Minimally Invasive, Image-Guided Therapy for Liver Cancer: What Every Oncologist Needs to Know

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Abstract

Liver cancer continues to be a growing healthcare challenge worldwide. Both primary and secondary liver cancers are among the most commonly reported causes of cancer-related death, and the incidence rates of primary liver cancer, or hepatocellular carcinoma (HCC), are expected to grow in the United States and Europe. The majority of patients' cancers are diagnosed at stages that are not amenable to surgical or curative therapy. However, alternative options for the treatment of HCC have expanded greatly in recent years, mostly due to technical innovations in interventional oncology. Advancements in imaging capabilities have allowed the integration of innovative, image-guided, catheter-based, intra-arterial therapies into clinical practice. New modalities of these minimally invasive therapies have become widely adopted, which has allowed larger-scale studies to clarify their appropriate role in the multidisciplinary clinical management of patients. In parallel, basic and translational research continue to break new ground in therapy paradigms, including the introduction of new generations of drug-eluting beads and radioembolic microspheres. This review highlights the history of these therapies, and discusses the value of novel, emerging, image-guidance technologies as well as the most recently presented data from prospective trials on the combination of local tumor therapies with systemically administered anticancer agents.

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Introduction

Hepatocellular carcinoma (HCC) ranks globally as the second most common cause of cancer-related death, and its incidence continues to rise.[1] The medical and surgical management of patients with HCC is often complicated by multiple factors, including progression to advanced disease by the time of diagnosis, lack of highly effective systemic therapies, and limited surgical options due to the high comorbidity of HCC and chronic liver disease.[2]

Interventional oncology (IO), a newly organized subspecialty of interventional radiology, offers several image-guided minimally invasive techniques to treat cancer, with the ultimate goal of improving patient outcomes with both curative and palliative intent (**Figure**). Among several therapeutic modalities that are at the disposal of an interventional oncologist, the catheter-based intra-arterial approach has become the most commonly used delivery route for anticancer agents, such as drugs and therapeutic radiation that can be delivered at high doses directly to the liver tumors while dramatically reducing systemic side effects. These techniques have been used and validated for the past 30 years and have been incorporated into all major guidelines and endorsed by several societies and study groups worldwide.[3,4] However, progress in the field continues, and the armamentarium of IO practices has continued to grow and improve in response to the need for improved management of patients with nonresectable liver cancer. The development of innovative technologies in image-guided procedures has allowed for widespread clinical adoption of previously niche, locoregional tumor therapies over the past decade.

Many of these therapies, specifically variations of transarterial chemoembolization (TACE) procedures, take advantage of the unique anatomy of HCC tumors, which are vascularized almost completely by the hepatic artery, with normal liver parenchyma supplied by the portal vein, which improves targeting and allows for the preservation of nontumoral tissues. There are various intra-arterial therapy (IAT) modalities currently in clinical use;

the most widely used is conventional TACE (cTACE), which employs a cocktail of chemotherapeutic agents, most commonly doxorubicin or cisplatin, suspended in an ethiodized oil, Lipiodol, followed by administration of additional embolic particles.[5] Other IAT options include bland transarterial embolization (TAE), drug-eluting bead TACE (DEB-TACE), and radioembolization with microspheres containing yttrium 90 (^{90}Y). This review highlights general principles, indications for use, and comparisons of efficacy between the various IATs, discusses imaging biomarkers of treatment response, and examines evidence from recent clinical trials of systemic therapies used in conjunction with IATs.

Rationale for Intra-Arterial Therapy and Patient Selection

Most patients with primary liver cancer are not considered to be candidates for curative surgical therapy at the time of diagnosis, and until today, there was no systemic chemotherapy, with the exception of sorafenib, that has been shown to improve patient survival. Locoregional tumor therapies offer an additional line of treatment and have demonstrated excellent local tumor control rates and an improved overall survival (OS) compared with best supportive care (BSC).[6] As such, and given the lack of therapeutic alternatives, embolotherapy continues to be the primary or secondary therapeutic choice in over 70% of all patients with liver cancer and is applied both in a palliative setting as well as in a bridge-to-transplant scenario.[7,8] Selection of patients for locoregional therapies requires a collaborative approach of a multidisciplinary team of experts, often composed of hepatologists, oncologists, transplant surgeons, radiation oncologists, and interventional radiologists.

