Diagnosis and Emerging Therapies in the Treatment of Colorectal Cancer

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ABSTRACT

PURPOSE: Although it ranks among the top 3 leading causes of cancer and cancer-related deaths in the United States, only 30% of patients receive adequate screening for colorectal cancer (CRC). Educating and referring patients for screening and for treatment is critical, as CRC can be effectively treated and often cured if identified in its earliest stages.

EPIDEMIOLOGY: In 2005 there will be an estimated 145 290 new cases (10% to 15% of all cancer cases) and 56 290 deaths (10% to 11% of all cancer deaths) from CRC. Apart from Australia and New Zealand, North America has the highest incidence of CRC worldwide.

REVIEW SUMMARY: This article describes the diagnostic and staging processes for CRC based on patient history, physical examination, and key diagnostic tests. However, often the disease is not diagnosed in its earliest stages. A number of new treatments, including adjuvant chemotherapy and radiation therapy, have doubled the lifespan of patients with metastatic disease in the past 10 years. Genetically engineered and individually tailored treatments may hold the key to the future treatment of this and other forms of cancer.

TYPE OF AVAILABLE EVIDENCE: Systematic reviews, randomized-controlled trials, cohort studies, unstructured reviews, nationally recognized treatment guidelines.

GRADE OF AVAILABLE EVIDENCE: Fair to good.

CONCLUSION: Future emphasis on screening, research into the complex genetic and environmentally linked etiologies for CRC, and development of new, more effective, less toxic chemotherapeutic regimens will continue to augment ever-advancing surgical techniques.

years or older at the time of diagnosis. The age-specific Surveillance, Epidemiology, and End Results (SEER) incidence rates for CRC show a dramatic increase at about age 50 years, and serve as the rationale for the recommendation to begin routine screening at this age. However, screening rates remain low, with fewer than half of all eligible candidates undergoing fecal occult blood testing and lower endoscopy. The prevalence of CRC has remained stable over the past 4 decades—in the healthy population with no known risk factors there is a 5% chance of developing this type of cancer over the lifetime. In other words, 1 in 20 individuals will develop CRC if they live to age 80, with some individuals at greater risk than others.

Colon cancers that are detected early on and are confined to the mucosa have an approximately 90% survival rate at 5 years. Unfortunately, because of low screening rates only 39% of CRCs are detected at this stage. Fifty percent of CRCs are metastatic—at which point the 5-year survival rate decreases to about 10%. 

**Risk Factors and Prevention of Colorectal Cancer**

Major risk factors for development of colorectal cancer include advancing age (age older than 50 years), a history of colonic polyps, a history of chronic inflammatory bowel disease, and unhealthy dietary practices, including a diet that is high in fat and calories and low in fruits, vegetables, and fiber. In a study of 47,927 men aged 40 to 75 years in 1986, among whom there were 411 confirmed colon cancer cases, Platz et al looked at modifiable risk factors to determine if their colon cancer could have been prevented. Risk factors considered were: obesity, physical inactivity, alcohol consumption, early adulthood cigarette smoking, red meat consumption, and low intake of folic acid from supplements. After adjusting for age and family history of CRC and comparing men with at least 1 risk factor with men who had no risk factors (3.1%), the population attributable risk percentage was 71% (95% confidence interval [CI] = 33-92). The data suggest that, if all the members of this cohort of middle-aged American men had a modifiable exposure distribution comparable to that of the men with low risk scores, a large proportion (71%) of colon cancer risk might be avoidable. This is based upon the following criteria for what would be considered suboptimal levels for risk factors: body mass index (>25 kg/m²), <15 metabolic equivalent task-hours per week of exercise, >3 pack-years of smoking, >15 g per day of alcohol, >2 servings per week of red meat, and <100 µg of folic acid intake per day. A recent published analysis of 148,600 patients enrolled in the Cancer Prevention Study II Nutrition Cohort demonstrated that long-term heavy consumption of red meat and processed meat was associated with an increased risk of distal colon and rectal cancer. Other risk factors include acromegaly as a result of increased growth hormone, type II diabetes (for proximal colon cancers), and low calcium intake (distal colon cancers).

