Colon and rectal cancer remains the second leading cause of cancer mortality in the United States. In 1999, an estimated 130,000 new cases and 50,000 deaths will occur. Curing patients with colorectal cancer depends on early diagnosis, successful operation and the appropriate use of adjuvant therapy. Currently, the most important aspect of therapy is appropriate and successful operation. In the past decade, though, adjuvant therapy has begun to play an increasingly important role. In 1990, the National Institutes of Health Consensus Panel recommended that chemotherapy become the "standard" adjuvant treatment for Stage III colon cancer. The panel also recommended adjuvant chemoradiation therapy for patients with Stage II or Stage III rectal cancer. Stage III colon cancer patients and Stage II and III rectal cancer patients are the patients at higher risk for recurrence following curative operation. The panel made their recommendations based on several studies that had shown an improved survival with adjuvant therapy for these higher risk patients. Presumably, the improved survival with adjuvant therapy in these patients was due to successful elimination of micrometastasis present but not removed at the time of surgery. Since these early trials, further studies have sought to clarify which patients, which agents, and which treatment regimens were most effective in improving survival in patients with colorectal cancer. In 1999, many questions remained to be answered, and investigations continue to evolve as more and more information is gained from ongoing randomized controlled trials. This review will update the current role of adjuvant therapy for colon and rectal cancer.

Colorectal Cancer
With very few exceptions, initial therapy for colon cancer is adequate surgical resection. Subsequent surgical and pathologic staging will dictate the need for adjuvant therapy. Currently, Stage I colon cancer patients enjoy a high cure rate after surgery alone (>80%), and there is no evidence that these patients will benefit from any adjuvant therapy. Large randomized clinical trials have been more interested in Stage II and Stage III colon cancer patients whose cure rate can be as low as 30% after surgery alone. Early chemotherapy trials for colon cancer used the chemotherapeutic agents available at the time. Eventually, fluorinated pyrimidines (5-Fluorouracil or 5-FU) were shown to have activity against metastatic colorectal cancer. This finding led to several trials evaluating 5-FU as adjuvant therapy for high risk patients after surgery (Stage II and III colon cancer). In 1988, Buyse and colleagues published a meta-analysis of all randomized controlled trials of adjuvant therapy with 5-FU for colorectal cancer. This analysis revealed a small overall survival benefit for adjuvant therapy with 5-FU. This finding was confirmed in a large randomized trial reported by the National Surgical and Adjuvant Breast and Bowel Project (NSABP).

Based on encouraging early results with levamisole (a presumed immunostimulant) in combination with 5-FU in a small trial of patients with colon cancer, a large trial was conducted through the intergroup mechanism. This intergroup trial enrolled over 300 Dukes' B2 and 900 Dukes' C patients. In the Dukes' B2 group of patients, although slightly more patients who had received adjuvant therapy with 5-FU and levamisole were alive after 7 years than those who had not (79% vs. 71%), this difference was not significant, and it would be difficult to recommend adjuvant chemotherapy to all patients with Dukes' B2 colon cancer on the basis of this study. On the other hand, in the Dukes' C group 5 year survival was 44% after operation alone compared to 61% after operation plus adjuvant therapy with 5-FU plus levamisole. This difference in survival was statistically and clinically significant. This 39% reduction in mortality would be expected to save ~6,000 lives per year in the United States if all Dukes' C patients were to receive this
adjunct chemotherapy regimen. Consequently, in 1990 the National Cancer Institute Consensus Conference on adjuvant therapy for colon cancer recommended that 5-FU plus levamisole be standard therapy for node-positive colon cancer (Dukes' C or Stage III).(2)

Because the mechanism of action of levamisole remains unknown, it has been proposed that levamisole may not be an active agent at all. Since the intergroup trial, several other trials have been conducted evaluating 5-FU plus levamisole and 5-FU plus leucovorin. These trials have found that in Dukes' C colon cancer patients, adjuvant therapy with 5-FU plus low or high dose leucovorin for 6 months is at least as effective as 5-FU plus levamisole for 1 year.(8)

