DEPARTMENT OF THE AIR FORCE
HEADQUARTERS UNITED STATES AIR FORCE

AIR1.941108.005

FROM: HQ AFMOA/SGPT
170 Luke Ave, Suite 400
Bolling AFB DC 20332-5113

24 Aug 93

SUBJ: Clinical Investigation Protocol 93-254 (Your Ltr, 12 Aug 93, 93HU099)

TO: David Grant Medical Center/SGI (Col Root)

1. For record-keeping purposes, we have assigned file number SGO 93-254 to the clinical investigation protocol entitled, "NSABP R-03, A Clinical Trial to Evaluate the Worth of Preoperative Mmultimodality Therapy (5FU-LV and RTX) in Patients with Operable Carcinoma of the Rectum." Please refer to this number in future correspondence regarding the study.

2. The Surgeon General's Clinical Investigation Committee concurred with your participation in the study on this date in accordance with AFR 169-6, Clinical Investigation and Human Test Subjects in the Medical Service, and HQ USAF/SG letter dated 20 Apr 93, Subject: Blanket Approval for Participation in National Cancer Institute Sponsored Groups. To assist in the proper accomplishment of this protocol you should assure compliance with AFR 169-6 as it pertains to annual progress reports, final reports, proper maintenance of records, and the application of written informed consent to all study participants.

3. Mrs. Darlene Casto, Clinical Investigation Program Manager, DSN 297-5078, is our point of contact for NCI-sponsored protocols.

Gerald J. Merritt

GERALD J. MERRITT, Col, USAF, BSC
Chief, Clin Investigations & Life Sci Div
Air Force Medical Operations Agency
Office of the Surgeon General

cc: HQ AMC/SG

93-254

DEPARTMENT OF THE AIR FORCE
DAVID GRANT USAF MEDICAL CENTER (AMC)
101 BODIN CIRCLE
TRAVIS AIR FORCE BASE, CALIFORNIA 94535-1800
CLINICAL INVESTIGATION FACILITY

FROM: DGMC/SGI (DSN 799-7400) 12 Aug 93

SUBJ: Institutional Review Committee Actions

TO: HQ AFMOA/SGPT
Bolling AFB, DC
20332-6188

1. The following new protocols were approved by the Institutional Review Committee on 26 Jul 93, and are forwarded for review by the Clinical
SGO# Investigation Committee, in accordance with AFR 169-6:

93-263 a. 93HU098, "Further Evaluation of 5-Hydroxytryptophol as a Marker of Recent Alcohol Use." Principal investigator: Capt Robert L. Hagan. Primary reviewer: Maj Rishi. Funding is requested for this protocol for $15,066.19, see Attachment 1 of the protocol for an accounting of supplies required. We understand O&M funds are depleted. We will use part of the $8,220.00 fall-out money you provided to initiate this project, with the remainder to be requested at the beginning of FY94.

93-254 b. 93HU099, "(NSABP-R-03)A Clinical Trial to Evaluate the Worth of Preoperative Multimodality Therapy (5FU-LV and RTX) in Patients With Operable Carcinoma of the Rectum." Principal investigator: Lt Col Kevin P. Ryan.

93-264 c. 93HU100, "The Effect of Oral d-Sotalol on Mortality in Patients With Atherosclerotic Coronary Heart Disease and Left Ventricular Dysfunction." Principal investigator: Maj Michael J. Keogh. Primary reviewer: Maj Foley.

93-240 d. 93HU101, "The Hypertension Optimal Treatment Study (HOT Study): A Prospective, Randomized, Multicenter, International Study." Principal investigator: Maj Robert Morrison. Primary reviewer: Capt Feller.

93-265 e. 93HU104, "Multi-Center Study of the Effect of Vitamin A on Lung Function in Patients With Pulmonary Disease." Principal investigator: Maj William J. Koenig.

93-266 f. CIF 93-E0064, EXEMPT, "Clinical Significance of MDR Gene Expression in Childhood Acute Lymphoblastic Leukemia." Principal investigator: Maj Mary M. Pelszynski. Funding support of $4,257.75 is requested from Maj Pelszynski to conduct this study. We will fund this with the $8,220.00 fall-out money your committee furnished to our Clinical Investigation Facility.

Charles F Root Jr

CHARLES F. ROOT, Jr., Col, USAF, BSC
Chairman, Institutional Review Committee

Atch
a/s

Approved/Disapproved

Robert W Gilmore

ROBERT W. GILMORE, Colonel, USAF, MC
Commander

93-254

PROTOCOL SUMMARY

David Grant USAF Medical Center (AMC)
101 Bodin Circle
Travis AFB, CA 94535-1800

TITLE: A Clinical Trial to Evaluate the Worth of Preoperative Multimodality Therapy (5FU-LV) and RTX) in Patients with Operable Carcinoma of the Rectum. (NSABP R-03)

I. PRINCIPAL INVESTIGATOR/OFFICE SYMBOL/PHONE EXTENSION:

Kevin P. Ryan, Lt Col, MC Department of Hematology/Oncology (707)423-5129

II. FACILITY:

David Grant USAF Medical Center
101 Bodin Circle
Travis Air Force Base, California 94535-1800

III. SUMMARY: This trial in patients with operable adenocarcinoma of the rectum compares the worth of seven cycles of 5-FU (FU) + leucovorin (LV) and radiotherapy (RTX), where the first three cycles are given preoperatively and the remaining four postoperatively, to seven cycles of FU-LV and RTX given postoperatively. The specific aims of this study are:

- To determine whether the administration of chemotherapy (FU-LV) with radiotherapy preoperatively is more effective than the administration of the chemotherapy and radiotherapy postoperatively in improving disease-free survival and survival in patients with operable carcinoma of the rectum.
- To determine if the administration of the above chemotherapy and radiotherapy preoperatively results in improvement in local recurrence rates when compared with the regimen administered postoperatively in this population of patients.
- To evaluate the response of rectal tumors to preoperative chemotherapy and radiotherapy and to correlate that response with disease-free survival and survival.
- To assess the down staging effect of preoperative chemotherapy and radiotherapy on the tumor size and the pathologic status of regional lymph nodes.
- To estimate the proportion of patients who can be converted to sphincter-saving surgical procedures from abdominoperineal resection. Furthermore, to estimate the proportion of patients who can be converted from sphincter-saving surgical procedures to local excision alone.

This research study is being conducted by the National Surgical Adjuvant Breast & Bowel Project (NSABP). It is anticipated that a total of 900 men and women will be entered into this trial throughout the United States and Canada. It is unknown how many of these patients will be enrolled at David Grant USAF Medical Center. The total length of time required to complete all the treatment cycles of this study is approximately 12 to 14 months. However, NSABP will attempt to follow patients for life.

IV. ADDITIONAL INFORMATION:

A. Drug Name: Both 5-Fluorouracil (NSC# 19893) and Calcium Leucovorin (NSC# 3590) are commercially available.

B. Investigation Use: Although both of these drugs have individually been approved by the Food & Drug Administration (FDA), their use in combination at these doses for the treatment of rectal cancer is considered to be experimental.

C. FDA Compliance: See para A. above.

D. Side Effects: The spectrum of toxicity includes stomatitis and esophagopharyngitis, that may lead to sloughing and ulceration. Diarrhea, anorexia, nausea, and emesis are commonly seen during therapy. Leukopenia usually follows every cycle of adequate therapy with fluorouracil. Alopecia and dermatitis may be seen in a substantial number of cases. The dermatitis most often seen is a pruritic maculopapular rash that usually appears on the extremities and; less frequently, on the trunk.

E. Dosage Rate Schedule: Dosage and duration of treatment for Group I and Group II can be found in Sections 13.0 and 14.0, pages 29-31 of the full protocol.

F. Modifications for Toxicity: Dose modification details can be found in Section 15.0, pages 31-33 of the full protocol.

G. Patient Selection: Eligible patients having histologic diagnosis by proctoscopic incisional biopsy of invasive rectal adenocarcinoma will be considered for entry in this study.

Eligibility Criteria:

- The patient must consent to be in the study. The informed consent form conforming to federal and institutional guidelines must be signed, witnessed, and dated prior to randomization.
- Patients in whom the diagnosis of invasive rectal cancer has been obtained by incisional (surgical or endoscopic) biopsy so that the majority of the tumor has not been removed are eligible.
- The interval between initial histologic diagnosis and randomization must be no more than 28 days.
- Patients must have a life expectancy of at least 10 years, excluding their diagnosis of cancer.
- The tumor should be either palpable by clinical rectal exam or be accessible by a proctoscope or sigmoidoscope, and its distal border should be located no more than 15cm from the anal verge.
- The tumor should be movable on clinical examination without evidence of fixation to the pelvis or to surrounding organs (vagina, prostate, bladder), beyond the limits of resection via exenteration.
- The patient must have no radiologic evidence of metastatic spread. The patient must have a CT of the abdomen and pelvis prior to randomization. Any suspicious findings, i.e., liver nodule, retroperitoneal adenopathy, will render the patient ineligible unless malignancy is ruled out by further tissue documentation (CT- or ultrasound-guided biopsy, laparoscopic biopsy, or open biopsy), prior to randomization.
- Evidence by CT scan of enlarged perirectal or pelvic lymph nodes is not a condition for ineligibility unless they appear to preclude adequate surgical removal.
- The WBC must be ≥ 4000/cu. mm and the platelet count must be ≥ 100,000/cu. mm.
- There must be evidence at randomization of adequate hepatic and renal function (bilirubin, SGOT or SGPT, and creatinine must be ≤ 1.5 times the upper limit of normal for the performing lab).
- Patients with more than one synchronous rectal lesion are eligible.

H. Data to be monitored before, during and after therapy include: All tables referenced below are found in the full protocol.

- **Prior to Randomization:** See Table 3, Columns 2 and 3, for those studies required prior to randomization, or prior to initiation of therapy.
- **Year 1:** See Table 3, Columns 4 through 8, for those studies required (a) every week prior to therapy, (b) every 8 weeks prito to beginning the next cycle, (c) every 3 months, (d) every 6 months, and (e) every 12 months during year 1.
- **Year 2:** See Table 4, Columns 2 through 4, for those studies required (a) every 3 months, (b) every 6 months, and (c) every 12 months during the second year following randomization.
- **Years 3-5:** See Table 4, Columns 5 and 6, for those studies required (a) every 6 months and (b) every 12 months during years 3 through 5 following randomization.
- **After Year 5:** Status of disease will be reported on a yearly basis. Treatment failures and the therapy instituted will be reported at the time of failure.

KEVIN P. RYAN, LtCol, USAF, MC
Chief, Hematology/Oncology

Approve/Disapprove

TERRENCE J. O'NEIL, Colonel, USAF, MC
Chairman, Department of Medicine

- Patients with a performance status of 0, 1, or 2 (see Appendix B of full protocol) are eligible.
- Patients presenting with intestinal obstruction are eligible, provided the only treatment prior to randomization is a decompressing colostomy.
- The patient must be accessible geographically for follow-up.

Ineligibility Criteria:

- Patients with malignant rectal tumors other than adenocarcinoma, i.e., sarcoma, lymphoma, carcinoid, squamous cell carcinoma, cloacogenic carcinoma, etc.
- Patients who have life expectancy of less than 10 years, excluding their diagnosis of cancer.
- Patients who demonstrate prior to randomization, evidence of free perforation, as manifested by free air or free fluid in the abdomen. (Patients with walled-off perforations are eligible.)
- Patients with a previous or concomitant malignancy, regardless of site, EXCEPT patients with squamous or basal cell carcinoma of the skin, or carcinoma in situ of the cervix that has been adequately treated.
- Patients who have received surgical treatment for rectal cancer, other than preliminary decompressing colostomy or diagnostic laparoscopy or laparotomy without any resection of primary tumor.
- Patients who have received any other therapy (radiation, chemotherapy) for rectal cancer prior to randomization.
- Patients in whom rectal cancer was diagnosed by excisional biopsy, (removal of polyp with adenocarcinoma, removal of villous adenoma with adenocarcinoma, etc).
- Patients in whom the interval between initial histologic diagnosis and randomization is greater than 28 days.
- Patients with a tumor whose distal border is located more than 15 cm from the anal verge.
- Patients whose tumor is fixed by clinical examination to surrounding structures, precluding the possibility of adequate surgical resection even with pelvic exenteration.
- Patients who show radiologic evidence of advanced disease (inoperable local-regional disease or metastatic disease). Evidence of biopsy-proven retroperitoneal lymph node involvement will deem a patient ineligible.
- Patients who demonstrate involvement of perirectal or pelvic lymph nodes with evidence of fixation to the pelvic side wall.
- Patients with a performance status of 3 or 4 (see Appendix B of full protocol)
- Patients having non-malignant systemic disease (cardiovascular, renal, hepatic, etc.), that would preclude their being subjected to the treatment (surgery, chemotherapy, and radiotherapy).
- Patients with active inflammatory bowel disease.
- Patients who are pregnant at the time of randomization.
- Patients with psychiatric or addictive disorders that would preclude obtaining informed consent.
- Patients who have multiple primary tumors involving both the colon and rectum that would preclude them from being classified as having only rectal cancer.
- Patients who are found, by endoluminal ultrasonography, to have a Duke's A lesion.

PROPOSAL FOR CLINICAL INVESTIGATION

David Grant USAF Medical Center (AMC)
101 Bodin Circle
Travis AFB, CA 94535-1800

TITLE OF INVESTIGATION: A Clinical Trial to Evaluate the Worth of Preoperative Multimodality Therapy (5FU-LV) and RTX) in Patients with Operable Carcinoma of the Rectum. (NSABP R-03)

I. Purpose of Investigation: This trial in patients with operable adenocarcinoma of the rectum compares the worth of seven cycles of 5-FU (FU) + leucovorin (LV) and radiotherapy (RTX), where the first three cycles are given preoperatively and the remaining four postoperatively, to seven cycles of FU-LV and RTX given postoperatively.

The reasons for employing preoperative radiotherapy as they relate to sphincter preservation and the reasons for the addition of preoperative chemotherapy are discussed in Section 2.2 of the full protocol. The justification for the study design in regards to the selection of three preoperative cycles (one cycle of FU-high dose LV followed by two cycles of FU-low dose LV and RTX) is based on clinical rationale. Because of the length of each cycle of therapy with FU-high dose LV (8 weeks with the rest period), attempting to administer all cycles preoperatively would result in delaying the operation for almost one year following diagnosis. Without proof of the value of chemotherapy in the preoperative setting, it would be difficult for physicians and patients to wait for such a prolonged period of time, especially if their is no complete response of the primary tumor.

Any development of metastatic disease during the administration of preoperative chemotherapy that may simply reflect natural history manifestation could be taken as progression of disease in the preoperative arm. Furthermore, after preoperative chemotherapy, the detection of residual pathologic disease in the lymph nodes following surgery may be viewed by patients and investigators as necessitating the administration of further chemotherapy.

The administration of the three cycles before operation (with radiotherapy given with cycles 2 and 3), certainly has the potential of inducing most of the expected tumor response prior to surgery, resulting in the desired down staging and sphincter preservation. On the other hand, the administration of one cycle of chemotherapy before radiotherapy and surgery tests the biological concept of suppression of micrometastatic tumor kinetics by chemotherapy following local tumor reduction by radiotherapy and surgery.

This research study is being conducted by the National Surgical Adjuvant Breast & Bowel Project (NSABP). It is anticipated that a total of 900 men and women will be entered into this trial throughout the United States and Canada. It is unknown how many of these patients will be enrolled at David Grant USAF Medical Center. The total length of time required to complete all the treatment cycles of this study is approximately 12 to 14 months. However, NSABP will attempt to follow patients for life.

II. Technical Approach:

A. TREATMENT REGIMEN FOR GROUP I: Preoperative and Postoperative FU-LV and Preoperative RTX

Initiation of Therapy

Patients must be randomized no later than 28 days after histologic diagnosis. The surgeon should state the intended surgical procedure prior to randomization. Cycle 1 of chemotherapy should begin no later than 3 weeks after randomization. Surgery will be performed within 8

weeks of the completion of radiotherapy when blood counts allow and when all toxicities have resolved. Acceptable surgical procedures include abdominoperineal resection, low anterior resection, coloanal resection, local excision (transanal, transacral, transphincteric).

Dosage and Duration of Treatment

Patients will receive seven cycles of therapy; the duration of cycles 1 and 4-7 is 8 weeks (chemotherapy during radiotherapy is considered cycles 2 and 3).

- LV -500 mg/m^2 diluted in 250 cc of normal saline administered i.v. as a 2-hour infusion weekly for 6 consecutive weeks (on days 1, 8, 15, 22, 29, 36), followed by a rest period. Repeat treatment begins 21 days after the date of administration of the sixth dose of the previous cycle (one cycle = 8 weeks).

- 5-FU -500 mg/m^2 administered i.v. bolus 1 hour after beginning the LV infusion, weekly for 6 weeks (on days 1, 8, 15, 22, 29, 36), followed by a rest period. Repeat treatment begins 21 days after the date of administration of the sixth dose of the previous cycle (one cycle = 8 weeks). The rest period between cycle 1 and RTX may vary, depending on the day of the week on which the last dose of cycle 1 was given, but it should not be less than 20 days or more than 26 days.

Regardless of dose modifications or delays, FU-LV therapy will not continue beyond 60 weeks from the time of initiation of treatment.

Timing of FU-LV and Radiotherapy

Patients will begin radiation therapy after completion of cycle 1 of FU-LV when WBC, platelet counts and symptoms allow (within 3 weeks after day 36 of cycle 1). Radiotherapy should start on a Monday.

During radiotherapy FU 325 mg/m^2 and LV 20 mg/m^2 will be given daily x 5 for the first and fifth week. FU-LV will be administered within 2 hours following the radiotherapy. LV should be diluted in 100 cc of normal saline and administered by iv infusion over 30 minutes and FU should be given as iv bolus 20 minutes later. FU-LV administered during radiotherapy will be considered cycles 2 and 3. Counts will be performed weekly during radiation therapy. Surgery will be performed after completion of the radiotherapy, provided any toxicity has resolved, but no later than 8 weeks after radiotherapy. Cycle 4 of FU-LV will begin after recovery from surgery is complete, but no later than 4 weeks postoperatively.

B. TREATMENT REGIMEN FOR GROUP 2: Postoperative FU-LV and RTX

Initiation of Therapy

Patients must be randomized no later than 28 days after histologic diagnosis. The surgeon should state the intended surgical procedure prior to randomization. Surgery will be performed within 3 weeks after randomization. Acceptable surgical procedures include: abdominoperineal resection, low anterior resection, coloanal resection, local excision (transanal, transacral, transphincteric). Chemotherapy will begin after recovery from surgery, but no later than 4 weeks postoperatively.

Dosage and Duration of Treatment

Patients will receive seven cycles of therapy; the duration of cycles 1 and 4-7 is 8 weeks (chemotherapy during radiotherapy is considered cycles 2 and 3).

- LV -500 mg/m^2 diluted in 250 cc of normal saline and administered i.v. as a 2-hour

infusion weekly for 6 consecutive weeks (on days 1, 8, 15, 22, 29, 36), followed by a rest period. Repeat treatment begins 21 days after the date of administration of the sixth dose of the previous cycle (one cycle = 8 weeks).

- 5-FU -500 mg/m^2 administered i.v. bolus 1 hour after beginning the LV infusion, weekly for 6 weeks (on days 1, 8, 15, 22, 29, 36), followed by a rest period. Repeat treatment begins 21 days after the date of administration of the sixth dose of the previous cycle (one cycle = 8 weeks). The rest period between cycle 1 and RTX may vary, depending on the day of the week on which the last dose of cycle 1 was given, but it should not be less than 20 days or more than 26 days.

Regardless of dose modifications or delays, FU-LV therapy will not continue beyond 60 weeks from the time of randomization.

Timing of FU-LV and RTX

Patients will begin radiation therapy after completion of cycle 1 of FU-LV 21 days after the date of administration of the sixth dose of cycle 1, once WBC, platelet counts, and symptoms allow. Radiotherapy should start on a Monday.

During radiotherapy FU 325 mg/m^2 and LV 20 mg/m^2 will be given daily x 5 for the first and fifth week. FU-LV will be administered within 2 hours following the radiotherapy. LV should be diluted in 100 cc of normal saline and administered by iv infusion over 30 minutes and FU should be given as iv bolus 20 minutes later. FU-LV administered during radiotherapy will be considered cycles 2 and 3. Counts will be performed weekly during radiation therapy. Cycle 4 of FU-LV will begin after completion of radiotherapy when counts allow, but no later than 5 weeks after radiotherapy.

III. Equipment and Supplies: None requested.

IV. Investigation Schedule:

A. Anticipated date investigation will begin: Upon SGO approval

B. Duration: 6.5 years

C. Time Phases: Not applicable

D. Approximate date of completion: 2000

V. Experimental Subjects: All subjects will be treated in compliance with AFR 169-6, MCR 169-1, and applicable FDA and HHS guidelines.

VI. Use of Investigational Drugs: Not applicable to this protocol.

VII. Personnel Data:

A. Medical Facility Commander: Col Robert W. Gilmore

B. Principal Investigator:

Kevin P. Ryan, LtCol, USAF, MC
Chief, Hematology/Oncology

C. Associate Investigators:

James M. Long, Maj, USAF, MC
Staff, Hematology/Oncology

Thomas Bradley, Maj, USAF, MC
Staff, Hematology/Oncology

Charles Goldman, Maj, USAF, MC
Chief, Surgical Oncology

VIII. Manpower:

1 Lt Col, AFSC R9386B	2 hrs/week duty time	1 off duty time/week
3 Major, AFSC R9386B	2 hrs/week duty time	1 off duty time/week

IX. Summary Sheet: See Attachment.

X. Bibliography: See Section 24.0, pages 57-60 of *full protocol*.

SGO # 23 June, 1993

INFORMED CONSENT DOCUMENT

DAVID GRANT USAF MEDICAL CENTER
101 Bodin Circle
Travis AFB, CA 94535-1800

TITLE OF STUDY: A Clinical Trial to Evaluate the Worth of Preoperative Multimodality Therapy (5FU-LV) and RTX) in Patients with Operable Carcinoma of the Rectum. (NSABP R-03)

1. INVESTIGATORS' NAMES, DEPARTMENTS, PHONE NUMBERS:

Kevin P. Ryan, Lt Col, MC	Department of Hematology/Oncology	(707)423-5129
James M. Long, Maj, MC	Department of Hematology/Oncology	(707)423-5129
Thomas Bradley, Maj, MC	Department of Hematology/Oncology	(707)423-5129
Charles Goldman, Maj, MC	Department of Hematology/Oncology	(707)423-5129

2. PURPOSE: I, _____, understand that I have been diagnosed with operable carcinoma of the rectum. I am being asked to participate in a research study to determine the best method for treating cancer such as mine. The purpose of this study is to determine whether 1) it is better to give radiotherapy and some of the chemotherapy before surgery and ~~more~~ additional chemotherapy after surgery rather than 2) to give all the therapy (chemotherapy and radiotherapy) after surgery.

