Published in final edited form as:
Gastroenterology. 2008 May ; 134(5): 1296–1310. doi:10.1053/j.gastro.2008.02.098.

Systemic Treatment of Colorectal Cancer

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Abstract

Colorectal cancer is the fourth most common non-cutaneous malignancy in the United States and the second most frequent cause of cancer-related death. Over the past 12 years, significant progress has been made in the systemic treatment of this malignant condition. Six new chemotherapeutic agents have been introduced, increasing median overall survival for patients with metastatic colorectal cancer from less than 9 months with no treatment to approximately 24 months. For patients with stage III (lymph node positive) colon cancer, an overall survival benefit for fluorouracil-based chemotherapy has been firmly established, and recent data have shown further efficacy for the inclusion of oxaliplatin in such 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 higher risk for disease recurrence. Ongoing randomized clinical trials are evaluating how best to combine currently available therapies, while smaller studies are evaluating new agents, with the goal of continued progress in prolonging life among patients with metastatic colorectal cancer and increasing cure rates among those with resectable disease.

Keywords

Colon cancer; chemotherapy; targeted therapy

I. Introduction

Colorectal cancer is the fourth most common non-cutaneous 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 were diagnosed and 52,180 people died from this disease[1]. Significant progress in the treatment of colorectal cancer has been achieved over the past twelve years, with the approval of six new therapeutic agents in the United States (Table 1). These compounds have greatly improved the outlook for patients diagnosed with resectable and metastatic disease. The current review focuses on advances in the systemic therapy of colorectal cancer.

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Conflicts of Interest: Brian Wolpin, M.D.: None Robert Mayer, M.D.: None.

II. 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)[2–4]. The depth of tumor invasion defines the T stage and increases from T1 (invasion of the submusosa) to T4 (invasion into the serosa or adjacent structures). As the depth of tumor invasion increases, the risk for nodal and distant spread also grows. Pathologic review of surrounding lymph nodes defines the three N categories: N0 (no lymph nodes involved), N1 (1–3 lymph nodes involved), and N2 (greater than 3 lymph nodes involved). Current guidelines recommend the identification of 12 or more lymph nodes in the resected specimen[5, 6], as the examination of fewer regional lymph nodes has been linked with poorer outcome in patients with node-negative and node-positive disease[7–11]. The examination of fewer lymph nodes may reflect a less complete operative procedure or an inadequate inspection of the pathologic specimen, mistakenly leading to “understaging” of the tumor and the subsequent omission of beneficial adjuvant therapy.

In patients with resectable colorectal cancer, several other pathologic and clinical features have been identified that are associated with an increased risk for tumor recurrence. These include poorly differentiated histology, lymphovascular invasion, perineural invasion, T4 tumor penetration, bowel perforation, clinical bowel obstruction, and an elevated preoperative plasma level of carcinoembryonic antigen (CEA)[12–16]. In contrast, hospitals and surgeons with higher patient volume have been associated with improved outcomes for resectable colorectal cancer[17–19].

Microsatellite instability and loss of heterozygosity at chromosome 18q are the two best-defined molecular prognostic markers[20]. Microsatellite instability results from mutations or promoter hypermethylation of DNA mismatch repair genes leading to errors in DNA replication and changes in short, repeated sequences of DNA. It is present in the vast majority of tumors from patients with hereditary nonpolyposis colon cancer (HNPCC), but is also found in 15 to 20 percent of patients with sporadic colon cancer[21, 22]. Patients with tumors possessing a high degree of microsatellite instability have a more favorable prognosis than those patients whose tumors are microsatellite stable[21, 23]. Loss of heterozygosity at chromosome 18q has been reported in approximately 50% of colon cancers and has been associated with a worse prognosis[24, 25]. Although these factors provide prognostic information on the risk of tumor recurrence after primary resection, they have not been prospectively validated as predictive markers for altered outcome with administration of specific chemotherapeutic regimens.

The rectum is located within the pelvis and extends from the transitional mucosa of the anal dentate line to the sigmoid colon, which measures between 10 and 15 centimeters 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, the local management of rectal cancer varies somewhat from that of colon cancer. Surgical resection of rectal cancer with sharp dissection of the mesorectum *en bloc* with the rectum, as part of a total mesorectal excision (TME), has resulted in a lower likelihood of local recurrence[26, 27]. The mesorectum is the rectal mesentery that contains the rectum’s vascular supply and lymphatic drainage and is the initial site of spread for rectal cancer. Additionally, radiotherapy administered preoperatively or postoperatively has been associated with a lower risk of local recurrence when compared to surgery alone, even when a TME has been performed[27, 28].

Spread of tumor beyond the colorectum and regional lymph nodes defines the M stage of the AJCC classification system, with M1 indicating the presence of tumor metastases to distant sites. Approximately 20% of patients present with metastatic disease and 30% to 40% of patients with localized disease ultimately develop metastases. The liver reflects the most common initial site of disease spread, but metastases to other organs during the course of the disease are common, including to the lungs, peritoneum, and intra-abdominal lymph nodes. Patients with a small number of isolated, organ-confined metastases may be cured of their disease by surgical resection[29]; decisions regarding metastatectomy should be made by a medical oncologist working in close conjunction with an experienced surgeon. Most patients with metastatic disease are candidates for systemic chemotherapy to palliate symptoms and prolong life. As the AJCC stage increases from stage I to stage IV, five-year overall survival declines dramatically: stage I, > 90%; stage II, 70–85%; stage III 25–80%; and stage IV, < 10% (Table 2)[2, 30, 31].

