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ACR Appropriateness Criteria[®] Rectal Cancer: Metastatic Disease at Presentation

Abstract: The management of rectal cancer in patients with metastatic disease at presentation is highly variable. There are no phase III trials addressing therapeutic approaches, and the optimal sequencing of chemotherapy, radiation therapy, and surgery remains unresolved. Although chemoradiation is standard for patients with stage II/III rectal cancer, its role in the metastatic setting is controversial. Omitting chemoradiation may not be appropriate in all stage IV patients, particularly those with symptomatic primary tumors. Moreover, outcomes in this setting are vastly different, as some treatments carry the potential for cure in selected patients while others are purely palliative. The American College of Radiology Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed every 3 years by a multidisciplinary expert panel. The guideline development and review include an extensive analysis of current medical literature from peer-reviewed journals and the application, by the panel, of a well-established consensus methodology (modified Delphi) to rate the appropriateness of imaging and treatment procedures. In instances in which evidence is lacking or not definitive, expert opinion may be used as the basis for recommending imaging or treatment.

Summary of Literature Review

Introduction/Background

According to the American Cancer Society, 40,000 new cases of rectal cancer were diagnosed in the United States in 2014.[1] Approximately 15% of these patients had metastatic disease at presentation.[2] The management of metastatic colorectal cancer (mCRC) has evolved over the past several decades with the introduction of improved surgical techniques, radiological and pathological staging, and regimens for systemic and radiation therapy (RT). As a result, the overall survival of patients with mCRC has improved significantly in recent years.[3] Furthermore, a small but important group of these patients potentially may be cured of their disease through multimodality management.[4] However, for the majority of patients with mCRC, the aim of therapy is to prolong survival and palliate symptoms.

Management of patients with newly diagnosed metastatic rectal cancer (mRC) may be complex, and treatment decisions benefit from multidisciplinary input. Management must be individualized based on the overall medical condition of the patient, the extent and distribution of metastatic disease, and the patient's wishes.

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Variant 1 Initial treatment of a 52-year-old man without a significant past medical history, with an asymptomatic, non-obstructing, uT3N0 primary rectal tumor 8 cm from the anal verge and a solitary, resectable, 4-cm metastasis in the right lobe of the liver. The patient's Karnofsky performance status (KPS) is 90.

Treatment	Rating ^a	Comments
Initial resection of the rectal primary by total mesorectal excision and of the liver lesion (either concurrent or sequential)	7	
Initial systemic 5-FU–based chemotherapy (FOLFOX/FOLFIRI) then surgery	7	Consider anti-EGFR agents with FOLFOX/FOLFIRI in wild-type <i>KRAS</i> tumors.
Initial systemic 5-FU–based chemotherapy (FOLFOX/FOLFIRI), then short-course pelvic RT, then surgery	7	Consider anti-EGFR agents with FOLFOX/FOLFIRI in wild-type <i>KRAS</i> tumors.
Initial systemic 5-FU–based chemotherapy (FOLFOX/FOLFIRI), then long-course chemoradiation, then surgery	7	Consider anti-EGFR agents with FOLFOX/FOLFIRI in wild-type <i>KRAS</i> tumors.
Initial long-course chemoradiation	6	
Resection of the liver lesion only	2	
Best supportive care	1	

^aRating Scale: 1,2,3 = usually not appropriate; 4,5,6 = may be appropriate; 7,8,9 = usually appropriate.

5-FU = 5-fluorouracil; EGFR = epidermal growth factor receptor; FOLFIRI = 5-FU/leucovorin [LV]/irinotecan;

FOLFOX = 5-FU/LV/oxaliplatin; RT = radiation therapy.

Management of the Primary Tumor

The optimal management of the primary tumor in patients with metastatic disease is controversial; however, the paradigm is changing with the substantial improvements in systemic therapy and the expected duration of survival. Given the potential for cure after resection of all locoregional and distant disease, the approach to the primary tumor is determined by the resectability of the metastatic lesions as well as the severity of symptoms from the primary rectal mass.

Resectable Metastatic Disease

After resection of the primary tumor and distant metastases, patients with mCRC may experience long-term survival, and a small subset may be cured. [4] Therefore, aggressive surgical management is warranted.