Previous studies have established that using a combination of chemotherapy (anticancer drug treatments) and radiotherapy (radiation treatment) after surgery is effective in the treatment of cancer of the rectum when the tumor penetrates through the bowel wall or when there is involvement of lymph nodes in the area. Studies have also shown that the combination of 5-fluorouracil (5-FU) and leucovorin (LV) appears to be an effective chemotherapy regimen. There is now information from the laboratory and from patients with locally advanced cancer that beginning the therapy before operation may be of increased benefit in decreasing the recurrence of further cancer and in improving the chances of survival. The administration of chemotherapy and radiotherapy before surgery may also reduce the tumor size so that less extensive surgery is necessary. It has been determined to the best of my physician's ability that my tumor has not spread to any other organs that would require surgical removal.

This research study is being conducted by the National Surgical Adjuvant Breast & Bowel Project (NSABP), an organization with significant experience in conducting clinical trials in patients with rectal cancer. It is anticipated that a total of 900 men and women will be entered into this trial throughout the United States and Canada. It is unknown how many of these patients will be enrolled at David Grant USAF Medical Center. The total length of time required to complete all the treatment cycles of this study is approximately 12 to 14 months. My treatment will be explained in detail later in this document.

3. PROCEDURES: If I agree to participate in this study, I will be assigned to receive <u>one</u> of the following treatments:

Group 1: Chemotherapy and radiotherapy treatments before surgery, followed by chemotherapy alone after surgery.
Group 2: Surgery, followed by chemotherapy and radiotherapy treatments.*

I will be placed by chance into one of these two groups. This chance selection process is called *randomization* (similar to the flipping of a coin) and is frequently used in experimental studies. I understand that I have approximately a 50-50 chance of receiving either treatment.

Dosing Procedure: In both groups, chemotherapy will consist of the following drugs: LV 500 mg/m^2 will be administered intravenously (in a vein in my arm) over a 2-hour period; one hour after the infusion begins, I will be given a second drug, 5-FU 500 mg/m^2, intravenously over a period of several minutes. Although both of these drugs have individually been approved by the Food & Drug Administration (FDA), their use in combination at these doses for the treatment of rectal cancer is considered to be experimental.

There will be seven treatment cycles of chemotherapy in this study. In cycles 1, 4, 5, 6, and 7, chemotherapy will be administered once a week for 6 weeks, followed by a two-week rest period. Treatment will be restarted 21 days after the day of the last dose of the previous cycle (each cycle = 56 days). As described above, the chemotherapy will consist of both LV and 5-FU administered intravenously.

In treatment cycles 2 and 3, I will receive radiotherapy 5 days a week for a total of 5 weeks and for 3 days during the sixth week, followed by a rest period of up to 8 weeks. During the radiotherapy, I will receive two more cycles of chemotherapy. In each cycle I will receive 5-FU 325 mg/m^2 and LV 20 mg/m^2 intravenously over a period of 30 minutes each day for 5 days during the first (cycle 2) and fifth (cycle 3) weeks of the radiotherapy.

If I am assigned to Group 1, I will have my surgery at the end of cycle 3. This will then be followed by a rest period of up to 4 weeks before I start cycle 4.

If I am assigned to Group 2, I will first have my surgery, followed by a rest period of up to 4 weeks, before I start any of my chemotherapy or radiotherapy.

The total length of time required to complete all the treatment cycles of this study is approximately 12 to 14 months.

**(Since the tumor has not yet been removed, it is impossible for my physician to know for sure whether it penetrates through the entire bowel wall or if the lymph nodes in the area are involved. From the testing done so far, there is a good possibility that one of these conditions is present. If I am randomized to Group 2 and the physician finds that I have a tumor that does not penetrate through the bowel wall and does not involve the lymph nodes in the area, then I will be treated at the discretion of my physician. Since the prognosis in such cases is generally good with surgery alone, further therapy may not be considered necessary. During my surgery, if I am found to have a tumor that involves other organs, or that is inoperable, then I will be treated at the discretion of my physician.)*

Testing & Exams: Laboratory tests and physical exams will be performed during each course of treatment to monitor my physical condition for continuation of therapy. For the lab tests, about 1-2 tablespoons of blood will be drawn from a vein in my arm with a needle. During the administration of chemotherapy and radiotherapy before surgery (Group 1), the size of the tumor will be assessed on two occasions in order to monitor my response to therapy. The first time will be after completion of the chemotherapy, before starting radiotherapy. The second time will be after completion of the radiotherapy and can be done right before surgery while I am asleep. It may be necessary for me to have another endoscopic or endorectal ultrasound to assess my tumor.

During the second year of my study participation, laboratory tests and a physical exam will be repeated every 3 months, then, during the third, fourth, and fifth years of the study, the tests and exams will be performed every 6 months.

During the 5 years after I am entered into this study, chest X-rays and a barium enema or endoscopy will be done every 12 months.

Additional laboratory tests or X-rays may be performed at any time should my physician feel they are medically necessary.

Duration of Participation: I understand that I am expected to complete all the cycles of therapy as described in the dosing procedure and to continue with the follow-up visits as described in the testing and examination section. I realize that, at this time, the NSABP wishes to continue to follow my medical condition at least annually for life.

4. BENEFITS: I understand that no benefit can be guaranteed. It has not been proven that either treatment regimen will increase my chances for permanent cure, and there is no evidence at this time that either treatment is better than the other. The potential benefit from this study is to decrease the recurrence rate and to improve the survival rate of patients with rectal cancer such as mine.

5. ALTERNATIVES: Alternative treatments might be radiotherapy alone or similar drugs given alone or in combination with the same or different schedules outside of this study, but there is no evidence these would work better than the treatments proposed here. I have discussed the alternatives with my physician and have been given the opportunity to ask questions.

6. RISKS/INCONVENIENCES: If I am a female of childbearing potential, my physician will do a pregnancy test before I participate in the study. I will not be allowed to participate in this research study if I am pregnant. I will be expected to use adequate birth control measures for the duration of the study. If I should become pregnant during the study, I will immediately inform my physician. If I have recently been pregnant and am lactating, upon entry into the protocol I will terminate breast-feeding.

I should expect that the chemotherapy will cause side effects in varying degrees and that some might be serious enough to require my being admitted to the hospital for supportive care. The combination of 5-FU and LV given in this trial may cause severe gastrointestinal toxicity. The symptoms may be exhibited as mild-to-severe mouth ulcers, as well as moderate-to-severe diarrhea. The mouth ulcers may be severe enough to inhibit taking an adequate amount of fluids or food by mouth, resulting in severe dehydration and weight loss. Other common side effects are nausea, vomiting, skin rash, and temporary hair loss.

The 5-FU may depress the function of the bone marrow, lowering my white blood count and platelet count. These conditions can increase the susceptibility to infections, bruising, and bleeding. Allergic sensitization has been reported in a few cases.

Risks Associated with Radiotherapy: Radiotherapy may cause transient nausea, vomiting, poor appetite, diarrhea, some irritation and burning of the skin, and, sometimes, urinary discomfort. Towards the end of treatment, fatigue may occur. These symptoms disappear after the completion of therapy. If necessary due to side effects, radiation therapy will be stopped temporarily or the chemotherapy dose will be decreased until the symptoms are alleviated. Once the symptoms are alleviated, radiation therapy and/or full-dose chemotherapy will be resumed. As a result of the study treatments, some months or years after therapy, there may be an increased risk of obstruction of the bowel, that may require surgery. Also, the capacity of the bladder may be reduced, and there is a possibility that some bleeding into the bladder could occur as a result of changes in the bladder blood vessels. The skin may show some pigmentation and scarring and, later, some slow healing after injury in the area exposed to radiation.

Risks Associated with Surgery: I am aware that any surgical procedure involves risks, including risks from anesthesia. Bleeding, infection, and clots in my veins that could travel to my lungs are some of the risks of surgical procedures. Surgery required for rectal cancer may result in bladder problems such as urinary incontinence, a temporary or permanent colostomy, or sexual impotence. Before my surgery, I will be required to sign another consent form required by the institution where I receive my surgery.

Other Risks: In studies where radiotherapy was given before surgery, there was evidence of a somewhat higher risk of developing skin infections in the area of radiation. This risk was low overall and, generally, these infections resolved with local care and antibiotics. However, should I develop this type of infection, it may prolong my hospital stay for a few days.

If my tumor becomes larger while I am undergoing chemotherapy before my surgery, then the chemotherapy will be stopped and I will be treated with radiotherapy followed by surgery. If my tumor becomes larger while I am receiving radiotherapy, then the radiotherapy will be interrupted and I will undergo surgery.

Mild pain or bruising may result from the needle sticks required for blood collections in this study. The risk of infection is minimal.

Precautions: Unanticipated side effects may occur with any of these drugs. It is extremely important that I report all symptoms that I experience to my physician.

Chemotherapy may cause harm to an unborn baby; therefore, I understand that, if I am a woman capable of becoming pregnant, I should use effective birth control measures while I am receiving treatment.

If any physician other than the study physician prescribes medication for me for another condition, I will inform the study staff.

7. PRIVACY ISSUES: *Records of my participation in this study may only be disclosed in accordance with federal law, including the Federal Privacy Act, 5 USC 552a, and its implementing regulations. DD Form 2005 contains the Privacy Act Statement for the records. I understand that records of this study may be inspected by the U.S. Food and Drug Administration (FDA), the National Cancer Institute (NCI), the NSABP, and/or their designee.*

8. EVENT OF INJURY: I understand that my entitlement to medical and dental care and/or compensation in the event of injury are governed by federal laws and regulations, and if I have questions about my rights or if I believe I have received a research-related injury, I may contact the Medical Center Patient Representative, at 423-3703 or the Director of the Clinical Investigation Facility at 423-7400 and/or the investigator _____ at _____.

9. EVENT OF UNANTICIPATED EVENT: In the event that an unanticipated event (clinical or medical misadventure) occurs during my participation in this study, I will be informed. If I am not competent at the time to understand the nature of the event, such information will be brought to the attention of my guardian or next of kin.

10. DECISION TO PARTICIPATE: The decision to participate in this study is completely voluntary on my part. No one has coerced or intimidated me into participating in this program. I am participating because I want to. _____ has adequately answered any and all questions I have about this study, my participation, and the procedures involved. I understand that the investigator will be available to answer any questions concerning procedures throughout this study. I understand that if significant new findings develop during the course of this study that may relate to my decision to continue participation, I will be informed. I further understand that I may withdraw this consent at any time and discontinue further participation in this study without prejudice to my entitlement to care. I also understand that the investigator of this study may terminate my participation in this study at any time if he/she feels this to be in my best interest.

(Subject's Printed Name)	(Subject's SSN)	
(Subject's Signature)	(Sponsor's SSN)	(Date)
(Advising Physician's Signature)	(Physician's SSN)	(Date)
(Witness) (Must witness all signatures above)	(Witness's SSN)	(Date)

Privacy Act of 1974 applies. DD Form 2005 filed in Clinical/ Medical Records.

Distribution: (1) CIF; (2) Subject's Medical Record, (to be maintained permanently); (3) Principal Investigator; (4) Subject.

DEPARTMENT OF THE AIR FORCE
DAVID GRANT USAF MEDICAL CENTER(AMC)

FROM: SGJ 23 Jun 93

SUBJ: Legal Review of Informed Consent Document

TO: SGI

I have reviewed the informed consent document titled, **"A Clinical Trial to Evaluate the Worth of Preoperative Multimodality Therapy (5FU-LV) and RTX) in Patients with Operable Carcinoma of the Rectum. (NSABP R-03)"** ***Principal Investigator: Dr. Kevin Ryan.*** *It has* been reviewed, approved and has been found to be in compliance with Air Force Regulation 169-6.

ERIC S. ISRAEL, CAPT, USAF
Judge Advocate
Medical Law Consultant

NSABP PROTOCOL NO. R-03

A CLINICAL TRIAL TO EVALUATE THE WORTH OF PREOPERATIVE MULTIMODALITY THERAPY (5FU-LV and RTX) IN PATIENTS WITH OPERABLE CARCINOMA OF THE RECTUM

NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT (NSABP)

OPERATIONS CENTER
Room 914 Scaife Hall
3550 Terrace Street
University of Pittsburgh
Pittsburgh, PA 15261

TELEPHONE: 412-648-9720
FAX: 412-648-1912

BIOSTATISTICAL CENTER
Suite 600
230 McKee Place
Pittsburgh, PA 15213

TELEPHONE: 412-624-2666
FAX: 412-624-1082

CLINICAL COORDINATING CENTER
Suite 601
230 McKee Place
Pittsburgh, PA 15213

TELEPHONE: 412-624-6221
FAX: 412-624-0862

NSABP Chairman: Bernard Fisher, M.D.
Director, NSABP Biostatistical Center: Carol K. Redmond, Sc.D.

PROTOCOL PREPARATION:
T. Mamounas, M.D.
H. Rockette, Ph.D.
N. Wolmark, M.D.
L. Wickerham, M.D.
N. Petrelli, M.D.
M. Deutsch, M.D.
M. Ketner, R.N.
D. Pollak, R.N., M.S.N.

CONTRIBUTORS:
Anatolio Cruz, M.D.
Philip Gordon, M.D.
David Hyams, M.D.
Samuel Jacobs, M.D.
Maureen Kavanah, M.D.
Harvey Lerner, M.D.
Marvin Wexler, M.D.

Final Version as of May 18, 1993 (PLEASE DESTROY ALL OTHER VERSIONS)

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1.0 SUMMARY OF THE STUDY

This trial in patients with operable adenocarcinoma of the rectum compares the worth of seven cycles of 5-FU (FU) + leucovorin (LV) and radiotherapy (RTX), where the first three cycles are given preoperatively and the remaining four postoperatively, to seven cycles of FU-LV and RTX given postoperatively (Figure 1).

1.1 Group 1: Preoperative and postoperative FU-LV and preoperative RTX (Figure 2).

Chemotherapy should begin no later than 3 weeks after randomization. In cycle 1, LV 500 mg/m^2 will be administered by i.v. infusion over 2 hours; FU 500 mg/m^2 will be given by i.v. bolus 1 hour after beginning LV infusion. Treatment will be given weekly for 6 weeks (on days 1, 8, 15, 22, 29, 36), followed by a rest period. **Treatment will be restarted 21 days after the date of administration of the sixth dose of the previous cycle (one cycle = 8 weeks).** Radiotherapy will begin after completion of cycle 1. Since radiotherapy should start on a Monday, the rest period after cycle 1 may vary from 20-26 days, based on the day of the week on which the last dose of cycle 1 was administered. FU 325 mg/m^2/day and LV 20 mg/m^2/day will be given for 5 days during the first and fifth weeks of radiotherapy (cycles 2 and 3). Surgery will be performed after completion of the radiation therapy, once any toxicity has resolved, but no later than 8 weeks after completion of radiotherapy. After recovery from surgery, but no later than 4 weeks, four more cycles of FU with LV will be given as in cycle 1, for a total of seven cycles.

1.2 Group 2: Postoperative FU-LV and RTX (Figure 2)

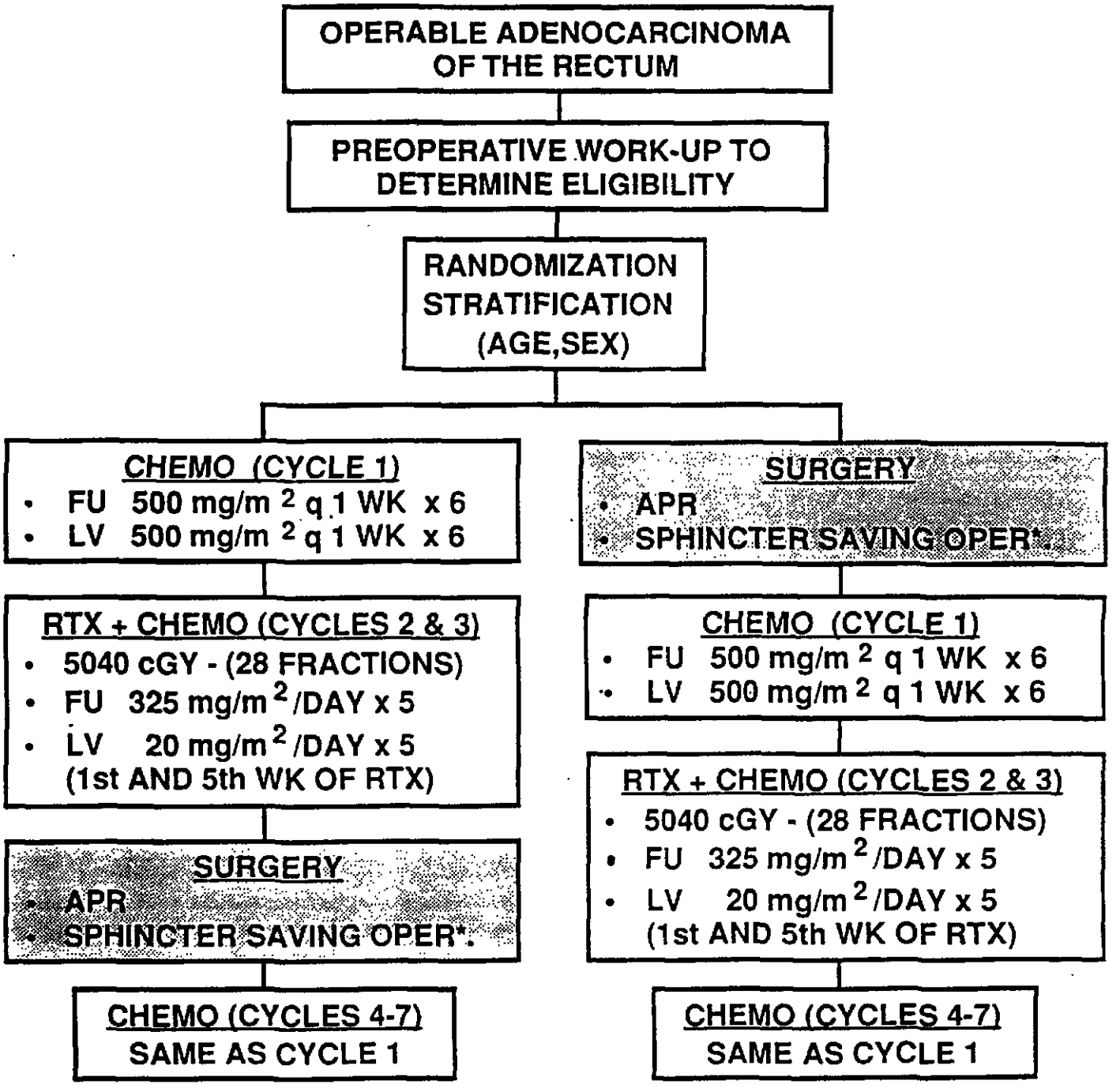
Surgery should be performed no later than 3 weeks after randomization. Chemotherapy will begin after recovery from surgery is complete but no later than 4 weeks postoperatively. In cycle 1 LV 500 mg/m^2 will be administered by i.v. infusion over 2 hours; FU 500 mg/m^2 will be given by i.v. bolus 1 hour after beginning LV infusion. Treatment will be given weekly for 6 weeks (on days 1, 8, 15, 22, 29, 36), followed by a rest period. **Treatment will be restarted 21 days after the date of administration of the sixth dose of the previous cycle (one cycle = 8 weeks).** RTX will begin after completion of cycle 1. Since radiotherapy should start on a Monday, the rest period after cycle 1 may vary from 20-26 days, based on the day of the week on which the last dose of cycle 1 was administered. FU 325 mg/m^2/day and LV 20 mg/m^2/day will be given for 5 days during the first and fifth weeks of radiotherapy (cycles 2 and 3). Cycle 4 of FU-LV will begin after completion of radiotherapy when counts allow, but no later than 5 weeks. Four more cycles of FU with LV will be given as in cycle 1, for a total of seven cycles.

2.0 BACKGROUND

2.1 Rationale for Selection of Chemotherapy with Radiotherapy as the Adjuvant Therapy Employed

Postoperative high-dose radiotherapy has been shown in randomized and nonrandomized studies to significantly decrease the rates of local recurrence in rectal cancer.[1-6] No

NSABP PROTOCOL R-03



* LAR, COLOANAL RESECTION OR LOCAL EXCISION

Figure 1

[redacted]

-03
ROUP 1)

& 3**	REST		REST	CYCLES 4–7
0,31,32,33 • •	UP TO 8 WKS.		UP TO 4 WKS.	SAME AS CYCLE 1
	← NO Rx →		← NO Rx →	FU: 500 mg/m^2 LV: 500 mg/m^2

(GROUP 2)

CYCLES 2 & 3**	REST	CYCLES 4–7
, 4, 5 • • • 29,30,31,32,33 • •	UP TO 5 WKS.	SAME AS CYCLE 1
25 mg/m^2 20 mg/m^2 RTX →	← NO Rx →	FU: 500 mg/m^2 LV: 500 mg/m^2

an 26 days, depending on the day of the

significant improvement has been demonstrated, however, in disease-free survival and in overall survival. Postoperative chemotherapy alone has been found to increase the disease-free survival and has demonstrated borderline survival benefit.[2] The combination of both has been evaluated in several prospective trials.[1,7] An indication of benefit in both reduction of local recurrence and improvement in disease-free survival and survival has been demonstrated. Results from large-scale trials currently in progress will provide definitive answers regarding the worth of the combined regimen.

