Overview of the management of primary colon cancer

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INTRODUCTION

Colorectal cancer is the third most common cancer affecting both males and females in the United States; approximately 70 percent of cases arise in the colon [1]. Globally, colorectal cancer is the third most commonly diagnosed cancer in males and the second in females; however, the incidence varies markedly. Country-specific incidence rates are available through the World Health Organization (WHO) GLOBOCAN database.

This topic review will provide an overview of the management and prognosis of primary colon cancer. Epidemiology, risk factors, clinical presentation, and diagnosis are addressed in detail separately. (See "Colorectal cancer: Epidemiology, risk factors, and protective factors" and "Clinical presentation, diagnosis, and staging of colorectal cancer".)

DIAGNOSIS

The diagnosis of colon cancer is usually made by colonoscopy. (See "Clinical presentation, diagnosis, and staging of colorectal cancer".)

STAGING

"Staging" a cancer provides a standard framework for describing disease extent. The stage of a colon cancer has three components, primary tumor (T), status of the regional nodes (N), and

distant metastasis (M), which together are combined to form stage groupings from I to IV. Stage groupings permit the stratification of prognosis, which is useful for the selection of treatment. The T, N, and M categories for colon cancer are assigned based upon:

- Whether there are signs of cancer spread on physical examination or radiographic imaging tests
- Findings from surgical resection and histologic examination of the resected tissues

The current combined American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM staging for colorectal cancer (eighth edition, 2017) is illustrated in the table (table 1) [2].

TNM staging for colorectal cancer is discussed in more detail elsewhere, and colon cancer prognosis, stratified according to stage, is discussed in more detail below. (See "Pathology and prognostic determinants of colorectal cancer", section on 'TNM staging' and 'Prognosis' below.)

THE CLINICAL STAGING EVALUATION

Pretreatment clinical staging is best accomplished by physical examination (with particular attention to ascites, hepatomegaly, and lymphadenopathy), computed tomography (CT) scan of the abdomen and pelvis, and chest imaging. (See "Clinical presentation, diagnosis, and staging of colorectal cancer", section on 'Clinical staging evaluation'.)

Radiographic imaging — In patients with newly diagnosed invasive colon cancer, preoperative chest, abdomen, and pelvis CT scans can demonstrate regional tumor extension, regional lymphatic and distant metastases, and tumor-related complications (eg, obstruction, perforation, fistula formation), findings that may assist in selecting the therapeutic approach. An important point is that the finding of isolated liver or lung metastases on preoperative studies may not necessarily alter the surgical approach to the primary tumor, particularly in patients who are symptomatic from bleeding or impending obstruction. (See 'Metastatic disease' below and "Locoregional methods for management and palliation in patients who present with stage IV colorectal cancer", section on 'Management of the primary cancer' and "Surgical resection of primary colon cancer", section on 'Preoperative evaluation'.)

The necessity of preoperative abdominal/pelvic CT for all patients with colon cancer is controversial, as is the clinical benefit of a staging chest CT. Nevertheless, the standard practice at most institutions is that all patients with stage II, III, or IV colon cancer undergo chest, abdomen, and pelvic CT either prior to or following resection, an approach that is endorsed by

the National Comprehensive Cancer Network (NCCN) [3], the American Society of Clinical Oncology (ASCO), and the European Society for Medical Oncology (ESMO). It is generally preferable to obtain these scans prior to, rather than after, operation, as the scan results will occasionally change surgical planning.

Contrast-enhanced magnetic resonance imaging (MRI) of the liver might identify more hepatic lesions than are visualized by CT and may be indicated to further define the extent of disease in patients who have suspected liver metastases on CT. (See "Clinical presentation, diagnosis, and staging of colorectal cancer", section on 'Liver magnetic resonance imaging'.)

Positron emission tomography (PET) scans do not appear to add significant information to CT scans for routine preoperative staging of colon cancer. PET scan may be helpful for patients who are thought to be candidates for resection of isolated colorectal cancer liver and lung metastases, in whom the routine use of PET reduces the number of nontherapeutic laparotomies. (See "Hepatic resection for colorectal cancer liver metastasis", section on 'Positron emission tomography' and "Surgical resection of pulmonary metastases: Benefits, indications, preoperative evaluation, and techniques", section on 'PET scans'.)

Tumor markers — A variety of tumor markers have been associated with colon cancer, especially carcinoembryonic antigen (CEA). Serum CEA levels should be obtained preoperatively in patients with colon cancer, particularly as an aid to post-treatment follow-up. Elevated preoperative CEA levels that do not normalize following surgical resection can imply the presence of persistent disease and the need for further evaluation. Serum CEA should **not** be used as a screening test for colon cancer due to low sensitivity and specificity for early stage disease. (See "Clinical presentation, diagnosis, and staging of colorectal cancer", section on 'Tumor markers'.)

Colonoscopy — Ideally, each patient should have visualization of the entire colon prior to surgery. Colonoscopy serves to localize the tumor, provide a tissue diagnosis, characterize the lesion as mucosal or submucosal, and evaluate the patency of the lumen, the presence of extrinsic colonic compression, and synchronous carcinomas and adenomas. Synchronous invasive colorectal cancers are found in 3 to 5 percent of cases, while the prevalence of synchronous adenomas is as high as 30 percent.

If full colonoscopy cannot be performed prior to elective colon resection because of obstruction or poor preparation, a barium enema, or (preferably) CT or magnetic resonance colonography can be used to evaluate the entire large bowel. Alternatively, the entire residual colon can be examined colonoscopically after resection. (See "Clinical presentation, diagnosis, and staging of colorectal cancer", section on 'Colonoscopy'.)

Family history — A family history of colorectal and other extracolonic cancers (going back three generations if possible, but at least first- and second-degree relatives) should be sought, as the patient may be a member of a kindred with a hereditary predisposition. This finding could alter the surgical approach, prompting consideration of subtotal or total colectomy in high-risk individuals. (See 'Genetic issues' below and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis" and "*MUTYH*-associated polyposis", section on 'Colonic manifestations'.)

However, use of family history alone is not sufficient to identify most patients with a hereditary colon cancer syndrome, particularly Lynch syndrome. Clinical practice guidelines from ASCO and others recommend testing of all colorectal cancers, independent of stage and age, for loss of mismatch repair protein expression (the underlying defect in Lynch syndrome) or microsatellite instability, the biologic consequence of mismatch repair protein deficiency [4-6]. (See 'Genetic issues' below and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Tumor characteristics'.)

MANAGEMENT OF LOCALIZED DISEASE

Surgical resection — Approximately 80 percent of cancers are localized to the colon wall and/or regional nodes. Surgery is the only curative modality for localized colon cancer. The goal of surgery for invasive cancer is complete removal of the tumor, the major vascular pedicle, and the lymphatic drainage basin of the affected colonic segment (figure 1). Surgical procedures for treatment of primary colon cancer are discussed in detail separately. (See "Surgical resection of primary colon cancer".)

Restoration of bowel continuity using a primary anastomosis can be accomplished in most patients undergoing an uncomplicated colectomy. However, a temporary proximal diverting colostomy or ileostomy may be necessary in cases of diffuse peritonitis or free perforation if the patient is medically unstable or, sometimes, for an obstructing left-sided colon cancer, although this is controversial. (See "Surgical resection of primary colon cancer", section on 'Colonic obstruction'.)

Laparoscopic-assisted colectomy, rather than open colectomy, is favored for patients with nonobstructed, nonperforated, non-locally advanced colon cancers who have not had prior extensive abdominal surgery. In experienced hands, appropriately selected patients have comparable oncologic outcomes, comparable perioperative morbidity and mortality, and faster recovery with laparoscopic as compared with open surgery. (See "Surgical resection of primary colon cancer".)

There are reports that robotic surgery has been performed safely for colon cancer, but there are no randomized trials comparing this approach with either laparoscopic or open colonic surgery. (See "Surgical resection of primary colon cancer".)

