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# **Image-Guided Therapies for Hepatocellular Carcinoma in Hepatocellular Carcinoma — Future Outlook**

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Additional information is available at the end of the chapter

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## **1. Introduction**

The use of image-guided locoregional therapies (LRTs) plays a key role in the management of patients with hepatocellular carcinoma (HCC). These therapies, classically used for palliation, are now more frequently being used with curative intent either as a bridge before the definitive therapy (surgical resection or orthotopic liver transplantation) or as a sole or combined therapy in selected patients for whom surgical options are precluded [1-3]. The refinement and development of new imaging technologies combined with recent advances in catheter technology, embolic agents, chemotherapeutic drugs, and delivery systems have been linked to further improved patients' outcomes, thus increasing the interest in this approach. In the first part of this chapter, an overview of the current available image-guided LRTs will be given. In the second part, indications for different LRTs according to tumor stage will be discussed. The third section will discuss the pivotal role of follow-up diagnostic imaging in the pre- and post-procedural care of patients with HCC. Finally, future directions with regard to the use of LRTs will also be presented and discussed.

## **2. Overview of currently available image-guided LRT options**

### **2.1. Transarterial therapies**

#### *2.1.1. Chemoembolization*

Hepatic transarterial embolization for the treatment of liver tumors was first performed in the 1970s to improve local disease control. The rationale behind this approach emerged from the peculiarities of blood flow to HCC, which is supplied preferentially via the hepatic

artery owing to the intense angiogenesis during disease progression. For transarterial chemoembolization (TACE), first described in 1977 by Yamada [4], one or more chemotherapeutic drugs are added to the embolic agent, on the basis of the theory that tumor ischemia caused by embolization of the dominant arterial supply has a synergistic effect with the chemotherapeutic drugs. Several chemotherapeutic agents are used for TACE, the two most commonly used doxorubicin and cisplatin, which can be mixed with one or several different embolic agents. Recently, the development of calibrated microparticles loaded with doxorubicin (DEBDOX-TACE) have gained acceptance. These drug-eluting microspheres allow more reliable distal occlusion of small vessels and delivery of high-dose chemotherapy to the tumor with a very low systemic circulation of the chemotherapeutic agent. A randomized phase II study [6] comparing conventional TACE with DEBDOX-TACE demonstrated a significant reduction in liver toxicity and serious adverse drug events in the latter arm and an insignificant trend of better antitumoral effect [5, 6].

### *2.1.2. Yttrium-90 microsphere radioembolization*

Transarterial radioembolization (TARE) is the transcatheter arterial delivery of microspheres loaded with yttrium-90 ( $^{90}\text{Y}$ ), a pure beta emitter with a physical half-life of 64.2 hours, after which it decays into stable zirconium. Like other transarterial therapies, TARE relies on the preferential arterial supply and enhanced microvascular density of hepatic neoplasms [7, 8]. Acting as carriers, these biocompatible microspheres can conceptually deliver radiation preferentially to tumors following hepatic artery delivery via embolization in the tumor-related arterioles. Additionally, employing high-energy beta radiation instead of traditional gamma radiation can potentially create an intense local radiotherapeutic effect that is proportional to the density of microsphere distribution. Hence, compared to nonselective extracorporeal x-ray radiotherapy, TARE allows the particles to be deposited predominantly within the tumor vasculature, thereby leading to tumor damage while preserving the surrounding liver parenchyma. This critical feature allows the delivery of substantially higher radiation doses than those that can be safely delivered via external beam radiotherapy.

In the United States, two Food and Drug Administration (FDA)-approved  $^{90}\text{Y}$  microsphere products are in current clinical use: TheraSphere® (MDS Nordion Inc., Kanata, Ontario, Canada), which consists of glass microspheres, and the resin-based SIR-Spheres™ (SIRTeX Medical Ltd., Sydney, New South Wales, Australia). The glass  $^{90}\text{Y}$  microspheres are approved in the United States for use in radiation treatment or as a neoadjuvant treatment before surgery or liver transplantation in patients with HCC under the auspices of a humanitarian device FDA exemption for orphan devices. TheraSphere has been used for neoplasia other than HCC under compassionate circumstances after adherence to FDA-related guidelines. The resin  $^{90}\text{Y}$  microspheres have premarket approval for the treatment of hepatic metastasis from colorectal primary cancers with adjuvant hepatic arterial infusion of floxuridine. However, globally, the regulatory approval of both products is more generic, and they are also commonly used for HCC therapy. The use of resin microspheres for an indication not included in the US FDA-specific labeling is considered off-label use. Clinicians should consult and adhere to their institutional and regulatory agencies before prescribing the treatment for off-label use with either device.

