ASCO special articles

Treatment of Metastatic Colorectal Cancer: ASCO Guideline

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abstract

PURPOSE To develop recommendations for treatment of patients with metastatic colorectal cancer (mCRC).

METHODS ASCO convened an Expert Panel to conduct a systematic review of relevant studies and develop recommendations for clinical practice.

RESULTS Five systematic reviews and 10 randomized controlled trials met the systematic review inclusion criteria.

RECOMMENDATIONS Doublet chemotherapy should be offered, or triplet therapy may be offered to patients with previously untreated, initially unresectable mCRC, on the basis of included studies of chemotherapy in combination with anti–vascular endothelial growth factor antibodies. In the first-line setting, pembrolizumab is recommended for patients with mCRC and microsatellite instability-high or deficient mismatch repair tumors; chemotherapy and anti–epidermal growth factor receptor therapy is recommended for microsatellite stable or proficient mismatch repair left-sided treatment-naive *RAS* wild-type mCRC; chemotherapy and anti–vascular endothelial growth factor therapy is recommended for microsatellite stable or proficient mismatch repair *RAS* wild-type right-sided mCRC. Encorafenib plus cetuximab is recommended for patients with previously treated *BRAF* V600E–mutant mCRC that has progressed after at least one previous line of therapy. Cytoreductive surgery plus systemic chemotherapy may be recommended for selected patients with colorectal peritoneal metastases; however, the addition of hyperthermic intraperitoneal chemotherapy is not recommended. Stereotactic body radiation therapy may be recommended following systemic therapy for patients with oligometastases of the liver who are not considered candidates for resection. Selective internal radiation therapy is not routinely recommended for patients with unilobar or bilobar metastases of the liver. Perioperative chemotherapy or surgery alone should be offered to patients with mCRC who are candidates for potentially curative resection of liver metastases. Multidisciplinary team management and shared decision making are recommended. Qualifying statements with further details related to implementation of guideline recommendations are also included.

Additional information is available at www.asco.org/gastrointestinal-cancer-guidelines.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common type of cancer diagnosed worldwide.[1] Almost 150,000 new cases and more than 50,000 deaths from CRC are reported each year in the United States.[2] In recent decades, the overall incidence of CRC has decreased among older adults because of screening and lifestyle factors; however, at the same time, incidence is increasing among younger adults.[3] The 5-year relative overall survival (OS) for patients with metastatic colorectal cancer (mCRC) is approximately 15%.[4] Approximately 33% of patients with CRC will develop metastases either at presentation or follow-up.[5] Evaluating treatment options is complex because of the heterogeneity of the patient population, including different molecular subtypes. Treatment has included conventional fluorouracil (FU)–based chemotherapy, and more recently, targeted therapies have been developed for specific molecular subtypes and primary tumor sidedness.[6] This guideline provides a review of the evidence for areas of uncertainty in the treatment of mCRC, including indications for targeted therapy, and treatment options for oligometastatic and liver-limited disease.

THE BOTTOM LINE

Treatment of Metastatic Colorectal Cancer: ASCO Guideline

Guideline Question

What is the recommended treatment for metastatic colorectal cancer (mCRC)?

Target Population

Patients with mCRC.

Target Audience

Medical oncologists and other health care professionals who treat patients with mCRC, patients, and caregivers.

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations on the basis of a systematic review of the medical literature.

Recommendations

Recommendation 1.1. Doublet (folinic acid, fluorouracil [FU], and oxaliplatin [FOLFOX], or folinic acid, FU, and irinotecan [FOLFIRI]) backbone chemotherapy should be offered as first-line therapy to patients with initially unresectable microsatellite stable (MSS) or proficient mismatch repair (pMMR) mCRC (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Qualifying statement. Treatment with capecitabine plus oxaliplatin may be substituted for folinic acid, FU, and oxaliplatin (FOLFOX) at the clinical discretion of the treating provider, and in shared decision making with the patient.

Recommendation 1.2. Triplet (folinic acid, FU, oxaliplatin, and irinotecan [FOLFOXIRI]) backbone chemotherapy may be offered as first-line therapy to selected patients with initially unresectable MSS or pMMR mCRC (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak).

Qualifying statements for Recommendations 1.1 and 1.2.

- All patients included in the evidence-base for Recommendations 1.1 and 1.2 received anti–vascular endothelial growth factor (VEGF) antibody bevacizumab in addition to doublet or triplet chemotherapy backbone.
- Shared decision making is recommended, including a discussion of the potential for benefit and risk of harm; while survival and recurrence outcomes are improved, number of grade 3 or greater adverse events are more frequent with triplet chemotherapy, compared with doublet chemotherapy (Table 1).

Recommendation 2.1. Pembrolizumab should be offered as first-line therapy to patients with microsatellite instability-high or deficient mismatch repair mCRC (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Recommendation 3.1. Anti–epidermal growth factor receptor (EGFR) therapy plus doublet chemotherapy should be offered as first-line therapy to patients with MSS or pMMR left-sided *RAS* wild-type mCRC (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Qualifying statements.

- Anti-EGFR therapy is not recommended as first-line therapy for patients with right-sided *RAS* wild-type mCRC, and consistent with the qualifying statements to Recommendation 1.1 and 1.2, these patients should be offered chemotherapy and anti-VEGF therapy.
- Anti-EGFR therapy is not recommended for patients with *RAS*-mutant mCRC.
- Anti-EGFR therapy with triplet chemotherapy is not recommended.
- Although anti-EGFR therapy is preferred, anti-VEGF therapy remains an active treatment option for patients with left-sided treatment-naive *RAS* wild-type mCRC in the first-line setting.
- Shared decision making is recommended, including a discussion of potential for benefit and risk of harms, such as the increased risk of treatment-related rash with anti-EGFR agents (Table 3).

Recommendation 4.1. Encorafenib plus cetuximab should be offered to patients with previously treated *BRAF* V600E–mutant mCRC that has progressed after at least one previous line of therapy (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

(continued on following page)

THE BOTTOM LINE (CONTINUED)

Recommendation 5.1. Cytoreductive surgery (CRS) plus systemic chemotherapy may be recommended for selected patients with colorectal peritoneal metastases (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak).

Qualifying statements.

- In the PRODIGE 7 trial, 15% of patients with isolated colorectal peritoneal metastases experienced no disease progression in the 5 years following surgery, indicating that CRS may be a curative option for an appropriately selected subgroup of patients.
- This recommendation applies to patients who have been deemed amenable to complete resection of colorectal peritoneal metastases, regardless of previous treatment, and who have no extraperitoneal metastases.
- Complete macroscopic cytoreduction was achieved in 91% of patients in the PRODIGE 7 trial, which is attributed to the majority of patients undergoing CRS at centers with substantial clinical experience.[8] CRS should be considered as a treatment option only within these specialized centers.
- Multidisciplinary team (MDT) management is recommended for patients with mCRC who are considered candidates for CRS. The MDT should include expertise in medical oncology, surgical oncology, radiology, and pathology.
- Shared decision making should include a discussion of the potential impact on quality of life and rate of adverse events associated with CRS (Table 5).

Recommendation 5.2. Oxaliplatin-based hyperthermic intraperitoneal chemotherapy is not recommended as an addition to CRS for treatment of patients with colorectal peritoneal metastases (Type: Evidence-based, harms outweigh benefits; Evidence quality: Moderate; Strength of recommendatio7n: Strong).

Recommendation 6.1. Stereotactic body radiation therapy may be recommended following systemic therapy for patients with oligometastases of the liver who are not considered candidates for resection (Type: Evidence-based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Recommendation 6.2. Selective internal radiation therapy is not routinely recommended for patients with mCRC and unilobar or bilobar metastases of the liver (Type: Evidence-based, harms outweigh benefits; Evidence quality: Low; Strength of recommendation: Weak).

Qualifying statement for Recommendations 6.1 and 6.2. MDT management is required for patients with mCRC who are considered candidates for stereotactic body radiation therapy or selective internal radiation therapy. The MDT should include expertise in medical oncology, radiation oncology, hepatobiliary surgery, and interventional radiology.

Recommendation 7.1. Surgery with or without perioperative chemotherapy should be offered to patients with mCRC who are candidates for potentially curative resection of liver metastases (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak).

Qualifying statements.

- Perioperative chemotherapy may be more likely to be recommended over surgery alone in patients with a greater number of metastases or with larger tumors. Shared decision making, including discussion of the potential for benefits and risks of harm outlined in Table 10, is recommended.
- The choice of perioperative chemotherapy or surgery alone, and coordination of treatment sequencing, should be discussed within a MDT that includes expertise in medical oncology and hepatobiliary surgery.
- Perioperative chemotherapy is recommended for a total preoperative and postoperative duration of 6 months, on the basis of total duration of chemotherapy in the EORTC 40983 trial.

Additional Resources

Definitions for the quality of the evidence and strength of recommendation ratings are available in Appendix Table A2 (online only). More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/gastrointestinal-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

GUIDELINE QUESTIONS

This clinical practice guideline addresses seven clinical questions:

1. For patients with previously untreated, initially unresectable mCRC who are candidates for chemotherapy plus bevacizumab, is doublet (folinic acid, FU, and oxaliplatin [FOLFOX], or folinic acid, FU, and irinotecan [FOLFIRI]) or triplet (folinic acid, FU, oxaliplatin, and irinotecan [FOLFOXIRI]) cytotoxic chemotherapy recommended?

2a. In the first-line setting, are outcomes for patients with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) mCRC improved with pembrolizumab immunotherapy versus chemotherapy with or without bevacizumab or cetuximab?

2b. Is pembrolizumab recommended as later-line therapy for patients with microsatellite stable (MSS) or proficient mismatch repair (pMMR) mCRC and high tumor mutational burden (TMB ≥ 10 mutations/Mb)?

3. For patients with treatment-naive *RAS* wild-type mCRC, are anti–epidermal growth factor receptor (EGFR) antibodies (ie, panitumumab and cetuximab) recommended for patients with right-sided or left-sided primary tumors?

4. For patients with previously treated *BRAF* V600E–mutant mCRC, does treatment with encorafenib plus cetuximab result in better outcomes compared with chemotherapy plus targeted therapy?