Older adult patients — Surgery for colon cancer (including laparoscopic resection [7,8]) should not be denied simply based on age. A comprehensive geriatric assessment may be useful in formulating an appropriate, individualized treatment plan for the older adult patient. (See "Comprehensive geriatric assessment for patients with cancer".)

Specific issues surrounding the use of adjuvant chemotherapy in older adult patients are discussed elsewhere. (See "Adjuvant therapy for resected colon cancer in older adult patients".)

Management of carcinoma in a polyp — The majority of colon cancers arise from polyps (adenomas). Benign adenomas, as well as those with severe dysplasia or carcinoma in situ (no evidence of invasive cancer, defined as invasion into the submucosa), can be effectively managed by endoscopic removal (polypectomy) alone as long as the resection margins are free of cancer. Endoscopic resection is also a reasonable alternative to radical surgery for selected favorable-risk early stage colon cancers arising in a polyp. The presence of any of the following factors should prompt consideration of radical surgery, as they indicate a higher risk of residual cancer and/or nodal metastases [9,10] (see "Surgical resection of primary colon cancer", section on 'Malignant polyp'):

- For both pedunculated and nonpedunculated (sessile) polyps:
  - Poorly differentiated histology.
  - Lymphovascular or perineural invasion.
  - Tumor budding (foci of isolated cancer cells or a cluster of five or fewer cancer cells at the invasive margin of the polyp). (See "Pathology and prognostic determinants of colorectal cancer", section on 'Tumor border and tumor budding'.)
  - Cancer at the resection margin or submucosal invasion depth ≥1 mm.

Locally advanced primary lesions

Multivisceral resection — Multivisceral resection is an appropriate option for locally advanced (ie, attached to or invading adjacent organs), potentially resectable primary colon cancers. The surgical approach to locally advanced colon cancer is reviewed separately. (See "Surgical resection of primary colon cancer", section on 'Locally advanced cancer'.)

Neoadjuvant therapy — There is no consensus as to which patients are suitable for neoadjuvant therapy rather than upfront surgery. Most patients with localized, resectable colon cancer should undergo upfront surgery, followed by adjuvant systemic therapy as clinically indicated. However, it may be appropriate to evaluate selected patients for neoadjuvant therapy, such as those with locally advanced tumors and potentially compromised surgical margins, or those with medically inoperable tumors. This position is consistent with consensus-based guidelines from the National Comprehensive Cancer Network (NCCN), which in 2016 included neoadjuvant chemotherapy as a treatment option for patients with bulky nodal disease or clinical T4b (table 1) colon cancer [3]. They are also consistent with updated guidelines on management of colon cancer from the American Society of Colon and Rectal Surgeons [10].

However, randomized trials have shown mixed results regarding the long-term benefits of neoadjuvant therapy compared with upfront surgery [11,12]. An unresolved problem is what criteria to employ preoperatively to select patients with locally advanced tumors that are not amenable to a complete (R0) resection with upfront surgery. Ideally, patients who are being evaluated for neoadjuvant therapy should be encouraged to enroll in clinical trials, where available. (See "Systemic therapy for nonoperable metastatic colorectal cancer: Selecting the initial therapeutic approach".)

For patients with locally advanced colon cancer, neoadjuvant systemic therapy is associated with several potential advantages:

- Early administration of systemic therapy may reduce the risk of micrometastases
- Reduction of the primary tumor can facilitate surgical resection
- Better compliance with systemic therapy when it is delivered preoperatively

Neoadjuvant (preoperative) chemoradiotherapy with or without chemotherapy, rather than initial surgery, is an accepted approach for locally advanced **rectal** cancer that is supported by data from randomized trials. Increasingly, "total neoadjuvant therapy" approaches are used in clinical practice, which utilize all planned systemic chemotherapy plus chemoradiotherapy in the preoperative setting to maximize the number of patients receiving chemotherapy in the context of curative resection and to downstage the rectal cancer. (See "Neoadjuvant therapy for rectal adenocarcinoma".)

The following data are available on the benefits of neoadjuvant treatment for locally advanced **colon** cancer.

- **Chemotherapy** – Observational studies suggest that perioperative chemotherapy is safe and does not worsen postoperative complications [13,14]. While some randomized studies demonstrate a consistent benefit with perioperative chemotherapy (eg, reduced rates of disease recurrence) [11], other studies failed to show improved disease-free survival over treatment with resection followed by adjuvant chemotherapy [12]:

  - In a phase III trial (FOxTROT) 1053 patients with a computed tomography (CT) scan-predicted, T3-4N0-2 primary colon cancer and no metastatic disease were randomly assigned to either upfront surgery plus six months of adjuvant oxaliplatin-based chemotherapy or perioperative oxaliplatin-based chemotherapy (six weeks of neoadjuvant [preoperative] oxaliplatin-based chemotherapy followed by surgery and 18 weeks of adjuvant [postoperative] chemotherapy) [11]. Chemotherapy regimens included FOLFOX (oxaliplatin plus short-term infusional fluorouracil [FU] and leucovorin [LV]; 72 percent) and CAPOX (capecitabine plus oxaliplatin; 28 percent). In addition, 279 patients with *RAS* wild-type tumors treated with perioperative chemotherapy were further randomly assigned to either the addition of panitumumab or not during the six weeks of neoadjuvant chemotherapy.

    At median follow-up of three years, compared with upfront surgery plus adjuvant chemotherapy, perioperative chemotherapy resulted in the following [11]:

    - **Disease recurrence** – Lower rates of residual or recurrent disease at two years (17 versus 22 percent, HR 0.72, 95% CI 0.54-0.98). Among patients with *RAS* wild-type tumors, the addition of panitumumab to neoadjuvant chemotherapy did not reduce the risk of residual/recurrent disease.

    - **Pathologic response** – Downstaging of both tumor and nodal stage (including a pathologic complete response rate [pathologic T0] of four percent) and a higher histopathologically complete (R0) resection rate (94 versus 89 percent). Among those treated with neoadjuvant chemotherapy, the risk of recurrence was lowest among those with significant disease regression.

    - **Surgical complications** – Fewer serious perioperative complications, including anastomotic leak, abdominal abscesses, or emergency reoperation.

    - **dMMR tumors** – Among patients with deficient MMR (dMMR) tumors, the rate of moderate or greater tumor regression after neoadjuvant FOLFOX was markedly reduced compared with those with MMR-proficient tumors (7 versus 23 percent) .

- In contrast, the multicenter OPTICAL trial did not demonstrate improved disease-free survival with the use of neoadjuvant chemotherapy. In this study, 752 patients with radiologically staged locally advanced (T3 with ≥5 mm invasion beyond the muscularis propria or T4) colon cancer were randomly assigned to three months of neoadjuvant FOLFOX or CAPOX followed by surgery and three additional months of chemotherapy, or immediate surgery followed by adjuvant chemotherapy given at the discretion of the treating clinicians [12]. In preliminary results, the pathologic complete response rate with neoadjuvant chemotherapy was 7 percent. Despite a lower pathologic disease stage overall, disease-free survival (DFS) for neoadjuvant chemotherapy was similar to that of surgery plus adjuvant chemotherapy (three-year DFS 79 versus 77 percent, HR 0.83, 95% CI 0.60-1.15).

- **Immunotherapy** – Patients with dMMR metastatic colon cancer respond to immune checkpoint inhibitors (immunotherapy). (See "Systemic therapy for nonoperable metastatic colorectal cancer: Selecting the initial therapeutic approach", section on 'Patients with deficient DNA mismatch repair/microsatellite unstable tumors' and "Systemic therapy for nonoperable metastatic colorectal cancer: Approach to later lines of systemic therapy", section on 'Microsatellite unstable/deficient mismatch repair tumors'.)

  In patients with localized dMMR colon cancer, data from observational studies and phase II trials suggest that upfront neoadjuvant immunotherapy can be effective in downstaging tumors [15-22]. In contrast, neoadjuvant chemotherapy has limited activity in this population, based on data from the FoxTROT trial [11]. While promising, further long-term studies are needed prior to incorporating neoadjuvant immunotherapy into routine clinical practice for resectable colon cancer. For patients with locally advanced unresectable dMMR colon cancer and an indication for neoadjuvant systemic therapy, neoadjuvant immunotherapy is an appropriate alternative to oxaliplatin-based chemotherapy (ideally in the context of a clinical trial).

