Randomized Trial of Postoperative Adjuvant Chemotherapy With or Without Radiotherapy for Carcinoma of the Rectum: National Surgical Adjuvant Breast and Bowel Project Protocol R-02

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Background: **The conviction that postoperative radiotherapy and chemotherapy represent an acceptable standard of care for patients with Dukes' B (stage II) and Dukes' C (stage III) carcinoma of the rectum evolved in the absence of data from clinical trials designed to determine whether the addition of radiotherapy results in improved disease-free survival and overall survival. This study was carried out to address this issue. An additional aim was to determine whether leucovorin (LV)-modulated 5-fluorouracil (5-FU) is superior to the combination of 5-FU, semustine, and vincristine (MOF) in men.** ***Patients and Methods:*** **Eligible patients (n = 694) with Dukes' B or C carcinoma of the rectum were enrolled in National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol R-02 from September 1987 through December 1992 and were followed. They were randomly assigned to receive either postoperative adjuvant chemotherapy alone (n = 348) or chemotherapy with postoperative radiotherapy (n = 346). All female patients (n = 287) received 5-FU plus LV chemotherapy; male patients received either MOF (n = 207) or 5-FU plus LV (n = 200). Primary analyses were carried out by use of a stratified log-rank statistic; *P* values are two-sided.** ***Results:*** **The average time on study for surviving patients is 93 months as of September 30, 1998. Postoperative radiotherapy resulted in no beneficial effect on disease-free survival (*P* = .90) or overall survival (*P* = .89), regardless of which chemotherapy was utilized, although it reduced the cumulative incidence of locoregional relapse from 13% to 8% at 5-year follow-up (*P* = .02). Male patients who received 5-FU plus LV demonstrated a statistically significant benefit in disease-free survival at 5 years compared with those who received MOF (55% versus 47%; *P* = .009) but not in 5-year overall survival (65% versus 62%; *P* = .17).** ***Conclusions:*** **The addition of postoperative radiation therapy to chemotherapy in Dukes' B and C rectal cancer did not alter the subsequent incidence of distant disease, although there was a reduction in locoregional relapse when compared with chemotherapy alone. [J Natl Cancer Inst 2000;92:388–96]**

It is commonly believed that the use of postoperative radiotherapy in addition to chemotherapy prolongs survival in patients with Dukes' B (stage II) or Dukes' C (stage III) carcinoma of the rectum. This conviction was encouraged by the conclusions of the National Institutes of Health Consensus Development Conference of April 1990 *(1)*.

Two principal randomized, prospective clinical trials provided evidence for the benefit of the combination therapy. The Gastrointestinal Study Group (GITSG) Protocol 7175 *(2)* began in 1975 and ended in 1980 after 227 patients had been randomly assigned to one of the following four arms after the resection of the primary tumor: 1) a control group consisting of no further treatment; 2) chemotherapy in the form of semustine [1-(2-chlorethyl-3-4-methyl-cyclohexyl)-1-nitrosourea] (or methyl-CCNU) and 5-fluorouracil (5-FU); 3) postoperative radiotherapy; and 4) a combination of chemotherapy and radiotherapy. When the results of this study were published in 1985, 58 eligible patients remained in the untreated arm and 46 patients remained in the group that received the combination therapy, with a median follow-up time of 80 months. A pairwise comparison demonstrated a statistically significant advantage for disease-free survival (DFS), and subsequently for overall survival *(3)*, in the group receiving combined radiation therapy and chemotherapy compared with the untreated control. Other pairwise comparisons did not reach statistical significance.

The second trial was the North Central Cancer Treatment Group (NCCTG)'s Protocol 79-47-51 *(4)*. In this two-arm trial, 204 patients were randomly assigned to receive either postoperative radiation therapy or radiation therapy combined with semustine and 5-FU. After a median follow-up of more than 7 years, there was a 34% reduction in tumor relapse (*P* = .002)

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See "Notes" following "References."

and a 36% reduction in cancer-related death ($P = .007$) in favor of the combined modality treatment.

Neither of these two trials was conclusive about whether the effect of radiotherapy and chemotherapy is additive when used in concert. Although GITSG 7175 showed a benefit for combination therapy, that study was underpowered and was unable to determine whether the same advantage would have been achieved with chemotherapy alone or radiation therapy alone. Similarly, since both groups in the NCCTG trial received radiotherapy, that trial did not answer whether the same benefit could be achieved with chemotherapy in the absence of radiotherapy.

The importance of this question was further underscored by the results from National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol R-01, which, at the time of publication in 1988, were regarded as enigmatic *(5).* From November 1977 through November 1986, 574 patients in that study were randomly assigned to receive one of three treatment options: 1) no further treatment postoperatively, 2) postoperative radiotherapy, or 3) postoperative chemotherapy consisting of a combination of semustine, vincristine, and 5-FU (MOF). After 5 years of follow-up, there was a statistically significant advantage in favor of the group that received postoperative adjuvant chemotherapy: 42% versus 30% for DFS and 53% versus 43% for overall survival. Curiously, this benefit seemed evident only in men. Patients who received radiotherapy alone demonstrated a decrease in locoregional relapse as an initial site of failure, from 24.5% to 16.3% ($P = .06$), but there was no statistically significant improvement in DFS or in overall survival. Although the disparate response to chemotherapy in men and women could not be explained, these results did demonstrate that, when used without radiotherapy, chemotherapy could alter the natural history of rectal cancer, whereas radiotherapy alone did not prolong DFS or overall survival.

Thus, the principal goal of NSABP Protocol R-02 was to ascertain whether the addition of radiotherapy to chemotherapy would enhance the benefits obtained with chemotherapy alone. An additional aim of this study was to determine whether leucovorin (LV)-modulated 5-FU was superior to MOF in men.

