Future Directions in Adjuvant Therapy for Rectal Cancer

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The US National Cancer Institute Gastrointestinal Intergroup has contributed to the development of chemotherapy and radiation regimens for the treatment of stage II and III rectal cancer. The first Intergroup trial demonstrated improvement in relapse-free and overall survival for patients who received protracted venous infusion fluorouracil (5-FU) with radiation compared to those treated with bolus 5-FU.

Through the years, the National Cancer Institute (NCI) Gastrointestinal Intergroup has designed a series of sequential clinical trials to explore chemotherapy and radiation regimens for patients with stage II and III rectal cancer. Intergroup participants have included Cancer and Leukemia Group B (CALGB), the Eastern Cooperative Oncology Group (ECOG), the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG), the National Surgical Adjuvant Breast and Bowel Project (NSABP), the North Central Cancer Treatment Group (NCCCTG), the Radiation Therapy Oncology Group (RTOG), and the Southwest Oncology Group (SWOG). Most recently, the American College of Surgery Oncology Group (ACOSOG) has joined the Intergroup network. This article summarizes the Gastrointestinal Intergroup continuum of rectal cancer trials, with an outline of current or planned future trials.

Improved Survival With Protracted Venous 5-FU Infusion

The first Intergroup trial of adjuvant therapy for rectal cancer, initiated in 1986, was coordinated by NCCTG and included CALGB, ECOG, RTOG, and SWOG.[1] A total of 660 patients with stage II or III rectal cancer were randomly assigned to receive bolus 5-FU with or without semustine (methyl-CCNU) for two cycles prior to radiation treatment. Protracted venous infusion 5-FU or bolus 5-FU was combined with radiation. After radiation, two additional 5-FU cycles with or without semustine were administered (Table 1). Results showed significantly improved relapse-free survival (63% vs 53%, P = .01) among 328 patients who received protracted venous infusion fluorouracil (5-FU) with radiation compared with 332 patients who received bolus 5-FU (Figure 1). Overall survival also favored the protracted venous infusion fluorouracil regimen (70% vs 60%, P = .005). The addition of semustine did not improve relapse-free or overall survival (P = .33, P = .61, respectively). The regimens were well tolerated, although diarrhea occurred more often in patients receiving protracted venous infusion fluorouracil with radiation and leukopenia was more predominant with the bolus regimen.

Identification of Tumor Risk Categories in INT 0114

Multiple analyses of results of the second Intergroup rectal cancer adjuvant therapy trial have been published (INT 0114). This study included the same cooperative group participants as the first, plus the NCIC-CTG.[2-4] It was designed to assess the role of biochemical modulation of 5-FU and that of levamisole (Ergamisol) in postoperative rectal cancer patients, building upon colon cancer adjuvant therapy data. Because the first Intergroup trial results were unavailable at the time of initiation, INT 0114 did not incorporate protracted venous 5-FU infusion during radiation. The same "sandwich" approach was taken, incorporating two cycles of chemotherapy prior to combined chemotherapy and radiation followed by two additional chemotherapy cycles. The four regimens tested included bolus 5-FU with or without leucovorin or levamisole vs the three drugs given as concomitant therapy (see Table 1).

Levamisole was not administered during radiation treatment, but 5-FU with or without leucovorin was. Accrual of 1,792 patients was completed in 1992, and 1,695 were evaluable. Patients had pathologically confirmed stage II or III rectal cancer (T3/4, N0-3, M0). With a median follow-up of 7.4 years,[4] overall disease-free survival was not statistically significantly different among the four treatment groups; however, there were significant differences by stage. High-risk (T3, N+; T4) and
low-risk (T1/2, N+; T3, N0) groups of patients were identified, who also had significant differences in 5- and 7-year survival rates ($P < .0001$). For example, 5- and 7-year survival rates were 76% vs 70% in the low-risk group, and 55% vs 45% in the high-risk group, respectively.

Results also showed a significant difference in risk of local failure in the low- and high-risk groups (9% vs 18%, respectively; $P < .0001$) (Table 2). The overall local failure rate increased over time (14% at 5 years vs 17% at 7 years). Patients with T4 disease had the highest risk of local failure, a 24% local failure rate at 5 years. This rate is of concern because it is significantly higher than reported in other studies (eg, study R-02).

Toxicities occurred significantly more frequently and were more severe in females than in males ($P < .001$). Grade 3 to 5 toxicity was noted in 81% of females and 69% of males, suggesting that females received a biologically higher dose. There was a nonsignificant trend to improved outcome in males who received 5-FU and leucovorin regimens; however, disease-free survival and local recurrence rates were not significantly different by gender. Overall survival was worse for males ($P = .03$).

