The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Treatment of Colon Cancer

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STATEMENT OF THE PROBLEM

In the United States, an estimated 96,000 and 38,000 new cases of colon and rectal cancer will be diagnosed in 2017.[1] Colorectal cancer is the third most common cancer and cause of cancer death in both men and women in the United States. The treatment of patients with colon cancer is largely guided by stage at presentation, emphasizing the importance of a comprehensive strategy of diagnosis, evaluation, and treatment. Surgery encompasses the primary form of treatment for colon cancer, whereas chemotherapy is used most commonly in the adjuvant setting. The 5-year overall survival for patients with localized, regional, and metastatic colon cancer is 91%, 72%, and 13%.[2]

The scope of this guideline is to address the issues related to the evaluation and treatment of patients who have been diagnosed with colon cancer. Matters pertinent to colon cancer screening and surveillance after colon cancer treatment,[3] as well as rectal cancer,[4] are addressed in separate documents.

METHODOLOGY

This guideline is based on the previous parameter published in 2012.[5] An organized search of MEDLINE, EMBASE, and the Cochrane Database of Collected Reviews was performed for the period of January 1, 1997 to April 21, 2017. The complete search strategy is included as an appendix (http://links.lww.com/DCR/A436). In brief, a total of 16,925 unique journal titles were identified. Initial review of the search results resulted in exclusion of 11,204 titles based on either irrelevance of the title or the journal. Secondary review resulted in exclusion of 5,480 titles considered irrelevant or outdated. A tertiary review of the remaining 241 titles included assessment of the abstract or full-length article. This led to exclusion of an additional 30 titles for which similar but higher-level evidence was available. The remaining 211 titles were considered for grading of the recommendations. A directed search of references

embedded in the candidate publications was performed. Emphasis was placed on prospective trials, meta-analyses, systematic reviews, and practice guidelines. Peer-reviewed observational studies and retrospective studies were included when higher-quality evidence was insufficient. The final source material used was evaluated for the methodological quality, the evidence base was examined, and a treatment guideline was formulated by the subcommittee for this guideline. A final grade of recommendation was assigned using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system (Table 1).[6] When agreement was incomplete regarding the evidence base or treatment guideline, consensus from the committee chair, vice chair, and 2 assigned reviewers determined the outcome. Members of the American Society of Colon and Rectal Surgeons (ASCRS) practice guidelines committee worked in joint production of these guidelines from inception to final publication. Recommendations formulated by the subcommittee were reviewed by the entire Clinical Practice Guidelines Committee. Final recommendations were approved by the ASCRS Clinical Guidelines Committee and ASCRS Executive Committee. In general, each ASCRS Clinical Practice Guideline is updated every 5 years.

RECOMMENDATIONS

Evaluation and Risk Assessment

1. **An assessment of disease-specific symptoms, past medical and family history, physical examination, and serum CEA level should typically be evaluated in patients with colon cancer. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.**

Sporadic, familial, and hereditary types of colon cancer account for approximately 65%, 30%, and <5% of new cancers in the United States.[7] Although often asymptomatic, colon cancer may also be heralded by symptoms of fatigue, blood in the stool, abdominal pain, or obstructive symptoms. These symptoms often correlate with more advanced stages of colon cancer and may be used to compliment the information that is subsequently gained during the process of staging the cancer and planning treatment. Comorbid conditions should be assessed to help determine operative risk and to identify opportunities for medical optimization before colon surgery. A careful history, including family history and colon cancer-specific history can guide the surgeon to suspect hereditary cancer syndromes, look for associated pathology or metastatic disease, and initiate additional workup such as mutational analysis. Patients meeting clinical criteria for or having family history of an increased susceptibility to colorectal cancer should be referred to a genetics counselor for formal evaluation, when possible, and consideration of genetics testing, because the results may impact surgical decision making. Physical examination should include assessment for an abdominal mass lesion, adenopathy, or surgical scars, all of which may influence diagnostic and treatment-related decisions. Selective rather than routine use of preoperative laboratory testing such as complete blood count, liver function tests, and coagulation studies are recommended for the evaluation of new patients with colon cancer.[8,9] Carcinoembryonic antigen levels should typically be assessed before elective surgery for colon cancer to establish a baseline value and during the surveillance period to monitor for signs of recurrence. A multivariate analysis of over 130,000 patients included in the National Cancer Database recently indicated that preoperative CEA is an independent predictor of overall survival in patients with stage I to III colon cancer.[10] Although higher CEA levels are generally associated with advanced cancer stage, conflicting evidence on the independent predictive value of this test should be acknowledged.[11–14]

2. **When possible, patients with presumed or proven colon cancer should undergo a full colonic evaluation with histologic assessment of the colonic lesion before treatment. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.**

When possible, the histologic diagnosis of colon cancer should be confirmed before elective surgical resection because nonneoplastic processes such as diverticulitis or IBD may be associated with the endoscopic or radiographic appearance of colon cancer. Lesions concerning for malignancy, but without histologic confirmation (eg, possible sampling error), that are not amenable to endoscopic removal warrant oncologic resection. When feasible, complete evaluation of the colorectal mucosa is typically advised before surgery to detect synchronous cancers, which were recently reported to be present in 4% of 2400 patients with stages I to III sporadic colon cancer.[15] Complete examination of the colorectal mucosa is also important to identify synchronous adenomas that are present in 30% to 50% of patients.[16,17]

