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Update on the Role of Imaging in Management of Metastatic Colorectal Cancer¹

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Abbreviations: ADC = apparent diffusion coefficient, CRC = colorectal cancer, DW = diffusion-weighted, EGFR = epidermal growth factor receptor, FDA = U.S. Food and Drug Administration, FDG = 2-[fluorine-18]fluoro-2-deoxy-D-glucose, 5-FU/LV = 5-fluorouracil/ leucovorin, Gd-BOPTA = gadolinium-benzyloxypropionicternacetate, Gd-EOB-DTPA = gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid, mCRC = metastatic colorectal cancer, MTT = molecular targeted therapy, NCCN = National Comprehensive Cancer Network, RECIST = Response Evaluation Criteria in Solid Tumors, VEGF = vascular endothelial growth factor

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> **TEACHING POINTS** See last page

Evolution in the treatment of metastatic colorectal cancer (mCRC) has led to significant improvement in the survival of these patients. Surgery is useful in patients with resectable disease. Liver-directed therapies such as hepatic arterial infusion, transarterial radio- and chemoembolization, and percutaneous ablation are sometimes used by oncologists when the liver is the only site of metastatic disease. Unresectable mCRC is typically treated with systemic chemotherapy. First-line systemic chemotherapeutic regimens for mCRC are FOLFOX (combination of 5-fluorouracil/leucovorin [5-FU/LV] and oxaliplatin) and FOLFIRI (combination of 5-FU/LV and irinotecan) combined with molecular targeted drugs. Molecular targeted therapies that are effective in treating mCRC include antiangiogenic agents such as bevacizumab-an antibody against vascular endothelial growth factor-and antibodies directed against epidermal growth factor receptor (EGFR). EGFR-directed antibodies such as cetuximab and panitumumab have been shown to produce activity only in wild-type KRAS tumors. Imaging modalities such as multidetector computed tomography (CT), magnetic resonance imaging, and positron emission tomography/CT play a major role in the selection of appropriate treatment strategies. Assessment of treatment response in patients who undergo liver-directed and systemic therapy requires imaging at regular intervals. Recent studies have shown that alternative treatment response criteria may be more predictive of pathologic response in mCRC than conventional criteria such as Response Evaluation Criteria in Solid Tumors. Awareness of unusual response patterns, as well as of complications and toxicities, is helpful in guiding patient management.

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Introduction

Colorectal cancer (CRC) is the fourth most common malignancy in the United States, with an estimated 143,460 new cases diagnosed in 2012 (1). CRC was the second most frequent cause of cancer-related death in 2012, accounting for a total of 51,690 deaths (1). Survival of patients with CRC depends primarily on disease stage. The 5-year relative survival rate is 90% for localized cancers but only 12%–19% for cancers with distant metastases (2–4). The management of stage I–III CRC is mainly surgical, with adjuvant chemotherapy in patients with high-risk stage II and stage III cancers. Chemotherapy is

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the main therapeutic modality for stage IV cancers. However, surgery and a variety of interventional radiologic techniques are also performed in selected patients with oligometastatic disease.

Stage IV CRC is defined as distant metastases that either (a) are confined to one organ or site (stage IVA), or (b) affect more than one organ or site or the peritoneum (stage IVB). The past decade has seen a paradigm shift in the management of stage IV or metastatic CRC (mCRC), leading to a significant increase in overall survival times for these patients, from less than 6 months to nearly 2 years (5). Much of this success can be attributed to the development of newer chemotherapeutic regimens, increased utilization of hepatectomy in patients with oligometastatic liver disease, and identification of new molecular targets and their inhibitors. Regimens such as FOLFOX (combination of 5-fluorouracil/leucovorin [5-FU/LV] and oxaliplatin) and FOLFIRI (combination of 5-FU/ LV and irinotecan) are now established as first-line treatments for mCRC (2,3). The identification of vascular endothelial growth factor (VEGF), a potent angiogenic factor, led to the development of bevacizumab, a VEGF antibody. Bevacizumab was approved by the U.S. Food and Drug Administration (FDA) in 2004 for use in the treatment of mCRC in combination with the FOLFOX and FOLFIRI regimens. Regorafenib, a tyrosine kinase inhibitor with an anti-VEGF effect, was approved by the FDA in 2012 for patients who have progressed through all other standard CRC regimens. Understanding the role of epidermal growth factor receptor (EGFR) and its intracellular signal cascades led to the development of cetuximab and panitumumab, monoclonal antibodies against EGFR (2,3). The understanding that mutations in KRAS, a downstream signaling protein in the EGFR pathway, is a predictor of nonresponsiveness to anti-EGFR antibodies led to the molecular classification of mCRC into KRAS-wild-type mCRC and KRAS-mutant mCRC (2,3).

Imaging plays an important role in the workup of patients with mCRC by helping enumerate the number and sites of metastases, determine resectability, assess response to systemic and liverdirected therapies, and detect drug toxicities and disease recurrences. Concurrent with advances in the treatment of mCRC, there have been major advances in radiology, with the development of new imaging modalities, functional imaging techniques, and contrast media and the proposal of alternative tumor response criteria (6,7). In this article, we review the management of mCRC, including the role of imaging in each treatment strategy, with emphasis on contemporary chemotherapeutic regimens and new molecular targeted therapies (MTTs).

Distribution of Distant Metastases in CRC

CRC most commonly metastasizes to the liver, with more than one-half of patients developing hepatic metastases either synchronously or metachronously. The lung is the second most common organ to harbor CRC metastases, followed by the peritoneal cavity (8). Peritoneal involvement is seen as peritoneal carcinomatosis and, in some cases, as pseudomyxoma peritonei, especially with the primary tumor arising from the appendix (9). Brain and bone metastases are uncommon (8,10).

Imaging of Metastases in CRC

Ultrasonography

Ultrasonography (US) is an inexpensive and readily available modality that in past years was widely used in the evaluation of liver metastases but has largely been supplanted by multidetector computed tomography (CT) and magnetic resonance (MR) imaging. Typical hepatic CRC metastases manifest as well-defined, solid, hypoechoic lesions-sometimes with a peripheral halo or a characteristic "target" or "bull's-eye" appearance—and are usually hypovascular at Doppler US (Fig 1) (11). Although contrastenhanced US has not received FDA approval for use in the United States, it does allow the assessment of dynamic enhancement characteristics of liver lesions with an accuracy comparable to that of multidetector CT in some studies (12). In a study of 271 consecutive patients with CRC, 21 of whom had liver metastases, contrast-enhanced US and multidetector CT both had a sensitivity of 87.5%, with a specificity of 97.6% and 95.6%, respectively (12). Intraoperative US has emerged as a valuable additional US technique and has been shown to have a higher sensitivity and specificity than preoperative transabdominal US, especially when combined with contrast-enhanced intraoperative US (13). Intraoperative US has been shown to help detect new metastases in 33%-42% of cases, with the addition of contrast-enhanced intraoperative US helping detect "disappearing" liver metastases after chemotherapy (14). Some of the limitations of US include operator dependence; ambiguity in segmental localization, which is crucial for surgical planning; and poor performance in the presence of hepatic steatosis and diffuse and chronic hepatic disease.

