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Interventional Oncology in Hepatocellular Carcinoma: Progress Through Innovation

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Abstract

The clinical management of hepatocellular carcinoma has evolved greatly in the last decade mostly through recent technical innovations. In particular, the application of cutting edge image guidance has led to minimally invasive solutions for complex clinical problems and rapid advances in the field of interventional oncology. Many image-guided therapies, such as transarterial chemoembolization and radiofrequency ablation have meanwhile been fully integrated into interdisciplinary clinical practice, while others are currently being investigated. This review will summarize and evaluate the most relevant completed and ongoing clinical trials, provide a synopsis of recent innovations in the field of intra-procedural imaging and tumor response assessment, and offer an outlook on new technologies, such as radiopaque embolic materials. In addition, combination therapies consisting of loco-regional therapies and systemic molecular targeted agents (e.g., sorafenib) remains of major interest to the field and will also be discussed. Finally, we will address the many substantial advances in immune response pathways that have been related to the systemic effects of loco-regional therapies. Knowledge of these new developments is crucial as they continue to shape the future of cancer treatment, further establishing interventional oncology along with surgical, medical, and radiation oncology as the 4th pillar of cancer care.

Keywords

Cone-beam computed tomography; Drug-eluting beads; EASL; Image-able beads; Irreversible electroporation; Microwave ablation; qEASL; Radioembolization; RECIST

Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related mortality worldwide with over 700,000 deaths in 2012.^{1,2} At the time of diagnosis, few patients are candidates for curative surgery or transplantation, and most will need loco-regional treatment during the course of their disease.³ Interventional oncology (IO), a subspecialty of

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interventional radiology, offers a variety of image-guided intra-arterial and percutaneous ablative therapies that are an essential part of the contemporary care for patients with HCC.^{3,4}

Intra-arterial therapies (IATs), notably transarterial chemoembolization (TACE), take advantage of the fact HCC tumors draw their blood supply almost exclusively from the hepatic artery while the remainder of the liver is supplied by the portal vein. As a result, by using the hepatic artery as a conduit to the tumor, anatomic targeting of HCC can be achieved while at the same time sparing the liver parenchyma. These therapies have been shown to improve local tumor control. Conventional TACE (cTACE) involves intra-arterial infusion of chemotherapy, suspended in Lipiodol, an iodinated poppy seed oil-based medium that works as an effective drug carrier, a tumor seeking and embolic agent all at once and is easily visualized under fluoroscopy and by computed tomography (CT). The intra-arterial administration of this emulsion of chemotherapy and Lipiodol is followed by embolization of tumor feeding vessels with calibrated particles or Gelfoam in order to protect the emulsion and prevent its separation thereby keeping the chemotherapy within the tumor for a longer period of time. Combining the delivery of the chemotherapy-Lipiodol emulsion with the embolization leads to local therapeutic cytotoxicity and ischemia.⁵ Other IATs include TACE with drug-eluting beads (DEB-TACE), where embolic microspheres are loaded with a chemotherapeutic drug, and radioembolization, which involves infusion of glass or resin microspheres (e.g., TheraSphere®, SIR-Spheres®) containing the radioactive isotope yttrium 90 (Y90) as a tumoricidal agent.

The most commonly used ablative therapy, radiofrequency ablation (RFA), is a locoregional thermal ablative tumor therapy that applies an electrical current within the radiofrequency spectrum generated from an electrode probe to a tumor lesion resulting in heat deposition and coagulative necrosis.⁵ Beyond serving as a bridge to liver transplantation, RFA effectively treats lesions up to 3 cm and shows significant survival benefit as a potentially curative therapy.^{6,7}

In this review of state-of-the-art therapies, we will highlight recent advances in image-guided loco-regional therapies as well as treatment assessment and strategy in HCC. Specifically, we will discuss new developments regarding the choice of intra-arterial therapy, evolution of embolic materials, imaging markers of tumor response, combined loco-regional and systemic therapies, clinical introduction and standardization of cone-beam CT (CBCT) imaging, and systemic effects of ablative therapies.