### 2.1.3. Embolization with $^{131}\text{I}$ iodine

The use of radioactive iodine ( $^{131}\text{I}$ ) has been proposed for internal radiotherapy for HCC. In this technique, ethiodized oil is tagged to the  $^{131}\text{I}$  via an atom-atom exchange.  $^{131}\text{I}$ -lipiodol then emits gamma radiation with energy of 374 KeV and penetration of up to 0.4 mm. The retention of lipiodol inside the HCC tumor cells allows a targeted dose-intensified radiation therapy to be delivered. Despite the reported efficacy of  $^{131}\text{I}$ -lipiodol [9, 10], its use in routine daily practice is limited owing to the lack of additional data and the complexity of this procedure when compared with other available therapies such as TACE and TARE. Patients are also required to be isolated for several days after the procedure for radiation safety. An initial randomized study comparing internal  $^{131}\text{I}$ -lipiodol radiation therapy versus supportive care in patients with HCC and portal vein thrombosis suggested the former conferred a survival benefit [9]. Considering the lack of clinical evidence and the possible severe side effects such as liver failure and pneumonia related to its use, this treatment method deserves further analysis.

## 2.2. Percutaneous ablative therapies

### 2.2.1. Ethanol injection

Percutaneous ethanol injection (PEI) is the prototypical technique used for percutaneous ablation. On this technique, absolute ethanol is injected inside the tumor and around it using a guiding needle inducing coagulative necrosis as a result of cell dehydration, protein denaturation and chemical occlusion of small vessels. PEI is a well-established technique for treating nodular types HCCs with the extent of necrosis obtained via this technique intrinsically correlated with the size of the lesions with complete necrosis achieved in 90%, 70%, and 50% of tumors measuring <2 cm, 2-3 cm, and 3-5 cm, respectively [11-13]. A possible explanation for the suboptimal response of larger tumors to PEI is the presence of intratumoral septa and/or a capsule that blocks the diffusion of ethanol. Recently, the introduction of a specific multipronged injection needle (Quadrafuse, RexMedical, Philadelphia, PE) for single-session PEI has resulted in a sustained complete response rate of 80%-90% in tumors measuring < 4cm [14].

### 2.2.2. Radiofrequency ablation

Radiofrequency ablation (RFA) has become the first-line choice for percutaneous ablation and has superseded PEI as the method of choice for ablative LRT mainly because it yields complete necrosis with fewer sessions than required for PEI, especially in larger tumors, thus leading to better local disease control [15-19]. This technology relies on its physical characteristics to deliver an alternating electrical current within the lesion via an electrode needle placed directly into the tumor. The resulting frictional heat and movement of electrons within the lesion and surrounding tissues generate heat in the immediate vicinity of the electrode which is then conducted to the surrounding environment, thereby resulting in the coagulative necrosis of a predetermined volume of tissue. RFA is performed by connecting a generator that provides an electric current to a metallic applicator probe (needle), which is inserted into the tumor percutaneously via computed tomography, fluoroscopy, magnetic resonance imaging, or

ultrasound guidance. Thermal energy is applied to tissues through the tip of the probe. The tissues surrounding the tip are destroyed within seconds as temperatures reach 55°- 60°C. Care is taken to avoid charring tissues, which limits heat propagation. Ideally, the ablation zone should encompass the tumor and a 5-10-mm margin of normal tissue, which might eliminate small, undetected satellite lesions. The size and shape of the ablation zone vary depending on the amount of energy, the type and number of electrodes, the duration of ablation, and inherent tissue characteristics [20].

Initial RFA indications included the treatment of small lesions (<3cm) in patients who were not surgical candidates and the palliation of large lesions. However, owing to the efficacy and safety profile of the technique, its use has greatly expanded and it is now offered to patients who are surgical candidates with comparable 5 year survival outcomes to resection [21]. The limitations of the technique include a “heat-sink” effect, whereby adjacent blood vessels produce perfusion-mediated attenuation of thermal energy deposition, potentially leading to incomplete ablation; large (>5 cm) lesions; and proximity to thermal sensitive structures, such as the gastrointestinal wall, gallbladder, diaphragm, and nerves.

### 2.2.3. Microwave ablation

Microwave ablation (MW) is an emerging hyperthermic ablative therapy that is a valuable alternative to RFA for the ablation of HCC. Several MW systems have been approved for clinical use in the United States [22], comprised by an energy generator that is connected via a coaxial cable to a percutaneous needle(s) that functions as an active antenna that delivers energy within the tumor. The application of electromagnetic microwaves in the matter creates heat by agitating water molecules in the surrounding tissue, thereby producing friction and heat and inducing cellular destruction via coagulative necrosis [23]. Compared with other available ablative technologies, MW creates larger tumor ablation volumes with consistently higher intratumoral temperatures, has faster ablation times, and an improved and a more favorable convection profile [22], thus resulting in a reduction in the “heat sink” effect created by vessels in proximity to the ablated zone [24]. Recent advances in MW engineering have resulted in better MW systems with the potential for creating more effective ablation zones.

