

# STRATEGIES FOR THE MANAGEMENT OF PATIENTS WITH COLORECTAL CANCER

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## INTRODUCTION

Our knowledge of colorectal cancer (CRC) and how to prevent and treat it has been enhanced in the last few years, uncovering new truths and dispelling commonly held myths. For example, a recent meta-analysis of 13 prospective cohort studies involving 725,628 adults followed for six to 20 years concluded that high dietary fiber is not associated with a reduced risk of colorectal cancer, thereby confusing a populace that has been indoctrinated to include more dietary roughage to ensure a healthy colon.<sup>1</sup>

The drugs available to treat the disease are changing, as well. Aimed at molecular targets such as epidermal growth factors, agents are becoming more widely researched both as monotherapy and in combination with traditional therapies. Pharmaceutical protectants like the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or “statins,” are also being assessed as means to protect one against CRC. Some say they work.<sup>2</sup> Others disagree with this approach.<sup>3,4</sup>

Another issue: Should adjuvant chemotherapy be offered to patients with stage II CRC? Not unless the patients are part of a clinical trial, according to a 1990 National Institutes of Health Consensus Panel.<sup>5</sup> On the other hand, in 2004 the American Society of Clinical Oncology recommended against the routine use of adjuvant therapy. However, for high-risk subsets of stage III patients, adjuvant therapy could be considered after thorough discussion with the patient about risks vs benefits.<sup>6</sup>

This article will review the current treatment options for CRC, including the advantages and disadvantages of adjuvant therapy in early stage CRC, as well as some of the newer molecules under consideration, and other issues that can impact therapeutic success.

## EPIDEMIOLOGY: THE BURDEN OF GENDER AND HERITAGE

Colorectal cancer is the third most common cancer and the second leading cause of cancer death in the United States, with approximately

145,290 new cases and 56,290 deaths from CRC estimated to have occurred in 2005.<sup>7</sup> Although the lifetime probability (magnitude of absolute risk) for the development of CRC in the United States is about 6%, the incidence and mortality of colorectal cancer increase with age. Over 90% of newly diagnosed cases and 94% of deaths from CRC occur in people over age 50.<sup>7</sup> The incidence rate of CRC is almost 60 times higher in men and 48 times higher among women aged 60 to 79 years than in those under the age of 39.<sup>8</sup> CRC incidence and mortality rates are more than 35% higher in men than in women.<sup>7</sup>

Racial disparities in the disease exist, as well. The incidence and mortality of CRC are highest in African Americans, with rates of incidence about 15% higher compared with non-Hispanic whites and mortality rates about 40% higher than for whites

(**Table 1**). Before 1987, the incidence rates for CRC were higher for non-Hispanic white males than for their African American counterparts. The current reversal of that trend may reflect historical underdiagnosis of CRC in African Americans, with some studies showing that members of this group were more likely to be diagnosed after the disease has metastasized and were less likely than white patients to receive surgical treatment and recommended adjuvant therapy.<sup>9,10</sup> Considerable variation exists across Asian/Pacific Islander and Hispanic white subgroups (**Table 2**). A study of American subgroups revealed that compared with non-Hispanic whites, African Americans, American Indians, Chinese, Filipinos, Koreans, Hawaiians, Mexicans, South/Central Americans, and Puerto Ricans were 10% to 60% more likely to be diagnosed with Stage III or

**Table 1. Colorectal Cancer Incidence and Mortality Rates\* According to Heritage and Gender, 1997-2001<sup>12</sup>**

Heritage	Incidence		Mortality	
	Male	Female	Male	Female
African Americans	72.9	56.5	34.3	24.5
Asian Americans/Pacific Islanders	56.3	38.6	15.8	10.8
Hispanics/Latinos	49.6	32.5	18.0	11.6
American Indians/Alaskan Natives	38.3	32.7	17.1	11.7
Non-Hispanic Whites	63.1	45.9	24.8	17.1
<i>All heritages</i>	<i>63.4</i>	<i>46.4</i>	<i>25.3</i>	<i>17.7</i>
*Per 100,000, age-adjusted to the 2000 U.S. Standard Population.				

**Table 2. Stage Distribution of Colorectal Cancer Diagnosed in 5 Heritage Populations, 1992-2000<sup>12</sup>**

Heritage	Stage distribution (%)			
	Local	Regional	Distant	Unstaged
African Americans	34.5	34.7	23.8	7.0
Asian Americans/Pacific Islanders	38.7	39.5	17.2	4.6
Hispanics/Latinos	34.9	38.4	21.4	5.3
American Indians/Alaskan Natives	34.8	38.7	23.3	3.2
Non-Hispanic whites	38.1	37.8	19.0	5.2

IV CRC.<sup>11</sup> Conversely, Japanese-Americans had a 20% lower risk of advanced-stage CRC. In addition to African Americans and American Indians, Hawaiians and Mexicans had a 20% to 30% greater risk of mortality, while Chinese, Japanese, and Indians/Pakistanis had a 10% to 40% lower risk. Although the etiology of these disparities was multifactorial, developing screening and treatment programs that target racial/ethnic populations with elevated risks of poor CRC outcomes may be an important means of reducing these disparities.

There is good news, however. In the United States, the overall incidence of CRC declined by 2.4% a year from 1998 through 2001.<sup>8</sup> Statistics also show that from the mid 1970s until the 1995-2000 period, the survival rate for CRC increased from 52% to 63% in women and from 50% to 64% in men, principally because of the introduction and use of 5-fluorouracil adjuvant therapy for resectable stage III

CRC, which reduced mortality by as much as 30%.<sup>12</sup>

#### **PATHOGENESIS: THE POLYP AS PRECURSOR TO DISEASE**

Most colorectal cancers begin with preexisting adenomatous polyps, or adenomas. While other types of polyps such as hamartomas and inflammatory polyps are present in the colon, only adenomas are believed to progress to CRC. The risk of subsequent CRC appears to depend on the histologic type, size, and number of adenomas found at the time of initial examination.<sup>13</sup>

From a histologic standpoint, early CRC and its precursor lesions are displayed as grossly visible elevated polyps or non-polypoid flat lesions. Macroscopically, precursor lesions are characterized by intraepithelial neoplasia and present as either pedunculated adenomas (attached by a narrow base and long stalk) or sessile (ser-

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rated) adenomas (attached by a long, flat base with no stalk).<sup>14</sup> In recent years, evidence has grown to identify the sessile adenomas as the probable precursor lesion for some cases of microsatellite unstable CRC.<sup>15</sup> They have a significant malignant potential; in an analysis of the clinicopathologic characteristics of 110 colorectal mixed hyperplastic adenomatous polyps, 11% contained foci of early carcinoma.<sup>16</sup> Approximately 55% to 66% of CRC arises from adenomatous polyps, while 10% to 30% originate from sessile adenomas.<sup>17</sup>

Autopsy studies have shown that adenomas are common and exist in more than 30% of persons over age 50 years, with their prevalence increasing with age.<sup>18</sup> However, only a fraction (2% at five years; 3% at 10 years) of adenomatous polyps ever becomes malignant.<sup>19</sup> After an adenomatous polyp is detected, the entire large bowel should be visualized endoscopically due to polyp recurrence. A study that assessed polyp recurrence among older, increased-risk patients who have been diagnosed and excised of colorectal polyps found that polyp recurrence rates for one, three, and five years were 11%, 38%, and 53%, respectively.<sup>20</sup> Males and younger patients were more likely to undergo surveillance and showed higher polyp recurrence rates.

The average time from onset of a polyp to onset of carcinoma, termed the “dwell time,” is 10 to 20 years. However, dwell time appears to vary with the location of the cancer. This period is longer in the distal colon than in the proximal colon, and shortest in the rectosigmoid segment.<sup>21</sup> Although rectosigmoid cancer develops more rapidly, its clinical manifestation is earlier because of associated

stool changes and hematochezia. This explains the lower mortality rate for rectosigmoid cancers compared with colon cancers.

A polyp’s potential for malignancy is based on its size. Relatively small polyps—5 mm or less in diameter—have a negligible malignant potential.<sup>17</sup> Polyps with a diameter of 5 mm to 10 mm are considered small. Very large lesions are considered to be greater than 20 mm in diameter with a prevalence of 0.8 to 5.2% in patients undergoing colonoscopy.<sup>22</sup> The prevalence of malignancy in these lesions is 5% to 22.1%.

Approximately one third of polyps and one half of colorectal cancers occur proximal to the splenic flexure.<sup>17</sup> Proximal lesions carry a poorer prognosis than distal cancers, partly because of delayed diagnosis secondary to the later development of hematochezia or obstruction. The rate of carcinomatous degeneration of polyps is low—about 2.5 cases per 1,000 polyps annually.<sup>17</sup>

**PREDISPOSITION TO DISEASE—GENETIC, SITUATIONAL, AND ENVIRONMENTAL**

The development of CRC is often a complex intertwining of environmental and genetic factors, as well as situational circumstances, such as ulcerative colitis. The majority of CRC is acquired sporadically. Almost one in four patients diagnosed with CRC has a family history of the disease, suggesting the involvement of a genetic factor. Two major forms of CRC predisposition are known to exist and both show autosomal dominant inheritance. They are familial adenomatous polyposis (FAP), which accounts for approximately 1% of cases of colon

cancer annually, and the more common hereditary nonpolyposis colorectal cancer (HNPCC), which accounts for 5% to 10% of cases.<sup>23</sup>

### **Familial Adenomatous Polyposis (FAP)**

FAP is characterized by the presence of multiple adenomas—hundreds or even thousands—in the colon starting in the second and third decades. FAP patients have an almost 100% risk of developing CRC by their 60s.<sup>24</sup>

FAP is associated with a deletion of chromosome 5q21, known as the adenomatous polyposis coli (APC) gene in neoplastic cells (somatic mutation) and normal cells (germline mutation); this deletion apparently leads to abnormal proliferative patterns in the colonic mucosa.<sup>25</sup> The different mutation sites in the gene are associated with varying severities of the disease. For instance, mutations at the 5' end and the 3' distal end and occasional specific mutations in other areas of the APC gene result in an attenuated form of FAP characterized by fewer adenomas, a proximal colonic distribution of polyps, a slightly delayed development of adenomas and cancer, and a decreased CRC risk.<sup>26</sup> Individuals with the same germline mutation may show different disease manifestations, suggesting that other factors, both genetic and/or environmental, may act as modifiers. Prophylactic surgery is offered to affected individuals, usually in their teens. Restorative proctocolectomy (RPC) eliminates the risk of colorectal adenocarcinoma in FAP patients, but desmoid tumors, duodenal adenomas, and ileal adenomas can still develop.<sup>27</sup> Close upper GI surveillance may help prevent duodenal malignancy. Once CRC is prevented, mesenteric desmoid

tumors are the principal cause of mortality, and the main reason for worsening functional results.