Multidetector CT

Multidetector CT is the most commonly used imaging modality in the workup of patients with mCRC. Multidetector CT offers the advantage of volumetric acquisition with isotropic voxels, which

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Figure 1. Liver metastases from colonic adenocarcinoma in a 65-year-old man who had undergone colectomy and presented for routine follow-up examination. (a) Transverse Doppler US image demonstrates solid hypoechoic liver lesions with a peripheral hypoechoic halo and no significant internal vascularity (arrows). (b) Contrast material–enhanced CT image shows multiple hypoattenuating liver lesions (arrows) consistent with liver metastases.





helps in generating high-quality reformatted images in multiple planes for improved detection of small lesions and accurate segmental localization of lesions. Hepatic metastases are hypovascular in the arterial phase, with a peripheral rim of hypervascularity in some cases, and are heterogeneously hypoattenuating in the portal venous phase (Fig 2) (15). The most reliable phase for the detection of hepatic metastases is the portal venous phase (approximately 60–70 seconds following initiation of intravenous contrast material administration), with a detection rate of 85% and a positive predictive value of 96% (16). In the arterial phase, CRC metastases can have peripheral rimlike enhancement. Calcification is noted in 11% of CRC liver metastases (17). Lung metastases are seen as pulmonary nodules, lymphangitis carcinomatosa, and pleural effusions (8). Peritoneal carcinomatosis manifests as soft-tissue deposits in the omentum and mesentery, with peritoneal thickening and ascites



Figure 3. Liver metastasis in a 47-year-old man with a history of resected stage II colonic adenocarcinoma. The patient had undergone hemicolectomy 2 years earlier and presented with an elevated carcinoembryonic antigen level. (a) Contrast-enhanced CT image shows an ill-defined lesion (arrows) in segment VIII of the liver. The lesion was difficult to characterize due to the underlying hepatic steatosis. (b, c) On axial in-phase (b) and out-of-phase (c) MR images, the lesion (arrows) is more clearly depicted on the out-of-phase image due to marked signal drop in the surrounding liver parenchyma owing to diffuse steatosis. (d) Axial gadolinium-enhanced fat-suppressed hepatocyte phase T1-weighted MR image obtained with gadoxetate disodium (Eovist; Bayer Schering Pharma, Berlin, Germany) after a 20-minute delay shows no uptake in the lesion (arrows), a finding that is consistent with metastasis. No other liver lesions were detected. The patient underwent neoadjuvant chemotherapy followed by right hepatectomy.

(sometimes loculated). Pseudomyxoma peritonei (low-attenuation mucinous peritoneal implants that scallop visceral surfaces) can be seen in some cases of appendiceal cancer (9). Bone metastases are typically lytic or mixed lytic-sclerotic lesions (8). Brain metastases from CRC are indistinguishable from metastases from other sites.

Detection of liver metastases at multidetector CT can be difficult in the presence of fatty liver, which is most often the result of concurrent chemotherapy (Fig 3) (18). Differentiation of small hemangiomas and cysts less than 1 cm in size from metastases can also be difficult at times due to volume averaging. The sensitivity of CT for detecting lesions less than 1 cm falls from 65%–95% to 31%–38% (19). Multidetector CT has a specificity of 67% in characterizing lesions as benign or malignant, compared with 81% for MR imaging (19).

MR Imaging

The heightened soft-tissue resolution provided by MR imaging makes it an invaluable problemsolving tool in the assessment of liver lesions. With T1- and T2-weighted sequences, hepatic metastases are hypo- and hyperintense, respectively, relative to normal liver parenchyma. The use of heavily T2-weighted images may help differentiate solid malignant lesions from hemangiomas and cysts. In-phase and out-of-phase gradient-recalled echo imaging offers an advantage over CT in the RadioGraphics

Table 1: Characteristics of Hepatocyte-specific MR Contrast Agents					
	Contrast Agent				
Characteristics	Gadobenate dimeglumine (Gd-BOPTA)	Gadoxetic acid (Gd-EOB-DTPA)			
Trade name	MultiHance	Eovist/Primovist			
Manufacturer	Bracco	Bayer			
Dose (mmol/kg)	0.1	0.025			
Excretion	95% renal, 3%–5% biliary	50% renal, 50% biliary			
Delayed imaging time	1–2 h	10–60 min			
Advantages	Better T1 relaxivity, greater enhance- ment during dynamic imaging	Better delineation of biliary tree			

presence of fatty liver (Fig 3). Intravenous administration of gadolinium-based contrast material helps in further characterizing known lesions and in detecting additional lesions. The appearance of metastatic lesions at MR imaging with extracellular gadolinium chelates is similar to their appearance at multidetector CT (ie, hypointense in the arterial and venous phases relative to normal liver parenchyma) (17). Hepatocyte-specific contrast agents are preferentially taken up by hepatocytes and excreted into the biliary tree. After their intravenous administration, these agents have a biphasic enhancement pattern, with the first phase occurring immediately after administration and the delayed phase occurring 10-120 minutes after administration (Fig 3) (17). Two hepatocytespecific contrast agents that are commonly used in the United States are gadolinium-benzyloxypropionictetraacetate (Gd-BOPTA), or gadobenate dimeglumine (MultiHance; Bracco, Milan, Italy), and gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA), or gadoxetate disodium (Eovist, Bayer). The differences between these two agents are summarized in Table 1. With use of hepatocyte-specific contrast agents, hepatic metastases typically appear hypointense relative to the surrounding liver parenchyma on delayed images, whereas hepatocyte-containing lesions such as focal nodular hyperplasia appear iso- or hyperintense (6). Hepatocyte-specific contrast-enhanced MR imaging helps detect more metastatic lesions than does conventional MR imaging (sensitivity of 95% versus 87%) and may be particularly useful for the follow-up of metastases after systemic or liver-directed therapies (20). Diffusion-weighted (DW) imaging measures the mobility of water molecules in tissues and reflects the cellular density of tissues. Apparent diffusion coefficient (ADC) values are quantitative estimates of diffusion restriction. Metastatic lesions have restricted diffusion and manifest as high-signal-intensity lesions with low ADC values (Fig 4). DW imaging helps detect lesions less than 1 cm (20). Overall,

the sensitivity of MR imaging for detecting CRC liver metastases is close to 95%, with an accuracy of 83% for detecting lesions less than 1 cm. In characterizing lesions less than 1 cm as benign or malignant, MR imaging surpasses CT, with an accuracy of 91% (19).

