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# Indian College of Radiology and Imaging Guidelines on Interventions in Hepatocellular Carcinoma

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## Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignancies and a significant cause of cancer-related death. Treatment of HCC depends on the stage of the tumor. As many patients with HCC are not deemed fit for surgical resection or liver transplantation, locoregional therapies play an essential role in the management. Image-guided locoregional treatments include percutaneous ablative therapies and endovascular therapies. The choice of an individual or a combination of therapies is guided by the tumor and patient characteristics. As the outcomes of image-guided locoregional treatments depend on the ability to achieve necrosis of the entire tumor along with a safety margin around it, it is mandatory to follow standard guidelines. In this manuscript, we discuss in detail the various aspects of image-guided locoregional therapies to guide interventional radiologists involved in the care of patients with HCC.

**Keywords**
- hepatocellular carcinoma
- interventional radiologists
- locoregional treatment

## Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and is the leading cause of cancer-related mortality.[1] As most HCCs occur in patients with cirrhosis, surveillance allows detection of these tumors at an early stage.[2] However, in countries where surveillance strategies are not effectively implemented, diagnosis at the advanced stage is not uncommon. There have been significant advances in the therapies for HCC over the past 20 years. The various management strategies include hepatic resection (HR), liver transplantation (LT), locoregional treatments (including percutaneous ablation, transarterial chemoembolization [TACE], radioembolization), stereotactic body radiation therapy, and systemic therapies.[3] A combination of one or more of these therapies is commonly utilized. The selection of a treatment method is based on the number and size of HCC, the status of the portal vein, changes in liver function, and patients' performance status (PS). Barcelona Clinic Liver Cancer (BCLC) is the most widely used algorithm guiding patient management.[3] Percutaneous ablation is the most common nonsurgical method for treating very early and early HCC. Among the various ablative techniques currently available, thermal ablation is the most popular method. Radiofrequency ablation (RFA) is the most extensively studied thermal ablative technique. Other thermal ablation techniques being increasingly utilized are microwave

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ablation (MWA) and cryoablation (CA). Irreversible electroporation (IRE), a nonchemical, nonthermal procedure, has a minimal destructive effect on the healthy tissues and is utilized for tumors at critical locations. The chemical ablative methods include percutaneous ethanol injection (PEI) and percutaneous acetic acid injection (PAI). Because of the high risk of recurrence and need for multiple sessions, these are currently utilized in resource-limited settings and very selected situations only.[4] The advantages are simplicity, cost-effectiveness, and safety profile.

TACE is the recommended treatment modality for nonsurgical, asymptomatic, large, or multifocal HCC without macrovascular invasion or extrahepatic metastasis (intermediate HCC, BCLC stage B). Conventional TACE (c-TACE) was evidenced first to treat intermediate-stage HCC patients. It combines the transcatheter delivery of chemotherapy using lipiodol-based emulsion plus an embolizing agent to achieve strong cytotoxic and ischemic effects.[5] Transarterial bland embolization (TAE) is a catheter-based delivery of embolizing agent (polyvinyl alcohol, gel foam, acrylic copolymer gelatin particles, or Embosphere) to the tumor-feeding artery to completely occlude the tumors' blood supply and achieve intense tumor hypoxia. Although TACE appears superior over TAE due to its strong cytotoxic effect, studies have failed to demonstrate any significant difference in the overall survival (OS) of patients undergoing TAE versus TACE.[6–8] TACE with drug-eluting beads (DEB–TACE) was primarily introduced to enhance the delivery of the chemotherapeutic agent while minimizing the systemic toxicity and to provide a standardized embolizing effect. DEBs are embolic microspheres loaded with a chemotherapeutic agent (mostly doxorubicin) with the ability to slow drug release, which should ensure high local and low systemic drug concentrations. In addition, DEB–TACE also has the important advantage of being a more-reproducible technique. Despite the use of drug-eluting particles of different sizes and volumes, this approach facilitates the standardization of treatment by decreasing the heterogeneity in the chemotherapeutic agent and embolic material used for conventional TACE. It has been noted that although systemic side effects are lesser with DEB–TACE as compared with c-TACE, the tumor response and OS rate are similar in both c-TACE and DEB–TACE.[9–13] TACE is an effective treatment in the management of intermediate-stage HCC. Although DEB–TACE is not superior to c-TACE in terms of efficacy, it is more reproducible with lesser systemic side effects.

Transarterial radioembolization (TARE) uses glass or resin microspheres labeled with radioisotopes, injected selectively into the hepatic artery or its branches supplying the tumor, like chemoembolization. There is growing evidence supporting TARE for intermediate BCLC stage B HCC as it provides a better safety profile, a better quality of life following treatment, and increased time to disease progression (TTP) compared with TACE.[14] TARE has shown reduced toxicity with better response in patients with portal vein thrombosis (PVT), which is a relative contraindication for TACE. TARE is also used as an alternative to the ablation of HCC (BCLC stage A) in difficult locations and to downstage tumors for LT subsequently.

## Classification of Ablative Methods

The classification of ablative techniques is based on the mechanism of cellular destruction.[15] Broadly, these include chemical, thermal, nonchemical, and nonthermal ablations. Overall, the most popular methods of thermal ablation of HCC are RFA and MWA. CA is being increasingly reported as a safe and effective method for HCC treatment. The other thermal ablation techniques less commonly utilized are high-intensity focused ultrasound (HIFU) and laser-induced thermotherapy. Although less widely used, IRE has a role in tumors located at critical locations where the thermal techniques can damage vital structures e.g., gallbladder (GB) and hilar structures. As chemical methods of ablation have limited penetration across the tumor, they are effective only for small lesions (<2 cm) and require multiple sessions of therapy. The recurrence rate compared with thermal ablation is exceedingly high, making them unsuitable for routine ablation in the current scenario. Percutaneous chemical ablation (PCA) procedures are curative in intent similar to other minimally invasive energy-based ablative techniques. However, they score higher only in terms of simplicity, cost-effectiveness, and safety profile.

## Indications

### Chemical Ablation

The classical indication for PEI is any BCLC 0 (single tumor < 2 cm, Child–Turcotte–Pugh [CTP] score A and PS 0) or BCLC A (single lesion up to 3 cm, multiple lesions up to 3, CTP score A–B, and PS 0–2) HCC that is not a candidate for resection due to poor hepatic functional reserve, anatomical complexity of the tumor, or presence of contraindications to surgery. In patients who are awaiting transplantation, ablation may be done as a bridging therapy to prevent the progression of the disease.[16,17]

PEI is best suited to single tumors measuring <3 cm in the largest dimension. However, the indications may be expanded to cover selected BCLC B (intermediate) tumors, although the rate of local recurrence is higher than in BCLC 0 and A lesions. Tumors up to 5 cm can be targeted using enhanced techniques. Multifocal tumors (up to 3) can be targeted over multiple sessions depending on the number of lesions as well as the size and complexity of the individual lesions.