Genetic testing is now the standard of care for FAP, although this is an evolving field. One small study showed that fecal DNA testing for APC gene mutations has a sensitivity of 57% and a specificity of 100%.<sup>28</sup> If the test result is positive or the test is not available, flexible sigmoidoscopy is performed at 10 to 12 years of age. During the procedure, mucosal biopsy specimens are taken to identify subtle adenomatous changes. Colonoscopy with mucosal biopsies is advisable at 18 to 20 years of age. If adenomas are detected, surgical prophylaxis should be considered. Routine gastroduodenoscopic surveillance is also recommended for patients with FAP, because these patients are at high risk for potentially precancerous gastric and duodenal adenomas.<sup>29</sup>

### **Hereditary Non-Polyposis Colorectal Cancer (HNPCC)**

HNPCC is caused by a fault in a DNA mismatch repair (MMR) gene; faults in the MMR genes account for over 90% of detectable mutations.<sup>30</sup>

The mean age at which adenomatous malignancies appear in HNPCC is age 45 years, which is 10 to 15 years younger than the median age at which they appear in the general non-HNPCC population.<sup>31</sup> Unlike FAP, HNPCC is associated with a very high frequency of neoplasms in the proximal large bowel. Also, families with HNPCC often include persons with multiple primary cancers; in women, an association between colorectal cancer and either endometrial or ovarian carcinoma is especially prominent.

Genetic testing for predisposing mutations in people with a strong fam-

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ily history of these cancers enables screening and prevention to be targeted at those individuals at highest risk. For those with a documented mutation, especially young patients with a family history of HNPCC, prophylactic surgery may be advisable. Pilot studies in CRC patients under 30 years old have shown that 41% have MMR gene mutations.<sup>32</sup> The risk for developing CRC by age 70 years in people with these mutations has been shown to be 91% for men and 69% for women.<sup>33</sup>

Apart from FAP and HNPCC, other conditions that predispose to CRC include rare polyposis autosomal dominant conditions such as Peutz-Jeghers syndrome and familial juvenile polyposis.<sup>34</sup>

**APC Mutations**

Despite the genetic predisposition of CRC in some people, the majority of persons who are diagnosed with CRC develop it as a result of environmental or other disease states. CRC occurs in conjunction with the accumulation of multiple mutations within a cell in the bowel lining, allowing it to escape the normal growth control mechanisms. The step-wise accumulation of mutations drives the histological transition from normal tissue to adenoma to carcinoma.<sup>34</sup> The most common genetic alterations in sporadic bowel cancers are activating mutations in the oncogene KRAS and mutation or loss of the tumor suppressor genes APC, SMAD4 and TP53. Evidence points to the strong likelihood that somatic mutations of the APC gene are associated with development of a great majority of colorectal tumors and that the occurrence of such APC mutations represents an initial step in CRC.<sup>35,36</sup> In an analysis of APC gene mutations in 63

colorectal tumors that developed in FAP and non-FAP patients, over 80% of tumors (14 adenomas and 39 carcinomas) had at least one APC gene mutation, of which more than 60% (nine adenomas and 23 carcinomas) had two mutations.<sup>35</sup> The APC protein has many vital functions including control of the Wnt developmental signalling pathway, cell adhesion, migration, apoptosis, and chromosomal segregation. Loss of APC causes stabilization of beta catenin which binds the TCF/LEF family of transcription factors, activating gene expression.<sup>37</sup> CRC arises through a gradual series of histological changes, each of which is accompanied by a specific genetic alteration. In general, an intestinal cell needs to comply with two essential requirements to develop into a malignancy: the acquisition of selective advantage to allow for its initial clonal expansion, and genetic instability to permit multiple hits in other genes that are responsible for tumor progression and malignant transformation. Inactivation of APC might fulfill both requirements.

**Inflammatory Bowel Disease**

Other conditions linked to an increased risk include the inflammatory bowel diseases, ulcerative colitis (UC) and Crohn's disease, estimated to be responsible for around 1% to 2% of CRC cases.<sup>38</sup> However, CRC is considered a serious complication of these bowel diseases and accounts for approximately 15% of all deaths in inflammatory bowel disease (IBD) patients. Statistical analyses suggest that the risk of CRC for people with IBD increases by 0.5% to 1.0% yearly in the eight to 10 years after diagnosis.<sup>38</sup> The magnitude of CRC risk

increases with early age at IBD diagnosis, longer duration of symptoms, and extent of the disease.

The morphological development of UC-related CRC differs from that of its sporadic counterpart. Recent research suggests that environmental factors related to long-term inflammation of the bowel may contribute more to the increased cancer risk in UC than inherited susceptibility.<sup>39</sup> UC-related CRC is likely a result of chronic inflammation, a mechanism that is still elusive.<sup>40</sup> Similarly, detailed molecular analyses have indicated that whereas many of the genetic alterations observed in sporadic colon cancers also occur in UC-associated malignancies, the timing and frequency of those changes in the UC arena are different. These histological and molecular signatures may very well be reflective of an inflammation-driven carcinogenesis process in UC patients. Studies in animal models of UC have partly unraveled the mechanisms of inflammation-driven CRC. The

available evidence implies that DNA damage caused by oxidative stress in the characteristic damage-regeneration cycle is a major factor in the development of CRC in UC patients.

### Environmental and Situational Factors

Specific factors that increase the CRC risk have been identified, as have factors that reduce risk (**Table 3**). Recent findings have sought to clarify clinical issues or to announce paradigm shifts in our present knowledge of CRC.

### Fiber is Not Protective for CRC

An analysis of 13 prospective cohort studies newly published by the Harvard School of Public Health and involving 725,628 adults revealed that high dietary fiber intake was not associated with a reduced risk of CRC.<sup>1</sup> The study population was followed for six to 20 years. These findings are discordant

**Table 3. Risk Factors for Colorectal Cancer<sup>12</sup>**

Increased risk	<ul style="list-style-type: none"> <li>• Age &gt;50 yrs</li> <li>• Male gender</li> <li>• African American heritage</li> <li>• Family history of CRC, colorectal polyps, or chronic inflammatory disease</li> <li>• Inherited genetic abnormalities, such as familial adenomatous polyposis, or hereditary nonpolyposis CRC</li> <li>• Sedentary lifestyle</li> <li>• Obesity</li> <li>• Diet that includes high amount of red and/or processed meat</li> <li>• Smoking</li> <li>• Alcohol consumption (&gt;4 drinks per week)</li> </ul>
Decreased risk	<ul style="list-style-type: none"> <li>• Hormonal replacement therapy</li> <li>• Moderate to vigorous physical activity most days per week</li> <li>• Diet that includes low-fat dairy products, fish, poultry</li> <li>• Diet rich in fruits and vegetables</li> <li>• Use of aspirin, non-steroidal anti-inflammatory drugs</li> </ul>

with previously published studies that tout the benefits of high-fiber diets. Even in this study, dietary fiber intake was inversely associated with risk of CRC until other dietary risk factors were considered. The researchers of the present study contend that persons who eat high-fiber diets also eat less red meat, take folate-rich multivitamins, and have otherwise healthier lifestyles. Even if fiber does not have a major impact on CRC, convincing evidence exists to show that dietary fiber helps to prevent heart disease, type 2 diabetes, diverticulitis, and other several chronic conditions.

#### **Dietary Acrylamide Does Not Increase CRC in Women**

Acrylamide is classified as a probable human carcinogen, and animal studies have shown an increased incidence of tumors in rats exposed to very high levels. The substance is found in coffee, fried potato products, pretzels, popcorn, and crisp bread. The first prospective study of acrylamide in food and CRC risk, done through Harvard Medical School, has shown that intake of food items associated with elevated levels of acrylamide was not associated with CRC risk.<sup>41</sup> The researchers comment that in light of the null findings of this study, an important question is why the epidemiologic data on dietary acrylamide thus far appear to contradict data from animal experiments and risk assessment models.

#### **Exercise Impacts CRC Survival**

While sedentary lifestyle and obesity increase the risk of CRC, new evidence shows that these risk factors also impact survival after CRC diagnosis.<sup>42</sup> A prospective cohort study of 526

Australians who had CRC showed that after adjusting for age, sex, and tumor stage, patients who reported regular exercise before their CRC were 31% less likely to die from the disease than were non-exercisers. In fact, 73% of exercisers survived at least five years, versus 61% of non-exercisers. Increasing percent body fat resulted in an increase in disease-specific deaths, (hazard ratio 1.33 per 10 kg [22 pounds]). Similarly, increasing waist circumference reduced disease-specific survival (hazard ratio 1.20 per 10 cm [four inches]).

