

RADIATION THERAPY ONCOLOGY GROUP

RTOG R-0012

**RANDOMIZED PHASE II TRIAL OF PREOPERATIVE COMBINED MODALITY
CHEMORADIATION FOR DISTAL RECTAL CANCER**

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RANDOMIZED PHASE II TRIAL OF PREOPERATIVE COMBINED MODALITY CHEMORADIATION FOR DISTAL RECTAL CANCER

SCHEMA (6/20/01)

S	R	
T	A	Arm 1: CVI 5-FU (225 mg/m ² /day, 7 days/week, until completion of RT)
R	N	+ Pelvic RT 45.6 Gy (1.2 Gy/b.i.d., ≥ 6 hour interval)
A	D	+ Boost to tumor (9.6 Gy for T3 and 14.4 Gy for fixed T4)*
T	O	+ Surgery**4-10 weeks after completion of RT. See Section 7.5 for
I	M	postoperative chemotherapy.
F	I	Arm 2: CVI 5-FU (225 mg/m ² /day, M-F, 120 hrs/weekly, until completion of RT) plus CPT-11
Y	Z	(50 mg/m ² , once weekly x 4)
	E	+ Pelvic RT 45 Gy (1.8 Gy/day)
		+ Boost to tumor (5.4 Gy for T3 and 9 Gy for fixed T4)*
		+ Surgery**4-10 weeks after completion of RT. See Section 7.5 for
		postoperative chemotherapy.

* Boost radiation may be delivered using conformal 3D techniques

** IORT (optional) may be delivered to areas of tumor fixation at time of surgery
Maintenance chemotherapy is recommended for all patients post radiation

Eligibility: (See Section 3.0 for details)[6/20/01]

- Adenocarcinoma of the distal rectum located from 0 to 9 cm from the dentate line (3-12 cm from the anal verge) without evidence of distant metastases
- Lesions may be either **mobile** cancers but stage T₃ by endorectal ultrasound, or **fixed** (defined as clinical T4 for this study) on palpation
- White blood count of > 4000 per ml and platelet count > 130,000 per ml; liver and renal function tests WNL.
- No prior chemotherapy or radiation therapy to the pelvis
- No evidence of distant metastasis
- No extension of malignant disease to the anal canal
- No concurrent malignancies or previous malignancy unless disease free for at least 5 years
- No other serious medical illnesses
- Not pregnant or lactating
- Signed study-specific informed consent prior to randomization

Required Sample Size: 100

Institution # _____

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ELIGIBILITY CHECK (6/20/01)

Case # _____

(page 1 of 2)

- _____(Y) 1. Does patient have adenocarcinoma?
- _____(Y) 2. Is tumor 0-9 cm from dentate line or 3-12 cm from anal verge?
- _____(N) 3. Is there tumor extension to the anal canal?
- _____(Y/N) 4. Is tumor fixed? (T4)
_____(Y) If no, is tumor T3 and mobile by endorectal ultrasound?
- _____(Y/ N/A) 5. If female, is patient non-pregnant and non-lactating?
- _____(≥ 4,000) 6. What is WBC?
- _____(> 130,000) 7. What is platelet count?
- _____(Y) 8. Is bilirubin ≤ 1.5 x upper limit normal limit?
- _____(Y) 9. Are liver functions normal (*alkaline phosphatase, SGOT, LDH and creatinine*)?
- _____(N) 10. Does patient have other serious illnesses?
- _____(N) 11. Did patient receive any prior chemotherapy or XRT to pelvis?
- _____(N) 12. Is patient taking any anti-epileptic or anti-seizure drugs?
- _____(Y/N) 13. Any prior malignancy?
_____(Y) If yes, disease free 5 years?
- _____(N) 14. Any concurrent malignancy other than non-melanoma skin cancer or *in situ* cancer of cervix?
- _____(N) 15. Any unresected synchronous Tis or T1 colonic cancer?
- _____(N) 16. Is there any evidence of distant metastases?
- _____(0-1) 17. What is Zubrod status?
- _____(Y) 18. Have pretreatment evaluations been completed as specified in Section 4.0?

(continued on next page)

Institution # _____

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ELIGIBILITY CHECK (6/20/01)

Case # _____

(page 2 of 2)

The following questions will be asked at Study Registration:

- _____ 1. Name of institutional person registering this case?
- _____ (Y) 2. Has the Eligibility Checklist (*above*) been completed?
- _____ (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 Name
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Social Security Number
- _____ 11. Gender
- _____ 12. Patient's Country of Residence
- _____ 13. Zip Code
- _____ 14. Patient's Insurance Status
- _____ 15. Will any component of the patient's care be given at a military or VA facility?
- _____ 16. Treatment Start Date
- _____ 17. Medical Oncologist
- _____ 18. Clinical Stage (*T3 vs. T4*)?
- _____ 19. Treatment Assignment

Completed by _____

Date _____

1.0 INTRODUCTION

1.1 Background

Rectal cancer remains a significant oncologic problem in the United States. In 2000, there are estimated to be 36,400 new cases of cancer of the rectum with an overall 5-year survival of 55%-60%. The prognosis in patients with early tumors (*stage T_pT₀*) is excellent (*greater than 80%*). However, prognosis becomes significantly more grave when tumors arise in the distal rectum and are of increasing stage of disease (*T₃T₄ or N positive*). Surgery has remained the mainstay of treatment of these cancers but because of high local recurrence rates (20-60%), adjunctive chemoradiation has become standard practice for treatment of advanced cancers ($\geq T_3$).¹ Until recently adjunctive therapy consisted primarily of postoperative chemoradiation as established by the GITSG², NCCTG³ studies and intergroup studies.⁴ However, data from the Swedish national trial⁵ indicates that preoperative radiation may be a potentially better approach to treatment of this disease than postoperative radiation, both in terms of local control and reduced toxicity. This is especially true for tumors with extension into the perirectal fat and involvement of adjacent structures (*stages T₃T₄ or N+*).

Historically preoperative radiation utilized in low dose regimens of 20-30 Gy in 1.8-2.0 Gy fractions had proven ineffective. More recent data utilizing high dose preoperative radiation appears to be significantly more effective in increasing resectability rates^{5,6}, improving the options for sphincter preservation surgery^{7,8}, reducing local recurrence and improving survival of patients.^{9,10} In single institutional studies preoperative radiation using a high total radiation dose of 45 Gy \pm boost has consistently yielded high rates of local control (< 90%) and overall survival in the 70%-80% range.^{11,12} Pathological complete response following preoperative radiation alone has been reported in approximately 10% of patients. More recently preoperative radiation has been combined with cytotoxic agents, especially 5-fluorouracil as a radiation sensitizer in an effort to increase the downstaging of tumors and improve the efficacy of treatment. A variety of chemotherapeutic approaches and radiation schedules have been utilized in single institutional studies and have resulted in a range of pathological complete responses of 10%-50%.¹³⁻¹⁸ Patient selection, radiation dose, treatment technique, and mode of drug delivery can significantly affect these rates of complete response. Reporting of treatment related toxicity also is variable and does not lend itself to comparison of the most effective regimen in the preoperative management of these cancers. This study is therefore proposed to examine, in a randomized phase II fashion, several of the currently available chemoradiation schedules to establish the most effective pre-operative treatment regimen as measured by pathological complete response rates and assess the toxicity of these regimens prior to considering a future phase III study for the management of this disease.

1.2 CPT-11 Rationale

The nuclear enzyme topoisomerase I has been recently recognized as the target for the anti-cancer drug irinotecan (*CPT-11*). CPT-11 (*7-ethyl-10-[4-(1-piperidino)-1-piperidinol carbonyloxy camptothecin*) is a water-soluble analogue of camptothecin synthesized in an attempt to identify camptothecin derivatives with aqueous solubility and antitumor activity. CPT-11 is a prodrug that undergoes deesterification *in vivo* to yield SN-38, a metabolite that is 1000-fold more potent than the parent compound *in vitro*.

1.3 Background on Camptothecins as Antitumor Agents

Camptothecin is a plant alkaloid obtained from the *Camptotheca acuminata* tree. The original clinical preparation, camptothecin sodium, was evaluated in clinical trials in the late 1960s and early 1970s but was abandoned due to severe and unpredictable hemorrhagic cystitis. Irinotecan (*CPT-11*) is a semisynthetic derivative of camptothecin that possesses greater aqueous solubility, greater *in vitro* and *in vivo* activity, and is associated with less severe and more predictable toxicity than camptothecin.¹⁶ Both camptothecin and CPT-11 are potent inhibitors of topoisomerase I, a nuclear enzyme that plays a critical role in DNA replication and transcription. The enzyme functions normally to cause transient breaks in a single strand of DNA that release the torsional strain caused by synthesis of a new strand of DNA or RNA around a double helix. The camptothecins target this topo I-DNA complex, known as the "cleavable complex." Once bound to the cleavable complex, the camptothecins inhibit realigning of the parent DNA, thereby halting nucleic acid synthesis in the cell and leading to cell death.¹⁶

1.4 Bioactivation of CPT-11 to SN-38

CPT-11 is converted by carboxylesterases to its more active metabolite, SN-38. *In vitro*, SN-38 is 250 to 1,000-fold more potent than CPT-11 as an inhibitor of topoisomerase I activity. Similar to camptothecin and its other analogues (*e.g., topotecan*), both CPT-11 and its more active metabolite, SN-38, are reversibly

hydrolyzed from active lactone forms to hydroxy acid (*carboxylate*) forms. This hydrolysis is pH-dependent, with equilibrium favoring the hydroxy acid form at physiological pH. The closed lactone ring is a structural requirement for activity of the camptothecins, since studies have demonstrated that the opening hydroxy acid form is a less potent inhibitor of topoisomerase I and a much less potent antitumor agent.¹⁶

