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Multifocal hepatocellular carcinoma: a narrative review assessing treatment options from the interventional radiologist's perspective※

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Background and Objective: It is estimated that 35–40% of hepatocellular carcinoma (HCC) patients present with multiple nodules at the time of diagnosis. Treating multifocal disease is difficult given patient population heterogeneity. Multiple interventional radiological (IR) options, including ablation, transarterial chemoembolization (TACE), and transarterial radioembolization (TARE), are available, each with its own merits and limitations. Our aim is to explore the current state of the literature to identify where each of these options is best applied to multifocal HCC management.

Methods: A narrative literature review of 107 papers was performed in PubMed. Articles from 2010 and newer were used for clinical data and for classification/scoring system details. The majority of the keywords for searches include the treatment modality name alongside terms such as "HCC", "multifocal", or "multinodular".

Key Content and Findings: Ablation is a curative option for Barcelona Clinic Liver Cancer (BCLC) A disease and is appropriate when liver transplantation (LT) is impractical. It is ideal in disease with ≤3 nodules (each <3 cm) preferably confined to one segment. TACE [conventional TACE (cTACE), drug-eluting bead TACE (DEB-TACE), balloon-occluded TACE (B-TACE), and less so hepatic arterial infusion chemotherapy (HAIC)] is the major workhorse for multifocal BCLC B disease, in pre-transplant downstaging, and in advanced disease palliation. The Kinki BCLC B subclassification can guide TACE subtype selection. TACE response can be assessed over 2–3 sessions per modified Response Evaluation Criteria in Solid Tumors (mRECIST) and patient session tolerance. TARE is an option for BCLC C disease, with BCLC A/B applications limited by radiation induced liver disease (RILD). Pseudo-ablative techniques like sub-selective TARE (sTARE) are promising but are unproven and less useful in multinodular disease. Finally, combination therapies [TACE + ablation, liver resection (LR) + ablation/TACE] are an exciting option but warrant further study.

Conclusions: Multifocal HCC remains challenging to manage. While BCLC is a useful starting point, the patient's tumor imaging characteristics and clinical circumstances must be considered when selecting the appropriate treatment modality.

Keywords: Hepatocellular carcinoma (HCC); ablation; transarterial chemoembolization (TACE); transarterial radioembolization (TARE); multifocal

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Introduction

Background

Primary liver cancer is the fifth most common cancer in the world and the third leading cause of cancer-related mortality (1). Of these primary liver cancer cases, 85–90% are attributable to hepatocellular carcinoma (HCC) (2). Unfortunately, 35–40% present with multiple nodules at the time of HCC diagnosis (3,4).

Multifocal HCC can be categorized into several stages, each with its own recommended treatment options. Early stage [Barcelona Clinic Liver Cancer (BCLC) A] multifocal HCC presents with up to 3 nodules (none >3 cm) and without macrovascular invasion, extrahepatic spread, or cancer-related symptoms [performance status (PS) 0] (5). Typical treatments for BCLC A multifocal HCC include liver transplant or ablation. Patients with multifocal HCC exceeding BCLC A criteria with preserved liver function and without cancer-related symptoms, extrahepatic disease, or vascular invasion are classified as intermediate or BCLC B stage. Within this diverse group, three subgroups are described: (I) those with well-defined HCC nodules that could be candidates for liver transplantation (LT) if they meet the "Extended Liver Transplant" criteria; (II) those with preserved portal flow and defined tumor burden that are candidates for locoregional therapy if LT is not possible; and (III) those with diffuse, infiltrative, extensive HCC liver involvement but who are still within BCLC B limits. It is well known that infiltrative HCC has worse outcomes than nodular HCC, with higher incidence of extrahepatic metastases, vascular invasion, higher alpha-fetoprotein (AFP) levels, and significant clinical symptoms (6). Most patients in this last subgroup do not benefit from transarterial chemoembolization (TACE) and systemic therapy is advised (5). Although recent guidelines only recommend TACE or LT for BCLC A/B patients, other options such as liver resection (LR) and other locoregional therapies have been successfully used (7). Each of these treatment options has its own merits and limitations that need to be carefully evaluated.

Rationale and knowledge gap

In patients with multifocal disease, both clinical and imaging factors must be considered before recommending a specific therapy. Clinically, the tumor burden, liver function, AFP levels, PS, age, pre-existing comorbidities, and any cancer-related symptoms need to be reviewed. From the imaging standpoint, the tumor number, size, and location are salient considerations, but other aspects, such as vascular invasion or extrahepatic disease also deserve attention. A rigorous multidisciplinary approach that considers all these factors in the treatment process is essential to offer each patient the best possible individualized therapy (5).

Objective

The objective of this narrative review is two-fold: first, to present an overview of each of the interventional radiology modalities available to treat multifocal HCC [broadly ablation, TACE, and transarterial radioembolization (TARE)]; and second, to identify suitable multidisciplinary guidelines to aid clinicians in selecting the ideal treatment option tailored to a given patient's clinical and imaging parameters and to objectively assess treatment response. We present this article in accordance with the Narrative Review reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-23-294/rc).

Methods

A narrative review of 107 English language papers from 1993 to 2022 was performed. Articles older than 2010 helped establish a modality's historical and procedural background, while newer articles provided recent clinical data and updated classification/scoring details. The literature search itself was conducted across the PubMed database. For each treatment option, the modality's name (type and/or subtype) was used alongside terms such as "HCC", "multifocal", or "multinodular". For combination therapies, the word "combined" was added to the search. When appropriate, classification and scoring system nomenclature ["BCLC", "Kinki", "up-to-7"/"up-to-seven", and Child-Pugh (CP) status modifiers] were included. Additional keywords used to answer specific clinical questions include BCLC stage (either "A/B/C" or "early/intermediate/advanced"), "downstaging/bridging" (in the context of transplant), as well as "palliative/palliation" (for advanced disease). Our detailed search strategy is presented in more detail in *Table 1*.

