

An ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists, and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those exams generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate

Clinical Condition:**Rectal Cancer—Metastatic Disease at Presentation****Variant 3:**

Initial treatment of a 60-year-old female without significant past medical history, with uT3N0 rectal cancer, bilobar hepatic metastases (50% liver replacement) and bilateral pulmonary metastases. Rectal lesion causing pain and early symptoms of obstruction. KPS 80.

| Treatment | Rating | Comments |
|---|--------|----------|
| Initial preoperative pelvic RT + concurrent 5-FU based chemotherapy | 7 | |
| Initial systemic 5FU-based chemotherapy (FOLFOX/FOLFIRI) | 6 | |
| Initial palliative stent or loop colostomy to relieve obstruction | 5 | |
| Initial systemic 5FU-based chemotherapy (FOLFOX/FOLFIRI + bevacizumab) | 4 | |
| Initial resection of rectal primary | 3 | |
| Initial pelvic RT alone | 2 | |
| Initial surgical debulking of metastatic disease | 1 | |
| Initial liver directed therapies (transarterial embolization, radiation, RFA) | 1 | |
| Best supportive care | 1 | |
| If Preoperative RT + Chemo Given: RT Dose | | |
| 45 Gy/1.8 Gy | 5 | |
| 50.4 Gy/1.8 Gy | 8 | |
| 54 Gy/1.8 Gy | 7 | |
| 59.4 Gy/1.8 Gy | 3 | |
| Rating Scale: 1=Least appropriate, 9=Most appropriate | | |

Variant 4:

Initial treatment of a 74-year-old female with history of coronary artery disease, severe emphysema, diabetes, now with an asymptomatic nonobstructing uT3N0 rectal primary with extensive hepatic metastases and abdominal carcinomatosis. Poor oral intake. KPS 50.

| Treatment | Rating | Comments |
|--|--------|----------|
| Best supportive care | 8 | |
| Systemic chemotherapy | 2 | |
| Resection of rectal primary | 1 | |
| Preoperative pelvic RT + concurrent 5FU-based chemotherapy | 1 | |
| Resection of metastatic disease | 1 | |
| Rating Scale: 1=Least appropriate, 9=Most appropriate | | |

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RECTAL CANCER—METASTATIC DISEASE AT PRESENTATION

Expert Panel on Radiation Oncology—Rectal/Anal Cancer: Joseph Herman, MD, MSc¹; Wells A. Messersmith, MD²; Peter A. Johnstone, MD³; A. William Blackstock, MD⁴; Andre A. Konski, MD⁵; Mohammed Mohiuddin, MD⁶; Matthew M. Poggi, MD⁷; William F. Regine, MD⁸; Tyvin A. Rich, MD⁹; W. Warren Suh, MD¹⁰; Bard C. Cosman, MD¹¹; Leonard Saltz, MD.¹²

Summary of Literature Review

In 2007, an estimated 41,420 new cases of rectal cancer will be diagnosed in the United States (23,840 men and 17,580 women) [1]. After decades of treating metastatic colorectal cancer (CRC) with 5-fluorouracil alone, newer agents have resulted in significant improvements in disease-free and overall survival rates. These improvements stem from combinations of newer cytotoxic agents (irinotecan and oxaliplatin) and targeted therapies (cetuximab and bevacizumab). Based on performance status and the burden of disease (resectable liver-only or lung-only vs widely systemic disease), metastatic CRC patients are generally treated with either curative or palliative intent.

Management of patients with newly diagnosed metastatic rectal cancer may be complicated, and will benefit in most cases from multidisciplinary specialty input pretreatment. Treatment decisions must be individualized based on the overall medical condition of the patient, the extent and distribution of extrapelvic metastatic disease, and the patient's wishes. As this is an uncommon presentation of rectal cancer, specific literature on the subject is sparse, and conclusions must be drawn from extrapolation of management principles for metastatic colon cancer.

Management of Patients with Colorectal Liver Metastases

Patients with resectable colorectal liver metastases and no evidence of any extrahepatic metastases have impressive 5-year survival rates of 30%-70% following resection. Unfortunately, only 20%-30% of patients with colorectal liver metastases are candidates for resection at initial presentation [2]. Management should be based on whether the patient has resectable disease and is an appropriate candidate for antitumor treatment, or whether debilitation

has progressed to the degree that supportive care is more appropriate. In general, patients with minimal comorbidities and a Karnofsky performance status (KPS) of 80%-100% should be managed aggressively. Otherwise, these patients may be more appropriate for less aggressive treatment, and in some extreme cases, they may be best served by supportive and/or comfort-oriented care only.