### 2.2.4. Cryoablation

The application of freezing temperatures to tumors can be also utilized to cause tissue destruction. Similarly to RFA and MW, a cryoablation probe is directly inserted into the target lesion. Argon circulates through the probe, causing a rapid drop in the local temperature around the probe, promoting local ischemia and a disruption of the cellular membrane. Ice crystals form within the cells and adjacent interstitium, causing cell dehydration and surrounding vascular thrombosis. Subsequently, when the tissues thaw, vascular occlusion leads to further ischemic injury [25]. Consistent tumor cell death is accomplished when the tissues are exposed to temperatures of at least -20°C within an area of approximately 3 mm inside the margins of the ice ball. As with RFA, the main limitations of cryoablation include proximity of the lesion to blood vessels, gastrointestinal organs, nerves, and skin. Treatment of large tumor volumes with cryoablation can lead to the development of rare but serious systemic



complications, such as ‘cryoshock’, a cytokine-mediated inflammatory response associated with coagulopathy and multiorgan failure, myoglobinuria, and severe thrombocytopenia [26-28]. Otherwise, most complications of cryotherapy are generally similar to those of RFA, such as hemorrhage and injury to adjacent organs.

### **2.3. Combination therapies**

The use of combined therapies, either a combination of different LRTs or LRT combined with systemic therapies, has gained particular attention in the last decade. Combining different modalities of LRT such as RFA and chemoembolization could increase the treatment success rate, particularly in large HCCs [29]. The rationale for this approach lies in the devascularization of large HCCs via embolization or chemoembolization, which reduces the possibility of having a deleterious “heat sink” effect in hypervascular tumors treated with RFA and thereby increases its therapeutic effect. This approach has been validated in several studies that demonstrated larger ablation zones when bland embolization or chemoembolization was performed before the ablative treatment [30-32]. Moreover, performing RFA before chemoembolization has been shown to increase the deposition of the chemoembolic agent in the periphery of the ablated tumor, the most common area for disease recurrence [33].

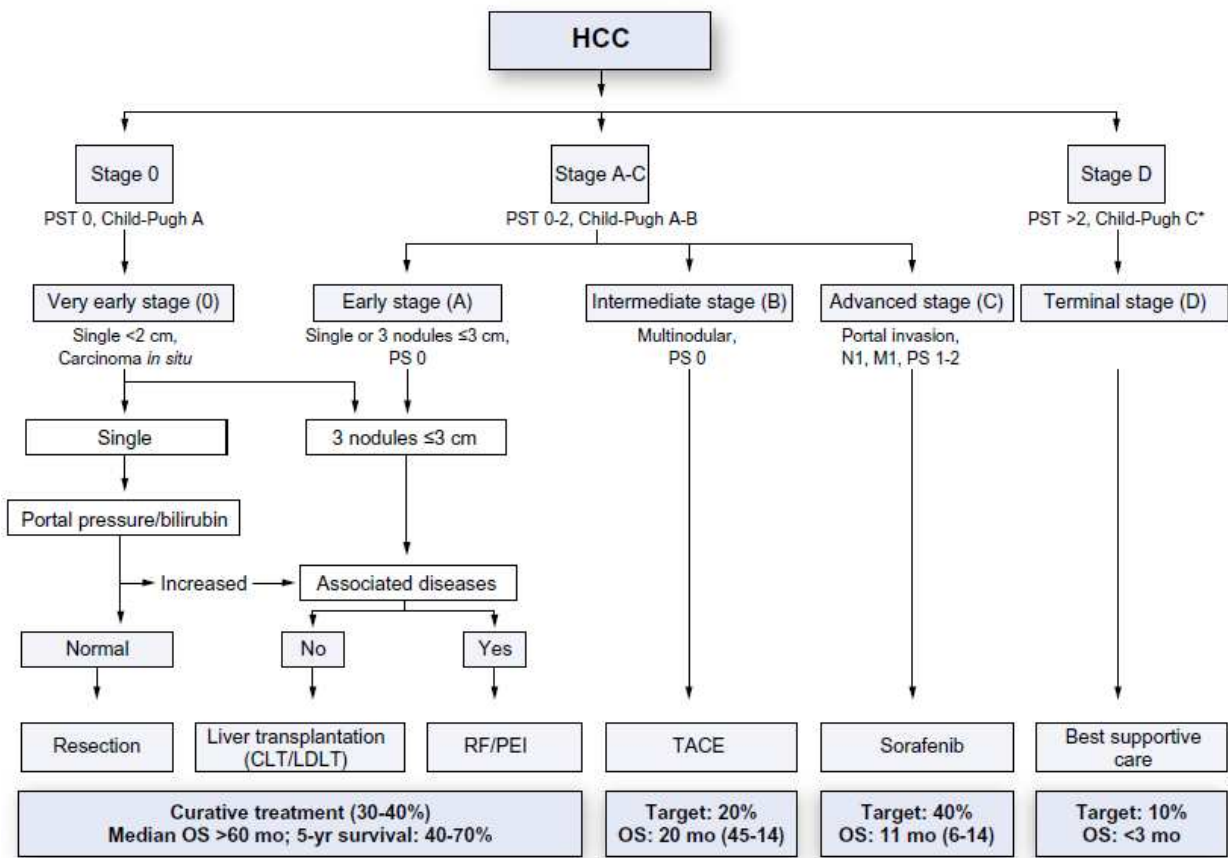
It is also suggested that the hypoxic environment after TACE may trigger the expression of neoangiogenic factors such as the vascular endothelial growth factor (VEGF), possibly leading to tumor growth and progression. Therefore, to avoid the development of a neoangiogenesis cascade and, by consequence, tumor progression systemic therapies in the form of chemotherapy or antiangiogenic drugs with the intent of acting in different fronts of neoangiogenesis have been proposed.