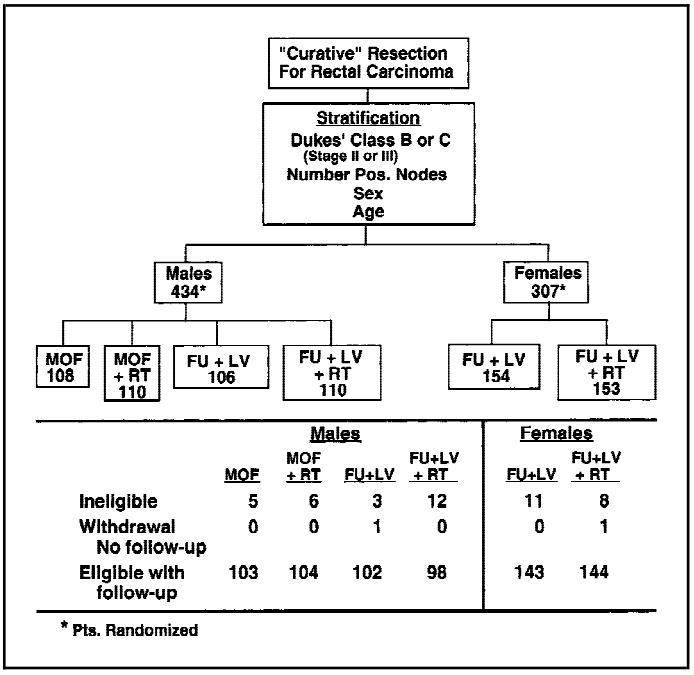

Fig. 1. National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol R-02 was designed in an attempt to determine whether the addition of radiation therapy (RT) to chemotherapy improves disease-free survival and overall survival in patients with Dukes' B or C carcinoma of the rectum. On the basis of findings from NSABP Protocol R-01, males were randomly assigned to one of four treatment regimens: 1) a combination of 5-fluorouracil, semustine, and vincristine (MOF); 2) MOF plus radiation therapy (RT); 3) 5-fluorouracil plus leucovorin (FU plus LV); or 4) FU plus LV plus RT. Females were randomly assigned to one of two treatment regimens: FU plus LV or FU plus LV plus RT. Specific aims were 1) to determine whether RT, when added to a chemotherapeutic regimen, prolongs disease-free survival and overall survival; 2) for males only, to compare MOF, with and without RT, to FU plus LV, with and without RT; and 3) for males and females, to compare FU plus LV without RT to FU plus LV with RT.

PATIENTS AND METHODS

The protocol schema for this study is provided in Fig. 1.

Selection of Patients

Patients from NSABP-affiliated institutions participated in this study (*see* Appendix). This study was approved by the Institutional Review Boards of the participating institutions and the National Cancer Institute. Patients provided written informed consent. Eligibility was restricted to those who had undergone curative abdominoperineal resection or anterior resection for Dukes' B or C carcinoma of the rectum *(6).* Rectal tumors were defined as those in which the opening of the pelvic peritoneum was necessary to define the distal extent of the lesion. Dukes' B tumors were characterized by invasion through the wall of the rectum with extension into the perirectal tissue but without involvement of lymph nodes. Dukes' C tumors manifested invasion of the wall of the rectum to any depth (including extension into perirectal tissue) with histologically positive regional lymph nodes. Patients with more than one synchronous rectal tumor were eligible, as were patients with intestinal obstruction, regardless of the need for preliminary or complementary colostomy. Primary tumor invasion of contiguous structures was not a disqualification as long as curative *en bloc* resection of the rectum and contiguous structures could be accomplished with uninvolved margins of resection. Patients with tumors other than carcinoma or those in whom there was free perforation of a carcinoma were not eligible. Patients treated by local excision, noncurative surgical resection, or prior treatment with radiation therapy, chemotherapy, or immunotherapy were not eligible. Pregnant patients and patients having nonmalignant systemic disease that would preclude protocol treatment were also excluded. The interval between surgery, randomization, and planned treatment onset was to be no more than 42 days, regardless of the presence or absence of postoperative complications. The surgical conduct, including abdominoperineal resection or anterior resection with tumor-free margins, was as described for Protocol R-01 *(5).*

Randomization

Randomization was conducted centrally at the NSABP Biostatistical Center (Pittsburgh, PA). Patients were stratified according to sex, number of positive lymph nodes (0, 1–4, or >4), age (≤59 years or >60 years), and institution. Male patients were randomly assigned to one of four postoperative treatment groups: 1) 5-FU plus LV; 2) 5-FU plus LV plus radiotherapy; 3) MOF; or 4) MOF plus radiation therapy. Female patients were randomly assigned to receive either 5-FU plus LV or 5-FU plus LV plus radiotherapy. Treatments were balanced across strata by use of a sequential treatment assignment similar to that described by Pocock and Simon *(7).* Thus, all patients, regardless of sex, received chemotherapy with or without radiotherapy.

Protocol-Specified Follow-up

During adjuvant therapy, patients were monitored for signs of hematologic and gastrointestinal toxicity, and chemotherapy dose was modified accordingly. During each cycle, blood cell counts were assessed on days 1, 22, 36, and 57 of MOF chemotherapy and weekly for patients receiving 5-FU plus LV. Physical examination, performance status evaluation, and blood chemistry studies were carried out during each cycle. Radionuclide scan, sonogram, or computerized tomography scan was performed for grossly abnormal liver function tests and/or hepatomegaly. These studies were repeated every 3 months for the 12 months after the completion of adjuvant treatment and then every 6 months, for a total

of 5 years. Over that period, a chest x-ray and carcinoembryonic antigen levels were required every 6 months. After 5 years, a barium enema and/or endoscopic examination were mandated every 12 months. Disease status was reported on a yearly basis. Histologic confirmation of relapse and new primary tumors was encouraged.