From a technical perspective, IATs exploit the fact that HCC tumors are almost exclusively fed by the hepatic artery, while normal liver tissue is mostly supplied by the portal vein. This difference in blood supply allows for a highly selective embolization of, and cytotoxic drug delivery to, tumors with relative sparing of surrounding normal tissue. Embolization of the vascular supply leads to ischemic necrosis of the tumor tissue while also slowing washout of chemotherapeutic agents, allowing higher levels of drug delivery to target tissues than would be possible with systemic therapy. Conversely, bland embolization is performed without any chemotherapeutic agent, while in ^{90}Y radioembolization, tumoricidal radiation is delivered locally into the tumor using radioactive microspheres. Regardless of payload, IATs carry substantial benefits in terms of quality of life and—across the board and regardless of the modality—are able to provide excellent local tumor control.[9]

Choice of Intra-Arterial Therapy

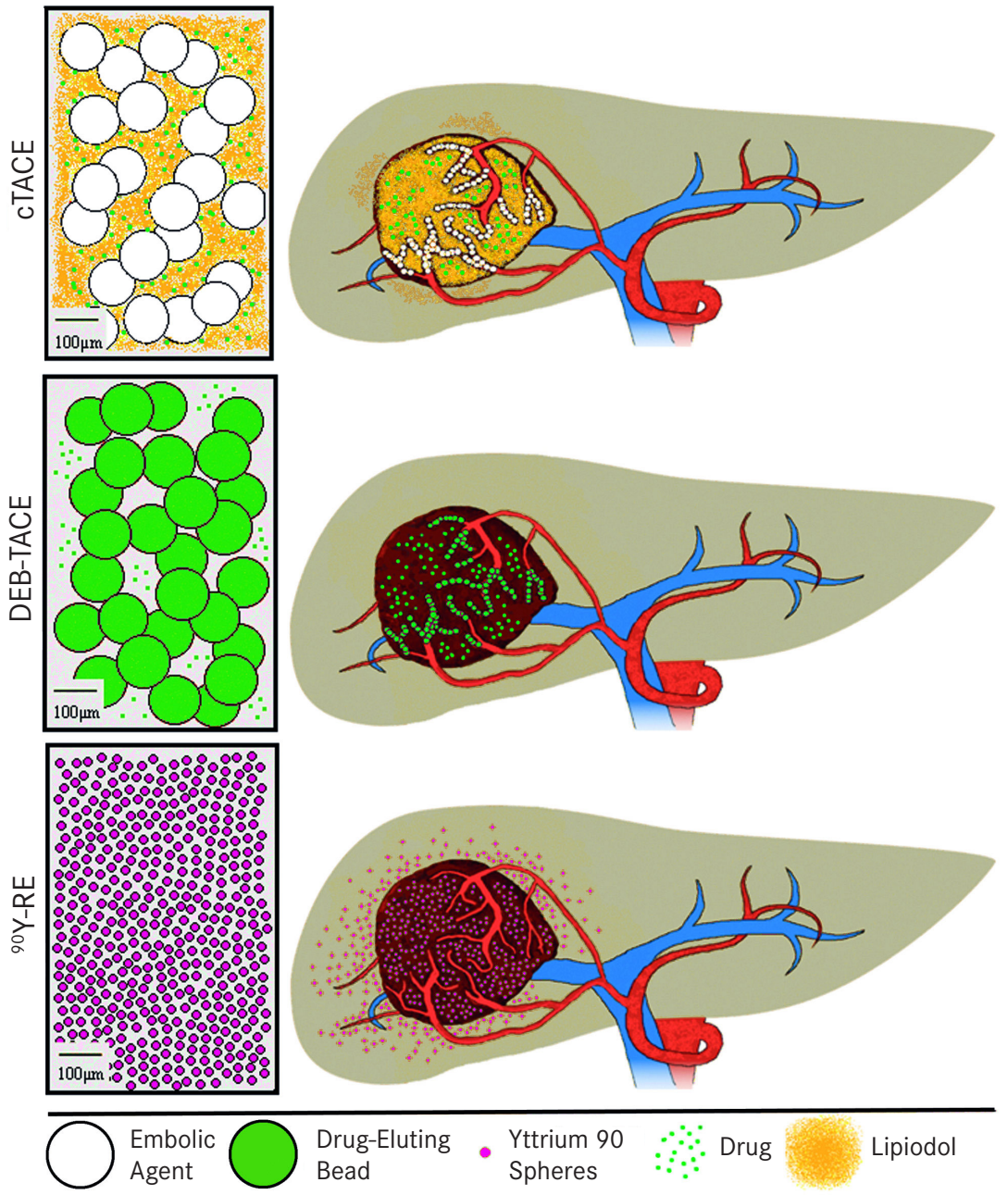
Multiple IAT modalities are available for tumor management, and the most commonly performed worldwide is cTACE, a Lipiodol-based embolotherapy. The procedure consists of an initial targeted infusion of a chemotherapeutic agent suspended in Lipiodol, an iodinated, poppy seed oil-based medium, followed by infusion of embolic particles or sterile compressed sponge. The suspension of Lipiodol increases the viscosity and x-ray visibility of the agent, and the embolic particles further delay washout of chemotherapy from the tumor. This promotes a slow, sustained delivery of the agent within the tumor while also promoting embolic blockade. Lipiodol therefore serves as an effective drug carrier, embolic agent, and imaging response biomarker while also minimizing systemic concentrations of chemothera-peutic agents.[10]

