Adjuvant Treatment of Colorectal Cancer

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ABSTRACT Colorectal cancer is the fourth most common noncutaneous malignancy in the United States and the second most frequent cause of cancer-related death. Approximately three quarters of patients are diagnosed with disease limited to the bowel wall or surrounding lymph nodes. Over the past decade, significant progress has been made in the treatment of localized colorectal cancer due to advances in surgery, radiotherapy, and chemotherapy. For patients with Stage III colon cancer, an overall survival benefit for fluorouracil-based chemotherapy has been firmly established, and recent data have shown further efficacy through the inclusion of oxaliplatin into adjuvant treatment programs. For patients with Stage II colon cancer, the use of adjuvant chemotherapy remains controversial, but may be appropriate in a subset of individuals at high risk for disease recurrence. In the treatment of patients with rectal cancer, improved outcomes have been noted with the use of total mesorectal excision and preoperative concurrent chemoradiotherapy. Current randomized clinical trials in the adjuvant therapy of colorectal cancer are examining the value of adding agents known to be active in metastatic disease, including those that modify specific molecular targets. (CA Cancer J Clin 2007;57:168–185.)

INTRODUCTION

Colorectal cancer is the fourth most common noncutaneous malignancy in the United States and the second most frequent cause of cancer-related death. In 2007, an estimated 153,760 cases of colorectal cancer will be diagnosed, and 52,180 people will die from the disease.1 Approximately 70% of these cancers will arise in the colon, whereas 30% will occur in the rectum. Significant progress in adjuvant therapy for colorectal cancer has been achieved since this topic was last reviewed in CA in 1999.2 Advances in chemotherapy (Table 1), surgery, and radiotherapy have improved outcomes for patients with colon and rectal cancer.

STAGING AND PROGNOSIS

Pathologic stage represents the most important prognostic factor for patients with colorectal cancer. The tumor-node-metastasis (TNM) system, as defined by the American Joint Committee on Cancer (AJCC), is the most commonly used staging system and is based on depth of invasion of the bowel wall, extent of regional lymph node involvement, and presence of distant sites of disease (Table 2).13–15 As the AJCC stage increases from Stage I to Stage IV, 5-year overall survival declines from greater than 90% to less than 10%.16,17

Several additional pathologic and clinical features have been identified that are associated with an increased risk for tumor recurrence, including poorly differentiated histology, lymphovascular invasion, perineural invasion, T4 tumor stage, clinical bowel obstruction or perforation, and an elevated preoperative plasma level of carcinoembryonic antigen (Table 3).18,19,23–25 Molecular features of colon cancer may also provide prognostic information. Mutations or promoter hypermethylation of deoxyribonucleic acid (DNA) mismatch repair genes can lead to errors in DNA replication and changes in short, repeated sequences of DNA, a condition known as microsatellite instability. Microsatellite instability
is present in the tumors of patients with hereditary nonpolyposis colon cancer (HNPCC), as well as 15% to 20% of sporadic colon cancers.\textsuperscript{20,26} Patients with tumors possessing a high degree of microsatellite instability have a more favorable prognosis than those patients whose tumors are microsatellite stable.\textsuperscript{26,27} In addition, loss of heterozygosity at chromosome 18q has been reported in approximately 50% of colon cancers and has been associated with a worse prognosis, possibly due to the loss of the putative tumor suppressor gene, “deleted in colon cancer” (DCC).\textsuperscript{21,28}

Several features related to surgical technique have also been associated with a poorer outcome. The examination of an inadequate number of lymph nodes has been linked with increased mortality in patients with node-negative and node-positive disease.\textsuperscript{29–33} In an analysis of 35,787 patients

| Regimen | Chemotherapy Dosing | Schedule |
|---------|---------------------|----------|
| LV5FU\textsuperscript{2} | 5-FU* 400 mg/m\textsuperscript{2} bolus on days 1 and 2 + 600 mg/m\textsuperscript{2} IVCI\textsuperscript{†} over 22 hours on days 1 and 2 LV\textsuperscript{†} 200 mg/m\textsuperscript{2} over 2 hours on days 1 and 2 | Every 2 weeks |
| Roswell Park\textsuperscript{4} | 5-FU 500 mg/m\textsuperscript{2} bolus LV 500 mg/m\textsuperscript{2} over 2 hours | Weekly for 6 of 8 weeks |
| Mayo Clinic\textsuperscript{5} | 5-FU 425 mg/m\textsuperscript{2} bolus on days 1 to 5 LV 20 mg/m\textsuperscript{2} bolus on days 1 to 5 | Every 4 to 5 weeks |
| Capecitabine\textsuperscript{6} | 1250 mg/m\textsuperscript{2} orally twice per day on days 1 to 14 | Every 3 weeks |
| Irinotecan | **5-FU = 5-fluorouracil.** **†LV = leucovorin.** **‡IVCI = intravenous continuous infusion.** §Other schedules of irinotecan have also been used with weekly cetuximab, including irinotecan 125 mg/m\textsuperscript{2} weekly for 4 of 6 weeks and irinotecan 350 mg/m\textsuperscript{2} on day 1 every 3 weeks.** |
with T3N0 colon cancer from the National Cancer Data Base, 5-year overall survival was positively associated with the number of lymph nodes identified (69%, 1–7 lymph nodes; 78%, 8–12 lymph nodes; 85%, ≥13 lymph nodes). A suboptimal number of examined lymph nodes may reflect a less complete operative procedure or an inadequate inspection of the pathologic specimen, and can mistakenly “understage” a tumor. Such inaccurate staging can lead to a higher than predicted rate of relapse due to the omission of adjuvant therapy. Based on the above data, current guidelines recommend the identification of 12 or more lymph nodes in the resected specimen for accurate colorectal cancer staging.

Studies have demonstrated that higher patient volume for a hospital or individual surgeon can decrease postoperative morbidity and mortality and improve outcomes for patients with colorectal cancer. In a linked analysis of the Surveillance, Epidemiology, and End Results (SEER) and Medicare databases, 30-day and 5-year mortality rates were higher by 2% and 4.4%, respectively, in patients treated at the lowest volume versus the highest volume hospitals. In addition, several studies of rectal cancer have demonstrated higher rates of sphincter-preserving surgery at high-volume hospitals.