## **3. LRT for HCC according to disease stage**

To review the available LRTs according to different stages of disease, we used the Barcelona Clinic Liver Cancer (BCLC) staging system, which has emerged in recent years as the standard means of classifying HCC. In this system, cases are classified into 5 different stages – very early (0), early (A), intermediate (B), advanced (C), and terminal (D) – according to pre-established prognostic variables, thereby allowing therapies to be allocated according to treatment-related status (Figure 1). Terminal-stage treatment options are beyond the scope of this chapter, as LRTs are not administered in that setting.

### **3.1. Very early stage (0)**

Patients diagnosed with very early-stage disease (performance status: 0, Child-Pugh score: A, single HCC <2 cm) on the BCLC staging system have the highest potential for cure. Surgical resection is the modality of choice for this stage and yields a 5-year survival rate of around 75% in these patients, with the anatomic resection—defined as the en bloc removal of a portion of liver supplied by a major branch of the portal vein and the hepatic artery



**Figure 1.** BCLC staging system and treatment strategy, 2011 [2]

utilized as the preferred surgical technique [34, 35]. Despite the improvements achieved with recent refinements in surgical technique and postoperative care, which resulted in a low mortality rate of 1%-3%, anatomic resection in patients with very early HCC is still limited depending on the volume of segments that need to be resected. Nodules smaller than 2 cm that are not subcapsular, perivascular, or adjacent to the gallbladder are the ideal indication for ablative therapies, and RFA is the standard technique in many institutions [2, 36, 37]. In a recent study, Cho and colleagues [38] concluded that RFA and hepatic resection are equally effective for the treatment of stage 0 HCC. Livraghi and colleagues [19] reported a complete response rate of 97.2% and a 5-year survival rate of 68% in 218 patients with very early-stage HCC treated using RFA. In another recent study [39] of 83 patients with very early HCC who were treated using different modalities of percutaneous ablation (33 PEI, 19 MW, and 31 RFA), the complete response rate was 95%, and the 5-year survival rate was 78%. Therefore, RFA is suggested by some authors as first-line therapy for very early-stage HCC, and surgical resection is reserved for when individual patient variables render RFA unfeasible or unsafe [40]. In selected cases of very early-stage HCC, when surgery or RFA cannot be offered because of increased bilirubin level, signs of portal hypertension, and risky tumor location, such as pericholecystic lesions and lesions near the hilum, PEI can still be offered as an alternative.

### 3.2. Early stage (A)

Patients with a solitary HCC or up to three lesions measuring less than 3 cm without associated diseases are the ideal candidates to be effectively treated with liver transplantation. On those where associated disease exists or where bridge therapy is required before liver transplantation, percutaneous ablation (PEI/RFA) is the modality of choice. Compared with PEI, RFA is consistently more effective and renders better local disease control. It also offers a survival benefit compared with PEI, as demonstrated by three independent meta-analyses that revealed 5-year survival rates of 51%-64% in patients who met the BCLC criteria for surgical resection [41-43].

