



Interventional Radiology in Hepatocellular Carcinoma: Current Status and Looking Ahead

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Indographics 2022;1:184–195.

Abstract

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide and its incidence is on the rise. Although transplantation and surgical resection remain the definitive curative treatment options, only a minority of patients are eligible for these owing to advanced stage of disease at diagnosis. Over the last two decades, various interventional radiology (IR) therapies such as ablative and transarterial therapies, have come to the forefront of HCC management. IR also plays a role in preoperative management of HCC patients with procedures such as portal vein embolization. The recently updated Barcelona Clinic Liver Cancer (BCLC) staging system for HCC provides a guideline for choosing the optimum treatment modality for individual patients, with IR playing a central role. This review summarizes the different IR treatment options in HCC, including various ablative therapies, Transarterial Chemoembolization (TACE), Transarterial Radioembolization (TARE), Portal Vein embolization, emphasizing patient selection, procedural considerations and response evaluation.

Keywords

- ▶ HCC
- ▶ interventional radiological therapies
- ▶ TACE
- ▶ microwave ablation
- ▶ radiofrequency ablation

Introduction

Hepatocellular carcinoma (HCC), is the seventh most common cancer in the world and the second most common cause of cancer-related mortality.¹ The incidence of HCC has been on the rise, particularly in the Asian population. The therapeutic options for HCC have evolved over the past two decades with early-stage tumors being treated with curative options such as surgical resection, liver transplantation, or ablative therapies. However, only a minority of patients are eligible for these therapies owing to the advanced stage at diagnosis and require other therapeutic options with a palliative intent such as TACE, TARE, stereotactic body radiation therapy (SBRT), and systematic immunotherapy. This review evaluates and summarizes the role of interventional radiology in the management of HCC, providing an outline of

the various available treatment options, chiefly ablative and transarterial therapies.

Barcelona Clinic Liver Cancer (BCLC) Staging System–2022 Update

The Barcelona Clinic Liver Cancer (BCLC) system, first proposed in 1999, is the most commonly used staging system for HCC and is endorsed by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD). The system stratifies patients based on general performance status, tumor burden and liver functional reserve, into five stages (0, A, B, C, D) and recommends treatment strategies accordingly.

The BCLC group recently released the 2022 update of the staging system (▶ **Fig. 1**).² It accords the interventional

DOI <https://doi.org/10.1055/s-0042-1759556>.

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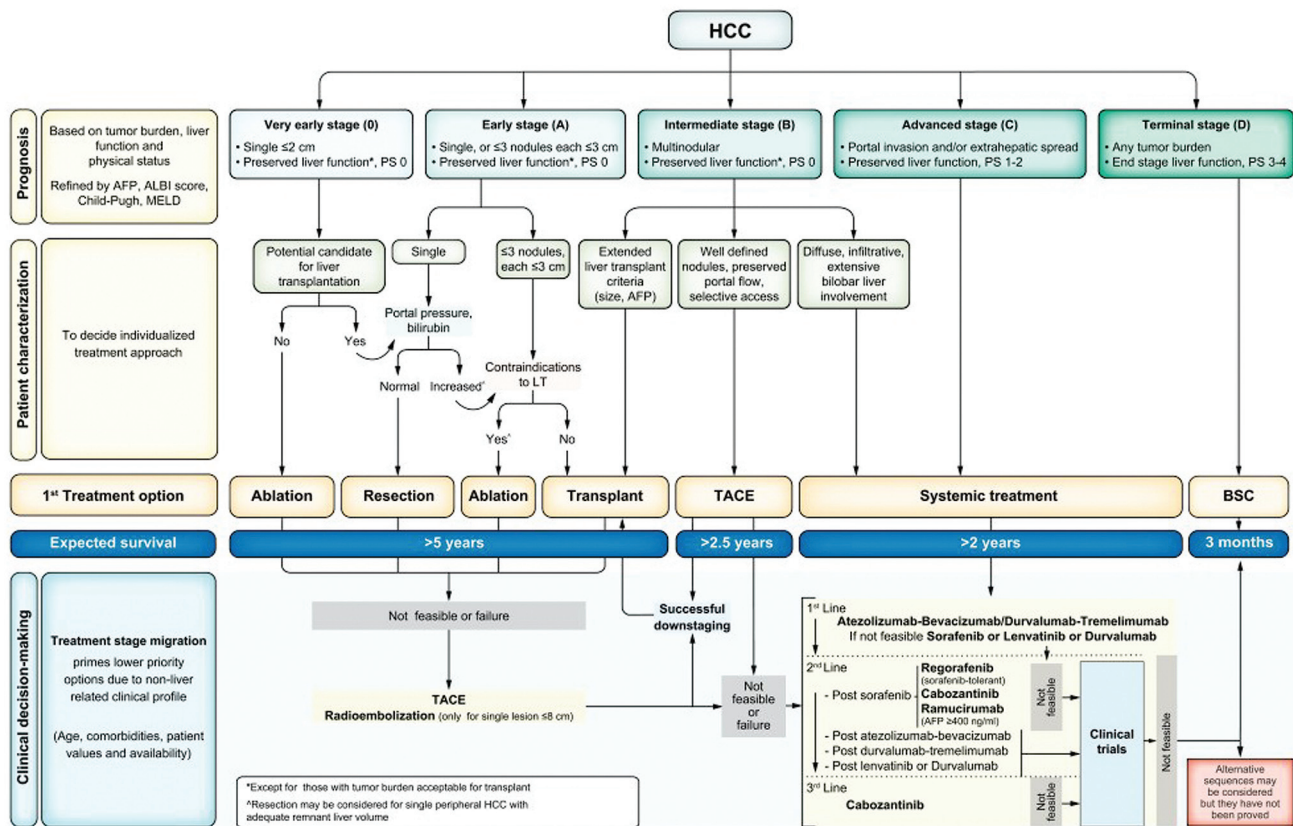


Fig. 1 BCLC staging and treatment strategy 2022 update (reproduced with permission from Elsevier).²

radiologists (IRs) an even more central role in HCC management. A major change in the recent update is the concept of treatment stage migration (TSM) and includes a clinical decision-making component, permitting tailoring of treatment based on individual patient and tumor characteristics, in lieu of the relatively rigid previous guidelines. TSM is applied when treatment failure or a specific patient profile causes a shift of the recommendation to a treatment option recommended for a more advanced stage.

