CLINICAL PRACTICE GUIDELINES

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

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The American Society of Colon and Rectal Surgeons (ASCRS) is dedicated to ensuring high-quality patient care by advancing the science, prevention, and management of disorders and diseases of the colon, rectum, and anus. The Clinical Practice Guidelines Committee is composed of society members who are chosen because they have demonstrated expertise in the specialty of colon and rectal surgery. This committee was created to lead international efforts in defining quality care for conditions related to the colon, rectum, and anus and develop clinical practice guidelines based on the best available evidence. While not proscriptive, these guidelines provide information on which decisions can be made and do not dictate a specific form of treatment. These guidelines are intended for the use of all practitioners, health care workers, and patients who desire information about the management of the conditions addressed by the topics covered in these guidelines. These guidelines should not be deemed inclusive of all proper methods of care nor exclusive of methods of care reasonably directed toward obtaining the same results. The ultimate judgment regarding the propriety of any specific procedure must be made by the physician in light of all the circumstances presented by the individual patient.

STATEMENT OF THE PROBLEM

The American Cancer Society estimated that roughly 105,000 Americans would be diagnosed with colon cancer and 43,000 with rectal cancer, and that 53,200 deaths would be attributed to these cancers in the year 2020.[1] In the United States, colorectal cancer remains the third most common cancer and the third most common cause of cancer-related death.[2] Approximately nine of 10 patients with colorectal cancer are diagnosed at 50 years of age or older. While the incidence and mortality rate of colorectal cancer are declining for individuals older than 50 years of age, both are on the rise for those younger than 50.[1] The treatment of patients with colon cancer is largely guided by the stage at presentation, emphasizing the importance of a comprehensive strategy for diagnosis, evaluation, and treatment. Surgery is the primary treatment for most patients with colon cancer, while chemotherapy is used most commonly in the adjuvant setting. In the United States cohort of the international CONCORD-2 study, five-year net (cancer-specific) survival was 90%, 70%, and 14% among those with localized, regional, or distant distribution of their colon cancer, respectively.[3]

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Colorectal cancer screening, bowel preparation, hereditary colon cancer, enhanced recovery pathways, surveillance and survivorship after curative treatment, and prevention of thromboembolic disease, while relevant to the management of patients with colon cancer, are beyond the scope of these guidelines and are addressed in other American Society of Colon and Rectal Surgeons (ASCRS) guidelines.[4–9]

METHODS

This guideline is based on the previous colon cancer parameter published in 2017.[10] Compared with 2017, this guideline has 11 new, 10 updated, and 2 excluded recommendations (Table 1). The literature searches were performed with PubMed using a combination of specialty-specific journal titles (Appendix 1, Supplemental Digital Content 1, http://links.lww.com/DCR/B798) organized under the subject headings of Gastroenterology, Imaging, Oncology and General Medicine, and Surgery, and the Medline Subject Heading (MeSH) "colorectal neoplasm" combined with the search limits of "journal article" or "guideline" or "controlled clinical trial" or "clinical trial" or "clinical study" or "meta-analysis" or "multicenter study" or "observational study" or "practice guideline" or "randomized controlled trial" or "systematic review," and the additional search limits of human studies, English language, and adults, and were limited to citations included in searches limited to the date range of April 8, 2015, to April 4, 2021. Additional subject-specific searches were performed with the PubMed search terms/phrases: 1) "incomplete colonoscopy" and 2) "conversion AND colorectal AND liver," both limited to English language, journal article, and date range of August 6, 2015, to April 4, 2021, and 3) "Oncotype DX OR coloprint OR ColDx OR ctDNA OR circulating tumor DNA AND colon cancer," limited to English language and journal article, with a date range of January 1, 2009, to June 27, 2021. An Embase query, inclusive of publication years 2017 to 2020, completed on December 2, 2020, with exclusion of titles also included in Medline/PubMed, resulted in 241 unique titles that were screened and resulted in the inclusion of 10 additional titles for the qualitative synthesis phase of the literature review. An additional 35 titles were identified from embedded references. These searches yielded a total of 7958 unique citations. A professional medical librarian provided consultation for the literature searches. The citations were then reviewed by the authors who selected the citations that they considered to be most relevant to the Clinical Practice Guideline. After screening and secondary and tertiary reviews, a total of 1921 individual citations were selected for potential inclusion in the Clinical Practice Guidelines (Appendix 2, Supplemental Digital Content 2, http://links.lww.com/DCR/B799). 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. Ultimately, Ultimately, a total of 328 unique citations were included in the reference list. The final source material used was evaluated for 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 2).[11] When agreement was incomplete regarding the evidence base or treatment guideline, consensus from the committee chair, vice chair, and two assigned reviewers determined the outcome. Members of the 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. The manuscript was additionally reviewed and edited by two ad hoc committee members (M.R.W. and G.J.C.). The submission was then approved by the ASCRS executive council and peer-reviewed in *Diseases of the Colon and Rectum*. In general, each ASCRS Clinical Practice Guideline is updated approximately every five years. No funding was received for preparing this guideline, and the authors have declared no competing interests related to this material. This guideline conforms to the Appraisal of Guidelines for Research and Evaluation (AGREE) checklist.

EVALUATION AND RISK ASSESSMENT

1. **A cancer-specific history should be obtained including disease-specific symptoms, past medical and family history, physical examination, and perioperative medical risk. Routine laboratory values, including carcinoembryonic antigen (CEA) level, should be obtained. Grade of recommendation: strong recommendation based on moderate-quality evidence, 1B.**

Sporadic, familial (ie, no identifiable germ-line mutation), and hereditary (ie, Lynch syndrome, familial adenomatous polyposis, and *MYH*-associated polyposis) types of colorectal cancer account for approximately 65%, 30%, and <5% of new colorectal cancers in the United States, respectively.[12] The personal and family history should include documentation of premalignant lesions and cancers, age of diagnosis, and the lineage of affected first- and second-degree relatives. Patients should be asked about known hereditary cancer predisposition syndromes, previous genetic testing, and family ancestry/ethnicity that may be relevant.[13] Patients with findings suggestive of an inherited susceptibility should be referred for genetic counseling given that the results may impact surgical decision-making. Among colon cancer patients younger than 50 years, up to one-third may carry a germline mutation associated with colon cancer; these patients often do

TABLE 1. What Is New in the 2021 ASCRS Colon Cancer Clinical Practice Guidelines

2021 New Recommendations	
Neoadjuvant therapy	#6. When neoadjuvant therapy is not included in the treatment plan, curative intent colectomy should be performed without unneeded delay. Grade of recommendation: strong recommendation based on low quality evidence, 1C.
Neoadjuvant therapy	#12. In patients with locally advanced colon cancer, neoadjuvant chemotherapy or radiotherapy can result in tumor regression and may facilitate margin-negative excision of locally advanced cancers. Grade of recommendation: weak recommendations based on moderate-quality evidence, 2B
Multidisciplinary discussion	#21. The treatment of patients with resectable stage IV colon cancer should be individualized and based on a comprehensive multidisciplinary discussion. Grade of recommendation: strong recommendation based on moderate quality evidence, 1B.
Resectable liver metastasis	#22. Patients with initially resectable colon cancer liver metastasis, an individualized decision on neoadjuvant chemotherapy followed by surgical resection or up-front surgery. Grade of recommendation: weak recommendation based on moderate-quality evidence, 2B.
Unresectable liver metastasis	#23. Patients with initially unresectable colon cancer liver metastasis should be considered for neoadjuvant chemotherapy to attempt to convert to resectability. Grade of recommendation: strong recommendation based on moderate-quality evidence, 1B.
Hepatic artery infusion of chemotherapy	#24. Hepatic artery infusion of chemotherapy combined with systemic chemotherapy or immunotherapy may increase resectability of colon cancer liver metastasis, but should only be performed in centers with the appropriate expertise. Strong recommendation based on moderate-quality evidence, 1B.
Combined or staged liver resection	#25. In patients with colon cancer and resectable liver metastasis, a single "combined" operation is generally recommended for relatively low complexity operations and sequential or "staged" operations are generally recommended for higher complexity cases. Grade of recommendation: weak recommendation based on moderate quality evidence, 2B.
Lung metastasis	#26. In patients with resectable colon cancer lung metastasis, resection of the lung lesions should be considered as it may prolong survival. Weak recommendation based on moderate-quality evidence, 2B.
Mismatch repair	#32. In patients with stage IV (dMMR or MSI-H colon cancer, immunotherapy with antibody to PD-L1 or PD-1 should be considered. Strong recommendation based on high quality evidence, 1A
Timing of adjuvant chemotherapy	#33. In general, and if possible, adjuvant chemotherapy should be started within 8 weeks of colon resection. Grade of recommendation: strong recommendation based on moderate quality evidence, 1B
Multigene assays	#34. The use of multigene assays, CDX2 expression analysis, and ctDNA may be used to complement multidisciplinary decision-making for patients with stage II or III colon cancer. Grade of recommendation: strong recommendation based on moderate-quality evidence, 1B.
2021 Updated Recommendations	
PET/CT	#4. PET/CT is generally not recommended for routine colon cancer staging but may be useful in surgical decision-making for patients with stage IV disease. Grade of recommendation: strong recommendation based on moderate-quality evidence, 1B.
T4b cancers	#10. For resectable colon cancers that adhere to or invade adjacent organs and are being treated with curative intent, complete and en bloc resection with negative margins is recommended. Grade of recommendation: strong recommendation based on moderate-quality evidence, 1B.
Oophorectomy	#11. Oophorectomy is typically advised for grossly abnormal ovaries or contiguous extension of colon cancer, but routine prophylactic oophorectomy is not recommended. Grade of recommendation: strong recommendation based on low-quality evidence, 1C.
Malignant polyp	#15. For patients with a "malignant polyp," either endoscopic excision or oncological resection may be appropriate, and is dependent largely on polyp histopathological features and completeness of excision. Grade of recommendation: strong recommendation based on moderate quality evidence, 1B.
Obstructing left-side colon cancer	#17. For patients with obstructing left-sided colon cancer and curable disease, endoscopic stent decompression, or diverting colostomy, with interval colectomy, are generally preferable to emergent colectomy. Grade of recommendation: strong recommendation based on moderate quality evidence, 1B.
Cancer perforation	#18. In the setting of perforation or impending perforation of the colon, resection following established oncological principles with a low threshold for performing a staged procedure is recommended when feasible. Grade of recommendation: strong recommendation based on low-quality evidence, 1C.
Cytoreductive surgery	#27. In patients with resectable colorectal cancer peritoneal metastases, cytoreductive surgery with or without intraperitoneal chemotherapy should be considered as part of a multimodality treatment plan. Strong recommendation based on moderate quality evidence, 1B.
Stage IV with asymptomatic primary tumor	#28. In patients with incurable stage IV colon cancer and an asymptomatic primary colon cancer, systemic chemotherapy is recommended as the initial treatment. Grade of recommendation: strong recommendation based on moderate quality evidence, 1B.
Obstructing colon cancer in palliative setting	#29. In patients with an obstructing colon cancer and incurable metastatic disease, or in other scenarios in which palliation is preferred over an attempt at cure, endoscopic stent placement or fecal diversion is preferable to colectomy when life expectancy is <1 year. Grade of recommendation: strong recommendation based on moderate-quality evidence, 1B
Stage II and adjuvant chemotherapy	#30. In patients with microsatellite stable/mismatch repair proficient stage II colon cancer and obstruction, or perforation, or <12 lymph nodes in the resection specimen, or poor differentiation, or lymphovascular invasion, or perineural invasion, or high-level tumor budding, adjuvant chemotherapy may offer a survival benefit. Weak recommendation based on moderate quality evidence, 2B

