Current Status of Adjuvant Therapy for Colorectal Cancer

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Adjuvant therapy with chemotherapy and/or radiation therapy in addition to surgery improves outcome for patients with high-risk carcinomas of the colon or rectum. For colon cancer, fluorouracil (5-FU) combined with leucovorin is a current standard of care that improves long-term survival. A recent European trial (MOSAIC) has documented significant improvement in 3-year disease-free survival when oxaliplatin (Eloxatin) was added to infusional 5-FU and leucovorin in the FOLFOX regimen. Two US cooperative group trials will evaluate the addition of antiangiogenesis therapy with bevacizumab (Avastin) to chemotherapy. A third trial will evaluate FOLFOX, irinotecan (Camptosar) combined with infusional 5-FU and leucovorin (FOLFIRI), and the sequential use of FOLFOX followed by FOLFIRI. In rectal cancer, postoperative 5-FU–based chemotherapy combined with irradiation can improve both local tumor control and survival. The German Rectal Cancer Group has recently reported that preoperative combined-modality therapy is less toxic and more effective in preventing local tumor relapse compared to similar treatment given postoperatively. A coordinated pair of cooperative group clinical trials will evaluate oral capecitabine (Xeloda) as a radiation enhancer in the preoperative setting, and the FOLFOX and FOLFIRI regimens compared to 5-FU and leucovorin following surgery. Predictive and prognostic molecular markers will be studied in these new adjuvant therapy clinical trials for both colon and rectal cancer with the goal of developing future regimens tailored to individual patients. There has been a recent and dramatic increase in the pace of drug development for colorectal cancer which holds promise to further improve curative therapy as part of a multidisciplinary approach in the surgical adjuvant setting.