Chemotherapy

The protocol stipulated that chemotherapy was to start between 21 and 42 days following definitive surgery. For patients assigned to MOF chemotherapy, five cycles of therapy were planned, with each cycle of 10 weeks' duration. 5-FU was administered daily on days 1–5 (325 mg/m^2 by intravenous bolus) and on days 36–40 (375 mg/m^2 by intravenous bolus) of each cycle. Semustine at a dose of 130 mg/m^2 was given orally on day 1 of each treatment cycle; vincristine at a dose of 1 mg/m^2 (to a maximum of 2 mg total dose) was administered intravenously before other chemotherapy on days 1 and 36, respectively. Chemotherapy was continued until five cycles were delivered or until evidence of treatment failure. Drug doses were adjusted according to the nadir of leukopenia and/or thrombocytopenia. The dose of 5-FU given on days 36–40 was determined by blood cell counts on days 22 and 36; dose modification in subsequent courses was considered after the evaluation of blood cell counts on days 57 and 70. Regardless of dose modifications or delays, MOF therapy was not continued beyond 1 year from the time of randomization.

For patients scheduled to receive chemotherapy with 5-FU plus LV, six cycles of therapy were planned for each course of treatment. LV (500 mg/m^2) was administered intravenously as a 2-hour infusion, and an intravenous bolus of 5-FU (500 mg/m^2) was given 1 hour after beginning the LV infusion. Both drugs were administered once a week for 6 consecutive weeks followed by 2 weeks with no drug. Dose modification of 5-FU plus LV was made on the basis of hematologic or gastrointestinal toxicity. Regardless of dose modifications or delays, 5-FU plus LV was not continued beyond 1 year from the time of randomization.

For patients receiving radiation therapy in either the MOF or 5-FU plus LV treatment arms, bolus infusions of 5-FU (400 mg/m^2) were given during each of the first 3 and last 3 days of radiation therapy.

Radiation Therapy Administration

Radiation therapy was initiated between 3 and 5 weeks following completion of cycle 1 of chemotherapy. The pelvis was treated with a four-field box technique (anterior–posterior and two laterals) by use of megavoltage photon beams; the entire tumor bed and lymph node groups were included, with the exception of the external iliac lymph nodes, unless pelvic organs with major external iliac drainage were involved by direct extension of tumor. The lateral borders of the anterior–posterior radiation fields were at least 1 cm lateral to the widest body margin of the true pelvic side walls; the superior border was at the L5-S1 interspace; and the lower border included the perineum in patients undergoing abdominoperineal resection and the inferior aspect of the obturator foramina in those with anterior resection. The posterior border of the lateral portals was at least 1.5 cm posterior to the anterior bony sacral margin, and the anterior margin was configured to reduce the amount of bladder and small bowel irradiated. If the external iliac lymph nodes were not included, the anterior margin of the lateral field was usually 2–3 cm anterior to the sacral promontory. In addition to the four-field box, a boost was administered by a multiple-field technique by use of either anterior–posterior and two lateral fields or posterior and two lateral fields. A boost was not administered in the few cases in which the small bowel could not be sufficiently shielded. In all instances, the small bowel was excluded from the boost volume. Total administered dose to the intersection of the fields was 4500 cGy in 25 fractions at 180 cGy per day. All fields were treated daily, 5 days per week. The boost volume was treated to a dose of 540 cGy in three fractions of 180 cGy per day. No modification in dose was made for interruption of therapy.

Quality Assurance

The NSABP quality-assurance program monitored surgical and adjuvant therapy compliance, acute toxicity, and long-term complications associated with protocol therapy. The hospital surgical reports and pathology reports were reviewed whenever necessary to verify information submitted on entry forms. Pathology specimens were submitted as blocks and/or slides. Copies of original treatment records, diagnostic procedures, discharge summaries, and other pertinent information were obtained, as necessary. An independent medical review was conducted at the NSABP for primary eligibility, adequacy of surgery, serious acute toxic side effects, treatment failures, the development of second primary cancers, and mortality. An institutional site-visit program was conducted to confirm compliance with federal regulations and with the treatment protocol by use of source documentation. Institutional performance relative to data submission was reviewed on a regular basis.

A radiation therapy quality-assurance program was instituted to review portal films for all patients who received radiotherapy. Simulation films of the anterior–posterior and posterior–anterior and lateral fields of the pelvis were submitted for review within 1 week of the start of radiotherapy. Simulation films of the boost portals with opacification of the small bowel were also submitted before the start of the radiation boost. At the conclusion of radiotherapy, follow-up evaluation was conducted through central review of the daily treatment records, dosimetry calculations, isodose curves, photographic documentation of the patient in the treatment position, portal films, and simulation films.

Diagnosis of Treatment Failure

Predetermined "acceptable" criteria for treatment failure were defined in the protocol document. Investigators were encouraged to document treatment failure with tissue biopsy when this was feasible. Alternate acceptable criteria included sequential enlargement of a mass on radiologic studies performed over an interval of 4 weeks or more. Isolated liver function test elevation or carcinoembryonic antigen elevation was not considered adequate evidence for recurrence or metastatic disease. A "suspicious" finding alone was not considered to be a treatment failure.

Statistical Analyses

The main statistical goal was to be able to detect a 10% increase in 5-year survival for patients who received radiation therapy compared with patients who did not receive radiation therapy. The sample size considerations and time of primary analysis were based on this hypothesis. Our two additional hypotheses to be tested were whether 5-FU plus LV offered a benefit over MOF and whether radiation therapy enhanced the effect of the 5-FU plus LV. The analysis plan called for the above comparisons to be performed for the end points of overall survival and DFS. All eligible patients were analyzed according to their assigned treatment group. In the calculation of DFS, an event is defined as the first occurrence of a tumor relapse, a second primary cancer (excluding basal cell carcinomas of the skin and carcinoma *in situ* of the cervix), or death. These analyses were supplemented by analyses of time to locoregional relapse (tumor in the pelvis, including the presacrum, pelvic sidewalls, base of the bladder and the perineum, or at the anastomotic site) and time to relapse (time to locoregional or distant relapse of rectal cancer). Application of the log-rank statistic stratifying for sex, age, number of lymph nodes, and other treatment was the method of primary analysis *(8,9).*

Plots showing the incidence of relapse and locoregional recurrence by time were generated by use of a cause-specific incident approach as defined by Gaynor et al. *(10).* Most of the other statistical analyses were carried out according to SAS procedures *(11).* The Kaplan–Meier method was used to construct curves for DFS and overall survival *(12).* The log-rank statistic was used to compare distributions; all follow-up data were utilized, although the survival curves are shown only to 8 years (*see* the "Results" section). All *P* values presented are two-sided unless otherwise stated. The Cox proportional hazards model was used for all multivariate analyses *(13).* A backward-regression analysis was used to identify significant prognostic factors; variables were kept in the model only if the standardized maximum-likelihood estimate statistic had a *P* value below .05. Relative hazard ratios were computed by use of the Cox proportional hazards model.