Patients with low-volume, stage T1-

T2N0 metastatic disease, or high rectal primary tumors may be treated ideally with upfront resection of the primary tumor and metastases or with preoperative chemotherapy alone followed by a synchronous or staged resection of the primary tumor and metastases. On the other hand, patients with T3-4, regional node-positive or low-lying primary tumors should be considered for preoperative combined-modality therapy (CMT) with 5-fluorouracil (5-FU) and pelvic RT to reduce the risk of pelvic recurrence. Although limited data exist to support this approach in mRC, the improved local control and decreased toxicity with preoperative vs postoperative CMT may be extrapolated from the data on patients with locally advanced rectal cancer.[5] In the United States, long-course chemoradiation (50.4 Gy in 28 fractions) is the standard preoperative management of rectal cancer; however, short-

course RT (25 Gy in 5 fractions) may be considered in the setting of mRC to reduce the delay before surgery and initiation of full-dose systemic therapy. [6] Any patient with an obstructing tumor should undergo surgical diversion prior to initiating CMT, regardless of the fractionation schedule used. A less preferable option for these patients would be endoscopic placement of a rectal stent.

Patients who have undergone upfront complete resection of both the primary tumor and all known metastatic disease can be considered candidates for the postoperative management routinely provided in stage II or III rectal cancer, which may include adjuvant chemotherapy with or without chemoradiation based on the stage and location of the primary tumor. Postoperative CMT should be strongly considered for any patient with T4 disease who did not receive preoperative pelvic RT.

Unresectable Metastatic Disease

The primary management of unresectable metastatic disease is chemotherapy. In the majority of cases, initiation of chemotherapy should not be postponed in favor of local therapy, given the high response rates and infrequency of rapid progression through first-line regimens. One important exception is patients with bowel obstructions, which require immediate diversion.

As with all scenarios, however, care plans must be individualized to the particular needs of the patient based on the pattern and pace of metastatic disease, degree of symptoms, risk of imminent obstruction, and comorbidities. For example, patients with a low burden of metastatic disease, a bulky rectal tumor, and a high likelihood of long-term survival may benefit from treatment of the primary tumor to prevent symptoms from progressive or recurrent pelvic disease. Since preoperative CMT followed by resection

may be the most effective approach for controlling the rectal primary, these patients may be appropriately treated with this regimen. Alternatively, chemotherapy may be provided upfront, and patients who achieve a favorable response may be treated subsequently with consolidative CMT and surgery to provide local control. On the other hand, patients with high-volume metastases and a small, asymptomatic rectal tumor are likely to die of their systemic disease before the primary tumor causes significant symptoms. In such patients, systemic chemotherapy is usually most appropriate, with local pelvic therapy reserved for palliation, if needed.

Management of Liver Metastases

The liver is the most frequent and often the only site of metastasis in CRC. Complete surgical resection of liver metastases can improve survival to an impressive 40% at 5 years and 25% at 10 years post treatment.[7] Therefore, patients who are candidates for surgery, have resectable liver metastases, and have minimal or resectable extrahepatic disease should be directed to operative treatment. Such patients may undergo either a staged or synchronous resection of the metastases and primary rectal tumor.[8-11] There is no consensus regarding the best sequence; rather, institutional philosophy tends to guide management.

The classic approach is surgical removal of the primary tumor, which is considered to be the nidus of metastatic disease, followed by chemotherapy and a second surgery to remove the liver metastases at a later date. If patients progress while on chemotherapy between the two surgeries, the second surgery may not be performed. This approach may be most appropriate for patients who are symptomatic from their primary tumor. Evidence to support this classic approach suggests that the primary tumor affects the liver to promote angiogenesis and metastasis.

Variant 2 Initial treatment of a 60-year-old woman without a significant past medical history, with uT3N0 rectal cancer 4 cm from the anal verge causing pain and early symptoms of obstruction, bilobar hepatic metastases (50% liver replacement), and bilateral pulmonary metastases. A colonoscope can be passed through the lesion. The patient's Karnofsky performance status (KPS) is 80.