#### **Chicken vs Processed Meats: Risk of Adenoma Recurrence**

Specific meats may have different effects in adenoma recurrence, a Dartmouth Medical School study has revealed.<sup>43</sup> Researchers found that among 1,520 adults with a history of colon polyps, those who ate a diet heavy in processed meats had a higher risk of polyp recurrence than those with the lowest intake. Conversely, patients who favored chicken had a lesser risk of new polyps than those who ate the least. Patients in the quartile with the highest intake of processed meat were 75% more likely to develop an advanced adenoma compared with the quartile that ingested the lowest amount of processed meat. In contrast, those with the highest chicken intake were 39% less likely than those who ate the least to develop an advanced polyp.

#### **Do Statins Prevent CRC?**

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, otherwise known as statins, are effective lipid-lowering agents. They can inhibit the growth of colon cancer cell lines, and secondary analyses of some, but not

all, clinical trials suggest that they reduce CRC risk. In 2005, the Molecular Epidemiology of Colorectal Cancer study, a population-based case-control study of 1,953 patients with CRC and 2,015 controls, compared the use of statins for at least five years versus the nonuse of statins, and concluded that statin use was associated with a 47% relative reduction in CRC risk after adjustment for other known risk factors.<sup>2</sup> In 2006, two more studies with conflicting results were published. One study, conducted by the American Cancer Society, examined the association between use of statins and CRC incidence among 132,136 men and women in the Cancer Prevention Study II Nutrition Cohort, and found that current use of such drugs for five years or more was only associated with a weak impact on CRC incidence (multivariable adjusted relative risk = 1.09).<sup>4</sup> The investigators did concede, however, that the small reduction in risk could be associated with only specific types or doses of statins. The other study looked at 27 trials of statins involving 86,936 patients and showed an even weaker association with a reduction in cancer incidence (overall risk [OR], 1.01) or in cancer mortality (OR, 1.01).<sup>3</sup> They concluded that no type of cancer was affected by statin use and no subtype of statin affected cancer risk. Undoubtedly, more studies will follow.

## TREATMENT OPTIONS

### Surgery

The greatest potential for cure in patients with CRC is curative resection.<sup>44</sup> Patients considered for such surgery are often elderly and should

be evaluated preoperatively for metastatic disease by thorough physical examination, biochemical studies, and imaging of the chest and pelvis. The identification of metastases does not constitute an absolute contraindication to surgery in patients experiencing tumor-induced gastrointestinal bleeding or obstruction, but evidence of metastasization often warrants a more conservative operative procedure designed primarily to relieve symptoms. Before surgery, the carcinoembryonic antigen (CEA) titer should be determined and, if possible, the entire bowel mucosa should be visualized by colonoscopy to detect synchronous polyps or neoplasms.<sup>44</sup>

### *The principles of surgery in treating CRC*

**Lymphadenectomy.** If lymphadenectomy is to be preformed, lymph nodes at the origin of the feeding vessels should be identified for pathologic exam.<sup>44</sup> Lymph nodes outside the field of resection considered suspicious should be biopsied or removed. Residual positive nodes indicate an incomplete (R2) resection. The new 2006 NCCN guidelines encourage surgeons to remove a minimum of 12 lymph nodes for examination to clearly establish stage II (T 3-4, N0) colon cancer.<sup>44</sup> Even for stage III disease, the number of lymph nodes correlates with overall survival, as demonstrated by a secondary survey of Intergroup trial INT-0089, which showed that the number of lymph nodes analyzed for staging colon cancers is, itself, a prognostic variable on outcome.<sup>45</sup>

**Laparoscopic-assisted colectomy.** A multi-institutional study conducted by the Clinical Outcomes of Surgical

Therapy Study Group showed the rates of recurrent cancer were similar after minimally invasive laparoscopically assisted colectomy and open colectomy, suggesting that the laparoscopic approach is an acceptable alternative to open surgery for colon cancer.<sup>46</sup> Laparoscopic-assisted colectomy may be considered if the surgeon has experience performing laparoscopically assisted colorectal operations.<sup>47,48</sup> Following that, additional criteria include no disease in rectum or prohibitive abdominal adhesions, and no advanced local or metastatic disease. The procedure is not indicated for acute bowel obstruction or perforation from cancer, and a thorough abdominal exploration is required. The surgeon may consider preoperative marking of small lesions.

#### *Principles for resectability of metastases*

**Liver.** Hepatic resection effectively controls hepatic tumor in a substantial number of patients.<sup>49,50</sup> Based on that finding, complete resection must be feasible based on anatomic grounds and the extent of disease; maintenance of normal hepatic function is required. There should be no unresectable extrahepatic sites of disease. Fong and colleagues used a five-criterion preoperative scoring system to produce a score that was highly predictive of outcome ( $P < .0001$ ):<sup>50</sup>

1. node-positive primary ( $P = .02$ )
2. disease-free interval from primary to metastases less than 12 months ( $P = .03$ )
3. number of hepatic tumors more than one ( $P = .0004$ )
4. largest hepatic tumor greater than 5 cm ( $P = .01$ )
5. CEA level greater than 200 ng/mL ( $P = .01$ )

A scoring system by Nordlinger and colleagues that included the most relevant disease characteristics was developed using data from 1,568 patients with resected liver metastases from CRC carcinoma.<sup>50a</sup> The prognostic value of different factors was studied through uni- and multivariate analyses. They found that two- and five-year survival rates were 64% and 28%, respectively, and were affected by age, size of largest metastasis or CEA level, stage of the primary tumor, disease free-interval, number of liver nodules, and resection margin. Giving one point to each factor, the population was divided into three risk groups with different two-year survival rates: 0-2 (79%), 3-4 (60%), or 5-7 (43%).

According to a study by Fujita et al,<sup>50b</sup> synchronous liver metastases should be resected with the primary lesion if the patient can tolerate the procedure. The only true prognostic factor is the number of regional lymph node metastases. When six or more distinct metastatic lymph nodes are detected during resection of the primary cancer, synchronous liver resection should be postponed. In such cases, resection of the liver tumors should be considered only when no new lesions and no recurrences are detected several months after the primary resection.

Re-evaluation for resection can be considered in otherwise unresectable patients after neoadjuvant therapy.<sup>51</sup> Hepatic resection is the treatment of choice for resectable liver metastases from CRC; radiofrequency ablation (RFA) alone or in combination with resection for unresectable patients does not provide survival comparable to resection, and only slightly superior to nonsurgical treatment.<sup>52</sup>

**Lung.** Complete resection of the lung is based on the anatomic location and extent of disease with maintenance of adequate function required. A Japanese study showed that the median interval between colorectal resection and lung resection was 33 months.<sup>53</sup> Overall, five-year survival was 48%; five-year survival was 51% for patients with solitary metastasis, 47% for patients with ipsilateral multiple metastases, and 50% for patients with bilateral metastases. Resectable extrapulmonary metastases do not preclude resection.<sup>54</sup> Re-resection can be considered in selected patients.

### Radiotherapy

Radiotherapy is advantageous to patients with stage II or III rectal tumors. Approximately 40% of these patients experience tumor recurrence following complete resection, compared with 7% for patients who receive postoperative radiotherapy.<sup>55</sup> This unusually high frequency of recurrence in non-radiation-treated patients is presumably the result of two factors: the loss of integrity of the serosa of the large bowel as it enters the pelvis facilitates the infiltration of tumor, and the rich lymphatic supply of the pelvic side wall immediately adjacent to the rectum enhances the early spread of malignant cells into surgically inaccessible tissue. Therefore, adjuvant radiation therapy was introduced to remove tumor cells from perirectal tissue and to boost the potential of cure.

The use of adjuvant radiation therapy to decrease pelvic recurrence appears rational, but controversy has existed as to whether such treatment should be administered prior to or after surgery. Patients with large, potentially

unresectable rectal cancers may need preoperative irradiation to shrink the tumor sufficiently to allow its resection. Survival is prolonged when adjuvant radiation therapy is combined with concomitant chemotherapy. Preoperative chemoradiation has now emerged as the treatment of choice for many stage II and stage III rectal cancer patients.

Radiation therapy fields should include the tumor bed, which should be defined by preoperative radiological imaging and/or surgical clips.<sup>44</sup> Radiation doses should be 45-50 Gy in 25 to 28 fractions; small bowel doses should be limited to 45 Gy. Chemotherapy based on 5-FU should be delivered concurrently with radiation. Intraoperative radiotherapy (IORT), if available, should be considered for patients with T4 or recurrent cancers as an additional boost. Preoperative radiation is preferred for these patients to aid resectability.

### Chemotherapy

After virtually having only one drug, 5-fluorouracil, to use against CRC for decades, the arrival of new and more effective agents has changed the approach to chemotherapy for the treatment of CRC. Although 5-FU remains the backbone of most regimens, the new agents—irinotecan, capecitabine, oxaliplatin, bevacizumab, and cetuximab—are being incorporated into frontline therapies for advanced CRC.

#### *5-Fluorouracil*

Synthesized in 1952 and approved by the FDA in 1962, 5-FU remains an important drug in the treatment of advanced CRC. At one time, it was given as a bolus injection, but today

permanent venous access devices and portable infusion pumps allow the continuous infusion of 5-FU on an outpatient basis. Such uninterrupted infusion increases the likelihood that 5-FU will be present during the S phase of the tumor cell cycle, when this agent is most effective.