Treatment options

Given the unique challenges that the presence of multiple nodules poses to treatment, we sought to review the various treatment modalities available in the interventional

Table 1 The search strategy summary

Items	Specification
Date of search	2022/10/9–2023/6/18
Databases and other sources searched	PubMed
Search terms used	"Hepatocellular Carcinoma" AND ("Multifocal" OR "Multinodular")
	"Hepatocellular Carcinoma" AND ("Multifocal" OR "Multinodular") AND "Ablation"
	"Hepatocellular Carcinoma" AND ("Multifocal" OR "Multinodular") AND ("Radiofrequency Ablation" OR "RFA")
	"Hepatocellular Carcinoma" AND ("Multifocal" OR "Multinodular") AND ("Microwave Ablation" OR "MWA")
	"Hepatocellular Carcinoma" AND ("Multifocal" OR "Multinodular") AND "Cryoablation"
	"Hepatocellular Carcinoma" AND ("Multifocal" OR "Multinodular") AND "Laser Ablation"
	"Hepatocellular Carcinoma" AND ("Multifocal" OR "Multinodular") AND ("Transarterial Chemoembolization" OR "TACE")
	"Hepatocellular Carcinoma" AND ("Multifocal" OR "Multinodular") AND ("Transarterial Radioembolization" OR "TARE" OR "Selective Internal Radiation Therapy" OR "SIRT")
	"Hepatocellular Carcinoma" AND ("Transarterial Chemoembolization" OR "TACE") AND "Kinki"
	"Hepatocellular Carcinoma" AND ("Transarterial Chemoembolization" OR "TACE") AND ("up-to-7" OR "up-to-seven")
	"Hepatocellular Carcinoma" AND ("Transarterial Chemoembolization" OR "TACE") AND ("BCLC B" OR "intermediate")
	"Hepatocellular Carcinoma" AND ("Transarterial Chemoembolization" OR "TACE") AND ("downstaging" OR "bridging")
	"Hepatocellular Carcinoma" AND "ALBI"
	"Hepatocellular Carcinoma" AND ("Transarterial Chemoembolization" OR "TACE") AND "ALBI"
	"Hepatocellular Carcinoma" AND ("Transarterial Chemoembolization" OR "TACE") AND "ART"
	"Hepatocellular Carcinoma" AND ("Transarterial Chemoembolization" OR "TACE") AND "Transaminitis"
	"Hepatocellular Carcinoma" AND ("Multifocal" OR "Multinodular") AND ("Transarterial Radioembolization" OR "TARE" OR "Selective Internal Radiation Therapy" OR "SIRT") AND ("palliation" OR "palliative")
	"Hepatocellular Carcinoma" AND ("Multifocal" OR "Multinodular") AND ("Transarterial Radioembolization" OR "TARE" OR "Selective Internal Radiation Therapy" OR "SIRT") AND "sorafenib"
Timeframe	1993–2022
Inclusion and exclusion criteria	Inclusion criteria: English language research articles (preferring meta-analyses and RCTs, with scattered retrospective analyses as needed) and review articles (for guidelines and historic background) about multifocal HCC and its various treatment modalities with a strong interventional radiology focus (ablation, TACE, TARE, and combination therapies)
	Exclusion criteria: any low-reliability articles or clinical data collected before 2010
Selection process	Literature review was conducted independently by Dr. Anish Narayanan, Dr. Andres Garza-Berlanga, and Dr. Jorge Lopera. The data selection is the resulting intersection of the searches of all three authors

RFA, radiofrequency ablation; MWA, microwave ablation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; ALBI, albumin-bilirubin; ART, assessment for retreatment with TACE; SIRT, selective internal radiation therapy; RCTs, randomized controlled trials; HCC, hepatocellular carcinoma.

radiologist's armament. In this paper, we will discuss four options: ablation, TACE, TARE, and combination therapies.

Ablation

Many ablative techniques have been developed to treat HCC. Outside of surgical options such as hepatic resection or transplant, ablation is uniquely curative. Ablation techniques include radiofrequency ablation (RFA), microwave ablation (MWA), lasers, cryoablation (CA), electroporation, and, more recently, histotripsy (8). Ablation, usually RFA or MWA, is mostly limited to BCLC A in multifocal HCC.

In conventional RFA, a thin electrode probe emitting radiofrequency waves is inserted into the tumor's center. The ablation target acts as a resistor, completing the electrical circuit. This current agitates ions around the electrode tip, resulting in focal frictional heating that is conducted deeper to adjacent tissues and causes irreversible heat-induced cell injury and death (9). Conventional monopolar techniques provide a limited necrotic volume, even with multiple ablation spheres (10). As a result, 5-year local tumor progression (LTP) rates with the conventional RFA approach are as high as 27% (11). This problem is further exacerbated with subcapsular tumors, which are prone to capsular breach and tumor seeding (12). The residual tumor rate in thermal ablation procedures ranges from 0.47% to 12%, likely due to microvascular invasion and satellite micro-metastases within 5–10 mm of the tumor. For this reason, a peritumoral margin of 10 mm is recommended (12). Some providers have used "no-touch" techniques to overcome this limitation, whereby multiple bipolar electrodes (NTmbpRFA) are placed at the tumor periphery rather than placing a monopolar (MonoRFA) electrode intratumorally (11,12).