Choice of Intra-arterial Therapy

Various IATs are available for HCC management, but cTACE remains the most commonly used treatment modality and continues to be the standard of care. In 2016, a systematic review reported the current efficacy and safety data of cTACE in the treatment of HCC.⁸ In over 10,000 patients treated with cTACE, the objective response rate was 53%, and overall survival was 70% at 1 year and 32% at 5 years (median: 19 months). Among over 20,000 adverse events reported from more than 15,000 patients, liver enzyme abnormalities were most common followed by post-embolization syndrome, and overall mortality rate was

0.6%, mostly related to acute liver insufficiency. These data support the efficacy of cTACE with no unexpected safety concerns. It is also important to mention that in 2014, the BRISK-TA trial, a Phase III randomized controlled trial (RCT) which investigated brivanib as an adjuvant therapy to cTACE, demonstrated that 253 HCC patients who received cTACE alone as the placebo arm treatment achieved a median overall survival of 26 months.⁹ This result from one of the largest trials ever conducted on HCC confirms the tremendous benefits of cTACE as a mainstay therapy.

Most recently, the GIDEON study, a large prospective, observational registry, has reported the highly prevalent use of TACE prior to and concomitantly with sorafenib in more than 3,000 HCC patients from 39 countries.¹⁰ It found that 47% patients underwent TACE prior to sorafenib and 10% concomitantly, with Lipiodol based cTACE accounting for 74% and 64% of TACE use, respectively, except in the U.S. where DEB-TACE was still more commonly administered. These results demonstrate the common clinical use of TACE globally, especially cTACE, especially in combination with sorafenib.

As for the embolic microsphere-based TACE, many studies examined drug-eluting beads or DEB-TACE and compared it to bland transarterial embolization (TAE) with the ultimate goal to identify the best technical alternative to cTACE. In 2016, a Phase II RCT in 101 patients directly compared DEB-TACE (LC Bead with 150 mg doxorubicin) with TAE (Bead Block microspheres) and found no apparent difference in response, survival, or adverse events.¹¹ This study suggested that adding chemotherapeutic agents to embolization may not elicit additional anti-tumor effects. As such, it challenged previous efficacy paradigms established with DEB-TACE. However, several issues with the trial design should be noted. First, stasis was chosen as the embolization endpoint, which precluded retreatment and potentially elevated hypoxia, likely contributing to the very short progression free survival (6.2 versus 2.8 months for DEB-TACE versus TAE). Second, Bead Block microspheres were additionally used in the DEB-TACE arm to achieve stasis, which deviate from the common DEB-TACE recommendations for using LC Beads. This drastically minimized the true technological difference between DEB-TACE and TAE and results of this study therefore cannot be generalized in a broader clinical context. Third, as the authors acknowledged, the study was not powered to detect small to moderate differences in outcome. In short, the cumulative trial evidence thus far has failed to show that TAE is truly equal to DEB-TACE. Of note, as the key studies on DEB-TACE were conducted in the West, its role in mostly Asian populations remains to be clarified in comparison to other IATs such as the well-established cTACE.

Radioembolization is another widely studied IAT with rising clinical use. From 2011 to 2015, retrospective studies showed longer time to progression (TTP), a better toxicity profile, and less hospitalization after radioembolization but no difference in survival, compared with TACE.¹²⁻¹⁵ Preliminary results in 43 patients from the PREMIERE study (NCT 00956930), a Phase II RCT, supported this TTP benefit of radioembolization over cTACE (not reached versus 6.4 months, $P=0.002$), but the trial was not appropriately powered and did not find significant difference in survival.¹⁶ Other prospective RCTs are thus underway further comparing radioembolization with TACE (NCT 01381211, NCT 02729506).

Evolution of Embolic Materials

Over the last decade, DEB-TACE has been clinically tested with the hope of eventually addressing some remaining issues with cTACE, such as drug dosing and extrahepatic drug toxicity.¹⁷ The most commonly used DEB is DC Beads loaded with doxorubicin (DEBDOX™), and there has been a trend to developing smaller-size DEB over time (e.g., from 500–700 µm to 100–300 µm in diameter) for greater distal penetration by accessing lesions perfused with smaller blood vessels.¹⁸ Recently, even smaller beads called M1 (LC Bead M1) have been developed with a diameter in the 70–150 µm range. LC Bead M1 has shown greater tumor penetration and drug delivery with a similar pharmacokinetic profile to larger beads in animal models¹⁹ and favorable short-term safety profile and promising results in objective response, tumor down-staging, and necrosis.²⁰ A clinical trial is now underway to further assess the feasibility and safety of doxorubicin-eluting LC Bead M1 for HCC (NCT 02007954). It may be that this smaller generation of drug-eluting beads could eventually fulfill the initial promise of DEB-TACE as the next-generation IAT.

