Radiation Therapy and Fluorouracil With or Without Semustine for the Treatment of Patients With Surgical Adjuvant Adenocarcinoma of the Rectum

By the Gastrointestinal Tumor Study Group

Purpose: To evaluate the contribution of semustine (MeCCNU) to adjuvant benefit, previously untreated patients with histologically proven adenocarcinoma of the rectum who had undergone curative resection were randomized to treatment with combination radiation therapy and fluorouracil (5-FU) followed by either 12 months of 5-FU and MeCCNU or 6 months of escalating 5-FU.

Patients and Methods: Between March 1981 and November 1985, 210 patients were randomized by Gastrointestinal Tumor Study Group (GITSG) investigators. Subsequent to randomization, 11 (5%) patients (six treated with 5-FU and MeCCNU; five with escalating 5-FU) were found to be ineligible and are excluded from survival analyses.

Results: About half the patients on each of the two treatment arms experienced at least one episode of severe or worse toxicity, and there was one treatment-related death on each arm. No episodes of leukemia have been reported. Median follow-up time for surviving patients is 5.8 years, and 3-year follow-up is available for all but five surviving patients. Recurrent disease has been reported in 54% (51 of 95) of 5-FU– and MeCCNU-treated patients compared with 43% (45 of 104) of escalating 5-FU–treated patients. Probability of 3-year disease-free survival for the two treatment cohorts is 54% and 68%, respectively. Ninety-one deaths have occurred: 46% (44 of 95) of 5-FU– and MeCCNU-treated patients and 45% (47 of 104) of escalating 5-FU–treated patients. Three-year postsurgery survival probabilities are 66% and 75%.

Conclusion: Substantial differences in survival or recurrence results between the two study arms are unlikely to be observed. We conclude that MeCCNU is not an essential component of effective postoperative combined modality treatment of adjuvant rectal cancer.

J Clin Oncol 10:549-557.

RECURRENCE OF rectal cancer in the pelvis after a complete resection represents a major contributor to morbidity and subsequent mortality.[1] Preoperative[2] and postoperative[3] radiation therapy alone, while reducing the local recurrence rate, has not been shown to improve survival. In 1985, the Gastrointestinal Tumor Study Group (GITSG; study GI 7175) reported that postoperative radiation and chemotherapy reduced the tumor recurrence rate for patients who had undergone a curative resection for rectal adenocarcinoma.[4] Treatment was limited to patients with tumors penetrating the full thickness of the rectal wall or with metastasis to regional lymph nodes. Although the superiority of combination radiotherapy and chemotherapy with fluorouracil (5-FU) and semustine (MeCCNU) was clearly shown in terms of both disease-free survival and, subsequently, overall survival,[5] the clinical impact of such treatment was tempered by the inclusion of MeCCNU in an adjuvant setting. The leukemogenic effect of MeCCNU was established subsequent to the initiation of GI 7175[6]; indeed, one patient who participated in GI 7175 developed acute myeloid leukemia after MeCCNU therapy. Consequently, the GITSG sought to assess the contribution of MeCCNU to the combined modality regimen in study GI 7180. The results of that study are the focus of this report.

A two-arm study was designed using the initial radiation/chemotherapy program of the previous study (GI 7175) for both arms of the new study (GI 7180) but offering MeCCNU to only half the patients during the postradiation period. The same postradiation regimen of 5-FU and MeCCNU as that used in GI 7175 was chosen for one arm, with the exception that the duration of treatment with postradiation 5-FU and MeCCNU was reduced from 18 months to 12 months in an attempt to reduce the leukemogenic potential of the MeCCNU. An escalating single-agent 5-FU regimen incorporating a theoretical maximum-tolerated dose was chosen as the alternative treatment option based on clinical evidence suggesting a dose response curve for 5-FU[7,8] and pilot data from the Dana-Farber Cancer Institute[9] suggesting added efficacy of 5-FU when given at higher dose levels.

From the Georgetown University Medical Center, Washington, DC; The EMMES Corporation, Potomac, MD; Roswell Park Memorial Institute, Buffalo, NY; Dana-Farber Cancer Institute, Boston, MA; Mount Sinai Medical Center, New York, NY; Instituto Nazionale, Milan, Italy; Hawaii Medical Association, Honolulu, HI; Wayne State University, Detroit, MI; University of Miami, Miami, FL; New York University/Montefiore Medical Centers, New York, NY; University of Chicago/Illinois Cancer Council, Chicago, IL; Yale University, New Haven, CT; Cleveland Clinic, Cleveland, OH; McGill Cancer Center, Montreal, Canada; Wisconsin Clinical Cancer Center, Madison, WI; and The Mallinckrodt Institute of Radiology, St Louis, MO.

Submitted May 29, 1991; accepted October 30, 1991.

Supported in part by United States Public Health Service contracts no. 1-CM 43794-43800, 07339, 07407-07411, 87193, and 17371.

Address reprint requests to Gastrointestinal Tumor Study Group Statistical Center, The EMMES Corp, 11325 Seven Locks Rd, Suite 214, Potomac, MD 20854.