PET/CT

The role of 2-[fluorine-18]fluoro-2-deoxy-Dglucose (FDG) positron emission tomography (PET)/CT in stage IV CRC is evolving, mainly due to the capacity of PET/CT to help detect additional sites of extrahepatic disease and thereby alter surgical management. PET/CT is highly sensitive for detecting liver metastases larger than 10 mm (78%-95%) (21). Its sensitivity drops to 36% for lesions less than 1 cm (19). False-negative results can occur with lesions with necrosis or mucinous contents (Fig 5) (22). In patients with potentially resectable liver disease, National Comprehensive Cancer Network (NCCN) guidelines recommend PET/CT for excluding occult metastatic disease (2). In metachronous hepatic or extrahepatic disease, PET/CT should be considered for the assessment of disease extent. PET/CT may also be used for detecting occult disease in patients with elevated carcinoembryonic antigen levels and negative anatomic workup (2).

Management of mCRC

Two different scenarios are encountered in the management of mCRC: (*a*) resectable or potentially resectable disease, and (*b*) unresectable disease.

Surgery in mCRC

Surgical resection is the only definitive treatment for mCRC and increases the 5-year survival rate to 25%–50% (23,24). However, only 10%–20% of liver metastases are resectable at presentation (2). The current definition of surgical resectability is evolving, with the mini-

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Figure 4. Liver metastases in a 58-year-old man with right colon cancer who had undergone right colectomy 5 years earlier. (a) Axial T2-weighted MR image demonstrates multiple hyperintense hepatic lesions (arrows). Note the perihepatic free fluid, consistent with ascites. (b, c) Axial DW ($b = 800 \text{ sec/mm}^2$) (b) and ADC (c) images demonstrate diffusion restriction in the periphery of the metastatic deposits as bright signal on the DW image and dark signal on the ADC image (arrows), findings that are consistent with viable tumor. The central portion of the lesion does not show diffusion restriction (ie, relatively higher signal compared with the periphery on the DW image and retention of high signal [T2 shine-through] on the ADC image), findings that are suggestive of necrosis.





b.





a

mum requirement being the ability to achieve complete resection with negative margins (R0 resection) and leave an adequate amount of liver for normal hepatic function (25). Patients with resectable or potentially resectable liver disease may benefit from perioperative chemotherapy that includes neoadjuvant and postoperative adjuvant chemotherapy (2). Neoadjuvant chemotherapy offers the advantages of eradicating micrometastatic disease preoperatively, assessing chemotherapy responsiveness, and allowing time to evaluate whether more metastatic lesions will develop outside the liver. The potential drawbacks of neoadjuvant chemotherapy include risk of progression with loss of surgical window; radiologic complete response (although viable

cancer can still be detected at histopathologic analysis), which can make surgical resection difficult; and risk of steatohepatitis and sinusoidal injury, which increases postoperative mortality and morbidity (2,26). Close collaboration between the radiologist and the medical and surgical oncologists is crucial for proper timing of surgery.

In selected patients, unresectable metastatic disease can be rendered resectable by administering "conversion chemotherapy" (in contrast to neoadjuvant chemotherapy) (25). The goal of conversion chemotherapy is to downsize the tumor to create an opportunity for surgical resection. As with neoadjuvant chemotherapy, the duration of conversion chemotherapy should be kept as short as possible, and surgery should be performed as soon as possible due to the risk of steatohepatitis and sinusoidal injury associated with chemotherapy.

Synchronous liver metastases from CRC can be managed with resection of the primary tumor and liver metastases either simultaneously or in stages (2). In some circumstances, patients with isolated lung metastases and no other sites of disease can be considered for surgical resection. Unresectable CRC metastases to lung are managed much like liver metastases. Peritoneal carcinomatosis is managed with palliative intent, with systemic chemotherapy for advanced mCRC (27). RadioGraphics

Figure 5. Hepatic metastasis with mucinous contents in a 49-year-old man with ascending colon cancer who had undergone right colectomy 3 months earlier. (a) Contrast-enhanced CT image shows a hypoattenuating lesion in the right hepatic lobe (arrows), a finding that is suspicious for metastasis. (b) Coronal maximum-intensity-projection image from an FDG PET/CT study demonstrates no increased uptake in the right hepatic lobe. (c) Axial gadolinium-enhanced fat-suppressed T1-weighted MR image depicts the lesion with a peripheral rim of enhancement (arrows). Results of biopsy confirmed hepatic metastasis with mucinous contents, which might explain the false-negative result at PET/CT.



a.

Role of Imaging in Surgical Planning for mCRC

The major determinants of resectability in mCRC are the number, size, and distribution of the liver metastases, which in turn determine the prospect of achieving negative surgical margins and adequate hepatic reserve. Thus, the primary goal of imaging in mCRC is to detect as many liver metastases as accurately as possible (6). Imaging also provides critical details about variations in the venous, arterial, and biliary anatomy. Reconstructed images act as road maps for surgical and radiologic interventions.

All lesions identified at pretreatment scanning must be mapped at preoperative imaging. Disappearing liver metastases are treated metastases that are not visualized at follow-up imaging due to their small size (radiologic complete response) (Fig 6) (18,25). Pathologic analysis of resected surgical specimens has shown such lesions to have viable tumor cells, especially at the tumorliver interface. Accurate preoperative mapping of these lesions is necessary, since they can be the site of recurrence if the margins are positive for microscopic disease. Studies have shown that MR imaging with hepatocyte-specific contrast agents is more sensitive than multidetector CT in the detection of these completely treated liver metastases. A recent meta-analysis of 11 studies that included 223 patients and 906 liver lesions found that MR imaging is the most appropriate investigation in the preoperative setting after neoadjuvant chemotherapy (28).



b.