### Thermal Ablation

#### Hepatocellular Carcinoma

1. Resectable: Very early (single lesion <2 cm) and early HCC (single lesion or up to three lesions each less than 3 cm). Recent studies support the use of RFA as a first-line treatment for selected patients with very early HCC. RFA has also been suggested as a substitute for surgical resection of early HCC.[18] A recent randomized control trial (RCT) showed that both surgery and RFA are equally effective and safe for HCCs <3 cm.[19] A systematic review and meta-analysis including 17 studies concluded that

 

RFA provided similar 3-year OS and disease-free survival (DFS) for very early HCC, at a lower cost.[20] A meta-analysis comprising 31 studies (including three RCTs) reported that the OS and DFS at 3 and 5 years were significantly higher in the HR group.[21] However, for tumors ≤2 cm, there was no significant difference in outcomes. Another meta-analysis of five RCTs showed no significant difference in OS between HR and RFA at 1 year and 3 years. However, RFA was associated with a decreased OS at 5 years, significantly higher intrahepatic recurrences, and overall recurrences.[22]

2. Unresectable: *In combination with TACE.*
   Ablation can be considered an alternative to surgery or transplantation in patients with early HCC who are surgically unfit. In the recent RCTs, there was no significant difference in the outcomes between the patient groups undergoing RFA and HR.[23,24] In one of these RCTs, tumor size >3 cm was associated with poor DFS.[24] For larger tumors, a combination of ablation with TACE is an effective treatment method. In a prospective study comprising large solitary HCCs (median size 4 cm), a combination of RFA and TACE had a similar OS at 1 year and 3 years as HR. However, tumor recurrence and local tumor progression (LTP) were higher in the combination of RFA and TACE groups. The effectiveness of RFA and DEB–TACE combination for large unresectable HCCs has also been reported by another study.[25] In a meta-analysis of eight RCTs, 306 patients who received RFA and TACE combination were compared with 292 patients who underwent RFA alone.[26] The significantly higher 1-, 2-, and 3-year OS was seen in the intermediate and large-sized HCCs treated with RFA–TACE combination. Different protocols for the combination of RFA with TACE have been evaluated. In one study, RFA performed 4 weeks after TACE was compared with TACE and RFA alone.[27] The combination group showed significantly lower local recurrence (compared with both RFA and TACE) and significantly higher OS at 1 year, 3 years, and 5 years (compared with RFA). In an RCT comparing TACE–RFA combination with TACE, RFA was performed within 5 days of TACE.[28] Significantly higher complete response (CR) rates at one month, and 1-year OS and DFS were reported in the patients receiving combination therapy. In another RCT, patients with solitary intermediate-sized HCC received either RFA or RFA–TACE combination (RFA performed on the same day).[29] LTP at 3 years was significantly lower in the combination group. There was no significant difference in the OS rates between the two groups.
3. *Bridging therapy for LT.*
   Several studies have shown the effectiveness of RFA as a bridging therapy in LT. In a study by Tsuchiya et al, 323 patients with early-stage HCC undergoing RFA were analyzed.[30] The cumulative OS and recurrence exceeding the Milan criteria were assessed. Recurrence within 1 year after initial ablation and α fetoprotein (AFP) level > 100 ng/mL were independently associated with recurrence exceeding the Milan criteria and OS. The authors suggested that patients with these risk factors should be considered for combination therapy and earlier transplant. In another study by Mazzaferro et al, the histologic response rate after one session of RFA was assessed to evaluate the efficacy and safety of RFA as a bridge to orthotopic LT.[31] Fifty patients with 60 HCCs were studied. All underwent a single session of RFA prior to transplant. None received any other tumor-directed therapy. Mean RFA to LT interval was 9.5 months. Overall CR was achieved in 55%. The response rate was higher (63%) for HCC <3 cm. Tumor size was the only prognostic factor associated with response. HCC >3 cm was significantly correlated with satellite nodules and new HCC foci. The probability of post-RFA tumor persistence increased with time. The authors concluded that RFA should not be considered an independent therapy for HCC. Brillet et al, however, reported that RFA allows most patients to undergo LT and does not impair posttransplantation outcomes.[32] In total, 26 patients with 35 HCCs were evaluated for LT. RFA was performed in 21 patients for 28 HCCs. Sixteen patients received transplants after a mean interval of 11.9 months. Three patients had distant tumor progression and were excluded. Two patients were excluded because of other reasons. After LT, the tumor recurred in one patient. Similar results were reported by Lu et al. In total, 52 patients with 87 HCCs considered for LT were studied.[33] After a mean waiting period of 12.7 months, 3 (5.8%) of 52 patients had tumor progression and were excluded from the transplant list. Forty-one patients who underwent OLT had 1- and 3-year post-LT survival rates of 85 and 76%, respectively. HCC recurrence occurred in none of the patients over the follow-up period.
4. *Residual and recurrent HCC.*
   Repeat ablation should be considered for focal residual lesion < 3 cm along the periphery or within the ablation zone.[34] Transarterial therapies are considered if the residual lesion is irregular or diffusely scattered along the margins of the ablated lesion, for subcapsular residual lesions, and lesions greater than 3 cm. There is no consensus on the treatment strategy for a recurrent lesion at present. Repeat RFA (rRFA), resection, and salvage liver transplantation (SLT) represent the two most important options.[35] rRFA has been shown to be associated with significantly lower DFS. Hence, an aggressive treatment strategy with resection or SLT should be considered whenever feasible.[35]

## Transarterial Chemoembolization

Factors taken into consideration while considering TACE for patients with HCC include tumor status, patient performance, and metabolic status.[36–38]The tumor characteristics include HCC not suitable for curative treatments such as HR, LT, or percutaneous ablation according to BCLC staging classification and treatment schedule, lack of extrahepatic spread, absence of main portal vein thrombus, and tumor involvement <50% of the liver parenchyma. Patients who demonstrate recurrence after potentially curative treatment

 

(HR and percutaneous ablation) or LT, who have measurable disease according to modified RECIST criteria, can also be considered for TACE. TACE is utilized in potential transplant recipients to decrease the dropout rate from the transplant list and limit recurrence. Finally, TACE may allow the downsizing of tumors before resection or transplantation.

Patients characteristics indicating suitability for TACE include well-preserved liver function (CTP class A/B) without encephalopathy and mild or severe ascites, serum creatinine $<2$ mg/dL (177 µmol/L), platelet count $>50{,}000/mm^3$, prothrombin activity $>50\%$, and Eastern Cooperative Oncology Group (ECOG) PS $<3$ or Karnofsky score $>70$.

