IO Learning Interventional Oncology

CLINICAL INSIGHTS

Liver-Directed Therapies for Transplant-Eligible and Near Transplant-Eligible Patients With Hepatocellular Carcinoma: An Institutional Approach

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INTRODUCTION

Hepatocellular carcinoma (HCC), the most common primary liver tumor, is the third leading cause of cancer-related death worldwide.[1] Orthotopic liver transplantation (OLT) is considered the most effective curative treatment option for HCC, with 5-year survival rates of 60%-80% in patients with early-stage disease.[2-5] However, only a minority of patients with HCC are eligible for transplantation at the time of diagnosis, necessitating alternative therapies to increase survival and prepare patients for transplantation.[6] Interventional radiology (IR) is a critical partner for patients with HCC, providing a means to bridge transplant-eligible patients and downstage near transplant-eligible patients. This is accomplished through various liver-directed interventions such as percutaneous ablation (PA), bland transarterial embolization (TAE), conventional transarterial chemoembolization (cTACE), drug-eluting bead chemoembolization (DEB-TACE), and transarterial radioembolization (TARE) with Yttrium-90 (Y-90).[7-9] In this article, we will discuss

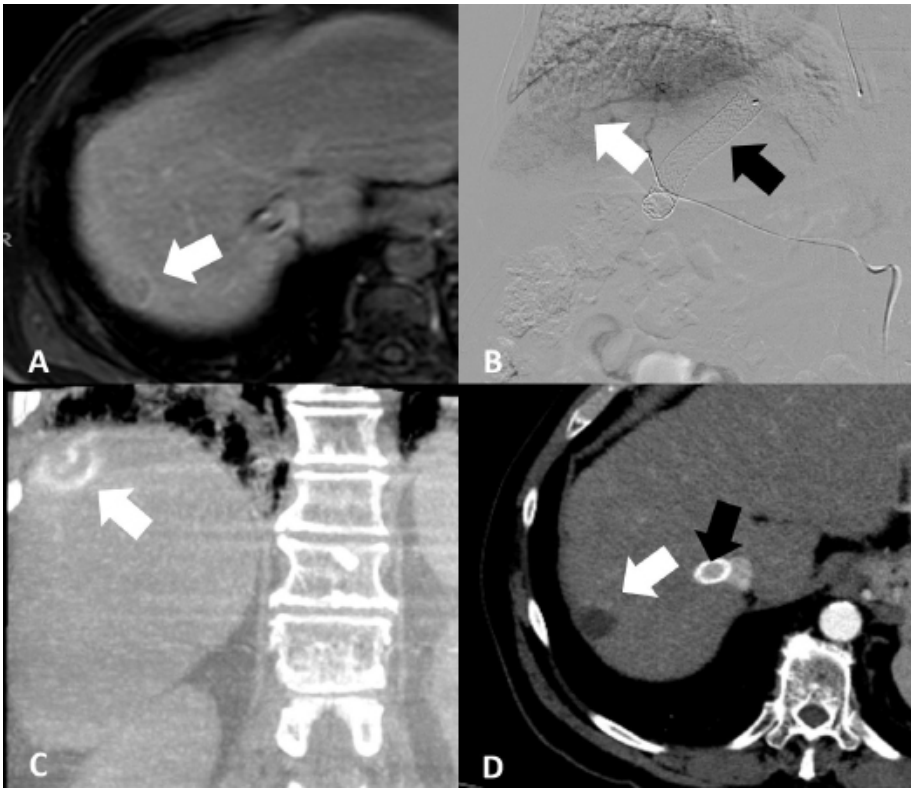

FIGURE 1. A 63-year-old man with cirrhosis secondary to hemochromatosis. (A) Axial slice from a T1-weighted, contrast-enhanced magnetic resonance imaging scan in portal venous phase demonstrates a 2.1 cm hepatocellular carcinoma (white arrow) in segment 7. (B) Digital subtraction angiogram from a branch of the right hepatic artery during drug-eluting bead chemoembolization (DEB-TACE) does not demonstrate obvious tumor vascularity. A transjugular portosystemic shunt (TIPS) stent is seen (black arrow). (C) Coronal reformatted image from a cone-beam computed tomography performed after DEB-TACE confirms tumor targeting with the embolic agent (white arrow). (D) Axial slice from a contrast-enhanced computed tomography in arterial phase demonstrates no residual enhancement in the tumor (white arrow), consistent with a complete response. The patient underwent successful liver transplantation approximately 10 months later. The TIPS stent is also seen (black arrow).

our approach to liver-directed therapies for transplant-eligible and near transplant-eligible patients at the University of Alabama in Birmingham, Alabama.