However, in addition to these general risk factors, about 15% to 20% of individuals have a genetic predisposition toward developing colorectal cancer. Individuals with a first-degree relative who has had colorectal cancer have 2 to 3 times the risk of developing the disease themselves. Inherited colon cancer syndromes are of 2 main types: familial adenomatous polyposis (FAP), which occurs in about 1% of all colon cancer patients, and hereditary nonpolyposis colorectal cancer (HNPCC), which is responsible for another 5% to 10% of all cases. Patients with either of these syndromes have approximately an 80% lifetime risk of developing colon cancer. Genetic testing is available for both FAP and HNPCC, and can identify affected individuals within families as well as new families that carry these mutations once a proband has been identified. Genetic counseling should be offered to patients along with genetic testing.

**Pathophysiology**

Nearly all of CRCs arise from preexisting adenomatous polyps. These adenomas may be of a villous or tubular type, or a combination of both. Polyps with a tubular histologic pattern have less potential for malignancy than do villous types. The larger the polyp size (>1 cm in diameter), the more likely it is to contain invasive carcinoma. Villous adenomas >2 cm in diameter have a 40% chance of harboring cancer at the time of discovery. Approximately one third of polyps and half of colorectal cancers occur proximal to the splenic flexure; the proportion of occurrence in this location increases with age. Therefore, older patients are more likely to present with occult anemia and advanced right-sided lesions, making screening of the entire colon (colonoscopy vs sigmoidoscopy) of particular importance in this group. Proximal lesions carry a poorer prognosis than do distal malignancies, which may be in part because of delayed diagnosis secondary to the later development of symptoms (see more discussion on this below). And, although cancers in the distal colon tend to progress more slowly, rectosigmoid cancer presents earlier because of associated stool changes and hematochezia and thus is associated with a better prognosis.

Growth rates are variable, but generally speaking, it takes 10 to 15 years for cancer to develop from a pre-
cancerous lesion. The evolution of a lesion from benign adenoma to adenomatous polyp with in situ cancer to invasive carcinoma is regulated by mutations in specific genes. Multiple genetic mutations are required. A typical pathway would be a mutation in the adenomatous polyposis coli (APC) gene, which allows for polypoid growth; a K-ras mutation, which is an intermediate step; and, finally, mutation in p53 or DCC (deleted in colon cancer) genes, which allow progression to frank carcinoma.

**CHEMOPREVENTION**

**Aspirin**

As our understanding of the molecular events of CRC has increased, opportunities to arrest or prevent progression to frank cancer have been closely studied. Epidemiologic studies also have suggested some viable prevention strategies. Aspirin, at moderate to high doses, has been shown to reduce the risk of polyp recurrence and colon cancer. However, in the Women’s Health Study of 40,000 women over 12 years, low-dose, every-other-day aspirin was not effective at preventing CRCs. Practitioners who recommend aspirin to their patients for chemoprevention should specify a daily dose of 325 mg.

**Cyclooxygenase-2 Inhibitors**

Nonsteroidal anti-inflammatory drugs other than aspirin are inhibitory to polyp growth through inhibition of cyclooxygenase-2 (COX-2) and production of prostaglandin E2, a promoter of cellular proliferation. This has been most clearly demonstrated in patients with FAP. The effect is less dramatic with sporadic polyps and there is no consensus on specific recommendations, particularly in light of the recent controversy about COX-2 inhibitors and coronary heart disease.

**HMG-CoA Reductase Inhibitors (Statins)**

Cholesterol inhibition as a cancer-preventing therapy has been hypothesized for many years, but analyses of cancer rates in patients on statin therapy have been inconclusive, particularly since most of these trials focused on coronary events as their endpoints. A recent study analyzing statin exposure in approximately 4000 Israeli patients suggested a 47% relative risk reduction in CRC occurrence in those who had used statins for at least 5 years.