In patients with colon cancer who have an endoscopically obstructing lesion or another reason for which complete colonoscopy was not performed, complete preoperative mucosal examination may be accomplished via a second attempt at conventional colonoscopy, CT colonography, or colon capsule endoscopy. When performed by expert endoscopists, 2 recent studies reported that repeat colonoscopy resulted in complete visualization of the colon in 75% and 95% of patients, adenoma detection in 24% and 53% of patients, and previously undetected colon cancer in 2% of patients.[16,18] Computed tomography colonography and colon capsule endoscopy are alternative techniques that have revealed meaningful mucosal lesions

TABLE 1. The GRADE system: grading recommendations

	Description	*Benefit vs risk and burdens*	*Methodological quality of supporting evidence*	*Implications*
1A	Strong recommendation, High-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B	Strong recommendation, Moderate-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C	Strong recommendation, Low- or very-low-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	Observational studies or case series	Strong recommendation but may change when higher-quality evidence becomes available
2A	Weak recommendation, High-quality evidence	Benefits closely balanced with risks and burdens	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B	Weak recommendations, Moderate-quality evidence	Benefits closely balanced with risks and burdens	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C	Weak recommendation, Low- or very-low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk and burden may be closely balanced	Observational studies or case series	Very weak recommendations, other alternatives may be equally reasonable

GRADE = Grades of Recommendation, Assessment, Development, and Evaluation; RCT = randomized controlled trial.
Adapted from Guyatt G, Gutermen D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians Task Force. *Chest*. 2006;129:174–181.[6] Used with permission.

in 11% to 13% and 24% to 44% of patients who had previous incomplete colonoscopy.[19–22] Intraoperative colonoscopy may be safely performed after resection of the tumor and restoration of intestinal continuity or creation of a colostomy.[17,23,24] Postoperative colonoscopy is another option for patients in whom preoperative or intraoperative evaluation of the colon and rectum was not possible or inadequate.[25] The use of contrast enema studies has relatively low yield for the detection colorectal mucosal pathology and therefore is generally not recommended.[18,26]

Staging of Colon Cancer

1. **Preoperative radiologic staging with a chest/abdomen/pelvis CT should typically be performed. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.**

Computed tomography scan of the chest, abdomen, and pelvis is recommended before the elective surgical resection of colon cancer.[27] Although the yield of chest CT in detecting colorectal cancer lung metastasis is low (6%), and increased when used selectively in patients with liver metastasis or mesenteric lymphadenopathy, its value in obtaining a "baseline" assessment of the chest generally warrants its routine use.[28–30] Preoperative CT imaging permits the detection and evaluation of the extent of synchronous metastases, which may require a change in the treatment strategy, eg, chemotherapy rather than surgery first or potential simultaneous resection of both the primary tumor and the metastatic sites. The preoperative CT scan findings may also result in the operative plan being altered based on accurate tumor localization and adjacent organ or abdominal wall involvement. In patients with hypersensitivity to the iodine contrast dye, or when it is necessary to further evaluate indeterminate lesions on CT, a positron emission tomography/CT scan (PET/CT) or noncontrast chest CT with an MRI of the abdomen and pelvis may be considered.[27,31,32]

2. **Positron emission tomography/CT (PET/CT) is generally not recommended for routine colon cancer staging. Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 2B.**

In 2011, a prospective analysis indicated that the sensitivity of CT and PET/CT for colorectal cancer liver me-

tastasis, on a lesion-by-lesion basis, was 89% and 55% ($p < 0.001$). In 2014, another prospective study indicated similar sensitivity for CT (≥75%) and PET/CT (85%) and overall accuracy of CT (86%–89%) and PET/CT (93%–95%) in the detection of colon cancer liver metastasis.[31] At present, it is not clear if CT/PET offers an advantage to contrast-enhanced CT for the detection of colon cancer lung metastasis.[31,33] Notwithstanding limited evidence from retrospective studies that the addition of PET/CT to routine colorectal cancer staging results in an alteration in treatment in as many as 20% of patients, the National Cooperative Cancer Network, the National Institute for Health and Care Excellence, and the European Society for Medical Oncology do not recommend PET/CT in the initial staging of colorectal cancer.[34–36] Alternatively, selective use of PET/CT is recommended for the evaluation of patients with an unexplained elevation in their CEA, for evaluation of indeterminate extrahepatic lesions detected by CT or MR, and when local recurrence of cancer is suspected but not confirmed.[32,37,38]

3. **Colon cancer staging should be performed according to the American Joint Committee on Cancer (AJCC)/TNM system and include an assessment of the completeness of surgical resection designated by the residual tumor code "R." Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.**

Tumor depth, nodal metastasis, and distant metastasis have been shown to be predictors of prognosis in colon cancer. These characteristics are described by the American Joint Committee on Cancer (AJCC)/TNM staging system and are presented in Table 2. The recently released eighth edition has expanded the definition of metastatic disease to include the M1c category for peritoneal implants, clarified the definition of tumor deposits, and also highlighted the importance of lymphovascular invasion, microsatellite instability (MSI) status, and mutations in KRAS, NRAS, and BRAF in treatment considerations.[39] As with previous editions, a positive lymph node is defined as one containing a ≥0.2-mm deposit of cancer cells. Although debate continues regarding the prognostic value of "isolated tumor cells" or clumps of tumor cells measuring <0.2 mm in regional lymph nodes, these terms are not included in the AJCC/TNM staging system.[40–42]

In addition to tumor-node-metastasis staging, the histologic grade of the tumor as well as the completeness of the resection should be assessed. Histologic grade has been shown to be an important predictor of outcome and is an important consideration for treatment recommendations. The absence or presence of residual tumor following resection is designated by the letter R in accordance with the AJCC prognostic factors as indicated below and, where possible, should be indicated in the operative report:

- R0—complete tumor resection with all margins histologically negative
- R1—incomplete tumor resection with microscopic surgical resection margin involvement (margins grossly uninvolved)
- R2—incomplete tumor resection with gross residual tumor that was not resected (primary tumor, regional nodes, macroscopic margin involvement)[43]