(*Continued*)

TABLE 1. What Is New in the 2021 ASCRS Colon Cancer Clinical Practice Guidelines (*Continued*)

2017 Recommendations Excluded	
Sentinel lymph nodes	SLN mapping for colon cancer does not replace standard lymphadenectomy. Grade of recommendation: strong recommendation based on moderate-quality evidence, 1B. A recommendation on this technique was excluded as its use has not been broadly adopted for clinical practice.
Minimally invasive surgery	Hand-assisted laparoscopic and robotic surgical techniques for right colon cancer result in oncological outcomes that are equivalent to open or straight laparoscopic techniques. Strong recommendation based on moderate-quality evidence, 1B. In 2021, hand-assisted laparoscopic and robotic colectomy techniques were included in recommendation #13: 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.

ctDNA = circulating tumor DNA; dMMR = mismatch repair deficient; MSI-H = microsatellite high; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death-ligand 1; PET = positron emission tomography; SLN = sentinel lymph node

TABLE 2. The GRADE System - Grading Recommendations

	Description	*Benefit vs risk and burdens*	*Methodologic 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, methodologic 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, methodologic 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.[11] Used with permission.

not have a clinical history that is typically associated with an identified hereditary cancer syndrome, supporting the recommendation that germline testing should be strongly considered for all young-onset colon cancer patients.[14] Guidelines on the management of patients with inherited colorectal cancer have been previously published by the society.[6,7] In keeping with the National Cooperative Cancer Network (NCCN) guidelines, all newly diagnosed colon cancers should be evaluated for microsatellite instability (MSI) or mismatch repair protein (MMR) expression.[15]

Colon cancer may be asymptomatic or heralded by symptoms of fatigue, blood in the stool, abdominal pain, changes in bowel habits, or obstructive symptoms. Recent retrospective, single-institution, American studies have reported that more than 75% of colon cancer diagnoses occurred after development of symptoms, and symptomatic cancers were associated with more advanced disease compared with cancers that were identified during screening colonoscopy.[16,17] Similar results, with nearly 70% of newly diagnosed cancers presenting with symptoms, were reported in a 2016 German population-based study.[18]

Patients' medical fitness and nutritional status should be assessed to guide perioperative management and identify opportunities for optimization before surgery. Inquiry about alcohol consumption and smoking is also advised, as these habits have been shown to both increase the risk of developing colorectal cancer and also the risk of postoperative complications.[19–22] Early mortality is infrequent among resected colon cancer patients but is more prevalent among patients with advanced age and an Eastern Cooperative Oncology Group performance status ≥2.[23,24] Frail patients may benefit from preoperative,

multimodality optimization (ie, prehabilitation), although the beneficial effect on postoperative complications and survival has not been firmly established.[25,26]

Physical examination should include assessment for an abdominal mass or surgical scars, which may influence diagnostic and treatment-related decisions. Routine serum laboratory evaluation should include a complete blood count, liver function tests, and a chemistry panel. A carcinoembryonic antigen (CEA) level should be obtained before elective surgery for colon cancer to establish a baseline value that is prognostic for recurrence and survival, and to provide a reference value for use during surveillance.[27] A multivariate analysis of more than 130,000 patients included in the National Cancer Database indicated that preoperative CEA is an independent predictor of overall survival in patients with stage I to III colon cancer.[28] Patients with an elevated CEA had a 62% increase in the hazard of death compared with patients with a normal preoperative CEA. Although preoperative CEA level is an independent prognostic factor, the optimal cutoff value to best determine prognostic significance is not clear.[29–32] In stage IV colorectal cancer, a decrease in CEA in response to treatment with chemotherapy has been associated with improved survival.[33]

2. Before colectomy, histologic confirmation of invasive adenocarcinoma should be established and, when feasible, the entire colorectal mucosa should be evaluated for synchronous pathology. 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 benign processes such as diverticulitis or inflammatory bowel disease may appear grossly similar to the endoscopic or radiographic appearance of colon cancer. Colonoscopy is the preferred evaluation method under these circumstances because it offers a therapeutic opportunity to treat synchronous polyps. Endoscopic biopsy may be nondiagnostic or incongruent with the clinical impression of invasive adenocarcinoma due to sampling error, in which case repeat endoscopic biopsy may be performed in the appropriate clinical circumstance. Lesions concerning for malignancy, but without histologic confirmation (eg, possible sampling error), that are not amenable to endoscopic removal warrant oncological resection. When feasible, a complete evaluation of the colorectal mucosa is advised before surgery to detect synchronous cancers, which are reported to be present in 4% of patients with stages I to III sporadic colon cancer.[34] Complete examination of the colorectal mucosa can also identify synchronous adenomas that are present in 30% to 50% of patients.[35,36] Endoscopic tattooing with documentation of tattoo location (ie, distal or proximal to the tumor) should be performed routinely to facilitate intraoperative localization.

In patients with a proximal cancer that cannot be passed with a colonoscope in whom an oncological resection would include the entire proximal colon (eg, obstructing distal ascending colon cancer), there is generally no need to examine the more proximal colon before colectomy. Alternatively, for patients with an endoscopically obstructing distal colon cancer (eg, sigmoid colon cancer) in whom oncological resection would spare the proximal colon, CT colonography or Fluro-2-deoxy-d-glucose positron emission tomography/computed tomography (FDG PET/CT) may be helpful. CT colonography is highly accurate for detecting synchronous advanced neoplasia (ie, high-grade or large adenoma or cancer) has a sensitivity of 94%, and is reported to affect the surgical plan in 2% to 21% of patients.[37–39] FDG PET/CT may also be sufficient to exclude proximal synchronous neoplasia, with a negative predictive value for advanced adenoma and colon cancer of 93% and 100%, respectively.[40] Alternatively, intraoperative colonoscopy to detect synchronous lesions is feasible and safe after resection of the tumor and restoration of intestinal continuity or creation of a colostomy.[41–43] Postoperative colonoscopy is another option for patients in whom preoperative or intraoperative evaluation of the colon was not possible or adequate.[44] Contrast enema studies have a relatively low yield for the detection colorectal mucosal pathology and therefore are generally not recommended.[45]

STAGING OF COLON CANCER

3. CT of the chest, abdomen, and pelvis with oral and intravenous contrast or noncontrast CT of the chest and abdominal MRI are recommended for colon cancer staging. Grade of recommendation: strong recommendation based on moderate-quality evidence, 1B.

CT scan of the chest, abdomen, and pelvis with intravenous iodinated and oral contrast is recommended before the elective surgical resection of colon cancer.[15,46] Preoperative CT imaging permits the detection of synchronous metastases, which often requires a change in the treatment strategy and may also alter the operative plan. While the yield of chest CT in detecting colorectal cancer lung metastasis is low (6%–8%), its superiority to standard chest x-ray and ability to detect indeterminate lesions that may demonstrate malignant progression on serial examinations support its use under these circumstances.[47–50] In patients with an allergy or other contraindication to the use of iodine contrast dye, a PET/CT or noncontrast chest CT with an MRI of the abdomen and pelvis are recommended alternatives.[51,52] Indeterminate liver lesions identified on CT should generally be further investigated by MRI with diffusion-weighted imaging.[46,53–56]

4. Positron emission tomography (PET)/CT is generally not recommended for routine colon cancer staging, but may be useful in surgical decision-making for patients with stage IV disease. Grade of recommendation: strong recommendation based on moderate-quality evidence, 1B.