In 2004, surgery remains the primary curative modality for treatment of cancers of the colon or rectum. It has been shown that outcome relates to the experience of the surgeon, particularly for cancer of the rectum. Furthermore, careful histopathologic evaluation of resected tumor specimens, including radial tumor margins and lymph nodes, is important in prognosis and selection of patients for adjuvant therapy. In spite of complete gross tumor removal (ie, "curative resection"), many patients will relapse and die of recurrent colorectal cancer. The risk of relapse following surgery correlates with stage of disease, and ranges from roughly 20% to 30% for stage II disease (Tx, N0) to 50% to 80% for stage III disease (Tx, N+). For patients with rectal cancer it has been shown that local tumor recurrence is highly correlated with both the depth of tumor penetration and the number of regional lymph nodes involved by metastatic disease.[1] There is general consensus that adjuvant therapy is indicated for most patients with stage III cancer of the colon or rectum and stage II cancer of the rectum. Opinion is divided whether patients with stage II colon cancer derive sufficient benefit to warrant adjuvant therapy on a routine basis.[2,3] The vast majority of tumor relapses occur in sites distant from the primary tumor following surgery for colon cancer. Therefore, the thrust of adjuvant therapy for colon cancer is on systemic treatment aimed at eradicating micrometastatic disease; radiation therapy has a very limited role. On the other hand, local tumor failure in the pelvis is a significant clinical problem for patients with rectal cancer treated with surgery alone, providing a rationale for regional adjuvant radiation therapy. Because distant metastasis is the predominant mode of tumor relapse in patients with rectal cancer who receive aggressive local therapy,[4,5] improved systemic therapy is also a principal focus of rectal cancer adjuvant trials. This paper will first provide a very brief overview of surgical adjuvant therapy for cancer of the colon, and then examine adjuvant therapy for rectal cancer. Emphasis will be placed on the current state-of-the-art and research questions that will be addressed in the next generation of cooperative group clinical trials in the United States. Adjuvant Therapy of Colon Cancer Substantive advances have been made in the surgical adjuvant therapy of colon cancer over the past 15 years. Fluorouracil (5-FU) and levamisole (Ergamisol) was shown by prospectively randomized clinical trials to significantly improve time to tumor recurrence and overall survival for patients with stage III (node-positive, Dukes 'C') colon cancer. The initial results of a North Central Cancer Treatment Group (NCCCTG) clinical trial[6] were confirmed by an Intergroup study published in 1990.[7] These results were endorsed by a National Institutes of Health (NIH) Consensus Development Panel, the US Food and Drug Administration (FDA) approved levamisole in combination with 5-FU for patients with stage III colon...
cancer, and this regimen became the standard of care in the United States. Meanwhile, the concept of biochemical modulation of 5-FU by leucovorin was shown to improve the efficacy of palliative chemotherapy for patients with advanced colorectal cancer compared to 5-FU alone.[8,9] Several cooperative group studies then evaluated 5-FU and leucovorin compared to observation following surgery in the adjuvant setting[10,11] and demonstrated an improvement in recurrence-free interval and overall survival. Several cooperative group studies then set out to compare 5-FU plus leucovamisole to 5-FU plus leucovorin, and combined modulation of 5-FU by both leucamisole and leucovorin.[12-14] This set of studies indicated at least equivalent (if not better) results with 5-FU and leucovorin, that the duration of adjuvant therapy could safely be reduced from 12 months to 6 months without decreasing survival benefits, and that the addition of leuvamisole to 5-FU plus leucovorin increased toxicity without improving outcome. Accordingly, the combination of 5-FU and leucovorin given for approximately 6 months has become the standard approach for surgical adjuvant therapy of colon cancer in the United States. The drugs irinotecan (Camptosar) and oxaliplatin (Eloxatin) have more recently been shown to significantly improve the palliative therapy of advanced colorectal cancer when combined with 5-FU and leucovorin.[15-18] Each of these drugs has now been approved by the FDA for the first and second-line treatment of metastatic colorectal cancer. The results of ongoing surgical adjuvant trials of irinotecan combined with 5-FU and leucovorin have not yet been reported, but are anticipated in the near future. However, very encouraging results from a large adjuvant study that evaluated oxaliplatin in combination with 5-FU and leucovorin were presented at the annual meeting of the American Society of Clinical Oncology (ASCO) in 2003.[19] This study demonstrated a significant improvement in 3-year disease-free survival for patients with stage II or III colon cancer who received treatment with a FOLFOX regimen compared to patients receiving infusional 5-FU plus leucovorin on the same schedule without oxaliplatin. Follow-up was sufficiently long to reliably conclude that disease-free survival has been significantly improved with the addition of oxaliplatin, but not long enough to determine the impact on overall 5-year survival. Statistical analyses are under way to determine under what conditions improvement in disease-free survival may be a reliable predictor of survival benefit, and investigators are considering whether disease-free survival may represent clinical benefit in its own right. Nevertheless, the use of oxaliplatin in the surgical adjuvant setting for patients with colon cancer has not been approved by the FDA at the time of this writing. For many years there has been great interest in antiangiogenesis therapy directed at tumor vasculature as a method of cancer treatment. Many preclinical models have shown that this approach had promise, but its value in the treatment of human cancer was not demonstrated until very recently. Bevacizumab (Avastin) is a humanized genetically engineered monoclonal antibody directed against vascular endothelial growth factor. The results of a phase III trial of bevacizumab added to chemotherapy with irinotecan, 5-FU, and leucovorin compared to the same chemotherapy alone for the first-line treatment of patients with metastatic colorectal cancer were reported at the 2003 ASCO meeting.[20] Highly significant improvements in tumor response rates, time to tumor progression, and survival were seen among patients receiving bevacizumab with chemotherapy. The FDA has approved bevacizumab combined with 5-FU-based chemotherapy for the first-line treatment of patients with metastatic colorectal cancer. These very positive results also provide a strong rationale for the study of bevacizumab in the colon cancer surgical adjuvant setting. Another monoclonal antibody with activity in advanced colorectal cancer is cetuximab (Erbitux). This antibody binds the epidermal growth factor receptor. It has been shown to cause tumor regression, especially when combined with irinotecan, in patients with metastatic colon cancer previously treated with chemotherapy.[21,22] It is approved by the FDA for second-line treatment of metastatic colorectal cancer, and is also a candidate for investigation in the surgical adjuvant setting. **Current and Planned Cooperative Group Trials:**