Prognostic calculators and nomograms that include the positive-to-total lymph node ratio and tumor location have been proposed and may be useful adjuncts to the TNM stage but are not currently included in the AJCC/TNM staging system.[44–47]

Surgical Treatment of the Primary Tumor

1. **A thorough surgical exploration should be performed and the findings documented in the operative report. Grade of Recommendation: Strong recommendation based on low- or very-low-quality evidence, 1C.**

The surgical exploration includes visual inspection and, when possible, palpation of the peritoneal cavity and the abdominal and pelvic organs to detect or rule out synchronous lesions, more advanced malignant disease (carcinomatosis, adjacent organ involvement, occult metastasis) or coexisting pathology (eg, adhesions, hernia, cholelithiasis, and cirrhosis).

2. **The extent of resection of the colon should correspond to the lymphovascular drainage of the site of the colon cancer. Grade of Recommendation: Strong recommendation based on high-quality evidence, 1B.**

The extent of a curative resection for colon cancer depends on 1) the site of the primary lesion and 2) its lymphovascular drainage. In the absence of synchronous pathology, a colon resection for cancer should generally include proximal and distal margins of 5 to 7 cm to ensure adequate removal of at risk pericolic lymph nodes.[48,49]

The mesentery to the tumor-bearing segment of bowel should be removed to the origin of the named primary feeding vessel(s) to enable removal of the draining intermediate and central lymph nodes.[50,51] This resection should be performed en bloc with preservation of the integrity of the colonic mesentery.[52,53]

Because the total number of lymph nodes evaluated at the time of resection has been associated with survival, the lymph node examination should be as complete as possible.[54,55] It is recommended that at least 12 lymph nodes be evaluated to assign N0 stage, and the examination of fewer than 12 lymph nodes is a high-risk feature for stage II colon cancer.[39,56] In the event that fewer than 12 lymph nodes are reported on the pathology report, the surgeon should request additional evaluation and processing and reporting of the specimen in accordance to

TABLE 2. TNM classification and AJCC 8th edition Staging of Colon Cancer

T Category	Definition of primary tumor (T) T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ, intramucosal adenocarcinoma (involvement of lamina propria, no extension through the muscularis mucosae)
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into the pericolonic tissue
T4a	Tumor penetrates to the surface of the visceral peritoneum (serosa)
T4b	Tumor invades and/or is adherent to other organs or structures
	Regional lymph node staging (N)
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	1 to 3 regional lymph nodes are positive (tumor in lymph nodes measuring ≥0.2mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
N1a	1 regional lymph node is positive
N1b	2–3 regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastases
N2a	4 or more regional lymph nodes are positive
N2b	7 or more regional lymph nodes are positive
	Distant metastasis staging (M)
M0	No distant metastasis
M1a	Metastasis confined to 1 organ or site is identified without peritoneal metastasis
M1b	Metastasis confined to 2 or more organs or sites is identified without peritoneal metastasis
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

Stage	*T*	*N*	*M*
0	Tis	N0	M0
I	1–2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2	N1-N1c	M0
	T1	N2a	M0
IIIB	T3-T4a	N1-N1c	M0
	T2-T3	N2a	M0
	T1-2	N2b	M0
IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b
IVC	Any T	Any N	M1C

AJCC = American Joint Committee on Cancer.

the guidelines set forth by the College of American Pathologists.[57–59] When suspected to be involved, the most apical central lymph nodes should be marked on the specimen because their metastatic involvement is a negative prognostic indicator.[60,61]

Colotomy and local excision of a colon cancer is an inadequate surgical technique for curative resection. It is associated with a risk of tumor spillage into the peritoneal cavity, and the lack of a lymphadenectomy increases the risk of tumor progression.

3. Routine performance of extended lymphadenectomy is not recommended. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.

Lymph node metastasis outside the standard field of resection (ie, proximal to primary feeding vessel and associated central (D2) nodes) occurs in 3% to 11% of colon cancers and is more likely with advanced T-stage cancers.[61–64] Central lymph node involvement in the absence of pericolic or intermediate lymph node involvement ("skip metastases") occurs in ≤2%

of cases.[65–67] "High ligation," "central vascular ligation," "complete mesocolic excision," and "D3 resection" are terms used to describe extended lymphadenectomy, beyond the primary feeding vessel and associated central (D2) lymph node basin, such as dissection and retrieval of the lymphatic tissue along the superior mesenteric artery and vein during right colon cancer resection, or at the level of the inferior mesenteric artery for sigmoid colon cancers. Although routine performance of extended lymphadenectomy is not supported by the data available,[68–70] dissection and retrieval, or at minimum, biopsy of clinically positive or suspicious lymph nodes outside the standard field of resection is recommended.[51]

4. **Resection of adherent or grossly involved adjacent organs should be en bloc. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.**

Local tumor control is achieved by complete resection of the tumor en bloc with contiguously involved structures.[50,71,72] Adhesions between a colon cancer and surrounding organs should not be divided because they have been shown to harbor malignant cells in 34% to 84% of patients.[71,73–75] The importance of an R0 resection was underscored in 2 recent large series of patients with colon cancer in whom margin-positive patients experienced significantly worse outcomes in terms of disease progression and disease-free and overall survival.[76,77] Tumor debulking in the setting of resectable disease should not be performed. Available diagnostic modalities (eg, CT scan or MRI scan) should be used to facilitate the identification of adjacent organ involvement before surgical exploration so that adequate preparation and assembly of a multidisciplinary team by be performed.[78]

5. **Synchronous colon cancers may be treated by 2 separate resections or subtotal colectomy. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.**