Prospective studies have not demonstrated superiority of PET/CT over standard intravenous contrast-enhanced CT in the detection of colorectal liver or peritoneal metastasis.[51,57,58] At present, it is not clear if PET/CT offers an advantage to contrast-enhanced CT for the detection of colon cancer lung metastasis.[59] Both the National Cooperative Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) do not recommend PET/CT in the initial staging of colorectal cancer.[15,46] On the contrary, PET/CT may be recommended for patients with known metastatic colon cancer who are being considered for curative resection as the identification of otherwise unrecognized metastatic disease may alter the treatment plan. A meta-analysis of 18 studies, including more than 1000 patients with hepatic colorectal metastases showed that PET or PET/CT findings led to a change in management in 24% of patients.[60] PET-CT may also be useful in the evaluation of patients with equivocal findings (eg, retroperitoneal lymphadenopathy) on CT or MRI.[52]

5. Colon cancer should typically be staged according to the American Joint Committee on Cancer, Tumor, Node, Metastasis (AJCC/TNM) system and should include an assessment of the completeness of surgical resection. Grade of recommendation: strong recommendation based on moderate-quality evidence, 1B.

The 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 TNM staging system and are included in Table 3. The current (8th) edition expanded the definition of metastatic disease to include the M1c category for peritoneal implants, clarified the definition of tumor deposits (N1c), and also highlighted the importance of lymphovascular and perineural invasion, microsatellite instability (MSI), tumor budding, and mutations in KRAS, NRAS, and BRAF in treatment considerations.[61] 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.[62–64]

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, particularly poor cellular differentiation, has been shown to be a predictor of outcome and is an important consideration for some treatment recommendations.[65] The absence or presence of residual tumor after resection is designated by the terms indeterminate (ie, margin of excision cannot be assessed), negative (ie, margin uninvolved with invasive adenocarcinoma) or positive (ie, invasive adenocarcinoma ≤1 mm from the excision margin) in accordance with the AJCC protocols for colorectal cancer pathology specimen processing.[66]

SURGICAL TREATMENT OF THE PRIMARY

6. When neoadjuvant therapy is not included in the treatment plan, curative intent colectomy should be performed without unneeded delay. Grade of recommendation: strong recommendation based on low quality evidence, 1C

The impact of the time interval from colon cancer diagnosis to curative intent surgery on oncological outcome remains unclear. While a recent retrospective analysis of Surveillance, Epidemiology, and End Results (SEER) and National Cancer Databases indicated that a delay in surgery of 3 to 6 weeks was associated with a decrease in overall survival, a Canadian population-based retrospective study and two recent single-center studies indicated that surgical delays of up to 12 weeks are not detrimental to disease-free or overall survival.[67–70] While a specific interval to surgery cannot be recommended with the available data, untreated cancer progresses over time, and as such, surgery should be completed without unneeded delay. Meanwhile, patients undergoing neoadjuvant therapy have a treatment timeline determined by the specifics of their care plan.

7. At the time of surgery, a thorough exploration should be performed and the findings should be documented in the operative report. Grade of recommendation: strong recommendation based on low-quality evidence, 1C.

The surgical exploration includes visual inspection and, when possible, during open surgery, palpation of the peritoneal cavity and the abdominal and pelvic organs to detect or rule out synchronous lesions, or more advanced malignant disease (eg, peritoneal metastasis or adjacent organ involvement). In the event that peritoneal metastases are incidentally discovered during exploration it is recommended that biopsies are obtained to confirm the diagnosis and that the extent and distribution of disease are determined and documented, ideally with use of the peritoneal cancer index.[71] In general, and in the absence of obstruction or perforation, both colectomy and cytoreductive surgery should be deferred until multidisciplinary discussion of treatment is completed and informed consent is obtained from the patient.[72]

The operative report should include a description of the relevant preoperative 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, severity of adhesions, occurrence and repair of unintended bowel injuries, extent of bowel and mesenteric resection, level of feeding vessel ligation, anastomotic

TABLE 3. The American Joint Committee on Cancer, Colorectal Cancer Staging System

Definition of primary tumor (T)

T category	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	One to three 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	One regional lymph node is positive
N1b	Two to three 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	Four or more regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive

Distant metastasis staging (M)

M0	No distant metastasis
M1a	Metastasis confined to one organ or site is identified without peritoneal metastasis
M1b	Metastasis confined to two 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; RCT = randomized controlled trial

technique, en bloc resection of contiguously involved organs, and an intraoperative assessment of the completeness of resection including margin status. Synoptic operative reports have been shown to improve the documentation of key surgical factors and are currently being developed by the American College of Surgeons Commission on Cancer.[73,74]

8. The extent of resection of the colon should correspond to the lymphovascular drainage of the colon cancer. Grade of recommendation: strong recommendation based on moderate-quality evidence, 1B.

The extent of a curative resection for colon cancer depends on the site of the primary lesion and its lymphovascular drainage. In the absence of synchronous pathology, a

colon resection for cancer should generally include proximal and distal longitudinal margins of 5 to 7 cm to ensure adequate removal of at risk pericolic lymph nodes.[75,76] In addition, the mesentery to the tumor-bearing segment of bowel should be removed up to the origin of the named primary feeding vessel(s) to enable removal of the draining intermediate and central lymph nodes.[77,78] For example, as long as there is no clinical lymphadenopathy outside of the standard field of resection, with a right-sided colon cancer, the ileocolic pedicle and right branch of the middle colic artery are divided at their origins. For a sigmoid colon cancer, the superior rectal artery and left colic artery are divided at their origins, and the inferior mesenteric vein is divided near the inferior edge of the pancreas. The resection should be performed with preservation of the integrity of the colonic mesentery[79,80] As 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.[81–84] It is recommended that at least 12 lymph nodes be evaluated to confidently assign an N0 stage, and the examination of fewer than 12 lymph nodes is a high-risk feature for stage II colon cancer.[85,86] 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 the guidelines set forth by the College of American Pathologists.[66,87]

Cancers of the transverse colon and splenic flexure deserve specific consideration regarding the extent of resection and what constitutes an appropriate lymphadenectomy. While a 2019 meta-analysis of patients with transverse colon cancer indicated that transverse colectomy and extended right or left colectomy resulted in comparable short- and long-term outcomes, a 2020 Italian national study concluded that, compared with patients undergoing extended resections, segmental resection patients had fewer postoperative complications, including anastomotic leak (2% vs 4%, $p < 0.05$) and improved three-year disease-free survival (86% vs 78% ($p < 0.05$)).[88,89] In a 2021 NCDB study of stages I to III transverse colon cancer, unadjusted five-year survival was similar for extended and segmental resection (40.7% vs 41.3%, $p = 0.34$), but after adjusting for covariates, extended colectomy for transverse colon cancer was associated with lower survival (HR 1.07; 95% CI 1.04–1.10; $p < 0.001$).[90] With this inconsistency in the reported data, an individual determination of resection extent based upon careful inspection of the tumor and its feeding vessel(s) and consideration of the functional outcomes related to each resection type is recommended.

Cancers of the splenic flexure usually metastasize to lymph nodes along the left colic pedicle.[91,92] However, positive lymph nodes have also been identified along the superior mesenteric artery and its tributaries, including the middle colic, right colic, and ileocolic arteries at a rate of up to 9%.[93] Despite this observation, retrospective studies and a meta-analysis suggest segmental resections are a reasonable alternative to extended colectomy under these circumstances.[90,94–96]

9. Routine extended lymphadenectomy is not recommended. Grade of recommendation: weak recommendation based on moderate-quality evidence, 2B.

Lymph node metastasis outside the standard field of resection (ie, at the level of the D3 lymph nodes) occurs in 3% to 11% of colon cancers and is more likely with advanced T-stage cancers.[97–100] Central lymph node involvement in the absence of pericolic or intermediate lymph node involvement ("skip metastases") occurs in 0% to 4% of cases.[101,102] Extended lymphadenetomy, which may be termed "central vascular ligation," or "D3 resection," refers to lymph node retrieval proximal to the primary feeding vessel and the associated central (D2) lymph node basin. This dissection retrieves lymphatic tissue along the superior mesenteric artery and vein during right colon cancer resection and at the origin of the inferior mesenteric artery for sigmoid cancer colectomy. In contrast, the term "complete mesocolic excision" refers to the completeness of the mesocolic envelop within a colon cancer resection specimen, and does not designate a particular level of vascular ligation.[103]

While extended lymphadenectomy has been shown to result in higher lymph node yields and potentially improved N-staging, it has also been associated with increased operative and postoperative complications.[97,104–107] Recent observational studies and a meta-analysis suggest that extended lymphadenectomy is associated with decreased rates of cancer recurrence and improved recurrence-free survival.[108–110] On the contrary, other studies, including a systematic review, have shown no survival benefit with extended lymphadenectomy.[104,106,111,112] With the equipoise in the current literature, further studies are needed before a strong recommendation on routine extended lymphadenectomy may be offered. Rather, as central/D3 lymph node positivity is associated with decreased recurrence-free survival, selective dissection and retrieval, including harvesting of clinically positive or suspicious lymph nodes outside the standard field of resection, is recommended.[113]

10. For resectable colon cancers that adhere to or invade adjacent organs and are being treated with curative intent, complete and en bloc resection with negative margins is recommended. 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.[114–117] Adhesions between a colon cancer and surrounding organs should not be divided as they have been shown to harbor malignant cells in 34% to 84% of patients.[114,118,119]

The importance of a margin-negative resection was underscored in three 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.[120–122] Available diagnostic modalities (eg, CT or MRI) can identify adjacent organ involvement before surgical exploration and facilitate operative planning and assembly of a multispecialty surgical team, as needed.[123] With appropriate experience, both laparoscopic and robotic approaches appear appropriate for en bloc resection.[124–129]

11. Oophorectomy is typically advised for grossly abnormal ovaries or contiguous extension of colon cancer, but routine prophylactic oophorectomy is not recommended. Grade of recommendation: strong recommendation based on low-quality evidence, 1C.

