Loco-Regional Treatment of Hepatocellular Carcinoma

Riccardo Lencioni

Loco-regional treatments play a key role in the management of hepatocellular carcinoma (HCC). Image-guided tumor ablation is recommended in patients with early-stage HCC when surgical options are precluded. Radiofrequency ablation has shown superior anticancer effects and greater survival benefit with respect to the seminal percutaneous technique, ethanol injection, in meta-analyses of randomized controlled trials, and is currently established as the standard method for local tumor treatment. Novel thermal and nonthermal techniques for tumor ablation—including microwave ablation, irreversible electroporation, and light-activated drug therapy—seem to have potential to overcome the limitations of radiofrequency ablation and warrant further clinical investigation. Transcatheter arterial chemoembolization (TACE) is the standard of care for patients with asymptomatic, noninvasive multinodular tumors at the intermediate stage. The recent introduction of embolic microspheres that have the ability to release the drug in a controlled and sustained fashion has been shown to significantly increase safety and efficacy of TACE with respect to conventional, lipiodol-based regimens. The available data for radioembolization with yttrium-90 suggests that this is a potential new option for patients with HCC, which should be investigated in the setting of randomized controlled trials. Despite the advances and refinements in loco-regional approaches, the long-term survival outcomes of patients managed with interventional techniques are not fully satisfactory, mainly because of the high rates of tumor recurrence. The recent addition of molecular targeted drugs with antiangiogenic and antiproliferative properties to the therapeutic armamentarium for HCC has prompted the design of clinical trials aimed at investigating the synergies between loco-regional and systemic treatments. The outcomes of these trials are eagerly awaited, because they have the potential to revolutionize the treatment of HCC. (HEPATOLOGY **2010;52:762-773**)

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related death.[1] Unlike most solid cancers, future incidence and mortality rates for HCC were projected to largely increase in several regions around the world over the next 20 years, mostly as a result of the dissemination of hepatitis C virus infection.[2,3] Early diagnosis of HCC can be achieved by surveillance of at-risk populations.[4-6] However, a careful multidisciplinary assessment of tumor characteristics, liver function, and physical status is required for proper therapeutic management even in patients with early-stage tumors.[7] Candidates for resection must be carefully selected to minimize the risk of postoperative liver failure and improve long-term results.[7] Access to liver transplantation has to be balanced between precise estimation of survival contouring individual tumor characteristics and organ availability.[8] When surgical options are precluded, image-guided tumor ablation is recommended as the most appropriate therapeutic choice and is considered a potentially radical treatment in properly selected candidates.[7]

Despite the widespread implementation of surveillance programs, more than half of the patients with HCC are diagnosed late, when curative treatments cannot be applied.[9] In addition, in a high proportion of cases, the disease recurs after radical therapy.[10,11] For patients presenting with multinodular HCC and

Abbreviations: CI, confidence interval; HCC, hepatocellular carcinoma; IRE, irreversible electroporation; MWA, microwave ablation; PEI, percutaneous ethanol injection; RCT, randomized controlled trial; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization.

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relatively preserved liver function, absence of cancer-related symptoms, and no evidence of vascular invasion or extrahepatic spread–i.e., those classified as intermediate-stage according to the Barcelona Clinic Liver Cancer (BCLC) staging system [12]–transcatheter arterial chemoembolization (TACE) is the current standard of care.[7] Systemic treatment with the multikinase inhibitor sorafenib is recommended for patients at a more advanced stage of the disease.[13]

Image-guided loco-regional therapies, including direct tumor ablation techniques and transcatheter treatments, play a major role in the clinical management of HCC. However, despite several recent advances and technical refinements, the long-term survival outcomes of patients managed with interventional techniques are not fully satisfactory, mainly as a result of the high rates of tumor recurrence. The recent addition of molecular targeted agents that inhibits tumor cell proliferation and angiogenesis to the therapeutic armamentarium for HCC has prompted the design of clinical trials aimed at investigating the synergies between loco-regional and systemic treatments. In this article, well-established and new loco-regional therapies for HCC are reviewed, and the rationale for combined strategies, including interventional techniques and systemically-active drugs, is discussed.