Summary of the various treatment recommendations in relation to IRs is as follows:

In BCLC 0, ablative therapy is the preferred option. If not feasible for ablation, resection to be considered first before TACE, in keeping with the concept of stage migration. TARE is recommended only in single lesion ≤ 8 cm³ and is considered as effective as TACE.

In BCLC A, for HCC > 2 cm, resection is favored over ablation due to the higher recurrence rates with the latter. In non-LT candidates with multifocal tumors, the update recommends ablation for HCCs ≤ 3 cm and TACE otherwise. In LT candidates with > 6 months of waiting time, bridging therapy is recommended in the form of either ablation, TACE or TARE.

The 2022 BCLC version divides the BCLC-B into three subgroups based on tumor burden and liver function. The first subgroup corresponds to patients who are candidates for LT if they meet the 'Extended Liver Transplant criteria' (commonly based on size and/or AFP) as laid down by each

institution/country. The second subgroup is composed of non-LT candidates but with preserved portal flow and well-defined nodules; they are candidates for TACE. The third subgroup consists of patients with diffuse and infiltrative bilobar involvement; systemic treatment is recommended for these patients. Patients with > 2 mg bilirubin or even mild fluid retention requiring diuretic treatment are also considered poor candidates for TACE. Type of TACE performed (conventional or using drug-eluting microsphere) is left to local discretion.⁴

In BCLC C patients, no role of IR has been recognized in the 2022 updates.

Treatment Modalities

Interventional therapies for HCC can broadly be divided into two categories

1. Percutaneous ablative therapy
 - a. Thermal ablation (radiofrequency/microwave/cryo-laser/HIFU)
 - b. Chemical ablation (ethanol, acetic acid)
 - c. Irreversible electroporation (IRE)
2. Transarterial therapy
 - a. Transarterial embolization/bland embolization with particles
 - b. Transarterial chemoembolization (TACE)
 - c. Transarterial radioembolization (TARE) or selective internal radiotherapy (SIRT)

Table 1 Summary of ablative therapies for HCC management

| Procedure | Mechanism | Advantages | Disadvantages |
|--|---|--|---|
| Thermal ablation | | | |
| • RFA | High-frequency alternating current causes ionic agitation and heat generation | Extensively studied modality with excellent safety profile | Ablation zone may be limited by tissue charring Susceptible to heat sink |
| • MWA | Generation of electromagnetic field with rapid oscillation of water molecules and frictional heating | Larger ablation zones, reaches higher temperature faster than RFA, no grounding pads, not susceptible to charring or heat sink | Limited studies showing superiority of MWA as compared to RFA |
| • Cryoablation | High-pressure gas when passed into larger volume at needle tip causes rapid cooling of tissues. Freeze–thaw cycles result in intracellular ice resulting in immediate cell death. | Safer for tissues adjacent to target lesion Formation of ice ball can be visualized on CT/USG | Limited published data regarding use in HCC Potential for serious adverse effects–“cryoshock” |
| • Laser | Nd-YAG lasers applied to target lesion via fiberoptic applicators. | Image guidance with MRI allows intraprocedural temperature monitoring | High procedural complexity, expensive |
| • High-intensity Focused ultrasound (HIFU) | High-intensity ultrasound causes cell death through thermal injury and mechanical cavitation injury | Completely non-invasive | Poor penetrance for deeper targets scatter causes complications, limited by respiratory movement. |
| Chemical ablation | Cytotoxic effects include protein denaturation, cytoplasmic dehydration, and small-vessel thrombosis | Inexpensive, fast, no additional equipment required, complication rate lower as compared to thermal ablation. | Requires multiple sessions. |
| Irreversible electroporation (IRE) | Short pulses of high-voltage electrical current cause nanopores in cell membranes and apoptosis. | Sparses extracellular matrix–no damage to adjacent vessels, bile ducts, not susceptible to heat sink. | Requires general anesthesia with deep neuromuscular blockade, requires ECG gating. |

In addition to these, preoperative intervention in the form of portal vein embolization (PVE) also forms an important tool in treatment of patients who are candidates for surgical resection.

Percutaneous Ablative Therapies

Image-guided ablative therapies are an important interventional radiological method in HCC management. These are minimally invasive procedures performed using a percutaneous approach, and are used for curative or palliative HCC treatment. Broadly, ablative therapies can be categorized as thermal or chemical techniques of ablation. The most commonly used ablative techniques are radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation. Chemical methods of ablation include percutaneous ethanol injection (PEI) and percutaneous acetic acid injection (PAI), which are infrequently used presently.⁵ The main advantages of these methods are percutaneous applicability, minimal invasiveness while preserving surrounding liver parenchyma, shorter hospital stay, and a low rate of morbidity and mortality. The various ablative techniques including less

commonly used techniques such as HIFU and laser ablation have been summarized in ► **Table 1**.

Image Guidance

Percutaneous ablation uses image guidance for accurate delivery of therapy to target lesions. USG, CT, and MRI may all be utilized; ultrasound and CT are most commonly used imaging modality for this purpose. In situations that require precise placement of multiple probes such as in IRE or MWA with multiple applicators, CT guidance may be preferred over USG.

Patient Selection

According to the BCLC classification, ablative therapies are recommended in patients with very early and early-stage HCC who are not candidates for liver transplantation (LT) or surgical resection. It provides a curative option or may be used as bridging therapy for patients awaiting LT. It is also commonly utilized in combination with TACE in patients with unresectable HCC.