III. Fluoropyrimidines

A. Intravenous Fluorouracil

Fluorouracil remains the cornerstone of systemic treatment for colorectal cancer. It is a fluorinated pyrimidine that acts primarily through inhibition of thymidylate synthetase, the rate-limiting enzyme in pyrimidine nucleotide synthesis[32] and is commonly administered with leucovorin, a reduced folate that is thought to stabilize fluorouracil's interaction with this enzyme[33–36]. A meta-analysis of 3,300 patients from 19 randomized trials found that the likelihood of a greater than 50% tumor shrinkage by bidimensional product measurement doubles when fluorouracil is administered with leucovorin in patients with metastatic colorectal cancer, with a modest but statistically significant improvement in overall survival, when compared to fluorouracil alone[37]. Among patients with metastatic colorectal cancer receiving fluorouracil and leucovorin, approximately 20% will have a reduction in tumor size by 50% or more, and median survival is increased from approximately 6 months to about 12 months[37, 38].

Fluorouracil can be administered by a variety of different schedules, with differing toxicity profiles. Neutropenia and stomatitis are the most frequent side effects when bolus fluorouracil and leucovorin are administered daily for five days every four to five weeks (the "Mayo Clinic regimen"). Higher rates of diarrhea are noted when bolus fluorouracil and leucovorin are administered weekly for six of eight weeks (the "Roswell Park regimen"). Schedules that administer fluorouracil as a continuous infusion are associated with less hematologic and gastrointestinal toxicity, but have a greater incidence of "hand-foot" syndrome, a tender, erythematous rash involving the palms and soles.

Although treatment programs that involve infusional fluorouracil were initially thought to be less convenient and more expensive than bolus regimens, little difference has been noted in quality of life or cost between these two types of regimens[39–41]. In addition, a meta-analysis of six randomized trials has demonstrated a modest improvement in response rate and median overall survival among patients with metastatic colorectal cancer who received infusional fluorouracil when compared with patients who received a more rapid, bolus approach[38].

B. Oral Fluoropyrimidines

Initial attempts to administer fluoropyrimidines orally were unsuccessful. A randomized comparison of oral versus intravenous fluorouracil in patients with metastatic colorectal cancer favored the intravenous route in terms of tumor response rate and mean duration of tumor response[42]. These differences in response were thought to result from erratic intestinal absorption of fluorouracil, due to differing mucosal concentrations of dihydropyrimidine

dehydrogenase (DPD), a major catabolic enzyme of the drug. Two strategies have been employed to circumvent this problem: the administration of an absorbable fluorouracil prodrug that is not catabolized by DPD[43] and the co-administration of an inhibitor of DPD with oral fluorouracil[44].

Capecitabine (Xeloda®) is an oral prodrug of fluorouracil that is absorbed intact through the gastrointestinal mucosa and undergoes a three-step enzymatic conversion to fluorouracil[43]. The side effect profile of this drug is similar to that seen with continuous infusion fluorouracil, with the hand-foot syndrome being most prominent. Studies have shown capecitabine to be therapeutically equivalent to bolus fluorouracil and leucovorin (Mayo Clinic schedule) as initial therapy in metastatic colorectal cancer, with no significant differences in median time to tumor progression or median overall survival[45, 46].

Tegafur uracil (UFT, [Orzel®]) circumvents the erratic intestinal absorption of fluorouracil by the co-administration of an oral fluoropyrimidine (tegafur) with an inhibitor of DPD (uracil), thereby allowing for a more uniform absorption and bioavailability of tegafur[47]. In two randomized studies of patients with metastatic colorectal cancer, treatment with UFT and oral leucovorin resulted in similar rates of response and median survival as parental fluorouracil and leucovorin[48, 49]. Although available in Europe and Asia, UFT is not available in the United States.

While capecitabine, at the recommended dose of 1,250 mg/m^2 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 (i.e. Roswell Park or infusional schedule). Additionally, results from recent studies of capecitabine administered with other intravenous chemotherapies, such as oxaliplatin and irinotecan, call into question the more favorable convenience and cost effectiveness profile that have been reported with single-agent capecitabine[50–52].

C. Adjuvant Therapy with Fluoropyrimidines for Stage III Colon Cancer

Fluorouracil was thought for many years to be ineffective as adjuvant treatment for colon cancer[53–56]; a meta-analysis of randomized trials published prior to 1987 demonstrated only a small, statistically insignificant benefit for such treatment[57]. In retrospect, these randomized trials suffered from heterogeneous patient populations, inadequate sample size, and poor compliance with therapy. Two subsequent approaches to adjuvant therapy for colon cancer revived interest in fluorouracil.

In an attempt to reduce the incidence of subsequent liver metastases, several clinical trials evaluated the administration of fluorouracil into the portal circulation during the immediate postoperative period[58–63]. Although these studies failed to reduce tumor spread to the liver, a meta-analysis of ten such trials did demonstrate a modest overall survival benefit, supporting the value of a short exposure to adjuvant fluorouracil, when compliantly administered[64].