  As an example, in a preliminary report of the NICHE-2 trial, 112 patients with locally advanced (64 percent T4) colon cancer were treated with a single dose of ipilimumab and two doses of nivolumab prior to attempted resection [20]. With a median time from the first dose of immunotherapy to surgery of only five weeks, a pathologic response was observed in 99 percent (major in 95 percent), and the pathologic complete response rate was 67 percent.

  Single-agent immunotherapy with agents such as pembrolizumab and nivolumab (among others) has also been investigated in the neoadjuvant setting for dMMR colon cancer [22].

- **Chemoradiotherapy** – Data addressing the benefit of neoadjuvant chemoradiotherapy in patients with colon primaries have been limited to isolated case reports and small case series [23-25]. While concurrently administered chemotherapy plus radiation therapy (RT) provides synergistic antitumor activity, it also increases treatment-related toxicity, which may be prohibitive if the radiation treatment volume includes a substantial amount of bowel.

Adjuvant chemotherapy

- **Stage III disease** – For patients who have undergone potentially curative resection of a colon cancer, the goal of postoperative (adjuvant) chemotherapy is to eradicate micrometastases, thereby reducing the likelihood of disease recurrence and increasing the cure rate. The benefits of adjuvant chemotherapy have been most clearly demonstrated in patients with stage III (node-positive) disease, who have an approximately 30 percent reduction in the risk of disease recurrence and a 22 to 32 percent reduction in mortality with modern chemotherapy. (See "Adjuvant therapy for resected stage III (node-positive) colon cancer".)

  Most treatments involve a combination of several oral or intravenous chemotherapy drugs in a specific order on specific days. For patients with node-positive colon cancer, a course of oxaliplatin-containing chemotherapy is generally recommended for most patients, although the benefits of oxaliplatin are controversial in older adults. (See "Adjuvant therapy for resected colon cancer in older adult patients", section on 'Oxaliplatin-based regimens' and "Adjuvant therapy for resected stage III (node-positive) colon cancer", section on 'Oxaliplatin-based therapy'.)

  The optimal duration of oxaliplatin-containing chemotherapy is evolving. Six months of therapy has been the standard approach, but the cumulative and dose-limiting neuropathy associated with oxaliplatin has prompted interest in a shorter duration of therapy. Results from the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration (six randomized trials of six versus three months of oxaliplatin-based adjuvant therapy) suggest that, given the small predicted loss of absolute disease-free survival benefit (absolute difference 0.9 percent at three years) and the significantly lower rates of oxaliplatin neuropathy seen in the IDEA collaboration analysis, adjuvant therapy can be limited to three months of therapy with capecitabine plus oxaliplatin in patients with low-risk disease (T1-3N1), which makes up approximately 60 percent of all stage III colon cancers [26]. On the other hand, for those with higher risk cancers (T4 or N2 (table 1)), six months of therapy may be preferred. These data are discussed in more

detail separately. (See "Adjuvant therapy for resected stage III (node-positive) colon cancer", section on 'Oxaliplatin-based therapy'.)

- **Stage II disease** – Among patients with resected node-negative (stage II) disease, the benefits of chemotherapy are controversial, as is the relative benefit of an oxaliplatin-based as compared with a non-oxaliplatin-based regimen. Treatment decisions must be individualized. Expert guidelines suggest that the risks and estimated benefits of adjuvant chemotherapy be discussed with patients who have higher-risk resected node-negative colon cancer. Among the issues that need to be taken into consideration when assessing the risk of recurrence and estimated benefit from specific chemotherapy regimens are the presence of high-risk clinicopathologic features (T4 stage (table 1), fewer than 12 nodes in the surgical specimen, perforated/obstructed tumor, poorly differentiated histology, lymphovascular or perineural invasion), mismatch repair enzyme status, assessment of comorbidities and anticipated life expectancy, and given the relatively good prognosis of stage II disease, the potential risks associated with treatment.

  If adjuvant chemotherapy is chosen, most patients receive a fluoropyrimidine alone, unless they have a tumor with deficient mismatch repair/high levels of microsatellite instability, in which case adjuvant fluoropyrimidines alone are ineffective. For patients receiving a non-oxaliplatin-based adjuvant therapy regimen (ie, a fluoropyrimidine alone), six months of adjuvant therapy remains the standard approach. In general, older adult patients gain as much benefit from adjuvant FU-based chemotherapy as do younger individuals, although it is used less often in older adults, and rates of treatment-related toxicity may be higher. The role of oxaliplatin as a component of adjuvant therapy in older adult patients is controversial. These issues are all discussed in detail elsewhere. (See "Adjuvant therapy for resected stage II colon cancer" and "Adjuvant therapy for resected colon cancer in older adult patients", section on 'Challenges specific to older adults' and 'Side effects' below.)

Side effects — Chemotherapy carries a risk of significant toxicities, including mucositis, emesis, diarrhea, febrile neutropenia, fatigue, hair loss, hand-foot syndrome (a condition in which there is soreness, redness, and peeling of the skin of the palms and soles of the feet), and cardiotoxicity. The frequency and severity of these side effects vary according to the specific drugs used and how they are administered. Fortunately, most of these symptoms are reversible with cessation of chemotherapy, and late and long-term effects are relatively infrequent, with the exception of oxaliplatin-related peripheral neuropathy, which may persist. In most modern trials, rates of treatment-related death range from 0.5 to 1 percent. (See "Overview of neurologic complications of platinum-based chemotherapy", section on 'Cumulative sensory

neuropathy' and "Fluoropyrimidine-associated cardiotoxicity: Incidence, clinical manifestations, mechanisms, and management" and "Toxic erythema of chemotherapy (hand-foot syndrome)", section on 'Hand-foot syndrome'.)

The most commonly used oxaliplatin-based regimens are FOLFOX and CAPOX. FOLFOX requires a central venous access catheter and the use of an ambulatory infusion pump. The oxaliplatin component of CAPOX can be administered via a peripheral vein as institutional practice allows, but sometimes patients require administration via a central line due to an infusion-related pain syndrome related to oxaliplatin. (See "Treatment protocols for small and large bowel cancer".)

Patients with stage II disease are more often offered a regimen that does not include oxaliplatin, typically LV-modulated FU or single-agent oral capecitabine. The range of treatment-related toxicity can be illustrated by the following clinical trial data:

- In the X-ACT study, severe toxicities associated with six months of adjuvant treatment with oral capecitabine alone included hand-foot syndrome in 17 percent, diarrhea in 11 percent, nausea or vomiting in 3 percent, and stomatitis in 2 percent [27]. (See "Adjuvant therapy for resected stage III (node-positive) colon cancer", section on 'Oral fluoropyrimidines' and "Toxic erythema of chemotherapy (hand-foot syndrome)", section on 'Hand-foot syndrome'.)

- In the control arm of the MOSAIC trial, which demonstrated the benefit of oxaliplatin (FOLFOX) in stage III disease, severe (grade 3 or worse) toxicity with infusional and bolus FU plus LV consisted of diarrhea (7 percent), neutropenia (5 percent), nausea (2 percent), and stomatitis (2 percent) [28]. Higher rates of diarrhea, nausea/vomiting, and myelosuppression are usually seen with bolus FU/LV regimens that do not require central venous access or an ambulatory infusion pump. (See "Adjuvant therapy for resected stage III (node-positive) colon cancer", section on 'Infusional versus bolus fluorouracil'.)

  In the experimental arm of this MOSAIC trial, the addition of oxaliplatin to infusional plus bolus FU/LV (the FOLFOX regimen) resulted in severe (grade 3 or worse) neutropenia (43 percent), diarrhea (11 percent), vomiting (6 percent), and stomatitis (3 percent) [28]. In addition, grade 3 sensory neuropathy developed in 13 percent during therapy but was still present at 48 months in fewer than 1 percent [29].

