Diseases of the Colon & Rectum

Practice Parameters

Practice Parameters for Colon Cancer

Prepared by
The Standards Practice Task Force
The American Society of Colon and Rectal Surgeons

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INTRODUCTION FOR CLINICAL PRACTICE GUIDELINES

It is estimated that there were 105,500 new colon cancers diagnosed in the United States in 2003: 49,000 in males and 56,500 in females.[1] This guideline will focus on colon cancer. Rectal cancer is presented in a separate guideline. In a national survey conducted by the American College of Surgeons Commission on Cancer, the most common presenting symptoms associated with colon cancer were abdominal pain, followed by change in bowel habits, rectal bleeding, and occult blood in the stool.[2] An individualized approach to the diagnosis that considers the patient's symptoms, age, personal history of inflammatory bowel disease, colon polyps, or colorectal cancer, and family history of colon cancer or predisposing genetic syndromes (*e.g.*, familial adenomatous polyposis or hereditary nonpolyposis colorectal cancer) should provide for the most cost-effective diagnostic evaluation.[3]

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I. DIAGNOSTIC EVALUATION

Current recommendations for screening and detection of colorectal neoplasms can be found in the So-

ciety's previously published practice parameters on this subject.[4] Once a colon cancer has been detected, prompt preoperative evaluation and treatment is warranted. A crucial part of this evaluation is to ensure that the patient's entire colon and rectum have been assessed with colonoscopy for the presence of synchronous neoplasms. In cases in which the colon cancer prevents the proximal bowel from being examined, colonoscopy should be performed within a few months of the definitive surgery. Most patients diagnosed with colon cancer will require an operation. Depending on the patient's age and health status, a variety of laboratory, radiologic, and cardiorespiratory tests may be appropriate to assess the patient's operative risk.

II. PREOPERATIVE ASSESSMENT

Guideline—Preoperative, carcinoembryonic antigen level should be obtained. Level of Evidence (Class II, Grade A)

Carcinoembryonic antigen (CEA) is known to be elevated in a variety of conditions, including colorectal cancer, proximal gastrointestinal cancers, lung and breast cancers, benign inflammatory conditions of the gastrointestinal tract, and smoking. It has never been useful as a screening tool but has proven useful in individuals diagnosed with colorectal cancer.

Drawing a CEA level has been recommended before and after resection of colorectal cancer.[5,6] Obtaining a preoperative CEA is thought to be beneficial for two reasons. First, postoperative return to normal of an elevated preoperative CEA is associated with complete tumor resection, whereas persistently elevated values indicate the presence of visible or occult residual disease.[7,8] The interval recommended most commonly is every three months for the first two years. This allows enough time for CEA to return to baseline. Second, elevated preoperative CEA levels have been found to be an independent prognosticator of poor outcome. In 572 patients undergoing curative resection for node-negative colorectal cancer, elevated CEA was demonstrated to be independently predictive of poor survival.[9] Also, disease-free survival is substantially lower in patients with elevated CEA before surgery. An elevated CEA was associated with future metastases in 37 percent of patients at five years *vs.* 7.5 percent of patients with normal CEA levels.[5]

Guideline—Evaluation with preoperative CT scanning of selected patients is indicated and routine preoperative CT scanning is optional. Level of Evidence (Class II, Grade B)

CT scanning is the modality of choice to evaluate metastatic, intra-abdominal colon cancer. Its use preoperatively has been debated. CT scans can be used to evaluate local extension of the tumor and regional lymphadenopathy, as well as for the presence of hepatic metastases. However, in most cases, the information gained does not impact the decision to operate or the operative approach, and is not comparable to a postoperative scan that may be used as a baseline. These factors limit its yield as a preoperative staging modality.

There is little data regarding accuracy of the CT scan in evaluating local extension. In individuals in whom there is a suspicion of invasion of an adjacent organ (because of the presence of a palpable mass, unusual abdominal pain or other symptoms, or unexplained chemical abnormalities), a CT scan may be useful for preoperative planning. The sensitivity of CT scans in detecting metastatic lymphadenopathy ranges from 19 to 67 percent.[10,11] Many series have reported the utility of CT in detection of liver metastases and cite sensitivities and specificities between 90 and 95 percent for lesions > 1 cm.[12] However, this rarely results in changes in operative strategy. Nearly all information obtained by preoperative abdominal CT scanning can be readily obtained at time of surgical resection. Based on these data, the routine use of CT before surgery is optional. A scan may be beneficial when the results will change the decision to operate or change the operative approach. Abnormalities such as a palpable mass or nearly obstructing cancer are more likely to have T4 involvement in which additional preoperative assessment is warranted.

