# Magnetic Resonance Imaging of the Liver After Loco-Regional and Systemic Therapy

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**KEYWORDS**

• Contrast-enhanced MRI • Diffusion-weighted imaging • Volumetric functional MRI
• Response to therapy • Biomarker • Loco-regional therapy

**KEY POINTS**

- Change in tumor size in the axial plane after loco-regional therapy might be delayed using the traditional criteria, whereas volumetric functional magnetic resonance imaging can detect tumor cellular and metabolic changes earlier after therapy.
- Volumetric functional magnetic resonance imaging may be used to assess early response of primary and secondary liver tumors to loco-regional and systemic therapy. These biomarkers could help to predict patient survival and outcome.

## INTRODUCTION

Surgical resection is the only curative therapeutic option for primary and secondary liver tumors. Unfortunately, because of many factors including poor hepatic reserve, only 10% to 20% of patients with hepatocellular carcinoma (HCC) or metastatic disease are eligible for surgical resection or liver transplantation.[1–3] Patients with unresectable HCC or those beyond Milan criteria (single nodule $\leq$5 cm or no more than 3 nodules, each measuring 3 cm or less[4] in patients with cirrhosis) who are being bridged to transplantation may be considered for loco-regional therapy (LRT). Patients treated with LRT have been shown to have improved survival, likely due to induction of tumor necrosis and resultant delay in disease progression.[5,6] Because of the high mortality associated with primary and secondary liver tumors, assessment of tumor response after LRT and systemic therapy is important in defining treatment success and in guiding future therapy.

The development of imaging-based response criteria in patients with primary and secondary liver tumors has evolved over the last 2 decades. The traditional radiographic criteria for determining tumor response—the World Health Organization (WHO)[7] and the Response Evaluation Criteria in

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Solid Tumors (RECIST)[8]—both rely primarily on changes in lesion size. However, some anticancer therapies including LRT cause tumor necrosis and tumor cell cycle arrest without early tumor shrinkage. The lack of tumor size change has shifted the focus to the assessment of tumor vascularity as a biomarker of response. In 2000, the European Association for the Study of the Liver (EASL) amended the response criteria used for HCC with the assumption that viable components of the tumor enhance in the arterial phase, whereas necrotic components do not.[9] In 2008, the RECIST criteria were modified for HCC (mRECIST) to adopt the EASL concept by measuring the size of the enhancing portion of the tumor, rather than the entire tumor size.[10] In 2009, the Liver Cancer Study Group of Japan proposed revised criteria for HCC response assessment (Response Evaluation Criteria in Cancer of the Liver, RECICL) incorporating a combination of tumor necrosis quantification and serum markers levels, such as α-fetoprotein (AFP) and des-γ-carboxy protein (DCP), and establishing the timing (3 months) for assessment.[11] However, these metrics may not detect early tumor necrosis, which predates tumor shrinkage.[12]

Newer biomarkers of tumor response have used changes in apparent diffusion coefficient (ADC), as measured by diffusion-weighted imaging (DWI) to detected early cellular changes after therapy, before changes in tumor size occur. DWI is based on the random microscopic motion of free water molecules and their interaction with structures such as cell membranes and macromolecules.[13] DWI and ADC maps provide information about the shift of water from extracellular to intracellular spaces, restriction of cellular membrane permeability, increased cellular density, and cellular membrane disruption.[14] These findings aid in quantifying tumor necrosis and therefore predicting tumor response.

Contrast-enhanced magnetic resonance (MR) imaging allows assessment of parenchymal and tumoral tissue vascularity, providing information about blood flow and tissue perfusion.

A reduction in tumor enhancement after LRTs represents disruption of tumor blood supply. Prior studies have demonstrated that these tumors become necrotic and eventually decrease in size resulting in improved patient survival.[15,16]

Response to treatment after LRT has been widely studied with most studies using tumor measurements based on the axial plane.[15–17] However, these measurements can mislead an accurate response to treatment.[18] Volumetric assessment of the tumor has been effectively assessed in the liver using DWI and enhancement after contrast administration[12,15,19–22] with better reproducibility than Region of Interest (ROI)-based axial measurements, or RECIST or EASL measurements.[23]

In this article the role of tumor size (RECIST), tumor enhancement (mRECIST, EASL), and volumetric functional (ADC and enhancement) MR imaging is described to assess tumor response after systemic therapy and LRT.

## LOCO-REGIONAL AND SYSTEMIC THERAPY

Although surgical resection and liver transplant offer the only chance for curative treatment in primary and secondary liver tumors, most patients are found to be ineligible for surgical treatment at the time of diagnosis. This ineligibility has resulted in increased utilization of minimally invasive strategies with or without the combination of systemic therapy.[24] The response assessment in the context of the most commonly used LRT (**Box 1**) and systemic therapies are discussed.

### *Transarterial Embolization*

Transarterial therapies take advantage of the dual blood supply of the liver (ie, the fact that the hepatic artery primarily supplies most liver tumors, whereas the liver parenchyma depends primarily on the portal vein).[25] Transarterial embolization without chemotherapy, also called bland

**Box 1**
**Loco-regional therapies**

Transarterial therapies

Conventional methods

- Without embolization
  - Intermittent chemotherapy infusion into the hepatic artery
  - Continuous infusion with a hepatic artery pump
- With embolization
  - Bland embolization
  - Transarterial chemoembolization

New techniques

- Embolization with drug-eluting microspheres
- Embolization with radiation-emitting microspheres

Radiofrequency ablation

- Chemical (ethanol)
- Thermal ($^{90}$Y-bearing microsphere)
- Cooling (cryoablation)