5. COLORECTAL CANCER TREATMENT

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The core references for this chapter include the textbook *Cancer Treatment* (Haskell, 1995), CancerNet PDQ Information for Health Care Professionals on colon cancer and rectal cancer (CancerNet, 1997), and recent review articles (Nogueras and Jagelman, 1993; Staniunas and Schoetz, 1993; Stein and Coller, 1993; Moertel, 1994; Kemeny et al., 1993; Levitan, 1993). Recent review articles were selected from a MEDLINE search identifying all English language review articles published on colorectal cancer diagnosis and treatment since 1992. Where the core references cited studies to support individual indicators, they have been included in the references. Whenever possible, they have been supplemented with the results of randomized controlled trials.

IMPORTANCE

Colorectal cancer (adenocarcinoma) is the second most frequent cause of cancer mortality in the United States. It is estimated that 133,500 people will be diagnosed with colorectal cancer in 1996 and 54,900 will die from the disease (Parker et al., 1996).

In addition, colorectal cancer is curable in approximately 50 percent of patients when it is diagnosed and treated while still localized to the bowel and amenable to surgery.

SCREENING

The quality indicators for colorectal cancer screening and the treatment of benign polyps is covered in Chapter 4.

DIAGNOSIS

Patients with colorectal cancer may be asymptomatic at presentation. A patient with a positive fecal occult blood test or with a large (> 1 cm) or adenomatous polyp discovered on sigmoidoscopy should undergo a full colonoscopy to look for neoplasm and to excise any polyps (Winawer et al., 1997). The symptoms associated with colorectal carcinoma depend upon the size
and location of the tumor. Tumors of the right colon, which contains fluid stool, tend to be larger on presentation and produce symptoms of abdominal pain, bleeding, and weight loss. As the left side of the colon contains semi-solid or solid stool, tumors there often cause obstructive symptoms, or a decrease in stool caliber, and may also be associated with bleeding. Patients over age 50 who present with the above symptoms should be evaluated for colon cancer with either barium enema or colonoscopy. However, because many of the above symptoms may be difficult to identify on chart review, we do not recommend this as a quality indicator.

**Staging and Preoperative Evaluation**

Stage of disease is the most important determinant of prognosis in colorectal cancer. Multiple staging systems exist. The Dukes and the Modified Astler-Coller (MAC) classification schemes are most often used in treatment decisions, though the American Joint Committee on Cancer has also developed a staging system (Table 5.1). Bowel obstruction, bowel perforation, and adhesion or invasion of adjacent structures are indicators of poor prognosis (Steinberg et al., 1986), as are elevated pretreatment levels of carcinoembryonic antigen and CA 19-9. However, since these indications do not usually affect the initial choice of therapy, we do not recommend including them in a quality indicator (Filella et al., 1992).
Table 5.1
Definition of Stages of Colorectal Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Dukes/ MAC</th>
<th>American Joint Committee on Cancer</th>
<th>Definitions of Stage for Quality Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td></td>
<td>Tis N0 M0 - carcinoma in situ</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>Stage I</td>
<td>Duke’s A</td>
<td>T1 N0 M0 - tumor confined to bowel wall, invades submucosa</td>
<td>Tumor is confined to bowel wall and does not invade all the way through the muscularis propria nor involve the subserosa or pericolic/perirectal tissues.</td>
</tr>
<tr>
<td></td>
<td>MAC A &amp; B1</td>
<td>T2 N0 M0 - tumor confined to bowel wall, invades muscularis propria</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>Duke’s B</td>
<td>T3 N0 M0 - tumor confined to bowel wall, invades through the muscularis propria into the subserosa</td>
<td>Tumor is confined to bowel wall but invades all the way through the muscularis propria or involves the subserosa or pericolic/perirectal tissues.</td>
</tr>
<tr>
<td></td>
<td>MAC B2 &amp; B3</td>
<td>T4 N0 M0 - tumor perforates the visceral peritoneum or invades other organs or structures</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>Duke’s C</td>
<td>Any T N1 M0 - metastases are present in 1-3 pericolic or perirectal lymph nodes</td>
<td>Tumor involves lymph nodes.</td>
</tr>
<tr>
<td></td>
<td>MAC C1-C2</td>
<td>Any T N2 M0 - metastases are present in ≥ 4 pericolic or perirectal lymph nodes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any T N3 M0 - metastases are present in any lymph node along the course of a named vascular trunk</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>Duke’s D</td>
<td>Any T Any N M1 - distant metastases are present</td>
<td>Distant metastases are present.</td>
</tr>
<tr>
<td></td>
<td>MAC D</td>
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</table>

Since surgery is the mainstay of treatment of colorectal cancer, preoperative evaluation and staging should focus on obtaining information that would alter the planned operation or preclude surgery entirely (Vignati and Roberts 1993; Cohen, 1992). Since the incidence of synchronous carcinoma has
been reported to be between two percent and 7.2 percent, all patients who undergo surgery should have a complete colonoscopy prior to the operation, to exclude a synchronous lesion that may necessitate a modification of the planned surgery (Vignati and Roberts 1993; Isler et al., 1987). If colonoscopy is unavailable, patients should be offered barium enema with sigmoidoscopy. Colonoscopy is preferred over barium enema because in a study of patients who had undergone both procedures, only half of the synchronous carcinomas found by colonoscopy were detected by barium enema (Isler et al., 1987). Our proposed indicator requires that all patients undergo colonoscopy or barium enema with sigmoidoscopy prior to surgical resection (Indicator 1).