**Colon Cancer** The dramatic benefit seen with the addition of bevacizumab to 5-FU-based chemotherapy in metastatic colorectal cancer serves as the basis for two colon cancer adjuvant therapy clinical trials. The first will be conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) in patients with stage II or III colon cancer. The plan is that all patients will receive chemotherapy with oxaliplatin, infusional 5-FU, and leucovorin (specifically, the mFOLFOX6 treatment schedule) for 6 months. Half of the patients will be randomized to receive bevacizumab in addition for a period of 1 year. The second trial will be coordinated by the Eastern Cooperative Oncology Group (ECOG) on behalf of the GI Intergroup. It will focus on high-risk stage II patients (identified by molecular markers expressed on the resected tumor). It is planned that all patients will receive 6 months of mFOLFOX6, and half of the patients will also receive bevacizumab for a period of 1 year. Analysis of numerous clinical trials of chemotherapy for metastatic colorectal cancer has indicated that the longest survival has been seen in patients who were able to receive multiple
effective agents as first-line or "salvage" therapy. Although this type of analysis is subject to selection bias, it raises the possibility that improved long-term survival might be seen in the adjuvant setting if multiple effective drugs were used "up front." The NCCTG will coordinate an Intergroup clinical trial that will evaluate this concept in patients with stage III colon cancer. Patients will be randomly assigned to receive treatment with oxaliplatin plus infusional 5-FU plus leucovorin (mFOLFOX6), irinotecan plus infusional 5-FU plus leucovorin (FOLFIIRI), or mFOLFOX6 followed by FOLFIRI. Treatment duration will be 6 months in each of the treatment arms. As can be seen, this trial will also afford the opportunity to directly compare irinotecan and oxaliplatin when combined with infusional 5-FU plus leucovorin. **Adjuvant Therapy of Rectal Cancer**

The same NIH Consensus Development Panel that recommended 5-FU and levamisole as adjuvant therapy for stage III colon cancer in 1990 also recommended postoperative combined-modality therapy with chemotherapy and irradiation for patients with stage II or III rectal cancer. These recommendations were based largely on the results of randomized clinical trials performed by the Gastrointestinal Tumor Study Group[23] and the NCCTG.[24] Improved local tumor control in the pelvis and improved survival were seen when both modalities were used compared to surgery or surgery followed by radiation therapy. The NSABP subsequently reported that chemotherapy could improve disease-free survival,[25] and that the addition of radiation therapy to chemotherapy could significantly decrease local tumor recurrence.[26] An Intergroup trial reported in 1994 demonstrated that the prolonged (continuous) infusion of 5-FU during radiation decreased local tumor failure and improved survival compared to bolus 5-FU during radiation as a component of sequential combined-modality postoperative adjuvant therapy.[4] This strategy was adopted by many oncologists as a standard approach to adjuvant therapy of rectal cancer in the United States. The improvements seen with adjuvant therapy of colon cancer using 5-FU modulated by either levamisole or leucovorin were tested in an Intergroup trial compared to the use of single-agent 5-FU as the systemic therapy.[5]