In patients with apparent direct colon cancer extension involving an ovary, en bloc oophorectomy should typically be performed as part of a curative-intent resection. In patients with suspected or known metastatic disease involving an ovary, oophorectomy has been associated with a survival benefit in retrospective series of selected patients.[130] In these situations, bilateral oophorectomy should typically be performed even if one ovary appears grossly normal.[130–132] In patients with grossly normal-appearing ovaries, the data do not support routine prophylactic oophorectomy at the time of colorectal cancer resection.[133] However, prophylactic oophorectomy should be considered in women with colon cancer with an inherited risk for developing ovarian cancer and in postmenopausal women desiring risk reduction. In breast cancer susceptibility gene 1 or 2 (BRCA1 or BRCA2) carriers, oophorectomy has been associated with an 80% reduction in the risk of ovarian, fallopian tube, or peritoneal cancer and a 77% reduction in all-cause mortality.[134]

12. In patients with locally advanced colon cancer, neoadjuvant chemotherapy or radiotherapy can result in tumor regression and may facilitate margin-negative excision of locally advanced cancers. Grade of recommendation: weak recommendations based on moderate-quality evidence, 2B.

Neoadjuvant chemotherapy and/or radiotherapy may be considered to facilitate complete excision of locally advanced colon cancers.[135–139] The current NCCN guidelines include a recommendation to consider neoadjuvant oxaliplatin-based chemotherapy for patients with "bulky nodal disease or clinical T4b" colon cancer.[15] In a 2020 systematic review of six studies, neoadjuvant chemotherapy resulted in tumor volume reduction in two-thirds of patients and major pathological tumor regression in 4% to 37% of patients, improved three-year disease-free survival in responders compared with nonresponders (94% vs 63%, $p = 0.005$), and a 23% lower rate of death at three years in matched patients with cT4b tumors who received neoadjuvant compared with adjuvant chemotherapy (HR 0.77, 95% CI 0.6–0.98; $p = 0.04$) but no benefit for cT3 or cT4a tumors.[140]

The FOxTROT trial, a prospective study from the United Kingdom, randomized 1053 subjects with cT3-4N0-3M0 colon cancer to receive either oxaliplatin-based adjuvant chemotherapy (12 cycles) or neoadjuvant therapy (3 cycles) followed by surgery and adjuvant chemotherapy (9 cycles).[137] Provisional results, published in abstract form, indicated no differences between groups in postoperative morbidity or mortality. Patients treated with neoadjuvant chemotherapy had significant T and N stage downstaging ($p < 0.001$), a pathological complete response rate of 3.8%, and a trend toward less recurrent or persistent disease at two years (14.0% *vs* 17.5%).[141] Publication of the full manuscript with longer follow-up may strengthen or change our recommendation.

The PRODIGE 22 trial, a French multicenter collaboration, included 104 patients with cT3-4 and/or N2 colon cancers randomized to curative resection followed by adjuvant chemotherapy (12 cycles) or neoadjuvant chemotherapy (four cycles) followed by surgery and then adjuvant chemotherapy (eight cycles).[142] Subjects in the neoadjuvant arm were more likely to achieve tumor regression grades 1-2 (44% vs 8%, $p < 0.001$) and had a significantly increased rate of pTNM downstaging. However, there were no differences in three-year overall survival (90.3% vs 90.4%) or three-year disease-free survival (76.8% vs 69.2%) in the neoadjuvant and adjuvant-only arms, respectively. A limitation of PRODIGE 22 was clinical overstaging in one-third of patients in the adjuvant therapy (control) arm, indicating that overtreatment may have occurred in the neoadjuvant (experimental) arm of the study

While both FOxTROT and PRODIGE 22 did not show a survival advantage with neoadjuvant chemotherapy, a 2018 retrospective analysis of the National Cancer Database (NCDB) found a three-year overall survival advantage (74% vs 66%, $p = 0.002$) among patients with cT4b colon cancers treated with neoadjuvant compared with adjuvant chemotherapy.[143] After propensity score matching, the improvement in overall survival among patients with clinical cT4b cancers was 23% higher in the neoadjuvant group (HR 0.77, 95% CI 0.60–0.98, $p = 0.004$). There were no survival advantages among the NCDB patients with cT3 or cT4a cancers related to the use of neoadjuvant therapy.

Neoadjuvant radiation therapy is not widely used; however, both a single-center study and a National Cancer Database study concluded that neoadjuvant radiation for cT4 disease may be associated with tumor downstaging, superior R0 resection rates, and improved overall survival.[138,139] In these complex scenarios, multidisciplinary decision-making is recommended.

13. Synchronous colon cancers may be treated by two segmental resections or subtotal colectomy. Grade of recommendation: strong recommendation based on moderate-quality evidence, 1B.

The term synchronous colon cancer is used to describe situations in which a second primary colon cancer is diagnosed at the same time, or up to 12 months after, as detection of the index colon cancer.[144] Synchronous cancers have been reported to occur in 4% to 5% of patients and have been associated with decreased overall survival.[34,145] Synchronous cancers in the same segment of the colon are removed with a segmental colectomy, whereas synchronous cancers in separate segments of the colon may be treated with an extended resection or two segmental resections.[146] Whereas extended resections do not incur increased surgical morbidity and have not been associated with a survival benefit, the functional outcomes associated with this approach may diminish the subsequent quality of life.[34,147]

When colon cancer is associated with an underlying colonic disease (eg, chronic ulcerative colitis or hereditary nonpolyposis colorectal cancer syndrome), the extent of resection should consider the underlying disorder. These considerations are beyond the scope of this Clinical Practice Guideline and are discussed in other Clinical Practice Guidelines.[7,148]

14. 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.

Minimally invasive surgical (MIS) approaches for colon cancer surgery include multiport, single-port, and hand-assisted laparoscopy and robotic techniques. Although certain lesions may not be amenable to a minimally invasive approach because of various factors (ie, large size or adjacent organ invasion), in most circumstances, MIS is preferred given appropriate expertise and experience. Most important, MIS procedures should achieve the same goals as open surgery; when this is not possible, conversion to open surgery is recommended. Several large multi-institutional randomized trials with experienced surgeons in the United States and internationally have demonstrated equivalent oncological outcomes with decreased length of hospital stay and other short-term outcome improvements with multiport laparoscopy compared with open surgical resection of localized colon cancer.[149–153] Although transverse colon cancers were excluded from the sentinel trials that compared laparoscopic and open colectomy for colon cancer, more recent nonrandomized data and meta-analyses indicate oncological equivalence and improved short-term outcomes with a laparoscopic technique in this setting.[154–157]

Observational studies and a meta-analysis of single-port laparoscopic surgery demonstrate equivalent surgical and oncological results as multiport laparoscopy.[158–161] In addition, two randomized controlled trials of 195 and 200 patients comparing single-port versus multiport laparoscopic surgery found no differences in operative times, number of harvested lymph nodes, lengths of resection margins or postoperative complications.[162,163]

Randomized controlled trials of hand-assisted laparoscopic surgery (HALS) versus open or conventional laparoscopic right colectomy for cancer indicate similar short-term outcomes for the laparoscopic and HALS techniques, less pain and faster recovery with hand-assisted laparoscopy compared with open surgery, and no differences in the long-term oncological outcomes.[164,165] A randomized controlled 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.[166] While numerous reports support HALS and robotic surgery for right colectomy, there remains insufficient evidence to allow meaningful recommendations for left-sided colon cancer resections using these techniques. However, as long as operations are performed according to the principals of colon cancer surgery, it is reasonable to conclude that left-sided colectomies are also suitable for a HALS or robotic approach.

15. For patients with a "malignant polyp," either endoscopic excision or oncological resection may be appropriate depending largely on polyp histopathological features and completeness of excision. Grade of recommendation: strong recommendation based on moderate-quality evidence, 1B.

Patients with a malignant polyp, a T1 cancer arising in an adenomatous polyp,[55] may be adequately treated by endoscopic excision or may require oncological colon resection. Conventional colonoscopic polypectomy techniques, endoscopic mucosal resection, endoscopic submucosal dissection, or combined endoscopic and laparoscopic surgery techniques have all been used safely and successfully to avoid colectomy in patients with low-risk malignant colon polyps.[167–171] An initial attempt at non-piecemeal complete endoscopic excision is typically warranted in selected patients as this will be curative in >80% of patients.[172–174] Polypectomy excision margin, depth of submucosal (SM) invasion of cancer cells, degree of cellular differentiation, lymphovascular and perineural invasion (LVI and PNI), and amount of tumor budding are the histopathological factors that require consideration when endoscopic excision or colectomy is being considered.