### 3 Poor Prognostic Indicators Following Complete Surgical Resection of Colorectal Cancer

| Poor Prognostic Indicators | Definition |
|----------------------------|------------|
| Tumor penetration through the bowel wall (T4 tumor stage) | Invasion of adjacent organs or structures |
| Regional lymph node involvement | Involvement of >1 lymph node |
| Four or more involved regional lymph nodes | Four or more lymph nodes involved |
| Poorly differentiated histology | Histology grade >2 |
| Lymphovascular invasion | Invasion of blood vessels |
| Perineural invasion | Invasion of nerves |
| Preoperative plasma CEA level > 5.0 ng/ml | Elevated CEA level |
| Bowel obstruction | Obstruction of bowel lumen |
| Bowel perforation | Perforation of bowel wall |
| Tumor involvement of surgical margins | Involvement of surgical margins |
| Specific chromosomal deletion (eg, chromosome 18q loss of heterozygosity) | Genetic abnormality |

CEA = carcinoembryonic antigen.

In the surgical resection of rectal cancer, sharp dissection of the mesorectum en bloc with the rectum, as part of a total mesorectal excision (TME), has been associated with a lower risk of local recurrence. The mesorectum is the rectal mesentery that contains the rectum’s vascular supply and lymphatic drainage. It is the initial site of spread for rectal cancer, making its complete removal in a single anatomic block an important feature of rectal cancer surgery.

The cornerstone of systemic treatment for colon cancer is fluorouracil, a fluorinated pyrimidine that acts primarily through inhibition of thymidylate synthetase, the rate-limiting enzyme in pyrimidine nucleotide synthesis. Yet, for many years, fluorouracil was thought to be ineffective as adjuvant treatment for colon cancer. Clinical trials published during the 1970s failed to demonstrate a survival benefit for the adjuvant administration of fluorouracil, and a meta-analysis of all randomized controlled trials (RCTs) published before 1987 demonstrated only a small, statistically insignificant benefit for adjuvant therapy. In retrospect, these randomized trials likely
suffered from heterogeneous patient populations, inadequate sample size, and poor compliance with therapy. In the setting of these initially discouraging results, two subsequent approaches to adjuvant therapy for colon cancer revived interest in fluorouracil.

In an attempt to reduce the incidence of liver metastases, several clinical trials were designed to administer fluorouracil into the portal circulation during the immediate postoperative period.45–50 Although these studies failed to achieve their primary objective of reducing tumor spread to the liver, a meta-analysis of 10 such trials did demonstrate a modest overall survival benefit, supporting the value of a short exposure to adjuvant fluorouracil when compliantly administered.51

Additionally, adjuvant treatment with fluorouracil was reassessed when levamisole, an anti-helminthic, was examined as an immunomodulating agent.52–54 The North Central Cancer Treatment Group (NCCTG)55 and subsequently the Eastern Cooperative Oncology Group (ECOG)56,57 compared the administration of fluorouracil and levamisole with observation in the adjuvant setting. Because levamisole was eventually shown to be inactive, these studies actually represented a reassessment of the adjuvant administration of fluorouracil. The NCCTG trial, involving 401 patients with Stage II or III colon cancer, demonstrated a 31% reduction in recurrence rate for patients with Stage III disease who received fluorouracil and levamisole.55 In the larger ECOG trial of 1,296 patients, adjuvant fluorouracil and levamisole reduced the risk of recurrence by 41% (P = 0.0001) and the risk of death by 33% (P = 0.006) compared with surgery alone in patients with Stage III disease.56 In contrast, no meaningful benefit was noted in the subset of patients with Stage II disease. In 1990, a National Cancer Institute consensus conference recommended fluorouracil-based adjuvant therapy as standard of care for patients with resected Stage III colon cancer.58

The antitumor activity of fluorouracil was subsequently shown to be enhanced when the drug was combined with leucovorin, a reduced folate that is thought to stabilize fluorouracil’s interaction with thymidylate synthetase.3–5,59 A meta-analysis of 3,300 patients from 19 randomized trials found that modulation of fluorouracil with leucovorin in patients with metastatic colorectal cancer doubles the response rate with a modest, but statistically significant, improvement in overall survival compared with fluorouracil alone.60 Thus, the combination of fluorouracil and leucovorin was evaluated in the adjuvant setting, where it was found to increase disease-free and overall survival.61–64 A pooled analysis of 7 randomized trials demonstrated an increase in 5-year disease-free survival from 42% to 58% and 5-year overall survival from 51% to 61% in patients with Stage III disease.65 Subsequent studies showed that adjuvant fluorouracil and leucovorin administered for 6 months was equivalent to fluorouracil and levamisole administered for 12 months, and that the addition of levamisole to fluorouracil and leucovorin did not provide added benefit.64,66,67 In addition, no administration schedule of fluorouracil was found to be superior to any other in the adjuvant setting,68–71 although different side effect profiles did emerge (Table 4). Neutropenia and stomatitis were the most frequent side effects when bolus fluorouracil and leucovorin were administered daily for 5 days every 4 to 5 weeks (the “Mayo Clinic regimen”), with mild alopecia and vomiting also commonly observed. Higher rates of debilitating diarrhea resulted when bolus fluorouracil and leucovorin were administered weekly for 6 of 8 weeks (the “Roswell Park regimen”). Schedules that administered fluorouracil as a continuous infusion were associated with less hematologic and gastrointestinal toxicity, but with the appearance of hand-foot syndrome (a tender, erythematous rash involving the palms and soles).

Colon Cancer in Elderly and Minority Populations

Although nearly 75% of patients diagnosed with colon cancer are age 65 or older,73 such patients have been underrepresented in clinical trials and are less likely to receive adjuvant therapy.74,75 Pooled data analyses have repeatedly demonstrated a consistent and equivalent survival benefit for adjuvant therapy in all age groups.76–78 An analysis of 3,351 patients with Stage II or III colon cancer from 7 RCTs showed that 5-year overall survival was improved by a
similar 24% in each of 4 age groups (less than age 50, age 51 to 60, age 61 to 70, greater than age 70; \( P \) for interaction = 0.61).77 Additionally, an assessment of 4,768 patients age 65 and older with Stage III colon cancer in the linked SEER-Medicare databases demonstrated a 34% reduction in risk of death with adjuvant fluorouracil-based chemotherapy.76 In contrast, increased treatment-related toxicity was not consistently observed in older patients.77,79–82 Taken together, these studies indicate that fluorouracil-based adjuvant therapy improves survival in older patients with Stage III colon cancer by a similar amount as it does in younger patients, without a clear increase in treatment-related toxicity.