While both Lipiodol-based cTACE and bland TAE have been used clinically for many years, there has yet to be a completed, well-controlled trial directly comparing the 2 therapies, and the determination of superiority of cTACE over TAE remains unclear.[11] While more recent randomized controlled trials (RCTs) have investigated the efficacy of DEB-TACE versus TAE, the latest available RCT that directly compared TAE, TACE, and BSC in patients with HCC was published in 2002, but was aborted after demonstrating clear superiority of cTACE over BSC. Follow-up in this trial was thus not sufficient to compare the TAE and cTACE arms.[6] However, today, Lipiodol-based cTACE remains the more widely utilized therapy, and is supported by a greater body of data demonstrating its efficacy. Although Lipiodol is currently only approved for imaging purposes in the United States, it has been used extensively for therapeutic purposes of primary and secondary liver cancer in both Europe and Asia for nearly 3 decades.

A 2016 systematic efficacy and safety review of Lipiodol-based cTACE, which drew data from over 10,000 patients with HCC, reported an objective response rate of 52.5% and an OS of 70.3% at 1 year, 51.8% at 2 years, and 32.4% at 5 years (median, 19.4 months).[12] Of more than 20,000 reported adverse effects, liver enzyme abnormalities were most common, followed by postembolization syndrome. Overall treatment-related mortality was 0.6%, most often attributed to acute liver insufficiency. These data re-established cTACE as the standard of care with respect to IAT for liver cancer, and demonstrated that this IAT modality continues to be the safest and more effective choice around the world.

In addition, data gathered recently from the GIDEON study,[13] a large observational registry that included more than 3000 patients with HCC, indicated that nearly half of these patients received cTACE at some point during

FIGURE. CT Scans of the Abdomen: Response of the Liver Lesions Over Time



cTACE indicates conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization; ^{90}Y-RE, yttrium 90 radioembolization.

their treatment course. It also re-established the findings of previous RCTs that demonstrated clinically significant survival benefits of cTACE over BSC.[6] The GIDEON registry additionally found that 47% of patients received TACE prior to systemic sorafenib, with Lipiodol-based cTACE accounting for up to 74% of these procedures. One notable discrepancy was in the United States, where DEB-TACE was administered more commonly. Additional and more recent evidence of efficacy was demonstrated with the data from the prospective BRISK-TA study (NCT00908752), a randomized phase III protocol that is investigating the impact of treatment with brivanib plus chemoembolization versus chemoembolization alone on OS in patients with advanced-stage HCC. This report, in one of the largest ever reported prospective cohorts of patients with HCC, demonstrated that patients undergoing chemoembolization alone within the control arm achieved a median OS of almost 26 months, which can now be seen as the new standard and benchmark, at least for patients with intermediate-stage disease.[14]

As for DEB-TACE, this technique has been introduced in hopes of addressing some of the challenges of cTACE, such as accurate drug dosing and systemic toxicities. Ever since the advent of DEB-TACE a decade ago, the technique has been thoroughly investigated in several prospective clinical trials and identified as safe and effective in terms of local tumor control.[15,16] In recent years, DEB-TACE has become universally accepted and integrated into clinical practice, effectively dominating the choice of therapy in many US care centers.[17] The most common drug-eluting beads (DEBs) currently used are DC Beads loaded with doxorubicin (DEBDOX), which range in size from 100 to 300 μm. Smaller beads such as the LC Bead M1 (diameter range, 70-150 μm range) are being investigated for their potential to penetrate more distally into the tumor vasculature, and have shown greater drug delivery to tumors in preclinical studies.[18] Despite high overall efficacy, DEB-TACE has not yet demonstrated the ability to fulfill the promise of improved survival outcomes over cTACE and, from a global perspective, has not yet reached the status of a standard-of-care therapy.