Global tests for interactions of covariates with treatment were done by comparing the log likelihood for the model with first-order terms (treatment and covariates) to the log likelihood with the same terms plus interaction terms. The study was designed to have a power of .83 to detect a 10% improvement in the 5-year survival of patients receiving radiation therapy (which translates into a 29% reduction in the annual death rate). There has been a sufficient number of deaths (i.e., 288) in this study to meet this power requirement. It was recognized that the study would be underpowered for detecting such a difference for the comparison of MOF to 5-FU plus LV, since this comparison would involve only males. For this reason, in addition to presenting the two-sided *P* values from the log-rank statistic for all comparisons, a 95% confidence interval (CI) for each relative hazard ratio is provided to indicate the range of values that is consistent with the observed data.

RESULTS

Follow-up

From September 2, 1987, through December 30, 1992, 741 patients were randomly assigned to NSABP Protocol R-02 (Table 1). Forty-five (6.1%) of those randomly assigned were subsequently determined to be ineligible. Of these, 21 patients were ineligible because of stage (19 with Dukes' A and two with Dukes' D), 17 had tumors located in the colon, seven patients did not meet one or more other protocol criteria, and two eligible randomly assigned patients withdrew consent immediately after randomization. Thus, 694 patients (93.7% of the randomly assigned patients) were eligible with follow-up. As of September 30, 1998, the average time in the study for surviving eligible patients with follow-up is 93 months. All patients but four have had at least 3 years of follow-up. The distribution of patients according to sex, Dukes' stage, number of positive lymph nodes, type of resection, and age was well balanced among the treatment groups. Of the Dukes' C cohort, 76% of the nonirradiated patients demonstrated full-thickness tumor penetration compared with 74% in the radiation therapy group.

Addition of Radiation Therapy to Chemotherapy

The addition of radiation therapy had no significant effect on the length of relapse-free survival (RFS) ($P = .38$), DFS ($P = .90$), or overall survival ($P = .89$) (Fig. 2). The estimated hazard ratios (95% CIs) for an event on the radiation therapy arms versus the no radiation therapy arms were 0.90 (0.71–1.14), 0.99 (0.80–1.22), and 0.98 (0.78–1.24), respectively. This lack of benefit was apparent regardless of whether the patients received MOF or 5-FU plus LV. When radiation therapy was compared with no radiation therapy in these two chemotherapy subgroups for the three end points described above (six analyses), the *P* value exceeded .41 in every case (data not shown).

Multivariate analyses indicated that the number of positive lymph nodes ($P<.001$ for DFS and overall survival) and age ($P = .008$ for DFS and $P = .02$ for overall survival) were statistically significant determinants of DFS and overall survival. Patients less than 60 years of age with fewer positive lymph nodes had the best prognosis. Only lymph node status ($P<.0001$) was prognostic of the length of the RFS. Sex and the surgical procedure were not significantly prognostic for any of the outcomes. Results were unaffected by whether patients with positive lymph nodes were evaluated as originally stratified (1–4 or >4) or by TNM (tumor–node–metastasis) stage (1–3 or >3) *(6)*.

A global test for the interaction of radiation therapy with the prognostic variables was significant (RFS, $P = .008$; DFS, $P = .04$; and overall survival, $P = .03$). The strongest interaction was between radiation therapy and age (RFS, $P = .007$; DFS, $P = .008$; and overall survival, $P = .007$), in that any potential benefit from radiation therapy would have occurred in patients who were less than 60 years of age. The estimated hazard ratios for an event on the radiation therapy arms versus the no radiation therapy arms were 0.65, 0.72, and 0.69, respectively, among patients who were less than 60 years of age and 1.20, 1.25, and 1.30, respectively, among patients who were 60 years of age or older. There was no difference in the amount of radiation therapy received as a function of age, nor was there a difference in the amount of chemotherapy received following radiation therapy as a function of age. There was an interaction between

Table 1. Distribution of characteristics of eligible patients with follow-up according to treatment groups in NSABP Protocol R-02*

	Treatment group			
	Males only		Males and females	
	MOF	MOF + RT	5-FU + LV	5-FU + LV + RT
Eligibility, No. of patients				
Randomized	108	110	260	263
Ineligible	5	6	14	20
Withdrawal, no follow-up	0	0	1	1
Eligible, with follow-up	103	104	245	242
Characteristic, %				
Sex				
Male	100	100	42	40
Female	0	0	58	60
Age y				
<60	50	48	48	46
⩾60	50	52	52	54
Race				
White	88	88	89	90
Black	5	10	7	6
Other	7	2	5	5
Lymph node status†				
Negative lymph nodes (Dukes' B)	28	30	30	30
Positive lymph nodes (Dukes' C)	72	70	70	70
1–3	45	38	42	41
⩾4	27	33	27	29
Surgical procedure				
Abdominoperineal resection	47	43	44	39
Anterior resection	53	57	56	61

*NSABP = National Surgical Adjuvant Breast and Bowel Project; MOF = combination of 5-fluorouracil, semustine, and vincristine; RT = radiation therapy; 5-FU = 5-fluorouracil; LV = leucovorin

†*See (6)* for staging information.