When disease outcomes have been analyzed by race and ethnicity, higher colorectal cancer–specific mortality has been noted in African American than in White patients.83 For patients diagnosed with colorectal cancer between 1995 and 2001, 5-year cancer-specific mortality was 65% in African Americans versus 55% in Whites.84 Several possible reasons for this discrepancy have been investigated, including differences in comorbid disease, sociodemographic factors, stage at presentation, tumor biology, and receipt of treatment.78,85–88 In subset analyses of RCTs, disease-free survival was similar in African American and White patients,89,90 suggesting that African Americans derive a similar degree of benefit from appropriately administered therapy as do Whites.

### Stage II Colon Cancer

No single randomized clinical trial has demonstrated a survival benefit for adjuvant therapy in patients with Stage II colon cancer. Subset analyses of trials that have included patients with Stage II and III disease have also repeatedly failed to demonstrate a statistically significant survival benefit for Stage II patients. A pooled analysis of 7 studies demonstrated a 5-year overall survival of 81% in patients who received fluorouracil-based adjuvant therapy and 80% in patients who underwent surgery alone (\( P = 0.11 \)).65

Two published reports have been cited as favoring the administration of adjuvant therapy in Stage II disease. A retrospective subset analysis of four consecutive National Surgical Adjuvant Breast and Bowel Project (NSABP) trials noted a similar proportional survival benefit for Stage II and Stage III patients who received fluorouracil-based adjuvant therapy and 80% in patients who underwent surgery alone (\( P = 0.11 \)).65

Results from the Quick and Simple and Reliable (QUASAR) study, a complex comparison of four different fluorouracil–based regimens with observation alone in a heterogeneous patient population, support a marginal survival benefit for patients with Stage II colon and rectal cancer; these results have thus far been reported only in abstract form.92

### Table 4

| Grade 3 or 4 Toxicity of Fluoropyrimidine-based Adjuvant Chemotherapy in Randomized Clinical Trials in Colon Cancer |
|---------------------------------------------------------------|
| **Adverse Event (%)** | **Intergroup Andre T, Colin P, Louvet C, et al.**62 | **Chau I, Norman AR, Cunningham D, et al.**70 | **X-Act**72 |
| | Mayo Clinic† | Roswell Park‡ | Mayo Clinic | LV5FU2§ | Mayo Clinic | PVII | Mayo Clinic | Capecitabine¶ |
| Diarrhea | 21 | 30 | 9 | 4 | 16 | 5 | 13 | 11 |
| Slomatitis | 18 | 1 | 7 | 2 | 18 | 4 | 14 | 2 |
| Hand-foot syndrome | — | — | 0 | 0 | 3 | 7 | <1 | 17 |
| Neutropenia | 24 | 4 | 16 | 7 | 55 | 1 | 26 | 2 |
| Nausea/vomiting | — | — | 3 | 1 | 2 | 2 | 3 | 3 |
| Any | 56 | 41 | 26 | 11 | — | — | — | — |

†Mayo Clinic: Fluorouracil 425 mg/m² + leucovorin 20 mg/m² for 5 days every 4 to 5 weeks.
‡Roswell Park: Fluorouracil 500 mg/m² + leucovorin 500 mg/m² weekly for 6 of 8 weeks.
§LV5FU2: Leucovorin 200 mg/m² over 2 hours followed by fluorouracil 400 mg/m² bolus followed by 600 mg/m² continuous infusion fluorouracil over 22 hours on days 1 and 2 every 14 days.
¶Capecitabine: 1,250 mg/m² orally twice per day for 14 of every 21 days.
After systematically reviewing the available literature, the Cancer Care Ontario Program in Evidence-Based Care,93 an expert panel convened by the American Society of Clinical Oncology (ASCO),94 and the National Comprehensive Cancer Network (NCCN)95 independently recommended against the routine administration of adjuvant therapy in patients with Stage II disease. In addition, the ASCO panel determined that a sample size of 9,680 patients per group would be required to detect a 2% survival difference between treatment and control arms (90% power with a significance level of 0.05).94

It has been proposed that adjuvant chemotherapy may benefit patients with Stage II disease and T4 tumor stage, bowel perforation, or clinical bowel obstruction.94 Although this hypothesis has not been validated in a prospective, randomized clinical trial, a retrospective subset analysis of 318 patients with Stage II disease enrolled in the ECOG INT -0035 study of fluorouracil and levamisole suggested a survival benefit for adjuvant therapy in these patient subgroups.25 Although other high-risk features, such as inadequate lymph node sampling, lymphovascular or perineural invasion, poorly differentiated histology, microsatellite stability, and loss of heterozygosity at chromosome 18q, are also known to carry a higher risk of recurrence,18 the potential benefit of chemotherapy is not known in patients with these factors.

Oral Fluropyrimidines

Attempts 30 years ago to administer fluorouracil orally proved unsuccessful; a randomized comparison of oral versus intravenous fluorouracil in metastatic colorectal cancer favored the intravenous route in terms of response rate and mean duration of response.96 These differences in response were thought to result from the erratic intestinal absorption of fluorouracil after oral administration, due to differing mucosal concentrations of dihydropyrimidine dehydrogenase (DPD), a major catabolic enzyme of the drug. Two strategies were developed to circumvent this problem: the administration of a fluorouracil prodrug that is not catabolized by DPD97 and the coadministration of an inhibitor of DPD with oral fluorouracil.98

Capecitabine is an oral prodrug of fluorouracil which is absorbed intact through the gastrointestinal mucosa and undergoes a three-step enzymatic conversion to fluorouracil.97 In RCTs, capecitabine was found to be therapeutically equivalent to bolus fluorouracil and leucovorin (Mayo Clinic schedule) as first-line therapy in metastatic colorectal cancer.6,72 In the adjuvant treatment of 1,987 patients with Stage III colon cancer, capecitabine (1,250 mg/m² administered twice daily on days 1 to 14 every 3 weeks) was also shown to be similarly effective when compared with the Mayo Clinic regimen of bolus fluorouracil and leucovorin.99 In these studies, treatment with capecitabine was associated with an increased rate of hand-foot syndrome and hyperbilirubinemia but less stomatitis and neutropenia (Table 4).