Additionally, the merits of adjuvant treatment with fluorouracil were reassessed when levamisole, an antihelminthic, was examined as a putative immunomodulating agent[65–67]. Since levamisole was eventually shown to be inactive, these studies actually represented a reassessment of the adjuvant administration of fluorouracil. A large trial of 1,296 patients conducted by the Eastern Cooperative Oncology Group (ECOG) demonstrated that adjuvant fluorouracil (and levamisole) reduced the risk of recurrence by 41% and the risk of death by 33% compared with surgery alone in patients with stage III disease[68]. After a median follow-up of 6.5 years, overall survival was increased from 47% to 60% by the addition of postoperative fluorouracil (and levamisole)[69].

Since the antitumor activity of fluorouracil was enhanced in the metastatic setting when administered with leucovorin[37], the combination of fluorouracil and leucovorin was evaluated in the adjuvant setting, where it was found to improve disease-free and overall survival[70–73]. A pooled analysis of seven randomized trials of postoperative fluorouracil-based therapy versus surgery alone demonstrated an increase in five-year disease-free survival from 42% to 58% and five-year overall survival from 51% to 61% in patients with stage III disease[74]. 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[73, 75, 76]. Furthermore, none of the various administration schedules of fluorouracil was found to be superior to any other in the adjuvant setting[77–80], although different side effect profiles were noted, similar to those observed in patients treated for metastatic disease.

Oral fluoropyrimidines have also been evaluated in the adjuvant therapy of colon cancer. In the "Xeloda in Adjuvant Colon Cancer Trial" (X-ACT), capecitabine (1,250 mg/m^2 administered twice daily on days 1 to 14 every three weeks) was shown to be equally effective when compared to the Mayo Clinic regimen of bolus fluorouracil and leucovorin, in a cohort of patients with stage III colon cancer[81]. A large, randomized trial comparing UFT and leucovorin with intravenous fluorouracil and leucovorin as adjuvant therapy also demonstrated similar rates of disease-free survival and overall survival between the two treatment arms[82].

Although nearly 75% of patients diagnosed with colon cancer are 65 years of age or older[83], such patients have been under-represented in clinical trials and are less likely to receive adjuvant therapy[84, 85]. Pooled data analyses and population-based studies have repeatedly shown a consistent and equivalent survival benefit for adjuvant therapy in all age groups[86–90], without an increase in treatment-related toxicity among older patients[87, 90–93]. When disease outcomes have been analyzed by ethnicity, higher colorectal cancer-specific mortality has been noted in African-American than in Caucasian patients[94]. Differences in comorbid disease, sociodemographic factors, stage at presentation, tumor biology, and receipt of treatment have been investigated as underlying reasons for the discrepancy in outcomes[88, 95–98]. Subset analyses of randomized treatment trials have demonstrated similar disease-free survival among African-American and Caucasian patients[99, 100], suggesting that African-Americans derive a similar degree of benefit from appropriately administered therapy as do Caucasians.

D. Adjuvant Therapy with Fluoropyrimidines for Stage II Colon Cancer

The benefit of adjuvant fluorouracil-based therapy in patients with stage II colon cancer is less clear. Subset analyses of trials that have included patients with stage II and III disease have repeatedly failed to demonstrate a statistically significant survival benefit for stage II patients receiving adjuvant therapy. A pooled analysis of seven studies demonstrated a five-year overall survival of 81% in patients who received fluorouracil-based adjuvant therapy and 80% in patients who underwent surgery alone ($p = 0.11$)[74].

Two studies have been cited in favor of the use of adjuvant therapy in patients with 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 patients with stage II and stage III disease who received fluorouracil-based therapy[101], although the statistical approach taken in this analysis has been questioned[102]. The "Quick and Simple and Reliable" (QUASAR) study, a complex comparison of four different fluorouracil-based regimens with observation alone, demonstrated a statistically significant 3.7% improvement in overall survival (80.8% vs. 77.1%) among patients with predominantly stage II colon and rectal cancer who received adjuvant treatment[103]. Interpretation of these data are clouded by: the lack of central pathologic review to verify tumor stage; a heterogeneous patient population

with inclusion of patients with both colon (71%) and rectal (29%) cancers, patients with stage III disease (8%), and patients who also received radiotherapy or portal vein infusion; multiple different chemotherapy regimens in the treatment arm; and a somewhat lower than expected survival in the two arms, when compared with other recently published adjuvant studies[104].

After systematically reviewing the available literature, the Cancer Care Ontario Program in Evidence-Based Care[105], an expert panel convened by the American Society of Clinical Oncology (ASCO) [106], and the National Comprehensive Cancer Network[107] 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, with 90% power and a significance level of 0.05[106].

It has been proposed that adjuvant chemotherapy may provide benefit to those patients with stage II disease and adverse clinical characteristics, such as T4 tumor penetration, bowel perforation, or clinical bowel obstruction[106]. Although this hypothesis has not yet been validated in a prospective, randomized clinical trial, a retrospective subset analysis of patients with stage II disease enrolled in the previously noted ECOG study which examined the adjuvant value of fluorouracil and levamisole, suggested a survival benefit for postoperative therapy in these high-risk patient subgroups[15]. 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[12], the potential benefit of chemotherapy has not been prospectively examined in patients with these risk factors.

