

# Hepatoma: Image-Guided Treatment Options in 2016

An overview of the interventional oncologist's arsenal.

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**G**lobally, primary liver cancer is the sixth most common cancer and is the second highest cause of cancer mortality.<sup>1</sup> Hepatoma, or hepatocellular carcinoma (HCC), accounts for approximately 80% of primary liver tumors. Major risk factors for the development of HCC include hepatitis B infection, hepatitis C infection, cirrhosis, heavy alcohol consumption, and nonalcoholic steatohepatitis.<sup>2</sup>

## PATIENT EVALUATION

Patients with HCC should be evaluated by a multidisciplinary group of specialists consisting of interventional oncology, hepatology, medical oncology, radiation oncology, and surgical oncology. The purpose of this group is to confirm tumor diagnosis, evaluate liver function, evaluate patient performance status, determine tumor stage, and ultimately propose the most appropriate therapeutic option available for each unique patient.

The diagnosis of HCC is made primarily with imaging characteristics of arterial-phase enhancement and venous-phase washout on contrast-enhanced CT or MRI (Figure 1). Biopsy is seldom necessary, but may be useful in difficult diagnostic cases.<sup>3</sup> Cross-sectional imaging can also define tumor size and number, delineate vascular invasion, and determine nodal or distant metastatic disease.

Liver function can be ascertained using the model for end-stage liver disease (MELD) score ([www.mayoclinic.org/gi-rst/mayomodel5.html](http://www.mayoclinic.org/gi-rst/mayomodel5.html)), as well as the Child-Pugh class (Table 1).<sup>4</sup> Additionally, a patient's overall functional ability to carry on activities of daily living is represented by the Eastern Cooperative Oncology Group (ECOG) performance status (Table 2).

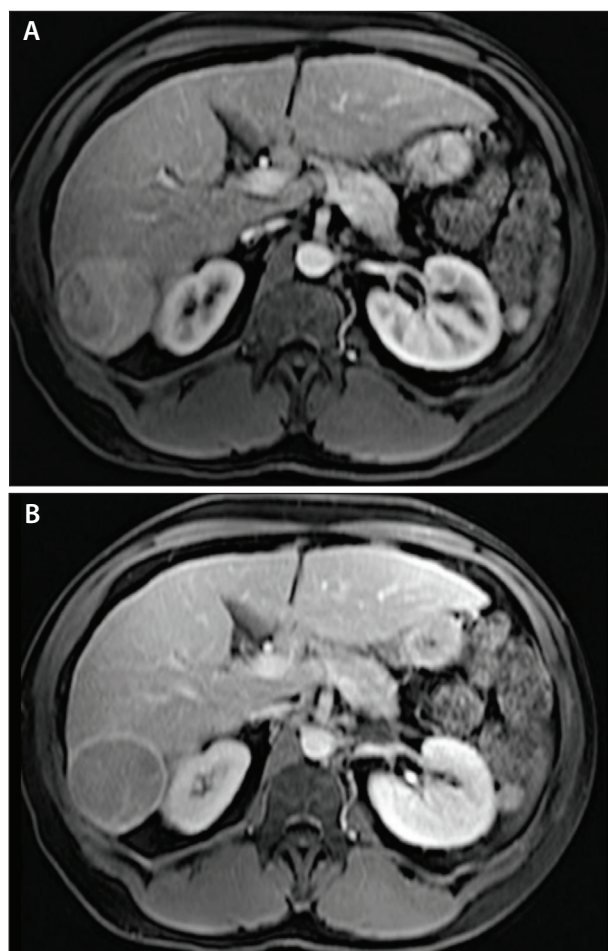


Figure 1. Arterial (A) and portal venous (B) phase images from a dynamic, contrast-enhanced MRI demonstrate a hypervascular mass with washout in segment VI of the right hepatic lobe, characteristic of HCC.