Imaging helps in the preoperative detection of conditions that can portend poor prognosis, including steatosis, biliary obstruction, parenchymal liver disease, and vascular complications such as portal vein thrombosis. CT- and MR imaging–based volumetry are helpful in estimating the volume of the future liver remnant (6). Several studies have shown that the use of correction factors in the preoperative assessment of liver volumes can help avoid over- or underestimation of volumes (29). Preoperative portal vein embolization, a technique that induces atrophy of the embolized liver lobe and compensa-

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Figure 6. Disappearing liver metastases in a 61-year-old man with mCRC to the liver who was treated with irinotecan and cetuximab. (a) Contrast-enhanced baseline CT image shows multiple hepatic lesions (arrows). (b) Contrast-enhanced CT image obtained 4 months after the start of chemotherapy demonstrates complete disappearance of two of the lesions seen in a and an interval decrease in the size of the third lesion (arrow). (c) Axial gadolinium-enhanced fat-suppressed T1-weighted MR image obtained 1 month later shows faint enhancement at the sites of the known lesions (arrows). Histopathologic analysis of the right hepatectomy specimen revealed fibrosis with foreign-body giant cell reaction and no microscopic residual tumor.





c.

tory hypertrophy of the contralateral lobe, can help in achieving a desirable future liver remnant in patients with suboptimal liver volume as predicted with cross-sectional imaging-based volumetrics (Fig 7). Portal vein embolization results in about 15% liver regeneration in 3–9 weeks (30).

Liver-directed Therapies in mCRC

The utilization of liver-directed therapies in the management of mCRC is a controversial and evolving field. Oncologists sometimes use liver-directed therapies when the liver is the only site of metastatic disease (2,3). Hepatic arterial infusion consists of surgical placement of a hepatic arterial port for infusion of chemotherapeutic drugs, taking advantage of the increased arterial supply to metastases and resulting in selective high-dose delivery. Proponents of hepatic arte-

rial infusion believe that it helps with local tumor control (31). Another liver-directed therapy is transarterial radioembolization with yttrium-90 (⁹⁰Y) microspheres, which can be used in selected patients without obvious extrahepatic disease who are refractory to first- and second-line treatments (Fig 8) (2,3). Percutaneous ablation of liver metastases can be considered in patients who are unfit for surgery due to comorbidities or an insufficient future liver remnant, or in conjunction with surgery to achieve tumor-free status (2,3). Options available for percutaneous ablation include radiofrequency ablation, cryoablation, and microwave ablation (Fig 9). Radiofrequency ablation is the most widely used local ablative procedure, with low morbidity and mortality. However, several retrospective studies have found radiofrequency ablation to be inferior to surgical resection in patients with resectable disease due to higher rates of local recurrence (32).

Role of Imaging in Liver-directed Therapies for mCRC

Most liver-directed therapies are performed under US and CT guidance. Imaging helps in selecting the type and approach of the radiologic intervention. In patients in whom ablation therapy is being contemplated, the relation of the target lesions to major vessels and the gallbladder plays a key role in treatment success by avoiding heat sink and biliary injury (33). The response to liver-directed therapies is different from the response to systemic chemotherapy. Percutaneous ablations usually result in **Figure 7.** Augmentation of the future liver remnant in a 43-year-old man with mCRC to the liver who was undergoing portal vein embolization prior to right hepatectomy. (a) Three-dimensional volume-rendered CT image shows the right hepatic lobe (brown) and the medial (purple) and lateral (pink) segments of the left hepatic lobe. The preembolization volume of the left lobe was 707 cm³. (b) Digital subtraction angiographic image obtained with portal vein injection following embolization of the right portal vein demonstrates opacification of the left portal vein and stasis of contrast material in the right portal vein. (c) Three-dimensional volume-rendered CT image obtained 2 months after embolization reveals enlargement of the left hepatic lobe (volume = 865 cm³). Green = right hepatic lobe, red = me-dial segment of left hepatic lobe, yellow = lateral segment of left hepatic lobe.

с.





a.

enlargement of the treated lesion in the first month due to intratumoral hemorrhage and coagulative necrosis (Fig 9). Transient periablational hyperemia is seen as a thin peripheral rim of enhancement in the immediate postablation period and disappears by 1 month (Fig 9) (33). This entity must be differentiated from residual or recurrent tumor, which is seen as a thick, irregular nodular rim of enhancement. Intralesional air bubbles and arterioportal shunting are also commonly encountered at imaging (33). Response following radiation therapy and chemoembolization is seen as a decrease in tumor size, tumor necrosis, and complete devascularization (angiographic complete response) of the tumor, although a transient increase in tumor size can occur due to peritumoral edema and hemorrhage (Fig 8). A ring of enhancement similar to postablation hyperemia represents posttreatment fibrosis rather than recurrence. Perivascular edema in the distribution of the embolized vessels is a transient phenomenon and should not be confused with infiltrative disease. Radio- or chemoembolization results in ischemia and hepatitis of the normal liver parenchyma, which in turn can result in abnormal patchy parenchymal enhancement of the treated liver segment, causing difficulty in interpreting treatment response (34). Capsular retraction and hepatic fibrosis resulting in portal hypertension have been reported following radio- and chemoembolization.

b.

Systemic Chemotherapy in mCRC

Chemotherapeutic Regimens

About 80%–90% of mCRCs are unresectable at presentation (2,3). The current treatment for most of these patients with unresectable and disseminated mCRC is palliative chemotherapy. The cytotoxic chemotherapeutic agents used in mCRC are 5-FU/LV, capecitabine, oxaliplatin, and irinotecan (Table 2). All of these drugs are often used in combination regimens and less commonly as monotherapies. Currently, the most widely used first-line regimens in mCRC are (*a*) combined 5-FU/LV and oxaliplatin (FOLFOX), and (*b*) combined



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Figure 8. Results of radioembolization in a 65-year-old man with metastatic rectal cancer and liver metastases who had progressed through all other standard chemotherapy options for CRC. (a) Contrast-enhanced baseline CT image demonstrates multifocal heterogeneous hepatic metastases with an ill-defined tumor-liver interface (arrows). Embolization was performed to isolate blood flow from the right hepatic and replaced left hepatic arteries into the liver. (b) Digital subtraction image from a superselective angiographic study of the right hepatic artery shows embolization of branches of the right and left gastric and gastroduodenal arteries (arrows) with 90Ycoated microspheres. (c) Anterior planar scintigraphic image demonstrates selective increased radiotracer uptake in the right hepatic lobe (arrows). The left hepatic lobe is not visualized, and no foci of increased uptake are seen in the lungs. (d) On a follow-up CT image obtained 1 month after radioembolization, the metastases in the right lobe (arrows) show a decrease in attenuation and a slight increase in size.





b.