**Calcium and Vitamins**

Data from the Nurses’ Health Study and the Health Professionals Follow-up Study suggest that moderate calcium intake (up to 700 mg/day) is associated with a lower risk of distal colon cancer. The mechanism may be that calcium binds bile salts and other colon toxins. The Nurses’ Health Study also suggested a protective effect from the use of multivitamins. This may be from an increase in folate and vitamin B6, or other vitamins. These studies demonstrate some interesting associations without clear understanding of what the protective mechanism might be. At this time, there are no specific recommendations regarding these vitamins in terms of colorectal cancer prevention.

**CLINICAL PRESENTATION**

**Findings Upon History and Physical Examination**

The clinical presentation of CRC varies greatly according to location. This is because stool is fairly liquid in consistency when on the right side of the colon, becoming more solid as it progresses to the transverse section and into the left side, where obstructive symptoms therefore are more likely to occur. Additionally, the colon narrows in caliber from right to left, reaching its narrowest caliber at the rectosigmoid junction. Tumors in the cecum and ascending colon therefore may become large and ulcerated before they are discovered. Right-sided colon cancers may in fact be quite advanced at the time of presentation; fewer than 25% in the ascending colon are diagnosed in stage I vs 90% of rectosigmoid cancers. Whereas patients may experience dark stools or melena, bleeding often is occult with the stool remaining normal in appearance and consistency. Inconsistently positive tests for fecal occult blood and complete blood counts consistent with iron deficiency anemia (ie, hypochromic, microcytic anemia) along with symptoms of anemia such as fatigue, weakness, dizziness, and palpitations may be the only signs and symptoms of right-sided colon cancer. If a lesion is present in the transverse or descending colon, the patient may develop symptoms of obstruction, including abdominal cramping and changes in bowel habits and stool caliber, whereas rectosigmoid cancers may cause urgency symptoms that are unproductive in defecation, as well as gross hematochezia. In advanced cases, obstruction may lead to abdominal distention, obstipation, and pain. There may be bowel ischemia, necrosis, and even perforation that may be the result of advanced disease. The staging of CRC based on clinical presentation, physical examination/diagnostic testing, and, ultimately, colon resection forms the foundation for therapeutic interventions.
come), and metastasis to distant sites (Figure). It is important that an adequate number of lymph nodes (at least 14) are found and examined to accurately determine node-negative vs node-positive disease.25 Without evidence of metastasis, staging can be completed only after bowel resection. Table 1 shows the American Joint Committee on Cancer (AJCC) depiction of the various stages of CRC based upon these 3 important criteria. The 5-year survival rates based on staging range from 90% for stage I to less than 5% for stage IV (Table 2).26 Predictors of a poor prognosis include the presence of ≥5 positive lymph nodes, a poorly differentiated histologic type of tumor, adhesion of the tumor to other organs, bowel obstruction or perforation, and/or venous invasion by the tumor. The presence of specific genetic markers and/or elevated carcinoembryonic antigen (CEA) levels (>5 ng/mL) also predicts a worse outcome for patients.12,27

**Therapies for Colorectal Cancer**

**Surgery: Still the Mainstay of Treatment**

In 1884 Ashhurst wrote that the treatment of cancer “consists in removal of the morbid growth, by the use of the knife.”28 More than a century has passed since he wrote those words, though surgery today remains the primary treatment for CRC and offers the greatest potential for cure. Preoperatively, it is important to perform certain diagnostic tests, including obtaining CEA levels. If elevated preoperatively the CEA level can be used as an indicator of recurrence during postoperative follow-up. Tumors of the rectum should be evaluated with endorectal ultrasound to determine the depth of the rectal cancer, assess whether the tumor has affected surrounding tissues, and indicate whether perirectal lymph nodes are positive. This is an important step in determining the type of surgery to be performed and whether neoadjuvant radiation and chemotherapy will be appropriate.