TRANSPLANTATION

OLT remains the most effective curative treatment for early-stage HCC, as it simultaneously treats the cancer and underlying liver disease. Studies have demonstrated that transplantation leads to superior survival outcomes when compared with other therapies, with 5-year survival rates as high as 60%-80% in patients with early-stage disease.[2-5] However, these success rates are contingent on patients meeting strict transplant criteria, as outlined by the Milan criteria.[10] Per these criteria, patients are eligible for OLT if they have either a single tumor ≤5 cm in diameter or ≤3 tumors (each ≤3 cm in diameter) without associated vascular invasion or extrahepatic metastatic disease.[10,11] Studies have found that patients who met these criteria had better post-transplant survival rates than patients with larger tumor burdens, emphasizing the importance of utilizing these tumor size and burden-based criteria.[3,12] Expanded criteria for transplant eligibility, such as the University of California San Francisco (UCSF), Pittsburgh, Hangzhou, Up-to-Seven, and Toronto criteria, have been explored to open the pathway of transplantation to more patients. The Milan criteria remain the most widely utilized transplant criteria for HCC patients, but continued investigation is warranted to develop less-exclusive criteria that can achieve similar or better clinical outcomes.[13]

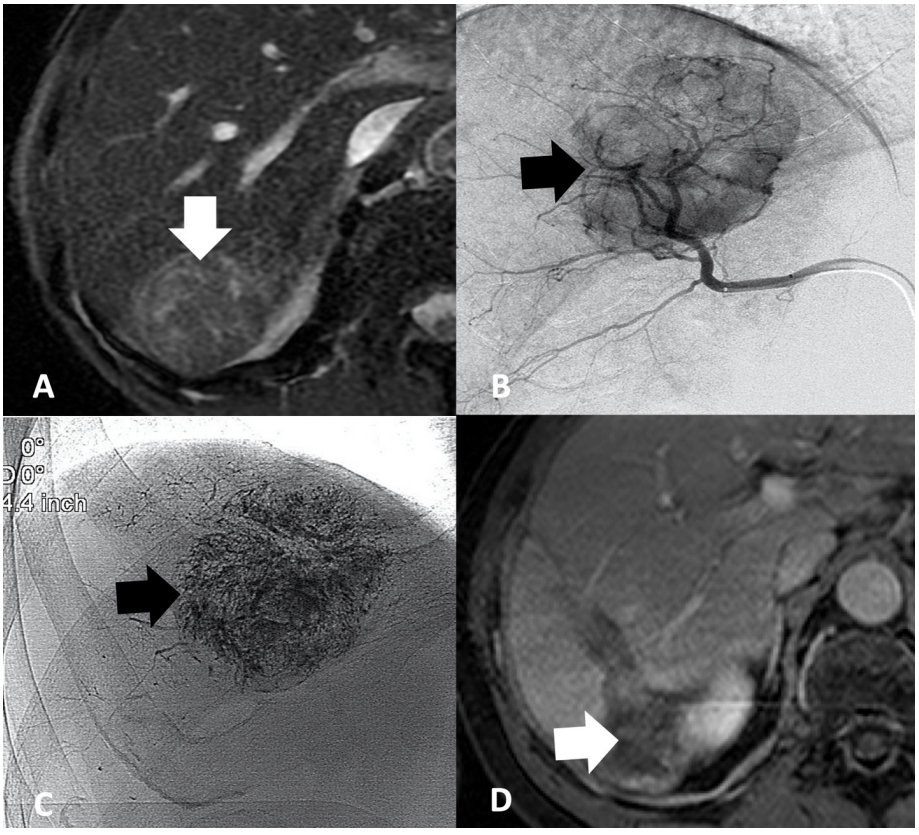

FIGURE 2. A 69-year-old man with cirrhosis secondary to hepatitis C. (A) Axial slice from a T2-weighted magnetic resonance imaging (MRI) scan demonstrates a well-defined, hyperintense mass in the right lobe of the liver (white arrow), measuring >5 cm. Prior to treatment, the patient was outside of Milan criteria. (B) Digital subtraction angiography from the right hepatic artery during conventional transarterial chemoembolization (cTACE) procedure demonstrates the hypervascular mass in the right lobe of the liver (black arrow). (C) Radiograph obtained after cTACE demonstrates excellent uptake of ethiodol/doxorubicin within the mass (black arrow). (D) Axial slice from a T1-weighted MRI scan after contrast administration in portal venous phase demonstrates no residual enhancement within the mass, consistent with a complete response to therapy and successful downstaging of the patient to be within Milan criteria. The patient underwent transplantation approximately 14 months after this MRI scan was obtained.

Aside from tumor-based criteria, patients must also undergo a thorough medical examination to ensure suitability for transplantation. A typical evaluation would include echocardiography, cardiac stress testing with potential catheterization depending upon risk factors, pulmonary function testing, and determination of functional status. Common medical contraindications to liver transplantation include functionally significant coronary artery disease not amenable to intervention, congestive heart failure with reduced ejection fraction, moderate to severe pulmonary hypertension, and severe pulmonary parenchymal disease. Age itself is not an absolute contraindication, although patients older than 70 years must have a very limited comorbidity burden and excellent functional status in order to qualify. Finally, a psychosocial evaluation ensures the patient's ability to comply with a complex medical regimen postoperatively, the absence of unstable psychiatric disease, no current substance abuse, and sufficient social support. These factors highlight the challenges of providing most HCC patients with the curative therapy of transplantation.