There is a trend toward the routine use of preoperative evaluation of patients with CT scans, especially in cancer centers in which synchronous resections of the primary and metastatic cancers are increasing. Also, investigational protocols using preoperative chemotherapy for asymptomatic Stage IV cancer are being investigated. As these and other protocols are implemented, operative strategy may be altered by the preoperative CT scan, which will be part of the routine preoperative evaluation in that setting.

Guideline—Routine performance of preoperative chest x-rays is acceptable. Level of Evidence (Class III, Grade C)

It is common practice among surgeons to obtain a chest x-ray preoperatively to evaluate the lungs for evidence of metastatic disease. Although the yield for metastatic disease is low, the cost is small, and the utility of the examination is part of an overall preoperative assessment.

III. PREPARATION FOR OPERATION

Once a decision is made that an operation is required and that the patient is a reasonable candidate for such, it is incumbent on the surgeon to ensure that the patient is well informed of what may be required and to make every effort to decrease the potential for postoperative complications.

A. Informed Consent

Guideline—Informed consent should be obtained preoperatively. Level of Evidence (Class III, Grade C)

All patients who are to undergo surgery for colon cancer need to be clearly informed of the reasons for and the extent of the proposed resection, the likely outcome of the surgery, the pertinent complications and their likelihood of occurring, expected length of hospitalization and recovery, alternatives to the proposed surgery, and prognosis. The patient and family must be given the opportunity to ask questions of their surgeon.

B. Mechanical Bowel Preparation

Guideline—Mechanical bowel preparation is nearly universally used in elective surgery. Level of Evidence (Class II, Grade A)

Despite its nearly universal use, the literature does not support a defined benefit for preoperative mechanical preparation of the bowel. There have been five, prospective, randomized, controlled studies comparing mechanical preparation to no preparation for elective colorectal surgery.[13–17] All of these have failed to demonstrate any appreciable decrease in infection rates, anastomotic leak, or mortality in patients undergoing mechanical bowel preparation. However, because of sample size, they all lack the statistical power required to exclude the presence of a Type II error. Even when compiled together and evaluated with meta-analysis, the numbers are still too few to reach a reliable conclusion.[18]

There is no doubt that preoperative mechanical bowel preparation is the common practice in North America. Surveys have demonstrated that for elective colorectal surgery, 100 percent of colorectal surgeons responding to the survey in the United States prefer to have their patients take some form of mechanical prep.[19–22] The persistence in using a preoperative bowel preparation may be justified simply on the basis of the advantages it affords in ease of handling the prepared colon, the proven safety of the methods used for bowel cleansing, and the relatively low cost.

Guideline—Outpatient bowel preparation is generally safe and cost effective. Level of Evidence (Class II, Grade A)

Because of continuing efforts to reduce the cost of medical care, preoperative bowel preparation is increasingly being performed on an outpatient basis the day before surgery. In two studies, one prospective and the other retrospective, outpatient bowel preparation was found to be safe and cost effective.[23,24] Patients who took their prep at home had no greater risk of operative complications and had a shorter hospital stay. However, these patients do tend to present for surgery in a relatively dehydrated state and should receive adequate intravenous fluid in the holding area before administration of anesthesia.

The potential fluid and electrolyte shifts that can occur with mechanical bowel preparations should be borne in mind when preparing an elderly or cardiac-compromised patient for surgery. It is at times more appropriate to admit such patients the day before operation for their bowel preparation.

C. Prophylactic Antibiotics

Guideline—Prophylactic antibiotics are recommended for patients undergoing colon resection. Level of Evidence (Class I, Grade A)

Prophylactic antibiotics have proven effectiveness in decreasing the rate of infection, mortality, and cost of hospitalization after colonic resection.[25] There are a wide variety of antibiotic regimens that are effective. Although the vast majority of colorectal surgeons in North America continue to use both oral and parenteral antibiotics,[22] it remains unclear whether using both has an additive effect in lowering infection rates.[26] Regardless which parenteral antibiotic regi-

men is selected, it is agreed that it must be given before the start of the operation to be effective.[27,28] In elective colon resection for cancer, the intravenous antibiotics need not be continued longer than 24 hours postoperatively.[29]

Although there are several studies proposing the use of a single preoperative dose of antibiotics,[30–34] most of these suffer from a lack of statistical power because of small study size. There is one large, prospective, randomized trial that has shown that a single preoperative dose of cefotaxime and metronidazole is as effective as three doses.[30]