E. Adjuvant Therapy with Fluoropyrimidines for Stage II and Stage III Rectal Cancer

Several clinical trials performed in the 1980's demonstrated that the addition of systemic chemotherapy to postoperative radiation reduced the risk of local recurrence and improved overall survival after the resection of stage II and stage III rectal cancers[108–110]. In a subsequent study, the administration of infusional fluorouracil with radiotherapy was noted to be more effective than similar radiotherapy with concurrent bolus fluorouracil[111]. More recently, the German Rectal Cancer Study Group demonstrated that preoperative combined chemoradiation therapy improved local control, decreased toxicity, and reduced the need for colostomy when compared to postoperative chemotherapy and radiation, among patients assessed by preoperative endoscope ultrasound and thought to have stage II and stage III rectal cancer[112]. No differences in disease-free or overall survival were observed between the preoperative and postoperative treatment arms. Therefore, standard of care for stages II and III rectal cancer is generally considered to be preoperative combined modality therapy with radiation and chemotherapy, followed by surgical resection with TME. Perhaps to parallel the six months of adjuvant therapy utilized among patients with resected colon cancer, an additional four months of postoperative fluorouracil-based chemotherapy are typically administered to patients with stage II or III rectal cancer.

IV. Irinotecan

Irinotecan (Camptosar®) is a semi-synthetic derivative of the natural alkaloid camptothecin that is converted by carboxylesterases to SN-38[113]. By inhibiting topoisomerase I, an enzyme that catalyzes breakage and rejoining of DNA strands during DNA replication, SN-38 causes DNA fragmentation and programmed cell death[114]. Metabolism of SN-38 occurs predominantly in the liver, where it is inactivated by glucuronidation and excreted through the biliary system. A polymorphism in the uridine diphosphate glucuronosyltransferase isoform 1A1 (UGTA1A) gene, which is responsible for glururonidation of SN-38, has been identified and leads to decreased inactivation of SN-38 with resultant increases in treatment-related

toxicity[115]. A diagnostic test for this genetic polymorphism is available, although not widely used in the clinic. Elevated serum bilirubin levels have also been associated with excess irinotecan-mediated toxicity and this drug is not typically administered to patients with hyperbilirubinemia[116]. The most commonly observed toxicities associated with irinotecan are diarrhea, myelosuppression, and alopecia[117, 118].

Randomized trials have demonstrated improvements in progression-free and overall survival when irinotecan has been added to either infusional (FOLFIRI)[119] or bolus (IFL)[120] fluorouracil and leucovorin in the initial treatment of patients with metastatic colorectal cancer. More recently, a randomized trial comparing FOLFIRI, IFL and irinotecan plus capecitabine (CAPIRI) demonstrated that those patients receiving FOLFIRI experienced longer progression-free and overall survival times, supporting the superiority of the infusional approach[121]. Additionally, CAPIRI was associated with approximately twice the rates of serious vomiting, diarrhea and dehydration, when compared with the two regimens that included intravenous fluorouracil.

Based on the encouraging results with irinotecan in patients with metastatic disease, it was anticipated that irinotecan would be an effective addition to adjuvant treatment programs for colon cancer. Three randomized trials of adjuvant irinotecan with either bolus or infusional fluorouracil and leucovorin have examined this premise[122–124]. Surprisingly, each of these studies demonstrated increased toxicity without a meaningful improvement in outcome among patients receiving irinotecan. This unanticipated failure of irinotecan to prove beneficial in the adjuvant setting has not been well explained, but underscores the importance of conducting rigorous, randomized clinical trials prior to making changes in clinical practice[125].

V. Oxaliplatin

Oxaliplatin (Eloxatin®) is a diaminocyclohexane platinum compound that forms DNA adducts, leading to impaired DNA replication and cellular apoptosis[126, 127]. 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[128–133], possibly due to oxaliplatin-induced “down-regulation” of thymidylate synthetase[134]. A cumulative sensory neuropathy, characterized by paresthesias of the hands and feet, is the primary toxicity associated with oxaliplatin.

In two randomized clinical trials in patients with metastatic colorectal cancer, the addition of oxaliplatin to infusional fluorouracil and leucovorin (FOLFOX) increased tumor response rates and disease-free survival, with a trend towards an improvement in overall survival[130, 131]. Further studies have compared the efficacy of oxaliplatin-containing and irinotecan containing combinations. In one such trial of patients with newly diagnosed metastatic disease, FOLFOX was associated with prolongations of progression-free and overall survival when compared with IFL or a combination of irinotecan and oxaliplatin[135]. Since this outcome may have been influenced by the superiority of infusional fluorouracil (as included in FOLFOX) over bolus fluorouracil (as included in IFL)[38, 121], two further studies have compared oxaliplatin and irinotecan in combination with an infusional fluorouracil schedule[133, 136]. In both of these studies, tumor response rate, progression-free survival and overall survival were statistically indistinguishable among patients receiving FOLFOX or FOLFIRI as first-line therapy. Importantly, patients receiving all three of these drugs – fluorouracil, oxaliplatin and irinotecan –were noted to have a median overall survival of approximately 20 months[133, 136, 137]. Recent randomized studies have examined whether capecitabine can replace fluorouracil and leucovorin in combination with oxaliplatin as initial therapy among patients with metastatic disease[138–140]. These trials have shown the two combinations to have similar therapeutic

benefit and toxicity, but the capecitabine-containing regimens to be more expensive due to the high cost of capecitabine[52].