Absolute contraindications to ablation therapy include uncorrectable coagulopathy, biliary dilatation, intravascular

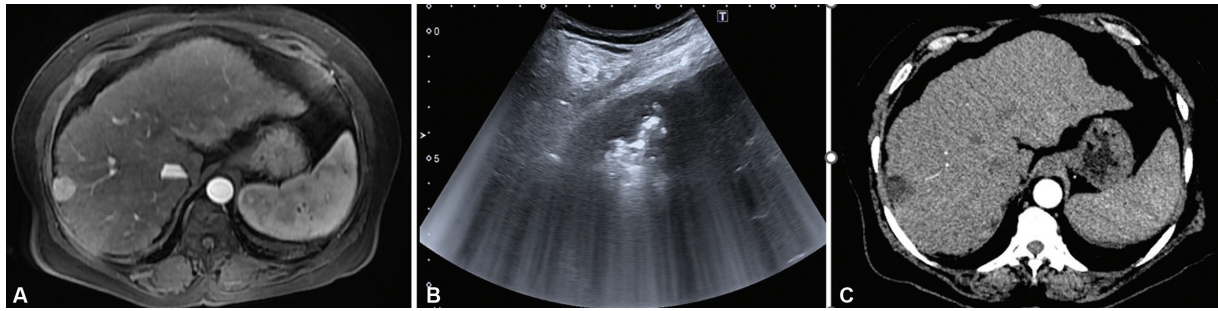


Fig. 2 Radiofrequency ablation: (A) Pre-procedural CE-MRI shows lesion with arterial phase hyperenhancement. (B) Ultrasound image depicts ablation of the lesion with the formation of echogenic bubbles during, with image showing typical artefacts caused due to RF interference. (C) Follow-up CT at 3 months post procedure showed complete ablation.

invasion, tumor within 1 cm of the main biliary duct. Relative contraindications include Child–Pugh class C cirrhosis/hepatic platelet count $< 50,000/\text{mm}^3$, failure, or pacemaker/defibrillator.⁵

Thermal Ablation

Thermal ablation aims to destroy tumor tissue by increasing or decreasing temperature to induce irreversible cellular injury. Hyperthermal ablation destroys tumors by heating to more than 50 to 60°C, causing irreversible cell death. In contrast, cryoablation achieves cell death by cooling to -20 to -40°C .⁶

Radiofrequency Ablation

Principles

Radiofrequency ablation (RFA) is the most commonly used ablative therapy in HCC.⁷ Radiofrequency energy is delivered as an alternating current at a frequency of about 400 MHz, causing ionic agitation and heat generation known via the Joule effect. Increase in the tissue temperature causes coagulation of proteins and eventual tissue death. To achieve optimal ablation, objective of RFA is to achieve and maintain a temperature of a 50 to 100°C throughout the entire target volume for at least 4 to 6 min. Heating to more than 100 to 110°C causes vaporization and reducing effectiveness of RFA.

Equipment

The basic RFA equipment consists of an RF generator, which is the source of alternating current, electrode and a grounding pad (in case of monopolar electrodes). Electrodes can be monopolar or bipolar and come in a variety of designs such as multitined expandable electrodes, internally cooled electrodes, and perfused electrodes. These innovations in electrode designs have resulted in larger ablation zones to enable RFA of tumors even in the range of 2 to 5 cm.⁸

Techniques

RFA is generally performed under ultrasound and CT guidance. It allows precise centering of the electrode within the tumor and enables continuous monitoring of the distribution of vapor bubbles. For locations that may be difficult to access on USG such as the diaphragmatic surface or caudate

lobe, CT guidance is especially useful. The probe is inserted into the target lesion under image guidance (**Fig. 2**), and the circuit is closed by placing the grounding pads in contact with the patient's body if using monopolar electrodes. The RFA generator modulates the radio frequency amplitude, and the energy is locally deposited within target tissue around the probe tip. RFA of liver lesions usually takes anywhere from 10 to 30 minutes per lesion.

Lesion size is the most important determinant of efficacy, with lesions up to 3 cm showing complete ablation rates of up to 90%.^{9–11} Another determinant of efficacy is lesion location. Central lesions are avoided because of the risk of the bile duct and vascular injury. Additionally, the lesions adjacent to large vessels may reduce the effectiveness of RFA due to the thermal protection provided by the adjacent blood flow, a phenomenon termed “heat-sink.” The heat sink effect can be prevented by temporary balloon occlusion of these branches, thus optimizing the ablation zone.^{12,13} For lesions at the liver surface or those abutting the stomach or colon, the technique of hydrodissection may be employed. It involves instillation of 5% dextrose in the plane between lesion and the bowel to avoid thermal injury to these structures.

Complications

Hepatic abscess is the most commonly reported complication after RFA with an incidence of 0.3 to 2%.¹⁴ Vascular complications such as pseudoaneurysm formation, portal and hepatic vein thrombosis or intraperitoneal bleeding have been reported.¹⁵ Bile duct injury or injury to adjacent structures including the gastrointestinal tract, gallbladder, and diaphragm may rarely occur. Delayed complications may be bile duct stricture or biloma formation. A dreaded but uncommon complication is tumor seeding along the needle tract, pleura, or peritoneum and may occur 3 to 12 months after RFA with a reported incidence of 0.2 to 1.4%.¹⁶ It is prevented by tract ablation during needle withdrawal.

Microwave Ablation

Principles

The use of microwave ablation (MWA) for thermal ablation has increased manifold over recent years. MWA causes hyperthermal cytotoxicity by generation of an

electromagnetic field with resultant rapid oscillation of water molecules trying to align themselves in the alternating electric field. This causes frictional heating and subsequent tissue coagulation. The action is most potent in high water content tissues.

Equipment and Technique

The device consists of a microwave generator, coaxial cable, and antenna. Microwave systems are currently available in two frequencies, 915 MHz and 2.54 GHz. One or more antennae are placed into the lesion and are connected to the generator using a coaxial cable. As compared to RFA, there is no current conduction in MWA, so grounding pads are not needed.