Image-Guided Tumor Ablation

The term "image-guided tumor ablation" is defined as the direct application of chemical or thermal therapies to a specific focal tumor(s) in an attempt to achieve eradication or substantial tumor destruction.[14] Although tumor ablation procedures can be performed at laparoscopy or surgery, most procedures aimed at treating HCC are performed with a percutaneous approach. Hence, several authors refer to these procedures as "percutaneous therapies". The concept of image guidance is stressed in the title to highlight that image guidance is critical to the success of these therapies. Over the past 25 years, several methods for chemical or thermal tumor destruction have been developed and clinically tested.[15] More recently, new options that use novel, nonchemical nonthermal ablative techniques have become subjects of clinical investigation.

Chemical Ablation

The seminal technique used for chemical ablation of HCC has been percutaneous ethanol injection (PEI). Ethanol induces coagulation necrosis of the lesion as a result of cellular dehydration, protein denaturation, and chemical occlusion of small tumor vessels. An alternate method for chemical ablation is acetic acid injection. However, acetic acid injection has been used by very few investigators worldwide.

Ethanol Injection. PEI is a well-established technique for the treatment of nodular-type HCC. HCC nodules have a soft consistency and are surrounded by a firm cirrhotic liver. Consequently, injected ethanol diffuses within them easily and selectively. The standard PEI protocol includes 4-6 sessions performed under ultrasound guidance by using fine noncutting needles. Although there have not been any randomized controlled trials (RCTs) comparing PEI and best supportive care or PEI and surgical resection, several retrospective studies have provided indirect evidence that PEI substantially improves the natural history of HCC: in patients with Child-Pugh class A cirrhosis and early-stage tumors, treatment with PEI has been shown to result in 5-year survival rates of 47%-53%.[16,17]

The major limitation of PEI is the high local recurrence rate, which may reach 33% in lesions smaller than 3 cm and 43% in lesions exceeding 3 cm.[18,19] The injected ethanol does not always accomplish complete tumor ablation because of its inhomogeneous distribution within the lesion, especially in the presence of intratumoral septa, and the limited effect on extracapsular cancerous spread. The recent introduction of a specific device for single-session PEI, a multipronged needle with three retractable prongs, each with four terminal side holes (QuadraFuse; Rex Medical, Conshohocken, PA), has been shown to overcome some of these limitations, by ensuring a more homogeneous ethanol perfusion throughout the whole tumor mass. In a recent study that included 141 patients with early-stage HCC, PEI performed with multipronged needles resulted in a rate of sustained complete response of 90% in tumors smaller than 3 cm and of 75% in tumors ranging 3-5 cm in diameter. Hence, the technique seems to offer a valuable alternative to thermal ablation.[20]

Acetic Acid Injection. Acetic acid injection has been proposed as a viable alternative to PEI for chemical ablation of HCC. Despite some initial promising reports, this method had limited diffusion and was not tested in large series of patients. The reported survival outcomes are not better than those obtained by several authors with PEI.[21]

Thermal Ablation

The thermal ablative therapies involved in clinical practice can be classified as either hyperthermic treatments—including radiofrequency ablation (RFA), microwave

ablation (MWA), and laser ablation—or cryoablation. The thermal damage caused by heating is dependent on both the tissue temperature achieved and the duration of heating. Heating of tissue at 50°C-55°C for 4-6 minutes produces irreversible cellular damage. At temperatures between 60°C and 100°C, near-immediate coagulation of tissue is induced, with irreversible damage to mitochondrial and cytosolic enzymes of the cells. At more than 100°C-110°C, tissue vaporizes and carbonizes.[22] On the other hand, the freezing of tissue with temperatures between −20°C and −60°C followed by rapid thawing results in cell membrane disruption and induces cell death. For adequate destruction of tumor tissue, the entire target volume must be subjected to cytotoxic temperatures.

Radiofrequency Ablation. The goal of RFA is to induce thermal injury to the tissue through electromagnetic energy deposition. In the more popular monopolar mode, the patient is part of a closed-loop circuit that includes a radio frequency generator, an electrode needle, and a large dispersive electrode (ground pads). An alternating electric field is created within the tissue of the patient. Because of the relatively high electrical resistance of tissue in comparison with the metal electrodes, there is marked agitation of the ions present in the target tissue that surrounds the electrode, because the tissue ions attempt to follow the changes in direction of alternating electric current. The agitation results in frictional heat around the electrode. The discrepancy between the small surface area of the needle electrode and the large area of the ground pads causes the generated heat to be focused and concentrated around the needle electrode. Several electrode types are available for clinical RFA, including internally cooled electrodes and multiple-tined expandable electrodes with or without perfusion.[22] An important factor that affects the success of RFA is the ability to ablate all viable tumor tissue and possibly an adequate tumor-free margin. Ideally, a 360-degree, 0.5-cm-thick to 1-cm-thick ablative margin should be produced around the tumor. This cuff would ensure that the peripheral portion of the tumor as well as any microscopic invasions located in its close proximity have been eradicated.[23]

