Review Article

Image-guided percutaneous locoregional therapies for hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the 3rd leading cause of cancer death worldwide. Treatment options include surgical resection, liver transplantation, image-guided percutaneous locoregional options, external beam radiation therapy (EBRT) and systemic therapies. Treatment choice depends on the stage of the disease and patient's characteristics including performance status and liver function. Barcelona Clinic Liver Cancer (BCLC) staging system, with its recent 2022 update, is one of the most widely endorsed staging system. Locoregional therapies (LRT) are recommended for very early stage (BCLC-0), early stage (BCLC-A), and the two first subgroups of intermediate stage (BCLC-B). Image-guided percutaneous locoregional therapies include ablation, mainly thermal ablation with radiofrequency (RFA), microwave ablations (MWA) and cryoablation, transarterial embolization (TAE, also known as bland embolization), transarterial chemoembolization (TACE), drug-eluding beads-transarterial chemoembolization (DEB-TACE), combination of ablation with embolization, transarterial radioembolization (TARE) also known as selective internal radioembolization therapy, and hepatic artery infusion (HAI). While ablation is recognized as a curative therapy, all intra-arterial therapies are considered non-curative options. There is growing evidence that TARE, through radiation segmentectomy, can be considered a curative intent treatment in appropriate selective patients. In this article, we will review indications, complications, and outcomes of locoregional therapies for HCC.

Keywords: Hepatocellular carcinoma (HCC); ablation; embolization; chemoembolization; radioembolization

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Introduction

In 2020, primary liver cancer was the sixth most frequently diagnosed cancer and the third leading cause of cancer death worldwide, with 830,180 deaths and an estimated incidence of 905,677, with hepatocellular carcinoma (HCC) accounting for 75–85% of cases and intrahepatic cholangiocarcinoma for approximately 10–15% (1). HCC incidence rates are highest in East Asia and sub-Saharan Africa, which together account for approximately 85% of all cases (2). In most cases, HCC develops in the presence of chronic liver disease and cirrhosis, most often caused by chronic viral hepatitis B and C, chronic alcohol abuse, and non-alcoholic fatty liver disease (NAFLD) (1-3).

HCC treatments are generally divided into curative and non-curative options (4). Liver transplantations (LT), surgical resection, and ablation are considered curative therapies. Non-curative therapies include transarterial embolization (TAE), transarterial chemoembolization

Table 1 The 2022 BCLC staging system (6)

BCLC stage	ECOG PS	Liver function	Tumor stage
Very early stage (0)	0	Preserved liver function*	Single ≤2 cm, without vascular invasion or extrahepatic spread
Early stage (A)	0	Preserved liver function*	Single, or ≤3 nodules, each ≤3 cm without macrovascular invasion or extrahepatic spread
Intermediate stage (B)	0	Preserved liver function*	Multinodular, no vascular invasion or extrahepatic spread
Advanced stage (C)	1–2	Preserved liver function*	Portal invasion and/or extrahepatic spread
Terminal stage (D)	3–4	End stage liver function	Any tumor burden

*, refined by AFP, ALBI, MELD. Liver function should be evaluated beyond the conventional Child-Pugh staging. ECOG PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; MELD, model of end-stage liver disease.

(TACE), transarterial radioembolization (TARE), hepatic artery infusion (HAI) and systemic therapies (5). There is growing evidence that radiation segmentectomy can be considered a curative intent treatment in appropriate selective patients.

Therapeutic decision is made by a multidisciplinary approach that includes hepatologists, medical oncologists, surgeons, radiation oncologist, diagnostic and interventional radiologists. Underlying liver function should always be assessed and considered.

Barcelona Clinic Liver Cancer (BCLC), with its recent 2022 update, is one of the most widely endorsed staging system (*Table 1*) (6). BCLC classification has been validated externally and endorsed by both European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD). Locoregional therapies (LRT) are only recommended for very early stage (BCLC-0), early stage (BCLC-A), and the two first subgroups of intermediate stage (BCLC-B). LRT have no role in advanced stage (BCLC-C), patients with portal invasion and/or extrahepatic disease (6). Other indications for LRT are "bridge to transplant" and "downstaging" in patient on the transplant list and advanced HCC patients without distant metastasis, respectively. While this is indeed the standard guideline for the European countries and the United States, other staging systems with treatment stratification exist, including the Hong Kong Liver Cancer (HKLC) staging system (*Table 2*) (7), the China Liver Cancer staging system (8), and the Japan Society of Hepatology-HCC guidelines (9). Compared to BCLC, these staging systems favor a more aggressive treatment approach. Because BCLC was developed in Western countries, where viral hepatitis C, alcohol abuse, and NAFLD, are the main factors attributable to HCC, it might not be the most appropriate staging system for Asian populations, in which hepatitis B virus chronic infection is the most common cause of cirrhosis and consequently HCC (10).

