ABSTRACT

BACKGROUND: Every 3.5 minutes, someone is diagnosed with colorectal cancer (CRC); every 9 minutes, someone dies from CRC; and every 5 seconds, someone who should be screened for CRC is not. The 5-year mortality for people diagnosed with CRC is approximately 40%; however, survival improves substantially if the cancer is diagnosed while still localized.

OBJECTIVE: To track and review the rapid progress researchers have made in CRC.

SUMMARY: Among patients who have CRC, approximately 50% will eventually develop liver metastases. The oncology field's significant advances in the last few years, especially in CRC, challenge clinicians and patients. Multiple facets of care intersect in CRC: medical management, pharmacy management, symptom management, case management, and patient advocacy. CRC develops over many years as environmental and genetic factors interact. The American Cancer Society recommends screening all men and women older than 50 years and those at high risk at an earlier age. In the past, patients presenting with the same stage of CRC were considered similar. The staging criteria of the American Joint Committee on Cancer recognizes that subsets of patients with varying survival statistics can be identified and that each patient requires a strategic approach. The U.S. Food and Drug Administration approval of irinotecan in 1996 and oxaliplatin in 2002 changed the landscape, and ultimately, the oral agent capecitabine and the biologics bevacizumab and cetuximab also significantly expanded treatment options.

CONCLUSION: Clinicians must consider all available treatment options and regimen sequences across multiple lines of therapy, creating an early plan for each patient to extend survival while minimizing side effects.

KEYWORDS: Bevacizumab, Capecitabine, Cetuximab, Colorectal cancer, FOLFOX, Irinotecan, Oxaliplatin, Panitumumab

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Oncology as a specialty has welcomed numerous successes since 2000, especially in colorectal cancer (CRC). These CRC advances, however, have not been without certain challenges for clinicians. Despite numerous advances, clinical researchers are still learning a great deal from ongoing clinical trials. Additionally, multiple facets of care intersect in the treatment of patients with CRC: medical management, pharmacy management, symptom management, case management, and patient advocacy. Any apt and timely discussion of these advances will not only highlight the implications of the multifaceted nature of the disease but also underscore recent scrutiny from employer groups, insurance companies, and government agencies about the appropriate use of new advances that those treating cancer and CRC are now facing. With articles such as a New York Times article, “Hope, at $4,200 a Dose” now reaching lay publications, we must expect to accommodate a much more proactive, discerning public and patient.

Colorectal Cancer Epidemiology

Every 7 seconds, someone turns 50 years old; every 3.5 minutes, someone is diagnosed with CRC; every 9 minutes, someone dies from CRC; and every 5 seconds, someone who should be screened for CRC is not. The 5-year mortality for people diagnosed with CRC is approximately 40%; however, survival improves substantially if the cancer is diagnosed while it is still localized. In a typical general practice with 500 patients older than 50 years, one would expect 100 to 250 of these patients to have colorectal adenomas. Ten to thirty of these patients would be expected to have CRC, and because only one third are apt to be screened, two thirds of these patients may die unnecessarily. Unfortunately, 20% of CRC patients who do receive screening may be diagnosed in the later, less-treatable stages.

The good news is that CRC's incidence rate declined by 2.9% annually from 1998 to 2001. Regardless, colorectal cancer remains the third most common cancer in men and women in the United States. The decline in incidence may have been due, in part, to increased screening and polypl removal. The National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program monitors the incidence of all cancers throughout the United States. For both men and women, the incidence of CRC begins to rise around the age of 40 years. Incidence sharply increases at age 50 years; 92% of CRCs are diagnosed in persons aged 50 years or older. People in their 80s clearly continue to be at risk for CRC, with 12.5% of cases diagnosed after age 85. Because age is a significant risk factor and the American population is aging, the population of individuals at risk for CRC is larger than it has ever been.

Author

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CRC is very common worldwide, with 850,000 people developing it annually and 500,000 dying of the disease. Its prevalence and preventable nature makes CRC a primary focus in the oncology community. In fact, estimates indicate that gastrointestinal cancers represent about 20% of all cancers. The broad diversity in the types of patients and stages at which the disease is diagnosed creates multidisciplinary challenges.

Among patients who have CRC, a majority will eventually develop liver metastases. In 30% to 40% of CRC patients, metastases are confined to the liver when they are initially found. One quarter to one third of patients who are able to undergo resection of liver metastases will live 5 years or longer; median survival after resection is between 24 and 40 months. This high rate of liver metastases has transformed treatment and evaluation in an effort to improve cure rates. More recent data indicate that survival rates may be increasing.

The risk factors for CRC for people who live in the United States are presented in Table 1. CRC does not discriminate by gender or ethnicity in terms of incidence or mortality. Socioeconomic groups in the lower income ranges tend to present with more advanced disease. Men tend to develop CRC slightly more often than women. The disease affects all ethnic groups, and epidemiologic studies confirm that environmental exposure is probably a factor. For example, people who immigrated to the United States from Japan—where CRC was once a low-incidence disease—eventually developed CRC at a rate similar to native-born Americans. Today, Japan’s incidence of CRC is rising dramatically, probably due to Western influence, particularly in diet: dietary intake of milk, meat, eggs, and fat/oil increased remarkably in Japan from 1950 to 1970, and it remains at this elevated level today. Globally, some differences in incidence remain related to location and low socioeconomic status.

Japan’s experience supports what we know: diet is a leading risk factor for CRC.

CRC is considered a completely preventable disease by most experts, and the fact that many of its risk factors are related to lifestyle reflect that belief. High-fat diets with few fruits and vegetables, inactivity, obesity, smoking, and alcohol use increase risk. Interest in chemoprevention is high, and trials suggest that nonsteroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen) and cyclooxygenase-2 (COX-2) inhibitors (such as rofecoxib or celecoxib) may reduce the risk of CRC. The CRC-related mortality has been reduced 40% to 50% in individuals who regularly take aspirin and other NSAIDs. Additionally, COX-2 is elevated in 85% to 95% of CRCs; overexpression has been shown to decrease cancer cell death. One study of a COX-2 inhibitor (celecoxib) showed a significant reduction in polypos.

Approximately 70% of CRCs are nonhereditary, or sporadic, and about 20% are familial. Two key hereditary syndromes are familial adenomatous polyposis (FAP) and hereditary nonpolyposis colon cancer (HNPPC). The FAP syndrome develops from inherited mutations of the adenomatous polyposis coli (APC) gene, and accounts for approximately 1% to 2% of all CRC cases. Patients with FAP develop hundreds to thousands of polyps before age 30, and inevitably develop CRC. Usually, CRC develops at an early age (average, 39 years) in FAP patients, but it can be prevented by surgically removing the colon.

