Combined-Modality Therapy for Rectal Cancer Using Irinotecan

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By Bruce D. Minsky, MD [2]

Preoperative or postoperative pelvic radiation plus concurrent fluorouracil-based chemotherapy is standard adjuvant treatment for patients with T3 and/or N1/2 rectal cancer. Newer chemotherapeutic regimens have been developed for the treatment of patients with metastatic disease.

Adjuvant Therapy With 5-FU-Based Regimens: Postoperative Therapy

Published results of randomized trials from the Gastrointestinal Tumor Study Group (GITSG)[1,2] and the Mayo/NCCTG (North Central Cancer Treatment Group, trial 79-47-51)[3] revealed significant improvements in local control and/or survival with postoperative radiation plus bolus 5-FU with or without semustine (methyl-CCNU) in patients with rectal cancer. Based on these findings, the National Cancer Institute Consensus Conference concluded in 1990 that combined-modality therapy with 5-FU-based regimens was the standard postoperative adjuvant treatment for patients with T3 and/or N1/2 rectal cancer.[4] While radiation therapy decreases local recurrence rates by half, the addition of 5-FU-based chemotherapy further decreases local recurrence rates to approximately 10% to 12%, and is responsible for increasing overall 5-year survival rates by approximately 10% to 15% above those achieved with surgery alone. Data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) R-02 randomized trial revealed that, although postoperative 5-FU-based chemotherapy alone decreased the local recurrence rate to 13%, the combination of chemotherapy plus radiation significantly decreased the local recurrence rate to 8%.[5]

Based on the positive results reported in the Mayo/NCCTG 86-47-51 trial that used continuous infusion 5-FU, the postoperative Intergroup trial INT 0144 was designed. The primary end point of this trial was to determine whether there was a benefit of continuous infusion 5-FU throughout the entire chemotherapy course (six cycles) as compared with continuous infusion only during the combined-modality segment (two cycles) and bolus 5-FU during the remaining four cycles. The control arm was bolus 5-FU/leucovorin/levamisole (Ergamisol). The trial closed to accrual in 2000 and the results are pending.

Until the results of INT 0144 are available, the choice of a postoperative adjuvant regimen in the nonprotocol setting remains controversial. If 5-FU alone is used, then it is probably best administered by continuous infusion. Otherwise, published data on 5-FU-based regimens indicate that they are probably equally effective; the choice of a regimen should be based on factors such as acute toxicity profiles and patient compliance.

Adjuvant Therapy With 5-FU-Based Regimens: Preoperative Therapy

Given the advantage of chemotherapy in the postoperative setting, several phase I/II preoperative combined-modality treatment programs have been developed. Most have used 5-FU-based chemotherapy. Retrospective data suggest that preoperative combined-modality therapy increases pathologic down-staging compared with preoperative radiation alone[6] and is associated with a lower incidence of acute toxicity compared with postoperative combined-modality therapy.[7] Preoperative therapy may also increase sphincter preservation. Seven series examining this issue have been reported. The studies were carried out in patients with clinically resectable rectal cancer whose surgeons had determined prospectively (based on a clinical office exam before beginning preoperative therapy) that they required abdominoperineal resection. All of the studied regimens
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used conventional radiation doses and techniques—three with radiation therapy alone[8-10] and four as combined-modality therapy.[11-14]

Results showed that the incidence of sphincter preservation after preoperative therapy was only 23% in the NSABP R-03 series[11] and 44% in the Lyon series[10]; however, approximately 70% of patients in the remaining five series had sphincter preservation. In the four series reporting functional outcome, the majority of patients (approximately 75%) had good to excellent sphincter outcome.

Some investigators have concluded that it is not necessary to add chemotherapy to preoperative radiation therapy. For example, in the Swedish Rectal Cancer Trial, patients received an intensive short course of preoperative radiation (5 Gy × 5) vs surgery alone.[15] Patients randomized to the preoperative radiation group had a significant decrease in local recurrence rate (12% vs 27%, $P < .001$) and an improved 5-year survival rate (58% vs 48%, $P = .004$).