### Transarterial Radioembolization

Indications for TARE have progressively evolved from palliation for unresectable HCC with or without PVT to bridge to transplantation, neoadjuvant therapy for resection, and as a definitive ablative radiotherapy for smaller lesions. Many centers have begun to use TARE as first-line treatment in the management of HCC not suitable for surgical interventions.[39,40] However, owing to the cost constraints, the general physical status of the patient, and overall prognosis, a personalized approach for each patient needs to be considered.

## Contraindications

### Chemical Ablation

#### Absolute

- Malignant portal vein thrombus.[16,17]
- Extrahepatic disease (lymph nodal or metastatic).
- Poor PS ($>2$).
- Severely deranged liver function (CTP class C).
- Sepsis and uncorrectable coagulopathy.

#### Relative

- Tumors larger than 5 cm.
- Correctable coagulopathy (platelet count $<50{,}000/\mu L$ and INR $>1.5$).
- Ascites.

### Other Ablations

#### Absolute

- Uncorrectable coagulopathy.[4]
- Intrahepatic biliary dilatation.
- Intravascular invasion or extrahepatic metastatic disease.
- Tumor within 1 cm of the main bile duct.
- Arrhythmias (for IRE).

#### Relative

- CTP B and C cirrhosis.
- Hepatic failure.
- Superficial lesions or lesions abutting any part of the gastrointestinal tract or GB.
- Pacemaker/ defibrillator (for RFA).
- Bilio-enteric anastomosis.

### Transarterial Chemoembolization

#### Absolute[36–38]

- Decompensated cirrhosis (CTP B 8 or higher) including:
  - Jaundice.
  - Clinical encephalopathy.
  - Refractory ascites.
  - Hepatorenal syndrome.
- Extensive tumor with massive replacement of both lobes.
- Severely reduced portal vein flow (e.g., nontumoral main portal vein occlusion or hepatofugal blood flow).
- Technical contraindications to hepatic intra-arterial treatment (e.g., untreatable arteriovenous fistula).
- Renal insufficiency (creatinine $\geq 2$ mg/dL or creatinine clearance $\leq 30$ mL/min).

#### Relative

- Tumor size $\geq 10$ cm.
- Comorbidities involving compromised organ function:
  - Active cardiovascular disease.
  - Active lung disease.
- Untreated varices at high risk of bleeding.

### Transarterial Radioembolization

#### Absolute

- Significant, immediate life-threatening extrahepatic disease[39,40]
- Decompensated cirrhosis, CTP C status (bilirubin $>4$, refractory ascites)
- Uncorrectable shunt/flow to the gastrointestinal tract.
- Hepato-pulmonary shunting.
  - For TheraSphere, the limitation is based on the dose delivered to lung, unlike the lung shunt fraction (30 Gy per infusion, 50 Gy cumulative dose to lungs).
  - For SIR-Spheres, the limiting dose is 20% lung shunt fraction.
- Contraindications for angiography.

#### Relative

- Main PVT.
- Tumor burden more than 70% of liver volume
- Poor PS, ECOG $>2$
- Poor hepatic reserve (serum bilirubin $>2$, biliary obstruction)

## Procedure Details

### Mechanism of Action

#### Chemical Ablation

Alcohol and acetic acid, when injected, selectively diffuse through the interstitium of the tumor. This effect is

 

augmented in HCC by the presence of increased diffusivity resulting from interstitial edema, necrosis, and distortion of the cellular scaffold. The ablative agents induce coagulative necrosis by means of cellular dehydration and cytoplasmic protein denaturation. In addition, they promote local ischemia by causing thrombosis of the tumor microvasculature. Studies on explanted livers have shown no difference in the pattern of coagulative necrosis between ethanol and acetic acid.[41] However, ethanol diffuses unevenly into the tumor, potentially leaving untreated areas. On the contrary, acetic acid has the property of dissolving interstitial collagen, which enables it to permeate through tumor septa/capsule and diffuse evenly throughout the tumor. Hence, acetic acid achieves more complete tumor necrosis at lower doses and requires fewer treatment sessions than ethanol. Higher rates of CR, lower rates of recurrence, and better OS have been observed with PAI.[42,43] Despite all this evidence, the completeness of ablation with chemicals is always unpredictable, which may explain the higher rates of margin recurrence associated with these techniques when compared with RFA in tumors larger than 2 cm.[16,17]

### Selective Role of Chemical Ablation in Hepatocellular Carcinoma

HCCs are "soft" tumors that primarily occur in "hard" cirrhotic livers. This along with the presence of a distinctive tumor capsule enables higher retention of the ablative agent within the tumor, which results in higher therapeutic efficacy and spares the normal surrounding parenchyma. This makes HCC the ideal tumor for chemical ablation. In contrast, metastases represent "hard" lesions within the normally "soft" liver and are not indications for PEI at present.[44]

### Thermal Ablation

Following the generation of heat, the tissues respond in a similar fashion regardless of the thermal ablation method.[45] Up to 40°C of temperature, cellular homeostasis can be maintained. The temperature of 42 to 45°C increases the susceptibility of cells to cytotoxic agents such as chemotherapy.[45] When the tissue is exposed to 46°C for 60 minutes, irreversible cell death occurs.[45] At temperatures of 50 to 52°C, cell death occurs in 4 to 6 minutes. Instantaneous cell death occurs between 60 and 100°C. Vaporization and carbonization occur above this temperature. Thus, for ablation by heating, the aim is to achieve a temperature of 50 to 100°C in the entire target tissue. Cell death by freezing (CA) occurs at temperatures between −20 and −50°C.[46] IRE induces cell death by exposing tissues to direct electric current at high voltage (up to 3,000 V) and high intensity (up to 50 A) in short pulses.[47]

RFA utilizes alternating current at frequencies of 400 MHz. This induces ionic agitation and frictional heat.[45] High-frequency microwaves create an electromagnetic field resulting in rapid and homogeneous heating of tissues by causing oscillation of water molecules.[48] CA leads to ice formation within the extracellular space. This creates an osmotic gradient and cellular dehydration.[49] The intracellular crystals cause cell membrane rupture. Additionally, the ablative effects of CA are potentiated by vascular stasis and thrombosis.[49] IRE creates pores in the lipid bilayer of cell membranes and produces irreversible cell death. The cells become leaky and body's own macrophages clear the tumor cells resulting in apoptosis-induced cell death. Normal tissues, including blood vessels, bile ducts, and tissue stroma, are relatively resistant to IRE.[50] Additionally, due to nonthermal cell damage, IRE is not affected by the heat sink effect.