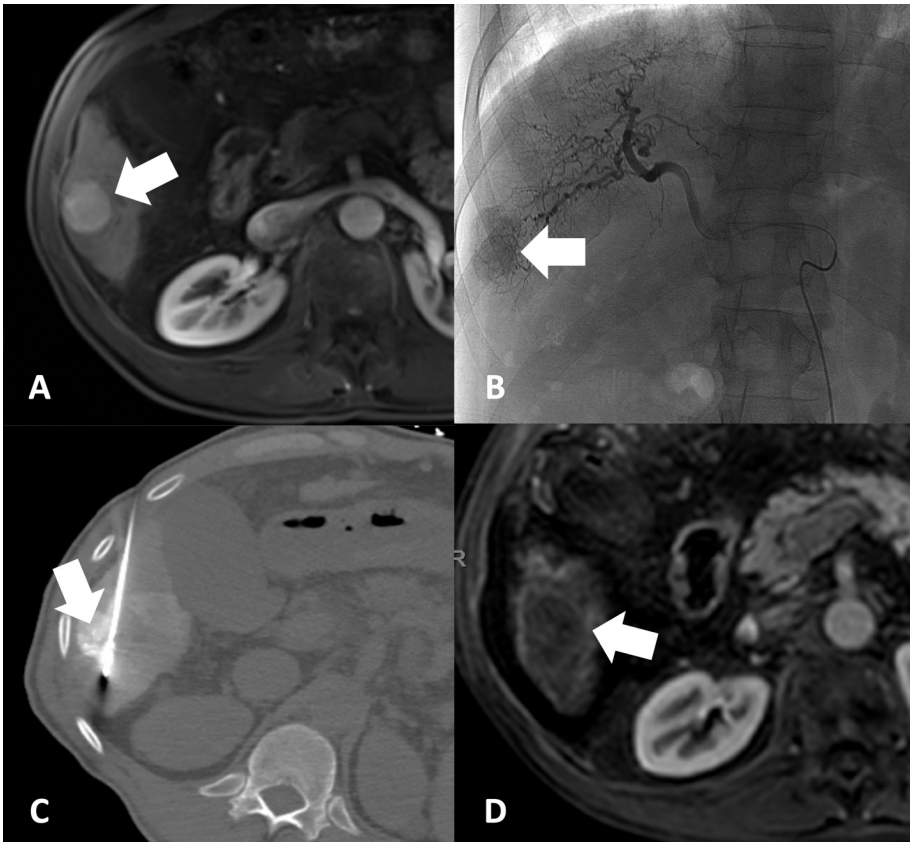

FIGURE 3. A 62-year-old man with cirrhosis secondary to hepatitis C. (A) Axial slice from a T1-weighted, contrast-enhanced magnetic resonance imaging (MRI) scan in arterial phase demonstrates a 3.2 cm hepatocellular carcinoma (white arrow) in segment 6. (B) Digital subtraction angiogram from the right hepatic artery during conventional transarterial chemoembolization (cTACE) demonstrates tumor hypervascularity (white arrow). (C) Axial slice from computed tomography obtained during percutaneous microwave ablation the day after cTACE shows retention of the radiopaque ethiodol in the tumor (white arrow) with the ablation probe adjacent to the tumor. Microwave ablation was performed with a 19 cm probe (AngioDynamics) at 140 watts for 6 minutes. (D) Axial slice from a T1-weighted, contrast-enhanced MRI scan in arterial phase 1 month after combined cTACE with percutaneous ablation demonstrates no residual enhancement (white arrow), consistent with a complete response. The patient is currently awaiting transplant.

THERAPEUTIC ALTERNATIVES FOR BRIDGING AND DOWNSTAGING PRIOR TO TRANSPLANTATION

Transplant-eligible and near transplant-eligible patients with HCC run the risk of losing the possibility of the curative therapy of transplantation due to disease progression from prolonged waiting periods.[14] Studies have shown that dropout rates from the transplant list are significantly higher for patients with tumors that are left untreated during the waiting period,[15,16] highlighting the value in bridging and/or downstaging therapies. Bridging therapies can be defined as treatments whose primary aim is to maintain the patient's tumor burden within Milan criteria. Examples of bridging therapies include surgical resection, PA, TAE, cTACE, DEB-TACE, TARE, and stereotactic body radiation therapy (SBRT). Downstaging