- The substitution of capecitabine for infusional FU/LV in combination with oxaliplatin increases the convenience of treatment but tends to be more toxic than FOLFOX. As an example, in one adjuvant trial, rates of grade 3 or worse toxicity with CAPOX included diarrhea (19 percent), sensory neuropathy (11 percent), neutropenia (9 percent), vomiting (6 percent), hand-foot syndrome (5 percent), and dehydration (3 percent) [30]. Rates of

severe diarrhea and dehydration were significantly higher in patients over the age of 65. By contrast, CAPOX was associated with less severe neutropenia than FOLFOX in all age groups.

Benefit of postoperative radiation therapy — Postoperative RT is not usually considered a routine component of care for completely resected colon cancer. This is in contrast to patients with rectal cancer, in whom effective adjuvant therapy for both transmural and node-positive disease includes RT. Local recurrence is more frequent with rectal cancer due to the local anatomy and the difficulty in obtaining adequate resection margins. (See "Adjuvant therapy for resected rectal adenocarcinoma in patients not receiving neoadjuvant therapy", section on 'Introduction'.)

Selected patients with colon cancer who are at high risk for local recurrence (ie, positive resection margins, perforation or abscess formation, T4 disease (table 1)) might potentially benefit from adjuvant RT. However, there is a paucity of high-quality evidence addressing the role of adjuvant RT (with or without concurrent chemotherapy) in patients with resected locally advanced colon cancer. A single randomized trial failed to show benefit but was closed prior to achieving its accrual goal because of slow accrual.

Despite the lack of evidence proving benefit from randomized trials, consensus-based guidelines from NCCN [3] suggest that adjuvant RT be "considered" for patients with T4 disease with penetration to a fixed structure. Others suggest that RT be considered on a case-by-case basis for positive resection margins and disease complicated by perforation or abscess formation. This topic is addressed in detail separately. (See "Adjuvant therapy for resected stage III (node-positive) colon cancer", section on 'Adjuvant radiation therapy'.)

Adjunctive therapies — The benefits of diet and exercise, aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDS), vitamin D, and coffee consumption on cancer outcomes are discussed separately. (See "Adjunctive therapy for patients with resected early stage colorectal cancer: Diet, exercise, NSAIDs, and vitamin D".)

Management in resource-constrained settings — There are few data to guide the treatment strategy for localized colorectal cancer in resource-constrained settings. ASCO has developed consensus-based guidelines for early detection and treatment of early stage (localized) colorectal cancer that stratify recommendations based on the available level of services (basic, limited, enhanced, and maximal (table 2)) [31-33].

METASTATIC DISEASE

Approximately 20 to 25 percent of newly diagnosed colon cancers are metastatic at presentation (synchronous metastasis). Others may develop metastatic disease after potentially curative treatment of localized disease. The most common distant metastatic sites are the liver, lungs, lymph nodes, and peritoneum. (See "Clinical presentation, diagnosis, and staging of colorectal cancer", section on 'Metastatic disease'.)

Although major advances in systemic chemotherapy have expanded the therapeutic options for these patients and improved median survival from less than one year in the single-agent fluoropyrimidine era to more than 30 months, fewer than 20 percent [34] of those treated with chemotherapy alone are still alive at five years, and only a few are free of disease, unless resection or ablation of metastases has been performed. (See "Systemic therapy for metastatic colorectal cancer: General principles", section on 'Systemic therapy versus supportive care' and "Systemic therapy for metastatic colorectal cancer: General principles".)

On the other hand, surgery provides a potentially curative option for selected patients with limited metastatic disease, predominantly in the liver and lung. Long-term survival can be achieved with metastasectomy in as many as 50 percent of cases, and an aggressive surgical approach to both the primary and the metastatic sites is warranted in conjunction with systemic chemotherapy. However, even after complete resection of metastases, most patients who are alive at five years are alive with active disease; only approximately 20 to 30 percent remain free of recurrence long term and may be cured. The timing of surgical intervention (particularly in patients who present with synchronous metastatic disease) is controversial. Management of potentially resectable hepatic metastases (including a discussion as to integration of systemic chemotherapy into the surgical paradigm) and resection of pulmonary metastases are discussed in detail separately. (See "Potentially resectable colorectal cancer liver metastases: Integration of surgery and chemotherapy" and "Surgical resection of pulmonary metastases: Outcomes by histology" and "Surgical resection of pulmonary metastases: Benefits, indications, preoperative evaluation, and techniques".)

Even patients who are not candidates for a curative resection can benefit from surgical palliation for symptoms of obstruction and bleeding from the primary tumor. On the other hand, the overwhelming majority of patients without symptoms who initiate chemotherapy never require palliative surgery, and there is no survival benefit for prophylactic primary tumor resection in this setting. (See "Locoregional methods for management and palliation in patients who present with stage IV colorectal cancer", section on 'Asymptomatic'.)

Resource-constrained settings — There are few data to guide the treatment strategy for metastatic colorectal cancer in resource-constrained settings. ASCO has developed consensus-based guidelines for treatment of late-stage colorectal cancer that stratify recommendations

based on the available level of services (basic, limited, enhanced, and maximal (table 2)) [35]. They include specific recommendations for initial diagnostic evaluation, systemic therapy in the first-line setting and beyond, surgical management of patients with potentially resectable disease, other liver-directed therapy options for late stage disease and liver metastases, and post-treatment surveillance.

PROGNOSIS

The various prognostic factors for patients with resected colon cancer are discussed in detail separately, but issues related to general prognosis will be briefly reviewed here. (See "Pathology and prognostic determinants of colorectal cancer", section on 'Prognostic determinants'.)

The most important indicator of outcome following resection of colon cancer is the pathologic stage at presentation [36,37]. Five-year survival rates according to tumor stage at diagnosis for patients with colon cancer, derived from the population-based Surveillance, Epidemiology, and End Results (SEER) database and stratified according to the 2010 American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) tumor, node, metastasis (TNM) staging classification, are illustrated in the figure (figure 2) [36].

For individual patients, a postoperative nomogram has been developed that permits prediction of the risk of a colon cancer recurrence based upon clinicopathologic factors and whether adjuvant chemotherapy was administered or not [38]. The nomogram, which has not yet been independently validated, is available online. It is one of two prognostic tools approved for use in patients with colon cancer by the AJCC, meeting all quality criteria [39].

An important point is that nomograms such as these may not be accurate in younger individuals with early onset colon cancer (diagnosed <age 50). In an analysis of data from six trials of three versus six months of adjuvant chemotherapy in stage II or stage III colorectal cancer (predominantly colon cancer), individuals with early onset high-risk stage III disease had a significantly worse five-year cancer-specific survival than did older individuals (76 versus 80 percent, hazard ratio for death 1.21, 95% CI 1.0-1.47) despite a better performance status, more distal tumors, and better adherence to and higher administered treatment intensity of adjuvant chemotherapy, suggesting true biological differences [40]. Furthermore, estimates of overall survival may overestimate outcomes relative to cancer-specific survival, particularly in younger individuals (ie, suggesting methodological biases). (See "Adjuvant therapy for resected stage III (node-positive) colon cancer".)

Most of the available prognostic estimates use five-year survival as the endpoint given that most recurrences develop within this time frame. In data derived from the 20,800-patient ACCENT database of patients undergoing adjuvant chemotherapy for stage II or III colon cancer, recurrence rates after five years never exceeded 1.5 percent annually, and after eight years, they were 0.5 percent per year [41].

As a result, conditional survival (eg, the survival probability after a given length of survival) improves dramatically after five years. As examples:

- In a study of over 83,000 colon cancer survivors derived from the SEER database, as the time alive increased to five years after diagnosis, the five-year disease-specific conditional survival probability was ≥80 percent for all disease stages except stage IV (48 percent) [42].
- Late recurrences may develop more often in men. In an analysis of 3622 patients with colon cancer derived from two French digestive cancer registries, among men with no recurrence five years after the diagnosis of colon cancer, 1 in 12 (8.3 percent) developed a subsequent recurrence between years 5 and 10; the corresponding rate for women was 1 in 19 (5.3 percent) [43].

