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INT 0147
RADIATION THERAPY ONCOLOGY GROUP
RTOG 94-01
CALGB 9483
ECOG R9401

**PHASE III INTERGROUP RANDOMIZED TRIAL OF PRE-OPERATIVE VS. POST-OPERATIVE COMBINED
MODALITY THERAPY FOR RESECTABLE RECTAL CANCER**

SCHEMA

- STRATIFY:** **Clinical Node Status** (*based on radiographic criteria*)
1. Negative (< 1.5 cm)
 2. Positive ([≥] 1.5 cm)

<u>RANDOMIZE</u>	
<p><u>Arm 1</u> Pre-Operative Therapy</p> <p style="padding-left: 20px;"><i><u>Pre-Operative Segment</u></i></p> <p>5-FU: 325 mg/m²/d days 1-5, 29-33</p> <p>LV: 20 mg/m²/d days 1-5, 29-33</p> <p>RT: 45 Gy whole pelvis followed by 5.4 Gy cone down at 1.8 Gy/d days 1-38 to a total dose of 50.4 Gy.</p> <p style="padding-left: 20px;"><i><u>Surgery</u></i></p> <p>4-6 weeks following the completion of RT</p> <p style="padding-left: 20px;"><i><u>Post-Operative Segment</u></i></p> <p>Begins 4-6 weeks following surgery</p> <p>5-FU: 425 mg/m²/d days 1-5, 29-33</p> <p> 380 mg/m²/d days 57-61 and 85-89</p> <p>LV: 20 mg/m²/d days 1-5, 29-33, 57-61, 85-89</p>	<p><u>Arm 2</u> Post Operative Therapy*</p> <p style="padding-left: 20px;"><i>(Begins 4-6 weeks following surgery)</i></p> <p style="padding-left: 20px;"><i><u>Pre-RT Segment</u></i></p> <p>5-FU: 425 mg/m²/d days 1-5, 29-33</p> <p>LV: 20 mg/m² /d days 1-5, 29-33</p> <p style="padding-left: 20px;"><i><u>Concurrent RT/Chemotherapy Segment</u></i></p> <p>5-FU: 400 mg/m²/d days 57-60, 85-88</p> <p>LV: 20 mg/m²/d days 57-60, 85-88</p> <p>RT: 45 Gy whole pelvis followed by 5.4 Gy cone down at 1.8 Gy/d days 57-95 to a total dose of 50.4 Gy</p> <p style="padding-left: 20px;"><i><u>Post-RT Segment</u></i></p> <p>Begins 28 days following completion of RT</p> <p>5-FU: 380 mg/m²/d days 1-5, 29-33</p> <p>LV: 20 mg/m²/d days 1-5, 29-33</p> <p>* Patients with pathologic T1-2, N0M0 disease will not receive postop therapy but will be followed per Section 11.5</p>

Eligibility: (*See Section 3.0 for details*)

- Histologically confirmed primary adenocarcinoma of the rectum
- The tumor must be at or below the peritoneal reflection
- Distal border of the tumor must be within 12 cm of the anal verge by proctoscopic exam
- Clinically resectable based on the routine examination
- Transmural penetration beyond the muscularis propria which must be confirmed by any two of the following tests: pelvic CT scan, pelvic MRI scan, transrectal ultrasound or physical exam
- Clinical estimate of the type of surgery needed (*APR, LAR, or LAR/coloanal anastomosis*)
- KPS ≥ 60
- WBC ≥ 4,000 cells/μl, platelets ≥ 150,000 cells/μl
- Age ≥ 18
- Non-pregnant, non-lactating
- Absence of high grade obstruction (*£1 cm lumen*)
- No prior chemotherapy, immunotherapy, or radiation therapy to the pelvis
- No evidence of metastatic (*M1*) disease
- Signed study-specific informed consent
- Treatment must start within 2 weeks after randomization

Required Sample Size: 770

RTOG Institution # _____

INT 0147

RTOG 94-01/ CALGB 9483/ECOG R9401

(circle one)

ELIGIBILITY CHECK

RTOG Case # _____

(page 1 of 2)

Other Sequence # _____

- _____(Y) 1. Histologically confirmed adenocarcinoma of the rectum?
- _____(Y) 2. Is the distal border of the tumor within 12 cm of the anal verge based on proctoscopic exam?
- _____(Y) 3. Is the tumor determined to be clinically resectable (*tumor mobile*) by the surgeon?
- _____(Y) 4. Is there transmural penetration beyond the muscularis propria based on two of the following tests: pelvic CT scan, pelvic MRI scan, transrectal ultrasound, or physical exam?
- _____(Y) 5. Is there an absence of high grade obstruction?
- _____(N) 6. Does the patient have any active inflammatory bowel disease?
- _____(N) 7. Is there any evidence of metastatic disease?
- _____(Y) 8. Is the Karnofsky performance status ≥ 60 ?
- _____(Y) 9. Is the patient ≥ 18 years of age?
- _____(Y/N) 10. Is the patient female?
_____(N) If yes, is the patient pregnant or lactating?
- _____(Y) 11. Is the WBC ≥ 4000 cells/ μ l?
- _____(Y) 12. Are the platelets $\geq 150,000$ cells/ μ l?
- _____(N) 13. Has the patient had any previous chemotherapy, immunotherapy, or radiation therapy to the pelvis?
- _____(Y/N) 14. Has the patient had a previous or concurrent malignancy except non-invasive cervical carcinoma or skin cancer (*excluding melanoma*)?(*If no, skip to Q16*)
_____(Y) If yes, has the patient been disease free for ≥ 5 years from the previous malignancy?
- _____(N) 15. Did the patient have multiple primary cancers involving both the colon and rectum that would preclude a patient from being classified as having only rectal cancer?
- _____(Y) 16. Will the patient be treated with a linear accelerator with energy ≥ 4 MV and which has a simulator capable of reproducing the treatment field geometry?

RTOG Institution # _____

INT 0147

RTOG Case # _____

(page 2 of 2)

Other Sequence # _____

_____(Y) 17. Will treatment start within 2 weeks?

_____(N) 18. Are there any serious medical illnesses or a psychiatric condition that would limit the ability of the patient to receive protocol therapy?

_____(Y) 19. Has the patient signed a study-specific informed consent form?

Patient's Name

Verifying Physician

Patient ID #

Referring Institution

Node status (*Radiographic*)

(negative [< 1.5 cm] vs. positive [≥ 1.5 cm])

Type of Surgery Planned

(AP resection vs. low anterior resection vs. low anterior resection/coloanal anastomosis)

Medical Oncologist

Birthdate

Sex

Race

Social Security Number

Zip Code

Method of Payment

Treatment Start Date *(within 2 weeks of randomization)*

Treatment Assignment *(Baseline QOL forms must be done pre RX)*

Completed by _____

Date _____

1.0 INTRODUCTION

1.1 Post-Operative Combined Modality Therapy

- 1.1.1** Most patients with transmural (*T3*) and/or node positive (*N1-2*) resectable rectal cancer receive adjuvant post-operative combined modality therapy. There are two major randomized trials of post-operative combined modality therapy vs. surgery alone. The GITSG randomized 202 patients to post-operative radiation therapy, 5-FU/MeCCNU, radiation + 5-FU/MeCCNU, or surgery alone.^{1,2} There was a significant increase in survival in those patients who received combined modality therapy compared with the surgery control arm (54% vs. 27%, $p=0.005$). There was no significant difference in survival in the radiation only or chemotherapy only arms compared with the surgery control arm.
- 1.1.2** In the Mayo/NCCTG #79-47-51 trial, 204 patients were randomized to either post-operative radiation therapy or post-operative radiation therapy + 5-FU/MeCCNU.³ There was no surgery only control arm. Patients who received combined modality therapy had a significant decrease in local failure (14% vs. 25%, $p=0.036$), distant failure (29% vs. 46%, $p=0.011$) and an increase in 5-year disease free survival (63% vs. 42%, $p=0.0016$) and overall survival (57% vs. 48%, $p=0.025$) compared with the radiation control arm.
- 1.1.3** In NSABP RO-1 trial, 528 patients were randomized to post-operative MOF chemotherapy, radiation therapy, or surgery alone.⁴ There was no combined modality therapy arm.
- 1.1.4** The Mayo Clinic/NCCTG 4 arm post-operative combined modality therapy trial #86-47-51 did not have a surgical control arm however did examine the value of MeCCNU as well as continuous infusion 5-FU. All patients received radiation therapy and were randomized to receive concurrent bolus 5-FU ± MeCCNU vs. continuous infusion 5-FU ± MeCCNU. The interim analysis suggested that MeCCNU does not add to the beneficial effects of 5-FU and radiation.⁵ Compared with bolus 5-FU, patients who received continuous infusion 5-FU had an improvement in 3-year relapse free survival (67% vs. 56%, $p=0.01$) and survival (76% vs. 68%, $p=0.02$). There was little difference in local failure (8% vs. 11%).⁵
- 1.1.5** The Intergroup adjuvant trial INT #0114 was a 4-arm trial in which all patients receive six cycles of post-operative chemotherapy and concurrent radiation therapy during cycles 3 and 4. The goal of this trial was to determine if combinations of 5-FU based chemotherapy (5-FU/low dose leucovorin (LV) vs. 5-FU/Levamisole vs. 5-FU/LV/Levamisole) were superior to 5-FU. The results are pending.
- 1.1.6** Despite the survival advantage of combined post-operative combined modality therapy, it is associated with substantial grade 3+ toxicity. For example, the incidence of grade 3+ toxicity in patients who received combined radiation plus chemotherapy in the GITSG trial was 26% hematological and 35% non-hematological.^{1,2} In the Mayo Clinic/NCCTG trial, the most significant grade 3+ toxicities included diarrhea (41%) and leukopenia (33%).³ The only grade 3+ toxicity in patients receiving radiation alone was diarrhea (5%). In both the GITSG and Mayo Clinic/NCCTG trials, 35% of the patients never finished all the planned cycles of chemotherapy due to toxicity. Furthermore, in the Mayo/NCCTG trial an additional 15% of patients did not finish due to patient refusal. Another measure of acute toxicity is the number of patients requiring a dose reduction. These data were not reported.

1.2 Pre-Operative Radiation Therapy

- 1.2.1** There are eight modern randomized trials of pre-operative radiation therapy for resectable rectal cancer.⁶⁻¹³ All use low to moderate doses of radiation. Some show a decrease in local failure, and in two of the series (*Stockholm*⁷ and *EORTC*⁶) this difference reached statistical significance. The Stockholm trial⁷ showed a significant advantage in disease-free survival and the EORTC combined radiation/5-FU trial¹¹ revealed a borderline advantage in survival ($p=0.06$). The most impressive improvement in results were reported from San Paulo Catholic University however a statistical analysis was not performed.¹³
- 1.2.2** There are significant flaws in the design of all the randomized trials. First, none use standard radiation doses (³45 Gy). Second, the interval between the completion of radiation and surgery is inadequate. An interval of 4-6 weeks is recommended for maximum tumor downstaging and the recovery of normal tissues. Third, the radiation techniques employed were suboptimal and are known to be associated with an increased incidence of complications. For example, all used AP/PA rather than multiple field

techniques and made no attempt to limit the dose to the small bowel. The superior border in most series was extended to L2 thereby further increasing the volume of small bowel in the radiation field. Furthermore, the fraction sizes were unconventional and were as high as 5.1 Gy/day. These inferior radiation techniques contributed to the significant increase in complications, most notably in the EORTC⁶ and Stockholm⁷ series.

1.3 Pre-vs. Post-Operative Radiation Therapy

1.3.1 The only randomized trial of pre-operative vs. post-operative radiation therapy for resectable rectal cancer was reported by Pahlman and Glimelius.¹⁴ In this multicenter randomized trial from Sweden, 471 patients were randomized to receive either 25.5 Gy pre-operatively (*in one week*) or 60 Gy (*split course*) post-operatively. Post-operative radiation was limited to patients with stages T3 and/or N1-2 disease. Those with stage T₁₋₂N₀ disease who were randomized to the post-operative radiation therapy arm did not receive radiation and were observed. The treatment results¹⁴ as well as the long term toxicity¹⁵ have recently been reported.

1.3.2 Patients who received pre-operative radiation therapy had a significant decrease in local failure (13% vs. 22%, $p=0.02$) however there was no difference in 5-year survival (42% vs. 38%). Although there was no increase in immediate radiation-related complications or post-operative mortality, there was a significant increase of perineal wound sepsis in the pre-operative group (33% vs. 18%, $p < 0.01$). Similar to other randomized trials of pre-operative radiation therapy, the excessively large fraction size (5.1 Gy/day) may have contributed to this complication. Despite the increased incidence of acute toxicity, the long term toxicity was decreased in patients receiving pre-operative radiation therapy. The incidence of small bowel obstruction was 5% in patients receiving pre-operative radiation and 11% in patients receiving post-operative radiation ($p=0.01$). In a historical surgical control group, the incidence was 6%. Likewise, the incidence of total Grade 3+ toxicity (*gastrointestinal, genitourinary, skin, neuro*) was 20% for the pre-operative group and 41% for the post-operative group. The incidence was 23% for the historical surgical control group.