5-FU/LV and irinotecan (FOLFIRI). Sequential treatment with FOLFOX and FOLFIRI (in either order) has been shown to improve median survival time to approximately 20 months (35). Although the two regimens do not differ in their efficacy, they have significantly different toxicity profiles: FOLFOX causes neuropathy, whereas FOLFIRI can cause severe diarrhea (36). For patients with

unresectable disease, oncologists individualize therapy for each patient and typically continue a regimen as long as the patient is benefiting radiologically and is able to tolerate the regimen. With chemotherapy, breaks are often necessary because of toxicity and fatigue. Oncologists will switch chemotherapy regimens when there is definitive radiologic proof of disease progression (37,38).

Figure 9. Results of cryoablation of residual metastasis in a 50-year-old woman with a liver metastasis from colon cancer. The patient had undergone right hepatectomy and nine cycles of treatment with FOLFOX and bevacizumab. (a) Axial gadolinium-enhanced fat-suppressed T1-weighted MR image obtained 1 week prior to ablation demonstrates a peripherally enhancing lesion (arrow) near the right margin of the liver. (b) Nonenhanced CT image demonstrates a Galil IceSphere cryoablation needle (Galil Medical, Arden Hills, Minn) in the lesion (arrows). (c) On an axial gadolinium-enhanced fat-suppressed T1-weighted MR image obtained 1 day after ablation, the lesion (arrow) is enlarged and has a thin peripheral rim of enhancement (arrowheads), findings that are consistent with the expected evolution of postablation changes. (d, e) On follow-up precontrast T1-weighted (d) and gadolinium-enhanced digital subtraction (e) MR images obtained 1 month later, the lesion demonstrates hyperintense signal (arrows in d) and no enhancement (arrows in e), findings that suggest coagulative necrosis and successful ablation, respectively.



a.

b.











e.

Class	Generic Name	Trade Name*	Year of FDA Approval	Туре	Mechanism of Action
CCT agents	5-FU	Efudex, Carac, Adrucil	Before 1984 [†]	Thymidylate synthase inhibitor	DNA synthesis inhi- bition (cytotoxic)
	Leucovorin	Wellcovorin	Before 1984 [†]	Folinic acid	Synergistic combina tion with 5-FU
	Capecitabine	Xeloda	1998	Oral prodrug of 5-FU	Conversion to 5-FU
	Irinotecan	Camptosar, Campto	1998	Prodrug of a topoisom- erase I inhibitor	DNA synthesis inhi- bition (cytotoxic)
	Oxaliplatin	Eloxatin	2002	Platinum compound	DNA synthesis inhi- bition (cytotoxic)
MTT agents	Bevacizumab	Avastin	2004	Anti–VEGF receptor mAb	Antiangiogenesis
	Cetuximab	Erbitux	2004	Anti-EGFR mAb	Cancer growth inhi- bition
	Panitumumab	Vectibix	2006	Anti-EGFR mAb	Cancer growth inhi- bition
	Ziv-aflibercept	Zaltrap		Recombinant protein (VEGF receptor inhibi- tor)	Antiangiogenesis
	Regorafenib	Stivarga	2012	Multiple TKIs	Antiangiogenesis, cancer growth inhibition

Note.—Commonly used combination regimens include FOLFOX (5-FU, leucovorin, and oxaliplatin [± bevacizumab or panitumumab]); FOLFIRI (5-FU, leucovorin, and irinotecan [± bevacizumab, panitumumab, or cetuximab]); and CAPEOX (capecitabine, leucovorin, and oxaliplatin [± bevacizumab]). CCT = conventional chemotherapeutic, mAb = monoclonal antibody, TKI = thyrosine kinase inhibitor.

*Manufacturers are as follows: Efudex: Valeant Pharmaceuticals, Bridgewater, NJ; Carac: Naman Pharma, Mumbai, India; Adrucil: TEVA Pharmaceutical, Petah Tikva, Israel; Wellcovorin: Bedford Laboratories, Bedford, Ohio; Xeloda: Hoffmann-LaRoche, Basel, Switzerland; Camptosar and Campto: Pfizer, New York, NY; Eloxatin: Sanofi Aventis, Bridgewater, NJ; Avastin: Genentech, South San Francisco, Calif; Erbitux: Bristol-Myers Squibb, New York, NY; Vectibix: Amgen, Deerfield, Ill; Zaltrap: Sanofi Aventis; Stivarga: Bayer. [†]FDA cannot verify year of approval before 1984.

Novel MTTs

Bevacizumab, a monoclonal antibody that binds to VEGF, was approved by the FDA for first-line treatment of mCRC in 2004. NCCN guidelines currently recommend the addition of bevacizumab to first-line combination chemotherapies with FOLFOX, FOLFIRI, and 5-FU/LV (2,3). Evidence supporting the use of bevacizumab beyond progression in second-line regimens recently emerged from the TML (Treatment through Multiple Lines) trial (39). Cetuximab (chimeric human-mouse monoclonal antibody) and panitumumab (fully humanized monoclonal antibody) are anti-EGFR antibodies that bind to the extracellular domain of EGFR and inhibit intracellular signal cascades such as the RAS/ RAF/MAPK pathways (2,3). Cetuximab and panitumumab were approved by the FDA in 2004 and 2006, respectively, for use in treating patients with mCRC.

Recent studies have shown that mutations in an intracellular signaling protein, KRAS (seen in 35%–45% of cases of CRC), result in constitutive activation of the EGFR pathway and determine response to anti-EGFR antibodies (2,3). In contrast to CRC without KRAS mutations (eg, wild-type KRAS), CRC with KRAS mutations is not responsive to EGFR inhibition with cetuximab and panitumumab. NCCN guidelines recommend KRAS genotyping in all patients with stage IV colon cancer (2). Mutations in B-RAF (V600E), another intracellular protein (seen in about 5%–9% of cases of colon cancer), have an effect similar to that of mutations in KRAS (2,3).