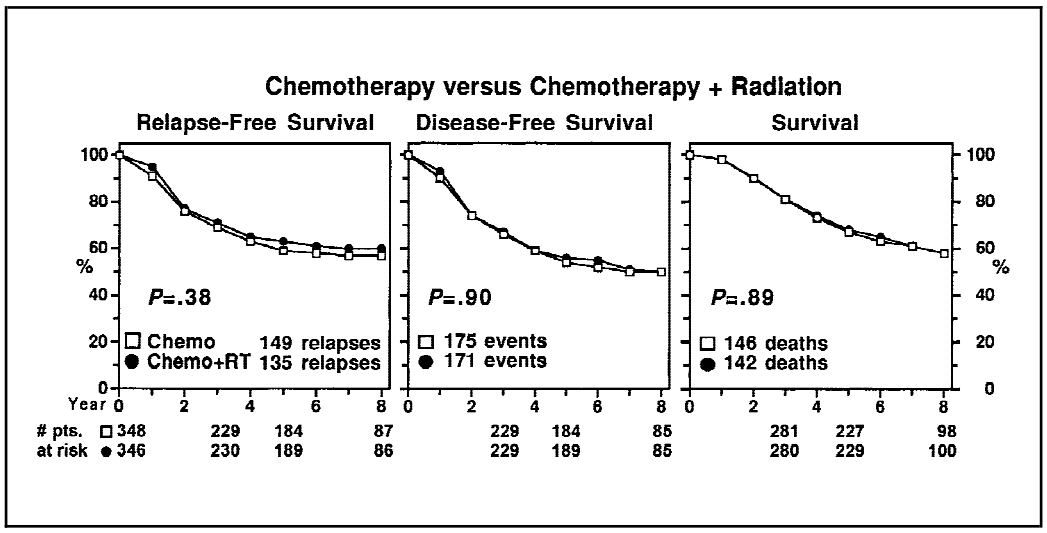

Fig. 2. Relapse-free survival, disease-free survival, and overall survival (survival) in patients (males and females) treated with chemotherapy with and without radiation therapy (RT). FU = 5-fluorouracil; LV = leucovorin; MOF = a combination of 5-FU, semustine, and vincristine; Chemo = chemotherapy. The addition of RT had no significant effect on the length of relapse-free survival (P = .38), disease-free survival (P = .90), or overall survival (P = .89). The estimated hazard ratios (95% confidence intervals) for an event on the RT arms versus the no RT arms were 0.90 (0.71–1.14), 0.99 (0.80–1.22), and 0.98 (0.78–1.24), respectively. This lack of benefit was apparent regardless of whether the patients received MOF or FU plus LV.

radiation therapy and the type of surgical resection (RFS, P = .007; DFS, P = .048; and overall survival, P = .07), in that any potential benefit from radiation therapy would have occurred in patients undergoing abdominoperineal resection.

When radiation therapy was added to chemotherapy, there was a reduction in the cumulative incidence of locoregional recurrence (P = .02; Fig. 3). The relative risk of locoregional recurrence was 0.57 for patients treated with radiotherapy, indicating that, at any point during follow-up, a patient treated with radiotherapy was estimated to have 0.57 times the likelihood of developing a locoregional failure as a similar patient not receiving radiotherapy (95% CI = 0.36–0.92). At 5 years, this was evident as a 5% absolute decrease in locoregional recurrence, from 13% without adjuvant radiation therapy to 8% with such therapy.

5-FU Plus LV Versus MOF Chemotherapy in Male Patients

Patients treated with 5-FU plus LV demonstrated a statistically significant benefit in RFS (P = .046) and DFS (P = .009) (Fig. 4). The 5-year DFS rate for male patients receiving 5-FU plus LV was 55% versus 47% for those receiving MOF. The estimated hazard ratio for 5-FU plus LV versus MOF was 0.70 (95% CI = 0.54–0.92). The 5-year RFS rate was 61% for 5-FU plus LV compared with 55% for MOF, with an estimated hazard ratio for 5-FU plus LV versus MOF of 0.74 (95% CI = 0.55–0.995). The 5-year survival was 65% for patients who received 5-FU plus LV versus 62% for those who received MOF (P = .17). The estimated hazard ratio for 5-FU plus LV versus MOF was 0.82 (95% CI = 0.61–1.09). There was no statistically significant interaction between radiation therapy and type of chemotherapy.

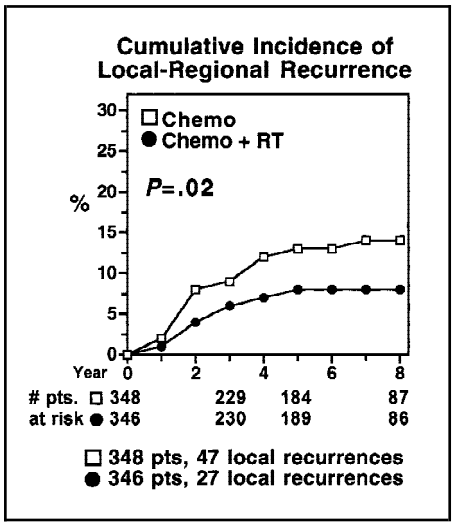

Fig. 3. Cumulative incidence of locoregional recurrence in patients (pts) (males and females) treated with chemotherapy (Chemo) with and without radiation therapy (RT). The relative risk of locoregional recurrence was 0.57 (95% confidence interval = 0.36–0.92) for patients treated with RT. At 5 years, this was evident as a 5% absolute decrease in locoregional recurrence, from 13% without adjuvant RT to 8% with such therapy.

First-Reported Site of Treatment Failure

Of patients developing a tumor relapse, more than two thirds presented with a metastatic lesion that was outside the field encompassed by the radiotherapy. Thirty-one percent of the irradiated group and 29% of the nonirradiated cohort developed such tumor recurrence as the first site of treatment failure (Table 2). The beneficial effect of LV-modulated 5-FU appeared to be evident for locoregional as well as for distant disease.

Toxicity

On each regimen, at least 95% of the patients experienced at least one toxic reaction, and nearly 40% had at least one severe reaction (Table 3). Thirty-one percent of those who received 5-FU plus LV experienced diarrhea greater than six stools per day compared with less than or equal to 9% in those receiving the MOF regimens. Patients receiving MOF had more leukopenia and thrombocytopenia. Men appeared to tolerate the 5-FU plus LV regimen better than women. For example, 34% of the women experienced grade III toxic effects compared with 22% of the men in the nonirradiated group; comparable grade III toxic effects were 32% versus 30% in irradiated patients. Radiation therapy was associated with more skin toxic effects and more leukopenia, but there was no consistent difference in the rate of diarrhea. Four deaths occurred on therapy.