1.4 Pre-Operative Radiation Therapy

1.4.1 The encouraging results seen in patients with resectable rectal cancer who receive adjuvant post-operative combined modality therapy^{1,3,16} has prompted increased interest in pre-operative combined modality therapy. There are a number of potential advantages of pre-operative combined modality therapy.

1.4.2 First, non-randomized data from Memorial Sloan Kettering Cancer Center (*MSKCC*) suggest the patients who receive radiation, 5 FU, and high dose (200 mg/m²) leucovorin are able to tolerate higher chemotherapy doses, experience lower acute toxicity¹⁷ and, in patients with unresectable disease, the addition of chemotherapy to pre-operative radiation therapy increases downstaging and resectability rates.¹⁸ Whether this same benefit is seen in patients receiving the low dose leucovorin regimen remains to be determined.

1.4.3 Second, there is no delay in starting systemic therapy.

1.4.4 Third is sphincter preservation. The experience with sphincter preservation has been limited to patients with resectable rectal cancer who receive pre-operative radiation therapy without chemotherapy.^{19,20} Pre-operative radiation therapy downstages the primary tumor in order to enable the surgeon to change the planned surgical procedure from an abdominoperineal resection (*APR*) to a low anterior resection (*LAR*)/coloanal anastomosis. A total of 22 patients with resectable, primary adenocarcinoma of the rectum enrolled on a phase I/II trial of pre-operative radiation followed by a low anterior resection(*LAR*)/coloanal anastomosis were reported by Minsky et al.²⁰ By pre-operative assessment, all patients had invasive tumors and required an APR.

1.4.5 Of the 21 patients who underwent resection, 10% had no tumor in the surgical specimen and 90% were able to successfully undergo a LAR/coloanal anastomosis. The crude incidence of local failure as a component of failure was 23%. The overall 4-year actuarial survival was 61%. No patients experienced grade 3+ toxicity while receiving radiation therapy, and 6% developed a partial disruption of the anastomosis. Of the 18 patients who underwent a LAR/coloanal anastomosis, 89% had a good or excellent functional result. Similar data were reported by Marks et al.²¹

- 1.4.6 Sphincter preservation has not been an endpoint of the pre-operative combined modality trials. Whether it will offer the same level of both sphincter preservation and function remains to be determined.
- 1.4.7 Finally, a theoretical reason for adding systemic chemotherapy at the time of diagnosis is to deliver therapy when the metastatic burden is the smallest.²²

1.5 Current Experience with Pre-Operative Combined Modality Therapy

- 1.5.1 The successful integration of chemotherapy and radiation therapy requires careful radiation techniques as well as a phase I dose escalation trial to determine the maximum tolerated dose (*MTD*) and the recommended doses of chemotherapy. A number of trials have used pre-operative combined modality therapy in a systematic fashion.²³⁻³³ Most did not use a phase I dose escalation trial to determine the *MTD* of chemotherapy. All have used bolus 5-FU based chemotherapy. The EORTC trial is a phase III trial and the remainder are single arm, non-randomized trials. Few trials have used conventional radiation doses and techniques.
- 1.5.2 The EORTC randomized 247 patients with clinically resectable rectal cancer to pre-operative radiation therapy + 5-FU (*375 mg/m² bolus days 1-4*) versus radiation therapy alone.¹¹ Similar to other European pre-operative randomized trials in resectable rectal cancer, the total dose (*34.5 Gy*), fraction size (*23 Gy/fraction*), field size (*extended to the superior border of L2*), technique (*AP/PA*) and the short radiation-surgery interval (*2 weeks*) were not conventional. There was no difference in local control however patients who received the combined modality therapy had a decrease in liver metastasis (*8% vs. 18%, p=0.07*). Overall, combined modality therapy had a negative impact on survival (*46% vs. 59%, p=0.06*). Since 5-FU was not employed as a systemic therapy with monthly cycles and the radiation techniques were unconventional, it is not surprising that it was a negative study.
- 1.5.3 Three consecutive phase I trials of pre-operative combined modality therapy have been performed at MSKCC. All 3 trials employed 5-FU/LV bolus daily x 5 (*2 cycles*) and radiation therapy (*50.4 Gy*) followed by surgery (*with or without intraoperative brachytherapy*) and post-operative 5-FU/LV bolus daily X 5.
- 1.5.4 The first MSKCC phase I trial was limited to patients with unresectable disease and was based on the experience from Erlichman, et al and used high dose LV (*200 mg/m²*).³⁴ With a median follow-up of 3 years, the local failure rate was 26% and the 3-year actuarial survival was 69%.³⁵ Since optimal doses of 5-FU to treat systemic disease could not be delivered until cycle 3, the high dose LV regimen was discontinued and a new trial using low dose LV (*20 mg/m²*) was developed.
- 1.5.5 The second MSKCC phase I trial was based on the Mayo Clinic/NCCTG experience in patients with metastatic colorectal cancer and used 5-FU and low dose LV (*20 mg/m²*).^{36,37} The identical treatment scheme used in the high dose LV trial was employed however low dose LV rather than high dose LV was used.²⁶ Once again, since optimal doses of 5-FU to treat systemic disease could not be delivered until cycle 3, this regimen was discontinued.
- 1.5.6 A third trial was developed in which the schedule rather than the chemotherapy dose was altered (*concurrent low dose LV*). In this trial, pre-operative radiation therapy, 5-FU and low dose LV was delivered concurrently (*from day 1*) rather than sequentially (*chemotherapy day 1 and radiation day 8*).²⁷ A total of 24 patients were entered. The resectability rate with negative margins in the 23 patients who underwent surgery was 100%. One patient refused surgery. The pathologic complete response rate was 13%. An additional four patients had negative nodes and a microscopic foci of tumor in the bowel wall. Therefore the total clinical complete response rate was 30%. The *MTD* of 5-FU for the pre-operative combined modality segment was 375 mg/m²; therefore, the recommended phase II dose level is 325 mg/m². The incidence of grade 3+ toxicity for the 22 patients treated at the recommended 5-FU dose level (*325 mg/m²*) during the pre-operative combined modality segment was; diarrhea: 14%, hematologic: 9%, and total: 18%.
- 1.5.7 A similar pilot to the MSKCC low dose LV/concurrent radiation therapy trial was reported by the

EORTC.^{33,38} In their trial, the results of 73 patients with resectable, residual, locally recurrent, or fixed rectal cancers were reported. Patients received treatment according to a similar schedule (*bolus daily x 5, days 1 and 29 of radiation therapy*). However, rather than performing a Phase I dose escalation trial, a phase II trial with a dose attenuation was performed. The 5-FU dose started at 425 mg/m² and was attenuated. LV remained constant at 20 mg/m². The recommended dose level of 5-FU was 350 mg/m². At that dose level the incidence of WHO grade 2+ toxicity during the pre-operative combined modality segment was 14%. Therefore, the EORTC and MSKCC low dose LV/concurrent radiation therapy trials recommend similar doses of chemotherapy and report comparable toxicity.

1.5.8 Both the MSKCC low dose LV/concurrent radiation therapy trial and Arm 2 of the prior Intergroup adjuvant post-operative rectal trial (*INT # 0114*) are based on the Mayo Clinic/NCCTG experience with 5-FU and low dose LV in patients with metastatic disease.^{37,39} In Arm 2 of the Intergroup trial, patients received the same doses and schedules of 5-FU and LV as in MSKCC low dose LV/concurrent radiation therapy trial. However, during the combined modality segment, (*cycles 3 & 4 of chemotherapy*), the chemotherapy dose and schedule is attenuated. The LV dose remained at 20 mg/m², however is given for only 4 days rather than 5 days. The 5-FU was decreased to 400 mg/m² x 4 days. With this schedule the total dose per cycle of LV was 80 mg/m² and 5-FU was 1600 mg/m². These doses are very similar with the 100 mg/m² of LV and 1625 mg/m² of 5-FU in the MSKCC low dose LV/concurrent radiation therapy trial.

1.5.9 Given the biological, physical, and functional advantages of pre-operative radiation therapy as well as 1) the clinical evidence of a significant improvement in local control and survival with post-operative combined modality therapy in patients with resectable rectal cancer, 2) the increased resectability and pathologic complete response rate with pre-operative combined modality therapy compared with pre-operative radiation therapy alone in patients with unresectable disease, and 3) the decreased acute toxicity of pre-operative compared with post-operative combined modality therapy, a phase III randomized trial of pre-operative vs. post-operative combined modality therapy for primary resectable rectal cancer will be activated. The MSKCC low dose LV/concurrent radiation therapy trial serves as the pre-operative combined modality therapy arm of this phase III trial. Arm # 2 of the prior Intergroup adjuvant post-operative rectal trial (*INT # 0114*) serves as the post-operative combined modality therapy arm.

1.6 Quality of Life

1.6.1 In view of the toxicities with combined modality therapy, consideration of how various treatments affect quality of life is warranted. Quality of life measurement augments morbidity and mortality evaluations and uniquely contributes to the "cost benefit" ratio involved in assessments of these treatments.⁴⁰ Not only are quality of life endpoints useful in therapy evaluations and treatment comparisons, but also in providing guidance in future clinical decisions.⁴¹

Upon general consensus, health related quality of life is viewed as a multidimensional construct, best assessed prospectively via the patient's perspective. Core quality of life domains within a health-oriented framework include, at the minimum, physical functioning, disease-related and treatment-related symptoms, social functioning, and psychologic functioning.⁴²

There have been few investigations of the quality of life of patients with rectal cancer. Those identified focused primarily upon post-treatment measurement of anorectal function alone.^{20,43,44} Some prior tools addressing functional status applied classifications ranging from "*bad*" to "*excellent*" based upon a combination of functional specifications.⁴⁵ While able to provide a gross description of preservation of sphincter function, specificity and sensitivity of such tools is low. Methods of assessment have varied from clinician ratings of continence, frequency, and evacuation, to investigation of bowel habits, urgency, continence, and socialization aspects through patient questionnaires. The most extensive investigation of quality of life in terms of anorectal function used laboratory, interview, and questionnaire methods.⁴⁶ Only one investigation of rectal cancer patients' quality of life (*consisting of pain, symptoms and adverse treatment effects, troublesome events, and tiredness items*) examined changes over time between treatment groups.⁴⁷

Although disturbance in the pattern of elimination is the most commonly reported complaint, others

include fatigue, discomfort, altered nutritional intake, impaired skin integrity, and sexuality.^{20,48} These disease or treatment-related concerns may impact quality of life in various ways.

None of the reviewed studies reported construct validity or reliability measures of any tools used. Neither was a quality of life measure incorporating the minimally recommended domains used or tool specific for rectal patients undergoing combined modality treatment found. An appreciation of the rectal patient as a whole, with specific-disease-related concerns, requires the use of multi-dimensional, disease and treatment-specific quality of life tools to address the unique impact upon this patient's sense of well-being and satisfaction with life. In this study, quality of life measurement using a cancer-specific instrument with demonstrated adequate reliability and validity, the FACT-C (version 2),⁴⁹ will be supplemented by the Anorectal Function Assessment Tool (AFAT) to provide a sufficient balance of measurement sensitivity, specificity, and generalizability.⁴² Due to differences in the sequence of these two treatment arms, possibly resulting in differences in sphincter function as well as acute and long term toxicities. In the absence of prior systemic study of a patient's quality of life who is undergoing therapy similar to that to be used in this investigation, no hypothesis is generated regarding how these treatments are expected to differ in terms of subsequent quality of life. However, because of the differences in the sequence of these two treatment arms, an appraisal of patient's quality of life will complement outcome and toxicity analyses.