5-FU is modulated by leucovorin, which raises the level of 5,10-methylenetetrahydrofolate and results in the formation of a stable ternary complex of the folate coenzyme thymidylate synthase with 5-FU in the form of its principal metabolite, fluorodeoxyuridine. The use of 5-FU with leucovorin has resulted in a higher response rate than with 5-FU alone. The NCCN guidelines recommend several 5-FU regimens, including a continuous infusion administered 24 hours a day for a protracted time (10 weeks or more).<sup>44,56</sup> Administration of 5-FU as a continuous infusion for protracted periods improves the therapeutic index for this agent in patients with advanced CRC with respect to response rate and reduced toxicity. The schedule appears workable in the community setting and yields response rates similar to those reported for 5-FU with high-dose leucovorin, but without the gastrointestinal toxicity profile of the latter combination. Other recommended regimens include bolus 5-FU given one hour after leucovorin and repeated weekly for six cycles, and 5-FU and leucovorin given daily for five days every four or five weeks for six cycles.<sup>44</sup>

#### *Irinotecan*

Irinotecan is a novel topoisomerase inhibitor that has significant therapeutic activity in metastatic CRC. It

is indicated for patients with metastatic CRC and for patients whose disease recurred or progressed following initial 5-FU-based therapy. The drug is used as first-line therapy in combination with 5-FU/leucovorin and considered standard chemotherapy for CRC.<sup>44</sup> In a phase 3 trial, irinotecan with an infusion 5-FU/leucovorin regimen increased median survival by 35% vs 22% ( $P<.005$ ) and improved overall survival (17.4 months vs 14 months;  $P>0.03$ )<sup>57</sup> In an intent-to-treat analysis, treatment with irinotecan, bolus 5-FU and leucovorin produced a significantly longer median progression-free survival (7.0 vs 4.3 months;  $P=.004$ ), compared with bolus 5-FU/leucovorin treatment.<sup>58</sup> The incidence of grade 4 diarrhea was more similar in both groups (<8%).<sup>58</sup> However, grade 4 neutropenia and grade 3 and grade 4 mucositis were less common in the triple drug regimen.

#### *Capecitabine*

Capecitabine is an oral fluoropyrimidine—specifically a prodrug of 5-FU—and appears to mimic continuous-infusion 5-FU. The drug is indicated for adjuvant treatment in patients with Dukes' C colon cancer who have undergone complete resection of the primary tumor. It is also approved as first-line treatment in patients with metastatic CRC. In two studies that compared capecitabine with bolus 5-FU/leucovorin in patients with advanced disease, capecitabine therapy was associated with an improved response rate (18.9% vs 15%;  $P=.0014$ ; and 24.8% vs 15%;  $P=0.005$ ), but there was not a significant benefit in survival (12.9 months vs 12.8 months).<sup>59-61</sup>

### *Oxaliplatin*

Although a platinum-based molecule, oxaliplatin differs in its preclinical activity profile from cisplatin and also has a distinct toxicity profile. In most patients, it causes no renal toxicity and minimal hematologic toxicity, but it is associated with both a reversible, acute, cold-related dysesthesia and a dose-limiting, cumulative, peripheral sensory neuropathy.

In 2004, the FDA approved oxaliplatin injection in combination with infusional 5-fluorouracil (5-FU) and leucovorin for the first-line treatment of patients with stage III CRC who have undergone complete resection of the primary tumor, as well as for the first-line treatment of advanced carcinoma of the colon or rectum. The combination including oxaliplatin was shown to shrink tumors in some patients and delay tumor growth. The approval was based on the efforts to find the best first-line regimen in advanced CRC in which the National Cancer Institute GI intergroup designed a six-arm study that compared various combinations of 5-FU, leucovorin, irinotecan, and oxaliplatin.<sup>62</sup> Data suggest that the combination of oxaliplatin and 5-FU infusion is superior to the combination of irinotecan and bolus 5-FU (response rate, 45% vs 31%; time to disease progression, 8.7 months vs 6.9 months; and overall survival, 14.5 months vs 15 months).<sup>62</sup>

### *Bevacizumab and cetuximab*

Bevacizumab and cetuximab are monoclonal antibodies that work by preventing angiogenesis. Both agents were approved by the FDA in 2004 for the treatment of advanced CRC. A pivotal study showed that

bevacizumab (5 mg/kg), when combined with irinotecan, 5-FU/leucovorin, produced a significantly higher response rate (45% vs 35%,  $P=0.004$ ), progression-free survival (10.6 months vs 6.2 months;  $P<0.001$ ), and median duration of survival (20.3 months vs 15.6 months;  $P<0.001$ ).<sup>63-65</sup> A pivotal phase 2 trial investigated the safety and efficacy of two doses of bevacizumab—5 mg/kg and 10 mg/kg every two weeks—plus 5-FU/LV vs 5-FU/LV alone in 104 treatment-naïve patients with metastatic CRC.<sup>66</sup> Compared with the 5-FU/LV control arm, treatment with bevacizumab (at both dose levels) plus FU/LV resulted in higher response rates (control arm, 17%; low-dose arm, 40%; high-dose arm, 24%), longer median time to disease progression (control arm, 5.2 months; low-dose arm, 9.0 months; high-dose arm, 7.2 months), and longer median survival (control arm, 13.8 months; low-dose arm, 21.5 months; high-dose arm, 16.1 months). Thrombosis was the most significant adverse event and was fatal in one patient.

A large randomized phase 2 trial, which became known as the BOND trial, compared cetuximab alone with cetuximab plus irinotecan in patients with irinotecan-refractory CRC.<sup>67</sup> While the response rates favored the combination over monotherapy in terms of response rate (23% vs 11%;  $P=.007$ ), disease control (56% vs 36%;  $P=.0001$ ), and median time to progression (4.1 vs 1.5 months;  $P<.0001$ ), the study was not designed or powered to address the survival advantage of cetuximab. Toxic effects were more frequent in the combination-therapy group, an observation that was attributed to the intrinsic toxicity of irinotecan.

[See Appendix for a review of relevant mechanisms of action.]

**Table 4. Estimates of 5-Year Disease-Free Survival (%) with Surgery Versus Surgery Plus Adjuvant Therapy<sup>68</sup>**

Nodal status	T Stage	Low Grade		High Grade	
		S	+AT	S	+AT
0 nodes	T3	79	81	72	76
	T4	70	74	62	66
	T1-T2	69	78	60	72
1-4 nodes	T3	58	70	48	62
	T4	45	59	34	49
	T1-T2	44	59	33	49
>5 nodes	T3	31	47	20	36
	T4	18	33	10	22
	T1-T2	44	59	33	49

S=surgery; AT=adjuvant therapy  
*Note: Referent age is 60-69 years.*

## TREATMENTS BY DISEASE STAGE

### Changes in Staging Classifications

Staging systems are changing so that treatment options can be more precisely targeted to the patient's disease risk status. The sixth edition of the American Joint Committee on Cancer Staging Manual includes several modifications to the colon and rectum TNM staging system, which have been incorporated into the NCCN treatment guidelines.<sup>44,69</sup> In the latest revision of the staging system, smooth metastatic nodules in the pericolic or perirectal fat are considered lymph node metastases and should be included in N staging. Irregularly contoured metastatic nodules in the peritumoral fat are considered vascular invasion.

Stage II is now subdivided into IIA (T3N0M0, if the primary tumor is T3) and IIB (T4N0M0 for T4 lesions).

Stage III is subdivided into IIIA (T1 to T2, N1, M0), IIIB (T3 to T4, N1, M0), and IIIC (any T, N2, M0). The number of nodes separates N1 and N2 disease: N1 lesions have one to three positive regional lymph nodes, whereas N2 tumors have four or more positive regional nodes. Understanding the significant differences in survival among diagnostic subsets is important when assessing individual patient treatment options and design of clinical trials.

For example, the difference in five-year disease-free survival (DFS) is substantial: stage IIIA is 59.8%, stage IIIB is 42.0%, and stage IIIC is 27.3%.<sup>69</sup> DFS decreases with higher T stage, greater extent of nodal involvement and high grade of tumor. Gill and colleagues have generated estimates suggesting that the addition of adjuvant chemotherapy to surgery can improve rates of DFS in all groups (**Table 4**).<sup>68</sup>

Treatment goals for CRC are based on the stage of disease at presentation.

Stages I, II, and III disease are considered potentially curable, and are best managed with the intent of eradicating known and micrometastatic sites to achieve remission and avoid recurrence. Because stage IV is considered incurable in most cases, efforts are directed to reducing symptoms and prolonging survival.

The latest version of NCCN's colon cancer guidelines includes several major changes to recommended courses of treatment based on recent relevant clinical studies and changing practice patterns. One significant change is the recommendation that all first-line therapy for advanced or metastatic disease should include bevacizumab in the treatment regimen. The panel also added a new regimen, capecitabine and oxaliplatin (a combination known as CAPOX) as a treatment option in first-line therapy (Category 2B).<sup>44</sup>

In addition to changing treatment recommendations in advanced or metastatic disease, there are also new options in the adjuvant setting. The panel added new treatment regimens for Stage IIA patients, including capecitabine, 5-FU/leucovorin or 5-FU/leucovorin/oxaliplatin (Category 2B) and the election of this regimen would be based on risk assessment discussions between physician and patient.

### Stage I

Because of its localized nature, stage I colon cancer has a high cure rate. The treatment of stage I colon cancer is usually wide surgical resection and anastomosis.<sup>44</sup> The treatment of early stage rectal cancer includes transabdominal resection or transanal excision.<sup>66</sup>

### Stage II

The treatment of stage II colon cancer is usually wide surgical resection and anastomosis. Following surgery, patients should be considered for entry into controlled clinical trials evaluating the use of systemic or regional chemotherapy, radiation therapy, biologic therapy, or observation without post-operative therapy. (Information about ongoing clinical trials is available from the NCI website at [www.cancer.gov/clinicaltrials](http://www.cancer.gov/clinicaltrials).)