In contrast to the experience with irinotecan, two randomized trials have demonstrated an improvement in disease-free survival when oxaliplatin has been added to fluorouracil and leucovorin in the adjuvant setting[141, 142]. Both the "Multicenter International Study of Oxaliplatin/Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer" (MOSAIC) study and the C-07 study of the NSABP have demonstrated a 20% reduction in the rate of colon cancer recurrence with the addition of oxaliplatin. With 6 years of follow-up, the MOSAIC study has also demonstrated a statistically significant 4.4% improvement in overall survival for those patients with stage III disease (73.0% vs. 68.6%)[104]. No such survival benefit was observed in patients with stage II colon cancer, for whom the likelihood of survival after 6 years was 87% in both treatment arms. However, a non-significant 26% reduction in disease recurrence with the addition of oxaliplatin was observed in patients with high-risk stage II disease, defined as the presence of T4 tumor stage, bowel obstruction, perforation, poorly differentiated histology, venous invasion, or examination of less than 10 lymph nodes in the resected specimen. The addition of oxaliplatin to fluorouracil and leucovorin in these trials did result in increased rates of neutropenia and neurotoxicity. Of note, approximately 10% of patients who received oxaliplatin continued to have symptomatic neuropathy 2 years after completing treatment on these clinical trials[104, 143].

VI. Angiogenesis Inhibitors

A more recently recognized strategy to control malignant proliferation and spread involves the inhibition of neoangiogenesis, or new blood vessel formation[144]. Currently, the most successful anti-angiogenic strategy has focused on inhibiting the vascular endothelial growth factor (VEGF), a soluble protein that stimulates blood vessel proliferation[145]. Bevacizumab (Avastin®) is a humanized monoclonal antibody directed against VEGF that has been examined in combination with chemotherapy in patients with advanced colorectal cancer (Table 3). In these patients, bevacizumab has been relatively well tolerated, with reversible hypertension and proteinuria representing two of the most common toxicities. Nonetheless, rare, yet serious side effects have been observed with bevacizumab, including a 1 to 2 percent risk of bowel perforation, a 3 percent risk of serious bleeding events, a 2 to 3 percent risk of arterial embolic events, and less than 1 percent risk of reversible posterior leukoencephalopathy syndrome[146–148].

Initial studies of bevacizumab demonstrated improvements in tumor response rate and progression-free survival among patients with metastatic colorectal cancer, when bevacizumab was added to fluorouracil and leucovorin[149, 150]. In subsequent randomized trials, bevacizumab was shown to prolong median overall survival (20.3 months versus 15.6 months) in combination with IFL[146] as initial treatment, and FOLFOX[151] after the failure of a prior irinotecan-containing regimen (12.9 months versus 10.8 months). Further studies have confirmed improved response rates and progression-free survival times with the addition of bevacizumab to FOLFIRI or FOLFOX in patients with untreated, metastatic colorectal cancer[121, 152].

Given the efficacy of bevacizumab in patients with metastatic colorectal cancer, the role of bevacizumab in adjuvant therapy is currently being examined in several randomized trials (Table 4). In the United States, the C-08 study of the NSABP is randomizing patients with stage II or III colon cancer to FOLFOX with or without bevacizumab, while a similar study of oxaliplatin-containing regimens with or without bevacizumab is ongoing in Europe. In addition, investigators of the ECOG have incorporated molecular markers into a large, randomized study of FOLFOX versus FOLFOX and bevacizumab in patients with high-risk

stage II colon cancer. Until the results of these trials are available, it is premature to recommend the incorporation of bevacizumab into adjuvant treatment programs for colon cancer.

VII. 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[153], and is expressed in malignancies of multiple tissues, including those of the colon, lung, breast, and head and neck[154]. In colorectal cancer, EGFR expression on the tumor cell surface has been demonstrated in up to 80% of tumors[155, 156] and tumors that express EGFR carry a poorer prognosis[157]. 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 (Erbitux®) and panitumumab (Vectibix®), have definitively demonstrated efficacy in colorectal cancer (Table 3)[158]. Although small molecule inhibitors of the intracellular tyrosine kinase domain of EGFR, such as erlotinib (Tarceva®), are effective in other solid tumors, they appear to be inactive in patients with colorectal cancer[159].

In a study of patients whose disease had progressed on a fluoropyrimidine, irinotecan, and oxaliplatin, weekly cetuximab demonstrated improvements in progression-free and overall survival (6.1 vs. 4.6 months), when compared with those treated with best supportive care alone[160]. Other studies of cetuximab in patients with irinotecan-refractory, metastatic colorectal cancer have confirmed tumor response rates of approximately 10% with cetuximab alone and 20% with cetuximab and irinotecan[161–163], indicating an ability of cetuximab to overcome irinotecan resistance in tumor cells. The main side effects of treatment with cetuximab are acneiform rash, hypomagnesemia, and infusion reactions, with approximately 3% of patients experiencing serious hypersensitivity reactions to cetuximab infusion. The presence of an acneiform rash has been positively associated with an improved response to cetuximab, among patients with metastatic colorectal cancer[164]. While initial studies mandated the immunohistochemical detection EGFR on the surface of tumor cells as a prerequisite for enrollment, the degree of surface EGFR expression has been found to correlate poorly with tumor response, and responses to cetuximab have been noted among patients without detectable EGFR by immunohistochemistry[165, 166].

