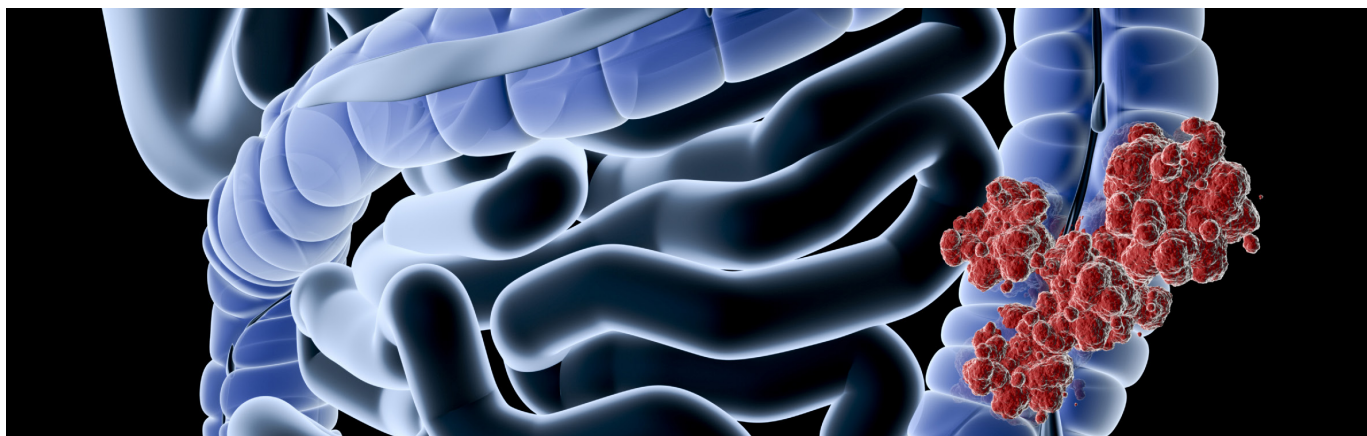


Metastatic Colorectal Cancer and Locoregional Therapies

By Patrick Middlebrook, M.D., and Hemant Mehta, M.D., Diagnostic Radiology · Updated for 2026 by Intrinsic Imaging



The American Cancer Society estimates about 158,850 new cases of colorectal cancer and 55,230 deaths in the United States in 2026, and the disease is now the leading cause of cancer death in adults under 50.¹ Roughly half of patients develop liver metastases, and for most of them the liver is what determines survival. Over the past decade the options for treating those metastases have multiplied: systemic therapy guided by molecular profiling, radioembolization, chemoembolization with drug-eluting beads, thermal ablation and, remarkably, liver transplantation. Each produces imaging changes that conventional size-based criteria handle poorly. This issue reviews the current evidence and what sponsors should build into trials of liver-directed therapy.

Systemic Therapy Has Fragmented by Biomarker

First-line treatment of metastatic colorectal cancer (mCRC) is still fluoropyrimidine-based chemotherapy with oxaliplatin or irinotecan plus a biologic, but the biologic is now chosen by molecular profile. Anti-EGFR antibodies are reserved for RAS and BRAF wild-type, left-sided tumors. Pembrolizumab is first-line standard for the roughly 5 percent of patients with microsatellite instability-high tumors after KEYNOTE-177 showed it doubled progression-free survival.² Encorafenib with cetuximab is approved for BRAF V600E-mutant disease, now including first-line use with chemotherapy, and KRAS G12C inhibitors combined with anti-EGFR therapy were approved in 2024 and 2025.^{3,4} Trials in mCRC therefore enroll ever smaller biomarker-defined populations, which places a premium on precise, reproducible imaging to detect differences in small samples.

Radioembolization: Lessons From Three Trials

Yttrium-90 radioembolization delivers beta radiation from microspheres lodged in the tumor's arterial supply. In first-line therapy, the combined analysis of the SIRFLOX, FOXFIRE and FOXFIRE-Global trials in more than 1,100 patients found no overall survival benefit from adding radioembolization to chemotherapy, although liver-specific

control improved.⁵ In the second line, the EPOCH trial showed that adding radioembolization to chemotherapy prolonged progression-free survival (hazard ratio 0.69) and hepatic progression-free survival (hazard ratio 0.59), establishing a role for the therapy in patients who have progressed on first-line treatment.⁶ Imaging in these trials used RECIST 1.1 for the primary endpoint, but the investigators noted that necrosis without shrinkage is common after radioembolization and that size criteria likely undercounted responses.