Image-guided percutaneous locoregional therapies has been proven to be safe and effective in treating hepatic metastases, especially for colorectal cancer metastases but also in neuroendocrine, thyroid, lung and breast. However, the focus of this review is HCC and therefore only treatment options for HCC will be reviewed here.

Here we review the indications, outcomes, and complications of the different locoregional therapies, which include percutaneous ablation, TAE and TACE, drug-eluding beads-transarterial chemoembolization (DEB-TACE), and TARE.

Percutaneous ablation

Indication

Percutaneous ablation, mainly thermal ablation with radiofrequency (RFA) and microwave ablations (MWA), are usually considered as curative options. In the recent 2022 BCLC update, ablation was recommended in BCLC-0 to BCLC-A patients (6). Patients should have preserved liver function, ECOG score of 0, no extrahepatic disease, no vascular invasion, and tumors ≤3 cm (6). For BCLC-0 patients, with a single nodule ≤2 cm, percutaneous ablation is the recommended therapeutic option (6). In BCLC-A patients with multifocal disease (up to 3 nodules, each ≤3 cm) and preserved liver function, ablation is recommended if the patient is not a LT candidate. For BCLC-A patients with a single HCC ≤3 cm, ablation represents a good option (6,11). Ablation has been suggested as "bridge to transplant" in patient on transplant list to prevent tumor progression and

Table 2 The 2014 HKLC staging system (7)

HKLC stage	ECOG PS	Liver function	EVM	Tumor status
I	0	Child-Pugh A	No	Early[1]
IIa	1[a]	Child-Pugh B[a]	No	Early[1]
IIb	0–1	Child-Pugh A	No	Intermediate[2]
IIIa	0–1	Child-Pugh B	No	Intermediate[2]
IIIb	0–1	Child-Pugh A/B	No	Locally advanced[3]
IVa	0–1	Child-Pugh A	Yes	Any
IVb	0–1	Child-Pugh B	Yes	Any
Va	2–4[b]	Child-Pugh C[b]	No	Early[1]
Vb	2–4[b]	Child-Pugh C[b]	Yes[c]	Intermediate[2] or locally advanced[3 c]

[a], at least one criterion: ECOG PS 1, Child-Pugh B; [b], at least one criterion: ECOG PS 2-4, Child-Pugh C; [c], at least one criterion: intermediate/locally advanced tumor, EVM. [1], early tumor: ≤5 cm, ≤3 tumor nodules and no intrahepatic vascular invasion. [2], intermediate tumor: (I) ≤5 cm, ≤3 tumor nodules and intrahepatic vascular invasion; (II) ≤5 cm, >3 tumor nodules and no intrahepatic vascular invasion; (III) >5 cm, ≤3 tumor nodules and no intrahepatic vascular invasion. [3], locally advanced: (I) ≤5 cm, >3 tumor nodules and intrahepatic vascular invasion; (II) >5 cm, ≤3 tumor nodules and intrahepatic vascular invasion; (III) >5 cm, >3 tumor nodules with or without intrahepatic vascular invasion; (IV) diffuse, any number of nodules, with or without intrahepatic vascular invasion. ECOG PS, Eastern Cooperative Oncology Group Performance Status; EVM, extrahepatic vascular invasion/metastasis; HKLC, Hong Kong Liver Cancer.

patient dropout from the waiting list, with a waiting list longer than 6 months (6).

In the 2014 HKLC staging system, ablation is the therapeutic option for patients with performance status (PS) of 0–1, stages I and IIa, with early tumor (≤5 cm, ≤3 tumor nodules and no intrahepatic or venous invasion), Child-Pugh A–B and without extrahepatic disease (7). However, the recent Hong Kong consensus has recommended ablation as an acceptable alternative to resection only for HCC <3 cm in Child-Pugh A–B patients (10). For 3–5 cm HCC in Child-Pugh A patients, resection is preferred over ablation. However, it recognizes that combination of TACE and ablation may be beneficial for 3–5 cm and 5–7 cm solitary tumors (10). For patients with a predominantly large mass in one lobe and 1 or 2 small HCCs in the other lobe, ablation is considered to ablate the small nodules in combination with the resection of the predominant mass (10).

Types of ablations

Radiofrequency ablation

RFA induces coagulation necrosis in the tumor by generating heat from ionic agitation of electrons caused by alternating current. Target tumor temperature should elevate to more than 60 degree centigrade. RFA is currently the most frequently used percutaneous technique for treatment of HCC and is considered the standard of care for percutaneous ablation (11). For very early HCC <2 cm, RFA demonstrated similar outcomes to resection (12,13). In patients with single HCC ≤2 cm and in the presence of two or three nodules ≤3 cm, RFA is more cost-effective than resection, with similar life-expectancy and quality-adjusted life-expectancy (14). In a study that included 218 patients with single HCC ≤2 cm, complete local response was seen in 97.2% with 5-year survival rate of 68.5% (15).