Although capecitabine, at the recommended dose of 1,250 mg/m² twice daily, appears therapeutically similar to monthly bolus fluorouracil and leucovorin with a somewhat less severe toxicity profile, it is uncertain whether the differences in toxicity profile would remain if capecitabine were compared with a more tolerable schedule of parenteral fluorouracil (ie, Roswell Park or infusional schedule). Additionally, it is unclear whether the more favorable convenience and cost-effectiveness profile that has been reported for capecitabine would persist if it were administered in combination with other intravenous chemotherapies, such as oxaliplatin.100

Tegafur uracil (UFT) circumvents the erratic intestinal absorption of fluorouracil by the coadministration of an oral fluoropyrimidine (tegafur) with an inhibitor of DPD (uracil), thereby allowing for a more uniform absorption and bioavailability of tegafur.101 In two randomized studies of patients with metastatic colorectal cancer, UFT and oral leucovorin resulted in similar response rates and overall median survival times as parenteral fluorouracil and leucovorin.102,103 A large, randomized trial comparing UFT and leucovorin with intravenous fluorouracil and leucovorin as adjuvant therapy demonstrated similar rates of disease-free survival and overall survival between the two treatment arms, with a comparable toxicity profile.104 Although available in Europe and Asia, UFT has been withdrawn by its pharmaceutical manufacturer in the United States.
Irinotecan

Irinotecan is a semisynthetic derivative of the natural alkaloid camptothecin and inhibits topoisomerase I, an enzyme that catalyzes breakage and rejoining of DNA strands during DNA replication. The efficacy of single-agent irinotecan was established in second-line treatment of metastatic disease, with a 2- to 3-month extension in median overall survival versus either best supportive care or continuous infusion fluorouracil. Diarrhea, myelosuppression, and alopecia were the most commonly observed side effects with use of irinotecan. Subsequent randomized trials demonstrated a benefit to combining irinotecan with either infusional or bolus fluorouracil and leucovorin. Based on these encouraging observations, it was anticipated that irinotecan would be useful in the adjuvant treatment of colon cancer.

Three randomized trials of adjuvant irinotecan with either bolus or infusional fluorouracil and leucovorin have been reported in abstract form. The Cancer and Leukemia Group B (CALGB) randomized 1,264 patients with resected Stage III colon cancer to receive either the Roswell Park regimen of fluorouracil and leucovorin or irinotecan with weekly bolus fluorouracil and leucovorin (IFL). Surprisingly, although IFL had proven superior to fluorouracil and leucovorin in patients with metastatic disease, it did not improve either disease-free or overall survival when administered as adjuvant therapy.

The Pan European Trials in Adjuvant Colon Cancer 3 (PETACC 3) trial randomized 3,278 patients with resected Stage III colon cancer to receive either the Roswell Park regimen of fluorouracil and leucovorin or irinotecan with weekly bolus fluorouracil and leucovorin. After a median follow up of 32 months, the addition of irinotecan did not significantly improve 3-year disease-free survival in 2,094 patients with Stage III disease (63.3% versus 60.3%, P = 0.09).

Oxaliplatin

Oxaliplatin is a diaminocyclohexane platinum compound that forms DNA adducts, leading to impaired DNA replication and cellular apoptosis. In preclinical testing, oxaliplatin was shown to be active as a single agent and synergistic when combined with fluorouracil in colorectal cancer cell lines, possibly due to oxaliplatin-induced downregulation of thymidylate synthetase. In patients with metastatic colon cancer, single-agent oxaliplatin has limited efficacy, but clinical benefit has been observed when it is administered with fluorouracil and leucovorin. A cumulative sensory neuropathy, characterized by paresthesias of the hands and feet and exacerbated by exposure to cold, is the primary toxic effect associated with oxaliplatin.

Oxaliplatin was evaluated in patients with metastatic colorectal cancer in two Phase III clinical trials, which demonstrated that the addition of oxaliplatin to infusional fluorouracil and leucovorin increased response rate and disease-free survival, with a trend toward improvement in overall survival. In a third study involving 795 patients with newly diagnosed metastatic disease, the combination of oxaliplatin, infusional fluorouracil, and leucovorin (FOLFOX) improved overall survival when compared with IFL or a combination of irinotecan and oxaliplatin (IROX).

Three clinical trials have been initiated to evaluate oxaliplatin and a fluoropyrimidine in the adjuvant treatment of colon cancer. In the Multicenter International Study of Oxaliplatin/Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) study, 2,246 patients with Stage II (40%) or Stage III (60%) colon cancer were randomized to receive 6 months
of infusional fluorouracil and leucovorin with or without oxaliplatin. After a median follow up of 49 months, the 4-year disease-free survival in patients with Stage III disease was statistically superior in those patients who received oxaliplatin (69.7% versus 61%). Although a statistically significant benefit was not observed in those patients with Stage II disease, a 5.4% absolute improvement in disease-free survival was noted in patients with high-risk Stage II disease, defined as the presence of T4 tumor stage, bowel obstruction, tumor perforation, poorly differentiated histology, venous invasion, or less than 10 examined lymph nodes. After 4 years of follow up, these improvements in disease-free survival have not yet resulted in a meaningful enhancement in overall survival (84.3% versus 82.7%) in patients with Stage II and III colon cancer.

