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PROTOCOL SUMMARY

David Grant USAF Medical Center (AMC)
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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:

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II. FACILITY:

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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.

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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 $\geq$ 4000/cu. mm and the platelet count must be $\geq$ 100,000/cu. mm.
- There must be evidence at randomization of adequate hepatic and renal function (bilirubin, SGOT or SGPT, and creatinine must be $\leq$ 1.5 times the upper limit of normal for the performing lab).
- Patients with more than one synchronous rectal lesion are eligible.

- 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 <u>both</u> the colon and rectum that would preclude them from being classified as having <u>only</u> rectal cancer.
- Patients who are found, by endoluminal ultrasonography, to have a Duke's A lesion.

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.

LtCol, USAF, MC
Chief, Hematology/Oncology

Appro /Disapprove

Colonel, USAF, MC
Chairman, Department of Medicine