5. For patients with colorectal peritoneal metastases, are outcomes improved with cytoreductive surgery

TABLE 1. Anti–Vascular Endothelial Growth Factor Antibody Bevacizumab Plus Triplet Chemotherapy (FOLFOXIRI) or Doublet Chemotherapy (FOLFOX or FOLFIRI) for Patients With Initially Unresectable Metastatic Colorectal Cancer[7]

Outcome, Time Frame	Study Results	Absolute Effect Estimates		Quality of Evidence (heterogeneity)	Plain Language Summary
		Doublet Chemotherapy/ Bevacizumab	Triplet Chemotherapy/ Bevacizumab		
OS, 24 months	HR, 0.81 (95% CI, 0.72 to 0.91) (1,697 participants in five studies)	500 deaths per 1,000	430 deaths per 1,000	Moderate[a]	Triplet chemotherapy improves OS, compared with doublet chemotherapy
		Difference: 70 fewer per 1,000 (95% CI, 107 fewer to 32 fewer)			
PFS, 24 months	HR, 0.74 (95% CI, 0.67 to 0.82) (1,697 participants in five studies)	894 deaths or progressions per 1,000	810 deaths or progressions per 1,000	Moderate[a] I^2 = 35%	Triplet chemotherapy improves PFS, compared with doublet chemotherapy
		Difference: 84 fewer per 1,000 (95% CI, 116 fewer to 53 fewer)			
ORR	OR, 1.57 (95% CI, 1.29 to 1.91) (1,697 participants in five studies)	536 responses per 1,000	645 responses per 1,000	Moderate[a] I^2 = 0%	Triplet chemotherapy improves ORR, compared with doublet chemotherapy
		Difference: 109 more per 1,000 (95% CI, 62 more to 152 more)			
Grade 3-4 neutropenia	OR, 3.16 (95% CI, 2.54 to 3.92) (1,674 participants in five studies)	215 events per 1,000	464 eventsper 1,000	Moderate[a]	Triplet chemotherapy worsens neutropenia, compared with doublet chemotherapy
		Difference: 249 more per 1,000 (95% CI, 195 more to 303 more)			
Grade 3-4 febrile neutropenia	OR, 1.76 (95% CI, 1.12 to 2.78) (1,674 participants in five studies)	37 events per 1,000	63 events per 1,000	Moderate[a]	Triplet chemotherapy worsens febrile neutropenia, compared with doublet chemotherapy
		Difference: 26 more per 1,000 (95% CI, 4 more to 60 more)			
Diarrhea	OR, 2.37 (95% CI, 1.75 to 3.21) (1,674 participants in five studies)	84 events per 1,000	179 events per 1,000	Moderate[a]	Triplet chemotherapy worsens diarrhea, compared with doublet chemotherapy
		Difference: 95 more per 1,000 (95% CI, 54 more to 143 more)			
Mucositis	OR, 1.83 (95% CI, 1.10 to 3.03) (1,674 participants in five studies)	29 event per 1,000	52 events per 1,000	Moderate[a]	Triplet chemotherapy worsens mucositis, compared with doublet chemotherapy
		Difference: 23 more per 1,000 (95% CI, 3 more to 54 more)			

Abbreviations: FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; FOLFOXIRI, folinic acid, fluorouracil, oxaliplatin, and irinotecan; HR, hazard ratio; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

[a]Risk of bias was found to be low to moderate for all trials, per Cremolini et al,[7] using the Method for Evaluating Research and Guideline Evidence.

(CRS) with or without hyperthermic intraperitoneal chemotherapy (HIPEC) plus chemotherapy, compared with chemotherapy alone?
6. For patients with unresectable liver-limited mCRC, are liver-directed therapies stereotactic body radiation therapy (SBRT) and selective internal radiation therapy (SIRT) recommended?
7. For patients with mCRC and potentially curable oligometastatic liver metastases, is perioperative chemotherapy recommended?

METHODS

Guideline Development Process

This systematic review-based guideline product was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology experience (Appendix Table A1, online only). The Expert Panel met via webinar and corresponded through e-mail. Based upon the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of 2 weeks allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then submitted to the *Journal of Clinical Oncology* (*JCO*) for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Evidence Based Medicine Committee before publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed by using a systematic review of evidence identified through online searches of PubMed and Cochrane Library until June 20, 2022. Articles were selected for inclusion in the systematic review on the basis of the following criteria:

- Population: patients with mCRC that is resectable or initially unresectable, including colorectal peritoneal metastases, and including molecular subtypes on the basis of microsatellite instability or mismatch repair deficiency (MSI-H, MSS, dMMR, and pMMR), *BRAF* V600E mutation status, and *RAS* mutation status, as well as primary tumor location (left-sided or right-sided).
- Interventions: doublet (FOLFOX or FOLFIRI) or triplet (FOLFOXIRI) chemotherapy; targeted therapy for molecular subtypes listed previously; CRS with or without HIPEC for patients with colorectal peritoneal metastases; SBRT; and SIRT, also known as transarterial radioembolization or Yttrium-90, for liver metastases.
- Comparisons: conventional chemotherapy, doublet chemotherapy, and no treatment.
- Outcomes: OS, progression-free survival (PFS), disease-free survival (DFS), response rate, local control, and adverse events.

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals within 2 years; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; and (3) published in a non-English language. For questions (1) to (5), included study designs were limited to randomized controlled trials (RCTs) or systematic reviews of RCTs. For questions (6) and (7), nonrandomized studies were also considered to be eligible. Where more than one systematic review or trial report was found that addressed the clinical questions, the most recent was retained for inclusion. The guideline recommendations are crafted, in part, using the *Guidelines Into Decision Support* methodology and the accompanying BRIDGE-Wiz software program.[9] In addition, a guideline implementability review was conducted. On the basis of the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for type and strength of the recommendation and evidence quality are provided with each recommendation. The evidence quality was assessed using the Cochrane Risk of Bias tool[10] and elements of the GRADE quality assessment and recommendations development process.[10,11] GRADE quality assessment labels (ie, high, moderate, low, and very low) were assigned for each outcome by the project methodologist in collaboration with the Expert Panel cochairs and reviewed by the full Expert Panel (Appendix Table A2). GRADE tables were created using the MAGICapp digital authoring platform.

Data Analysis

Hazard ratios (HRs) were extracted, where available, for time-to-event data; for other dichotomous outcomes, relative risk (RR) or odds ratio was extracted where available or calculated using reported events and population totals in the treatment and control groups, using RevMan 5.3. Heterogeneity was assessed using the I^2 statistic, and informally categorized according to the Cochrane Handbook as low (40%), moderate (30%-60%), substantial (50%-90%), or considerable (75%-100%).[10]

Guideline Updating

The ASCO Expert Panel and guidelines staff will work with cochairs to keep abreast of any substantive updates to the guideline. On the basis of formal review of the emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at https://www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

A systematic review with meta-analysis of five RCTs met the inclusion criteria for studies of doublet versus triplet chemotherapy.[7] One phase III RCT of pembrolizumab versus standard-of-care chemotherapy with or without bevacizumab or cetuximab met the inclusion criteria for question (2) related to immunotherapy as first-line therapy in patients with MSI-H or dMMR tumors.[12] One systematic review was included in the evidence-base for patients with *RAS* wild-type mCRC; this review included a meta-analysis of the PRIME, CRYSTAL, and TAILOR RCTs comparing anti-EGFR therapies (panitumumab or cetuximab) versus chemotherapy alone, and a meta-analysis of the FIRE-3, PEAK, and CALGB 80405 trials comparing chemotherapy plus anti-EGFR versus chemotherapy plus bevacizumab.[13] Three additional RCTs were available to inform question (3).[14-16] Data from the BEACON trial of second-line therapy in patients with *BRAF* V600E mutations were included.[17]

Two RCTs were available to inform the question related to CRS with or without HIPEC for patients with colorectal peritoneal metastases.[8,18] One systematic review of phase III RCTs[19] and one phase III RCT[20] were available to inform the question regarding SIRT. A systematic review of noncomparative studies addressed the question of SBRT.[21] Finally, two RCTs[22,23] and a pooled analysis that looked at neoadjuvant and/or adjuvant therapy for patients with mCRC met the inclusion criteria for question (7).[24]

A flow diagram of the search results and tables of study characteristics are available in the Data Supplement (online only). Quality ratings for the outcomes of included studies are found in the subsequent data tables and explained in table footnotes.

RECOMMENDATIONS

Clinical Question 1

For patients with previously untreated, initially unresectable mCRC who are candidates for chemotherapy plus bevacizumab, is doublet (FOLFOX or FOLFIRI) or triplet (FOLFOXIRI) cytotoxic chemotherapy recommended?

Recommendation 1.1. Doublet (FOLFOX or FOLFIRI) backbone chemotherapy should be offered as first-line therapy to patients with initially unresectable MSS or pMMR mCRC (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Qualifying statement. Treatment with capecitabine plus oxaliplatin may be substituted for FOLFOX at the clinical discretion of the treating provider, and in shared decision making with the patient.

Recommendation 1.2. Triplet (FOLFOXIRI) backbone chemotherapy may be offered as first-line therapy to selected patients with initially unresectable MSS or pMMR mCRC (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak).

Qualifying statements for Recommendations 1.1 and 1.2.

- All patients included in the evidence-base for Recommendations 1.1 and 1.2 received anti–vascular endothelial growth factor (VEGF) antibody bevacizumab in addition to doublet or triplet chemotherapy backbone.
- Shared decision making is recommended, including a discussion of the potential for benefit and risk of harm; while survival and recurrence outcomes are improved, number of grade 3 or greater adverse events are more frequent with triplet chemotherapy, compared with doublet chemotherapy (Table 1).