A similar statement can be made about ^{90}Y radioembolization, which utilizes far smaller particles (with a range of 30 to 60 μm, depending on the product) to deliver a tumoricidal dose of beta-radiation directly to the tumor.[19] Several retrospective studies and small RCTs have compared radioembolization to cTACE and have shown some improvements in time to progression (TTP), but no difference in OS.[20,21] On the horizon are some potentially impactful improvements to microsphere-based therapies, including the use of radiopaque beads (LC Bead LUMI), which allow more accurate intraprocedural visualization of microsphere delivery and embolic endpoints. However, as of today, cTACE continues to be the clinical standard of care, both from a standpoint of worldwide utilization as well as available data.

Intraprocedural Image Guidance With Cone-Beam Computed Tomography

Combinations of ultrasound, computed tomography (CT), magnetic resonance imaging, fluoroscopy, and digital subtraction angiography (DSA) have conventionally been used in the process of planning, performing, and postoperatively assessing IATs. While 2-dimensional DSA imaging has often been the mainstay of intraprocedural guidance, its diagnostic potential is hampered by suboptimal anatomic differentiation due to superimposed vessels and poor soft-tissue contrast. The intraprocedural utilization of 3D imaging modalities may therefore allow for more accurate treatment delivery and improved outcomes.

Cone-beam CT (CBCT) is an imaging modality that has been increasingly integrated into clinical practice over the past decade, and has been used with high success in the guidance of complex intra-arterial procedures. Intraprocedural visualization of 3D images of vessels and soft tissue enables the operator to better reach and map the tumor tissue, while also allowing immediate and improved postprocedural validation of therapeutic endpoints. Operatively, CBCT imaging is based on rotational image acquisition around the patient by a C-arm machine with an x-ray source and flat panel detector with subsequent 3D reconstruction. Immediate generation of high-accuracy 3D CT-like images allows for super-selective catheterization and much more accurate vessel targeting. This has greatly improved intraoperative catheter guidance, detection of feeding vessels, and assessment of embolization endpoints.[22] CBCT has also shown benefit in early detection of treatment response after cTACE.[23] More importantly, CBCT has become an independent determinant of OS, with patients receiving Lipiodol TACE under CBCT guidance, demonstrating significantly higher OS and local progression-free survival (PFS) compared with patients under angiography guidance alone (OS, 74% vs 44% at 3 years).[24-26] With this in mind, CBCT has been widely incorporated into clinical practice, and is now becoming a platform for advanced image-guided approaches to treating liver cancer and beyond.

Imaging Biomarkers of Response

Evaluation of embolotherapy response is an integral part of the treatment course and informs further therapeutic decision making. While survival continues to be the ultimate endpoint in clinical trials, therapeutic efficacy and decisions on whether or not to re-treat a patient with

a particular therapy must rely on surrogate markers for therapeutic efficacy. Both for IO and beyond, imaging biomarkers for tumor response have been widely accepted as an integral part of the therapy assessment algorithm. In addition, outcome surrogates such as PFS and TTP, which are often used as endpoints, rely completely on accurate radiographic response evaluation. Thus, a rigorous and standardized imaging schedule is typically required for all IO procedures, with baseline imaging being performed 2 to 3 weeks prior to treatment and follow-up imaging being obtained 4 to 6 weeks afterward.[27]

Changes in anatomic lesion size or diameter have historically been used to evaluate tumor response; however, no universal consensus on evaluation criteria existed in the past.[28] The World Health Organization (WHO) first published 2D tumor response criteria in 1981, based on the sum of 2 long-axis measurements of the tumor diameter to calculate percentage of shrinkage in tumor size.[29] Since that time, multiple new criteria have been proposed and validated; one of the most widely accepted has been the Response Evaluation Criteria In Solid Tumors (RECIST) system for evaluation of systemic chemotherapy, which relies upon single longest plane measurements.[30] However, most IATs induce tumor ischemia and necrosis, with little to no immediate tumor shrinkage. As such, purely anatomic markers of tumor change were ineffective in near-term response evaluation to embolotherapy.[31]