A web-based tool is available to determine conditional survival expectancy based upon initial stage at diagnosis, ethnicity, age, gender, and histologic grade.

Prognosis for patients with advanced (metastatic) colorectal cancer is highly variable and dependent on many factors, including age and performance status, site and number of metastases, molecular factors such as *RAS* or *BRAF* mutations and deficient DNA mismatch repair/microsatellite instability (MSI), eligibility for surgery or additional chemotherapy, and tumor location. Nomograms for overall and progression-free survival based on several of these clinicopathologic factors have been developed that can assist in aiding prognostication and patient-clinician communication; however, they do not include tumor location or MSI status and only apply to patients who are not candidates for or do not undergo metastasectomy [44].

POST-TREATMENT SURVEILLANCE

Following potentially curative treatment for a stage II or III colon cancer, post-treatment surveillance usually consists of periodic history and physical examination, with serial assay of the serum concentrations of the tumor marker carcinoembryonic antigen (CEA), annual surveillance computed tomography (CT) scans, and colonoscopy to detect metachronous adenomas and primary tumors. Guidelines are available from several groups and are compared and contrasted in the table (table 3). Whether or not post-treatment surveillance is needed

after resection of a stage I colon cancer is controversial, and the guidelines differ on this point (table 3). However, most recommend only periodic history and physical examination and colonoscopy.

The rationale for and evidence supporting these guidelines are discussed elsewhere, as are issues that arise in long-term survivors of colon cancer. (See "Post-treatment surveillance after colorectal cancer treatment" and "Approach to the long-term survivor of colorectal cancer".)

GENETIC ISSUES

Although most colorectal cancers are sporadic, specific genetic disorders have been identified, most of which are autosomal dominant, that are associated with a very high risk of developing the disease. Familial adenomatous polyposis (FAP; 90 percent risk of colorectal cancer by the age of 45 in the absence of prophylactic colectomy) and Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]; lifetime risk of colorectal cancer 25 to 75 percent) are the most common of the familial colorectal cancer syndromes, but together these two conditions account for fewer than 5 percent of cases. (See "Colorectal cancer: Epidemiology, risk factors, and protective factors", section on 'Hereditary CRC syndromes' and "Clinical manifestations and diagnosis of familial adenomatous polyposis" and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis".)

Lynch syndrome is more common than FAP and accounts for approximately 2 to 3 percent of all colonic adenocarcinomas. The term "Lynch syndrome" is now commonly used for families who have been genetically determined to have a disease-causing defect (inherited or de novo) in one of the mismatch repair (MMR) genes. The biologic footprint of a defect in MMR capacity is microsatellite instability (MSI), detected by polymerase chain reaction. Testing of all colorectal cancers is routinely used to help establish the diagnosis of Lynch syndrome. Some institutions perform MSI testing and/or immunohistochemistry (IHC) testing for MMR protein expression (which are absent when a disease-causing genetic defect is present) in colorectal cancers in young patients (diagnosed prior to age 50 years) or in those who meet the Bethesda criteria (table 4). However, increasingly, universal testing of all colorectal cancers for MSI or loss of MMR protein expression by IHC is performed, a practice that is supported by guidelines from the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the United States Multi-Society Task Force on Colorectal Cancer [4-6]:

- Absence of MSI and intact expression of all four MMR proteins on IHC rules out Lynch syndrome.

- Although over 90 percent of Lynch syndrome-related colorectal cancers will demonstrate MSI, 15 percent of sporadic colorectal cancers also have MSI. Thus, the finding of MSI in a colorectal cancer does not indicate Lynch syndrome but, instead, identifies those patients who should be referred for additional testing (IHC or germline mutational testing).

- For individuals with evidence of high MSI (MSI-H) or loss of expression of an MMR protein by IHC, further evaluation is based on the MSI/IHC results and is outlined in the suggested algorithm (algorithm 1):

  - Absence of protein expression of MLH1 and PMS2, MLH1 alone, or PMS2 alone (which is rare) may be associated with either sporadic or inherited disease. If these proteins are not expressed in a tumor, the next step is analysis of *BRAF* V600E mutation or analysis of methylation of the MLH1 promoter. The presence of a *BRAF* mutation suggests sporadic rather than inherited disease, and there is no need to refer for genetic testing. If there is methylation of the MLH1 promoter and no *BRAF* mutation, then a disease-causing genetic defect should be considered, as 5 to 10 percent of these patients may harbor a germline mutation [45,46].

  - On the other hand, loss of expression of MSH2 alone, MSH2 in combination with MSH6, or MSH6 alone is highly specific for a disease-causing germline defect, and referral for genetic testing (for the genes corresponding to the absent proteins) is appropriate. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis" and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management".)

  - Biallelic somatic mutations in the MMR genes also can explain MSI in the tumors of patients where there is no germline mutation noted in the MMR genes.

Extracolonic cancers are very common in Lynch syndrome, particularly endometrial carcinomas, which may occur in up to 60 percent of female mutation carriers in some families. Other sites at increased risk of neoplasm formation include the ovaries, stomach, small bowel, hepatobiliary system, brain, renal pelvis or ureter, and sebaceous neoplasms of the skin, such as sebaceous adenomas or carcinomas. Periodic screening is recommended by expert groups. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management", section on 'General measures'.)

The development of one or more of these cancers in a family member of a colon cancer survivor may prompt consideration for genetic testing. Family history is seldom updated regularly during follow-up. However, regularly updating a three-generation family history pedigree from cancer survivors can be valuable to help determine the potential risk of cancer in family

members, as well as the survivor's own risk of subsequent cancers that may be associated with a previously unrecognized hereditary syndrome.

Importantly, the identification of MSI-H/deficient MMR also identifies patients with metastatic colon cancer who might be candidates for treatment with an immune checkpoint inhibitor. (See "Systemic therapy for nonoperable metastatic colorectal cancer: Approach to later lines of systemic therapy", section on 'Microsatellite unstable/deficient mismatch repair tumors'.)

MANAGEMENT OF LOCALLY RECURRENT DISEASE

Selected patients with locally recurrent colon cancer can be cured, typically with multimodality therapy. Prognostic factors for outcome in patients with recurrent colon cancer were addressed in a large database series of 17,381 patients who were enrolled in 18 randomized phase III trials testing adjuvant chemotherapy for stage II or III colon cancer conducted mainly before 2000 in the era when treatment was mainly limited to fluorouracil (FU) [47]. The median survival of all patients experiencing a recurrence was 13 months. Survival was significantly better in patients with initial stage II rather than stage III tumors (median 18 versus 13 months), in those with a longer disease-free interval, and in those who did not receive FU-based adjuvant chemotherapy following resection of the primary tumor.

Although there are no prospective trials to guide therapy, the management of these patients is typically multidisciplinary and may include chemotherapy, chemoradiotherapy, or intraoperative radiation therapy in addition to surgery. While guidelines from the National Comprehensive Cancer Network (NCCN) [3] recommend six months of adjuvant chemotherapy after resection of colorectal cancer liver metastases, they do not address the utility of chemotherapy after resection of a local recurrence. The decision must be individualized and is based in part on whether adjuvant therapy (particularly an oxaliplatin-containing regimen) was administered previously. (See "Potentially resectable colorectal cancer liver metastases: Integration of surgery and chemotherapy", section on 'Systemic chemotherapy'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Colorectal cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Colon and rectal cancer (The Basics)" and "Patient education: Colectomy (The Basics)")
- Beyond the Basics topics (see "Patient education: Colon and rectal cancer (Beyond the Basics)" and "Patient education: Colorectal cancer treatment; metastatic cancer (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Diagnosis and staging**
  - The diagnosis of colon cancer is usually made by colonoscopy. (See 'Diagnosis' above.)
  - Pretreatment clinical staging is best accomplished by physical examination and computed tomography (CT) scan of the chest, abdomen, and pelvis. Serum levels of the tumor marker carcinoembryonic antigen (CEA) should be obtained preoperatively in most patients. (See 'Radiographic imaging' above and 'Tumor markers' above.)
  - Each patient should have a colonoscopic examination of the entire colon prior to surgery. If full colonoscopy cannot be performed because of obstruction or poor preparation, CT or magnetic resonance colonography can be done, or alternatively, the entire residual colon should be examined colonoscopically soon after resection. (See 'Colonoscopy' above.)
- **Family history and genetic issues**

- A family history of colorectal and other extracolonic cancers should be sought prior to therapy, as an inherited predisposition to colon cancer may alter the surgical approach, prompting consideration of subtotal or total colectomy in high-risk individuals. (See 'Family history' above.)