Two further studies have evaluated the addition of cetuximab to first-line regimens in patients with previously untreated metastatic colorectal cancer[167, 168]. Initial results from a CALGB trial have shown an improvement in tumor response rate with the addition of cetuximab to FOLFIRI or FOLFOX (RR, 52% vs. 38%)[167]. The CRYSTAL trial, a randomized evaluation of FOLFIRI with or without cetuximab, has demonstrated improvements in tumor response rate (RR, 47% vs. 39%) and progression-free survival (median PFS, 8.9 months vs. 8.0 months), among those patients receiving cetuximab[168]. Although these results do support the efficacy of including cetuximab in first-line treatment programs, how these regimens compare with bevacizumab-containing regimens is currently unknown. Several ongoing studies, described below, have been designed to investigate this question.

The role of cetuximab in the adjuvant therapy of colon cancer has not yet been defined. The North Central Cancer Treatment Group (NCCTG) and the European Organization for Research and Treatment of Cancer (EORTC) are each registering over 2,000 patients with resected stage III colon cancer and randomizing them to receive FOLFOX alone or FOLFOX with cetuximab (Table 4). Until the results of these trials become available, the inclusion of cetuximab in adjuvant treatment programs cannot be recommended outside of a clinical trial.

Panitumumab is a humanized monoclonal antibody to EGFR that has shown similar single-agent activity as cetuximab in metastatic colorectal cancer, but with a biweekly (rather than

weekly) administration schedule[158, 169]. In an initial study, 9% of patients whose cancers had progressed after treatment with fluorouracil and either irinotecan or oxaliplatin experienced a tumor response to panitumumab[170]. In a randomized trial of 463 patients previously treated with a fluoropyrimidine, irinotecan and oxaliplatin, single-agent panitumumab improved progression-free survival when compared with best supportive care (median PFS, 8.0 vs. 7.3 weeks)[169], similar to the previously described experience with cetuximab[160]. Two ongoing studies are evaluating the addition of panitumumab to FOLFOX and FOLFIRI in patients with metastatic colorectal cancer. Panitumumab has not yet been tested in adjuvant treatment programs among patients with colon cancer, and cannot be recommended in this setting.

As only a subset of patients' tumors treated with cetuximab or panitumumab will respond to this drug, the identification and characterization of molecular markers to predict tumor response is an area of active investigation. Two such tumor characteristics have emerged from initial studies: EGFR copy number as determined by fluorescence in situ hybridization (FISH), and *K-ras* gene mutation status. Among patients treated with cetuximab or panitumumab, high EGFR gene copy number by FISH has been associated with higher tumor response rates and prolongation of disease-free and overall survival[171, 172]. In contrast, patients with tumors having mutations in *K-ras* appear to be relatively resistant to treatment with cetuximab[173–175] or panitumumab[176], with lower response rates and poorer survival. These and other molecular features may help define a subset of patients who will derive benefit from treatment with an inhibitor of EGFR.

VIII. Combined Targeted Therapy

Several ongoing studies are assessing the efficacy of combined treatment with monoclonal antibodies to VEGF and EGFR in patients with metastatic colorectal cancer (Table 3). Initial data supporting this treatment approach arose from two studies, in which patients received combinations of irinotecan, cetuximab and bevacizumab[161, 177]. Those patients receiving both cetuximab and bevacizumab had improvements in tumor response rate and progression-free survival.

In the "Panitumumab Advanced Colorectal Cancer Evaluation" (PACCE) trial, patients with previously untreated, metastatic colorectal cancer received FOLFOX and bevacizumab with or without panitumumab[178]. Surprisingly, the first planned efficacy interim analysis demonstrated an inferior outcome for those patients receiving panitumumab, with shorter survival times and increased side effects. Since patients receiving panitumumab experienced greater treatment-related toxicity, it remains uncertain whether the combination is therapeutically inferior or whether the toxic effects resulted in less exposure to active drugs. This question should be answered by an ongoing randomized trial coordinated by the National Cancer Institute (CALGB/SWOG 80405), in which patients with previously untreated, metastatic colorectal cancer are receiving FOLFOX or FOLFIRI with the addition of cetuximab; bevacizumab; or cetuximab and bevacizumab.

IX. Summary and Future Directions

Currently available data in 2008 support the use of a fluoropyrimidine, irinotecan, oxaliplatin, bevacizumab, and either cetuximab or panitumumab, in the treatment of patients with metastatic colorectal cancer. The optimal sequence of administration of these drugs remains under investigation, but patients who receive all of these available therapies can now expect a median overall survival of approximately two years (Figure 1). The success of chemotherapy in prolonging survival in the metastatic setting is also being translated to improved cure rates among patients with stage III disease. The goal of ongoing adjuvant trials evaluating

bevacizumab and cetuximab is to increase even further the improved rates of survival provided by fluorouracil, leucovorin, and oxaliplatin (Table 5).