TABLE 1. CHILD-PUGH SCORE

Finding	1 Point	2 Points	3 Points
Encephalopathy grade	None	Mild	Severe
Ascites	Absent	Mild to moderate	Severe, refractory
Total bilirubin (mg/dL)	< 2	2–3	> 3
Serum albumin (g/dL)	> 3.5	2.8–3.5	< 2.8
INR	< 1.7	1.71–2.20	> 2.20

Child-Pugh class A = 5–6 points, class B = 7–9 points, class C = 10–15 points. Abbreviation: INR, international normalized ratio.

TABLE 2. ECOG PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry out all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair
5	Dead

TABLE 3. BCLC HCC STAGE

Stage	Description
Very early (stage 0)	PS 0, Child-Pugh A, single HCC < 2 cm
Early (stage A)	PS 0, Child-Pugh A-B, single HCC or 3 nodules < 3 cm
Intermediate (stage B)	PS 0, Child-Pugh A-B, multinodular HCC
Advanced (stage C)	PS 1–2, Child-Pugh A-B, portal vein invasion, nodal metastases, distant metastases
Terminal (stage D)	PS > 2, Child-Pugh C

Abbreviation: PS, ECOG performance status.

Many different classification and staging systems are available to stratify HCC and assist providers with determination of prognosis and treatment.<sup>5</sup> The Barcelona Clinic Liver Cancer (BCLC) classification has emerged as the standard staging system for the clinical management of patients with HCC (Table 3).<sup>6</sup>

## TREATMENT OPTIONS

There are many treatment options available to patients diagnosed with HCC, including surgical therapy, medical therapy, radiotherapy, and image-guided locoregional therapy.

### Surgical Therapy

Surgical resection and liver transplantation are the gold standard with regard to curative therapies for BCLC stage 0 and stage A HCC. However, the majority of patients are not surgical candidates due to decompensated liver function, medical comorbidities, extrahepatic spread of tumor, and a lack of donor organs.<sup>7</sup>

### Medical Therapy

Sorafenib, a tyrosine kinase inhibitor, has been shown to improve overall survival in both the SHARP trial and the Asia-Pacific trial.<sup>8,9</sup> However, systemic chemotherapy has not increased survival in patients with advanced disease. Additionally, patient tolerability may be a limiting factor to its long-term use as a first-line treatment. Sorafenib is indicated for BCLC stage C HCC.

### Radiotherapy

Although HCC is a radiosensitive tumor, conventional external beam radiotherapy is not an often-utilized treatment modality. This is due to the corresponding radiosensitivity of surrounding noncancerous liver parenchyma and the propensity for radiation-induced liver damage. Stereotactic body radiation therapy allows for more targeted delivery of external radiation and may provide a survival benefit for unresectable HCC in the setting of compensated cirrhosis.<sup>10,11</sup>

### Image-Guided Locoregional Therapy

Locoregional techniques have evolved with the intention to control tumor growth with targeted destruction, while minimizing collateral damage to the surrounding liver in patients who are not deemed to be surgical candidates. These minimally invasive techniques are most commonly image guided and can be

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divided into percutaneous ablative therapies and intra-arterial, catheter-based embolic therapies.

### Ablation

Image-guided, percutaneous ablation is an approach designed to treat focal tumors by inducing irreversible cellular damage with the administration of thermal energy, nonthermal energy, or denaturing chemicals. The goal is to achieve uniform ablation of the visible tumor in addition to a 1-cm ablative margin of normal liver tissue. Ablative therapy is indicated for BCLC stage A HCC.

### Radiofrequency Ablation

Radiofrequency ablation (RFA) delivers high-frequency alternating currents at the active portion of an ablation probe, which causes local ionic agitation and generates frictional heat.<sup>12</sup> As tissue temperatures increase between 60°C to 100°C there is instantaneous coagulation necrosis of the exposed tissue (Figure 2).<sup>13</sup> Temperatures > 100°C can cause tissue charring, which may decrease the size of the ablation zone.<sup>14</sup> The efficacy of RFA may be limited in subcapsular tumors adjacent to nearby structures due to the risk of thermal injury to these structures. Also, tumors in close proximity to high-flow blood vessels > 3 mm in diameter are susceptible to a heat sink effect, whereby flowing blood dissipates thermal energy.