Ziv-aflibercept is a recombinant protein consisting of human VEGF receptors 1 and 2 fused to the Fc portion of human immunoglobulin G1 that prevents activation of VEGF receptors by inhibiting ligand binding (2,3). Ziv-aflibercept combined with FOLFIRI has been shown to be an effective second-line regimen following progression with first-line non-irinotecan-containing regimens such as FOLFOX (2). Regorafenib is a multitargeted kinase inhibitor with activity against VEGF receptors, Kit, platelet-derived growth factor receptors, and several other kinases

Teaching Point

Table 3: Treatment Response Patterns and Toxicities/Complications in mCRC					
Treatment	Treatment Response Patterns	Toxicities/Complications			
Cytotoxic che- motherapy	Usual pattern: decrease in size and enhance- ment, homogeneous appearance, sharp tumor-liver interface Unusual patterns: new hypoattenuating lesion that was previously inconspicuous, increase in size with decrease in attenuation and enhancement, cavitation of lung nodules and pneumothorax, decrease in ascites	Hepatotoxicity (hepatic steatosis, steatohepa- titis, sinusoidal obstruction syndrome), interstitial lung disease, neuropathy, my- elosuppression (opportunistic infection or neutropenic colitis)			
МТТ	Same as for cytotoxic chemotherapy	Pneumatosis intestinalis, perforation, wound dehiscence, tumor-bowel fistula, thrombo- embolic events, cholecystitis, pancreatitis, interstitial lung disease			
Liver-directed therapy	Complete or partial devascularization, coagulative necrosis	 Hepatic arterial infusion: acalculous chole- cystitis, gastrointestinal perforation, biliary ischemia, sclerosing cholangitis Radioembolization: radiation hepatitis, cho- lecystitis, gastritis, biliary necrosis, hepatic fibrosis Percutaneous ablation: hepatic abscess, intraperitoneal hemorrhage, biliary injury, tumor seeding, liver failure, pneumothorax, pleural effusions 			

(40). Regorafenib has been shown in recent trials to have a modest 6-week survival advantage in patients with mCRC that is refractory to all chemotherapeutic drugs and was approved by the FDA in 2012.

Role of Imaging in Systemic Chemotherapy

Evaluation of response to treatment in patients with mCRC plays a critical role in treatment decisions. Multidetector CT is the most widely used modality for assessing treatment response. Conventionally, multidetector CT evaluation of response to treatment in solid tumors has made use of the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (41). In recent years, the RECIST guidelines have been updated to RECIST 1.1 to standardize and simplify the criteria (41). Both RECIST and RECIST 1.1 are size-based criteria that define response to treatment as a 30% decrease in unidimensional measurement. Studies have shown the inadequacy of RECIST in assessing treatment response, especially response to MTT. To overcome these inadequacies, several alternative criteria have been proposed that take morphology as well as size into account (42). Choi et al (43) suggested the use of modified criteria based on a combination of size and attenuation changes ($\geq 10\%$ decrease in size or $\geq 15\%$ decrease in attenuation) in assessing response to treatment in gastrointestinal

stromal tumors. Smith et al (44,45) proposed the use of size and attenuation CT criteria and of MASS (*morphology*, *a*ttenuation, *size*, and *s*tructure) criteria for metastatic renal cell carcinoma treated with sunitinib.

Several studies have shown the interpretation of response to the treatment of liver metastases from CRC using RECIST to be suboptimal, since it does not reflect the pathologic response. Pathologic response refers to the percentage of residual viable tumor cells and has been shown in recent studies to correlate with clinical outcome (46). In a study of 59 patients who underwent chemotherapy with (n = 30) or without (n = 29) bevacizumab, Chung et al (47) found that using modified CT criteria ($\geq 10\%$ decrease in size or $\geq 15\%$ decrease in attenuation) helped identify more good responders than did RECIST 1.1 criteria.

Bevacizumab is an antiangiogenic agent that causes decreased enhancement and attenuation with or without concurrent changes in size. In some studies of patients with mCRC, chemotherapy with and chemotherapy without bevacizumab have been shown to have similar effects on tumor morphology (47). At multidetector CT, response to treatment is characterized by decreases in size, attenuation, enhancement, and internal heterogeneity, and a sharp tumor-liver interface (Fig 2). In a study of 234 lesions in 50 patients, Chun et al (7) described three patterns of morphologic response in liver metastases treated



Figure 10. Treatment response in a 58-year-old man with mCRC to the liver. (a) Coronal reformatted contrast-enhanced baseline CT image demonstrates multiple heterogeneous liver metastases with an irregular tumorliver interface (arrows). (b) On a follow-up CT image obtained after three cycles of treatment with FOLFIRI and bevacizumab, the lesions (arrows) demonstrate a slight increase in size, a concurrent decrease in attenuation, relative homogeneity, and a sharp tumor-liver interface. The size increase can be confused with disease progression (pseudoprogression). However, the other morphologic changes, taken together with a decrease in the tumor markers, favor true treatment response. (c) Follow-up CT image obtained 2 months later shows a decrease in the size of the lesions (arrows), a finding that indicates continued treatment response.



b.

with a bevacizumab-containing regimen. In their study, metastases with a decrease in attenuation, a homogeneous appearance, and a sharp tumorliver interface represented a good or optimal morphologic response. The disappearance of a peripheral rim of enhancement that was present at pretreatment scanning was also considered to represent a good response. The absence of any of these changes was defined as absent morphologic response. Partial changes in morphology that did not fulfill the criteria for optimal response were described as partial morphologic response. The authors found significant correlation between the three morphologic patterns of response and good pathologic response (7).

Instead of using morphologic criteria, a novel approach to evaluating treatment response to antiangiogenic agents is assessing physiologic changes in tumor vascularity. Dynamic contrastenhanced CT provides qualitative and quantitative perfusion data in liver metastases and has been shown to be an innovative and reliable tool in monitoring perfusion changes in response to antiangiogenic agents (48,49). Therapy-induced

changes in perfusion parameters such as permeability, blood volume, and blood flow have been shown to precede changes in tumor size in some studies (48). The main limitation of dynamic contrast-enhanced CT is the additional radiation exposure it entails and the lack of standardization of the technique and parameters.

Unusual patterns of response that can mimic disease progression may occur in liver metastases treated with neoadjuvant chemotherapy (Table 3). In our experience, three such patterns of "pseudoprogression" can occur (50). First, lesions that were isoattenuating on pretreatment scans tend to become apparent on posttreatment scans because they become hypoattenuating and can therefore be misinterpreted as new lesions. Second, some lesions increase in size after treatment, with a concurrent decrease in attenuation and enhancement due to intratumoral edema or visualization of a previously isoattenuating component of the lesion (Fig 10) (47). The increase in size according to conventional response criteria may be confused with disease progression. Third, intratumoral hemorrhage due to

Teaching Point



a.