Compliance

Two eligible patients withdrew their consent to be followed before chemotherapy was initiated, and 12 other eligible patients never began chemotherapy but agreed to be followed (six pa-

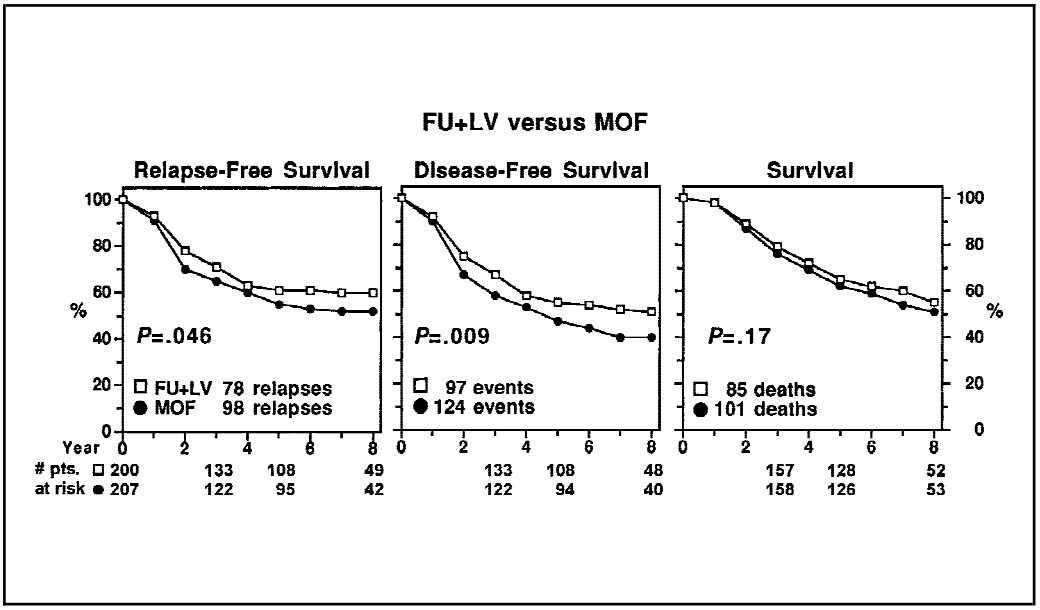

Fig. 4. Relapse-free survival, disease-free survival, and overall survival (survival) in patients (pts) (males only) treated with 5-fluorouracil and leucovorin (FU plus LV) or the combination of 5-FU, semustine, and vincristine (MOF). The 5-year disease-free survival rate for male patients receiving FU plus LV was 55% versus 47% for those receiving MOF. The estimated hazard ratio for 5-FU plus LV versus MOF was 0.70 (95% confidence interval [CI] = 0.54–0.92). The 5-year relapse-free survival rate was 61% for FU plus LV versus 55% for MOF, with an estimated hazard ratio for FU plus LV versus MOF of 0.74 (95% CI = 0.55–0.995). The 5-year survival was 65% for patients who received FU plus LV versus 62% for those who received MOF (P = .17). The estimated hazard ratio for FU plus LV versus MOF was 0.82 (95% CI = 0.61–1.09).

Table 2. Percent distribution of first sites of treatment failure* in different treatment groups in NSABP Protocol R-02†

Site	No RT	RT	5-FU + LV‡	MOF‡
Total relapse	43	39	39	47
Locoregional	14	8	10	14
Anastomotic	5	3	3	5
Pelvic	9	4	7	8
Distant	29	31	30	34
Liver only	11	10	13	10
Lung only	9	10	7	9
At least one distant site other than liver or lung	9	11	10	15

*For entire period of follow-up.

†NSABP = National Surgical Adjuvant Breast and Bowel Project; RT = radiation therapy; 5-FU = 5-fluorouracil; LV = leucovorin; MOF = combination of 5-fluorouracil, semustine, and vincristine.

‡Men only.

tients [MOF], one patient [MOF plus radiation therapy], three patients [5-FU plus LV], and two patients [5-FU plus LV plus radiation therapy). Another 155 patients discontinued therapy in the absence of a documented treatment failure or second primary cancer before completing the protocol-specified regimen. Of these withdrawals, 87 were attributed to toxicity or other medical reasons, and another 64 were simply called "patient withdrawal." In total, the distribution of eligible patients who did not complete protocol-specified chemotherapy was as follows: 22 (21.4%) of 103 in MOF; 20 (19.2%) of 104 in MOF plus radiation therapy; 58 (23.6%) of 246 in 5-FU plus LV; and 69 (28.4%) of 243 in 5-FU plus LV plus radiation therapy.

Fig. 5 shows the proportion of patients who received the full dose of 5-FU chemotherapy during each cycle of treatment. For this analysis, "full dose" was defined as more than 80% of the protocol-mandated dose of 5-FU. 5-FU was chosen for these comparisons because of its use in all arms of the protocol and because it was the principal drug undergoing dose reduction. The amount of LV delivered was consistent at 500 mg/m^2 for any 5-FU dose, except for the cycle administered during radiotherapy in which no LV was given. All eligible patients with follow-up were included until an event such as treatment failure, death, or second primary cancer intervened.

Radiotherapy appeared not to reduce the proportion of those who received the full dose of 5-FU plus LV chemotherapy; this was the case for both men and women receiving 5-FU plus LV. There was a suggestion that men were more likely to receive full-dose 5-FU plus LV than were women, but this proportion was not influenced by radiotherapy and did not affect outcome. Compliance with the prescribed radiation therapy was similar for the two chemotherapy regimens, as shown in Table 4. Of patients randomly assigned to receive radiation therapy, 7.5% underwent no radiation therapy and 11% deviated from the protocol.