2.1.1 Role of Postoperative Radiotherapy

Several randomized[1-3] and nonrandomized[4-6] studies have demonstrated a reduction in the rate of local recurrence with the use of adjuvant postoperative radiotherapy (Table 1). However, no impact on the 5-year survival rates has been observed.

TABLE 1. STUDIES OF POSTOPERATIVE RADIOTHERAPY IN RECTAL CANCER

Source	5-Year Survival (%)		Local Recurrence (%)	
Randomized	Surgery	Surgery + RTX	Surgery	Surgery + RTX
GITSG[1]	45	51	24	20
NSABP R-01[2]	43	41	25	16
Dutch[3]	57	45	33	24

Gastrointestinal Tumor Study Group (GITSG) Protocol 7175:[1] This trial was a four-arm study comparing the effect in the postoperative setting of no therapy, radiotherapy, chemotherapy (MeCCNU and FU), and a combination of both in the disease-free survival and overall survival of patients with Dukes' B and Dukes' C rectal cancers. Randomization was discontinued before the accrual of the originally designed sample size, due to the fact that the surgery-alone arm showed inferior outcome when compared to the other three arms. Twenty percent of patients developed local-regional recurrence in the radiotherapy group versus 24% of patients in the surgery-only group. This difference was not statistically significant. There was no impact from radiotherapy on disease-free survival or survival.

National Surgical Adjuvant Breast and Bowel Project, Protocol R-01:[2] Protocol R-01 was a three-arm study in 555 patients with Dukes' stage B and C carcinoma of the rectum, comparing surgery alone to surgery followed by postoperative radiotherapy and surgery followed by postoperative chemotherapy. The group receiving postoperative radiotherapy (4600-4700 cGy) demonstrated an overall reduction in local-regional recurrence from 25% to 16% ($p=0.06$) when compared to the group that received surgery alone. There was no significant benefit in overall disease-free survival or survival.

Dutch Multicenter Trial:[3] In a prospective randomized multicenter trial in the Netherlands, 172 patients who had undergone surgical resection for rectal adenocarcinoma received either 5000 cGy of postoperative radiation in 5 weeks or no adjuvant therapy. After 5 years of follow-up, more local recurrences were seen in the control group (33%) than in the radiation therapy group (24%), but the difference was not statistically significant. No influence on disease-free survival or survival could be detected. The improvement in local disease-free survival rate was negligible (73% vs 70%) in patients with B_2 lesions but was greater (62% vs 46%) in patients with C_1 and C_2 lesions.

2.1.2 Role of Postoperative Chemotherapy

Gastrointestinal Tumor Study Group (GITSG), Protocol 7175:[1] There was no improvement in the rate of local failure or in disease-free survival or survival between the group receiving postoperative chemotherapy (MeCCNU and FU) and the group receiving surgery alone.

National Surgical Adjuvant Breast and Bowel Project, Protocol R-01:[2] Findings from this study show a significant 5-year disease-free survival advantage in the group receiving chemotherapy (MeCCNU, VCR, FU) when compared to the control group; this was translated to a statistically significant survival advantage ($p<0.05$). Further subgroup analysis indicates that this effect was restricted to male patients. There was no significant reduction in the rate of local failure in the chemotherapy group when compared to the surgery group (21% vs 25%).

2.1.3 Role of the Combination of Chemotherapy with Radiotherapy:

Gastrointestinal Tumor Study Group (GITSG), Protocol 7175[1]: After 8 years of follow-up, findings from this study continue to show a disease-free survival and survival advantage in favor of the combined therapy arm when compared to the surgery-alone arm (60% vs 45%; $p=0.005$). These results, based on only a small number of patients, indicate the value of postoperative combination therapy in the treatment of rectal cancer and require further confirmation.

North Central, Duke, and Mayo Clinic Sequential Chemotherapy Radiation Protocol[7]: This two-arm study of 209 patients compared postoperative radiotherapy (4500-5040 cGy) to radiotherapy with chemotherapy (MeCCNU and FU). The radiotherapy was deferred until a full cycle of chemotherapy was administered. Findings from this study also demonstrated that the time-to-recurrence was significantly prolonged in the combination group when compared to the radiotherapy-alone group. Furthermore, the 5-year survival rates were significantly improved with chemotherapy in combination with radiotherapy (55% vs 45%; $p=0.025$).

National Surgical Adjuvant Breast and Bowel Project, Protocol R-02: In order to further establish the efficacy of the combination of postoperative chemotherapy and radiotherapy, protocol R-02 compared the efficacy of postoperative chemotherapy with and without radiotherapy. In male patients, the LV-modulated FU was compared to MeCCNU, VCR, and FU with and without radiotherapy. Female patients were randomized only to the arms containing FU-LV. Preliminary results from this study indicate that the combination of chemotherapy and radiotherapy significantly reduced the rates of local recurrence but did not affect disease-free survival and survival when compared to chemotherapy alone.

2.2 Rationale for the Use of Preoperative Chemotherapy and Radiotherapy

2.2.1 Role of Preoperative Radiotherapy

In several randomized and nonrandomized studies,[8-14] preoperative radiotherapy has been shown to decrease the rate of local recurrence and, in some non-randomized studies, to prolong survival when compared to surgery-alone historical control groups.

In the EORTC trial,[8] 466 patients with T_2, T_3, T_4, N_x, M_o rectal cancer were randomized to receive 3450 cGy of preoperative radiotherapy (15 doses of 230 cGy) and radical surgery or surgery alone. There was no difference in the 5-year survival rates between the two groups (49% and 52% for the control group and the combined modality group, respectively). In patients who received surgical resection with a curative aim, the local recurrence rates were significantly reduced at 5 years in the preoperative radiotherapy group (30% vs 15%; $p=0.003$). Taking into account all randomized patients, the 5-year local recurrence rate was still significantly lower for the group receiving preoperative radiotherapy ($p=0.023$). Postoperative morbidity was reported slightly more frequently and at higher degrees of severity after preoperative radiotherapy. Overall, however, the difference was not statistically significant. The perineal wound-healing duration and the median duration of hospitalization tended to be longer for irradiated patients.

At Thomas Jefferson University,[10] 220 patients with adenocarcinoma of the rectum were treated with high-dose (4000-6000 cGy) preoperative radiotherapy followed by radical surgical resection. The overall incidence of local recurrence was 15%. Patients with fixed and unresectable tumors had a higher incidence of local recurrence (20%) as compared with patients who had mobile and partially fixed tumors (10%). Overall 5-year survival of the total group was 67%. The 5-year survival by pathologic stage of disease was 90% for those with stages O, A, and B disease, and 71%, 75%, and 47%, respectively, for those with stages B2, C1, and C2 disease. Nine percent of patients had no residual cancer following preoperative radiation. There was no surgical mortality, nor did any

patient require lengthening of the time between radiation and surgery for enteritis. Four percent of patients had adhesive/obstructive complications post-surgery. Wound healing was delayed in six patients (3%), and anastomotic breakdown was observed in 3 patients (1.5%); 3 patients (1.5%) developed rectovaginal fistula. The overall incidence of grade 3/4 radiation-related complications was 6%, and those caused by surgery was 4%.

At Washington University Medical Center in St. Louis[12], 112 patients with adenocarcinoma of the rectum were treated by preoperative radiation followed by excisional surgery between 1975-1986. Preoperative radiation consisted of 2000 cGy from 1975-1980 (22 patients) and 4500 cGy from 1980-1986 (90 patients). With the high-dose radiotherapy, after a mean follow-up of 46 months, the local recurrence rate was 18%. There was no surgical mortality, and the overall surgical complication rate was 9%. There was no need for a colostomy because of the use of preoperative radiotherapy. No anastomotic leaks were encountered.

At the University of Florida,[13] from 1975-1986, 148 patients with resectable rectal cancers were treated with three different regimens of preoperative radiotherapy (3500 cGy in 20 fractions, 4000-5000 cGy at 180 cGy per fraction, and 3000 cGy in 10 fractions). There were no differences in the rates of local control, absolute survival, or complications among the three preoperative radiotherapy protocols. In the group receiving high-dose radiotherapy (78 patients), no patient required a diverting colostomy for obstruction during radiotherapy or before the planned operation after preoperative radiation therapy.

At the University of Oregon,[14] 97 patients with adenocarcinoma of the recto-sigmoid were treated with high-dose (5000-6000 cGy) preoperative radiotherapy from 1960-1972. Surgical excision of the tumor occurred between 4 to 7 weeks following the completion of irradiation. The regimen was very well tolerated. The incidence of complications was no different from that in a previous series of patients with rectal tumors treated with surgical resection at the same institution. There were 10% pathologic complete responses. Among 57 patients that underwent potentially curative resection, there were no pelvic recurrences noted.

Preoperative radiotherapy was compared directly to postoperative radiotherapy. In a Swedish randomized multicenter trial,[15] moderate-dose preoperative radiotherapy (2550 cGy in 5-7 days) was compared with high-dose postoperative radiotherapy (6000 cGy in 8 weeks) in 471 patients with rectal and rectosigmoid carcinoma. The local recurrence rate was significantly lower after preoperative radiotherapy than after postoperative radiotherapy (12% vs 21%; $p=0.02$), but there were no significant differences in survival between the two groups.

Preoperative radiotherapy may have several theoretical advantages: sterilization of circumferential margins can be achieved, which is especially important in areas

where surgical access to the tumor is made technically difficult by anatomic restrictions. Involved pelvic sidewall lymphatics and iliac nodes can be sterilized by high-dose preoperative radiotherapy, thus preventing the dissemination and seeding that usually occur during surgical manipulations or transecting. However, the main advantage of preoperative radiotherapy may be related to its potential for the need of reduced longitudinal and circumferential surgical tissue removal in order to obtain free surgical margins by shrinking the tumor, thereby allowing sphincter-saving procedures to be performed.

2.2.2 Sphincter Preservation

If improvement in survival rates is the most important aim of any cancer treatment strategy, preservation of anal sphincter function without increase in local recurrence or decrease in survival rates should be one of the most important goals of any strategy for the management of rectal carcinoma. Besides anal continence, additional potential benefits of sphincter-conserving surgery include preservation of bladder function and of normal sexual function. The development of endoluminal stapling devices has brought technical ease and confidence to surgeons in performing anastomoses in the distal rectum and has also increased their frequency. Furthermore, both clinical observations that sphincter competence remains after anastomoses performed in the terminal 1-2 cm of the rectum and scientific studies that demonstrated the reflex arm of continence originating in the puborectalis muscle further encourage the performance of lower rectal and anal anastomoses. In the last decade, the old concept of the need for 5-cm distal margins, as proposed by Cole[16] in 1913, has been challenged as a result of recognition of the importance of circumferential margins, with the consensus currently being that a 2-cm distal margin is adequate. Circumferential margins are limited, however, because the space between the muscular coat of the rectum and the pelvic sidewall is too narrow. It appears from the above that the involvement of the pelvic sidewall and microlymphatics when the tumor arises in the very distal rectum is the limiting factor in considering sphincter preservation for cancer of the distal rectum.

Adjuvant radiotherapy, with its proven ability to sterilize the perirectal lymphatics, can be an important factor in performing sphincter-preserving surgery without compromising the chance for cure for cancers arising in the distal rectum. Adjuvant postoperative radiotherapy has been shown to be effective in reducing local-regional recurrence, indicating that rectal tumors are sensitive to radiotherapy when it is administered in adequate doses. Several studies have tested the worth of postoperative radiotherapy with or without the addition of FU (as a radiosensitizer) in allowing the performance of sphincter-preserving procedures with carcinomas of the distal rectum without adversely affecting the local and distant recurrence rates, when compared to the standard treatment with abdominoperineal resection (Table 2). Although excellent local recurrence rates have been obtained, the occurrence of distant metastases without local recurrence is not infrequent in patients with T_2 and T_3 lesions.

TABLE 2. STUDIES OF SPHINCTER-PRESERVING SURGERY FOLLOWED BY POSTOPERATIVE RTX IN THE TREATMENT OF DISTAL RECTAL CARCINOMA

Source	No. Pts.	Depth of Lesion	RTX Dose	Follow-up Time (months)	Type of Excision	Local Recurrence (%)	Distant Recurrence
Summers[17]	17	T1-T2	4500 cGy	64	Transanal Transacral	12	0/17
Wood[18]	20	T1-T3	4500 cGY±5FU	47	Transanal Transacral Transphincteric	0	2/20*
Jessup[19]	19	T2-T3	4500 cGy±5FU	25	Transanal Transacral Coloanal	0	2/19†
Ota[20]	46	T1-T3	4500 cGy±5FU	36	Transanal Transphincteric Transacral	10	5/46

*Both patients had T_2 lesions
†Both patients had T_3N_2 lesions

Several studies have demonstrated the ability of preoperative radiotherapy to allow the performance of sphincter-saving procedures with low rates of local recurrence and survival rates comparable to those obtained with abdominoperineal resection.

At Memorial Sloan-Kettering,[21] 22 patients with resectable primary adenocarcinomas of the lower rectum (3-7 cm. from the anal verge) were given 5040 cGy preoperative radiotherapy followed by total rectal excision with coloanal anastomosis. Most of the patients underwent protective colostomy, but it is of interest that so did also most of the patients in this institution who underwent the same surgical procedure without preoperative radiotherapy. Ten percent of the patients had no residual cancer within the specimen and 90% underwent resection with coloanal anastomosis with negative margins. At 23 months of follow-up, the incidence of pelvic recurrence as the only site of recurrence was 5% and was 14% as a component of both distant and pelvic recurrence. The 3-year actuarial disease-free survival rate was 69%. Partial anastomotic disruption occurred in 6% of patients.

At Thomas Jefferson University,[22] 43 patients received preoperative radiotherapy (4000-6000 cGy) followed by a variety of sphincter-preserving operative approaches (abdominosacral approach, low anterior resection, transanal excision) 4-6 weeks later. It is not clear in this report what percent of patients underwent a protective colostomy. Fourteen percent of patients were initially considered to have "fixed" disease and 65% had "unfavorable pathology." After a median follow-up of 51 months, there was a 16% local recurrence rate, most of which came from the "fixed" tumors. The 5-year actuarial survival rate was 72%. Anastomotic failure occurred in three patients. Sphincter function was maintained in 86% of the patients. Fecal diversion for late-occurring problems of suppuration or tumor recurrence was necessary in three patients (7%).

In conclusion, it appears from several clinical studies that high-dose preoperative radiotherapy is safe, with a low rate of complications due to radiation injury and delayed anastomotic healing.

2.2.3 Role of Preoperative Chemotherapy

The value of preoperative chemotherapy in the treatment of rectal cancer has not yet been evaluated in the clinical setting. There is clinical information, however, to suggest the value of such chemotherapy in other malignancies such as osteosarcoma,[23] breast cancer,[24-26] esophageal cancer,[27] and head and neck carcinoma.[28] Studies with locally advanced breast cancer have demonstrated a correlation between tumor response to chemotherapy and disease-free survival and survival.[29] Ongoing prospective randomized trials of preoperative versus postoperative chemotherapy evaluate the impact of preoperative chemotherapy on disease-free survival and survival as well as on organ preservation.[30]

Several biological premises provide justification for considering the use of preoperative chemotherapy. Ample evidence is available from experimental systems to indicate that noncurative reduction of tumor cell burden results in an increase in the proliferation of residual tumor cells.[31-33] Recent investigations from six different tumor-host systems have demonstrated that, 24 hours after removal of a primary tumor, there is an increase in the labeling index (LI) of the metastases which persists for a variable period of time and results in a decrease in tumor doubling time with a measurable increase in tumor size. Radiation of a primary tumor, sufficient to retard growth, also results in kinetic changes in distant tumor similar to those obtained following tumor removal.[33] Studies directed toward elucidating the mechanism whereby removal or radiation exerts an effect on metastases have indicated the presence of a serum growth factor. Further investigations from animal models indicate that chemotherapy given prior to operation completely prevents the increase in the labeling index, more effectively suppresses tumor growth, and prolongs survival.[34] Further justification for preoperative chemotherapy is based on the Goldie-Coldman hypothesis that, as a tumor cell population increases, an ever-expanding number of drug-resistant phenotypic variants arises due to spontaneous somatic mutations which become more difficult to eradicate.[35] Thus, it is possible that drug-resistant phenotypic variants may arise in the sites of micrometastases present at the time of surgery because of the increase in tumor proliferation as a result of surgical removal or radiation-induced primary tumor reduction. This can be potentially prevented by the administration of chemotherapy prior to any local intervention in the primary tumor (radiation, surgery).

2.3 Rationale for Selection of FU-LV

Although results from protocol R-02 comparing the efficacy of MOF vs FU-LV are not yet available, the selection of FU-LV as the adjuvant chemotherapy for this protocol is based on information from several other studies.

The superiority of FU-LV over FU alone has been well demonstrated in the metastatic setting. Results from a recent meta-analysis using nine randomized prospective clinical trials and a total of 1381 patients with advanced colorectal cancer indicate that FU-LV is superior to FU alone relative to overall tumor response. Twenty-three percent of patients who received FU-LV demonstrated an objective decrease in measurable tumor size, compared to 11% for FU alone ($p < 10^{-7}$).[36] There was, however, no overall survival advantage. Results from protocol C-03 [37] demonstrate that FU-LV is superior to MOF in the adjuvant setting for patients with colon cancer. There was a 9% greater disease-free survival (73% vs 64%) and a 7% greater overall survival (84% vs 77%) in patients who received FU-LV when compared to those who received MOF. It is important to state that the MOF regimen was shown to be an active regimen in protocol C-01.

The combination of FU+levamisole has demonstrated activity in patients with Dukes' C colon cancer. Whether FU-LV is as effective as or more effective than the combination of FU+levamisole in the adjuvant treatment of rectal cancer is unknown at present. A direct comparison between FU-LV, FU+levamisole and the combination FU-LV+levamisole was made in protocol C-04 for patients with colon cancer, but results from that trial are not yet available. The Intergroup rectal adjuvant protocol compares FU, FU-LV, FU+levamisole, and FU-LV+levamisole (all with the addition of radiotherapy) in the treatment of rectal cancer. This study was activated in August 1990 and is to accrue roughly 1335 patients within 4 years.

There is evidence for an increase in cytotoxicity of radiation therapy by the addition of 5-FU. It has been shown that this increase is related to the duration and concentration of drug exposure. The addition of LV to 5-FU by the stabilization of the ternary complex could theoretically increase the cytoxicity of 5-FU in combination with radiotherapy.

The regimen of preoperative radiotherapy with 5-FU low-dose LV (for 5 days every 4 weeks x 2) has been piloted (Minski, personal communication) and can be given at the proposed doses with reasonable toxicity.

A systemic effect from this regimen of FU-LV is also expected in conjunction with its effect as a radiation sensitizer.

2.4 Use of Preoperative Therapy Without Pathologic Staging

Treatment in this study will not be related to pathologic staging as derived from the depth of penetration of tumor and from the status of the perirectal nodes, since this information will not be available at the time of randomization. Currently there is justification for the use of adjuvant chemotherapy and radiotherapy in the treatment of patients who present with Dukes' B and C tumors. Every effort will be made prior to randomization to identify and exclude Dukes' A and D tumors. Prior to randomization, CT scan of the abdomen and pelvis will be mandated and the use of endoluminal ultrasonography will be strongly encouraged. In fact, in order to be eligible, patients who present with villous adenomas or polyps containing adenocarcinoma are required to undergo endoluminal ultrasonography, which must demonstrate unequivocally either penetration through the muscularis propria or involvement of the perirectal nodes.

2.4.1 Endoluminal Ultrasonography

Endoluminal ultrasonography has been shown to be a valuable tool in predicting the depth of wall penetration of rectal cancers. Its accuracy rate ranges between 80-92%.[38-44] Factors affecting the diagnostic accuracy include both the examiner's experience and elements intrinsic to the neoplasm, such as peritumoral edema and superficial lesions. Furthermore, ultrasonography can assess the status

of mesorectal lymph nodes with a sensitivity of 81%, a specificity of 80%, and positive and negative predictive values of 74% and 80%, respectively.[3] Some studies have shown better accuracy with endoluminal ultrasonography compared to CT scan in staging of primary rectal cancers and recurrent rectal cancers.[42,45,46] In a recent study, endoluminal ultrasonography provided valuable information in the direct biopsy of pararectal lymph nodes and appeared to be more useful than CT in assessing the extent of local recurrence in the pelvis.[47]

In this trial, endoluminal ultrasonography will be evaluated wherever possible. Its use will be encouraged, but not mandated, prior to a patient's entry in the study. However, if and when it is performed, the results in staging of the rectal cancers will be taken into consideration in determining a patient's eligibility. Patients who, by endoluminal ultrasonography, demonstrate a tumor classified as Dukes' A will be ineligible for randomization.

2.5 Justification for the Study Design

The reasons for employing preoperative radiotherapy as they relate to sphincter preservation have already been mentioned. The reasons for the addition of preoperative chemotherapy have also been discussed. The selection of three preoperative cycles (one cycle of FU-high dose LV followed by two cycles of FU-low dose LV and RTX) is based on clinical rationale. Because of the length of each cycle of therapy with FU-high dose LV (8 weeks with the rest period), attempting to administer all cycles preoperatively would result in delaying the operation for almost one year following diagnosis. Without proof of the value of chemotherapy in the preoperative setting, it would be difficult for physicians and patients to wait for such a prolonged period of time, especially if there is no complete response of the primary tumor.

Any development of metastatic disease during the administration of preoperative chemotherapy that may simply reflect natural history manifestation could be taken as progression of disease in the preoperative arm. Furthermore, after preoperative chemotherapy, the detection of residual pathologic disease in the lymph nodes following surgery may be viewed by patients and investigators as necessitating the administration of further chemotherapy.

The administration of the three cycles before operation (with radiotherapy given with cycles 2 and 3), certainly has the potential of inducing most of the expected tumor response prior to surgery, resulting in the desired downstaging and sphincter preservation. On the other hand, the administration of one cycle of chemotherapy before radiotherapy and surgery tests the biological concept of suppression of micrometastatic tumor kinetics by chemotherapy following local tumor reduction by radiotherapy and surgery.