Figure 11. Treatment response in a 53-year-old woman with pulmonary metastases from rectal cancer. (a) Baseline CT image of the chest demonstrates bilateral lower lobe lung nodules (arrows). (b) Follow-up CT image obtained 2 months after the start of treatment with FOLFIRI and bevacizumab demonstrates cavitation in the metastatic deposits (*), a known treatment effect, with an apparent increase in the size of the lesions (arrows).

antiangiogenic agents can cause an increase in the size and attenuation of metastatic lesions and can be interpreted as progressive disease even according to the modified criteria. Recognizing pseudoprogression is critical because failure to do so can result in discontinuation of effective treatment. Pitfalls in interpreting unusual response patterns can be avoided by correlating imaging findings with the clinical status of the patient, tumor markers, and response to treatment at other disease sites. Careful attention to the internal architecture of the lesions (eg, fluid-fluid levels or a change in a lesion from homogeneous to heterogeneous) and use of unenhanced CT or MR imaging can be helpful in cases of intratumoral hemorrhage. Follow-up imaging can demonstrate a gradual decrease in the size and attenuation of responding metastatic lesions; consequently, nonacute treatment-related decisions should always be deferred until follow-up imaging in patients who are suspected of having pseudoprogression. An unusual pattern of response is also known to occur in lung metastases treated with bevacizumab-containing regimens. The metastases typically demonstrate central lucency and cavitation due to central necrosis, despite a size increase (Fig 11). Spontaneous pneumothorax can occur with cavitation in subpleural metastases (51). Similarly to hepatic metastases, peritoneal deposits show a decrease in size and enhancement in response to chemotherapy. A decrease in ascites and relief of bowel obstruction may be indirect signs of treatment response in peritoneal carcinomatosis. Treated bone metastases are typically more sclerotic on follow-up scans (8).

The role of MR imaging in the assessment of treatment response is less defined. At our institution, MR imaging is used as a problem-solving

tool in cases of suspected pseudoprogression. Pseudoprogression due to intratumoral hemorrhage manifests with high signal intensity on T1-weighted images. MR imaging with hepatocyte-specific contrast agents can help detect disappearing liver metastases, which remain hypointense in the hepatobiliary phase. MR imaging is also useful in the detection of liver metastases in the setting of chemotherapy-induced hepatic steatosis, especially if surgical resection is being contemplated. In a study of 20 patients with CRC liver metastases who underwent preoperative multidetector CT and MR imaging in the setting of neoadjuvant chemotherapy-induced fatty infiltration followed by surgical resection of the metastases, Kulemann et al (18) found that MR imaging detected more lesions less than 1 cm than did multidetector CT (66% versus 11%). Hepatocyte-specific contrast agents were used in 14 of the 20 patients in their study (18). Some recent studies have shown dynamic contrast-enhanced MR imaging to act as a surrogate marker for measuring the efficacy of bevacizumab-containing chemotherapy regimens, since it allows in vivo measurement of capillary perfusion, which determines delivery of drugs to the tumor cells. Dynamic contrast-enhanced MR imaging can help predict treatment response by measuring the volume transfer constant $K_{\rm trans}$ and rate constant K_{ep} . A high baseline K_{trans} has been shown to correlate with better outcome with cytotoxic agents in CRC (52). In a study by De Bruyne et al (53), a decrease in K_{trans} of more than 40% after bevacizumab-containing chemotherapy was associated with better progression-free survival, although this has not been corroborated in other studies. DW imaging can also help detect small lesions (<10 mm) that are



Figure 12. Hepatic steatosis in a 65-year-old man with metachronous liver metastases from rectal cancer. (a) Contrast-enhanced CT image obtained before the start of nine cycles of treatment with FOLFIRI and bevacizumab demonstrates multiple hypoattenuating liver metastases (arrows). (b) Posttreatment follow-up CT image demonstrates partial obscuration of the liver metastases (arrows) secondary to the development of hepatic steatosis.

not detectable with other modalities (54). An increase in the ADC values in metastatic lesions at DW imaging has also been reported as an indicator of physiologic treatment response (54). Some studies have shown that software-based volumetric changes in enhancement and ADC values at postcontrast and DW MR imaging, respectively, can help predict the response of liver tumors to various therapies (55). The role of PET/CT in monitoring mCRC therapy has not yet been established. A decline in metabolic activity during treatment is indicative of favorable treatment response. However, complete resolution of metabolic activity is not always indicative of pathologic complete response. PET/CT has less sensitivity for detecting lesions under 10 mm. In a recent meta-analysis, van Kessel et al (28) found that the sensitivity of PET/CT for detecting liver metastases after neoadjuvant chemotherapy dropped from 71% to 52%, most likely due to the small size of the treated lesions and to central necrosis (28). The NCCN guidelines do not recommend PET/CT for assessing treatment response, since both false-negative (necrotic lesions) and false-positive (inflammation and surgery) results are known to occur (2,3).

Complications and Toxicities Associated with Treatment of mCRC

Several unexpected side effects are known to occur with the use of both conventional chemotherapeutic drugs and MTT in patients with mCRC (Table 3). Oxaliplatin-based regimens are known to cause endothelial injury with resultant veno-occlusive disease or sinusoidal obstruction syndrome (56). Sinusoidal obstruction syndrome causes disruption of the sinusoidal wall, fibrosis,

and nodular regenerative hyperplasia. At imaging, sinusoidal obstruction syndrome manifests as hepatosplenomegaly, portal hypertension, and sluggish portal venous flow, increasing the risk of portal vein thrombosis (6). Early detection of sinusoidal injury can be achieved by monitoring signs of portal hypertension, especially splenic enlargement (25). Sinusoidal obstruction syndrome can result in postresection liver failure in patients with a poor future liver remnant, in spite of portal vein embolization (6). 5-FU-based chemotherapy is known to cause steatosis. Hepatic steatosis results in a diffuse decrease in liver attenuation, which may obscure metastatic lesions (Fig 12) (18). Quantification of hepatic steatosis can be performed with unenhanced CT and chemical shift MR imaging. Irinotecan has been shown to cause steatohepatitis (steatosis with hepatic inflammation) (2,3). Steatohepatitis may progress to cirrhosis; early signs of such transformation include abnormal enhancement and restriction of diffusion on DW images (6). Chemotherapy-associated steatohepatitis has been shown to increase the risk of postoperative morbidity and mortality.

Other toxicities associated with conventional chemotherapeutic agents include neuropathy (oxaliplatin), severe diarrhea (irinotecan), and hand-foot syndrome (capecitabine) (36). Pulmonary toxicity in the form of interstitial lung disease or organizing pneumonia associated with oxaliplatin is a rare complication but may be mistaken for progressive disease in patients with lung metastases (57).

Bevacizumab has been associated with bowel and vascular complications. Gastrointestinal perforation is seen in up to 2% of patients receiving **Figure 13.** Bowel perforation in a 63-yearold woman with mCRC. The patient had undergone right hemicolectomy, partial hepatectomy, and nine cycles of treatment with irinotecan and bevacizumab. Coronal reformatted contrast-enhanced CT image demonstrates pneumatosis of the colon (white arrows) and free intraperitoneal air (black arrows), findings that are suggestive of perforation.





a.

b.