Literature review and analysis. One systematic review with meta-analysis of five phase II or III RCTs[25-30] comparing doublet chemotherapy (FOLFIRI or FOLFOX) to triplet chemotherapy (FOLFOXIRI) met the inclusion criteria.[7] In four of five studies and 74% of patients, doublet chemotherapy consisted of FOLFOX, with the remaining control arm patients receiving FOLFIRI. The duration of induction chemotherapy ranged from 4 to 6 months, and was followed by maintenance with a fluoropyrimidine (FU or capecitabine) plus bevacizumab until disease progression, patient refusal, unacceptable adverse events, or withdrawal of consent. OS (HR, 0.81; 95% CI, 0.72 to 0.91), PFS (HR, 0.74; 95% CI, 0.67 to 0.82), and objective response rate (ORR; odds ratio, 1.57; 95% CI, 1.29 to 1.91) were significantly improved in the triplet chemotherapy group, compared with doublet chemotherapy. Adverse events including diarrhea, neurotoxicity, and neutropenia were significantly more likely with triplet chemotherapy, although in a subgroup analysis, the rate of neurotoxicity did not differ between groups of patients treated with FOLFOXIRI versus FOLFOX (Table 1).

Clinical interpretation. The goals of first-line chemotherapy include prolonging survival by stopping cancer progression, palliation, and in some patients who have a moderate burden of disease, it may allow for consideration of other subsequent locoregional options. Doublet chemotherapy has previously been shown to be superior to FU and folinic acid[31]; therefore, this analysis focused on the potential for additional benefit with triplet chemotherapy, compared with FOLFOX or FOLFIRI. The comparison of chemotherapy and bevacizumab versus chemotherapy alone was outside the scope of this systematic review; however, the Expert Panel acknowledges that previous studies have established this combination as the standard initial treatment for mCRC.[32,33] Doublet-chemotherapy continues to be the preferred backbone chemotherapy; however, on the basis of evidence of improved efficacy, triplet chemotherapy may be recommended, following a shared decision-making discussion between the patient and clinician that includes the potential for benefit and risk of higher incidence of adverse events.

Clinical Question 2

a. In the first-line setting, are outcomes for patients with MSI-H or dMMR mCRC improved with pembrolizumab immunotherapy versus chemotherapy with or without bevacizumab or cetuximab?
b. Is pembrolizumab recommended as later-line therapy for patients with MSS or pMMR mCRC and high TMB (≥ 10 mutations/Mb)?

Recommendation 2.1. Pembrolizumab should be offered as first-line therapy to patients with MSI-H or dMMR mCRC (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Literature review and analysis. Keynote-177 is a phase III RCT of pembrolizumab compared with FOLFOX with or without bevacizumab, or FOLFIRI with or without bevacizumab or cetuximab, in patients with MSI-H or dMMR mCRC. PFS was significantly improved with pembrolizumab (HR, 0.60; 95% CI, 0.45 to 0.80), while there was no significant difference between arms for overall response rate (RR, 1.32; 95% CI, 0.99 to 1.76). Grade 3 or greater adverse events were significantly lower in the pembrolizumab arm (Table 2).[12] OS results reported in a subsequent abstract showed no significant difference between treatment and control groups (HR, 0.74; 95% CI, 0.53 to 1.03).[34]

Clinical interpretation. *MSI-H or dMMR.* MSI-H or dMMR is present in approximately 4% of patients with advanced colorectal cancer (CRC).[35] The Keynote-177 trial compared programmed cell death protein-1 blockade with pembrolizumab to conventional treatment with chemotherapy for patients with MSI-H or dMMR tumors in the first-line setting.[12] On the basis of a PFS advantage, compared with chemotherapy with or without bevacizumab or cetuximab, and a reduction in the rate of adverse events, pembrolizumab is recommended for patients with MSI-H or dMMR mCRC. There was no difference in OS for this comparison, which may be due to the high rate of crossover (60%) from chemotherapy to pembrolizumab in the intention-to-treat population.[34] The ORR was also not significantly different between groups; however, in those who had a complete or partial response, ongoing response at 24 months was 83% versus 35% for pembrolizumab and chemotherapy, respectively. The rate of progressive disease in the pembrolizumab arm was 29%, compared with 12% in the chemotherapy arm. In addition, pembrolizumab monotherapy led to clinically meaningful improvements in health-related quality of life compared with chemotherapy.[36] On June 29, 2020, pembrolizumab was approved by the US

TABLE 2. Pembrolizumab Versus FOLFOX With or Without Bevacizumab; FOLFIRI With or Without Bevacizumab or Cetuximab for Patients With Microsatellite Instability-High or Deficient Mismatch Repair Stage IV Colorectal Cancer[12,34]

Outcome, Time Frame	Study Results	Absolute Effect Estimates		Quality of Evidence	Plain Language Summary
		Chemotherapy ± Bevacizumab or Cetuximab	Pembrolizumab		
PFS (coprimary outcome), 24 months	HR, 0.60 (95% CI, 0.45 to 0.80) (296 patients in one study)	814 deaths or progressions per 1,000	635 deaths or progressions per 1,000	Moderate[a]	Pembrolizumab probably improves PFS compared with chemotherapy ± bevacizumab or cetuximab
		Difference: 179 fewer per 1,000 (95% CI, 283 fewer to 74 fewer)			
OS (coprimary outcome) at data cutoff (median 32.4 months)	HR, 0.74 (95% CI 0.53 to 1.03)[34] (296 patients in one study)	448 deaths per 1,000	356 deaths per 1,000	Low[a,b,c]	Pembrolizumab may improve OS compared with chemotherapy ± bevacizumab or cetuximab
		Difference: 92 fewer per 1,000 (95% CI, 178 fewer to 10 more)			
ORR	RR, 1.32 (95% CI, 0.99 to 1.76) (296 patients in one study)	331 responses per 1,000	437 responses[d] per 1,000	Moderate[a]	Pembrolizumab may improve ORR compared with chemotherapy ± bevacizumab or cetuximab
		Difference: 195 more per 1,000 (95% CI, 3 fewer to 513 more)			
Grade ≥ 3 AEs	RR, 0.72 (95% CI, 0.61 to 0.85) (296 patients in one study)	780 eventsper 1,000	562 events per 1,000	Moderate[a]	Pembrolizumab probably improves grade ≥ 3 AEs, compared with chemotherapy ± bevacizumab or cetuximab
		Difference: 218 fewer per 1,000 (95% CI, 304 fewer to 117 fewer)			

Abbreviations: AE, adverse event; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; FOLFIRI, folinic acid, fluorouracil, and irinotecan; HR, hazard ratio; ORR, objective response rate (complete or partial radiographic response [RECIST 1.1] by central review); OS, overall survival; PFS, progression-free survival; RR, relative risk.

[a]Downgrade: inadequate/lack of blinding of participants and personnel.

[b]Indirectness: crossover to pembrolizumab was 60% in the intention-to-treat population.

[c]For OS significance, a *P* value of .0246 (one-sided) was required: The *P* value in final analysis was .0359, that is, not statistically significant. *P* value for PFS (.0002) met the prespecified *P* value boundary for superiority of pembrolizumab over chemotherapy ($P = .0117$).

[d]MagicApp was used to calculate the ORR in the pembrolizumab subgroup.

Food and Drug Administration as first-line therapy for patients with unresectable or metastatic MSI-H or dMMR CRC, on the basis of the results from Keynote-177.[37]

In addition, the phase II nonrandomized Checkmate 142 study of nivolumab plus ipilimumab showed promising results,[38] and is being followed up with the Checkmate 8HW randomized phase III study of this combination compared with nivolumab alone or chemotherapy.[39] Full publication of the results of this study may affect guideline recommendations in the future.

High TMB. No other randomized studies of immunotherapy for patients with advanced CRC met the inclusion criteria for this review. The Expert Panel acknowledges the Keynote-158 phase II trial of pembrolizumab as later-line therapy in 10 tumor types.[40] This analysis did not include patients with CRC; however, on June 16, 2020, the US Food and Drug Administration approved pembrolizumab for patients with metastatic or unresectable solid tumors including colon cancer with a high TMB, defined as ≥ 10 mutations per megabase, who have experienced progression with prior treatment and who have no other satisfactory treatment options.[41] In a subsequent retrospective analysis in patients with CRC, study authors found that there was no benefit of pembrolizumab in patients with high TMB and pMMR or without pathogenic mutations in polymerase ε or polymerase δ1.[42] On the basis of this limited evidence, pembrolizumab is not recommended for patients with mCRC and TMB ≥ 10 mutations per megabase.

Clinical Question 3

For patients with treatment-naive *RAS* wild-type mCRC, are anti-EGFR antibodies (ie, panitumumab and cetuximab) recommended for patients with right-sided or left-sided primary tumors?

Recommendation 3.1. Anti-EGFR therapy plus doublet chemotherapy should be offered as first-line therapy to patients with MSS or pMMR left-sided *RAS* wild-type mCRC (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Qualifying statements.

- Anti-EGFR therapy is not recommended as first-line therapy for patients with right-sided *RAS* wild-type mCRC, and consistent with the qualifying statements to Recommendation 1.1 and 1.2, these patients should be offered chemotherapy and anti-VEGF therapy.
- Anti-*EGFR* therapy is not recommended for patients with RAS-mutant mCRC.
- Anti-EGFR therapy with triplet chemotherapy is not recommended.
- Although anti-EGFR therapy is preferred, anti-VEGF therapy remains an active treatment option for patients with left-sided treatment-naive *RAS* wild-type mCRC in the first-line setting.
- Shared decision making is recommended, including a discussion of potential for benefit and risk of harms, such as the increased risk of treatment-related rash with anti-EGFR agents (Table 3).

Literature review and analysis. *Anti-EGFR antibodies plus doublet chemotherapy compared with doublet chemotherapy in* RAS *wild-type right-sided or left-sided mCRC.* The meta-analysis by Ciliberto et al found a significant benefit in terms of OS and PFS for anti-EGFR antibodies (ie, panitumumab and cetuximab) plus chemotherapy compared with chemotherapy alone as first-line therapy for *RAS* wild-type mCRC (Data Supplement).[13] When the results were stratified by tumor side in post hoc subgroup analyses, the OS and PFS results remained significant for left-sided tumors only. Grade 3-4 adverse events, including skin toxicity and rash, were more likely with anti-EGFR antibodies plus doublet chemotherapy versus chemotherapy alone (Table 3).