In a second study, the NSABP randomized 2,407 patients with resected Stage II (29%) or Stage III (71%) colon cancer to receive adjuvant therapy with the Roswell Park regimen of fluorouracil and leucovorin with or without oxaliplatin (85 mg/m² on weeks 1, 3, and 5 of each 8-week cycle) for 24 weeks. After a median follow up of 34 months, the probability of 3-year disease-free survival was significantly improved in patients who received oxaliplatin (76.5% versus 71.6%, \(P = 0.004\)) by nearly an identical amount to that seen in the MOSAIC trial. This similarity in outcome is noteworthy because the NSABP administered fluorouracil in a bolus manner, rather than the infusional program utilized in the MOSAIC study.

The addition of oxaliplatin in both the MOSAIC and NSABP trials resulted in increased treatment-related toxicity. In the MOSAIC study, Grade 3 or 4 neutropenia was more common in patients receiving FOLFOX (41.1% versus 4.7%), although neutropenia complicated by fever or infection was relatively uncommon in both groups (1.8% versus 0.2%). Grade 3 paresthesia (severe objective sensory loss or paresthesias that interfere with function) was also more frequent in patients treated with FOLFOX (12.4% versus 0.2%), but was reported in only 1% of patients 12 months after completion of treatment. Patients receiving oxaliplatin as part of the NSABP protocol also experienced higher rates of neurotoxicity associated with pain or interfering with activities of daily living (Grade 3 on Sanofi National Cancer Institute neurotoxicity scale, 8% versus 1%). In these patients, 0.5% had persistent Grade 3 neurotoxicity 1 year after completing treatment. Additionally, increased gastrointestinal toxicity was reported in the NSABP trial when oxaliplatin was added to bolus fluorouracil and leucovorin.

A third study, known as the XELOXA trial, randomized 1,886 patients with resected Stage III colon cancer to receive either capecitabine and oxaliplatin or bolus fluorouracil and leucovorin. At present, only safety data are available from this study. Similar to the MOSAIC and NSABP trials, higher rates of neurologic toxicity have been noted in the oxaliplatin-containing arm (Grade 3 or 4 neurotoxicity, 8.1% versus 0%).

Because disease recurrence is fatal in the vast majority of patients, disease-free survival has been proposed as a surrogate for overall survival. In an analysis of individualized patient data from 18 RCTs of adjuvant fluorouracil-based chemotherapy, 3-year disease-free survival was highly correlative with 5-year overall survival. At present, the MOSAIC and NSABP trials have demonstrated improved disease-free survival when oxaliplatin is added to fluorouracil and leucovorin, but an overall survival benefit has not yet been observed in either of these two studies (Table 5).

### Epidermal Growth Factor Receptor Inhibitors

The epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein that interacts with signaling pathways affecting cellular growth, proliferation, and programmed cell death. It is expressed in malignancies of multiple tissues, including those of the colon, lung, breast, and head and neck. In colorectal cancer, EGFR expression has been demonstrated in up to 80% of tumors, and tumors that express EGFR carry a poorer prognosis. Antibodies directed against the extracellular domain of EGFR and small molecular inhibitors of the intracellular tyrosine kinase domain have been developed to inhibit the function of this transmembrane receptor. Thus far, only the anti-EGFR monoclonal
antibodies, cetuximab and panitumumab, have definitively demonstrated efficacy in colorectal cancer; experience to date with oral tyrosine kinase inhibitors has been disappointing.133–135 In preclinical studies, antitumor activity was noted in colon cancer cell lines for cetuximab alone and in combination with chemotherapy.136 In addition, synergistic activity was observed with the combination of cetuximab and irinotecan in tumor cells sensitive to and resistant to irinotecan, suggesting that EGFR inhibition may overcome cellular resistance to irinotecan.137 Due to these preclinical observations, trials of cetuximab were initiated in patients with metastatic colorectal cancer.

In an initial Phase II study of 121 patients whose tumors expressed EGFR and were refractory to irinotecan, treatment with the combination of cetuximab and irinotecan resulted in a response rate of 17%.11 To determine whether this anti-neoplastic effect was due to synergy between the 2 drugs or independent activity of cetuximab, 57 similar patients were treated with cetuximab alone, resulting in a 9% response rate.138 Confirming this synergistic activity, a randomized Phase II trial of 329 patients with irinotecan-refractory, metastatic colorectal cancer demonstrated response rates of 22.9% with cetuximab and irinotecan and 10.8% with cetuximab alone.139

The role of cetuximab in adjuvant therapy of colon cancer has not yet been defined. The NCCTG and the European Organization for Research and Treatment of Cancer (EORTC) are each randomizing over 2,000 patients with resected Stage III colon cancer to receive FOLFOX alone or FOLFOX with cetuximab. These two randomized trials will provide data on the efficacy of cetuximab in the adjuvant setting.

The most common side effects of cetuximab are dermatologic, including an acne-like rash, xerosis (dry skin), and fissures of the skin.139,140 Although some degree of acneiform rash occurs in most patients, severe eruptions resulting in significant pain or infectious sequelae are less common. Interestingly, the presence and severity of the cetuximab-induced rash, but not the degree of EGFR expression on the surface of tumor cells, appear to correlate with the likelihood of response.139 In addition to dermatologic toxicities, severe hypersensitivity infusional reactions can occur with administration of cetuximab, although these reactions are uncommon, occurring in less than 3% of patients.

Panitumumab is a humanized monoclonal antibody to EGFR that has shown similar single-agent activity as cetuximab in metastatic colorectal cancer. In a Phase II trial, 9% of 148 patients whose cancers had progressed after treatment with fluorouracil and either irinotecan or oxaliplatin experienced a partial response to panitumumab.141 This response rate is comparable to response rates observed in clinical trials of cetuximab in a

| Trial | Treatment Arms | Patients | Three-year Disease-free Survival | Three-year Overall Survival |
|-------|----------------|---------|-------------------------------|---------------------------|
| MOSAIC*121 | FOLFOX† | 1123 | 78.2 | 0.002 | 87.7 | NS# |
| | LV5FU2‡ | 1123 | 72.9 | 86.6 | | |
| NSABP§ C-0710 | FLOX¶ | 1200 | 78.5 | 0.004 | NR** | |
| | Roswell Park¶ | 1207 | 71.6 | | NR | |