In a patient deemed fit for aggressive intervention, a determination must be made as to whether the patient is potentially treatable for cure, or whether treatment is strictly palliative. Potentially curable patients, for all practical purposes, are those with metastatic disease that is confined to a single organ (usually liver or lung) in a distribution permitting complete resection [3-5]. Patients with metastases in multiple organs can sometimes receive aggressive local and systemic therapies if fit for treatment and have limited extrahepatic tumor burden [6]. Whether patients with multiple liver lesions can undergo a curative resection is based on the number, size, and location of the lesions. Otherwise patients with unresectable disease are approached with palliative local or systemic therapy and/or supportive care.

Curative Surgical Intent in Patients with Colorectal Liver Metastases

In a patient treated with curative intent, the potential for such curability is confirmed by noninvasive imaging and/or surgical exploration to exclude unsuspected metastases to intra-abdominal organs, lymph nodes, and peritoneal surfaces. If the primary rectal tumor and metastatic disease are resectable and the primary lesion is nonobstructing, patients may undergo a staged resection in which the liver tumor is resected first. If this is accomplished successfully, then resection of the primary is undertaken. A single (synchronous) procedure can be performed if a metastatic liver lesion can be removed through the same midline procedure as the lower anterior resection without compromising the quality of the liver resection. Patients undergoing abdominal-perineal resection and/or patients requiring a subcostal or other additional incision for resection of the metastases should usually undergo staged procedures.

Adjuvant/Neoadjuvant Chemotherapy for Liver Metastases

There is a clear survival benefit from resection in patients with limited hepatic metastases from CRC; however, the role of systemic or regional therapy following resection of metastases is less clear. Perioperative FOLFOX for three months prior to and after resection of liver metastases appears safe, and an advantage in 3-year disease-free survival rates has been demonstrated [7]. Patients with

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solitary or a small number of lung metastases may also benefit from aggressive resection, but data are limited [8].

Currently, only retrospective data support the use of neoadjuvant chemotherapy and/or liver-directed therapies to increase the likelihood of resecting initially unresectable liver-limited metastasis [2,9]. The advantages of potential downstaging with neoadjuvant chemotherapy must be weighted against potential adverse effects such as steatohepatitis and vascular changes, which may increase surgical complications [10].

Unresectable Liver Metastases

The primary management of unresectable metastatic disease is systemic chemotherapy. Some uncontrolled trials have investigated liver-directed therapies such as transarterial embolization (TACE), chemoradiation, radiofrequency ablation, and cryotherapy in the palliative or, in rare cases, neoadjuvant setting in colorectal cancer. Randomized studies with long-term follow-up are needed to determine the efficacy of these modalities [11-15].

Management of the Primary in Patients with Resectable Metastatic Disease

The optimal management of this patient population is controversial; however, the paradigm is changing with the substantial improvements that have occurred over the last decade with chemotherapy. In patients with small-volume, resectable metastatic disease and T3-4 rectal (or obstructive) primary tumors, preoperative combined-modality therapy (5-FU/RT) may be an acceptable option. In these cases, resection of both the rectal primary tumor and metastases is often performed after the combined-modality therapy and before systemic postoperative chemotherapy. Although there are limited data to support this regimen in patients with metastatic CRC, one could extrapolate the improved local control and decreased toxicity with preoperative versus postoperative chemoradiation reported by Sauer et al [16]. Patients who have undergone complete resection of both the primary rectal cancer and all known metastatic disease can reasonably be considered to be candidates for standard postoperative management consistent with that given to patients with stage II or III rectal cancer.

Management of the Primary in Patients with Unresectable Metastatic Disease

The primary management of unresectable metastatic disease is systemic chemotherapy. Given the high response rates and low rates of overt rapid progression through current first-line regimens, this approach should be strongly considered in all cases except for those patients who are overtly obstructed or are extremely close to obstruction. 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 immanent

obstruction, and comorbidities. Patients who have metastatic disease with small-volume unresectable metastases may be considered for palliative combined-modality management of the pelvic disease. Since preoperative chemoradiotherapy followed by resection is the most effective modality for control of the rectal primary, patients who are judged to be at reasonable risk for survival long enough to develop symptoms from progressive or recurrent pelvic disease may be appropriately palliated with combined-modality therapy. Alternatively, systemic combination chemotherapy may be used first, with consideration of consolidative radiation and concurrent chemotherapy for more definitive local control in those patients who respond to therapy. In patients with bulky metastatic cancer, demise from metastatic cancer is more likely to occur before pelvic symptoms become a problem. In such patients, systemic chemotherapy is usually most appropriate, with local therapy best reserved following systemic chemotherapy for treating symptomatic complications as needed.

