Adjuvant Postoperative Combined-Modality Therapy for Rectal Cancer

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A number of advances have been made in the use of adjuvant chemotherapy for resectable rectal cancer. Whereas pelvic radiation therapy has been shown to increase local control in patients with clinically resectable

Introduction

For patients with T3 and/or nodepositive rectal cancer, postoperative combined-modality therapy significantly improves local control and survival. The focus of the Intergroup trials of postoperative combined radiation/chemotherapy has been the identification of the optimal chemotherapeutic agents and their method of administration. Data from ongoing and recently completed randomized trials in the postoperative setting will be discussed in this article. Preoperative chemotherapy in clinically resectable disease[1] and locally advanced/unresectable disease[2] has been previously reviewed and will not be examined here.

Postoperative Combined-Modality Therapy Rationale

The majority of patients with rectal cancer in the United States undergo surgery and, if necessary, receive postoperative adjuvant chemotherapy plus radiation therapy. The most compelling benefit achieved with this approach is the opportunity for pathologic staging. Although advances in preoperative imaging techniques allow for more accurate patient selection than was previously possible, surgical staging still remains the most common approach to treatment. Disadvantages include an increased amount of small bowel in the radiation field,[3] a potentially hypoxic postsurgical bed, and, if the patient has undergone an abdominoperineal resection, extension of the radiation field to include the perineal scar.

Results

Based on nonrandomized data, conventional doses of radiation alone (4,500 to 5,500 cGy) have been reported to decrease local failure to between 4% and 31% in patients with stage T3-4, N0, M0 rectal cancer and to between 8% and 53% in patients with stage T3-4, N1-2, M0 disease.[4-6] Data from five randomized trials failed to show improvement in overall survival when adjuvant postoperative radiation therapy was used alone in stages T3 and/or N1-2 rectal cancer,[7-13] although local failure rates decreased in two trials (National Surgical Adjuvant Breast and Bowel Project [NSABP] R-01: 16% vs 25%, P = .06[7]; and the Medical Research Council: 21% vs 34%, P = .001[12]). Of the five trials, the NSABP is the only one in which radiation was delivered as a continuous course with full doses and modern techniques.

Randomized trials from the Gastrointestinal Tumor Study Group (GITSG)[14] and Mayo/North Central Cancer Treatment Group (NCCTG) 79-47-51[15] revealed a significant improvement in local control (GITSG and Mayo/NCCTG) and survival (GITSG and Mayo/NCCTG) among patients with rectal cancer who received postoperative radiation plus bolus 5-fluorouracil (5-FU)/semustine (MeCCNU). Based on these results, in 1990, the National Cancer Institute Consensus Conference concluded that combined-modality therapy is the standard postoperative adjuvant treatment for patients with T3 and/or N+ disease.[16] Since that time, Intergroup postoperative trials have focused on identifying the optimal chemotherapeutic agents and their methods of administration.

In a follow-up study to NCCTG 79-47-51, the Mayo/NCCTG designed a four-arm trial (86-47-51) to determine if MeCCNU benefits the treatment regimen and to compare the relative efficacy of bolus vs continuous-infusion 5-FU. Since MeCCNU did not improve local control or survival, it is no longer recommended for use in the adjuvant treatment of rectal cancer.[17]
Continuous Infusion vs Bolus
Compared with bolus 5-FU (±MeCCNU), patients who received continuous-infusion 5-FU experienced a significant decrease in overall tumor relapse rate (37% vs 47%, P = .01) and distant metastasis (31% vs 40%, P = .03), and realized an improvement in 4-year survival (70% vs 60%, P = .005). These data suggest that single-agent 5-FU is more effective as a continuous infusion than as a bolus when combined with radiation therapy. There also are differences in the acute toxicities of continuous-infusion and bolus 5-FU. For example, during combined-modality treatment, patients who received continuous-infusion 5-FU had significantly more grade 3+ diarrhea (24% vs 14%, P < .01) but significantly less grade 3+ leukopenia (2% vs 11%, P < .01) than did patients receiving bolus 5-FU.