For larger HCC, resection is generally favored (16). In event of local recurrence after ablation, repeat RFA is safe and efficient (17,18). Compared to monopolar RFA, multi-bipolar RFA with the "no-touch" method potentially allows for better pathological response (19), and was associated with a better sustained local tumor response in patients with HCC ≤5 cm (20).

Microwave ablation

MWA generates heat using high frequency (>900 MHz) electromagnetic energy via interaction with protons predominately within water molecules and generates a more uniform and larger ablation zones, particularly when adjacent to large vessels. MWA achieves higher and faster temperature peaks when compared to RFA and is less sensitive to heat sink effect (11). Therefore, MWA could safely and efficiently

be used to treat larger HCC (3–8 cm) (21-23). Phase II randomized controlled trial (RCT) comparing MWA with RFA in patients with ≤4 cm HCC demonstrated similar results. Local tumor progression (LTP) at 2-year was 6% and 12% in the MWA and RFA group, respectively (24). These results were further confirmed in a Phase III RCT in HCC patients with tumor size ≤5 cm and tumor number ≤3. No significant differences in terms of 1-, 3- and 5-year LTP, overall survival (OS), disease-free survival (DFS) and major complication rates (25) were reported. A recent meta-analysis, including 26 studies and 4,396 patients with a median tumor size ranging from 1.6 to 3.6 cm, found that MWA exhibited similar therapeutic effects as RFA in the treatment of early stage HCC, with no significant difference in terms of progression, OS or DFS (26). However, the median ablation time was significantly shorter in the MWA group (12 min) compared with RFA group (29 min) (26).

Both RFA and MWA are thermal-ablation techniques that induce lesion coagulative necrosis. They are mainly used to ablate small HCC lesions, typically <3–5 cm. More data with RFA are currently available, as MWA is a newer technology (27). To our best knowledge, there are no clear data supporting that MWA is superior or equivalent to RFA, however it is commonly accepted that MWA allows larger ablation than monopolar RFA, allowing MWA to treat lesions even larger than 5 cm (23). The 2022 BCLC update indeed suggests that MWA technique is potentially the best ablative option for the treatment of 2–4 cm HCC (6). Furthermore, whereas the ablation zone may be limited with RFA due to "heat-sink effect" through adjacent vessels, MWA demonstrates less susceptibility to this effect and has been shown to be effective and safe in treating HCC tumors adjacent to large vessels (28). These are the reasons why MWA is increasingly replacing RFA for HCC ablation in current clinical practice.

Cryoablation (Cryo)

Cryo uses argon or helium gas to decrease the temperature using the "Thomson effect" inducing tissue freezing and vascular injury, ultimately resulting in tumor cell death. The main advantage of Cryo is that the ice ball can be easily visualized during ablation and allows for real time monitoring of the ablation margin (11). Cryo has been compared to RFA and MWA and has demonstrated similar outcomes and complications (29-31). A recent retrospective propensity-matched population study analyzed 3,239 patients with HCC and showed no significant difference in OS between Cryo, RFA and MWA (32).

Percutaneous ethanol injection (PEI)

PEI is a non-thermal ablation technique. PEI causes dehydration of tumor cells accompanied by small vessel thrombosis, leading to tumor ischemia and destruction. RFA has demonstrated better OS, DFS and lower recurrence rates when compared to PEI, especially for HCC >2 cm (33-35). Additionally, RFA requires fewer sessions than PEI to achieve tumor necrosis. Therefore, PEI has been replaced by RFA and MWA (11). PEI remains an option for small HCC <2 cm and lesions that are not suitable for thermal ablation, such as hilar lesions, lesions located near the main biliary duct or nodules abutting large vessels (6,10).

Irreversible electroporation (IRE)

IRE is a nonthermal ablation modality that results in the irreversible formation of nanopores across the cellular bi-lipid membranes, leading to cell death, mainly by apoptosis (11,36). Patients with normal cardiac rhythm are candidates for this modality and ablation is synchronized with the heartbeat to avoid cardiac arrhythmia (37). Compared to thermal ablation technics, the advantage of IRE is the near complete absence of heat. Therefore, the risk of thermal injury to structures adjacent to the tumor is minimized and the blood vessels and particularly the adjacent bile ducts are preserved. This allows for treatment of more central HCC that are located near bile ducts (11,38,39). In addition, IRE is not affected by heat sink effect. Further studies are required to valid survival benefits of IRE.

Contraindications

(I) Tumors located within 1 cm from the main biliary ducts (for thermal ablation modalities) (40).
- ❖ Risk of delayed bile duct stenosis or perforation from thermal ablation.
- ❖ Overall biliary stricture rate is 2% after RFA of lesions close to central biliary tree (41).
- ❖ IRE represents a good alternate to thermal method for central HCC (11,38,39,42).