The enzymatic cleavage (*hydrolysis*) of the carbamyl bond of CPT-11 to form the active species SN-38 has been shown to be mediated by hepatic microsomal and serum carboxyl-esterase in animals. These serine hydroxylases were found in hepatic microsomes, kidney, lung, intestine, brain, and erythrocytes. The ability of various human tissues to produce SN-38 from CPT-11 was also compared. Enzymatic hydrolysis was fastest in human liver (*42.4 ng SN-38/mg protein/hour*) with the kidney showing the second highest activity at 24% of the liver value. Activity in normal spleen, lung, and pancreatic tissue ranged between 16% to 18% of the liver value. Liver tumors produced significant, but slightly lower, amount of SN-38 than normal liver tissue. Based on these results, human liver was proposed to be the major site of bioactivation of CPT-11, with extrahepatic metabolism in other normal and tumor tissues likely.¹⁶

1.5 Clinical Pharmacokinetics of CPT-11 and SN-38

The mean terminal half-life of SN-38 in plasma is slightly longer than that for CPT-11: 11.5 @ 3.8 hours versus 6.3 ± 2.2 hours (*lactone forms*). Peak plasma concentrations for CPT-11 occur at the end of the infusion. The time to peak SN-38 concentration is highly interpatient dependent and occurs 30-90 minutes after the end of infusion.¹ Murine studies suggest that the liver may concentrate CPT-11, convert CPT-11 to SN-38, and eliminate via biliary excretion CPT-11, SN-38 and the glucuronide conjugate of SN-38 (*SN-38G*). In rats, 55% of radiolabeled CPT-11 was excreted unchanged in the bile within 24 hours while 21.7% was transferred to SN-38. Overall, 73% of the radioactivity could be recovered from the feces of rats and 25% from the urine. It recently was demonstrated that plasma concentrations of SN-38G in patients occur 0.5 to three hours after the SN-38 peak and that plasma levels generally exceeded that of SN-38. In one patient, bile concentrations of CPT-11 were 10 to 560-fold higher than plasma concentrations during the first six hours following administration, whereas bile concentrations of SN-38 were 2 to 9 fold higher. Renal clearance has not been reported to be a major route of elimination for these compounds in humans.¹⁶

1.6 Phase II Trials of CPT-11 in Previously Untreated Patients

At the Memorial Sloan-Kettering Cancer Center (*M6475-0010*), 41 patients with previously untreated metastatic colorectal cancer were enrolled and treated. There were 25 females and 16 males with a median age of 60 years (*range, 19 to 84 years*). All patients enrolled in this trial had aggressive malignancies as documented by the presence of metastatic disease (*Dukes stage D*) at primary diagnosis. Metastatic sites included liver in 36 patients and lung in 11 patients. Of 41 treated patients, 32% (*13/41, 95% CI: 18-46%*) achieved partial responses. Eighteen patients had stable disease and ten had disease progression. The median time to tumor progression was 4.0 months. For the 13 responders, the median duration of response was 4.9 months. The median survival time for all patients was 10.9 months. The most common serious medical events were Grade 3 or 4 late (*occurring >24 hour post-infusion*) diarrhea (25%); leukopenia (12%); neutropenia (20%), and nausea/vomiting (9.8%). The incidence of grade 3 or 4 late diarrhea, initially 56% (*10/18*), was reduced to 9% (*2/23*) with early and frequent use of loperamide and diphenhydramine.¹⁷

The North Central Cancer Treatment Group (*NCCTG*) completed enrollment in a multicenter phase II study (*M6475-0003N*) of 31 patients with previously untreated colorectal cancer. There were 24 males and seven females with an average age of 66 years (*range, 32 to 81 years*). Most had measurable disease in the liver (74%). In these patients the response rate was 20% (*9/31, 95% CI: 13-45%*); all were partial responses. Sixteen patients had stable disease and six had disease progression. The median time to tumor progression was 4.4 months. The median survival time for all patients was 11/7 months. Late diarrhea and myelosuppression were the most common serious toxicities. Grade 3 or 4 late diarrhea was observed in 25.8% of the patients. Grade 3 or 4 leukopenia and neutropenia were also observed in 25.8% of the patients.¹⁸

1.7 CPT-11 and Irradiation

Preliminary preclinical and clinical studies demonstrate a synergistic effect of CPT-11 and radiation and suggest radiosensitizing activity of CPT-11. It has been suggested that CPT-11 may potentiate the lethal effects of ionizing radiation by attaching to the DNA-topoisomerase I adducts in sites of DNA single strand breaks (*SSBs*). Subsequently, the stabilized CPT-11-TOPO1-DNA complexes interact with advancing

replication forks during the S-phase of the cell cycle converting SSBs into irreversible DNA double strand breaks resulting in cell death. Fractionated irradiation synchronizes and resorts the tumor cell population, leaving the majority of cells in the S phase of the cell cycle, and thus more sensitive to CPT-11 treatment. Although radiation enhancement with CPT-11 has been demonstrated *in vivo*, the optimal dose and sequencing of irradiation with CPT-11 has not been examined.

A phase I/II study of weekly irradiation irinotecan in patients with local advanced non-small cell lung cancer demonstrated responses and manageable toxicities. Doses of CPT-11 started at 30 mg/m² and was escalated to 45 and 60 mg/m²/week. Twenty-six eligible patients, the DLT were esophagitis, pneumonitis and diarrhea. The MTD was estimated to be 60 mg/m² and the recommended dose for phase II study was 45 mg/m². In this phase II study, out of 24 evaluable patients, 2 achieved a CR and 16 attained a PR, resulting in over all response rate of 76%. The conclusion was that a combination of concurrent weekly CPT-11 and RT is feasible and active for locally advanced NSCLC.

1.8 Completed Studies

Phase I study was done at Memorial Sloan-Kettering Cancer Center to determine the maximal tolerated divided dose (*MTD*) for bolus administered schedule of CPT-11 (Monday-Friday, weeks 1,2,4, and 5 during a standard 6-week RT cycle (50.4 Gy) for preoperative treatment of locally advanced or unresectable rectal cancer. 2 of 3 patients at 13 mg/m²/day had dose-limiting diarrhea. and thus 10 mg/m²/day was declared MTD. Additional patients were then treated at this dose level. Diarrhea and neutropenia have been dose-limiting toxicities. All patients had a complete resection of their rectal tumor. Following recovery from resection, patients received weekly CPT-11 125 mg/m², leucovorin 20 mg/m², and fluorouracil 500 mg/m² for 4 weeks, repeated q 6 weeks X 3 cycles. One patient withdrew from the study and declined to receive post-operative chemotherapy. Two patients developed grade 3 diarrhea and discontinued postoperative treatment. No grade 4 neutropenia or other grade 3-4 non-hematologic toxicities were seen. In summary, this combined modality CPT-11-based schedule is safe and well-tolerated.¹⁹

Phase I study was initiated at Thomas Jefferson University Hospital to determine the maximal tolerated dose (*MTD*) of weekly CPT-11 combined a continuous infusion (*CI*) of 5-FU and concomitant RT in rectal cancer. The treatment regimen was as follows: Escalating doses of CPT-11 30-60mg/m² over 90 minutes on days 1, 8, 15, and 22; 5 FU as a protracted CI 300 or 225 mg/m²/day on days 1-5 weekly during the period of RT. The external dose of RT was 45.0 Gy given at 1.8 Gy daily. Surgery was performed 8-10 weeks following completion of CMT. The toxicities observed per dose level are as followed:

Level	# of Patients	CPT-11 dose mg/m ²	5-FU dose mg/m ²	Grade 3-4 Toxicity
1	5	30	300	2
2	4	35	300	0
3	5	40	300	2
4	5	40	225	1
5	2	50	225	1

Hematological toxicities were mild with 1 grade-4 neutropenia in the noncompliant patient. The major dose-limiting toxicities were diarrhea and intravenous catheter infections and thrombi. This combination was well tolerated. Of 20 patients who have undergone surgery, 5 complete pathological remissions and 6 minimal residual disease were observed; 2 are awaiting surgery.²⁰ The phase I trial was subsequently completed with total of 34 patients. It established the MTD for CPT-11 as 50 mg/m² with this combined program.²¹

2.0 OBJECTIVES

- 2.1 To evaluate pathological complete response to preoperative combined modality chemoradiation in cancer of the rectum.
- 2.2 Secondary endpoints include acute and late normal tissue morbidity, patterns of failure, and complete resection rates.

3.0 PATIENT SELECTION

3.1 Patient Eligibility Criteria (6/20/01)

- 3.1.1 Adenocarcinoma of the distal rectum located from 0 to 9 cm from the dentate line (*3 to 12 cm from the anal verge*) without evidence of distant metastases
- 3.1.2 Lesions may be either **mobile** cancers but stage T₃ by endorectal ultrasound, or **fixed** (*defined as clinical T4 for this study*) on palpation
- 3.1.3 Non-pregnant, non-lactating due to the combined effects of chemotherapy and pelvic irradiation
- 3.1.4 White blood count of > 4000 per ml and platelet count > 130,000 per ml; liver and renal function tests (*See Section 4.3*) WNL. Bilirubin ≤ 1.5 x upper normal limit
- 3.1.5 Zubrod performance status 0-1
- 3.1.6 No concurrent malignancies except inactive non-melanoma skin cancer, *in situ* carcinoma of the cervix, synchronous colonic cancer if the synchronous tumor is Tis or T1 and has been completely resected; no previous invasive cancer unless the patient has been disease free for at least 5 years
- 3.1.7 No other serious medical illnesses
- 3.1.8 Signed study-specific informed consent prior to randomization
- 3.1.9 Pretreatment evaluations must be completed as specified in Section 4.0.