For most obstructing lesions, a resection with a primary anastomosis generally is performed, unless peritonitis is present. In cases where peritonitis is present a resection with a diverting colostomy usually is appropriate. The regional lymph nodes and associated blood vessels also should be included. During laparotomy, the surgeon examines the entire abdomen, with particular attention to the liver and pelvic structures in addition to the entire bowel. An important quality-of-life issue for patients is the avoidance of a permanent colostomy. With modern stapling devices and skilled surgical technique, a permanent colostomy can almost always be avoided except when very low rectal tumors involve the anal sphincter. Some patients—even those with low rectal cancers—can undergo sphincter-sparing surgery following neoadjuvant radiation and chemotherapy. Nevertheless, patients may benefit from a temporary colostomy, in particular if they have perforation and peritonitis at the time of their surgery, if they have a near-obstructing rectal cancer and will undergo neoadjuvant therapy, or if they have a difficult anastomosis that the surgeon wishes to protect with a diverting ileostomy.

Some patients with rectal cancers are candidates for local, transanal excision, an option of particular importance for those patients who are at poor surgical risk. However, to be eligible for this procedure lesions must be node-negative T1-T2 (confirmed by endorectal ultrasound), must be <4 cm in size, must be located <8 cm from the anal verge, and cannot extend more than one third of the circumference of rectum.

**Laparoscopic Colectomy**

First described in 1991 in a case report, laparoscopic colon surgeries are now performed in large numbers.29 The procedure involves four key steps: identifying and ligating the distal and proximal mesenteric vessels, transecting the mesentery to take down the specimen, completing the anastomosis, and closing the abdominal incision. Benefits include a shorter hospital stay, less pain, and a faster return to normal activities. However, the procedure is more technically demanding and requires additional equipment.

![Figure. Stages of Colon Cancer](https://www.merck.com/pubs/mmanual_ha/figures/fg51_2.html)
numbers worldwide, although they still constitute only 5% of all colectomies performed. Applications of laparoscopic surgery for colon cancer (aside from colon cancer resection) also include laparoscopic stoma formation for patients with unresectable stage IV cancer and laparoscopic placement of a hepatic artery catheter for intraarterial chemotherapy in cases of hepatic metastases, although the latter rarely is performed today.

This procedure has been studied extensively in clinical trials in the United States and Europe and good clinical data are now available. After conducting a review of the current literature and obtaining expert opinions, the European Association of Endoscopic Surgery reported in 2002 that advanced age, obesity, and previous abdominal operations are not considered absolute contraindications for laparoscopic colon cancer surgery; however, it is not an advantageous procedure for large or extensively invasive tumors. They noted that the laparoscopic operation takes longer to perform than does laparotomy, with similar outcomes in terms of specimen size, pathologic examination, and short-term postoperative morbidity and mortality. However, the laparoscopic patients experienced less postoperative pain and had better-preserved pulmonary function, earlier restoration of gastrointestinal function, and an earlier discharge from the hospital. The incidence of port site metastases was <1%. Survival after laparoscopic resection of colon cancer appears to be at least equal to survival after open resection. However, the costs of laparoscopic surgery for colon cancer are higher than those for open surgery, mainly because of the longer operating times and complex instrumentation required for the former, and the long-term prognosis compared with laparotomy is yet to be determined.