Compared to RFA, MWA is newer and promises reduced treatment times and larger ablation zones, while retaining RFA's ideal properties such as causing heat-induced cell death (13). In a 2020 meta-analysis by Facciorusso *et al.*, MWA and RFA were compared across a number of outcome parameters. No significant difference in terms of the complete treatment response [relative risk (RR): 1.01, 95% confidence interval (CI): 0.99–1.02], 5-year OS (RR: 0.91, 95% CI: 0.81–1.03), and local recurrence (RR: 0.70, 95% CI: 0.43–1.14) rates was noted. However, both the distant recurrence rate (RR: 0.60, 95% CI: 0.39–0.92) and 5-year DFS (RR: 3.66, 95% CI: 1.32–42.27) were both significantly in favor of MWA. Complication rates were similar between both treatment modalities (RR: 1.06, 95% CI: 0.48–2.34) (14). On the other hand, LR suffered more major complications than MWA (22.1% *vs.* 5.9%; P=0.004), likely due to deep (≥3 cm from liver capsule) tumors resulting in increased blood and normal liver parenchyma intra-operative losses (15). However, this latter study only explored patients with single HCC lesions ≤3 cm, not multifocal disease.

Other ablation treatment modalities have been developed in addition to RFA and MWA. One such option is CA. This uniquely hypothermic technique has multiple benefits, enabling direct ablation zone visualization as an ice ball, not causing severe pain, and avoiding gallbladder and vascular injury risks (16). Since then, a 2021 meta-analysis of 6 randomized controlled trials (RCTs) and 13 observational studies found no significant difference in 3-year OS between CA and RFA [hazard ratio (HR): 0.90, 95% CI: 0.48–1.64] (17). However, adoption of this modality has been limited by the potential life-threatening risk of cryoshock, where melting of the ablation ice ball releases cellular debris into the systemic circulation and results in multi-organ failure, severe coagulopathy, and disseminated intravascular coagulation (18).

Another potential option is laser thermal ablation (LTA). By focusing laser optical fibers onto a target lesion, temperatures >60 ℃ are achieved, resulting in coagulative necrosis (19). While some report that LTA could serve a role ablating multiple small or variably sized lesions, clinical adoption is limited and few studies have been performed (20-22). A recent [2015] randomized control trial comparing RFA and LTA by Di Costanzo *et al.* found similar complete tumor ablation rates (RFA: 97.4%, 95% CI: 91.0–99.3%; LTA: 95.7%, 95% CI: 88.1–98.5%) and comparable (P=0.591) mean time to LTP (RFA: 42.0 months, 95% CI: 36.8–47.3 months; LTA: 46.7 months, 95% CI: 41.5–51.9 months). The mean OS was nearly identical in both arms (RFA: 42.8 months, LTA: 42.2 months, P=0.346), with 3-year survivals of 89% and 80% in the RFA and LTA arms (23). While initial results are promising, further study is required to verify LTA efficacy in managing HCC.

Recently, BCLC 2022 recommended ablation for ≤3 nodules (each ≤3 cm) as an alternative for patients with preserved liver function who are not candidates for LT (5). In general, resection and ablation are more limited in multifocal HCC than with solitary tumors given the tumor's tendency for aggressive behaviors such as intrahepatic metastasis, multicentric recurrence, higher

vascular invasion, and more advanced cirrhosis (5,24). Most studies suggest that a higher tumor number increases the likelihood of having more radiologically occult lesions. In a study by Aufhauser *et al.*, of 3,696 patients from the United States who underwent LT, 37% had occult metastasis on explant pathology (25).

A study of 150 patients by Zhang *et al.* evaluated the overall survival (OS) and relapse-free survival (RFS) in 154 HCC patients who met Milan criteria with multifocal disease and without extrahepatic disease or vascular invasion (26). In this study, 77 patients had a percutaneous RFA, 19 had laparoscopic approach RFA, and 58 had open surgical RFA. The 1-, 3-, and 5-year OS rates were significantly higher (P=0.001) in patients with tumors in the same segment (93.2%, 77.4%, and 50.8%) than those in different segments (82.4%, 54.8%, and 23.0%). This also held for 1-, 3-, and 5-year RFS rates (same segment: 84.5%, 49.4%, and 32.5%; different segments: 78.4%, 36.4%, and 7.6%). These investigators also noted that while the RFS rates for patients with two tumors was like those reported in single tumor patients at the same time endpoints (85.2%, 44.7%, and 24.0% respectively), having three tumors resulted in worse OS and RFS rates.

In a Western study by Preel *et al.*, 281 HCC patients were separated into unifocal (n=216), bifocal (n=46), and trifocal (n=16) tumor groups and were treated with RFA (43%) or MWA (57%) (27). During follow-up, 145 patients (51.6%) developed at least one distant recurrence, including 94 unifocal (43.5%), 37 bifocal (75.5%), and 14 trifocal (87.5%) patients. The median RFS for the unifocal, bifocal, and trifocal groups were 23.3, 7.7, and 5.2 months. The 1-, 2-, and 3-year OS rates were 96.9%, 83.9%, and 74.7%. This study showed that patients with more tumors had higher distal recurrence and shorter OS rates than those with fewer tumors. Early (within 1 year) and very early (within 6 months) recurrence rates were also higher in the bifocal and trifocal patients compared with the unifocal ones. The elevated rate of very early recurrence (50% for trifocal, 39% for bifocal, and 11% for unifocal) reveals a high frequency of radiologically occult metastases. The OS of trifocal disease was particularly poor, ranging between that of BCLC A and of BCLC B patients, resulting in the authors concluding that LT should be considered earlier in this sub-population.