About 55% of all cases of colon cancer presently diagnosed are either stage II or stage III disease, and therefore eligible for adjuvant chemotherapy.<sup>71,72</sup> However, adjuvant therapy is not indicated for most stage II colon cancer patients unless they are entered into a clinical trial. The principles of risk assessment for stage II colon cancer include asking the patient how much information he or she would like to know regarding prognosis. Following that, a patient/physician discussion should ensue regarding the potential risks of therapy compared with potential benefits. This should include discussion of evidence supporting treatment, assumptions of benefit from indirect evidence, morbidity associated with treatment, high-risk prognostic characteristics, and patient preferences.

When determining whether adjuvant therapy will offer clinical benefits, the following points should be considered: the number of lymph nodes analyzed after surgery; poor prognostic features (eg, T4 lesion, perforation, peritumoral lymphovascular involvement, poorly differentiated histology); assessment of other comorbidities; anticipated life expectancy.

The potential value of adjuvant therapy for patients with stage II colon cancer remains controversial.

Although subgroups of patients with stage II colon cancer (including those with anatomic features such as tumor adherence to adjacent structures, perforation, complete obstruction, emergency presentation, a primary tumor site in the left colon, pT3 tumors with a depth of invasion of greater than 15 mm beyond the outer border of the muscularis propria, and pT4 lesions<sup>73</sup>) may be at relatively increased risk for recurrence, the evidence is conflicting as to whether adjuvant chemotherapy based on 5-FU is associated with an overall improved survival compared to surgery alone. Investigators from the National Surgical Adjuvant Breast and Bowel Project (NSABP) have indicated that the reduction in risk of recurrence by adjuvant therapy in patients with stage II disease is of similar magnitude to the benefit seen in patients with stage III disease treated with adjuvant therapy.<sup>74</sup> The Intergroup 0035 Trial, which randomized stage II patients to either follow-up only or 5-FU plus levamisole, showed no survival advantage to postoperative adjuvant chemotherapy in that patient population.<sup>75</sup> In its meta-analysis of 1,000 stage II patients, the International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) found a 2% advantage in overall survival at five years when adjuvant patients were treated with 5-FU/leucovorin, compared with untreated controls.<sup>76</sup>

The SEER Medicare Cohort study of 3,151 cases of resected stage II colon cancer distinguishes between the great majority of patients (92%) who have T3N0 disease and “usual” risk and a small number (8%) at high risk (T4N0 disease, obstruction or perforation).<sup>77</sup> Among the “usual” risk group, 27% received chemotherapy; 33%

high-risk patients were treated. Treatment was started at a median of 5.5 weeks from surgery. Of those patients who consulted with a medical oncologist, 54% received adjuvant therapy. Survival curves between treated and untreated patients in this SEER cohort are identical until three years from surgery, when the curve for chemotherapy-treated patients starts to diverge. However, the absolute difference in survival at five years among this non-randomized population is only around 3%.

A panel convened by the American Society of Clinical Oncology (ASCO), in partnership with the Cancer Care Ontario Program in Evidence-Based Care Gastrointestinal Cancer Disease Site Group, made recommendations on adjuvant therapy for stage II colon cancer patients based on a literature meta-analysis that included 37 trials, 11 meta-analyses, and 20,317 patients.<sup>6,78</sup> The panel concluded that while a 5% to 10% improvement in the DFS was observed with adjuvant treatment, no significant improvement was seen in overall survival. Thus, the panel did not recommend the routine administration of adjuvant chemotherapy for stage II colon cancer patients. The panel did emphasize the importance of a discussion outlining the risks vs benefits of adjuvant therapy to help guide the decision process. Patients with stage II colon cancer remain candidates for clinical trials in which surgery alone represents standard therapy.

The efficacy of postoperative radiation and 5-FU-based chemotherapy for stage II and III rectal cancer was established by a series of prospective, randomized clinical trials (the Gastrointestinal Tumor Study Group (GITSG) Protocol 7175, the Mayo/North Central Cancer

Treatment Group (NCCTG) Protocol 79-47-51, and the National Surgical Adjuvant Breast and Bowel Project (NSABP) R-01.<sup>79-81</sup> These studies showed an increase in both disease-free interval and overall survival when radiotherapy is combined with chemotherapy following surgical resection.

A recent randomized trial from the German Rectal Cancer Study Group included 823 stage II and stage III rectal cancer patients randomized to receive either preoperative chemoradiotherapy or postoperative chemoradiotherapy. The study demonstrated comparable overall five-year survival (76% vs 74%, respectively). However, local relapse rate favored preoperative chemoradiotherapy (6% vs 13%;  $P=0.006$ ), with less acute and long-term toxicity (14% vs 24%;  $P=0.01$ ).<sup>82</sup>

### Stage III

The treatment options for colon cancer include wide surgical resection and anastomosis as well as chemotherapy and radiation. The results of the MOSAIC trial demonstrated the benefit of adding oxaliplatin to 5-FU and leucovorin (FOLFOX) in adjuvant therapy for stage II and III disease.<sup>83</sup>

Some of the newer regimens in phase 3 trials presented at the 2005 ASCO meeting included:

- A phase 3 trial in which XELOX was compared with bolus 5-FU/LV (the standard regimen at the start of the study) as adjuvant therapy for stage III colon cancer.<sup>84</sup> Patients with resected stage III colon cancer received XELOX (capecitabine 1000mg/m<sup>2</sup> bid d1-14 + oxaliplatin 130mg/m<sup>2</sup> d1, q3w x8) or IV bolus 5-FU/LV (Mayo Clinic, LV 20mg/m<sup>2</sup> + 5-FU 425mg/m<sup>2</sup> d1-5, q4w x6; or Roswell Park [RP], LV 500mg/m<sup>2</sup> + 5-FU 500mg/m<sup>2</sup> d1, w1-6

in 8w cycles x4). Early safety data from the largest population of patients treated with XELOX indicate that XELOX causes less myelosuppression (neutropenia – XELOX 5.3% vs 5-FU/LV 10.9%) and stomatitis (0.6% vs 7.9%), but more skin (hand-foot syndrome (3.6% vs 0.2%) and neurosensory toxicity (8.1% vs 0%) than 5-FU/LV, and compares favorably with FOLFOX4. XELOX has now been incorporated in the three-arm AVANT adjuvant trial (FOLFOX4 vs FOLFOX4 + bevacizumab vs XELOX + bevacizumab).

The NSABP recently reported three-year disease-free survival results from a randomized trial comparing bolus 5-FU and leucovorin with 5-FU and oxaliplatin (FLOX) in patients with stage II and stage III colon cancer. Results favored the FLOX regimen and were comparable to data from the MOSAIC trial.<sup>85</sup>

Various adjuvant regimens are now recommended by the NCCN.<sup>44</sup> These include 5-FU/leucovorin given in various cycles<sup>86,87</sup> (most recently without the use of levamisole, which had been included in 5-FU/leucovorin in the past<sup>88</sup>). Also, capecitabine used as monotherapy, and mFOLFOX6, which adds oxaliplatin to a 5-FU/leucovorin regimen are also proposed as standard adjuvant therapy.<sup>85,89</sup>

Based on results from the MOSAIC trial presented at the American Society of Clinical Oncology meeting in 2005, adjuvant FOLFOX4 demonstrated prolonged four-year survival over 5-FU/leucovorin (69.7% vs 61.0% translating into a relative risk reduction of 25% in the subset of stage III patients).<sup>90</sup> FOLFOX4 is now considered a standard treatment for patients with stage III CRC.

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### Stage IV

- Stage IV CRC represents distant metastatic disease. Treatment of recurrent CRC depends on the sites of recurrent disease demonstrable by physical examination and/or radiographic studies.<sup>44</sup>

Treatment options include:

- Surgical resection of locally recurrent cancer.
- Surgical resection/anastomosis or bypass of obstructing or bleeding primary lesions in selected metastatic cases.
- Resection of liver metastases or ablation in selected metastatic patients.
- Resection of isolated ovarian or pulmonary metastases in selected patients.
- Palliative radiotherapy and/or chemotherapy.
- Clinical trials evaluating new drugs, biological therapy, or comparisons of different chemotherapy regimens which may include biologic agents

In stage IV and recurrent colon cancer, chemotherapy has been used for palliation. For patients who can tolerate intensive therapy, recommended first-line regimens for advanced or metastatic CRC include:<sup>44</sup>

- FOLFOX (5-FU, leucovorin, oxaliplatin) plus bevacizumab.
- FOLFIRI (5-FU, leucovorin, irinotecan) plus bevacizumab.
- IFL (or Saltz regimen irinotecan, 5-FU, leucovorin) plus bevacizumab.
- 5-FU/leucovorin plus bevacizumab.
- CAPOX (capecitabine, oxaliplatin) plus bevacizumab.

For patients who cannot tolerate intensive therapy, recommended first-line regimens for advanced or metastatic CRC are:

- Capecitabine.
- Bolus 5-FU/leucovorin with or without bevacizumab.
- Infusional 5-FU with or without leucovorin and/or bevacizumab.
- Protracted 5-FU with or without leucovorin.

**Table 5. Selected Prognostic Factors and 5-Year Relapse-Free Survival<sup>45,94,100</sup>**

Prognostic factors*	Stage	5-yr relapse-free survival (%)
T3N0 (11-20 nodes analyzed) Stage IIa	IIA	79
T3N0 low grade	IIA	73
T3N0 (10 nodes analyzed)	IIA	72
T3N0 high grade	IIA	65
T4N0 low grade Stage IIb	IIB	60
T4N0 high grade	IIB	51
T3N1	IIIB	49
T3N2	IIIC	15

\*All stages in this table are M0. Results derived from [www.mayoclinic.com/calcs](http://www.mayoclinic.com/calcs) using a referent age of 60-69 years old.