D. Blood Cross Match and Transfusion

Guideline—Blood transfusion should be based on physiologic need. Level of Evidence (Class III, Grade C)

Preoperative blood transfusions may be required for patients undergoing resection for colorectal cancer.[35–38] The need for transfusion is primarily based on the starting hemoglobin, the patient's physiologic status, and extent of intraoperative blood loss.[39,40]

The immunosuppressive effect of transfusion is well established.[41–44] A number of studies have shown that patients who receive perioperative blood transfusions have a greater incidence of infection.[35,45–47]

The use of autologous blood or leukocyte poor cells (washed red blood cells) may decrease this risk.[47,48] Whether the immunosuppressive effect of transfusion is of a magnitude to actually increase the rate of cancer recurrence is still unproved. Many studies have reported that patients receiving a perioperative blood transfusion have a greater risk of cancer recurrence and subsequent decreased survival.[35,37,49,50] However; meta-analysis studies have strongly questioned whether there is a true causal effect present.[39,51] Other factors (extent of resection required, location of tumor, experience of surgeon) in patients requiring transfusion may actually be the cause for the increased recurrence rate.

E. Thromboembolism Prophylaxis

Guideline—All patients undergoing surgery for colon cancer should receive prophylaxis against thromboembolic disease. Level of Evidence (Class I, Grade A)

Patients undergoing colon resection for cancer have a high incidence of venous thromboembolism, including deep venous thrombosis and pulmonary embolism.[52,53] There is strong evidence that the prophylactic use of unfractionated heparin reduces this risk.[52] Multiple studies also have demonstrated the effectiveness of low molecular weight heparin (LMWH) for this purpose.[54–57] A recently published, prospective, randomized trial in colorectal surgery patients demonstrated that LMWH and subcutaneous heparin were equally effective for preventing thromboembolism, with the patients receiving LMWH having a slightly higher rate of minor bleeding events.[57] Economic analysis on this data favored the use of subcutaneous heparin as more cost effective.[58]

By meta-analysis, intermittent pneumatic calf compression has been shown to be effective in reducing the risk of thromboembolism in cancer patients.[59] Whether there is an additive effect by use of more than one mode of prophylaxis for patients undergoing colonic resection is yet to be determined. However, many surgeons advocate the use of compression devices and chemical agents for prophylaxis in high-risk patients. For a more in-depth discussion of the risks and preventative measures available the reader is referred to the Society's previously published practice parameters on this subject.[60]

IV. OPERATIVE ISSUES

A. Operative Technique

Guideline—The extent of resection of the colon should correspond to the lymphovascular drainage of the site of the colon cancer. Level of Evidence (Class II, Grade B)

The determinant of adequate bowel resection for colon cancer is removal of the primary feeding arterial vessel and its corresponding lymphatics. Extended resections have not been shown to confer additional survival benefit.[61] However, tumors located in border zones should be resected with the neighboring lymphatic regions to encompass both possible directions of spread. In a study randomizing 260 patients to a left hemicolectomy or segmental resection for left colon cancer, median survival between the two groups was similar, with the only difference being the longer segment of intestine removed in the hemicolectomy group.[61] Complications and operative mortality were not significantly different.

The length of bowel resected is usually governed by the blood supply to that segment. Ligation of the

origin of the primary feeding vessel ensures the inclusion of the apical nodes, which may convey prognostic significance for the patient.[62] A comparison of patients with involvement of the apical lymph nodes revealed a 2.5 times more likely mortality than those patients without involvement.[62] This finding is supported by a prospective study of 1,117 patients from Australia, demonstrating a decreased five-year survival from 54 to 26 percent in patients with spread to the apical lymph nodes.[63] High ligation, resulting in extended lymphadenectomy, has not been shown to result in improved survival.[64]

The value of the "no touch" technique has not been proven, although there is a theoretic basis for its use. Concern regarding intraoperative manipulation of the tumor with shedding of cancer cells into the portal circulation led to a study by Hayash *et al.*[65] In a small group of 27 patients, they identified tumor cells in the portal vein in 73 percent of patients operated on by conventional techniques *vs.* 14 percent in patients using the "no touch" technique. However, in a randomized, prospective study by Wiggers *et al.*,[66] there was no significant difference in the five-year survival rate between the two techniques.