MW ablation is emerging as a viable alternative to RFA in patients with early-stage HCC owing to its larger tumor ablation volumes, because the inherent characteristics of this technique are less affected by the “heat-sink” effect created by vessels in proximity to the tumor. To date, the only randomized control trial comparing RFA and MW ablation did not reveal any differences in the effectiveness of the two techniques, with a trend toward RFA in respect achieving tumor ablation in fewer sessions [44]. Nevertheless, the recent advances in MW engineering along with improvements in the learning curve of this technology will potentially create a more effective ablation zone and better local disease control when compared to RFA.

Although not specified in the BCLC guidelines, a combination of ablative and transarterial treatments could be considered for cases in which the target lesion measures between 3 and 5 cm in its longest axis in view of the suboptimal response of larger lesions to ablative therapies alone [30, 31, 45, 46]. The recent results of a randomized control trial [46] assessing the efficacy of combining RFA with subsequent conventional TACE (lipiodol plus epirubicin at 30-50 mg followed by introduction of gelatin sponge) in patients with HCCs measuring 3.1-5.0 cm showed that the rate of tumor progression was significantly lower in the combination group than in the ablation-only group (39% versus 6%,  $P=0.012$ ) [46]. DEB-TACE administered after RFA has also been studied and yielded a potential increase of  $60.9\% \pm 39.0$  in treatment-induced necrosis on imaging [33]. Further studies to determine the ideal sequence of techniques and the real impact of this approach are needed.

When percutaneous ablative therapies such as RFA and MW are not feasible or safe, TACE can be performed as an alternative. This can be a valuable tool in patients with solitary large ( $>5$  cm) lesions, for whom the benefits of combining different LRTs seems negligible. In a recent study, DEB-TACE administered before liver transplantation yielded complete necrosis in 77% of treated tumors on pathology (mean size:  $3.2 \text{ cm} \pm 1.54 \text{ cm}$ ) with no serious adverse events observed.

#### 3.2.1. Intermediate stage (B)

TACE is the standard of care for patients with stage B disease, according to BCLC guidelines. This indication is based on the improved survival rates demonstrated in a meta-analysis of six randomized clinical trials that compared TACE with the best supportive care or suboptimal therapies [47]. Of note, however, the studies included in this meta-analysis were considerably heterogeneous (particularly with regard to the patient populations and the TACE techniques



used), and the cases of intermediate-stage HCC comprised a heterogeneous population of patients whose liver function and tumor burden varied widely. Therefore, not all patients included in BCLC stage B will have the same benefits from TACE, as demonstrated by a recent meta-analysis of randomized control trials [48]. On a recent study by Burrel et al [49], a median survival of 42.8 months was achieved with the use of DEB-TACE in patients classified as BCLC-B after censoring follow-up at the time of liver transplantation, sorafenib treatment and TARE. A sub-stratification of this patient population, along with the comparison of TACE with other LRTs and systemic therapies, should be encouraged in future research.

The combination of DEB-TACE with sorafenib in patients with intermediate-stage HCC was assessed in a phase II randomized, double-blind, placebo-controlled trial. Patients who received sorafenib combined with DEB-TACE had a longer time to progression than did the control group, to whom DEB-TACE was administered in combination with placebo (hazard ratio: 0.797). Nonetheless, the difference in median survival was only 3 days in favor of the sorafenib group (169 versus 166 days), and the difference in overall survival between two groups was 6 days in favor of the placebo group (562 versus 554 days). Evidence from ongoing phase III trials is expected to clarify the clinical efficacy of this combination.

The use of radioembolization with  $^{90}\text{Y}$  in patients with intermediate to advanced stage HCC has been investigated in a phase II study [50]. In this study, 17 patients with intermediate-stage HCC without portal vein thrombosis were treated with a lobar delivery of 120 Gy. Nine (52.9%) patients had complete response (CR) or partial response (PR) accordingly to the European Association for the Study of Liver (EASL) criteria. Disease control (CR, PR or stable disease [SD]) was achieved in 15 patients (88.2%). Time to progression was 13 months, and overall survival was 18 months (range, 12–38 months) [50]. In a recent multicenter trial [51] assessing the use of radioembolization with  $^{90}\text{Y}$  in patients with HCC, 87 patients with BCLC stage B HCC treated with  $^{90}\text{Y}$  had a median survival of 16.9 months (95% CI 12.8–22.8). Of note, this study demonstrated that radioembolization with  $^{90}\text{Y}$  appears to be particularly promising for the subset of patients with intermediate-stage HCC who are considered poor candidates for TACE (median survival: 15.4–16.6 months) as well for those for whom prior TACE or bland embolization was ineffective (median, 15.4 months). The results of this study emphasize the possibility of using radioembolization as a complementary therapy to TACE in the HCC armamentarium.