2.0 OBJECTIVES

- 2.1 A phase III study of pre-operative vs. post-operative combined modality therapy in patients with clinically resectable primary rectal adenocarcinoma will be activated. Combined modality therapy will include bolus 5-FU, leucovorin (LV), and pelvic radiation therapy.
- 2.2 The endpoints of the trial will be sphincter preservation, function and quality of life, tolerance of treatment, patterns of failure, disease free survival, and overall survival.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

- 3.1.1 Histologically confirmed primary adenocarcinoma of the rectum.
- 3.1.2 The distal border of tumor must be at or below the peritoneal reflection. Since patients will be entered on the study prior to surgery this decision will be based on proctoscopic exam. The distal border of the tumor must be within 12 cm of the anal verge by proctoscopic exam.
- 3.1.3 The tumor must be clinically resectable. Clinically resectable is defined as a tumor, which by examination by the surgeon, is mobile and therefore negative margins would likely be obtained at operation. *This definition is based on the routine examination of the non-anesthetized patient. It cannot be based on an examination of the patient while he or she is under anesthesia.* At the time of the examination, the surgeon must make his or her best clinical estimate of the type of surgery the patient will require (*either APR, low anterior resection or low anterior resection/coloanal anastomosis*). This decision must be recorded on the Eligibility Checklist.
- 3.1.4 Transmural penetration beyond muscularis propria. The presence of transmural penetration by the tumor must be confirmed by any two of the following tests: pelvic CT scan, pelvic MRI scan, transrectal ultrasound and physical exam.
- 3.1.5 KPS performance status ≥ 60 .
- 3.1.6 WBC ≥ 4000 cells/ μ l, platelets $\geq 150,000$ cells/ μ l.
- 3.1.7 Absence of a high grade obstruction (*bowel lumen ≥ 1 cm*).
- 3.1.8 Age ≥ 18 years.
- 3.1.9 Non-pregnant, non-lactating. Patients with reproductive potential should use appropriate contraception.
- 3.1.10 Patient must have a signed study-specific informed consent form. No other serious medical illness, other than that treated by this study, which would limit the ability of the patient to receive protocol therapy, or psychiatric condition which would prevent informed consent.
- 3.1.11 No prior chemotherapy, immunotherapy, or radiation therapy to the pelvis.
- 3.1.12 No evidence of metastatic (MI) disease (*see Appendix III*). If there are any suspicious findings (*i.e., liver metastasis, lung nodule, retroperitoneal adenopathy*) the patient is ineligible unless malignancy is ruled out by tissue documentation (*biopsy*) prior to randomization.
- 3.1.13 No previous or concurrent malignancy is allowed except a) inactive non-invasive cervical carcinoma and skin cancer (*excluding melanoma*), or b) other cancer if the patient has been disease free for ≥ 5

- years.
- 3.1.14** Treatment must start within 2 weeks of randomization.
- 3.1.15** Patients randomized to the post-operative therapy (*Arm 2*) who have pathologic stage T1-2, N0M0 will not receive chemotherapy or radiation therapy however will be followed.
- 3.1.16** The patient must be treated at an institution with a linear accelerator with energy of ≥ 4 MV and which has a simulator capable of reproducing the treatment field geometry.

3.2 Ineligibility Criteria

- 3.2.1** Non-histologically confirmed primary adenocarcinoma of the rectum.
- 3.2.2** If the tumor is entirely above the peritoneal reflection. Since patients will be entered on the study prior to surgery this decision will be based on protoscopic exam.
- 3.2.3** Active inflammatory bowel disease.
- 3.2.4** Karnofsky performance status < 60 .
- 3.2.5** WBC $< 4,000$ cells/ μ l, PLT $< 150,000$ cells/ μ l.
- 3.2.6** Presence of a high grade obstruction (*bowel lumen ≤ 1 cm*).
- 3.2.7** Age < 18 years.
- 3.2.8** Pregnant or lactating.
- 3.2.9** Serious medical illness or psychiatric condition.
- 3.2.10** Prior chemotherapy, immunotherapy, or radiation therapy to the pelvis.
- 3.2.11** Evidence of metastatic (*M1*) disease.
- 3.2.12** Multiple primary cancers involving both the colon and rectum that would preclude a patient from being classified as having only rectal cancer.

4.0 PRETREATMENT EVALUATIONS

- 4.1** Complete history and physical examination including proctoscopic exam.
- 4.2** Laboratory evaluations to include CBC, Platelet count, BUN, Creatinine, Bilirubin, SGOT, Alkaline Phosphatase, Total Protein, Albumin, LDH, and CEA. If liver function tests are elevated beyond their normal range, every attempt must be made to exclude liver metastases.
- 4.3** Chest x-ray and abdominal/pelvic CT or MRI within the previous month.
- 4.4** Barium enema or colonoscopy.
- 4.5** *Optional but strongly recommended:* Transrectal ultrasound, Pelvic MRI.
- 4.6** If any one of the radiographic exams (*CT, transrectal ultrasound, or MRI*) reveal evidence of positive pelvic or mesorectal lymph nodes (≥ 1.5 cm) the patient will be considered to have clinically positive nodes and will be stratified accordingly.
- 4.7** If a pelvic MRI is obtained, the use of a Helmholtz coil or endorectal coil is highly recommended. The use of these coils will improve sensitivity, resolution, and allow the use of a small field of view compared with that achieved with a body coil alone.
- 4.8** Baseline quality of life assessments. The patient who is unable to communicate in English or Spanish may not be able to complete the quality of life assessments but this does not affect enrollment in the treatment study but must be appropriately documented. (*see Section 11.6.4*)

5.0 REGISTRATION PROCEDURES

5.1 Randomization

It is the responsibility of each participating Cooperative Group to decide which of its member institutions may participate in this protocol. Each participating Cooperative Group must ensure that IRB approval was obtained prior to accession of cases. Patients who meet the eligibility criteria in Section 3.0, sign the consent form, and pass the pretreatment evaluation, may be entered into the study prior to any protocol therapy. Member institutions will phone their respective Cooperative Group headquarters Mondays through Fridays. The following information will be required at the time of patient entry:

- Institution's Name and RTOG Institution Identification Number
- Patient's name and ID Number
- Verifying Physician's Name
- Eligibility Criteria Information
- Stratification Information
- IRB Approval Date
- Name of Medical and Radiation Oncologists
- Demographic Data

- Treatment Start Date (*must be within 14 days of randomization*)

5.2 Where to Call:

5.2.1 CALGB (919) 286-4704, 9:00am - 5:00 pm, Eastern Time
CALGB Randomization will be accepted through the Main Institution only, prior to initiation of therapy. Confirm all selection criteria listed in Section 3.0. Call the CALGB Data Management Center (919/286-4704, Monday to Friday, 9 am to 5 pm Eastern Time). The CALGB Registration Desk will then contact RTOG Headquarters to enter the patient. RTOG will forward a confirmation of randomization and a Forms Due Calendar to the CALGB Data Management Office/CALGB Restistra for routing to the participating CALGB institution.

5.2.2 ECOG (617) 632-2022, 8:30 am - 4:30 pm, Eastern Time

Note: A signed HHS 310 Form for this protocol must be on file at the ECOG Operations Office before any ECOG institution may enter a patient.

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

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

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

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

6.0 RADIATION THERAPY

6.1 Radiation Therapy Schedule

6.1.1 Large pelvic field - 45 Gy (as described in Section 6.4.1)

The tumor dose will be calculated at the isocenter of the multiple fields. The dose will be delivered at 1.8 Gy per day, five days per week, to give a total of 25 fractions over a period of five weeks for a total of 45 Gy. At least two fields per day should be treated.

6.1.2 Boost Field - 5.4 Gy (as described in Section 6.4.4)

6.1.2.1 A minimum tumor boost of 5.4 Gy at 1.8 Gy per fraction (50.4 Gy cumulative, including contribution from large pelvic fields) is required for all patients.

6.2 Equipment and General Techniques

Linear accelerators with a minimum energy of 4 MV will be used. Multiple field techniques (*usually four-field, [PA:AP and laterals] or three-field [PA and laterals]*) should be designed to exclude as much small bowel as possible. In male patients (*where the genitalia are commonly in the treatment field*), if there is large volume of small bowel in the pelvis, or if a colostomy is present, a 3-field technique (*PA + laterals*) is highly recommended. In general, wedges should be used on the lateral fields to improve dose homogeneity. At least two fields should be treated per day. Radiation will be delivered 5 days/week, once per day, at 1.8 Gy/day.

6.3 General Simulation Techniques

6.3.1 All fields must be simulated using a machine that duplicates the geometry of the actual treatment machine. Radiation simulation will be performed prior to radiation therapy.

6.3.2 The patient should be simulated and treated in the prone position. Simulation and treatment with the patient in the prone position has an advantage over the supine position in that bony landmarks (*especially sacrum*) are more easily visualized, positional shifts in small bowel can occur, and after abdominoperineal resection the perineal scar can be bolused more easily. In the very rare circumstance when the patient cannot tolerate simulation and treatment in the prone position, the supine position may be used. If the patient is treated supine, the pelvis should be raised off the simulation and treatment table with styrofoam or similar material to help delineate bony structures and posterior field margins.

6.3.3 For patients who have an intact rectum, at the time of simulation, they should have barium or other contrast material placed within the rectum. The perineum should be marked with a radio-opaque marker and a block placed to exclude the perineal skin where possible. Rectal contrast (*barium sulfate*)

is injected using a # 16 French foley catheter. A wire is placed on the catheter to identify the anal verge.

6.3.4 Perineal Scar following APR: Patients who have had an APR should have the perineal scar marked with a radio-opaque marker in order to include it in all radiation fields. The inferior (*caudad*) and posterior field edges should be 1.5-2 cm beyond the scar. Inferolaterally, the margin should be the lateral aspect of the ischial tuberosities (*at that level*). Bolus material (*typically 1-2 cm depending on the machine energy*) is necessary during the treatment to bring the dose to 100%. This is preferable to taping the buttocks together.

6.3.4.1 The perineum should be included to a dose level of 45 Gy. In males, elevation of the penis and scrotum cephalad in front of the symphysis, or altering the penis position during treatment, may help decrease skin reaction. A 3-Field technique (*PA and 2 laterals*) is helpful in decreasing the dose to the penis and scrotum and should be used whenever possible. Because of skin reactions, patients occasionally require a 7-10 day rest during treatment and the use of sitz baths, Aquaphor ointment, or other non-metallic creams. Most finish on schedule and limited skin reactions resolve within 1-2 weeks of completion. Never use an electron boost for the perineum - there can be overlap between the electron and photon fields.

6.3.4.2 It is not necessary to have complete healing of the perineal wound prior to starting radiation. If the perineum is initially packed open after resection, the time interval to complete closure can be 3-3 1/2 months or longer. Treatment can be started as soon as there is granulation tissue and a maximum defect 1.5-2 cm wide and 3-4 mm deep. While complete closure of the defect will be delayed by the radiation, problems with lack of healing or secondary perineal hernias have not been encountered.

6.4 Radiation Therapy Fields (See Appendix VI)

6.4.1 Large pelvic field - Tumor bed + nodes (45 Gy)

Areas to be treated - The intent of the treatment is to include the tumor bed with margin plus iliac (*internal ± external*) and presacral lymph node groups. The external iliac nodes should not be included in the radiation therapy field unless, at the time of surgery, pelvic organs with major external iliac drainage (*bladder, prostate, cervix, or vagina*) are found to be involved by direct extension (*pathologic T4*).

6.4.2 PA:AP Fields

6.4.2.1 Lateral borders: At least 1.5 cm lateral to the widest bony margin of the true pelvic side walls with a wider margin being used if it is necessary to cover the external iliac nodes secondary to other pelvic organ involvement or adherence.

6.4.2.2 Superior border: At the L5/S1 junction, approximately 1 1/2 cm above the level of the sacral promontory.

6.4.2.3 Inferior border: The inferior border will be determined by the distal extent of the primary tumor and the operative procedure. Corner blocks will be used to exclude extra-pelvic normal tissues. In patients who have undergone an APR, the lower border of the field will include the perineum with at least a 1.5 cm margin. At the time of simulation, radiopaque markers will be placed to define precisely the perineal scar to insure that this region is covered by the radiation field. The perineum will be included in all of the radiation fields.

6.4.2.4 In patients receiving pre-operative radiation therapy or those patients who receive post-operative radiation therapy following an LAR or LAR/coloanal anastomosis, the distal border of the radiation field will be 3 cm. below the primary tumor or at the inferior aspect of the obturator foramina; whichever is the most inferior. The perineum will not be included.

6.4.3 Lateral Fields

Following an APR, the entire perineal scar should be included with a 1.5 posterior, anterior, and inferior margin.

6.4.3.1 Posterior border: should be a minimum of 1.5 cm behind the anterior bony sacral margin and can be shaped with blocks to spare posterior muscle and soft tissues.

6.4.3.2 Anterior border: The external iliac nodes will normally not be included therefore the anterior margin should be at the most posterior aspect of the symphysis pubis. The external iliac lymph nodes will be included only if there is evidence of invasion of an adjacent organ or structure (*pathologic T4*). In this case, the anterior margin can also be shaped to reduce the amount of dose inferior to the symphysis pubis and to decrease the amount of small bowel superiorly and anteriorly. This will vary depending on the location of the primary lesion. The lateral presurgical barium enema films as well as the barium enema performed at the time of simulation should be used to determine the exact anterior border.

6.4.3.3 Superior border: same as the PA and AP fields.

6.4.3.4 Inferior border: same as the PA and AP fields.

6.4.4 Boost field (5.4 Gy)

6.4.4.1 All patients must receive a minimum tumor boost dose of 5.4 Gy (*50.4 Gy cumulative including contribution from large pelvic fields*). A boost tumor dose of 5.4 Gy will be delivered to the primary tumor bed. The boost fields will commonly be 10 x 10 or 12 x 12 cm. to insure adequate coverage. The intent is to treat the primary tumor and not to include the nodal groups. The perineum should not be included in the boost field. Therefore, the exact size and field arrangement will be determined by the size and location of the primary tumor. The boost field should be treated with opposed lateral fields, a wedge pair, or a 3 field technique. The advantage of using lateral fields for the boost is that field shaping can be done to avoid small bowel. Small corner blocks can be used as needed.