B. Synchronous Colon Cancer

Guideline—Synchronous colon cancers can be treated by two separate resections or subtotal colectomy. Level of Evidence (Class II, Grade B)

The reported incidence of synchronous carcinoma of the colon is 2 to 9 percent.[67] Whether to resect the two lesions separately or by performing a subtotal colectomy is a decision that is based on the location of the tumors and a variety of patient factors. There does not seem to be a difference in outcome or complication rate between the two techniques.[67] It has been shown that synchronous bowel resections can be performed with the same clinical leak rate and mortality as patients undergoing resection with a single anastomosis.[68]

C. Contiguous Organ Attachment

Guideline—Colon cancers adherent to adjacent structures should be resected *en bloc*. Level of Evidence (Class II, Grade A)

Fifteen percent of patients with colon cancer will have tumors adherent to adjacent organs.[69] At the time of surgery, it often is impossible to distinguish between malignant and inflammatory adhesions. Because it has been demonstrated that these adhesions harbor malignant cells at least 40 percent of the time, an *en bloc* excision is necessary to achieve a tumor-free resection.[70]

In a series of 121 patients with multivisceral organ involvement, the five-year survival was similar for *en bloc* resections regardless of whether the adhesion was inflammatory or malignant (54 *vs.* 49 percent). However, the survival rate was reduced to 17 percent if the surgeon inadvertently divided a malignant adhesion.[71] This finding was confirmed by Hunter *et al.*[72] in a study of 43 patients with adjacent organ involvement. Five-year survival was 61 percent when an *en bloc* resection was performed compared with a 23 percent five-year survival when the adhesions were surgically separated.

D. Synchronous Resection of Liver Metastases

Guideline—Resection of synchronous liver metastases may be reasonable to perform at the time of the initial colon resection. Level of Evidence (Class III, Grade B)

Between 10 and 20 percent of patients will have liver metastases at the time of their colon resection. Surgical excision or ablation of these tumors, when amenable, remains the only means of obtaining long-term survival in this group of patients. It is generally believed that such anatomic resections are best performed at a later date after recovery from the initial colonic resection. However, if at the time of the primary colon resection the patient is found to have limited metastatic disease in the liver, which is amenable to subsegmental resection or metastasectomy, it may be preferable to proceed with this additional procedure at the time of colectomy. To ensure that the patient will be left with no gross residual hepatic disease, evaluation of the extent of metastases should include intraoperative ultrasound and a careful bimanual palpation of the liver before resection. Removal of the metastasis can proceed if the following conditions are met[73]: 1) colon resection has proceeded with minimal blood loss or contamination, 2) the medical condition of the patient will permit combining both procedures, 3) resection can be accomplished with at least 1-cm margin, 4) the incision is appropriate for hepatic resection, and 5) the surgeon is comfortable with performing the hepatic resection.

A variety of retrospective studies have demon-

strated that resection of such synchronous lesions is safe and can yield five-year survival of 25 to 40 percent.[74–77] Provided a 1-cm margin can be obtained, there does not seem to be any advantage of performing a wider resection.

E. Role of Oophorectomy

Guideline—Bilateral oophorectomy is advised when one or both ovaries are grossly abnormal or involved with contiguous extension of the colon cancer. However, prophylactic oophorectomy is not recommended. Level of Evidence (Class II, Grade B)

The incidence of synchronous metastases to the ovaries in cases of colon cancer is 2 to 8 percent. As such, the ovaries should be inspected at the time of laparotomy for colon cancer. If the ovaries are grossly abnormal or involved with contiguous extension, then they should be removed *en bloc* with the tumor, similar to contiguous involvement of other adjacent organs. However, there is no proven survival advantage associated with prophylactic oophorectomy in patients with colon cancer, because the risk of occult microscopic disease seems to be low.[78,79] If one ovary is grossly involved, then bilateral oophorectomy is advised because of the risk of bilateral ovarian metastatic disease.[80] The possible need to perform bilateral oophorectomy should be fully discussed with the patient before surgery.

F. Role of Laparoscopic Resection

Guideline—Relative merits of laparoscopic *vs.* open resection for colon cancer remain unproved at this time. Level of Evidence (Class II, Grade B)

Multiple studies have been performed demonstrating the feasibility and safety of laparoscopic colorectal resection for cancer. Adherence to oncologic principles is possible and adequate lymphadenectomy with disease-free margins can be achieved comparable to open surgery.[81–86] However, concerns have been raised about port site recurrence with laparoscopic techniques.[87,88] Conversely, laparoscopic technique may facilitate better preservation of immune function compared with open surgery.[89,90] Ongoing clinical trials should clarify the relative merit of the laparoscopic approach for colon cancer resection.[91]