It should be emphasized that the overall survival of patients with metastatic colorectal cancer represents a continuum of care and correlates with the availability of all active agents over the course of a patient's illness.<sup>91</sup>

Cetuximab plus FOLFOX4 (oxaliplatin, leucovorin, 5-FU) has been used in patients with metastatic EGFR-positive CRC who had progressed on prior first-line irinotecan therapy with an ECOG performance status 2.<sup>92</sup> Response rates and progression-free survival showed a trend toward improvement with the combination of FOLFOX4 and cetuximab in irinotecan-refractory patients with advanced CRC. Another study presented at the 2005 ASCO meeting assessed irinotecan versus FOLFOX4 in 5-FU-experienced patients.<sup>93</sup> In patients failing prior 5-FU, overall survival was not significantly different based on whether second-line therapy began with either irinotecan or FOLFOX4 (HR=1.04, 95% CI 0.9-1.3). However, second-line FOLFOX4 produced a higher response rate than irinotecan (27% vs 15%;  $P<.01$ ) and a trend toward longer time to progression.

### ADVANCED

Tournigand and colleagues compared irinotecan-based and oxaliplatin-based chemotherapy in patients with newly diagnosed advanced CRC.<sup>92</sup> In this study, patients were crossed over from one regimen to the other at the time of progression. These two first-line treatments for metastatic and advanced CRC demonstrated similar response rates and acceptable toxic effects profiles with no differences in median time to first progression (eight months vs

8.5 months;  $P=.26$ ) or overall survival (20.6 months vs 21.5 months;  $P=.99$ ) for FOLFOX6 followed by FOLFIRI regimen versus FOLFIRI followed by FOLFOX regimen, respectively. However, the toxicity profiles were different. In first-line therapy, National Cancer Institute Common Toxicity Criteria 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.

### SURVEILLANCE

Surveillance after curative treatment of CRC commonly includes periodic history taking and physical examinations; some combination of laboratory tests (eg, CEA tests, liver-function tests, complete blood counts, and fecal occult-blood tests); diagnostic imaging studies (eg, chest radiography, ultrasonography, computed tomography, magnetic resonance imaging, and barium enema); and endoscopic procedures (eg, sigmoidoscopy and colonoscopy).<sup>94</sup> Is such an exhaustive list the standard of care and does intensive follow-up improve survival and preserve quality of life?

The ASCO Expert Panel published a 2005 surveillance guideline update based on results from three independently reported meta-analyses of randomized controlled trials.<sup>95</sup> These trials compared low-intensity and high-intensity programs of colorectal cancer surveillance with recent analyses of data from major clinical trials in colon and rectal cancer.<sup>78,96,97</sup> The Panel recommended the following:

- Annual computed tomography (CT) of the chest and abdomen for three years after primary therapy for patients who are at higher risk of

recurrence and who could be candidates for curative-intent surgery.

- Pelvic CT scan for rectal cancer surveillance, especially for patients with several poor prognostic factors, including those who have not been treated with radiation.
- Colonoscopy at three years after operative treatment, and, if results are normal, every five years thereafter.
- Flexible proctosigmoidoscopy every six months for five years for rectal cancer patients who have not been treated with pelvic radiation.
- History and physical examination every three to six months for the first three years, every six months during years 4 and 5, and subsequently at the discretion of the physician.
- CEA every three months postoperatively for at least three years after diagnosis, if the patient is a candidate for surgery or systemic therapy.
- Chest x-rays, CBCs, and liver function tests are not recommended, and molecular or cellular markers should not influence the surveillance strategy based on available evidence.

For individuals with familial or inherited risk, ASCO recommends the following based on a report by Winawer and colleagues:<sup>98</sup>

- Colonoscopy every five years for a person with two or more first-degree relatives with CRC, or a single first-degree relative with CRC or adenomatous polyps at age <60 years.
- Annual sigmoidoscopy beginning at age 10-12 years for a gene carrier of (or at risk for) FAP.
- Colonoscopy every one to two years, beginning at age 20-25 years or 10 years younger than the first diagnosis in the family, whichever comes first, for a gene carrier of (or at risk for) HNPCC.

## PATIENT INVOLVEMENT

An ongoing working relationship between patient and oncologist is essential for survival. An analysis of patient data from 15 large adjuvant CRC trials showed that 85% of CRC recurrences are diagnosed within the first three years following initial treatment.<sup>99</sup> Based on that, the 2005 ASCO Surveillance Guidelines recommend seeing the patient every three to six months for the first three years after treatment, with longer intervals possible during the fourth and fifth years, to determine symptoms and to offer counseling.<sup>95</sup>

Risk assessment should also be reviewed with the patient, using the latest TMN classifications as mentioned above. This is especially important for stage II and III patients in whom the subsets within these stages have varying relapse-free survival rates (**Table 5**) based on Internet-based predictive tools such as those found at [www.mayoclinic.com/calcs](http://www.mayoclinic.com/calcs) and [www.adjuvantonline.com](http://www.adjuvantonline.com).<sup>100,101</sup>

Stage II patients who opt for adjuvant treatment must understand that the magnitude of benefit is less than 5% in overall survival at five years. Treatment decision-making with all stage II patients should include an assessment of comorbid conditions and life expectancy. When life expectancy is limited, then adjuvant treatment offers less benefit.<sup>6</sup>

Other than stage and stage subsets, no single pathological feature or statistical model exists in CRC to build a surveillance strategy with the patient. Likewise, no predictive markers exist in CRC that can show who is most likely to benefit from therapy.<sup>95</sup> Yet, risk assessment should be part of the patient discussion

to prepare a surveillance strategy for that patient.

## CONCLUSIONS

While the treatment of CRC is advancing as research continues to forge ahead, fulfilling specific needs should be the focus of our efforts. This includes designing individualized treatment strategies and developing molecular CRC classification subtypes, as well as creating and assessing new molecules that can prevent and treat CRC, particularly the use of molecularly targeted agents and combinations of drugs and/or treatment modalities. Also, diagnostic accuracy should be enhanced using the newest imaging technology to identify precancerous and cancerous lesions as well as to noninvasively assess treatment effects. In the future, functional imaging might detect molecular activity in cells and their surroundings and could, potentially, signal the interaction of a treatment agent with its intended molecular target.

Finally, methods are needed to subtype tumors on the basis of genetic and molecular alterations to help define the biologic characteristics of normal, premalignant, and malignant lesions that indicate the likelihood of neoplastic transformation, recurrence after initial treatment, and positive response to a particular treatment.

## DISCLOSURE

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## REFERENCES

1. Park Y, Hunter DJ, Spiegelman D, et al. Dietary fiber intake and risk of colorectal cancer: a pooled analysis of prospective cohort studies. *JAMA*. 2005;294:2849-2857.
2. Poynter JN, Gruber SB, Higgins PD, et al. Statins and the risk of colorectal cancer. *N Engl J Med*. 2005;352:2184-2192.
3. Dale KM, Coleman CI, Henyan NN, et al. Statins and cancer risk: a meta-analysis. *JAMA*. 2006;295:74-80.
4. Jacobs EJ, Rodriguez C, Brady KA, et al. Cholesterol-lowering drugs and colorectal cancer incidence in a large United States cohort. *J Natl Cancer Inst*. 2006;98:69-72.
5. NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer. *JAMA*. 1990;264:1444-1450.
6. Benson AB 3rd, Schrag D, Somerfield MR, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. *J Clin Oncol*. 2004;22:3408-3419.
7. American Cancer Society. *Cancer Facts & Figures 2005*. Available at: <http://www.cancer.org>. Accessed January 17, 2006.
8. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. *CA Cancer J Clin*. 2005;55:10-30.
9. Cooper GS, Yuan Z, Landefeld CS, et al. Surgery for colorectal cancer: Race-related differences in rates and survival among Medicare beneficiaries. *Am J Public Health*. 1996;86:582-586.
10. Potosky AL, Harlan LC, Kaplan RS, et al. Age, sex, and racial differences in the use of standard adjuvant therapy for colorectal cancer. *J Clin Oncol*. 2002;20:1192-1202.
11. Chien C, Morimoto LM, Tom J, et al. Differences in colorectal carcinoma stage and survival by race and ethnicity. *Cancer*. 2005;104:629-639.
12. American Cancer Society. *Colorectal Cancer Facts & Figures 2005*. Available at: <http://www.cancer.org/downloads/STT/CAFF2005CR4PWSecured.pdf>. Accessed January 17, 2006.
13. Atkin WS, Morson BC, Cuzick J. Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. *N Engl J Med*. 1992;326:658-662.
14. Geboes K, Ectors N, Geboes KP. Pathology of early lower GI cancer. *Best Pract Res Clin Gastroenterol*. 2005;19:963-978.
15. Wynter CVA, Walsh MD, Higuchi T, et al. Methylation patterns define two types of hyperplastic polyp associated with colorectal cancer. *Gut*. 2004;53:573-580.
16. Longacre TA, Fenoglio-Preiser CM. Mixed hyperplastic adenomatous polyps/serrated adenomas. A distinct form of colorectal neoplasia. *Am J Surg Pathol*. 1990;14:524-537.
17. Winawer SJ, Fletcher RH, Miller L, et al. Colorectal cancer screening: clinical guidelines and rationale. *Gastroenterology*. 1997;112:594-642.
18. Rickert RR, Auerbach O, Garfinkel L, et al. Adenomatous lesions of the large bowel: an autopsy survey. *Cancer*. 1979;43:1847-1857.
19. Levi F, Randimbison L, La Vecchia C. Incidence of colorectal cancer following adenomatous polyps of the large intestine. *Int J Cancer*. 1993;55:415-418.
20. Amonkar MM, Hunt TL, Zhou Z, et al. Surveillance patterns and polyp recurrence following diagnosis and excision of colorectal polyps in a Medicare population. *Cancer Epidemiol Biomarkers Prev*. 2005;14:417-421.
21. Launoy G, Smith TC, Duffy SW, et al. Colorectal cancer mass-screening: estimation of faecal occult blood test sensitivity, taking into account cancer mean sojourn time. *Int J Cancer*. 1997;73:220-224.
22. Fukami N, Lee JH. Endoscopic treatment of large sessile and flat colorectal lesions. *Curr Opin Gastroenterol*. 2006;22:54-59.
23. Rustgi AK. Hereditary gastrointestinal polyposis and non-polyposis syndromes. *N Engl J Med*. 1994;331:1694-1702.
24. Ionescu DN, Papachristou G, Schoen RE, et al. Attenuated familial adenomatous polyposis: a case report with mixed features and review of genotype-phenotype correlation. *Arch Pathol Lab Med*. 2005;129:1401-1404.
25. Cottrell S, Bicknell D, Kaklamanis L, et al. Molecular analysis of APC mutations in familial adenomatous polyposis and sporadic colon carcinomas. *Lancet*. 1992;340:626-630.