Cytotoxic and Targeted Therapies

5-fluorouracil (5-FU) has been the basis of standard chemotherapy for treating CRC for the last five decades. Overall, prolonged infusion schedules appear to be more effective and less toxic, and bolus regimens should rarely be used at this time. Capecitabine, an oral fluoropyrimidine, has been shown to have superior response rates and lower incidence of adverse events, but no significant differences in survival when compared to the Mayo Clinic schedule of bolus 5-FU/LV [17]. This oral agent has a dose-limiting toxicity causing hand-foot syndrome, which appears to be more common in the U.S. population than in Europe, where most of the studies were done. 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 [18]. Oxaliplatin is a third-generation platinum compound and has emerged as a superior regimen to bolus 5-FU-irinotecan regimens [19]. When faced with treating a patient with advanced CRC in the first-line setting, there are multiple options, and comparative trials have indicated that both FOLFOX (oxaliplatin-based) and FOLFIRI (irinotecan-based) are acceptable first-line regimens [20].

New “targeted” therapies such as cetuximab (ErbixTM), panitumumab (VectibixTM), and bevacizumab (AvastinTM) have increased the options available for treating

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metastatic disease. Cetuximab and panitumumab are monoclonal antibodies directed against the epidermal growth factor receptor (EGFR). Cetuximab received FDA approval for treatment of irinotecan-resistant disease. A 22% response rate was seen in patients treated with cetuximab/irinotecan, and an 11% response rate with cetuximab as a single agent [21]. Panitumumab was recently FDA-approved after demonstrating improved progression-free survival vs best supportive care in patients with chemotherapy-refractory disease [22]. Bevacizumab is directed against the vascular endothelial growth factor (VEGF). In a randomized phase III trial, adding bevacizumab 5mg/kg to IFL in patients with advanced CRC improved overall survival by 4.5 months [23]. However, in a larger phase III trial of oxaliplatin-based front-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 survival [24].

Bevacizumab has a half-life of 20 days. The safe interval between administration of bevacizumab and an operation has not been determined. The common practice of waiting 6-8 weeks (2-3 half-lives) between bevacizumab and an elective operation is consistent with an approval study in which the longest interval between bevacizumab and wound dehiscence was 56 days. A large study including unplanned operations had a mean of 20 days between bevacizumab and any wound-healing complication. A small study of planned hepatectomy after bevacizumab, with a mean interval of 6.9 weeks, found no increase in wound-healing complications when compared with matched controls. Delaying a planned operation 6-8 weeks after bevacizumab is today's reasonable consensus practice [25-27].

Supportive care

Patients with widespread unresectable metastatic rectal cancer, poor performance status, and multiple comorbidities are often best managed with supportive, comfort-oriented intent.

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Appendix 1. AJCC 2002 Staging Classification for Cancer of the Anal Region

| Primary Tumor (T) | | | |
|---------------------------------|--|-------|----|
| TX | Primary tumor cannot be assessed | | |
| T0 | No evidence of primary tumor | | |
| Tis | Carcinoma <i>in situ</i> , intraepithelial or invasion of lamina propria | | |
| T1 | Tumor invades submucosa | | |
| T2 | Tumor invades muscularis propria | | |
| T3 | Tumor invades through the muscularis propria into the subserosa, or into nonperitonealized pericolic or perirectal tissues | | |
| T4 | Tumor directly invades other organs or structures, and/or perforates visceral peritoneum | | |
| Regional Lymph Nodes (N) | | | |
| NX | Regional lymph nodes cannot be assessed | | |
| N0 | No regional lymph node metastasis | | |
| N1 | Metastasis in 1-3 regional lymph nodes | | |
| N2 | Metastasis in 4 or more regional lymph nodes | | |
| Distant Metastasis (M) | | | |
| MX | Presence of distant metastasis cannot be assessed | | |
| M0 | No distant metastasis | | |
| M1 | Distant metastasis | | |
| Stage Grouping | | | |
| Stage 0 | Tis | N0 | M0 |
| Stage I | T1 | N0 | M0 |
| | T2 | N0 | M0 |
| Stage IIA | T3 | N0 | M0 |
| Stage IIB | T4 | N0 | M0 |
| Stage IIIA | T1 | N1 | M0 |
| | T2 | N1 | M0 |
| Stage IIIB | T3 | N1 | M0 |
| | T4 | N1 | M0 |
| Stage IIIC | Any T | N2 | M0 |
| Stage IV | Any T | Any N | M1 |

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