Lynch syndrome, or HNPPC, is caused by inherited mutation in any 1 of 5 mismatch repair (MMR) genes, and accounts for 3% to 5% of all CRC cases. The term nonpolyposis does not mean that the cancer does not emanate from polyps; it is used to distinguish HNPPC from FAP. Polyps do not develop earlier in people with HNPPC, but once they do, their tendency to become malignant more rapidly leads to a 70% to 80% lifetime risk of CRC. In these patients, CRC occurs at early age (average 44 years). Some patients with HNPPC also elect to have a complete colectomy because of their increased risk of rapid development of colon cancer. Experts stress the need for detailed family history to identify individuals who are at risk to provide appropriate screening, genetic counseling, and treatment. It has been recommended that people who have a first-degree relative who has had CRC should be screened annually beginning at age 40, rather than at age 50. Family members of patients who developed CRC very early (i.e., before age 50) should be screened 10 years before the age at which the relative developed CRC. For example, if a patient’s brother, or other first-degree relative, developed CRC at age 45, the patient should begin screening at age 35.

### The Biology

Approximately 70% to 90% of CRCs arise from adenomatous polyps. Between 15% and 30% of people in the United States eventually develop polyps—about 30% of all polyps are hyperplastic with no malignant potential. Others are adenomatous and

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Risk Factors for Colorectal Cancer (CRC)</th>
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<tbody>
<tr>
<td>- Age older than 50 years</td>
<td></td>
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<tr>
<td>- Previous CRC</td>
<td></td>
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<tr>
<td>- Polyps</td>
<td></td>
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<tr>
<td>- Family history of CRC or adenomatous polyps</td>
<td></td>
</tr>
<tr>
<td>- Inflammatory bowel disease</td>
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<tr>
<td>- Ulcerative colitis</td>
<td></td>
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<tr>
<td>- Crohn's disease</td>
<td></td>
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<tr>
<td>- Preventable risk factors</td>
<td></td>
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<tr>
<td>- High-fat diet</td>
<td></td>
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<tr>
<td>- Diet low in fruits and vegetables</td>
<td></td>
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<tr>
<td>- Physical inactivity</td>
<td></td>
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<tr>
<td>- Obesity</td>
<td></td>
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<tr>
<td>- Smoking</td>
<td></td>
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<tr>
<td>- Alcohol</td>
<td></td>
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<tr>
<td>- Possible chemoprevention</td>
<td></td>
</tr>
<tr>
<td>- NSAIDs, COX-2 inhibitors</td>
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</tbody>
</table>

COX-2 = cyclooxygenase isoenzyme 2; NSAID = nonsteroidal anti-inflammatory drug.
are considered premalignant. Polyps larger than 2 cm in diameter have a 50% chance of becoming malignant. Polyp removal, although not perfect, dramatically reduces the incidence of colorectal cancer. Previous CRC increases risk for a new primary tumor at least 4-fold; therefore, regular screening with colonoscopy becomes a lifelong requirement for these patients. In addition, people with inflammatory bowel disease, particularly ulcerative colitis and Crohn’s disease, must be screened very carefully because of their substantial risk of developing cancer.19-21

Our understanding of the molecular biology of colon cancer has grown exponentially in recent years. Colorectal cancer develops over many years as environmental and genetic factors interact. Environmentally, a high-fat diet plays a role in the development of CRC, especially in the descending and sigmoid colon. Fat makes up 40% to 50% of total caloric intake in Western countries.9 Animals fed high-fat diets develop more carcinogetic-induced colon cancers than do animals on low-fat diets.22-23 Dietary fats are converted into potentially carcinogenic substances and enhance cholesterol and bile acid synthesis by the liver. Bacterial flora convert these compounds to secondary bile acids, cholesterol metabolites, and other potentially toxic metabolites. Bile acids may activate protein kinase C—an enzyme involved in the transfer of cell signals that, when activated, induce excess cellular production.24

Colorectal cancer arises as genetic alterations that cause abnormal cellular proliferation, resulting in progression from normal colonic mucosa to adenomas or adenomatous polyps to adenocarcinoma. This progression can be induced by a series of inherited or noninherited mutations involving oncogenes and tumor suppressor genes. Inherited APC and MMR mutations are responsible for the 2 most common types of hereditary CRC. These genes are also involved in noninherited mutations, along with Kirsten-ras (K-ras), p53, and other genes. Noninherited mutations of the APC gene are also present in 60% to 80% of sporadic CRC and adenomas.

- hMLH1 is the MMR gene most commonly mutated in sporadic CRCs, especially those occurring in the right or transverse colon.
- K-ras is an important proto-oncogene involved in the regulation of cell proliferation. K-ras mutations are present in about 40% of CRCs.
- p53 is a tumor suppressor gene normally involved in preventing cells with damaged DNA from progressing through the cell cycle. This gene also inhibits angiogenesis, possibly by decreasing expression of vascular endothelial growth factor (VEGF). Loss of p53 is present in approximately 75% of CRC and is involved in the conversion of adenoma to adenocarcinoma.21

The sequence of molecular events is not a linear, but rather a collection of events that occurs over time. Using large tumor banks (repositories for tissue specimens), researchers may someday link colon cancer clinical trial efficacy data to develop both prognostic and predicted strategies based on the tumor’s molecular biology.

This information will allow clinicians to fine-tune the approach for each individual patient.

### Diagnosis and Screening

Symptoms of CRC can be nonspecific or quite fulminant. Patients may interpret occult blood in stool as hemorrhoids and fail to pursue treatment. Then again, blatant hematochezia (bloody stool) or melena (dark tarry feces containing blood) may cause patients to seek immediate treatment. Anemia may be identified serendipitously or during routine physical examination, and subsequent evaluation may find otherwise asymptomatic colon cancer. Change in bowel habits is a common symptom, particularly among individuals whose tumors grow in the sigmoid colon or rectum.

The American Cancer Society recommends screening all men and women older than 50 and those at high risk at an earlier age. Unfortunately, many Americans fail to schedule screenings. Currently, colonoscopy remains the gold standard for screening and diagnosis. Sigmoidoscopy can only evaluate the rectum and the left side of the colon, and this is a serious limitation. For example, people with HNPPC syndrome are much more likely to have a silent right-sided colon cancer. Flexible sigmoidoscopy may be done every 5 years but must be coupled with fecal occult blood testing annually. If an individual has a positive fecal occult blood test even with a negative sigmoidoscopy, that individual must be fully evaluated with the colonoscopy. Also, double contrast barium enema is occasionally used as a screening tool. The standard approach to preventing CRC is to employ routine screening and remove colon polyps.