Anti-EGFR antibodies plus doublet chemotherapy compared with anti-VEGF antibodies plus doublet chemotherapy in RAS *wild-type right-sided or left-sided mCRC.* In the included meta-analysis,[13] anti-EGFR antibodies significantly improved OS, compared with chemotherapy plus bevacizumab for left-sided and right-sided patients combined. For PFS, there was considerable heterogeneity, which was potentially attributable to the variety of agents used in the treatment and control groups (Data Supplement).

In patients with left-sided tumors, treatment with anti-EGFR therapy resulted in a significantly better OS (HR, 0.71; 95% CI, 0.58 to 0.85), while the HR for OS in right-sided tumors was 1.35 (95% CI, 1.0 to 1.8). PFS for left-sided tumors nonsignificantly favored chemotherapy plus anti-EGFR, compared with chemotherapy plus bevacizumab (HR, 0.86; 95% CI, 0.73 to 1.02), while PFS for right-sided tumors was more favorable with the chemotherapy plus bevacizumab combination (HR, 1.53; 95% CI, 1.16 to 2.01; Table 4).

There was a similar likelihood of grade 3-4 adverse events in the chemotherapy plus anti-EGFR versus chemotherapy plus bevacizumab groups (Table 4). In a network meta-analysis, Ciliberto et al[13] found that the combination of chemotherapy plus cetuximab was most likely to induce a grade 3-4 adverse event, compared with other treatment combinations.

In the PARADIGM trial, authors reported a significant benefit for OS (HR, 0.82; 95.798% CI, 0.68 to 0.99) and ORR (HR, 1.17; 95% CI, 1.06 to 1.29), although no benefit in PFS (HR, 0.98; 95% CI, 0.82 to 1.17), and no difference in rate of grade 3 or greater adverse with panitumumab plus FOLFOX versus bevacizumab plus FOLFOX in patients with left-sided primary tumors (Data Supplement). In an exploratory analysis, the HR for OS in the right-sided *RAS* wild-type population of PARADIGM was 1.09 (95% CI, 0.79 to 1.51).[52]

Anti-EGFR antibodies plus triplet chemotherapy compared with triplet chemotherapy in RAS wild-type mCRC. In a small phase II RCT, investigators found a significantly improved investigator-assessed ORR for patients treated with panitumumab plus triplet chemotherapy, compared with triplet chemotherapy alone; however, there was no significant difference in PFS or OS, and a higher incidence of grade 3 or greater adverse events in the panitumumab plus triplet chemotherapy group (Data Supplement).[14]

Anti-EGFR antibodies plus triplet chemotherapy compared with anti-EGFR antibodies plus doublet chemotherapy in RAS wild-type mCRC. Data from a phase III RCT of triplet chemotherapy plus panitumumab versus doublet chemotherapy plus panitumumab showed that the ORR and PFS were not significantly different between groups, and the triplet chemotherapy group experienced more gastrointestinal adverse events (Data Supplement).[15]

Clinical interpretation. As it has been previously established that *RAS* mutations are predictive of resistance to anti-EGFR therapy, this analysis focused on treatment options for *RAS* wild-type mCRC.[13,53] A significant interaction effect has previously been found for patient tumor location and treatment with anti-VEGF or anti-EGFR therapy.[54] Compared with doublet chemotherapy and bevacizumab, which were previously considered the standard initial treatment for mCRC,[32,33] doublet chemotherapy plus anti-EGFR significantly improved OS in a post hoc analysis of patients with left-sided tumors; in patients with right-sided *RAS* wild-type mCRC, chemotherapy plus bevacizumab was superior in a post hoc analysis. Data from the PARADIGM trial, published as an abstract and as conference proceedings, provide additional support for anti-EGFR therapy, specifically panitumumab plus doublet chemotherapy for patients with *RAS* wild-type left-sided mCRC. A qualifying statement recommending against anti-EGFR therapy plus triplet chemotherapy is included, supported by recent results from the TRIPLETE phase III RCT.

TABLE 3. Anti-EGFR Therapy Plus Doublet Chemotherapy Versus Doublet Chemotherapy for First-Line Treatment of RS or LS *RAS* Wild-Type Metastatic Colorectal Cancer[13]

Outcome, Time Frame	Study Results	Absolute Effect Estimates		Quality of Evidence (heterogeneity)	Plain Language Summary
		Doublet Chemotherapy	Anti-EGFR Plus Doublet Chemotherapy		
OS (left-side), 24 months	HR, 0.69 (95% CI, 0.60 to 0.80) (916 patients in three studies)	500 deaths[43] per 1,000	380 deaths per 1,000	Low[a,b]; I^2 = 0%	Anti-EGFR plus doublet chemotherapy probably improves OS compared with doublet chemotherapy for left-sided tumors
		Difference: 87 fewer per 1,000 (95% CI, 160 fewer to 74 fewer)			
OS (right-side), 24 months	HR, 0.95 (95% CI, 0.72 to 1.26) (255 patients in three studies)	600 deaths[43] per 1,000	581 deaths per 1,000	Low[a,b]; I^2 = 0%	Anti-EGFR plus doublet chemotherapy probably has little or no effect on PFS OS compared with doublet chemotherapy for right-sided tumors
		Difference: 19 fewer per 1,000 (95% CI, 117 fewer to 85 more)			
PFS (left-side), 12 months	HR, 0.65 (95% CI, 0.54 to 0.79) (916 patients in three studies)	620 deaths or progressions[43] per 1,000	467 deaths or progressions per 1,000	Low[a,b]; I^2 = 25.9%	Anti-EGFR plus doublet chemotherapy probably improves PFS compared with doublet chemotherapy for left-sided tumors
		Difference: 153 fewer per 1,000 (95% CI, 213 fewer to 86 fewer)			
PFS (right-side), 12 months	HR, 0.77 (95% CI, 0.57 to 1.04) (255 patients in three studies)	830 deaths or progressions[43] per 1,000	744 deaths or progressions per 1,000	Low[a,b]; I^2 = 0%	Anti-EGFR plus doublet chemotherapy probably has little or no effect on PFS compared with doublet chemotherapy for right-sided tumors
		Difference: 86 fewer per 1,000 (95% CI, 194 fewer to 12 more)			
Grade 3-5 AEs[44-47]	RR, 1.24 (95% CI, 1.18 to 1.3) (2,741 participants in four studies)	601 per 1,000	745 per 1,000	Moderate; I^2 = 57%	Anti-EGFR plus doublet chemotherapy probably worsens grade 3-5 AEs, compared with doublet chemotherapy
		Difference: 144 more per 1,000 (95% CI, 108 more to 180 more)			
Grade 3 skin toxicity[47]	RR, 118.4 (95% CI, 16.59 to 844.7) (1,202 participants in one study)	2 per 1,000	197 per 1,000	High	Anti-EGFR plus doublet chemotherapy increases the risk of grade 3 skin toxicity, compared with doublet chemotherapy
		Difference: 195 more per 1,000 (95% CI, 31 more to 1,687 more)			
Grade 3 acne-like rash[47]	(1,202 participants in one study)	In the cetuximab group, 16% experienced grade 3 acne-like rash; no cases of acne-like rash were experienced in the control group		High	Anti-EGFR plus doublet chemotherapy increases the risk of acne-like rash, compared with doublet chemotherapy

Abbreviations: AE, adverse event; EGFR, epidermal growth factor receptor; HR, hazard ratio; LS, left-sided primary tumor; OS, overall survival; PFS, progression-free survival; RR, relative risk; RS, right-sided primary tumor.

[a]Downgrade: open label trials; post hoc subgroup analyses.

[b]Risk of bias assessment from Ciliberto et al.[13]

Clinical Question 4

For patients with previously treated *BRAF* V600E–mutant mCRC, does treatment with encorafenib plus cetuximab result in better outcomes compared with chemotherapy plus targeted therapy?

Recommendation 4.1. Encorafenib plus cetuximab should be offered to patients with previously treated *BRAF* V600E–mutant mCRC that has progressed after at least one previous line of therapy (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Literature review. Approximately 8% of patients with mCRC have *BRAF* V600E mutations, and these patients have poorer prognoses compared with patients with wild-type disease.[55] The BEACON phase III RCT with 441 patients met the inclusion criteria for treatment options for patients with previously treated *BRAF* V600E mCRC.[56] In the encorafenib plus cetuximab group, 95% received prior oxaliplatin, and within the control group (cetuximab plus irinotecan-based chemotherapy), 91% received prior oxaliplatin.[57] Nine percent and five percent within the encorafenib plus cetuximab group and the chemotherapy group were MSI-H, respectively. OS (HR, 0.61; 95% CI, 0.48 to 0.77), PFS (HR, 0.44; 95% CI, 0.35 to 0.55), and ORR (RR, 13.18; 95% CI, 4.64 to 37.42) were significantly improved in the encorafenib plus cetuximab group, compared with cetuximab plus chemotherapy. There were

TABLE 4. Anti-EGFR Therapy Plus Doublet Chemotherapy Versus Anti-VEGF Therapy Plus Doublet Chemotherapy for First-Line Treatment of RS or LS *RAS* Wild-Type Metastatic Colorectal Cancer[13]

Outcome, Time Frame	Study Results	Absolute Effect Estimates		Quality of Evidence (heterogeneity)	Plain Language Summary
		Anti-VEGF + Doublet Chemotherapy	Anti-EGFR + Doublet Chemotherapy		
OS (left-sided tumors), 24 months	HR, 0.71 (95% CI, 0.58 to 0.85) (689 patients in three studies)	400 deaths[48] per 1,000	304 deaths per 1,000	Moderate[a]; $I^2 = 0$	Anti-EGFR plus chemotherapy probably improves OS compared with anti-VEGF plus chemotherapy for left-sided tumors
		Difference: 96 fewer per 1,000 (95% CI, 144 fewer to 48 fewer)			
OS (right-sided tumors), 24 months	HR, 1.35 (95% CI, 1.0 to 1.8) (404 patients in three studies)	575 deaths[48] per 1,000	685 deaths per 1,000	Moderate[a]; $I^2 = 0$	Anti-EGFR plus chemotherapy may have no effect or worsen OS compared with anti-VEGF plus chemotherapy for right-sided tumors
		Difference: 110 more per 1,000 (95% CI, 0 fewer to 211 more)			
PFS (left-sided tumors), 24 months	HR, 0.86 (95% CI, 0.73 to 1.02) (689 patients in three studies)	900 deaths or progressions per 1,000	814 deaths or progressions per 1,000	Moderate[a]; $I^2 = 0$	Anti-EGFR plus chemotherapy may improve PFS compared with anti-VEGF plus chemotherapy for left-sided tumors
		Difference: 86 fewer per 1,000 (95% CI, 38 fewer to 5 more)			
PFS (right-sided tumors), 24 months	HR, 1.53 (95% CI, 1.16 to 2.01) (689 patients in three studies)	920 deaths or progressions per 1,000	979 deaths or progressions per 1,000	Moderate[a]; $I^2 = 0$	Anti-EGFR plus chemotherapy may worsen PFS compared with anti-VEGF plus chemotherapy for right-sided tumors
		Difference: 59 more per 1,000 (95% CI, 27 more to 74 more)			
Grade 3 or greater AEs	RR, 1.11 (95% CI, 1.02 to 1.20) (870 participants in two studies[49,50])	530 events[48] per 1,000	588 events per 1,000	Moderate[a]; $I^2 = 0\%$	Anti-EGFR plus chemotherapy may increase grade 3 or greater AEs compared with anti-VEGF plus chemotherapy
		Difference: 58 more per 1,000 (95% CI, 11 more to 106 more)			