can be defined as treatments whose primary aim is to bring the patient's tumor burden within Milan criteria. Examples of downstaging therapies include TAE, cTACE, DEB-TACE, TARE, and SBRT. Treatment selection is principally driven by patient-specific factors, although institutional preferences and experience are important to consider, as few data exist to support one therapy over another. Also, multidisciplinary tumor boards consisting of liver transplant surgeons, hepatologists, oncologists, radiologists, interventional radiologists, radiation oncologists, and pathologists are important for treatment planning in these patients, further optimizing therapeutic interventions for HCC patients.[17]

Surgery is the most widely accepted primary intervention for early-stage HCC, making resection a powerful method of bridging.[18] However, in our experience, a minority of patients have the hepatic reserve required for a successful resection. In that regard, PA represents an attractive option, since both randomized trials and cohort studies have shown that oncologic outcomes are similar to those of surgery for tumors up to 5 cm in size, with greater preservation of hepatic function.[19] PA of HCC is most commonly performed using either radiofrequency ablation (RFA) or microwave ablation (MWA).[20] Other less commonly used technologies for ablation of HCC include irreversible electroporation (IRE), cryoablation, and high-intensity focused ultrasound (HIFU).[21] However, the use of ablation for bridging is limited in many centers due to the risk of tumor seeding outside the liver, which can occur in ~1% of cases and results in the patient losing transplant eligibility.[22] Given this, the majority of patients at our transplant center are referred for intra-arterial liver-directed therapies when

either bridging or downstaging is necessary.