In an effort to find improved markers of response to embolotherapy, the European Association for the Study of the Liver (EASL) guidelines were published with the inclusion of bi-dimensional tumor contrast enhancement as a relative biologic marker of change due to tumor necrosis.[4] Modified RECIST criteria (mRECIST) were introduced soon after to improve EASL guidelines by incorporating enhancing tumor single-axis measurements into the previous RECIST criteria. Unfortunately, frequent variation of tumor anatomy and the inhomogeneity of necrotic tumor volumes often limit the reliable application of these criteria, and they are subject to large inter- and intra-observer variability. Nevertheless, both EASL and mRECIST criteria have demonstrated superior efficacy in evaluating treatment response and predicting survival outcomes.[32]

Even with the inclusion of enhancing diameters, both single-axis and bi-dimensional criteria are still hampered by similar challenges and can only provide surrogate volumetric assessment of tumors. Currently under investigation are 3D volumetric assessment criteria, which attempt to address the problems associated with lower dimensional analysis. Initial studies have demonstrated the feasibility and efficacy of 3D quantitative analysis in the locoregional therapy response assessment of liver tumors. Further investigation found that quantitative 3D volumetric analysis correlated well with histopathologic findings.[33] Most recently, a 2016 study compared the predictive correlations of non-3D methods (RECIST, EASL, mRECIST) with quantitative 3D criteria, and found that the non-3D criteria were unable to distinguish treatment responders from nonresponders, while the quantitative 3D method demonstrated significant between-group differences.[27] The quantitative 3D criteria, primarily quantitative EASL, are currently the most predictive response criteria of patient survival, and their adoption into clinical practice may prove beneficial in therapeutic decision making.

Combination Therapies

The basic mechanism of action for all embolotherapies is the induction of an ischemic insult to the tumor tissue. While instantaneously effective, this mechanism may also induce severe tissue hypoxia followed by a massive surge of pro-angiogenic mediators, such as the vascular endothelial growth factor, a molecule known to promote vascular proliferation, and thus revascularization of the tumor tissue. Therefore, combining locoregional therapies with molecular targeted inhibitors of this pathway is theoretically appealing. As of today, sorafenib, an orally active multi-tyrosine kinase inhibitor, continues to be the only systemically applicable therapy for HCC, and has demonstrated both survival benefit and activity along the aforementioned molecular pathway. Established in 2 large prospective trials, the SHARP and the Asia-Pacific trials, sorafenib is able to modestly improve median OS in patients with advanced-stage HCC by no more than 3 months compared with placebo.[34]

As a result, several trials that combined sorafenib with TACE followed around the world. The previously mentioned GIDEON registry demonstrated that nearly half of patients received TACE before starting sorafenib (37% in the United States, 71% in Japan), and 10% received TACE while taking sorafenib.[35] A recent phase II trial found that the combination of TACE and sorafenib was well tolerated and effective, reporting an 83% survival at 3 years, while a separate retrospective study found that combination therapy increased TTP compared with sorafenib alone, but did not significantly affect OS.[36-38] Most importantly, the recently published multicenter RCT, the SPACE study,[39] which investigated safety and efficacy of DEB-TACE combined with sorafenib, failed to demonstrate a survival benefit of the combination when compared with DEB-TACE alone. While the combination of sorafenib with TACE continues to be of questionable benefit, several ongoing clinical trials are investigating the combination of ^{90}Y radioembolization with sorafenib,[40] including the SORAMIC (NCT01126645), SARAH (NCT01482442), and STOP-HCC (NCT01556490) trials.

Conclusion and Future Perspectives

Over the past 2 decades, IO has become an innovative and clinically indispensable pillar of cancer care around the globe, with liver cancer being the central scope of expansion. While young as a profession, IO is driven by technical progress and interdisciplinary collaboration, which transcends professional boundaries and limitations. In this regard, basic and translational research into the therapeutic mechanisms of local tumor therapies and their interactions with systemic therapies are vital for continued development in the field. Further understanding of the systemic effects of locoregional therapies is also necessary, and will lead the way toward broader acceptance within the oncology community. Emphasis should be placed on the discovery of novel, molecularly targeted, pharmacologic therapies that will enhance and improve the efficacy of IO therapies in an adjuvant setting. As for the future of clinical practice, further work is needed to accurately direct treatment recommendations, improve and standardize radiographic evaluation criteria, and further advance drug carrier systems and their delivery using novel image-guidance instruments. While developments in technology can be expected to shape the future of the IO landscape, all advancements must be measured by the benefit they ultimately bring to patient survival and quality of life.

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