Staging has evolved over time, and we currently use the TNM system, an evaluation system based on 3 variables: primary tumor (T), regional nodes (N), and metastasis (M). Table 2 provides the newest CRC staging. In the past, patients presenting with the same stage of CRC were considered similar. The new staging criteria recognize that they are usually quite different. Within the confines of the staging system, subsets of patients with varying survival statistics can be found. Stage II colon cancer is now subdivided into stage IIA and stage IIB, and stage III into Stages IIIA, IIB, and IIIC. Fewer than one quarter of patients present with early disease (Stage I) that is curable by surgical resection. Staging appropriately dramatically improves survival. In large part, the present discussion focuses on stage IV disease, which represents more than 20% of CRC patients at diagnosis.

Managed care pharmacists may be unfamiliar with cancer terminology in general, and treatment of CRC specifically. Table 3 defines some terms necessary to understand recent changes in its diagnosis and treatment. Surgery has always been the treatment of choice for CRC. Radiation generally is restricted to rectal cancers. Additionally, readers should keep in mind that until the mid-1990s, chemotherapy for CRC was limited to leucovorin and fluorouracil combinations. The U.S. Food and Drug Administration (FDA) approval of irinotecan in 1996...
Epidemiology, Disease Progression, and Economic Burden of Colorectal Cancer

### Table 2: American Joint Committee on Cancer (AJCC) Staging Guidelines for Colorectal Cancer (CRC)

<table>
<thead>
<tr>
<th>Disease development</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staging</td>
<td>T1 N0 M0</td>
<td>A: T3 N0 M0</td>
<td>A: T1-2 N1 M0</td>
<td>Any T Any N M1</td>
</tr>
<tr>
<td></td>
<td>T2 N0 M0</td>
<td>B: T4 N0 M0</td>
<td>B: T3-4 N1 M0</td>
<td>C: Any T N2 M0</td>
</tr>
<tr>
<td>Definition</td>
<td>Invades submucosa (T1)/muscular propria (T2)</td>
<td>Invades subserosa, nonpertenalized pericolic/peripectal tissues (T3) |</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Invades other organs or structures/visceral peritoneum (T4)</td>
<td>Involves 1-3 (N1) or more (N2) lymph nodes</td>
<td>Involves distant metastases</td>
<td></td>
</tr>
<tr>
<td>Usual treatment</td>
<td>Surgery</td>
<td>Surgery + chemotherapy</td>
<td>Surgery + chemotherapy</td>
<td>Chemotherapy + surgery</td>
</tr>
</tbody>
</table>


and oxaliplatin in 2002 changed the landscape, and ultimately, the biologics bevacizumab and cetuximab also significantly expanded treatment options. Oncology is also a field that uses many (and sometimes confusing) acronyms. These, too, are addressed in Table 3. Sometimes, clinicians, researchers, or institutions modify standard regimens, and they are then given a similar but new name (e.g., FOLFOX4, FOLFOX6).

The most common treatment for patients with localized CRC is surgery, which is frequently curative. Although adjuvant chemotherapy in stage II disease has been investigated, its use remains controversial, with overall survival ranging from approximately 75% to 80% with surgery alone. Surgery and adjuvant chemotherapy are common treatments for patients with stage III disease. Conversely, the overall survival among individuals with stage IIIC colon cancer, even after surgical resection, is as low as 15%. The differences in survival are striking. Combination chemotherapy is given for metastatic disease when possible. Chemotherapy with radiation is given before (favored) or after surgery in most patients with stage II or III rectal cancer. Thus, one strategy for all patients is inappropriate. Staging involves separating patients into 3 groups: those with liver metastases, those with lung metastases, and those with more disseminated disease.

For patients presenting with liver metastases at the first diagnosis, clinicians can select one of several pathways. Treatment might begin with chemotherapy with a biologic, and depending on patient response, make a decision about whether to proceed with the primary tumor removal and liver resection. Alternatively, the oncologist might schedule surgery to remove the primary colon lesion and perhaps remove the liver lesion. Liver resection, if feasible, can also be scheduled for a later time. Another option is colectomy followed by neoadjuvant chemotherapy and then liver resection.

Patients unable to undergo curative resection must be evaluated for symptoms. Bleeding or obstruction may be an indication for surgery before chemotherapy. In relatively asymptomatic patients, proceeding with chemotherapy can shrink the primary tumor as well as metastatic disease. Oncologists generally find that among patients with hepatic metastases, approximately 70% are considered resectable at diagnosis. However, a sizable number of patients even with multiple lesions may be able to undergo successful surgery.

Numerous studies have examined surgical rates in patients with metastatic colon cancer who have had surgical resection, and the 5-year survival rate (the point at which oncologists consider a patient cured) ranges from 25% to nearly 60%, compared with patients with metastatic disease who have not had resection; their 5-year survivorship rate is between 5% and 10%.

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TABLE 3  Colorectal Cancer Terms and Acronyms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Adjuvant chemotherapy</td>
<td>Chemotherapy treatment that is given after complete surgical resection of cancer. Its aim is to treat presumed residual micrometastatic disease.</td>
</tr>
<tr>
<td>CEA</td>
<td>Carcinoembryonic antigen, a serum marker often elevated in people with some adenocarcinomas, in particular colon cancer. It may also be present in the serum of patients with pancreas, breast, ovary, or lung cancer. CEA is normally produced during the development of a fetus. Production stops before birth, and it usually is minimally present in the blood of healthy adults.</td>
</tr>
<tr>
<td>CapIri</td>
<td>A regimen similar to FOLFOX (see below) that substitutes oral capecitabine for intravenous fluorouracil</td>
</tr>
<tr>
<td>CapOx</td>
<td>A regimen similar to FOLFOX (see below) that substitutes oral capecitabine for intravenous fluorouracil</td>
</tr>
<tr>
<td>Downstage</td>
<td>Employment of chemotherapy or chemoradiation to reduce tumor burden and thus reduce the clinical stage of the disease</td>
</tr>
<tr>
<td>FOLFOX</td>
<td>A chemotherapy regimen for treatment of advanced colorectal cancer or adjuvant treatment, consisting of concurrent treatment with fluorouracil, leucovorin (folinic acid), and oxaliplatin. Patients typically receive a treatment every 2 weeks, and leucovorin and oxaliplatin are administered as an infusion lasting 2 hours, followed by fluorouracil, which is administered in 2 different ways: a bolus injection and a continuous infusion lasting 46 hours.</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>A chemotherapy regimen for treatment of advanced colorectal cancer, consisting of concurrent treatment with irinotecan, leucovorin (folinic acid), and fluorouracil. A standard regimen would include irinotecan as a 90-minute infusion concurrently with a fluorouracil bolus, then fluorouracil intravenous infusion over 46 hours. This cycle is typically repeated every 2 weeks.</td>
</tr>
<tr>
<td>IFL</td>
<td>A chemotherapy regimen for treatment of colorectal cancer that employs bolus fluorouracil and leucovorin with irinotecan—IFL is no longer recommended as a treatment regimen.</td>
</tr>
<tr>
<td>IROX</td>
<td>A chemotherapy regimen using irinotecan and oxaliplatin without fluorouracil</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>A chemotherapy treatment that is given before surgery</td>
</tr>
</tbody>
</table>