The definition of a negative polypectomy excision margin is a point of debate, with earlier reports indicating the need for a ≥2 mm margin.[175] A 2012 USA single-center review of 143 patients with a malignant polyp who underwent endoscopic excision and subsequent colectomy

found residual cancer at the polypectomy site or regional lymph nodes in 0%, 9%, 16% and 5%, 21% and 7% of patients with polypectomy excision margins of ≥1mm, <1mm, or indeterminate.[172] A 2013 analysis of the north of England NORCCAG (NORthern Colorectal Cancer Audit Group) database found malignant polyp excision margins of 0 and >0 mm resulted in residual cancer at the polypectomy site or regional lymph nodes in 34% and 5% of patients, respectively.[173] In a 2018 Scottish national study, patients with complete polyp excision were subsequently found to have residual cancer at the polypectomy site or regional lymph nodes in 7% and 7%, respectively, whereas, in patients with incomplete polyp excision, residual cancer at the polypectomy site or regional lymph nodes occurred in 29% and 9%. This Scottish study also showed that a polyp excision margin of ≥1 mm did not reduce the risk of residual cancer after polypectomy when compared with a negative margin of ≥0 mm.[174]

Submucosal invasion depth is an important prognostic factor for malignant polyps. This depth may be stratified as superficial, intermediate, or deep invasion (ie, SM 1, 2, or 3) or by the measured depth into the submucosa (eg, <500, 500–1000, or >1000 μm).[176,177] In a 2013 systematic review, SM 1, 2, and 3 invasion were associated with lymph node metastasis in 3.4%, 8.5%, and 22.6% of patients, respectively.[178] Additional studies, cited above, add further support to the poor prognostic value of SM3/>1000 μm invasion depth and may be used to support oncological resection when present. The Haggitt classification may also be used to stratify risk for lymph node metastasis or other adverse outcomes related to a malignant polyp. As Haggitt reported in 1985, when malignant invasion was limited to the head, neck, or stalk (ie, level 1, 2, or 3) of a pedunculated polyp, there were no lymph node metastases and only one of 101 patients (1%) died with colorectal cancer.[179] As a result, it is generally accepted that complete excision of a pedunculated malignant polyp with level 1-3 invasion is adequate, providing that no other adverse factors (eg, LVI, poor differentiation, etc). Alternatively, for patients with Haggitt level 4 invasion, defined as cancer cells in the submucosa at the base of a pedunculated or sessile polyp, seven of 28 (25%) of Haggitt patients were diagnosed with lymph node or systemic metastasis. Subsequent studies noted lymph node metastasis in as many as 13% of patients with "level 4" malignant polyps, which supported the idea that colectomy was required in these patients.[180,181] However, we now know that SM depth and Haggitt level are only two of many variables that should be considered when a malignant polyp is categorized as low or high risk and when endoscopic excision or oncological resection is appropriate.

A 2013 systematic review and meta-analysis of patients with pT1 colorectal cancer who underwent oncological resection revealed that 11% overall had lymph node involvement and that LVI, submucosal invasion depth ≥1 mm, poorly differentiated cancer, and tumor budding were associated with lymph node metastasis in 22%, 12%, 24%, and 21% of cases, respectively.[178]

A low-risk malignant pedunculated or sessile polyp may be defined as one with well- or moderately differentiated cancer, no LVI or PNI, no or low tumor budding, a negative resection margin, and <1 mm submucosal invasion depth. Endoscopic endoscopic excision is generally considered definitive treatment for these malignant polyps as the risk of residual disease in the colon wall or cancerous lymph nodes is negligible. Alternatively, when a sessile or pedunculated malignant polyp contains a poorly differentiated cancer, a positive or indeterminate margin, or >1 mm depth of submucosal invasion, segmental oncological resection is generally warranted, as the risk of recurrence in the colon wall or regional lymph node involvement is unacceptably high.[171,172,174,182–184]

COLON CANCER-RELATED EMERGENCIES

Approximately 20% of patients with colon tumors present with surgical emergencies such as bleeding, perforation, or obstruction.[185] The goals of treatment in these situations are to: 1) avert the immediate negative impacts of the complication (eg, death or sepsis), 2) achieve the best possible tumor control, and 3) ensure timely recovery to permit initiation of appropriate systemic treatment, as needed.

16. For patients with obstructing left-sided colon cancer and curable disease, the choice of endoscopic stent decompression, diverting colostomy with interval colectomy, or initial treatment with oncological segmental colectomy should be individualized based upon patient factors and local expertise of the institution. grade of recommendation: strong recommendation based on moderate-quality evidence, 1B.

A 2020 systematic review and meta-analysis of 27 studies and nearly 4000 patients, the majority of whom had an obstructing left-sided colon cancer, indicated that initial stenting in curative cases resulted in more frequent use of a primary anastomosis, decreased morbidity and 30-day mortality, and no significant differences in three- or five- disease-free years or overall survival.[186] A 2017 meta-analysis of eight randomized controlled trials comparing stenting as a bridge to surgery with emergency resection limited to left-sided cancers demonstrated a 60-day mortality of 9.6% and 9.9% ($p > 0.05$), 60-day morbidity of 34% and 51% ($p = 0.02$), a temporary ostomy rate of 34% and 51% ($p < 0.001$), and primary anastomosis rates of 70% and 54% ($p = 0.04$), respectively.[187] Further, in this 2017 analysis, the emergency resection group required a permanent ostomy more frequently (35% vs 22%). Notwithstanding these data, initial treatment of these patients with oncological segmental resection may be appropriate for select

patients in whom the risks of a nondiverted anastomosis are low or when a temporary diverting ileostomy is acceptable to both the patient and surgeon.

While successful stent placement has been reported in 77% to 81% of patients, stenting carries a perforation rate of 2% to 9%. Patients who develop a perforation related to stenting are at increased risk of locoregional cancer recurrence.[188–191]

A diverting colostomy may be an alternative to stenting for patients with an obstructing left-side colon cancer. In recent Dutch national population-based cohort studies of matched patients with obstructing left-side colon cancer who underwent initial diverting ostomy or initial endoscopic stent decompression, the patients who were initially treated with a diverting stoma were more likely to undergo subsequent laparoscopic resection of the obstructed colon segment (57% vs 9%, $p < 0.001$), had more primary anastomoses (88% vs 41%, $p < 0.001$), reduced 90-day mortality (1.7% vs 7.2%, $p = 0.03$), a significant improvement in three-year overall survival (79% vs 73% (95% CI 0.20–0.65)) and fewer permanent stomas (22% vs 42%, $p < 0.0010$).[192,193]

Ultimately, the condition of the patient, surgeon experience, available endoscopic expertise, and informed decision-making by the patient should all be considered to select the optimal treatment option for each patient who presents with an obstructing left-side colon cancer.

17. For patients with obstructing right or transverse colon cancer and curable disease, initial colectomy or initial endoscopic stent decompression with subsequent 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, oncological segmental resection with ileocolic anastomosis can be safely performed in most cases.[194] 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.

While most studies evaluating stenting as a bridge to surgery (SBTS) have focused on left-sided obstructions, recent retrospective studies demonstrate that selected patients with right-sided lesions can be safely and effectively stented. Successful right-sided stent placement has been reported in 87% to 96% of cases.[195,196] In a Japanese national database study of 1500 matched patients who underwent emergent right colectomy or SBTS, the SBTS group utilized laparoscopy more often (50% vs 25%, $p < 0.001$), had fewer stomas created (1.7% vs 5.1%, $p < 0.001$), and had decreased length of stay (13 vs15 days, $p < 0.001$).[197] A 2020 systematic review and meta-analysis of emergent colectomy or SBTS for obstructing right-sided colon cancer demonstrated similar five-year disease-free and overall survival between the treatment groups.[198]

nonsurgical methods fail to control bleeding from a colon cancer, surgical intervention is generally required. Under these circumstances, an oncological resection is recommended, when it can be safely performed, in keeping with established surgical principles.

MANAGEMENT OF LOCOREGIONAL RECURRENCE

20. Treatment options for patients with local or local-regional recurrence of colon cancer should be considered in a multidisciplinary setting. Grade of recommendation: strong recommendation based on moderate-quality evidence, 1B.

The true incidences of local and local-regional recurrence (LRR) for colon cancer are difficult to determine as series often combine these outcomes with patients with distant disease and report on colon cancer patients together with rectal cancer patients. The most recent, robust studies report LRR in 4-7% of patients, half of whom have concurrent systemic disease. The median interval between initial resection and LRR is 18 to 24 months.[209–211] Risk factors for LRR include higher T and N stages, left-sided tumors, omission of chemotherapy, a positive surgical margin at the index operation, and lymphovascular invasion.[185,209,210] Asymptomatic LRRs may be heralded by an elevated CEA level or discovered on surveillance colonoscopy or computed tomography, while others present with symptoms of bleeding, pain, or obstruction.[212] LRRs may occur at the anastomosis, but more often occur outside the lumen and may adhere to adjacent organs.[213] In patients with LRR, CT, MRI, and FDG PET/CT are employed to determine disease extent and resectability.[46,55] When LRR occurs in isolation, or in the presence of resectable metastases, salvage surgery can be attempted with reasonable short and long-term outcomes. These outcomes vary based on disease burden and the ability to achieve an R0 resection, but are predictably better for patients with isolated anastomotic recurrences compared with patients requiring multivisceral resection or who have oligometastatic disease.[211,212,214]

A 2016 systematic review evaluated overall survival following resection of locally recurrent colon cancer. The review included data on 550 patients from eight retrospective cohort studies and one population-based registry.[212] More than half of patients had a multivisceral resection. Rerecurrence occurred in 41 of 188 patients (22%). The median overall survival for patients who underwent resection ranged from 14 to 42 months, the pooled overall five-year survival was 52%, and patients who had an R0 resection had the best outcomes. The postoperative morbidity rate ranged from 21% to 68%, but most complications were considered minor. Factors predictive of prolonged survival after resection for LRR included having an R0 resection, early stage of initial disease, no associated distant disease, and a single site of recurrence. Chemotherapy and radiotherapy were commonly employed in the included series, but the timing and specifics of therapy were variable.[212] One study included 15 selected patients with locally recurrent colon cancer adherent to other structures and used neoadjuvant chemoradiation to achieve an 87% R0 resection rate and a 100% three-year survival rate.[213] While another study identified preoperative chemotherapy or radiation as a predictor of having an R0 resection.[215] Intraoperative radiation therapy has also shown improved outcomes with low morbidity in small series with recurrent and locally advanced disease.[212]

MANAGEMENT OF STAGE IV COLON CANCER

A. Resectable or Potentially Resectable Stage IV Colon Cancer

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

When considering treatment for stage IV patients, it is important to distinguish between clearly resectable metastatic disease and disease that is potentially convertible to resectable if tumors regress after chemotherapy. Conversion to resectability has been described with standard chemotherapy regimens usually with the addition of bevacizumab or cetuximab.[216,217] When metastatic disease is considered resectable or potentially resectable, resection of the primary tumor should be considered as, in general, medically fit patients with resectable hepatic and/or pulmonary metastases will benefit from curative resection of the metastases.[218,219] The utilization of a multidisciplinary conference has been shown to increase the use of metastasectomy and increase survival in patients with stage IV colorectal cancer.[220,221]

22. Patients with initially resectable colon cancer liver metastasis can be treated with neoadjuvant chemotherapy followed by surgical resection or up-front surgery. Grade of recommendation: weak recommendation based on moderate-quality evidence, 2B.