A large Japanese cohort study by Shiina *et al.* found similar long-term survival rates between patients with 2–3 tumors (5-year: 54%, 10-year: 20%) and those with ≥4 tumors (5-year: 53%, 10-year: 17%) treated with RFA. Both were much shorter than the 64% and 32%, 5- and 10-year survival of patients with a solitary tumor (24). However, in this study, the group used a combination of TACE and ablation for patients with ≥4 tumors or tumors >3 cm, severely limiting the evaluation of ablation's utility as a single therapy for patients with multiple and larger tumors.

TACE

Approximately 20% of all HCC patients present with intermediate-stage HCC (28). TACE, has generally been considered the first line treatment option for intermediate HCC ever since the BCLC guidelines were first published in 1999. However, this blanket recommendation fails to capture the nuances of the various TACE methodologies available and the characteristics of the patient population that these techniques treat.

In conventional TACE (cTACE), a chemotherapeutic agent (doxorubicin or alternatively cisplatin) is emulsified in iodized oil (usually lipiodol) and locally and intra-arterially injected (29,30). The oil is preferentially absorbed by cancer cell wall pumps and transported intracellularly, where it is retained longer in tumoral cells (up to 1 year) than normal liver cells (around 4 weeks) (30). This is followed with careful vessel embolization with particulate agents (30). The result is a cytotoxic effect from the chemotherapeutic agent that is potentiated by local ischemia from the embolization process (29). When performing cTACE, selective/superselective catheterization is ideal to reduce total lipiodol dose and minimize hepatotoxicity (31). Selective TACE yields a higher degree of tumoral necrosis (67.0%±28.7%) than lobar treatments (48.1%±31.4%, P=0.029) in patients with multiple sub-5 cm tumor nodules (32). Furthermore, in HCC patients with tumors <7 cm and ≤5 lesions, the 5-year OS is significantly (P=0.0034) better with selective rather than non-selective embolization (40.8% *vs.* 25.7%) (33).

cTACE has several limitations, including lipiodol's liquid mobility preventing chemotherapeutic agent concentration and the lack of sustained and controlled chemotherapeutic agent release (30). To improve cTACE's effectiveness, practitioners have used drug-eluting bead TACE (DEB-TACE). In DEB-TACE, uniformly sized microbeads are delivered to target tissues and release the chemotherapeutic agent over a prolonged (1 week) duration, allowing higher targeted tumoral drug delivery and lower toxicity (30,34).

While 75 mg of doxorubicin loaded in 2 mL vial of beads is adequate for patients meeting the Milan criteria, patients with multifocal disease usually fall outside of Milan criteria and may require two vials instead (30,35). Smaller

beads (100–300 μm) are preferred in DEB-TACE, as the increased surface area results in higher doxorubicin level delivery and the beads better penetrate the tumor vascular bed's distal vessels for a more targeted embolization (36). Of note, bilobar disease, large tumors, or >50% liver volume tumor burden typically requires two consecutive treatment sessions, 2–4 weeks apart (35,37).

One newer TACE option is balloon-occluded TACE (B-TACE). B-TACE is identical to cTACE, except that a microballoon catheter occludes feeding arteries during embolization, allowing denser lipiodol emulsion accumulation by blocking proximal embolization materials leakage and modifying local hemodynamics at the intrahepatic collateral arteries (38,39). Measuring the balloon-occluded arterial stump pressure (BOASP) is critical, with values >64 mmHg indicating the presence of thick collateral arteries which reduce tumoral lipiodol accumulation (40). One multicenter comparison of B-TACE *vs.* cTACE showed that although the complete response (CR) rate for B-TACE is lower than cTACE for smaller (<3 cm) nodules (56.3% *vs.* 61.9%, P=0.680), B-TACE is superior for intermediate-sized (3–5 cm) nodules (72.3% *vs.* 54.1%, P=0.047) and equally poor for larger (>5 cm) ones (23.1% *vs.* 22.6%; P=1.000) (38).

Finally, for palliation, hepatic arterial infusion chemotherapy (HAIC) can be considered. Rather than performing on-demand chemoembolization, a catheter-port system is percutaneously placed at the hepatic artery. An implanted pump is used to prevent chemotherapeutic agent reflux (41). The port is then accessed regularly in the outpatient setting to refill the pump. Unlike systemic chemotherapy, HAIC exploits the liver's first-pass metabolism, minimizing systemic toxicity (42).

There are several absolute and relative contraindications to TACE. Absolute contraindications include decompensated cirrhosis, reduced renal function, or extensive bilobar disease. Relative contraindications include large (>5 cm) tumors, poor expected survival, impaired portal venous flow, untreated high-risk esophageal varices, and elevated liver enzymes (37,43). Extrahepatic metastatic disease is another relative contraindication, although TACE can be useful as typically the intrahepatic, rather than extrahepatic, disease is lethal (44).