(II) Exophytic tumors for which only a direct access is feasible.
- ❖ Higher risk of tumor seeding especially for undifferentiated HCC (40).

(III) Unmanageable coagulopathy.
(IV) Significant ascites interposed along the track (40).
(V) Contraindications to IRE are cardiac arrhythmia and pacemakers.

Complications

(I) Post-ablation syndrome.
- ❖ Majority of the patients develop low-grade fever, nausea, vomiting. These symptoms are considered post-ablation syndrome and are not considered complications (40). The duration is usually short and can be treated by symptomatic management.

(II) Pain at the treatment site or right shoulder is frequently reported (43).
- ❖ While it is generally not severe and subsides within a few days, the intensity and frequency may be greater with the size of the ablation, or with the proximity to the liver capsule (40,43).

(III) Bleeding.
- ❖ Include hemoperitoneum, liver hematoma, hemobilia, and hemothorax.

(IV) Pneumothorax.
(V) Tumor track seeding.
- ❖ Occurs in 0.5% to 3.2% of cases and is more commonly seen in direct puncture of subcapsular or exophytic HCC (11,44-46).
- ❖ Ablation track traversing through non-tumor parenchyma and track ablation are recommended to decrease the risk of tumor seeding (45,46).

(VI) Bowel perforation, diaphragmatic injury, and pleural effusion.
- ❖ The risk of bowel or diaphragmatic injury, and pleural effusion, is related to the location of the tumor. They can be avoided by using thermo-protective methods, such as gas, hydrodissection or balloon interposition (47).

(VII) Liver abscess.
- ❖ Liver abscess occurs is patients with history of sphincterotomy or bilio-enteric anastomosis (48). These patients should receive prophylactic antibiotics prior and after the procedure (49,50).

(VIII) Bile duct stricture or perforation and cholecystitis.
- ❖ This complication is seen when tumors located less than 1 cm from the common or left/right hepatic ducts are treated with thermal ablation. Endoluminal biliary cooling has been shown to help prevent this complication (40,47).

(IX) Ascites and liver failure (11,40).
- ❖ The risk of developing liver failure and ascites depends on the patient's underlying liver function and the size of ablation.

(X) Cryoshock.
- ❖ Cryoshock phenomenon which is characterized by severe coagulopathy and multi-organ failure is seen with Cryo (51). Risk of occurrence is proportional to the volume of treated tumor (40).

Trans-arterial treatments: TAE, TACE, DEB-TACE and TARE

Embolization of any type should be performed as selective as possible to maximize treatment effect, preserve the nontumoral parenchyma and minimize the risk of complication.

TAE

TAE also known as hepatic artery embolization or bland embolization is performed using only embolic agents without the addition of chemotherapy drug. Arterial supply to the tumor is blocked resulting in tumor ischemia. Most common particle sizes used range from 40 to 120 and 100 to 300 μm (52). No human study has compared outcome and survival benefits of different particle sizes. In Oncopig model, TAE using 40–120 μm demonstrated significantly more decrease in tumor size when compared to 100–300 μm (53). Endpoint of embolization is complete stasis with absolutely no flow in the tumor target vessels.

TACE

TACE is commonly described by the intra-arterial delivery of chemotherapy emulsified in ethiodized oil (Lipiodol® Ultra Fluid (UF), Guerbet, France) followed by the administration of an embolic agent (6,54-56). This is also known as conventional TACE or cTACE. TACE has been shown to decrease the relative risk of death comparted to best supportive care and improved OS in two RCTs and confirmed by two meta-analysis studies (57-60). Lipiodol®UF is oil-based radiopaque contrast agent, that has a high affinity for primary hepatic tumors and demonstrates

embolic effect (61-63). Since most chemotherapeutic drugs are water-soluble, once Lipiodol®UF forms an emulsion with the drug, it performs as a drug-delivery system to the tumor (63). The drug is "loaded" as droplets inside the Lipiodol®UF. Chemotherapy regimen varies between centers and countries, with doxorubicin, idarubicin, epirubicin and cisplatin being the most commonly used drugs for HCC. Drugs have been used alone and in combination. The most common combination used is Doxorubine and Cisplatin (54). Emulsion preparation is essential, and one of the most important steps is using the perfect drug/oil ratio. Most authors recommend 1:2 to 1:3 ratio (56,64,65). The drug should be first pushed towards the Lipiodol®UF. A minimum of 20 pumping exchanges is required to promote the production of "large" droplets with a target size of 70–100 µm (62). Following emulsion injection, the tumor vascular bed should be saturated (66). The visualization of peripheral portal branches around the tumor during cTACE has been recognized as a predictive factor for tumor response to cTACE and is associated with lower local recurrence rates particularly in tumors less than 5 cm (67,68). Additional embolization after administration of the emulsion, to provoke tumor ischemia and prevent drug washout has shown better results when compared to injecting the emulsion alone and is recommended by majority of interventionalists (69). Different embolic agents can be used, including gelatin sponge, polyvinyl alcohol, or calibrated microspheres (70). The recommended particles size is 100–300 µm for non-resorbable calibrated microspheres, since it allows both distal occlusion (intra-tumoral ischemia) and preservation of the segmental arteries patency (extra-tumoral arteries) and limits the risk of complications such as biliary ischemia or pulmonary embolism (71,72).