The potential benefits of MWA over RFA include higher intratumoral temperature, larger ablation zones (→Fig. 3) (>5 cm) faster ablation time, ability to use multiple applicators, and less procedural pain. MWA is also less susceptible to heat sink effects than RFA, and thus is more effective in treating tumors near larger vessels.¹⁷

Complications with MWA are similar to those seen with RFA.

Cryoablation

Principles

Cryoablation is one of the oldest techniques of thermal ablation. In cryoablation, tissue damage occurs via various mechanisms. Immediate cell death is the result of freezing and thawing cycles, creating a hyperosmotic environment and causing cell death by dehydration. Delayed tissue damage also results from cellular anoxia due to vascular stasis.¹⁸ Target temperatures are in the -20 to -40°C range. The sensitivity of tissues to freezing differs. As connective tissue is relatively resistant, cryoablation is safer for tissues adjacent to target lesion.

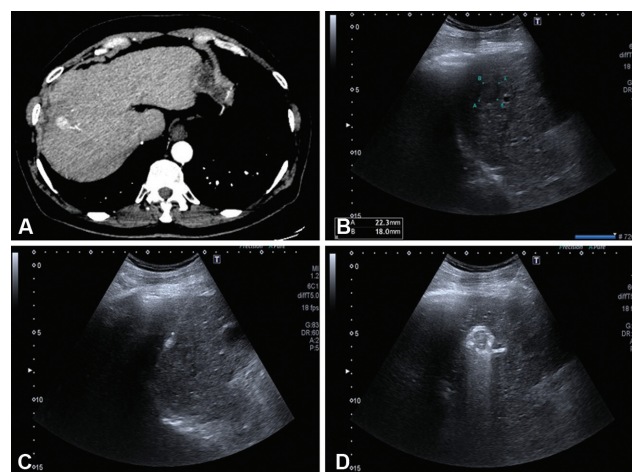


Fig. 3 Microwave Ablation: (A) Axial arterial phase CT shows small enhancing nodule in segment 8. (B) Ultrasound image depicts the same hypoechoic nodule. (C) MWA antenna deployed within target lesion with echogenic tip in the center of the nodule. (D) Post procedural image shows an echogenic ablation zone.

Equipment and Techniques

Cryoablation utilizes an argon-based unit with cryoprobes. Multiple probes can be used for ablation of larger tumors. The cryoprobes should be placed within 1 cm of the tumor edge and at least two freeze–thaw cycles are generally performed. An ice ball is created around the tip of the probe, which can be imaged with computed tomography or ultrasound in real-time.¹⁹

Despite the availability of percutaneous cryoprobes, cryotherapy has not been as widely used in the treatment of HCC compared with RFA and MWA, due to higher complication rate compared to RFA in older studies including “cryoshock,” which is a severe systemic reaction specific to cryotherapy characterized by cytokine release and multi-organ failure.²⁰

Irreversible Electroporation

Principles

Irreversible electroporation (IRE) is a relatively new technology that has recently been applied in HCC treatment. It involves delivering short pulses of high-voltage electrical current up to 3 kV to tumor cells. It results in the creation of nanopores in cell membranes. This irreversible damage causes cell death by apoptosis.²¹ The advantage of this modality is that it does not affect the extracellular matrix, thus making tissues adjacent to target lesion relatively resistant to its effects. Being a non-thermal ablative technique, it also does not exhibit the heat sink effect.

Equipment and Techniques

IRE electrodes are monopolar 19 G electrodes. The procedure is performed under general anesthesia and deep neuromuscular blockade. The electrical pulses need to be synchronized with the refractory phase of the myocardium.

Chemical Ablation

Percutaneous Ethanol Injection

Percutaneous ethanol injection (PEI) is one of the earliest methods devised to ablate liver. Ethanol causes coagulative necrosis due to its multiple cytotoxic effects including protein denaturation, cytoplasmic dehydration, and small-vessel thrombosis.²² It is administered with a fine needle using imaging guidance. The alcohol is relatively restricted to tumor tissue, sparing normal parenchyma. The main advantages of the procedure are its low cost and simple methodology. Disadvantages include need for multiple sessions to treat each lesion, even tumors smaller than 3 cm. Complications of hemorrhage, liver necrosis, portal vein thrombosis, and gallbladder injury, have been reported with PEI. PEI allows the treatment of tumors near sensitive organs and tissues and does not suffer from the “heat-sink” effect as compared to RFA. The applicability of PEI in other situations is limited.

Percutaneous Acetic Acid Injection (PAI)

Acetic acid is characterized by better tissue diffusion than ethanol. Fewer treatment sessions and smaller volume of

acetic acid per session can achieve the same degree of tumor ablation as ethanol²³ Acetic acid has a higher diffusion capacity; it is easily available and cheap. Additionally, percutaneous acetic acid injection (PAI), also helps in infiltrating the tumor septae, and capsule. The procedure of PAI is similar to PEI, wherein 50% acetic acid is injected in multiple sessions (1–2 mL per tumor per session per week) using a fine needle (23 G spinal/Chiba needle). Uncommon side effects such as transient hemoglobinuria, fever, segmental hepatic infarction, and metabolic acidosis can occur.²³

Transarterial Therapies

Principle

Transarterial liver-directed therapies are based on the basic concept of dual blood supply to the liver. HCCs derive almost 90% of their blood supply from the hepatic artery. Therefore, selective delivery of bland particles, chemotherapeutic agents, or radioactive spheres into the hepatic artery branches results in intratumoral localization while relatively sparing the healthy liver parenchyma. The embolization induces ischemia and hence tumor necrosis.

Transarterial Chemoembolization

Transarterial chemoembolization (TACE) is considered a standard locoregional treatment for a large group of patients with HCC who are not candidates for resection/transplant or ablation. It combines transarterial delivery of chemotherapeutic agents to the tumor bed and embolization of the tumor vascularity. The infusion of chemotherapeutic agents results in the delivery of higher concentration of the drug to the tumor as compared to systemic route with fewer systemic side effects.

Patient Selection

TACE is one of the recommended treatment strategies in BCLC stage B patients who are non-LT candidates. Secondary indications include use as bridging therapy for patients awaiting LT or for downstaging of disease to meet resection/transplant criteria.