These impressive results should be analyzed in the context of other published literature: First, given that the other 11 randomized trials of preoperative radiation therapy did not report a survival benefit, these data clearly need to be confirmed by additional studies.[16] Second, even if future trials confirm a survival benefit, there are other equally important end points in rectal cancer that need to be addressed. These include morbidity, mortality, and sphincter preservation and function, all of which are adversely affected by intensive short-course preoperative radiation.[17,18] Lastly, the Dutch CKVO 95-04 trial, in which a total mesorectal excision was mandated and patients underwent the same intensive short-course preoperative randomization to 5 Gy × 5 vs surgery alone, reported a significant decrease in local recurrence rate with preoperative radiation (2% vs 8%); however, the survival advantage reported in the Swedish Rectal Cancer Trial was not demonstrated.[19]

To address whether chemotherapy (bolus 5-FU/leucovorin) is necessary either concurrently with preoperative radiation and/or postoperatively, the European Organization for Research and Treatment of Cancer (EORTC) is conducting the definitive randomized trial (EORTC 22921). The results are pending at this time.

When the goal of preoperative therapy is sphincter preservation, conventional doses and techniques of radiation are recommended. These include multiple-field techniques to a total dose of 4,500 to 5,040 cGy at 180 cGy/fraction. Surgery should be performed a minimum of 4 weeks following completion of radiation. Unlike the intensive short course of radiation, this conventional design allows for recovery from acute side effects of radiation and enhances tumor down-staging. Data from the Lyon trial of preoperative radiation suggest that an interval greater than 2 weeks following completion of radiation increases the chance of downstaging.[10]

Clearly, randomized trials are needed to confirm the suggestion of decreased acute toxicity and enhanced sphincter preservation with preoperative therapy. Three randomized trials of preoperative vs postoperative combined modality therapy for clinically resectable T3 rectal cancer have been developed. Two are from the United States (INT 0147, NSABP R-03) and one is from Germany (CAO/ARO/AIO 94). The three studies used conventional doses and techniques of radiation therapy and concurrent 5-FU-based chemotherapy. A preoperative clinical assessment to determine the type of operation indicated was also required.

Unfortunately, low accrual has resulted in early closure of both the INT 0147 and NSABP R-03 trials. The German CAO/ARO/AIO 94 trial completed accrual of more than 800 patients. It is the only trial that can adequately address the issues of toxicity, efficacy, and sphincter preservation. A preliminary analysis of the NSABP R-03 trial, albeit underpowered with only 300 of the planned 900 patients accrued, revealed that patients who received preoperative therapy had a higher chance of having sphincter-sparing surgery and achieving disease-free status (44% vs 34%); however, this group also had an unexplained increase in grade 4 + toxicity (34% vs 23%).[20]

**Preoperative Therapy Using Newer Chemotherapeutic Regimens**

Several phase I/II trials of preoperative combined-modality therapy using newer chemotherapeutic agents such as raltitrexed (Tomudex),[21] UFT (uracil and tegafur)/leucovorin,[22] irinotecan,[23-27] oxaliplatin,[28] and capecitabine (Xeloda)[29] for patients with both resectable and unresectable disease are under way. Additional trials are also examining targeted therapies such as C225 and SU5416 (Iressa).

The significant survival advantage of irinotecan/5-FU/leucovorin vs 5-FU/leucovorin or irinotecan alone in patients with metastatic colorectal cancer has generated considerable interest in integrating irinotecan into preoperative combined-modality therapy regimens for rectal cancer.[30] Five phase I
or II trials are using combined irinotecan with radiation therapy. Two of the trials assessed irinotecan as monotherapy[23,24] and three assessed irinotecan combined with 5-FU.[25-27]

**Irinotecan Alone in Combined-Modality Therapy**

Minsky et al[23] reported results of a phase I trial of escalating doses of weekly irinotecan (8 to 13 mg/m² daily) administered weeks 1, 2, 4, and 5, plus concurrent radiation at 50.4 Gy in 28 patients with T3/4 rectal cancer. Among 16 patients treated at the recommended dose of 10 mg/m², the pathologic complete response rate was 5% and the grade 3 + acute toxicity rate was 29%. Because these results were inferior to those achieved previously with 5-FU/leucovorin-based regimens tested at Memorial Sloan-Kettering Cancer Center,[14] this single-agent irinotecan regimen was not tested in the phase II setting.