Based on tumor assessment and liver function, cTACE can be repeated at intervals of 2–3 months and that it should be stopped when there is no residual viable tumor, or when there is liver impairment, serious complications, or progression, despite adequate drug administration (10).

cTACE should be performed as selective as possible. This maximizes the anti-tumor effect and minimizes collateral damage to surrounding parenchyma (73,74). Selective embolization leads to significantly higher levels of tumor necrosis and a higher rate of complete necrosis in comparison with lobar cTACE and has demonstrated a significant survival benefit (75).

Reported objective tumor response rate for cTACE is within 50% with OS of 70% at 1 year, 52% at 2 years, 40% at 3 years, and 32% at 5 years. Median OS is 19.4 months and median time to progression ranges from 3.1 to 13.5 months (54).

DEB-TACE

DEB-TACE corresponds to the administration of calibrated microspheres onto which chemotherapeutic medication, generally an anthracycline for HCC (doxorubicin, epirubicin, idarubicin), is loaded or absorbed with the intention of sustained *in vivo* drug release (76,77). The recommended standard size of microspheres is 100–300 µm since smaller microspheres increase the risk of biliary complications (55,78).

The PRECISION V randomized trial found higher rates of complete response, objective response, and disease control with DEB-TACE than with the cTACE (79). However, the hypothesis of superiority was not met. In the 67% of patient with more advanced disease (Child-Pugh B, ECOG 1, bilobar disease or recurrent disease) objective response and disease control rates were statistically higher in the DEB-TACE group (79). In the PRECISION Italia randomized trial, DEB-TACE was compared with cTACE and no differences were found in local and overall tumor response between the two groups. Both arms had a median time-to-tumor progression of 9 months and the 1- and 2-year survival rates were also similar: 86.2% and 56.8% after DEB-TACE and 83.5% and 55.4% after TACE (80). A meta-analysis, including 4 RCTs and 8 observational studies found non-significant trends in favor of DEB-TACE over cTACE for 1-, 2- and 3-year survival (81).

The benefit of the administration of a chemotherapeutic agent remains debated. A RCT compared the outcome of TAE using microspheres alone with DEB-TACE using doxorubicin-eluting microspheres (52). No significant difference in RECIST response, median progression free survival and OS (19.6 in TAE group *vs.* 20.8 months in DEB-TACE group) was detected (52).

Indication

Based on updated BCLC:

(I) BCLC-0 and BCLC-A that are not surgical candidates (6).
- ❖ Recommended in patients with preserved liver function, PS score of 0, no extrahepatic spread and no vascular invasion.
- ❖ Not surgical candidates and LT candidates with a waiting list > 6 months

(II) BCLC-B group, in patients without the option of LT, who have preserved portal flow and defined tumor burden (well-defined nodules) with feasible selective access to feeding tumor arteries (6).
(III) Small HCC, difficult to treat with ablation due to high-risk location or medical comorbidities.

Based on HKCL staging system:

(I) Recommended in patient with no extrahepatic vascular invasion or metastasis, with PF 0–1.
(II) Stage IIIa and stage IIIb: unresectable, large or multifocal HCCs, with no vascular invasion or extrahepatic spread, and with satisfactory liver function (Child-Pugh A or B).
    ❖ These patients are Child-Pugh B, with intermediate tumor <5 cm, either >3 tumor nodules or with intrahepatic venous invasion, or tumors larger than 5 cm, ≤3 tumor nodules, and no intrahepatic venous invasion.
    ❖ Locally advanced tumor sizes up to 5 cm, >3 tumor nodules and with intrahepatic venous invasion, or >5 cm, >3 tumor nodules or/and with intrahepatic venous invasion, or diffuse tumor) (7,10).

Contrary to BCLC system, for which macrovascular invasion is always a contraindication for TAE, TACE and DEB-TACE, the Hong Kong consensus statements considered that these embolization techniques can be performed in patients with unresectable HCC with segmental vein invasion.