Treatment	Rating ^a	Comments
Initial systemic 5-FU–based chemotherapy (FOLFOX/FOLFIRI)	8	Consider anti-EGFR agents with FOLFOX/FOLFIRI in wild-type <i>KRAS</i> tumors.
Initial long-course chemoradiation	7	
Initial palliative stent or loop colostomy to relieve obstruction	5	Given the low location, diversion may be better due to complications and pain related to stent placement.
Initial systemic 5-FU–based chemotherapy (FOLFOX/FOLFIRI plus bevacizumab)	4	
Initial resection of rectal primary	3	
Initial palliative pelvic RT alone	2	
Initial surgical debulking of metastatic disease	1	
Initial liver-directed therapies (transarterial embolization, radiation, RFA)	1	
Best supportive care	1	

^aRating Scale: 1,2,3 = usually not appropriate; 4,5,6 = may be appropriate; 7,8,9 = usually appropriate. 5-FU = 5-fluorouracil; EGFR = epidermal growth factor receptor; FOLFIRI = 5-FU/leucovorin (LV)/irinotecan; FOLFOX = 5-FU/LV/oxaliplatin; RFA = radiofrequency ablation; RT = radiation therapy.

[12] A synchronous resection of primary tumor and liver metastases obviates the need for two separate operations, but the more arduous surgery may not be suitable for patients with a poor performance status. A more contemporary approach, commonly referred to as “liver-first,” is initial excision of the liver metastases, which demonstrates the genetic mutations and capacity to metastasize, then later resection of the local tumor. Frequently, the primary rectal disease is locally advanced, warranting neoadjuvant CMT; in select patients with a complete clinical response, close observation may delay or abrogate the need for rectal surgery.[13,14] In addition to resection of the primary tumor and liver metastases, systemic che-

motherapy improves disease-free and progression-free survival.[15-17] Administration of chemotherapy before or after hepatectomy results in equivalent disease-free and overall survival.[18]

Unfortunately, 70% to 80% of patients with CRC liver metastases are not candidates for resection at initial presentation. Upfront management of patients with unresectable metastases is

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Variant 3 Initial treatment of a 60-year-old woman without a significant past medical history, with an asymptomatic, non-obstructing, uT3N0 rectal cancer, bilobar hepatic metastases (50% liver replacement), and bilateral pulmonary metastases. The patient's Karnofsky performance status (KPS) is 90.

Treatment	Rating ^a	Comments
Systemic 5-FU–based chemotherapy (FOLFOX/FOLFIRI ± bevacizumab) ± surgery	9	Consider anti-EGFR agents with FOLFOX/FOLFIRI in wild-type <i>KRAS</i> tumors.
Systemic 5-FU–based chemotherapy (FOLFOX/FOLFIRI ± bevacizumab) followed by short-course pelvic RT (± surgery)	6	Consider anti-EGFR agents with FOLFOX/FOLFIRI in wild-type <i>KRAS</i> tumors.
Systemic 5-FU–based chemotherapy (FOLFOX/FOLFIRI ± bevacizumab) followed by long-course chemoradiation (± surgery)	5	Consider anti-EGFR agents with FOLFOX/FOLFIRI in wild-type <i>KRAS</i> tumors.
Best supportive care	2	
Surgical debulking of metastatic disease	1	
Resection of rectal primary	1	
Liver directed therapies (transarterial embolization, radiation, RFA)	1	

^aRating Scale: 1,2,3 = usually not appropriate; 4,5,6 = may be appropriate; 7,8,9 = usually appropriate.
 5-FU = 5-fluorouracil; EGFR = epidermal growth factor receptor; FOLFIRI = 5-FU/leucovorin (LV)/irinotecan; FOLFOX = 5-FU/LV/oxaliplatin; RFA = radiofrequency ablation.

chemotherapy. Primarily unresectable liver metastases may become resectable after responding to chemotherapy. [19-21] Portal vein embolization or hepatic arterial infusion with floxuridine/

dexamethasone may increase the rates of conversion to resectability and thus improve long-term survival.[22,23] For tumors that remain unresectable, non-surgical liver-directed therapies have

Variant 4 Initial treatment of a 74-year-old woman with a history of coronary artery disease, severe emphysema, and diabetes, now with an asymptomatic, non-obstructing uT3N0 rectal primary cancer, extensive hepatic metastases, and abdominal carcinomatosis. The patient's Karnofsky performance status (KPS) is 50.