Absolute contraindications include decompensated cirrhosis or Child–Pugh class C, severe cardiac or renal insufficiency and uncorrectable coagulopathy. Main portal vein thrombosis or significant arteriovenous shunting between hepatic artery and portal or hepatic vein are seen as relative contraindications.

Procedure

Chemoembolization is most commonly performed via the transfemoral route. Transbrachial or transradial route may be used in cases of difficult transfemoral access. A careful review of pre-procedural triphasic CT scan is required to map out the arterial anatomy including presence of any variations. It is vital to target all the arterial feeders of the tumor for getting a good response. Cone beam CT is a recent technical breakthrough in DSA systems, wherein it provides CT-like images during the angiographic evaluation.^{24,25} After

completely mapping the arterial supply to the tumor, superselective catheterization of the feeding arteries is done with a microcatheter, and the chemoembolic mixture is infused into the feeder branches. This is followed by embolization with either polyvinyl alcohol particles or Gelfoam slurry. The end point of chemoembolization is complete stasis. A completion angiogram is obtained. Hemostasis is achieved at the arterial puncture site either by manual compression or use of vascular closure devices. For large tumors or tumors reaching the hepatic capsular surface, angiographic evaluation of the extrahepatic arteries, such as the inferior phrenic, intercostals, and internal mammary arteries also needs to be performed.^{26,27}

TACE is mainly of two types – conventional TACE (cTACE) or TACE using drug-eluting beads (DEB-TACE).

Conventional Transarterial Chemoembolization

In conventional transarterial chemoembolization (TACE), a mixture of chemotherapeutic drug(s) and lipiodol is delivered transarterially to hepatic artery branches supplying the tumor. Lipiodol acts as a carrier for the chemotherapeutic drug and also functions as a microembolic agent. In normal liver parenchyma, lipiodol is cleared by Kupffer cells, while it is retained in the tumor bed due to lack of Kupffer cells in the tumor.²⁸ It causes occlusion of the downstream capillaries and has a lethal effect on tumor cells. Being radiopaque, it allows for easy visibility under fluoroscopy or CT^{29,30} (→ Fig. 4). Lipiodol can be used in combination with multiple chemotherapeutic agents including doxorubicin, epirubicin, cisplatin, carboplatin, mitomycin, and mitoxantrone. The mixture is injected through a microcatheter after selective catheterization of subsegmental branches of the hepatic artery supplying the tumor. After injecting the drug–lipiodol emulsion, embolization is done polyvinyl alcohol particles (100–300 microns) or Gelfoam slurry.

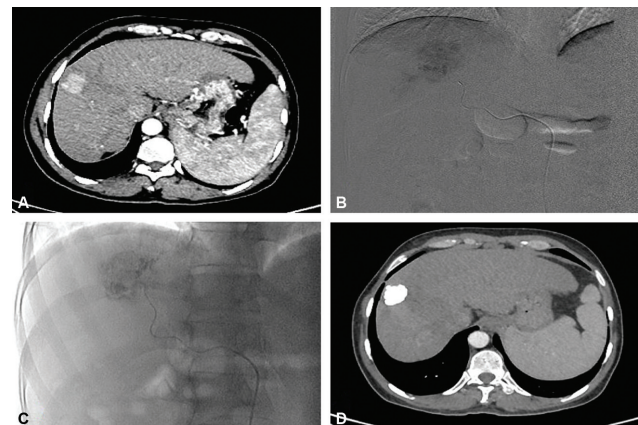


Fig. 4 Conventional TACE: (A) Axial CT scan showing the arterial phase enhancing lesion in segment VIII of the right lobe of the liver. (B) Tumor blush after superselective cannulation of the feeding vessel. (C) Post-chemoembolization angiogram showing complete stasis within tumor with lipiodol deposition within. (D) Response evaluation CT scan confirms homogenous lipiodol deposition in tumor with sparing of the surrounding normal parenchyma.

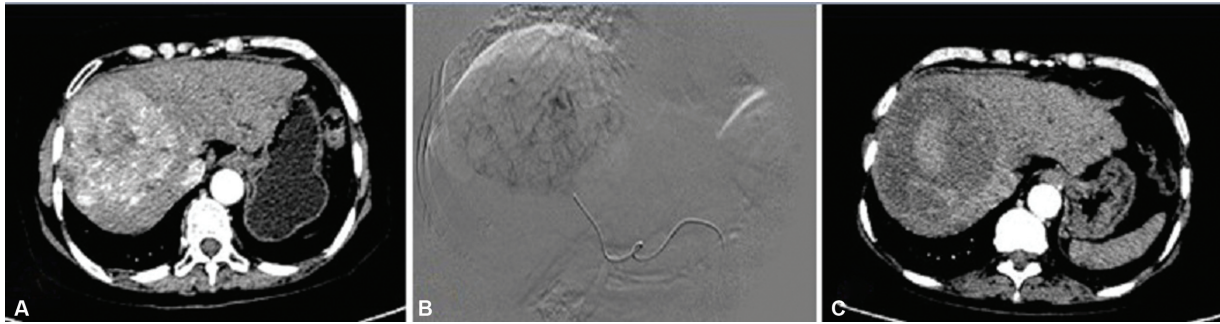


Fig. 5 DEB-TACE: (A) Axial CT scan showing large arterial phase enhancing lesion in the right lobe of the liver. (B) Tumor blush after selective cannulation of feeding vessel. (C) Response evaluation CT scan shows necrosis of the tumor.