The term synchronous colon cancers has been used to describe situations in which a second primary colon cancer is diagnosed at the same time or up to 12 months after detection of the index colon cancer.[79,80] Synchronous cancers were recently reported to occur in 4% of patients,[15] with earlier series indicating an incidence of 0.5% to 11% of patients.[17,81] Synchronous cancers in the same segment of the colon are removed with a segmental colectomy. Synchronous cancers in separate segments of the colon may be treated on an individualized basis with an extended resection or 2 separate resections. Whereas extended resections do not incur increased surgical morbidity and have not been associated with a survival benefit, functional outcomes and quality of life may be diminished following extended resection.[15,82,83]

When associated with underlying colonic disease (eg, chronic ulcerative colitis or hereditary nonpolyposis colorectal cancer syndrome), the extent of resection should consider treatment of the underlying disorder. For example, carcinoma arising in the setting of chronic ulcerative colitis, in general, should be treated with a proctocolectomy, whereas carcinoma arising in the setting of Lynch syndrome may be treated by either tumor-directed segmental resection or by a more extensive resection tailored to the underlying risk of the patient.[84,85]

6. **Sentinel lymph node mapping for colon cancer does not replace standard lymphadenectomy. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.**

A recent meta-analysis[86] and systematic review[87] have indicated that the sensitivity of sentinel lymph node mapping in patients with colon cancer is in the range of 78% to 93% (false-positive rate, 7%–22%). Aberrant sentinel nodes (outside the planned extent of resection) occurred in 4% (range, 0%–15%) of cases.[87] Ultra staging of sentinel nodes considered negative by standard hematoxylin and eosin staining has resulted in upstaging in 7% to 19% of patients depending on the definition used for node positivity. While not a component of the recently updated AJCC colon cancer staging system, the presence of micrometastatic lymph node disease detected by ultra staging has been associated with disease recurrence and decreased survival in patients with otherwise lymph node-negative cancer evaluated by standard methods.[41]

7. **When expertise is available, a minimally invasive approach to elective colectomy for colon cancer is preferred. Grade of Recommendation: Strong recommendation based on high-quality evidence, 1A.**

Although certain lesions may not be amenable to a minimally invasive approach because of various factors (ie, large size, locally advanced), in most circumstances, minimally invasive surgery is preferred given appropriate expertise and experience. Most importantly, the laparoscopic procedure should achieve the same goals as the open approach; and when this is not possible, conversion to a laparotomy approach is recommended. Several large multi-institutional randomized trials with experienced surgeons in the United States and internationally have demonstrated equivalent oncologic outcomes including overall and recurrence-free survival rates after laparoscopic compared with open surgical resection of localized colon cancer.[88–92]

Although transverse colon cancers were excluded from the sentinel trials that compared laparoscopic and open colectomy for colon cancer, more recent nonrandomized data and a meta-analysis indicate oncologic noninferiority and improved short-term outcomes with the laparoscopic in comparison with the open surgical approach when performed by experienced surgeons.[88,93–96] Similarly, nonran-

domized and retrospective data indicate that laparoscopic resection of T4 colon cancer may be performed safely and effectively with long-term oncologic outcomes that did not differ in comparison with open surgery.[97]

8. **Hand-assisted laparoscopic and robotic surgical techniques for right colon cancer result in oncologic outcomes that are equivalent to open or straight laparoscopic techniques. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.**

Randomized prospective trials of hand-assisted laparoscopic versus open or conventional laparoscopic right colectomy for cancer indicate similar short-term outcomes for the laparoscopic and hand-assisted laparoscopic techniques, less pain and faster recovery with hand-assisted laparoscopy compared with open surgery, and no differences in the long-term oncologic outcomes.[98,99] A randomized prospective trial of robotic versus laparoscopic right colectomy for colon cancer indicated no differences in postoperative morbidity or short-term cancer-related outcomes but increased operative time and costs for the robotic group.[100] Despite numerous reported studies of hand-assisted laparoscopic and robotic colectomy, there remains insufficient evidence to allow meaningful recommendations for left-sided colon cancer resections using these techniques.

9. **Treatment of the malignant polyp is determined by the morphology and histology of the polyp. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.**

A malignant adenomatous polyp is defined as one in which cancer is invading through the muscularis mucosa into the submucosa (T1). It is estimated that up to 5% of endoscopically resected and up to 20% of endoscopically unresectable colorectal adenomas contain invasive cancer.[101–103] Advanced polyp size, patient age, high-grade dysplasia, and nonlifting with submucosal injection are risk factors for invasive cancer in a colon adenoma.[101,104] Endoscopic management has been reported to be sufficient for pedunculated or sessile malignant polyps that can be removed in 1 piece and have the following "low-risk" features: resection margins free of dysplasia or cancer, well or moderately differentiated cancer without angiolymphatic invasion, and limited submucosal invasion with cancer cells ≤2 mm below the muscularis mucosa.[27,105–107] Nodal metastases have been reported in up to 8% of malignant polyps.[107] Poor differentiation, cribiform pattern, invasive depth >2 mm, lymphatic invasion, and tumor budding are associated with increased risk of nodal disease.[107,108]

The definition of a negative polypectomy resection margin is a point of controversy with earlier reports indicating the need for a ≥2-mm margin.[108] More recent evidence supports a ≥1-mm margin,[109,110] and most recently, in the largest reported review of malignant polyps to date, the authors reported that a negative resection margin of any measure is adequate.[111] Conventional colonoscopic polypectomy techniques, endoscopic mucosal resection, endoscopic submucosal dissection, or combined endoscopic laparoscopic surgery techniques have all been used safely and successfully to avoid colectomy in patients with low-risk malignant colon polyps regardless of their morphology.[101,112–114] Alternatively, malignant polyps that do not meet low-risk criteria or cannot be adequately removed via endoscopic techniques should in general be treated with an oncologic resection, because the risk of residual cancer in the colon wall and/or lymph node metastases is unacceptably high.[107,110]