Before combination chemotherapy and new treatment strategies were available, researchers identified several adverse prognostic factors that might preclude surgical resection. Prognosis is poorer when

- the patients’ original tumor is stage III or higher;
- patients have multiple lesions;
- the lesions are larger than 3 cm, involve satellite lesions, or occur in both lobes of the liver;
- metastases occur within the first 12 to 30 months; and/or
- metastases occur outside the liver and primary colon site.

Sidebar 1

Case 1: Patient Presentation

A 62-year-old nurse presented 10 months ago with a sigmoid colon lesion. She had a moderately differentiated, ulcerated 3×2 cm lesion (Stage II). After successful surgical resection, she received 6 months of adjuvant fluorouracil and leucovorin. Last month her carcinoembryonic antigen (CEA, used as a tumor marker for CRC) was elevated to 6.8 ng/mL. After seeing this individual, how would you proceed? Would you do a colonoscopy, a computed tomography (CAT) scan of the chest and abdomen and pelvis, a positron emission tomography (PET) scan, or an anti-CEA nuclear medicine scan?

A CAT scan is appropriate. This patient’s rise in CEA in less than a year suggests the development of metastatic disease. Current surveillance strategies after surgery and adjuvant therapy for CRC are imperfect. Testing for CEA is the most widely used test, and it can be an early warning of metastases. Once it rises, the patient needs a full evaluation for metastatic disease. Colonoscopy is appropriate. In most individuals, the National Comprehensive Cancer Network (NCCN)26 recommends colonoscopy 1 year after surgery to identify new polyps or a second primary tumor.

Although a PET scan would not be the first tool to evaluate metastatic disease, it can be helpful, particularly if further surgery to resect metastatic disease is being considered. The anti-CEA scan is available but is not widely used in the United States and certainly would not be a first choice.

The patient’s colonoscopy was normal, but a CAT scan revealed 2 lesions (3×3 cm) in the right lobe of the liver. The PET scan confirmed the 2 lesions and found no other evidence of metastatic disease. The clinical team and patient chose surgical resection following chemotherapy. The only opportunity to cure the person is with surgery, although the benefit of postoperative chemotherapy in this setting is unknown.

Prognostic factors, however, may be evolving with the introduction of modern chemotherapy approaches.⁵

Approaches for Liver Metastases

Hepatic artery infusion (HAI) is the infusion of chemotherapy into the hepatic artery via a surgically implanted pump. Chemotherapy drugs can be injected periodically into the chamber of the pump, which then employs a gas-driven bellows to send chemotherapy by a hepatic artery catheter directly into the liver. Fluorodeoxyuridine (FUDR) has been the chemotherapy of choice for many years for HAI; compared with other agents, FUDR has the highest rate of extraction by the liver. Trials have compared HAI to systemic therapy with fluorouracil.³⁴-⁴⁰ They have certain limitations and do not confirm a definitive survival benefit, but prior to the introduction of intravenous combination therapy, HAI produced the highest response rate seen in colon cancer: 50% to 60%. Since response rates with FOLFOX and FOLFIRI are similar to HAI, there may be a more limited role for HAI-delivered therapy.

Hepatic artery infusion has been tested for patients whose liver metastases have been resected.³⁴-⁴⁰ These trials are also imperfect; however, they show without question that HAI recipients tend to experience less hepatic recurrence than those who did not.
Experience with radiofrequency ablation (RFA, the use of electrodes to heat and destroy abnormal tissue) in patients with hepatic metastasis from CRC is increasing. Open surgery, percutaneous RFA, and laparoscopic RFA have been studied. Findings cannot confirm that RFA is curative—recurrence rates range from very low to almost 50% depending on the underlying presentation and number of lesions. If cure is the goal, surgical resection remains the gold standard, but in patients who are not good surgical candidates, RFA may be an option. Currently, many surgical patients have a combination of surgical resection with concurrent operative RFA for lesions that cannot be resected; the cure rate is unknown.

Adam et al. evaluated the long-term survival of patients who initially had inoperable colorectal liver metastases that subsequently responded to systemic chemotherapy and eventually allowed surgical resection. They used prognostic factors of outcome to create a model predicting survival in a preoperative setting. In a consecutive series of 1,439 patients with colorectal liver metastases from 1988 to 1999 at one hospital, 335 (23%) received initial resection, and 1,104 (77%) initially unresectable patients were treated with oxaliplatin-based or irinotecan-based chemotherapy, although 12% of patients received fluorouracil and leucovorin alone. After a documented response to chemotherapy was observed, 138 (12.5%) of patients underwent secondary hepatic resection resulting in a 33% 5-year survival. An average of 10 courses of chemotherapy were administered preoperatively. The 5-year survival was 48% for the initial surgical resection group. Four preoperative risk factors (a rectal tumor, an elevated CA 19-9, tumor larger than 10 cm, and 3 or more metastatic sites) predicted poorer outcome from this strategy. Neoadjuvant therapy results are changing the way oncologists think about patients with metastatic disease, introducing the concept of surgical resection for patients with previously unresectable disease. Survival expectancy at 5 years for patients with risk factors was also reported: 1 risk factor, 23% to 41%; 2 risk factors, 14%; and 3 or 4 risk factors, 0% to 1%. Although chemotherapy can produce a complete response as measured by CAT scan, most patients will have residual tumor cells visible in pathology specimens; therefore, we cannot say at this time that neoadjuvant chemotherapy alone is curative.