For colon cancer, the value of routine preoperative imaging of the abdomen with either CT, MRI, or endocolic ultrasound, though often obtained, remains ill-defined. While there is consensus that patients with Stage I, II, and III colon cancer should undergo surgical resection with intent to cure, experts do not agree on the role of palliative surgical resection of the primary tumor in patients with Stage IV disease (CancerNet, 1997; Haskell and Berek, 1995). The extent of disease can be determined intraoperatively by palpation and ultrasound. The sensitivity of intraoperative ultrasound for detecting liver metastases is about 98 percent compared with 77 percent for CT scan (Parker et al., 1989). Therefore, if surgical resection is planned regardless of the stage of disease, preoperative imaging may not provide additional prognostic information. In addition, the accuracy of CT for predicting stage is poor, ranging from 48 percent to 64 percent (Balthazar et al., 1988; Freeny et al., 1986). Therefore, we do not recommend that routine preoperative imaging be included as a quality indicator.

For rectal cancer, the benefits of preoperative staging are clearer. In rectal cancer, preoperative evaluation centers on trying to determine if the tumor is limited (Stage I that may benefit from immediate local resection) or locally advanced (Stage II or III). The latter may benefit from preoperative radiation therapy to downstage the tumor and allow a sphincter-sparing operation, whereas a larger resection may have been required without it. Finally, if a patient already has metastatic disease (Stage IV), especially if the primary tumor is not causing symptoms, surgery may needlessly produce a loss of continence.
To guide initial treatment decisions, preoperative staging has an important role to play in rectal cancer. Clinical staging of rectal cancer includes a digital rectal exam with rigid proctoscopy. Using these techniques, a rectal tumor is considered to be at least a T3 lesion (making it at least Stage II cancer) if on digital rectal exam it is noted to be fixed in the pelvis. The accuracy of digital rectal exam in determining tumor penetration ranges from 48 percent to 85 percent, approaching the accuracy of pelvic CT (Beynon, 1986; Konishi et al., 1990; Milsom, 1990; Cohen et al., 1991; Glaser et al., 1990; Waizer et al., 1989). However, there is considerable inter-observer variation in the assessment of the stage of rectal carcinoma, and many lesions are not within reach of the examining finger (Nicholls et al., 1982). Unfortunately, digital rectal exam and proctoscopy do not allow for the assessment of lymph nodes (except for inguinal nodes which are not usually involved) or metastases.

Other techniques for the staging of rectal cancer include pelvic CT and MRI and endorectal ultrasound. While initial reports of pelvic CT in staging rectal cancer were extremely promising (Koehler et al., 1984; Theoni et al., 1981), inter-observer reliability has been reported to be only about 37 percent and test-retest reliability (reading of the same scan multiple times by the same radiologist) only 51 percent (Shank et al., 1990). In series comparing endorectal ultrasound with CT scan, endorectal ultrasound was better at detecting transmural penetration and lymph node spread, although CT was better at detecting liver metastases. In a comparative trial of MRI and CT, MRI did not compare favorably. The sensitivity of detecting lymph node metastases was 40 to 57 percent with CT and only 13 to 43 percent with MRI, with a specificity of 90 percent for both (Hodgman et al., 1986; Guinet et al., 1990).

Of the various imaging modalities, endorectal ultrasound has the best sensitivity and specificity at determining the extent of tumor penetration (67 to 97 percent and 50 to 92 percent, respectively) (Saitoh et al., 1986; Beynon et al., 1987; Konishi et al., 1990; Dershaw et al., 1990; Hildebrandt et al., 1990; Glaser et al., 1990; Beynon, 1989; Cohen et al., 1991; Di Candio et al., 1987; Milsom, 1990; Napolean et al., 1991; Dershaw et al., 1990). However, it is not as effective at evaluating lymph node metastases. Nonetheless, of the various imaging modalities, endorectal ultrasound probably has the greatest
role in the preoperative staging of rectal cancer as it allows the surgeon to assess the degree of penetration, thus determining which tumors will be amenable to local excision, which will require wide excision, and which will benefit from preoperative radiation for downstaging in order to allow a sphincter saving operation. However, endorectal ultrasound is extremely operator dependent and is not yet widely available in the United States for the staging of rectal cancer (Hawes, 1993).

Given the complexity of the various clinical situations in rectal cancer that may or may not warrant preoperative imaging with endorectal ultrasound or CT scan, and the alternative surgical approaches that are largely at the discretion of the surgeon, we do not recommend a quality indicator for the routine use of any imaging studies in the preoperative evaluation of rectal cancer.

Other tests that are often obtained prior to surgery for colorectal cancer include liver function tests and the serum level of carcinoembryonic antigen (CEA) (Vignati and Roberts, 1993). However, the sensitivity and specificity of liver function tests do not make them useful for predicting metastatic disease in colorectal cancer. In one study of patients with elevated liver function tests prior to surgery for colorectal cancer, fewer than 50 percent had demonstrable metastatic disease at laparotomy, and, in long term follow-up they were no more likely to have metastases to the liver than patients without abnormal liver function tests (Tartter et al., 1984). Therefore, we do not recommend that routine screening of liver function tests be included in a quality indicator for the preoperative evaluation of colon cancer. CEA is a protein present in fetal tissue and in tumors of the gastrointestinal tract but not in normal adult intestinal tissue. Plasma concentrations of CEA may be elevated in colorectal tumors but they may also be normal, and CEA may also be elevated in non-malignant conditions such as in patients with chronic active hepatitis or in patients who smoke. Nonetheless, several large case series of patients with colorectal cancer have shown that an elevated preoperative CEA correlates with poorer survival, independent of stage of disease at diagnosis (Sener et al., 1989).

In practice, however, the level of the preoperative CEA does not change the initial management of patients with colorectal cancer. A preoperative CEA may be desirable if the clinician is going to be following the CEA
postoperatively. However, since we are not recommending that serial CEA measurements be included in a quality indicator for follow-up (see discussion later), we do not recommend that they be included in a preoperative quality indicator either.