The Clinical Outcomes of Surgical Therapy (COST) Study Group randomized 872 patients to undergo laparoscopic-assisted colectomy (LAC) vs open colectomy at 48 institutions. They found statistically significant reductions in median hospital stay, and briefer use of parenteral narcotics and oral analgesics (1-day reduction in each case). Recurrence (including wound or port-site recurrence), survival, and complications were statistically identical in both groups and for all stages of cancer. The conversion rate was 21% and operative time approximately 55 minutes longer in the laparoscopic group. The study validates LAC as equal to open colectomy in terms of long-term results and also demonstrates a modest decrease in surgical trauma as measured by hospital stay and narcotic use. This and other studies confirm that survival rates after surgery are essentially equal among patients who undergo open vs LAC, in terms of: cancer-specific mortality, recurrence, wound metastasis, the adequacy of surgical margins, or the number of lymph nodes resected. Thus, today the overwhelming evidence points toward these 2 approaches as being essentially equivalent—in the hands of experienced surgeons.

**Table 2. Colorectal Cancer: Five-Year Survival**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>90%</td>
</tr>
<tr>
<td>Stage II</td>
<td>60%-80%</td>
</tr>
<tr>
<td>Stage III</td>
<td>20%-50%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

**Sentinel Lymph Node Mapping**

Coming upon the heels of its successful use with breast cancer and melanoma patients, sentinel lymph...
node (SLN) mapping also is being studied for CRC staging. In some cancers, SLN mapping predicts with high sensitivity and specificity whether a regional lymph node basin is positive, thereby potentially upstaging the patient from stage II to stage III colon cancer. The result is the addition of chemotherapy, but SLN mapping does not affect recommendations for surgical therapy. Unlike patients with breast cancer who may be able to avoid radical and extensive lymph node resection, SLN mapping for CRC is not intended to minimize the need for therapeutic lymphadenectomy. Lymph nodes are always removed in the case of CRC, because lymph node channels parallel blood supply. The intent of SLN mapping in CRC, therefore, is to improve the accuracy of nodal staging by evaluating anywhere between 1 and 4 sentinel nodes more thoroughly for micrometastases, and provide a more accurate prognosis, keeping in mind that 20% to 30% of patients with stage I/II cancers will die of metastatic disease despite “curative” resection.

The average number of positive lymph nodes found in any single specimen is 1 or 2, and these can be difficult to find because they are often not enlarged (the average positive node size is approximately 0.6 cm). A number of drawbacks exist to SLN mapping for patients with CRC. These include poor concordance between the results of the SLN and the presence of regional metastasis as well as a high false-negative rate (24% in one study, meaning regional lymph nodes are positive yet sentinel nodes are negative). In addition, micrometastatic disease may not predict outcome. Thus, SLN mapping for CRC remains in an investigational stage and, with additional research, may be determined to hold little or no benefit for patients.

**Chemotherapy for Metastatic Disease**

In general, chemotherapy is recommended for stage III (node-positive) colon cancer and stage II rectal cancer. Chemotherapy in stage II colon cancer patients remains controversial. Prospective studies have shown that the use of chemotherapy in patients with metastatic disease prolongs survival and improves quality of life. In 2000, a meta-analysis of a subset of 13 randomized-controlled trials representing a total of 1365 patients demonstrated that palliative chemotherapy was associated with an improvement in 1-year survival from 34% to 50% and an improvement in median survival of 3.7 months. However, the reviewers indicated that the quality of evidence relating to treatment toxicity, symptom control, and quality of life was poor, and further investigation was needed to determine whether chemotherapy provides a palliative benefit.

At present, a number of agents are Food and Drug Administration (FDA) approved for the treatment of metastatic CRC. These include: 5-fluorouracil (5-FU), leucovorin, capecitabine, irinotecan (CPT-11), oxaliplatin, bevacizumab, and cetuximab. First-line therapies are 5-FU, leucovorin, and irinotecan (FOLFIRI); 5-FU, leucovorin, and oxaliplatin (FOLFOX); and