0732-183X/92/1004-0008$3.00/0

PATIENTS AND METHODS

Eligibility and Exclusion Criteria

Patients were considered eligible for entry onto the study provided they had histologically proven adenocarcinoma of the rectum and had undergone a surgical procedure at which time all gross tumor had been removed and no evidence of tumor had been present at the resection margins. The distal edge of the primary tumor must have been $\leq$ 12 cm from the anal verge as measured by sigmoidoscopy with the patient in the knee-chest position. Patients must have recovered from the acute effects of surgery, been capable of starting treatment within 60 days after resection, had no evidence of active infection, had adequate performance and nutritional status to tolerate protocol treatment, and had no preexisting or concurrent malignant tumors except basal cell or superficial squamous cell carcinomas of the skin. Presence of ascites, peritoneal seeding, residual pelvic tumor, positive paraaortic lymph node biopsy, or distant metastases excluded patients from study, as did previous chemotherapy or pelvic irradiation or any active and significant coexistent disease that, in the judgment of the investigator, would make the risks of chemotherapy or radiation therapy prohibitive.

Only patients with Dukes pathologic stage B_2 (negative nodes, disease extension into the perirectal fat), C_1 (positive nodes, no disease extension into the perirectal fat), and C_2 (positive nodes, disease extension into the perirectal fat) were eligible, and slides must have been available for review. Normal hepatic, renal, and bone marrow function (ie, bilirubin level < 2.5 mg/dL, BUN level < 25 mg/dL, or creatinine level < 1.5 mg/dL; leukocyte and platelet counts > 4,500/μL and 125,000/μL, respectively) must have been documented before study entry.

Randomization

Patients considered eligible received a full explanation of the purpose, procedures, and risks of the study, signed a statement of informed consent approved by the local institutional review board, and were then randomized by telephoning a central coordinating center. Random assignment to treatment was performed by the coordinating center after confirmation of eligibility criteria using a preestablished randomization table.

Radiation Therapy

Supervoltage radiation therapy with the treatment volume to encompass the true and false pelvis was specified by the study protocol. The superior border of the field was to be the top of the fifth lumbar vertebral body, the lateral border 2 cm lateral to the true pelvic side wall, and the inferior margin of the field was to be determined clinically. The inferior margin included the perineum in all patients who underwent an abdominal-perineal resection and whose tumor was $\leq$ 5 cm from the dentate line. Parallel-opposed three- or four-field techniques were allowed. For all other patients, inclusion of the perineum in the radiation field was at the discretion of the investigator. In cases of perineal exclusion, the inferior margin of the field must have included the lower margin of the ischial tuberosity. The treatment volume as defined must have received 4,140 cGy at a rate of 180 cGy/d, five treatments per week.

Chemotherapy

All patients were to receive intravenous 5-FU 500 mg/m^2 given in a rapid infusion on the first 3 days and last 3 days of radiation therapy. After the completion of radiation therapy and 5-FU, no chemotherapy was given for 5 weeks. After this 5-week period, patients received one of the two chemotherapy schedules.

5-FU and MeCCNU. The first course on this treatment arm consisted of intravenous 5-FU 300 mg/m^2, days 1 to 5 and 375 mg/m^2, days 36 to 40 given in a rapid infusion. One dose of MeCCNU 100 mg/m^2 was to be given orally on day 1. Second and subsequent courses were to be given on the same schedule but with the dose of 5-FU increased to 325 mg/m^2 intravenously, days 1 to 5; 375 mg/m^2, days 36 to 40; and MeCCNU to 130 mg/m^2 orally on day 1. Courses were to be repeated at 10-week intervals for a total of 18 months of treatment. One year after study activation, treatment duration was decreased to a total of 12 months of treatment due to concerns about the leukemic potential of MeCCNU.[6]

Escalating 5-FU. The first course of treatment for patients randomized to this arm consisted of 5-FU 350 mg/m^2 intravenously given in a rapid infusion on days 1 to 5. Courses were to be repeated at 4-week intervals for a total of six courses of postradiotherapy treatment. If tolerated, 5-FU doses were escalated in 50 mg/m^2 increments each course during the second through the fourth cycle to a maximum of 500 mg/m^2. This dose was not to be exceeded for the fifth and sixth courses.

Dose Reduction Criteria

Temporary interruption of radiation therapy was required for leukocyte depression below 2,000/μL and platelet count depression below 100,000/μL. Concomitant administration of 5-FU during the last 3 days of radiation therapy was to be omitted if the leukocyte count was below 4,000/μL or if the platelet count was below 125,000/μL. During postradiotherapy chemotherapy, moderate or severe nausea or vomiting required a 50% dose reduction of all chemotherapy for one course; mild stomatitis or diarrhea, continued but not escalated therapy; and moderate or worse stomatitis, reduction of the next course of chemotherapy by 25%.

Separate criteria for dose reduction were specified for the two postradiation treatment arms. Each course of treatment was not to be instituted until leukocyte counts were greater than 4,000/μL and platelet counts were above 150,000/μL. Dose reductions of 5-FU by 25% were required for patients assigned to the 5-FU and MeCCNU treatment arm who experienced a leukocyte count nadir of below 2,000/μL during the first 3 weeks. MeCCNU dose reductions of 25% and 50% were required if, after 5 weeks, leukocyte nadirs were below 2,500/μL and 1,000/μL, respectively. If at any time the platelet count nadir was between 25,000/μL and 50,000/μL, MeCCNU was to be reduced by 25%, and by 50% if the platelet count was below 25,000/μL. Repetition of severe marrow depression (leukocyte count < 1,500/μL) or thrombocytopenia (platelet count < 25,000/μL) after dose reduction or persistent leukopenia (leukocyte count < 4,000/μL) or thrombocytopenia (< 100,000/μL) at 10 weeks after the last dose of MeCCNU disqualified a patient from any further treatment with MeCCNU. Treatment with 5-FU was to be continued at 5-week intervals.