6.5 Treatment Relationships

The ability to reconstruct tumor volumes from pre-operative studies (*physical exam, proctoscopy, barium enema, CT scan, MRI scans etc.*), operative notes, pathology reports and/or surgical clips demarcating tumor volume is critical in defining the tumor bed for the boost.

6.5.1 Small Bowel Series

6.5.1.1 A small bowel series in the simulation position is required for all patients participating in this study. This study can be helpful in minimizing both acute and chronic toxicity by influencing both portal design and radiation dose.

6.5.1.2 Technique for small bowel series during simulation

NPO for 4 hours prior to the simulation.

Patient drinks 8 oz. of barium sulfate at least 20 minutes prior to the simulation.

If a post-simulation CT scan is performed, the following mixture should be substituted for barium: 2 oz. Gastrograffin plus water (*and flavoring if desired*) to a total volume of 8 oz.

When home, the patient should take a laxative (i.e. 30 cc milk of magnesia) to help clear the bowel of the contrast.

6.5.2 Bladder Distension

6.5.2.1 The value of bladder distension to displace small bowel has been more useful than placing the patient in the Trendelenburg position. Its use in all patients is encouraged. The exception is the category of patients with tumor adherence to or invasion of the dome of the bladder in whom bladder distension could displace not only small bowel but also the necessary tumor volume out of the radiation field.

6.5.2.2 Approximately 1 to 2 hours prior to treatment, the patient is instructed to void and then drink 4 glasses (*approximately 1 liter*) of water or other liquid. The patient should not empty his/her bladder until after treatment. Mild discomfort at the time of treatment is preferred and generally indicates satisfactory bladder distention. Extreme discomfort is to be avoided as this leads to difficulty in patient positioning. Patients will need to adjust their intake of liquid prior to treatment as needed.

6.5.2.3 As an alternative to bladder distention, patients may be simulated and treated on a false table top device (*with or without compression*), designed to allow small intestine to be mobilized anteriorly and superiorly out of the pelvis. Simulation films of PA and lateral fields with the patient on the false table top device should be submitted for quality control review.

6.6 Quality Control

6.6.1 Films of the initial treatment fields are to be sent to the RTOG quality assurance office for review. Patient contours and isodose plots are required and are to be sent after completion of therapy. Isodose plots must account for the effect of all treated fields. Wedges or compensation devices must be used to bring the dose within the treated volume (*exclusive of penumbra*) to within 5% of that specified in Section 6.4. Deviations of 5%-10% will be classified as a minor protocol violation and deviations of greater than 10% will result in a major protocol violation.

6.7 Radiation Checklist

6.7.1 Initial simulation is to be performed within three weeks prior to the start of radiation therapy and films and other information are to be forwarded to the RTOG Operations Office.

6.7.2 During radiation therapy, patients should be seen in status check at least once a week with notation of tolerance, weight and blood counts.

6.7.3 Field verification films will be taken of each field at the initiation of treatment. Such port films should be repeated at least every other week during treatment or more often (especially with lateral fields) to ensure field accuracy.

- 6.7.4 Radiation Therapy Reporting Form (TI) should be completed after the completion of radiation therapy.
- 6.7.5 Treatment modifications - For any GI or hematologic toxicity of Grade 3 or greater, radiation treatments will be held until toxicity has decreased to Grade 2 or lower. Treatment will then resume as previously planned. Improvement of diarrhea to Grade 2 or lower by medication is acceptable for continuing the radiation therapy except if there is profuse loose watery diarrhea.

7.0 CHEMOTHERAPY

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

7.1 5-Fluorouracil (5-FU)

- 7.1.1 Dose Formulation: 5-FU is available in 10-ml ampules, as a colorless to faint yellow aqueous solution containing 500 mg 5-FU, with pH adjusted to approximately 9.0 with sodium hydroxide. Administration of 5-FU should be only by the intravenous route taking care to avoid extravasation.
- 7.1.2 Pharmacology: 5-FU is a marketed drug available in 500 mg vials. It is fluorinated pyrimidine belonging to the category of antimetabolites. 5-FU resembles the natural uracil molecule in structure, except that a hydrogen atom has been replaced by a fluorine atom in the 5 position. There is evidence that the metabolism of fluorouracil in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to the thymidylic acid. In this fashion 5-FU interferes with the synthesis of DNA and to a lesser extent inhibits the formation of ribonucleic division and growth, the effect of fluorouracil may be to create a thymidine deficiency which provides unbalanced growth and death of the cell.
- 7.1.3 Drug Availability: 5-FU is available commercially.
- 7.1.4 Storage: Although 5-FU solution may discolor slightly during storage, the potency and safety are not adversely affected. Store at room temperature (49-86 °F). Protect from light. If a precipitate occurs due to exposure to low temperatures, resolubilize by heating to 140 °F with vigorous shaking; allow to cool to body temperature before using.
- 7.1.5 Side Effects and Toxicities: The spectrum of toxicity includes stomatitis and esophagopharyngitis (which may lead to sloughing and ulceration), diarrhea, anorexia, nausea and emesis are commonly seen during therapy. Leukopenia usually follows every course of adequate therapy with fluorouracil. The lowest white blood cell counts are commonly observed between the 9th and 14th days after the first dose, although uncommonly the maximal depression may be delayed for as long as 20 days. By the 30th day the count has usually returned to the normal range. Alopecia and dermatitis may be seen. The dermatitis most often seen is a pruritic maculopapular rash usually appearing on the extremities and less frequently on the trunk.

7.2 Leucovorin (LV) (folinic acid)

- 7.2.1 Dose Formulation: 20cc vials - Sterile powder. Equivalent to 100 mg Leucovorin. Reconstitute with 10 (ten) ml Bacteriostatic Water for Injection USP which contains benzyl alcohol. Each ml contains Leucovorin calcium equivalent to Leucovorin (ten) 10 mg and sodium chloride 8 mg.
- 7.2.2 Pharmacology: Leucovorin is the formal derivative and active form of folic acid used to counteract the hematologic and other toxicities of Methotrexate and other antifols. Allergic sensitization has been reported following both oral and parenteral administration of folic acid. Leucovorin is also available as a 25 mg oral tablet used to protect against potential toxicities from methotrexate.
- 7.2.3 Drug Availability: Calcium Leucovorin is available commercially.
- 7.2.4 Storage: Use within 7 days. If reconstituted with sterile water for injection USP, use within 8 hours.
- 7.2.5 Side Effects and Toxicities when given in combination with 5-FU: Mild nausea and vomiting, stomatitis, anorexia, diarrhea, skin rash, alopecia, myelosuppression have been observed.

7.3 Dose

7.3.1 *Patients in both arms will receive six cycles of 5-FU and leucovorin.*

7.3.1.1 Treatment Arm 1 (Pre-operative Therapy)

7.3.1.1.1 Treatment during radiation therapy will consist of 5-FU and leucovorin given for 2 cycles during five consecutive days on week 1 and week 5 of the radiation therapy. Leucovorin should be given as an i.v. bolus preferable within 2 hours after the completion of that day's radiation, 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 at a dose of 325 mg/m²/day. Treatment will be given on days 1-5 and 29-33.

7.3.1.1.2 Treatment after surgery will consist of 5-FU and leucovorin given for 4 cycles during five

consecutive days on days 1-5, 29-33, 57-61, and 85-89 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. For cycles 3 (*days 1-5*) and 4 (*days 29-33*) the 5-FU dose will be 425 mg/m²/day. For cycles 5 (*days 57-61*) and 6 (*days 85-89*) the 5-FU dose will be 380 mg/m²/day.

7.3.1.2 Treatment Arm 2 (Post-operative Therapy)

7.3.1.2.1 Treatment prior to radiation therapy will consist of five consecutive days of chemotherapy given as an i.v. bolus for 2 cycles on days 1-5 and 29-33. Leucovorin will be given at a dose of 20mg/m²/day. This will be followed immediately on each day by 5-FU given as an i.v. bolus at a dose of 425 mg/m²/day.

7.3.1.2.2 Treatment during radiation therapy will consist of 5-FU and leucovorin given for 2 cycles during four consecutive days on week 1 and week 5 of the radiation therapy. Leucovorin should be given as an i.v. bolus preferably within 2 hours after the completion of that day's radiation, at a dose of 20 mg/m²/day for each of the four days in each cycle. This will be followed immediately on each day by 5-FU given as an i.v. bolus at a dose of 400 mg/m²/day. Treatment will be given on days 57-60 and 85-88.

7.3.2 Treatment after radiation therapy will consist of 5-FU and leucovorin given for 2 cycles during five consecutive days on days 1-5 and 29-33 starting 28 days after the completion of the radiation therapy. Leucovorin should be given as an i.v. bolus at a dose of 20 mg/m²/day for each of the five days in each cycle. This will be followed immediately on each day by 5-FU given as an i.v. bolus at a dose of 380 mg/m²/day.

7.3.3 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.

7.3.4 If the patient develops grade 3+ toxicity during the course of radiation therapy, (*excluding stomatitis which is due exclusively to chemotherapy*) all treatment (*radiation and chemotherapy*) will be stopped for one week. The patient will be re-evaluated after one week and if grade 3+ toxicity is no longer present radiation therapy and chemotherapy will resume. Dose attenuation of chemotherapy will be performed as outlined in Sections 7.3.4.1.2, 7.3.4.2.2.1 and 7.3.4.2.3. The daily and total dose of radiation will NOT be attenuated. If after a one week break the patient has persistent 3+ toxicity radiation therapy and chemotherapy will not resume until grade 3+ toxicity is no longer present.

7.3.4.1 **Dosage modification for chemotherapy when given ALONE (*not during combined radiation therapy and chemotherapy*):**

7.3.4.1.1 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 chemotherapy (*given alone, not during radiation therapy and chemotherapy*). The dose of Leucovorin is not modified for chemotherapy toxicity.

7.3.4.1.2 Percent of Dose Resulting in Toxicity

Toxicity	5-FU	Leucovorin
<i>Hematology Nadirs (/mm³)</i>		
WBC 1000-2500	80%	100%
WBC < 1000	70%	100%
PLT 25,000-75,000	80%	100%
PLT < 25,000	70%	100%
<i>Diarrhea</i>		
Grade 2	80%	100%
Grade 3-4	70%	100%
<i>Stomatitis</i>		
Grade 2	80%	100%
Grade 3-4	70%	100%

7.3.4.1.3 If Grade 2 or greater diarrhea or stomatitis is present at the scheduled time for the next cycle, chemotherapy should be held until the toxicity clears.

7.3.4.1.4 If WBC < 3,500/mm³ and/or platelets < 100,000/mm³ at the start of a treatment cycle, hold

therapy and repeat counts weekly x 2. If the blood counts are still below these levels, chemotherapy should be discontinued.

7.3.4.2 Chemotherapy treatment modifications during COMBINED radiation therapy and chemotherapy:

7.3.4.2.1 If multiple toxicities are seen the dose administered should be based on the most severe toxicity experienced. If the radiation therapy is delayed, the chemotherapy should be delayed similarly so that the chemotherapy is always given during the first and fifth week of radiation therapy. Different dose modifications will be made depending on whether the toxicity is the maximum toxicity seen during the interval between the two doses of chemotherapy or the toxicity at the time of delivery of the second dose of chemotherapy (*with week 5 radiation therapy*).

7.3.4.2.2 Maximum toxicity during INTERVAL BETWEEN COURSES of 5-FU given during radiation therapy.

7.3.4.2.2.1 Percent of dose resulting in toxicity.

Toxicity	5-FU	Leucovorin
<i>Hematology Nadirs (/mm³)</i>		
WBC 1000-2500	80%	100%
WBC < 1000	70%	100%
PLT 25,000-75,000	80%	100%
PLT < 25,000	70%	100%
<i>Diarrhea</i>		
Grade 3	80%	100%
Grade 4	70%	100%
<i>Stomatitis</i>		
Grade 2	80%	100%
Grade 3-4	70%	100%

7.3.4.2.3 Toxicity AT TIME OF SECOND DOSE of chemotherapy during the radiation therapy

Toxicity	5-FU/LV Dose Reduction
Stomatitis - Grade 2-4	Do not administer second course
WBC < 3500/m ³ PLT < 75,000	Do not administer second course
Diarrhea - Grade 2 (<i>if associated with loose, watery bowel movements</i>) or Grade 3-4	Delay chemotherapy with the radiation therapy delay

7.4 Toxicity Management

7.4.1 Patients should receive ice chips by mouth to decrease the incidence and severity of stomatitis during the administration of 5-day courses of chemotherapy.

7.4.2 Patients should start taking ice chips by mouth five minutes prior to each 5-FU/LV administration. They should be asked to place and retain a spoonful of ice chips in their mouth. Before the ice chips have completely melted, they should place another spoonful of ice chips into their mouth and repeat the process for a total of 30 minutes. Patients with dentures should remove them prior to and throughout the period of ice chip administration.