- Family history alone is insufficient to identify most patients with a hereditary colon cancer syndrome, particularly Lynch syndrome. Clinical practice guidelines from American Society of Clinical Oncology and others recommend testing of all colorectal cancers, independent of stage and age, for loss of mismatch repair protein expression. (See 'Genetic issues' above.)

- **Treatment**

  - Surgical resection is the only curative modality for localized colon cancer. Endoscopic resection is a reasonable alternative for selected early stage colon cancers arising in a polyp, as long as they meet certain criteria for favorable risk. (See 'Surgical resection' above and 'Management of carcinoma in a polyp' above.)

  - There is no consensus as to which patients are suitable for neoadjuvant approaches rather than upfront surgery. (See 'Neoadjuvant therapy' above.)

    - Most patients with localized, resectable colon cancer should undergo upfront surgery, followed by adjuvant systemic therapy as clinically indicated. However, it may be appropriate to evaluate selected patients for neoadjuvant therapy such as those with locally advanced tumors and potentially compromised surgical margins, or those with medically inoperable tumors.

    - For patients with localized, unresectable colon cancers with deficient mismatch repair (dMMR) and an indication for neoadjuvant systemic therapy, immunotherapy is an appropriate alternative to chemotherapy (ideally in the context of a clinical trial.)

  - Following potentially curative resection, postoperative (adjuvant) chemotherapy eradicates micrometastases, reduces the likelihood of disease recurrence, and increases cure rates. The benefits have been most clearly demonstrated in patients with stage III (node-positive) disease. (See 'Adjuvant chemotherapy' above.)

  - Most patients who present with metastatic disease are not surgical candidates, and palliative chemotherapy is generally recommended. However, surgery may provide a

potentially curative option for selected patients with limited metastatic disease, predominantly in the liver and lung. (See 'Metastatic disease' above.)

- The most important indicator of outcome following resection of colon cancer is pathologic stage (figure 2) (see 'Prognosis' above).

- **Post-treatment surveillance**

  - Selected patients with locally recurrent or limited metastatic colon cancer can be cured, typically with multimodality therapy. (See 'Management of locally recurrent disease' above and 'Metastatic disease' above.)

  - Following potentially curative treatment for a stage II or III colon cancer, post-treatment surveillance to detect recurrent disease usually consists of periodic history and physical examination and assay of the serum CEA, annual surveillance CT scans, and periodic colonoscopy (table 3).

  - Following treatment for stage I colorectal cancer, post-treatment surveillance consists only of periodic history and physical examination and colonoscopy. (See 'Post-treatment surveillance' above.)

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Topic 2507 Version 86.0

GRAPHICS

Colorectal cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*, intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4	Tumor invades* the visceral peritoneum or invades or adheres¶ to adjacent organ or structure
T4a	Tumor invades* through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades* or adheres¶ to adjacent organs or structures
* Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (ie, respectively, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix, or vagina). ¶ Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classification should be used to identify the presence or absence of vascular or lymphatic invasion whereas the PN prognostic factor should be used for perineural invasion.	
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis

N1	One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the: ▪ Subserosa ▪ Mesentery ▪ Nonperitonealized pericolic, or perirectal/mesorectal tissues
N2	Four or more regional nodes are positive
N2a	Four to six regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive

Distant metastasis (M)

M category	M criteria
M0	No distant metastasis by imaging, etc; no evidence of tumor in distant sites or organs. (This category is not assigned by pathologists.)
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
M1a	Metastasis to one site or organ is identified without peritoneal metastasis
M1b	Metastasis to two or more sites or organs is identified without peritoneal metastasis
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

Prognostic stage groups

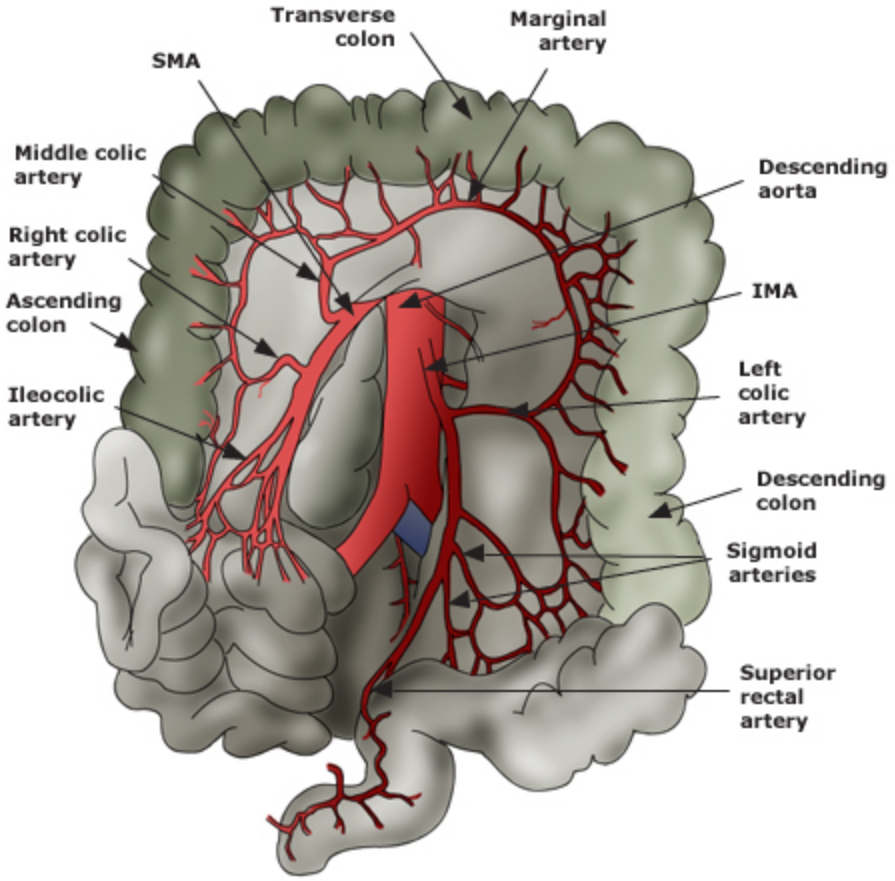
When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1, T2	N0	M0	I
T3	N0	M0	IIA
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T1-T2	N1/N1c	M0	IIIA
T1	N2a	M0	IIIA
T3-T4a	N1/N1c	M0	IIIB

T2-T3	N2a	M0	IIIB
T1-T2	N2b	M0	IIIB
T4a	N2a	M0	IIIC
T3-T4a	N2b	M0	IIIC
T4b	N1-N2	M0	IIIC
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVB
Any T	Any N	M1c	IVC

TNM: Tumor, Node, Metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Graphic 111438 Version 10.0

Arterial circulation to the large bowel



IMA: inferior mesenteric artery; SMA: superior mesenteric artery.

Graphic 64156 Version 2.0

American Society of Clinical Oncology (ASCO) framework of resource stratification[1,2]

Setting	Description
Basic	Core resources or fundamental services are absolutely necessary for any public health/primary health care system to function; basic-level services typically are applied in a single clinical interaction.
Limited	Second-tier resources or services are intended to produce major improvements in outcome, such as incidence and cost effectiveness, and are attainable with limited financial means and modest infrastructure; limited-level services may involve single or multiple interactions. Universal public health interventions are feasible for a greater percentage of the population than the primary target group.
Enhanced	Third-tier resources or services are optional but important; enhanced-level resources should produce further improvements in outcome and increase the number and quality of options and individual choice (perhaps ability to track patients and links to registries).
Maximal*	May use high-resource-setting guidelines.
	High-level/state-of-the-art resources or services may be used or are available in some high-resource countries and/or may be recommended by high-resource-setting guidelines that do not adapt to resource constraints, but that nonetheless should be considered a lower priority than those resources or services listed in the other categories on the basis of extreme cost and/or impracticality for broad use in a resource-limited environment.