Chemoembolization With Drug-Eluting Beads

Irinotecan-eluting beads (DEBIRI) deliver high intratumoral drug concentrations with embolic ischemia. A randomized trial of DEBIRI versus systemic FOLFIRI in previously treated patients reported median overall survival of 22 versus 15 months, and a subsequent randomized study found that adding DEBIRI to first-line FOLFOX and bevacizumab improved response rate and downsizing to resection.^{7,8} Both were small, and DEBIRI remains a second-line or bridging option rather than a standard, but the imaging findings are instructive: treated lesions frequently develop central necrosis, peripheral enhancement and transient enlargement that mimic progression on size criteria.

Ablation, Resection and Transplantation

Surgery remains the only reliably curative treatment, but the COLLISION trial has shown that for small resectable colorectal liver metastases up to 3 cm, thermal ablation is non-inferior to resection for overall survival, with fewer serious adverse events (7 versus 20 percent) and a shorter hospital stay.⁹ At the other end of the spectrum, the Trans-Met trial randomized patients with definitively unresectable, chemotherapy-responsive liver-only metastases to liver transplantation plus chemotherapy or chemotherapy alone and reported five-year overall survival of 57 versus 13 percent, an unprecedented result that has reopened transplantation for metastatic disease.¹⁰ Imaging determined eligibility in both trials and defines the follow-up endpoints: local tumor progression at the ablation margin, new intrahepatic disease and extrahepatic recurrence.

Assessing Response After Locoregional Therapy

The common theme is that size is an inadequate measure of response after liver-directed therapy. Morphologic CT criteria developed at MD Anderson, which grade lesions by attenuation homogeneity and tumor-liver interface, correlated with pathologic response and survival after bevacizumab-containing therapy better than RECIST did.¹¹ mRECIST and the LI-RADS treatment response algorithm, developed for hepatocellular carcinoma, measure only viable enhancing tumor and are increasingly adapted to metastases after ablation and embolization. Diffusion-weighted MRI, contrast-enhanced MRI with hepatobiliary agents and FDG-PET each detect viable tumor and small lesions that CT misses. A trial protocol should state which criteria govern the primary endpoint, how necrosis and post-ablation zones are to be measured, and how 'disappearing' metastases after chemotherapy are handled, since many still harbor viable tumor.

Guidance for Sponsors

Imaging a liver-directed therapy trial

- **Choose criteria for the therapy.** RECIST 1.1 as the regulatory anchor, with mRECIST, morphologic or volumetric criteria pre-specified as secondary endpoints.^{6,11}
- **Define the ablation zone rules.** Specify how the treated zone is measured and what constitutes local tumor progression.⁹
- **Use liver-optimized imaging.** Multiphase CT or MRI with hepatobiliary contrast and DWI at fixed intervals.
- **Account for pseudoprogression.** Expect transient enlargement and peripheral enhancement after embolization; require confirmation.⁷
- **Track extrahepatic disease.** Include chest CT and whole-body assessment, because liver control alone did not improve survival in first-line radioembolization.⁵
- **Read centrally.** Blinded independent review with readers experienced in post-treatment liver imaging.¹²

Summary

Colorectal liver metastases are now treated with a wider range of tools than any other metastatic site, from molecularly matched drugs to microspheres, ablation probes and donor livers. Each changes the imaging appearance of the tumor in its own way. Sponsors who pre-specify how those changes will be measured, and who read them centrally with experienced eyes, will be able to show what their therapy achieves.

About the Authors

Dr. Patrick Middlebrook and Dr. Hemant Mehta, radiologists at Intrinsic Imaging, wrote the original edition of this issue. Both completed residencies in diagnostic radiology with fellowship training in body and oncologic imaging, and both interpret abdominal CT, MRI and PET for oncology trials, with particular expertise in hepatic imaging after locoregional therapy. Both are board-certified in diagnostic radiology.

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