Second Primary Cancers

Forty-one (5.9%) of the 694 patients developed at least one second primary cancer: 11 (4.5%) of 245 of those assigned to receive 5-FU plus LV; 13 (5.4%) of 242 of those assigned to receive 5-FU plus LV plus radiation therapy; nine (8.7%) of 103 of those assigned to receive MOF; and eight (7.7%) of 104 of those assigned to receive MOF plus radiation therapy. Eleven patients had a second primary cancer in the colon, and seven had subsequent prostate cancer (one following a rectal cancer relapse). Each of these tumor sites was distributed across the four regimens without obvious imbalance. Seven patients had a second primary cancer in the lung (two following a rectal cancer relapse), three with bladder cancer, three with breast cancer, and two with malignant melanoma (one who had relapsed). Eight other patients had a second primary cancer, each with a different first site of presentation. To date, there have been no reported leukemias or other blood dyscrasias in any of the treatment arms.

Discussion

While the addition of postoperative radiotherapy to chemotherapy significantly reduced the cumulative incidence of locoregional recurrence from 13% to 8% at 5 years, there was no concomitant prolongation in DFS or in overall survival. These results support the previously reported findings from NSABP Protocol R-01, in which the use of postoperative radiotherapy without chemotherapy also reduced locoregional disease without affecting DFS and overall survival *(5)*. The preponderance of

Table 3. Toxic effects of chemotherapy in different treatment groups in NSABP Protocol R-02*

Greatest toxicity per patient, all cycles of therapy	Males only, %		Males and females, %	
	MOF	MOF + RT	5-FU + LV	5-FU + LV + RT
Thrombocytopenia				
$<100 \times 10^3$ cells/mm^3	55	31	3	4
$<50 \times 10^3$ cells/mm^3	16	9	0	0
Leukopenia				
$<4 \times 10^3$ cells/mm^3	76	89	26	65
$<2 \times 10^3$ cells/mm^3	9	18	1	3
Fever				
Any	11	2	10	9
>40 °C or hypotension	0	0	1	1
Infection				
Any	8	6	11	14
Systemic and/or sepsis	1	0	1	3
Nausea and vomiting				
Any	66	60	58	59
Severe or with hospitalization	5	6	5	4
Diarrhea				
Any	46	57	82	81
⩾3 stools/day	21	28	63	61
⩾7 stools/day	9	6	31	31
Stomatitis				
Any	17	13	26	21
Severe or worse	0	0	0	0
Dermatitis				
Any	11	22	19	25
Severe	0	2	1	3
Alopecia				
Any	21	15	5	9
Total	0	0	0	<1
Summary				
Any toxic effects†	96	95	95	97
Severe or worse	33	39	37	39
Life threatening or death	7	6	8	8
Death	0	1	0	1

*NSABP = National Surgical Adjuvant Breast and Bowel Project; MOF = combination of 5-fluorouracil, semustine, and vincristine; 5-FU = 5-fluorouracil; LV = leucovorin; RT = radiation therapy.

†Total percentage of patients with any toxic effects.

evidence from these two sequential studies indicates that postoperative radiotherapy, administered alone or in concert with chemotherapy, is unsuccessful in altering the subsequent incidence of distant disease, an observation that appears to contradict findings from GITSG 7175 *(2)*. However, it may be argued that the results from the NSABP trials and those of GITSG 7175 are not inconsistent. Although the latter study demonstrated that the combination of chemotherapy and radiotherapy was able to prolong DFS and overall survival when compared with an untreated control, it was underpowered to ascertain whether this benefit could have been achieved with chemotherapy alone. The data from the present NSABP trial raise the possibility that the advantage attributable to the combined modality arm of GITSG 7175 was a consequence of the chemotherapy. This assertion is strengthened by the NSABP Protocol R-01 findings that the use of MOF chemotherapy, without radiotherapy, achieved a prolongation in DFS and overall survival *(5)*. While the data are convincing with respect to the inability of radiotherapy to enhance DFS and overall survival, interpretation of the interaction of the effect of radiation therapy with prognostic variables is more challenging, in particular the clinical significance of the interaction of this effect with age or type of surgical resection.

Although the use of preoperative radiotherapy for low-lying lesions of the rectum has become more frequent, only one randomized prospective clinical trial assessing this modality has demonstrated a statistically significant survival advantage. The data from the Swedish Rectal Cancer Trial are unique in suggesting that a 5-day course of preoperative radiotherapy (without chemotherapy) results in a survival advantage when compared with no treatment *(14)*. Whether the greater proportion of patients with more favorable Dukes' stage in the preoperative group in that study was a result of downstaging because of the radiotherapy or was a consequence of an imbalance in the randomization is unclear. It would be surprising if the use of radiotherapy in the preoperative setting were shown to have a unique biologic role.

Unlike the controversy associated with the role of adjuvant radiotherapy in rectal cancer, the benefit of chemotherapy in the postoperative adjuvant setting is generally accepted and has been confirmed in several randomized prospective clinical trials. Although the utility of chemotherapy for this cancer is recognized in the United States, an optimum regimen has not been established. The results of NCCTG 86-47-51 suggested that the addition of semustine to a 5-FU regimen did not provide an