### Microwave Ablation

Microwave thermal ablation (MWA) involves inserting antennae for an externally applied energy source into a tumor. There is a resultant oscillation of polar

molecules that produces frictional heat.<sup>15</sup> MWA can reach higher temperatures in shorter periods of time compared to RFA and is not limited by tissue charring. MWA is not hampered by perivascular heat sink.

### Irreversible Electroporation

Irreversible electroporation (IRE), a nonthermal technique, uses an electrical field to induce apoptosis through irreversible cell membrane damage.<sup>16</sup> IRE is not affected by heat sink from nearby blood vessels and also appears to limit damage to surrounding tissue. IRE requires general anesthesia and induced paralysis.

### Cryoablation

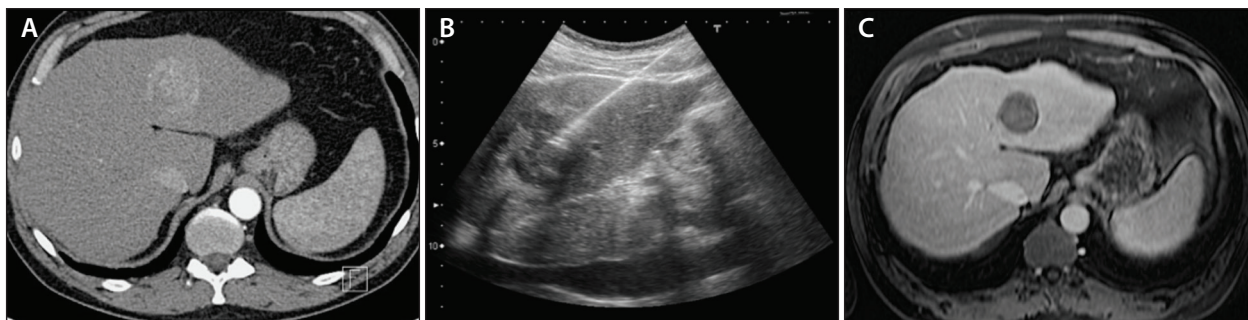
Cryoablation is a thermal ablative technique that uses argon gas, traveling through a percutaneous probe, to cool the target lesion. Temperatures of –20°C to –40°C are reached, and cell death is induced by intracellular and extracellular ice crystal formation.<sup>17</sup> Cryoablation may be associated with disseminated intravascular coagulation and cryoshock syndrome, a life-threatening multiorgan failure.<sup>18</sup>

### Chemical Ablation

Chemical ablation, percutaneous ethanol injection, and percutaneous acetic acid injection, is mostly of historical value in the current landscape of interventional oncology. These procedures involve the direct, image-guided injection of a chemical into a hepatoma.<sup>19</sup>