Building on the positive results reported with continuous-infusion 5-FU, an Intergroup trial (INT 0144) was designed to determine whether there is benefit associated with postoperative continuous-infusion 5-FU throughout the complete 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. A control arm (arm 4) included bolus 5-FU/levamisole (Ergamisol). The trial opened in 1993 and is actively accruing patients.

The NSABP R-01 was a three-arm trial comparing outcome with postoperative MeCCNU/vincristine (Oncovin)/5-FU (MOF) vs radiation therapy vs surgery alone. The investigators reported a significant improvement in 5-year disease-free survival (42% vs 30%, P = .006) and overall survival (53% vs 43%, P = .05) among patients receiving postoperative MOF chemotherapy compared with those undergoing surgery alone.[7] The advantage in overall survival associated with chemotherapy was most evident in males (60% vs 37%), particularly males < 65 years of age (44% vs 26%). In contrast, chemotherapy was associated with a lower survival than surgery alone among treated women (37% vs 54%).

Randomized by Gender
The NSABP subsequently designed a four-arm trial (R-02) in which patients were randomized, depending on gender, to either MOF ± radiation or 5-FU/calcium folinate ± radiation. Preliminary analysis revealed a significant decrease in local failure in the two combined-modality therapy arms compared with chemotherapy alone (7% vs 11%, P = .045).[18] Median survival, however, did not improve. Other results are pending.

The most recent Intergroup trial was INT 0114.[19] In this four-arm trial, all patients received six cycles of postoperative chemotherapy plus concurrent radiation therapy during cycles 3 and 4, with the goal of determining whether 5-FU-based combination chemotherapy (5-FU/low-dose calcium folinate vs 5-FU/levamisole vs 5-FU/calcium folinate/levamisole) is superior to single-agent 5-FU. At a median follow-up of 4 years, there were no significant differences in local control or survival between the four arms (Table 1). Although the total incidence of acute grade 3+ toxicity was similar for the four arms, there were differences between the regimens. The 5-FU arm had a higher incidence of hematologic toxicity, whereas the 5-FU/levamisole arm had a higher incidence of diarrhea.[19] A subset analysis revealed that women had a significantly greater incidence of acute grade 3+ toxicity than did men in all four arms. The reason for this difference in toxicity by gender is uncertain.

The adjuvant regimen of choice in the nonprotocol setting remains unclear. Given that results from the Mayo/NCCTG 86-47-51 trial suggested that continuous-infusion 5-FU is more effective than bolus 5-FU, regardless of modulation with calcium folinate, levamisole, or both (INT 0114), continuous-infusion 5-FU might seem the preferred regimen. A direct comparison of continuous-infusion 5-FU with bolus 5-FU/calcium folinate/levamisole in INT 0144 has not yet yielded results, however. Therefore, acceptable regimens for patients not enrolled in a clinical trial at this time include either continuous-infusion 5-FU or bolus 5-FU plus modulation with calcium folinate. These regimens probably have equal efficacy and the choice of a regimen should be based on factors such as their acute toxicity profiles and patient compliance.

Combined-Modality Therapy With New Chemotherapeutic Agents
Among the new chemotherapeutic agents with activity in colorectal cancer either in development or approved by the Food and Drug Administration are CPT-11 (Camptosar), raltitrexed (Tomudex), trimetrexate (Neutrexin), oxaliplatin, and UFT plus oral calcium folinate (Orzel).[20-23] Clinical phase I and II trials examining the combination of some of these agents with pelvic radiation are under way.[24,25] Marsh et al have combined chronobiologically shaped 5-FU infusion with preoperative radiation therapy in the treatment of patients with unresectable disease.[26]

Postoperative UFT/Calcium Folinate Plus Radiation Therapy
A phase I dose-escalation trial of postoperative treatment with UFT/oral calcium folinate plus concurrent radiation therapy for patients with primary or recurrent rectal or colon cancer has been developed at Memorial Sloan-Kettering Cancer Center (Figure 1). The goal of this study is to compare the efficacy of the oral regimen of UFT/oral calcium folinate (Orzel) with a continuous-infusion 5-FU-based regimen in combined-modality therapy. The doses and schedules of drugs are similar to those used in current Intergroup postoperative adjuvant rectal trials. Patients receive two cycles of 5-FU-based chemotherapy, followed by two cycles concurrent with pelvic radiation and a 4-week rest, after which two additional cycles are administered.