3.0 SPECIFIC AIMS

3.1 To determine whether the administration of chemotherapy (FU-LV) with radiotherapy preoperatively is more effective than the administration of the chemotherapy and radiotherapy postoperatively in improving disease-free survival and survival in patients with operable carcinoma of the rectum.

3.2 To determine if the administration of the above chemotherapy and radiotherapy preoperatively results in improvement in local recurrence rates when compared with the regimen administered postoperatively in this population of patients.

3.3 To evaluate the response of rectal tumors to preoperative chemotherapy and radiotherapy and to correlate that response with disease-free survival and survival.

3.4 To assess the downstaging effect of preoperative chemotherapy and radiotherapy on the tumor size and the pathologic status of regional lymph nodes.

3.5 To estimate the proportion of patients who can be converted to sphincter-saving surgical procedures from abdominoperineal resection. Furthermore, to estimate the proportion of patients who can be converted from sphincter-saving surgical procedures to local excision alone.

4.0 DEFINITIONS

4.1 Rectal Tumors

For purposes of this study, rectal tumors will be tumors located within 15 cm from the anal verge, as defined by proctoscopic examination.

4.2 Classification of Tumors

For purposes of this study, pathologic categories of the primary tumor will be designated as Dukes' A, B, C, and D and are defined as follows:

Dukes' A - The tumor is confined within the muscular wall of the rectum, i.e., the tumor has not extended into the perirectal tissue and has not involved the regional lymph nodes. (Modified Astler-Coller A, B_1; AJCC Stage I [$T_1N_0M_0$, $T_2N_0M_0$].)

Dukes' B - The tumor has invaded <u>through</u> the wall of the rectum or has extended into the perirectal adipose tissue but <u>without</u> involvement of regional lymph nodes. (Modified Astler-Coller B_2, B_3; AJCC Stage II [$T_3N_0M_0$, $T_4N_0M_0$, excluding free perforation].)

Dukes' C - The tumor has invaded the wall of the rectum to any depth with involvement of the regional lymph nodes. (Modified Astler-Coller C_1,C_2,C_3; AJCC Stage III [T_{any} $N_{1-3}M_0$].)

Dukes' D - The tumor has extended beyond the scope of curative operative resection. This may be either on the basis of distant metastasis or unresectable local/regional disease. Patients with isolated distant or noncontiguous intra-abdominal metastases, even if resected, are considered to have Dukes' D tumors. (Modified Astler-Coller D, AJCC Stage IV [T_{any} N_{any} M_1].)

4.3 Additional Therapy

4.3.1 Prophylactic Therapy

No prophylactic therapy will be employed beyond that specified by protocol without evidence of documented local, regional, or distant treatment failure.

4.3.2 Therapy for Treatment Failure

Therapy for treatment failure will be given at the discretion of the investigator. All additional therapy will be reported to the NSABP Biostatistical Center and should be recorded on the follow-up forms.

5.0 END POINTS

The primary end points to be used for statistical analysis are as follows: 1) disease-free survival and 2) survival. In the group receiving preoperative and postoperative therapy, an additional end point will be the assessment of local-regional response to preoperative chemotherapy and radiotherapy.

5.1 Disease-Free Survival

The following events are to be used in the analysis of disease-free survival:

5.1.1 Local Recurrence

Following completion of therapy (including surgery), evidence of tumor in the anastomosis or in the perineal or perirectal area. Treatment following local recurrence will be at the discretion of the investigator.

5.1.2 Regional Recurrence

Following completion of therapy (including surgery), evidence of tumor in the pelvic or retroperitoneal nodes. Further treatment following regional recurrence will be at the discretion of the investigator.

5.1.3 Distant Recurrence

Evidence of tumor in any area, with the exception of those described above (5.1.1 and 5.1.2). Further treatment for distant metastasis, with or without evidence of local-regional recurrence, will be at the discretion of the investigator.

5.1.4 Inoperable Progressive Disease

Patients in Group 1 who, while on chemotherapy or radiotherapy prior to surgery develop progressive disease which becomes inoperable, will be considered to have a treatment failure. (See Section 11.0).

5.1.5 Second Primary Cancer

Any histologically proven second primary cancer other than squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix will be considered an event in the analysis of disease-free survival.

5.1.6 Death From Any Cause Other Than Cancer

5.2 Survival

The end point for survival analysis is death from any cause.

5.3 Response of Primary Tumor and Regional Nodes to Preoperative Therapy (Group 1 Only)

Clinical response to preoperative therapy will be assessed at completion of the first cycle of chemotherapy and at the completion of the radiotherapy (i.e., prior to operation). The clinical response will be classified as complete, partial, stable, or progressive disease. For an explanation of tumor measurement and monitoring procedures, refer to Section 10.0. **Patients in Group 1 who, while on chemotherapy or radiotherapy before surgery, develop progressive disease which is operable will not be considered to have a treatment failure.** The management of progressive disease, either operable or inoperable, is described in Section 11.0.

6.0 PATIENT ELIGIBILITY AND INELIGIBILITY

Eligible patients having histologic diagnosis by proctoscopic incisional biopsy of invasive rectal adenocarcinoma will be considered for entry in this study.

6.1 Patient Eligibility

Patients who satisfy the conditions stated below are the only patients who will be considered to be eligible.

6.1.1 The patient must consent to be in the study. The informed consent form conforming to federal and institutional guidelines must be signed, witnessed, and dated prior to randomization.

6.1.2 Patients in whom the diagnosis of invasive rectal cancer has been obtained by incisional (surgical or endoscopic) biopsy so that the majority of the tumor has not been removed are eligible.

6.1.3 The interval between initial histologic diagnosis and randomization must be no more than 28 days.

6.1.4 Patients must have a life expectancy of at least 10 years, excluding their diagnosis of cancer.

6.1.5 The tumor should be either palpable by clinical rectal exam or be accessible via a proctoscope or sigmoidoscope, and its distal border should be located no more than 15 cm from the anal verge.

6.1.6 The tumor should be movable on clinical examination without evidence of fixation to the pelvis or to surrounding organs (vagina, prostate, bladder), beyond the limits of resection via exenteration.

6.1.7 The patient must have no radiologic evidence of metastatic spread. The patient must have a CT of the abdomen and pelvis prior to randomization. Any suspicious findings, i.e., liver nodule, retroperitoneal adenopathy, will render the patient ineligible unless malignancy is ruled out by further tissue documentation (CT- or ultrasound-guided biopsy, laparoscopic biopsy, or open biopsy), prior to randomization.

6.1.8 Evidence by CT scan of enlarged perirectal or pelvic lymph nodes is not a condition for ineligibility unless they appear to preclude adequate surgical removal.

6.1.9 The WBC must be ≥ 4000/cu. mm and the platelet count must be $\geq 100{,}000$/cu. mm.

6.1.10 There must be evidence at randomization of adequate hepatic and renal function (bilirubin, SGOT or SGPT, and creatinine must be ≤ 1.5 times the upper limit of normal for the performing lab).

6.1.11 Patients with more than one synchronous rectal lesion are eligible.

6.1.12 Patients with a performance status of 0, 1, or 2 (see Appendix B) are eligible.

6.1.13 Patients presenting with intestinal obstruction are eligible, provided the only treatment prior to randomization is a decompressing colostomy.

6.1.14 The patient must be accessible geographically for follow-up.

6.2 Patient Ineligibility

The following patients are ineligible for randomization into the study:

6.2.1 Patients with malignant rectal tumors other than adenocarcinoma, i.e., sarcoma, lymphoma, carcinoid, squamous cell carcinoma, cloacogenic carcinoma, etc.

6.2.2 Patients who have life expectancy of less than 10 years, excluding their diagnosis of cancer.

6.2.3 Patients who demonstrate prior to randomization, evidence of free perforation, as manifested by free air or free fluid in the abdomen. (Patients with walled-off perforations are eligible.)

6.2.4 Patients with a previous or concomitant malignancy, regardless of site, EXCEPT patients with squamous or basal cell carcinoma of the skin, or carcinoma in situ of the cervix that has been adequately treated.

6.2.5 Patients who have received surgical treatment for rectal cancer, other than preliminary decompressing colostomy or diagnostic laparoscopy or laparotomy without any resection of primary tumor.

6.2.6 Patients who have received any other therapy (radiation, chemotherapy) for rectal cancer prior to randomization.

6.2.7 Patients in whom rectal cancer was diagnosed by excisional biopsy, (removal of polyp with adenocarcinoma, removal of villous adenoma with adenocarcinoma, etc).

6.2.8 Patients in whom the interval between initial histologic diagnosis and randomization is greater than 28 days.

6.2.9 Patients with a tumor whose distal border is located more than 15 cm from the anal verge.

6.2.10 Patients whose tumor is fixed by clinical examination to surrounding structures, precluding the possibility of adequate surgical resection even with pelvic exenteration.

6.2.11 Patients who show radiologic evidence of advanced disease (inoperable local-regional disease or metastatic disease). Evidence of biopsy-proven retroperitoneal lymph-node involvement will deem a patient ineligible.

6.2.12 Patients who demonstrate involvement of perirectal or pelvic lymph nodes with evidence of fixation to the pelvic side wall.

6.2.13 Patients with a performance status of 3 or 4 (see Appendix B).

6.2.14 Patients having nonmalignant systemic disease (cardiovascular, renal, hepatic, etc.), which would preclude their being subjected to the treatment (surgery, chemotherapy, and radiotherapy).

6.2.15 Patients with active inflammatory bowel disease.

6.2.16 Patients who are pregnant at the time of randomization.

6.2.17 Patients with psychiatric or addictive disorders that would preclude obtaining informed consent.

6.2.18 Patients who have multiple primary tumors involving both the colon and rectum that would preclude them from being classified as having only rectal cancer.

6.2.19 Patients who are found, by endoluminal ultrasonography, to have a Dukes' A lesion.

7.0 PATHOLOGY STUDIES

Pathology studies are to be performed on all patients randomized into this study. One staff pathologist at each participating institution should supervise all pathology examinations, which will be recorded on Form D-1. This form, attached to a copy of the institution's official pathology report(s), will be forwarded to the NSABP Biostatistical Center together with the materials listed below:

7.1 Blocks

7.1.1 Block of primary tumor from the incisional biopsy

7.1.2 Block of primary tumor from the surgical excision of site of apparent deepest presentation

7.1.3 Block from normal rectal mucosa

7.2 Sections

7.2.1 Sections from the incisional biopsy

7.2.2 Sections from the surgical excision specimen:

- site of deepest penetration
- tumor-rectum interface
- lines of resection
- lymph nodes
- other disease, if present
- polyps, if present
- other organ sites of metastases, if present

7.3 Submission of NSABP Pathology Material

Submit all NSABP pathology material to:

NSABP Biostatistical Center
Suite 600, 230 McKee Place
Pittsburgh, PA 15213

8.0 ALLOCATION OF PATIENTS TO TREATMENT GROUPS

8.1 Stratification

Prior to randomization, patients will be stratified according to the following criteria for the purposes of ensuring equal distribution of patients possessing possible prognostic factors:

8.1.1 Sex

8.1.2 Age (0-59, 60+)

8.2 Randomization

Random allocation of patients will be accomplished by direct communication (telephone or otherwise) with a randomization specialist at the NSABP Biostatistical Center (412) 624-2666.

8.3 Patient Identification Number

Each patient will have a nine-digit identification number. The first two digits will refer to the protocol, the next four will be assigned sequentially, and the last three refer to the institution.

9.0 REQUIRED ENTRY AND FOLLOW-UP STUDIES

9.1 Prior to Randomization: See Table 3, Columns 2 and 3, for those studies required prior to randomization, or prior to initiation of therapy.

9.2 Year 1: See Table 3, Columns 4 through 8, for those studies required (a) every week prior to therapy, (b) every 8 weeks prior to beginning the next cycle, (c) every 3 months, (d) every 6 months, and (e) every 12 months during year 1.

9.3 Year 2: See Table 4, Columns 2 through 4, for those studies required (a) every 3 months, (b) every 6 months, and (c) every 12 months during the second year following randomization.

9.4 Years 3-5: See Table 4, Columns 5 and 6, for those studies required (a) every 6 months and (b) every 12 months during years 3 through 5 following randomization.

9.5 After Year 5

- Status of disease will be reported on a yearly basis on the follow-up form.
- Treatment failure and the therapy instituted will be reported at the time of failure.

10.0 TUMOR MEASUREMENTS AND MONITORING PROCEDURES

Clinical tumor response to preoperative therapy in Group 1 will be assessed after completion of the first cycle of chemotherapy (within 2 weeks before the beginning of RTX) and after completion of radiotherapy (no sooner than 2 weeks after completion of RTX, but prior to tumor removal). These tumor measurements will be compared to tumor measurements obtained before initiation of chemotherapy. The length and width of tumor will be measured either by direct transanal approach (anoscope) or by proctoscopy. All three measurements should be performed by the same method and, if possible, by the same person. Measurements of the tumor by endorectal ultrasound, CT, or MRI will be acceptable, provided that the same modality is used for all three points of the evaluation. If one of these modalities is used, and if there are enlarged perirectal lymph nodes, measurements of the larger of the perirectal lymph nodes should be included in all points of the evaluation. If one of the parameters (length or width) of the tumor cannot be measured, the evaluation will be based on the one existing parameter. The clinical tumor response will be classified as complete, partial, stable disease, or progressive disease.

10.1 Complete Response

Complete disappearance of any tumor as evidenced by clinical or proctoscopic examination.

10.2 Partial Response

Decrease in the product of tumor measurements (length x width) by at least 50% when compared to the measurement before initiation of therapy.

10.3 Stable Disease

Any tumor changes that do not meet the criteria for classification as progressive disease or partial response.

10.4 Progressive Disease

Any increase in the product of tumor measurements (length x width) by at least 25%, or the appearance of new lesions, either local-regional or distant.

11.0 MANAGEMENT OF PROGRESSIVE DISEASE, RESPONSIVE DISEASE, DUKES' STAGES D AND A (See TABLE 5)

11.1 Group 1 patients who develop progressive inoperable (advanced local-regional or distant) disease while on chemotherapy or radiotherapy prior to surgery will be considered to have a treatment failure. Further therapy for these patients will be at the discretion of the investigator.

11.2 Group 1 patients who are found to have progressive operable disease after the completion of the first cycle of chemotherapy will receive the radiotherapy and chemotherapy (cycles 2 and 3), as per protocol guidelines, followed by surgery.

11.3 Group 1 patients who develop progressive operable disease while on cycle 1 of chemotherapy will have this cycle interrupted and will be started on the radiotherapy and chemotherapy (cycles 2 and 3), per protocol guidelines, followed by surgery.

11.4 Group 1 patients who develop progressive operable disease while on radiotherapy and possibly chemotherapy (cycles 2 and 3) will have the radiotherapy and, if necessary, chemotherapy, interrupted and will be offered surgery. After the operation they will receive the remaining four cycles of chemotherapy according to protocol guidelines.

11.5 Group 1 patients who are found at the time of surgery to have inoperable or metastatic disease will be classified as treatment failures and will be treated at the discretion of the investigator. Continuing protocol therapy (± surgery + FU-LV x four cycles) is recommended but not mandated.

11.6 Group 2 patients who are found at the time of surgery to have inoperable or metastatic disease will be classified as treatment failures (they actually represent protocol diagnostic failures) and will be treated at the discretion of the investigator. Continuing protocol therapy (± surgery, FU-LV (cycle 1), RTX and chemotherapy (cycles 2 and 3), FU-LV x four cycles) is recommended but not mandated.

TABLE 3. STUDIES REQUIRED PRIOR TO RANDOMIZATION AND DURING YEAR 1

	Year 1						
	Before Therapy		During Therapy		Post-Therapy		
Required Studies	Prior to Randomization	Prior to Initiation of Therapy	Every Week Prior to Therapy	Every 8 Weeks Prior to Next Cycle	Every 3 Mos	At 6 Mos	At 12 Mos
History & Physical Examination	X			X	X		
•Height and Weight	X		X	X	X		
•Tumor measurements*		X					
Hematologic Studies							
•CBC and Diff	X		X	X	X		
•Platelet count	X		X	X	X		
Chemistries							
•BUN & serum creatinine	X			X	X		
•Bilirubin, total	X			X	X		
•Alkaline phosphatase	X			X	X		
•SGOT or SGPT	X			X	X		
•CEA†		X				X	X
Roentgenologic Exam							
•Chest (PA & Lat.)	X						X
•CT scan (abdomen and pelvis)	X						
•Liver scan, sonogram, abdominal CT, or MRI‡							
•Barium enema and/or full colonoscopic exam	X					X	X
•Endorectal ultrasound (optional)§	X						
Performance Status	X		X	X	X		

*Baseline tumor measurements will be performed in both groups prior to initiation of therapy (before or after randomization). In the preoperative group, additional tumor measurements will be obtained after completion of cycle 1 (prior to RTX) and after completion of cycle 3 (prior to surgery).

†For both groups, CEA tests will be performed preoperatively and postoperatively. In Group 1, an additional CEA test will be performed prior to cycle 1 of chemotherapy. The baseline CEA value can be obtained either before or after randomization.

‡Performed only in the presence of abnormal liver function tests and/or hepatomegaly. Biopsy confirmation of the presence or absence of metastases is indicated with an abnormal scan.

§Required in patients that present with polyps or villous adenomas.

TABLE 4. STUDIES REQUIRED AFTER YEAR 1

	Year 2			Years 3-5		After Year 5
Required Studies	Every 3 Months	Every 6 Months	Every 12 Months	Every 6 Months	Every 12 Months	Every 12 Months
Physical Examination	X			X		
•Weight	X			X		X
Hematologic Studies						
•CBC and Diff	X			X		
•Platelet count	X			X		
Chemistries						
•BUN & serum creatinine	X			X		
•Bilirubin, total	X			X		
•Alkaline phosphatase	X			X		
•SGOT or SGPT	X			X		
•CEA		X		X		
Roentgenologic Exam						
•Chest (PA & Lat.)			X		X	
•Liver scan, sonogram, abdominal CT, or MRI*						
•Barium enema and/or endoscopic exam			X		X	
•Performance Status	X			X		X

*Performed only in the presence of abnormal liver function tests and/or hepatomegaly. Biopsy confirmation of the presence or absence of metastases is indicated with an abnormal scan.

11.7 Patients in both groups who undergo incomplete resection or incomplete local excision (including presence of tumor at the margins of resection) will be classified as treatment failures and treated at the discretion of the investigator (protocol therapy is recommended but not mandated). Patients with margin involvement following sphincter-preserving surgery (including local excision) will be allowed to have another procedure (APR, LAR, reexcision) in order to obtain clear margins. If the margins are uninvolved after the second surgery, the patient will continue protocol therapy, as specified.

11.8 Group 1 patients who are found, after surgery, to have a Dukes' A tumor will continue protocol therapy since it will not be evident in which patients this is a true Dukes' A tumor and in which this is a result of downstaging effect of chemotherapy-radiotherapy on a previous Dukes' B or C tumor.

11.9 Group 2 patients who are found, after surgery (APR, LAR, coloanal), to have a Dukes' A tumor will be treated at the discretion of the investigator. Protocol therapy is recommended for T_2 lesions with unfavorable pathology. Patients in this group who, after local excision, are found to have tumor confined to the wall of the rectum will continue protocol therapy since their pathologic lymph-node status would be unknown.

12.0 DIAGNOSIS OF TREATMENT FAILURE

The diagnosis of a first treatment failure can be made only when the clinical and laboratory findings meet the criteria of "acceptable" as defined below. Suspicious findings do not constitute criteria for treatment failure, nor are they an indication to alter protocol therapy. The following table is offered as a guide. Anything not listed as acceptable should be considered unacceptable for evidence of treatment failure. ANY RECURRENCE OF MALIGNANT DISEASE SHOULD BE PROVEN BY BIOPSY WHENEVER POSSIBLE.

AT THE TIME OF TREATMENT FAILURE, THE INVESTIGATOR SHOULD CLEARLY INDICATE BOTH THE SITE OF TUMOR RECURRENCE AND WHETHER MULTIPLE SITES ARE INVOLVED.

12.1 Abdominal and/or Pelvic Sites

If a treatment failure occurs within the fields of prior radiation therapy, this should be indicated on follow-up forms.

12.1.1 Anastomotic

- Acceptable: positive cytology or biopsy
- Suspicious: abnormal barium enema, change in bowel habit, palpable mass, abnormal endorectal ultrasound

12.1.2 Abdominal, pelvic and retroperitoneal nodes

- Acceptable: (i) positive cytology or biopsy, (ii) progressively enlarging node as evidenced by two CT or MRI scans or two endorectal ultrasound, separated by at least a 4-week interval, or (iii) ureteral obstruction in the presence of a mass as documented on CT or MRI scans, or endorectal ultrasound

- Suspicious: (i) abnormal sonogram, CT scan, or MRI scan, or endorectal ultrasound, or (ii) ureteral obstruction without mass

12.1.3 Peritoneum (including visceral and parietal peritoneum, omentum)

- Acceptable: (i) positive cytology or biopsy, or (ii) progressively enlarging intraperitoneal solid mass as evidenced by two CT or MRI scans separated by at least a 4-week interval

- Suspicious: abnormal sonogram or CT scan without solid mass

12.1.4 Ascites

- Acceptable: positive cytology

- Suspicious: ascites without proof of tumor cells present

12.1.5 Liver

- Acceptable: (i) positive cytology or biopsy or (ii) three of the following which are not associated with benign disease:

  - recent or progressive hepatomegaly, abnormal liver contour
  - positive radionuclide liver scan, sonogram, or CT scan
  - abnormal liver function studies
  - elevated CEA: A persistent rise in CEA titer of 10 times the upper normal value, confirmed on two determinations separated by a 4-week interval, in patients who had a normal postoperative CEA value. The determination should be performed by the same laboratory using the same method.