Abbreviations: AE, adverse event; EGFR, epidermal growth factor receptor; FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HR, hazard ratio; LS, left-sided primary tumor; OS, overall survival; PFS, progression-free survival; RR, relative risk; RS, right-sided primary tumor; VEGF, vascular endothelial growth factor.

[a]Downgrade: inadequate/lack of blinding of participants and personnel; sidedness analyses were retrospective post hoc. Comparisons in included studies: FOLFOX plus panitumumab versus FOLFOX plus bevacizumab,[49] FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab,[50] and FOLFOX6 or FOLFIRI plus cetuximab versus FOLFOX6 or FOLFIRI plus bevacizumab.[51]

significantly fewer grade 3 or greater adverse events in the encorafenib plus cetuximab group, compared with the control group (Data Supplement).

Clinical interpretation. On the basis of positive results from the BEACON trial, the Expert Panel agrees that the combination of *BRAF* inhibitor encorafenib plus anti-EGFR monoclonal antibodies cetuximab or panitumumab are recommended for patients with *BRAF* V600E–mutant mCRC previously treated with chemotherapy.

Clinical Question 5

For patients with colorectal peritoneal metastases, are outcomes improved with CRS with or without HIPEC plus chemotherapy, compared with chemotherapy alone?

Recommendation 5.1. CRS plus systemic chemotherapy may be recommended for selected patients with colorectal peritoneal metastases (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak).

Qualifying statements.

- In the PRODIGE 7 trial, 15% of patients with isolated colorectal peritoneal metastases experienced no disease progression in the 5 years following surgery, indicating that CRS may be a curative option for an appropriately selected subgroup of patients.
- This recommendation applies to patients who have been deemed amenable to complete resection of colorectal peritoneal metastases, regardless of previous treatment, and who have no extraperitoneal metastases.
- Complete macroscopic cytoreduction was achieved in 91% of patients in the PRODIGE 7 trial, which is attributed to the majority of patients undergoing CRS at centers with substantial clinical experience.[8] CRS should be considered as a treatment option only within these specialized centers.
- Multidisciplinary team (MDT) management is recommended for patients with mCRC who are considered candidates for CRS. The MDT should include expertise

in medical oncology, surgical oncology, radiology, and pathology.
- Shared decision making should include a discussion of the potential impact on quality of life and rate of adverse events associated with CRS (Table 5).

Recommendation 5.2. Oxaliplatin-based HIPEC is not recommended as an addition to CRS for treatment of patients with colorectal peritoneal metastases (Type: Evidence-based, harms outweigh benefits; Evidence quality: Moderate; Strength of recommendation: Strong).

Literature review and clinical interpretation. Approximately 20% of new cases of mCRC present with synchronous peritoneal metastases.[59] One systematic review included four studies of the effect of CRS plus HIPEC for patients with colorectal peritoneal metastases and mCRC, three of which were published as abstracts.[60] The fully published phase III RCT by Verwaal et al was included in the present analysis, along with the subsequent full publication from the PRODIGE 7 trial.[8]

CRS plus HIPEC and systemic chemotherapy (FU plus folinic acid) compared with systemic chemotherapy. The Verwaal et al[58] RCT of 105 patients, originally published in 2003, was designed to assess the impact of CRS followed by HIPEC, plus adjuvant systemic chemotherapy (FU plus folinic acid) following a postoperative recovery period, compared with chemotherapy with FU plus folinic acid (and surgery in cases of intestinal obstruction). OS was significantly improved in the CRS plus HIPEC and chemotherapy group (HR, 0.55; 95% CI, 0.32 to 0.95), compared with chemotherapy alone (Table 5). Treatment-related mortality was 8% in the CRS plus HIPEC arm and appeared to be related to the extent of disease, which reportedly was difficult to determine preoperatively. The main factor affecting long-term survival was completeness of cytoreduction; after a median follow-up of 21.6 months, one of 18 patients with absence of residual tumor after resection had died. By comparison, 66% (14 of 21) of patients with limited residual disease, and 70% (7 of 10) of patients with extensive residual disease had died over the same period. The authors of this study note that HIPEC can only affect the superficial layers of the peritoneal surface, and thus can be effective only in the scenario of minimal residual disease. Therefore, the possibility that the significant effect on survival was due to aggressive cytoreduction could not be ruled out in this study.

CRS compared with CRS plus HIPEC. The more recent PRODIGE 7 phase III RCT included 256 patients with colorectal peritoneal metastases and < 1 mm of residual disease after CRS. Following CRS, a 30-minute administration of oxaliplatin-based HIPEC was compared with no administration of HIPEC,[8] and patients also received systemic therapy (FU plus folinic acid) before or after surgery, with or without targeted therapy. Study authors found no difference in OS (HR, 1.00; 95% CI, 0.63 to 1.58) or relapse-free survival (HR, 0.91; 95% CI, 0.71 to 1.15) between groups . There was no significant difference in rate of grade 3 or greater adverse events at 30 days after treatment; however, at 60 days, grade 3 or greater adverse events were more common in the CRS plus HIPEC group (RR, 1.69; 95% CI, 1.03 to 2.77), compared with CRS alone (Table 6). In addition, 15% of patients with isolated colorectal peritoneal metastases experienced no disease progression in the 5 years following surgery, indicating that CRS may be a curative option for an appropriately selected subgroup of patients. The duration of HIPEC was limited to 30 minutes in the PRODIGE 7 study; this guideline will be updated if future studies of longer-duration HIPEC produce different results. On the basis of the results of previous studies, the authors of PRODIGE 7 speculate that the results of their trial would not have differed had they used mitomycin-C, another common HIPEC drug.

Clinical Question 6

For patients with unresectable liver-limited mCRC, are liver-directed therapies SBRT and SIRT recommended?

Recommendation 6.1. SBRT may be recommended following systemic therapy for patients with oligometastases of the liver who are not considered candidates for resection (Type: Evidence-based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Recommendation 6.2. SIRT is not routinely recommended for patients with mCRC and unilobar or bilobar metastases of the liver (Type: Evidence-based, harms outweigh benefits; Evidence quality: Low; Strength of recommendation: Weak).

Qualifying statement for Recommendations 6.1 and 6.2. MDT management is required for patients with mCRC who are considered candidates for SBRT or SIRT. The MDT should include expertise in medical oncology, radiation oncology, hepatobiliary surgery, and radiology.

Literature review and analysis. *SBRT.* SBRT delivers a high dose of radiation therapy to specific liver lesions while minimizing irradiation of surrounding tissue; therefore, it may be considered as a therapeutic option for patients with mCRC who are not candidates for resection.[61] One systematic review with a meta-analysis of SBRT met the inclusion criteria for this systematic review.[21] Eighteen nonrandomized studies published between 2006 and 2017 were included in this review, which assessed SBRT patients with one to five oligometastases of the liver (mostly 1-2) who were not suitable for surgery, and had for the most part previously received chemotherapy. OS was 67% and 57% at 1 and 2 years, respectively. Local control was 67% and 59% at 1 and 2 years, respectively. The correlation between SBRT dose and OS at 2 years was poor, at 0.29. A moderate correlation of 0.47 was found for the relationship between SBRT biologically effective dose and local control.

TABLE 5. CRS Plus HIPEC and Chemotherapy (FU plus folinic acid) Versus Chemotherapy for mCRC Patients With Colorectal Peritoneal Metastases and No Distant Metastases[58]

Outcome, Time Frame	Study Results	Absolute Effect Estimates		Quality of Evidence	Plain Language Summary
		FU Chemotherapy	CRS + HIPEC + FU Chemotherapy		
OS, 24 months	HR, 0.55 (95% CI, 0.32 to 0.95) (105 participants in one study)	902 deaths per 1,000	721 deaths per 1,000	Moderate[a]	Risk of death was lower for patients with mCRC and colorectal peritoneal metastases treated with CRS plus HIPEC, compared with chemotherapy alone
		Difference: 181 fewer per 1,000 (95% CI, 378 fewer to 12 fewer)			
Treatment-related mortality	The mortality rate was 8% in the CRS plus HIPEC arm, attributable at least partially to the extent of surgery, which was related to the extent of peritoneal metastases. Extent of disease was reportedly difficult to predict preoperatively			High	Treatment-related mortality risk is increased with CRS plus HIPEC, compared with chemotherapy alone
Grade ≥ 3 AEs and surgical complications	Rate of grade 3-5 adverse events was 65%, and rate of surgical complications (ie, postoperative events needing reintervention) was 35% among patients undergoing CRS plus HIPEC			High	Risk of adverse events and surgical complications are increased with CRS plus HIPEC

Abbreviations: AE, adverse event; CRS, cytoreductive surgery; FU, fluorouracil; HIPEC, hyperthermic intraperitoneal chemotherapy; HR, hazard ratio; mCRC, metastatic colorectal cancer; OS, overall survival.

[a]Downgrade: the effect on OS may have been due to the impact of CRS alone.

Toxicities were mostly mild to moderate, as described in Table 7.