Contraindications

No absolute contraindications have been recognized by the society of interventional radiology (SIR) (77). Unlike the SIR, several absolute contraindications for TACE are listed in CIRSE Standards of Practice guidelines including portal vein neoplastic thrombosis or hepatofugal blood flow, impaired hepatic function (Child-Pugh B8 or greater), poor performance status (PF ≥2), contraindication for arteriography (uncorrectable thrombocytopenia, coagulopathy, severe renal insufficiency or severe reaction to contrast media) (55).

Relative contraindications based on SIR guidelines are:

(I) Inability to undergo arteriography.
    ❖ Due to uncorrectable thrombocytopenia, coagulopathy, renal insufficiency, or severe allergy to contrast).
(II) Decompensated liver disease or liver insufficiency (total bilirubin >3.0 mg/dL).
(III) Poor performance status (PS ≥3).
    ❖ Poor performance status: PF ≥2 is an absolute contraindication based on CIRSE Standards of Practice guidelines (55).
(IV) Large tumor burden (>50% liver replacement by tumor, diffuse infiltrative tumor).
(V) Biliary abnormality (obstruction, biliary-enteric anastomosis, or indwelling biliary stent).
(VI) Active systemic infection.
(VII) Main portal vein thrombosis.
    ❖ Neoplastic thrombosis in the portal vein or hepatofugal blood flow is an absolute contraindication based on CIRSE Standards of Practice guidelines (55).
(VIII) Life expectancy <3 months.
(IX) Contraindication to chemotherapy agent that may be used in TACE.
(X) Poor hepatic arterial flow due to atherosclerosis or damaged vessels.
(XI) Poor tolerance of prior procedures (77).

Complications

Post-embolization syndrome (PES) is characterized by fever, pain, nausea, vomiting, and fatigue. It generally resolves within the first two weeks after treatment. It is not considered a complication, but rather an expected outcome, occurring in about 80% of cases (55,77). Procedure related complications are divided in two groups of hepatic and extrahepatic complications. Hepatic complications are hepatic failure, liver infarction, biloma and liver abscess. Liver abscess is more common in patient with compromised sphincter of Oddi including patients with history of sphincterotomy and bilio-enteric anastomosis. History of transpapilary biliary drainage or biliary stent across the papilla are also considered as sphincter compromise and thus risk factors for post treatment liver abscess. Extrahepatic complications include cholecystitis, hematologic suppression, pulmonary embolism, gastrointestinal ulceration, or hemorrhage, contrast induced nephropathy or acute renal failure, and death (55,77).

Combination of ablation with embolization

TAE or TACE prior to thermal ablation is mainly performed for solitary HCC >3 cm and <5 cm, to increase tumor control (10,40,77). The embolization of the vessels within and adjacent to the tumor can indeed reduce the heat loss due to heat-sink effects and increase the

therapeutic effect of thermal ablation (82). Lipiodol®UF accumulation in the tumor in TACE and particle/contrast retention in TAE, helps with targeting the tumor for ablation when using CT or CBCT is used for guidance. A systematic review and meta-analysis, that included 8 trials suggested that RFA plus TACE was associated with a significant advantage in recurrence-free survival and OS for intermediate and large HCCs (83). Higher 1-, 3-, and 5-year OS were also found with the use of TACE plus RFA compared to RFA or TACE alone in another meta-analysis, including 21 studies (84). TAE plus ablation has been compared to surgical resection in HCC patients with tumors up to 7 cm and has demonstrated to be as effective as surgery with similar survival outcomes (85).

TARE

TARE, also called selective radiation therapy (SIRT), consists in the intra-arterial delivery of radioactive substances such as 131-Iodine-labelled Lipiodol or microspheres containing Yttrium-90 (Y90) or more recently Holmium-166 (Ho166) (86-88). Both Y90 and Ho166 being beta-emitting radionuclides (89). Close collaboration between interventional radiologists, nuclear medicine specialists, radiopharmacists, and physicists, is necessary to carry out this treatment. Currently, the most popular radioactive agents for TARE are resin Y90 and glass Y90 microspheres.

Indication

(I) BCLC-0 patients.
- ❖ TARE is considered as effective as TACE and can be proposed when ablation and resection are not feasible.
- ❖ This new recommendation is based on the results of the LEGACY study, and therefore TARE is recommended only for single HCC ≤8 cm (6,90).

(II) BCLC-A patients.
- ❖ Patients who are not candidates for the first recommended approaches and if they meet the LEGACY inclusion criteria (6,90).
- ❖ In some BCLC-A patients with large tumor and small future liver remnant, radiation lobectomy could be considered to increase remnant liver volume.

(III) Bridge to transplant in LT candidates.
- ❖ TARE can be considered in LT candidates with a waiting list longer than 6 months (6).

In the new 2022 update, no role for TARE is recognized for BCLC-B and BCLC-C patient.