    NOTE: **An elevated CEA level will, in itself, not be considered acceptable evidence of treatment failure. Non-protocol therapy will not be instituted on the basis of an abnormal CEA level. It is suggested that, when CEA elevations occur without other corroborative evidence of treatment failure (hepatomegaly, elevated liver function studies, positive radionuclide scans, etc.), the following investigations should be considered:**

5. MANAGEMENT OF PROGRESSIVE DISEASE, RESPONSIVE DISEASE, DUKES' STAGES D AND A

Time	Response/Stage	Classification	Treatment Recommendation
cycle 1 valuation RTX (cycles 2	•Progressive inoperable disease (advanced local-regional or distant)	•Treatment failure	•At the discretion of the investigator
valuation RTX)	•Progressive operable disease	•Progressive disease on chemo	•Continue protocol therapy (RTX and chemotherapy [cycles 2 and 3] - Surgery - FU-LV x 4)
cycle 1	•Progressive operable disease	•Progressive disease on chemo	•Interrupt chemo. Continue protocol therapy (RTX and chemotherapy [cycles 2 and 3] - Surgery - FU-LV x 4)
RTX (cycles 2	•Progressive operable disease	•Progressive disease	•Interrupt RTX. Continue protocol therapy (Surgery - FU-LV x 4)
y	•Inoperable disease •Metastatic disease	•Dukes' D (treatment failure)	•At the discretion of the investigator (recommend continuation of protocol treatment - FU-LV)
y	•Inoperable disease •Metastatic disease	•Dukes' D (diagnostic failure)	•At the discretion of the investigator (recommend protocol therapy)
y ogic exam ery	•Incomplete resection •Positive margins of resection*	•Treatment failure	•At the discretion of the investigator (recommend protocol therapy)
ogic on	•Tumor confined to muscular wall of the rectum, negative lymph nodes	•Dukes' A (possible partial response)	•Continue protocol therapy (FU-LV x 4)
ogic on	•Tumor confined to muscular wall of rectum, negative lymph nodes†	•Dukes' A (diagnostic failure)	•At the discretion of the investigator (recommend protocol therapy for T_2 with unfavorable pathology)

margins will be allowed an additional resection. If there is no evidence of residual disease after the second procedure, nued as per protocol and patients will not be classified as treatment failure.

p who, after local excision, is found to have tumor confined to the muscle wall will continue protocol therapy since the pathologic s would be unknown.

- **contrast and/or endoscopic exam,**
- **abdominal and pelvic CT scan or sonogram,**
- **celiac and mesenteric arteriography,**
- **exploratory celiotomy.**

DOCUMENTATION OF THE ABOVE BY BIOPSY IS STRONGLY RECOMMENDED.

12.1.6 Pelvic mass not otherwise specified (NOS)

- Acceptable: positive cytology or biopsy, progressively enlarging intrapelvic solid mass as evidenced by two CT or MRI scans or two endorectal ultrasound, separated by at least a 4-week interval

- Suspicious: abnormal sonogram or CT or MRI scans without solid mass

12.1.7 Abdominal wall, perineum, and scar

- Acceptable: positive cytology or biopsy

12.2 Non-Abdominal and Non-Pelvic Sites

12.2.1 Skeletal

- Acceptable: (i) x-ray evidence of lytic, blastic, or mixed lytic/blastic lesions on skeletal films with or without bone scan confirmation, (ii) biopsy proof of bone metastasis, (iii) bone scan consistent with bone metastases in a patient with bone pain, or (iv) progressive bone scan changes over at least a 4-week period are necessary in asymptomatic patients with only bone scan abnormalities.

NOTE: In the absence of progressive disease by scan, a biopsy is strongly recommended. Any positive bone scan in the joints or in a recent area of trauma (surgical or otherwise) cannot be used as an indication of treatment failure.

12.2.2 Lung

- Acceptable: (i) positive cytology or biopsy or (ii) the presence of multiple pulmonary nodules which are felt to be consistent with pulmonary metastases.

NOTE: If a solitary lung lesion is found and no other lesions are present on lung tomograms or on CT or MRI scans, further investigations such as biopsy, needle aspiration, or resection should be performed. Proof of neoplastic pleural effusion should be established by cytology or pleural biopsy.

12.2.3 Bone Marrow

- Acceptable: positive cytology, aspiration, or biopsy
- Suspicious: unexplained depression of peripheral counts and/or erythroblastic blood picture

12.2.4 Central Nervous System

- Acceptable: (i) positive CT or MRI scan, usually in a patient with neurological symptoms, or (ii) biopsy or cytology (for a diagnosis of meningeal involvement)

12.3 Second Primary Cancer

The diagnosis of a second primary cancer must be confirmed histologically whenever possible. Representative slides should be submitted to the NSABP Biostatistical Center for review.

12.4 Postmortem Examination

Whenever possible, autopsies should be secured and reports submitted to the NSABP Biostatistical Center. A copy of the death certificate should also be forwarded to the Biostatistical Center.

13.0 TREATMENT REGIMEN FOR GROUP 1: PREOPERATIVE AND POSTOPERATIVE FU-LV AND PREOPERATIVE RTX

13.1 Initiation of Therapy

Patients must be randomized no later than 28 days after histologic diagnosis. The surgeon should state the intended surgical procedure prior to randomization. Cycle 1 of chemotherapy should begin no later than 3 weeks after randomization. Surgery will be performed within 8 weeks of the completion of radiotherapy when blood counts allow and when all toxicities have resolved. Acceptable surgical procedures include abdominoperineal resection, low anterior resection, coloanal resection, local excision (transanal, transacral, transphincteric).

13.2 Dosage and Duration of Treatment

13.2.1 Patients will receive seven cycles of therapy; the duration of cycles 1 and 4-7 is 8 weeks (chemotherapy during radiotherapy is considered cycles 2 and 3).

- LV -500 mg/m^2 diluted in 250 cc of normal saline administered i.v. as a 2-hour infusion weekly for 6 consecutive weeks (on days 1, 8, 15, 22, 29,

36), followed by a rest period. Repeat treatment begins 21 days after the date of administration of the sixth dose of the previous cycle (one cycle=8 weeks).

- 5-FU -500 mg/m^2 administered i.v. bolus 1 hour after beginning the LV infusion, weekly for 6 weeks (on days 1, 8, 15, 22, 29, 36), followed by a rest period. Repeat treatment begins 21 days after the date of administration of the sixth dose of the previous cycle (one cycle=8 weeks). The rest period between cycle 1 and RTX may vary, depending on the day of the week on which the last dose of cycle 1 was given, but it should not be less than 20 days or more than 26 days.

Regardless of dose modifications or delays, FU-LV therapy will not continue beyond 60 weeks from the time of initiation of treatment.

13.2.2 Timing of FU-LV and Radiotherapy

Patients will begin radiation therapy after completion of cycle 1 of FU-LV when WBC, platelet counts and symptoms allow (within 3 weeks after day 36 of cycle 1). Radiotherapy should start on a Monday.

During radiotherapy FU 325 mg/m^2 and LV 20 mg/m^2 will be given daily x 5 for the first and fifth week. FU-LV will be administered within 2 hours following the radiotherapy. LV should be diluted in 100 cc of normal saline and administered by iv infusion over 30 minutes and FU should be given as iv bolus 20 minutes later. FU-LV administered during radiotherapy will be considered cycles 2 and 3. Counts will be performed weekly during radiation therapy. Surgery will be performed after completion of the radiotherapy, provided any toxicity has resolved, but no later than 8 weeks after radiotherapy. Cycle 4 of FU-LV will begin after recovery from surgery is complete, but no later than 4 weeks postoperatively.

14.0 TREATMENT REGIMEN FOR GROUP 2: POSTOPERATIVE FU-LV AND RTX

14.1 Initiation of Therapy

Patients must be randomized no later than 28 days after histologic diagnosis. The surgeon should state the intended surgical procedure prior to randomization. Surgery will be performed within 3 weeks after randomization. Acceptable surgical procedures include: abdominoperineal resection, low anterior resection, coloanal resection, local excision (transanal, transacral, transphincteric). Chemotherapy will begin after recovery from surgery, but no later than 4 weeks postoperatively.

14.2 Dosage and Duration of Treatment

14.2.1 Patients will receive seven cycles of therapy; the duration of cycles 1 and 4-7 is 8 weeks (chemotherapy during radiotherapy is considered cycles 2 and 3).

- LV -500 mg/m^2 diluted in 250 cc of normal saline and administered i.v. as a 2-hour infusion weekly for 6 consecutive weeks (on days 1, 8, 15, 22, 29, 36), followed by a rest period. Repeat treatment begins 21 days after the date of administration of the sixth dose of the previous cycle (one cycle = 8 weeks).

- 5-FU -500 mg/m^2 administered i.v. bolus 1 hour after beginning the LV infusion, weekly for 6 weeks (on days 1, 8, 15, 22, 29, 36), followed by a rest period. Repeat treatment begins 21 days after the date of administration of the sixth dose of the previous cycle (one cycle = 8 weeks). The rest period between cycle 1 and RTX may vary, depending on the day of the week on which the last dose of cycle 1 was given, but it should not be less than 20 days or more than 26 days.

Regardless of dose modifications or delays, FU-LV therapy will not continue beyond 60 weeks from the time of randomization.

14.2.2 Timing of FU-LV and RTX

Patients will begin radiation therapy after completion of cycle 1 of FU-LV 21 days after the date of administration of the sixth dose of cycle 1, once WBC, platelet counts, and symptoms allow. Radiotherapy should start on a Monday.

During radiotherapy FU 325 mg/m^2 and LV 20 mg/m^2 will be given daily x 5 for the first and fifth week. FU-LV will be administered within 2 hours following the radiotherapy. LV should be diluted in 100 cc of normal saline and administered by iv infusion over 30 minutes and FU should be given as iv bolus 20 minutes later. FU-LV administered during radiotherapy will be considered cycles 2 and 3. Counts will be performed weekly during radiation therapy. Cycle 4 of FU-LV will begin after completion of radiotherapy when counts allow, but no later than 5 weeks after radiotherapy.

15.0 DOSE MODIFICATIONS

15.1 Groups 1 and 2 (cycles 1 and 4-7)

NOTE 1: Should toxicity of any type result in a dose delay after week 4 in any treatment cycle, discontinue therapy for that cycle, begin the rest period, then institute the next cycle (e.g., skip weeks 5 and/or 6, maintain the rest period, and begin the next cycle of therapy 1 or 2 weeks earlier than scheduled).

NOTE 2: It is important to understand that the FU-LV is not simply a weekly FU schedule; it requires a very high level of attention to gastrointestinal (GI) toxicity. If FU-LV is continued or if toxicity is left untreated, fatal toxicity may occur. Nevertheless, correctly used, the FU-LV regimen will be less toxic than loading FU. Patients should be thoroughly instructed in the assessment of potential toxicity to improve their role as historians. Patients should be urged to keep a diary-record of side effects and weights in order to minimize risk of over-dosage due to failure to report GI toxicity. Weekly observation or contact is mandatory to ensure against failure to recognize worsening nadir toxicity.

15.1.1 Dose Modifications for Hematologic Toxicity (Cycles 1 and 4-7)
(See Tables 6A and 6C)

15.1.2 Dose Modifications for Gastrointestinal Toxicity (Cycles 1 and 4-7)
(See Tables 7A, 7C, and 7E)

15.1.3 Clinical Precautions and Additional Dose Modifications for Other Related Symptoms (Cycles 1 and 4-7)
(See Table 8A)

15.1.4 Interruption of Chemotherapy for Reasons Other Than Toxicity (Group 1: Cycles 4-7; Group 2: Cycles 1 and 4-7)
(See Table 9A)

15.2 Groups 1 and 2 (cycles 2 and 3 [during radiotherapy])

In the event of development of grade 3 or greater toxicity during cycle 2, all therapy (chemotherapy and radiation therapy) should be held. When the toxicity resolves, radiotherapy will resume and the rest of cycle 2 will be deleted. In this case, cycle 3 will be given with the FU dose decreased by 50 mg/m^2. Cycle 3 should still be given 28 days after the beginning of cycle 2. The days of radiotherapy that were not given due to toxicity will follow cycle 3. If grade 3 or greater toxicity develops after cycle 2, the radiation therapy should be held until toxicity resolves. Cycle 3 should still be given 28 days after the beginning of cycle 2 at a dose reduction of FU by 50 mg/m^2. The days of radiotherapy that were not given due to toxicity will follow cycle 3. In the event of grade 3 skin reaction secondary to RTX, the radiation should be held until resolution of toxicity, but there will be no dose reduction in cycle 3. Cycle 3 should still be given 28 days after the beginning of cycle 2.

If any grade 3 or greater toxicity develops during cycle 3, all therapy (chemotherapy and radiation therapy) should be held. When the toxicity resolves, radiotherapy will resume and the rest of cycle 3 will be deleted. There will be no dose reduction in cycle 4 because of toxicity that developed during cycle 3.

15.2.1 Dose Modifications for Hematologic Toxicity (Cycles 2 and 3 [during radiotherapy])
(See Tables 6B and 6D)

15.2.2 Dose Modifications for Gastrointestinal Toxicity (Cycles 2 and 3 [during radiotherapy])
(See Tables 7B, 7D, and 7F)

15.2.3 Clinical Precautions and Additional Dose Modifications for Other Related Symptoms (Cycles 2 and 3 [during radiotherapy])
(See Table 8B)

15.2.4 Interruption of Chemotherapy for Reasons Other than Toxicity (Group 2: Cycles 2 and 3 [during radiotherapy])
(See Table 9B)

16.0 DOSE DETERMINATIONS

The drug dose for each cycle of therapy will be calculated after the determination of WBC and platelet count before the onset of each cycle of therapy. PATIENT'S BODY SURFACE AREA (BSA) WILL BE CALCULATED BEFORE EACH COURSE. The patient's body surface area will be calculated using actual body weight but with a maximum BSA of $2m^2$ for any patient (see Appendix C).

Total dose of chemotherapy will be adjusted as follows:

16.1 FU should be rounded up to the next 25 mg. Ex: 918 mg = 925 mg

16.2 LV - I.V. doses of LV during cycles 1 and 4-7 should be rounded to the nearest 25 mg.

Ex: 570 mg = 575 mg
560 mg = 550 mg

16.3 LV - I.V. doses of LV during cycles 2 and 3 should be rounded to the nearest 5 mg.

Ex: 36 mg = 35 mg
48 mg = 50 mg

17.0 ADVERSE DRUG REACTIONS (ADRs)

Any severe or unusual toxicity should be reported immediately to the NSABP Clinical Coordinating Center (412/624-6221). A written report, using the NSABP Toxicity/Adverse Drug Reaction Report Form (Appendix D), should then be completed by the attending physician and be submitted to the NSABP within 2 days. The guidelines listed below should also be followed.

17.1 The following ADRs attributed to commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days:

- Any ADR that is both serious (life-threatening or fatal) and unexpected.
- Any increased incidence of a known ADR that has been reported in the package insert or the literature.
- Any death on study that is clearly related to the commercial agent(s).
- The ADR report should be documented on Form FDA 1639. This form should be mailed to:

Investigational Drug Branch
P.O. Box 30012
Bethesda, MD 20824

NSABP Headquarters will forward the appropriate information to the Investigational Drug Branch of the NCI.

18.0 SURGICAL TECHNIQUE

18.1 Preparation of the Rectum Prior to Surgery

A mechanical prep is recommended. The use of antibiotics will be left to the discretion of the surgeon. Their use will be recorded on Form OR.

18.2 Technique of Rectal Resection

18.2.1 Abdominoperineal Resection

In those situations where an abdominoperineal resection is carried out:

- The sigmoid vessels should be ligated and the attached mesentery should be resected.
- The tumor should be completely resected and the margins of the resection should be tumor-free as determined by the pathologist. The margins of the resected tissue, including perianal skin, should be tumor-free.
- The levators should be transected at the pelvic wall when possible.
- The pelvic peritoneum should be closed, unless technically impossible, to prevent small bowel from entering into the pelvic field of radiation. The use of mesh to prevent small bowel from adhering to the pelvis is encouraged but is not mandatory.
- The use of drains or perineal packing is optional but should be recorded.
- The number, type, and date of blood transfusions given preoperatively, perioperatively, and postoperatively should be recorded on Form OR.

TABLE 6A. Groups 1 and 2: Dose Modifications for Hematologic Toxicity
CYCLES 1 and 4-7

WBC		Platelet Count	FU-LV
$\geq 3000/mm^3$	and	$\geq 75,000/mm^3$	500 mg/m^2 FU + 500 mg/m^2 LV
$2000/mm^3$ - $2999/mm^3$	or	$50,000/mm^3$ - $74,999/mm^3$	HOLD treatment and repeat counts weekly; when WBC ≥ 3000 and platelets $\geq 75,000$, THEN resume FU 400 mg/m^2 with 500 mg/m^2 of LV for the remaining weeks of that treatment cycle. If this occurs after week 4 of any cycle, begin the rest period. **Begin the next cycle (21 days after the last dose) at 400 mg/m^2 of FU with 500 mg/m^2 of LV.** Return to the 500 mg/m^2 dose of FU on day 1 of the next 8-week cycle. Should leukopenia (WBC <3000) occur at any time at the 400 mg/m^2 dose of FU, the dose will be reduced in 100 mg/m^2 increments (300 mg/m^2, 200 mg/m^2, etc.). In an effort to deliver the maximum tolerated dose, the dose of FU for subsequent cycles should be increased at 100 mg/m^2 intervals until 500 mg/m^2 is reached. Should frequent dose reductions occur, permanent dose reductions may be considered. Contact the NSABP Clinical Coordinating Center at (412) 624-6221 prior to such permanent reductions.

TABLE 6B. Groups 1 and 2: Dose Modifications for Hematologic Toxicity
CYCLES 2 and 3 (during radiotherapy)

WBC		Platelet Count	FU-LV
$\geq 3000/mm^3$	and	$\geq 75,000$	325 mg/m^2 FU + 20 mg/m^2 LV
$2000/mm^3$ - $2999/mm^3$	or	$50,000/mm^3$ or $74,999/mm^3$	If such counts are obtained: • At the beginning of cycle 2, hold chemotherapy and radiotherapy; repeat counts weekly; when WBC ≥ 3000 and platelets $\geq 75,000$, start cycle 2 and radiotherapy. • During radiotherapy, continue radiotherapy. • At the starting date of cycle 3, hold cycle 3 but continue radiotherapy; repeat counts at weekly intervals. If after 1 week WBC ≥ 3000 and platelets $\geq 75,000$, proceed with cycle 3. If after 1 week the counts are not back to that level, delete cycle 3 and begin the rest period.

TABLE 6C. Groups 1 and 2: Dose Modifications for Hematologic Toxicity
CYCLES 1 and 4-7

WBC		Platelet Count	FU-LV
$\leq 1999/mm^3$	or	$\leq 49,999/mm^3$	Delay therapy for at least 3 weeks from last dose and until WBC ≥ 3000 and platelets $\geq 75,000/mm^3$, THEN begin the next cycle at 400 mg/m^2 of FU with 500 mg/m^2 LV for that full cycle. Observe closely for nadir complications. In the absence of further limiting toxicity, return to 500 mg/m^2 FU for the next cycle. Should leukopenia (WBC <3000) occur at any time at the 400 mg/m^2 dose of FU, the dose will be reduced in 100 mg/m^2 increments (300 mg/m^2, 200 mg/m^2, etc.). In an effort to deliver the maximum tolerated dose, the dose of FU for subsequent cycles should be increased at 100 mg/m^2 intervals until 500 mg/m^2 is reached. Should frequent dose reductions occur at the 500 mg/m^2 dose, additional permanent dose reductions may be considered. Contact the NSABP Clinical Coordinating Center at (412) 624-6221 prior to such permanent reductions.

Table 6D. Groups 1 and 2: Dose Modifications for Hematologic Toxicity
CYCLES 2 and 3 (during radiotherapy)

WBC		Platelet Count	FU-LV
$\leq 1999/mm^3$	or	$\leq 49,999/mm^3$	If such counts are obtained: • At the beginning of cycle 2, hold chemotherapy and radiotherapy; repeat counts weekly; when WBC ≥ 3000 and platelets $\geq 75,000$, start cycle 2 and radiotherapy. • During radiotherapy, hold radiotherapy until WBC ≥ 2000 and platelets $\geq 50,000$; give cycle 3, 28 days after cycle 2 with an FU dose reduction by 50 mg/m^2 and complete radiotherapy after cycle 3. • At the starting date of cycle 3, hold both chemotherapy and radiotherapy; repeat counts weekly. If after 1 week WBC 2000-2999 and platelets 50,000-74,999, resume radiotherapy only and delete cycle 3. If after 1 week WBC ≥ 3000 and platelets $\geq 75,000$, resume radiotherapy and give cycle 3 at a 50 mg/m^2 FU reduction. If none of the above occurs, delete cycle 3 and complete radiotherapy when WBC ≥ 2000 and platelets $\geq 50,000$. If this does not occur within 2 weeks after the last radiation treatment, delete the rest of the radiotherapy and begin the rest period.

TABLE 7A. Groups 1 and 2: Dose Modifications for Gastrointestinal Toxicity
CYCLES 1 and 4-7

IT IS IMPORTANT TO UNDERSTAND THAT, IN CONTRAST TO GENERAL EXPERIENCE, THE FIRST CYCLE OF THERAPY REQUIRES THE MOST ATTENTION AND CAUTION. GI TOXICITY CAN BE FATAL IF MONITORING ADJUSTMENT OR TREATMENT IS DELAYED. TOXICITY IS REPRODUCIBLE BUT RARELY CUMULATIVE.

Standard antidiarrheal medications, e.g., Lomotil, etc., should not be used prophylactically but should be used once diarrhea occurs.

Grade	Toxicity	FU-LV
1	•nausea (able to eat) or vomiting (1 x day) •stomatitis (mild, moderate ulcers) or •diarrhea (watery stools) 2-3 x per day. If symptoms are present at the time treatment is due, hold treatment. If symptoms occur between treatments and patient presents with no symptoms, no adjustments should be made •mild abdominal pain	HOLD treatment until recovery. Early i.v. supportive care is indicated, even as an inpatient if necessary. This is necessary in order to prevent serious toxicity. Observe closely for nadir complications, THEN resume 400 mg/m^2 of FU with 500 mg/m^2 of LV for remaining weeks of the treatment cycle. If this occurs after week 4 of any cycle, begin the rest period and begin the next cycle at 400 mg/m^2 of FU with 500 mg/m^2 of the LV. In the absence of further limiting toxicity, return to the originally calculated drug dosage of 500 mg/m^2 of FU for the next cycle of therapy.