### Transarterial Chemoembolization

TACE aims to induce tumor ischemia and necrosis by reducing blood flow to the tumor and increasing the dwell time of the injected chemotherapeutic agent in the vicinity of the tumor.[51] The ethiodized oil (Lipiodol) used for c-TACE is selectively taken up and retained by HCC. It acts as a carrier for the chemotherapeutic agent and embolizes small vessels. Lipiodol microdroplets also reach the peritumoral portal veins thus further enhancing the effect of TACE. The embolization agents injected at the end of the procedure increase the hypoxic effect on the tumor cells as well as decrease systemic drug toxicity. DEB–TACE, as opposed to c-TACE, offers simultaneous drug delivery and embolization. The drug release in DEB–TACE is controlled and sustained compared with c-TACE.

### Transarterial Radioembolization

TARE delivers a high dose of radiation to the tumor, avoiding the dose to the noninvolved liver. This is achieved by intra-arterial delivery of Y-90 particles followed by microembolization of the feeding artery.[39]

## Technique and Hardware

### Chemical Ablation

In most cases, US is used for guidance since it enables real-time visualization and is cheap, widely available, and rapidly performed. Typically, a low-frequency (3–5 MHz) curvilinear probe is used. If the lesion is not visible on US, computerized tomography (CT) guidance may be used. In such cases, contrast is mixed with the ablative agent in a ratio of 1:9 to enable visualization of the ablated zone.[42] If the lesion is not visualized on unenhanced CT, a lipiodol TACE may be performed prior to the ablation to help target the tumor on unenhanced CT. Magnetic resonance imaging (MRI) guidance may be used if the lesion is not visible on US and unenhanced CT. MRI is the ideal guidance modality for tumors located near the dome of the diaphragm since it enables coronal or sagittal plane imaging to track cranial needle angulation, obviating the need for pleural or lung transgression.[52]

### Infusion Needles

Since the effectiveness of PCA depends on the precise and uniform distribution of the therapeutic agent throughout the tumor, the orientation and pattern of holes on the needle are important. The most commonly used needles used for access and infusion are 20- to 22-G end-hole stainless steel needles with a beveled tip since they are cheap and easily available.

 

These include lumbar puncture needles (standard length: 9 cm) and Chiba needles (standard length: 15–25 cm; for deep-seated lesions). However, in ex-vivo studies, end-hole needles were observed to form an elongated and nonuniform zone of distribution oriented along the direction of the needle.[53] Hence to target larger tumors (3–5 cm), multiple needles must be placed across the tumor or the same needle can be repositioned and placed at different sites within the tumor to produce multiple overlapping zones of ablation. Treatment of these larger lesions is usually done in multiple sessions since each session is limited by the maximum dose of ethanol. To circumvent this, Livraghi et al described the "one-shot" technique wherein a larger dose of ethanol was injected under the cover of intravenous fructose 1,6-diphosphate and glutathione infusion to increase the rate of hepatic oxidation of ethanol and reduce local/systemic toxicity.[54] This technique, being more painful, is typically performed under general anesthesia.

Larger zones of distribution can also be obtained using a closed conical-tip multiside-hole infusion needle (Bernadino needle; Cook, Bloomington, Indiana, United States), which also demonstrated better visibility and linear tracking than end-hole needles. However, the best results were obtained using an 18-G multipronged (array) needle with an adjustable array diameter (Quadra-Fuse; Rex Medical, Radnor, Pennsylvania, United States). Each of the three prongs of this needle measures 27-G, is retractable and contains four fluid exits, thus totaling 12 points of simultaneous infusion. This produces a spherical zone of distribution and is capable of treating tumors up to 5 cm in a single pass.[55] If MRI guidance is required, titanium needles are preferred to minimize susceptibility artifact.[52]

### Determining the Dose of Ablating Agent

The volume of the drug is estimated so that it covers the tumor as well as a 1-cm-margin of normal liver around it. This is analogous to the surgical margin used to achieve R0 resection and ensures coverage of microscopic seedlings along the tumor margin/capsule. Ethanol is typically used at a concentration of more than 95% w/v (absolute alcohol) and acetic acid at 50% w/v. For ethanol, volume (in milliliter) is calculated using equation $4/3\pi(r+0.5)$,[3] where "r" is the radius of the tumor in centimeters and 0.5 cm is the correction for the safety margin. Acetic acid requires a lower volume as compared with ethanol which is calculated by adding 1 mL to the largest tumor dimension (e.g., a 2-cm tumor requiring 3 mL) or using equation $4/3\pi(r+0.5)^3 \times ⅓$.[43]

### Injection

After local anesthesia, the needle is advanced into the lesion using a freehand technique or a needle guide. Considering the oblong zone of distribution seen with end-hole needles, care needs to be taken to direct the needle along the maximum diameter of the tumor to obtain optimal tumor ablation. The needle is advanced through the center of the lesion till it reaches the margin of the tumor farthest from the transducer. Subsequently, the infusion is started, preferably using a 1-mL insulin syringe, in 0.1- to 0.2-mL aliquots under continuous ultrasound monitoring. Once the area becomes echogenic, suggesting ablation, the needle is slowly withdrawn in a stepwise manner into the unablated area closer to the transducer and infusion is restarted. Care must be taken to not introduce air, since acoustic shadowing can hinder the visualization of needle tip position and real-time ablation. If opacification of an arterial, venous, or biliary structure is seen at any point, the infusion should be stopped, and the needle is withdrawn and repositioned. Visualization of GB filling is an indication for immediate termination of the procedure since it is associated with hemobilia. The endpoint to the infusion is the echogenic transformation of the entire tumor or when the target volume is reached. US is known to overestimate the zone of ablation. If CT guidance is used, infusion can be stopped once the entire tumor is opacified. On MRI, ablation is identified by the transformation of the T2 signal of tissue from hyperintense to hypointense, secondary to desiccation. After completion of ablation, the needle is kept in place for 1 to 2 minutes and withdrawn under aspiration to prevent drug spillage into normal tissue along the track. In each session, up to 10 mL may be injected for both ethanol and acetic acid.[42] In case of multiple lesions requiring multiple sessions, up to four sessions may be performed over the period of a month.[42]

## Thermal Ablation

*RFA:* The equipment comprises a generator (capable of producing alternating current), electrode (probe), and a grounding pad (for monopolar RFA). The grounding pad acts as a large dispersive electrode allowing the current to pass freely without significant heat production. Four types of RF electrodes are commercially available.[15] *Retractable-needle electrodes* (model 70 and model 90 Star-burst XL needles, RITA Medical Systems, Mountain View, California, United States; LeVeen needle electrode, Boston Scientific, Boston, Massachusetts, United States) have multiple curved electrodes that upon deployment assume the shape of an "umbrella." *Internally cooled electrode* (Cool-Tip RF electrode; Medtronics, Minneapolis, Minnesota, United States) has a 17-G insulated, hollow, needle with two internal channels for chilled water perfusion. The *clustered electrode* (Octopus; STARmed, Goyang, Korea) is characterized by switching of RF energy between a pair of electrodes producing a large ablation zone in a shorter time.