HCC multifocality is a fuzzy term, with differing definitions in the literature of tumor size (>3 to >10 cm), tumor number (4 to >10–20 bilobar tumors), and liver function (CP score 5 to 9) (45). One score that considers both tumor size and number is the up-to-7 criterion, where seven represents the sum of the largest tumor's diameter (in cm) and the number of tumors present. In a retrospective analysis by Mazzaferro *et al.* examining HCC patients who fell outside of the Milan criteria but nevertheless underwent transplantation, patients who met this more relaxed up-to-7 criterion still retained a 5-year OS of 71.2% (95% CI: 64.3–77.0%) (46). When the up-to-7 and the CP scores are combined, the result is a simple BCLC B subclassification system that balances tumor response and post-treatment liver damage. Called the Kinki system, patients are subdivided into B1, B2, and B3 based on their CP score (CP 5–7 or CP 8–9) and up-to-7 criteria (IN or OUT) status (45). When applying the Kinki classification to stage B patients, significant differences (P<0.001) in median OS were noted for the B1 (4.3 years; 95% CI: 3.7–4.9), B2 (2.9 years; 95% CI: 2.2–3.4), and B3 (1.1 years; 95% CI: 0.5–1.8) classes (47). B1 patients (CP: 5–7, up-to-7: IN) are treated with curative intent and, if considered for TACE (alongside resection or ablation), should be presented with superselective cTACE (or alternatively DEB-TACE or B-TACE). B2 patients (CP: 5–7, up-to-7: OUT) are treated with non-curative or palliative intent with DEB-TACE, HAIC, or Sorafenib (or alternatively cTACE). B3 (CP 8–9) patients are split into B3-a (up-to-7: IN) and B3-b (up-to-7: OUT). B3-a patients should be treated curatively with transplant, ablation, or superselective cTACE (or alternatively DEB-TACE, B-TACE, or HAIC). B3-b patients on the other hand should be treated palliatively with HAIC, selective DEB-TACE, or best supportive care (45).

As early as 2003, TACE's survival benefit was known, demonstrating significantly improved 2-year survival compared to contemporary best supportive care for unresectable HCC (48,49). More recent studies have confirmed this, with untreated BCLC stage B patients presenting with an OS of 16 months and with TACE extending patient survival to a median OS of 19–20 months (50). Compared to LR, while TACE sported a lower post-procedural complication rate (18.5% *vs.* 28%, P=0.04), OS rates were statistically (P=0.001) inferior at 1 year (69% *vs.* 84%), 3 years (29% *vs.* 59%), and 5 years (14% *vs.* 37%) (51). However, this may be less applicable to multifocal disease as 77% of the included cases were solitary tumors (51). Even larger meta-analyses such as by Hyun *et al.* in 2018, which showed superior 5-year survival rates for LR *vs.* TACE in BCLC stage B and C patients, enrolled patient populations with predominantly 1–2 larger tumors (52). The observation that TACE is more practical for patients with multifocal disease has been

proven in other subgroup analyses comparing LR to TACE, where although patients with 1–3 tumors showed better 1-, 3-, and 5-year OS rates if they underwent LR rather than TACE, no significant difference was noted for patients with >3 tumors (53).

TACE is often used for pre-transplant downstaging as the majority of HCC patients present outside the Milan criteria (54). One pooled meta-analysis found a downstaging success rate of 48% (95% CI: 39–58%) (54). While both TARE and TACE were used in that meta-analysis, no significant difference in recurrence between these treatments was identified (54). The rate of LT also decreased if patients received ≥3 *vs.* <3 TACE procedures (21.6% *vs.* 48.6%, P<0.001) (55). While this can enable more patients to receive curative options like transplant, the post-transplant recurrence rate of 16% (95% CI: 11–23%) is higher in this group than in patients who initially met transplant criteria (54). This was redemonstrated by Toso *et al.* in 2019, where although downstaged transplanted patients had non-inferior 5-year DFS compared to their non-downstaged counterparts (76% *vs.* 86% using Milan criteria, P=0.258), they had statistically higher recurrence rates (11% *vs.* 1.5%, P=0.001) (56).

Even in BCLC C and CP B patients, TACE significantly improved the median OS compared with BSC (6.0 *vs.* 2.0 months, P≤0.01) (57). When offering palliative TACE, however, the potential benefit must be balanced with the risk of dangerous complications such as post-embolization syndrome (associated with two-fold increased risk of death) and acute liver failure (seen in 13.4% of overall cases and increases to 38% in CP B patients) (58,59). Despite these risks, TACE remains the most frequently used first-line option for both BCLC B and C stages (60).

Following TACE, treatment response must be accurately assessed. Even after consecutive superselective TACE sessions, HCC may remain viable or even undergo progression due to collateral or distal portal venous blood supply (61). Both large (>5 cm) and multiple (>3) tumors were statistically (P<0.05) independently associated with failure to achieve CR after initial TACE (62). Critically, at least two TACE sessions should be performed prior to discontinuing TACE, as approximately half (47%) of patients who do not respond in the initial TACE session achieved a favorable response after the second session (63).

Unfortunately, what constitutes TACE failure remains unclear. A 2022 review article by Zhang *et al.* reviewed the definitions for TACE failure across 23 different studies (61). Laboratory markers have been used to assess TACE response post-treatment. One commonly used scoring system is albumin-bilirubin (ALBI) grade. Initially developed in 2015 by Johnson *et al.*, this simple model offered an evidence-based and globally validated method of assessing liver function in HCC without reliance on subjective consideration of variables such as ascites and encephalopathy (64). Using just the serum bilirubin and albumin, patients were stratified into three grades, each with progressively decreasing median survival (grade 1: 18.5–85.6 months, grade 2: 5.3–46.5 months, and grade 3: 2.3–15.5 months) (64). ALBI has since been applied to the post-TACE setting by Chi *et al.* in 2021. There, it was found that the risk of acute ALBI-grade migration was 24.3% and chronic ALBI-grade migration was 16% for BCLC B HCC patients (65). In particular, migration to grade 3 *vs.* just to grade 2 was directly shown to have an adverse effect on median OS for acute migration (grade 2: 30.9 months, grade 3: 8.9 months, P<0.001) and chronic migration (grade 2: 30.9 months, grade 3: 5.7 months, P<0.001) (65). In the same study, HBV infection and meeting up-to-7 (or the modified up-to-11) criteria were factors for acute ALBI grade migration, while bilobar burden had a high risk of chronic ALBI grade migration (65).