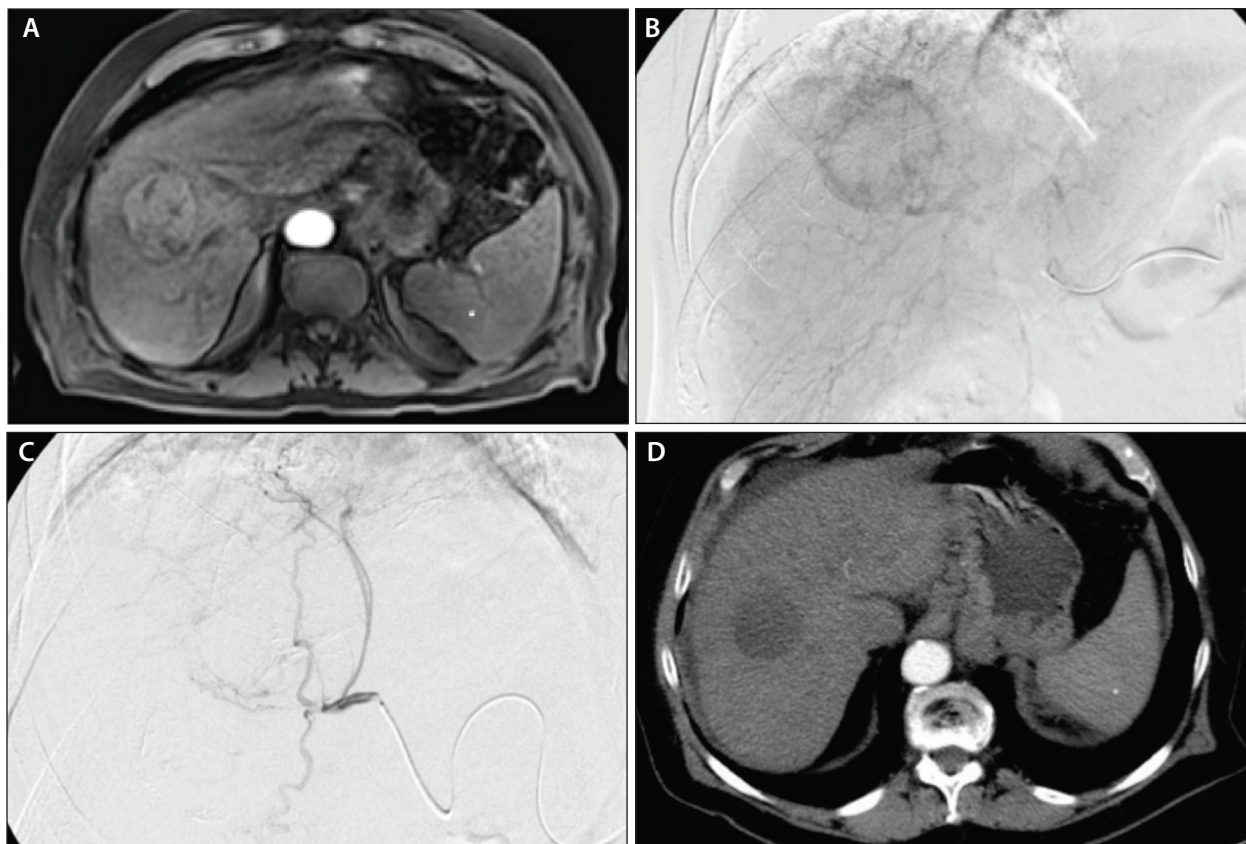
### Catheter-Based Therapy

The normal liver receives 75% of its blood supply from the portal vein and 25% from the hepatic artery. Conversely, HCC is supplied predominantly by the hepatic artery.<sup>20</sup> Intra-arterial embolotherapies exploit this nuance and can selectively deliver embolic materials to tumor tissue while relatively sparing normal surrounding parenchyma. Endovascular techniques are recommended for BCLC stage B HCC.



**Figure 2.** A hypervascular HCC in segment II of the left hepatic lobe (A). An intraprocedural ultrasound image demonstrates an RFA probe entering the hypoechoic tumor (B). An area of necrosis at the treatment site 24 months after ablation (C).





**Figure 3.** Hypervascular HCC in segment VIII of the right hepatic lobe (A). Hypervascular tumor blush in the region of the hepatic dome (B). Subselective catheterization of the segmental VIII right hepatic arterial branch (C). Area of necrosis at the treatment site 12 months after DEB-TACE (D).

### Transarterial Chemoembolization

Conventional transarterial chemoembolization (cTACE) involves selective hepatic arterial delivery of a mixture of lipiodol with a cytotoxic agent(s) followed by bland particle embolization.<sup>21</sup> Lipiodol is a poppy seed oil that accumulates in tumor cells due to a lack of Kupffer cells found in a normal liver. The most commonly used chemotherapeutic agents are doxorubicin, mitomycin C, and cisplatin. The exact combinations are highly variable between institutions. Some may use only one agent, whereas others combine two or three. After chemoinfusion, bland permanent or temporary particles ranging from 100 to 500  $\mu\text{m}$  in diameter are infused into the same hepatic arterial distribution to decrease washout and prolong tissue dwell of the chemotherapeutic. A meta-analysis of randomized controlled trials comparing cTACE to conservative treatment over a 24-year period found a significant 2-year survival benefit with cTACE.<sup>22</sup>