### 3.3. Advanced stage (Stage C)

According to the BCLC guidelines, the use of the systemic multi tyrosine-kinase inhibitor, sorafenib, is the cornerstone for patients with advanced HCC [2]. The benefit of this therapy was demonstrated in two randomized control trials [52, 53] in which this new therapy was compared with placebo. Both studies revealed an improvement in the median overall survival and the median time to disease progression on imaging. Although LRTs are not recommended for patients with BCLC stage C disease, many patients who undergo LRT in the form of TACE or radioembolization are in fact classified as having advanced-stage disease according to the aforementioned criteria. This subclass of patients is characterized by the presence of tumoral invasion of a branch vein with or without limited extra-hepatic disease and a performance

status 1-2. Combination therapy using TACE and sorafenib is technically feasible and generally well tolerated in patients with unresectable HCC [54-56]. In a recent phase II study of concurrent conventional TACE and sorafenib, Park et al. [55] demonstrated a median time to progression of 7.3 and 5 months for patients with BCLC stage B and C disease, respectively. Compared with unpublished data from the same group, the combination of sorafenib with conventional TACE yielded increased time to progression in both patients with BCLC stages B and C when compared with conventional TACE (cTACE) alone (4.5 and 2.8 months, respectively).

Concurrent therapy with DEB-TACE and sorafenib has also been investigated [56]. DEB-TACE promotes a lesser degree of serum aminotransferase elevation than does conventional TACE, which is the most common cause for delaying therapy with sorafenib. Of note, sorafenib should ideally be administered as soon as possible after TACE is administered to prevent an early surge of vascular endothelial growth factor and other angiogenic factors. Pawlik et al. [56] assessed the safety and response rate of combination therapy using DEB-TACE and sorafenib in patients with advanced-stage HCC. The results of this study demonstrated that the combination of sorafenib and DEB-TACE was well tolerated and safe, and most toxic effects related to sorafenib were manageable with dose adjustment. Disease control was achieved in 95% of patients (SD+PR), according to Response Evaluation Criteria in Solid Tumors (RECIST) with an objective response of 58% (according to the EASL).

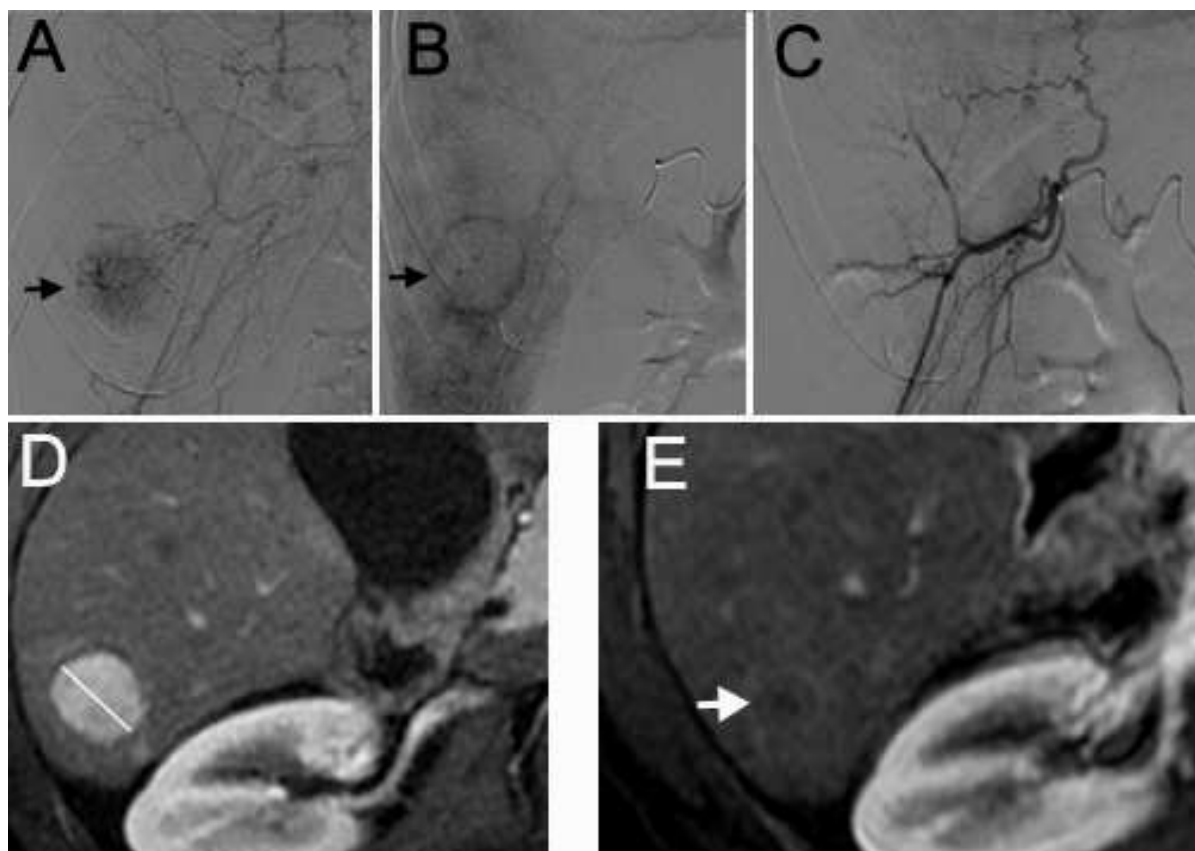
#### **4. Imaging response assessment for LRT**