In this context, another important advance in embolic material comes from LC Bead LUMI™, which is a radiopaque image-able microsphere labeled with iodine that can be visualized by fluoroscopy and CT. LC Bead LUMI™ have been designed to address the lack of imaging feedback in DEB-TACE, which uses radiolucent microspheres, in contrast to Lipiodol used in cTACE that is radiopaque. When performing DEB-TACE, soluble contrast medium is mixed with the beads to help visualize the delivery of these beads. The addition of contrast medium is critical to ensure that the beads do not reflux along the catheter shaft and also to gauge the degree of bead retention within the tumor as a sort of predictor of tumor response, realizing however that the bead location may not be truly reflected by contrast deposition within the tumor as the contrast medium washes out.^{21–23} On the other hand, because the LUMI™ beads enable direct visualization of bead location, It may be possible in the future to assess efficacy (i.e., completeness of target tissue embolization) and safety (i.e., unintentional embolization of non-target tissue) (Figure 1). Compared to conventional beads, LUMI™ beads have been shown to allow for better conspicuity to determine target and non-target embolization in pre-clinical studies²⁴ and to enable real-time geographic localization of embolization during treatment;²⁵ these results suggest that LUMI™ beads may help determine embolization endpoints more effectively. The imaging characteristics of LUMI™ beads are now studied in an ongoing clinical trial of hepatic tumors (NCT 02649868).

It was with much expectation that LC Bead M1 and LUMI™ beads were developed to improve DEB-TACE in treating HCC. However, as recent trial evidence has not demonstrated any dramatic increase of DEB-TACE efficacy over cTACE, it can be questioned if these incremental technological improvements may ever suffice to establish DEB-TACE as a true alternative to cTACE.

Imaging Markers of Tumor Response

Imaging biomarkers increasingly play an important role to evaluate treatment efficacy and guide therapeutic decisions. Response used to be measured with the World Health

Organization (WHO) and Response Evaluation Criteria in Solid Tumors (RECIST) guidelines for anatomic changes in lesion size.^{26,27} These criteria, however, cannot measure antitumor activity other than changes in tumor size, such as necrosis induced by loco-regional therapies. Newer guidelines proposed by the European Association for the Study of the Liver (EASL)²⁸ considered bi-dimensional (2D) area changes in enhancing tumor tissue using contrast-enhanced radiologic imaging as the optimal response assessment. More recently, the modified RECIST (mRECIST) criteria²⁹ was created, using a single long-axis measurement of enhancing tumor tissue, and has shown improved performance in treatment response assessment and survival prediction in HCC patients, compared to RECIST guidelines.^{30,31}

However, the existing 1 and 2D measurements, which estimate the overall tumor volume, are susceptible to high inter- and intra-rater variability,³²⁻³⁴ and tumor necrosis does not often conform to heterogeneous change in distribution or contrast enhancement. Therefore, a 3D quantitative enhancement-based response assessment method, quantitative EASL (qEASL), was developed (Figure 2) and has been shown to strongly correlate with pathological examinations of HCC lesion necrosis and better predict overall survival in treated HCC with TACE than using RECIST, mRECIST, or EASL guidelines.³⁵⁻³⁷ More recently, the feasibility of whole liver based volumetric enhancement assessment has been presented with favorable results for studying treatment response and survival in infiltrative and multifocal HCC, where tumor response is not quantifiable by any current guidelines.³⁸ Overall, current trends will bring about increasingly automated, machine-assisted techniques to assess tumor response with the ultimate goal of improving measurement objectivity and achieving higher standardization in clinical practice.