Another trial of irinotecan alone with preoperative radiation was reported by Volter and colleagues from Lausanne.[24] A total of 20 patients with T3/4 rectal cancer were entered in this phase I trial. The irinotecan dose was escalated from 30 to 105 mg/m² weekly × 3; hyperfractionated radiation (1.6 Gy bid to a total dose of 41.6 Gy) began on week 2. There was a high incidence of anastomotic leak and/or abscess (30%), which may have been partly related to the hyperfractionated radiation. The recommended dose level of irinotecan was 90 mg/m².

**Irinotecan Combination Regimens in Combined-Modality Therapy**

In the remaining three trials of irinotecan in combined-modality therapy, 5-FU was added to the preoperative radiation/irinotecan combination. Klautke and associates from the University of Rostock performed a phase II trial in 26 patients with various stages of rectal cancer.[26] Doses were fixed: irinotecan (40 mg/m² weekly), 5-FU (250 mg/m² by continuous infusion), and radiation therapy (50.4 Gy). Grade 3 + toxicities were hematologic (15%) and diarrhea (35%). The 15 patients who underwent surgery had an impressive complete response rate (26% pathologic and 26% clinical). Even higher complete response rates were reported in a phase II trial from Metha and coworkers from Stanford University Medical Center.[25] A total of 22 patients with T3 disease received irinotecan (50 mg/m² weekly × 4), 5-FU (200 mg/m² by continuous infusion), and radiation at 50.4 Gy. Grade 3 + acute toxicities were diarrhea (20%) and mucositis (15%). Among 18 patients who underwent surgery, the complete response rates were 67% pathologic and 17% clinical. The largest study was reported by Mitchell and colleagues from Thomas Jefferson University.[27] In this phase I trial, 46 patients with T3/4 rectal cancer received irinotecan (30 to 60 mg/m² weekly × 4), 5-FU (225 to 300 mg/m² by continuous infusion), and radiation therapy (45 to 54 Gy). This trial had both escalation and attenuation of the irinotecan, 5-FU, and radiation doses. Overall, there was a 24% pathologic complete response rate and a 15% clinical complete response rate. Interestingly, patients whose tumors had evidence of microsatellite instability had a higher complete response rate compared with those without microsatellite instability. The recommended dose levels were irinotecan at 50 mg/m² weekly × 4, 5-FU at 225 mg/m² daily × 5, and radiation therapy at 54 Gy. This regimen is being compared with a regimen of preoperative continuous infusion 5-FU plus radiation bid in the randomized phase II Radiation Therapy Oncology Group (RTOG) protocol R-0012.

**Conclusions**

In summary, the ideal irinotecan-based preoperative combined-modality regimen has not been determined. Results from phase I/II trials suggest that preoperative irinotecan plus radiation therapy is most effective when used in combination with 5-FU. This is consistent with data from the randomized trial that revealed a significant survival benefit in patients with advanced colorectal cancer.[30] While preliminary data reveal encouragingly high complete response rates, it should be emphasized that these rates need to be compared with those achievable with 5-FU-based therapy in randomized trials.

5-FU-based combined-modality therapy remains the standard of care for patients with T3/4 rectal cancer. In addition to irinotecan, a number of newer chemotherapeutic agents are available and should be examined in preoperative and postoperative combined-modality therapy regimens in patients with rectal cancer.

**References:**


2. Gastrointestinal Tumor Study Group: Adjuvant therapy of colon cancer: Results of a prospectively


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