7.4.3 Loperamide, diphenoxylate or other anti-diarrheal agents may be used for control of diarrhea. Caution should be observed with the combination of 5-FU and LV as this combination has been reported to have severe diarrhea leading to death when used with higher doses of LV.

7.4.4 All patients who require hospitalization for chemotherapy-induced diarrhea should be considered for somatostatin analogue therapy 100 µg subcutaneously every eight hours for five days, in addition to standard medical management of the diarrhea. The number of stools per day should be recorded starting the day prior to receiving somatostatin analogue and for each day that somatostatin analogue is administered. The daily stool frequency should be recorded on the data forms.

7.4.5 Prochlorperazine or other antiemetics may be used as needed for control of nausea and vomiting.

7.4.6 Appropriate infectious precautions, antibiotic therapy and cell replacement should be employed in

instances of severe bone marrow depression.

7.5 Adverse Drug Reaction Reporting/RTOG and CALGB (6/12/95, 11/13/95)

- 7.5.1** The following ADR's attributed to commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days:
- 7.5.1.1** Any ADR which is both serious (*life threatening, fatal*) and unexpected.
- 7.5.1.2** Any increased incidence of a known ADR which has been reported in the package insert or the literature.
- 7.5.1.3** Any death on study if clearly related to the commercial agent(s).
- 7.5.2** The ADR report should be documented on Form FDA 3500 (*Appendix V*) and mailed to:

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

- 7.5.3** CALGB's participants should telephone the CALGB Central Office within 24 hours of the Adverse Event (*312/702-9860*). The original report should be sent to the CALGB Central Office of the Chairman, 208 S. LaSalle St., Suite 2000, Chicago, IL 60604-1104. A copy of the report will then be forwarded to the RTOG Headquarters.

7.6 Adverse Drug Reaction Reporting/ECOG Members (6/12/95)

- 7.6.1** All toxicities should be coded according to the Cooperative Group Common Toxicity Criteria (*Appendix IV*).
- 7.6.2** Written Adverse Drug Reaction reports are to be submitted ONLY on the Adverse Reaction (ADR) Form for Investigational Drugs (*Form 39IRF*) and the form must be signed by the treating investigator. RTOG will accept this form in lieu of FDA Adverse Drug Reaction (ADR) Form 3500. All ADR reports are to be accompanied by copies of supporting documentation. In addition, your institution's Investigational Review Board must be notified.
- 7.6.3** This protocol contains COMMERCIAL AGENTS only. Events indicated below must be reported in the manner specified for:
- Any death while on treatment if clearly related to commercial agent:
 - Any ADR which is BOTH serious (*life threatening [grade 4] or fatal [grade 5]*) AND unexpected.
 - Any increased incidence of a known ADR.
 - Occurrences of second malignancies (*include protocol reference number, time from diagnosis to development of second malignancy and any characterization of the second malignancy, such as AML-FAB sub type, cytogenetics, etc.*)
- 7.6.4** Call the ECOG Data Management Office within 24 hours of the event. Submit original written ADR form to ECOG Data Management Office within 5 working days of the event. In addition a copy must be mailed to the Investigational Drug Branch within 10 days and your institutional Review Board (*IRB*) must be notified.
- 7.6.5** The ECOG Data Management Office will call the RTOG office to report ADR telephone calls and will forward ADR reports to RTOG.
- NCI Telephone Number: (301) 230-2330 ECOG Telephone Number: (617) 632-3610
NCI Fax Number: (301) 230-0159 ECOG Data Management Office

NCI Mailing Address:	ATTN: ADR
IDB	303 Boylston Street
P.O. Box 30012	Brookline, MA 02146-7215
Bethesda, MD 20824	

8.0 SURGERY

8.1 General Operative Evaluation

- 8.1.1** Perform thorough examination of the abdomen to detect metastatic disease. Negative as well as positive findings should be mentioned in the operative report.
- 8.1.2** To help orientate the specimen for pathologic examination, a suture should be placed on the distal anterior rectal wall.

8.2 Biopsies

- 8.2.1** In addition to marking the resected specimen for pathologic correlation, obtain separate biopsy(*ies*) of unresected tissue at the closest tumor margins to rule out histologically residual tumor and submit in a separate bottle.
- 8.2.2** Biopsy suspicious areas on the peritoneum, liver, or any other suspicious sites.
- 8.3** Patients who are randomized to pre-operative therapy will undergo surgery four to six weeks following the completion of radiation therapy.
- 8.4** Patients will be explored even if there are no gross signs of tumor regression. The finding at surgery of unresectable hepatic metastases, will preclude radical resection. However, since it is likely the pre-treatment scans will have ruled out this possibility, at most it is felt that minimal liver metastasis will be present. Under these circumstances, radical resection will still be undertaken to try to effect local control and control of long-term symptoms related to the primary tumor. The finding of biopsy-proven peritoneal seeding will also preclude radical surgery.
- 8.5** The choice of operative procedure (*abdomioperineal resection [APR], low anterior resection [LAR], or LAR/coloanal anastomosis*) is at the discretion of the surgeon. It is strongly recommended that the entire mesorectum be removed and that a distal rectal margin of at least 2 cm be obtained for sphincter-preserving operation in both treatment arms.
- 8.6** APR will involve resection of the rectum and mesorectum from the pelvic floor to at least the aortic bifurcation. The ureters will be identified bilaterally and preserved. A hysterectomy and vaginectomy will be performed if felt to be indicated. The pathologist will be asked to ink the specimen for radial margin determination. Biopsies will be taken of any gross residual area suspicious for tumor or any tumor bed at risk.
- 8.7** Pelvic reconstruction - Any operative maneuver which can decrease the volume of small bowel that will be in the pelvis should be used in patients who are randomized to receive post-operative radiation. These include the following: peritonealize pelvic floor, omental sling or pedicle flap, retrovert uterus into pelvis, or the use of absorbable mesh or temporary prosthetic devices. The method used to exclude small bowel must be documented.
- 8.8** When APR is necessary, some form of closure of the perineum should be used unless problems with hemostasis exist.
- 8.9** If a temporary colostomy is performed, it should not be closed until at least 6-8 weeks after the completion of all cycles of chemotherapy.
- 8.10** **Surgical Procedure for LAR/Coloanal Anastomosis**
- 8.10.1** If a LAR/coloanal anastomosis is performed, the entire left colon to the level of the middle colic artery is mobilized, with ligation of the inferior mesenteric artery and vein. The distal left colon is divided with a linear stapler at a level to ensure adequate length to reach to the pelvic floor. A radical resection of the rectum with wide mobilization of the mesorectum on all sides and from the levators is performed from the abdominal incision. The rectosacral fascia is incised posteriorly to mobilize the entire rectum to the level of the anorectal ring. Using the technique of Parks,¹⁸ the mucosa is stripped from the dentate line to just above the levators. At the level of the anorectal ring the muscular rectal wall is divided by cautery and the specimen removed.
- 8.10.2** The colon is brought into the anal canal, the staple line excised, and a direct anastomosis performed to the dentate line (*including some internal sphincter muscle*) with interrupted sutures. In patients who have received pre-operative combined modality therapy, unirradiated colon from outside the pelvis should be used for the anastomosis. The colon is replaced into the sacral hollow. The pelvis is drained from above with two closed suction drains. A temporary transverse colostomy is brought to the skin, and primarily matured following abdominal closure. A petrolatum-impregnated gauze roll is placed in the anal canal to prevent "side-to-side" healing, and removed 4 to 5 days later.
- 8.10.3** If a temporary colostomy is performed, it should not be closed until at least 6-8 weeks after the completion of all cycles of post-operative chemotherapy. Following closure, patients should be kept on a regular diet with Metamucil twice daily, as tolerated.
- 8.11** **Metastatic Disease at Surgery**
- 8.11.1** See Section 11.5.

9.0 OTHER THERAPY

Not applicable to this study.

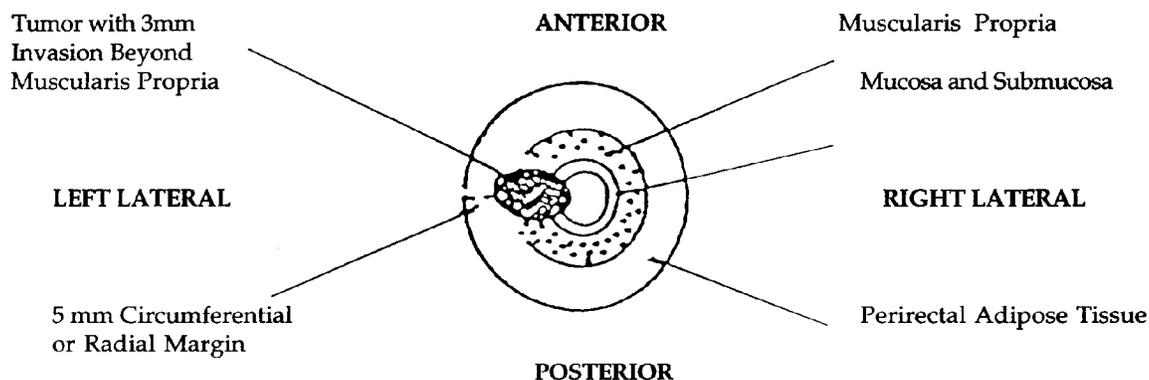
10.0 PATHOLOGY (10/1/96)

10.1 Pathology Review

- 10.1.1 Central pathology review of diagnostic materials *will not* be undertaken as part of this protocol.
- 10.1.2 The surgical pathology report(s) must be submitted for all preoperative biopsies and subsequent resections.
- 10.1.3 In cases where review of an outside pathology report does not allow for the necessary pathologic evaluation, slides may be requested (*see Section 10.2*) by RTOG Headquarters.
- 10.1.4 Laboratory correlative studies are planned for this protocol. Every effort should be made to obtain a representative paraffin tissue block or unstained slides as outlined in Section 10.3 for an additional RTOG case credit.

10.2 Pathology Evaluation

The depth of tumor invasion beyond the rectal wall (*muscularis propria*) and the minimum circumferential (*radial*) margin of normal tissue should be indicated on the pathology report. The pathologist must be able to define the margins of resection to assure that there are no microscopically positive margins. Example:



10.3 Fixed Tumor Repository Study (Optional)

- 10.3.1 Patients entered on this study are eligible for the Fixed Tumor Repository.
- 10.3.2 To receive an additional RTOG case credit (*only RTOG members can receive the RTOG credit*), the following must be provided to RTOG:
 - 10.3.2.1 One paraffin block of tumor, with a representative H&E stained slide, OR 15 unstained slides (*maximum thickness of 5 microns each*). Block/slides must be clearly labeled with the pathology identification number that agrees with the Pathology Report.
 - 10.3.2.2 Pathology report documenting that submitted block or slides contain tumor.
 - 10.3.2.3 A Pathology Submission Form must be included and must clearly identify the enclosed materials as being for the Fixed Tumor Repository.
- 10.3.3 To encourage compliance, your Pathology Department could be reimbursed for obtaining blocks or cutting slides.
- 10.3.4 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*).
- 10.3.5 Materials will be sent to:

**Pathology Coordinator
RTOG Headquarters
1101 Market Street
Philadelphia, PA 19107
215/574-3192**

- 10.3.6 ECOG members will send pathology materials (*with submission form*) to the ECOG Pathology Office for tissue banking:

**ECOG , Frontier Science
ATT: PATHOLOGY
303 Boylston Street
Brookline, MA 02146-7648**

All material must be labeled with the patient's ID number, study number and both the RTOG and

ECOG case numbers. The materials will be retained indefinitely at the ECOG Central Tumor Repository for use in future studies.

10.4 Fresh Tissue Repository (Optional), RTOG Members Only

10.4.1 Fresh specimens from patients on Arm 2 (*post-operative therapy*) are eligible for RTOG 93-08, the fresh/frozen tumor repository study.

11.1 Study Parameters (6/12/95, 11/13/95)

Tests/Procedures	Pre-op	Within 14 days prior to randomization	During treatment	During Radiation	F/U q 3 months first 24 mos after completion of all therapy. ^c
History and phys. KPS		X	Prior to each course of chemo & RT	Weekly ^a	X
CBC		X	Weekly	Weekly	X
SMA-12 ^b		X	Day 1 & 29 of chemo	Prior to starting	X
CXR		X	Prior to post-RT chemo		3 mos after completion of all therapy, then annually.
CEA		X			X
Proctoscopy	X				X
Barium Enema or colonoscopy	X				At 1,3, and 5 yrs post-op
Abdominal/Pelvic CT or MRI	X				At the 6 month F/U visit & at 1st relapse
Pregnancy test (<i>pre-menopausal women</i>)		X			
Port films of at least 2 fields				Weekly	
Quality of Life Tools	X				X ^d

- a) To include weight, toxicity
- b) BUN, creatinine, electrolytes, SGOT, bilirubin, alkaline phosphatase, total protein, albumen, LDH
- c) Starting at 24 mos q 6 mos for 3 years then yearly
- d) Every 6 months after completion of all therapy for 5 years, then yearly until death.

