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Treatment of Metastatic Colorectal Cancer

ASCO Guideline

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1 Background & Methodology

Introduction

- Colorectal cancer is the third most common type of cancer diagnosed worldwide.[1] Almost 150,000 new cases and over 50,000 deaths from CRC are reported each year in the US.[2]
- In recent decades, the overall incidence of CRC has decreased among older adults due to screening and lifestyle factors. At the same time, incidence is increasing among younger adults.[3]
- The 5-year relative OS for patients with metastatic colorectal cancer (mCRC) is ~15%.[4]
- Approximately 33% of patients with CRC will develop metastases either at presentation or follow-up.[5]
- Evaluating treatment options is complex due to the heterogeneity of the patient population, including different molecular subtypes. Treatment has included conventional fluorouracil-based CT, 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.

ASCO Guideline Development Methodology

- The ASCO Evidence Based Medicine Committee (EBMC) guideline process includes:
  - a systematic literature review by ASCO guidelines staff
  - an expert panel provides critical review and evidence interpretation to inform guideline recommendations
  - final guideline approval by ASCO EBMC

- The full ASCO Guideline methodology manual can be found at: www.asco.org/guideline-methodology

Clinical 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 (FOLFOX of FOLFIRI) or triplet (FOLFOXIRI) cytotoxic chemotherapy recommended?
2. (a) In the first-line setting, are outcomes for patients with MSI-H or dMMR mCRC improved with pembrolizumab immunotherapy vs. 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 mutation/Mb)?
3. For patients with treatment-naïve RAS wild-type mCRC, are anti-EGFR antibodies (i.e. panitumumab, cetuximab) recommended for patients with right- 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 to chemotherapy plus targeted therapy?

Clinical Questions

5. For patients with colorectal peritoneal metastases, are outcomes improved with CRS with or without HIPEC plus chemotherapy, compared to chemotherapy alone?
6. For patients with unresectable liver-limited mCRC, are liver-directed therapies SBRT, or SIRT recommended?
7. For patients with mCRC and potentially curable oligometastatic liver metastases, is perioperative chemotherapt recommended?

Target Population and Audience

Target Population

- Patients with mCRC

Target Audience

- Medical oncologists and other healthcare professionals who treat patients with mCRC, patients, and caregivers

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2 Summary of Recommendations

Summary of 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.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate	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.*

Summary of Recommendations

Recommendation 1.2

- Triplet (FOLFOXIRI) backbone chemotherapy may be offered as first-line therapy to selected patients with initially unresectable MSS or pMMR mCRC.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate	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-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 to doublet chemotherapy (See Table 1 in the guideline publication).*

Summary of Recommendations

Clinical Question 2

a. In the first-line setting, are outcomes for patients with MSI-H or dMMR mCRC improved with pembrolizumab immunotherapy vs. 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 mutation/Mb)?

Recommendation 2.1

- Pembrolizumab should be offered as first-line therapy to patients with MSI-H or dMMR mCRC.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Note: *Pembrolizumab is not recommended for patients with mCRC and TMB ≥ 10 mutations per megabase. See full guideline for discussion of patients with MSS or pMMR mCRC and high TMB.*

Summary of Recommendations

Clinical Question 3

- For patients with treatment-naïve RAS wild-type mCRC, are anti-EGFR antibodies (i.e. panitumumab, cetuximab) recommended for patients with right- 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.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Summary of Recommendations

Qualifying statements for Recommendation 3.1 :

- *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-naïve 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 (See Table 3 in the guideline publication).*

Summary of Recommendations

Clinical Question 4

- For patients with previously treated BRAF V600E-mutant mCRC, does treatment with encorafenib plus cetuximab result in better outcomes compared to 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.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Summary of Recommendations

Clinical Question 5

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

Recommendation 5.1

- Cytoreductive surgery plus systemic chemotherapy may be recommended for selected patients with colorectal peritoneal metastases.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Summary of Recommendations

Qualifying statements for Recommendation 5.1:

- *In the PRODIGE 7 trial, 15% of patients with isolated colorectal peritoneal metastases experienced no disease progression in the five 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.[7] CRS should be considered as a treatment option only within these specialized centers.*
- *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 in the guideline publication).*

Summary of Recommendations

Recommendation 5.2

- Oxaliplatin-based HIPEC is not recommended as an addition to CRS for treatment of patients with colorectal peritoneal metastases.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Summary of Recommendations

Clinical Question 6

- For patients with unresectable liver-limited mCRC, are liver-directed therapies SBRT or 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.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Low	Weak

Summary of Recommendations

Recommendation 6.2

- SIRT is not routinely recommended for patients with mCRC and unilobar or bilobar metastases of the liver.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate	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.*

Summary of Recommendations

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.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate	Weak

Summary of Recommendations

Qualifying statements for Recommendation 7.1 :

- *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 (in the guideline publication) is recommended.*
- *The choice of perioperative chemotherapy or surgery alone, and coordination of treatment sequencing, should be discussed within a multidisciplinary team that includes expertise in medical oncology and hepatobiliary surgery.*
- *Perioperative chemotherapy is recommended for a total pre- and postoperative duration of 6 months, based on total duration of chemotherapy in the EORTC 40983 trial.*