*MWA:* The generators are available in two frequencies: 915 MHz and 2.45 GHz.[4] MWA can be performed using single or multiple applicators. Ablation using multiple applicators produces larger but irregular ablation zone and requires independent generators and precise placement of multiple probes. Different protocols are recommended based on the generator setting and size of the lesion.

*CA:* Currently, argon-based units are used.[46] The basic principle of CA-induced tissue damage is the Joule–Thompson effect. Following the passage of argon gas through a thin probe, the rapid expansion creates an extremely low temperature. An ice ball is formed around the tip of the probe. Cell death is maximized by passive thawing. Typically, two freeze-thaw cycles are employed. The probe removal

 

requires active thaw at the end of the procedure with helium. Depending on the size of the lesion, multiple probes can be used simultaneously.[46]

*IRE:* NanoKnife (AngioDynamics, New York, United States) system is the most commonly used system for IRE.[50] The IRE electrodes are monopolar 19 G electrodes. The active tip length (5–40 mm) is adjustable. An essential component of the IRE system is a cardiac synchronization device that allows the delivery of electrical pulses in the ST segment of the ECG. All IRE procedures are performed under general anesthesia with muscle relaxation.

## Transarterial Chemoembolization

Under strict aseptic precautions, common femoral artery access is obtained. Selective catheterization of the celiac artery and hepatic artery is done, and angiogram is obtained. Further, superselective cannulation of arteries supplying the tumor is done. Special attention should be paid to identify arteries at the risk of nontarget embolization. In difficult cases, cone-beam CT may be helpful in superselective delivery. In c-TACE, lipiodol is admixed with chemotherapeutic agents at a ratio of 2 to 4:1 to create water in oil emulsion. The lipiodol–drug emulsion is injected into arteries supplying the tumor. The choice and dose of the chemotherapeutic agent in TACE have not been standardized.[56] The most common agent used worldwide is doxorubicin. Cisplatin is the second most widely used agent. A combination regimen comprising doxorubicin (50 mg), cisplatin (100 mg), and mitomycin C (10 mg) has also been reported. Epirubicin is the other preferred agent. The common pharmacokinetic feature of chemotherapeutic agents for TACE is preferential hepatocyte extraction. The available literature does not support the use of one agent over the other. The choice of the agent will continue to be determined by the institutional/interventional radiologists' preference. The dosages of doxorubicin and cisplatin reported in the literature are 50 to 150 mg and 10 to 100 mg per procedure, respectively.[57] There are no data to suggest a relationship between the dose of the chemotherapeutic agent and the toxicity. The dose is adjusted by the interventional radiologists based on the patients' liver function status.[57] The drug–lipiodol combination is followed by embolization of the vessel supplying tumor mostly using gel foam slurry. In DEB–TACE, DEBs loaded with chemotherapeutic agents are injected into arteries supplying the tumor. TACE is considered complete once the flow of drug/beads becomes sluggish or if reflux of contrast is seen. In large tumors, injection of the drug should be stopped once the maximum dose of the drug as per the body weight has been injected. Hemostasis at the access site should be secured, and the lower limb used for arterial access should be kept immobilized and monitored for 8 to 12 hours.

## Transarterial Radioembolization

The most commonly used and studied radioisotope is Yttrium 90 (Y90), an unstable isotope that undergoes decay into more stable element zirconium-90 with the emission of pure β minus particles. The average half-life of Y90 is approximately 64 hours. The average tissue penetration of β particles is 2.5 mm, with maximum penetration up to 10 to 11 mm. Since the tissue penetration of β particles is less, irradiation of the adjacent normal liver parenchyma is minimal, and limited radiation protection is required once the drug has been delivered.[58] There are two commercially available Y90 products for treatment at present, SIR-Spheres resin microspheres (Sirtex Medical, Woburn, Massachusetts, United States), and TheraSphere glass microspheres (BTG, Canada).

### Glass Microspheres

The mean diameter of insoluble glass microspheres impregnated with Y90 ranges from 20 to 30 μm with an activity of 2,500 Bq per microsphere. Owing to the smaller size, each milligram contains 22,000 to 73,000 microspheres, and approximately 1.2 million microspheres are required to produce 3 Gbq of delivered dose. TheraSphere has been approved by Food and Drug Administration (FDA) under a Humanitarian Device Exemption for inoperable HCC and HCC with PVT.[59]

### Resin Microspheres

Resin microspheres received approval from the FDA in 2002 for the treatment of colorectal metastases to the liver in conjunction with floxuridine.[60] The size of the biocompatible resin-based microsphere ranges between 20- and 60-μm diameter with an activity of 50 Bq per microsphere. Since there is a lower density of Y90 per sphere with reduced activity compared with glass microspheres, more spheres are required to administer a given dose, producing a higher embolic effect and early stasis in the arteries.[61] To create 3-Gbq activity, 40 to 80 million resin microspheres are required (50 Bq per sphere).

Based on the size, location, and extent of vascular invasion by the tumor, the decision will be made on segmental, lobar, or sequential lobar TARE. Hence, TARE is generally performed in two sessions, the first session of treatment planning and dose calculation followed by drug delivery in the second session that is 1 to 3 weeks later. Based on the availability of Y90 microspheres, TARE can now be performed in a single day (both planning and delivery sessions) as an outpatient basis procedure.