11.2 Criteria for Toxicity

- 11.2.1** Possible toxicities related to radiation therapy: fatigue, dysuria, myelosuppression, diarrhea, skin erythema, sterility, and small bowel obstruction.
- 11.2.2** Possible toxicities related to chemotherapy: reduction in radiation dose due to combined toxicity, surgical complications in patients with relative leukopenia, nausea, vomiting, diarrhea, stomatitis, peptic ulcer, gastritis, decreased renal function, or pancytopenia.
- 11.2.3** Possible toxicities related to surgery: pelvic abscess, hemorrhage, inability to void, erectile impotence.
- 11.2.4** The RTOG toxicity scales will be used (*Appendix IV*).

11.3 Patient Evaluations

11.3.1 Evaluation During Radiation Therapy

- 11.3.1.1** Patients will be seen in status check at least weekly during radiation with notation of tolerance, weight and blood counts. If clinically indicated other blood tests (*SMA-20, BUN, Creatinine*) will be obtained.
- 11.3.1.2** If the patient experiences grade 3+ toxicity or if the WBC is < 2.0 or the platelet count is < 100,000, the radiation therapy will be held and the patient will be reassessed at weekly intervals. There will be no dose attenuation for radiation therapy.
- 11.3.1.3** Weekly port films will be taken of at least two fields.

11.3.2 Evaluation Following Treatment

- 11.3.2.1** Evaluation will be supervised by surgery, medical, and radiation oncology according to the schedule outlined in Section 11.1.

11.3.3 Criteria For Response

11.3.3.1 Treatment evaluation must be performed at an approved institution according to the schedule specified in the schema.

11.3.3.2 At the time of re-evaluation, patients will be classified in the following manner:

No evidence of disease (*NED*)

Relapse of disease (*PROG*). Biopsy confirmation should be obtained when this can be accomplished with minimum risk. Interval to relapse or progression will be measured from the date of randomization until clinical diagnosis of locally recurrent or metastatic disease. Thorough staging of the patient at the time of the relapse, including CT scan or MRI of the abdomen and pelvis, is recommended to determine patterns of failure and to evaluate for local tumor control. If pelvic recurrence occurs at some point after an initial metastasis, this should be clearly stated on the flow sheets. A clear demonstration of a progressive pelvic mass on CT scan will be accepted without biopsy. Fine needle biopsy is encouraged.

11.3.3.3 Survival will be calculated from the date of randomization to the date of death. Patients who die without evidence of recurrent or metastatic disease will be censored for evaluation of site of failure at the date of the last evaluation. Autopsies are strongly encouraged in order to document the exact patterns of failure to aid in the design of future trials.

11.3.3.4 Patients will be evaluated every 3 months for the first 3 years, every 6 months for the next two years, then yearly thereafter.

11.3.3.5 At each visit the patients will have an interval history and complete physical examination including rectal exam.

11.3.3.6 Patients will undergo quality of life assessment at each 6 month follow-up (*See Section 11.4*). Patients with an intact sphincter will undergo an analysis of sphincter function as part of the quality of life assessment.

11.3.3.7 CBC, screening profile (*SMA-12*) and CEA will be drawn at each visit.

11.3.3.8 Chest X-ray yearly.

11.3.3.9 An abdominal/pelvic CT or MRI will be performed at 6 months following the completion of the last cycle of chemotherapy. In addition, it will be performed whenever indicated by history, examination, or CEA results.

11.4 Sphincter Function Criteria

11.4.1 The Anorectal Function Assessment Tool (*AFAT*) will supplement other assessments. This tool is based on the Memorial Sloan Kettering anal sphincter function criteria previously used in toxicity assessments of post-therapy rectal cancer patients.²⁰ The Memorial tool identified functional aspects of interest. The aspects included on the AFAT include continence, day or night episodes of defecation, stool consistency and frequency and completeness of evacuation. For each criteria, patients select the ranked number which most closely corresponds to the most severe problem the patient has experienced during the prior week. The tool is scored cumulatively with a possible score from zero to 21. A higher score signifies less functional normalcy.

Although anorectal function is a complex and integrated function, differences in sphincter mechanisms and rectal physiologic function reflect subtle yet important distinctions related to clinical functional outcome. Whereas continence is primarily a function of the sphincter complex, stool consistency is highly related to rectal function, and stool frequency or completeness of evacuation is affected by neorectal capacity. Subsequently, the specific aspects of bowel function are known to result in different problems in a patient's daily life and alterations in lifestyle.⁵² For these reasons the Memorial tool has been revised to more clearly discriminate between the various functional aspects. Because this tool has not previously been used in a study setting, validity and reliability analyses will concurrently be performed.

Patients who do not have a colostomy will be administered and requested to complete the AFAT tool in the same manner in which the FACT-C is completed. This is described in Section 11.6.3. Because of the nature of these tools, a clinician interviewer familiar with the tools should administer the tool. The administrator will make sure instructions for both tools have been read and understood by the patient prior to the patient beginning the questionnaires.

11.4.2 Documentation of any patient dietary or elimination education should be complete for all patients. To avoid or minimize problems with intake or elimination, choice of intervention is dependent upon patient needs. However, complete documentation of dietary or elimination interventions is required, both medical and nonmedical.

11.5 Management of Progressive, Responsive, or Stage T1-2N0M0 Disease

- 11.5.1 All patients will continue to be followed.
- 11.5.2 Patients treated on Arm 1 (*Pre-operative Therapy*) in whom progressive metastatic (*abdominal or distant*) disease develops either prior to surgery or is found at the time of surgery will be considered to have treatment failure. Further therapy for these patients will be at the discretion of their physician. For those patients who have both their primary disease and metastatic disease resected it is recommended that they continue protocol therapy (*5-FU/leucovorin x 4 cycles*).
- 11.5.3 Patients treated on Arm 1 (*Pre-operative Therapy*) who develop progressive local only (*within the pelvis*) disease prior to surgery should have their therapy interrupted and undergo surgery. After the operation they will have the remaining 4 cycles of chemotherapy as per protocol.
- 11.5.4 Patients who are treated on Arm 2 (*Post-operative Therapy*) who have metastatic disease (*abdominal or distant*) at the time of surgery will be considered to have a treatment failure (*actually they represent a protocol diagnostic failure*). Continuing protocol therapy (\pm *surgery + 5-FU/leucovorin x 6 cycles with radiation during cycles 3 and 4*) is recommended however further therapy for these patients will be at the discretion of their physician.
- 11.5.5 Patients who are treated on either Arms 1 or 2 who undergo an incomplete resection of their primary tumor (*microscopic or gross positive margins*) without evidence of metastatic disease will be considered to have a treatment failure. Continuing protocol therapy is recommended however further therapy for these patients will be at the discretion of their physician.
- 11.5.6 Patients who are treated on Arm 1 (*Pre-operative Therapy*) who are found, after surgery, to have T0-2N0M0 disease will continue with protocol therapy since this downstaging may be the result of the pre-operative therapy.
- 11.5.7 Patients who are treated on Arm 2 (*Post-operative Therapy*) who are found, after surgery, to have T1-2N0M0 disease will not receive protocol therapy and will undergo follow-up only.

11.6 Quality of Life Assessments

- 11.6.1 *The Functional Assessment of Cancer Therapy (FACT - C version 2)* is the primary quality of life assessment instrument. The FACT-C scale is a 43- item self-report quality of life tool. Using a Likert-type format, the first 33 items are grouped into five subscales assessing physical well-being, and fulfillment/contentment. Additionally, ten colorectal disease-specific items are included. Within each subscale an experimental item attempts to reflect patients' perception of the degree in which his/her quality of life is affected by a subscale's domain. These additional items may be used to weight subscale scores in the composite quality of life score.⁴⁹ A Spanish version of the FACT-C is available.
- 11.6.2 *Prior use of the FACT-C* with 630 cancer patients supports tool construct validity with correlations to a shortened Taylor Manifest Anxiety Scale (.57), Brief Profile of Mood States (.69), ECOG Performance Status Rating of anxiety level (-.56) and no correlation with the brief Marlowe-Crowne Social Desirability Scale (.22). A high correlation with the Functional Living Index-Cancer (.80) supports concurrent validity. Internal consistency (*coefficient alpha*) of .89 was found with the 28-item FACT; the individual subscale alpha ranged from .65 to .82.^{49,50}
- 11.6.3 Consistent with the belief that the most meaningful information is elicited from the patient, both the FACT-C and AFAT are designed for self administration and self-report of the patient's perceived quality of life and function . The patient alone must supply responses to these items. Assistance from family members is not permitted. However, assistance by the tool administrator through reading the items and responses to the patient or circling responses indicated by the patient is allowed in cases where the respondent is unable to read or writing capacity is hindered. If assistance is provided in any manner, the type and reason for assistance is to be noted on the QOL form. The patient will complete this tool while alone in an undisturbed setting. The same clinical individual should administer the tool to the patient each time if possible. The administrator will avoid influencing responses. If the patient is unable to complete these forms due to language barriers, this must be appropriately documented on the QOL form. Note that the FACT-C is available in Spanish for administration, if required.

If the due date of a QOL assessment does not coincide with a scheduled appointment, the QOL Assessment Forms may be mailed to the patient with appropriate information/instructions and preferably with an enclosed self-addressed, stamped return envelope. Another method is to conduct a telephone "interview", reading each item verbatim. If this is done, a form should be mailed to the patient in advance.

The following will be read to the patient at each administration: "As part of our evaluation of your treatment, we would like to learn about how you see your quality of life at several points in time, both

before and after treatment. That is why we are asking you to take a few minutes to respond to these statements. Please read the directions at the top of the page." After the patient reads the instructions: "Do you have any questions about how to complete this form?" Address individual questions/concerns as needed. Then state, "please try not to skip any items." Upon completion, review the forms to ensure all items have one and only one response.

12.0 DATA SUBMISSION

12.1 Summary of Data Submission (10/1/96)

All material with the exception of initial Dosimetry and initial Medical Oncology data will be sent to the appropriate Cooperative Group office according to the following schedule and then forwarded to RTOG Headquarters. **Preliminary (and final for ECOG) dosimetry material (T2, T3, T4) and the Medical Oncology Treatment Planning Form (M2) must be sent directly to RTOG Headquarters, 1101 Market Street, 14th Floor, Philadelphia, PA 19107.** All dosimetry material (*films, etc.*) must be identified with labels available from your Cooperative Group. **All data items must be identified with both RTOG and other Group's study and case number. Unidentified data/films will be returned.**

<u>Item</u>	<u>Due</u>
Demographic Form (A5) Medical Oncology Treatment Planning Form (M2) QOL Baseline FACT-C Form (FA) Anorectal Function Assessment Tool (QL)	Within 1 week of study entry
Initial Evaluation Form (I1) Pathology Report (P1)	Within 2 wks of study entry
Pathology Form (P4) Surgery Form (S1) Operative Notes (S2) Surgical Pathology Report (S5)	Within 2 wks of surgery
<u>For Fixed Tumor Repository</u> (see Section 10.3) Pathology Report (P6) Pathology Block/Slides (P7)	Within 4 weeks of randomization
<u>Preliminary Dosimetry Information:</u> RT Prescription (Protocol Treatment Form) (T2) Films (<i>simulation and portal</i>) (T3) Calculations (T4)	Within 1 wk of start of RT
Radiotherapy Form (T1) <u>Final Dosimetry Information:</u> Daily Treatment Record (T5) Isodose Distribution (T6) Boost Films (<i>simulation and portal</i>) (T8) Post Induction Evaluation Form (F0) (<i>Arm 1</i>)	Within 1 week of RT end
Chemotherapy Flow Sheets (M1)	After each cycle
Follow-up Form (F1)	Every 3 months for the first 24 months after the completion of all therapy; q 6 months x 3 years, then annually. Also at progression/ relapse and at death.
FACT-C Form (QF) Anorectal Function Assessment Tool (PF)	Every 6 months to year 5 then annually.

12.2 Data Forms

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

**American College of Radiology
Radiation Therapy Oncology Group - 14th Floor
1101 Market Street
Philadelphia, PA 19107**

- 12.2.1** CALGB participants should submit forms to the CALGB Data Management Center. Forms will then be forwarded to RTOG Headquarters. The CALGB Data Management Center address:

CALGB Data Management Center
First Union Plaza, Suite 340
2200 West Main Street
Durham, NC 27705

12.3 Rapid Review Items

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

M2 - Medical Oncology Treatment Planning Form
T2- Protocol Treatment Form
T3 Photon localization film (*for all fields treated initially*)
T4 - Photon dose calculations (*for all fields treated initially*)

12.4 Request for Study Information and Forms Request

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

13.0 STATISTICAL CONSIDERATIONS**13.1 Endpoints**

- 13.1.1** Overall Survival (*Failure: death from any cause*)
13.1.2 Disease Free Survival (*Failure: disease relapse or second primary or death without progression*);
13.1.3 Sphincter preservation surgery
13.1.4 Toxicity
13.1.5 Quality of life

13.2 Sample Size

To calculate the sample sizes, a number of assumptions must be made. At the 1993 ASTRO meeting, a three year survival rate of 67% was reported for the recently closed intergroup rectal study NCCTG 86-47-51/RTOG 88-11 and will be used in sample size calculation.⁵¹ We assume the failures will approximately follow an exponential distribution for the first five years. Based on the three year survival rate of 67%, the hypothesized exponential distribution for control arm has a parameter lambda 0.133, which leads to an estimated five year overall survival rate of 51%. The patient accrual period is set for four years with five years of follow-up post accrual. Thus to detect a 10% difference from 51% in overall survival rate at five years at the significance level of 0.05 and with power of 0.85, a total of 700 patients would be needed for a two-sided log-rank test. To guard against patients ineligible or lost to follow-up, **the sample size was**

increased by approximately 10% to 770 patients.