* To be useful, maximal-level resources typically depend on the existence and functionality of all lower-level resources.

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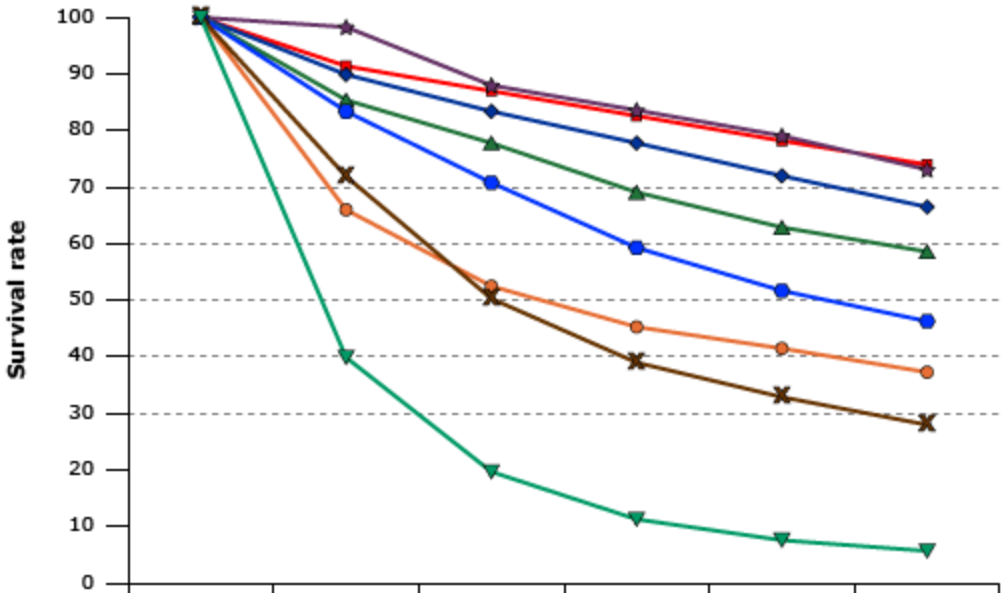
Graphic 120538 Version 1.0

Observed survival rates for 28,491 cases with adenocarcinoma of the colon



	0	1	2	3	4	5
I	100.0	91.4	87.0	82.6	78.2	74.0
IIA	100.0	89.9	83.4	77.8	72.0	66.5
IIB	100.0	85.4	77.8	69.1	62.9	58.6
IIC	100.0	66.0	52.5	45.3	41.5	37.3
IIIA	100.0	98.3	88.0	83.6	79.1	73.1
IIIB	100.0	83.4	70.8	59.3	51.7	46.3
IIIC	100.0	71.9	50.3	39.0	32.9	28.0
IV	100.0	39.9	19.7	11.3	7.6	5.7

Years from diagnosis

Data from the SEER 1973 to 2005 Public Use File diagnosed in years 1998 to 2000. Stage I includes 7417; Stage IIA, 9956; Stage IIB, 997; Stage IIC, 725; Stage IIIA, 868; Stage IIIB, 1492; Stage IIIC, 2000; and Stage IV, 5036.

SEER: Surveillance, Epidemiology, and End Results.

Graphic 81414 Version 14.0

Summary of professional guidelines regarding posttreatment surveillance for resected colon and rectal cancer

Organization	History and physical examination	CEA testing	CT scanning	Endoscopic surveillance	C
ASCO[1] and CCO[2]	Every 3 to 6 months for 5 years.	Every 3 to 6 months for 5 years.	Abdomen and chest annually for 3 years; pelvis: rectal cancer only, annually for 3 to 5 years.	Colonoscopy at 1 year*; subsequent studies dictated by prior findings. If negative, every 5 years. Proctosigmoidoscopy every 6 months for 2 to 5 years if rectal cancer and no pelvic RT.	Posttre surveill guided risk of functio recomm for rese III colo cancer. Recom provide stage I to lack recomm
American Cancer Society[3]	Every 3 to 6 months for the first 2 years, then every 6 months to 5 years.	Every 3 to 6 months for the first 2 years, then every 6 months to 5 years if the patient is a potential candidate for further intervention.	Abdomen/pelvis and chest every 12 months for 5 years for stage III and high-risk stage I/II disease.	Colonoscopy in year 1; if advanced adenoma, repeat in 1 year; otherwise, repeat in 3 years. If no advanced adenoma in year 4, repeat every 5 years.	High-ri disease
NCCN[4]	Every 3 to 6 months for 2 years, then every 6 months for 3 years.	Every 3 to 6 months for 2 years for ≥T2 disease, then every 6 months for 3 years. For resected metastatic disease, every 3 to 6	Colon: Abdomen/pelvis and chest every 6 to 12 months for up to 5 years for those at high risk of recurrence¶. For rectal cancer, CT chest/abdomen	Colonoscopy at 1 yearΔ; subsequent studies dictated by prior findings. If no advanced adenoma, repeat at 3 years, then every 5 years; if advanced adenoma at 1 year, repeat at 1 year.	Recom to stag resecte cancer, II, III, o IV recta

		months for 2 years, then every 6 months for 3 to 5 years.	and pelvis every 3 to 6 months for 2 years, then every 6 to 12 months for up to 5 years for those at high risk of recurrence¶. For resected metastatic disease, CT abdomen/pelvis and chest every 3 to 6 months for 2 years, then every 6 to 12 months up to a total of 5 years.	Flexible sigmoidoscopy with EUS or MRI every 3 to 6 months for 2 years, then every 6 months to complete 5 years for patients with rectal cancer undergoing transanal excision only.	
ESMO colon cancer[5]	Every 3 to 6 months for 3 years, then every 6 to 12 months for 2 more years.	Every 3 to 6 months for 3 years, then every 6 to 12 months for 2 years.	Abdomen, chest, and pelvis every 6 to 12 months for 3 years, then every 12 months for 2 more years.	Colonoscopy at 1 year; every 3 to 5 years thereafter.	Guideli localize do not applica stage I More ir surveill years f metast Refer t on "Sur colorec resecti
ESMO rectal cancer[7]	Every 6 months for 2 years◇.	Every 6 months for the first 3 years.	A minimum of 2 CT scans of the chest, abdomen, and pelvis in the first 3 years.	Colonoscopy every 5 years up to age 75.	High-ri circum resecti positive more p surveill recurre

					More ir surveill years f metast Refer t on "Sur colorec resecti
New Zealand[8]	Clinical assessment§ stratified according to risk of recurrence: ▪ *High-risk cancer (stage IIB, III):* Every 6 to 12 months for 3 years, then annually for 2 years. ▪ *Lower risk (stage I, IIA), or with comorbidities restricting future surgery:* Annual review for 5 years or when symptoms occur.	*For high-risk cancer (stage IIB, III):* Every 6 to 12 months for 3 years, then annually for 2 years. *For lower risk (stage I, IIA), or with comorbidities restricting future surgery:* Annually for 5 years.	All individuals with stages I to III colorectal cancer should have liver imaging between years 1 and 3.	Colonoscopy at 1 year¥; colonoscopy every 6 to 12 months for 3 years for high-risk patients (stages IIB, III), then annually for at least 5 years. For low-risk patients, colonoscopy every 3 to 5 years. For rectal cancer, proctoscopy or sigmoidoscopy at 3, 6, 12, and 24 months postsurgery; colonoscopy at 3- to 5-year intervals thereafter.	Recom stages colorec
US Multi-Society Task Force on Colorectal Cancer[9]				Colonoscopy 1 year after surgery (or 1 year after the clearing perioperative colonoscopy). The interval to the next colonoscopy should be 3 years and then 5 years. If neoplastic polyps are	