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**Table 3. Comparison of Approved Agents for the Treatment of Colorectal Cancer**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Other Mechanism</th>
<th>Adjuvant</th>
<th>Advanced</th>
<th>Route</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorouracil</td>
<td>5-FU</td>
<td>Thymidylate synthase inhibitor</td>
<td>Yes</td>
<td>Yes</td>
<td>IV-bolus or continuous</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Xeloda</td>
<td>Prodrug of 5-FU</td>
<td>No</td>
<td>Yes</td>
<td>Oral</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>CPT-11, Camptosar</td>
<td>Topoisomerase I inhibitor</td>
<td>No</td>
<td>Yes</td>
<td>IV</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Eloxatin</td>
<td>Forms bulky DNA adducts and induces apoptosis</td>
<td>Yes</td>
<td>Yes</td>
<td>IV</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Avastin</td>
<td>Vascular endothelial growth factor antibody</td>
<td>No</td>
<td>Yes</td>
<td>IV</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Erbitux</td>
<td>Epidermal growth factor receptor antibody</td>
<td>No</td>
<td>*</td>
<td>IV</td>
</tr>
</tbody>
</table>

*In cancers with demonstrated expression of epidermal growth factor receptor.
ADJUVANT CHEMOTHERAPY

In the treatment arena, the recent development and introduction of new chemotherapeutic agents in addition to traditional fluorouracil and/or leucovorin has increased the median life expectancy for people with metastatic CRC from 10 to 12 months to 14 to 16 months when either irinotecan or oxaliplatin is added to a fluorouracil-based treatment regimen. Combination therapy with 3 drugs can further increase life expectancy to an average of 20 months, as can targeted therapy (e.g., adjuvant immunotherapy with monoclonal antibodies such as bevacizumab or cetuximab) in combination with a cytotoxic drug. (Six months is the median survival for untreated patients.) Adjunct chemotherapy and radiation before or after surgery also may enhance survival. In addition, efforts are under way to develop individually tailored treatment regimens based on what may be most effective and least toxic for that patient. Ultimately, the success of this approach may be linked to unraveling and understanding the genetic complexities that determine the specific pathophysiology of cancer for each patient. Specifically, microsatellite instability, which occurs in 15% to 20% of sporadic CRC and in the majority of hereditary nonpolyposis CRCs, has been targeted as a specific genetic alteration for which tailored chemotherapy may be appropriate.

ADJUVANT CHEMOTHERAPY

Large, prospective, randomized trials conducted over the past 2 decades have demonstrated an increased overall survival for patients with resected stage III colon cancer who are treated with adjuvant 5-FU–based chemotherapy. The benefit of adjuvant chemotherapy for patients with stage II disease remains controversial except in cases of rectal cancer. There is indirect evidence to support adjuvant chemotherapy after resection of metastatic disease. Gill et al conducted a pooled analysis of 3302 patients with stage II and III colon cancer from 7 randomized trials that compared 5-FU–based therapies plus surgery with surgery alone for patients with stage III disease. The investigators found that adjuvant chemotherapy increased the probability of recurrence-free survival after 5 years from 42% to 58% and the likelihood of 5-year overall survival from 51% to 64%. In addition, treatment benefited stage III patients to a greater extent than stage II patients.

The use of irinotecan and oxaliplatin in addition to 5-FU and leucovorin has been extensively studied in the adjuvant setting. A recent study of 1264 patients randomized to irinotecan with 5-FU and leucovorin vs 5-FU and leucovorin alone showed no benefit with the addition of irinotecan. The results of the MOSAIC (Multi-center International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) trial of 2246 patients randomized to 5-FU and leucovorin alone vs 5-FU and leucovorin with oxaliplatin demonstrated statistically significantly improved disease-free survival at 3 years. At this time, irinotecan is not appropriate in the adjuvant setting although the addition of oxaliplatin can be recommended in most instances with the understanding that it is more toxic than 5-FU and leucovorin alone.

NEOADJUVANT CHEMOTHERAPY AND RADIATION THERAPY FOR RECTAL CANCER

In patients with rectal tumors, adjuvant or neoadjuvant chemotherapy and radiation therapy play an important role, as the local recurrence rate is between 20% and 40% in patients receiving no adjuvant therapy. Increasingly, neoadjuvant chemotherapy and radiation are used with success for rectal cancer, and have been shown to decrease locoregional recurrence and improve the ability to perform sphincter-sparing surgery. Overall survival also may be improved.