Combined Loco-regional And Systemic Therapies

To date, the only systemic antineoplastic therapy in HCC with proven survival benefit in Phase III trials is sorafenib. This oral multi-tyrosine-kinase inhibitor was tested and supported in the SHARP and Asia-Pacific studies that established its role in treating advanced stage HCC.^{39,40} The recently published data from the GIDEON study has demonstrated the excellent safety profile of sorafenib in both Child-Pugh A and B patients.⁴¹ Because TACE can induce extensive tumor hypoxia and thus lead to increased levels of pro-angiogenic factors, blocking VEGF expression and other pro-angiogenic downstream pathways with sorafenib may prevent disease recurrence or progression after therapy.^{42,43} Empirically, nearly half of the patients receive TACE before initiating sorafenib (e.g., 37% in the US, 71% in Japan), and one in ten receives TACE while on sorafenib (e.g., 13% in the US, 12% in Japan).⁴⁴ Early clinical trials support the safety and efficacy of combining TACE with sorafenib in both intermediate and advanced stage HCC.⁴⁵⁻⁴⁹ Notably, a single-arm Phase II study in 197 patients with intermediate stage HCC evaluated the combination of cTACE on demand and sorafenib on an interrupted treatment schedule and found this combination well tolerated and efficacious (86% estimated 3-year overall survival).⁵⁰ A retrospective study using propensity score analysis in 355 patients with advanced stage HCC found that the addition of TACE to sorafenib showed longer TTP than sorafenib alone (2.5 versus 2.1 months, $P=0.008$) but no significant difference in survival.⁵¹

Recently, the SPACE trial, a Phase II RCT in 307 patients compared sorafenib with placebo plus DEB-TACE in intermediate stage HCC. It confirmed the technical feasibility and safety of this combination but failed to find a difference in TTP between treatment groups (169 versus 166 days in the sorafenib arm versus placebo).⁵² This negative result is in part due to the conservative TACE treatment protocol by which over one third of patients in the sorafenib group received only one TACE; in fact, later evidence in separate studies suggested that many patients failing initial TACE would respond to a second TACE and have greater survival than nonresponders to both TACEs.⁵³ Furthermore, a larger percentage of non-Asian patients in the sorafenib arm received only the first TACE, compared to those in the placebo arm (42% versus 18%), in contrast to more balanced TACE administration in the Asian group. This heterogeneity may have contributed to the overall null result, especially given that greater TTP and a trend in increased overall survival were observed in the Asian patients. In addition, median overall survival, the ultimate oncological outcome, was not reached in either group.⁵² As a result, no definitive conclusion can be truly drawn from this study on the efficacy of DEB-TACE and sorafenib combination therapy.

In 2016, an interim futility analysis of the TACE 2 trial, a Phase III RCT studying the efficacy of sorafenib in addition to DEB-TACE in 294 patients led to the trial's termination. No evidence was found for improved progression free survival in patients with intermediate stage HCC (7.8 versus 7.7 months) who also received sorafenib.⁵⁴ While the results of another Phase III RCT testing combined TACE-sorafenib therapy (NCT 01004978) are pending, future research may be needed to identify alternative systemic therapies in combination with TACE to treat intermediate stage HCC.

In advanced stage HCC, however, combined TACE-sorafenib therapy seems safe and effective. For example, the GIDEON study reported that 85% patients experienced adverse events but there was no difference associated with TACE treatment administration.¹⁰ Importantly, patients with concomitant use of TACE and sorafenib achieved 22 months of overall survival, in comparison to 10 months in non-concomitant-TACE patients.

Another area of active research is the combination of radioembolization with sorafenib in intermediate and advanced stage HCC. A single-arm, Phase II trial in 29 patients studied the sequential treatment of radioembolization with Y90 resin microspheres followed by sorafenib 14 days after. Its findings supported the safety of this treatment regimen (28 patients experienced ≥ 1 toxicities; 52% grade ≥ 3 toxicity) and potential efficacy (25% best overall response rate; 100% and 65% disease control rates in intermediate and advanced stage HCC, respectively).⁵⁵ This was also supported by the safety and toxicity data in the first 40 patients from the SORAMIC trial, an RCT comparing radioembolization followed by sorafenib 3 days after with sorafenib alone (no significant difference in total or grade 3 or 4 toxicity).⁵⁶ However, this initial safety result was rated as very low for quality of evidence by Cochrane Reviews due to 1) high risk of performance and reporting biases and 2) unclear risk of attrition, selection, and detection biases.⁵⁷ Results of ongoing RCTs are awaited to provide further safety and efficacy data; these studies include SORAMIC (NCT 01126645), SARAH (NCT 01482442), and SIRveNIB (NCT 01135056) using resin microspheres and STOP-HCC (NCT 01556490) and YES-P (NCT01887717) using glass microspheres.