TREATMENT

Polyps

The quality indicators for the treatment of benign polyps are covered in Chapter 4. The incidence of carcinoma in situ in a polyp is approximately seven percent, while the incidence of invasive cancer in a polyp is approximately five percent (Stein and Coller, 1993). For a polyp that contains carcinoma in situ, curative treatment consists of complete excision of the polyp as there is no appreciable risk of spread (Stein and Coller, 1993). For polyps with invasive cancer, multiple case series have demonstrated that with favorable histologic conditions, the risk of developing recurrent or metastatic cancer is extremely low (approximately 2%) with complete polypectomy alone as treatment. Given that the operative mortality of a segmental colectomy is reported to be between 2.5 percent to 4.4 percent, the operative risks outweigh the potential benefits. However, in patients with unfavorable histologic features, the risk of cancer recurrence ranges from 15 percent (for invasion into the submucosa below the stalk or Level 4 invasion) to 48 percent (for a positive margin) (Stein and Coller, 1993). Other histologic features that predict cancer recurrence include lymphatic or venous invasion (45% risk) and Grade 3 differentiation (38% risk). Given the high risk of recurrent or metastatic disease from a polyp with unfavorable histologic features, experts recommend that these patients be offered a wide surgical resection (see sections on Localized Colon Cancer and Localized Rectal Cancer). Based upon this evidence, the American College of Gastroenterology recommends that only those polyps that are completely excised, not poorly differentiated, without vascular or lymphatic invasion, and with negative margins be treated with polypectomy alone; and for patients with polyps with poor prognostic features, the risk of surgical resection be weighed against the risk for death from metastatic cancer (Bond, 1993).

We recommend that the quality indicator for the treatment of malignant polyps specify that patients be offered a wide surgical resection if:
• the polyp is not completely excised,
• the margins are positive,
• lymphatic or venous invasion is present, or
• histology is Grade 3 or poorly differentiated (Indicator 2).

For patients who are treated with polypectomy alone (presumably those with favorable histologic features) the American College of Gastroenterology recommends a follow-up colonoscopy in three months to be sure that there is no abnormal residual tissue at the polypectomy site, followed by standard surveillance (Bond, 1993) (Indicator 3).

Localized Colon Cancer (Stage I, II, & III)

The standard treatment for colon cancer is surgery with wide resection and anastamosis (Nogueras and Jagelman, 1993). The aim of surgical treatment for cure is to remove the tumor and its lymphatic drainage and to provide adequate clear margins ensuring removal of the entire tumor burden. Wide surgical resection involves removing the entire tumor with a margin of bowel on either side along with the mesentery that contains the lymphatic drainage for that region of bowel. Retrospective studies have shown poorer survival rates with margins beyond the tumor of less than approximately 5 cm. However, since histopathologic studies have not identified intramural spread of tumor beyond 1.2 cm, most surgeons currently accept a 2 cm clear margin on either side of the tumor. Direct extension to surrounding organs does not preclude resection with curative intent as histopathologic examination of such “en bloc” resections confirms actual involvement only 48 to 84 percent of the time (Staniunas and Schoetz, 1993). Case series have shown a five year survival of 49 to 79 percent with en bloc resection compared with zero to 17 percent without (McGlone et al., 1982; Gall, 1987).

Approximately 25 percent of patients have distant metastases and are not candidates for surgical resection with curative intent. Several case series have suggested a benefit in survival and symptoms from a surgical resection with palliative intent; however, experts disagree on the merits of this approach (O'Connell, 1997). For this reason, we will limit our quality indicator for the surgical treatment of colon cancer to those cases where the intent is cure (Stages I to III). Wide surgical resection should be offered to all patients with Stages I to III colon cancer, including those with
locally invasive disease, unless coexisting medical problems substantially increase the mortality risk of the surgical procedure itself. In order to operationalize this as an indicator, evidence of wide resection will be obtained from the pathology report as follows: The surgical specimen must include the tumor with at least 2 cm of bowel on either side, and there must be lymph nodes present. Age alone is not a contraindication to aggressive treatment for colorectal cancer as acceptable mortality and morbidity are achieved even in patients over age 70 (Fitzgerald, 1993) (Indicator 4). As an assessment of the technical quality of the surgical resection, for patients with Stage I colon cancer or Stage II and III colon cancer that does not invade other organs, the surgical specimen should have negative margins (Indicator 5).

**Adjuvant Therapy of Colon Cancer**

Randomized trials have shown a benefit for adjuvant chemotherapy in Stage III colon cancer (The Medical Letter, 1996; Moertel, 1994). Results of two randomized controlled trials that demonstrated approximately a 30 percent reduction in the overall mortality for patients with Stage III colon cancer treated with 5-FU and levamisole (Moertel et al., 1990; Laurie et al., 1989; Moertel, 1995). Based on these results, an NIH Consensus Conference convened in 1990 recommended that all patients with Stage III colon cancer be offered adjuvant chemotherapy for one year (5-FU with levamisole) within six weeks of their surgical resection (NIH Consensus Statement Online, 1990). In addition, the combination of 5-FU with leucovorin has been shown to have a similar benefit on overall and disease-free survival in several randomized trials when compared with a 5-FU, semustine, and vincristine regimen, and when compared with no adjuvant treatment (Wolmark et al., 1993; IMPA of Colon Cancer Trials 1995; O'Connell, 1997). Maturing data from trials comparing various dosage schedules of 5-FU and leucovorin with the now standard 5-FU and levamisole did not demonstrate a significant difference between them (Haller et al., 1996; Wolmark, 1996).

For Stage II colon cancer, there was a non-significant trend toward improved disease-free and overall survival in one of the trials of adjuvant 5-FU and leucovorin (Moertel, 1990). Similarly, analysis of pooled data from several National Surgical Adjuvant Breast and Bowel Project (NSABP) trials suggested a survival advantage comparable to that seen in Stage III patients.
with adjuvant chemotherapy (Mamounas et al., 1996). None of the studies to date have demonstrated a clear benefit for adjuvant chemotherapy in Stage II patients (Laurie et al., 1989; International Multicentre Pooled Analysis of Colon Cancer Trials, 1995). In keeping with these data, the NIH Consensus Conference in 1990 did not make a recommendation regarding adjuvant chemotherapy in Stage II colon cancer (NIH Consensus Statement Online, 1990).