Drug-eluting bead chemoembolization (DEB-TACE) is a derivative of cTACE in which microspheres are loaded

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with a chemotherapeutic agent, most commonly doxorubicin (Figure 3). DEB-TACE may result in prolonged chemotherapy exposure of the target tumor compared to cTACE.<sup>23</sup> The PRECISION V study showed improved tolerability of DEB-TACE in patients with BCLC stage B HCC compared to cTACE, but did not demonstrate an improved therapeutic response.<sup>24</sup>

### Radioembolization

Radioembolization uses glass or resin microspheres loaded with beta-emitting yttrium-90 (Y-90) for selec-

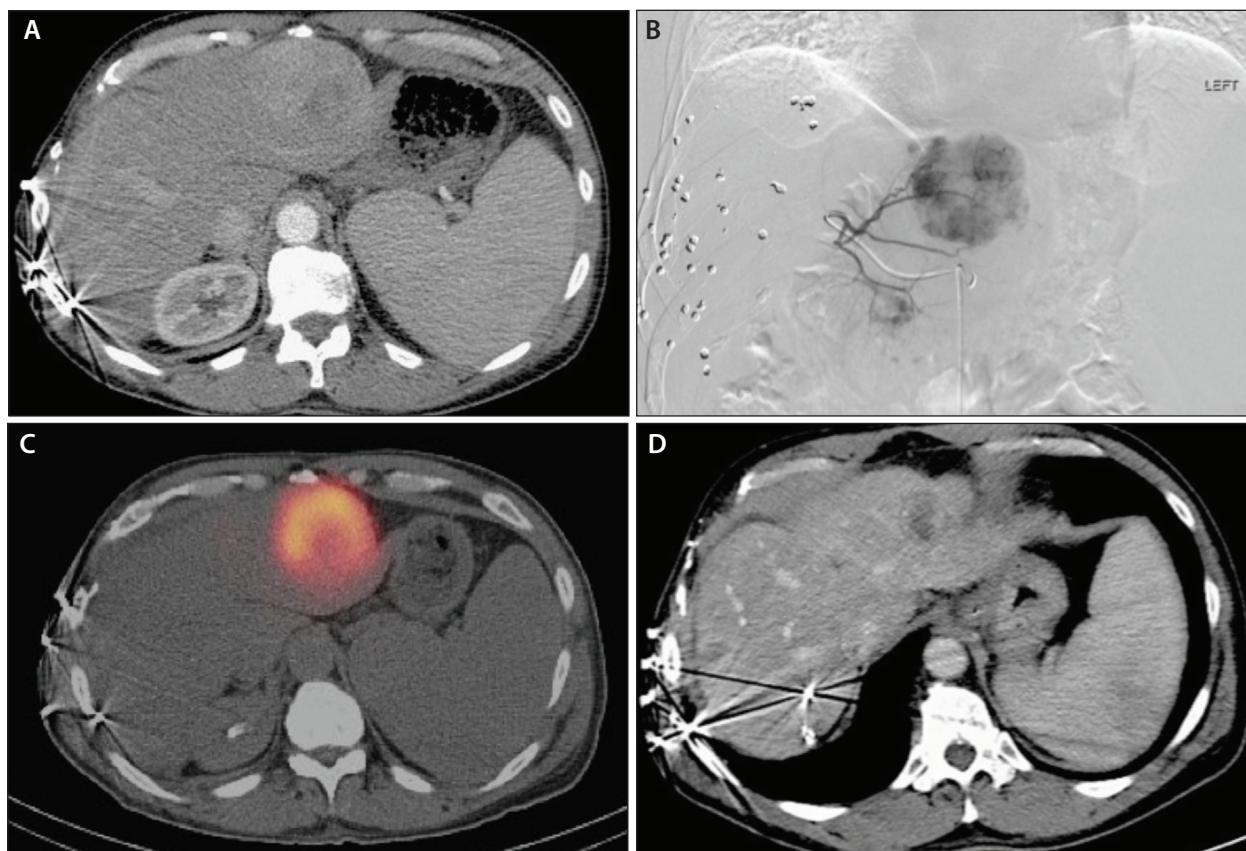


Figure 4. Hypervascular HCC in segment II of the left hepatic lobe (A). Selective catheterization of the left hepatic artery shows the hypervascular mass (B). Fused SPECT and CT shows uptake of Tc-99m MAA into the mass (C). Shrunken, necrotic mass 12 months after radioembolization (D).