TABLE 7B. Groups 1 and 2: Dose Modifications for Gastrointestinal Toxicity
CYCLES 2 and 3 (during radiotherapy)

Standard antidiarrheal medications, e.g., Lomotil, etc., should not be used prophylactically but should be used once diarrhea occurs.		
Grade	Toxicity	FU-LV
1	•nausea (able to eat) or vomiting (1 x day) •stomatitis (mild, moderate ulcers) or •diarrhea (watery stools) 2-3 x day •mild abdominal pain	No adjustments in chemotherapy or radiotherapy

TABLE 7C. Groups 1 and 2: Dose Modifications for Gastrointestinal Toxicity
CYCLES 1 and 4-7

Grade	Toxicity	FU-LV
2	•nausea (decrease intake) or vomiting (2-5/24 hours) •stomatitis (severe ulcers) that does not totally prevent alimentation and nutrition, or •moderate-to-severe diarrhea (watery stools) 4-6 x per day; intravenous hydration not required; no evidence of occult blood •moderate abdominal pain	HOLD treatment at least 2 weeks and until full recovery, THEN begin the next cycle of therapy at 400 mg/m^2 of FU with 500 mg/m^2 of LV. Aggressive i.v. supportive care and, most likely, hospitalization are indicated in order to prevent more serious toxicity. In the absence of further dose-limiting toxicity during that cycle, return to the originally calculated drug dosage of 500 mg/m^2 of FU for the next cycle of therapy. Should grade 2 or grade 3 GI toxicity occur at the 400 mg/m^2 dose of FU, the dose will be reduced in 100 mg/m^2 increments (300 mg/m^2, 200 mg/m^2, etc.). In an effort to deliver the maximum tolerated dose, the dose of FU for subsequent cycles should be increased at 100 mg/m^2 intervals until 500 mg/m^2 is reached. Should frequent dose reductions occur, permanent dose reductions may be considered. Contact the NSABP Clinical Coordinating Center at (412) 624-6221 prior to such permanent reductions.

TABLE 7D. Groups 1 and 2: Dose Modification for Gastrointestinal Toxicity
CYCLES 2 and 3 (during radiotherapy)

Grade	Toxicity	FU-LV
2	•nausea (decrease intake) or vomiting (2-5/24 hours) •stomatitis (severe ulcers) that does not totally prevent alimentation and nutrition, or •moderate-to-severe diarrhea (watery stools) 4-6 x per day; intravenous hydration not required; no evidence of occult blood •moderate abdominal pain	If such toxicity occurs: • At the beginning of cycle 2, hold both chemotherapy and radiotherapy and assess the patient weekly. Start cycle 2 and radiotherapy when toxicity has resolved. • During cycle 2, delete the rest of cycle 2 and continue radiotherapy. Give cycle 3, 28 days after the beginning of cycle 2 at an FU dose reduction by 50 mg/m^2. • During radiotherapy, continue radiotherapy and give cycle 3, 28 days after the beginning of cycle 2 at an FU dose reduction by 50 mg/m^2. • At the beginning of cycle 3, hold cycle 3 but continue radiotherapy and evaluate the patient weekly. If in one week the toxicity has resolved, proceed with cycle 3 at a 50 mg/m^2 dose reduction. If the toxicity has not resolved in 1 week, delete cycle 3 and begin the rest period.

TABLE 7E. Groups 1 and 2: Dose Modifications for Gastrointestinal Toxicity
CYCLES 1 and 4-7

Grade	Toxicity	FU-LV
3-4	•nausea (inability to eat) and vomiting (6-10 episodes/day)	Standard antiemetic therapies may be used as required in order to reduce/control nausea and vomiting. If these symptoms cannot be controlled, subsequent dosages of FU will be reduced as required in increments of 100 mg/m^2.
	•vomiting (> 10 episodes/day or requiring parenteral support) •stomatitis (severe ulcers) that makes the patient unable to eat •GI bleeding (occult or gross) •incapacitating diarrhea (watery stools) ≥ 7 x per day •severe abdominal pain	Discontinue further protocol therapy. Hospitalization with aggressive i.v. supportive care is indicated to prevent more serious toxicity. Observe closely for nadir complications. Examine for evidence of postural hypotension, decreased urine output, and occult GI opportunistic infection. Contact the NSABP Clinical Coordinating Center at (412) 624-6221 to report all such toxicity.

TABLE 7F. Groups 1 and 2: Dose Modifications for Gastrointestinal Toxicity
CYCLES 2 and 3 (during radiotherapy)

Grade	Toxicity	FU-LV
3-4	•nausea (inability to eat) and vomiting (≥6 episodes/day or requiring parenteral support) •stomatitis (severe ulcers) that makes the patient unable to eat •GI bleeding (occult or gross) •incapacitating diarrhea (watery stools) ≥7 x per day •severe abdominal pain	If such toxicity occurs: • At the beginning of cycle 2, hold both chemotherapy and radiotherapy and assess the patient weekly. Start cycle 2 and radiotherapy when toxicity has resolved. • During cycle 2, stop both chemotherapy and radiotherapy. Delete the rest of cycle 2. Restart radiotherapy when the toxicity decreases to grade 2 or less. Give cycle 3, 28 days after the beginning of cycle 2 at a dose reduction of FU by 50 mg/m^2. Complete radiotherapy after cycle 3. • During radiotherapy, stop radiotherapy until toxicity resolves. Then resume radiotherapy and give cycle 3, 28 days after the beginning of cycle 2 at a dose reduction of FU by 50 mg/m^2. Complete radiotherapy after cycle 3. • At the beginning of cycle 3, hold both chemotherapy and radiotherapy and evaluate at weekly intervals. If in one week the toxicity has resolved, resume radiotherapy and proceed with cycle 3 at an FU dose reduction of 50 mg/m^2. If the toxicity has not resolved in 1 week, delete cycle 3 and resume radiotherapy when the toxicity has decreased to grade 2 or less. If this does not occur within 2 weeks after the last radiation treatment, delete the rest of the radiotherapy and begin the rest period.

TABLE 8A. Clinical Precautions and Additional Dose Modifications for Other Related Symptoms
CYCLES 1 and 4-7

•Neurologic Toxicity	FU may produce cerebellar ataxia. Patients should be examined and questioned about the possible side effects before each treatment. Therapy should be delayed if neurologic toxicity is present and reinstituted at 400 mg/m^2 when symptoms resolve. Should symptoms recur at the lower dose, additional therapy should be discontinued and the NSABP Clinical Coordinating Center (412/624-6221) notified. In the absence of further toxicity at 500 mg/m^2, administer 400 mg/m^2 FU for the remaining cycles.
•Generalized Skin Rash or •Decreased Performance Status (3)	Hold treatment at least 2 weeks and until full recovery, THEN begin the next cycle of therapy at 400 mg/m^2 of FU with 500 mg/m^2 of LV. In the absence of further dose-limiting toxicity during that cycle, return to the originally calculated drug dosage of 500 mg/m^2 of FU for the next cycle of therapy. If symptoms reappear at the 400 mg/m^2 dose of FU, the dose will be reduced in 100 mg/m^2 increments (300 mg/m^2, 200 mg/m^2, etc.) In an effort to deliver the maximum tolerated dose, the dose of FU for subsequent cycles should be increased at 100 mg/m^2 intervals until 500 mg/m^2 is reached. Should frequent dose reductions occur, permanent dose reductions may be considered. Contact the NSABP Clinical Coordinating Center at (412) 624-6221 prior to such permanent reductions.
•Exfoliative Dermatitis or •Decreased Performance Status (4)	Discontinue further protocol therapy. Observe closely for nadir complications. Contact the NSABP Clinical Coordinating Center at (412) 624-6221 to report all such toxicity.

TABLE 8B. Clinical Precautions and Additional Dose Modifications for Other Related Symptoms
CYCLES 2 and 3 (during radiotherapy)

•Neurologic Toxicity (Grade 2) or •Generalized Skin Rash or •Decreased Performance Status (3)	If such toxicity occurs: • At the beginning of cycle 2, hold both chemotherapy and radiotherapy and assess the patient weekly. Start cycle 2 and radiotherapy when toxicity has resolved. • During cycle 2, delete the rest of cycle 2 and continue radiotherapy. Give cycle 3, 28 days after the beginning of cycle 2 at an FU dose reduction by 50 mg/m^2. • During radiotherapy, continue radiotherapy and give cycle 3, 28 days after the beginning of cycle 2 at an FU dose reduction by 50 mg/m^2. • At the beginning of cycle 3, hold cycle 3 but continue radiotherapy and evaluate the patient weekly. If in one week the toxicity has resolved, proceed with cycle 3 at a 50 mg/m^2 dose reduction. If the toxicity has not resolved in 1 week, delete cycle 3 and begin the rest period.
•Neurologic Toxicity (Grades 3-4) or •Exfoliative Dermatitis (excluding radiation-induced) or •Decreased Performance Status (4)	If such toxicity occurs: • At the beginning of cycle 2, hold both chemotherapy and radiotherapy and assess the patient weekly. Start cycle 2 and radiotherapy when toxicity has resolved. • During cycle 2, stop both chemotherapy and radiotherapy. Delete the rest of cycle 2. Restart radiotherapy when the toxicity decreases to grade 2 or less. Give cycle 3, 28 days after the beginning of cycle 2 at a dose reduction of FU by 50 mg/m^2. Complete radiotherapy after cycle 3. • During radiotherapy, stop radiotherapy until toxicity resolves. Then resume radiotherapy and give cycle 3, 28 days after the beginning of cycle 2 at a dose reduction of FU by 50 mg/m^2. Complete radiotherapy after cycle 3. • At the beginning of cycle 3, hold both chemotherapy and radiotherapy and evaluate at weekly intervals. If in one week the toxicity has resolved, resume radiotherapy and proceed with cycle 3 at an FU dose reduction of 50 mg/m^2. If the toxicity has not resolved in 1 week, delete cycle 3 and resume radiotherapy when the toxicity has decreased to grade 2 or less. If this does not occur within 2 weeks after the last radiation treatment, delete the rest of the radiotherapy and begin the rest period.

TABLE 9A. Interruption of Chemotherapy for Reasons Other Than Toxicity
Group 1: CYCLES 4-7
Group 2: CYCLES 1 and 4-7

Closure of Colostomy	The time for closure of the colostomy will be at the discretion of the surgeon. Timing of closure of colostomy should be arranged to minimize time off chemotherapy. Closure of colostomy following completion of chemotherapy is encouraged. The total number of cycles should be retained. Reason for delay of treatment will be reported on Form T.

TABLE 9B. Interruption of Chemotherapy for Reasons Other Than Toxicity
Group 2: CYCLES 2 and 3 (during radiotherapy)

Closure of Colostomy	Although the time of closure of colostomy is at discretion of the surgeon, interruption in radiation and cycles 2 and 3 for colostomy closure should be avoided.

18.2.2 Low Anterior Resection (including coloanal resection)

When an anterior resection is carried out:

- The sigmoid vessels should be ligated and the attached mesentery removed.
- The margins of resection should be demonstrated to be tumor free.
- Preferably the proximal part of colon used in the anastomosis should come from non-irradiated field.
- The type of suture material employed in the anastomosis is optional but must be recorded.
- The use of drains is optional but must be recorded.
- The number, type, and date of blood transfusions given preoperatively, perioperatively, and postoperatively should be recorded on Form OR.

18.2.3 Local Excision

Local excision may be performed in the following manner:

- Local excision through the anal canal after dilatation of the rectal sphincter. Complete excision is required with full thickness removal of the tumor and frozen section confirmation of clear margins.
- Transsphincteric excision with a single surgical incision through the external anal sphincter muscle. Complete excision is required with full thickness removal of the tumor and frozen section confirmation of clear margins.
- Transsacral approach to the rectum with removal of coccyx or lower sacrum and sleeve resection of the bowel containing the tumor. Frozen section confirmation of free margins is required.

If the margins of resection are found to be involved in the permanent sections, then one reexcision procedure will be allowed. The second procedure can also be an abdominoperineal resection if deemed appropriate by the surgeon.

18.2.4 Placement of Permanent Colostomy Following APR

The colostomy should be placed out of the field of radiation, i.e., cephalad to a horizontal line drawn from the anterior superior iliac spines.

18.2.5 Creation of Temporary Colostomy

Creation of a temporary colostomy is permitted with low anterior resection, coloanal resection, or other sphincter-preserving operations.

NOTE: Form OR should be completed immediately after operation by the surgeon and submitted to the NSABP Headquarters Office within 45 days from surgery, accompanied by a copy of the institution's dictated operative report.

19.0 RADIATION THERAPY ADMINISTRATION

19.1 Only megavoltage photon beams will be used. The minimum energy will be 4MV and Co-60. Radiotherapy will start within 3 weeks following cycle 1 and only after hematopoietic recovery from the first course of chemotherapy.

19.2 All irradiated patients will receive 4500 rad/25 fractions to the pelvis as described below. A smaller volume, excluding small bowel, will then be treated with an additional 540 rad/3 fractions to give a total dose of 5040 rad/28 fractions. Treatments will be administered 5 days/week in a continuous course. Radiotherapy should start on a Monday.

19.3 Volume to be Irradiated.

The irradiated volume will be the same for preoperative and postoperative patients. Similarly, the same fields will be used after AP resection, anterior resection, or local excision. The perineum does not have to be included in the irradiated volume. Preliminary data from R-02 indicate that the rate of perineal recurrence without radiotherapy in patients receiving APR is very low (<3%).

The pelvis will be treated using a four-field box technique (anterior-posterior and two lateral fields). It is the intent of therapy to include the entire tumor bed with a margin, plus the nodal groups. The external iliac nodes are not to be included unless pelvic organs with major external iliac drainage are involved by direct extensions, i.e., invasion of bladder, prostate, cervix, or vagina. The lateral borders of the anterior-posterior radiation fields will be at least 1 cm lateral to the widest bony margin of the true pelvic side walls. The superior border of the radiation fields will be at the L5-S1 interspace. The lower border will be at the inferior aspect of the obturator foramen. The superior and inferior borders of the lateral fields will be as for the anterior/posterior fields. The posterior border of the lateral portals will be at least 1.5 cm posterior to the anterior bony sacral margin. The anterior margin can be shaped to reduce the amount of bladder irradiated and also to decrease the amount of small bowel superiorly and anteriorly. If the external iliac lymph nodes do not have to be included, the anterior margin of the lateral field is 2-3 cm anterior to the sacral promontory and includes approximately two-thirds of the femoral heads. It is recommended that all patients be treated in the prone position.

19.4 Boost Volume

The boost volume will be treated with a multiple-field technique using either anterior-posterior and two lateral fields, posterior and two lateral fields, or two lateral fields. In patients with complete or nearly complete mobilization of the small bowel out of the pelvis, the fields for the boost may be nearly as large as the initial pelvic fields, using additional blocking or modest reduction of field size to minimize small bowel irradiation. The fields for the boost should be as large as possible while excluding the small bowel. In the occasional instance where small bowel cannot be sufficiently shielded, a boost will not be administered. It is to be emphasized that small bowel is to be excluded from the boost volume.

19.4.1 Suggested Small Bowel Studies

A small bowel series can be helpful in minimizing acute and chronic toxicity by influencing portal design. The small bowel series should be performed either before or during the first few weeks of radiotherapy.

It is suggested that the patient be instructed in the technique of bladder distension. Approximately 1-2 hours before therapy, the patient is instructed to void, then to drink approximately 1 liter of fluid. The patient should not empty his/her bladder until after therapy.

For a small bowel series, the patient drinks approximately 500 cc of fluid plus 500 cc of barium sulfate 2-4 hours before simulation; films are then taken of the anterior-posterior and lateral fields with bladder distension. A second set of films is taken after the patient voids. Bladder distention produces some degree of small bowel displacement in most patients. For some patients, bladder distention may be extremely uncomfortable or difficult.

19.5 Doses

Using the four-field box technique, 4500 rad/25 fractions at 180 rad per day will be administered to the intersection of the axes. All fields will be treated daily. The boost volume will receive 540 rad in 3 fractions at 180 rad per day calculated at the ISO center. Therapy will be administered 5 days/week in a continuous course. No modification in dose will be made for interruptions in therapy.

19.6 Radiation Checklist

There will be rapid review of portal films for all patients receiving radiotherapy on this study. Simulation films of the AP-PA and lateral fields of the pelvis will be submitted within one week of starting radiotherapy. Simulation film of the boost portals with opacification of the small bowel will also be submitted before the irradiation of the boost volume. All films and quality-assurance material are to be sent to the NSABP Biostatistical Center, Suite 600, 230 McKee Place, Pittsburgh, PA 15213.

At the conclusion of radiotherapy, the completed RT form with daily treatment records, dosimetry calculations, isodoses, photographs of the patient in the treatment position, and portal and simulation films will be submitted.

20.0 DRUG INFORMATION

20.1 5-Fluorouracil: (NSC #19893)

20.1.1 Description

5-FU is a marketed drug available in 500 mg vials. It is a fluorinated pyrimidine belonging to the category of antimetabolites and 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 deoxyribonucleic acid (DNA) and, to a lesser extent, inhibits the formation of ribonucleic acid (RNA). Since DNA and RNA are essential for cell division and growth, the effect of fluorouracil may be to create a thymine deficiency, which provides unbalanced growth and death of the cell.

20.1.2 Toxicity

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 cycle 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 in a substantial number of cases. The dermatitis most often seen is a pruritic maculopapular rash that usually appears on the extremities and, less frequently, on the trunk.

20.1.3 Special Precaution

Administration of 5-FU should be only by intravenous route, taking care to avoid extravasation.

20.1.4 How Supplied

5-FU is available in 10-ml vials, as a colorless-to-faint-yellow aqueous solution

containing 500 mg 5-FU, with pH adjusted to approximately 9.0 with sodium hydroxide.

20.1.5 Storage

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

20.1.6 Procurement

5-FU is available commercially and should be obtained from such sources.

20.2 Calcium Leucovorin - (NSC #3590)

20.2.1 Description

Leucovorin is the formal derivative and active form of folic acid used to counter the hematologic and other toxicities of methotrexate and other antifols. Allergic sensitization has been reported following both oral and parenteral administration of folic acid.

20.2.2 Clinical Formulation

Calcium leucovorin is available in 20 cc vials as a sterile powder and is equivalent to 100 mg leucovorin. Reconstitute with 10 ml bacteriostatic water for injection USP, which contains benzyl alcohol. Each ml contains leucovorin calcium equivalent to leucovorin 10 mg and sodium chloride 8 mg. Use within 7 days. If reconstituted with sterile water for injection USP, use within 8 hours.

20.2.3 Procurement

Calcium leucovorin is available commercially and should be obtained from such sources.

21.0 RECORDS TO BE KEPT

FORM TYPE	DESCRIPTION	REQUIRED FOR SUBMISSION
Consent	Informed Consent Form (signed and dated)	Immediately after patient randomization
A	Patient Entry Form	Immediately after patient randomization
B	Patient History, Physical Exam, Preoperative Studies Form	Within 30 days of randomization
TR	Tumor Measurement and Treatment Response Form	Groups 1 and 2: Before initiation of therapy. Group 1: After completion of first cycle of chemotherapy (prior to RTX) and after completion of RTX (prior to surgery).
OR	Operative Report Form	Within 45 days of surgery
Dictated Operative Report		Within 45 days of surgery
D	Pathologist's Report Form	Within 45 days of surgery
Dictated Pathology Report		Within 45 days of surgery
Pathology Blocks and Slides		Within 45 days of surgery
T	Chemotherapy Report Form	At the end of each cycle of therapy
ADR	Toxicity/Adverse Drug Reaction Report Form	At the end of each cycle of therapy and/or in the event of a severe or unusual reaction; also submit one ADR form 3 months after completion of protocol therapy
RT	Radiation Therapy Report Form	At the end of radiation therapy
OFF	Off-Protocol Therapy Form	When a patient permanently discontinues protocol therapy for reasons other than 1) completion of therapy per protocol or 2) documented treatment failure or second primary
F1	Follow-Up Form (For positive or suspicious tests, provide documentation.)	Every 3 months for the first 2 years (even though T forms will also be submitted during part of this time); every 6 months for years 3 through 5; yearly thereafter

22.0 PATIENT CONSENT

The consent form must be signed by the patient, witnessed, and dated before the patient is randomized. All pages of the consent form are to be initialed by the patient. All institutional, NCI, and federal regulations concerning informed consent and peer judgment will be fulfilled.

23.0 STATISTICAL CONSIDERATIONS

23.1 Stratification

Patients randomized into this study will be stratified by age (0-59, 60+) and sex.

23.2 End Points

There are two primary end points: 1) disease-free survival and 2) survival. For disease-free survival, an event is defined as documented evidence of treatment failure, a second primary cancer or non-cancer death. When overall survival is an end point, death from any cause is considered to be an event. A secondary end point is the proportion of patients with local-regional recurrence as a first event.

23.3 Sample Size Estimates

Patients who received FU-LV and RTX in protocol R-02 had a yearly rate for disease-free survival of .115 and a death rate of .06. However, because patients will be randomized prior to surgery some Dukes' A and Dukes' D patients will be entered into the trial. We estimate these numbers to be 10% for Dukes' D patients and 15% for Dukes' A patients. We have no information available on the rates of recurrence and/or death of Dukes' A and Dukes' D patients on FU-LV and RTX. Based on failure rates of Dukes' A and Dukes' D patients in protocol R-01, we estimate that such a mixture of stages in R-03 (15% Dukes' A, 75% Dukes' B and Dukes' C, and 10% Dukes' D) would result in a range of annual death rate between .075 and .11 for the total group..