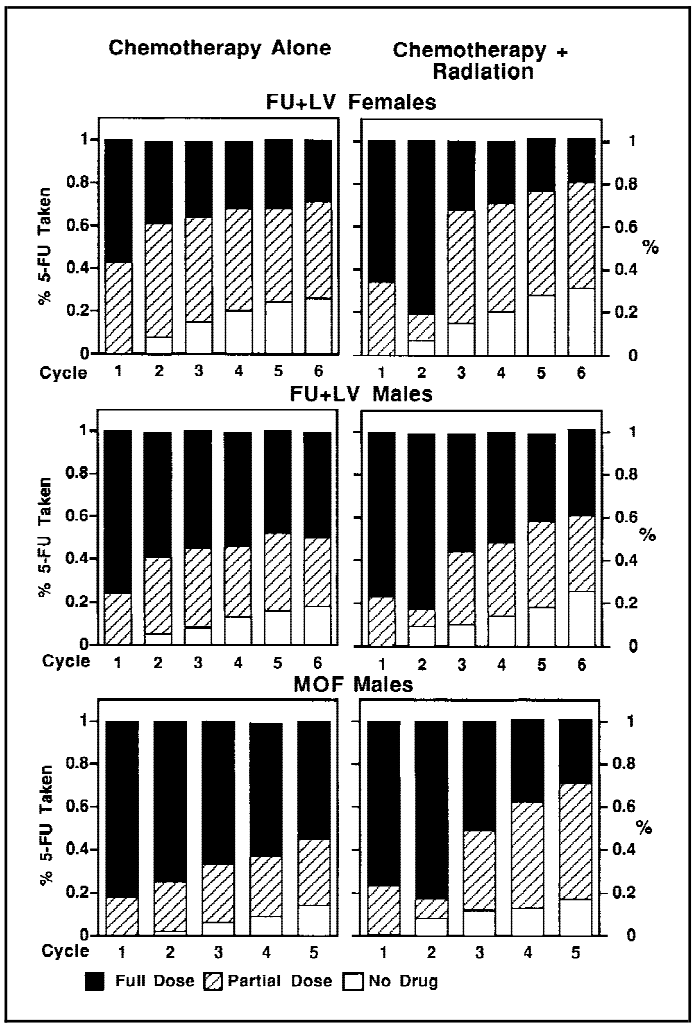

Fig. 5. Percentage of patients receiving a "full dose" of protocol-mandated 5-fluorouracil (5-FU) during each cycle of treatment. LV = leucovorin; MOF = the combination of 5-FU, semustine, and vincristine.

Table 4. Compliance with radiation therapy regimen in different treatment groups in NSABP Protocol R-02*

	MOF + RT (104 patients), %	5-FU + LV + RT (242 patients), %
Patients who started radiation therapy	94	92
Dose to pelvis (excluding boost)†		
⩽5% deviation from protocol	93	91
>5% deviation from protocol	6	9
>10% deviation from protocol‡	1	4
Unknown	1	1
Pelvic volume irradiated		
According to protocol	97	96
Inadequate volume	3	4
Radiation therapy		
According to protocol	91	88
Violating protocol	8	11
Unknown	1	1

*NSABP = National Surgical Adjuvant Breast and Bowel Project; MOF = combination of 5-fluorouracil, semustine, and vincristine; 5-FU = 5-fluorouracil; LV = leucovorin; RT = radiation therapy.

†Recommended dose was 450 cGy.

‡Included in the 5% noted above.

incremental benefit beyond that offered by 5-FU alone *(15)*. Data from Intergroup Trial 0114 indicated that the addition of LV to 5-FU-containing regimens did not result in additional benefit, and it appears unlikely that substantial benefit will result from the addition of LV *(16)*. The results from NSABP Protocol R-02 underscore the efficacy of 5-FU plus LV and lend support for its use in the treatment of carcinoma of the rectum. The advantage of LV-modulated 5-FU over the MOF regimen is consistent with findings from NSABP Protocol C-03, in which clinically (and statistically) significant DFS and survival prolongation were demonstrated in patients with Dukes' B and C carcinoma of the colon *(17)*.

These findings from NSABP Protocol R-02 have potential relevance to the commonly accepted standard of care for carcinoma of the rectum. While a logical argument may be made for the elimination of radiotherapy in the postoperative setting on the basis of the outcome from the study described here, enthusiasm for this approach must be tempered by the confirmed demonstration that radiotherapy is effective in reducing the incidence of locoregional recurrence, an event that can be associated with substantial morbidity and an attenuation in quality of life. Whether the 5% absolute decrease in the cumulative incidence of locoregional relapse is sufficient to justify the routine use of postoperative radiotherapy is a decision that must be made by the clinician. It will undoubtedly be argued that had more aggressive radiotherapy been utilized in this study, or had a more effective radiosensitizer been employed, a survival advantage would have been apparent. Until such assertions can be substantiated by well-conducted clinical trials, however, our conclusion that postoperative radiotherapy appears not to affect survival cannot be dismissed.

Appendix. Institutions contributing 10 or more patients to NSABP Protocol R-02*

Institution	Principal investigator
Baptist Regional Cancer Institute, Jacksonville, FL	Neil Abramson
Billings Interhospital Oncology Project, MT†	David Meyers
CCOP, Allegheny, Pittsburgh, PA‡	Reginald Pugh
CCOP, Columbia River Oncology Program, Portland, OR	Keith S. Lanier
CCOP, Columbus, OH	J. Philip Kuebler
City of Hope Medical Center, Duarte, CA	Lawrence D. Wagman
Glens Falls Hospital, NY	Robert W. Sponzo
Hartford Hospital, CT	Patricia A. DeFusco
Hotel-Dieu, Montreal, ON, Canada	Andre Robidoux
Illinois Masonic Medical Center, Chicago	Samuel G. Taylor IV
Jewish General Hospital, Montreal	Richard G. Margolese
Lehigh Valley Hospital, Allentown, PA	Herbert C. Hoover, Jr
L'Hopital Laval, Quebec, Canada	Stephan Lebel
Michigan State University, East Lansing	Nikolay V. Dimitrov
Roswell Park Cancer Institute, Buffalo, NY	Nicholas J. Petrelli
Royal Victoria Hospital, Montreal	Henry R. Shibata
St. Mary's Hospital Center, Montreal	Paul Donald Ahlgren
University of Cincinnati, OH	Elizabeth A. Shaughnessy
University of Iowa, Iowa City	Peter Jochimsen
University of Kentucky, Lexington	Edward H. Romond
University of Pittsburgh, PA	Victor Gerald Vogel III
University of Texas, San Antonio	Anatolio B. Cruz, Jr

*A list of institutions that contributed fewer than 10 patients is available from the National Surgical Adjuvant Breast and Bowel Project (NSABP) headquarters.

†Affiliate member status inactive; now participating as a Community Clinical Oncology Program (CCOP).

‡CCOP inactive; now participating as an affiliate member.

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