3.2 Patient Ineligibility Criteria

- 3.2.1 Any evidence of distant metastasis
- 3.2.2 Extension of malignant disease to the anal canal
- 3.2.3 Prior chemotherapy or radiation therapy to the pelvis
- 3.2.4 Administration of anti-epileptic drugs

4.0 PRETREATMENT EVALUATIONS (6/20/01)

- 4.1 Complete physical examination
- 4.2 Biopsy of tumor to establish diagnosis, tumor location, size and extent
- 4.3 Laboratory evaluations (*within four weeks prior to study entry*):
 - 4.3.1 CBC, platelets and differential, CEA
 - 4.3.2 Liver and renal functions (*alkaline phos., SGOT, LDH, bilirubin, and creatinine*)
- 4.4 Scans (*within eight weeks prior to study entry*): **(3/13/02)**
 - 4.4.1 Sigmoidoscopy/colonoscopy to determine the location and extent of the tumor from the anorectal junction and to rule out multiple synchronous primaries
 - 4.4.2 Chest films (*AP and lateral*)
 - 4.4.3 CT scan of abdomen and pelvis to determine the location, extent, size pretreatment and extent of involvement of adjacent tissues as well as possible metastasis to the liver
 - 4.4.4 Endorectal ultrasound (*TRUS*) for TNM staging of mobile cancers
 - 4.4.5 MRI scan of pelvis for corroboration of TNM staging (*optional*)

5.0 REGISTRATION PROCEDURES

- 5.1 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. 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.

6.0 RADIATION THERAPY

6.1 Fractionation and Total Dose

6.1.1 Hyperfractionated (Arm 1)

1.2 Gy per fraction, two fractions per day with a ≥ six-hour interval, 5 days per week delivered to all fields every day. Total dose will be 45.6 Gy. Clinical stage T3 patients will receive a boost dose of 9.6 Gy; fixed T4 patients will receive a boost dose of 14.4 Gy which will be delivered to a conedown volume including the posterior half of the pelvis or by a 3D conformal technique (*tumor plus 2-2.5 cm*).

6.1.2 Conventional (Arm 2)

Conventional doses of 1.8 Gy per fraction, five fractions per week delivered with all fields treated every day. The total dose will be 45 Gy/25 fractions/five weeks. Clinical stage T3 patients will receive a boost dose of 5.4 Gy; fixed T4 patients will receive a boost dose of 9.0 Gy which will be delivered to a conedown volume including the posterior half of the pelvis or by a 3-D conformal technique (*tumor plus 2-2.5 cm*).

- 6.1.3** Modality: External beam photon radiation shall be used.
Energy: Megavoltage radiation shall be used i.e., accelerator beams of energy no less than 6 MV. Equipment of 10 MV or higher energy is strongly recommended.
- 6.1.4** Field Definition
 The fields are designed to cover the primary disease, pelvic soft tissue, principal nodal drainage areas and perineum. Shaped fields or blocks will be used to shield non-essential tissue.
- 6.1.5** Minimum boundaries of whole pelvic fields:
- 6.1.5.1** Standard opposed anterior-posterior portals:
Inferior - The minimum would be at least a 5 cm margin from the inferior extent of the cancer or the anal verge for the distal cancers as identified by a marker on simulation.
Lateral - 2 cm lateral to the bony pelvis taken at its widest point.
Superior – L5-S1 junction.
- 6.1.5.2** Standard opposed lateral portals:
Superior - To correspond to A/P fields.
Inferior - To correspond to A/P fields.
Anterior - This will cover the lower common and external iliac to 1 cm anterior to the symphysis pubis for anterior wall lesions and be at the mid symphysis for posterior lesions.
Posterior - This must include the entire sacrum with a 1 cm margin for T4 lesions or 2 cm posterior to the presacrum for T3 lesions.
- 6.1.6** The boost field shall have a 3 cm margin around the tumor but must include the whole of the sacral hollow.

6.2 Treatment Planning

6.2.1 Treatment Dose

For the following portal arrangements, the target dose shall be specified as follows:

- 6.2.1.1** For two opposed co-axial equally-weighted beams: on the central ray at mid-separation of beams
6.2.1.2 For an arrangement of two or more intersecting beams: at the intersection of the central ray of the beams
6.2.1.3 For complete rotation or arc therapy: in the plane of rotation at the center of rotation
6.2.1.4 Other or complex treatment arrangements: at the center of the target volume
6.2.1.5 The technique of using two opposing co-axial unequally-weighted fields is not recommended due to unacceptable hot spots and unacceptable dose inhomogeneity.

6.2.2 Total Treatment Dose

- 6.2.2.1** Original Treatment Volume: The total dose to the prescription point shall be 45 Gy in 25 (1.8 Gy/fx) fractions for conventional RT and 45.6 Gy in 38 twice daily fractions (1.2 Gy/fx) for hyperfractionated RT.
6.2.2.2 Boost Volume: The cumulative dose within the boost volume to the prescription point shall be 50.4 to 54 Gy with conventional RT and 55.2-60 Gy with hyperfractionated RT.

6.2.3 Time-Dose Considerations

- 6.2.3.1** Daily Dose: The daily dose to the prescription point of original and boost volumes shall be 1.8 Gy daily with conventional RT and 1.2 Gy twice daily (≥ 6 hour intervals) with hyperfractionated RT.
6.2.3.2 Fractionation: Treatment shall be given five days per week. All radiation fields shall be treated once each day with conventional RT and twice a day with a ≥ 6 -hour interval with hyperfractionated RT.
6.2.3.3 Dose Homogeneity: The dose throughout the treatment volume will be within 10% of the prescribed dose.
6.2.3.4 Treatment Modification: Uninterrupted treatment is planned. Treatment may be interrupted for acute toxicity. The specific reason(s) for treatment interruption will be recorded in the treatment summary. Treatment may be interrupted for grade ≥ 3 diarrhea or other grade ≥ 3 regional symptoms. No modifications in dose will be made for interruptions in therapy. (See Sections 7.2 and 7.4). (2/25/03)
6.2.3.5 The patient will be examined at least once a week during the course of radiation with a CBC and platelets. RT interruption is to be minimized and is allowed only for regional symptoms. (6/20/01)

6.2.4 Protocol Compliance Criteria

	FIELD BORDERS		SCORE
$\leq 5\%$	2 cm to ≤ 2.5 cm		Per Protocol
$> 5\%$ to $\leq 10\%$	<u>MIN</u> 1.5 to < 2 cm	OR <u>MAX</u> > 2.5 to ≤ 3.5 cm	Minor Variation, Acceptable
$> 10\%$	< 1.5 cm	OR > 3.5 cm	Major Deviation, Unacceptable

7.0 DRUG THERAPY

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

7.1 5-Fluorouracil (5-FU)

7.1.1 *Dose:* 5-FU will begin on day 1 of RT until completion of RT or patient intolerance. See Section 7.2. 5-FU will be given as an i.v. continuous infusion by an infusion pump. Acute toxicity of 5-FU will be closely monitored and may indicate, where necessary, any dose modifications. The main toxicity anticipated are nausea, diarrhea, and mucocutaneous reactions. Antiemetics and adequate fluid intake greatly ameliorate acute toxicity.

7.1.1.1 Infusional 5-FU Treatment Schedule (6/20/01)

Agent	Dose	Route	Schedule
Arm 1 (CVI 5-FU) 5-FU	225 mg/m ² /day	Continuous infusion	Daily (7 days each week) for entire duration of radiation
Arm 2 (CVI 5-FU/ CPT-11) 5-FU	225 mg/m ² /day	Continuous infusion	Daily (5 days, 120 hours) each week for entire duration of radiation

7.1.1.2 Continuous infusion of 5-FU will be initiated on Day 1 of irradiation and continue according to schedule. It should end within 24 hours of the last radiation treatment.

7.1.1.3 Venous access must be established utilizing venous access device (*for example, Hickman, Infusaport*). An ambulatory infusion pump will be utilized for this regimen. The specific pump will be selected by the treating investigator.

7.1.1.4 Because of the increased risk of catheter thrombosis, anticoagulation is recommended. Heparin 10,000 can be co-administered, mixed in the same infusion, with the dose of 5-FU to be delivered over one week's time. Alternatively, oral coumadin anticoagulants 1 – 2 mg daily can be prescribed. Platelets and coagulation parameters (*Prothrombin Time, PT*) should be monitored weekly for four weeks and then monthly, If heparin associated thrombocytopenia is noted heparin should be deleted. The dose of coumadin anticoagulants should be adjusted to be low enough so as not to prolong PT. Anticoagulation administration should be recorded on the flow sheet.

7.1.2 Chemistry

5-Fluorouracil is a fluorinated pyrimidine differing from the normal RNA substrate, uracil, by a fluorinated number 5 carbon. The chemical has a pH of 8.1, and the commercially available solution is buffered with NaOH to obtain an alkaline solution with a pH of around 9.0. The drug is both light sensitive and will precipitate at low temperatures or, occasionally, after a prolonged period at room temperature. The melting range of the solid is 280-284°C. At 25°C the solubility is 12.2 mg/ml in water, 5.5 mg/ml in 95% ethanol, and less than 0.1 mg/ml in chloroform. The molecular weight is 130.08.

7.1.3 Mechanism of Action

The metabolism of 5-FU in the anabolic pathway blocks the methylation reaction of deoxyuridilic acid to thymidylic acid. In this fashion, 5-FU interferes with the synthesis of DNA. This creates a thymine deficiency that provides unbalanced growth and cell death. Prolonged administration of 5-FU by continuous infusion may favor 5-FU incorporation into RNA. 5-FU is rapidly absorbed by the tissues. Studies with radioactively labeled 5-FU administered i.v. have indicated passage of the drug through the blood brain barrier. Intravenous administration gives a half time of 5-7.5 minutes at a 15mg/kg dose. Following the i.v. administration of a single 14 mg/kg dose radioactively labeled drug, levels of 28 mcg/ml, 2-8 mcg/ml, and 0.72 mcg/ml in plasma were observed at 10 minutes, 2 hours, and 24 hours, respectively. The drug is largely catabolized in the liver and excreted in the form of nontoxic metabolites. Eighty percent of the drug is excreted as CO₂ from the lungs, and approximately 15% is excreted intact in the urine in 6 hours. Of this 90% is excreted in the first hour.

7.1.4 Known Side Effects and Toxicities

Mild nausea and vomiting, stomatitis, anorexia, diarrhea, alopecia, myelosuppression, cerebellar, skin, and cardiac toxicity have been observed.

7.1.5 Formulation

Each 10 ml ampule contains 500 mg of the drug (50 mg/ml), adjusted to a pH of approximately 9 with sodium hydroxide. 5-FU is stored at room temperature.