The role of adjuvant chemotherapy for patients with Dukes' B2 colon cancer remains unclear. The intergroup trial showed only a marginal (not statistically significant) improvement in survival with adjuvant therapy. Perhaps some but not all Dukes' B2 colon cancer patients would benefit from adjuvant treatment and further stratification of low and high risk Dukes' B2 patients is necessary. Factors that have been found to be correlated with a higher risk of recurrence include but are not limited to perforation, poorly differentiated histology, high S-phase fraction and presence of 18q deletion. Although there currently is no good data demonstrating a survival benefit for Dukes' B2 patients with one or more "high risk" factors, it would seem reasonable to offer chemotherapy to younger patients with high risk Dukes' B2 colon cancer. Future clinical trials hopefully will resolve which Dukes' B2 patients and which chemotherapeutic regimens are most effective in improving survival in this group of patients.

Colon cancer patients with metastatic disease (Dukes' D or Stage IV) may benefit from further surgery such as liver or lung resection for localized metastasis. With respect to adjuvant therapy in patients with Dukes' D colon cancer, 5-FU plus leucovorin in younger patients or patients with symptomatic disease has been shown to stabilize the disease and improve quality of life.(9) For patients who fail 5-FU based therapy for metastatic disease, a new agent, irinotecan or CPT-11 has been shown to be effective and has recently been approved for use in the United States for patients with metastatic disease who have failed standard 5-FU therapy.

Although 5-FU based chemotherapy for adjuvant treatment of colon cancer is clearly effective in reducing mortality, adjuvant therapy is far from curing every patient. More effective adjuvant regimens are needed and investigators are currently exploring a number of different approaches. Portal vein infusion with 5-FU has been investigated in several large trials. These trials have shown a small but statistically significant survival advantage for portal vein infusion of 5-FU for 1 week following surgery versus surgery alone.(10) Unfortunately, these studies have not shown a reduction in hepatic metastasis between the treatment and no treatment groups suggesting that the improvement in survival with treatment may be the result of the systemic activity of the intraportally administered chemotherapy.

Intraperitoneal chemotherapy results in high drug concentrations in both the portal vein and the peritoneal cavity. This approach has been shown to reduce the incidence of peritoneal metastasis but not mortality in a study reported by Sugarbaker. Investigators continue to evaluate intraperitoneal chemotherapy for colon cancer. Although the preliminary results are encouraging, long-term randomized controlled trials need to be completed to determine if intraperitoneal chemotherapy adds any benefit over systemic chemotherapy.

Adjuvant therapy using monoclonal antibodies against colon cancer cells has also been recently investigated by Riethmüller and colleagues. In this trial, the 17-1A antibody was given postoperatively in 5 doses over 4 months. Survival was significantly improved in the group receiving the antibody (30% reduction in mortality). Adjuvant therapy with monoclonal antibodies deserves further investigation.
Antitumor vaccines administered to enhance the body's immunologic response to colon cancer have also been developed. Although only a small number of patients have been treated, Hoover et al. have shown that survival is improved in patients with colon cancer who received immunologic stimulation with a combination of BCG and a preparation of their own irradiated tumor cells. Additional studies are necessary to determine the role of antitumor vaccines against colon cancer.

**Rectal Cancer**

Adjuvant therapy of rectal cancer utilizes both radiation therapy and chemotherapy. Rectal cancer patients with either tumor penetration through the bowel wall (T3) or positive lymph nodes (N1) are recommended to undergo adjuvant chemoradiation. Radiation therapy has been shown to decrease local recurrence, increase the chance of sphincter preservation and, with locally advanced tumors, increase the resectability rate. Chemotherapy administered concomitantly with radiation enhances the effectiveness of the radiation and improves patient survival presumably by eradicating distant microscopic metastasis. Adjuvant therapy for rectal cancer can be administered either preoperatively or postoperatively. Indications for adjuvant therapy are modified after local excision of small rectal cancers. For locally advanced rectal cancer, adjuvant therapy is utilized preoperatively to allow for surgical resection.