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3 Discussion

Patient and Clinician Communication

- Studies have demonstrated the value of effective communication between a patient and their healthcare team and provider.
- The modern patient's needs are growing
- Early referral to palliative and supportive care services benefits patients' psychological 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.[8]
- For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[9]

Health Disparities

- A 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 US.[10]
- Socioeconomic status was also associated with treatment delays in a UK study.[11]
- To address these issues, a targeted approach that meets the specific needs of individual populations is recommended.[12]
- Additionally, there is a global rise in early-onset CRC.
- Awareness of these disparities in access to care should be considered in the context of this guideline, and clinicians should strive to deliver the highest level of care to these vulnerable populations.
- Stakeholders should work towards achieving health equity by ensuring equitable access to both high-quality cancer care and research, and addressing the structural barriers that preserve health inequities.[13]

Cost Implications

- Specific to recommended treatment options in this guideline, there are cost-effectiveness analyses for KRAS and NRAS screening to identify appropriate patients for anti-EGFR therapy.
- 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 per QALY. [14]
- Authors of another analysis that looked at the cost-effectiveness of selecting patients for anti-EGFR therapy based on tumor location 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.[15]
- Likewise, a study found that while the addition of bevacizumab improved survival, it would not be cost-effective at a threshold of $100,000 per QALY unless the price could be reduced.[16]

Additional Resources

- More information, including a supplement and clinical tools and resources, is available at www.asco.org/gastrointestinal-cancer-guidelines

- Patient information is available at www.cancer.net

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Abbreviations

- ASCO, American Society of Clinical Oncology
- CRC, colorectal cancer
- CRS, cytoreductive surgery
- dMMR, deficient mismatch repair
- EBMC, Evidence Based Medicine Committee
- EGFR, epidermal growth factor receptor
- FOLFIRI, folinic acid, fluorouracil, and irinotecan
- FOLFOX, folinic acid, fluorouracil, and oxaliplatin
- FOLFOXIRI, folinic acid, fluorouracil, oxaliplatin, and irinotecan
- HIPEC, hyperthermic intraperitoneal chemotherapy
- mCRC, metastatic colorectal cancer
- MDT, multidisciplinary team
- MSI-H, microsatellite instability-high
- MSS, microsatellite stable
- OS, overall survival
- pMMR, proficient mismatch repair
- QALY, quality adjusted life year
- SBRT, stereotactic body radiation therapy
- SIRT, selective internal radiation therapy
- TMB, tumor mutational burden
- UK, United Kingdom
- US, United States

References

1. Sung H, Ferlay J, Siegel RL, et al: Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 71:209-249, 2021
2. Siegel RL, Miller KD, Fuchs HE, et al: Cancer Statistics, 2021. CA Cancer J Clin 71:7-33, 2021
3. American Cancer Society: Colorectal cancer facts and figures: 2020-2022. Atlanta, GA, American Cancer Society, 2020
4. Centers for Disease Control and Prevention: Cancer Stat Facts: Colorectal Cancer SEER 18 2011–2017. 2022 https://seer.cancer.gov/statfacts/html/colorect.html
5. Väyrynen V, Wirta E-V, Seppälä T, et al: Incidence and management of patients with colorectal cancer and synchronous and metachronous colorectal metastases: a population-based study. BJS Open 4:685-692, 2020
6. Baran B, Mert Ozupek N, Yerli Tetik N, et al: Difference Between Left-Sided and Right-Sided Colorectal Cancer: A Focused Review of Literature. Gastroenterology Res 11:264-273, 2018
7. Quénet F, Elias D, Roca L, et al: Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 22:256-266, 2021
8. Horlait M, Chambaere K, Pardon K, et al: What are the barriers faced by medical oncologists in initiating discussion of palliative care? A qualitative study in Flanders, Belgium. Support Care Cancer 24:3873-81, 2016
9. Gilligan T, Coyle N, Frankel RM, et al: Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline. Journal of Clinical Oncology 35:3618-3632, 2017
10. Baxter NN, Kennedy EB, Bergsland E, et al: Adjuvant Therapy for Stage II Colon Cancer: ASCO Guideline Update. Journal of Clinical Oncology 40:892-910, 2022
11. Lejeune C, Sassi F, Ellis L, et al: Socio-economic disparities in access to treatment and their impact on colorectal cancer survival. Int J Epidemiol 39:710-7, 2010
12. Jackson CS, Oman M, Patel AM, et al: Health disparities in colorectal cancer among racial and ethnic minorities in the United States. J Gastrointest Oncol 7:S32-43, 2016
13. Patel MI, Lopez AM, Blackstock W, et al: Cancer Disparities and Health Equity: A Policy Statement From the American Society of Clinical Oncology. J Clin Oncol 38:3439-3448, 2020
14. Behl AS, Goddard KA, Flottemesch TJ, et al: Cost-effectiveness analysis of screening for KRAS and BRAF mutations in metastatic colorectal cancer. J Natl Cancer Inst 104:1785-95, 2012
15. Wong WWL, Zargar M, Berry SR, et al: Cost-effectiveness analysis of selective first-line use of biologics for unresectable RAS wild-type left-sided metastatic colorectal cancer. Curr Oncol 26:e597-e609, 2019
16. Parikh RC, Du XL, Robert MO, et al: Cost-Effectiveness of Treatment Sequences of Chemotherapies and Targeted Biologics for Elderly Metastatic Colorectal Cancer Patients. J Manag Care Spec Pharm 23:64-73, 2017

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