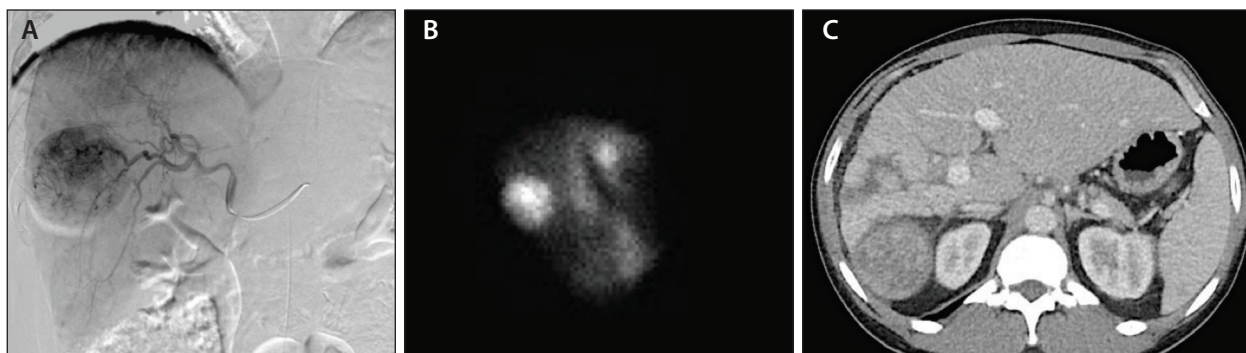


Figure 5. Same patient as in Figure 1. A hepatic arteriogram demonstrates the hypovascular HCC (A). Planar SPECT imaging shows accumulation of Tc-99m MAA at the expected location of the mass (B). Hypovascular mass 12 months after radioembolization (C).

tive injection into the hepatic arteries feeding an HCC. Treatment can be lobar or selective. Unlike other transarterial therapies, radioembolization requires a pre-treatment planning arteriogram to determine precise vascular supply to the tumor and to detect possible extrahepatic shunting. Prophylactic embolization of various arteries, such as the gastroduodenal artery and

right gastric artery, may be necessary to prevent non-target radioembolization. Technetium-99m macroaggregated albumin (Tc-99m MAA) is administered into the target hepatic artery during planning arteriography to assess for potential Y-90 shunting to the lungs.<sup>25</sup> After obtaining the planning arteriogram, a single-photon emission computed tomography (SPECT) scan is



TABLE 4. mRECIST CLASSIFICATION OF TUMOR RESPONSE

Response	Description
Complete response	Disappearance of any intratumoral arterial enhancement in all target lesions
Partial response	At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
Stable disease	Any cases that do not qualify for either partial response or progressive disease
Progressive disease	An increase of at least 20% of the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started

obtained to demonstrate the degree of tumor uptake, degree of pulmonary shunting, and possible sites of extrahepatic radiotracer uptake. The patient returns for therapeutic Y-90 administration after appropriate dose calculation (Figures 4 and 5).<sup>26</sup> Radioembolization has been shown to improve survival for intermediate-stage HCC at a rate similar to cTACE and DEB-TACE.

### Tumor Response

The assessment of HCC response to locoregional therapies has evolved during the past decade. The modified Response Evaluation Criteria in Solid Tumors (mRECIST) is currently accepted and takes into account intratumoral arterial enhancement on follow-up imaging (Table 4).<sup>27</sup>

### CONCLUSION

HCC is a unique tumor in that it often develops on a backdrop of underlying liver disease. As a result, most patients are not candidates for curative surgical therapies. Image-guided locoregional interventions have continued to progress and provide both a survival benefit and an encouraging safety profile. ■

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