Over the past fifteen years, deaths due to colorectal cancer in the United States have decreased by approximately nine percent[1, 179]. This decline in mortality highlights the advances made in screening, prevention, and treatment for colorectal cancer, brought about by the collaboration of gastroenterologists, medical oncologists, pathologists, primary care physicians, and surgeons. Although this progress has occurred relatively rapidly, such cancer care and new chemotherapeutic agents, in particular, have not come without a significant cost to the health care system (Table 6)[180, 181]. In the near future, physicians and society may be faced with difficult decisions regarding resource allocation and innovative cancer treatment, as we work to maintain our current trajectory of progress[181].

Glossary of Relevant Terms

AJCC TNM system
: American Joint Committee on Cancer, Tumor-Node-Metastasis Cancer Staging System

adjuvant treatment
: Treatment delivered after resection of the primary tumor, with the goal of reducing the risk of tumor recurrence by eliminating micrometastatic disease

IFL
: Irinotecan, bolus Fluorouracil (5-FU), and Leucovorin (LV)

FOLFIRI
: Infusional 5-FU, LV, and Irinotecan

CAPIRI
: Capecitabine and Irinotecan

FOLFOX
: Infusional 5-FU, LV, and Oxaliplatin

XELOX
: Capecitabine (Xeloda®) and Oxaliplatin

targeted therapy
: Therapeutic agents designed to perturb specific molecular pathways critical for tumor cell growth and survival

EGFR
: Epidermal growth factor receptor – a transmembrane protein on the surface of tumor cells, targeted by cetuximab and panitumumab

VEGF
: Vascular endothelial growth factor – a serum protein involved in stimulating new blood vessel formation, targeted by bevacizumab

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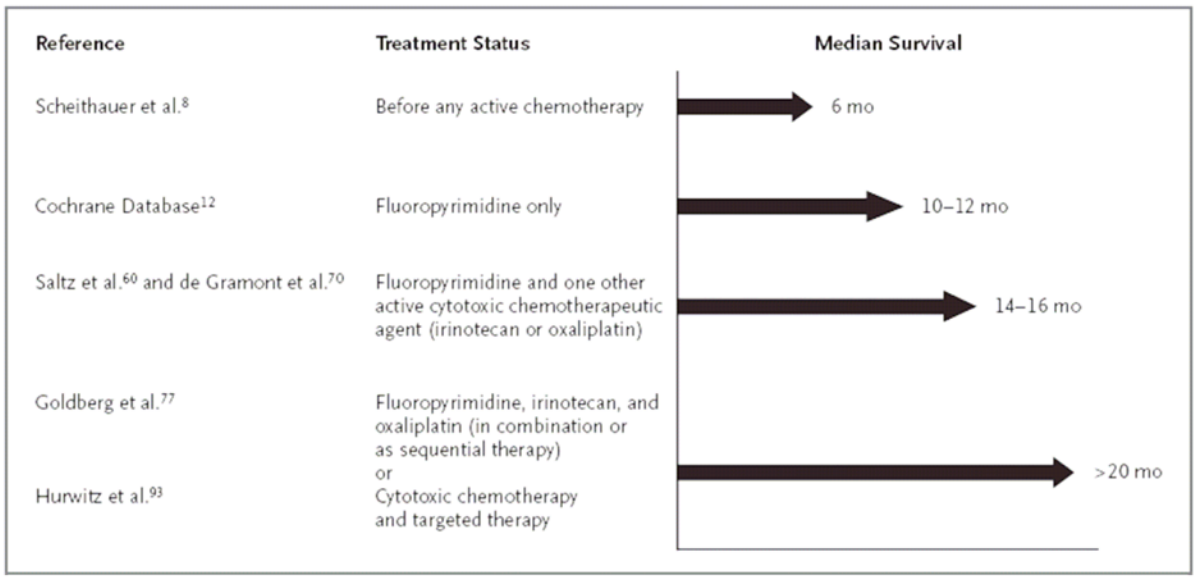

Figure 1. Trends in Median Survival Among Patients with Metastatic Colorectal Cancer
Adapted with permission from Meyerhardt and Mayer[31]
Scheithauer et al.[182]
Cochrane Database[183]
Saltz et al.[120] and de Gramont et al.[131]
Goldberg et al.[135] and Fuchs et al.[121]
Hurwitz et al.[146]

Table 1

New Chemotherapeutic Agents in the Systemic Treatment of Colon Cancer

Drug	Current Indications*			
	Metastatic Disease	FDA-approval Date	Adjuvant Therapy	FDA-approval Date
Irinotecan (Camptosar®)	Yes	Jun 1996	No	-
Capecitabine (Xeloda®)	Yes	Apr 2001	Yes	Jun 2005
Oxaliplatin (Eloxatin®)	Yes	Aug 2002	Yes	Nov 2004
Cetuximab (Erbitux®)#	Yes	Feb 2004	No	-
Bevacizumab (Avastin®)	Yes	Feb 2004	No	-
Panitumumab (Vectibix®)#	Yes	Sept 2006	No	-

* U.S. Food and Drug Administration (FDA) data accessed at www.accessdata.fda.gov

Approved for use in patients with tumors that express the epidermal growth factor receptor

Table 2

TNM Staging System for Colorectal Cancer[3–5, 30, 31]