With FOLFOX, the maximum reduction in tumor size is usually seen within 3 months. In addition, longer periods of chemotherapy administration can produce liver toxicity with nonalcoholic steatohepatitis, which can potentially increase surgical morbidity. Therefore, NCCN currently recommends administering approximately 3 months of chemotherapy, then surgery, and then additional chemotherapy after surgery. Clinical trials are currently exploring this approach. The strategy is identical for people with isolated lung metastases.

Advanced metastatic disease is usually terminal. NCCN recommends that for patients who present with, for example, abdominal peritoneal disease, clinicians first rule out obstruction. Chemotherapy is an immediate option in nonobstructing disease, but other options (colon resection, colostomy, bypass, or stenting) must be considered if an obstruction is present. Cases 2 and 3 demonstrate some of these principles (see Sidebar 2).

In 2002, the FDA approved oxaliplatin, a third-generation platinum analog that induces DNA cross-links and results in apoptosis. Currently, it is approved for both the first- and second-line therapies of CRC. The biologics made their entry shortly thereafter. Bevacizumab is a humanized monoclonal antibody to VEGF, a key regulator of tumor angiogenesis. Approved in 2004, it is used in combination with fluorouracil regimens as first-line or second-line treatment for metastatic CRC. Cetuximab is a chimeric antibody to the epidermal growth factor receptor (EGFR) and was approved in 2004 for the treatment of second-line
metastatic CRC in patients who over-express EGFR. Cetuximab in combination with irinotecan is indicated for patients who are refractory to irinotecan-based chemotherapy. As a single agent, cetuximab is indicated for patients who are intolerant to irinotecan-based chemotherapy.

Grothey and colleagues analyzed data from 7 phase 3 trials (N = 3,187) in advanced CRC to compare the proportion of patients receiving fluorouracil-leucovorin, irinotecan, and oxaliplatin administered over time with median overall survival (OS), using a weighted analysis. They reported median OS correlated significantly with the percentage of patients who received all 3 drugs (but no biologics) in the course of their disease. It did not correlate with the percentage of patients who received any second-line therapy. The use of combination therapies as first-line therapy was associated with an improvement in median survival of 3.5 months (95% confidence interval [CI], 1.27-5.73 months; \( P = 0.0083 \)). This represented a dramatic shift in survivorship from roughly 13% to nearly 22% and in median survivorship at 2 years. Their conclusion: the 3 active drugs should be available to all appropriate patients with advanced CRC to maximize OS. They also proposed that OS is not the most appropriate endpoint to assess the efficacy of a first-line treatment in CRC.

An updated report including 4 additional phase 3 trials (for a total of 11 studies, N = 5,768) validated the initial analysis. It confirmed that the percentage of patients with advanced CRC receiving 3 drugs during the course of their disease were likely to have longer OS. Again, the researchers gathered data on exposure to fluorouracil/leucovorin, irinotecan, and oxaliplatin. They concluded that a strategy of making all active agents available to patients with advanced CRC appears to be more important than the use of an individual therapy, and that combination therapy should remain the standard of care for first-line treatment.

### The Treatment Continuum

Clinicians now have more options for treating patients with CRC. This treatment continuum defines a strategic approach for each patient. It encourages consideration of all available treatment options and regimen sequences across multiple lines of therapy, creating an early plan for each patient to extend survival while minimizing side effects. Flexibility is crucial, too, so patients who experience oxaliplatin neurotoxicity, for example, can be shifted to a different but equally effective regimen. This replaces the “treat as you go” approach used historically. The treatment continuum concept is consistent with the current NCCN guidelines for metastatic CRC treatment and puts the guidelines in the context of patient benefits.

Safety and efficacy are emphasized as researchers have examined not only different drugs, but also different administration techniques. For example, in Europe, there is traditionally more emphasis on continuous infusion fluorouracil; this regimen is believed to be safe, more efficacious, and more conducive to combination therapy. This belief led to the development of infusion regimens, including FOLFOX and FOLFIRI. In the United States, researchers and clinicians emphasized bolus therapy. The evidence, however, now indicates continuous intravenous infusion (CIV) is clearly safer.

The Meta-analysis Group in Cancer conducted a meta-analysis of all randomized trials (N = 1,219) that compared fluorouracil bolus with CIV, including toxicities, especially grades 3 to 4 anemia, thrombocytopenia, leukopenia, neutropenia, nausea/vomiting, diarrhea, mucositis, and hand-foot syndrome. They found that fluorouracil bolus was more likely to cause hematologic toxicity, mainly neutropenia (31% with bolus versus 4% with CIV; \( P < 0.0001 \)) but less likely to be associated with hand-foot syndrome (13% with bolus versus 34% with CIV; \( P < 0.001 \)). The other nonhematologic toxicities did not differ significantly between groups. Independent prognostic factors were age, gender, and performance status for nonhematologic toxicities; they were performance status and treatment for hematologic toxicities and age, gender, and treatment for hand-foot syndrome.

Saltz et al. showed that irinotecan prolongs survival in CRC patients. They compared cohorts receiving either a combination of irinotecan and bolus fluorouracil and leucovorin (IFL) or bolus doses of fluorouracil and leucovorin as first-line therapy for metastatic CRC. A third group of patients received irinotecan alone. Endpoints were progression-free survival and overall survival. Patients were randomly assigned to receive:

- irinotecan (125 mg/m\(^2\) IV), fluorouracil (500 mg/m\(^2\) bolus), and leucovorin (20 mg/m\(^2\) bolus) weekly for 4 weeks every 6 weeks (N = 231); or
- fluorouracil (425 mg/m\(^2\) bolus) and leucovorin (20 mg/m\(^2\) bolus) daily for 5 consecutive days every 4 weeks (N = 226); or
- irinotecan alone (125 mg/m\(^2\) IV) weekly for 4 weeks every 6 weeks (N = 226).

In an intention-to-treat analysis, treatment with irinotecan, fluorouracil, and leucovorin resulted in significantly longer progression-free survival (median, 7 months versus 4.3 months; \( P = 0.004 \)), a higher rate of confirmed response (39% versus 21%; \( P < 0.001 \)), and longer overall survival (median, 14.8 months versus 12.6 months; \( P = 0.04 \)) than irinotecan alone or fluorouracil and leucovorin. Results for irinotecan alone were similar to those for fluorouracil and leucovorin. On the basis of analysis of adverse events, adding irinotecan to the regimen of fluorouracil and leucovorin did not compromise the quality of life.