Intra-arterial liver-directed therapies for HCC include TAE, cTACE, DEB-TACE, and TARE. cTACE is the only intra-arterial liver-directed therapy that has been shown in randomized trials to provide a survival advantage for patients with unresectable HCC.[23,24] As such, it is considered a first-line treatment for intermediate-stage disease and is commonly used as a bridging therapy.[25] However, recent studies have challenged the superiority of cTACE for HCC management, with varied results throughout. For example, DEB-TACE has been found to be associated with a reduction in liver toxicity and drug-related adverse effects when compared with cTACE.[26,27] Furthermore, there were no significant differences in radiologic response, progression-free survival, or overall survival in one randomized trial comparing TAE with DEB-TACE.[28] TARE has also emerged as a comparable liver-directed therapy for HCC management, with at least one study showing no significant difference in overall survival between TARE and cTACE for patients with intermediate-stage HCC, but longer time to progression (TTP) and better tolerance with TARE.[29] TARE may also be particularly useful in cases involving tumor extension into the portal vein, since the radiolabeled spheres are not truly embolic within the hepatic artery.[30,31] Studies have even supported the use of radiation segmentectomy as a possible curative therapy for early-stage disease patients who are not resection or ablation candidates.[32,33] There is also growing evidence that supports the usefulness of SBRT for patients with unresectable, locally advanced, or recurrent HCC.[34,35] Combinations of liver-directed therapies are often utilized in HCC management as well, with the combination of TACE and PA shown to lead to better outcomes than either modality alone for solitary HCC <7 cm in diameter.[36]

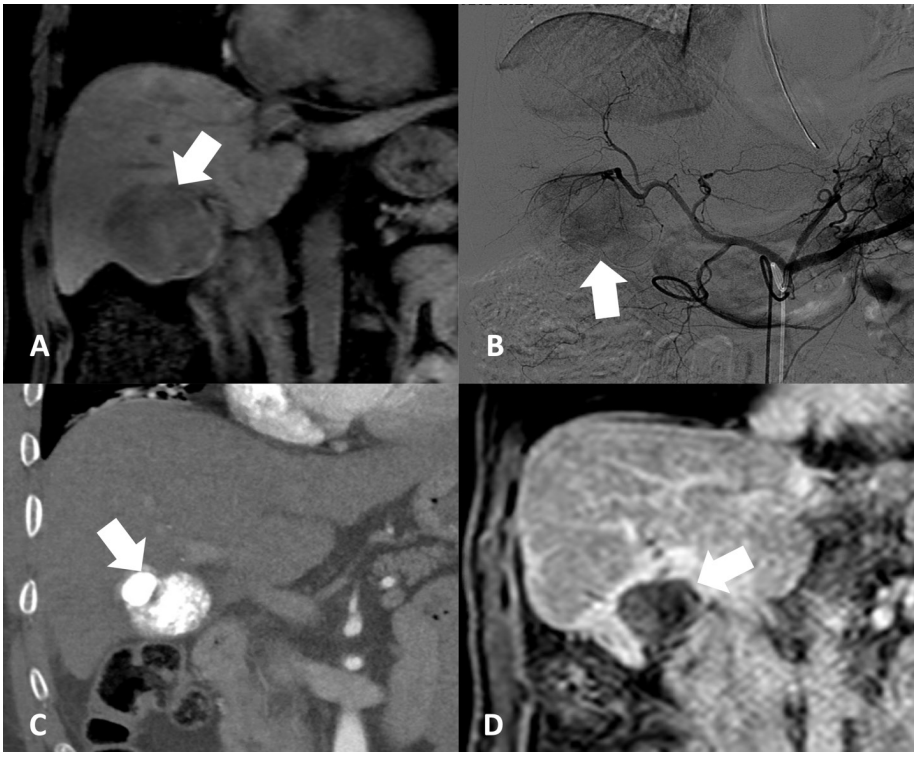

FIGURE 4. A 54-year-old man with cirrhosis secondary to alcohol use. (A) Coronal image from a T1-weighted magnetic resonance imaging (MRI) scan without contrast demonstrates a 6.2 cm hepatocellular carcinoma (HCC) in the inferior right hepatic lobe (white arrow). (B) Digital subtraction angiogram from the celiac artery during conventional transarterial chemoembolization (cTACE) demonstrates tumor hypervascularity (white arrow), consistent with preprocedural imaging. (C) Coronal reformatted image from a contrast-enhanced computed tomography scan in arterial phase shows excellent coverage of the tumor with radiopaque ethiodol (white arrow). (D) Coronal slice from a T1-weighted, contrast-enhanced MRI scan in portal venous phase obtained approximately 1 year after cTACE followed by stereotactic body radiation therapy (SBRT) demonstrates no residual enhancement in the tumor (white arrow), consistent with a complete tumor response. The patient began SBRT approximately 3 months after cTACE. The patient received a total dose of 45 Gy in 3 fractions over 8 days.