SIRT (radioembolization). SIRT involves the binding of beta-particle-emitting Yttrium-90 bound to resin or glass microspheres and delivered to liver metastases via branches of the hepatic artery. One systematic review with a meta-analysis of SIRT met the inclusion criteria for this systematic review.[19] It included three multicenter phase III RCTs of patients recruited between 2006 and 2014 that assessed SIRT in patients with liver-dominant (ie, mostly liver; 38%) or liver-only metastases (62%). In this study, there was no significant difference between groups in terms of OS or PFS. There was a higher rate of grade ≥ 3 adverse events in the SIRT plus FOLFOX group, compared with

TABLE 6. CRS Plus Oxaliplatin-Based HIPEC and Chemotherapy Versus CRS Plus Chemotherapy for Patients With Colorectal Peritoneal Metastases With Less Than 1-mm Residual Tumor[8]

Outcome, Time Frame	Study Results	Absolute Effect Estimates		Quality of Evidence	Plain Language Summary
		CRS + Chemotherapy	CRS + HIPEC + Chemotherapy		
OS, 12 months	HR, 1.00 (95% CI, 0.63 to 1.58) (265 patients in one study)	144 deaths per 1,000	144 deaths per 1,000	High	CRS plus HIPEC and chemotherapy may have little or no effect on OS compared with CRS plus chemotherapy
		Difference: 0 fewer per 1,000 (95% CI, 51 fewer to 74 more)			
RFS, 12 months	HR, 0.91 (95% CI, 0.71 to 1.15) (265 patients in one study)	553 recurrences or deaths per 1,000	519 recurrences or deaths per 1,000	High	CRS plus HIPEC and chemotherapy has little or no effect on RFS compared with CRS plus chemotherapy
		Difference: 34 fewer per 1,000 (95% CI, 118 fewer to 51 more)			
Grade ≥ 3 AEs, 30 days	RR, 1.32 (95% CI, 0.96 to 1.82) (265 patients in one study)	320 events per 1,000	422 events per 1,000	High	CRS plus HIPEC and chemotherapy has little or no effect on or may worsen grade ≥ 3 AEs at 30 days compared with CRS plus chemotherapy
		Difference: 102 more per 1,000 (95% CI, 13 fewer to 262 more)			
Grade ≥ 3 AEs, 60 days	RR, 1.69 (95% CI, 1.03 to 2.77) (261 patients in one study)	150 events per 1,000	254 events per 1,000	High	CRS plus HIPEC and chemotherapy probably worsens grade ≥ 3 AEs at 60 days compared with CRS plus chemotherapy
		Difference: 104 more per 1,000 (95% CI, 5 more to 266 more)			

Abbreviations: AE, adverse event; CRS, cytoreductive surgery; HIPEC, hyperthermic peritoneal chemotherapy; HR, hazard ratio; OS, overall survival; RFS, relapse-free survival (peritoneal or distant relapse or death); RR, relative risk.

TABLE 7. SBRT for Pretreated Patients With Oligometastatic Colorectal Cancer[21]

Outcome	Study Results	Quality of Evidence	Plain Language Summary
OS (1-year)	67.18% (95% CI, 42.1 to 92.2); 11 studies, I^2 = 0%	Low[a]	OS was approximately 67% at 1 year for patients treated with SBRT
OS (2-year)	56.5% (95% CI, 36.7 to 76.2); 13 studies, I^2 = 0%	Low[a]	OS was approximately 57% at 2 years with for patients treated with SBRT
LC (1-year)	67% (95% CI, 43.8 to 90.2); 13 studies, I^2 = 0%	Low[a]	LC was approximately 67% at 1 year for patients treated with SBRT
LC (2-year)	59.3% (95% CI, 37.2 to 81.5); 13 studies, I^2 = 0%	Low[a]	LC was approximately 59% at 1 year for patients treated with SBRT
Safety (toxicity)	Acute liver toxicity of up to 90%, usually mild-moderate Pooled grade 1-2 and grade 3-4 liver toxicity: 30.7% and 8.7%, respectively Other toxicities: Mild nausea and fatigue Liver failure: 0.6% Treatment-related deaths: 0.004%	Moderate	The toxicity profile was relatively manageable and limited for patients treated with SBRT

Abbreviations: LC, local control; OS, overall survival; SBRT, stereotactic body radiation therapy.
[a]Downgrade: no comparison group. No clear dose-response gradient.

FOLFOX alone (Table 8). First progression events were more likely to occur in the liver for patients treated with FOLFOX only, compared with patients treated with FOLFOX plus SIRT (HR, 0.51; 95% CI, 0.43 to 0.62).

More recently, the EPOCH study assessed the comparison of SIRT with Yttrium-90 glass microspheres plus oxaliplatin or irinotecan-containing chemotherapy to chemotherapy alone as a second-line therapy option for patients who had progressed following first-line therapy.[20] A significant benefit was noted for the coprimary outcomes, PFS and hepatic PFS, with HRs of 0.69 (95% CI, 0.54 to 0.88) and 0.59 (95% CI, 0.46 to 0.77), respectively. ORR was also significantly improved, while there was no difference in OS (HR, 1.07; 95% CI, 0.86 to 1.32), and adverse events were significantly more frequent in the SIRT plus chemotherapy arm (Table 9).

Clinical interpretation. Twenty to 30% of patients with CRC and liver metastases are candidates for surgical resection, which is the only potentially curative treatment option for liver-limited mCRC.[62] A discussion of selection criteria to identify appropriate patients for surgery and timing of surgery are outside the scope of this systematic review. On the basis of this review, SBRT may be considered an option for unresectable liver metastases, given the OS rates of 67% at 1 year and 57% at 2 years after treatment. Using a different subset of studies, local control reportedly was 67% and 59% at one and 2 years after treatment, respectively. The randomized phase II SABR-COMET trial did not meet the inclusion criteria for this review, as it included a small proportion of patients with CRC.[63]

SIRT is an option to explore for improving local control and downstaging hepatic metastases to operability; however, the included meta-analysis found no difference in OS or local control with the addition of SIRT to FOLFOX either in the overall study population or the subgroup without extrahepatic metastases in the first-line setting.[19] The results were more promising in the second-line setting; however, the significantly greater rate of adverse events with SIRT compared with chemotherapy alone resulted in the Expert Panel recommending against the routine use of SIRT for unresectable mCRC.

Clinical Question 7

For patients with mCRC and potentially curable oligometastatic liver metastases, is perioperative chemotherapy recommended?

Recommendation 7.1. Surgery with or without perioperative chemotherapy should be offered to patients with mCRC who are candidates for potentially curative resection of liver metastases (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak).

Qualifying statements.

- Perioperative chemotherapy may be more likely to be recommended over surgery alone in patients with a greater number of metastases or with larger tumors. Shared decision making, including discussion of the potential for benefits and risks of harm outlined in Table 10, is recommended.
- The choice of perioperative chemotherapy or surgery alone, and coordination of treatment sequencing, should be discussed within a MDT that includes expertise in medical oncology and hepatobiliary surgery.
- Perioperative chemotherapy is recommended for a total preoperative and postoperative duration of

TABLE 8. First-Line FOLFOX Plus SIRT Versus FOLFOX for Unselected Patients With Liver-Only or Liver-Dominant Metastases and Limited Extrahepatic Metastases[19]

Outcome	Study Results	Absolute Effect Estimates		Quality of Evidence	Plain Language Summary
		FOLFOX	First-Line FOLFOX + SIRT		
OS	HR, 1.04 (95% CI, 0.90 to 1.19) (1,103 participants in three studies)	749 deaths per 1,000	763 deaths per 1,000	Low[a,b]	FOLFOX plus SIRT probably has little or no effect on OS compared with FOLFOX alone
		Difference: 14 more per 1,000 (95% CI, 37 fewer to 58 more)			
PFS	HR, 0.90 (95% CI, 0.79 to 1.02) (1,103 participants in three studies)	851 deaths or progressions per 1,000	82 deaths or progressions per 1,000	Low[a,b]	FOLFOX plus SIRT probably has little or no effect on PFS, compared with FOLFOX alone
		Difference: 31 fewer per 1,000 (95% CI, 73 fewer to 6 more)			
Grade ≥ 3 AEs	OR, 1.42 (95% CI, 1.09 to 1.85) (1,078 participants in three studies)	670 events per 1,000	742 events per 1,000	Moderate[a]	FOLFOX plus SIRT worsens grade ≥ 3 adverse events during treatment, compared with FOLFOX alone
		Difference: 72 more per 1,000 (95% CI, 19 more to 120 more)			

Abbreviations: AE, adverse event; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HR, hazard ratio; OR, odds ratio; OS, overall survival; PFS, progression-free survival; SIRT, selective internal radiation therapy.

[a]Downgrade: indirectness (38% with extrahepatic metastases).

[b]Downgrade: imprecision.

TABLE 9. SIRT Versus Chemotherapy for Patients With Unresectable Liver Metastases Who Have Progressed on First-Line Chemotherapy[20]

Outcome, Time Frame	Study Results	Absolute Effect Estimates		Quality of Evidence	Plain Language Summary
		Chemotherapy	SIRT + Chemotherapy		
PFS (coprimary outcome), 12 months	HR, 0.69 (95% CI, 0.54 to 0.88) (428 participants in one study)	868 deaths or progressions per 1,000	753 deaths or progressions per 1,000	Moderate[a]	SIRT plus chemotherapy may improve PFS compared with chemotherapy alone
		Difference: 115 fewer per 1,000 (95% CI, 203 fewer to 36 fewer)			
Hepatic PFS (coprimary outcome), 12 months	HR, 0.59 (95% CI, 0.46 to 0.77) (428 participants in one study)	868 deaths or progressions per 1,000	697 deaths or progressions per 1,000	Moderate[a]	SIRT plus chemotherapy may improve hepatic PFS compared with chemotherapy alone
		Difference: 171 fewer per 1,000 (95% CI, 262 fewer to 78 fewer)			
OS, 12 months	HR, 1.07 (95% CI, 0.86 to 1.32) (428 participants in one study)	376 deaths per 1,000	396 deaths per 1,000	Moderate[a]	SIRT plus chemotherapy probably has little or no effect on OS compared with chemotherapy alone
		Difference: 20 more per 1,000 (95% CI, 43 fewer to 87 more)			
ORR	RR, 1.61 (95% CI, 1.17 to 2.21) (428 participants in one study)	211 responses per 1,000	340 responses per 1,000	Moderate[a]	SIRT plus chemotherapy increases the ORR compared with chemotherapy alone
		Difference: 129 more per 1,000 (95% CI, 36 more to 255 more)			
Grade 3 or 4 AEs, 12 months	RR, 1.39 (95% CI, 1.17 to 1.64) (394 participants in one study)	493 events per 1,000	685 events per 1,000	High	SIRT plus chemotherapy increases the rate of grade 3 or 4 AEs compared with chemotherapy alone
		Difference: 192 more per 1,000 (95% CI, 84 more to 316 more)			

Abbreviations: AE, adverse event; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RR, relative risk; SIRT, selective internal radiation therapy.