Drug-Eluting Beads Transarterial Chemoembolization (DEB-TACE)

Drug-eluting microspheres are composed of polyvinyl alcohol hydrogel. They are biocompatible, hydrophilic, and non-absorbable. The drug-eluting beads are loaded with chemotherapeutic agent such as doxorubicin hydrochloride. They sequester doxorubicin from solution by ion exchange and release it in tissues. This allows for a slow and sustained release of the drug over a long period of time. The half-life for 100 to 150 micron microspheres is 150 hours, while 700 to 900 micron microspheres have a maximum half-life of 1,730 hours.³¹ There is substantial increase in the contact time of drugs with tumor as compared to lipiodol with lower systemic concentration of the drugs. This results in decreased systemic side effects and decreased rates of liver failure.³²

Follow-Up

Response evaluation with imaging is typically done at 4 to 6 weeks (► **Fig. 5**). Dynamic CE-MRI or triphasic CT is obtained for assessing treatment response and detect new lesions if any. With cTACE, dense lipiodol accumulation and the absence of internal enhancement are markers of complete necrosis. Focal areas of nonopacification with lipiodol and persistent nodular arterial enhancement with portal venous phase washout indicate residual disease and call for retreatment. Reduction in size can also be documented.

TACE cycles are repeated at 4 to 6 weeks interval until imaging shows complete necrosis. If the tumor does not respond after two cycles of TACE, the therapy is discontinued.

Complications of TACE

The most common nonvascular complication is post embolization syndrome, which presents with abdominal pain, nausea, vomiting, and fever. It usually resolves within 2 to 3 days and only requires symptomatic treatment. The duration of post embolization syndrome in DEB-TACE has been found to be shorter than that seen with cTACE. Other complications include liver abscess, biliary stricture, or hepatic decompensation resulting from nontarget hepatic artery embolization. Nontarget embolization of cystic artery or gastric arterial branches may result in cholecystitis or

gastritis. Vascular complications also include access site injury, hepatic artery dissection, or rupture.

Transarterial Radioembolization/Selective Internal Radiotherapy

Radioembolization is a form of interstitial radiotherapy, which combines radiotherapy with the interventional radiology technique of hepatic artery cannulation. Transarterial radioembolization (TARE)/selective internal radiotherapy (SIRT) is a locoregional therapy that is based on the principle of intra-arterial brachytherapy using infusion of yttrium-90 containing microspheres into the hepatic artery.

Indications

Indications for TARE in HCC include BCLC-B stage with diffuse or large HCC not responding to TACE. As per the 2022 update of BCLC system, it can also be considered as a bridging therapy option in BCLC-A patients in waiting for LT.

Procedure

TARE entails intra-arterial injection of yttrium-90 microspheres (Y-90). There is preferential trapping of these microspheres in the tumor capillary bed owing to its small size (20–60 μm). These spheres can deliver up to 150 Gy of β radiation to cause tumor necrosis by radiation and by microscopic embolization due to obstruction of the tumor capillary bed. Radiation exposure to adjacent healthy tissue from the microspheres is limited, given half-life of 62 h and small radius of action of up to 1 cm.³³

TARE planning requires certain pre-treatment procedures. A preparatory arteriogram is done to map the hepatic arterial anatomy to avoid nontarget delivery of microspheres. Hepatofugal arteries supplying nonhepatic sites may be prophylactically embolized with coils. The ^{99m}Tc-MAA SPECT scan is done to evaluate the amount of hepatopulmonary shunting. The hepatopulmonary shunt should be less than 30 Gy per session up to a maximum total dose of 50 Gy to avoid radiation pneumonitis. Tumor volumetry is done to calculate the optimum therapeutic dose. The dose for radioembolization is based on tumor perfusion volume and hepatopulmonary shunt, to achieve a target dose of 120 to 140 Gy. The Y-90 microspheres are available in two forms—

TheraSphere glass sphere (BTG International, London, UK) or SIR-Spheres Resin microspheres (Sirtex Medical, MA, USA).

Follow-up

Post procedure PET scan is done within 24 hours to identify Y90 distribution within tumor. Response evaluation is done after 6 weeks with triphasic CT or dynamic MRI.

Complications

Common complications include fever, nausea and pain which are self-resolving in most cases. Nontarget delivery of Y-90 may result in deleterious effects such as gastrointestinal ulceration, radiation pneumonitis, cholecystitis, and pancreatitis.

Multimodal Treatment of HCC

Multimodal treatment or combination therapies for HCC involve different modalities and treatment durations. These are tailored based on various factors such as number, location, and size of lesions, the degree of liver function, presence of vascular invasion or extrahepatic spread and the availability of different techniques. Combination therapies may either be concomitant, where different treatments are administered during the same session or sequential, when different modalities are applied one after another. By combining different synergistic treatment modalities, the aim is to increase the efficacy of treatment as compared to monotherapy, such as for large or difficult lesions, to prevent tumor recurrence, or to slow tumor progression, and reduce tumor size in patients awaiting transplantation.³⁴

Percutaneous Ablation with TACE

Effectiveness of ablative procedures reduces with increasing tumor size, possibly due to increased vascularity in large lesions, which results in heat loss and incomplete ablation. Performing TACE before RFA has a synergistic effect of the ischemic cytotoxicity induced by TACE and the thermal injury caused by ablation, which enables effective ablation of bigger lesions than seen with RFA alone.³⁵ A 2008 RCT by Cheng et al demonstrated that combined therapy with TACE and RFA was superior to TACE or RFA monotherapy, with improved overall survival and a better complete response rate.³⁶

Sorafenib with TACE

Sorafenib was the first oral multikinase inhibitor to be approved for use in HCC and still remains the recommended treatment as per the BCLC staging in advanced HCC. The antiangiogenic effect of sorafenib is particularly important in HCC due to its hypervascular nature. It is also proposed that the hypoxia caused by embolization triggers tumor neoangiogenesis resulting in recurrence. Therefore, multiple studies have evaluated the potential synergistic effect of TACE combined with systemic administration of sorafenib. The TACTICS trial, a recent RCT comparing the effects of sorafenib with TACE versus TACE alone, demonstrated a statistically significant increase in time to unTACEable

progression (TTUP), in the TACE plus oral sorafenib group as compared with the group that received only TACE (25.2 vs. 13.5 months; hazard ratio, 0.59; 95%; $p = 0.006$).³⁷ Although TTUP is a novel endpoint to evaluate treatment efficacy, the TACTICS trial points toward a clinical benefit of this synergistic approach.