V. OPERATIVE ISSUES—EMERGENT

A. Obstructing Colon Cancer

Guideline—Patients with an obstructing right or transverse colon cancer should undergo a right or extended right colectomy. A primary ileocolic anastomosis can be performed in the appropriate clinical setting. Level of Evidence (Class II, Grade C)

Multiple nonrandomized, noncontrolled case series of right-sided colon obstruction caused by malignancy have demonstrated that right hemicolectomy with anastomosis (without a colonic lavage) is safe and effective.[92–94] Performing an anastomosis in this setting is dependent on the patient's general condition at the time of resection and the absence of other factors that indicate the need for a stoma to be created. Although there are no studies specifically looking at outcomes of extended right colectomies for obstruction, this procedure with a primary ileodescending colon anastomosis has been advocated in standard surgery texts.[95]

Guideline—For the patient with a left-sided colonic obstruction, the procedure selected should be individualized from a variety of appropriate operative approaches. Level of Evidence (Class II, Grade C)

For patients who present with a left-sided colon obstruction from cancer, there have been a variety of surgical options advocated. The most frequently used are resection with end colostomy and Hartmann's pouch, resection with on-table colonic lavage and primary anastomosis, and subtotal colectomy with ileorectal anastomosis. Each of these has its proponents.[96] The literature does not strongly support the use of any one of these over the others. There is a single, randomized, control study of left colonic malignant obstruction comparing subtotal colectomy *vs.* segmental resection, intraoperative colonic irrigation, and primary anastomosis.[97] This study, published in 1995 by the SCOTIA group, reported that although the mortality and complication rate of these two procedures was the same, the bowel function at four months was worse in patients undergoing subtotal colectomy. Based on this finding, the authors recommended segmental resection with on-table lavage and anastomosis as the preferred choice for left colonic obstruction.

However, in the presence of cecal perforation or synchronous neoplasms, a subtotal colectomy was their preferred option.

The three-stage approach of performing proximal diversion, then resection, then colostomy closure is generally thought to be less advantageous because of its high mortality and morbidity rates.[98] Although rarely advocated, reports of its use (and preference) still appear in the literature.[99] A randomized, controlled trial published in 1995 compared the three-stage procedure to the two-stage Hartmann resection and colostomy closure.[100] The author advocated the three-stage procedure primarily on the basis of finding a smaller risk of permanent colostomy. Most surgeons would rarely use proximal diversion alone as the initial step in managing a patient with left-sided obstruction. This has been thought to be a procedure of last resort for patients with unresectable cancer or who are prohibitive operative risks.

The most recent development in the management of patients with malignant obstruction is the option of inserting a colonic wall stent. This device, when used in the appropriately selected patient, may relieve the acute obstruction thereby permitting an elective colonic oral lavage, colonoscopy, and subsequent resection with primary anastomosis. Multiple nonrandomized, noncontrolled case series have demonstrated that colonic stenting for acute obstructions is safe and allows for a single-stage surgery to be subsequently performed.[101–104] No randomized, controlled trial has been performed to compare stenting *vs.* immediate surgical resection.

B. Colonic Perforation

Guidelines—The site of a colonic perforation caused by colon cancer should be resected, if at all possible. Level of Evidence (Class III, Grade C)

There is no Level I evidence in the literature that addresses the surgical treatment of perforated colon cancer. Most of the management principles are based on uncontrolled case series and expert opinion.[92–95,105] Right-sided colon perforation from a right colon cancer should be resected. If there is a free perforation with peritonitis, an anastomosis may be unwise and the patient is probably best left with an end ileostomy. The distal end may be brought out as a mucous fistula or stapled off as a Hartmann's pouch. Alternatively, if there is limited fecal spillage, the surgeon may choose to reanastomose the bowel with or without fecal diversion.

When a left colon cancer perforates resulting in peritonitis, a Hartmann's resection is the indicated operation in most settings. In cases in which there is massive proximal colonic distention and/or ischemia, a subtotal colectomy may be the best choice. If there is a limited degree of peritoneal contamination, the surgeon may choose to perform an ileorectal or ileosigmoid anastomosis with (usually) or without a diverting loop ileostomy.[92–95] The older literature had advocated proximal diversion with suturing of the perforation for left colonic perforations. This approach has been criticized as insufficient in ridding the patient of their source of sepsis and leaving the malignancy in place.[95,105]

In the case of a right colon perforation caused by a left-sided colon cancer, most experts advocate a subtotal colectomy. Whether an anastomosis or a loop ileostomy to protect the anastomosis are performed is dependent on the surgeon's judgment about the degree of contamination and the patient's clinical status.