[a]Downgrade: 13% did not receive planned SIRT. Open-label trial (independent central review) inconsistency.

6 months, on the basis of total duration of chemotherapy in the EORTC 40983 trial.[64]

Literature review and analysis. The search results included the EORTC Intergroup trial 40983, which looked at perioperative chemotherapy with FOLFOX,[22] the JCOG0603 study of postoperative chemotherapy versus surgery alone,[23] and a meta-analysis that included two studies of preoperative chemotherapy with FU plus folinic acid.[24]

Perioperative chemotherapy compared with surgery alone. In the 364-person EORTC study, 94% and 79% of randomly assigned patients started and completed six cycles of preoperative chemotherapy, respectively. PFS was not significantly different for perioperative chemotherapy versus surgery alone in the intention-to-treat study population (HR, 0.79; 95% CI, 0.62 to 1.02); however, in an exploratory analysis of the 83% of randomly assigned patients who ultimately underwent surgery, the HR for PFS favored the perioperative chemotherapy group (HR, 0.73; 95% CI, 0.55 to 0.97). There was no significant difference in OS between groups, and reversible postoperative complications were more likely in the perioperative chemotherapy group (Table 10). The definition of reversible postoperative complications was not provided.

Hepatectomy plus postoperative FOLFOX compared with hepatectomy alone. In the JCOG0603 study, OS was not significantly different for patients who received hepatectomy plus postoperative FOLFOX, or hepatectomy alone (HR, 1.25; 95% CI, 0.78 to 2.0); however, for the primary outcome DFS, the HR was 0.67 (95% CI, 0.50 to 0.92), favoring the postoperative chemotherapy group.[23] Adverse events were more likely in the group that received FOLFOX, compared with surgery alone (Table 11). In this trial, there was an imbalance in postrecurrence interventions; the proportion of patients receiving oxaliplatin-based therapy was higher in the hepatectomy-only arm, and the proportion receiving irinotecan was higher in the chemotherapy arm.

Single-agent chemotherapy (FU plus folinic acid) after potentially curative resection of metastases from CRC versus resection alone. There were no significant differences found in DFS or OS in a pooled univariate analysis of two trials of FU plus folinic acid following potentially curative resection of CRC metastases, compared with resection alone.[24] In a multivariate analysis controlling for number of metastases, previous adjuvant chemotherapy, and maximum size of metastases, DFS showed a significant benefit in favor of postoperative FU plus folinic acid (HR, 0.72; $P = .026$; CIs not provided). In a multivariate analysis controlling for number of metastases, disease-free interval, maximum size of metastases, and WHO performance status, the estimate of the association of treatment group for OS also showed a significant benefit in favor of postoperative chemotherapy (HR, 0.72; $P = .046$; CIs not provided). Risk of recurrence or death was significantly elevated in patients with two or more metastases, compared with one metastasis.

Clinical interpretation. Because relapse after surgical resection occurs in approximately 75% of patients, there is a need for additional treatment options that may reduce the risk of recurrence and improve OS.[24] The EORTC 40983 trial, conducted between 2000 and 2004, met its accrual targets because of the inclusion of patients from a large number of centers. The finding of a small but significant PFS benefit of perioperative chemotherapy within the resected group of patients in this trial suggests that chemotherapy in addition to surgery may be an option for patients with resectable liver metastases from CRC. The lack of an OS difference in the intention-to-treat population may be associated with the significant percentage of patients who were unresectable, which was mostly because of the discovery during operation of more advanced disease than expected on the basis of the findings from imaging. Imaging techniques have improved since the time period of this study, resulting in improved ability to identify appropriate patients for surgery and perioperative chemotherapy. Both studies that were included in the pooled analysis of postoperative FU plus folinic acid compared with surgery alone, failed to meet accrual targets; however, the significant benefits found in the multivariable analysis indicate that single-agent FU may also be an option for resectable patients. The significantly greater benefit of chemotherapy in patients with two or more metastases may be a factor to consider during shared decision making. In addition, a significant benefit of adjuvant doublet chemotherapy was found in the JCOG0603 study.

Given the limited data available to support the recommendation for either perioperative or postoperative chemotherapy, the option of surgery alone is also noted for consideration within the recommendation, and the potential for benefit and risks of adverse events should be considered. The rate of peripheral neuropathy in a trial of patients with stage II CRC ranged from 13% to 36% with 3 or 6 months of oxaliplatin-containing chemotherapy, respectively.[65] Nordlinger et al[22] note the consideration of hepatotoxicity, which varies on the basis of the drugs used for chemotherapy, and can include the development of vascular lesions after treatment with oxaliplatin. Karoui et al[66] found that among patients who received chemotherapy, the risk of morbidity was increased when ≥ 6 cycles of chemotherapy were administered, compared with < 6 cycles. The trial by Nordlinger et al was likely the last to have a study arm with patients undergoing surgery alone.

DISCUSSION

This guideline adds to previous resource-stratified guidance from ASCO for patients with mCRC,[67] and previous ASCO guidance for systemic therapy for patients with stage II[77] and stage III CRC.[68] The scope of this guideline was designed to address selected outstanding areas of uncertainty in the treatment of mCRC; thus, not all possible

TABLE 10. Perioperative Chemotherapy Versus Surgery Alone for Patients With Liver Metastases From Colorectal Cancer[22]

Outcome, Time Frame	Study Results	Absolute Effect Estimates		Quality of Evidence	Plain Language Summary
		Surgery Alone	Perioperative Chemotherapy		
PFS (ITT, primary outcome), 3 years	HR, 0.79 (95% CI, 0.62 to 1.02) (364 participants in one study)	719 deaths or progressions per 1,000	633 deaths or progressions per 1,000	Moderate[a]	Perioperative FOLFOX may have little or no effect on PFS compared with surgery alone
		Difference: 86 fewer per 1,000 (95% CI, 174 fewer to 7 more)			
PFS (resected patients), 3 years	HR, 0.73 (95% CI, 0.55 to 0.97) (303 participants in one study)	668 deaths or progressions per 1,000	553 deaths or progressions per 1,000	Low[a,b]	For patients who ultimately undergo resection, perioperative chemotherapy may improve PFS compared with surgery alone
		Difference: 115 fewer per 1,000 (95% CI, 213 fewer to 11 fewer)			
OS (ITT), 5 years	HR, 0.88 (95% CI, 0.69 to 1.14) (303 participants in one study)	522 deaths[64] per 1,000	478 deaths per 1,000	Moderate[a]	Perioperative chemotherapy may have little or no effect on OS compared with surgery alone
		Difference: 44 fewer per 1,000 (95% CI, 123 fewer to 47 more)			
Reversible postoperative complications	RR, 1.58 (95% CI, 1.02 to 2.45) (329 participants in one study)	160 per 1,000	253 per 1,000	Moderate[a,c]	Perioperative chemotherapy increases the rate of reversible postoperative complications
		Difference: 93 more per 1,000 (95% CI, 3 more to 232 more)			

Abbreviations: FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; RR, relative risk.

[a]Downgrade: lack of blinding of participants, personnel, or assessors.

[b]Exploratory subgroup analysis not specified in study protocol; planned before data analysis.

[c]≥ 5% of patients in the perioperative group experienced biliary fistula (8%), hepatic failure (7%), and intra-abdominal infection (7%). ≥ 5% of patients in the surgery alone group experienced hepatic failure (5%).

treatment options have been addressed, particularly for liver-directed therapy.

Testing for molecular subtypes was also outside the scope of this guideline; ASCO has an existing Provisional Clinical Opinion that supports tumor testing in a Clinical Laboratory Improvement Amendments–certified laboratory for mutations in both *KRAS* and *NRAS* exons 2 (codons 12 and 13), 3 (codons 59 and 61), and 4 (codons 117 and 146).[69] It is assumed that patients will have access to molecular testing to implement this guideline's recommendations for specific molecular subtypes. Although sufficient evidence to recommend treatment on the basis of other molecular subtypes such as human epidermal growth factor receptor 2/neu amplified CRC and TRK-fusion CRC was out of scope for this iteration of the guideline, these targets will be considered in future updates.

Another important point that applies across guideline recommendations is the necessity of implementation within the context of a MDT, and the membership of this team is detailed following several of the recommendations. The recommendation related to CRS is also qualified by a statement that the procedures should only be performed at higher volume or specialized centers by individuals with significant experience with the procedure. Many recommendations within this guideline have been given a strength of weak, on the basis of moderate or lower quality evidence. According to the GRADE system, a weak recommendation is one for which most informed people would choose the recommended course of action, but a substantial number would not. For this reason, a shared decision-making approach is advised across recommendations, considering performance status, contraindications to therapies such as anti-VEGF antibodies, values and preferences, and other factors, as several of the recommended treatment options have a significant risk of adverse events, which needs to be carefully weighed along with the potential for benefit.