TARE is not mentioned in the 2014 HKLC staging system. However, the Hong Kong consensus statements for the management of unresectable HCC recognizes the role of TARE as a bridge to LT in suitable candidates, for Child-Pugh A patients with multifocal or large HCC, for HCC >5 cm not amenable to resection or ablation, and for Child-Pugh A and selected Child-Pugh B patients with small burden HCC not responding to cTACE (10). In contrast to 2022 BCLC, in which there is no role for TARE (or other locoregional therapy) in presence of vascular invasion, the Hong Kong consensus recognizes the usefulness of TARE for Child-Pugh ≤7 patients with vascular invasion, and liver dominant disease, and who have bilirubin <2 mg/dL (10).

Contraindications

Absolute contraindications to TARE, as listed by the European Association of Nuclear Medicine (EANM) include:

(I) Pregnancy and breastfeeding.
(II) Life expectancy <3 months.
(III) Liver failure (i.e., ascites, icterus, encephalopathy).
(IV) Disseminated extrahepatic malignant disease.
(V) Extrahepatic perfusion that cannot be corrected.
- ❖ The gallbladder, lymph nodes or the falciform ligament are excluded (89).

Relative contraindications are as follows (89):

(I) Child-Pugh >7.
(II) High intrahepatic tumor burden.
(III) High extra-hepatic tumor burden.
(IV) Main portal vein thrombosis with poor targeting evidenced by scintigraphy.
(V) Acute or severe chronic renal failure (creatinine clearance <30 mL/min).
(VI) Contraindications to hepatic artery catheterization (uncorrectable coagulation disorder, renal failure, severe allergy to contrast media, or vascular abnormalities)
(VII) Lung shunting, determined by pretreatment ^{99m}Tc-MAA scintigraphy, that would lead to a lung dose >30 Gy per session or >50 Gy cumulatively.
- ❖ The latter does not represent an absolute contraindication, as lung shunting is overestimated by planar ^{99m}Tc-MAA and no reliable safety limit has yet been established (89).

(VIII) Caution is warranted in patients with history of prior liver EBRT.

- ❖ TARE is considered safe only in patients with limited exposure to prior EBRT. A study found that the fraction of liver exposed to ≥30 Gy (V30) was a strongest predictor for post TARE hepatotoxicity (91).

Outcomes

A randomized phase II trial, including BCLC A or B patients compared TARE with TACE and found no significant difference in OS between the two group, with median OS of 18.6 months for TARE and 17.7 months for cTACE (92). A meta-analysis, including 9 observational studies and 2 RCT compared the effect and safety of cTACE and TARE (93). A better 2-year OS rate was found for TARE in the observational subgroup. TARE resulted also in better OR rates, with a lower risk of adverse events (93). However, in a recent meta-analysis that evaluated the effects of DEB-TACE, TARE and cTACE, the comparison of DEB-TACE with TARE found that DEB-TACE had a better OS than TARE at 2 years, whereas TARE had significant better OS than cTACE at 2 and 3 years (94).

TARE has been used in treatment of advanced HCC both alone and in combination with systemic options including tyrosine kinase inhibitors (TKI) and checkpoint inhibitors (CPI). The SARAH trial, in patients with locally advanced or intermediate-stage HCC, and SIRveNIB trial, in locally advanced HCC, both evaluated sorafenib *vs.* Y90-resin TARE (95,96). OS did not differ significantly between the TARE and sorafenib groups, with median OS of 8.0 and 8.8 months in the TARE groups and 9.9 and 10.0 months in the sorafenib groups, respectively. However, there were significantly fewer grade 3–4 side effects in the TARE groups (95,96). The palliative cohort of SORAMIC trial included patients with advanced HCC not eligible for TACE who were randomized to Y90-resin TARE plus sorafenib or sorafenib alone (97). OS survival did not differ significantly between the two groups. Different authors proposed explanations for these negative results, including the fact that the work-up phase was performed after rather than before randomization, which is why a large proportion of patients in the TARE arms did not actually receive TARE, and the lack of personalized dosimetry (98-100).

Dosimetry has an important impact on the outcome of TARE. A study that evaluated the impact of dosimetry on TARE outcome found a median OS of 18.2 months for patients with portal vein invasion (101). Among these patients, a much higher median OS (24.5 months) was observed in the subgroup of patients in which the tumor radiation dose was >205 Gy, highlighting the importance of pre-treatment dosimetry (101). In a retrospective study, including HCC patients with right, left, and/or main portal vein invasion, those patients treated with ablative TARE, with high radiation dose selectively delivered to the hepatic segment or lobe where the tumor was located, presented significantly longer median OS compared to the group treated with lower dose: 45.3 *vs.* 18.2 months (102).