A second trial also examined the efficacy of irinotecan and fluorouracil to treat 387 previously untreated patients. They were randomly assigned to irinotecan plus infusion fluorouracil and leucovorin (N = 199) or an infusion fluorouracil-leucovorin combination alone (N = 188). Investigators could prescribe a once-weekly or every-2-weeks treatment cycle. The response rate was significantly higher in patients in the irinotecan group than in those in the no-irinotecan group (49% as opposed to 31%; \( P < 0.001 \)), as was time-to-progression (median 6.7 as opposed to 4.4 months; \( P < 0.001 \)). Overall survival was also higher in the irinotecan group (15.6 months as opposed to 13.7 months; \( P < 0.001 \)).

In summary, the treatment continuum is a strategic approach for treating patients with CRC. It emphasizes safety and efficacy, and allows for flexibility in treatment options. The use of continuous infusion regimens, such as FOLFOX and FOLFIRI, is associated with improved outcomes compared to bolus therapy. The choice of treatment regimen should be individualized based on patient characteristics and treatment goals.
higher (median 17.4 as opposed to 14.1 months). Patients receiving irinotecan were more likely to develop some grade 3 and 4 toxic effects, but did so in a predictable manner. Adverse events were reversible, noncumulative, and manageable. The investigators suggested that the combination therapy be considered as a reference first-line treatment for metastatic CRC.

Evolving First-Line Treatments

Goldberg et al. looked at 3 different 2-drug combinations in patients with advanced metastatic CRC who were previously untreated.\(^5^4\) Patients were randomly assigned to receive

- irinotecan and bolus fluorouracil plus leucovorin (IFL, control combination), or
- oxaliplatin and infused fluorouracil plus leucovorin (FOLFOX), or
- irinotecan and oxaliplatin (IROX).

The investigators accrued 795 patients between May 1999 and April 2001. FOLFOX was associated with a median time-to-progression of 8.7 months, response rate of 45%, and median survival time of 19.5 months. These results were significantly superior to all endpoints observed for IFL (6.9 months, 31%, and 15 months, respectively) and for first-to-progression and response for IROX (6.5 months, 35%, and 17.4 months, respectively). The FOLFOX regimen’s adverse event profile was significantly better in terms of severe nausea, vomiting, diarrhea, febrile neutropenia, and dehydration. It was, however, associated with more sensory neuropathy and neutropenia. Thus, the investigators found the FOLFOX regimen active and comparatively safe. In addition to supporting FOLFOX as first-line treatment for metastatic CRC, the irinotecan/oxaliplatin regimen is an appropriate alternative for fluorouracil-intolerant individuals.

In Europe, the FOLFOX and FOLFIRI infusion schedules were both used. An Italian research group compared FOLFIRI with FOLFOX in previously untreated patients (N = 360) with advanced CRC.\(^5^5\) Patients were randomly assigned to receive, every 2 weeks, either

- arm A (N = 164) FOLFIRI: irinotecan 180 mg/m\(^2\) on day 1 with leucovorin 100 mg/m\(^2\) administered as a 2-hour infusion before fluorouracil 400 mg/m\(^2\) administered as an intravenous bolus injection, and fluorouracil 600 mg/m\(^2\) as a 22-hour infusion immediately after fluorouracil bolus injection on days 1 and 2 (LV5FU2) or
- arm B (N = 172) FOLFOX4: oxaliplatin 85 mg/m\(^2\) on day 1 with the LV5FU2 regimen).

Overall response rates were 31% in arm A and 34% in arm B. Median time-to-progression, duration of response, and overall survival were similar in both arms. Patients in arm A reported more alopecia and gastrointestinal disturbance; those in arm B experienced more thrombocytopenia and neurosensory adverse effects. Serious toxicity was uncommon for both regimens. Both therapies are equally effective as first-line treatments, although their toxicity profiles differ.

Tournigand et al. randomized patients to FOLFOX6 or FOLFIRI and allowed crossover to the other regimen after disease progression.\(^5^6\) In arm A, 109 patients received FOLFIRI and 81 of these patients were treated with second-line FOLFOX upon progression. In arm B, 111 patients received FOLFOX and 69 of these patients were treated with second-line FOLFOX upon progression. Median survivals were similar in the arms: 21.5 months in arm A versus 20.6 months in arm B. Median second progression-free survival was 14.2 months in arm A versus 10.9 months in arm B. First-line response rates were similar, 54% and 56%, respectively. Grade 3/4 mucositis, nausea/ vomiting, and grade 2 alopecia were more frequent with FOLFIRI, and grade 3/4 neutropenia and neurosensory toxicity were more frequent with FOLFOX6. This trial indicates that the sequence used is irrelevant; overall survivorship of about 21 months is expected with either approach. Either regimen is an appropriate platform on which to build other treatment approaches. The differences in toxicities may guide treatment choice.

Enter Oral Agents

Two randomized phase 3 trials compared oral capecitabine monotherapy with the Mayo regimen of intravenous bolus fluorouracil and leucovorin (daily for 5 days) as first-line therapy in patients with newly diagnosed metastatic CRC.\(^5^7,5^8\) Data obtained from each trial were pooled.\(^5^9\) Patients received either capecitabine 2,500 mg/m\(^2\) daily (1,250 mg/m\(^2\) twice daily) on days 1 to 14 every 21 days, or fluorouracil 450 mg/m\(^2\) plus leucovorin 20 mg/m\(^2\) IV daily on days 1 to 5 every 28 days. The primary endpoint was the overall objective tumor response rate (RR: complete response and partial response). Capecitabine treatment was associated with significantly higher RR than fluorouracil and leucovorin (25.7% versus 16.7%, respectively). However, no difference in overall survival (median of 12.9 months with each) between treatments was observed. Subgroup analysis indicated that the difference in response was observed irrespective of previous adjuvant therapy, site of metastasis, or age.\(^5^9\)

A dose of capecitabine 2,500 mg/m\(^2\) daily is higher than would be generally used in clinical practice in the United States, with most practitioners administering 2,000 mg/m\(^2\). By observation, clinicians have determined that people in the United States do not tolerate capecitabine in the same doses that Europeans do. One theory is that the heavily fortified diet in the United States is folate-rich, accounting for increased fluoropyrimidine toxicity.

Studies of combinations of capecitabine identical to those using FOLFOX and FOLFIRI have been reported. Building on their previous work, Grothey et al. designed a randomized phase 2 trial whereby patients received either XELOX (N = 80) or XELIRI (N = 77) and upon progression were then treated with the alternative regimen: XELIRI (N = 34) or XELOX (N = 31).\(^6^0\) The doses for each 22-day cycle included capecitabine, 1,000 mg/m\(^2\) twice daily on days 1 to 14; irinotecan,
1,000 mg/m² twice daily on days 1 and 8; and oxaliplatin, 70 mg/m² on days 1 and 8. Overall survival for the 2 sequential regimens was similar for first-line XELOX versus XELIRI (16.5 months versus 18.8 months, respectively) as was initial response rate (51% versus 41%, respectively) and progression-free survival (6.2 months versus 7.1 months, respectively).