Treatment	Rating ^a	Comments
Best supportive care	8	
Systemic biologic therapy or chemotherapy	6	This treatment may be appropriate based on individual patient characteristics.
Palliative pelvic RT	3	
Resection of rectal primary	1	
Preoperative pelvic RT plus concurrent 5-FU–based chemotherapy	1	
Resection of metastatic disease	1	

^aRating Scale: 1,2,3 = usually not appropriate; 4,5,6 = may be appropriate; 7,8,9 = usually appropriate.
 5-FU = 5-fluorouracil; RT = radiation therapy.

yielded promising results and may be considered. For example, high-dose stereotactic body RT is well tolerated and provides local control rates of ≥ 77% at 1 year.[24-26] Radiofrequency ablation (RFA) yields excellent local control of small (< 3 cm) CRC liver metastases.[27-29] Radioembolization, using yttrium-90 microspheres in combination with systemic therapy, results in a greater reduction in hepatic metastases than treatment with systemic therapy alone.[30,31] The addition of chemoembolization or cryotherapy to chemotherapy may also improve outcomes and is the topic of ongoing study[32-34] (see Variant 1 and Variant 2).

Cytotoxic and Targeted Therapies

5-FU has been the basis of standard chemotherapy for CRC for the last 5 decades. Continuous-infusion schedules have replaced bolus regimens because they were shown to be more effective and less toxic.[35] Capecitabine, an oral fluoropyrimidine, may be used in place of intravenous 5-FU. Capecitabine is associated with superior response rates and a lower incidence of adverse events, but no significant survival differences are observed when compared to bolus 5-FU/leucovorin (LV).[36] Capecitabine has a dose-limiting toxicity of hand-foot syndrome, which appears to be more common in the US population than in Europe, where most of the studies were conducted. In addition, capecitabine requires a highly motivated and reliable patient who will take oral medication correctly, will not miss or duplicate doses, and will hold medications at appropriate levels of toxicity.

Combining 5-FU/LV or capecitabine with newer agents, including irinotecan and oxaliplatin, has resulted in improved outcomes. Irinotecan, a topoisomerase I inhibitor, can be used independently in 5-FU–resistant advanced CRC or can be combined with 5-FU/LV as first-line therapy in patients with metastatic disease.[37] Oxaliplatin, a

third-generation platinum compound, has been shown to be a superior regimen to bolus 5-FU/irinotecan regimens.[38] FOLFOX (5-FU/LV/oxaliplatin), FOLFIRI (5-FU/LV/irinotecan), or FOLFOXIRI (5-FU/LV/oxaliplatin/irinotecan) are acceptable first-line regimens to treat mCRC in patients appropriate for intensive therapy.[39,40] In patients receiving CMT, addition of oxaliplatin to 5-FU and RT increases toxicity without improving primary tumor response rates, as shown in three randomized controlled trials: STAR (Studio Terapia Adjuvante Retto)-01, ACCORD (Actions Concertées dan les Cancers Colorectaux et Digestifs), and National Surgical Adjuvant Breast and Bowel Project (NSABP) trial R-04.[41] In the metastatic setting, sequential therapy with multiagent chemotherapy before and/or after 5-FU–based CMT is an option to control systemic disease.

New “targeted” therapies such as cetuximab, panitumumab, and bevacizumab have increased the options available for treating metastatic disease. Cetuximab and panitumumab are monoclonal antibodies directed against the epidermal growth factor receptor (EGFR). Cetuximab initially received US Food and Drug Administration (FDA) approval for treatment of irinotecan-resistant disease, in which a 22% response rate was associated with cetuximab/irinotecan therapy vs 11% with cetuximab as a single agent.[42] Panitumumab was FDA-approved after demonstrating improved progression-free survival vs best supportive care in patients with chemotherapy-refractory disease.[43] The discovery that patients with *KRAS*-mutated tumors do not derive benefit from EGFR-targeted agents has ushered in an era of “personalized” therapy in CRC. For instance, in the large CO.17 study of cetuximab vs best supportive care in chemotherapy-resistant advanced CRC, patients harboring a *KRAS* mutation had a response rate of 1% and median overall survival time of 4.5 months, whereas those with *KRAS*

wild-type tumors had a response rate of 13% and median overall survival of 9.5 months.[44] In a retrospective meta-analysis of the CRYSTAL and OPUS studies, the addition of cetuximab to chemotherapy resulted in a significant improvement in progression-free and overall survival in patients with *KRAS* wild-type tumors.[45] Conversely, in a phase III study (COIN) comparing cetuximab in combination with capecitabine or intravenous 5-FU and oxaliplatin vs chemotherapy alone as first-line treatment in mCRC, the former did not meet its primary endpoint of improved overall survival in *KRAS* wild-type patients (17 months vs 17.9 months; hazard ratio [HR] = 1.04; 95% confidence interval [CI], 0.90–1.20; *P* = .68).[46] Two recent studies, OPUS[47] and PRIME,[48] demonstrated a progression-free survival benefit with the addition of cetuximab or panitumumab, respectively, to FOLFOX in the first-line setting; however, no benefit was shown for patients with *KRAS* mutations. These studies collectively suggest that EGFR inhibitors should be considered in treating *KRAS* wild-type tumors but should not be offered to *KRAS*-mutant patients. Furthermore, emerging data suggest that patients with *KRAS* wild-type mCRC receiving FOLFIRI and cetuximab as a first-line treatment experience improved overall survival when compared to those receiving FOLFIRI and bevacizumab.[49]