Clinical Introduction and Standardization of Cone-beam CT Imaging

Traditionally, a combination of ultrasound, CT, fluoroscopy, digital subtraction angiography (DSA), and magnetic resonance imaging techniques are used for planning, guiding, and assessing intra-arterial and percutaneous ablative therapies. For IATs, diagnostic validity of 2D DSA images is hampered by suboptimal identification of anatomy due to superimposed vessels and limited soft-tissue contrast. Thus, making cross-sectional 3D imaging datasets available during the procedure may provide the key advantage to achieve a better and more complete treatment. CBCT is a new imaging modality that has been introduced to clinical practice over the last decade and has gained wide clinical acceptance throughout the world. The ability to intra-procedurally acquire 3D CT-like images of vessels and soft tissue in an angiography suite allows the treating physician to see, reach, and treat targeted tumor tissue with greater diagnostic accuracy while additionally introducing the element of improved and immediate post-procedural evaluation of treatment success (Figure 3). The CBCT technique is based on the rotational image acquisition of a C-arm system equipped with an X-ray source and flat panel detector around the patient and 3D image reconstruction.^{58,59} Specifically, CBCT enables virtual 3D roadmapping developed from superimposed angiographic and fluoroscopic images. It dramatically improves lesion and feeding vessel detection, catheter navigation, and assessment of procedure technical success or embolization endpoint. It has also shown value in early prediction of treatment response.^{59,60}

CBCT has helped improve both local progression-free and overall survival^{61,62} and is currently recommended by the CardioVascular and Interventional Radiological Society of Europe and Society of Interventional Radiology for selective TACE.⁶³ In addition, the more recent contrast-enhanced dual-phase CBCT, based on the accumulation of information provided by consecutive acquisitions performed at different phases (e.g., arterial, portal venous, or delayed), has allowed more sensitive detection of liver tumors and improved assessment of tumor-feeding vessel devascularization after DEB-TACE.^{64,65} Furthermore, the feasibility of ultrafast CBCT, which uses the rotation of a double x-ray tube detector to acquire faster 3D volume data, has been studied with promising results for tumor and feeding vessel detection and catheter localization.⁶⁶

Of note, previous research on CBCT radiation exposure suggested that the use of CBCT during TACE increases the dose-area product greater than DSA alone.⁶⁷ This, however, is highly dependent on CBCT acquisition parameters.⁶⁸ With optimized parameters and advanced image processing algorithms, radiation exposure can be significantly reduced for TACE without increasing radiation time or decreasing DSA image quality.⁶⁹

To a lesser extent, CBCT in percutaneous ablation has been tested in several pilot studies.⁷⁰⁻⁷³ It has been proposed for targeting tumors that are difficult to locate by conventional means of ultrasound or CT and for post-procedural assessment of the ablation zone and margins. However, larger studies are needed to optimize technical specifications and confirm benefit in patient outcome.

Novel Techniques and Systemic Effects of Ablative Therapies

In addition to RFA, microwave ablation (MWA) has been established as an alternative thermal ablative option for treating HCC. It uses electromagnetic energy to cause rapid and homogeneous tissue heating and subsequent coagulation necrosis with less susceptibility to heat sink phenomenon to potentially achieve larger ablation volumes in a shorter procedural time.^{74,75} MWA may thus be successful in treating larger tumors, likely in combination with TACE,⁷⁶⁻⁷⁸ although this combination has not been directly compared to RFA with TACE.

Irreversible electroporation (IRE) is an emerging non-thermal ablative technology. It uses electric pulses to create nanoscale cellular membrane pores leading to cell death with more predictable ablation boundary than RFA and allows for preservation of tissue architecture and vital structures like blood vessels and nerves.⁷⁹ IRE, however, tends to require longer procedure times and is associated with higher complication rates, although this may result from selection bias of existing studies.⁸⁰ Furthermore, IRE followed by TACE has been studied in experimental porcine models with promising results showing enhanced intranuclear accumulation of doxorubicin in the reversible electroporation zone.⁸¹

In understanding the biology of ablation, increasing evidence has suggested that RFA is associated with acute increase in interleukin-6 and hepatocyte growth factor (HGF), thereby promoting tumor growth in distant, non-target tissues.⁸²⁻⁸⁴ Recent research confirmed this RFA “off-target” effect with rigorously designed mouse experiments and found that RFA activates innate immune response with myofibroblast activation and macrophage accumulation, leading to periablation inflammation and global liver regeneration.⁸⁵ Experiments using a chronic-inflammation-induced HCC mouse model (*Mdr2* knockout) found that this liver regeneration promotes c-met/HGF-dependent tumor formation, and blocking this liver regeneration by a c-met inhibitor modulates the RFA tumorigenic effect.⁸⁶ This raises the potential for introducing c-met inhibitor therapy to reduce HCC recurrence after RFA.