Primary tumor (T)		
T_x	Primary tumor cannot be assessed	
T_{is}	Carcinoma in situ	
T_1	Tumor invades submucosa	
T_2	Tumor invades muscularis propia	
T_3	Tumor invades through the muscularis propria into the subserosa	
T_4	Tumor directly invades other organs or structures, or perforates visceral Peritoneum	
Regional lymph nodes (N)		
N_x	Regional lymph nodes cannot be assessed	
N_0	No regional lymph node metastases	
N_1	Metastases in one to three regional lymph nodes	
N_2	Metastases in four or more regional lymph nodes	
Distant metastases (M)		
M_x	Presence or absence of distant metastases cannot be determined	
M_0	No distant metastases detected	
M_1	Distant metastases detected	
Stage Grouping and Five-year Survival		
Stage	TNM classification	Five-year survival
I	$T_{1–2}$, N_0, M_0	> 90 %
IIA	T_3, N_0, M_0	80–85%
IIB	T_4, N_0, M_0	70–80%
IIIA	$T_{1–2}$, N_1, M_0	65–80 %
IIIB	$T_{3–4}$, N_1, M_0	50–65 %
IIIC	$T_{1–4}$, N_2, M_0	25–50 %
IV	$T_{1–4}$, $N_{0–2}$, M_1	5–8 %

Table 3

Trials of Targeted Therapies in Metastatic Colorectal Cancer

Study	Study Type	No. of Patients	Response Rate (%)	Median DFS (mo.)	Median OS (mo.)
Cetuximab					
Cunningham et al.[161]	Phase II*				
Cetuximab		111	11	1.5	6.9
Cetuximab + irinotecan		218	23	4.1	8.6
NCIC CO.17[160]	Phase III∏				
Best supportive care		285	0	N/A	4.6
Cetuximab		287	8	N/A	6.1
CRYSTAL[168]	Phase III$^{\Sigma}$				
FOLFIRI		609	39	8.0	N/A
FOLFIRI + cetuximab		608	47	8.9	N/A
Panitumumab					
Van Cutsem et al.[169]	Phase III∏				
Best supportive care		232	0	1.8	N/A
Panitumumab		231	10	2.0	N/A
Bevacizumab					
Hurwitz et al.[146]	Phase III$^{\Sigma}$				
IFL		402	35	6.2	15.6
IFL + bevacizumab		411	45	10.6	20.3
ECOG E3200[151]	Phase III#				
FOLFOX		291	9	4.7	10.8
FOLFOX + bevacizumab		286	23	7.3	12.9
Bevacizumab + Anti-EGFR					
BOND-2[124]	Phase II*				
Cetuximab + bevacizumab		40	20	4.9	11.4
Irinotecan + cetuximab + bevacizumab		43	37	7.3	14.5
PACCE[178]	Phase III$^{\Sigma}$				
FOLFOX + bevacizumab		410	46	11.0	20.6
FOLFOX + bevacizumab + panitumumab		413	45	9.5	19.3

N/A denotes that data are not available

EGFR = epidermal growth factor receptor; DFS = disease-free survival; OS = overall survival

*Second or third-line therapy after progressive disease on an irinotecan-containing regimen

∏After progressive disease on a fluoropyrimidine, irinotecan, and oxaliplatin

#Second-line therapy after progressive disease on an irinotecan-containing regimen

$^{\Sigma}$First-line therapy in previously untreated patients

Table 4

Ongoing Trials of Targeted Therapies in Resected Colon Cancer

Clinical Trial	AJCC Stage[#]	Randomization[∞]
NSABP C-08	II, III	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 +/− Bevacizumab Standard risk: observation
NCCTG N0147	III	FOLFOX +/− Cetuximab
PETACC-8	III	FOLFOX +/− Cetuximab

[#] AJCC = American Joint Committee on Cancer

[∞] FOLFOX = fluorouracil, leucovorin, and oxaliplatin

MSS = miscrosatellite stable

MSI-L = microsatellite instability – low

18q LOH = loss of heterozygosity at chromosome 18q

Table 5

Postoperative Treatment of Patients with Resected Stage II and Stage III Colon Cancer

Stage III disease: • Randomized clinical trials support six months of postoperative fluorouracil, leucovorin, and oxaliplatin • Capecitabine and intravenous bolus fluorouracil and leucovorin appear to have similar efficacy, if a fluoropyrimidine is to be used alone as postoperative therapy, • Current data do not support the use of irinotecan, cetuximab, or bevacizumab in postoperative treatment programs
Stage II disease: • Randomized clinical trials have not demonstrated a clear survival benefit to postoperative therapy in patients with standard risk stage II disease • While certain features can predict an elevated risk for disease recurrence, the benefit of postoperative therapy in patients with high risk stage II disease has not been prospectively validated in clinical trials

Table 6

Costs of Systemic Treatments for Colorectal Cancer

Regimen*	Cost per 6 Months# ($)
Bolus Fluorouracil/Leucovorin (Mayo Clinic schedule)	96
Infusional Fluorouracil/Leucovorin	352
Capecitabine	11,648
Irinotecan (every 3 weeks)	30,100
FOLFIRI	23,572
FOLFOX	29,989
Bevacizumab	23,897
Cetuximab	52,131
Panitumumab	44,720

Adapted with permission from Meropol and Schulman[181].

*FOLFIRI = infusional fluorouracil, leucovorin, and irinotecan

FOLFOX = infusional fluorouracil, leucovorin, and oxaliplatin

#Only drug costs included. Costs based upon average sales price for 70 kg patient with body-surface area of 1.7 m^2. Wholesale acquisition costs provided for panitumumab.