Tumor-Related Emergencies

Approximately 20% of patients with colon tumors present with surgical emergencies, such as bleeding, perforation, or obstruction.[115] The goals of treatment in these situations are to 1) avert the immediate negative impacts of the complication (eg, death, sepsis), 2) achieve the best possible tumor control, and 3) ensure timely recovery to permit initiation of appropriate adjuvant or systemic treatment. It is important to note that emergency presentation of patients with colon tumors is an independent predictor of adverse disease-free survival.[115]

Bleeding

1. **When a colon cancer is the source of an acute lower GI bleed, in general, the initial management includes attempts to control the bleeding with nonsurgical approaches. In general, when surgery is required, an oncologic resection should be performed. Grade of Recommendation: Strong recommendation based on low- or very-low-quality evidence, 1C.**

Although chronic blood loss is more common, acute massive lower GI bleeding from a colon cancer is a rare, but potentially life-threatening complication. Management of acute bleeding includes resuscitation of the patient followed by attempts to localize the site of bleeding. Options for preoperative localization include radionuclide imaging, CT angiography, conventional angiography, and colonoscopy. In studies of GI bleeds that result from various pathologies, CT angiography has proven superior to radionuclide imaging with a sensitivity of 85% in comparison with 20% to 60% for radionuclide imaging.[116–119] Angiography detects bleeding in 40% to 90% of patients and can be combined with angiographic embolization, which results in cessation of bleeding in 70% to 90% of patients.[120] Urgent colonoscopy has a yield of 20% to 40% in patients with a lower GI bleed and, like angiography,

has the advantage of being both diagnostic and therapeutic.[121] When nonsurgical methods fail to localize or control bleeding from a colon cancer, surgical intervention is generally required. An oncologic resection is recommended, when it can be safely performed, in keeping with established surgical principles

Perforation

1. **In the setting of perforation, resection following established oncologic principles with a low threshold for performing a staged procedure is recommended. Grade of Recommendation: Strong recommendation based on low- or very-low-quality evidence, 1C.**

In a recent retrospective comparative analysis of 52 patients with perforated colon cancer and 1206 patients with nonperforated colon cancer, patients with a perforation were significantly less likely to have a primary anastomosis (67% vs 99%) and had increased postoperative morbidity (56% vs 22%) and mortality (15% vs 3%). Additionally, the patients with perforated cancers had significantly lower disease-free 5-year survival (43% vs 73%) and overall survival (48% vs 67%).[122]

When perforation of uninvolved colon proximal to an obstructing tumor has occurred, resection of the tumor following usual oncologic principles should be performed. In addition, the perforated segment should be addressed by repair or resection with or without bypass or diversion according to standard surgery principles. A primary anastomosis (with or without proximal diversion) may be considered in select patients with minimal contamination, healthy tissue quality, and clinical stability. The use of a self-expanding metal stent is contraindicated in the setting of perforated colon cancer.[123]

Obstruction

1. **For patients with obstructing left-sided colon cancer and curable disease, initial colectomy or initial endoscopic stent decompression and interval colectomy may be performed. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.**

In patients with malignant colon obstruction, individualized treatment decisions are based on the intent of surgery (curative or palliative), the age and risk profile of the patient, the degree of obstruction (clinical or endoscopic), and the therapeutic resources available. The appeal of endoscopic stent decompression is that it offers the potential to convert an emergent situation into a nonemergent situation and, as a result, decrease the morbidity of the colectomy and decrease the need for an ostomy. Concerns about initial stenting include colon perforation during and after stent insertion and compromise of cancer-related outcomes.

A 2011 Cochrane review of 5 randomized prospective trials comparing stent as a "bridge to surgery" versus immediate surgery indicated technical success of stent placement in 86%, clinical success in 78% patients (versus 99% with immediate surgery, $p = 0.001$), stent-related perforation in 6%, and no differences in overall complications (39% and 46%) or mortality, and concluded that stenting offered no benefit compared with proceeding directly with surgery.[124] A similar, more recent meta-analysis of 7 randomized prospective trials comparing stenting versus resection demonstrated successful stent placement in 77% of patients and that patients with stents had higher rates of primary anastomosis, decreased use of a permanent ostomy, and decreased wound infections, but no difference in mortality.[125] In this meta-analysis, colon perforation during stent insertion occurred in 7% of patients, and another 14% of patients had "silent perforation" discovered incidentally in the colectomy specimen.[125]

In patients with obstructing left-sided colon cancer, comparative analyses of the oncologic outcomes of initial stenting versus initial surgery have produced variable results, with 1 subgroup analysis of a randomized prospective trial indicating decreased recurrence-free survival in the 6 of 26 patients who sustained immediate or delayed stent-related colon perforation. However, on an intention-to-treat basis, there were no differences in disease-free or overall survival.[126] Retrospective studies have demonstrated decreased disease-free but similar overall survival for initially stented patients ≤75 years old[127] and worse overall and cancer-specific survival.[128] On the contrary, multiple other retrospective trials have indicated that initial stenting does not compromise cancer-related outcomes.[129–133] Concerns about the oncologic outcomes of initially stented, obstructed but curable average surgical risk patients is the underlying explanation for the recommendation against this practice by both the European Society of Gastrointestinal Endoscopy (endorsed by the American Society of Gastrointestinal Endoscopy) and the French Society of Digestive Endoscopy.[123,134] On the contrary, in high-risk surgical patients, initial stenting followed by optimization for interval colectomy is recommended by these societies and should be considered on an individualized basis.