Patients with Stage III colon cancer should be offered adjuvant chemotherapy with one of the following published 5-FU-containing regimens, beginning 21 days to six weeks after surgery (The Medical Letter, 1996) (Indicator 6):

1. 5-FU 450 mg/m² rapid intravenous injection daily for five consecutive days followed by weekly 5-FU treatments, at the same dose, beginning 28 days from the start of treatment and continuing for 48 weeks, and levamisole 50 mg orally every eight hours for three days beginning with the first dose of 5-FU and repeated every two weeks for 52 weeks.

2. Leucovorin 200 mg/m² followed by 5-FU 370-400 mg/m² rapid intravenous injection daily for five consecutive days repeated every 28 days for at least six cycles and not more than 12 cycles (International Multicentre Pooled Analysis of Colon Cancer Trials 1995, Haller et al., 1996; Wolmark et al., 1996)

3. Leucovorin 20 mg/m² followed by 5-FU 370-425 mg/m² rapid intravenous injection daily for five consecutive days repeated every 28 days for at least six cycles and not more than 12 cycles.

4. Leucovorin 500 mg/m² followed by 5-FU 500 mg/m² intravenous infusion weekly, for six weeks of an eight week cycle, for at least six cycles and not more than 12 cycles.

Localized Rectal Cancer

Like colon cancer, the mainstay of treatment for rectal cancer is wide surgical resection of the primary and regional lymph nodes with anastomosis, provided there is sufficient distal rectum to allow for it. Surgery can be accomplished either by the sphincter-sparing low anterior resection (usually necessitates tumor at least 7 to 8 cm of the anal verge) or the sphincter-sacrificing abdominal perineal resection for lesions too distal to permit low anterior resection. Overall survival is comparable with the two approaches,
though a greater number of local recurrences occur with the abdominal perineal resection (18-21% versus 7% for low anterior resection) (Butcher, 1971; Malt, 1974; Slanetz, 1972; Mayo, 1960; Mayo, 1958; Balsley, 1973).

Stage I rectal cancer has a high cure rate with surgery alone, with 90 to 95 percent disease-free survival at five years (Heald et al., 1986). While the standard surgical procedure would be a low anterior resection or abdominal perineal resection as described in the proceeding paragraph, retrospective series suggest that patients with small (< 4 cm) well- to moderately-well differentiated adenocarcinoma with no lymphatic or venous invasion treated with full-thickness local excision that results in negative margins have comparable outcomes in selected populations, with or without radiation therapy (Minsky, 1995; Buess, 1995; Scholefield et al., 1995; Heimann, 1992; Bailey et al., 1992; Willett et al., 1994). Other treatments including endocavitary irradiation and electrofulguration have been described; however, these have not been compared in randomized trials to surgery (CancerNet PDQ, 1997). Our proposed quality indicators for Stage I rectal cancer require that patients be offered definitive surgical treatment with low anterior resection or abdominal perineal resection, or have a full-thickness local excision described in the pathology report to have “negative margins” (Indicators 7 and 9).

Patients with Stage II and III rectal cancer are at high risk for local and systemic recurrences. While only five to ten percent of patients with Stage I disease will recur, 25 to 30 percent of those with Stage II will relapse. Up to 50 percent of patients with Stage III rectal cancer will recur (Heald et al., 1986). It is believed that the principal reason for patients with rectal cancer having a higher local recurrence rate than patients with colon cancer is the difficulty in obtaining clear radial margins given the constraints of the pelvic anatomy. Randomized trials of preoperative or postoperative radiation therapy alone have demonstrated a significant decrease in local recurrence rates without any impact on overall survival (Gerard, 1988; Thomas, 1988; Fisher et al., 1988; Mohiuddin et al., 1991). However, several studies have demonstrated an increase in both disease-free survival and overall survival for patients with Stage II and III rectal cancer when chemotherapy is combined with radiation therapy in the postoperative period (Thomas, 1988; The Medical Letter, 1996; Pahlman, 1995; Freedman et al., 1995; Krook et al., 1991; Gastrointestinal Tumor Study Group, 1992; Moertel, 1994).
This lead the NIH Consensus Conference on colorectal cancer in 1990 to conclude that all patients with Stage II or III rectal cancer should be offered perioperative combined modality therapy with chemotherapy and high-dose pelvic radiation therapy (4500 to 5500 cGy). While the initial studies of combined modality therapy used 5-FU and semustine, subsequent randomized trials have found that 5-FU alone is equally effective (and semustine has been shown to be leukemogenic) (Gastrointestinal Tumor Study Group 1984 and 1992). Though one study did demonstrate a modest survival with prolonged 5-FU infusion over bolus infusion of 5-FU during radiation therapy, either protocol with or without the addition of leucovorin is considered standard (O’Conell et al., 1994). For patients with low rectal tumors, one study has shown that high-dose preoperative radiation therapy may allow preservation of anal sphincter function (and continence) upon resection of the tumor (Mohiuddin et al., 1991). Our recommended quality indicators for the treatment of Stage II and III rectal cancer state that patients should be offered complete surgical resection with either a low anterior resection or abdominal perineal resection (Indicator 8), followed by postoperative 5-FU and radiation therapy of 4500 to 5500 cGy to the pelvis, or preoperative radiation therapy, with or without 5-FU chemotherapy, followed by complete surgical resection (Indicator 10).