				detected, the intervals between colonoscopies should be shorter and in accordance with published guidelines for polyp surveillance intervals[10]. These intervals do not apply to patients with Lynch syndrome. For rectal cancer, flexible sigmoidoscopy or EUS every 3 to 6 months for the first 2 to 3 years after surgery for patients at high risk for local recurrence. Refer to UpToDate topic on "Surveillance after colorectal cancer resection."	
British Columbia Medical Association[11]	Every 3 to 6 months for 2 years, then every 6 months for 3 years.	Every 3 months for 3 years, then every 6 months for 2 years.	Liver ultrasound or CT scans (preferred) every 6 months for 3 years, then annually for 2 years. Annual chest CT for 3 years.	Colonoscopy at 1 year; if normal, repeat 3 years later and, if normal, every 5 years thereafter.	These g resecte colon a Patient comorb advanc 5-year are not surveill
American Society of Colon and Rectal Surgeons[12]	Every 3 to 12 months for 2 years, then every 6 to 12 months for 3 years.	Every 3 to 12 months for 2 years, then every 6 to 12 months for 3 years.	Twice in 5 years or up to annually for 5 years.	Colonoscopy at 1 year (or 1 to 6 months after surgery if inadequate colonoscopy preoperatively, and depending on findings, repeat at 3 years, then every 5 years or more	Recom to high (eg, rec posttra colorec endosc only, or based t stage I disease

				frequently as indicated). Proctoscopy ±endoscopic ultrasound every 6 to 12 months after rectal cancer resection with anastomosis (no RT), or every 6 months following local excision for 3 to 5 years.	curativ UpToD "Survei colorec resecti

CEA: carcinoembryonic antigen; CT: computed tomography; ASCO: American Society of Clinical Oncology; CCO: Cancer Care Ontario; RT: radiation therapy; NCCN: National Comprehensive Cancer Network; EUS: endoscopic ultrasound; MRI: magnetic resonance imaging; ESMO: European Society for Medical Oncology.

* Except if no preoperative colonoscopy because of obstructing lesion; do as soon as possible after completion of adjuvant chemotherapy rather than waiting until 1 year.

¶ Features suggesting a high risk of recurrence: poorly differentiated histology, lymphatic or venous invasion.

Δ Except if no preoperative colonoscopy because of obstructing lesion; recommend at 3 to 6 months rather than waiting until 1 year.

◇ Minimum provisional recommendation.

§ Clinical assessment for patients with colon cancer includes physical examination, CEA, chest/abdominal and pelvic CT scans, colonoscopy, and liver ultrasound. Clinical assessment for rectal cancer patients includes physical examination, CEA, chest/abdominal and pelvic CT scans, colonoscopy, and proctoscopy or sigmoidoscopy.

¥ If no complete colonoscopy before surgery, perform colonoscopy within 6 months.

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Graphic 91618 Version 21.0

The revised Bethesda guidelines for testing colorectal tumors for microsatellite instability (MSI)

Tumors from individuals should be tested for MSI in the following situations:
1. Colorectal cancer diagnosed in a patient who is less than 50 years of age.
2. Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors*, regardless of age.
3. Colorectal cancer with the MSI-H¶-like histologyΔ diagnosed in a patient who is less than 60 years of age◇.
4. Colorectal cancer diagnosed in a patient with one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 years.
5. Colorectal cancer diagnosed in a patient with two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age.

HNPCC: hereditary nonpolyposis colorectal cancer; MSI-H: microsatellite instability-high.

* HNPCC-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratocanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.

¶ MSI-H in tumors refers to changes in two or more of the five National Cancer Institute-recommended panels of microsatellite markers.

Δ Presence of tumor infiltrating lymphocytes. Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.

◇ There was no consensus among the Workshop participants on whether to include the age criteria in guideline 3 above; participants voted to keep less than 60 years of age in the guidelines.

Graphic 72965 Version 5.0

Approach to screening for Lynch syndrome in individuals with colorectal and/o

CRC: colorectal cancer; IHC: immunohistochemistry; MSI: microsatellite instability; MMR: mismatch repair.

* Germline genetic evaluation may be appropriate in individuals with any one of the following: 1) Family can Bethesda guidelines; 2) >2.5% chance of an MMR gene mutation by prediction models; 3) First-degree relati

¶ Normal IHC is only approximately 85% sensitive for Lynch syndrome. Consider MSI testing to confirm or ru

Δ The presence of MLH1 promoter methylation or BRAF V600E mutation is suggestive of sporadic CRC.

◇ Endometrial tumors are not eligible for BRAF V600E testing, so those with loss of MLH1/PMS2 on IHC shou

§ Lynch syndrome should be suspected in individuals with synchronous or metachronous CRC, CRC prior to CRC and endometrial, ovarian, stomach, small intestine, or renal pelvis/ureter), and in cases of familial cluste

¥ Other important considerations include ethnicity, the prevalence of particular genetic founder mutations i

‡ Refer to UpToDate content on genetic evaluation for Lynch syndrome.

† Individuals with bi-allelic somatic inactivation (by mutation and/or loss of heterozygosity) of MMR genes d

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Graphic 130015 Version 1.0

Contributor Disclosures

Michael J Overman, MD Grant/Research/Clinical Trial Support: BMS [Colon cancer]; Lilly [Small bowel adenocarcinoma]; Medimmune [Colon and pancreas cancer]; Merck [Colon cancer and MSI-high cancers]; Nouscom [Colon and gastric cancers]; Roche [MSI-high colon cancer]; Takeda [MSI-high cancers]. Consultant/Advisory Boards: 3D Medicines [Tumor-agnostic and MSI-high cancers]; AgilVax [Colon cancer]; BMS [Colon cancer]; Gilead Sciences [Colon cancer]; GlasxoSmithKline [Colon cancer]; Gritstone [Colon cancer]; Ipsen Biopharmaceuticals [Colon cancer]; Janssen research [Colon cancer]; Medimmune [Colon and pancreas cancer]; Merck [Colon cancer]; Novartis [Colon cancer]; Pfizer [Colon cancer]; Phanes [Colon cancer]; Promega [Tumor-agnostic and colon cancer]; Roche [Colon cancer]; Simcere [Tumor-agnostic cancer and colon cancer]; Takeda [Colon cancer]; Tempus [Tumor-agnostic cancer]. All of the relevant financial relationships listed have been mitigated. **Kenneth K Tanabe, MD** Patent Holder: EGF SNP to determine risk for HCC [Cirrhosis, hepatocellular carcinoma]; Use of EGFR inhibitors to prevent HCC [Cirrhosis, hepatocellular carcinoma]. Consultant/Advisory Boards: Cancer Expert Now [GI cancers, melanoma]; GSK [GI Cancers]; Imvax [GI cancers]; Leidos [Melanoma, GI cancers]; Teledoc [GI cancers, melanoma]. Other Financial Interest: American Cancer Society [Honoraria as editor of Cancer]. All of the relevant financial relationships listed have been mitigated. **Richard M Goldberg, MD** Equity Ownership/Stock Options: Advanced Chemotec Inc [Pancreatic cancer]; Compass Therapeutics [Biliary tract and colorectal cancer]. Consultant/Advisory Boards: AbbVie [GI cancers]; Advanced Chemotherapy Technologies [GI cancer]; AstraZeneca [GI cancer]; Bayer [GI cancer]; Compass Therapeutics [GI cancer]; Eisai [GI cancer]; G1 Therapeutics [GI cancer]; GSK [Colorectal cancer]; Innovative Cellular Therapeutics [Colorectal cancer]; Inspirna [Colorectal cancer]; Merck [GI cancer]; Modulation Therapeutics [Lymphoma]; Novartis [GI cancer]; Sorrento Therapeutics [GI cancer]; Taiho [GI cancer]. Other Financial Interest: Taiho [Expert testimony GI cancer]. All of the relevant financial relationships listed have been mitigated. **Sonali M Shah, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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