**Enter the Biologics**

The next major advancement for CRC was the introduction of biologics, a form of targeted therapy. Bevacizumab is an antibody directed against VEGF, a soluble protein instrumental in angiogenesis. Use of targeted therapies in combination with cytotoxic agents is expanding options within the lines of therapy.

To determine whether the addition of bevacizumab to IFL improves survival among metastatic CRC patients, Hurwitz and colleagues randomly assigned 813 patients in a blinded fashion with previously untreated metastatic CRC to receive either IFL (the standard at the time) plus bevacizumab (N=402) or IFL plus placebo (N=411). A third arm included fluorouracil and leucovorin plus bevacizumab. After a predetermined interim safety analysis confirmed the safety of the IFL regimen with bevacizumab, the fluorouracil and leucovorin arm of the trial was discontinued. Patients received 5 mg/kg bevacizumab every 2 weeks. The primary endpoint was overall survival, and secondary endpoints were progression-free survival, response rate, duration of response, safety, and quality of life.

Adding bevacizumab to irinotecan plus bolus fluorouracil and leucovorin (IFL) resulted in a significant and clinically meaningful improvement in survival (20.3 versus 15.6 months; P<0.001). Median duration of therapy was 9.3 months in the arm receiving irinotecan plus fluorouracil and leucovorin plus bevacizumab and 6.4 months in the arm receiving irinotecan plus fluorouracil and leucovorin. The discontinuation rate due to adverse events was 8.4% in the irinotecan plus fluorouracil and leucovorin plus bevacizumab arm and 7.1% in the irinotecan plus fluorouracil and leucovorin arm. The incidence of any grade 3 or 4 adverse events was approximately 10% higher among patients receiving IFL plus bevacizumab than among those receiving IFL plus placebo; this was largely due to patients receiving the IFL plus bevacizumab regimen having higher incidences of grade 3 hypertension (11% versus 2.3%), as well as grade 4 diarrhea (32.4% versus 24.7%) and leucopenia (37% versus 31.1%).

In an abstract presenting a subsequent subgroup analysis, Hedrick et al. looked at use of irinotecan plus bolus fluorouracil and leucovorin plus bevacizumab followed by oxaliplatin second-line therapy. They found that irinotecan plus bolus fluorouracil and leucovorin plus bevacizumab followed by oxaliplatin second-line can prolong survival to 25.1 months. This subset analysis also suggests that a treatment strategy incorporating all active agents over the course of disease optimizes overall survival. Exposing patients to more active drugs, now including biologics, may push median survivorship even farther.

The Eastern Cooperative Oncology Group sponsored a trial for CRC patients who progressed after therapy with either fluorouracil or irinotecan plus fluorouracil. Patients were randomized to receive (1) bevacizumab plus FOLFOX4 or (2) FOLFOX4 alone or (3) bevacizumab alone. Response rate, progression-free survival, and overall survival were improved when bevacizumab was added to FOLFOX. The addition of second-line bevacizumab 10 mg/kg every 2 weeks to FOLFOX significantly improved median overall survival from 10.7 to 12.5 months. As a single agent, however, bevacizumab had minimal, if any, activity and therefore is not recommended as a therapeutic choice outside the clinical trial.

A randomized phase 2 trial by Hochster et al. added bevacizumab to oxaliplatin combination chemotherapy in patients with metastatic CRC. This randomized study assesses the safety and tolerability of each of 3 oxaliplatin plus fluoropyrimidine regimens (bolus, infusional, or oral fluoropyrimidine) alone in TREE1, and with bevacizumab in TREE2. Regardless of the chemotherapy employed, adding bevacizumab improved the response rate. These data with bevacizumab in colon cancer are consistent across trials and across chemotherapy regimens. The trial by Hochster et al. also suggested that the bolus fluorouracil/oxaliplatin regimen is inferior for patients with advanced colon cancer and cannot be recommended.

Clinicians need to monitor bevacizumab for its potential adverse events. There is a risk of bleeding, which often manifests as mild epistaxis. The risk of venous thromboembolism does not differ between the groups who received bevacizumab and who did not, so previous history of venous thromboembolism does not preclude its use. Bevacizumab may be administered to patients who are anticoagulated for venous thrombosis. Proteinuria is a concern, as is hypertension, and must be monitored. The most recent warning for bevacizumab alerts clinicians to the possibility of reversible posterior leukoencephalopathy (RPLS), a condition similar to what is associated with malignant hypertension or eclampsia during pregnancy. Even mild hypertension or a change in blood pressure (e.g., from 90/60 to 120/85), can result in RPLS and will require discontinuing bevacizumab.

The risk of gastrointestinal perforation secondary to bevacizumab is rare, but real and potentially life threatening. It has been seen across trials. Episodes with or without intra-abdominal abscesses have occurred throughout treatment (i.e., they did not correlate with duration of exposure). Typical presentation was reported as abdominal pain associated with symptoms (e.g., constipation and vomiting). Bevacizumab therapy should be permanently discontinued in patients with gastrointestinal perforation.

Wound-healing complication (wound dehiscence) is also possible and is an important consideration in patients undergoing
surgery. Because of its long half-life, patients receiving bevacizumab-containing regimens must be bevacizumab-free for a minimum of 6 weeks before surgery. The risk of arterial thromboembolism is a concern, particularly for the elderly with a previous history of arterial thromboembolism, such as cardiovascular accident, myocardial infarction, transient ischemic attacks, or angina.66

One of the most significant findings in modern colon cancer therapy is that chemotherapy compared with best supportive care (BSC) is superior even when toxicity is considered. Two trials have also examined irinotecan as second-line therapy.67,68 A British study compared irinotecan to BSC prospectively; 279 patients with metastatic CRC who had failed fluorouracil therapy were randomized 2:1 to receive either BSC plus treatment with irinotecan 350 mg/m² every 3 weeks, or BSC alone. In the BSC group, 14% of patients were still alive at 1 year compared with the 36% of patients alive at 1 year after treatment with irinotecan (P = 0.001).67 Patients receiving irinotecan lived significantly longer without performance status deterioration; and deterioration in quality of life (50% reduction from baseline) occurred significantly later in the irinotecan-treated patients than in controls.