**Preoperative Radiation**

The advantages of preoperative radiation for rectal cancer include: (1) increasing the chance of resectability and probability of cure in locally advanced disease, (2) "downstaging" of the rectal tumor increasing the likelihood of a sphincter-saving procedure, and (3) decreasing viable malignant cells resulting in a decreased probability of local or distant recurrence after surgery. The disadvantages of preoperative radiation therapy include: (1) loss of accurate surgical staging, (2) delay in performing curative surgery, (3) potential increase in postoperative morbidity and mortality, and (4) possibility of exposing some patients (T1 and T2) to the risks of radiation unnecessarily. A number of trials have evaluated preoperative radiation for rectal cancer comparing this treatment to either surgery alone or postoperative radiation.

The European Organization for Research and Treatment of Cancer (EORTC) randomized close to 500 patients and found that preoperative radiation decreased local recurrence but had no effect on overall survival. The Stockholm I trial[11] and the multicenter trial reported by Pahlman and Glimelius also found that preoperative radiation decreased local recurrence but had no effect on overall survival. The latter trial also found that preoperative radiation decreased local recurrence more than postoperative radiation (12% vs. 21%). Studies have also shown that preoperative radiation therapy is not without complications. In contrast to patients treated with surgery alone, both Holm et al. and the Stockholm I trial[11] reported increased postoperative morbidity and mortality (mortality: 8% vs. 2% for surgery alone) after preoperative radiation therapy. Subsequently, a nationwide Swedish trial and the Stockholm II trial[12] have shown that using a 3 or 4 portal radiation technique rather than a 2 portal technique decreases postoperative morbidity and reduces postoperative mortality to the rate seen in nonirradiated patients. Finally, the Stockholm II trial[12] and the recently reported Swedish Rectal Cancer Trial[13] have found that compared to surgery alone, preoperative radiation not only decreases local recurrence (11% vs. 27%) but also increases overall survival (58% vs. 48%).

**Postoperative Radiation**

The advantages of postoperative radiation therapy for rectal cancer include (1) allows for accurate staging and avoids unnecessary treatment of T1 and T2 tumors, (2) allows for better treatment planning and localization if clips are placed at the time of surgery, and (3) does not delay operation. The disadvantages of postoperative radiation therapy include: (1) it has no effect
on cells spread at the time of operation, (2) residual malignant cells may be rendered hypoxic after operation and consequently would be less susceptible to radiation, and (3) postoperative complications or prolonged perineal wound healing may result in a delay in the initiation of radiation.

The Gastrointestinal Tumor Study Group (GITSG) trial found that postoperative radiation in combination with chemotherapy not only decreased local recurrence (from 24% to 11%) but it also improved overall survival (from 43% to 59%).(14) The NSABP Protocol R-01 trial also found that postoperative radiation decreased local recurrence (16% vs. 25%).(15) Subsequent studies have shown that postoperative radiation is also associated with complications such as small bowel obstruction but that these complications can be reduced by using a multiple radiation portal technique. In contrast to preoperative radiation, none of the randomized trials utilizing postoperative radiation therapy have shown a survival benefit without the addition of chemotherapy.

Chemoradiation
Since the NSABP Protocol R-01 trial(15) had found a survival benefit for postoperative chemotherapy in rectal cancer patients, investigators began pursuing adjuvant treatment regimens using radiation plus chemotherapy in order to reduce both local recurrence and increase survival. Both the GITSG(14) and NCCTG 794751(16) trials reported a decrease in local recurrence rates (14% vs. 23%) and improved survival (53% vs. 38%) with combined modality adjuvant therapy. A subsequent Intergroup study reported by O'Connell et al. has shown that continuous infusion 5-FU chemotherapy is superior to bolus therapy in terms of overall survival (70% vs. 60%).

Recommendation
Patients with Stage II or III rectal cancer are at high risk for local and systemic relapse. Trials have confirmed that radiation (45-55 Gy) plus 5-FU chemotherapy are effective and should be considered standard adjuvant treatment.(17) This recommended chemoradiation can be given either preoperatively or postoperatively. Combined modality adjuvant therapy results in lower local failure rate and an improved survival rate than either radiation or chemotherapy alone.