TACE with Radiotherapy

The effects of combination therapy of TACE and external beam radiation therapy (EBRT) versus TACE alone have been compared in several nonrandomized studies. These studies have shown that patients with portal vein tumor thrombosis who received combination therapy had better survival compared with those who received radiotherapy or TACE alone.³⁸

A recently introduced approach of local tumor ablation in the liver is interstitial brachytherapy with computed tomography-guided high-dose rate brachytherapy (CT-HDRBT), which has shown advantageous results in HCC not feasible for RFA owing to lesion size and location. A recent study by Schnapauff et al demonstrated promising survival rates in patients with unresectable HCC who received interstitial brachytherapy following TACE.³⁹

Special Scenarios

HCC with Portal Vein Tumor Thrombosis

Portal vein tumor thrombosis (PVTT) occurs commonly in HCC in up to 35 to 50% of patients⁴⁰ at the time of diagnosis and is a strong negative prognostic factor, with high recurrence risk. The BCLC staging system classifies these patients as advanced disease and recommends systemic treatment as the standard of care. However, use of sorafenib monotherapy has shown less than satisfactory results in these patients. It is a complex clinical condition that includes a wide range of patients with varied prognosis and treatment possibilities based on the degree of the portal system involvement, patient's clinical features, severity of liver dysfunction, and complications due to portal hypertension. To date, there are no consensus guidelines regarding ideal treatment strategy for HCC with PVTT.

PVTT has been classified into four grades by the Liver Cancer Study Group of Japan (LCSGJ)⁴¹ as follows:

- Vp1: Presence of a tumor thrombus distal to second-order branches of portal vein;
- Vp2: invasion of second-order branches of portal vein;
- Vp3: Presence of the thrombus in first-order branches;
- Vp4: Tumor thrombus in the main trunk of the portal vein and/or a portal vein branch contralateral to the primarily involved lobe.

Various treatment strategies, including surgical options such as hepatic resection and thrombectomy and nonsurgical approaches have been attempted in PVTT with variable results. Conventionally, PVTT of the main trunk has been considered a contraindication for TACE, due to the potential risk of ischemia related post-TACE deterioration in liver function. However, TACE is a viable treatment option in Vp1 or Vp2 PVTT. Various studies have evaluated TACE

monotherapy as well as combined TACE therapies in PVTT. Xue et al⁴² in their meta-analyses compared TACE and conservative treatment in 1,601 patients with PVTT, showed better survival rates in TACE group as compared to the supportive therapy group. The START trial performed in Asia assessing the effectiveness of the combination of TACE with sorafenib showed promising results in PVTT patients in terms of 3-year overall survival (OS).⁴³ TACE combined with RT is another approach that has shown encouraging results in a few studies.

As compared to TACE, in which there is a potential risk of hepatic ischemia, especially with Vp3/Vp4 stage PVTT, TARE can be safely performed in patients with PVTT without major concerns, owing to the minimal embolic effect of 90Y-glass microspheres and lower risk of liver ischemia. However, two phase III trials SARAH (Sorafenib versus Radioembolization in Advanced Hepatocellular carcinoma) and SIRveNIB (Selective Internal Radiation Therapy Versus Sorafenib) have failed to demonstrate significant superiority of TARE as compared to sorafenib.^{44,45}

HCC with Hepatic Vein Tumor Thrombosis

Hepatic vein tumor thrombosis (HVTT) has a lower incidence in HCC as compared to PVTT, but may be associated with potentially life-threatening complications such as thrombus extension into the IVC or right atrium, intrapulmonary dissemination, or pulmonary embolism. As per the BCLC system, HVTT constitutes advanced disease and recommends systemic treatment as standard of care. However, surgical treatments such as liver resection combined with thrombectomy or radiation therapy have been used, particularly in Asia with promising results. In addition to curative-intent surgery, TACE, EBRT, or combined treatment have also been advocated in these patients with varying results.

Spontaneous HCC Rupture

Spontaneous rupture is a potentially lethal complication of HCC. The mortality due to rupture of HCC in the acute phase is reported to be high at 25 to 75%.⁴⁶ Management of ruptured HCC involves multidisciplinary care where achieving hemostasis is the primary concern. Transarterial embolization (TAE) has been shown to effectively induce hemostasis in the acute stage with a high success rate and a lower 30-day mortality as compared to open surgical methods.⁴⁶ PVA particles or Gelfoam slurry is commonly used to occlude the tumoral bed.

Response Evaluation after Locoregional Therapy

Response evaluation after locoregional therapies for HCC is recommended to be done using the LI-RADS treatment response algorithm.⁴⁷ The earlier treatment response systems such as mRECIST or EASL provided criteria for overall patient response and were better suited for clinical trials and studies assessing treatment response. The LI-RADS treatment response algorithm is a practical system as it assesses response in individual lesions and may be better suited for

Table 2 LI-RADS CT/MRI treatment response table

| Response category | Criteria |
|-------------------|--|
| LR-TR non-viable | No lesion enhancement OR Treatment-specific expected enhancement pattern |
| LR-TR equivocal | Enhancement atypical for treatment-specific expected enhancement pattern and not meeting criteria for probably or definitely viable |
| LR-TR viable | Nodular, mass-like, or thick irregular tissue in or along the treated lesion with any of the following: <ul style="list-style-type: none"> • Arterial phase hyperenhancement OR • Washout appearance OR • Enhancement similar to pretreatment |

routine clinical practice. It is to be applied in patients to assess response for path-proven or presumed (LR-4, LR-5, or LR-M lesions) malignancy after locoablative, transarterial, or external beam radiation therapies. Post-treatment imaging is performed with multiphase CT or MRI with extracellular contrast agents or MRI with hepatobiliary contrast agents (HBA). If a treated observation is evaluable, treatment response categories are allotted for individual lesions as outlined in ►Table 2.⁴⁷ Schedule of follow-up imaging after treatment may vary, depending on institution protocol, but is generally performed at 1 month, 3 months, 6 months, 9 months, and 12 months, and every 3 to 6 months thereafter, and further treatment sessions are planned according to treatment response.