7.1.6 Supply

Commercially available.

7.2 **5-FU Dose Modifications** (6/20/01)

7.2.1 If Grade ≥ 3 toxicity is encountered, the 5-FU will be withheld and RT interrupted. Treatment should be resumed when toxicity has resolved to Grade 1.

5-FU Toxicity

- \geq Grade 3 nausea and vomiting
- \geq Grade 3 stomatitis or Grade 3 diarrhea not controlled with medications
- \geq 10% weight loss
- \geq Grade 3 hand-foot syndrome (*desquamation and burning*)
- \geq Grade 3 hepatic toxicity
- \geq Grade 3 neutropenia and thrombocytopenia

Change

Temporarily discontinue 5-FU and resume according to the following table and text.

5-FU Dose Modification		
Toxicity	Parameters	Modification
Diarrhea	Grade 3: increase of ≥ 7 stools/day or incontinence; or need for parenteral support for dehydration	Decrease by 25%
Diarrhea	Grade 4: Physiologic consequences requiring intensive care; or hemodynamic collapse	Decrease by 25%
Stomatitis	Grade 3: Painful erythema edema, or ulcers requiring <i>i.v.</i> hydration	Decrease by 25%
Stomatitis	Grade 4: severe ulceration or requires parenteral or enteral nutritional support or prophylactic intubation	Decrease by 25%
Skin	Grade 3: Confluent moist desquamation, ≥ 1.5 cm diameter, not confined to skin folds; pitting edema	Decrease by 25%
Skin	Grade 4: Skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion	Decrease by 25%
Dehydration	Grade 3: Requiring <i>i.v.</i> fluid replacement (<i>sustained</i>)	Decrease by 25%
Dehydration	Grade 4: Requiring intensive care; hemodynamic collapse	Decrease by 50%
5-FU Dose Modification		
Toxicity	Parameters	Modification
Nausea	Grade 3: No significant intake, requiring <i>i.v.</i> fluids	Add anti-emetics; no dose reduction
Vomiting	Grade 3: ≥ 6 episodes in 24 hrs. over pretreatment; or need for <i>i.v.</i> fluids	Add anti-emetics; no dose reduction
Vomiting	Grade 4: Requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse	Add anti-emetics; no dose reduction

- 7.2.2** Stomatitis will be managed with oral and systemic analgesics, but when it severely limits oral caloric intake, 5-FU therapy will be withheld for 3-7 days. Erythema of the palms and sole associated with pain is also a side effect that may require treatment cessation, but usually does not occur during the early phases (*week 1-3*) of treatment. Patients with pre-existing peripheral neuropathy and diabetic patients will be instructed to report any subtle changes in their conditions.
- 7.2.3** If hemoglobin falls below < 10.5 g/dL and the cause is determined to be related to chemotherapy, the use of Procrit or Epogen (*epoetin alpha*) should be considered. Blood transfusions should be carefully recorded. No dose modifications will be required for toxicity Grades 1 or 2.
- 7.2.4** Nutritional counseling should occur if caloric intake declines or if weight loss $> 5\%$ of pretreatment weight occurs during the combined radiation and chemotherapy. Nutritional support will be provided via enteral alimentation if possible, but parenteral hyperalimentation may be employed during this period if it is deemed clinically necessary to complete protocol therapy safely.

7.2.5 If radiotherapy is interrupted due to treatment toxicity, chemotherapy will be delayed until radiotherapy resumes. If Grade 3 toxicity persists longer than two weeks, discontinue chemotherapy and consult study chair. If a Grade 3 toxicity recurs, consult study chair.

7.3 Irinotecan (CPT-11/CAMPTOSAR™)-Arm 2 only (6/20/01)

7.3.1 Dose

CPT-11 given as an *i.v.* infusion over 60 minutes once weekly at a dose of 50 mg/m². Treatment will be given once weekly for four weeks for a total of four doses.

7.3.2 Drug Administration

CPT-11 is diluted with 5% dextrose (D₅NS) to a total volume of 500 ml and infused intravenously over 60 minutes. Nothing else should be added to the bag. Dosage is based on actual weight. Treatment during radiation therapy will consist of prolonged continuous infusion (PCI) 5-FU, 225 mg/m²/day on Mondays through Fridays. CPT-11 will be given on Treatment Days 1, 8, 15, and 22. **CPT-11 will be given immediately prior to radiation therapy on each day of administration.**

7.3.3 Chemistry

Irinotecan hydrochloride trihydrate [CPT-11, (4S)-4,11 diethyl-4-hydroxy-9-[(4-piperidinopiperidino) carbonyloxy]-1H-pyrido [3',4': 6,7] indolizino [1,2-b] quino line-3,14(4H,12H)dione hydrochloride trihydrate] is a topoisomerase I inhibitor.

7.3.4 Toxicity

Virtually all phase I and II studies of irinotecan have reported neutropenia and diarrhea as the dose-limiting toxicities. It is expected that these toxicities will also be encountered in this trial. Other Grade 2-3 toxicities seen include nausea and vomiting, anorexia, abdominal cramping, cumulative asthenia, thrombocytopenia, renal insufficiency, increase in transaminase level and hair loss. Sporadic cases of pulmonary toxicity, manifested as shortness of breath and nonproductive cough, have also been reported.

7.3.5 Formulation

The drug is supplied in two forms: 2 ml vials containing 40 mg of drug and 5 ml vials containing 100 mg of drug. The drug is supplied in brown vials and appears as a pale yellow transparent solution. CPT-11 vials must be stored in a cool, dry place, protected from light in a locked cabinet accessible only to authorized individuals. It is stable for at least three years at room temperature. Irinotecan is stable for at least 24 hours in glass bottles or plastic bags after reconstitution with D₅W.

7.3.6 Supply for U.S. Sites (3-13-02)

Commercially available.

7.3.7 Camptosar®/CPT-11 and Loperamide Distribution for Canadian Study Sites (3-13-02)

The CPT-11 supplied for this study will not be used for any other purpose other than for this study or administered other than as described in the protocol.

Shipments to Canada

Pharmacia Canada Inc. will ship CPT-11 and loperamide from its corporate office in Mississauga, Ontario, to participating Canadian institutions after Pharmacia Canada Inc. has received the following documentation from RTOG:

- Ethics committee approval letter clearly identified with protocol title and study-specific consent form, version dated;
- Ethics Committee approved informed consent;
- Completed Site Information Sheet including the drug shipment address;
- Clinical Trial Site Information Form that has been filed with the Health Products and Food Branch (HPFB).

An initial drug shipment of 25 vials of CPT-11 (100 mg per vial; 20mg/ml) will be provided along with 15 blisterpacks of loperamide (Imodium; 2 mg caplets in packs of 12 per blister pack). The trial inventory of CPT-11 at each site should always have sufficient supply for 3 patients to complete 4 weeks of treatment.

To request additional supplies of CPT-11 and/or loperamide, complete the Request for Trial Drug Shipment Form that is included with your original drug shipment and fax the request to the Pharmacia Canada, Clinical Trials Supply Manager at FAX number 905-755-3151. The site pharmacist must confirm the receipt of CPT-11 and/or loperamide, and to comply with this request, the site pharmacist must sign and date the Drug Shipment Invoice and fax the invoice to the Pharmacia Canada Inc. Clinical Trials Supply Manager at FAX number 905-755-3151.

7.4 CPT-11 Dose Modification (6/20/01)

- 7.4.1 If Grade ≥ 3 toxicity is encountered, the CPT-11 will be withheld and RT interrupted. Treatment should be resumed when toxicity has resolved to Grade 1. See the table below. (2/25/03)
- 7.4.2 No dose modification will be required for changes in hemoglobin (See Section 7.2.3).
- 7.4.3 No dose modification will be made for Grade 1 or 2.
- 7.4.4 For Grade 3 or 4 neutropenia, the dose of CPT-11 should be held until toxicity resolves to Grade 1 and then should be reduced to 40 mg/m².
- 7.4.5 For Grade 3 or 4 febrile neutropenia, the dose of CPT-11 should be held until toxicity resolves to Grade 1 and then should be reduced to 40 mg/m².
- 7.4.6 For Grade 1 or 2 diarrhea, loperamide should be initiated (See Section 7.6.1).
- 7.4.7 For Grade 3 or 4 diarrhea while taking loperamide, see Section 7.2.5.

CPT-11 Dose Modification		
Toxicity	Parameters	Modification
Diarrhea	Grade 3: increase of ≥ 7 stools/day or incontinence; or need for parenteral support for dehydration	Decrease to 40 mg/m ²
Diarrhea	Grade 4: Physiologic consequences requiring intensive care; or hemodynamic collapse	Decrease to 40 mg/m ²
Stomatitis	Grade 3: Painful erythema edema, or ulcers requiring <i>i.v.</i> hydration	Decrease to 40 mg/m ²
Stomatitis	Grade 4: severe ulceration or requires parenteral or enteral nutritional support or prophylactic intubation	Decrease to 40 mg/m ²
Skin	Grade 3: Confluent moist desquamation, ≥ 1.5 cm diameter, not confined to skin folds; pitting edema	Decrease to 40 mg/m ²
Skin	Grade 4: Skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion	Decrease to 40 mg/m ²
Dehydration	Grade 3: Requiring <i>i.v.</i> fluid replacement (<i>sustained</i>)	Decrease to 40 mg/m ²
Dehydration	Grade 4: Requiring intensive care; hemodynamic collapse	Omit CPT-11 for remainder of protocol
CPT-11 Dose Modification		
Toxicity	Parameters	Modification
Nausea	Grade 3: No significant intake, requiring <i>i.v.</i> fluids	Add anti-emetics; no dose reduction
Vomiting	Grade 3: ≥ 6 episodes in 24 hrs. over pretreatment; or need for <i>i.v.</i> fluids	Add anti-emetics; Decrease to 40 mg/m ²
Vomiting	Grade 4: Requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse	Add anti-emetics; Omit CPT-11 for remainder of protocol