Pathologic assessment of lymph nodes in the surgical specimens yielded important results. While no differences were noted among lymph node-positive patients, relapse-free and overall survival differed significantly among lymph node-negative patients as determined by the number of lymph nodes examined. For example, 5-year survival rate was 68% for patients with more than 0 but under 5 lymph nodes analyzed, compared with 82% for patients with > 14 lymph nodes analyzed (Table 3).[2]

**Ongoing Trial of Postoperative Infusional 5-FU (S9304)**

The third Intergroup trial, coordinated by SWOG (S9304), completed accrual in 2000 with 1,700 patients. The treatment design was based on the previous Intergroup trials. The control arm included bolus 5-FU given before and after radiation with protracted venous infusion 5-FU throughout radiation. An experimental arm incorporated protracted venous infusion 5-FU throughout the treatment course. The third arm included 5-FU, leucovorin, and levamisole, with bolus 5-FU and leucovorin during radiation, similar to INT 114 (see Table 1). Results of this trial, when available, should help define the role of infusional 5-FU for rectal cancer patients in the postoperative setting.

**NSABP Adjuvant Therapy Trials in Rectal Cancer**

The NSABP has conducted three trials of adjuvant therapy for rectal cancer. In the first trial (R-01), 574 patients with stage II or III rectal cancer were recruited from 1977 to 1986.[5] Patients were randomly assigned to receive no further therapy after surgery, postoperative adjuvant chemotherapy with MOF (semustine [methyl-CCNU], vincristine [Oncovin], and 5-FU), or postoperative radiation therapy without chemotherapy (see Table 1). Results demonstrated improved disease-free survival (42% vs 30%, $P = .006$) and overall survival (52% vs 43%, $P = .05$) in the MOF arm compared with the surgery-alone arm (Figure 2). Only males, however (particularly younger males), experienced this survival benefit. Radiation therapy was shown to reduce locoregional recurrence (25% vs 16%, $P = .06$), but provided no advantage in disease-free or overall survival.

In another trial conducted by the NSABP (R-02) from 1987 through 1992,[6] 694 stage II and III rectal cancer patients were randomly assigned to receive adjuvant chemotherapy with or without radiation. The adjuvant chemotherapy for females consisted of 5-FU and leucovorin; in males it was MOF vs 5-FU and leucovorin (see Table 1). As in R-01, the addition of radiation did not improve disease-free or overall survival, while it significantly reduced risk of locoregional recurrence from 13% to 8% at 5 years ($P = .02$) (Figure 3). Disease-free survival at 5 years was significantly improved for male patients who received 5-FU and leucovorin compared to MOF (55% vs 47%, respectively; $P = .009$), but overall survival was not affected (65% vs 62%, respectively; $P = .17$).

Diarrhea was noted more often in patients treated with 5-FU and leucovorin than in those receiving MOF, while leukopenia and thrombocytopenia were seen in more MOF than 5-FU/leucovorin patients. Grade 3 toxicities occurred more frequently in women than in men (34% vs 22%, respectively). The rate of grade 3 toxicities was comparable (approximately 30%) in patients receiving chemotherapy alone or the combination of radiation and 5-FU/leucovorin.

The NSABP attempted to compare preoperative chemoradiation to postoperative combined-modality therapy in the R-03 trial (see Table 1). A similar trial was attempted by the Intergroup (R-9401). Preoperative chemoradiation is of considerable interest because of the potential to down-stage patients, increasing the possibility of sphincter-sparing surgery. This approach may also reduce chronic toxicities because irradiated tissue can be removed during surgery. On the other hand,
postoperative therapy provides the opportunity for pathologic staging, thereby avoiding radiation therapy in patients with stage I disease. Accrual was not completed in either of these trials. Preliminary results of R-03 were reported at the annual American Society of Clinical Oncology meeting in 2001.[7] A total of 267 patients were enrolled from 1993 to 1999. At 1-year of follow-up, sphincter-saving surgery was possible in more patients who received preoperative 5-FU, leucovorin, and radiation than in those who received postoperative therapy (44% vs 34%, respectively). Among the preoperative therapy group, 23% had a complete clinical response and 16.2% had a complete pathologic response. More of the preoperatively treated patients had grade 4/5 toxicities (34% vs 22%, respectively), although disease-free survival was comparable in the preoperative (83%) and postoperative (78%) therapy arms.

It is doubtful that a large, definitive, randomized trial comparing preoperative chemoradiation to postoperative combined therapy will be achievable at least not in the United States. A recent meta-analysis of preoperative chemoradiation vs surgery alone demonstrated a significant reduction in overall mortality favoring preoperative radiation (14 randomized trials, \( P = .03 \)).[8] The meta-analysis also reviewed cancer-related mortality and local recurrence in 11 of the randomized trials, which revealed an advantage for both parameters favoring preoperative therapy \((P < .001\) for both parameters).