Neoadjuvant therapy is not used for colon cancers, with the exception of those cancers that have invaded the abdominal wall—usually right-sided lesions. There are many potential advantages of chemotherapy and radiation therapy prior to, as compared with after, surgery for rectal cancer. Preservation of the anal sphincter can be accomplished with neoadjuvant therapy in many patients who would otherwise require a permanent colostomy. A good response to neoadjuvant therapy often makes for easier and less morbid surgery as the tumor shrinks away from the pelvic sidewall and other organs. Treatment with radiation therapy prior to surgery allows the surgeon to resect the irradiated rectum and then bring the unirradiated colon down into the pelvis for anastomosis, thus avoiding some of the problems of radiation enteritis. Furthermore, following rectal surgery, loops of small intestine will fall into the pelvis and then be irradiated postoperatively. By treating with radiation first, no small bowel is irradiated. A final theoretic advantage of administering radiation therapy preoperatively is that radiation depends on a good blood and oxygen supply to the irradiated field. After surgical dissection, the field is relatively hypoxic due to the interruption of blood vessels, which may make radiation less effective. Preoperative chemotherapy and radiation is thought to “sterilize” the operative field prior to operative manipulation, thus decreasing the risk that undetectable cancer cells may be spread during surgery.

However, neoadjuvant chemotherapy also may pose several drawbacks, including the possible need for a diverting ostomy, a more difficult surgical dissection...
secondary to postradiation inflammation, and the possibility that a tumor might be overstaged on preoperative imaging and be irradiated when it is actually a stage I lesion. In any case, most surgeons and oncologists favor preoperative chemo and radiation therapy whenever it is determined that a stage II lesion is present because of the locoregional control advantage demonstrated with preoperative therapy.

**Ablative and Other Therapies for Metastases**

Common sites for CRC metastasis are the lungs and liver. Resection of isolated liver metastases can confer 5-year survival rates of 25% to 30%. In fact, aggressive surgeons have re-resected liver metastases and/or lung metastases, and continue to show a renewed 5-year survival of 25% to 40%. However, indicators of a poor outcome include high or rising levels of CEA (>5 ng/mL) and CA19-9 (37 U/mL), 2 tumor markers.

A variety of ablative therapies have been employed for liver metastases including cryotherapy, chemoradiation, radiofrequency ablation, and SIR-Spheres. The latter are radioactive, microscopic glass beads that can deliver radiation to very selective areas of the liver—directly into the artery feeding a tumor. Locoregional approaches such as radiation, hepatic arterial infusion, or portal vein chemotheraphy remain investigational.

These therapies are experimental. They all have demonstrated some short-term efficacy, but the long-term effects are still unclear at this point.

**Long-term Follow-up and Care**

Following treatment for CRC, the American Society of Clinical Oncology (ASCO) recommends obtaining a CEA assay (if levels were elevated with the primary tumor) every 3 months for 3 years, and annually thereafter. If CEA levels are elevated, clinicians should proceed with an extensive metastatic workup. ASCO also recommends colonoscopy every 3 years after a colon cancer is found.

**The Future of Screening, Staging, and Therapy**

Because advanced CRC remains incurable, the best approach and the best hope still lies in effective screening, which includes various methods of fecal occult blood testing to be conducted annually, flexible sigmoidoscopy every 5 years, or fiber-optic colonoscopy every 10 years. Unfortunately, according to the ACS, overall only 30% of the population participates in any kind of screening. Virtual colonoscopy is a technique that is in its relative infancy but is showing promise—depending upon the experience of the radiologist—as a less invasive and perhaps more appealing screening modality. Patients overwhelmingly favor computed tomography over colonoscopy in terms of perceived invasiveness, however a full bowel preparation and infusion of large amounts of air via the rectum are still required for virtual colonoscopy. Virtual colonoscopy is excellent at picking up lesions of at least 10 mm in size, but is much less sensitive than colonoscopy for lesions smaller than 10 mm.