Dose reduction criteria for the 5-FU escalating arm included no escalation if leukocyte count nadir was below 2,000/μL but at least 1,000/μL and platelet count nadir between 75,000/μL and 99,999/μL and a 25% reduction in the next course for leukocyte nadir below 1,000/μL and platelet count nadir below 75,000/μL.

Assessment of Radiation Therapy Quality

Central review of radiotherapy treatment records including contour and isodose curves, dosimetry calculations, simulation films, verification films for each port displaying treatment fields, and dose prescription was conducted by Dr P.R.M. Thomas. Deviations in dose and fractionation of up to 5% were considered satisfactory for protocol compliance. Deviations greater than 5% but $\leq$ 10% were considered minor deviations, and deviations greater than 10% were regarded as major deviations. Variations of field placement were also categorized into minor and major clinical deviations.

Patient Follow-Up

The study protocol stated that all patients were to be reevaluated at 3-month intervals for 3.5 years and every 6 months thereafter. Evaluations were to consist of pertinent medical history, physical examinations, peripheral hemogram, blood chemistries, and chest x-rays at 6, 12, and 18 months, and then annually. Gastrointestinal series and small bowel follow-up were to be performed at 12 months and barium enema and proctoscopy (if rectum is in place) at 6, 12, and 18 months, and then annually. Verification that these criteria were followed is unavailable.

Criteria for Recurrence

Disease recurrence required histologic or cytologic documentation with the exception that radiographic techniques could be used to establish the presence of metastases to the lung, liver, bony structures, or brain. Perineal pain, if preceded by a pain-free interval, was considered indicative of recurrence, and time of recurrence was listed as the time of pain onset. Only the first site of recurrence was reported. Recurrence status for patients identified as dead of recurrent disease without adequate documentation was determined by group review, with the examiners blinded to treatment assignment.

Statistical Considerations

The primary objective of this study was to evaluate the effectiveness of an adjuvant treatment with radiation therapy and escalating 5-FU and to compare it with a combination of 5-FU and MeCCNU. A major goal was to assess the contribution of MeCCNU to adjuvant benefit. The original design called for the enrollment of 134 patients per arm, and the primary end point was to detect a difference in the 30-month disease-free survival rate from .65 for the MeCCNU-containing arm to .80 for the escalating 5-FU arm. Despite early termination of accrual due to loss of funding, the results of this study provide important information regarding the potential effectiveness of the escalating 5-FU regimen compared with a MeCCNU-containing regimen. Given the leukemic potential of MeCCNU, it is important to find a treatment that is at least as effective as a treatment containing MeCCNU. Using the techniques of Makuch and Simon,[10] it can be shown that a sample size of 100 patients per arm has an 80% power to exclude differences in treatments as great as .19 assuming $\alpha = .05$ and a 30-month rate of .65. The potential for MeCCNU to contribute to a result superior to that obtained with escalating 5-FU can be assessed by examining the lower bound of the 95% confidence intervals of relative risk.

Probability distribution estimates of survival and disease-free survival were performed using the product-limit method of Kaplan and Meier.[11] When estimating disease-free survival, patients were censored if they were disease-free at last contact (or died free of disease). All patients who died, regardless of disease status, were counted as events in the survival analysis. The contribution of variables and treatment effect was tested using the proportional hazards procedures of Cox[12] and the log-rank test.

RESULTS

Patient Cohort

Between March 1981 and November 1985, 210 patients were enrolled in this study; 101 were randomized to the 5-FU and MeCCNU regimen, and 109 to the escalating 5-FU arm. Eleven patients (six receiving 5-FU and MeCCNU and five receiving escalating 5-FU), comprising 5% of the registered population, are not included in the primary analysis as they were determined to be ineligible by an independent review. Reasons for ineligibility were as follows: colon cancer rather than rectal cancer (five patients), prior history of cancer (two), and incomplete resection (four). The remaining 199 patients (95% of the registered population) are included for survival analysis in the study group to which they were randomized regardless of whether or not protocol treatment was administered. Four patients received no protocol treatment and are excluded from the toxicity analyses but are included in the survival and disease-free survival analyses.

Although the protocol required treatment to begin within 60 days of surgery, 20 patients evenly distributed between the two treatment arms began treatment more than 60 days postsurgery; 16 of the 20 individuals received their initial therapy within 64 days. The longest delay was 82 days in a patient who developed an intestinal fistula after surgery. All of these patients are included in the analyses.

Patient Characteristics

Of the 199 patients who comprised the cohort for primary analysis, 95 were randomized to receive postradiation 5-FU and MeCCNU, and 104 were randomized to receive postradiation escalating 5-FU. Selected patient characteristics show that 58% had disease extension involving the perirectal fat with at least one positive lymph node, 60% of patients are male, and 59% underwent an abdominal-perineal resection (Table 1). The median age of the 199 patients analyzed was 59 years. The clinical characteristics were well balanced between the treatment arms, with a slightly higher percentage of patients having disease extension into perirectal fat randomized to receive 5-FU and MeCCNU (61%) compared with escalating 5-FU (56%), and a higher percentage of males randomized to escalating 5-FU