2. **For patients with obstructing right or transverse colon cancer and curable disease, initial colectomy or initial endoscopic stent decompression and interval colectomy may be performed. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.**

For patients with obstructing cancers of the right or transverse colon, oncologic segmental resection with ileocolic anastomosis can be safely accomplished in most cases.[135] Creation of a primary anastomosis in this setting depends on the patient's general condition at the time of resection and the absence of other factors that indicate the need for

a defunctioning or end stoma. As an alternative to emergent colectomy, recent retrospective studies indicate that endoscopic stent decompression of obstructing right-sided colon cancers can be safely and effectively performed, with an increased the likelihood that a laparoscopic technique could be used for the interval colectomy and that stenting in these situations does not diminish long-term oncologic outcomes.[136,137]

3. **When emergent surgery is performed for an obstructing colon cancer, intraoperative colonic lavage is not required. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.**

Consideration of the fecal load in patients with obstructing colon cancer has led to studies comparing intraoperative colonic lavage with simpler methods to decompress the colon (eg, manual evacuation of stool from the open end of the divided colon) that differ little from how the colon is handled in the nonurgent setting. Both a prospective trial[138] and a systematic review of 7 trials[139] have indicated similar postoperative outcomes in patients who underwent colonic irrigation or manual decompression.

Management of Stage IV Disease

The treatment of patients presenting with synchronous or metachcronous stage IV colon cancer should be individualized and guided by a multidisciplinary team. Patients may be classified as initially *resectable*, *potentially resectable*, and *unresectable* with respect to both their primary tumor site and metastases.

Resectable Stage IV Disease

1. **The treatment of patients with resectable stage IV colon cancer should be individualized and based on a comprehensive multidisciplinary approach. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.**

When considering preoperative treatment for stage IV patients, it is important to distinguish between clearly resectable metastatic disease and disease that is potentially convertible to resectability if tumor regression is obtained through chemotherapy. Conversion to resectability has been described with standard chemotherapy regimens for unresectable metastatic disease, including biologic therapies (ie, antiangiogenesis medications).[140,141]

When metastatic disease is considered resectable or potentially resectable, resection of the primary tumor should be performed by using standard oncologic principles. In general, medically fit patients with resectable hepatic and/or pulmonary metastases will benefit from curative resection of the metastases.[142,143] The sequence of chemotherapy, resection of the primary tumor, and resection of metastases should be individualized and determined by multidisciplinary consensus. Neoadjuvant approaches to systemic chemotherapy before resection may assist in identifying patients who are better candidates for surgery.[144–146]

The role of systemic chemotherapy in the setting of resectable liver metastases was addressed in EORTC 40983. Patients with resectable liver metastases were randomly assigned to surgery alone versus combined therapy with 3 months of preoperative 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) followed by surgery and then 3 months of postoperative FOLFOX.[147] One of the benefits of the neoadjuvant regimen appears to be the downsizing that facilitates performing a complete resection. Patients in the chemotherapy arm who obtained an R0 resection had a statistically significant improvement in 3-year disease-free survival of 9.2% over surgery alone. However, this did not translate into improved overall survival.[148] Nevertheless, the results support the perioperative use of FOLFOX or capecitabine and oxaliplatin in patients with resectable colorectal liver metastases to help allow for R0 resection.

2. **Oophorectomy is recommended for grossly abnormal ovaries or contiguous extension of the colon cancer, but routine prophylactic oophorectomy is not necessary. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.**

In women with colon cancer who have normal ovaries and have average risk for ovarian cancer, prophylactic oophorectomy is not recommended. Alternatively, prophylactic oophorectomy should be considered when there are other risk factors for ovarian pathology such as HNPCC or BRCA and in postmenopausal woman. The ovaries are the site for colorectal cancer metastasis (Krukenberg tumor) in 3% to 8% of patients.[149] Oophorectomy is recommended in patients with suspected or confirmed ovarian metastasis, either by direct extension or metastasis. If 1 ovary is involved with metastatic disease, a bilateral oophorectomy should be performed with the expectation of prolonged survival in affected women who receive adjuvant chemotherapy.[149,150]

3. **The treatment of patients with isolated peritoneal carcinomatosis should be multidisciplinary and individualized, and may include cytoreductive surgery with intraperitoneal chemotherapy. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.**

Colorectal cancer-associated peritoneal carcinomatosis is most often one of multiple sites of metastatic cancer. However, in as many as 35% of patients, the abdominal cavity is the only location of metastatic cancer.[151,152] In patients with such isolated colorectal peritoneal carcinomatosis, treatment options include systemic chemotherapy and/or resection of the peritoneal cancer in combination with intraperitoneal chemotherapy. Modern chemotherapeutic agents and targeted biologic therapies have improved the outcome of pa-

tients with colorectal cancer-associated carcinomatosis, with median survival currently in the range of 16 to 24 months.[153] Unfortunately, 5-year overall survival with systemic oxaliplatin-based chemotherapy alone is less than 5%, with minimal benefit from the addition of bevacizumab.[154,155]