*MOSAIC = Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer.
†FOLFOX = leucovorin 200 mg/m2 over 2 hours on days 1 and 2, simultaneous with oxaliplatin 85 mg/m2 over 2 hours on day 1, followed by fluorouracil 400 mg/m2 bolus with subsequent 600 mg/m2 continuous infusion fluorouracil over 22 hours on days 1 and 2 every 14 days.
‡LV5FU2 = leucovorin 200 mg/m2 over 2 hours followed by fluorouracil 400 mg/m2 bolus followed by 600 mg/m2 continuous infusion fluorouracil over 22 hours on days 1 and 2 every 14 days.
§NSABP = National Surgical Adjuvant Breast and Bowel Project.
¶FLOX = fluorouracil 500 mg/m2 + leucovorin 500 mg/m2 weekly for 6 of 8 weeks and oxaliplatin 85 mg/m2 on weeks 1, 3, and 5 of every 8 weeks.
¶Roswell Park = fluorouracil 500 mg/m2 + leucovorin 500 mg/m2 weekly for 6 of 8 weeks.
#NS = not statistically significant.
**NR = not reported.
similar patient population. In a randomized Phase III trial of 463 patients with previously treated metastatic colorectal cancer, preliminary results have suggested a progression-free survival benefit for panitumumab when compared with best supportive care.

Angiogenesis Inhibitors

The inhibition of new blood vessel formation has been explored as a strategy to control malignant proliferation and spread. Currently, the most successful antiangiogenic therapy has focused on inhibiting the vascular endothelial growth factor (VEGF), a soluble protein that stimulates blood vessel proliferation. Bevacizumab is a humanized monoclonal antibody directed against VEGF that has been examined in combination with chemotherapy in patients with advanced colorectal cancer. In a randomized, Phase III trial of 815 previously untreated patients with metastatic disease, the addition of bevacizumab to IFL led to a statistically significant improvement in response rate (44.8% versus 34.8%, \( P = 0.004 \)) and a 4.7-month prolongation in median overall survival (20.3 months versus 15.6 months, \( P = 0.001 \)). In patients with metastatic colorectal cancer who have received fluorouracil and irinotecan, the combination of FOLFOX and bevacizumab has also demonstrated a statistically significant improvement in progression-free survival and overall survival when compared with FOLFOX alone. Bevacizumab was relatively well tolerated in both trials, with reversible hypertension and proteinuria representing two of the most common adverse events attributable to bevacizumab. Nonetheless, rare but serious side effects have been observed with bevacizumab, including a 1% to 2% risk of bowel perforation, a 3% risk of serious bleeding events, a 2% to 3% risk of arterial embolic events, and less than 1% risk of reversible posterior leukoencephalopathy syndrome.

The role of bevacizumab in adjuvant therapy for colon cancer is under examination in several randomized trials in the United States and Europe. Until the results of these trials are available, it is premature to recommend the incorporation of bevacizumab into adjuvant treatment programs for colon cancer.

Recommendations and Future Questions in the Adjuvant Treatment of Colon Cancer

Currently available data in 2006 (Table 6) support the use of 6 months of postoperative fluorouracil, leucovorin, and oxaliplatin in patients with Stage III colon cancer. Such adjuvant therapy appears to be equally effective in older and younger patients. If a patient is to receive therapy with a fluoropyrimidine alone, then capecitabine is an acceptable alternative to intravenous fluorouracil and leucovorin. Current data do not support the use of irinotecan, cetuximab, or bevacizumab in the adjuvant treatment of colon cancer, outside of a clinical trial.

In patients with Stage II colon cancer, prospective data have not demonstrated a benefit for adjuvant therapy, and current guidelines do not recommend its routine use. Administration of adjuvant therapy to patients with Stage II disease and one or more high risk features appears to be reasonable, but the value of such treatment has not yet been prospectively validated.

Several questions remain unanswered regarding adjuvant therapy for colon cancer, including whether capecitabine can be used in place of intravenous fluorouracil in combination adjuvant chemotherapy regimens, such as with oxaliplatin; how best to incorporate new, targeted agents into current cytotoxic treatments; and whether specific subgroups of patients with Stage II disease may benefit from adjuvant treatment. Ongoing RCTs are addressing some of these questions (Table 7).

RECtAL CANCER

Differences in Management of Colon and Rectal Cancer

The rectum is located within the pelvis and extends from the transitional mucosa of the anal dentate line to the sigmoid colon at the peritoneal reflection, which measures between 10 and 15 cm from the anal verge by rigid sigmoidoscopy. The bony constraints of the pelvis limit surgical access to the rectum, leading to a lower likelihood of achieving widely negative margins and a higher risk of local recurrence. Due to the increased risk of local recurrence and a poorer overall prognosis, the management of rectal
Adjuvant Treatment of Colorectal Cancer

Cancer varies somewhat from that of colon cancer, including differences in surgical technique, the use of radiotherapy, and method of chemotherapy administration.

Surgical Management of Rectal Cancer

In rectal cancer, the surgical approach to resection varies with the location of the tumor. Proximal tumors are resected by a low anterior resection (LAR) and primary anastomosis. Most midrectal tumors can also be resected by a LAR, although when the anastomosis is low in the pelvis, a temporary ileostomy or colostomy may be required to divert the fecal stream from the anastomosis and facilitate proper healing. Distal rectal tumors typically require an abdominoperineal resection (APR) with permanent colostomy because the anal sphincter cannot be preserved. A small subset of superficial, distal rectal tumors with favorable histologic features may be amenable to local excision.

Total mesorectal excision has become accepted as the standard surgical technique in rectal cancer resection. Historically, rectal cancer surgery involved blunt dissection within the rectal mesentery, known as the mesorectum, which contains the rectum’s vascular supply and lymphatic drainage. TME requires sharp dissection beyond the plane of the mesorectum with well-defined circumferential margins, so that the rectum with its surrounding perirectal fat and lymph nodes is removed as a single specimen. In a study conducted by the Dutch Colorectal Cancer Group, the local recurrence rate 2 years after TME was 8.2%, substantially less than historically reported rates of 20% to 25%.