The “off-target” effect of IRE has also been recently studied.⁸⁷ Compared to RFA, IRE allows more patent vasculature to retain in the coagulation zone and thus invokes greater infiltration of macrophages and myofibroblasts with significantly higher serum interleukin-6 levels. Experiments using *Mdr2* knockout mice and subcutaneous BNL 1ME hepatocarcinoma xenografts found that IRE induced more pronounced systemic effects than RFA, both negative tumorigenic and desired immunogenic (abscopal) effects. This suggests that the ablation energy source may be selected to modulate systemic effects for improved clinical outcomes, if tumor can be profiled *a priori* for classifying response. Overall, the prospect of systemic, immunologically mediated effects of loco-regional therapies is rapidly gaining interest of the IO community.

Future Directions

First and foremost, more basic and translational studies are needed to further elucidate the systemic effects of loco-regional therapies, including the potential “off-target” effects of various IATs. Further investigation into the underlying mechanisms of these phenomena is

crucial. Strong focus should be placed on developing molecular imaging techniques capable of detecting these effects early within the course of therapy in order to devise strategies to mitigate undesired tumorigenic consequences. This effort shall also be closely linked to the development of novel molecular targeted agents to modulate the immune system and the tumor microenvironment in an adjuvant setting.

As for the choice of intra-arterial therapy, cTACE continues to be the most commonly used modality worldwide. Although DEB-TACE has undergone incremental advances in technology and protocol, this technique has yet to prove itself as a true alternative for cTACE. As such, further research is necessary to evaluate new generations of embolic and drug delivery materials, ablative technologies, and peri-procedural imaging modalities developed to achieve higher precision of targeted treatment. Along these lines, it is important to emphasize that not only should future advances be guided by what is technologically possible, they must take into account the value added to clinical care and patient survival. This aim is especially vital in the establishment of IO as the 4th pillar of cancer care.

With respect to clinical trials, the next goal for the IO community should be to broaden the application of established therapeutic modalities for the treatment of HCC. Therefore, we should expand treatment to both early stage disease as well as more advanced stages, which currently is seen by many as an exclusive domain of sorafenib. The knowledge gained from these efforts will work to improve current treatment algorithms such as the Barcelona Clinic Liver Cancer system and aid in investigation of additional guidelines such as the Hong Kong Liver Cancer staging system.⁸⁸ These future studies will require higher quality and greater numbers of prospective RCTs with overall survival as the final endpoint.

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Figure 1. LUMI™ beads applied in a rabbit with VX2 tumor implanted in the liver
Three dimensional volume rendered CBCT imaging, acquired post-euthanasia, was windowed to highlight the 1.1 mL of LUMI™ Beads (0.055 mL packed bead volume). The beads were suspended in iodinated soluble contrast medium and delivered intra-arterially. Note the hepatic arteries, non-target delivery, and the tumor located in the right hepatic lobe. CBCT: cone-beam computed tomography.

Figure 2. qEASL showing tumor response after DEB-TACE

A 58-year-old male with hepatocellular carcinoma underwent 1 session of DEB-TACE. Based on pre- and post-procedure magnetic resonance imaging, qEASL showed that the tumor volume reduced from 297.3 cm³ with 71.9% enhancement down to 197.1 cm³ with 2.7% enhancement. DEB-TACE: transarterial chemoembolization with drug-eluting beads.

Figure 3. CBCT imaging post TACE in comparison to MR imaging

A 55-year-old male with biopsy-proven hepatocellular carcinoma underwent 2 sessions of TACE with immediate post-procedure CBCT imaging that illustrates embolization endpoints, in comparison to MR imaging 4-6 weeks after TACE. CBCT: cone-beam computed tomography; DSA: digital subtraction angiography; MR: magnetic resonance; TACE: transarterial chemoembolization.