Additional laboratory parameters have also been considered for prognostic use. In a 2021 retrospective analysis by Granito *et al.*, 70 patients (55.7% BCLC B) status post cTACE were evaluated both in the immediate phase with clinical lab values and one month later with modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria to assess radiological response. In this cohort, it was found that transient aspartate aminotransferase (AST) and alanine aminotransferase (ALT) increases of ≥46% and ≥52% respectively were significantly correlated with objective (P=0.03 and P=0.04) and complete (P=0.02 and P=0.02) target lesion treatment responses (66). Given the reported use of superselective technique and lack of clinical symptoms or liver function deterioration post-treatment, this self-resolving transaminitis is likely attributable to tumoral hepatic cytolysis (66) and could serve as a valuable positive prognostic marker to predict cTACE response.

While most accept that insufficient imaging response of treated tumors represents treatment refractoriness, and while standard imaging criteria like mRECIST can follow target HCC lesions over time, contentious factors such as portal vein tumor thrombosis, extrahepatic spread, and interval lesion development remain. While more holistic scores like assessment for retreatment with TACE (ART)

claim to objectively determine TACE failure by weighting factors like CP increase, AST change, and target tumor imaging response, multiple follow-up articles have reported that ART failed to predict OS in their local populations, likely due to patient heterogeneity (67-70). Zhang's review (61) consensus therefore suggested assessing target tumor response after three TACE sessions, with several additional recommendations regarding tumor response. If target tumor disease progressed, then TACE failed, and other options should be pursued. If the target tumor disease showed stable or partial response, additional TACE sessions could be considered. If the target tumor completely responded, only routine follow-up was recommended. If new lesions were found, TACE could be repeated on demand. Finally, if there was extrahepatic spread or portal vein thrombus, CP status could help the decision-making process, with CP A/B patients receiving systemic therapy + on-demand TACE and CP C patients receiving either transplantation when feasible or supportive care.

One common clinical question is regarding whether there is a role for systemic therapies in patients who remain refractory after multiple TACE sessions. This phenomenon, which has recently been labeled as "untraceable progression" in the literature, is characterized broadly by intrahepatic growth or non-response of target lesions after two TACE sessions, stage progression (development of extrahepatic spread or macrovascular invasion), or continued decline in liver function (increasing PS or CP ≥ B8) (71). In such intermediate stage refractory patients, it has been shown in a 2015 retrospective cohort study by Arizumi *et al.* that patients who converted to sorafenib demonstrated a significantly (P=0.002) median OS compared to those two remained in the TACE group (sorafenib: 24.7 months, TACE: 13.6 months) (72,73). This directly translated into increasing median OS (20.5 *vs.* 15.4 months, HR: 2.04, 95% CI: 1.20–3.48) and 3-year OS (33.4% *vs.* 3.5%) when comparing combined therapy to TACE alone (73).

TARE

Traditional radiotherapy with external beam technology is limited in treating hepatic tumors due to the liver's high sensitivity to radiation-induced injury. TARE, also known as selective internal radiation therapy (SIRT) or yttrium-90 (Y-90), is a different form of radiotherapy. Following histopathologic animal model studies from the 1960s, TARE exploits observations showing liver tumors primarily derive their supply from the arterial system while functional parenchyma is preferentially fed by the portal venous system. TARE uses the liver's characteristic dual blood supply to deliver tumoricidal radiation doses to the targeted tumors while sparing functional liver tissue. More recent observations indicated that, after transarterial particle embolization, the preferential arterial flow to the tumor results in around a 3:1 particle deposition in tumor over normal liver (74,75). Another characteristic of TARE is the use of Y-90 as the source of energy. These particles produce ionizing energy capable of tissue destruction, but the energy penetrates tissues only a few millimeters from the particle location allowing for a good toxicity delimitation. These properties allow TARE to achieve effective tumoricidal doses to the targeted liver tumors and to avoid hepatotoxicity to the remaining functional liver.

The TARE technique that has been in clinical practice for the last decade in the United States prescribes doses of 100 to 140 Gy to the affected liver. Assuming a preferential 3:1 ratio of deposition of the Y-90 particles in the tumor *vs.* the unaffected liver tissue, the tumor is expected to receive an effective tumoricidal dose while the functional liver tissue gets spared with non-toxic doses. Whole liver treatments in a single session have been considered difficult to achieve safely as the proximal position of the delivery catheter would need to be in the proper hepatic artery, near the origin of extrahepatic branches like gastroduodenal or pancreatic branches, and reflux or accidental flow of Y-90 particles into extrahepatic branches can result in major complications. The targets in multifocal disease have been typically the right liver lobe, the left liver lobe, or both lobes sequentially. Targeting liver lobes allows position of the delivery catheter farther downstream into the lobar arterial branches reducing the risk of accidental extrahepatic Y-90 leakage.

The resin or glass particles used as vectors to deliver the attached Y-90 are small enough to not cause significant local arterial hemodynamic changes. This characteristic is particularly useful in the setting of advanced HCC due to portal vein tumor invasion. In this situation, the functional liver becomes dependent on the arterial system to compensate for the lack of portal flow. TACE would be considered contraindicated due to the likely ischemic hepatotoxicity produced with the occlusion of the local arterial system, now the sole support of the liver. TARE emerged as an alternative locoregional therapy option for patients with HCC in this setting. This stage of HCC has a poor prognosis, with a life expectancy of 10 months on best supportive care and 13 months with TARE or systemic

chemotherapy with sorafenib (76-78). Recently, newer immunotherapy agents have demonstrated promising results in advanced stage HCC. However, the presence of vascular invasion in HCC has been shown to be a key indicator of aggressive clinicopathological behavior, portending poor response to treatments and rapid progression, even more so than the presence of extrahepatic disease. The effect of immunotherapies in this subset of aggressive advanced stage HCC patients remains unknown.