Perioperative Radiation Therapy Alone

To further reduce the risk of local recurrence, clinical trials have evaluated 3 schedules of radiation therapy administered in addition to

### TABLE 6  Recommendations for Adjuvant Treatment of Stage II and Stage III Colon Cancer

| Clinical Trial | AJCC Stage | Randomization |
|---------------|------------|---------------|
| NCCTG* N0147 | III        | FOLFOX# versus FOLFOX + cetuximab |
| PETACC†-8    | III        | FOLFOX versus FOLFOX + cetuximab |
| NSABP‡ C-08  | II, III    | FOLFOX versus FOLFOX + bevacizumab |
| AVANT§       | II, III    | FOLFOX versus FOLFOX + bevacizumab versus capecitabine + oxaliplatin + bevacizumab |
| ECOG| E5202     | II          | Molecular high risk (MSS** or MSI-L†† and 18q LOH‡‡): FOLFOX versus FOLFOX + bevacizumab |

*NCCTG = North Central Cancer Treatment Group.

†PETACC = Pan European Trials in Adjuvant Colon Cancer.

‡NSABP = National Surgical Adjuvant Breast and Bowel Project.

§AVANT = International Phase III study of Avastin(R) (bevacizumab), XELOX, and FOLFOX chemotherapy regimens in early-stage colon cancer.

| ECOG | E5202 | II |

||
| N0147 | III | FOLFOX# versus FOLFOX + cetuximab |
| PETACC†-8 | III | FOLFOX versus FOLFOX + cetuximab |
| NSABP‡ C-08 | II, III | FOLFOX versus FOLFOX + bevacizumab |
| AVANT§ | II, III | FOLFOX versus FOLFOX + bevacizumab versus capecitabine + oxaliplatin + bevacizumab |
| ECOG| E5202 | II | Molecular high risk (MSS** or MSI-L†† and 18q LOH‡‡): FOLFOX versus FOLFOX + bevacizumab |

| Randomization |
|---------------|
| Standard risk: observation |

**MSS = microsatellite stability.

††MSI-L = microsatellite instability—low.

‡‡18q LOH = loss of heterozygosity at chromosome 18q.
surgery: a postoperative protracted-course therapy over 4 to 6 weeks; a protracted preoperative regimen; and a preoperative short-course, high-dose fraction therapy delivered over 1 week. In the postoperative setting, radiation was administered to a total dose of 40 to 50 Gy in 1.8- to 2-Gy fractions over 4 to 7 weeks and resulted in an improvement in the rate of local control, but not overall survival. Preoperatively, the EORTC evaluated a total dose of 34.5 Gy administered as 15 daily fractions of 2.3 Gy and also noted a decrease in local recurrence rate, without a significant improvement in overall survival. Short-course preoperative therapy was evaluated in the Swedish Rectal Cancer Trial, in which patients receiving radiotherapy to a total dose of 25 Gy over 5 days experienced enhanced local control and prolonged survival compared with patients who underwent surgery alone.

To compare preoperative and postoperative schedules, a Swedish trial randomized 471 patients to surgery with either preoperative (25.5 Gy in 5 5.1-Gy fractions over 1 week) or postoperative (60 Gy in 2-Gy fractions over 6 to 7 weeks) radiation. Local recurrence was lower in the preoperative radiation group (12% versus 21%, \( P = 0.02 \)), but no difference was noted in overall survival. The Colorectal Cancer Collaborative Group (CCCG) performed a meta-analysis of radiation therapy in 8,507 patients from 22 randomized trials. After 5 years of follow up, both preoperative and postoperative radiation approaches were associated with a lower risk of local recurrence when compared with surgery alone, although neither schedule of radiotherapy resulted in a statistically significant improvement in overall survival. In the subsequent Dutch Colorectal Cancer Group study of TME with or without radiation, patients who underwent preoperative radiotherapy had a lower risk of local recurrence (8.2% versus 2.4%, \( P = 0.001 \)), confirming the benefit of radiation, even in the setting of TME. This reduction in risk was most notable in patients with tumors located in the distal rectum. The addition of radiation therapy, however, did not prolong survival.

**Postoperative Chemoradiotherapy**

Randomized studies published in the late 1980s and early 1990s established combined postoperative chemotherapy and radiation as the standard of care for patients with resected Stage II or III rectal cancer. The Gastrointestinal Tumor Study Group (GITSG) randomized 227 patients with resected T3 to T4 or node-positive rectal adenocarcinoma to 1 of 4 treatment arms: observation, radiation alone, chemotherapy alone, or combined radiation and intravenous fluorouracil. Combined modality therapy resulted in a statistically significant reduction in the rate of local recurrence and an increase in the rate of overall survival when compared with surgery alone—an outcome that was not observed for patients receiving either adjuvant chemotherapy or radiotherapy alone.

These improvements in local control and overall survival for combined modality therapy were confirmed in a subsequent NCCTG trial. Due to the findings of these 2 studies, a National Cancer Institute consensus conference in 1990 recommended the use of adjuvant chemoradiotherapy for Stage II and III rectal cancer. This recommendation was refined when a comparison of radiotherapy given concurrently with either infusional or bolus fluorouracil demonstrated that continuous infusion fluorouracil was associated with a lower risk of tumor recurrence (37% versus 47%, \( P = 0.01 \)) and an improvement in 4-year overall survival (70% versus 60%, \( P = 0.005 \)). Interestingly, the rate of local recurrence was not significantly different between the two groups, implicating more effective treatment of distant disease as the cause of the overall survival benefit.

Two subsequent cooperative group studies conducted in North America demonstrated that the addition of leucovorin to fluorouracil during radiation did not improve disease-free or overall survival. In addition, two studies performed by the NSABP showed that postoperative chemotherapy alone was associated with an increased risk of local recurrence when compared with postoperative radiation alone or combined modality therapy.

Perhaps to parallel the 6 months of adjuvant therapy in colon cancer, an additional 4 months of fluorouracil-based chemotherapy are typically administered in association with concurrent chemoradiation. Although it has not been validated in randomized clinical studies, a “sandwich”
Approach to therapy has been employed most commonly, in which bolus fluorouracil is administered both before and after concurrent chemoradiation therapy.164

Preoperative Chemoradiotherapy

The efficacy of adjuvant combined modality therapy led investigators to evaluate preoperative chemotherapy and radiation. Due to shrinkage of the tumor before resection, preoperative treatment was thought to allow for a greater number of sphincter-preserving surgeries. In addition, it had the potential to cause less gastrointestinal toxicity because less small bowel would typically be located in the radiation field at the time of treatment. The merits of the preoperative therapeutic approach, however, could only be established through a randomized clinical trial.