Table 1. Distribution of Patient Characteristics by Treatment Group

Characteristic	Treatment Group (%) RT + 5-FU + MeCCNU	RT + Escalating 5-FU	Total (%)
Total no. of patients	95 (100)	104 (100)	199 (100)
Stage*			
B2 (negative nodes, extension)	25 (26)	26 (25)	51 (26)
C1 (positive nodes, no extension)	12 (13)	20 (19)	32 (16)
C2 (positive nodes, extension)	58 (61)	58 (56)	116 (58)
Resection			
Abdominal-perineal	56 (59)	62 (60)	118 (59)
Anterior	39 (41)	42 (40)	81 (41)
Sex			
Male	53 (56)	66 (63)	119 (60)
Female	42 (44)	38 (37)	80 (40)
Age (median years)	59.5	57.9	59.2
Distance to nearest margin (cm)			
≤ 3	42 (44)	36 (35)	78 (39)
> 3	47 (49)	61 (59)	108 (54)
Unknown	6 (6)	7 (7)	13 (7)

*According to Dukes' classification as modified by the GITSG.

compared with 5-FU and MeCCNU (63% *v* 56%, respectively). None of these differences were statistically significant. The median follow-up time for the 108 surviving patients is 5.8 years with 3 years of follow-up available for all but five surviving patients.

Treatment Administration

Two patients on each treatment arm received no adjuvant therapy, and 16 patients assigned to the 5-FU and MeCCNU arm and 18 patients assigned to the escalating 5-FU regimen received no postradiation chemotherapy. An additional three patients on the 5-FU and MeCCNU arm received no MeCCNU after radiation therapy but continued to receive 5-FU. Reasons for postradiation chemotherapy termination were evenly distributed between patient refusal and toxicity. As planned in the protocol design, patients on the 5-FU and MeCCNU arm were treated for a longer duration than patients who received escalating 5-FU (median, 11.3 months *v* 7.5 months, respectively). Also as planned, among patients who received chemotherapy, dose intensity of 5-FU was greater on the escalating 5-FU arm versus the 5-FU and MeCCNU arm. Although patients received a median total dose of 12.4 g/m^2 of 5-FU on the escalating 5-FU arm (25% < the planned level of 16.5 g/m^2) and 13.1 g/m^2 of 5-FU on the 5-FU and MeCCNU arm (23% < the planned level of 16.9 g/m^2), the median monthly dose of 5-FU on the escalating arm was 1.74 g/m^2, compared with 1.40 g/m^2 on the 5-FU and MeCCNU arm ($P < .001$). Patients randomized to 5-FU and MeCCNU received a median total dose of MeCCNU of .37 g/m^2 (25% < the planned level of .49 g/m^2), and a median of .08 g/m^2 of MeCCNU per 10-week course. Approximately one third of patients (41 of 104) randomized to the escalating 5-FU arm were escalated to at least one 5-day course of 500 mg/m^2 of 5-FU.

Central review of compliance with radiation therapy confirmed that the majority of patients were treated as per protocol, with discrepancies occurring equally in each treatment arm. In all, 16% of patients were found to have clinical deviations. Dosimetry deviations were limited to 5% of the cases. No patients were excluded from analysis due to deviations from the radiotherapy protocol.

Toxicity

Toxicities experienced by patients on the two arms are comparable; 53% of patients on the 5-FU and MeCCNU arm (52 of 99) and 50% of those assigned to the escalating 5-FU arm (54 of 107) experienced at least one episode of severe or worse toxicity as defined by the GITSG toxicity scale. Life-threatening toxicities were reported in six (6%) 5-FU and MeCCNU patients and 11 (10%) escalating 5-FU patients. Leukocyte depression below 1,000/μL accounted for a majority of these episodes (eight patients on the escalating 5-FU arm and three on the 5-FU and MeCCNU arm). Platelet count depression below 20,000/μL was reported for two patients receiving 5-FU and MeCCNU. Toxicity resulted in either a temporary or permanent decrease in dose, interruption of part of therapy, or interruption of all therapy in 62% of 5-FU and MeCCNU patients and 53% of escalating 5-FU patients. Permanent interruption of all therapy due to toxicity occurred in 11% of 5-FU and MeCCNU patients and 14% of escalating 5-FU patients.

Two treatment-related deaths were reported, one on each treatment arm. One event occurred in a 50-year-old man assigned to receive escalating 5-FU. Twelve days after treatment initiation and after receiving the initial 3 days of 5-FU and 4 days of radiation therapy, he experienced life-threatening episodes of myelosuppression, stomatitis, and seizures. The patient died of septicemia and pneumonia 24 days after treatment initiation. At the time of death the patient's leukocyte count was below 500/μL. One patient on the 5-FU and MeCCNU arm is reported to have died of complications of intestinal obstruction, although confirming evidence documenting this event is not available. This patient was free of disease by computed tomography scan, and the death is considered treatment-related. Six patients are reported to have experienced severe (three) or life-threatening

(three) treatment-related intestinal obstructions, two receiving the 5-FU and MeCCNU regimen and four on escalating 5-FU (Table 2). Three patients were successfully treated with nasogastric suction and supportive therapy alone and three underwent surgical reexploration. In three patients the small bowel obstruction appeared to occur at an anatomic site remote from the radiation field. One patient developed intestinal obstruction during the radiation therapy.

No episodes of acute myeloid leukemia have been reported on either arm of the study.