Since the schedule of chemotherapy with UFT/oral calcium folinate (28 days of daily treatment followed by a 1-week rest) is different from both bolus and continuous-infusion 5-FU-based regimens, modifications have been made to reflect these differences. Two separate determinations of the maximum tolerated dose will be made. First, the maximum tolerated dose of UFT (tegafur and uracil) with fixed doses of oral calcium folinate and concurrent radiation will be defined. Then the maximum tolerated dose of UFT with fixed doses of oral calcium folinate following completion of concurrent UFT/oral calcium folinate and radiation therapy will be determined.

During cycle 1 (before radiation therapy), chemotherapy is delivered at the full recommended dose with no dose escalation: calcium folinate 25 mg orally (po) every 8 hours, concurrent with each UFT dose of 300 mg/m²/day for 28 consecutive days. Each cycle is followed by a 1-week rest. During chemotherapy cycle 2 (with radiation therapy), the calcium folinate dose is fixed at 25 mg po every 8 hours and is given concurrently with each UFT dose, which begins lower than the recommended dose at 175 mg/m²/day po in divided doses every 8 hours for 28 consecutive days followed by a 2-week rest.

Since the maximum tolerated dose of UFT/oral calcium folinate may be different when given with concurrent radiation compared with postirradiation, the maximum tolerated dose of UFT/oral calcium folinate is determined during cycle 2 (MTD 1) independently of cycles 3 to 5 of chemotherapy (MTD 2). To determine each maximum tolerated dose, radiation and calcium folinate doses are kept constant and the UFT dose alone is increased 50 mg/m²/day with each subsequent level until the maximum tolerated dose is reached. The trial is open to accrual.

**Adjuvant Therapy Following Total Mesorectal Resection**

Some physicians contend that if patients undergo more extensive surgery, postoperative adjuvant therapy is not necessary. In one series, total mesorectal excision, involving sharp dissection around the integral mesentery of the hind gut, decreased the local recurrence rate to 5%.[27] These data must be interpreted with caution, however, because they derive from personal series, include highly selected patients, and the procedure allows the identification and exclusion of patients with more advanced disease.

In comparison, patients treated in the adjuvant trials usually did not receive mesorectal excision.[28,29] Furthermore, some patients received adjuvant radiation therapy ± chemotherapy (ie, 28% in the series from Enker et al.[30] and 18% in the series by Haas-Kock et al.[31]). Total mesorectal excision also may be associated with higher complication rates. In the Basingstoke Hospital experience, 16% of 219 patients who underwent a total mesorectal resection had anastomotic leaks.[32] In the series from Aitken, operative deaths were excluded from the analysis.[33]

Although total mesorectal excision is controversial, advocates of the procedure have increased awareness of the importance of surgical technique. Careful surgical techniques are central to the successful management of rectal cancer. However, they should be considered a valuable component of therapy, not competitive with adjuvant therapy. The relative benefits and risks of total mesorectal excision (focusing on local control, survival, sphincter preservation and function, surgical morbidity and mortality, and quality of life) need to be more carefully defined.

**Summary**

The standard management of patients with T3 and/or N1-3 rectal cancer is postoperative combined-modality therapy, including six cycles of 5-FU-based chemotherapy and concurrent pelvic irradiation during cycles 3 and 4. Ongoing trials will help determine the ideal chemotherapeutic agents and methods of administration.

**References:**


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