Bevacizumab is a monoclonal antibody directed against the vascular endothelial growth factor (VEGF). In a randomized phase III trial, adding bevacizumab to bolus 5-FU/LV/irinotecan in patients with advanced CRC improved overall survival by 4.5 months.[50] However, in a larger phase III trial of oxaliplatin-based first-line chemotherapy, the addition of bevacizumab resulted in a modest but significant improvement in progression-free survival but no improvement in response rate and no significant impact on overall survival.[51] In addition, although

Summary

- Survival of patients with metastatic colorectal cancer (mCRC) has improved significantly in recent years.

- Management of patients with metastatic rectal cancer (mRC) benefits from multidisciplinary input.

- Operative candidates with resectable metastatic disease should undergo resection of the primary tumor and metastases, and should receive chemotherapy.

- Pelvic irradiation with concurrent 5-fluorouracil (5-FU) prior to resection of the rectal tumor is appropriate in patients with bulky, low-lying primary tumors, limited metastatic disease, and a long life expectancy.

- Patients with unresectable metastases should receive upfront chemotherapy.

- Multiple nonsurgical therapies are available to target unresectable liver metastases.

- A combination of cytotoxic and targeted systemic therapies is used in mCRC and has significantly improved outcomes.

- Patients with widespread disease, poor performance status, or multiple comorbidities may be best managed with comfort-oriented, supportive care.

there were promising initial results with “double biologic” strategies of combining bevacizumab and EGFR-targeting monoclonal antibodies, both the PACCE (panitumumab) and CAIRO2 (cetuximab) trials showed shorter sur-

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vival times and greater toxicity in the arms with double biologics.[52,53] Thus, bevacizumab should not be combined with other biologic agents but may be used in combination with chemotherapy to treat mCRC. Based on work in animal models, there is concern that administration of an anti-angiogenic agent preoperatively may increase the risk of surgical complications. However, multiple groups have retrospectively shown that surgeries, including liver resections, are safe after bevacizumab delivery.[54,55] Delaying an elective operation until 6–8 weeks (2–3 bevacizumab half-lives) after treatment with bevacizumab is a reasonable consensus practice.

Researchers continue to investigate the role of new targeted therapies in the management of mCRC. Recently, some of these agents have been shown to provide small but statistically significant survival benefits. For example, addition of aflibercept to FOLFIRI resulted in a median overall survival of 13.5 months vs 12.06 months with FOLFIRI and placebo.[56] In a study of patients whose mCRC had progressed on standard therapy, treatment with regorafenib yielded a median overall survival of 6.4 months vs 5.0 months in the placebo group.[57] These and other new targeted agents may play an increasing role in the management of mCRC. Clinical trials should be considered for patients with a good performance status, with the goal of developing more effective therapeutic regimens and rational combinations of chemotherapy, targeted agents, and radiotherapy for patients with mRC (see Variant 3).

Supportive Care

Patients with widespread unresectable mCRC, poor performance status, and multiple comorbidities are often best managed with supportive, comfort-oriented intent. The goals of care should be made clear to these patients, the majority of whom may not understand that their cancer is incurable and

treatment is intended to provide palliation only.[58] Local therapies may be valuable for symptomatic relief. For example, palliative RT or CMT achieves at least temporary relief in 80% of patients with mCRC who are suffering from pain, bleeding, or obstruction, with more durable palliation provided by doses ≥ 40 Gy.[59] Stents may also be used to palliate obstruction but may be poorly tolerated in the distal rectum (see Variant 4).

The American College of Radiology seeks and encourages collaboration with other organizations on the development of the ACR Appropriateness Criteria through society representation on expert panels. Participation by representatives from collaborating societies on the expert panel does not necessarily imply individual or society endorsement of the final document.

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