A secondary analysis of SARAH trial data showed that higher tumor radiation-absorbed dose computed at Tc99m MAA SPECT/CT was associated with better OS and disease control. The participants who received at least 100 Gy had significantly longer OS than those who received <100 Gy; median OS 14.1 *vs.* 6.1 months. The recent DOSISPHERE-01 randomized phase II trial also highlighted the importance of personalized dosimetry which significantly improved the objective response rate and median OS (26.7 *vs.* 10.7 months) in patients with locally advanced HCC compared to standard dosimetry approach with Y9 glass microspheres (103). Personalized therapeutic activity prescription in TARE that aims to maximize tumor response while sparing non-target tissues from undesired toxicity by tailoring the treatment according to patient-specific parameters is also recommended with Y-90 resin microspheres (104).

Radiation segmentectomy and lobectomy

There is a growing interest in the use of higher radiation doses to achieve segmentectomy or lobectomy. An ablative dose is delivered into the target segment or lobe. This approach is used to treat localized disease with a curative intent, such as BCLC-0 and BCLC-A HCC patients (100,104,105). Radiation segmentectomy has resulted in high response rates and longer PFS (90,106,107). The higher dose that is delivered increases the rate of complete pathologic necrosis, making this approach useful in the setting of bridging/downstaging to LT (108,109). It is also of interest in patients with unresectable solitary HCC not amenable to ablation, such as nodules in suboptimal location for ablation (110,111). As long as the volume of parenchyma infused is low compared to the total liver volume, this approach is considered safe (107,112,113). The use of cone-beam CT or angio-CT to precisely assess the perfused volume is necessary to allow accurate dosimetry calculations (104,105,114).

For patients presenting with unilobar disease, with uni- or multi-focal HCCs, for whom resection is often

not possible due to small anticipated future liver remnant, radiation lobectomy approach is a reported effective option (100,104,105). The high radiation dose delivered to the lobe may induce hypertrophy of the contralateral lobe, while allowing tumor control or downstaging of the treated lesions (115-117). This approach could represent an alternative to portal vein embolization (118,119).

Complications

Common side effects are usually mild to moderate fatigue, nausea, abdominal pain, fever, chills, transitory elevation of liver enzymes and/or decline in lymphocytes and occur in approximately 10% of patients (89).

The main severe complications are relatively rare, occurring <5%, and include the radioembolization-induced liver disease (REILD) and non-target irradiation. The REILD syndrome combines hyperbilirubinemia, hypoalbuminemia, ascites, that typically occur 2–6 months after treatment, with no evidence of disease progression (89,120,121). It results from the excessive radiation to the functional liver parenchyma.

Non-target irradiation occurs when microspheres are delivered directly or indirectly (reflux) into extra-hepatic arteries, that can lead to radiation gastritis, gastrointestinal ulceration, upper gastrointestinal bleeding, and pancreatitis. Radiation pneumonitis can occur in presence of a significant lung shunt (89).

Conclusions

The therapeutic armamentarium for HCC includes different LRT options. Multidisciplinary approach is highly recommended when deciding on the best treatment option. Additionally, the level of experience of each center and the available techniques should be considered.

LRT has been recommended in treatment of different stages of HCC, ranging from single small HCC in BCLC-0 patients, to more advanced stages including multifocal liver disease, BCLC-B patients. LRTs can downstage HCC to resection or can be used to bridge to transplant. Although the 2022 BCLC, unlike the Hong Kong consensus, does not suggest LRT as an option for treatment of advanced stage HCC, the literature provides encouraging results for TARE in treating patients with portal vein invasion and therefore is beneficial to these patients.

There are overlaps in the indications of the different LRTs and techniques. For instance, although ablation is recognized as the standard of care for most BCLC-0 HCC patients and BCLC-A with unresectable HCC, ablative TARE with radiation segmentectomy may provide curative treatment, particularly for lesions whose location is not amenable to ablation.

Combination of LRTs or LRT with resection could also be applicable in some patients. Further studies are needed to determine the most appropriate therapy for each individual case. With the recent advances in immunotherapy treatments, including monoclonal antibodies targeting immune checkpoints, there is a growing interest in combining LRT with immunotherapy. In addition to tumor cells destruction, LRTs also have an immunomodulating role by releasing tumor-associated antigens. This can lead to synergic relationship with immunotherapy. Trials combining locoregional treatment with immunotherapies are currently underway, with their results being eagerly awaited (122,123).

Overall, in our opinion, percutaneous ablation remains the best locoregional therapy for small single HCCs <2–3 cm or in the presence of less than 3 nodules <3 cm, whereas radioembolization is particularly interesting for larger single nodules, in the case of unilobar disease or in the presence of a nodule not accessible to ablative treatment. The role of TAE/TACE remains multinodular disease, especially when super selective therapy is possible. The role of these therapies is much more limited in cases of tumor thrombosis, diffuse and infiltrative disease, with nevertheless, possible good results obtained by radioembolization in the presence of tumor thrombosis.

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Footnote

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