Recently, quantitative and functional imaging modalities are being studied for response evaluation in HCC. Diffusion-weighted imaging (DWI) and metabolic imaging have been shown to detect tumor response earlier than routinely employed morphological criteria.^{48,49} ADC quantification may help evaluate the degree of tumor necrosis after locoregional therapy, as necrotic tissue shows higher ADC values than viable tumors.⁵⁰ Similarly, ¹⁸F-FDG uptake on PET is closely related to the therapeutic response in HCC. An early metabolic response on ¹⁸F-FDG PET may be correlated to post-therapy survival and could help guide treatment options and follow-up management.

Intravoxel incoherent motion (IVIM) is another promising MR technique that can be used to study both diffusion and perfusion characteristics of masses without the use of intravenous contrast agents, which is of special importance in patients with impaired renal function or severe contrast allergy. IVIM-derived parameters include diffusion coefficient (D), pseudo-diffusion coefficient (D*), and perfusion fraction (f). Woo et al⁵¹ demonstrated a significant correlation between perfusion fraction and arterial enhancement of HCC in pretreatment diagnosis or after locoregional therapy.

Despite the promising results, functional and quantitative imaging techniques are not routinely used in clinical practice

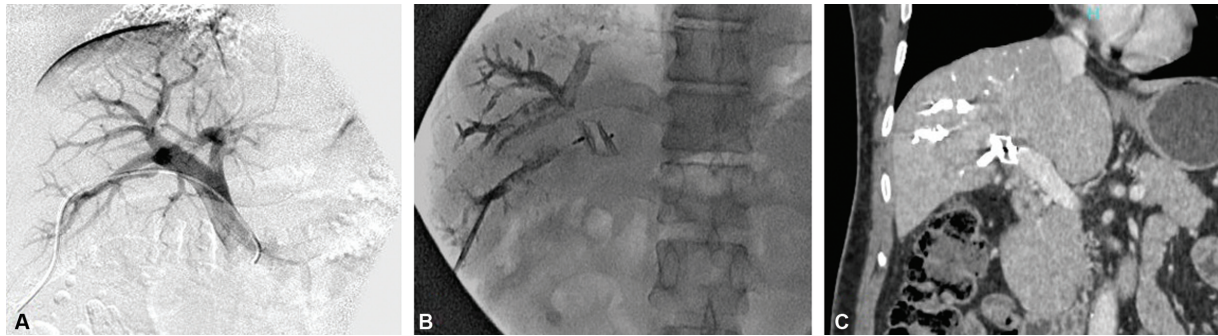


Fig. 6 Portal vein embolization: (A) Portal venogram done after access to the portal venous system via transhepatic approach, shows ramifications of the portal venous tree. (B) PVE was performed in the right lobe branches with NBCA and lipiodol mixture and vascular plug was deployed just distal to bifurcation of the portal vein. (C) Postembolization CT shows satisfactory occlusion of right PV branches by the glue cast and depicts the vascular plug in place.

for response assessment as they have certain limitations such as availability, lack of standardization, and suboptimal reproducibility.

Pre-operative Intervention-Portal Vein Embolization

Principle

Surgical resection is one of the primary therapeutic options for patients with very early or early stage HCC. However, the risk of postoperative liver failure precludes surgery in some patients with inadequate future liver remnant (FLR) volume. Portal vein embolization (PVE) causes progressive atrophy of the embolized lobe and compensatory hypertrophy in the contralateral lobe to increase the future liver remnant.⁵²

Patient Selection

PVE is recommended when estimated FLR is less than 20% to 30% in normal liver or noncirrhotic diffuse parenchymal disease or FLR of less than 40% in cirrhotic livers.

Absolute contraindications include established portal hypertension, widespread portal vein thrombosis in liver segment to be embolized, or metastatic disease. Relative contraindications include uncorrectable coagulopathy, biliary obstruction with biliary dilatation, or renal insufficiency.

Procedure

Pre-procedural CT or MRI is acquired to quantify the FLR volume. Access to the portal vein is most commonly through a percutaneous transhepatic approach or rarely via transileocolic approach that requires a mini-laparotomy to be performed in the right lower quadrant.

In the transhepatic approach portal vein, radicles are accessed percutaneously under USG guidance using a fine needle. Flush portal venogram is then performed with a catheter placed in the MPV for mapping the portal venous branches. Embolization of sectoral portal veins of selected hepatic segments is then done until complete occlusion of the target portal vein branches with diversion of blood flow toward the future remnant portal venous system is achieved. A repeat portal venogram is done to evaluate completion of

PVE (→**Fig. 6**). After completion of embolization the transhepatic tract is usually occluded with coils. Various embolic materials have been used for PVE such as Gelfoam, PVA particles, coils and n-butyl cyanoacrylate (NBCA), with no consensus regarding the best option. FLR hypertrophy is measured after 3 to 5 weeks of PVE.

Complications

Major complications may be puncture related such as vascular injury, hemoperitoneum, biloma formation, pneumothorax or related to embolization such as nontarget embolization and thrombosis of the main portal vein.

Future Perspective

Currently, research in HCC is focused on immune mechanisms of the tumor microenvironment that plays a crucial role in patient outcome. Locoregional therapies such as TACE and TARE have shown to have a synergistic effect on immunotherapy.⁵³ Animal studies carried out on TACE combined with sorafenib eluting microspheres have shown reassuring results.⁵⁴

Conclusion

Interventional therapy is a vital tool in the armamentarium against HCC and its role continues to grow with rapid advances in the field. IR therapies are generally better tolerated and offer therapeutic options with reduced morbidity and costs for palliation and cure. Ablative therapies and embolization also act as bridging or downstaging treatment for patients awaiting surgical resection and liver transplantation. Ongoing trials focused on multimodal treatments with immunotherapy have shown promising results and the potential for newer innovations in this field remains vast.

Funding

None.

Conflict of Interest

None declared.

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