The use of TARE has been extended to intermediate and early BCLC stages of HCC. However, the use in intermediate stage disease remains controversial. Currently, TACE is the gold standard for intermediate stage HCC achieving an OS of 2 to 3 years (79,80). On the other hand, despite the good tumor control observed with TARE, OS rates remain worse than those reported for TACE, ranging between 1.5 to 2 years (81,82). This may be attributable to radiation induced liver disease (RILD) negatively impacting long-term survival in this subgroup of patients, even when there is good tumor response. Similar findings have been observed in studies evaluating TARE in treating cancers with longer survival prognosis like tractable colorectal cancer with limited liver metastasis (83). Furthermore, in a long-term retrospective study of TARE for the treatment of neuroendocrine neoplasia metastatic to the liver, where patients typically have no chronic underlying liver disease and survival expectancies of >5 years, liver toxicity was reported in >50% of patients, with 5% developing symptoms of decompensated liver dysfunction like jaundice, encephalopathy, or tense ascites. The subclinical liver toxicity signs found on follow-up imaging consisted of contracted liver lobes and stigma of portal hypertension (84). These observations have led to questions regarding whether TARE adequately preserves the normal liver parenchyma and what its clinical effects are in patients with longer expected survival rates. The safety for hepatotoxic delayed adverse events remains unknown.

Recent studies have observed over 200 Gy are required for adequate tumoricidal effects while doses to liver tissue should be under 50 Gy to prevent the short-term adverse events (74,75). This would be difficult to achieve with a lobar dose from TARE with a possible 3:1 distribution. Therefore, a modified version of TARE called sub-selective TARE (sTARE) or Y-90 segmentectomy has been developed. In this version, higher doses of over 200 Gy are prescribed to a smaller, more selective region of liver containing the HCC lesions. By doing this, sTARE destroys both the tumor and normal tissue within the targeted region, simulating a targeted tissue ablation or resection. The technique attempts to preserve liver function by exclusively selecting the tumor-containing distal vascular regions of liver and has proven excellent long-term results in the treatment in early BCLC stage single HCC lesions.

The clinical benefits of sTARE were recently observed to be comparable to those obtained by more established treatment alternatives like surgical resection and thermal ablation as part of the LEGACY study (85). In this multicenter retrospective study, patients (n=162) with solitary HCC lesions ≤8 cm, CP A, and Eastern Cooperative Oncology Group (ECOG) 0–1 status underwent sTARE alone (72.2%) or alongside either transplant (21.0%) or LR (6.8%). These patients had excellent tumor response per localized mRECIST (best response ORR of 88.3%; 95% CI: 82.4–92.4%), with 62.2% (95% CI: 54.1–69.8%) exhibiting a duration of response (DoR) of ≥6 months. The 3-year OS was also impressive, measuring 86.6% across all patients and 92.8% for patients where TARE was paired with resection or transplant. On dose-pathology correlation in the LT/LR subset, patients exhibited complete pathological necrosis with doses >400 Gy. Unfortunately, the sub-selective condition for the safety of this technique narrows its utility in multifocal intermediate BCLC stage of the disease, where typically a larger proportion of liver segments are affected.

Combination therapies

TACE's curative effect is often stymied by incomplete embolization of the multiple branches that feed the tumors and the potential for post-embolization recanalization and angiogenesis (86). By comparison, ablation's curative effect is limited in tumors >3 cm and/or close to major vessels. The combination of transcatheter therapies such TACE, TAE, and DEB-TACE have been used to increase the potential curative effect of ablative techniques, especially for tumors over 3 cm. Transarterial therapies produce tumor cell ischemia, hypoxia, and apoptosis. Furthermore, when using iodized oil or radiopaque beads, TACE stains the tumors, improving visualization during subsequent ablation. The synergistic effects of these two therapies have been explored for patients with larger or multiple tumors. TACE before the ablation improves the ablation size due to reducing tumor vascularity and the resulting heat sink effect. TACE after the ablation helps treat residual tumoral cells, resulting in tumor-free ablation margins.

Studies exploring combined TACE + RFA have shown

improved tumoral response, OS, RFS, and LTP rates compared to TACE alone in early-stage disease (87,88). In a study of 211 patients with BCLC B disease, TACE combined with RFA also compared favorably to TACE alone, achieving a higher complete tumor necrosis rate (76.9% *vs.* 46.5%), lower major complication rate (1.8% *vs.* 2.6%), higher total tumor control rate (74.5% *vs.* 54.5%), and higher survival rates (89). A study by Ren at al. treated HCC patients with <3 tumors without size cutoffs, including tumors over 10 cm. RFA was performed 1–2 weeks after the TACE. They included a total of 399 BCLC A/B patients, with 128 assigned to the TACE-RFA group and 271 assigned to the TACE group. Patients in the TACE/RFA group showed better OS and PFS regardless of tumor size, without increased risk of death or major complication incidence (90). Similarly, several meta-analyses have shown that TACE + RFA results in longer OS and RFS that RFA alone (91-93).

Similar studies have been performed with MWA instead of RFA. One study compared TACE + MWA with TACE alone and showed better tumor response and time to progression, but no clear OS benefit for tumors ≤5 cm (94). Another showed that for unresectable larger tumors >5 cm, combination therapy with TACE + MWA showed statistically higher (P<0.001) OS rates than TACE alone at 1-year (87.5% *vs.* 62.5%), 3-year (50.0% *vs.* 17.5%), and 5-year (10.0% *vs.* 5.0%) endpoints (95). Other studies have shown combination therapy was superior to MWA alone (96). Comparisons between TACE + RFA *vs.* TACE with MWA have shown higher CR with MWA than RFA for tumors 3–5 cm in size (97). Results of superiority of combination therapy to CA alone also have been published but are limited (98).