At our institution, we use DEB-TACE as our therapy of choice for bridging and downstaging (Table 1), as this technique has similar efficacy and less toxicity than cTACE.[26,27] DEB-TACE can be performed with a variety of bead sizes and chemotherapy combinations. We prefer using a single drug, doxorubicin, since there is no clear advantage to a triple-drug regimen (Figure 1).[37] The beads are bound with 50-100 mg of doxorubicin, depending on the patient's tumor burden. Regarding bead size, DEB-TACE is typically performed using 40-300 µm beads. The most commonly used beads in our practice are Oncozene (Varian) and LC Beads (Boston Scientific). Smaller bead sizes theoretically penetrate deeper into the tumor, but may come with an increased risk of biliary necrosis.[38,39] A recent

Table 1. Institutional approach for bridging transplant-eligible and downstaging near transplant-eligible patients with hepatocellular carcinoma.

Liver-Directed Therapy	Notes
Monotherapy	
DEB-TACE	Preferred method for bridging/downstaging[a]
TARE	Reserved for cases with main branch portal vein thrombus, radiation segmentectomy, and radiation lobectomy prior to surgical resection
Combination Therapies	
cTACE + PA	If PA is feasible and tumor size is 3-5 cm
cTACE + SBRT	If PA is not feasible[b] or tumor size is >5 cm

[a]Treatment selection is driven by patient-specific factors, and a multidisciplinary approach is taken to optimize therapeutic interventions on a case-by-case basis. [b]Lesions within 1cm of critical structures or major blood vessels where a safe ablation zone cannot be created via common displacement techniques such as hydrodissection.
cTACE = conventional transarterial chemoembolization; DEB-TACE = drug-eluting bead chemoembolization; PA = percutaneous ablation; SBRT = stereotactic body radiation therapy; TARE = transarterial radioembolization.

study from our institution demonstrated the safety and efficacy of using as small as 75 µm for DEB-TACE in unresectable HCC.[40] Currently, our practice is to use 75 µm beads for selective (ie, sublobar) embolization while reserving larger beads (ie, 100-300 µm beads) for lobar therapies.

cTACE involves mixing ethidiozed oil with a chemotherapeutic agent, creating a radiopaque emulsion. After this emulsion is delivered, embolization is performed with either a gelatin foam slurry or beads. The radiopaque ethiodol is cleared by normal hepatocytes but retained by the HCC, helping the emulsion preferentially target cancerous cells. Moreover, the emulsion improves the concentrations of the chemotherapeutic agent within the target tissue (Figure 2).[41] Finally, its radiopaque nature makes it an excellent target for computed-tomography guided PA (Figure 3) or SBRT (Figure 4). If PA is technically feasible for an HCC measuring 3-5 cm in size, our typical practice is to perform cTACE followed by PA, as the combination of these therapies improves oncologic outcomes.[36] PA is most commonly performed either on the same day or the day following cTACE. If PA is not technically feasible or tumor size exceeds 5 cm, the radiopaque ethiodol can be used to localize the tumor for SBRT. Our institutional results demonstrated improvements in both local recurrence and overall survival in patients with unresectable HCC measuring ≥3 cm treated with TACE and SBRT versus those treated with TACE alone.[42] We reserve TARE for patients with main-branch portal vein thrombus, radiation segmentectomy, and radiation lobectomy prior to surgical resection.[32,33] In our practice, we primarily use glass-based spheres (TheraSphere; Boston Scientific) in patients with HCC.

CONCLUSION

Interventional radiology provides a means to bridge transplant-eligible patients and downstage near transplant-eligible patients to curative therapies through liver-directed therapies Various liver-directed therapies have emerged as options for bridging and downstaging HCC patients, with no clear support for one therapy over another. Therefore, treatment selection is strongly driven by patient-specific factors, as well as institutional preferences and experience. As therapeutic innovations continue to outpace randomized trials, continued investigation is warranted to further elucidate the role and comparative efficacy of each liver-directed therapy as bridging and downstaging therapies for HCC patients.

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