**Isolated Liver Metastases (Stage IV)**

For patients who have isolated liver metastases, either at the time of initial diagnosis or who later develop them as the only site of recurrence, surgical resection, if it is technically feasible, offers a hope of cure and in multiple case series has a five year survival of approximately 25 percent (Fong, 1995; Taylor, 1996; Steele et al., 1991; Pedersen et al., 1994; Coppa et al., 1985; Adson et al., 1984; Scheele et al., 1990; Gayowski et al., 1994; Scheele et al., 1991). The number of historical controls that have lived beyond five years are strikingly few. Randomized trials have not been performed because the investigators have not believed them to be ethical. The operative mortality has been reported between three and seven percent (Fong, 1995; Taylor, 1996). Factors that predict a more favorable course after liver resection of colorectal metastases include tumor size less than 4 cm, fewer than four metastases, unilobar involvement, and original stage of disease (Gayowski et al., 1994; Scheele et al., 1991). This evidence suggests that
selected patients will benefit from resection of colorectal metastases to the liver. From chart review alone, however, it would prove difficult to identify those patients who would possibly have benefitted. In addition, only five percent of patients with colorectal cancer develop isolated liver metastases that appear amenable to surgical resection (Scheele et al., 1990). Therefore, given the small numbers of patients affected, and the difficulty in identifying those patients who would benefit, we have not included resection of isolated liver metastases as a quality indicator.

Hepatic artery infusion of chemotherapy is another treatment occasionally used in the treatment of colorectal liver metastases. Studies have shown that while this approach achieves a higher response rate, there is no improvement in overall survival (Kemeny et al., 1987; Chang, 1987; Wagman, Rougier et al., 1992; Kemeny et al., 1993; Meta-analysis Group in Cancer, 1996).

Metastatic Colorectal Cancer (Stage IV)

Approximately 50 percent of patients have metastatic disease on presentation. Unfortunately, there is no therapy for metastatic colon cancer that has been shown to improve survival. Chemotherapy has been used for palliation of symptoms with the hope of prolonging survival (The Medical Letter, 1996; Moertel, 1994; Kemeny et al., 1993). 5-FU based regimens are the standard, and multiple trials have been conducted comparing 5-FU alone with 5-FU modulated by varying agents including methotrexate, leucovorin, and interferon alpha, all in varying dosage schedules. While generally the modulation of 5-FU with these agents improved the response rate (number of cases where the tumor size decreases during the course of treatment), there has not been a consistent improvement in overall survival demonstrated with any of these protocols, and treatment-related toxicities have generally been worse with the combination and higher dosage regimens (Erlichman et al., 1988; Doroshow et al., 1990; Petrelli et al., 1989; Petrelli et al., 1987; Leichman et al., 1995; Buroker et al., 1994; Poon et al., 1989; Advanced Colorectal Cancer Meta-analysis Project, 1994; Hill et al., 1995; Corfu-A Study Group, 1995). Likewise, continuous infusion of 5-FU via an ambulatory infusion pump has been associated with a modest increase in the response rate but no improvement in overall survival (Lokich et al., 1989; Leichman, 1995).

Irinotecan is a new drug that was approved by the FDA in June of 1996, under
the provisions of the accelerated approval process, for use in metastatic colorectal cancer that has recurred or progressed on standard chemotherapy (Micromedex Healthcare Series Drug Information DRUGDEX(R) System 1975-1997). In phase II studies, irinotecan had a response rate of 23 percent to 32 percent in metastatic colorectal cancer. However, no randomized studies of its efficacy have been performed, and no data are available on its effect on disease-free or overall survival (Rothenberg, 1996; Conti, 1996).

Surprisingly, given that the goal of therapy in metastatic disease is palliation, few studies have included performance status, symptoms, or quality of life as endpoints (Buroker et al., 1994; Poon, 1989; Sullivan, 1995; Laufman et al., 1993). One study comparing 5-FU modulated by high versus low dose leucovorin found no difference in quality of life outcomes. Another study included six arms of 5-FU modulated by varying doses of leucovorin, methotrexate, or cisplatin. The low dose leucovorin arm demonstrated a higher response rate for improvement in performance status, weight gain, and palliation of symptoms (Buroker et al., 1994; Poon et al., 1989). This regimen also had the lowest drug cost (Poon, 1989).

Palliative surgery also has a role in metastatic colorectal cancer, especially to relieve obstruction or treat bleeding or perforation. In addition, several case series have suggested a benefit in survival and symptoms from a surgical resection with palliative intent. However, experts disagree on the merits of this approach (CancerNet PDQ, 1997; Haskell, 1995).

Given the variety of clinical scenarios, the absence of strong evidence that any treatment improves survival or quality of life in all or even most patients, and the lack of expert consensus, we do not recommend a quality indicator for the treatment of metastatic colorectal cancer.

Toxicity

Most chemotherapy regimens for colorectal cancer, whether adjuvant or palliative, include 5-FU, and the main toxicities of those regimens are secondary to the 5-FU. 5-FU toxicity varies with the dose and the schedule (daily, weekly, continuous infusion), but may include nausea, vomiting, diarrhea, leukopenia, stomatitis, and erythrodysesthesis (hand foot syndrome) (The Medical Letter, 1996). The dose limiting toxicity (Grade 3 or 4) for the five-daily fast intravenous infusion is generally neutropenia (3 to 47 percent
of patients) or stomatitis (3 to 28 percent), and for the weekly intravenous infusion, diarrhea (13 to 40 percent). These effects require that chemotherapy be withheld until symptoms resolve and often result in dose reduction as well (The Medical Letter, 1996; Erlichman et al., 1988; Doroshow et al., 1990; Petrelli et al., 1989; Petrelli et al., 1987; Leichman et al., 1995; Poon et al., 1989; Moertel et al., 1990; Laurie et al., 1989; Wolmark et al., 1993; International Multicentre Pooled Analysis of Colon Cancer Trials, 1995). The fatal complications of therapy with 5-FU are usually related to sepsis with neutropenia or severe diarrhea. We recommend two quality indicators for all patients receiving chemotherapy with 5-FU. The first requires that all patients have a CBC not more that 48 hours prior to the first day of 5-FU in each cycle of chemotherapy (Indicator 11). The second states that patients with Grade 3 or 4 toxicity (a WBC less than 2,000, stomatitis that prevents eating, or diarrhea of seven or more stools a day) should have chemotherapy withheld until the symptoms resolve (Indicator 12).