### Pretreatment Angiography

To map the arterial supply of the tumor, assess arterioportal shunting, hepatic vasculature, and surrounding structures, pretreatment angiography of aorta, celiac trunk, and SMA is required.[62] Since HCC is known to parasitize blood supply from adjacent vessels, it is important to identify all the branches supplying the tumor to reduce the risk of treatment failure or incomplete treatment. It is also important to determine the extrahepatic blood flow from the hepatic arteries to avoid nontarget deposition of the radioactive isotopes, especially within the GB through cystic arteries or gastrointestinal tract through right/left gastric arteries, which may result in adverse events. Embolization of these arteries may be performed with coils based on the proximity

 

to the location of drug delivery and reflux; however, it is not recommended routinely.[63]

### $^{99m}$Technetium Macroaggregated Albumin Nuclear Scan

HCCs are hypervascular tumors commonly associated with arteriovenous communications and direct shunting of blood flow into lungs, which may lead to inadvertent deposition of radioactive isotopes in the lungs in sufficient doses to cause radiation pneumonitis. Hence, $^{99m}$Tc-macroaggregated albumin (MAA) scan is performed to assess the amount of blood shunting into the lungs, which may not be indicated on routing conventional angiogram. Since the size of MAA (20–50 µm) is like Y90 microspheres (20–40 µm), $^{99m}$Tc-labeled MAA acts as a surrogate in demonstrating the Y90 deposit during treatment. After tumor mapping and selective cannulation of the desired artery through which Y90 needs to be delivered, approximately 4 to 5 mCi of $^{99m}$Tc-labeled MAA is injected into the desired artery, and a high-resolution single-photon emission computed tomography/CT scan is acquired. The radiation dose of >30 Gy in a single session or a cumulative dose of 50 Gy to the lungs after radioembolization significantly increases the risk of radiation pneumonitis.[64] Correlation of angiography findings with that of $^{99m}$Tc-MAA scan is utmost important to look for any shunting into the gastrointestinal tract or elsewhere.

### Dose Calculation

Dose calculation varies based on the manufacturers' prescription and, however, depends on the assumption that Y90 microspheres undergo uniform distribution throughout the liver and complete decay in situ. For glass microspheres, it is based on the dose delivered to the injected liver parenchymal volume (considering equal volume of tumor and nontumoral tissues), and for resin-microspheres, the dosing is based on the body surface area. In neither case, the amount of dose distribution between tumoral and nontumoral tissues is taken into consideration. The desired dose of glass microspheres can be calculated using the following formula:

A (GBq) = [D x M]/50

where A is the activity to be administered to the target area in gigabecquerel, D is the dose administered in grays, and M is treated liver volume/mass in kilograms. Target liver volume, including tumoral and nontumoral tissue, is calculated using CT and, subsequently, converted to mass using a conversion factor (1.03 mg/cc). The recommended activity of the delivered dose is 80 to 150 Gy.[14]

For resin microspheres, there are many dose calculation methods that are aimed at keeping the absorbed dose to the targeted nontumoral volume below 70 and 50 Gy for lobar and total liver treatment, respectively, and the recommended dose of 120 Gy for the tumor.[14,65] Most preferred method of dose calculation incorporates body surface area and is represented by the formula:

A (GBq) = BSA ($m^2$) - 0.2+ (% Tumor burden/100)

where BSA is the body surface area in square meters and % tumor burden is the percentage of liver involved by tumor. Recently, there are modifications with the personal dosimetry approach wherein the intended dose to the tumor is aimed at >205 Gy, ensuring that the dose to the normal liver parenchyma is less than 120 Gy.[66]

### Drug Delivery

Based on the tumor burden and extent, the treatment paradigm like TACE is recommended with lobar or segmental infusions. In large tumors with multiple feeders or bilobar distribution, the dose can be divided and delivered sequentially by superselective cannulation, preserving normal parenchyma as much as possible. For dose administration, the catheter is advanced into the treatment vessel determined by pretreatment angiography and the drug administration device provided by the manufacturer is used for the infusion of Y90 microspheres. After achieving hemostasis at the puncture site, positron emission tomography (PET)-CT scan may be considered to confirm dose distribution at the expected sites.

## Preprocedure Preparation

### Preprocedural Work Up and Patient Preparation

Careful patient selection produces optimal results with minimum complications. The patient is assessed for PS, and detailed blood investigations, including hemogram and liver function tests, are performed. Planning the procedure requires a multiphase CT or MRI to assess the tumor number, size, location, as well as the presence and extent of PVT. Additionally, a thorough search is done for extrahepatic disease. Ideally, the procedure should be scheduled within 4 weeks of the imaging. Since US is the most common imaging tool used for guidance of ablative therapies, screening US should be done at the time of scheduling and immediately prior to the procedure for assessing visibility of the lesion, planning the approach, and screening for ascites. On the day of the procedure, the patient is admitted, and the following checklist is adhered to

- Informed written consent.
- Investigations: complete blood count, coagulogram, liver, and renal function tests.
- Preanesthetic checkup.
- At least 6 hours of fasting prior to the procedure.
- Antibiotics: prophylactic antibiotics should be considered for patients at a high risk of infection, particularly those with bilio-enteric anastomosis.[67]
- Patent vascular access (at least 20 G)

## Image Guidance

The utilization of US or CT is based on the tumor visibility and operator preference and experience. Less commonly, the use of MR guidance has also been reported. In a study comparing the effectiveness of US versus CT guidance for RFA, all the patients had complete tumor ablation and there was no significant difference in the OS and tumor recurrence at 1 year, 2 years, and 3 years between the two groups.[68] The US group required a median of two sessions versus the single session for the CT group. There was no difference in the complication rates. In another study comparing US, CT, and MR guidance for RFA, there was no difference in the technical success, technical effectiveness, as well as OS.[69]

 

### Protection of Adjacent Structures from Collateral Damage

Hydrodissection is the most common method to reduce damage to adjacent structures, including GB, gastrointestinal tract, pericardium, or diaphragm.[70] Hydrodissection separates the target tissue and adjacent structures by a fluid layer. The fluid most commonly employed is 5% dextrose. A variable volume of fluid ranging from 100 to 1,500 mL is used.[71] The aim is to achieve 5-mm separation between the target site and the adjacent critical structure. In a study comprising 181 HCCs, 148 lesions were found to be in high-risk locations with potential for thermal injury to adjacent structures.[72] Complete necrosis was achieved in 91.2% of HCCs following hydrodissection with 5% dextrose. There were no major complications. The other methods that have been used less frequently are balloon placement, use of thermoprotective gel, and carbon dioxide insufflation. Hermida et al employed carbon dioxide pneumothorax for the ablation of HCCs abutting the domes of the diaphragm.[73] After a median follow-up of 13.8 months, LTP was significantly reduced in patients who underwent ablation after carbon dioxide pneumothorax (10.7 vs. 25%).

### Technical Effectiveness

The ablative procedure is considered technically effective when the entire tumor and a safety margin are covered in the ablation zone. Achieving an ablative margin around the lesion is critical as the tumor margin may contain microscopic foci of the tumor. The targeted ablative margin of 5 to 10 mm should be achieved circumferentially around the entire lesion.[74] In an RCT comparing LTP and intrahepatic recurrences following a wide margin (ablative margin $\geq$ 10 mm) versus a narrow margin (ablative margin, 5–10 mm), the authors reported an ablative margin $\geq$10 mm in 40 out of the 48 patients randomized to achieve wide margin ablation.[74] The outcomes were significantly better in the patients who achieved the targeted ablative margin of $\geq$10 mm.