The RECIST and the world health organization (WHO) criteria are the standard criteria for assessing imaging response in patients who undergo systemic therapies using cytotoxic drugs. These criteria assess the response of target lesions solely on the basis of their measurement in diameters and their changes after systemic therapy. In the setting of LRT, tumor response as determined via simple measurement in diameters is not accurate enough since tumor necrosis, a common endpoint for all LRTs, is not taken into consideration.

The inconsistency of using these response evaluation criteria for systemic therapy in patients undergoing LRTs was first addressed by a panel of experts on HCC from the European Association Study of Liver in 2000, which suggested that response assessment should be based on the estimation of the reduction in viable tumor, as recognized by arterial-phase enhancement on radiologic imaging. The concept of achieving complete necrosis (complete response) after LRT is a good surrogate for excellent outcome and has been confirmed by a number of different studies [57-60].

More recently, the addition of molecular targeted therapies such as sorafenib, bevacizumab, and erlotinib to the anticancer armamentarium rendered an improvement in overall survival without showing any significant imaging response rate according to the RECIST criteria [54, 61]. This finding can also be explained by the ability of these new agents to cause necrosis in the target lesions without any significant significantly affecting the reduction of the size of the lesions. In fact, it is now known that some lesions tend to increase in volume after the use of

molecularly targeted therapies owing to the presence of massive necrosis and edema on their interior.

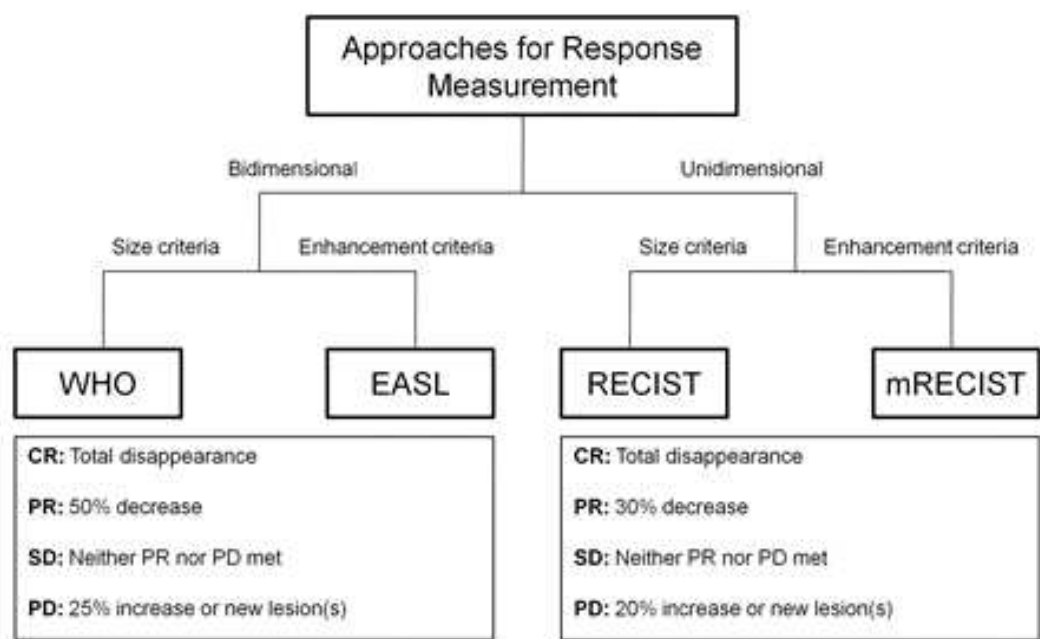


**Figure 2.** TACE and magnetic resonance imaging follow-up utilizing the mRECIST: (A) Digital subtraction angiography (DSA) demonstrating the hypervascular lesion (black arrow) located in the segment VI. (B) Parenchymal phase showing the encapsulated pattern of the lesion (black arrow). (C) post DEB-TACE DSA no longer characterizing the hypervascular tumor. (D) Baseline magnetic resonance imaging (MRI) showing the hypervascular tumor in the arterial phase (white line) measuring 3.2 cm. (E) post DEB-TACE MRI arterial phase, showing the absence of arterial enhancement at the lesion (white arrow) after the DEB-TACE, configuring a complete response according to the mRECIST. Liver explant analysis confirmed complete necrosis of the treated