26. Soravia C, Berk T, Maklensky L, et al. Genotype phenotype correlations in attenuated adenomatous polyposis coli. *Am J Hum Genet.* 1998;62:1290-1301.
27. Parc Y, Piquard A, Dozois RR, et al. Long-term outcome of familial adenomatous polyposis patients after restorative colectomy. *Ann Surg.* 2004;239:378-382.
28. Traverso G, Shuber A, Levin B, et al. Detection of APC mutations in fecal DNA from patients with colorectal tumors. *N Engl J Med.* 2002;346:311-320.
29. Sarre RG, Frost AG, Jagelman DG, et al. Gastric and duodenal polyps in familial adenomatous polyposis: a prospective study of the nature and prevalence of upper gastrointestinal polyps. *Gut.* 1987;28:306-314.
30. Liu B, Parsons R, Papadopoulos N, et al. Analysis of mismatch repair genes in hereditary non-polyposis colorectal cancer patients. *Nat Med.* 1996;2:169-174.
31. Vasen HF, Watson P, Mecklin JP, et al. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative Group on HNPCC. *Gastroenterology.* 1999;116:1453-1456.
32. Farrington SM, Lin-Goerke J, Ling J, et al. Systematic analysis of hMSH2 and hMLH1 in young colon cancer patients and controls. *Am J Hum Genet.* 1998;63:749-759.
33. Dunlop MG, Farrington SM, Carothers AD, et al. Cancer risk associated with germline DNA mismatch repair gene mutations. *Hum Mol Genet.* 1997;6:105-110.
34. Fearhead NS, Wilding JL, Bodmer WF. Genetics of colorectal cancer: hereditary aspects and overview of colorectal tumorigenesis. *Br Med Bull.* 2002; 64:27-43.
35. Miyoshi Y, Nagase H, Ando H, et al. Somatic mutations of the APC gene in colorectal tumors: mutation cluster region in the APC gene. *Hum Mol Genet.* 1992;1:229-233.
36. Powell SM, Zilz N, Beazer-Barclay Y, et al. APC mutations occur early during colorectal tumorigenesis. *Nature.* 1992;359:235-237.
37. Fodde RR, Smits R, Clevers H. APC, signal transduction and genetic instability in colorectal cancer. *Nat Rev Cancer.* 2001;1:55-67.
38. Munkholm P. Review article: the incidence and prevalence of colorectal cancer in inflammatory bowel disease. *Aliment Pharmacol Ther.* 2003;18(Suppl 2):1-5.
39. Wong NA, Harrison DJ. Colorectal neoplasia in ulcerative colitis-recent advances. *Histopathology.* 2001;39:221-234.
40. Seril DN, Liao J, Yang GY, et al. Oxidative stress and ulcerative colitis-associated carcinogenesis: studies in humans and animal models. *Carcinogenesis.* 2003;24:353-362.
41. Mucci LA, Adami HO, Wolk A. Prospective study of dietary acrylamide and risk of colorectal cancer among women. *Int J Cancer.* 2006;118:169-173.
42. Haydon AM, Macinnis RJ, English DR, et al. Effect of physical activity and body size on survival after diagnosis with colorectal cancer. *Gut.* 2006;55:62-67.
43. Robertson DJ, Sandler RS, Haile R, et al. Fat, fiber, meat and the risk of colorectal adenomas. *Am J Gastroenterol.* 2005;100:2789-2795.
44. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology - v.2.2006. *Colon Cancer.* Version 2.2006. [http://www.nccn.org/professionals/physician\\_gls/pdf/colon.pdf](http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf). Accessed February 22, 2006.
45. Le Voyer TE, Sigurdson ER, Hanlon AL, et al. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. *J Clin Oncol.* 2003;21:2912-2919.
46. Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med.* 2004;350:2050-2059.
47. Wishner JD, Baker JW, Jr., Hoffman GC, et al. Laparoscopic-assisted colectomy. The learning curve. *Surg Endosc.* 1995;9:1179-1183.
48. Nelson H, Weeks JC, Wieand HS. Proposed phase III trial comparing laparoscopic-assisted colectomy versus open colectomy for colon cancer. *J Natl Cancer Inst Monogr.* 1995:51-56.
49. Hughes KS, Simon R, Songhorabodi S, et al. Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of patterns of recurrence. *Surgery.* 1986;100:278-284.
50. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg.* 1999;230:309-318.
- 50a. Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. *Cancer.* 1996;77:1254-1262.
- 50b. Fujita S, Akasu T, Moriya Y. Resection of synchronous liver metastases from colorectal cancer. *Jpn J Clin Oncol.* 2000;30:7-11.
51. Rivoire M, De Cian F, Meeus P, et al. Combination of neoadjuvant chemotherapy with cryotherapy and surgical resection for the treatment of unresectable liver metastases from colorectal carcinoma. *Cancer.* 2002;95:2283-2292.
52. Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg.* 2004;239:818-825.
53. Sakamoto T, Tsubota N, Iwanaga K, et al. Pulmonary resection for metastases from colorectal cancer. *Chest.* 2001;119:1069-1072.
54. Mohiuddin M, Marks G. Adjuvant radiation therapy for colon and rectal cancer. *Semin Oncol.* 1991;18:411-420.
55. Rena O, Casadio C, Viano F, et al. Pulmonary resection for metastases from colorectal cancer: factors influencing prognosis. Twenty-year experience. *Eur J Cardiothorac Surg.* 2002;21:906-912.
56. Lokich JJ, Ahlgren JD, Gullo JJ, et al. A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a Mid-Atlantic Oncology Program Study. *J Clin Oncol.* 1989;7:425-432.
57. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomized trial. *Lancet.* 2000;355:1041-1047.
58. Saltz LB, Blanke JV, Rosen C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med.* 2000;343:905-914.
59. Van Cutsem E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: Results of a large phase III study. *J Clin Oncol.* 2001;19:4097-4106.
60. Van Cutsem E, Hoff PM, Harper P, et al. Oral capecitabine vs intravenous 5-fluorouracil and leucovorin: Integrated efficacy data and novel analyses from two large, randomized, phase III trials. *Br J Cancer.* 2004;90:1190-1197.
61. Hoff PM, Ansari R, Batist G. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: Results of a randomized phase III study. *J Clin Oncol.* 2001;19:2282-2292.
62. Goldberg RM, Sargent DJ, Morton RF. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol.* 2004;22:23-30.
63. Kabbinnar FF, Hambleton J, Mass RD, et al. Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. *J Clin Oncol.* 2005;23:3706-3712.
64. Hurwitz HI, Fehrenbacher L, Hainsworth JD, et al. Bevacizumab in combination with fluorouracil and leucovorin: an active regimen for first-line metastatic colorectal cancer. *J Clin Oncol.* 2005;23:3502-3508.
65. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med.* 2004;350:2335-2342.
66. Kabbinnar F, Hurwitz HI, Fehrenbacher L, et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. *J Clin Oncol.* 2003;21:60-65.
67. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med.* 2004;351:337-345.
68. Gill S, Loprinzi CL, Sargent DJ, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III