## Expected Outcomes

*Chemical ablation:* Initial CR has been reported in 66 to 100% of the tumors, with majority of the studies reporting the CR in the lower range. OS at 1- and 3-year OS has been reported to be 61 to 96% and 50 to 73%, respectively.[75–77]

*RFA:* OS following RFA at 1 year has been reported to be consistently higher between 90 and 99%.[78] OS at 3 years has been reported to be 60 to 87%. OS of 40 to 70% at 5 years and 20 to 30% at 10 years has been reported.[79] A recent study reported 10-year OS of 74.2% following RFA of a single HCC $<$ 3 cm.[80] The local recurrence rates following RFA are variably reported, ranging from 3.2 to 27% at 5 years.

*MWA:* OS at 3 and 5 years following MWA has been reported to be 50.5 to 82.7% and 51 to 57%, respectively.[81,82] A recent retrospective study reported 10-year OS of 23.8% and 10-year recurrence-free survival of 8.1%.[83]

*CA:* OS at 1 year, 3 years, and 5 years has been reported to be 81.3 to 98.6%, 47.6 to 80.6%, and 39 to 60.3%, respectively.[84–86] The corresponding LTP rates have been reported to be 3, 7, and 7%, respectively.

*IRE:* The long-term data for OS and PFS are not available. Most of the studies have reported short-term follow-up data. Studies have usually reported data for liver tumors including HCC and metastasis. OS at 1 year and 3 years has been reported to be 56.6 to 97% and 50.7 to 52%, respectively.[50,87] The corresponding 1- and 3-year PFS have been reported to be 44 to 74.8% and 68.3%, respectively.

*TACE:* In one of the largest series, median survival was 34 months. In another large series, the median OS and 5-year survival were 3.3 years and 34%, respectively.[88,89]

*TARE:* The published literature regarding TARE in HCC has shown consistent results in survival. Salem et al in their study of patients with CTP A disease reported OS of 17.2 months, and Hilgard et al in their study of lobar TARE in 108 patients with BCLC B (47%) and BCLC C (51%) status achieved median OS of 16.4 months.[90,91] A study by Sangro et al on TARE in patients with BCLC B status and poor candidature for TACE due to bilobar disease or five tumors reported a median OS of 16.9 months, and it was 15.4 months in patients who had failed response to prior TACE.[92] Many studies have compared TARE with TACE for OS; however, no prospective RCTs have shown a statistically significant difference in OS between the two therapies. A retrospective study of BCLC B and C HCC patients by Soydal et al showed an OS advantage with TARE compared with TACE: mean OS 39 months for TARE versus 31 months for TACE ($p = 0.014$).[93] Meta-analysis of 1,499 patients with HCC also yielded an OS advantage in favor of TARE (hazard ratio $= 0.74$; 95% confidence interval [CI]: 0.61–0.90).[94] As compared with TACE, multiple studies have shown improvement in other end points like safety profile, time to tumor progression (TTP), and quality of life. OS was 63% (95% CI: 56–70%) and 27% (95% CI: 21–33%) at 1 year and 3 years, respectively, in intermediate-stage HCC, whereas OS was 37% (95% CI: 26–50%) and 13% (95% CI: 9–18%) at the same time intervals in patients with sufficient liver function (CTP A-B7) but with an advanced HCC because of the presence of PVT. When an intermediate and advanced case mix was considered, OS was 58% (95% CI: 48–67%) and 17% (95% CI: 12–23%) at 1 year and 3 years, respectively. The median time to progression was 2.4 years (95% CI: 2.1–5.7), with 72% of patients having no target lesion progression at 5 years. Median OS was 6.7 years (95% CI: 3.1–6.7); survival probability at 1 year, 3 years, and 5 years was 98, 66, and 57%, respectively. OS probability at 1 year, 3 years, and 5 years was 100, 82, and 75%, respectively, in patients with baseline tumor size less than or equal to 3 cm ($n = 45$) and was significantly longer than in patients with tumors greater than 3 cm ($p = 0.026$).

## Complications

### Chemical Ablation

PCA is a safe procedure, well-tolerated by patients. Minor complications like fever, local pain, and malaise are common, transient, and easily managed with nonsteroid anti-inflammatory drugs. Major complications associated with both PEI

 

and PAI include needle-related factors (peritoneal hemorrhage, hemopneumothorax, and tumor seeding) and those which result from local (hepatic necrosis, bilioma, abscess, chemical cholangitis, and cholecystitis with hemobilia) or systemic effects (hypotension, hemolysis resulting in hematuria/ hemoglobinuria, and renal failure) of the ablative agent. The incidence of major complications with PEI has been reported to be 3.2%.[95,96] Complications are higher for the "one-shot" PEI technique.[97] PAI is associated with a higher incidence of complications than PEI.[96] Hemolysis and hemoglobinuria are much more common in PAI than PEI. Minor transient hemolysis is frequently seen even with routine therapeutic doses of acetic acid, causes no derangement in serum creatinine levels, and clears spontaneously with several voids.[97] Metabolic acidosis is unique to acetic acid. Renal failure is also more common, possibly from direct renal injury by acetic acid, though it is usually multifactorial.

#### Thermal Ablation

The major complication rate is reported to be 2.2 to 3.1%.[70] Major early complications include intra-abdominal bleed, hollow viscus perforation, pneumothorax or hemothorax, liver abscess, and bile duct stenosis. An important late complication is needle track seeding. The rate of needle track seeding is 0.5 to 1%.[70,98] Skin burns from grounding pads are reported in <1% of the RFA procedures. Proper shaving of the skin, avoidance of pressure on the grounding pads, and frequent checking of the temperature of the local skin are effective in avoiding this complication. Minor complications include pain, fever, small self-limiting intraperitoneal hemorrhage, and small pleural effusions.

There are concerns about severe bleeding, liver fractures, and cryoshock with CA, but these complications were mostly reported in the early surgical CA series. Recent studies have reported an excellent safety profile of CA comparable to other ablative methods.[99,100]

Although IRE is considered to have no effect on the major vascular and biliary structures, mild-to-moderate cholestasis is reported in 24% patients in a study.[101] The additional risk with IRE is cardiac arrhythmias.[102]

#### Transarterial Chemoembolization

The most common adverse events are related to the postembolization syndrome and include liver enzyme abnormalities, fever, abdominal pain, vomiting, nausea, renal failure, liver abscess, liver failure, acute hepatic decompensation, variceal bleeding, acute cholecystitis and acute pancreatitis.[103,104] Most of these complications are self-limiting and improve with conservative treatment consisting of hydration, antiemetic, and antipyretic medications.