7.5 Post-Operative Chemotherapy

- 7.5.1** Post-operative chemotherapy should be given to all patients with pathologic evidence of residual disease. Patients with a complete pathologic response may have their post-operative chemotherapy omitted at the discretion of the treating physicians. If significant treatment toxicity has occurred during the course of induction treatment, then the administration of the post-operative chemotherapy will be at the discretion of the treating physician.
- 7.5.2** Treatment can consist of 5-FU and leucovorin given for 4 cycles during five consecutive days on days 1-5, 29-33, 57-61, and 86-89 starting 4-6 weeks post-operatively. Leucovorin should be given as an i.v. bolus at a dose of 20 mg/m²/day for each of the 5 days in each cycle. This will be followed immediately on each day by 5-FU given as an i.v. bolus.²²
- 7.5.3** For the first 2 courses of postoperative chemotherapy, the 5-FU dose will be 425 mg/m²/day. For the last 2 courses the 5-FU dose will be 350 mg/m²/day. In the event chemotherapy is scheduled to be delivered during five consecutive days in a given week and there are only four working days in that week (*i.e. national holiday*) then day 5 of chemotherapy should be given on the next available working day.
- 7.5.4** Alternatively, weekly bolus 5-FU 500 mg/m² given at the midpoint of a 2-hour infusion of leucovorin 500 mg/m² can be delivered weekly for 21 weeks. Dose modifications can be made at the discretion of the treating physician.²²
- 7.5.5** If multiple toxicities are seen, the dose administered should be based on the most severe toxicity experienced. Dose reductions are based on the dose of chemotherapy given on the preceding treatment cycle, and should be based on toxicities observed since the previous dose of post-operative chemotherapy.
- 7.5.6** The dose of leucovorin will not be adjusted due to toxicity. It should remain at 20 mg/m² for all courses. Leucovorin will be given immediately prior to each 5-FU dose; thus, if 5-FU is delayed, leucovorin will be delayed. This applies only to the Mayo Schedule. If using the RPMI schedule per Section 7.4.3, this specific dosage does not apply.
- 7.5.6.1** Leucovorin toxicities are rare. Hypersensitivity reactions have been reported in < 1% of patients.

7.5.7 Dose reduction steps for 5-FU/leucovorin

Dose Reduction Steps for 5-FU/leucovorin				
	Starting Dose	Dose Level - 1	Dose Level - 2	Dose Level - 3
5-FU	425 mg/m ²	340 mg/m ²	255 mg/m ²	170 mg/m ²

* leucovorin dose remains fixed at 20 mg/m² (*not adjusted*).

7.6 Supportive Therapy

- All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) and documented on each institution's case report as source documentation.
- 7.6.1** Loperamide (Imodium®)
All patients should be instructed to begin taking loperamide at the earliest signs of diarrhea and/or abdominal cramping that occur more than eight hours after receiving CPT-11. Patients will be instructed to begin taking loperamide at the earliest signs of (1) a poorly formed or loose stool, (2) the occurrence of 1 to 2 more bowel movements than usual in one day, or (3) unusually high volume of stool. Loperamide should be taken in the following manner: 4 mg at the first onset of diarrhea, then 2 mg every two hours around the clock until diarrhea-free for at least 12 hours. Patients may take 4 mg of loperamide every four hours during the night. Additional antidiarrheal measures may be used at the discretion of the treating physician.
- 7.6.2** Atropine
Lacrimation, diaphoresis, abdominal cramping, diarrhea, or other symptoms of early cholinergic syndrome that occur during or within one hour after receiving CPT-11 can be treated with i.v. atropine (0.25 to 1 mg i.v. or as indicated). Patients experiencing recurrent difficulties with cholinergic

symptoms may be given prophylactic atropine. Atropine should be used with caution in patients with potential contraindications (*e.g., obstructive uropathy, glaucoma, tachycardia, etc.*).

7.6.3

Antiemetics

Antiemetics should be prescribed by the treating physician as clinically indicated if a patient develops nausea and/or vomiting. Patients should receive dexamethasone (*Decadron®*) 10 mg i.v. as a pretreatment antiemetic unless there is a relative or absolute contraindication to corticosteroids (*e.g., diabetes, known sensitivity to corticosteroids, severe muscle weakness, etc.*). The addition of lorazepam (*Ativan®*) at 1-2 mg i.v. or p.o., ondansetron (*Zofran®*) at 32 mg i.v., or granisetron (*Kytril®*) at 10 µg/kg i.v. may also be considered if clinically indicated.

7.6.4

Prochlorperazine (Compazine®)

Compazine® should not be given on the day of CPT-11 treatment due to its potential association with akathisia (*motor restlessness*). There are no restrictions on the use of this drug on other days within the treatment course.

Because late nausea and vomiting may occur for several days following CAMPTOSAR administration, prochlorperazine (*Compazine®*) 10 mg p.o. every 6 hours as needed might be considered to ameliorate these events. Other antiemetics, such as 5HT₃ antagonists, or dexamethasone 4 mg to 8 mg p.o. b.i.d. x 48-72 hours may be used at the discretion of the investigator for late nausea and vomiting.

7.6.5

Anticoagulants

Patients who are taking Coumadin® may participate in this study; however, it is recommended that prothrombin time be monitored carefully (*at least weekly*). Subcutaneous heparin or fractionated heparin products are also permitted.

7.6.6

Growth Factor

Routine prophylactic use of G-CSF is not generally recommended; however, prophylactic administration of G-CSF in a patient who is experiencing recurrent difficulties with neutropenia or therapeutic use in patients with serious neutropenic complications such as tissue infection, sepsis syndrome, fungal infection, etc., may be considered at the investigator's discretion.

7.6.7

Other Concomitant Medication

Other concomitant medications should be avoided except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems. If possible, the use of drugs with laxative properties should generally be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact the physician to discuss any laxative use.

7.6.8

Oral Hydration

Oral fluids containing approximately 100 grams of sucrose and 2 grams of sodium chloride should be given on the day of CPT-11 administration and on day following CPT-11 administration.

7.7 **Toxicity Reporting** (6/20/01)

7.7.1

The revised NCI Common Toxicity Criteria Version 2.0 (3/98) will be used to score chemotherapy and acute radiation (*≤ 90 days*) toxicities. The following guidelines for reporting adverse drug reactions (*ADRs*) apply to any research protocol, which uses commercial anticancer agents (*also see Appendix V*). The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days.

7.7.1.1

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

7.7.1.2

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

7.7.1.3

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

7.7.1.4

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

7.7.2

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

**Investigational Drug Branch
P.O. Box 30012
Bethesda, Maryland 20824
Telephone (301) 230-2330
available 24 hours
Fax (301) 230-0159**

7.8 SAE Reporting for Canadian Study Sites (3-13-02)

7.8.1 Definition of Adverse Event

All serious adverse events, regardless of relationship to study drugs, must be reported to RTOG in an expedited manner (*see next section for reporting instructions*).

A serious adverse event (SAE) is any adverse event that:

7.8.1.1 Results in death;

7.8.1.2 Is life-threatening;

7.8.1.3 Requires inpatient hospitalization or prolongation of existing hospitalization (*excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care*);

7.8.1.4 Results in persistent or significant disability or incapacity;

7.8.1.5 Results in a congenital anomaly/birth defect in infants born to women treated on this protocol.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in those situations that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the patient or require intervention to prevent one of the events listed above.

If the investigator becomes aware of an SAE that occurs (*regardless of relationship to study drug*) within 30 days after stopping protocol therapy (*i.e., after last dose*); or more than 30 days after stopping protocol therapy, and is considered related to protocol therapy, the SAE must be reported in accordance with procedures specified in this protocol.

7.8.2 Serious Adverse Event Reporting Instructions

All serious adverse events must be reported as follows:

7.8.2.1 Within 24 hours (*of investigator knowledge of event*) report event by faxing the FDA Form 3500 to:

RTOG Data Management
1101 Market Street, 14th floor
Philadelphia, PA 19107
1-800-227-5463 Ext. 4189
Fax: 215-928-0153

Investigational Drug Branch (NCI/CTEP)
P.O. Box 30012
Bethesda, MD 20824
301-230-2330
Fax: 301-230-0159

If necessary, the initial report is to be followed by submission of more detailed adverse event information on the same FDA Form 3500 within 5 working days of the event.

7.8.2.2 RTOG Reporting Responsibilities

RTOG will forward a copy of all serious adverse events by fax, regardless of relationship to protocol treatment, to Pharmacia Canada Inc. within 24 hours of receipt by RTOG.

Reporting Information:

Ruth Bell
Drug Surveillance Associate
Pharmacia Canada Inc.
555 Standish Court, Suite 1200
Mississauga, Ontario L4W 5J5
FAX: 800-353-0942
Phone: 888-391-2222

The Therapeutic Products Directorate (TPD) of the Canadian Health Protection Branch will be notified by RTOG in an expedited manner of **serious adverse events considered unexpected and related to protocol treatment**. In addition, RTOG will inform all investigators of all serious adverse events reported to TPD and request that local ethics boards (*REB/IRB/IEC*) be notified of the same.

7.8.2.3 Reporting Serious Adverse Events to Local Ethics Boards

Investigators must notify their Research Ethics Boards (*REB/IRB/IEC*) of any serious adverse events sent by RTOG for the purpose of reporting to REBs (*as outlined in previous section*). Documentation from the REB of receipt of these reportable serious adverse events must be kept on file in the centre.

8.0 SURGERY

8.1 Surgical Technique

8.1.1 Surgery will consist of a radical resection either by anterior resection or an abdominal perineal resection with preferably a total mesorectal resection four to ten weeks after completion of the chemoradiation therapy.

9.0 OTHER THERAPY

Not applicable to this study.

10.0 PATHOLOGY

10.1 RTOG Tissue Bank (for patients who have consented to participate in the tissue component of the study [3/13/02])

10.1.1 Materials for patients entered on this study must be submitted to the RTOG Tissue Bank.

10.1.2 The following must be provided:

10.1.2.1 One H&E stained slide.

10.1.2.2 A paraffin-embedded tissue block of the tumor or 15 unstained slides. Block/slides must be clearly labeled with the pathology identification number that agrees with the pathology report.