Disease Recurrence

Disease recurrence has been documented in 48% of eligible patients including 54% (51 of 95) of patients randomized to receive 5-FU and MeCCNU and 43% (45 of 104) of patients randomized to receive escalating 5-FU (Table 3). Of the 96 recurrent patients, 10 died of disease without adequate documentation and were classified as recurrences by group review. Recurrences involving local sites occurred in 17% of 5-FU and MeCCNU patients and 16% of escalating 5-FU patients. Significantly ($P = .05$) more recurrences involving distant sites have been documented on the 5-FU and MeCCNU arm (40%) compared with the escalating 5-FU arm (26%). The probability of 3-year disease-free survival on the two arms is 54% and 68% for patients assigned to the 5-FU and MeCCNU arm and the escalating 5-FU arm, respectively; median time to recurrence is estimated to be 4 years and greater than 4 years, respectively (Fig 1). The difference in disease-free survival favors the escalating 5-FU arm, but this difference is not statistically significant ($P = .20$, two-tailed).

The prognostic importance of Dukes stage, resection type, distance to the nearest margin, age, sex, and Eastern Cooperative Oncology Group (ECOG) performance status score on disease-free survival was examined in the cohort of eligible patients. When included in the Cox model, Dukes stage, resection type, distance to the nearest margin (≤ 3 cm *v* other), and the interaction between resection type and distance to the nearest margin were found to be significant without adjustment for multiple comparisons in predicting disease-free survival ($P < .05$). After adjustment for these variables, the 5-FU and MeCCNU and the escalating 5-FU treatment

Table 3. Initial Recurrence by Treatment Group and Site

	Treatment Group (%)		
	RT + 5-FU + MeCCNU	RT + Escalating 5-FU	Total (%)
Total no. of patients	95 (100)	104 (100)	199 (100)
Total no. of recurrences	51 (54)	45 (43)	96 (48)
Regional recurrence only	10 (11)	16 (15)	26 (13)
Regional and distant recurrences	6 (6)	1 (1)	7 (4)
Distant only	32 (34)	26 (25)	58 (29)
Liver only	10	8	18
Lungs only	7	7	14
Bone only	5	1	6
Brain only	4	3	7
Other	6	7	13
Any liver	19 (20)	13 (13)	32 (16)
Any lung	15 (16)	13 (13)	28 (14)
Unknown	3 (3)	2 (2)	5 (3)

Table 2. Summary Listing of Reported Obstructions

Case No. by Treatment	Comment
MeCCNU + 5-FU	
71386	Enteritis and subacute intestinal obstruction on day 43 of treatment; resolved without surgery.
71437	Small bowel obstruction on day 96 of treatment; underwent surgery to resolve.
Escalating 5-FU	
71316	Partial small bowel obstruction (adynamic ileus process) on day 25 of treatment; used nasogastric tube.
71367	Enteritis and acute intestinal obstruction due to radiation on day 118 of treatment; underwent surgery to resolve.
71382	Subacute organic small intestine obstruction on day 248 of treatment; underwent surgery to resolve.
71419	Radiation proctitis, constipation flatus, and obstruction; used nasogastric tube to clear on day 215 of treatment.

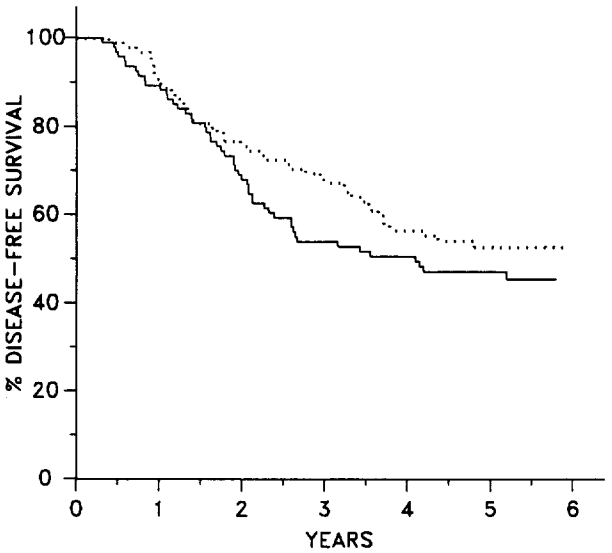

Fig 1. Probability of disease-free survival by treatment: —, radiation plus 5-FU plus MeCCNU; ····, radiation plus escalating 5-FU.

results remained statistically indistinguishable ($P = .30$, two-tailed). In fact, the adjusted relative risk (RR) for tumor recurrence associated with the 5-FU and MeCCNU arm is 1.25 (95% confidence interval [CI], .84 to 1.66); when considered individually without adjustment for covariates, it is estimated to be 1.30 (95% CI, .87 to 1.94).

A secondary analysis of disease-free survival considering all patients randomized regardless of eligibility status resulted in an estimated RR attributed to treatment with 5-FU and MeCCNU and adjusted for important covariates of 1.21 (95% CI, .83 to 1.88). Similarly, when only eligible patients who received post–radiation-therapy drug treatment were considered (84 escalating 5-FU and 72 5-FU and MeCCNU patients), no difference in direction or magnitude of the RR estimate was observed (RR = 1.17; 95% CI, .74 to 1.85).

Mortality

A total of 91 deaths have been reported; 46% (44 of 95) on 5-FU and MeCCNU and 45% (47 of 104) on 5-FU. Eighty-one of the deaths were attributed to progressive disease, and one death was reported without documented cause; the causes of death for the remaining nine patients were attributed to treatment (two patients; discussed above), myocardial infarctions (five; three of whom had a suspected recurrence), stroke (one), and metastatic disease resulting from a new primary tumor arising in the bile duct (one). Six of the deaths unrelated to disease occurred in patients receiving escalating 5-FU and three in patients receiving 5-FU and MeCCNU. The one death with no cause reported was on the escalating 5-FU arm. Kaplan-Meier estimates of 3-year survival probabilities for patients assigned to 5-FU and MeCCNU and escalating 5-FU are 66% and 75%, respectively (Fig 2). There is no difference between the two arms with respect to the survival distributions ($P = .58$, two-tailed). The RR for death associated with 5-FU and MeCCNU adjusted for stage, resection type, and distance to the nearest margin is 1.10 (95% CI, .68 to 1.52; $P = .67$). Median survival has not been reached in either treatment arm.