#### Transarterial Radioembolization

In comparison to TACE, radioembolization is well tolerated with less common postembolization syndrome, characterized by nausea, vomiting, abdominal pain, and fever. Conservative management with analgesics and antipyretics is recommended. Severe complications like gastrointestinal ulceration, cholecystitis, pancreatitis, and radiation-induced pneumonia have been reported due to accidental non-target embolization, with few cases of radiation-induced hepatitis.[93] Common practice is to give a loading dose of proton pump inhibitors at the start of drug delivery and follow-up with infusion for 7 days as a standard of care or if there is evidence of nontarget deposition of radioisotope on postprocedure PET-CT. Fluoroquinolones are indicated for 7 to 10 days in patients treated with radioembolization of the entire right lobe with the presence of GB. Cholecystostomies may be warranted in patients with acute severe radiation-induced cholecystitis if conservative management fails. Similarly, surgery is indicated for a nonhealing gastrointestinal ulcer.

## Follow-Up

#### Chemical Ablation

Patients who undergo ablation must remain under close follow-up using imaging and serum AFP levels to detect untreated residual disease or recurrence. The first follow-up imaging is performed 4 to 8 weeks after imaging, usually using multiphase CT or MRI.[105–107] Successful ablation is seen as complete T1/T2 hypointensity and hypoenhancement of the tumor as well as the safety margin (1 cm beyond the tumor). Thus, the final ablation zone is larger than the original tumor. Air bubbles may be seen in early posttreatment CT and do not necessarily represent infection. A thin rim of peripheral enhancement with a smooth margin represents a benign inflammatory reaction to the ablation. On the other hand, nodular, eccentric, and peripheral areas of arterial phase hyperenhancement are seen in recurrent disease.[106] Further imaging is typically performed at 3, 6, 9, 12 months, and longer intervals thereafter. Contrast-enhanced ultrasound has been found to be inferior to multiphase CT in the follow-up after ablation.[107]

#### Other Ablations

First follow-up scan should be performed at 1 month after ablation.[108] Thereafter, follow-up imaging should be performed every 3 months for the first year. After the first year, surveillance is performed every 6 months. The ablation zone should appear as a nonenhancing area. Smooth enhancing peripheral rim may be present and does not represent residual disease.

#### Transarterial Chemoembolization

The protocol for follow-up imaging is similar to that for ablative therapies. First follow-up scan is done at 1 month. Four types of lipiodol distribution have been described on CT.[109] These correlate with the treatment response. A thin rim of enhancement secondary to reactive hyperemia has been described around the treated lesion for first few days after TACE. Imaging following TACE is preferably done with multiphasic MRI.

#### Transarterial Radioembolization

No universally accepted standard protocol exists currently for post-TARE imaging. Cross-sectional imaging with either

 

**Table 1** Comparison of various ablative methods

| Characteristics | Radiofrequency ablation | Microwave ablation | Cryoablation | Irreversible electroporation |
|---|---|---|---|---|
| Principle | Thermal | Thermal | Thermal | Nonthermal |
| Mechanism of cell death | Necrosis | Necrosis | Apoptosis | Apoptosis |
| Collateral damage[a] | Yes | Yes | No | No |
| Anesthesia | Local/General | Local/General | Local/General | General |
| Post procedure pain | Yes | Yes, less than RFA | Less than RFA and MWA | Less than RFA and MWA |
| Specific complication | Skin burns | None | Cryoshock | Arrythmias |
| Procedure time | + | +, less than RFA | ++ | +++ |
| Cost | + | + | ++ | +++ |
| Clinical utilization | Routine | Routine | Tumors adjacent to critical structures | |

Abbreviations: MWA, microwave ablation; RFA, radiofrequency ablation.
[a]Damage to connective tissue framework adjacent to the liver tumor.

contrast enhanced CT or MRI and PET/CT are used varyingly at the discretion of the treating interventional radiologist. Most commonly these patients are subjected to CT/MRI at 2 months after the treatment, and PET CT at the third month as the imaging response may take up to 2- to 3-months post-TARE. Boas et al have proposed the optimal posttreatment imaging schedule at 2, 4, 6, 8, 11, 14, 18, and 24 months, with a higher frequency of imaging in the first year due to 6.5 times greater chance of recurrent disease within this period.[109]

The response to various forms of locoregional therapies may be assessed using the European Association for the Study of Liver, modified response evaluation criteria for solid tumors, or liver imaging reporting and data system treatment response assessment criteria.

### Combination Locoregional Therapies

#### Ablation with Transarterial Chemoembolization

*PEI–TACE:* TACE-induced tumor necrosis is hypothesized to facilitate the diffusion of ablative agents, thereby enhancing the efficacy of chemoablation. Studies have observed the need for fewer treatment sessions when PCA was combined with TACE. In addition, combination therapy was associated with a lower incidence of recurrence and higher survival rates than either of the therapies used alone.[110] Lipiodol–TACE also helps in increasing the tumor visibility if CT guidance is subsequently used for PCA.

*RFA/MWA–TACE:* The combination of thermal ablation with TACE potentiates tumor necrosis. This translates into a reduced recurrence rate and improved OS and PFS.[111]

A meta-analysis comprising eight RCTs demonstrated that patients who underwent RFA–TACE had significantly better 1-, 2- and 3-year OS and PFS versus RFA alone. There was no significant difference in the major complications. TACE–MWA has been shown to be associated with a higher CR rate than TACE–RFA for 3- to 5-cm lesion.[112] However, no survival benefit has been demonstrated.

The comparative efficacy of simultaneous TAE-ablation versus sequential TACE followed by ablation for large HCC is being evaluated.[113]

*PEI–RFA:* The combination of RFA with PEI could increase the ablation zone, thereby reducing local recurrence rates and augmenting therapeutic efficacy. A combination of PEI with RFA has been observed to increase the OS in tumors of size 3 to 5 cm.[114] PEI can also be used to treat post-RFA recurrences resulting from tumor proximity to vessels (heat sink effect). Chemical ablation can also be used to treat small residual or recurrent lesion after RFA or TACE.

*TACE–Sorafenib:* Previous trials (SPACE, Korea-Japan post-TACE trial, TACE-2 trials) showed no benefit of the addition of sorafenib to TACE compared with TACE alone.[115–117] However, a recent trial from Japan (TACTICS trial) showed significantly longer PFS and TTP in the TACE–sorafenib group compared with sorafenib alone.[118]

The various ablative methods are compared in ►**Table 1**.

## Conclusion

Image-guided therapies are integral to the management of HCC. The choice of therapies depends on the tumor and patient characteristics. To achieve optimal results, the procedures must be performed meticulously. Follow-up imaging allows the detection of local tumor recurrence as well as the new lesions.

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None declared.

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