Whereas fecal occult blood testing is inexpensive and has good compliance, it may miss early cancers that do not bleed, or it can lead to expensive workups for false-positive results. Newer types of immunochemical fecal occult blood tests are more accurate, do not require following special diets, and remain inexpensive. Scientists are also working to develop the ability to detect DNA mutations in stool, because the genetic association in CRC is well established. However, this is extremely difficult in that in stool, only 1 in 1 billion DNA strands are human, and the problem may lie with a single gene mutation out of 35,000. Yet, strides are being made in the field. For example, Traverso et al attempted to utilize fecal DNA samples to identify mutations in the APC gene that initiate colorectal tumors. APC mutations were identified in 26 of the 46 patients with neoplasia (57%; 95% CI, 41%-71%) and in none of the 28 control patients (0%; 95% CI, 0%-12%; P < .001). In patients with positive tests, mutant APC genes made up 0.4% to 14.1% of all APC genes in the stool. In another investigation, Doolittle et al developed a new technique for extracting DNA using tetracycltrimethylammonium oxalate to identify K-ras mutations that occur in 46% to 50% of all CRCs. The authors were successful in detecting this mutation in 87% of cases.

Finally, Ahlquist et al devised a method of detecting multiple markers (APC, K-ras, p53) in a single panel. The authors examined stool specimens from 22 patients with CRC, 11 with adenomas, and 28 control subjects with no evidence of gastrointestinal abnormalities. The sensitivity of the test was 91% (95% CI, 71%-99%) for cancer and 82% (48%-98%) for adenomas, with a specificity of 93% (76%-99%). Excluding K-ras from the panel, sensitivities for cancer were unchanged but decreased slightly for adenomas to 73% (39%-94%), whereas specificity increased to 100% (88%-100%).

In order to improve staging, genetic techniques also may be utilized to detect micrometastasis in patients with known CRC. In a recent study, reverse transcriptase-polymerase chain reaction techniques were utilized to look for colon cancer markers on pathologically negative lymph nodes. This is a technique of using the enzyme reverse transcriptase to amplify and convert RNA in a specimen to DNA and then pick out a specific piece of DNA by using a probe that looks for a specific DNA sequence. Thus, it can detect a tiny amount of a specific RNA in a specimen. An example is a study in which 37% of a group of

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patients with stage II colon cancer with a confirmed K-ras oncogene within their primary tumor were found to have detectable K-ras mutations within clinically negative lymph nodes. These patients went on to have a much poorer survival than their counterparts in whom no K-ras mutations in the lymph nodes were detected. Therefore, future genetic research may assist in identifying metastatic disease earlier and more accurately than can routine lymph node analysis.

**Conclusion**

CRC is the third-leading cause of cancer and the second-leading cause of cancer-related mortality in both men and women, resulting in 11% of all cancer deaths. Though the prognosis for CRC in its early stages is favorable, only 5% to 7% of all patients with advanced CRC survive for 5 years or more. Part of the problem lies with bringing all patients up to current standards of care, including the latest adjuvant therapies, but most important, with compliance with screening. Continued development of more accurate and less invasive screening modalities hopefully will increase the number of patients who are screened for CRC. Other challenges will continue to be the development of new and better chemotherapeutic agents, as well as resolution of the controversies that revolve around which subset of patients with stage II colon cancer might benefit from adjuvant therapy, how to maximize the benefit to immunotherapy in lieu of or in addition to cytotoxic agents, and how locoregional therapies come into play as compared with systemic therapies. Finally, the development of genetically engineered and individually tailored treatment regimens poses an ambitious but exciting agenda for researchers and clinicians alike as they battle against this formidable foe.

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**References**