Figure 3 compares the survival prognosis of patients undergoing abdominal-perineal resections and patients undergoing anterior resection with distance to margin of resection (as determined by the pathologist on fresh specimen) of $\leq$ 3 cm and greater than 3 cm. Patients undergoing anterior resection with distance to the margin greater than 3 cm experienced improved survival compared with patients undergoing anterior resection with distance to the nearest margin $\leq$ 3 cm, suggesting

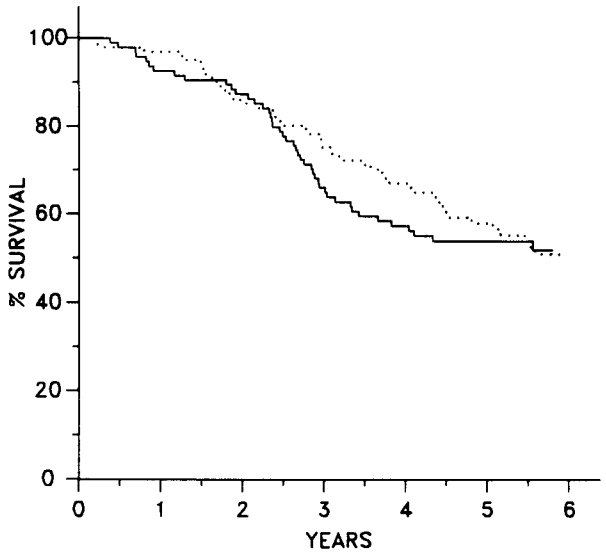

Fig 2. Probability of survival by treatment: —, radiation plus 5-FU plus MeCCNU; ····, radiation plus escalating 5-FU.

that abdominal-perineal resection should be considered when the distal margin for resection with the low anterior route would be $\leq$ 3 cm.

As in the disease-free analysis, secondary analyses of survival considering either all patients randomized or only patients who received treatment after the completion of radiation therapy, resulted in no meaningful change in direction or magnitude of the RR attributed to treatment with the 5-FU and MeCCNU regimen

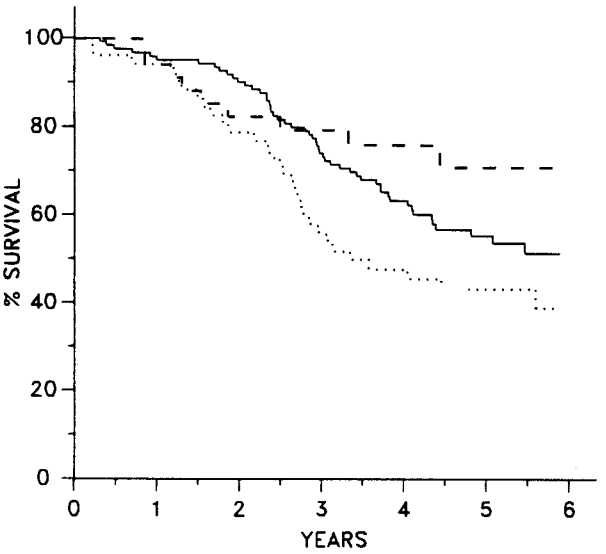

Fig 3. Probability of survival by resection type and distance to the nearest margin: —, abdominal-perineal resection; ····, anterior resection with distance ≤ 3 cm; ---, anterior resection with distance > 3 cm.

(RR = 1.10, 95% CI, .72 to 1.67; and RR = 1.04, 95% CI, .65 to 1.67, respectively).

A stage-wise comparison of the results of this study with GI 7175 in which the same staging criteria of GI 7175 were applied to GI 7180 shows that reducing the chemotherapeutic regimen of 5-FU and MeCCNU from 18 months to 12 months did not significantly alter the survival outcome for patients. There were no differences between the radiation and escalating 5-FU arm of GI 7180 and the radiation and 5-FU and MeCCNU arm of GI 7175 with respect to survival within any stage (Fig 4).

DISCUSSION

The results of this study indicate that treatment after surgical resection of Dukes B2 and C rectal cancer with escalating 5-FU postradiation therapy provides similar survival and recurrence outcomes as a postradiation chemotherapeutic regimen including the leukemogen MeCCNU. Both survival and disease-free survival results favor the escalating 5-FU arm, although these differences did not reach statistical significance. Fewer recurrences involving distant sites occurred on the escalating 5-FU arm compared with the 5-FU and MeCCNU arm, further suggesting that MeCCNU is not an essential component of the postradiation chemotherapy treatment. Although similar rates of local recurrence were experienced on the two study arms, the similarity in outcome is not surprising as both arms used identical postsurgery radiation therapy regimens including 5-FU.

In any adjuvant study, toxicity of therapy must be carefully assessed. Toxicity in GI 7180 was nontrivial with one treatment-related death reported in each arm and half of the patients in both arms experiencing at least one episode of severe or worse toxicity. As expected, myelosuppression was the most common toxicity seen in both arms. Although there were twice as many intestinal obstructions among patients receiving escalating 5-FU, no association with type of chemotherapy can be drawn from these small samples. Because of toxicity, patients often received no therapy beyond the initial radiation treatment. The risk to the patient, however, is balanced by the expected survival benefit. To date, no patient treated with 5-FU and MeCCNU in this study has developed leukemia.