The role of systemic chemotherapy in the setting of resectable liver metastases was addressed in EORTC 40983 in which patients with up to four resectable liver metastases were randomly assigned to either liver surgery alone (ie, no neoadjuvant or adjuvant chemotherapy) or to six cycles of neoadjuvant 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX), then metastasectomy, and then six cycles of adjuvant FOLFOX.[222] Complications of liver resection were increased in the chemotherapy arm (25% *vs* 16% ($p = 0.04$)). At three-year follow-up, there was a 7% better progression-free survival in the perioperative chemotherapy group compared with the surgery-alone group

(35% vs 28%, $p = 0.04$). At a median follow-up of 8.5 years (interquartile range 7.6–9.5), five-year overall survival did not significantly differ among treatment groups (51% for those who received perioperative chemotherapy and 48% among those who underwent surgery alone).[223] Due to the improvement in progression-free survival in the perioperative chemotherapy group, the EORTC investigators recommended this treatment paradigm. In the current NCCN guidelines, up-front surgery or neoadjuvant chemotherapy then surgery followed by adjuvant therapy are recommended approaches for patients with resectable synchronous or metachronous colon cancer liver metastasis.[15]

23. Patients with initially unresectable colon cancer liver metastasis should be considered for neoadjuvant chemotherapy to attempt to convert to resectability. Grade of recommendation: strong recommendation based on moderate-quality evidence, 1B.

A 2017 systematic review and meta-analysis of 11 studies demonstrated that oxaliplatin (FOLFOX) or irinotecan (FOLFIRI)-based neoadjuvant chemotherapy combined with bevacizumab effectively converted 39% (27–53%) of patients with initially unresectable colon cancer liver metastasis to resectable, and of these "converted" patients, an R0 resection was achieved in 28% (18–41%).[224] In the FIRE-3 trial, reported in 2018, patients with metastatic colorectal liver tumors were assessed before and after treatment with irinotecan-based chemotherapy (FOLFIRI) and bevacizumab or cetuximab (for KRAS wild-type cancers), and resectability increased from 22% to 53% ($p < 0.001$).[225] A 2020 systematic review of 20 trials has shown that neoadjuvant use of FOLFOX or FOLFIRI or a combination of 5-FU, oxaliplatin, and irinotecan (FOLFIRINOX) plus bevacizumab or cetuximab (for KRAS wild-type cancers) will result in an overall response rate of 55% to 85%, a conversion to resectability in 10% to 61%, and an RO-resection rate of as high as 54%.[226]

24. Hepatic artery infusion of chemotherapy combined with systemic chemotherapy or immunotherapy may increase resectability of colon cancer liver metastasis, but should only be performed in centers with the appropriate expertise. Grade of recommendation: strong recommendation based on moderate-quality evidence, 1B.

In the single-arm OPTILIV trial, of patients with KRAS wild-type unresectable colorectal liver metastases, hepatic artery infusion (HAI) of irinotecan, oxaliplatin, and 5-FU, plus systemic cetuximab, enabled R0 or R1 metastasectomy in 19 of 64 patients (29.7%). These 19 responders had a median overall survival, of 35 (33–38) months.[227] Two reports of a single phase 2 trial indicated that HAI of floxuridine, in combination with systemic oxaliplatin or irinotecan-based chemotherapy, with or without bevacizumab produced response rates of 76% and 73% and conversion to resectability in 47% and 52%.[228,229] In one of these reports, the patients who ultimately underwent resection had a three-year overall survival (OS) rate of 80%, which compared favorably with the 30% OS in patients who did not undergo resection.[228] In the other report, the five-year OS of resected patients was 63.3% (95% CI 43.6–77.7%) and 12.5% for unresected patients (95% CI 3.5–27.3%) ($p \leq 0.001$).[229] Notably, treament-related toxicity was high in these studies, as 77% of patients in the OPTILIV trial and 41% of the phase 2 trial patients whose regimen included bevacizumab had grade 3 or 4 toxicity (eg, neutropenia, abdominal pain, and diarrhea). Further, in the OPTILIV trial, major complications (eg, hepatic artery thrombosis or arteritis) led to interruption of HAI delivery in nearly one-half of the study patients.

25. In patients with colon cancer and resectable liver metastasis, a single "combined" operation is generally recommended for relatively low complexity operations and sequential or "staged" operations are generally recommended for higher complexity cases. Grade of recommendation: weak recommendation based on moderate-quality evidence, 2B.

Patients with resectable stage IV disease limited to the liver should undergo resection of both the primary tumor as well as the metastatic foci and the sequence of resection should be individualized for each patient, but it is important that the procedure be done in a center with the expertise to handle both the colon surgery and the liver resection. In 2003, a retrospective study by Martin and colleagues showed that combined resections (n=134) were less complex (ie, more right colectomies and smaller and fewer liver lesion) than the staged resections ($n = 106$) and had lower overall morbidity (49% *vs* 67%, $p<0.003$) and decreased total hospital stay (10 vs 18 days, $p < 0.001$).[230] A subsequent multicenter retrospective study by Reddy et al that included 475 staged and 135 combined colorectal and liver resections showed that the addition of a colorectal resection to a minor hepatectomy resulted in no increase in severe morbidity (12.5% vs 14.1%) but that the addition of a colorectal resection to a major hepatectomy resulted in an increase in severe morbidity compared with major liver resection alone (36.1% vs 15.1%, $p < 0.05$), and that major hepatectomy was a independent predictor of severe morbidity (HR 3.4, $p = 0.008$).[231] A 2015 NSQIP study provided evidence in favor of combined operations for relatively low-complexity operations and staged operations for more complex cases.[232] In this study, estimated cumulative postoperative morbidity ranged from as low as 25% for a low-risk colectomy (eg, right colectomy) combined with a low-risk hepatic resection (eg, left hepatectomy) to as high as 39% for a high-risk colectomy (eg, total abdominal colectomy) combined with high-risk hepatic resection (eg, right hepatectomy). Meanwhile, in another more recent retrospective study that included 145 simultaneous and 53 staged colorectal and liver resections, severe complications (Calvien-Dindo grade III-IV) occurred in 15% and 19% of patients ($p = 0.51$),

respectively. In a subgroup analysis, patients who underwent simultaneous or staged major hepatectomy, 63% and 56% experienced a postoperative complication of any grade ($p = 0.70$), including 23% and 18% that were severe (p value not provided), suggesting that simultaneous resections may be safe even for more complex cases when performed at centers with appropriate expertise.[233]

26. In patients with resectable colon cancer lung metastasis, resection of the lung lesions should be considered as it may prolong survival. Grade of recommendation: weak recommendation based on moderate-quality evidence, 2B.

A 2019 retrospective study of 345 patients with colorectal cancer lung metastasis who underwent anatomical or non-anatomical lung resection demonstrated a median overall survival of 101 months, with the best outcomes in patients with KRAS wild-type cancers and those who underwent anatomical resection.[234] A Japanese national retrospective study of 553 patients who underwent colorectal cancer lung metastasectomy reported five-year recurrence-free survival in 49% and 36% and five-year overall survival in 80% and 68% of patients who underwent segmentectomy ($n = 98$) or wedge resection ($n = 455$), respectively.[235] In a Spanish national registry study (2008–2010), in which a variety of excision types were performed in 522 patients, median disease-free and disease-specific survival were 28 and 55 months, respectively, with the best outcomes in patients who had a major resection with lymphadenectomy.[219] A 2015, Japanese, single-center retrospective study of 94 patients reported a five-year overall survival of 45%, a significantly better rate of five-year survival for colon compared with rectal metastasis (62% vs 24%, $p = 0.03$) but cancer recurrence (local or distant) in 69% of patients at a median of 11.5 (0–50) months[236] In the Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) Cohort Study, which randomly assigned patients with resectable colorectal cancer lung metastases to metastasectomy or no metastasectomy, median overall survival was 3.5 (3.1–6.6) years and 3.8 (3.5–4.6) years, respectively, supporting the position that nonsurgical treatment of these patients should also be considered.[237] Stereotactic body radiation therapy (SBRT) may also be considered in these cases but appears to be less efficacious than resection in terms of both progression-free and overall survival when compared with metasectomy.[238]

27. In patients with resectable colorectal cancer peritoneal metastases, cytoreductive surgery with or without intraperitoneal chemotherapy should be considered in a multidisciplinary setting with appropriate expertise. Grade of recommendation: strong recommendation based on moderate-quality evidence, 1B.