- colon cancer: who benefits and by how much? *J Clin Oncol.* 2004;22:1797-1806.
69. Greene FL, Stewart AK, Norton HJ. A new TNM staging strategy for node-positive (stage III) colon cancer 2002. An analysis of 50,042 patients. *Am Surg.* 2002;236:416-442.
  70. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology – v.2.2006. *Rectal Cancer*. Version 2.2006. [http://www.nccn.org/professionals/physician\\_gls/PDF/rectal.pdf](http://www.nccn.org/professionals/physician_gls/PDF/rectal.pdf) Accessed February 22, 2006.
  71. Hobday TJ. An overview of approaches to adjuvant therapy for colorectal cancer in the United States. *Clin Colorectal Cancer.* 2005; 5(Suppl 1): S11-S18.
  72. Mattar M, Frankel P, David D, et al. Clinicopathologic significance of synchronous and metachronous adenomas in colorectal cancer. *Clin Colorectal Cancer.* 2005;5:274-278.
  73. Merkel S, Wein A, Günther K, et al. High-risk groups of patients with Stage II colon carcinoma. *Cancer.* 2001;92:1435-1443.
  74. Mamounas E, Wieand S, Wolmark N, et al. Comparative efficacy of adjuvant chemotherapy in patients with Dukes' B versus Dukes' C colon cancer: results from four National Surgical Adjuvant Breast and Bowel Project adjuvant studies (C-01, C-02, C-03, and C-04) *J Clin Oncol.* 1999;17:1349-1355.
  75. Moertel CG, Fleming TR, Macdonald JS, et al. Intergroup study of fluorouracil plus levamisole as adjuvant therapy for stage II/Dukes' B2 colon cancer. *J Clin Oncol.* 1995; 13:2936-2943.
  76. International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) Investigators. Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer. *J Clin Oncol.* 1999;17:1356-1363.
  77. Schrag D, Rifas-Shiman S, Saltz L, et al. Adjuvant chemotherapy use for Medicare beneficiaries with stage II colon cancer. *J Clin Oncol.* 2002;20:3999-4005.
  78. Figueredo A, Charette ML, Maroun J, et al. Adjuvant therapy for stage II colon cancer: a systematic review from the Cancer Care Ontario Program in evidence-based care's gastrointestinal cancer disease site group. *J Clin Oncol.* 2004;22:3395-3407.
  79. Thomas PR, Lindblad AS. Adjuvant postoperative radiotherapy and chemotherapy in rectal carcinoma: a review of the Gastrointestinal Tumor Study Group experience. *Radiother Oncol.* 1988;13:245-52.
  80. Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N Engl J Med.* 1991;324:709-715.
  81. Fisher B, Wolmark N, Rockette H, et al. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. *J Natl Cancer Inst.* 1988;80:21-9.
  82. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med.* 2004;351:1731-1740.
  83. Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med.* 2004;350:2343-2351.
  84. Sastre J, Massuti B, Tabernero JM, et al. Preliminary results of a randomized phase III trial of the TTD Group comparing Capecitabine and Oxaliplatin (CapeOx) vs Oxaliplatin and 5-Fluorouracil in continuous infusion (5-FU CI) as first line treatment in advanced or metastatic colorectal cancer (CRC) [abstract 3524]. Presented at the 41st Annual Meeting American Society of Clinical Oncology; May 13-17, 2005; Orlando, Florida.
  85. Wolmark N, Wieand HS, Kuebler JP, et al. A phase III trial comparing FULV to FULV + oxaliplatin in stage II or III carcinoma of the colon: Results of NSABP Protocol C-07 [abstract 3500]. Presented at the 41st Annual Meeting American Society of Clinical Oncology; May 13-17, 2005; Orlando, Florida.
  86. O'Connell MJ, Mailliard JA, Kahn MJ, et al. Controlled trial of fluorouracil and low-dose leucovorin given for 6 months as postoperative adjuvant therapy for colon cancer. *J Clin Oncol.* 1997;15:246-250.
  87. International multicentre pooled analysis of colon cancer trials (IMPACT) investigators. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. *Lancet.* 1995; 345:939-944.
  88. Haller DG, Catalano PJ, Macdonald JS, et al. Phase III study of fluorouracil, leucovorin, and levamisole in high-risk stage II and III colon cancer: final report of Intergroup 0089. *J Clin Oncol.* 2005;23:8671-8678.
  89. Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med.* 2005;352:2696-2704.
  90. de Gramont A, Boni C, Navarro M, et al. Oxaliplatin/5FU/LV in the adjuvant treatment of stage II and stage III colon cancer: Efficacy results with a median follow-up of 4 years [abstract 3501]. Presented at the 41st Annual Meeting American Society of Clinical Oncology; May 13-17, 2005; Orlando, Florida.
  91. Grothey A, Sargent D, Goldberg RM, et al. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol.* 2004;22:1209-1214.
  92. Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol.* 2004;22:229-237.
  93. Jennis A, Polikoff J, Mitchell E, et al. Erbitux (Cetuximab) plus FOLFOX for colorectal cancer (EXPLORE): Preliminary efficacy analysis of a randomized phase III trial [abstract 3574]. Presented at the 41st Annual Meeting American Society of Clinical Oncology; May 13-17, 2005; Orlando, Florida.
  94. Pfister DG, Benson AB 3rd, Somerfield MR. Clinical practice. Surveillance strategies after curative treatment of colorectal cancer. *N Engl J Med.* 2004;350:2375-2382
  95. Desch CE, Benson AB 3rd, Somerfield MR, et al. American Society of Clinical Oncology. Colorectal cancer surveillance: 2005 update of an American Society of Clinical Oncology practice guideline. *J Clin Oncol.* 2005;23:8512-8519.
  96. Renehan AG, Egger M, Saunders MP, et al. Impact on survival of intensive follow up after curative resection for colorectal cancer: Systematic review and meta-analysis of randomised trials. *BMJ.* 2002;324:813.
  97. Jeffery GM, Hickey BE, Hider P. Follow-up strategies for patients treated for non-metastatic colorectal cancer *Cochrane Database Syst Rev.* 2002;(1):CD002200.
  98. Winawer S, Fletcher R, Rex D, et al. Colorectal cancer screening and surveillance: Clinical guidelines and rationale—Update based on new evidence. *Gastroenterology.* 2003;124:544-560.
  99. Sargent DJ, Wieand S, Benedetti J, et al. Disease-free survival (DFS) vs overall survival (OS) as a primary endpoint for adjuvant colon cancer studies: Individual patient data from 12,915 patients on 15 randomized trials [abstract 3502]. Presented at the 40th Annual Meeting of the American Society of Clinical Oncology; June 5-8, 2004; New Orleans, La.
  100. Adjuvant systemic therapy tools; 2005. [www.mayoclinic.com/calcs](http://www.mayoclinic.com/calcs). Accessed January 23, 2006.
  101. Adjuvantonline.com; 2005. [www.adjuvantonline.com](http://www.adjuvantonline.com). Accessed January 23, 2006.

<b>Appendix. Mechanisms of Action of Agents Currently Used in Colorectal Cancer</b>	
<b>Drug</b>	<b>Mechanism of Action</b>
<b>Bevacizumab</b>	<ul style="list-style-type: none"> <li>• Humanized MAb.</li> <li>• Binds to VEGF.</li> <li>• Reduces the ability of the VEGF ligand for its receptor and thus prevents receptor activation.<sup>a</sup></li> </ul>
<b>Capecitabine</b>	<ul style="list-style-type: none"> <li>• In the liver, drug is hydrolyzed to 5-FU.<sup>99</sup></li> <li>• Both normal and tumor cells metabolize 5-FU to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP).</li> <li>• This causes cell injury by forming a complex with thymidylate synthase, which inhibits the formation of thymidylate, the necessary precursor of thymidine triphosphate (TT), and essential for DNA synthesis.</li> <li>• TT deficiency inhibits cell division.</li> <li>• Also, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate during the synthesis of RNA.</li> <li>• This metabolic error can interfere with RNA processing and protein synthesis.</li> </ul>
<b>Cetuximab</b>	<ul style="list-style-type: none"> <li>• When the external binding domain of EGFR, a transmembrane glycoprotein, binds to specific ligands, such as EGF, receptor dimerization occurs, which in turn stimulates phosphorylation of the tyrosine kinases.<sup>b</sup></li> <li>• This initiates a signaling cascade that regulates cell proliferation and survival.</li> <li>• Cetuximab, a chimeric immunoglobulin G<sub>1</sub> MAb, recognizes the bind to the extracellular domain of EGFR.<sup>c</sup></li> <li>• This results in a steric interference with the ligand binding site and prevents ligand activation of the receptor.</li> </ul>
<b>5-Fluorouracil</b>	<ul style="list-style-type: none"> <li>• Incorporated into DNA during DNA synthesis.</li> <li>• This promutagenic DNA lesion is excised by the base excision repair enzyme uracil DNA glycosylase (UDG).</li> <li>• 5-FU, as the free base, specifically binds in vivo to the UDG in noncycling human cells, thereby inhibiting its activity.<sup>d</sup></li> </ul>
<b>Irinotecan</b>	<ul style="list-style-type: none"> <li>• Semi-synthetic, water-soluble derivative of camptothecin, a cytotoxic alkaloid extracted from plants such as <i>Camptotheca acuminata</i>.<sup>e</sup></li> <li>• Along with its active metabolite, SN-38, they inhibit the action of topoisomerase I, an enzyme that produces reversible single-strand breaks in DNA during DNA replication.</li> <li>• These single-strand breaks relieve torsional strain and allow DNA replication to proceed. Irinotecan and SN-38 bind to the topoisomerase I-DNA complex and prevent relegation of the DNA strand, resulting in double-strand DNA breakage and cell death.</li> <li>• Cell cycle phase-specific (S-phase).<sup>f</sup></li> </ul>
<b>Oxaliplatin</b>	<ul style="list-style-type: none"> <li>• A platinum-based chemotherapeutic agent with a 1,2-diaminocyclohexane (DACH) carrier ligand.<sup>g</sup></li> <li>• Retention of the bulky DACH ring by activated oxaliplatin is thought to result in the formation of platinum-DNA adducts, which appear to be more effective at blocking DNA replication and are more cytotoxic than adducts formed from cisplatin.</li> </ul>
EGF, endothelial growth factor; EGFR, endothelial growth factor receptor; MAb, monoclonal antibody; UDG, uracil DNA glycosylase; VEGF, vascular endothelial growth factor.	

**REFERENCES**

- a. Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. *Endocr Rev.* 2004;25:581-611.
- b. Ciardiello F, Tortora G. A novel approach in the treatment of cancer: targeting the epidermal growth factor receptor. *Clin Cancer Res.* 2001;7:2958-2970.
- c. Thomas SM, Grandis JR. Pharmacokinetic and pharmacodynamic properties of EGFR inhibitors under clinical investigation. *Cancer Treat Rev.* 2004;30:255-268.
- d. Wurzer JC, Tallarida RJ, Sirover MA. New mechanism of action of the cancer chemotherapeutic agent 5-fluorouracil in human cells. *J Pharmacol Exp Ther.* 1994;269:39-43.
- e. Camptosar [prescribing information]. New York, NY: Pfizer, Inc.; 2005.
- f. Rothenberg ML, Kuhn JG, Schaaf LJ, et al. Alternative dosing schedules for irinotecan. *Oncology* (Huntington). 1998;12(8 Suppl 6):68-71.
- g. Raymond E, Faivre S, Woynarowski JM, Chaney SG. Oxaliplatin: mechanism of action and antineoplastic activity. *Semin Oncol.* 1998;25(2 Suppl 5):4-12.