**Recurrent Colon Cancer**

One third of patients diagnosed with colorectal cancer will develop recurrent disease (Asbun, 1993; Safi, 1993). Most will have distant metastases, but 21 percent will have an isolated local recurrence. Local recurrence is more common in rectal cancer, comprising approximately 50 percent of recurrences. An additional 25 percent have isolated hepatic metastases, and approximately four percent present with isolated pulmonary lesions. Local recurrences may present at the site of the anastomosis or more commonly in the bed of the primary carcinoma. Surgery is the only hope for cure in these patients. Case series of selected patients who have undergone a second resection report median lengths of survival after resection of 35 to 85 months (Michelassi et al., 1990). The approach to isolated liver metastases is discussed above. For the rare case of an isolated pulmonary metastasis, wedge excision is an option with curative potential. In a series of 139 patients with solitary pulmonary metastases who underwent resection, the five year survival rate was 30.5 percent and the 20 year-survival rate was 16.2 percent (McAfee, 1992). Again, given the variety of clinical scenarios for a relatively few number of patients, we believe it would be difficult to
implement a quality indicator for recurrent colorectal cancer and do not recommend one.

**FOLLOW-UP AND POSTOPERATIVE SURVEILLANCE**

Of patients who undergo a surgical resection with curative intent, 30 percent to 50 percent will develop recurrent disease (Vignati et al., 1993; Safi et al., 1993). The goal of postoperative surveillance after curative resection for colorectal carcinoma is the detection of recurrent tumor at a stage when it is still curable and the prevention or early detection of a metachronous carcinoma. However, to date there have been no large-scale randomized trials to document the efficacy of a postoperative monitoring program and intensive surveillance of colorectal cancer patients after resection with curative intent remains controversial (Steele, 1993; Safi, 1993; Moertel et al., 1993).

As there is no literature on the efficacy of surveillance of patients with metastatic colorectal cancer, we recommend that the quality indicator be limited to patients with potentially curable disease (Stages I to III). Methods of surveillance commonly used to follow patients with colorectal cancer who have undergone a curative resection include periodic history and physical examination, serial CEA measurements, periodic imaging studies, and colonoscopy (Vignati et al., 1993).

In two studies, positive findings on a thorough history and physical exam provided the first indication of recurrent disease in up to 48 percent of patients (Beart et al., 1983; Deveney et al., 1984). As periodic history and physical examination can be accomplished without special technology and is relatively inexpensive we will include it in our quality indicator for the follow-up of Stages I to III colorectal cancer. Since 85 percent of colorectal cancers recur in the first three years, our proposed quality indicator for follow-up requires a history and physical exam by a physician at least every six months for three years after initiation of treatment (Indicator 13) (Vignati et al., 1993).

Serial measurement of serum CEA levels has been widely accepted as a way to identify recurrences while they may still be resectable for cure. In one analysis of 146 asymptomatic patients who underwent a second look operation only because of a rise in CEA, 95 percent had recurrences and, of these, 58
percent were resectable for potential cure. Of those patients who were reoperated upon, the five year survival rate was approximately 30 percent (Martin et al., 1985). However, other large retrospective studies found a year disease-free survival rate after salvage surgery of two percent in CEA-monitored patients; the one year disease free survival of patients who underwent salvage surgery with no CEA monitoring was identical (Moertel et al., 1995; Minton et al., 1985). No randomized prospective trials have been performed to evaluate the efficacy of CEA in the postoperative surveillance of colorectal cancer. While many physicians may choose to follow CEA levels in their patients with colorectal cancer, given the absence of clear data in the literature, we will not include CEA monitoring in our quality indicators for the follow-up of colorectal cancer.

Periodic imaging studies, including CT or MRI of the abdomen, chest x-ray or CT of the chest, and endorectal ultrasound are all used to detect recurrent colorectal cancer. Unfortunately, there are no controlled studies to provide information on the efficacy of these studies in monitoring patients with colorectal cancer (Vignati et al., 1993; Kagan et al., 1991). We will therefore not include any imaging studies in our quality indicators for the follow-up of colorectal cancer.

There are no controlled studies of postoperative surveillance for colorectal cancer with colonoscopy. Recent consensus guidelines, developed by the American Gastroenterological Association (AGA) and endorsed by the American Cancer Society and the American Society of Colon and Rectal Surgeons recommend a colonoscopy or double contrast barium enema (DCBE) within a year of curative surgery if it did not occur preoperatively (Indicator 14). If the colonoscopy or DCBE is normal at three years post-surgery, the test should then be performed every five years (Indicator 15) (Winawer et al., 1997). This indicator is similar to the AGA recommendations for adenomatous polyps, which are based upon randomized controlled trials in that population. A retrospective study of 290 patients who underwent resection with curative intent for colorectal cancer and were followed with colonoscopy (initially every six months, and every one to two years after the first year) suggests that there might be a benefit for routine postoperative surveillance with colonoscopy (Winawer et al., 1997). These authors found that 75 percent of patients who had asymptomatic recurrences identified by colonoscopy were able
to undergo a second resection compared with only 16 percent of patients whose recurrences were identified when they presented with symptoms (Lautenbach et al., 1994). Several other case series have found that up to ten percent of patients may have metachronous cancers discovered by screening colonoscopy, although, a much smaller percentage were actually asymptomatic at the time (Barlow et al., 1993; Patchett et al., 1993). Even though conclusive data regarding the efficacy of postoperative surveillance for colorectal cancer with either colonoscopy or double contrast barium enema are lacking, given the current evidence in its favor and its widespread acceptance as the standard of care, we will include it in the quality indicator for follow-up of patients with Stage I to III colorectal cancer (Indicator 15).
REFERENCES


Bond JH, and for the Practice Parameters Committee of the American College of Gastroenterology. 1993. Position paper. Polyp guideline: diagnosis,
treatment, and surveillance for patients with nonfamilial colorectal polyps. *Archives of Internal Medicine* 19: 836-843.