Based on our accrual in R-02 in the years 1989-1991, we believe 180 patients/year is a conservative estimate of accrual for this protocol. The main statistical goal is to be able to detect a 33% reduction in death rate in the preoperative therapy treatment arm. Assuming a baseline death rate of .075, such a reduction, if maintained for 5 years, would be equivalent to an absolute difference in survival of 9.1% between the two treatment groups. Assuming an a=.05 two-sided test, using stratum specific death rates and proportions of patients within strata from R-02, we estimate a power of .81 to detect a 33% reduction in hazard rate at the end of the 6.5 years. We have assumed a uniform accrual of 180 patients/year for 5 years, an additional 1.5 years of follow-up, and have applied the Bernstein and Lagakos method of estimating sample size.[48] If the death rate corresponds to .11, then we estimate power of .84 of detecting a 33% reduction in mortality rate at the end of 5.5 years (5 years of accrual and .5 years of follow-up).

23.4 Interim Analysis

Toxicity and accrual information will be reviewed quarterly. Disease-free survival and survival will be analyzed semiannually starting at year 2.5. At that time we will also re-evaluate the sample size estimates. We will then have improved estimates of the percentage of Dukes' A and Dukes' D patients and of the survival rates of Dukes' D patients on LV+RTX. These estimates will be based only on data from the postoperative treatment arm. We feel that our estimate of 5 years of accrual at 180 patients/year and 1.5 years of additional follow-up represents a worst-case scenario and that a final analysis at 5.5 years is more likely. Note that we will be able to reevaluate the sample size estimates before initiating comparison of treatment groups. If one of the treatments demonstrates a significant survival advantage before the proposed final analysis, it will be presented to the NSABP Executive Committee, which will make a decision on early termination and early reporting of results.

To protect against problems with multiple comparisons resulting from nine possible interim analyses, we will conduct the interim testing at a=.02 and require two conservative rejections at this reduced a-level. These results were obtained by Hussein[49] and follow the suggestion by Falissard and Lellouch[50] to define interim stopping rules for rejection regions based on a succession of significant tests. The decision for early termination of the trial will be based on survival as an end point and a comparison based on the totality of randomized patients in the two treatment groups. Thus, early stopping will not be based on differences in treatment efficacy in subgroups of patients.

23.5 Strategy for Final Analysis

The primary end points are disease-free survival and survival. The analyses will be based on time from randomization to first event. Our ineligible rate has been less than 1% in previous rectal protocols. For this protocol, if eligibility is defined by stage of disease (i.e., exclusion of either Dukes' A or Dukes' D lesions), an analysis based on only eligible patients may be biased since preoperative chemotherapy may "downstage" the disease. To test the primary hypothesis we will use the logrank test,[51,52] adjusted for the stratification variables applied to all randomized patients, including ineligibles.

The Cox regression model[53] will be the primary tool for determining differences in efficacy among patient subgroups. Log-minus-log survival plots will be used to check the proportionality assumption of the model. Initially, terms for the stratification variables and treatments will be included in the model. If the global likelihood ratio test for all interactions of covariates with treatments is significant, individual interactions will be tested using the Gail and Simon procedure.[54] Subgroup differences in treatment efficacy will be further investigated only if the global test for interaction is significant.

Secondary aims of this protocol include a comparison of local recurrences in the two groups, a correlation of the therapy response of the primary rectal tumor to disease-free

survival and survival, an assessment of the downstaging effect of preoperative therapy and an estimate of the proportion of patients who can be converted to sphincter-saving surgical procedures. Although each of these will be addressed in the final analysis, in some cases we may not have sufficient statistical power to answer completely all of the questions related to these issues.

Present results from R-02 indicate that LV+5FU in combination with radiation results in a lower local recurrence rate than chemotherapy alone. Although we still do not have precise estimates of the local recurrence rate as a first event, the final estimate of local recurrence on the combination therapy arm from R-02 is likely to be less than 10%. We will compare time-to-local recurrence in the two treatment arms using Kaplan-Meier plots.

The response of rectal tumors to preoperative therapy will be classified as complete, partial, stable disease, or progressive disease. In addition, estimates of clinical tumor size will be made at entry and prior to each course of therapy. Within the preoperative groups, comparisons among the four categories of response will be made using Kaplan-Meier plots supplemented by the log-rank test. Such analysis will include control for selected tumor and/or patient characteristics. One factor that we feel must be adjusted for in the analysis is tumor size. If tumor response is not predictive of outcome other than through a possible correlation with tumor size, then the use of tumor response as a marker of subsequent long- term outcome may not be justified. Conversely, if tumor response provides independent information on long-term patient outcome, then it may have use as a marker of response to therapy in the design of future protocols. In addition to the category of response, we will attempt to relate reduction in initial tumor size and the rate of reduction to long-term outcome.

We expect preoperative treatment will downstage the disease in some patients. Estimates of the amount of downstaging can be obtained by comparing the distribution of Dukes' stage and the distribution of nodal classification in the preoperative and postoperative groups.

Prior to randomization, the surgeons will be asked to estimate which type of operation would be sufficient. We will then estimate the proportion of sphincter-saving surgical procedures which are due to preoperative therapy. This will be obtained by subtracting the baseline rate observed in the postoperative group. Assuming 450 patients within each group, we will be able to estimate the proportion of sphincter-saving surgical procedures with 90% confidence to a precision of $\pm .04$. In estimating this precision, we have been conservative by using the maximum variance of an estimate of a proportion which occurs when $p=.5$.

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NSABP PROTOCOL R-03

[*To be included with submission of consent form document to local IRB*]

TO: Local Institutional Review Boards

FROM: Bernard Fisher, M.D.
Chairman, National Surgical Adjuvant Breast & Bowel Project

DATE: April 5, 1993

RE: Local IRB Review of Multicenter Clinical Trials

The NSABP understands and agrees with the position of the Office for Protection from Research Risks (OPRR) that, "Only the local IRB is familiar with the particular circumstances of its research setting and is in a position to weigh critical considerations like state and local laws, professional and community standards, institutional policies, and the needs of differing patient or subject populations." In order to conform to OPRR guidelines regarding local IRB review of multicenter clinical trials (effective November 9, 1992), and to provide local IRBs with flexibility in conforming to local standards, the NSABP provides the following instructions regarding the IRB approval process of this multicenter clinical trial:

The protocol and model consent form provided by the NSABP have been reviewed and approved by the Division of Cancer Treatment/National Cancer Institute. Local IRBs and the investigator are permitted to make changes to the consent form; however, the editorial changes must not alter the overall content or the intent of the information in the model consent form. Should an investigator or local IRB delete or make a substantive modification of the information contained in the risks or alternative treatments sections of the consent form, this must be justified in writing by the investigator or the IRB and then approved by the IRB. The IRB is responsible for reflecting in the IRB minutes the justification for, and approval of, such deletions or modifications. The investigator is responsible for forwarding copies of such IRB-approved changes with their justifications to the NSABP Headquarters at the address provided below. It is the responsibility of the principal investigator and the IRB to determine what constitutes a substantive change. Any conflict between the two groups concerning this decision would be resolved at NSABP Headquarters.

NSABP Operations Center
Room 914 Scaife Hall
3550 Terrace Street
Pittsburgh, PA 15261

Phone: (412) 648-9720
Fax: (412) 648-1912

Upon receipt of these documents at NSABP Headquarters, Operations Center staff will review and approve the changes and their justifications with input (as needed) from the Quality Assurance staff or NSABP Headquarters staff.

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University of Pittsburgh
SCHOOL OF MEDICINE
Department of Surgery

NSABP R-03
Page 1 of 6
Approved: 05/04/93
Biomedical IRB
University of Pittsburgh

CONSENT TO ACT AS A SUBJECT IN AN EXPERIMENTAL STUDY

TITLE: A Clinical Trial to Evaluate the Worth of Preoperative Multimodality Therapy (5FU-LV and RTX) in Patients with Operable Carcinoma of the Rectum

INVESTIGATOR(S): Bernard Fisher, M.D.
Distinguished Service Professor
Department of Surgery
University of Pittsburgh
(412) 648-9720

SOURCE OF SUPPORT: National Cancer Institute

DESCRIPTION: Dr. _____ has explained to me that I have rectal cancer; therefore, I am being asked to participate in a research study to determine the best method for treating cancer such as mine, which is classified as operable. The purpose of this study is to determine whether 1) it is better to give radiotherapy and some of the chemotherapy before surgery and more chemotherapy after surgery rather than 2) to give all the therapy (chemotherapy and radiotherapy) after surgery.

Background: Previous studies have established that using a combination of chemotherapy (anticancer drug treatments) and radiotherapy (radiation treatment) after surgery is effective in the treatment of cancer of the rectum when the tumor penetrates through the bowel wall or when there is involvement of lymph nodes in the area. Studies have also shown that the combination of 5-fluorouracil (5-FU) and leucovorin (LV) appears to be an effective chemotherapy regimen. There is now information from the laboratory and from patients with locally advanced cancer that beginning the therapy before operation may be of increased benefit in decreasing the recurrence of further cancer and in improving the chances of survival. The administration of chemotherapy and radiotherapy before surgery may also reduce the tumor size so that less extensive surgery is necessary. It has been determined to the best of my physician's ability that my tumor has not spread to any other organs that would require surgical removal.

This research study is being conducted by the National Surgical Adjuvant Breast & Bowel Project (NSABP), an organization with significant experience in conducting clinical trials in patients with rectal cancer. It is anticipated that a total of 900 men and women will be entered into this trial throughout the United States and Canada.

Patient's Study Number: _____ Patient's Initials: _____

Treatment Groups: If I agree to participate in this study, I will be assigned to receive one of the following treatments:

Group 1: Chemotherapy and radiotherapy treatments before surgery, followed by chemotherapy alone after surgery.

Group 2: Surgery, followed by chemotherapy and radiotherapy treatments.*

I will be placed by chance into one of these two groups. This chance selection process is called *randomization* and is frequently used in experimental studies.

Dosing Procedure: In both groups, chemotherapy will consist of the following drugs: LV 500 mg/m^2 will be administered intravenously (in a vein in my arm) over a 2-hour period; one hour after the infusion begins, I will be given a second drug, 5-FU 500 mg/m^2, intravenously over a period of several minutes. Although both of these drugs have individually been approved by the Food & Drug Administration (FDA), their use in combination at these doses for the treatment of rectal cancer is considered to be experimental.

There will be seven treatment cycles of chemotherapy in this study. In cycles 1, 4, 5, 6, and 7, chemotherapy will be administered once a week for 6 weeks, followed by a two-week rest period. Treatment will be restarted 21 days after the day of the last dose of the previous cycle (each cycle = 56 days). As described above, the chemotherapy will consist of both LV and 5-FU administered intravenously.

In treatment cycles 2 and 3, I will receive radiotherapy 5 days a week for a total of 5 weeks and for 3 days during the sixth week, followed by a rest period of up to 8 weeks. During the radiotherapy, I will receive two more cycles of chemotherapy. In each cycle I will receive 5-FU 325 mg/m^2 and LV 20 mg/m^2 intravenously over a period of 30 minutes each day for 5 days during the first (cycle 2) and fifth (cycle 3) weeks of the radiotherapy.

If I am assigned to Group 1, I will have my surgery at the end of cycle 3. This will then be followed by a rest period of up to 4 weeks before I start cycle 4.

If I am assigned to Group 2, I will first have my surgery, followed by a rest period of up to 4 weeks, before I start any of my chemotherapy or radiotherapy.

The total length of time required to complete all the treatment cycles of this study is approximately 12 to 14 months.

**[Since the tumor has not yet been removed, it is impossible for my physician to know for sure whether it penetrates through the entire bowel wall or if the lymph nodes in the area are involved. From the testing done so far, there is a good possibility that one of these conditions is present. If I am randomized to Group 2 and the physician finds that I have a tumor that does not penetrate through the bowel wall and does not involve the lymph nodes in the area, then I will be treated at the discretion of my physician. Since the prognosis in such cases is generally good with surgery alone, further therapy may not be considered necessary. During my surgery, if I am found to have a tumor that involves other organs, or that is inoperable, then I will be treated at the discretion of my physician.]*

Testing & Exams: Laboratory tests and physical exams will be performed during each course of treatment to monitor my physical condition for continuation of therapy. For the lab tests, about 1-2 tablespoons of blood will be drawn from a vein in my arm with a needle. During the administration of chemotherapy and radiotherapy before surgery (Group 1), the size of the tumor will be assessed on two occasions in order to monitor my response to therapy. The first time will be after completion of the chemotherapy, before starting radiotherapy. The second time will be after completion of the radiotherapy and can be done right before surgery while I am asleep. It may be necessary for me to have another endoscopic or endorectal ultrasound to assess my tumor.

During the second year of my study participation, laboratory tests and a physical exam will be repeated every 3 months, then, during the third, fourth, and fifth years of the study, the tests and exams will be performed every 6 months.

During the 5 years after I am entered into this study, chest X-rays and a barium enema or endoscopy will be done every 12 months.

Additional laboratory tests or X-rays may be performed at any time should my physician feel they are medically necessary.

Duration of Participation: I understand that I am expected to complete all the cycles of therapy as described in the dosing procedure and to continue with the follow-up visits as described in the testing and examination section. I realize that, at this time, the NSABP wishes to continue to follow my medical condition at least annually for life.

RISKS & BENEFITS:

Risks Associated with Chemotherapy: I should expect that the chemotherapy will cause side effects in varying degrees and that some might be serious enough to require my being admitted to the hospital for supportive care. The combination of 5-FU and LV given in this trial may cause severe gastrointestinal toxicity. The symptoms may be exhibited as mild-to-severe mouth ulcers, as well as moderate-to-severe diarrhea. The mouth ulcers may be severe enough to inhibit taking an adequate amount of fluids or food by mouth, resulting in severe dehydration and weight loss. Other common side effects are nausea, vomiting, skin rash, and temporary hair loss.

The 5-FU may depress the function of the bone marrow, lowering my white blood count and platelet count. These conditions can increase the susceptibility to infections, bruising, and bleeding. Allergic sensitization has been reported in a few cases.

Risks Associated with Radiotherapy: Radiotherapy may cause transient nausea, vomiting, poor appetite, diarrhea, some irritation and burning of the skin, and, sometimes, urinary discomfort. Towards the end of treatment, fatigue may occur. These symptoms disappear after the

completion of therapy. If necessary due to side effects, radiation therapy will be stopped temporarily or the chemotherapy dose will be decreased until the symptoms are alleviated. Once the symptoms are alleviated, radiation therapy and/or full-dose chemotherapy will be resumed. As a result of the study treatments, some months or years after therapy, there may be an increased risk of obstruction of the bowel, which may require surgery. Also, the capacity of the bladder may be reduced, and there is a possibility that some bleeding into the bladder could occur as a result of changes in the bladder blood vessels. The skin may show some pigmentation and scarring and, later, some slow healing after injury in the area exposed to radiation.

Risks Associated with Surgery: I am aware that any surgical procedure involves risks, including risks from anesthesia. Bleeding, infection, and clots in my veins that could travel to my lungs are some of the risks of surgical procedures. Surgery required for rectal cancer may result in bladder problems such as urinary incontinence, a temporary or permanent colostomy, or sexual impotence. Before my surgery, I will be required to sign another consent form required by the institution where I receive my surgery.

Other Risks: In studies where radiotherapy was given before surgery, there was evidence of a somewhat higher risk of developing skin infections in the area of radiation. This risk was low overall and, generally, these infections resolved with local care and antibiotics. However, should I develop this type of infection, it may prolong my hospital stay for a few days.

If my tumor becomes larger while I am undergoing chemotherapy before my surgery, then the chemotherapy will be stopped and I will be treated with radiotherapy followed by surgery. If my tumor becomes larger while I am receiving radiotherapy, then the radiotherapy will be interrupted and I will undergo surgery.

Mild pain or bruising may result from the needle sticks required for blood collections in this study. The risk of infection is minimal.

Precautions: Unanticipated side effects may occur with any of these drugs. It is extremely important that I report all symptoms that I experience to my physician.

Chemotherapy may cause harm to an unborn baby; therefore, I understand that, if I am a woman capable of becoming pregnant, I should use effective birth-control measures while I am receiving treatment.

If any physician other than the study physician prescribes medication for me for another condition, I will inform the study staff.

Benefits: It has not been proven that either treatment regimen will increase my chances for permanent cure, and there is no evidence at this time that either treatment is better than the other. The potential benefit from this study is to decrease the recurrence rate and to improve the survival rate of patients with rectal cancer such as mine.

ALTERNATIVE TREATMENTS: Alternative treatments might be radiotherapy alone or similar drugs given alone or in combination with the same or different schedules outside of this study, but there is no evidence these would work better than the treatments proposed here. I have discussed the alternatives with my physician and have been given the opportunity to ask questions.

NEW INFORMATION: If any significant new information about the study drugs and/or therapies develops, my doctor will tell me, and my options concerning therapy will be discussed at that time.

COST AND PAYMENTS: Blood tests, laboratory fees, and X-ray procedures will be billed to me in the same fashion as if I were not a part of the study. These tests are felt to be part of good medical care and may or may not be covered by most major insurance companies. The medications and all physicians' and hospital costs will be charged to me in the same fashion as if I were not part of this study.

CONFIDENTIALITY: I understand that any information about me obtained from this research will be kept strictly confidential and will never be identified in any report. I do understand that my research records, just like hospital records, may be subpoenaed by court order. Pathologic slides and blocks will also be made available for review. I consent to the publication of study results as long as the information is anonymous and/or disguised so that I cannot be identified. I also understand that authorized representatives of the National Cancer Institute (NCI), the FDA, and the NSABP may examine my records.

RIGHT TO WITHDRAW: I understand that I am free to refuse to participate in this study or to withdraw at any time for any reason and that my decision will not adversely affect my care at this institution or cause a loss of benefits to which I might otherwise be entitled.

Should I withdraw from this study, I understand there are no anticipated side effects that I may experience as a result of withdrawal from the treatments delivered in this study.

I also understand that, at any time, my doctor can withdraw me from this study because further participation would not be in my best interest. My doctor can stop the treatments even if I am willing to continue.

COMPENSATION FOR ILLNESS OR INJURY: I understand that, in the event of a physical injury or illness resulting from my participation in this study, no monetary compensation will be made, but any immediate emergency medical treatment which may be necessary will be provided at my own expense. In the case of injury related to this research study, I should contact _____ at _____, or _____ at _____.

Patient's Study Number: _____ Patient's Initials: _____

Appendix A

ETHICAL AND REGULATORY CONSIDERATIONS

The following principles must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations. In seeking informed consent, the following information shall be provided in a language understandable to the subject.

1. Basic Elements of Informed Consent

   The following are the basic elements of informed consent which should be provided to each subject:

   a. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

   b. A description of any reasonably foreseeable risks or discomforts to the subject.

   c. A description of any benefits to the subject or to others which may reasonably be expected from the research.

   d. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

   e. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the FDA may inspect the records.

   f. For research involving more than minimal risk, an explanation regarding compensation and the availability of medical treatments in the event of injury, what these treatments consist of, or where further information may be obtained.

   g. An explanation of whom to contact for answers to pertinent questions about the research and subject's rights, and whom to contact in the event of a research-related injury to the subject.

   h. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the

subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

2. Additional Elements of Informed Consent

When appropriate, one or more of the following elements of information shall also be provided to each subject:

a. A statement that the particular treatment or procedure may involve currently unforeseeable risks to the subject (or to the embryo or fetus, if the subject is, or may become, pregnant).

b. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

c. Any additional costs to the subject that may result from participation in the research.

d. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

e. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

f. The approximate number of subjects involved in the study.

A subject (or the subject's legally authorized representative) must give his/her written consent to participate in the study. This consent must be witnessed and dated and retained by the investigator as part of the study records.

If Experimental Subject's Bill of Rights is applicable in your state, this form must also be prepared and signed by each subject and retained as part of the required study records.

A copy of the proposed consent form must be submitted to the Institutional Review Board together with the protocol for approval. Each subject's signed informed consent form must be kept on file by the investigator for FDA inspection at any time.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 56).

The protocol and informed consent form for this study must be approved in writing by the appropriate Institutional Review Board. Prior to study implementation, a consent form which has been approved by the National Cancer Institute will be provided to each clinical center as a guideline for preparation of consent forms for individual IRB approval.

Institutional Review Board approval must be obtained for each participating clinical center to take part in the trial. Local IRB review of this protocol and consent form must adhere to the policy guidelines set forth by The Office for Protection from Research Risks (OPRR) in their directive of November 9, 1992. These procedures complement the informed consent requirements of Department of Health and Human Services (DHHS) regulations as follows:

- The Office for Protection from Research Risks (OPRR) now requires that each local IRB receive a copy of the NIH-approved sample informed consent document and the full NIH-approved protocol as a condition for review and approval of the local informed consent document.

- Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

- The justification for and approval of such deletions or modifications must be reflected in the IRB minutes. For trials sponsored by the National Cancer Institute (NCI), investigators must forward copies of such IRB-approved changes, with their justifications, to the appropriate Cooperative Group headquarters. [Lin, MH and Miller, JG. NIH-OPRR letter to institutional officials and institutional review board (IRB) chairpersons, 9 November, 1992.]

A memorandum directed to local IRBs detailing these responsibilities has been provided with the consent form as part of this protocol.

The letter of approval from the Board must include the statement that "The Institutional Review Board is in compliance with the requirements in Part 56, Subchapter D, Part 312 of the 21 Code of Federal Regulations published January 27, 1981." If the Institutional Review Board uses an approval form which does not contain this or a similar statement, the investigator should request from the Chairperson of the Institutional Review Board a separate letter or memo which does include this statement.

Significant changes to the protocol, as well as a change of principal investigator, must also be approved by the Board and documentation of this approval provided to the study monitor. Records of the Institutional Review Board review and approval of all documents pertaining to this study must be kept on file by the investigator and are subject to FDA inspection at any time during the study. Periodic status reports must be submitted to the Institutional Review Board at least yearly, as well as notification of completion of the study and a final report within three months of study completion or termination. The investigator must maintain an accurate and complete record of all submissions made to the Institutional Review Board, including a list of all reports and documents submitted.

Drug Accountability

For each drug supplied for a study, an accountability ledger containing current and accurate inventory records covering receipt, dispensing, and the return of study drug supplies must be maintained.