Figure 14. Anastomotic dehiscence in a 76-year-old woman with rectal cancer and liver metastasis who underwent low anterior resection followed by 4 months of treatment with FOLFIRI and bevacizumab. Treatment was interrupted for 2 months for reversal of ileostomy, which resulted in progression of liver metastasis. (a) Contrast-enhanced CT image obtained 1 month after the resumption of treatment demonstrates scattered foci of air adjacent to the anastomotic site (arrows) and a small amount of presacral fluid (arrowheads). Two months after the start of treatment, the patient presented with pelvic pain and discharge of fecal matter through the vagina. (b) Unenhanced CT image obtained during this acute presentation reveals a breakdown of the anastomotic site, with a rectovaginal fistula (black arrows) and a large, presacral feculent collection containing fluid and gas (white arrows).

bevacizumab therapy and usually occurs in the setting of recent surgery, colonoscopy, peritoneal carcinomatosis, or primary tumor in situ (58). Pneumatosis intestinalis is a class-specific toxicity of anti-VEGF MTT and is postulated to result from ischemia induced by microvascular thrombosis. Pneumatosis is asymptomatic in the early stages but can result in complications such as bowel perforation (Fig 13) and tumor-bowel fistula (59). Management of bevacizumab-associated pneumatosis and bowel perforation includes prompt discontinuation of the drug. In a study by Shinagare et al (59), 22 of 24 patients with MTT-associated pneumatosis or bowel perforation required discontinuation of MTT. Other bowel complications associated with bevacizumab include anastomotic dehiscence caused by impaired wound healing due to anti-VEGF effect (Fig 14) (60). The NCCN guidelines recommend discontinuation of bevacizumab at least 6 weeks prior to elective surgery (2,3). Anti-VEGF agents increase the risk of both thromboembolic and hemorrhagic events (Fig 15). Venous thromboembolism increases the risk of pulmonary embolism (51). Careful attention to





c.

b.

thromboembolic complications is required, since pulmonary embolism in oncology patients is often asymptomatic and incidentally detected on restaging scans. The risk of arterial events, including stroke, is significantly increased in patients over 65 years of age (2). Bevacizumab is associated with hypertensive encephalopathy (posterior reversible encephalopathy syndrome), which is characterized by subcortical white matter changes in the occipital and posterior temporoparietal lobes (51). Uncommon class-specific complications associated with antiangiogenic agents such as bevacizumab include acute cholecystitis (61).

Cetuximab and panitumumab have been associated with severe infusion reactions in 3% and 1% of patients, respectively (62,63), and severe skin reactions have been reported with both EGFR agents. Pulmonary complications, including interstitial lung disease (Fig 16), have been reported with cetuximab (64).

Complications Associated with Liver-directed Therapies

Hepatic arterial infusion has been associated with acute acalculous cholecystitis, gastrointestinal perforation, biliary ischemia, and sclerosing cholangitis (Table 3). Radioembolization and stereotactic body radiation therapy can result in radiation hepatitis, cholecystitis, gastritis, gastric and duodenal ulcers, biliary necrosis, and lobar atrophy of the liver. Late complications associated with radiation include hepatic fibrosis, bile duct necrosis, and eventual portal hypertension (34). Major complications associated with percutaneous ablation include hepatic abscess, intraperitoneal hemorrhage, biliary injury, vascular thrombosis (Fig 17), tumor seeding, liver failure, gastrointestinal perforation, and pulmonary complications such as pneumothorax and pleural effusions (65).

Conclusion

In this era of personalized cancer care, imaging plays a critical role in the management of patients with mCRC. The development of new treatment regimens necessitates more rigorous imaging strategies for diagnosis and surveillance of mCRC, making radiologists an integral part of the multidisciplinary team caring for these patients. Multidetector CT and MR imaging are crucial in the diagnosis and treatment evaluation of mCRC. PET/CT is useful in ruling out **Figure 16.** Interstitial lung disease in a 42-year-old man with metastatic colon cancer. The cancer was refractory to FOLFIRI and cetuximab, and the patient was switched to panitumumab. Chest CT image obtained 2 months after the start of treatment demonstrates patchy consolidation and ground-glass opacities, predominantly in the left lung (arrowheads), findings that are consistent with drug toxicity (interstitial lung disease–cryptogenic organizing pneumonia). Note the large conglomerate deposit in the right lung (arrows).





Figure 17. Vascular thrombosis in a 66-year-old woman with sigmoid colon cancer. (a) Contrast-enhanced baseline CT image demonstrates a hypoattenuating metastatic deposit (black arrow) in the right hepatic lobe. Note the normal enhancement of the portal vein branches (white arrow). The patient underwent laparoscopic sigmoid colectomy followed by percutaneous ablation of the liver metastasis. (b) Postablation follow-up CT image demonstrates a large, hypoattenuating ablation zone (black arrows) associated with thrombosis of the posterior division of the right branch of the portal vein (white arrow).

extrahepatic disease when hepatectomy is being considered. Patients with unresectable disease are treated with systemic chemotherapy, most commonly FOLFOX and FOLFIRI in combination with bevacizumab, cetuximab, or panitumumab. There is growing evidence that response to systemic therapy is best assessed with alternative treatment response criteria. Attention must be paid to complications and toxicities associated with treatment for mCRC when imaging studies are being interpreted.

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Teaching Points



Update on the Role of Imaging in Management of Metastatic Colorectal Cancer

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Page 1909

The past decade has seen a paradigm shift in the management of stage IV or metastatic CRC (mCRC), leading to a significant increase in overall survival times for these patients, from less than 6 months to nearly 2 years.

Page 1912

Overall, the sensitivity of MR imaging for detecting CRC liver metastases is close to 95%, with an accuracy of 83% for detecting lesions less than 1 cm. In characterizing lesions less than 1 cm as benign or malignant, MR imaging surpasses CT, with an accuracy of 91%.

Pages 1916-1917

Currently, the most widely used first-line regimens in mCRC are (a) combined 5-FU/LV and oxaliplatin (FOLFOX), and (b) combined 5-FU/LV and irinotecan (FOLFIRI).

Page 1919

In contrast to CRC without KRAS mutations (eg, wild-type KRAS), CRC with KRAS mutations is not responsive to EGFR inhibition with cetuximab and panitumumab.

Page 1921

Unusual patterns of response that can mimic disease progression may occur in liver metastases treated with neoadjuvant chemotherapy.