10.1.2.3 Pathology report documenting that submitted block or slides contain tumor.

10.1.2.4 A Pathology Submission Form must be included and must clearly state that it is being submitted for the RTOG Tissue Bank.

10.1.3 RTOG will reimburse pathologists from submitting institutions \$100. per case if proper materials are submitted (*reimbursement is handled through an invoice submitted to RTOG Administration, ATT: Path Reimbursement*).

10.1.4 Patient consent form should give the Pathology Department authority and responsibility to comply with this request (*pathology blocks belong to the patient from whom tissue has been removed*).

10.1.5 Materials will be sent to:

**LDS Hospital
Dept. of Pathology
E.M. Laboratory
8th Ave & C Street
Salt Lake City, UT 84143
(801) 408-5626
FAX (801) 321-5020
Ldafurne@ihc.com**

10.2 Tissue Preparation

10.2.1 A complete pathologic assessment of the primary cancer will be made to assess depth of invasion, grade, mucin production, and blood vessel (*with special stains wherever possible*), lymphatic or perineural invasion. The deep and lateral margins will be assessed in millimeters and specifically defined as deep, lateral, superior, or inferior margins. Intra-operative frozen section will be used to assess the adequacy of the margin of resection.

10.2.2 The circumferential margins will be inked prior to fixation. The size of the specimen will be measured in length, width and thickness following fixation. The size of the tumor will be measured in length, width and thickness in fixed condition. The pathology report will indicate the absence of microscopic tumor at the proximal, distal, lateral, and deep margins of resection. The central portion of the tumor will be serially sectioned to determine the maximum depth of cancer penetration.

10.2.3 The pathology report will specify the presence or absence of mucin production. A cancer will be scored as mucin positive if 30% or more of cells are producing mucin. The pathology report will specify the presence or absence of signet ring cell morphology and a cancer will be considered a signet ring cell cancer if 90% or more of cells exhibit this morphology. The pathology report will report the presence or absence of colloid cancer morphology.

The pathology report will specify depth of invasion of tumor in a fashion such that it is clear whether the tumor is:

- 1) Confined to the mucosa
- 2) Confined to submucosa
- 3) Confined to muscularis propria
- 4) Transmural into perirectal fat grossly or microscopically

10.2.4 The pathology report will specify histologic grade as follows:

- a. Well differentiated, 70-100% of tumor forming glands
- b. Moderately differentiated, 25-75% of tumor forming glands
- c. Poorly differentiated or undifferentiated, less than 25% of tumor forming glands or tumors which contain foci which are undifferentiated or anaplastic, even if the majority of tumor forms recognizable glands.
- d. The pathology report will comment on the presence or absence of endothelial lined space invasion with cancer and the presence or absence of perineural and/or lymphatic invasion. An endothelial lined space containing both cancer and mature blood cells will be reported as blood vessel invasion.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (6/20/01) (3-13-02)

MONTHS POST SURGERY

Assessment	Study Entry^c	Pre Surg	3	6	9	12	18	24	30	36	42	48	54	60
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CEA, CBC, Platelets, Diff ^a	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ALK PHOS, LDH, SGOT, Bilirubin, Creatinine	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CT Scan (<i>abd/pelvis</i>) to include liver	X	X	As indicated											
MRI pelvis	X ^b		As indicated											
TRUS	X		As indicated											
CXR	X		X		X	X	X	X	X	X	X	X	X	
Sigmoidoscopy	X		X ^d	X	X	X	X	X	X	X	X	X	X	X
Colonoscopy	X		As indicated											

- a. CBC and platelets will be done weekly during RT.
- b. For corroboration of TNM staging (*optional*)
- c. Labs within four weeks prior to study entry; scans within eight weeks prior to study entry.
- d. Recommended for follow-ups, not required.

11.2 Documentation of Tumor Response

Tumor response to high-dose preoperative radiation will be evaluated following surgical resection and pathological assessment of the specimen and categorized according to the following criteria:

11.2.1 Complete response: No evidence of residual cancer.

11.2.2 Partial response: > 50% regression of tumor.

11.2.3 No response: No change in size.

11.2.4 Progression: Increase in size.

11.3 Documentation and Diagnosis of Tumor Relapse

11.3.1 The following terminology will be used to document evidence of locally recurrent or metastatic disease:

11.3.1.1 Local Failure: recurrence or persistence of disease within radiation portals.

11.3.1.2 Regional Failure: failure outside of treatment field on basis of direct and/or lymphatic spread to include aortic nodes.

11.3.1.3 Distant Failure: includes both peritoneal seeding (*PS*) and distant metastasis (*DM*) on hematologic basis.

11.3.1.4 Disease Relapse: will be documented by biopsy whenever possible, together with clinical or radiographic evidence.

11.3.1.5 Progression: defined as one of the following:

- a. Evidence of new areas of malignant disease (*palpable or measurable*).
- b. Liver metastasis diagnosed by clinically significant hepatomegaly and/or positive liver scan.
- c. Other evidence of progression, e.g., jaundice, ascites, pleural effusion- Class V, persistent sacral pain with or without x-ray verification of bone destruction, neurologic changes consistent with metastatic disease with positive brain or CT scan.

11.3.2 At the time of disease progression while undergoing treatment, the patient will be taken off protocol treatment; however, follow-up for evaluation will continue until death. The patient can be treated at the discretion of their physician. (2/25/03)

11.4 Assessments

11.4.1 Complications of treatment will be recorded as to site and severity.

11.4.2 The major complaint is most likely to be GI related, and documentation of this will be extremely important to help evaluate treatment complications. Treatment will be conservative whenever possible, with surgical intervention called upon only when conservative methods fail.

11.4.3 Patients who have evidence of locoregional failure either by scans or clinical examination will undergo exploratory laparotomy and radical resection if possible. The radical resection will be appropriate for the site of recurrence.

Patients will receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. Treatment with chemotherapeutic agents or radiation can be administered as necessary for recurrent or metastatic disease.

11.4.4 Associated medical disease will be evaluated and treated as per accepted practice.

12.0 DATA COLLECTION

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

12.1 Summary of Data Submission

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 2 weeks of study entry
Initial Evaluation Form (I1)	
Pathology Report (P1)	
Pathology Slides/Block (P2)	
<u>Preliminary Dosimetry Information:</u>	Within 1 week of start of RT
RT Prescription (<i>Protocol Treatment Form</i>) (T2)	
Films (<i>simulation and portal</i>) (T3)	
Calculation Form (T4)	
<u>Final Dosimetry Information:</u>	Within 1 week of RT end
Daily Treatment Record (T5)	
Isodose Distribution (T6)	
Boost Films (<i>simulation and portal</i>) (T8)	
Treatment Summary Form (TF)	At end of chemoradiation
Surgery Form (S1)	Within 2 weeks of surgery
Operative Notes (S2)	
Surgical Pathology (S5)	
Follow-up Form (F1)	Every 3 months for 2 years; q 6 months x 3 years, then annually. Also at progression/relapse and at death.
Long Term Follow-up Form (FF)	Yearly after 5 years in place of the F1 form, as applicable. See FF Form for instructions.
Autopsy Report (D3)	As applicable

13.0 STATISTICAL CONSIDERATIONS

13.1 Endpoints

13.1.1 Pathologic Complete Response (*Primary outcome*)

13.1.2 Toxicity

13.1.3 Complete Resection Rate

13.1.4 Patterns of Failure

13.1.5 Survival

13.2 Sample Size

The sample size consideration is based on the pathological complete response (*pCR*). A disease progression or death before surgery will be considered as a less than pCR (*even without surgical specimen*), and will be included in the denominator where the path CR rate is calculated. A search of available literature shows that the pCR rate in this disease has been reported in the 10-20% range overall. An experimental arm that results in a pCR rate of less than 20% would not merit further study. Patients will be randomized to one of two experimental arms. We are targeting 45 patients for each of the two arms. Confidence intervals corresponding to various potential pCR rates are listed in Table 1. With type I error of 0.05 (*one sided*) and statistical power of more than 90%, this sample size is will be able to detect a minimum of 20% increase in pCR compared with historical pCR (*which can be as high as 20%*). Adjusting the sample size by 10% guarding against ineligible cases, we will need to randomize 50 patients per each arm. **Thus the targeted study size will be 100.**

Table 1: 95% confidence interval of pCR rate of 45 patients.*

# of pCRs	5	7	9	11	13
CR rate (%)	11.1	15.6	20.0	24.4	28.9
95% C.I.* (%)	(3.7, 24.1)	(6.5, 29.5)	(9.6, 34.6)	(12.9, 39.5)	(16.4, 44.3)
# of pCRs	15	17	19	21	23
CR rate (%)	33.3	37.8	42.2	46.7	51.1
95% C.I.* (%)	(20.0, 49.0)	(23.8, 46.3)	(27.7, 57.9)	(31.7, 62.1)	(35.8, 66.3)

* Exact method is used.²⁶

The Fleming design will be used to identify early if either or both arms have unacceptably lower response rate.²³ If both arms yield an estimated pCR > 20%, we will use statistical selection theory to choose the arm for further testing in the follow-up phase III trial.²⁴ Briefly, its criterion is to select the treatment arm with highest response regardless how small or “nonsignificant” its advantage over the other treatment is. With 45 patients in each arm, we have greater than a 90% probability of correctly selecting the better treatment when there is an absolute difference of 15% in response rates between the two experimental arms.²⁵

13.3 Drug Modifications for Unacceptable Toxicity

Because of limited phase I testing with both treatment plans, they will separately be monitored for excessive toxicity using the method of Fleming.²³ The toxicities, that will be monitored, are grade 3 and 4 and are anticipated to occur during treatment.

The frequency of grade 3 or 4 toxicities would be acceptable if it is no more than 10%. Modifications to either treatment plan will be considered if its frequency is more than 30%. If there five or more patients with grade 3 or 4 toxicities among the first 15 patients in a treatment arm, or if there are seven or more such cases among the first 30 patients entered, the treatment plan may be modified for the remaining patients to be entered. The modification will be only made after a conference call or meeting of the GI Steering Committee and the study chairs.