Results from the previous GITSG study (GI 7175) of adjuvant therapy after surgical resection of Dukes B2 or C rectal cancer demonstrated improved survival and disease-free survival in patients treated with combination radiation therapy and post radiation therapy using 5-FU and MeCCNU when compared with surgery alone,

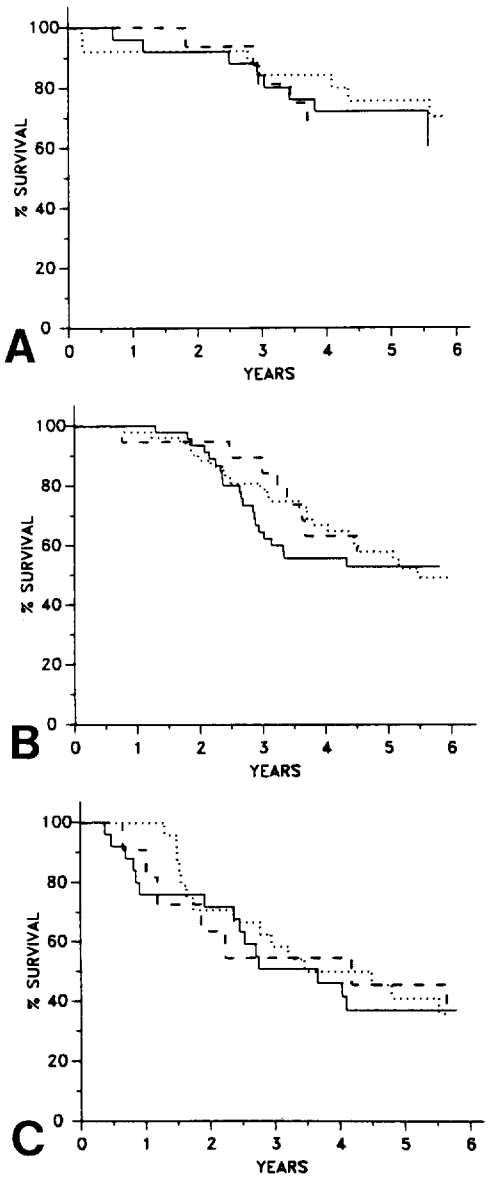

Fig 4. Probability of survival by Dukes stage (A, stage B2 [no nodes]; B, stage C1 [< five nodes]; C, stage C2 [≥ five nodes]) and study therapy (—, 7180: radiation plus 5-FU plus MeCCNU; ····, 7180: radiation plus escalating 5-FU; ----, 7175: radiation plus 5-FU plus MeCCNU).

and improved disease-free survival for patients treated with this combined modality therapy compared with radiation therapy alone. The results of the present study confirm the expected survival and disease-free survival probabilities observed in the combination therapy arm of the previous GITSG study, while the recent report by the North Central Cancer Treatment Group (NCCTG)[13] further demonstrates the advantage of combination radiation therapy and chemotherapy compared with

radiation therapy alone in reducing recurrence rates and improving survival. Although data from the initial rectal cancer adjuvant trial conducted by the National Surgical Breast and Bowel Project (NSABP RO1)[14] suggested improved survival and disease-free survival in patients treated with chemotherapy alone compared with surgery alone, that study did not include a combined modality treatment arm.

Progress has clearly been made in the adjuvant treatment of rectal cancer. A recent National Institutes of Health consensus conference on adjuvant therapy for patients with colon and rectal cancer concluded that combined postoperative chemotherapy and radiation therapy improved local control and survival in stage B2 and C patients with rectal cancer and that treatment with combined modality therapy in these patients is recommended.[15] The only combined modality regimens examined until now have included MeCCNU. The results of this study show that comparable results can be achieved using a combination regimen that does not include MeCCNU; this conclusion is also supported by preliminary data reported by the NCCTG.[16]

GI 7180, a protocol designed more than a decade ago, used a treatment plan that most likely is now outdated. The protocol-mandated radiotherapy dose (4140 cGy) may be suboptimal. Different methods of 5-FU administration (eg, rapid infusion, prolonged continuous infusion) have been compared in an attempt to maximize radiation sensitization and further reduce the rate of locoregional recurrence. Furthermore, studies in metastatic colorectal disease demonstrating enhanced efficacy of 5-FU when administered with leucovorin,[17,18] as well as a recent report indicating a reduction in the rate of recurrence in colon cancer when levamisole was added to adjuvant 5-FU,[19] have led to an intergroup trial assessing the value of such combinations as adjuvant therapy for rectal cancer (Intergroup Rectal Adjuvant protocol; Int 0114; activated August 1990).

It appears highly unlikely that further follow-up in GI 7180 will result in 5-FU and MeCCNU treatment being superior to escalating 5-FU. The increased leukemic potential of MeCCNU makes the drug additionally undesirable to include in the adjuvant setting. Therefore, we conclude that MeCCNU is not an essential component of effective postoperative combined modality treatment of adjuvant rectal cancer and should not be included in future treatment regimens.