In patients with stage IV disease, as many as 25% will have metastatic disease that is limited to the peritoneum.[239,240] In these patients, initial treatment options include systemic chemotherapy and/or resection of the peritoneal cancer with or without intraperitoneal chemotherapy. Systemic therapy using modern chemotherapeutic agents and targeted biologic therapies has improved outcomes of patients with colorectal cancer-associated carcinomatosis, who now have a median survival in the range of 16 to 24 months.[241] Unfortunately, the five-year overall survival with systemic oxaliplatin-based chemotherapy alone is less than 5%, and there is minimal benefit from adding bevacizumab.[242,243]

The surgical approach to colorectal cancer associated peritoneal metastases generally includes the combination of cytoreductive surgery in conjunction with hyperthermic intraperitoneal mitomycin-C or oxaliplatin with or without hyperthermia.[71,244] With this approach, in more than 500 patients treated in France, five-year overall and disease-free survival were 27% and 10%, respectively, with survival inversely proportional to the extent of peritoneal disease as described by the Peritoneal Cancer Index (PCI).[71] Other studies have reported median survival in the range of 22 to 63 months, and five-year overall survival in 19% to 51% of patients with this approach.[245–250] In the first randomized trial of cytoreductive surgery and intraperitoneal chemotherapy versus systemic oxaliplatin-based chemotherapy in this setting, two- and five-year overall survival rates were 54% and 38% ($p = 0.04$) and 33% and 4% $p = 0.02$), respectively.[249] The completeness of surgical cytoreduction is also directly related to overall survival after hyperthermic intraperitoneal chemotherapy (HIPEC).[251] In 2021, the results of the PRODIGE-7 multicenter randomized, controlled trial that compared cytoreduction alone ($n = 132$) versus cytoreduction and HIPEC ($n = 133$) raised doubts about the value of HIPEC given the higher rates of severe adverse events in the HIPEC arm but no associated overall survival benefit (41–42 months in both arms).[252] The 2020 Chicago Consensus on the management of peritoneal metastasis of colorectal cancer acknowledged the PRODIGE-7 results (unpublished at the time) and recommended preoperative systemic chemotherapy (± immunotherapy in MSI-H cancers) for high-risk cases, initial cytoreductive surgery for low-risk cases with or without the use of intraperitoneal chemotherapy.[253]

B. Unresectable Stage IV Colon Cancer

Patients who present with widely metastatic colon cancer are usually not candidates for surgical cure. Meanwhile, other patients may not be candidates for radical, curative resection due to systemic comorbidities. In these situations, a multidisciplinary management approach to potential palliation is recommended. In patients with incurable metastatic colon cancer who have an asymptomatic colon primary, 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. Palliative therapy often includes 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. The individual patient's overall life expectancy should also be considered when making palliative intervention decisions.

28. In patients with incurable stage IV colon cancer and an asymptomatic primary colon cancer, systemic chemotherapy is recommended as the initial treatment. Grade of Recommendation: Strong recommendation based on moderate quality evidence, 1B.

For patients with incurable stage IV colon cancer and an asymptomatic primary colon tumor, there are conflicting reports on the value of primary tumor resection. A strong argument in favor of an initial nonoperative approach may be based on the prospective multicenter phase NSABP C-10 trial, which evaluated patients with colon cancer, an intact primary colon tumor, and unresectable metastases who were treated with up-front FOLFOX chemotherapy and bevacizumab.[254] In this trial, with 21-month follow-up, 14% of patients experienced major morbidity related to the primary colon tumor and 12% required operation, most often for colon obstruction. In addition, a SEER database (1998–2013) analysis of 4692 patients with stage IV colorectal cancer (74% colon and 26% rectal) unplanned operations were also required in 12% of patients.[255] In this SEER analysis, the probability of requiring unplanned surgery between six and 12 months, 12 and 24 months, and >24 months were 8.1%, 6.7%, and 5.3%, respectively, and female gender, left-side colon tumors, and younger age were risk factors for unplanned operation. Further, 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.[256] Finally, in 2021, the results of the JCOG1007- iPACS trial, in which 165 patients stage IV colorectal cancer and an asymotomatic primary tumor were randomly assigned to either chemotherapy alone (84 patients) or primary tumor resection (PTR) plus chemotherapy (81 patients) were reported. With a median follow-up of 22 months, the median overall survival was 25.9 months (95% CI 19.9–31.5) in the PTR plus chemotherapy arm and 26.7 (95% CI 21.9–32.5) in the chemotherapy-alone arm (HR 1.10; 95% CI 0.76–1.59; $p = 0.69$).[257]

On the contrary, the evidence in favor of initial operative treatment is relatively weak and comes from a 2016 single-center adjusted retrospective analysis, a 2016 observational study of Canadian provincial data, and a 2019 meta-analysis that each reached the conclusion that palliative resection of the primary tumor was associated with improved survival compared with chemotherapy alone and without significant increase in morbidity.[258–260] Additional evidence in favor of initial resection of the primary tumor may be obtained from a 2018 analysis of eight randomized trials included in the ARCAD database, which showed improved progression-free (9.7 vs 7.9 months, HR 1.31 (1.19–1.44) and overall survival (22.2 vs 16.4 months, HR 1.60 (1.43–1.78)) in patients who underwent resection of the primary colon tumor.[261] In this ARCAD analysis, the majority of patients had colon cancer, all received oxaliplatin or irinotecan-based systemic chemotherapy, most were also treated with targeted, antibody therapies, but it was not clear precisely how often the colon primary was actually asymptomatic. This same limitation was present in a 2018 analysis of the NCDB (2004–2012) that showed improved overall survival (22 vs 13 months) in the primary tumor resection group. The most recently published data in favor of initial surgery in this setting comes from a 2020 Korean prospective multicenter trial of 48 patients who were randomized to upfront primary resection versus chemotherapy alone and revealed a two-year cancer-specific survival rate of 72% in the resection group and 47% in the chemotherapy group ($p = 0.05$) with a clinically relevant but statistically insignificant improvement in overall survival (69% vs 45%, $p = 0.06$), respectively. The primary tumor-related complication rate was 23% in the chemotherapy group and postoperative complications developed in five patients (19%; 4% major) after colon resection.[262] However, while results this study are noteworthy it is also notable that the trial was stopped early due to insufficient enrollment and that four of the 48 enrolled patients were lost to follow-up.

Thus, with the currently available evidence, although an argument may be made in favor of initial surgical treatment for these patients, a stronger case may be made for initial chemotherapy, evaluation of response, estimation of prognosis, and repeat discussion in the multidisciplinary setting. The results of ongoing prospective clinical trials (CAIRO4 and GRECCAR 8) are awaited as they may provide additional data to guide decsion-making in these patients.

29. In patients with an obstructing colon cancer and incurable metastatic disease, or in other scenarios where palliation is preferred over an attempt at cure, endoscopic stent placement or diverting colostomy is preferable to colectomy when life expectancy is less than one year. 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 as it has been shown to result in decreased mortality, ostomy use, and interval to initiation of chemotherapy with no difference in survival.[202,263–266] Compared with patients without peritoneal metastases, patients with peritoneal metastases are less likely to have successful colonic

stent placement and experience a higher complication rate.[267–269] Endoluminal stenting in the palliative setting, has a median duration of patency of 106 (68–288) days and one-, six-, and 12-month stent patency rates of 69%, 54%, and 50%, respectively.[270,271] When tumor ingrowth results in recurrent obstruction, placing a stent through the obstructed stent has proven safe and effective in the majority of patients.[272,273] An observational cohort study assessed the outcomes of 345 patients who required urgent or emergent hospitalization for obstructing colorectal cancer who were treated with an ostomy or a stent without plans for further resection.[274] Patients who were treated with a stent were significantly less likely to experience a prolonged length of stay and were more likely to be discharged to their usual residence. Readmission rates were similar for the two groups, as were reoperations at 90 days but reoperation at one year was more often needed in the stent group. With regard to bevacizumab in patients who are treated by an endoluminal stent, a meta-analysis published in 2014 showed a higher rate of colon perforations in patients whose treatment included bevacizumab (12.5%) compared with chemotherapy alone (7%), but more recent retrospective studies have demonstrated no increase in stent-related perforation among bevacizumab treated patients.[269,275,276]

CHEMOTHERAPY, IMMUNOTHERAPY, AND MOLECULAR ADJUNCTS

30. In stage II colon cancer patients with microsatellite stable/mismatch repair proficient cancer, obstruction, perforation, <12 lymph nodes in the resection specimen, poor differentiation, lymphovascular invasion, perineural invasion, or high-level tumor budding, adjuvant chemotherapy may offer a survival benefit. Grade of recommendation: weak recommendation based on moderate-quality evidence, 2B

Stage II colon cancer patients are a heterogeneous group with an expected five-year overall survival that ranges from as high as 90% for a patient with a T3, well-differentiated cancer to as low as 74% for a patient with a poorly differentiated, T4b cancer.[70] High-risk stage II colon cancers include those that present with obstruction or perforation, or have <12 lymph nodes in the resection specimen, a close or positive resection margin, T4b tumor depth, poor differentiation, lymphovascular invasion, perineural invasion, or high-level tumor budding, or are microsatellite stable/mismatch repair proficient on histopathology.[55,277–285] There is conflicting data regarding the role of adjuvant chemotherapy in stage II colon cancer. Most of the randomized trials studying adjuvant therapy for colon cancer enrolled both stage II and stage III patients and some 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 in the stage II patients.[286–289] However, the proportion of patients with stage II cancers was approximately 20% to 25% in these trials, limiting the ability to draw definitive conclusions. Although initial subgroup analysis of the MOSAIC trial suggested a benefit of adding oxaliplatin to adjuvant chemotherapy for high-risk stage II patients, a more recent analysis 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.[290,291] A 2016, pooled analysis of five prospective trials, in which fluorouracil-based adjuvant chemotherapy was compared with oxaliplatin-based adjuvant chemotherapy in patients with stage II colon cancer, indicated that the addition of oxaliplatin resulted in an improvement in feve-year disease-free recurrence (10.3% vs 15.3%, $p < 0.05$) but no difference in deaths at five years (9.4% ˆ 10.2%, $p > 0.05$).[292] Conversely, in another recent analysis of more than 150,000 stage II colon cancer patients included in the National Cancer Database (NCDB), the use of adjuvant chemotherapy was associated with improved survival irrespective of pathological risk factors.[293] In this NCDB study, after covariate adjustment, patients with low or high-risk stage II colon cancer, treated without or with adjuvant fluorouracil or oxaliplatin-based chemotherapy, had a median survival of 8.8 and 13.2 years ($p < 0.001$) and 6.9 and 11.0 years ($p < 0.001$), respectively. Notwithstanding this NCDB data, with its methodology limitations related to its retrospective design, most data suggest that there is minimal to no benefit to adjuvant treatment in patients with "low-risk" stage II colon cancer. Stage II patients with one or more high-risk features have a risk of recurrence which approaches stage IIIa colon cancer and are routinely considered for adjuvant chemotherapy.[277,279,282] Multigene assays and measurement of circulating tumor DNA (ctDNA) are emerging technologies that may also play a role in adjuvant therapy decisions in patients with stage II colon cancer (see Recommendation #34).