There are two quality of life tools in this trial, The Functional Assessment of Cancer Therapy (*FACT-C*) and Anorectal function Assessment tool (*AFAT*). *FACT-C* is a multi-dimensional questionnaire that qualitatively assesses how the patient feels with respect to physical, social, and emotional well-being and relationship with doctor fulfillment. *AFAT* is a quantitative assessment of function.

FACT-C and *AFAT* will be administered according to the schedule in Section 12.1. Global quality of life change, the total score of the first 33 questions of *FACT-C* will be measured at each time point with a difference of ≥ 5.4 being clinically significant.⁵⁰ Sufficient sample size will be required to compare changes in quality of life for: Pre-Op vs. Post-Op, sphincter preserved vs. non-sphincter preserved; T1-2 N0 Pre-Op vs. Post-Op. The variance and *FACT-C* participation rates for each time point and each group will be determined at each interim analysis point. Completion of *FACT-C* will be requested of all patients, unless accrual to this portion of the trial to terminated early (*Section 13.5.1*). *AFAT* is experimental, accrual to this tool will be terminated to conjunction with *FACT-C*.

Based on the NCCTG 86-47-51/RTOG 88-11 study, the disease free survival rate of 57% at three year was also reported.⁵¹ Assuming an exponential distribution for the first five years, the parameter is estimated to be .187, which leads to an estimated five year disease free survival rate of 39%. The number 770 will provide a power of 0.85 to detect a difference of 10% from 39% in disease free survival at five year between the two arms, using a two-sided log rank test. In the case of statistical equivalence of overall survival and disease free survival, the treatment arm with the increased frequency of sphincter preservation, lower incidence of worst toxicity per patient, and higher quality of life will be recommended. These three components will be analyzed separately. Based on the data from NCCTG 86-47-51 study, the overall toxicity of 3+ grade is 30%, and the proportion of sphincter preservation surgery, both abdominal/perineal and anterior, is 50% (*personal communication with NCCTG statistical unit*). To detect a difference of 2%, 4%, 6%, 8%, and 10% from 30% of overall toxicity of 3+ grade, the target sample size will provide a power of 0.09, 0.21, 0.39, 0.61, and 0.79. Similarly, to detect a difference of 2%, 4%, 6%, 8%, and 10% from 50% of sphincter preservation surgery, the target sample size will provide a power of 0.08, 0.19, 0.36, 0.57, and 0.76. The comparisons of both sphincter preservation and toxicity between two treatment arms will be made using a z statistic for binomial proportions. However, in the case of no statistical differences in overall survival, disease free survival, sphincter preservation, 3+ grade toxicity, and quality of life, the treatment of choice will depend on clinicians' preference.

In conformance with the National Institute of Health (*NIH*) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have also considered the possible interaction between gender/to race and treatments. The NCCTG #79-47-51 adjuvant rectal trial revealed that there were no significant differences between males (60%) and females (40%) in overall (*p-value = 0.39*) and disease free (*p-value = 0.23*) survival outcomes (*personal communication with NCCTG statistical unit*). Nevertheless, if 60% of patients recruited in this study are male, the powers to detect 51% of overall survival at five years from 61%, 66%, and 71% are respectively 66%, 95%, and 100%. Likewise, if 40% of patients recruited in this study are female, the powers to detect 51% from 61%, 66%, and 71% are respectively 49%, 83%, and 97%. Since there are no prior data on racial proportion and difference, if any, in treatment efficacy, it is difficult to have a valid assessment. However, the power analysis can still be performed in the similar manner for the gender effect. Assuming this study will accrue 90% whites and 10% non-whites, the powers to detect 51% from 61%, 66%, and 71% are respectively 83%, 99%, and 100% for whites, and 16%, 31%, and 50% for non-whites. If this study can accrue 80% whites and 20% non-whites, the powers to detect 51% from 61%, 66%, and 71% are respectively 78%, 98% and 100% for whites, and 28%, 54%, and 79% for non-whites.

13.3 Accrual for the Study.

RTOG has completed a pre-operative study (*RTOG 81-15*) with ECOG participating. The average annual accrual rate was 71 patients over the last four years of accrual. The currently closed intergroup rectal study #0114 had an average annual accrual rate of 796 patients. (*CALGB spring 1993 Statistical Report*). Thus, the required accrual of 200/year for this study appears reasonable with members from other groups participating. If the patient accrual rate is less than 150 cases per year, the RTOG Research Strategy Committee will review the feasibility of continuing the study.

13.4 Randomization Schema.

The treatment allocation will be used in a randomized permuted block within strata to balance the patient factor other than institutions, as Zelen has described.⁵³ Patients will be stratified by clinical nodal involvement (N^- vs N^+) prior to randomization.

13.5 Analyses Plan.

13.5.1 Interim Analyses to Monitor Study Progress

Interim reports with statistical analyses will be prepared every six month until the initial paper reporting the treatment results has been submitted. In general, the interim report will contain information about the patient accrual rate with a projected completion date for the accrual phase, data quality, compliance rate of treatment delivery, FACT-C and AFAT completion, distribution of important prognostic baseline variables and the frequencies and severity of the toxicities. Measures of treatment efficacy such as overall survival (*Section 13.1.1*) and disease free survival (*Section 13.1.2*) will be reported by blinded treatment code to RTOG Data Monitoring Committee (DMC) at time points specified below.

After 200 patients are randomized (*100 per arm*), the variance and completion rated for FACT-C at each time point (*see Section 12.1*) will be computed. Assuming a clinically significant difference for global quality of life change is 5.4 the power will be calculated with the variance estimate and completion rate at the time of analysis for each group and time point of interest (*see Section 13.2*). The results of this analysis will be presented to the DMC.

The first test of statistical significance for overall survival differences between the two arms will be performed after 75% of the patients have been randomized to the study. If the treatment arms are significantly different (*log-rank test $p < .001$, two sided*), the recommendation will be made to the DMC to stop further patient accrual and report the study results. The second test of statistical significance for overall survival differences between the two arms will be performed when the last patient entry has been followed for at least one year. If the treatment arms are significantly different (*log-rank test $p < .001$, two sided*), the recommendation will be made to the DMC to report the study results immediately. The third test will be performed for all eligible cases with a minimum of three years of follow-up. Again, if the treatment arms are significantly different (*log-rank test $p < .001$, two sided*), the recommendation will be made to the DMC to report the study results immediately. Otherwise, the results will be reported after the last patient entry has been followed for at least five years and the treatment comparison then will use a significance level of .047. This level have been selected in order to preserve an overall significance level of .05 for the study.

13.5.2 Analysis for Reporting the Results

The primary hypothesis for the study is whether the control and the experimental arms have different effects on overall survival. All eligible patients randomized will be included in the comparison regardless of whether or not the patients fully receive their assigned protocol, the surgical findings of the stage of the disease, the positive margin, and the occurrence of metastasis. The overall survival may be shifted downward due to the inclusion of patients with metastasis and/or positive margin. On the other hand, the inclusion of patients with better prognosis into analysis may have a favorable effect upon the survival curve. We anticipate that the survival rates stay the same given both groups of patients are similarly distributed. All eligible patients randomized will be grouped by assigned treatment arm in the analysis. The primary hypothesis of treatment benefit will be tested using the Cox proportional hazard model with the stratification factor of clinical nodal involvement included as a covariate. Additional analyses of treatment effect will include modifying factors such as age, sex, surgical stage, and other patient characteristics. These analyses will also use the Cox proportional hazard model. The treatment comparison on disease free survival will be analyzed in a similar fashion.

The treatment comparison on the proportions of sphincter preservation and of 3+ grade toxicity will use the z-statistic for testing binomial proportions.

Analysis of quality of life data will be performed on all patients that complete baseline questionnaires. The analysis will utilize analysis of variance, repeated measures and analysis of variance, and quality adjusted survival methods for comparing treatments, and sphincter preserved vs. non-preserved. FACT-C with concentration on the additional concerns questions will be examined for responsiveness in follow-up. AFAT will be examined for internal consistency, content and construct validity, and responsiveness. Subgroup analysis of global quality of life will be undertaken for groups with sufficient

sample size

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APPENDIX I

**INT 0147
RTOG 94-01
CALGB 9483
ECOG R9401**

PHASE III INTERGROUP RANDOMIZED TRIAL OF PRE-OPERATIVE VS. POST-OPERATIVE COMBINED MODALITY THERAPY FOR RESECTABLE RECTAL CANCER

Sample Patient Consent Form

RESEARCH STUDY

I have the right to know about the procedures that are used in my participation in clinical research so as to afford me an opportunity to make the decision whether or not to undergo the procedure after knowing the risks and hazards involved. This disclosure is not meant to frighten or alarm me; it is simply an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

It has been explained to me that I have rectal cancer. The purpose of this study is to develop better ways to treat rectal cancer. At present, patients who have tumors originating in the rectum receive additional therapy after surgical removal of their tumor if the tumor is found to have extended through the wall of the bowel or if there is evidence of lymph node disease. This is done because of the known risk for a small number of tumor cells to remain, even after the best possible surgery. Patients with these tumors receive a combination of radiation therapy and chemotherapy in order to decrease the chance of the tumor recurring and to increase the chance of being cured of the tumor. A common chemotherapy treatment consists of 2 drugs: 5-Fluorouracil (*5-FU*) and leucovorin.

There is increasing evidence that patients who receive radiation therapy with concurrent chemotherapy before surgery rather than after surgery have fewer acute side effects as well as experience tumor shrinkage which makes surgery easier.

This investigational study is being done to try to determine whether combined chemotherapy and radiation therapy is better tolerated and more effective when given before surgery or after surgery. The doses and techniques of chemotherapy and radiation therapy used in both treatment programs are conventional and are very similar. The primary difference is the sequence in which they are delivered. In the pre-operative treatment program the radiation and some chemotherapy is delivered before surgery. The remainder of the chemotherapy is delivered after surgery. In the post-operative treatment program, the radiation and all of the chemotherapy is delivered after surgery. I will be assigned at random to either the pre-operative treatment program or the post-operative treatment program.

Treatment for cancer of the rectum may affect my life and how I feel in many ways. It is important to understand how I view my quality of life. In the future this information will help health care providers and patients make more informed treatment decisions.

DESCRIPTION OF PROCEDURES (6/12/95)

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

Chemotherapy will be performed as an outpatient. Each month (*cycle*) of chemotherapy requires an injection of drugs into my vein once a day for 5 days and requires approximately 2 hours each day. The chemotherapeutic drugs will include the

combination of 5-Fluorouracil (5-FU) and leucovorin.

Radiation therapy will be delivered to my pelvis 5 times/week for 25 treatments. This will be followed by another short course (*three treatments*) of radiation to the area of my tumor only (*known as a cone down or boost*).

The sequence of the surgery, radiation therapy and chemotherapy depends on which treatment program to which I am assigned. The 2 treatment programs are as follows:

1. Pre-Operative Treatment Program

Prior to surgery I will receive 2 months of chemotherapy. Radiation therapy will be delivered concurrently with chemotherapy. Following a 4-5 week rest period, surgery will be performed. Following an additional 4-6 week rest period, I will receive an additional 4 months of chemotherapy for a total of 6 months of chemotherapy.

2. Post-Operative Program

Following surgery, I will receive 2 months of chemotherapy followed by another 2 months of chemotherapy combined with radiation therapy, followed by 2 additional months of chemotherapy, for a total of 6 months of chemotherapy. At the beginning of the third month of chemotherapy, radiation therapy will begin. It will be delivered concurrently with chemotherapy. If the tumor is confined to the muscle wall of the rectum and the lymph nodes do not contain tumor, then I will not receive post-operative chemotherapy and radiation therapy since surgery alone is adequate therapy.

I will be asked to complete quality of life and functional assessment forms at several points in time before and after I complete treatments. It will take approximately 10 minutes each time to complete each of these forms.

Also, at the time of my diagnosis by biopsy, all or some of my tumor was removed. As is usually done, this tissue went to the hospital's pathology department for routine testing and diagnosis. After that process was complete, remaining tumor samples were stored in the pathology department. I am being asked for permission to use the remainder of the tumor for additional tests. Since this tissue was removed at the time of surgery or biopsy, the permission to use my tissue will not involve any additional procedure or expense to me. The tumor tissue's cells will be examined to see if any special "markers", tests which predict how a patient with tumors like mine responds to treatment, can be identified.