APPENDIX

Contributors: Georgetown University Medical Center, Washington, DC: Paul V. Woolley, Russell Nauta, and Frederick P. Smith; The EMMES Corporation, Potomac, MD: Anne S. Lindblad*; Roswell Park Memorial Institute, Buffalo, NY: Nicholas Petrelli, Lemuel Herrera, and Harold O. Douglass, Jr; Dana-Farber Cancer Institute, Boston, MA: Robert J. Mayer*; Mount Sinai Medical Center, New York, NY: Howard W. Bruckner and Jack Dalton; Instituto Nazionale, Milan, Italy: Gianni Bonadonna and Leondro Gennari; Hawaii Medical Association, Honolulu, HI: Thomas C. Hall; Wayne State University, Detroit, MI: Donald W. Weaver*† and Lawrence Leichman; University of Miami, Miami, FL: Martin H. Kalser and Pasquale Benedetto; New York University/Montefiore Medical Centers, New York, NY: Franco M. Muggia, Michael Green, and Edward Greenwald; University of Chicago/Illinois Cancer Council, Chicago, IL: Bernard Levin, Ellen Gaynor, and Jules Harris; Yale University, New Haven, CT: John C. Marsh, Kenneth Barwick,† Arthur H. Knowlton, and Elliot M. Livstone; Cleveland Clinic, Cleveland, OH: Ronald M. Bukowski†; McGill Cancer Center, Montreal, Canada: Antoine Loutfi; Wisconsin Clinical Cancer Center, Madison, WI: Guillermo Ramirez; and The Mallinckrodt Institute of Radiology, St Louis, MO: Patrick R.M. Thomas.†

Also contributing: Provisional members—State University of New York Upstate Medical Center; members of the Community Clinical Oncology Program: Twin Tiers, Binghamton, NY; New England Collaborative, Boston, MA; San Gabriel Valley, Pasadena, CA; Newark Beth Israel, Newark, NJ; San Joaquin Valley, Fresno, CA; Central Los Angeles, Los Angeles, CA; Southwest Virginia, Roanoke, VA; Eastern Maine, Bangor, ME; Nassau/Winthrop University, Mineola, NY; and Northern New Jersey, Morristown, NJ.

*Writing committee.

†Study Chairman.

REFERENCES

1. Gunderson L, Sosin H: Areas of failure found at reoperation (second or symptomatic look) following "curative surgery" for adenocarcinoma of the rectum. Cancer 34:1278-1292, 1974

2. Gerard A, Buyse M, Nordlinger B, et al: Preoperative radiotherapy as adjuvant treatment in rectal cancer. Final results of a randomized study of the European Organization for Research and Treatment of Cancer (EORTC). Ann Surg 208:606-614, 1988

3. Bentzen SM, Balslev I, Pederson M, et al: A regression analysis of prognostic factors after resection of Dukes B and C carcinoma of the rectum and rectosigmoid. Does postoperative radiotherapy change the prognosis? Br J Cancer 58:195-201, 1988

4. Gastrointestinal Tumor Study Group: Holyoke ED, Stablein DM, Thomas PRM, et al: Prolongation of disease-free interval in surgically treated rectal carcinoma. N Engl J Med 312:1465-1472, 1985

5. Douglass HO Jr, Mayer RJ, Lindblad AS, et al: Survival after postoperative combination treatment of rectal cancer. N Engl J Med 315:1294-1295, 1986 (letter)

6. Boice JD Jr, Greene MH, Killen JY Jr, et al: Leukemia and pre-leukemia after adjuvant treatment of gastrointestinal cancer with methyl-CCNU. N Engl J Med 309:1079-1084, 1983

7. Horton J, Olson J, Sullivan J, et al: 5-Fluorouracil in cancer: An improved regimen. Ann Intern Med 73:897-900, 1970

8. Ansfield F, Klotz J, Nealon T, et al: A phase III study comparing the clinical utility of four regimens of 5-fluorouracil. A preliminary report. Cancer 39:34-40, 1977

9. Mayer RJ, MacIntyre JM, Steele GJ Jr: High-dose bolus 5-fluorouracil (5-FU) for metastatic colorectal carcinoma. Proc Am Soc Clin Oncol 2:127, 1983 (abstr)

10. Makuch R, Simon R: Sample size requirements for evaluating a conservative therapy. Cancer Treat Rep 62:1037-1040, 1978

11. Kaplan E, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-458, 1958

12. Cox DR: Regression models and life tables. J Stat Soc B 34:187-200, 1972

13. Krook JE, Moertel CG, Gunderson LL, et al: Effective surgical adjuvant therapy for high risk rectal carcinoma. N Engl J Med 324:709-715, 1991

14. Fisher B, Wolmark N, Rockette H, et al: Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: Results from NSABP protocol R-01. J Natl Cancer Inst 80:21-29, 1988

15. National Institutes of Health Consensus Conference: Adjuvant therapy for patients with colon and rectal cancer. JAMA 264:1444-1450, 1990

16. O'Connell M, Wieand H, Krook J, et al: Lack of value for methyl-CCNU (MeCCNU) as a component of effective rectal cancer surgical adjuvant therapy. Interim analysis of Intergroup protocol 86-47-51. Proc Am Soc Clin Oncol 10:134, 1991 (abstr)

17. Poon MA, O'Connell MJ, Moertel CG, et al: Biochemical modulation of fluorouracil; evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. J Clin Oncol 7:1407-1417, 1989

18. Gastrointestinal Tumor Study Group: The modulation of fluorouracil with leucovorin in metastatic colorectal carcinoma: A prospective randomized phase III trial. J Clin Oncol 7:1419-1426, 1989

19. Moertel CG, Fleming TR, Macdonald JS, et al: Levamisole and fluorouracil for surgical adjuvant therapy of colon carcinoma. N Engl J Med 322:352-358, 1990