The ledger will be maintained routinely for all studies, regardless of study design, and will identify for each shipment the subject number (as applicable) and the quantity of drugs contained in the shipment. The ledger will consist of drug Accountability Records Forms supplied by the NCI. One form for each investigational drug used on each research protocol will be kept. If a protocol contains more than one investigational drug, a separate Accountability Form should be used. A separate drug Accountability Form should also be maintained for each different strength or dosage form of the particular drug being used.

The Accountability Form will be used at each location at which the drug is stored for patient administration, i.e., main pharmacy, satellite pharmacy, physician's office or other dispensing areas. The form is also designed to accommodate both dispensing accountability and any other types of drug transactions (receipts, transfers, returns, broken vials, etc.). The Accountability Form requires information related to the specific protocol and drug transactions such as dispensing to individual patients, drug receipts, transfers to and returns from satellite pharmacies and drug returns.

Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions. During the course of the study, the following information must be noted on the accountability ledger: the quantity of drug dispensed to the subject and the date(s) and quantity of drug returned by the subject. Subjects should return empty containers to the investigator, and the return should be noted in the ledger. These Accountability Forms must be readily available for inspection and are open to FDA inspection at any time.

One copy of all Accountability Forms and the return statement are retained by the investigator for his or her files; the ledger containing copies of the inventory sheets is included in the return shipment of drug supplies.

Adverse Experiences

An unexpected adverse experience, if deemed therapy related, must be reported to the NSABP Operations Center (412-648-9720), which will notify the NCI study monitor immediately by telephone. Such report of an unexpected adverse experience must be followed up within 10 working days by a written report to the NSABP (using form FDA 1639), followed by a full description of the event and any sequelae. All deaths considered drug related must also be reported immediately to the Operations Center, which will report to the NCI study monitor.

Any unexpected adverse experience must also be reported to the Institutional Review Board within 10 days and documentation of this report sent to the Operations Center.

Appendix B

PERFORMANCE STATUS KEY

0 - normal activity

1 - symptoms but ambulatory

2 - in bed $\leq 50\%$ of time

3 - in bed $> 50\%$ of time

4 - 100% bedridden

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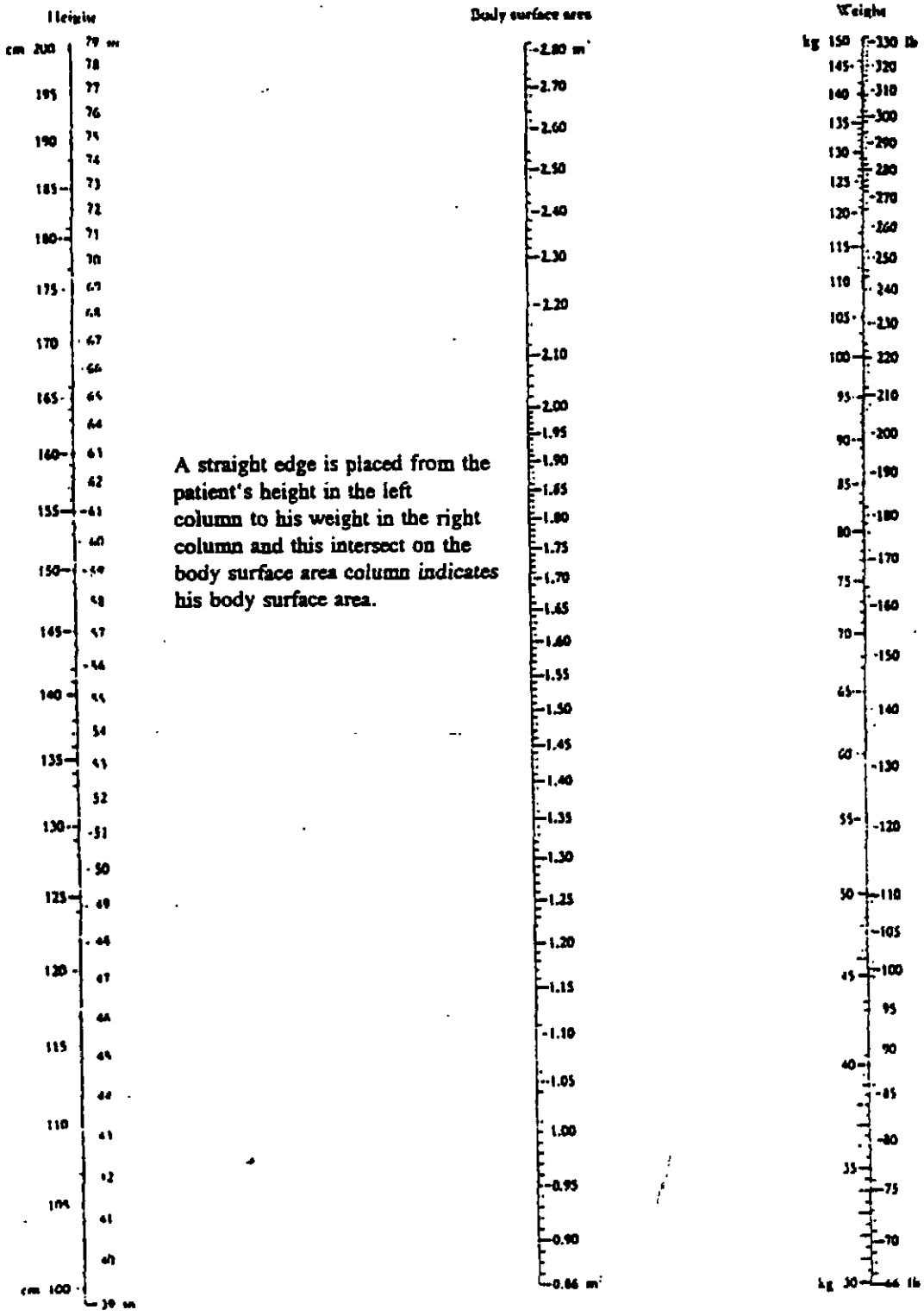
BODY SURFACE AREA OF ADULTS

Nomogram for determination of body surface area from height and weight.



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NSABP TOXICITY REPORT FORM

Complete this form for ALL patients even if no toxicity is experienced. Submit one form to correspond to each course of therapy while the patient is on therapy and up to 3 months after protocol therapy ends. "COURSE #" refers to chemotherapy cycle. For tamoxifen or placebo given without chemotherapy, code course = 77. If post-therapy, code course = 88. Complete and submit forms immediately if the patient experiences a Grade 3, 4, or 5 toxicity. If these more severe reactions occur, also complete the top portion of the reverse side of this form. All hematologic and chemistry data should be reported on the protocol therapy form. For appropriate dose modifications, refer to protocol.

STUDY NUMBER ☐☐☐☐☐☐☐☐☐ 1-9 COURSE # ☐☐ 10-11 PATIENT NAME _____

PT's LAST NAME ☐☐☐ 12-14 (1st 3 Letters) ANY TOXICITY? ☐ 15 (1=YES, 2=no) REPORT DATE ☐☐☐☐☐☐ 16-21 Mo. Day Yr. TO ☐☐☐☐☐☐ Mo. Day Yr. 22-27

CODE MAX. GRADE OR INTERVAL* ↓	CRITERIA	TOXICITY GRADE** (Code "5" if Toxicity-Related Death) 1	2	3	4
☐ 28	HEMORRHAGE	Mild	1-2 Units	3-4 Units	>4 Units
☐ 29	INFECTION/SEPSIS	Mild	Moderate	Severe	Life-threatening
☐ 30	NAUSEA	Able to eat	Decr. intake	No intake	—
☐ 31	VOMITING	1 q. 24 hrs.	2-5 q. 24 hrs.	6-10 q. 24 hrs.	Parenteral support
☐ 32	DIARRHEA	Incr. 2-3 q. 24 hrs.	Incr. 4-6 q. 24 hrs. (Moderate)	Incr. 7-9 q. 24 hrs. (Severe)	Incr. 10+ q. 24 hrs.; bloody; support
☐ 33	STOMATITIS	Mild	Ulcers	Cannot eat	Support required
☐ 34	HEMATURIA	Micro	No clots	Gross with Clots	Transfusion
☐ 35	ALOPECIA	Mild	Pronounced	Total	—
☐ 36	PULMONARY	Asympt. w/abn. PFTs	Exertion Dyspnea	Normal Activity Dyspnea	Rest Dyspnea
☐ 37	PHLEBITIS/PULM. EMB.	Superficial	Deep Vein Thrombosis w/o Hosp.	DVT w/hosp.	Pulmonary Embolism
☐ 38	CARDIAC DYSRHYTHM.	Transient	Recurrent	Therapy Required	Monitoring
☐ 39	CARDIAC FUNCTION	Asympt; <20% Decr., in Lt. V.F.	>20% Decr. in Lt. V.F.	Mild CHF.	Severe CHF.
☐ 40	CARDIAC ISCHEMIA	Flat T-wave	Addn. EKG changes	Angina	Myocardial Infarction
☐ 41	CARDIAC PERICARDIAL	Asymptomatic	Pericarditis	Drainage	Tamponade
☐ 42	HYPERTENSION	Transient	20+ Incr. Diastolic	Therapy Required	Crisis
☐ 43	HYPOTENSION	No therapy	Output; fluids required	Rx. Req./Hosp.	Rx/Hosp Req >48 hrs
☐ 44	NEURO-SENSORY	Mild	Moderate	Severe	—
☐ 45	NEURO-MOTOR	Subjective	Mild Objective	Impaired Function	Paralysis
☐ 46	NEURO-CORTICAL	Mild	Moderate	Severe	Coma/Seizures
☐ 47	NEURO-CEREBELLAR	Slight Incoord.	Tremor, slurred speech, nystagmus	Ataxia	Necrosis
☐ 48	NEURO-MOOD	Mild	Moderate	Severe	Suicidal
☐ 49	NEURO-HEADACHE	Mild	Moderate	Unrelenting	—
☐ 50	NEURO-CONSTIPATION	Mild	Moderate	Severe	Ileus >96 hrs.
☐ 51	NEURO-HEARING	Loss on Audiometry	Tinnitus	Impaired Function	Deafness
☐ 52	NEURO-VISION	Transient	Asympt., Measurable Change	Subtotal Loss	Blindness
☐ 53	SKIN	Eruption	Eruption w/pruritis	Gen'lized Eruption	Ulcerative Dermatitis
☐ 54	ALLERGY	Rash	Urticaria	Therapy Required	Anaphylaxis
☐ 55	FEVER	<38°C	38-40°C	>40°C	With Hypotension
☐ 56	LOCAL COMPLICATION or EXTRAVASATION	Pain	Pain w/inflam.	Ulceration	Surgery
☐ 57	OTHER. Describe.	_____			
☐ 58	OTHER. Describe.	_____			

*GRADE 3, 4, OR 5 = Complete Reverse Side **GRADE 5 = DEATH 59-73 ☐☐☐☐ ☐☐☐☐ ☐☐☐☐ ☐☐☐☐ ☐

☐ (OVER)

STUDY NUMBER ____________________

COMPLETE THIS SECTION ONLY IN THE EVENT OF A GRADE 3, 4, OR 5 TOXICITY AS REPORTED ON FORM ADR AND FORWARD IMMEDIATELY TO NSABP BIOSTATISTICAL CENTER. ATTACH ANY PERTINENT DOCUMENTATION.

REPORTING DATE ________________ REACTION ONSET DATE ________________________

DESCRIPTION OF SUSPECTED REACTION(S):

INCLUSIVE DATES OF REACTION(S):

SEVERITY: 1=MILD 2=MODERATE 3=SEVERE 4=LIFE-THREATENING 5=DEATH ☐ 76

OUTCOME OF REACTIONS TO DATE:

☐ Alive with Sequela

☐ Recovered

☐ Still under Treatment for Reaction

☐ Died (Report Cause and Date)

WAS *OUTPATIENT* TREATMENT FOR REACTION REQUIRED? 1 = Yes 2 = No ☐ 77

WAS HOSPITALIZATION TREATMENT FOR REACTION REQUIRED? 1 = Yes 2 = No ☐ 78

SUSPECTED DRUG(S), DOSES AND DATES OF ADMINISTRATION:

IF HOSPITALIZED, NUMBER OF DAYS (Count day of admission <u>and</u> day of discharge).
888 = Still Hospitalized ☐☐☐ 79-81

TESTS/LABORATORY DATA CONFIRMING REACTION:

☐☐☐☐ 82-85

FOR BIOSTATISTICAL CENTER USE
(TO BE COMPLETED BY HEADQUARTERS MEDICAL REVIEWER)

<u>PRIMARY PROBLEM</u>

Date of Primary Problem ☐☐☐☐☐☐ 86-91 (Mo. Day Yr.)

ICDA-8 CODE ☐☐☐.☐ 92-95

Description of Primary Problem ☐☐☐☐☐☐☐☐☐☐☐☐☐ ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ 96-129

Was protocol therapy stopped? 1 = Yes; 2 = No ☐ 130

Was this problem related to protocol therapy? 1 = Yes; 2 = No ☐ 131

GRADE OF TOXICITY ☐ 132

If reviewed for "septic episode", indicate result of review. (If judged to be septic episode, ICDA-8 code should be "038.9".)

1 = Septic Episode
2 = <u>Not</u> Septic Episode ☐ 133

REVIEWER'S INITIALS ________________

DATE OF REVIEW ☐☐☐☐☐☐ (Mo. Day Yr.)

☐ (OVER)

*GRADE 3, 4, OR 5 = [illegible] **GRADE 5=DEATH ☐☐☐☐ ☐☐☐☐ ☐☐☐☐ ☐☐☐☐ ☐

COMMON TOXICITY CRITERIA

	TOXICITY	GRADE 0	1	2	3	4
Blood/Bone Marrow	WBC	≥4.0	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	<1.0
	PLT	WNL	75.0 - normal	50.0 - 74.9	25.0 - 49.9	<25.0
	Hgb	WNL	10.0 - normal	8.0 - 10.0	6.5 - 7.9	<6.5
	Granulocytes/Bands	≥2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	<0.5
	Lymphocytes	≥2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	<0.5
	Hemorrhage (clinical)	None	Mild, no transfusion	Gross, 1-2 units transfusion per episode	Gross, 3-4 units transfusion per episode	Massive, >4 units transfusion per episode
	Infection	None	Mild	Moderate	Severe	Life-threatening
Gastrointestinal	Nausea	None	Able to eat Reasonable intake	Intake significantly decreased but can eat	No significant intake	—
	Vomiting	None	1 episode in 24 hrs.	2-5 episodes in 24 hrs.	6-10 episodes in 24 hrs.	>10 episodes in 24 hrs. or requiring parenteral support
	Diarrhea	None	Increase of 2-3 stools/day over pre-Rx	Increase of 4-6 stools/day, or nocturnal stools, or moderate cramping	Increase of 7-9 stools/day, or incontinence, or severe cramping	Increase of ≥10 stools/day or grossly bloody diarrhea, or need for parenteral support
	Stomatitis	None	Painless ulcers, erythema, or mild soreness	Painful erythema, edema, or ulcers, but can eat	Painful erythema, edema, or ulcers, and cannot eat	Requires parenteral or enteral support
Liver	Bilirubin	WNL	—	<1.5 x N	1.5 - 3.0 x N	>3.0 x N
	Transaminase (SGOT, SGPT)	WNL	≤2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	>20.0 x N
	Alk Phos or 5'nucleotidase	WNL	≤2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	>20.0 x N
	Liver (clinical)	No change from baseline	—	—	Precoma	Hepatic coma
Kidney, Bladder	Creatinine	WNL	<1.5 x N	1.5 - 3.0 x N	3.1 - 6.0 x N	>6.0 x N
	Proteinuria	No change	1+ or <0.3 g% or <3 g/l	2 - 3+ or 0.3 -1.0 g% or 3 - 10 g/l	4+ or 1.0 g% or 10 g/l	Nephrotic syndrome
	Hematuria	Neg	Micro only	Gross, no clots	Gross + clots	Requires transfusion
	Alopecia	No loss	Mild hair loss	Pronounced or total hair loss	—	—
	Pulmonary	None or no change	Asymptomatic, with abnormality in PFT's	Dyspnea on significant exertion	Dyspnea at normal level of activity	Dyspnea at rest

COMMON TOXICITY CRITERIA

	TOXICITY	GRADE 0	1	2	3	4
Heart	Cardiac dysrhythmias	None	Asymptomatic, transient, requiring no therapy	Recurrent, or persistent, no therapy required	Requires treatment	Requires monitoring; or hypotension, or ventricular tachycardia, or fibrillation
	Cardiac function	None	Asymptomatic, decline of resting ejection fraction by less than 20% of baseline value	Asymptomatic, decline of resting ejection fraction by more than 20% of baseline value	Mild CHF, responsive to therapy	Severe or refractory CHF
	Cardiac-ischemia	None	Nonspecific T-wave flattening	Asymptomatic, ST and T-wave changes suggesting ischemia	Angina without evidence for infarction	Acute myocardial infarction
	Cardiac-pericardial	None	Asymptomatic effusion, no intervention required	Pericarditis (rub, chest pain, ECG changes)	Symptomatic effusion; drainage required	Tamponade; drainage urgently required
Blood Pressure	Hypertension	None or no change	Asymptomatic, transient increase by greater than 20 mm Hg (D) or to >150/100 if previously WNL. No treatment required	Recurrent or persistent increase by greater than 20 mm Hg (D) or to >150/100 if previously WNL. No treatment required	Requires therapy	Hypertensive crisis
	Hypotension	None or no change	Changes requiring no therapy (including transient orthostatic hypotension)	Requires fluid replacement or other therapy but not hospitalization	Requires therapy and hospitalization; resolves within 48 hrs of stopping the agent	Requires therapy and hospitalization for >48 hrs after stopping the agent
Neurologic	Neuro-sensory	None or no change	Mild paresthesias, loss of deep tendon reflexes	Mild or moderate objective sensory loss, moderate paresthesias	Severe objective sensory loss or paresthesias that interfere with function	—
	Neuro-motor	None or no change	Subjective weakness; no objective findings	Mild objectie weakness without significant impairment of function	Objective weakness with impairment of function	Paralysis
	Neuro-cortical	None	Mild somnolence or agitation	Moderate somnolence or agitation	Severe somnolence, agitation, confusion, disorientation, or hallucinations	Coma, seizures, toxic psychosis
	Neuro-cerebellar	None	Slight incoordination, dysdiadokinesis	Intention tremor, dysmetria, slurred speech, nystagmus	Locomotor ataxia	Cerebellar necrosis
	Neuro-mood	No change	Mild anxiety or depression	Moderate anxiety or depression	Severe anxiety or depression	Suicidal ideation
	Neuro-headache	None	Mild	Moderate or severe but transient	Unrelenting and severe	—
	Neuro-constipation	None or no change	Mild	Moderate	Severe	Ileus >96 hrs.
	Neuro-hearing	None or no change	Asymptomatic hearing loss on audiometry only	Tinnitus	Hearing loss interfering with function but correctable with hearing aid	Deafness not correctable
	Neuro-vision	None or no change	—	—	Symptomatic subtotal loss of vision	Blindness

COMMON TOXICITY CRITERIA

TOXICITY		GRADE 0	1	2	3	4
	Skin	None or no change	Scattered macular or papular eruption or erythema that is asymptomatic	Scattered macular or papular eruption or erythema with pruritus or other associated symptoms	Generalized symptomatic macular, papular, or vesicular eruption	Exfoliative dermatitis or ulcerating dermatitis
	Allergy	None	Transient rash, drug fever <38c, 100.4F	Urticaria, drug fever =38c, 100.4F, mild bronchospasm	Serum sickness, bronchospasm, req parenteral meds	Anaphylaxis
	Fever in absence of infection	None	37.1 - 38.0c 98.7 - 100.4F	38.1 - 40.0c 100.5 - 104.0F	>40.0c, >104.0F for less than 24 hours	>40.0c (104.0F) more than 24 hrs or fever accompanied by hypotension
	Local	None	Pain	Pain and swelling, with inflammation or phlebitis	Ulceration	Plastic surgery indicated
	Weight gain/loss	<5.0%	5.0 - 9.9%	10.0 - 19.9%	≥20.0%	—
Metabolic	Hyperglycemia	<116	116 - 160	161 - 250	251 - 500	>500 or ketoacidosis
Metabolic	Hypoglycemia	>64	55 - 64	40 - 54	30 - 39	<30
Metabolic	Amylase	WNL	<1.5 x N	1.5 - 2.0 x N	2.1 - 5.0 x N	>5.1 x N
Metabolic	Hypercalcemia	<10.6	10.6 - 11.5	11.6 - 12.5	12.6 - 13.5	≥13.5
Metabolic	Hypocalcemia	>8.4	8.4 - 7.8	7.7 - 7.0	6.9 - 6.1	≤6.0
Metabolic	Hypomagnesemia	>1.4	1.4 - 1.2	1.1 - 0.9	0.8 - 0.6	≤0.5
Coagulation	Fibrinogen	WNL	0.99 - 0.75 x N	0.74 - 0.50 x N	0.49 - 0.25 x N	≤0.24 x N
Coagulation	Prothrombin time	WNL	1.01 - 1.25 x N	1.26 - 1.50 x N	1.51 - 2.00 x N	>2.00 x N
Coagulation	Partial thromboplastin time	WNL	1.01 - 1.66 x N	1.67 - 2.33 x N	2.34 - 3.00 x N	>3.00 x N

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Attachment 7
December 1990

GUIDELINES FOR REPORTING ADVERSE DRUG REACTIONS OCCURRING WITH COMMERCIAL AGENTS

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

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

The ADR report should be documented on the attached ADR form (Form FDA 1639). The completed form should be mailed to:

Investigational Drug Branch
P.O. Box 30012
Bethesda, Maryland 20824

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFD-730)
ROCKVILLE, MD. 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0230
See OMB Statement on the Reverse

FDA CONTROL NO

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID / INITIALS *(In Confidence)*

2. AGE YRS

3. SEX

4.-6. REACTION ONSET — MO. | DA | YR.

8.-12. CHECK ALL APPROPRIATE
- ☐ PATIENT DIED
- ☐ REACTION TREATED WITH R_x DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S)

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

17. INDICATION(S) FOR USE

18. DATES OF ADMINISTRATION *(From/To)*

19. DURATION OF ADMINISTRATION

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check all that apply)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT?
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.