Rougier and colleagues evaluated 101 patients randomized to receive 1 of 3 second-line regimens68:

- irinotecan 180 mg/m² on day 1 followed by a leucovorin 200 mg/m² infusion, before a fluorouracil 400 mg/m² bolus followed by a 5-FU 600 mg/m² infusion (LV5FU2 regimen), on days 1 and 2 every 2 weeks (N = 35); or
- oxaliplatin 85 mg/m² on day 1 followed by the LV5FU2 regimen on days 1 and 2 every 2 weeks (N = 33); or
- oxaliplatin 85 mg/m² followed by irinotecan 200 mg/m², both on day 1 every 3 weeks (N = 33).

Overall survivals were 12.2 months (95% CI, 9.2-16.0), 11.5 months (95% CI, 9.0-14.1), and 11.0 months (95% CI, 8.1-12.2), respectively. These researchers determined that second-line treatment with irinotecan/LV5FU2, oxaliplatin/LV5FU2, or oxaliplatin/irinotecan controls tumor growth well, increases survival, and is safe. The intention-to-treat objective response rates (ORRs) were 11.4% (95% CI, 3.2-26.7), 21.2% (95% CI, 9.0-38.9), and 15.2% (95% CI, 5.1-31.9), respectively, in the 3 arms. Tumor growth control was ≥60% for all 3 combinations.

**Cetuximab**

Cetuximab is a monoclonal antibody that specifically blocks EGFR. Cunningham et al. examined cetuximab’s efficacy in combination with irinotecan with that of cetuximab alone in metastatic CRC refractory to irinotecan.69 Patients (N = 329) whose CRC progressed during or within 3 months of treatment with an irinotecan-based regimen were randomized to receive cetuximab plus irinotecan (N = 218) or cetuximab monotherapy (N = 111). The combination-therapy group was significantly more likely to respond than the cetuximab-alone group (22.9% versus 10.8%; P = 0.007). Median time-to-progression was also significantly greater in the combination therapy group. The addition of irinotecan increased toxicity (i.e., diarrhea and neutropenia) as expected. Thus, cetuximab’s activity alone (unlike that of bevacizumab alone) or in combination with irinotecan was determined to be significant. Because this work is from phase 2 trials, we do not have survivor statistics for cetuximab.

Cetuximab’s complete prescribing information indicates that cetuximab is appropriately used in tumors that stain positive for EGFR; however, neither EGFR-staining nor the percentage of cells expressing EGFR correlate with response rate.70 Furthermore, there are now data to support the use of cetuximab for EGFR-negative patients.71

With cetuximab and other EGFR-targeted therapies, skin toxicity may actually be a surrogate for efficacy. Trials have shown that those who develop the most pronounced acneiform rash are those who are most likely to benefit.72 Because cetuximab and bevacizumab have different toxicity profiles and biologic targets, theoretically it would be appropriate to look at cetuximab and bevacizumab combinations. A randomized phase 2 trial examined cetuximab and bevacizumab with or without irinotecan.73 The response rate was significant for patients receiving second-line or third-line treatment and superior for patients treated with the irinotecan-cetuximab-bevacizumab combination (38%, 8.5 months time-to-progression, compared with 23% time-to-progression for cetuximab and bevacizumab).

These data have stimulated the development of additional randomized phase 3 trials. It is now clear that second-line and third-line treatment can extend the benefit of first-line treatment. It increases response rates across treatment lines, extends overall survival using combinations of cytotoxic and targeted therapies, and appears to sensitize previously refractory tumors.

The challenge of these new regimens is that toxicity can be significant and patients grow weary of ongoing treatment. To address this problem, researchers are now examining “stop and go” approaches. One particular strategy drops the oxaliplatin after a defined period of time, introducing it again at disease progression.74 Initial studies suggest doing so is safe and uncompromising of the overall strategy. This suggests that at maximum response, patients might be afforded either complete breaks in therapy or less intensive therapy until the disease progresses. At progression, combination therapy can be reintroduced. This may alleviate toxicities and reduce costs.

The many choices for advanced metastatic CRC are reflected in the NCCN guidelines. NCCN has identified choices for people who cannot tolerate intensive therapy with agents such as capecitabine or infusional fluorouracil. For the less fit patient, it is important to weigh the risk of therapy, including combination therapy, with the need to achieve the best response as an effort to most effectively achieve disease control and improved performance status.
**Most Recent Approval: Panitumumab**

The FDA approved panitumumab in September 2006 (just a week before the symposium upon which the supplement is based). Panitumumab binds specifically to EGFR on normal and tumor cells, competitively inhibiting ligand-binding. After panitumumab binds to EGFR, ligand-mediated receptor site autophosphorylation is inhibited, as is activation of receptor-associated kinases. Cell growth is inhibited, and apoptosis is induced. Proinflammatory cytokines and vascular epithelial growth factor production decrease.\(^{75}\) Panitumumab differs from cetuximab, which is a chimeric antibody, in that it is a fully human monoclonal antibody. Some researchers believe that there is less risk for infusion reactions with fully human monoclonal antibodies.

Panitumumab’s pivotal trial was a phase 3 multicenter, randomized controlled trial. Peeters and colleagues compared the effect of panitumumab 6 mg/kg every 2 weeks and BSC (N = 231) with BSC alone (N = 232) in patients with progressive metastatic CRC during or following treatment with fluoropyrimidine, irinotecan, and oxaliplatin.\(^{75,76}\) All patients had at least 1% tumor cell membrane positive staining for EGFR by centrally read immunohistochemistry. Tumor responses were determined at weeks 8, 12, 16, 24, 32, 40, 48, and every 12 weeks thereafter until progression. Responses were confirmed more than 4 weeks after criteria were first met. This design is somewhat flawed in that people were allowed crossover and many patients had crossover before the first analysis. Patients receiving panitumumab plus BSC showed a significant improvement in progression-free survival, with a 46% lower relative progression rate versus the BSC-alone group. At as early as 8 weeks into treatment, a higher percentage of panitumumab plus BSC-treated patients were alive without progression than in the BSC group alone. This difference in favor of the panitumumab plus BSC group versus the BSC group alone continued through week 32 of the study.

**Conclusion**

Clearly, many choices are available to clinicians who treat patients who have CRC. They will need to balance concerns about toxicity with those about cost (see Table 4). In the coming months and years, the results from numerous ongoing clinical trials will further refine our choices. The experts at NCCN will continue to refine and update their guidelines to reflect these changes and to give patients the longest and best life after a diagnosis of CRC.

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**DISCLOSURES**

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REFERENCES

Epidemiology, Disease Progression, and Economic Burden of Colorectal Cancer
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