C. Massive Colonic Bleeding

Guideline—Acutely bleeding colon cancers that require emergent resection should be removed following the same principles as in elective resection. Level of Evidence (Class III, Grade C)

Hematochezia from a colon carcinoma necessitating urgent operation is an unusual complication.[106] Great effort should be made to identify the site of bleeding preoperatively or intraoperatively using the variety of techniques described in the literature.[106] When the cause of a massive lower gastrointestinal bleed is a colon carcinoma, its location can usually be identified by these means. Once the site of the cancer has been identified, a segmental resection with its adjacent lymphovascular supply should be performed.[95,106,107] Because of the cathartic effect of the bleeding, the bowel has been effectively cleansed of the bulk of fecal matter and a primary anastomosis can be considered. Whether to proceed with an anastomosis or elect to perform an end stoma and mucous fistula (or Hartmann's pouch) is based on the surgeon's judgment about the current clinical condition of the patient. There are no randomized studies that have looked at whether one of these two options is preferable.

In cases in which the site of the bleeding cannot be

Table 1.
Pathologic TNM Staging Nomenclature

Primary tumor (T)
T_x—Primary tumor can not be assessed
T_0—No evidence of primary tumor
T_{is}—Carcinoma *in situ*: intraepithelial or invasion of lamina propria
T_1—Tumor invades submucosa
T_2—Tumor invades muscularis propria
T_3—Tumor invades through the muscularis propria to the subserosa, or into the nonperitonealized pericolic/perirectal tissues
T_4—Tumor directly invades other organs or structures and/or perforates visceral peritoneum
Regional lymph nodes (N)
N_x—Regional lymph nodes can not be assessed
N_0—No regional lymph node metastases
N_1—Metastasis in one to three lymph nodes
N_2—Metastasis in four or more lymph nodes
Distant metastasis (M)
M_x—Distant metastasis cannot be assessed
M_0—No distant metastasis
M_1—Distant metastasis

T = tumor; N = nodes; M = metastasis.
Source: AJCC Staging Manual[114]

identified, retrospective series have shown that a subtotal colectomy is the preferred procedure.[106–108] The rate of rebleeding is less after a subtotal colectomy, and in the series reported by Farner *et al.*,[108] the morbidity and mortality of this procedure was not significantly different than from a randomly selected limited colon resection.

VI. STAGING OF COLON CANCER

Guideline—Colon cancers should be staged using the TNM staging system. Level of Evidence (Class II, Grade B)

Tumor depth, nodal metastasis, and presence of tumor metastasis have been shown to be the most significant variables in determining prognosis in colon cancer.[109–113] These characteristics are best described by the TNM system of staging. The American Joint Committee on Cancer (AJCC) recently revised this system and recommend subdividing Stages II and III based on the T Stage of the primary tumor. This updated edition of the TNM staging system is presented in Tables 1 and 2.[114]

It is important that accurate pathologic evaluation of the radial margin of resection be performed. The AJCC recommends that each operation be given a resection code to denote completeness of resection: R_0, complete tumor resection with all margins negative; R_1, incomplete tumor resection with microscopic involvement of the margin; R_2, incomplete tumor resection with gross residual tumor that was not resected.[114]

Table 2.
Pathologic Staging

Stage	T	N	M
0	T_{is}	N_0	M_0
I	T_1	N_0	M_0
	T_2	N_0	M_0
IIA	T_3	N_0	M_0
IIB	T_4	N_0	M_0
IIIA	T_1–T_2	N_1	M_0
IIIB	T_3–T_4	N_1	M_0
IIIC	Any T	N_2	M_0
IV	Any T	Any N	M_1

T = tumor; N = nodes; M = metastasis.
Source: AJCC Staging Manual[114]

Other factors that are not specifically included in the TNM staging system can have an impact on the patient's risk of recurrence and survival. Microscopic venous or lymphatic invasion within the specimen worsen the prognosis for every stage.[109,115] Histologic grade, histologic type, serum carcinoembryonic antigen, and cytokine levels are all independent prognostic factors that are well supported in the literature.[109,113,114] In the future, DNA analysis and the intratumoral expression of specific chemical substances (18q/DCC, p27, p53, aneuploidy, S-phase fraction, microsatellite instability, thymidylate synthase) may be used routinely to further assess prognosis or response to therapy.[114,116,117]

Guideline—To be properly evaluated, one should strive to have a minimum of 15 lymph nodes examined microscopically. Level of Evidence (Class II, Grade B)

The accuracy of colon cancer staging improves with increasing the number of lymph nodes evaluated microscopically.[118–123] Ten or more lymph nodes can be found in 98 percent of colon specimens and 13 or more lymph nodes can be found in 91 percent of specimens without using fat-clearing techniques.[119] Four separate studies have verified that 15 to 21 lymph nodes need to be evaluated to identify a nodal metastasis in 95 percent of patients in whom a nodal metastasis is present.[120–123] Using fat-clearing techniques, the mean number of lymph nodes available for examination increased as high as 58 per specimen.[119] Finding these small lymph nodes seems to be important. In patients without distant disease, 91 percent of lymph nodes containing metastases are < 6 mm in size.[124] Equally important for prognosis is finding all of the metastatic lymph nodes.