If there is any fatal treatment related toxicity on a treatment arm, it will be immediately reviewed by the study chairs and followed by a conference call with the GI Steering Committee to determine if a dose modification is warranted. If there are two such fatal treatment toxicities on a treatment arm, accrual will be immediately suspended pending such review.

13.4 Accrual for the Study

Based upon wider use of pre-operative radiation therapy for rectal cancer and the results of the RTOG institutional survey, we estimate a monthly accrual for this study of five patients and anticipate that the accrual can be achieved in 18 months allowing two months for institutional IRB approvals. If the monthly accrual rate is less than 2.5 cases a month after the first year, the study will be re-evaluated.

13.5 Randomization Plan

Patients will be stratified before randomization with respect to tumor clinical stage (*T3 vs. T4*). The treatment allocation scheme described by Zelen will be used because it balances patient factors other than institution.²⁷

13.6 Analyses Plan

13.6.1 Early Termination of Treatment Arms

There will be two interim looks at the data. The first will come after the first 15 patients have been entered onto an arm. If at that time only 1 patient has experienced a path CR, we will accept the null hypothesis and the arm will be dropped from further randomization. The second look will come after a total of 30 patients have been entered onto a treatment arm. We will accept the null hypothesis if there are 7 or fewer pCRs at that time.²³ Alternately, the boundary for stopping an arm and rejecting the null hypothesis will be reached if there are 8 pCRs among the first 15 patients or 11 among the first 30 patients. If this boundary is crossed, the results will be forwarded to the GI Committee, which will determine whether the arm should be closed and considered in a future phase III study.

13.6.2 Interim Analysis

Interim reports with statistical analyses are prepared every six months until the initial manuscript reporting the treatment results has been submitted. In general, the interim reports will contain information about:

- a. The patient accrual rate with a projected completion date for the accrual phase;
- b. The compliance rate of treatment delivery with respect to protocol prescription;
- c. The quality of submitted data with respect to timeliness and completeness, and accuracy;
- d. The frequency and severity of toxicities;

Through examining the above items, the study chairs and the statistician can identify problems with the execution of the study. These problems will be reported to the RTOG GI committee responsible for the study and, if necessary, to the RTOG Research Strategy Committee, so that corrective action can be taken.

13.6.3 Analysis for Reporting the Initial Treatment Results (2/25/03)

To preserve the overall 0.05 type I error adjusting for the two early looks, we will reject the null hypothesis of 20% path CR rate for any given treatment arm if there are at least 14 pCRs achieved. The initial analysis of treatment results will be performed after all patients have been followed at least 3 months post surgery. All eligible patients (*as per Section 3.0*) that begin protocol treatment will be included in the analysis. It should be noted that patients who had disease progression or died before surgery will be considered as a less than pCR (*even without surgical specimen*) and will be included in the denominator when the pCR rate is calculated. The usual components of this analysis are:

- a. Tabulation of all cases entered, and any excluded from the analysis along with reasons for the exclusion;
- b. Institutional accrual;
- c. Distribution of important prognostic baseline variables;
- d. Distribution of treatment related toxicities;
- e. Observed results with respect to the endpoints described above. The 95% confidence interval for the treatment's pCR rate will be estimated.
- f. Selection of the treatment arm with higher pCR rate if both are greater than 20%. If the difference between the two arms is less than 10%, toxicity differences will be considered in finalizing the treatment selection.

13.6.4 Analysis for Reporting the Long Term Treatment Results (2/25/03)

The second analysis of treatment results will be performed after all patients have been followed at least 3 years. All eligible patients (*as per Section 3.0*) that begin protocol treatment will be included in the analysis. It should be noted that patients who had disease progression or died before surgery will be included in the analysis. The focus of this analysis will be on disease recurrence patterns. It will include items a-d from Section 13.6.3.

13.7 Inclusion of Women and Minorities

We would anticipate a similar distribution of race and gender in this study as was seen in INT 0144/RTOG 94-03. In that study, 36% of the patients were women and 15% were non-white. The projected race/gender distribution for this study is shown in Table 2.

Table 2: Projected distribution of race and gender

	American Indian or Alaskan Native	Asian	Black or African American	Hispanic Or Latino	Native Hawaiian or Pacific Islander	White	Other Or Unknown	Total
Female	0	1	4	1	0	30	1	37
Male	0	3	3	3	1	52	1	63
Total	0	4	7	4	1	82	2	100

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APPENDIX I (6/20/01)

RTOG R-0012

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE

Randomized Phase II Trial of Preoperative Combined Modality Chemoradiation for Distal Rectal Cancer

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. You are being asked to take part in this study because you have cancer of the rectum.

Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, *Taking Part in Clinical Trials: What Cancer Patients Need To Know*, is available from your doctor.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to examine two different ways to give chemotherapy and radiation therapy to patients before they undergo surgery. We want to find out what effects (good and bad) each of these treatment schedules has on rectal cancer.

This research is being done because although surgery is the standard treatment for advanced rectal cancer, there is a high rate of recurrence. We want to find out if radiation and chemotherapy given prior to surgery will help control this disease. Having chemotherapy and radiotherapy before surgery may also reduce the tumor size so that less extensive surgery may be necessary.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

Nationally, about 100 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

You will be “randomized” into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. Which group you are put in is done by a computer. Neither you nor the researcher will choose what group you will be in. You will have an equal chance of being placed in one of the following two groups.

Arm 1: Radiation Therapy: Twice a day (*6 hours apart*), five days per week for five weeks.

	Chemotherapy:	Beginning on the first day of radiation therapy, 5-FU delivered continuously by an intravenous pump until the end of radiation therapy. The pump will be portable allowing you to get around.
	Surgery:	Removal of tumor four to ten weeks after radiation ends.
Arm 2:	Radiation Therapy:	Once a day, five days per week for six weeks.
will	Chemotherapy:	Beginning on the first day of radiation therapy, 5-FU delivered continuously (<i>5 days a week</i>) by an intravenous pump until the end of radiation therapy. The pump be portable allowing you to get around.
		Irinotecan (<i>CPT-11</i>) will be given intravenously over 60 minutes once a week for 4 weeks just prior to your radiation therapy treatment.
	Surgery:	Removal of tumor four to ten weeks after radiation ends.

If you take part in this study, you will have the following tests and procedures:

- Procedures that are part of regular cancer care and may be done even if you do not join the study:
 - Physical Exam
 - Blood Counts and Chemistries
 - Chest X-ray
 - Endoscopy & Biopsy
 - Endorectal Ultrasound
 - MRI of Pelvis
 - CT of abdomen and pelvis including the liver
 - Sigmoidoscopy/Colonoscopy
- Procedures being done because you are in this study:
 - Tumor specimens will be sent to a central repository for future analysis if you agree to participate in the tissue component of the study. **(3/13/02)**

HOW LONG WILL I BE IN THE STUDY?

You will receive radiation therapy and chemotherapy for five to six weeks and six to eight weeks later you will undergo surgery. After your surgery you will be seen by your doctor once every three months for two years, then every six months for three years and after that once a year for the rest of your life.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

If you do not complete the prescribed treatment you will still have regular checkups with your doctor for the rest of your life unless you choose to remove yourself from the study. You will have these checkups once every three months for two years, then once every six months for three years and then once a year after that.

The researcher may decide to take you off this study if your disease gets worse despite the treatment, the side effects of the treatment are too dangerous for you, or new information about the treatment becomes available and this information suggests the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be stopped early due to lack of funding or participation.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the radiation therapy and chemotherapy are stopped, but in some cases side effects can be serious or long-lasting or permanent.

Risks Associated with Radiation Therapy

Very Likely

Skin irritation
Diarrhea
Tiredness
Nausea
Temporary loss of pubic hair
For Women: Sterility in pre-menopausal women. Hormones may be given orally to replace hormones normally produced by the ovaries

Less Likely, But Serious

Intestinal obstruction and/or intestinal bleeding which may require surgery
For Men: Permanent sterility

Risks Associated with 5-FU Chemotherapy

Very Likely

Lower blood counts, which can lead to risk of infection and bleeding
Headaches
Loss of appetite
Mouth sores
Sore throat
Nausea and/or vomiting
Diarrhea with cramping or bleeding
Weakness/fatigue
Skin rash
Loss of hair, which is temporary

Less Likely

Confusion
Inflammation of fingers and toes
Increased sensitivity to light
Darkening of skin, nails, or veins
Loss of coordination or balance

Less Likely, But Serious

Chest pain that may indicate heart damage
Infection at the catheter entry site

Risks Associated with Irinotecan (CPT-11) Chemotherapy

Very Likely

Nausea and/or vomiting
Weakness/fatigue
Loss of appetite
Urinary problems
Weakness
Diarrhea
Skin irritations
Lower blood counts
Loss of hair

Less Likely, But Serious

Lung toxicity

Other risks: In studies where radiotherapy was given before surgery, there was evidence of a somewhat higher risk of developing skin infections in the area of radiation. This risk was low overall and, generally, these infections resolved with local care and antibiotics. However, should you develop this type of infection, it may prolong your hospital stay for a few days. . Allergic reactions have been reported in less than one percent of patients.

Reproductive risks: Because the radiation and drugs in this study will affect an unborn baby, you should not become pregnant or father a baby while on this study. You should not nurse your baby while on this study. Ask about counseling and more information about preventing pregnancy

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with rectal cancer in the future.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) radiation therapy; (2) chemotherapy; (3) surgery; or (4) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread. These treatments could be given either alone or in combination with each other.

Another option may be to get the treatment plan described in this study at this center or another center even if you do not take part in the study.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (*RTOG*). Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (*FDA*), the National Cancer Institute (*NCI*), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

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

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A Data Safety and Monitoring Board, an independent group of experts, may be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

For information about your disease and research-related injury, you may contact:

Name

Telephone Number

For information about this study, you may contact:

Name

Telephone Number

For information about your rights as a research subject, you may contact:

(OPRR suggests that this person not be the investigator or anyone else directly involved with the research)

Name

Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI’s Cancer Information Service at
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

Visit the NCI’s Web sites for comprehensive clinical trials comprehensive clinical trials information <http://cancertrials.nci.nih.gov> or for accurate cancer information including PDQ <http://cancernet.nci.nih.gov>.

SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (*full study plan*).

Patient Signature (*or legal Representative*)

Date

TISSUE AND BLOOD TESTING (RTOG R-0012)

I agree to the use of my tissues/other samples for research studies related to my cancer.

Yes No

Patient Signature (*or legal Representative*)

Date

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

ZUBROD PERFORMANCE SCALE

0	Fully active, able to carry on all predisease activities without restriction (<i>Karnofsky 90-100</i>).
1	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 (<i>Karnofsky 70-80</i>).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (<i>Karnofsky 50-60</i>).
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (<i>Karnofsky 30-40</i>).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (<i>Karnofsky 10-20</i>).

APPENDIX III

AJCC Staging Colon and Rectum, 5th Edition

DEFINITION OF TNM

The same classification is used for both clinical and pathologic staging.

Primary Tumor (*T*)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma <i>in situ</i> : intraepithelial or invasion of lamina propria*
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into the subserosa, or into nonperitonealized pericolic or perirectal tissues
T4	Tumor directly invades other organs or structures, and/or perforates visceral peritoneum**

* *Note:* Tis includes cancer cells confined within the glandular basement membrane (*intraepithelial*) or lamina propria (*intramucosal*) with no extension through the muscularis mucosae into the submucosa.

** *Note:* Direct invasion in T4 includes invasion of other segments of the colorectum by way of the serosa; for example, invasion of the sigmoid colon by a carcinoma of the cecum.

Regional Lymph Nodes (*N*)

NX	Regional lymph nodes cannot be assessed
NO	No regional lymph node metastasis
N1	Metastasis in 1 to 3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes

Distant Metastasis (*M*)

MX	Distant metastasis cannot be assessed
MO	No distant metastasis
M1	Distant metastasis

STAGE GROUPING

AJCC/UICC				Dukes	
Stage 0	Tis	N0	M0	-	Dukes B is a composite of better (<i>T3 N0 M0</i>) and worse (<i>T4 N0 M0</i>) prognostic groups, as is Dukes C (<i>Any TN1 M0</i> and <i>Any TN2 M0</i>).
Stage 1	T1	N0	M0	A	
	T2	N0	M0	-	
Stage II	T3	N0	M0	B	
	T4	N0	M0	-	
Stage III	Any T	N1	M0	C	
	Any T	N2	M0	-	
Stage IV	Any T	Any N	M1	-	

APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

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

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
 - a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.
2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.
3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).
4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.
5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

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

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.
7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.
8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
2. All life-threatening (grade 4) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS DRUG AND BIOLOGICS

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

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

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

Commercial and Non-Investigational Agents

- i. Any fatal (*grade 5*) or life threatening (*grade 4*) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.
- ii. Unknown adverse reactions (\geq *grade 2*) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.
- iii. All neurotoxicities (\geq *grade 3*) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.
- iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

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

Investigational Agents

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

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

i. Phase I Studies Utilizing Investigational Agents

- | | |
|--|--|
| - All deaths during therapy with the agent. | Report by phone within 24 hours to IDB and RTOG Headquarters.
**A written report to follow within 10 working days. |
| - All deaths within 30 days of termination of the agent. | As above |

- All life threatening (*grade 4*) events which may be due to agent. As above
 - First occurrence of any toxicity (*regardless of grade*). Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters. ****A written report may be required.**
- ii. *Phase II, III Studies Utilizing Investigational Agents*
- All fatal (*grade 5*) and life threatening (*grade 4*) known adverse reactions due to investigational agent. Report **by phone** to RTOG Headquarters and the Study Chairman within 24 hours ****A written report must be sent to RTOG within 10 working days with a copy to IDB. (*Grade 4 myelosuppression not reported to IDB*)**
 - All fatal (*grade 5*) and life threatening (*grade 4*) unknown adverse reactions resulting from or suspected to be related to investigational agent. Report **by phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**. ****A written report to follow within 10 working days.**
 - All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent. ****Report in writing** to RTOG Headquarters and IDB within 10 working days.

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

APPENDIX VI (3-13-02)

DRUG SUPPLY PROCEDURE FOR CAMPTOSAR® AND LOPERAMIDE

Initial Drug Shipment:

<i>Site study coordinator</i>	<ul style="list-style-type: none"> • Sends originals of the trial site regulatory documents to the Radiation Therapy Oncology Group (RTOG) Registration/Randomization Department
<i>RTOG Registration/Randomization Department</i>	<ul style="list-style-type: none"> • Informs the Therapeutic Area Manager at Pharmacia Canada Inc. of local trial site activation by faxing (FAX number: 905 890-8522) the following documentation: <ul style="list-style-type: none"> Ethics Committee approval letter Ethics Committee approved Informed Consent Site Information Sheet HPFB Clinical Trial Site Information Form
<i>Pharmacia Canada Inc. Therapeutic Area Manager or designee, Medical Marketing/Clinical Research (MMCR)</i>	<ul style="list-style-type: none"> • Completes the request for initial trial drug shipment (Camptosar® and Loperamide). Forwards the request for initial trial drug shipment to the Clinical Trial Supplies Manager.
<i>Pharmacia Canada Inc. Clinical Trials Supplies Manager</i>	<ul style="list-style-type: none"> • Requests the Clinical Research Coordinator, MMCR, to notify the trial site of the shipment. • Ships the following supplies to the trial site pharmacist. The initial shipment will supply enough study drug for 4 weeks of treatment for 3 patients entered in Study Arm 2: <ol style="list-style-type: none"> 1. 25 vials of Camptosar® (Irinotecan; 100 mg per vial; 20mg/ml) 2. 15 blister packs of Loperamide (Imodium®; 2 mg caplets in packs of 12 per blister pack)
<i>Pharmacia Canada Inc. Clinical Research Coordinator, MMCR</i>	<ul style="list-style-type: none"> • Notifies the study site pharmacist and coordinator of the shipment by fax. • Sends the following documents by courier to the study site pharmacist: <ol style="list-style-type: none"> 1. Investigational Medication Distribution Forms (drug accountability log) 2. Additional trial drug request forms 3. Product monographs: Camptosar®
<i>Trial site pharmacist</i>	<ul style="list-style-type: none"> • Confirms receipt of the trial drugs by signing and dating the Drug Shipment Invoice that accompanies the trial drug supplies. • Sends a signed/dated copy of the Drug Shipment Invoice to the Clinical Trial Supplies Manager, Pharmacia Canada Inc. @ FAX number (905) 755-3151.

Requests for trial drug resupply:

<i>Trial site pharmacist</i>	<ul style="list-style-type: none"> • Manages trial drug inventory ensuring sufficient supplies are maintained for 4 weeks of treatment for 3 patients • Completes the request for trial drug shipment on an “as needed” basis, depending upon patient accrual. • Sends the request for trial drug shipment to the Pharmacia Canada Inc. Clinical Trial Supplies Manager @ FAX number (905) 755-3151 .
<i>Pharmacia Canada Inc. Clinical Trial Supplies Manager</i>	<ul style="list-style-type: none"> • Forwards the request to the Therapeutic Area Manager, MMCR.
<i>Pharmacia Canada Inc. Therapeutic Area Manager, MMCR</i>	<ul style="list-style-type: none"> • Approves and signs the request for trial drug shipment. • Forwards the request for trial drug shipment to the Clinical Trial Supplies Manager.
<i>Pharmacia Canada Inc. Clinical Trial Supplies Manager</i>	<ul style="list-style-type: none"> • Ships drug supplies to the trial site. • Requests the Clinical Research Coordinator, MMCR to notify the trial site of the shipment.
<i>Pharmacia Canada, Clinical Research Co-ordinator, MMCR</i>	<ul style="list-style-type: none"> • Notifies the trial pharmacist and site study coordinator of the shipment by fax.
<i>Trial site pharmacist</i>	<ul style="list-style-type: none"> • Confirms receipt of the trial drugs by signing and dating the Drug Shipment Invoice that accompanies the trial drug supplies. • Sends a signed/dated copy of the Drug Shipment Invoice to the Clinical Trial Supplies Manager, Pharmacia Canada @ FAX number (905) 755-3151.

Return of trial drug supplies:

<i>Pharmacia Canada Inc. Clinical Research Co-ordinator, MMCR</i>	<ul style="list-style-type: none"> • Forwards the “Return of Clinical Supplies” form to the trial site. • Sends written instruction to the trial site regarding shipment of returned goods to Pharmacia Canada offices for destruction.
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APPENDIX VII (3-13-02)

RTOG R-0012/ CPTAIV-0020-359

SITE INFORMATION SHEET

To facilitate the timely receipt of drug shipments, supplies and correspondence, we ask that you complete and promptly return this form to RTOG by faxing 215-574-0300. Your careful attention to the accuracy of this form will ensure the correct delivery of all items associated with this clinical trial.

INVESTIGATOR:	
INSTITUTION/ORGANIZATION:	
ADDRESS:	
CITY/PROVINCE:	
POSTAL CODE:	
PHONE NUMBER:	FAX NUMBER:
<u>SUB-INVESTIGATOR(S):</u>	
<u>ADDRESS (if different form Investigator):</u>	
PHONE NUMBER:	FAX NUMBER:
<u>SUB-INVESTIGATOR(S):</u>	
<u>ADDRESS (if different form Investigator):</u>	
PHONE NUMBER:	FAX NUMBER:

<u>PHARMACIST:</u>	
<u>ADDRESS (if different form Investigator):</u>	
PHONE NUMBER:	FAX NUMBER:
<u>STUDY COORDINATOR:</u>	
<u>ADDRESS (if different form Investigator):</u>	
PHONE NUMBER:	FAX NUMBER:
INSTITUTIONAL REVIEW BOARD	
NAME:	
ADDRESS (IF DIFFERENT FORM INVESTIGATOR):	