Adjuvant Therapy after Local Excision
Local excision can be appropriate and complete treatment for small, early (T1) rectal cancer with no unfavorable pathologic features (poorly differentiated, blood or lymphatic vessel invasion or positive margin). Patients with T1 tumors that are excised locally that have unfavorable pathologic features or patients with T2 tumors that invade the muscularis propria may benefit from adjuvant chemoradiation. Small trials have found that survival for T2 rectal cancer after local excision plus chemoradiation is equivalent to T1 rectal cancer after local excision alone. The results of a larger trial, CALGB 8984, in which patients with T1 tumors underwent local excision alone and patients with T2 tumors underwent postoperative chemoradiation are awaited. Early results of this trial suggest that although the local recurrence rate is acceptably low for the T1 tumors, local recurrence after local excision plus chemoradiation for T2 tumors may be unacceptably high (15-20%).

Adjuvant Therapy for Locally Advanced Rectal Cancer
The two goals of treatment for locally advanced rectal cancer are to accomplish local control (to prevent disabling pain) and to provide cure. In contrast to the adjuvant setting where the benefits of preoperative versus postoperative radiation therapy continue to be debated, for locally advanced rectal cancer preoperative radiation is essential for tumor downstaging and to increase tumor resectability. Although some studies have shown that preoperative radiation does increase the risk of postoperative complications, the magnitude of this risk is small and far outweighed by
its benefits. In addition to preoperative radiation, preoperative chemotherapy may enhance tumor downstaging, improve resectability and decrease tumor dissemination. Frykholm reported a greater curative resectability rate for patients receiving preoperative chemoradiation (71%) than for patients receiving radiation therapy alone (34%).

Despite the improvements reported by many investigators using preoperative combined modality therapy, local failure rates as high as 33% for advanced rectal cancer are still reported. To improve this failure rate, intraoperative radiation therapy (IORT) or intraoperative high dose brachytherapy (IOHDR) directed at areas where there is a "close" margin or microscopic residual disease has been utilized. In studies from the Massachusetts General Hospital and the Mayo Clinic, this localized boost of 1000-2000 cGy has been shown to improve both local control and disease-free survival.(18,19) Complications from IORT are few as this extra boost of radiation is directed at a limited area. Peripheral neuropathy and ureteral stricture have been reported, though, and appear to be related in part to the IORT. For locally advanced rectal cancer, preoperative chemoradiation followed by surgical resection with IORT and postoperative chemotherapy is associated with the lowest rate of local failure and highest rate of disease-free survival.

Summary
Adjuvant therapy for colon cancer is recommended for all node positive (Stage III) patients. Adjuvant chemotherapy with continuous infusion 5-FU plus either low or high dose leucovorin for 6 months or levamisole for 1 year should result in a 25-35% reduction in mortality in this group of patients. It is unclear whether some Dukes' B2 patients would also benefit from adjuvant therapy. Adjuvant therapy with 5-FU can stabilize metastatic disease (Stage IV) in some patients. For other patients with metastatic disease, irinotecan or CPT-11 may be effective. Further studies of intraportal chemotherapy, intraperitoneal chemotherapy, monoclonal antibodies and antitumor vaccines for colon cancer are warranted.

Adjuvant therapy for rectal cancer is recommended for all T3 or node positive patients (Stages II and III). Combined modality therapy with 45-55 Gy of pelvic radiation and continuous infusion 5-FU decreases local recurrence and improves overall survival. Although it is unclear whether radiation therapy should be given preoperatively or postoperatively, it is clear that a multiple portal technique is important to reduce morbidity and mortality. Small rectal cancers treated with local excision may benefit from adjuvant therapy if high risk pathologic features are present. For locally advanced rectal cancer, preoperative chemoradiation followed by surgical resection with IORT and postoperative chemotherapy is associated with the lowest rate of local failure and highest rate of disease-free survival.

References