The ideal wait time between the TACE and the ablation is unknown. While some perform the procedures sequentially the same day, others prefer waiting 1–7 weeks before the ablation. The rationale for the delay is that the TACE can affect liver function. The disadvantage is that waiting risks interim vessel recanalization and neo-angiogenesis, reducing the combination therapy's effectiveness (86). One study by Feng *et al.* suggested a period of 3–5 weeks between therapies, but further studies are needed to establish the best interval between therapies. Alternatively, iodized oil, when used alone, has limited embolization effects, alters liver function alteration less than TACE, and no waiting period is needed (99).

Although LR alone in patients with HCC within the Milan criteria has been reported with encouraging survival results, BCLC 2022 does not recommend resection for multinodular HCC within Milan criteria (5,100). However, hepatectomy has been successfully combined with ablation using RFA or MWA for tumors <3–6 cm in size and ≤5 in number located deep to the resection or in the contralateral lobe, resulting in an OS between 22–65% at 5 years (101-103). TACE, when combined pre-operatively with LR, improved OS compared to LR alone in BCLC B patients (1-year: 90.6% *vs.* 73.3%; 3-year: 61.7% *vs.* 43.5%; 5-year: 52.9% *vs.* 33.8%, P<0.001) (104). Another study employing TACE + LR *vs.* TACE alone in large/multifocal HCC also found that the OS was higher in the combined treatment group (47.00±2.87 *vs.* 20.00±1.85 months, P<0.001) (105). Interestingly, in patients with poor response after pre-operative TACE, there was no significant difference in OS between the TACE + LR and the TACE only groups (median OS: 35.0 months, 95% CI: 14.3–55.7 months, P=0.135) (105).

Finally, in patients with more advanced HCC, one potentially effective combination therapy is sorafenib plus SIRT. This option has been recently explored in the 2019 SORAMIC randomized control trial's palliative cohort. These patients, who were not eligible for TACE, were randomized to either SIRT + sorafenib (n=216) or sorafenib alone (n=208). The study found that there was no significant difference (P=0.9529) in median OS between the SIRT + sorafenib arm (12.1 months) and the sorafenib only arm (11.4 months) (106). Similar results of equivalence between SIRT and sorafenib was published in 2017 in the multicenter French SARAH RCT. Although combination therapies were not evaluated, this study also found no significant difference in median OS (HR: 1.15, 95% CI: 0.94–1.41, P=0.18) between the SIRT (8.0 months, 95% CI: 6.7–9.9 months) and sorafenib (9.9 months, 95% CI: 8.7–11.4 months) (77). However, additional subgroup analyses in the SORAMIC trial revealed survival benefits in non-cirrhotic patients (HR: 0.46, P=0.02), non-alcoholic cirrhotic patients (HR: 0.63, P=0.012), and younger patients ≤65 years old (HR: 0.65, P=0.05), suggesting that further study is warranted in these patient sub-populations (106).

Conclusions

Multifocal HCC is challenging to treat given the extensive patient population heterogeneity and treatment modality diversity. Alongside clinical status, imaging features such as tumor number, size, location, and vascular invasion play a critical role in selecting the appropriate treatment strategy.

Regarding ablation techniques, data is only available for RFA or MWA. While RFA and MWA are comparable in terms of OS, PFS, complication rate, or LTP, MWA is preferred to reduce treatment times, ablate larger zones, attain higher ablation temperatures, and reduce the heat sink effect. BCLC guidelines advocate for treating ≤3 lesions (each <3 cm) with ablation when other curative options like LT are not possible. However, even ablating three lesions can lead to poorer OS and RFS and LT should be considered for these patients. Lesions in different segments are also less amenable to ablation.

TACE is the main option for intermediate stage HCC. The Kinki BCLC B subclassification system (using CP and up-to-7 scores) can stratify patients and dictate TACE treatment subtype (cTACE, DEB-TACE, B-TACE, or HAIC). cTACE should be performed in a selective/superselective manner to improve tumor necrosis and OS. DEB-TACE and B-TACE allows for more targeted intratumoral drug administration. B-TACE is a newer alternative to cTACE, with cTACE being slightly favored for smaller tumors and B-TACE being preferred for larger ones. In extensive disease (bilobar, >5 cm lesions, >50% liver tumor burden), two consecutive sessions should be performed. Pre-transplant TACE can downstage disease with a nearly 50% success rate. TACE has a role in palliation, but post-embolization syndrome and acute liver failure risks warrant discussion. TACE response can be assessed in terms of patient tolerance, mRECIST response in selected target tumors, presence of new lesions, and development of extrahepatic spread or portal vein thrombosis. Two TACE sessions are often needed to derive benefit, but no more than three sessions should be performed.

TARE is an option in advanced HCC. Recent studies have shown encouraging results if higher (>400 Gy) can be delivered to tumor. If chosen, a lobar rather than whole liver approach is preferred to avoid gastroduodenal or pancreatic branch artery reflux. TARE has seen some use in BCLC A/B disease; however, benefits here may be outweighed by the long-term risks of RILD and liver toxicity. sTARE, while effectively simulating a targeted ablation zone, is unsuited for multi-segment disease.

Finally, combination therapies are promising. TACE, performed either before or after, helps potentiate ablation and can be superior to TACE alone. LR, although not recommended in BCLC 2022, can improve survival when combined with ablation or TACE, with the IR technique targeting the deep or contralateral lobe tumors outside of the resection margins. These and other modality combinations are an exciting prospect that should be explored in future studies.

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Footnote

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