31. In patients with stage III colon cancer, adjuvant chemotherapy is generally recommended. Grade of recommendation: strong recommendation based on high-quality evidence: 1A.

In patients with stage III colon cancer, with MSI-high or MSI-low tumors, large multi-institutional US and international randomized clinical trials have demonstrated a survival benefit with adjuvant oxaliplatin-based chemotherapy.[292,294–296] Oral capecitabine (Xeloda) is a safe and effective alternative to infusional 5-FU in this setting and, in combination with oxaliplatin (CAPOX), has outcomes similar to other established regimens (FOLFOX).[295,297] Since 2004, a 6-month regimen of adjuvant chemotherapy has been the standard recommendation;[286,290] however, the duration of adjuvant chemotherapy has recently been reassessed in part due to the toxicity (eg, neuropathy) associated with oxaliplatin use.[298] In 2018, the

International Duration Evaluation of Adjuvant Therapy (IDEA) collaboration reported no difference in outcomes for patients with T1-3N1 colon cancer who received three or six months of oxaliplatin-based adjuvant chemotherapy (three-year disease-free survival was 83% in both groups). However, in patients with T4 and/or N2 cancer, disease free survival was superior with six months of treatment.[299] Therefore, duration of adjuvant chemotherapy should be decided based on patient characteristics, tumor stage, and an understanding of chemotherapy-related toxicity using a shared decision approach. Current evidence does not support the use of irinotecan-based chemotherapy.[300–303] The addition of bevacizumab or certulizumab to FOLFOX for adjuvant therapy for stage III colon cancer is also not recommended as randomized trials have shown these agents increase the risk of severe adverse events without offering a survival advantage.[304,305]

32. In patients with stage IV mismatch repair deficient (dMMR) or microsatellite high (MSI-H) colon cancer, immunotherapy targeting programmed cell death-ligand 1 (PD-L1) or programmed cell death protein 1 (PD-1) should be considered. Grade of recommendation: strong recommendation based on high-quality evidence, 1A.

In 2020, the KEYNOTE-177 trial, in which 307 patients with dMMR/MSI-H stage IV colorectal cancer were randomized to first-line chemotherapy or pembolizumab (anti PD-1), demonstrated improved progression-free survival (median 16.5 versus 8.2 months; $p = 0.0002$) in the pembrolizumab trial arm.[306] In the CheckMate 142 trial, second line treatment (after cancer progression during treatment with FOLFOX or FOLFIRI or intolerance to these drugs) of 74 patients with dMMR/MSI-H stage IV colorectal cancer resulted in an objective response in 23 of 74 patients (31%) of whom eight (11%) had responses lasting 12 months.[307] The KEYNOTE-164 trial involved a study population similar to the CheckMate 142 trial (ie, cancer progression on standard chemotherapy ± anti-VEGf or anti-EGFR), and showed that pembrolizumab resulted in a response to treatment in 32% of patients and a 12-month progression-free survival of 41%.[308] Atezolizumab, a monocolonal antibody to the programmed cell death-ligand 1 (PD-L1), is currently being studied in the ATOMIC trial in which patients with stage III dMMR colon cancer are randomized to adjuvant oxaliplatin-based chemotherapy with or without Atezolizumab. Meanwhile, therapies targeting PD-1 and PDl-1 are ineffective for the treatment of microsatellite stable/MMR proficient colorectal cancers.[309]

33. In general, adjuvant chemotherapy should be started within 8 weeks of colon resection. Grade of recommendation: strong recommendation based on moderate-quality evidence, 1B.

US National Cancer Database analyses of patients with stage III colon cancer from 2016 and 2018 demonstrated maximal overall survival benefit of when adjuvant chemotherapy was started within six to eight weeks of resection, but adjuvant therapy remained beneficial even when started as long as 24 weeks after resection.[310,311] A 2015 national study from the Netherlands also indicated that overall survival was decreased when adjuvant chemotherapy was started greater than eight weeks after resection of stage III colon cancer.[312]

34. The use of multigene assays, CDX2 expression analysis, and circulating tumor DNA (ctDNA) may be used to complement multidisciplinary decision-making for patients with stage II or III colon cancer. Grade of recommendation: strong recommendation based on moderate-quality evidence, 1B.

Oncotype DX is an assay that quantifies the expression of five reference genes and seven recurrence risk genes as a prognostic classifier of low, intermediate, or high probability of colon cancer recurrence.[313] Oncotype DX used on tumor samples for patients with stage II colon cancer who were enrolled in the Cancer and Leukemia Group B (CALGB) 9581 study demonstrated that the recurrence score (RS, derived from a mathematical function combining the expression values of selected cancer–related genes) ranged from two to 78 (median 31.4), and that an increase in the RS by 25 was significantly associated with cancr recurrence (HR 1.52 (95% CI 1.09–2.12; $p = 0.013$)).[314] In a similar analysis of tumor samples from patients with stages II and II colon cancer enrolled in the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 study, continuous RS predicted cancer recurrence and that cancer recurrences were increased in the high RS group compared with the low RS group of patients (HR 2.11 (95% CI 1.54–2.88, $p < 0.001$)) and that higher RS was associated with decreased disease-free and overall survival and increased benefit to oxaliplatinbased adjuvant cchemotherapy.[315] In another study, in which a 13-gene assay, that used an analysis similar to Oncotype-DX, was used in stage II patient tumor samples from the Quick and Simple and Reliable (QUASAR) study, cancer recurrence at three years was reported in 12%, 18%, and 22% of patients in the low, intermediate, amd high RS groups (HR 1.94, $p < 0.001$) but this information was not predictive of adjuvant chemotherapy benefit.[316] ColoPrint is a multigene assay that quantifies the expression of 18 genes into low or high probability of cancer recurrence. In a study of 206 patients with stage I-III colon cancer whose tumors were evaluated with ColoPrint, the five-year recurrence-free survival rates for low and high-probablity groups were 88% (CI 81–94%) and 67% (CI 55–79%), respectively.[317] ColDx is an additional multigene assay that utilizes 634 probes-based and helps identify stage II colon cancer patients at high risk for recurrence.[318] In one study of stage II patients, those identified by ColDx as having a high risk of recurrence had a decreased recurrence-free survival when compared with low risk patients (HR 2.13 CI 1.3–3.5, $p < 0.01$).[319] CDX2

is a transcription factor that has recently been shown to be important in identifying high risk stage II colon cancer patients who may benefit from adjuvant chemotherapy. In stage II colon cancer, patients with CDX2-negative tumors had significantly lower five-year disease-free survival than patients with CDX2-positive tumors HR 3.44 CI 1.60–7.38; $p = 0.002$. The rate of five-year disease-free survival was higher in patients with CDX2-negative tumors who were treated with adjuvant chemotherapy versus those who were not (91% vs 56%, $p = 0.006$).[320]

Circulating tumor DNA (ctDNA) is fragments of cancer DNA that have entered the bloodstream and may be used as a marker for residual or recurrent disease. The presence of ctDNA may be used for both risk-assessment and to identify patients with resected colon cancer who may be at higher risk of recurrence.[321] In one study of 178 patients with stage II colon cancer, 14 (7.9%) had ctDNA detected postoperatively and 11 (79%) were diagnosed with cancer recurrence at a median follow-up of 27 months. In comparison, of 164 patients in whom ctDNA was not detected, only 16 (9.8%) recurred ($p < 0.001$).[322] Additionally, ctDNA may be helpful in surveillance after resection or chemotherapy to detect recurrences more rapidly than with standard surveillance.[321,323–325] Studies have shown a correlation between a decrease in ctDNA during systemic therapy in metastatic colon cancer with tumor response.[326–328] Thus, ctDNA is being studied in an effort to determine if it will be a useful maker for benefit from adjuvant treatment. In a prospective observation study of stage II patients, detection of ctDNA immediately after completion of adjuvant chemotherapy was associated with lower recurrence-free survival (HR 11, CI 1.8–68, $p = 0.001$).[322] In a similar study of stage III patients, patients with detectable ctDNA after completion of adjuvant treatment had a three-year recurrence-free survival of 30% vs 77% if ctDNA was not detectable (HR 6.8; CI 11–157, $p < 0.001$).[325] An additional study reported a 17-fold higher risk of recurrence if ctDNA remained detectable after completion of adjuvant chemotherapy (HR 17.5 CI 5.4–56.5, $p < 0.001$).[321] These studies provide early support for the use of ctDNA to inform the use of adjuvant chemotherapy; however, they had limited sample size and a variety of different ctDNA assay platforms were used. Ongoing trials will address whether ctDNA will be a useful marker of survival, recurrence, and adjuvant therapy effectiveness (NCT04068103, COBRA; NCT04120701, CIRCULATE; ACTRN12615000381583, DYNAMIC-II). Nothwistanding these thought-provoking data on multigene asays, the current NCCN colon cancer guidelines state these tests "can further inform the risk of cancer recurrence over other risk factors," but that there is insufficient data to recommend their use to estimate recurrence or determine adjuvant treatment.[15] The European Society for Medical Oncology (ESMO) guidelines are similar to NCCN in that the routine use of these tests is "not warranted" but that their use "might be considered in complementing clinicopathological information on intermediate risk stage II (colon cancer) scenarios."[46]

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