Five-year survivals are significantly decreased for those patients with more than three metastatic lymph nodes.[125] Many retrospective studies have found an increased incidence of lymph node metastasis using immunohistochemistry and polymerase chain reaction techniques.[126–130] The majority show significantly decreased five-year and ten-year survival for those found to have micrometastases. At the present time, there is no evidence that the emerging sentinel node technology improves the survival in colon cancer patients. However, this field of inquiry is still being actively pursued.

VII. ADJUVANT THERAPY

A. Chemotherapy

Guideline—Postoperative adjuvant systemic chemotherapy has a proven benefit in Stage III colon cancer and may be beneficial in certain high risk Stage II patients. Level of Evidence (Class I, Grade A)

Treatment failure of colon cancer most commonly occurs in the liver, peritoneal cavity, or other distant sites. True isolated local failure is rare, because there are few obstacles to obtaining adequate margins of resection within the peritoneal cavity.

Accordingly, systemic chemotherapy is the mainstay of adjuvant therapy for resectable colon cancer. Patients with Stage III colon cancer are recognized to be at high risk for recurrence, and administration of 5-fluorouracil (5-FU)/leucovorin for six months postoperatively has proven benefit in decreasing recurrence and improving survival.[131] The addition of levamisole does not seem to add any benefit.[132] The addition of interferon alpha-2a does not improve disease-free survival or overall survival, but does increase toxicity.[133,134]

There is conflicting data regarding the role of adjuvant chemotherapy in Stage II colon cancer. Between 1990 and 1999, four trials have shown no survival advantage to adjuvant therapy over surgery alone for Stage II colon cancer, whereas two others did report an advantage. A recent NSABP meta-analysis has claimed a benefit for Dukes B2 colon cancer patients.[135] Others reviewing this report contested the conclusion. Patients with Stage II colon cancer who are considered at higher risk for recurrence include those with one or more of the following characteristics: tumor perforation, adherence, or invasion of adjacent organs; nondiploidy by flow cytometry; poorly differentiated tumor; or venous, lymphatic, and perineural invasion.[136,137] It may be advantageous for these patients to receive adjuvant chemotherapy. Ideally, this should be performed within the confines of a clinical trial.

The role of oral chemotherapy agents, in particular capecitabine, is still being defined. Capecitabine is an oral fluoropyrimidine carbamate preferentially converted to 5-FU in tumor cells. In two, large, phase III trials in advanced colorectal cancer, capecitabine was superior to 5-FU/leucovorin in terms of tumor response rate, and similar in terms of time to disease progression and overall survival.[138] Capecitabine is now in clinical trial for single agent adjuvant therapy in Dukes C colon cancer.

B. Immunotherapy

Guideline—The value of immunotherapy for colon cancer is undetermined. Its use is recommended within the setting of a clinical trial. Level of Evidence (Class II, Grade C)

A variety of approaches to use immunotherapy against colon cancer are presently being pursued. Active-specific immunotherapy immunizes the patient against his/her own cancer cells. Several small trials (98 patients, 412 patients, 254 patients) have failed to show an overall benefit.[139–141] The trial from Belgium, of 254 patients, showed no benefit in Stage III disease, but in Stage II disease recurrence-free survival was significantly longer, and there was a trend toward a longer recurrence-free period and improved overall survival. The small number of patients limited the power of this study.

Treating tumor cells with neuraminidase increases their immunogenicity. This vaccine was given after curative resection of colorectal cancer and compared with surgical control.[142] A total of 301 patients were randomized. No difference was found in relapse-free survival or overall survival.

Monoclonal antibodies specific for tumor antigens also have been investigated. These are cytotoxic by themselves, and their effect does not depend on the cell cycle, allowing cytotoxicity to micrometastases,

which often are in a quiescent phase. A study of 189 patients with resected Dukes C colorectal cancer were randomly assigned to receive monoclonal antibody 17-1A postoperatively or observation only.[143] After seven years of follow-up, treatment reduced overall mortality by 32 percent and recurrence rate by 23 percent. Distant metastases were significantly reduced, but not local relapse rate.