The surgical approach to colorectal cancer-associated peritoneal carcinomatosis includes the combination of cytoreductive surgery in conjunction with perioperative intraperitoneal mitomycin-C or oxaliplatin with or without hyperthermia.[156,157] With this approach, in over 500 patients treated in France, 5-year overall and disease-free survival was 27% and 10%, with survival inversely proportional to the extent of peritoneal disease (peritoneal cancer index).[157] Other studies have reported median survival in the range 22 to 63 months, and 5-year overall survival in the range of 19% to 51% with this approach.[158–162] In the only randomized prospective trial of cytoreductive surgery and intraperitoneal chemotherapy versus systemic oxaliplatin-based chemotherapy, 2- and 5-year overall survival was 54% vs 38% ($p = 0.04$) and 33% vs 4% ($p = 0.02$).[162] A linear relationship between the extent of peritoneal cancer (peritoneal cancer index) and overall survival was reported in 2016.[163] The completeness of surgical cytoreduction is also directly related to overall survival after heated intraperitoneal chemotherapy.[164] Although there is limited evidence that systemic adjuvant chemotherapy may lead to improved overall survival, the value of systemic neoadjuvant chemotherapy remains unclear.[165]

Unresectable Stage IV Disease

Patients who present with widely metastatic colon cancer are usually not candidates for surgical cure. Other patients with technically resectable disease may not be candidates for radical, curative resection because of systemic comorbidities. In these situations, a multidisciplinary approach to palliation is recommended. In patients with incurable metastatic colon cancer who have an asymptomatic colon lesion, the value of colectomy is debatable. The goals of palliation should be relief of symptoms caused by the cancer and maintenance of quality of life. Often this involves a multidisciplinary approach that may include systemic chemotherapy. Palliative surgical interventions for obstruction of the GI tract or intractable bleeding caused by colon cancer include resection, endoluminal stent therapy, ablative procedures, internal bypass, or creation of a diverting stoma. An individual patient's overall life expectancy should also be considered when deciding the type of palliative intervention (eg, resection or stent).

1. **Resection of an asymptomatic primary colon cancer in patients with incurable metastatic cancer is generally not recommended. Grade of Recommendation: Weak recommendation based on high-quality evidence, 2A.**

Numerous studies have evaluated the risks and benefits of resection of an asymptomatic primary tumor in patients with incurable metastatic colorectal cancer. These observational and retrospective studies are often limited by a significant influence of selection bias and have inconsistent results in terms of survival benefit. A 2017 multivariate analysis of the National Cancer Database that included adjustments for potential cofounder effects indicated no survival benefit with resection of the asymptomatic primary tumor compared with chemotherapy alone.[166] Similarly, another recent report (retrospective with propensity matching) indicated that resection of the primary tumor in the setting of incurable metastases failed to prolong survival.[167] A 2012 Cochrane Systematic Database Review that included 7 nonrandomized studies including nearly 1100 patients also reached the conclusion that resection of the primary tumor in asymptomatic patients with unresectable stage IV colorectal cancer who are managed with chemoradiotherapy is not associated with a consistent improvement in overall survival. In addition, resection does not significantly reduce the risk of complications from the primary tumor (ie, obstruction, perforation, or bleeding).[168] On the contrary, a 2016 large single-center adjusted retrospective analysis,[169] a 2016 observational study of Canadian provincial data,[170] and a 2014 meta-analysis[171] all reached the conclusion that palliative resection of the primary tumor *may be* associated with improved overall survival. No prospective randomized trials of resection and chemotherapy versus chemotherapy alone for patients with incurable metastatic colon cancer and an asymptomatic primary tumor have been reported.

2. **In patients with a large bowel obstruction caused by colon cancer who have incurable metastatic disease, or in other scenarios where palliation is the aim, decompressive stent insertion is preferable to colectomy or diversion. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.**

In the palliative setting, endoscopic stent decompression of an obstructing colon cancer is preferable to initial colectomy or diversion because it has been shown to decrease mortality, ostomy use, and the interval to initiation of chemotherapy with no difference in survival.[123,172–175] In the palliative setting, median duration of stent patency has been reported to be 106 (68–288) days with 1-, 6-, and 12-month patency rates of 69%, 54%, and 50%.[176,177] When tumor ingrowth results in recurrent obstruction, stenting through the obstructed stent has proven safe and effective in the majority of patients.[178,179]

Management of Locoregional Recurrence

1. **The treatment of patients with locoregionally recurrent colon cancer should be multidisciplinary. Potentially curative resection, including multivisceral resection, should be performed when indicated to improve overall survival. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.**

The risk for locoregional recurrence as the first and only site of recurrence following curative resection of localized colon cancer is low, approximately 2% to 3%. Salvage surgical resection is possible in approximately 30% of patients. A recent systematic review evaluated overall survival following resection of locally recurrent colon cancer. The review was based on 8 retrospective cohort studies and 1 population-based registry and included data from 550 patients.[180] Median overall survival for patients undergoing resection ranged from 14 to 42 months; however, patients who had R0 resections had a survival of 19 to 66 months compared with 8 to 23 months in patients with R2 resections. Although the use of multimodality treatment with chemotherapy and radiotherapy was variable with regard to timing, its use was common.[180] One study used a standardized protocol including preoperative 5-fluorouracil infusion and simultaneous external beam radiation. Using this protocol, the authors reported 87% R0 resection rate and a 100% 3-year survival rate.[181] Multivisceral resection rates ranged from 33% to 100%, with a median rate of 57% in 5 of the included studies. Postoperative morbidity ranged from 21% to 68% in all patients undergoing surgical resection; however, most complications were considered minor. Finally, the pooled recurrence rate was 25%.[180] Factors predictive of prolonged survival following surgical salvage include R0 resection, early stage of initial disease, no associated distant disease, and single site of recurrence.[180] One study identified preoperative chemotherapy or radiation as a predictor of R0 resection.[182] Intraoperative radiation therapy has also shown improved outcomes with low morbidity in small series with recurrent and locally advanced disease.[180]

Recommendations Regarding Documentation

1. **The operative report for colorectal cancer should include information regarding the diagnostic workup, intraoperative findings, and technical details of the procedure. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.**