To address all the limitations associated with the RECIST criteria in assessing therapy response, especially that of HCC, novel imaging correlative endpoints were proposed by different investigators [61-63]. One of the initial proposals created was the amendment of enhancement criteria to the WHO criteria (EASL criteria), which use the enhancement observed in the arterial phase by the intravenous contrast as a surrogate for viable tumor, whereas the absence of arterial enhancement within the tumor indicates tumor necrosis. Despite the initial enthusiasm, recent studies have demonstrated that these criteria cannot provide prognostic data to enable differentiation between the survival outcomes of patients who achieved partial response and those who had stable disease. This is possibly explained by the different thresholds for therapy response extrapolated from the WHO criteria. Therefore, a new proposal suggested for assessing therapy response for HCC was made by the modification of the conventional RECIST criteria with the incorporation of the concept of viable tumor (Figure

2). These criteria, also known as the modified RECIST (mRECIST) [63], have been demonstrated to be an accurate tool for assessing response for both locoregional and systemic therapies [59, 60, 64] and should be used as the method of choice for assessing treatment response in patients with HCC [2]. Although mRECIST helps to predict survival outcomes in patients undergoing LRTs, further data are needed to establish these criteria for assessing survival in the setting of systemic therapies with molecularly targeted drugs. A summary of the different response criteria are summarized in Figure 3.

Radiographic response criteria used to assess the clinical effects of HCC treatment.



Shim J H et al. Radiology 2012;262:708-718

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**Figure 3.** Radiographic response criteria used to assess the clinical effects of HCC treatment [59]. Adapted from: Shim, J.H., et al., Which response criteria best help predict survival of patients with hepatocellular carcinoma following chemoembolization? A validation study of old and new models. Adapted from Radiology, 2012. 262(2): p. 708-18.

5. Future directions

The last few decades were characterized by establishing the limits of outcomes of liver directed therapies for HCC. Recent therapeutic advances exploiting molecular biological pathways have created new vistas in our collective approaches towards this disease. Certain distinct

clinical scenario will remain the focus of future endeavors such as recurrence and cancer prevention. Tumor recurrences are a major drawback in patients with very early and early stages HCC submitted to ablative therapies or resection. Effective preventive agents in the form of better ablative technologies or combined loco-regional and systemic therapies are needed given the projected increase in patients at risk for developing HCC. Irreversible electroporation (IRE) is a new ablative therapy that increases cell membrane permeability by changing the transmembrane potential and subsequently disrupts the lipid bilayer integrity resulting in cell death [65, 66]. Currently there is one IRE system available on the market. Similarly to an RFA system, this system consists of two major components: a generator that delivers energy of up to 3000 V and a needle-like electrical probe. Compared with other available ablative technologies, this technology can create a sharper boundary between the treated and untreated area in vivo within microsecond or milliseconds; moreover, because it is a non-thermal technique, issues associated with perfusion-mediated tissue cooling or heating are not relevant. Preclinical investigations [67] focused on HCC have demonstrated the great potential of this technology for targeted ablation of HCC and have prompted its clinical evaluation.

Light-activated drug therapy uses light-emitting diodes to activate talaporfin sodium, a small molecule synthesized from a chlorophyll derivate that has the ability to concentrate within the tumors when administered intravenously and activated by placing a percutaneous light emitter intratumorally under imaging guidance. Talaporfin is capable of absorbing long-wavelength light, resulting in singlet oxygen that causes apoptotic cell death through oxidation and permanent tumor vessel occlusion. Preclinical animal studies suggested that the production of large apoptotic masses in tumor with light-activated drug therapy yields tumor-specific clones of CD8<sup>+</sup> T cells which infiltrate distant, untreated tumors. A phase III clinical trial is currently assessing the use of talaporfin for HCC.

In patients with advanced-stage HCC, future research will hopefully better delineate the indications for TACE and TARE, either in the form of isolated therapy or combined with sorafenib with possible improvements in slowing disease progression. Finally, advances in molecular cell biology will identify new therapeutic strategies for patients with advanced-stage HCC. For these advances to take place, a multidisciplinary continuous clinical and experimental research is vital.

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