In 2004, the German Rectal Cancer Study Group published the results of such a randomized trial comparing preoperative and postoperative therapy in 823 patients with T3 to T4 or node-positive rectal cancer.169 Patients randomized to preoperative therapy received 50.4 Gy in 28 fractions with a 120-hour infusion of fluorouracil at 1000 mg/m²/day during the first and fifth weeks of radiation. One month after surgery, patients received adjuvant chemotherapy, consisting of 4 cycles of bolus fluorouracil at 500 mg/m²/day for 5 days every 4 weeks. Patients randomized to receive surgery as initial treatment received the same chemoradiation and subsequent fluorouracil postoperatively, with the exception of an additional 5.4-Gy radiation boost to the tumor bed.

This study demonstrated that preoperative chemoradiation therapy doubled the rate of sphincter-sparing operations and lowered the rates of local recurrence, acute toxicity, and long-term toxicity (Table 8). However, no difference in disease-free or overall survival was observed between the two treatment arms. Although all patients underwent a preoperative endorectal ultrasound, nearly 20% of patients who were randomized to initial surgery were found to have Stage I disease on pathologic review of the surgical specimen, implying that approximately 20% of patients in the preoperative treatment arm were likely “over”-treated.

Recommendations and Future Questions in the Treatment of Rectal Cancer

The clinical management of rectal cancer in 2006 (Table 9) is performed most effectively by a multidisciplinary team, which includes representatives from gastroenterology, medical oncology, radiation oncology, radiology, and surgical oncology. Early and accurate determination of tumor location within the rectum and AJCC TNM stage is particularly important because such

| Treatment Arm | Overall Survival | Disease-free Survival | Local Recurrence | Acute Toxicity† | Long-term Toxicity‡ | Sphincter-sparing Surgery§ |
|---------------|-----------------|----------------------|------------------|----------------|-------------------|--------------------------|
| Preoperative (%) | 76              | 68                   | 6                | 27             | 14                | 39                       |
| Postoperative (%) | 74            | 65                   | 13               | 40             | 24                | 19                       |
| P value       | 0.80            | 0.32                 | 0.006            | 0.001          | 0.01              | 0.004                    |

Adapted from Fisher B, Wolmark N, Rockette H, et al.167

*Survival and recurrence rates were determined at 5 years.
†The proportion of patients who developed any Grade 3 or 4 adverse event during treatment.
‡The proportion of patients with any Grade 3 or 4 adverse event documented at 1, 3, and 5 years after treatment.
§A subset of 194 patients thought to require abdominoperineal resection (APR) with permanent colostomy at preoperative surgical evaluation.
information will determine the type of surgery that is performed and the need for chemoradiation. For patients with Stage II or III rectal cancer, data support the use of preoperative concurrent radiation and continuous infusion fluorouracil, and resection performed by total mesorectal excision. Chemoradiation and surgery are typically followed by four months of adjuvant chemotherapy. Currently, randomized data are not available to support the use of bevacizumab, capecitabine, cetuximab, irinotecan, or oxaliplatin in the adjuvant treatment of rectal cancer.

Several questions remain unanswered regarding therapy for rectal cancer, including whether capecitabine can be used in place of intravenous fluorouracil and whether the incorporation of newer cytotoxic and targeted agents into current treatment regimens can decrease morbidity and mortality associated with this disease. Several clinical trials are currently underway to address some of these questions (Table 10).

**CONCLUSIONS**

During the past 10 years, substantial progress has been made in the treatment of colorectal cancer. In patients with metastatic disease, the incorporation of new cytotoxic drugs and targeted agents has led to an increase in median overall survival from less than 9 months without treatment to greater than 20 months. In patients with potentially resectable tumors, advances in surgery, radiation, and chemotherapy have all contributed to increased rates of cure. Higher volume medical centers have become models for improving surgical quality, and the use of total mesorectal excision has decreased rates of local recurrence in rectal cancer. Oxaliplatin has been incorporated into adjuvant treatment programs for colon cancer, and new targeted agents are currently in preclinical development and ongoing clinical trials. The precision of radiation delivery has improved, and the benefits of preoperative chemoradiotherapy have been established in rectal cancer. The same statement can be made today. As in the past, further progress depends on the completion of well-designed RCTs.

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**TABLE 10** Ongoing Clinical Trials in Adjuvant Treatment of Rectal Cancer

| Trial                | Setting                      | Randomization                                      |
|---------------------|------------------------------|----------------------------------------------------|
| NSABP R-04          | Preoperative chemoradiation  | 5-FUT versus capecitabine with or without oxaliplatin |
| Accord-12           | Preoperative chemoradiation  | Capecitabine versus capecitabine + oxaliplatin    |
| RTOG 0247           | Preoperative chemoradiation  | Capecitabine and irinotecan versus capecitabine and oxaliplatin |
| French Intergroup R98 | Adjuvant chemotherapy        | 5-FU/LV/S versus 5-FU/LV/irinotecan                 |
| US Gastrointestinal Intergroup | Adjuvant chemotherapy       | 5-FU/LV/oxaliplatin versus 5-FU/LV/oxaliplatin/bevacizumab |

*NSABP = National Surgical Adjuvant Breast and Bowel Project.
†RTOG = Radiation Therapy Oncology Group.
‡5-FU = 5-fluorouracil.
§LV = leucovorin.
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Erratum

In the March/April 2007 issue, in the article “American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography” (CA Cancer J Clin 2007;57:75–89), an error appeared in the text on page 86. The sentence that read, “However, in view of data suggesting that tumor doubling time in women with an inherited risk decreases with age, it is conceivable that older women can safely be screened less frequently than younger women” was incorrect. It should read, “However, in view of data suggesting that tumor doubling time in women with an inherited risk decreases with age, it is conceivable that older women can safely be screened less frequently than younger women.” The authors regret the error and apologize for any confusion it may have caused.