Although each approach has had its share of successes, none have reached the point of clear clinical acceptance. Therefore, use of this mode of treatment is recommended within the setting of a clinical trial.

C. Intraperitoneal/Intraportal Chemotherapy

Guideline—Intraperitoneal and intraportal infusions of chemotherapy are recommended only in the confines of a clinical trial. Level of Evidence (Class II, Grade C)

In hopes of aiming therapeutic agents more directly to the site of disease, efforts have been made to infuse chemotherapeutic agents intraportally or intraperitoneally. The four most recent, large, multicenter trials of portal vein infusion (EORTC; Swiss Group for Clinical Cancer Research; UK Coordinating Committee on Cancer Research; Studio Multicentrico Adjuvante Colon)[144–147] have not shown any survival advantage for portal vein infusion in patients with resected colon cancer.

A multicenter phase III trial from France randomized 267 patients after resection of Stage II or III colon cancer to resection alone or resection followed by intraperitoneal 5-FU for six days and intravenous 5-FU during surgery. Intraperitoneal chemotherapy was well tolerated, reduced the risk of recurrence in Stage II cancers, but did not reduce the risk of death.[148]

Combined intravenous and intraperitoneal chemotherapy with fluorouracil (FU) plus leucovorin (LV) *vs.* FU and levamisole was performed with a total of 241 Stage II or III colon cancer patients randomly assigned to standard therapy with FU and levamisole, given for a duration of six months, or to an investigative arm, consisting of LV 200 mg m(−2) plus FU 350 mg m(−2) both administered intravenously (Days 1'4) and intraperitoneally (Days 1 and 3) every four weeks for a total of six courses.[149] In patients with Stage II disease, no significant difference was noted. In patients with Stage III disease, both an improvement in disease-free survival (P = 0.0014) and a survival advantage (P = 0.0005) with an estimated 43 percent reduction in mortality rate (95 percent confidence interval, 26'70 percent) was observed in the investigational arm. The results of this trial suggest that combined intraperitoneal plus systemic intravenous chemotherapy is a promising treatment strategy in patients with surgically resected Stage III colon cancer.[149]

D. Radiation Therapy

Guideline—The role for radiation therapy in colon cancer is limited. Level of Evidence (Class II, Grade C)

Radiation is rarely used in the treatment of colon cancer. Radiation's potential for injury to the abdominal viscera limits its usefulness. There have been a few small studies that have evaluated external beam radiation as an adjuvant therapy. ECOG PA-285 study was a pilot study of the effect of large-field external beam abdominal irradiation as adjuvant treatment for resectable Dukes C1 and C2 colon cancer.[150] Eligible patients would receive 45 Gy to the tumor bed and periaortic lymph nodes, as well as 30 Gy to the liver. Fourteen patients were enrolled. One refused radiation after surgery; one died of acute hepatic radiation toxicity after a major deviation from protocol. Of the 12 remaining patients, 7 survived for more than 10 years. This study demonstrates the feasibility and acceptable toxicity; however, the numbers are too limited to evaluate survival benefit. A retrospective study of adjuvant irradiation of the tumor bed in 79 patients with T4N0 or T4N+ resected colon cancers showed improved local control in patients with less extensive disease.[151]

A small Phase II clinical trial treated 45 patients with resected B2-3 or C1-3 colon cancer with a 21-week course of intraperitoneal 5-FU and two courses of 22.5 Gy external beam radiation to the tumor bed and periaortic nodes.[152] Therapy was tolerable. Local and regional relapse showed a trend toward reduction with treatment, but there was no improvement in survival.

Radiation therapy remains unproved as effective adjuvant therapy for colon cancer. Although used selectively for patients with a perforated tumor or focal positive margin, its use for generalized abdominal application should be limited to clinical trials.

Appendix A.
Levels of Evidence

Level I:	Evidence from properly conducted randomized, controlled trials
Level II:	Evidence from controlled trials without randomization or Cohort or case-control studies or Multiple time series, dramatic uncontrolled experiments
Level III:	Descriptive case series, opinions of expert panels

Appendix B.
Scale Used for Evidence Grading

Grade	Explanation
A	High-level (level I or II), well-performed studies with uniform interpretation and conclusions by the expert panel.
B	High-level, well-performed studies with varying interpretations and conclusions by the expert panel.
C	Lower level evidence (level II or less) with inconsistent findings and /or varying interpretations or conclusions by the expert panel.

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