PATIENT AND CLINICIAN COMMUNICATION

Studies have demonstrated the value of effective communication between a patient and their health care team and provider. The modern patient's needs are growing: early referral to palliative and supportive care services benefits patients' psychologic and physical well-being and improves survival, as well as benefits caregivers. However, doctors can find it difficult to initiate discussions about palliative care, particularly if they have close emotional bonds with the patient and their family.[70] For

TABLE 11. Hepatectomy Plus Postoperative FOLFOX Versus Hepatectomy Alone in Patients With Liver-Only Colorectal Cancer Metastases[23]

Outcome, Time Frame	Study Results	Absolute Effect Estimates		Quality of Evidence	Plain Language Summary
		Hepatectomy	Hepatectomy + Postoperative FOLFOX		
DFS (primary outcome), 3-year	HR, 0.67 (95% CI, 0.50 to 0.92) (300 participants in one study)	574 recurrences, secondary cancers or deaths per 1,000	435 recurrences, secondary cancers or deaths per 1,000	Moderate[a]	Hepatectomy plus postoperative FOLFOX probably improves DFS
		Difference: 139 fewer per 1,000 (95% CI, 227 fewer to 30 fewer)			
OS, 3-year	HR, 1.25 (95% CI, 0.78 to 2.00) (300 participants in one study)	82 deaths per 1,000	101 deaths per 1,000	Low[a,b]	We are unsure of the effect of hepatectomy plus postoperative FOLFOX on OS. The addition of FOLFOX to hepatectomy may worsen OS
		Difference: 19 more per 1,000 (95% CI, 17 fewer to 75 more)			
AEs	—			High	Hepatectomy plus postoperative FOLFOX worsens adverse events, compared with hepatectomy alone

Abbreviations: AE, adverse event; DFS, disease-free survival; HR, hazard ratio; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; OS, overall survival.
[a]Downgrade: inconsistency of results between OS and DFS; open-label trial; trial terminated early according to protocol.
[b]Insufficient follow-up of this end point noted by Kanemitsu et al.

recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[71]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care and/or receive fragmented care. Factors such as race and ethnicity, age, socioeconomic status, sexual orientation and gender identity, geographic location, and insurance access are known to affect cancer care outcomes.[72] Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial/ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving fragmented care or poor-quality care than other Americans.[73-76] Another recent ASCO guideline for stage II colon cancer outlined disparities in incidence, access to care, and outcomes, including a higher rate of occurrence and mortality among Black residents of the United States.[77] Potential reasons for these disparities included lack of family history knowledge, unequal access, insufficient data needed to address the underlying issues, biological factors, and travel burden. Socioeconomic status was also associated with treatment delays in a UK study.[78] In the United States, a recent study looking at claims data showed that among patients who sought chemotherapy or surgery, Black patients waited an average of eight days longer (67 days after diagnosis) than White patients (59 days after diagnosis). Black patients were also more likely (6.8%) to experience 60 or more days of delayed treatment after diagnosis. In total, more than a third of Black patients experienced this delay.[79] To address these issues, a targeted approach that meets the specific needs of individual populations is recommended.[80] With respect specifically to mCRC, authors of one study that used data from a large database found that a significantly lower percentage of patients who were Black (41.8%) received next-generation sequencing genetic testing, compared with patients who were White (51.6%).[81] Authors of one study found that disparities in outcomes for minority patients with mCRC and lower socioeconomic status can potentially be overcome by equalizing access to care, which may result in outcomes being on par with clinical trials.[82]

In addition to addressing race and inequitable care for mCRC, it is worth highlighting the global rise in early-onset CRC. Authors of one article found that early-onset patients age 35-49 years were most likely to present with symptoms of metastatic disease within 30 days of diagnosis. Roughly 8% of patients age younger than 35 years were found to have sought care at least once for a secondary neoplasm indicative of metastatic disease within 30 days of their initial CRC diagnosis. The rate of concurrent secondary neoplasm at presentation was 13.7% within the 35-49 years age group, and 9.63% in the 50 years or older age group.[83]

Authors of a recent JAMA article reported that by 2030, it is predicted that CRC will be the number one cause of deaths for those between ages 20 and 49 years in the United States, as it associated with aggressive tumor characteristics.[84] Recently, *The Lancet* produced an extensive two-part series providing insight into the unique challenges faced by this patient population, which included the role of energy balance, biological and genomic mechanisms (including microbiome aspects), and the treatment of early-onset CRC, as well as psychosocial challenges of being diagnosed with CRC cancer at younger age, and the potential financial toxicities faced by younger patients.[85]

Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations. Additionally, stakeholders should work toward achieving health equity by ensuring equitable access to both high-quality cancer care and research, and addressing the structural barriers that preserve health inequities.[72]

COST IMPLICATIONS

Despite health insurance, almost three fourths of patients in the United States experienced financial hardship within the first year after diagnosis, according to the authors of a recent study.[86] For this reason, screening for medical financial hardship is critically important. Many providers and practices use lack of insurance at a single visit to screen patients; however, within that study, this approach would miss or exclude the majority of the patients with mCRC who reported financial hardship. A review of this study notes that financial hardship is dynamic and often cumulative. They recommend routine and comprehensive screening for financial hardship and social needs using validated instruments and documentation of referrals in electronic health records. [87]

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[88,89] Higher patient out-of-pocket costs are a barrier to initiating and adhering to recommended cancer treatments.[90,91] Discussion of cost can be an important part of shared decision making.[92] Clinicians should discuss with patients all treatment alternatives. It is important to patients to understand both the cost implications as well the time commitment and feasibility to ensure informed decision making. It is especially important to have this discussion when there are two or more treatment options that are comparable in terms of benefits and harms.[92]

Patient out-of-pocket costs may vary depending on insurance coverage, and medication prices may vary markedly, depending on negotiated discounts and rebates. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even within the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services, industry-funded patient assistance programs, as well as nonprofit organizations both locally and nationally that are available to support patients and their families facing this complex and heterogeneous landscape.[92]

As part of the guideline development process, ASCO may opt to search the literature for published cost-effectiveness analyses that might inform the relative value of available treatment options. Excluded from consideration are cost-effective analyses that lack contemporary cost data; agents that are not currently available in either the United States or Canada; and/or are industry-sponsored. ASCO has previously published a guidance that recommends *KRAS* and *NRAS* screening to identify appropriate patients for anti-EGFR therapy and to avoid the treatment costs and other adverse effects of anti-EGFR therapy in patients with these mutations.[69] A cost-effectiveness analysis of screening for *KRAS* and *NRAS* in mCRC found that, while screening reduced overall costs associated with anti-EGFR therapy, the cost-effectiveness ratio was above the generally accepted maximum value of $100,000 US dollars per quality-adjusted life-year (QALY).[93] Authors of another analysis that looked at the cost-effectiveness of selecting patients for anti-EGFR therapy on the basis of tumor location (ie, left-sided tumors) found that including this variable improved cost-effectiveness, although the cost per QALY was still well above the acceptable threshold. These authors suggest that the price of anti-EGFRs could be reduced to meet the effectiveness threshold.[94] Likewise, a study found that while the addition of bevacizumab improved survival, it would not be cost-effective at a threshold of $100,000 US dollars per QALY unless the price could be reduced.[95]

OPEN COMMENT

The draft recommendations were released to the public for open comment from March 1 through March 15, 2022. Response categories of "Agree as written," "Agree with suggested modifications" and "Disagree. See comments" were captured for every proposed recommendation with written comments received. The Expert Panel members reviewed comments and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. The majority of the 26 respondents either agreed or agreed with slight modifications to Recommendations 1 through 4. A significant percentage (28%) of respondents disagreed with Recommendation 5.1 related to CRS. The Expert Panel added wording to clarify that CRS is only appropriate for select patients in specialized centers, and added further text to clarify that CRS is recommended *without* HIPEC.

Several respondents commented on the importance of MDT management of patients, particularly for the recommendations related to liver-directed therapy. All changes were incorporated before Evidence Based Medicine Committee review and approval.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guidelines Implementation Network (PGIN) on the panel. The additional role of this PGIN representative on the guideline panel is to assess the suitability of the recommendations to implementation in the community setting, but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a Supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/gastrointestinal-cancer-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Integration of Palliative Care into Standard Oncology Care[96] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[71] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Treatment of Patients with Late-Stage Colorectal Cancer[67] (http://ascopubs.org/doi/10.1200/JGO.19.00367)
- Adjuvant Therapy for Stage II Colon Cancer[77] (http://ascopubs.org/doi/10.1200/JCO.21.02538)
- Duration of Oxaliplatin-Containing Adjuvant Therapy for Stage III Colon Cancer[68] (http://ascopubs.org/doi/10.1200/JCO.19.00281)

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EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/gastrointestinal-cancer-guidelines.

EQUAL CONTRIBUTION

V.K.M. and C.E. were expert panel cochairs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Treatment of Metastatic Colorectal Cancer: ASCO Guideline

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APPENDIX

TABLE A1. Metastatic Colorectal Cancer Guideline Expert Panel Membership

Name	Affiliation	Role or Area of Expertise
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Chiara Cremolini, MD, PhD	University of Pisa, Pisa, Italy	Medical Oncology
Anjee Davis, MPPA	Fight Colorectal Cancer, Springfield, MO	Patient Representative
Dustin A. Deming, MD	University of Wisconsin Carbone Cancer Center, Madison, WI	Medical Oncology
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Sepideh Gholami, MD	UC Davis Health, Davis, CA	Liver Cancer Surgery
Theodore S. Hong, MD	Massachusetts General Hospital, Boston, MA	Radiation Oncology
Ishmael Jaiyesimi, DO	Beaumont Hospital, Royal Oak, MI	Medical Oncology, Practice Guidelines Implementation Network Representative
Kelsey Klute, MD	University of Nebraska, Omaha, NE	Medical Oncology
Christopher Lieu, MD	CU Medicine, Denver, CO	Medical Oncology
Hanna Sanoff, MD, MPH	University of North Carolina, Chapel Hill, NC	Medical Oncology
John H. Strickler, MD	University Medical Center, Durham, NC	Medical Oncology
Sarah White, MD	Medical College of Wisconsin, Milwaukee, WI	Interventional Radiology
Jason A. Willis, MD, PhD	University of Texas MD Anderson Cancer Center, Houston, TX	Medical Oncology
Erin B. Kennedy, MHSc	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

TABLE A2. Recommendation Rating Definitions

Term	Definitions
Quality of evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Strength of recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects All or almost all informed people would make the recommended choice for or against an intervention
Weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. Most informed people would choose the recommended course of action, but a substantial number would not