Interestingly, there were no significant differences between single-agent 5-FU and 5-FU modulated by levamisole, levamisole, or the combination when used as a component of postoperative combined-modality therapy for rectal cancer. An Intergroup clinical trial coordinated by the Southwest Oncology Group that further evaluated the continuous 5-FU infusion theme was reported at the 2003 ASCO annual meeting.[27] This study evaluated continuous infusion 5-FU given during radiation only; infusion 5-FU before, during, and after radiation; and a regimen using bolus 5-FU modulated by levamisole and leucovorin without continuous infusion 5-FU at all. There was no significant difference in outcome between these approaches. Because previous studies failed to show any advantage in adding levamisole to leucovorin-modulated 5-FU in the adjuvant therapy of colon cancer or rectal cancer, levamisole cannot be recommended. With the exception of levamisole, any of the regimens in this study would be reasonable as postoperative adjuvant therapy for patients with rectal cancer. It should be noted that there may be advantages in avoiding the need for a central venous catheter and ambulatory infusion pump necessary for the administration of continuous infusion 5-FU by selecting the 5-FU plus leucovorin chemotherapy regimen. Preoperative (neoadjuvant) therapy has been preferred over postoperative adjuvant therapy for rectal cancer in Europe for some period of time. Studies in the United States have also suggested less acute and chronic gastrointestinal toxicity from preoperative radiation therapy,[28] and practice patterns are shifting toward preoperative radiation therapy in this country. A prospectively randomized clinical trial comparing preoperative vs postoperative combined-modality therapy was reported at the 2003 meeting of the American Society of Therapeutic Radiology by the German Rectal Cancer Group.[29]

This study demonstrated a significant reduction in local tumor relapse and less toxicity from preoperative combined-modality therapy as compared to similar treatment given postoperatively. These data provide a strong rationale to consider sequencing radiation prior to surgery for operable T3 or T4 rectal cancer. **Current and Planned Cooperative Group Trials: Rectal Cancer**

Members of the North American cooperative groups investigating adjuvant therapy for rectal cancer have designed two complementary clinical trials to address several critical questions. The first is an Intergroup study coordinated by ECOG. It will examine whether the addition of either oxaliplatin or irinotecan to the 5-FU plus leucovorin combination (using FOLFOX or FOLFIRI) will be more effective than 5-FU plus leucovorin in decreasing the rate of distant metastasis, thereby improving long-term survival. This study will allow radiation therapy with concomitant fluorinated pyrimidine chemotherapy to be given either preoperatively or postoperatively at the discretion of the patient and physician. The second study is an NSABP study that will evaluate oral capecitabine (Xeloda) as an enhancer of radiation therapy in the preoperative setting. The goal is to improve the tolerability and effectiveness of combined-modality therapy in preventing local tumor failure by using a drug preferentially activated in tumor tissue. Patients participating in this trial will also be eligible to...
participate in the ECOG trial that is addressing systemic tumor failure as described above. **Summary and Conclusions**

The therapy of colorectal cancer has advanced dramatically since 1990. The long-term survival rates of patients with primary colon cancer have unequivocally improved with the use of effective surgical adjuvant chemotherapy. The incorporation of oxaliplatin, irinotecan, and the monoclonal antibodies bevacizumab and cetuximab into surgical adjuvant regimens holds the prospect for further advances in the next few years. From a longer-range perspective, one can realistically anticipate additional new agents emanating from the pharmaceutical industry pipeline that will further add to our armamentarium. Local tumor recurrences, which can produce devastating symptoms for patients with primary rectal cancer, have been greatly reduced with the use of combined radiation therapy and chemotherapy when added to complete surgical resection. There is evidence that preoperative combined-modality therapy is better tolerated and more effective in providing local tumor control compared to postoperative adjuvant therapy. Hopefully, incorporation of new drugs shown to be effective in metastatic colorectal cancer will also decrease the problem of distant metastasis when used in the surgical adjuvant setting for patients with rectal cancer. Finally, it is important never to be satisfied with the status quo. Correlative science studies aimed at identifying prognostic and predictive markers must be undertaken to facilitate selection of patients that truly need surgical adjuvant therapy, and specific treatments best suited to individual patients. As in the past, future progress will depend on well-conducted clinical trials supported by community physicians and patients alike. We presently have the good fortune of a number of promising avenues to investigate.

**Disclosures:** The author is on the scientific advisory boards of Sanofi Pharmaceuticals, Novartis Pharmaceuticals, and Genentech.

**References:**


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