomed occupation or usual tasks.

## APPENDIX IV

### AJCC CANCER STAGING SYSTEM, ANAL CANAL (AJCC, 2002, 6<sup>TH</sup> Edition)

#### **Primary Tumor (T)**

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ
- T1: Tumor 2 cm or less in greatest dimension
- T2: Tumor more than 2 cm but not more than 5 cm in greatest dimension
- T3: Tumor more than 5 cm in greatest dimension
- T4: Tumor of any size that invades adjacent organ(s), e.g., vagina, urethra, bladder\*

[Note: \*Direct invasion of the rectal wall, perirectal skin, subcutaneous tissue, or the sphincter muscle(s) is not classified as T4.]

#### **Regional Lymph Nodes (N)**

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis in perirectal lymph node(s)
- N2: Metastasis in unilateral internal iliac and/or inguinal lymph node(s)
- N3: Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes

#### **Distant Metastasis (M)**

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

#### **Stage Grouping**

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage IIIA	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
	T4	N0	M0
Stage IIIB	T4	N1	M0
	Any T	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

## APPENDIX V

### **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 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 VI (5/31/07)(6/2/09)**

**SPECIMEN COLLECTION KITS AND INSTRUCTIONS**

**Peripheral Blood**

**Instructions** for use of serum, plasma, or buffy coat collection kit (collected as required by protocol):

This kit includes:

- Ten (10) 1 ml cryovials
- Biohazard bags
- Absorbent shipping material
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Pre-paid shipping label(s)

**Serum (if requested):**

- Using four (4) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials “serum”.

Process:

1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at room temperature.
3. Aliquot a minimum of 0.5 ml serum (optimal 1ml) into each cryovial labeled with RTOG study and case numbers, collection date/time, timepoint collected, and clearly mark specimen as “serum”.
4. Place cryovials into biohazard bag and immediately freeze at –70 to –80° Celsius.
5. Store serum at –70 to –80° Celsius until ready to ship.
6. Ship on dry ice.

**PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.**

**Plasma (If requested):**

- Using three (3) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials “plasma”.

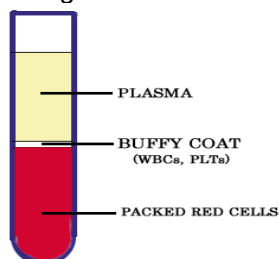
Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at room temperature.
3. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot a minimum of 0.5 ml plasma (optimal 1 ml) into each cryovial labeled with RTOG study and case numbers, collection date/time, timepoint collected and clearly mark specimen as “plasma”.
5. Place cryovials into biohazard bag and immediately freeze at –70 to –80° Celsius.
6. Store plasma at –70 to –80° Celsius until ready to ship.
7. Ship on dry ice.

**PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.**

**Buffy coat (if requested):**

*For a visual explanation of Buffy coat, please refer to diagram below.*



- ❑ Using one (1) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovial(s) “buffy coat”.

Process:

1. Centrifuge EDTA (purple top) tube within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at room temperature.
2. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is performed.
3. Carefully remove plasma close to the buffy coat and set plasma aside (*can be used to send plasma samples – see above instructions*).
4. Remove the buffy coat cells carefully and place into cryovials labeled “buffy coat” (*it is okay if a few packed red cells are inadvertently collected in the process*). Clearly mark the tubes with date/time of collection and timepoint collected.
5. Place cryovials into biohazard bag and freeze immediately at -70 to -80° Celsius.
6. Store buffy coat samples frozen (-70 to -80° Celsius) until ready to ship.
7. Ship on dry ice.

**PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.**

Shipping/Mailing:

- ❑ Ship specimens overnight **Monday-Wednesday** to prevent thawing due to delivery delays. Saturday and holiday deliveries will not be accepted.
- ❑ Include all RTOG paperwork in a sealed plastic and tape to the outside top of the Styrofoam box.
- ❑ Wrap frozen specimens of same type (i.e., all serum together, plasma together and buffy coats together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with dry ice (4-5lbs/2-2.5kg minimum). Ship ambient specimens in a separate envelope/cooler. Place Styrofoam coolers into outer cardboard box, and attach shipping label to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag.*
- ❑ For questions regarding collection, shipping or to order a Blood Collection Kit, please email [RTOG@ucsf.edu](mailto:RTOG@ucsf.edu) or contact the RTOG Biospecimen Resource by phone 415-476-RTOG (7864) or Fax at 415-476-5271.

URINE COLLECTION KIT INSTRUCTIONS

**This Kit contains:**

- One (1) Sterile Urine collection cup
- Biohazard bags

**Urine Specimens:**

Preparation for collecting **Urine:**

- A clean catch urine specimen will be collected.

Process

- To collect the specimen, use the following instructions:
  - Males should wipe clean the head of the penis and females need to wipe between the labia with soapy water/cleansing wipes to remove any contaminants.
  - After urinating a small amount into the toilet bowl to clear the urethra of contaminants, collect a sample of urine in the collection cup.
  - After 10-25 mL urine has been collected, remove the container from the urine stream without stopping the flow of urine.
  - Finish voiding the bladder into the toilet bowl.
  - Place the cap on the collection cup and tighten the container. Make sure the cap is not cross-threaded or placed on incorrectly or leaking will occur.
- Label the specimen with the RTOG study and case number, collection date and time, timepoint of collection, and clearly mark specimen as “urine”.
- If available, use parafilm to seal the cap of the urine cup and to prevent leakage.
- Place urine cup into biohazard bag and seal the bag.
- Immediately freeze urine sample at -20°C.

- Store specimens frozen at -20°C until ready to ship.

**Shipping Instructions for all specimens:**

**Urine Specimens:** Urine cups must be wrapped in an absorbent material (e.g., paper towels) and placed in an airtight plastic freezer bag (i.e., re-sealable bag). Urine specimens may be sent in batches, if within 30 days of collection. Pack the frozen specimens in a heavy grade Styrofoam box with dry ice (4-5 lbs/2-2.5 mg minimum). Seal the box with plastic tape. All RTOG paperwork should be placed in a plastic bag, sealed, and taped to the outside of the Styrofoam box. Pack the Styrofoam box in a cardboard box. Note: Specimens requiring specific infectious precautions should be clearly labeled, with specific sources of infectious concerns listed, if known. Mark the outer cardboard box "biohazard".

**Send specimens by overnight express to the address below. Specimens only should be shipped Monday through Wednesday to prevent thawing due to delivery delays. Saturday and holiday deliveries will not be accepted. Samples received thawed will be refrozen and held. A notification will be sent immediately to the Principal Investigator and Clinic Research Assistant of the submitting institution. The institution should send a subsequent sample, collected as close as possible to the original planned collection date, if possible.**

**Notes:**

- *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag*
- Sites must submit the required documentation with specimens. All specimens will be shipped to:

**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**