**RECOMMENDED QUALITY INDICATORS FOR COLORECTAL CANCER TREATMENT**

The following apply to men and women age 18 and over who have colorectal cancer.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Quality of Evidence</th>
<th>Literature</th>
<th>Benefits</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
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<tr>
<td>1. Patients who have undergone surgical resection for colon or rectal cancer should have documentation in the chart that colonoscopy or barium enema with sigmoidoscopy was offered within the preceding 12 months.</td>
<td>II-2, III</td>
<td>Vignati and Roberts 1993; Isler et al., 1987</td>
<td>Promote complete cure.</td>
<td>Identifies synchronous lesions so that surgery can be appropriately modified. Between 2% and 7% of patients with colon cancer have a synchronous lesion.</td>
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<td><strong>Treatment</strong></td>
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<tr>
<td>2. Patients diagnosed with a malignant polyp should be offered a wide surgical resection within 6 weeks if any of the following are true: a. the colonoscopy report states that the polyp was not completely excised; b. the margins are positive; c. lymphatic or venous invasion is present; d. histology is grade 3 or poorly differentiated.</td>
<td>II-2, III</td>
<td>Stein and Coller 1993; Bond, 1993</td>
<td>Promote complete cure.</td>
<td>Offers option of curative treatment for persons at high risk of developing recurrent or metastatic disease. Adverse histologic features predict 40-50% rate of recurrence or metastases.</td>
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<td>3. Patients with a malignant polyp treated with polypectomy alone should be offered colonoscopy within 6 months of the polypectomy.</td>
<td>III</td>
<td>Bond, 1993</td>
<td>Decrease risk of recurrence.</td>
<td>Ensures that all of the carcinoma has been excised. American College of Gastroenterology recommendation.</td>
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<td>Indicator</td>
<td>Quality of Evidence</td>
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<td>Benefits</td>
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<td>4. Patients who are diagnosed with colon cancer and do not have metastatic disease should be offered a wide resection with anastomosis within 6 weeks of diagnosis.</td>
<td>II-2, III</td>
<td>CancerNet 3/97, Haskell 1995; Nogueras and Jagelman et al., 1993; Staniunas and Schoetz 1993; McGlone et al., 1982; Gall et al., 1987</td>
<td>Decrease mortality.</td>
<td>Surgical resection is the only curative treatment.</td>
</tr>
<tr>
<td>5. Patients who undergo a wide surgical resection should have “negative margins” noted on the most recent final pathology report or have documentation that they were offered a repeat resection if they meet either of the following criteria:</td>
<td>II-2, III</td>
<td>Haskell 1995; Nogueras and Jagelman, et al., 1993</td>
<td>Decrease risk of recurrence.</td>
<td>Ensures adequate surgical therapy. Risk of recurrence is higher with positive margins.</td>
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<tr>
<td>a. Stage I colon cancer;</td>
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<td>b. Stage II or III colon cancer that is not invading into other organs (not a T4 lesion).</td>
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<td>Indicator</td>
<td>Quality of Evidence</td>
<td>Literature</td>
<td>Benefits</td>
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<td>6. Patients with Stage III colon cancer who have undergone a surgical resection should be offered adjuvant chemotherapy(^*) within 6 weeks of surgery and not before 21 days after surgery with a published 5-FU-containing regimen.</td>
<td>I, II-2, III</td>
<td>The Medical Letter 1996, Moertel, 1994; Moertel et al., 1990; Laurie et al., 1989; Moertel et al., 1995; NIH 1990; Wolmark et al., 1993; IMPA of Colon Cancer Trials, 1995; O'Connell, et al., 1997; Haller, et al., 1996; Wolmark, et al., 1996</td>
<td>Decreases the risk of recurrence.</td>
<td>Randomized controlled trials have demonstrated approximately a 30% reduction in the overall mortality for patients with Stage III colon cancer treated with 5-FU and levamisole or 5-FU and leucovorin.</td>
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</tbody>
</table>
| 7. Patients who are diagnosed with rectal cancer that appears clinically to be Stage I, should be offered one of the following surgical resections within 6 weeks of diagnosis:  
• low anterior resection;  
• abdominal perineal resection;  
| 8. Patients who are diagnosed with rectal cancer that appears clinically to be Stage II or III, should be offered one of the following surgical resections within 6 weeks of diagnosis:  
• low anterior resection;  
• abdominal perineal resection. | II-2, III | Butcher Jr., 1971; Malt and Nundy, 1974; Slanetz et al., 1972; Mayo and Cullen,1960; Mayo et al., 1958; Balsley and Fenger , 1973; | Promotes complete cure. | Surgical resection is the only curative treatment. |
<table>
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<th>Benefits</th>
<th>Comments</th>
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<tr>
<td>9. Patients who undergo a wide surgical resection should have “negative margins” noted on the most recent final pathology report or have documentation that they were offered a repeat resection if they meet either of the following criteria: a. Stage I rectal cancer; b. Stage II or III rectal cancer that is not invading into other organs (not a T4 lesion).</td>
<td>II-2, III</td>
<td>Butcher, 1971; Malt and Nundy, 1974; Slanetz et al., 1972; Mayo and Cullen, 1960; Mayo, et al., 1958; Balsley and Fenger, 1973; Heald and Ryall, 1986; Minsky, 1995; Buess, 1995; Scholefield, 1995; Heimann et al., 1992; Bailey et al., 1992; Willett et al., 1994;</td>
<td>Promotes complete cure.</td>
<td>Ensures adequate surgical therapy. Risk of recurrence is higher with positive margins.</td>
</tr>
<tr>
<td>10. Patients with Stage II and III rectal cancer (defined pathologically) who undergo surgical resection should be offered one of the following treatments (this indicator only applies to patients who have had a surgical resection): • postoperative radiation therapy of 45-55 Gy to the pelvis with chemotherapy containing 5-FU to begin not sooner than 4 weeks after surgery and not more than 12 weeks after surgery; • preoperative radiation therapy to the pelvis to begin not more than 6 weeks after diagnosis; • preoperative radiation therapy with chemotherapy containing 5-FU to begin not more than 6 weeks after diagnosis.</td>
<td>I, II-2, III</td>
<td>Heald, 1986; Gerard, et al., 1988; Thomas and Lindblad, 1988; Fisher et al., 1988; Mohiuddin, 1991, Thomas and Lindblad, 1988; The Medical Letter, 1996; Pahlman, 1995; Freedman, 1995, Krook, et al., 1991; GTS Group, 1992; Moertel, 1994; GTS Group, 1984; O’Conell et al., 1994</td>
<td>Decreases risk of recurrence.</td>
<td>NIH Consensus Conference recommendation (1990).</td>
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<td>Indicator</td>
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<td>11. Patients receiving 5-FU chemotherapy should have a CBC checked not</td>
<td>II-2, III</td>
<td>The Medical Letter 1996; Erlichman, 1988; Doroshow et al., 1990; Petrelli et al., 1989; Petrelli et al., 1987; Leichman et al., 1995; Poon et al., 1989; Moertel et al., 1990; Laurie et al., 1989; Wolmark et al., 1993; IMPA of Colon Cancer Trials 1995</td>
<td>Avoid excess morbidity and mortality from chemotherapy toxicity.</td>
<td>Most common dose-limiting side-effect of the five-day daily 5-FU fast infusion is neutropenia.</td>
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<td>more than 48 hours prior to the first dose in each cycle.</td>
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<td>12. Patients should not receive 5-FU chemotherapy if any of the following</td>
<td>II-2, III</td>
<td>The Medical Letter 1996; Erlichman, 1988; Doroshow et al., 1990; Petrelli et al., 1989; Petrelli et al., 1987; Leichman et al., 1995; Poon et al., 1989; Moertel et al., 1990; Laurie et al., 1989; Wolmark et al., 1993; IMPA of Colon Cancer Trials 1995</td>
<td>Avoid excess morbidity and mortality from chemotherapy toxicity.</td>
<td>Grade 3 or 4 toxicity is an indication to hold chemotherapy and reduce the dosage.</td>
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<td>are documented in the past 2 days:</td>
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<tr>
<td>a. WBC &lt; 2,000;</td>
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<td>b. stomatitis that prevents them from eating;</td>
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<td>c. diarrhea of seven or more stools a day.</td>
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<td>Follow-up</td>
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<td>13. Patients with Stages I, II, and III colorectal cancer should receive</td>
<td>II-2, III</td>
<td>Vignati and Robert, 1993; Safi et al., 1993; Steele, 1993; Beart et al., 1983; Deveney et al., 1984</td>
<td>Decrease mortality.</td>
<td>Identifies patients with recurrent disease or a metachronous cancer early. 85% of colorectal cancers recur in the first 3 years.</td>
</tr>
<tr>
<td>Indicator</td>
<td>Quality of Evidence</td>
<td>Literature</td>
<td>Benefits</td>
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<tr>
<td>14. Patients with Stages I, II, and III colorectal cancer should receive colonoscopy or double contrast barium enema within a year of curative surgery if it did not occur within 12 months preoperatively.</td>
<td>II-2, III</td>
<td>Winawer et al., 1997; Lautenbach et al., 1994; Barlow and Thompson 1993; Patchett et al., 1993</td>
<td>Decrease mortality.</td>
<td>Identifies patients with recurrent disease or a metachronous cancer early. 85% of colorectal cancers recur in the first 3 years.</td>
</tr>
<tr>
<td>15 Patients with Stages I, II, and III colorectal cancer should receive colonoscopy or double contrast barium enema three years after surgery and every five years thereafter.</td>
<td>II-2, III</td>
<td>Winawer et al., 1997; Lautenbach et al., 1994; Barlow and Thompson, 1993; Patchett, et al., 1993</td>
<td>Decrease risk of recurrence.</td>
<td>Identifies patients with recurrent disease or a metachronous cancer early. 85% of colorectal cancers recur in the first 3 years.</td>
</tr>
</tbody>
</table>
Definitions and Examples