RISKS AND DISCOMFORTS (6/12/95)

Cancer treatments often have side effects. The treatment used in this program may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

Radiation Therapy: May cause loss of pubic hair, skin irritation, diarrhea, tiredness and nausea. These side effects usually resolve shortly after the treatment has been completed. Later on some more serious complications, which rarely occur, may also develop. These include intestinal obstruction and/or intestinal bleeding which may require surgery. If surgery is required later on, the risks involved may be slightly increased due to the radiation therapy. Radiation therapy to the pelvis will also cause sterility in fertile females and may require the use of hormones given orally (*by mouth*) to replace the hormones normally produced by the ovaries. Radiation therapy to the pelvis may rarely result in permanent sterility in males. In pregnant females, administration of radiation therapy to the pelvis will cause damage to the fetus (unborn child). If I am female and potentially pregnant I must have a negative pregnancy test before participation in the study. If I am not currently pregnant I must practice contraception.

Chemotherapy: 5-Fluorouracil (*5-FU*) may cause nausea, loss of appetite, vomiting, diarrhea, skin rash, inflammation of the fingers and toes, mouth sores, reversible hair loss, chest pain, increase sensitivity to sunlight, skin or nail darkening, and a depression of the bone marrow (*the blood forming organ*) which increase the risk of anemia, infection, or bleeding. If the bone marrow is depressed extensively, transfusions may be required to correct the problem. Escape of drug from the injection site may cause chronic ulceration of the skin or severe local reaction. It is also possible that changes may occur in the sperm of males which might produce birth defects in future children. Additional, more serious side effects which rarely occur include chest pain with some damage to the heart, loss of coordination or balance, or other manifestations of brain or

nerve damage. Leucovorin, when given in combination with 5-FU, may cause mild nausea, vomiting, soreness of the mouth, loss of appetite, diarrhea, hair loss, skin rash, and lowered blood counts.

Surgery: Possible risks of surgery include prolonged nausea or inability to eat, infection, non-healing tissues, and scarring around the intestines leading to blockage, bleeding, and pain which may require an operation for relief.

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

CONTACT PERSONS

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

_____ the investigator in charge at _____
_____. In addition, I may contact _____
_____ at _____ for information regarding patients' rights in research studies.

BENEFITS

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

It is hoped that the pre-operative treatment program will be associated with fewer side effects, decrease my tumor size, decrease the chance of my tumor recurring in my pelvis, and increase survival. However, I cannot be assured that these will occur.

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

ALTERNATIVES

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

My physician will explain any procedures related solely to research which would not otherwise be necessary. Some of these procedures may result in added costs but may be covered by insurance.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. No compensation for participation will be given. I understand that I am free to withdraw my consent to participate in this treatment program at any time without prejudice to my subsequent care. Refusal

to participate will involve no penalty, or loss of benefits. I am free to seek care from a physician of my choice at any time. If I do not take part in or withdraw from the study, I will continue to receive care. In the event of a research-related injury, I understand my participation has been voluntary.

CONFIDENTIALITY

I understand that records of my progress while on the study will be kept in a confidential form at this institution and also in a computer file at the headquarters of the Radiation Therapy Oncology Group (*RTOG*). The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (*FDA*), the National Cancer Institute (*NCI*), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in the conduct of this study may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including tissue and/or slides, may be sent to a central office for review and research investigation associated with this protocol.

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

Patient Signature (*or Legal Representative*)

Date

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

APPENDIX III
Rectal, AJCC 1992, 4th Edition

DEFINITION OF TNM

Primary Tumor (T)

- TX** Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma *in situ*: intraepithelial or invasion of the lamina propria *
T1 Tumor invades the submucosa
T2 Tumor invades the 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 the 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.

** Note: Direct invasion of other organs or structures includes invasion of other segments of colorectum by way of 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
N0 No regional lymph node metastasis
N1 Metastasis in one to three pericolic or perirectal lymph nodes
N2 Metastasis in four or more pericolic or perirectal lymph nodes
N3 Metastasis in any lymph node along the course of a named vascular trunk and/or metastasis to apical node(s) (*when marked by the surgeon*)

Distant Metastasis (M)

- MX** Presence of distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Histopathologic Grade (G)

- GX** Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

APPENDIX III (cont 'd)

STAGE GROUPING				Modified	
<u>AJCC/UICC</u>				<u>DUKES</u>	<u>Astler-Coller</u>
Stage 0 Tis	N0	M0	–	A	
Stage I T1	N0	M0	A	B1	
	T2	N0	M0		B1
Stage II T3	N0	M0	B	B2	
	T4	N0	M0		B3*
Stage III	T1-2	N1-3	M0	C	C1
	T3	N1-3	M0		C2
	T4	N1-3	M0		C3*
Stage IV	Any T	Any N	M1	–	

* B3 or C3 if lesion is adherent to or invades an adjacent organ or structure (*T4b*) but B2 or C2 if lesion perforates the visceral peritoneum (*T4a*) without adherence or invasion.

Note: Dukes B is a composite of better (*T3, N0, M0*) and worse (*T4, N0, M0*) prognostic groups, as is Dukes C (*Any T, N1, M0*) and Any T, N2, N3, M0.

APPENDIX V

ADVERSE DRUG REACTION REPORTING GUIDELINES

General Toxicity Reporting Guidelines

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates.

1. The Principal Investigator will report to the RTOG Group Chairman, the details of any unusual, significant, fatal or life-threatening protocol treatment reaction. In the absence of the Group Chairman, the report should be made to the Headquarters Data Management Staff (215/574-3214).
2. The Principal Investigator will also report to the Study Chairman by telephone the details of the significant reaction.
3. When directed, a written report containing all relevant clinical information concerning the reported event will be sent by the Principal Investigator to RTOG Headquarters. This must be mailed within 10 working days of the discovery of the toxicity unless specified sooner by the protocol.
4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures.
5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), when feasible, the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

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

6. When telephone reporting is required, the Principal Investigator should have all relevant material available. See attached reporting form for the information that may be requested.
7. See the specific protocol for criteria utilized to grade the severity of the reaction.
8. The Principal Investigator when participating in RTOG sponsored intergroup studies is obligated to comply with all additional reporting specifications required by the individual study.
9. Institutions must also meet their individual Institutional Review Board (IRB) policy with regard to their toxicity reporting procedure.
10. Failure to comply with reporting requirements in a timely manner may result in suspension of participation, of application for investigational drugs or both.

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.

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

a known side effect.

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. Form 3500 is to be used in reporting details (see attached). 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 and 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 only a reasonable suspicion.

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

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 <u>drug</u> monitor and RTOG Headquarters.
**A written report <u>may</u> be required. |

ii. Phase II, III Studies Utilizing Investigational Agents

- | | |
|--|---|
| - All fatal (grade 5) and life threatening | Report by phone to RTOG Headquarters and |
|--|---|

(grade 4) known adverse reactions due to investigational agent.

the Study Chairman within 24 hours
**A written report must be sent to RTOG within working days with a copy to IDB. (Grade 4 myelosuppression not reported to IDB)

- All fatal (grade 5) and life threatening (grade 4) unknown adverse reactions resulting from or suspected to be related to investigational agent.

Report by **phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**.
**A written report to follow within 10 working days.

- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent.

Report **in writing to RTOG Headquarters and IDB within 10 working days.

** See attached NCI Adverse Drug Reaction Reporting Form

APPENDIX VI

IDEALIZED RADIATION THERAPY FIELDS

FIGURE 1. Treatment fields (whole pelvis and conedown) for pre-operative radiation therapy for a low lying $T_3N_xM_0$ (or following a LAR for a $T_3N_1M_0$) rectal cancer. In this example the distal border is extended 3 cm beyond the primary tumor and the perineum is blocked. Since the tumor was a T_3 , the anterior field is at the posterior margin of the symphysis pubis (to treat only the internal iliac nodes).

APPENDIX VI

IDEALIZED RADIATION THERAPY FIELDS

FIGURE 2. Treatment fields (whole pelvis and conedown) for pre-operative radiation therapy for $T_3N_xM_0$ (or following a LAR for a $T_3N_1M_0$) rectal cancer. In this example the distal border is at the bottom of the obturator foramen and the perineum is blocked. Since the tumor was a T_3 , the anterior field is at the posterior margin of the symphysis pubis (to treat only the internal iliac nodes).

APPENDIX VI
IDEALIZED RADIATION THERAPY FIELDS

FIGURE 3. Treatment fields following an APR for a $T_3N_1M_0$ rectal cancer 2 cm. from the anal verge. In this example the distal border is extended to include the perineal scar. Since the distal border is being extended only to include the scar, the remaining normal tissues can be blocked.

APPENDIX VII

INTERGROUP PARTICIPATION IN RTOG STUDIES

GENERAL GUIDELINES

- I. REGISTRATION:** RTOG will be responsible for all registration/ randomizations. The procedure is:
- Each institution affiliated with a Cooperative Group will phone their group and supply the eligibility check information.
 - The participating Cooperative Group will then telephone RTOG 215/574-3191 between 8:30 a.m. and 5:00 p.m. ET and supply the necessary eligibility and stratification information. RTOG will then assign a case number and treatment assignment. The participating Cooperative Group will then inform its member institution.
 - RTOG will send a Confirmation of Registration and a Forms Due Calendar to the participating Cooperative Group for each case registered. The participating Group forward a copy of the calendar to the participating institution.
- II. PROTOCOL DISTRIBUTION:** Each participating cooperative group is responsible for distribution of the protocol to its members. All protocol amendments will be sent by RTOG to each participating Group office for distribution to member institutions. All communication with NCI regarding this protocol will be routed through the RTOG.
- III. INSTITUTIONAL PARTICIPATION:** It is the responsibility of each participating Cooperative Group to decide which of its member institutions may participate in this protocol. Each participating Cooperative Group must ensure that IRB approval was obtained prior to accession of cases.
- IV. CONFIRMATION/CALENDARS:** A Confirmation of Registration notice and a Data Collection Calendar is produced for each case registered and/or randomized. These will be distributed by RTOG to the appropriate cooperative group office for distribution to their members, if appropriate.

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

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

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

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

- V. FORMS:** Forms packages may be obtained from the participating Cooperative Group office. Attached is a list (Forms Package Index) of all data collection forms used in the study, the toxicity criteria for this study, if applicable and a sample of the data collection forms.

The RTOG assigned case and study number must be recorded on all data items submitted. Except for material which requires rapid review (see below), data should be routed according to the mechanism set up by the participating Group. Generally the participating group will require forms to be routed through their office and they will send the forms to

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- VI. **LABELS:** Preprinted labels are available for source document data items (radiographic reports, etc.) Supplied white labels are to be used for film identification.

The blank labels will be supplied to the participating Group for distribution to the individual institutions as patients are registered at RTOG.

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

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

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

Patients who receive no treatment whatsoever may be cancelled, however, written notification and an explanation must be received at RTOG Headquarters as soon as this has been determined. We must receive this notification not later than two weeks after registration. We will notify you of the determination made regarding the status of the case and instructions regarding subsequent data submission.

- VI. **RAPID REVIEW ITEMS:** Time critical data which requires rapid submission must be sent directly to RTOG (See Section V). These items are:

M² - Medical Oncology Treatment Planning Form (if required by the Protocol)
T2 - Protocol Treatment Form
T3 - Photon Localization film (for all fields treated initially)
T4 - Photon dose calculations (for all fields treated initially)

- IX. **REQUEST FOR STUDY INFORMATION**

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

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

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

- X. **QUESTIONS REGARDING:**

Randomization/Registration	Registration Secretary (215) 574-3191
Pathology	Pathology Coordinator (215) 574-3161
Protocols/Amendments	Protocol Administrator (215) 574-3195

**Data/Eligibility/Treatment/
Adverse Reactions/Data Management Procedures**

Data Manager (215)574-3214

**Radiotherapy data items (films,
radiographs, isodose summations,
treatment records, scans,
reports and calculations)**

Dosimetry Clerk (215) 574-3219

If you are unable to reach the person noted, and your call is urgent, ask to speak to any data manager.

XI. ADVERSE REACTIONS/AND TOXICITY

- From Radiotherapy:** Unusual toxicities, and all grade 4-5 toxicities are to be reported by telephone to RTOG Headquarters, the Group Chairman Dr. James Cox and to the Study Chairman. If the Chairman is unavailable, ask to speak to the Data Manager for this study.
- From Investigational Agents:** Are to be reported according to NCI guidelines. In addition, RTOG Headquarters and the Study Chairman are to receive notification as outlined by the NCI procedures, i.e. if telephone notification is necessary, RTOG and the Study Chairman must also be called.
- Copies of all toxicity reports and forms submitted to NCI must be sent to RTOG Headquarters also.
- From Commercial Drugs:** Are to be reported according to NCI/FDA guidelines. A copy of the reports and forms submitted to FDA must be sent to RTOG.