**Other Ongoing and Planned Trials**

The Medical Research Council (MRC) CR07 trial, being conducted in the United Kingdom, will attempt to explore further preoperative radiation vs selective postoperative chemo/radiotherapy. Patients will be randomly assigned to receive 25 Gy of radiation therapy (in five fractions) followed by surgery with local pathology assessment, and adjuvant therapy per physician discretion. The second study arm will also include pathologic assessment for postoperative patients. Select patients in the postoperative chemo/radiotherapy arm considered to be at high risk of local recurrence following surgery will receive 45 Gy of radiation therapy (in five fractions) plus a chemotherapy regimen chosen by their physician. The target accrual is 1,800 patients, and the study end point is local recurrence.

German researchers are planning a trial of 800 stage II and III rectal cancer patients who will receive preoperative treatment with 50.4 Gy of radiation plus continuous infusion 5-FU administered during the first and fifth weeks of radiation, or the same regimen postoperatively. In addition, both regimens will incorporate four cycles of 5-day 5-FU administered in the postoperative setting. Future and ongoing trials in the United States will evaluate the contribution of new agents and incorporate tissue acquisition for correlative laboratory projects. For example, ECOG is conducting a phase I trial for patients with T3 or T4 rectal carcinoma. Treatment consists of 50.4 Gy of radiation therapy with protracted venous infusion 5-FU and oxaliplatin, and postoperative weekly high-dose leucovorin plus 5-FU.

Another trial being planned by the entire US Gastrointestinal Intergroup, including NSABP, allows the physician and patient to choose between preoperative or postoperative chemoradiation. Chemotherapy administered during radiation may include capecitabine, bolus 5-FU with or without leucovorin or continuous infusion 5-FU. Randomization will compare a standard regimen of high-dose leucovorin (500 mg/m²) and 5-FU (500 mg/m²) administered weekly for 6 weeks for a total of four cycles, vs irinotecan, 5-FU, and leucovorin using a European infusion regimen (Figure 4). This every-other-week infusion schedule was chosen in part because of toxicity concerns with weekly bolus irinotecan and a suggestion that toxicity may be reduced with an infusion program.[9,10] Efforts to develop oral fluoropyrimidines as potential alternatives to protracted venous infusion 5-FU are continuing. Capecitabine (Xeloda), a prodrug converted to 5-FU by a three-enzyme pathway, is the only commercially available oral drug for the treatment of advanced colorectal cancer. In two large randomized trials for patients with advanced colorectal cancer, oral capecitabine produced a higher response rate than the 5-day bolus regimen of 5-FU/leucovorin (eg, 24.8% vs 15.5%, respectively; \( P = .005 \)) with a more favorable toxicity profile.[11,12] Furthermore, time to disease progression and survival rates were similar with the two regimens. In addition, capecitabine is viewed as a potential radiosensitizer because it results in selective concentration of 5-FU in tumor tissue, and 5-FU is a known radiation sensitization. Phase I data from Germany suggest using a phase II capecitabine dose of 825 mg/m² bid during radiation therapy for rectal cancer (50.4 Gy).[13] The NSABP has designed the R-04 trial, which is a preoperative chemoradiation trial comparing radiation (45 Gy) plus oral capecitabine at 825 mg/m² bid throughout radiation vs protracted venous infusion 5-FU at 225 mg/m² (Figure 5). End points include toxicity assessment and rates of pathologic

**Figure 5**
complete response and successful sphincter-saving surgery. A second randomization will include administration of epoetin alfa in conjunction with preoperative radiation and chemotherapy to determine whether it improves hemoglobin levels, quality of life, and local tumor control. Tumor tissue samples will be available to evaluate gene expression profiles.

The RTOG is exploring the use of irinotecan and continuous infusion 5-FU with preoperative radiation in patients with T3 or T4 rectal cancer (R-0012). This randomized phase II trial will evaluate protracted venous infusion 5-FU (250 mg/m²/d) with radiation versus irinotecan (50 mg/m² IV every week for four courses) plus protracted venous infusion 5-FU (225 mg/m²/d Monday through Friday) combined with radiation.

Many trials will continue to explore biologic correlates for predictors of survival and response and for potential therapeutic intervention. For example, in the R-01 study, thymidylate synthase (TS) expression was evaluated by immunohistochemistry: patients with low TS staining intensity had improved disease-free (49% vs 27%, P < .01, respectively) and overall survival (60% vs 40%, P < .01, respectively).[14] In addition, patients with high TS expression were more likely to benefit from chemotherapy: in high-TS patients, 54% of those treated with chemotherapy survived compared with 31% treated with surgery alone (P < .01). Prospective analyses of the predictive power of TS and other markers (eg, dihydropyrimidine dehydrogenase, thymidine phosphorylase) are planned for both Intergroup and NSABP trials.

Recent molecular data from trials assessing adjuvant therapy for colon cancer suggest that patients with retention of the 18q allele and those with microsatellite instability with TGF-beta1 RII mutation have significant improvement in 5-year survival when treated with 5-FU-based adjuvant therapy.[15] Trials of adjuvant therapy for both colon and rectal cancer will now prospectively analyze these and other molecular markers to clarify these provocative observations.

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