1 Metastatic disease - A patient shall be considered to have metastatic disease if a chest x-ray, CT scan of the abdomen, abdominal ultrasound, bone scan, or plain films of the bones show evidence of metastatic disease as follows:
   a. Chest X-ray - nodules or masses
   b. CT scan of the abdomen - nodules or masses in the liver
   c. Abdominal Ultrasound - hypoechoic lesions in the liver
   d. Bone Scan - increased uptake
   e. Plain Films - lytic or blastic bone lesions.

2 Wide Resection with Anastamosis - evidence of wide resection will be obtained from the pathology report as follows: The surgical specimen must include the tumor with at least 2cm of bowel on either side, and there must be lymph nodes present.

3 To be clinically Stage I, all of the following criteria must be met:
   a. On digital rectal exam, tumor is not fixed to pelvis.
   b. If endorectal ultrasound is performed there is no transmural penetration of tumor.
   c. No evidence of metastatic disease.

4 To be clinically Stage II or III, all of the following criteria must be met:
   a. On digital rectal exam, tumor is fixed to pelvis.
   b. If endorectal ultrasound is performed there is transmural penetration of tumor
   c. No evidence of metastatic disease.

5 T4 lesion - tumor penetrates the visceral peritoneum or invades other organs or structures.

6 Adjuvant chemotherapy: Acceptable 5-FU containing regimens include the following:
   5-FU 300-600mg/m² intravenous, daily for 5 days repeated every 28 days OR weekly, plus Levamisole 50mg orally 3 times a day for 3 days every 2 weeks OR Leucovorin 20-500mg/m² intravenous with each dose of 5-FU.

Quality of Evidence Codes:
I Randomized controlled trials
II-1 Nonrandomized controlled trials
II-2 Cohort or case analysis
II-3 Multiple time series
III Opinions or descriptive