The operative report should clearly communicate the evaluation, intraoperative findings, and technical details of the procedure. The report should include a description of preoperative treatments and relevant workup and findings on exploration, including the presence of synchronous metastases or gross involvement of mesenteric lymph nodes, tumor site, and adjacent organ involvement. The report should also describe treatment details including type of incision, extent of bowel and mesenteric resection, anastomotic technique, en bloc resection of contiguously involved organs, and an intraoperative assessment of the completeness of resection including margin status. Synoptic operative reports improve documentation of key surgical factors.[183,184] Video documentation of laparoscopic colon cancer operations may complement the written operative note and may be considered when technically feasible in selected situations.[185]

Adjuvant Therapy

Adjuvant chemotherapy is used to eradicate micrometastasis after curative resection of colon cancer. Decisions regarding adjuvant treatment following curatively resected colon cancer should be based on the clinical findings at resection, including stage of disease and patient comorbidities. The choice of the adjuvant chemotherapy regimen should be made jointly by the patient and the physician. Radiation therapy plays a minimal role in the adjuvant treatment of colon cancer.

1. **Adjuvant chemotherapy is typically recommended for patients with stage III colon cancer. Grade of Recommendation: Strong recommendation based on high-quality evidence, 1A.**

Several large multi-institutional US and international randomized clinical trials have demonstrated the survival benefit with adjuvant chemotherapy. Pooled data from randomized trials demonstrates a 30% reduction in the risk for recurrence and a 26% reduction in the risk for death with fluoropyrimidine-based therapy administered for 6 months.[186–191] More recently, the addition of oxaliplatin to fluoropyrimidine (eg, 5-fluorouracil (5-FU)) chemotherapy has been shown to effect an additional approximately 20% reduction in relative risk for recurrence or death corresponding to an approximately 5% absolute survival benefit at 5 years with combination 5-FU and leucovorin (LV) with oxaliplatin when compared with 5-FU alone.[186–189] Therefore, the first-line adjuvant chemotherapy regimen for stage III colon cancer, in general, should include a fluoropyrimidine (5-FU/LV or capecitabine) and oxaliplatin. However, grade 3 peripheral sensory neuropathy occurs in approximately 12% of patients who receive oxaliplatin, making it unsuitable for some patients.[190]

In patients with high-frequency MSI (MSI-high) stage III colon cancer, fluorouracil-based chemotherapy had no benefit in terms of overall survival.[191] On the contrary, more recent data indicate significant improvement in disease-free survival in patients with MSI-high stage III colon cancer who are treated with oxaliplatin-based adjuvant chemotherapy.[192]

The addition of irinotecan in combination with 5-FU was studied in several phase 3 randomized controlled trials in the United States and internationally and was demonstrated to yield no survival benefit when compared with 5-FU/LV alone.[193–195] Presently, there is no role for the addition of irinotecan in the adjuvant setting after curative resection of localized colon cancer.

Finally, the role of the biologic agents such as the vascular endothelial growth factor inhibitor bevacizumab or the epidermal growth factor receptor inhibitors cetuximab

and panitumumab, along with other targeted agents, have been the subject of recent randomized prospective multicenter trials. Unfortunately, these trials have failed to demonstrate added benefit with the addition of either bevacizumab[196–198] or the epidermal growth factor receptor inhibitor cetuximab[199,200] to FOLFOX alone. At present, there is no evidence to support the routine addition of biologic agents in the adjuvant treatment of stage III colon cancer.

2. **Adjuvant chemotherapy may be considered for patients with high-risk stage II colon cancer. Grade of Recommendation: Weak recommendation based on high-quality evidence, 2A.**

Data from SEER (Surveillance, Epidemiology, and End Results) indicates 5-year overall survival ranging from 37% for patients with T4b cancer to 66% for patients with T3 cancer.[201] There are conflicting data regarding the role of adjuvant chemotherapy in stage II colon cancer. Most of the randomized trials of adjuvant therapy for colon cancer enrolled both stage II and stage III patients, and some have demonstrated a small difference corresponding to a potential absolute improvement in overall survival of approximately 2% to 3% with 5-FU/LV and 3% to 4% with FOLFOX.[187,202–204] However, the proportion of patients with stage II cancers was approximately 20% to 25% in these trials, and definitive conclusions have not been possible. Although initial subgroup analysis of the MOSAIC trial[186] suggested a benefit of adding oxaliplatin to adjuvant chemotherapy for high-risk stage II patients, a more recent update of these data showed no benefit to oxaliplatin in the treatment of stage II disease, regardless of whether the patients were classified as low or high risk.[205] A recent, pooled analysis of oxaliplatin-based chemotherapy for patients with stage II colon cancer indicated improved short-term recurrence-free survival but no benefit in long-term disease-free or overall survival.[189] Conversely, in another recent analysis of over 150,000 patients with stage II colon cancer included in the National Cancer Database, the use adjuvant chemotherapy was associated with improved survival irrespective of pathologic risk factors.[206]

Most data suggest that there is minimal to no benefit to adjuvant treatment in patients with "good-risk" stage II colon cancer. Patients with one or more risk factors (eg, T4 primary, perforating or obstructing lesion, poorly differentiated histology, resection with <12 lymph nodes harvested) are considered to have "high risk" stage II disease and a risk of recurrence that approaches stage IIIA colon cancer.[207] Thus, high-risk stage II patients are routinely considered for adjuvant chemotherapy.[30,186,208,209]

Although recently developed and commercially available, genomic profiling tools have demonstrated prognostic information in patients with stage II colon cancers, their utility for determining treatment response has not been established, and there is no clear role for their use in treatment stratification.[210,211]

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