RFA has been the most widely assessed alternative to PEI for local ablation of HCC. Five RCTs have compared RFA versus PEI for the treatment of early-stage HCC. These investigations consistently showed that RFA has higher anticancer effect than PEI, leading to a better local control of the disease[24-28] (Table 1). The assessment of the impact of RFA on survival has been more controversial. Although a survival benefit was identified in the three RCTs performed in Asia, the two European RCTs failed to show statistically significant differences in overall survival between patients who received RFA and those treated with PEI, despite the trend favoring RFA (Table 1). In patients with early-stage HCC treated with percutaneous ablation, long-term survival is influenced by multiple different interventions, given that about 80% of the patients will develop recurrent intrahepatic HCC nodules within 5 years of the initial treatment and will need additional therapies.[29] Nevertheless, three independent meta-analyses including all RCTs have confirmed that treatment with RFA offers a survival benefit as compared with PEI, particularly for tumors larger than 2 cm, thus establishing RFA as the standard percutaneous technique.[30-32] For studies that reported major complications, however, the incidence in RFA-treated patients was 4.1% (95% confidence interval [CI], 1.8%-6.4%), compared to 2.7% (95% CI, 0.4%-5.1%) observed in PEI-treated patients.[33] This difference was not statistically significant; nevertheless, this safety profile should be taken into consideration as part of the overall risk/benefit profile in each individual case.

Recent reports on long-term outcomes of RFA-treated patients have shown that in patients with Child-Pugh class A and early-stage HCC, 5-year survival rates are as high as 51%-64%, and may reach 76% in patients who meet the BCLC criteria for surgical resection[29,34-36] (Table 2). Therefore, an open question is whether RFA can compete with surgical resection as first-line treatment for patients with small,

Table 1. Randomized Controlled Trials Comparing RFA Versus PEI for the Treatment of Early-Stage HCC

Author and Year (Reference)	Initial CR	Treatment Failure*	Overall Survival (%)		
			1-Year	3-Year	*P*
Lencioni et al., 2003 (24)					
RFA ($n = 52$)	91%	8%	88	81	NS
PEI ($n = 50$)	82%	34%	96	73	
Lin et al., 2004 (25)					
RFA ($n = 52$)	96%	17%	82	74	0.014
PEI ($n =52$)	88%	45%	61	50	
Shiina et al., 2005 (26)					
RFA ($n = 118$)	100%	2%	90	80	0.02
PEI ($n = 114$)	100%	11%	82	63	
Lin et al., 2005 (27)					
RFA ($n = 62$)	97%	16%	88	74	0.031
PEI ($n = 62$)	89%	42%	96	51	
Brunello et al., 2008 (28)					
RFA ($n = 70$)	96%	34%	88	59	NS
PEI ($n = 69$)	66%	64%	96	57	

*Includes initial treatment failure (incomplete response) and late treatment failure (local recurrence).

CR, complete response; HCC, hepatocellular carcinoma; NS, not significant; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation.

Table 2. Studies Reporting 5-Year Survival of Patients with Early-Stage HCC Who Received RFA as the Sole First-Line Nonsurgical Treatment

Author and Year (Reference)	Patients (Number)	Overall Survival (%)		
		1-Year	3-Year	5-Year
Lencioni et al., 2005 (29)				
Child-Pugh A	144	100	76	51
Child-Pugh B	43	89	46	31
Tateishi et al., 2005 (34)				
Child-Pugh A	221	96	83	63
Child-Pugh B-C*	98	90	65	31
Choi et al., 2007 (35)				
Child-Pugh A	359	NA	78	64
Child-Pugh B	160	NA	49	38
N'Kontchou et al., 2009 (36)				
BCLC resectable†	67	NA	82	76
BCLC unresectable	168	NA	49	27

*Only 4 of 98 patients had Child-Pugh C cirrhosis.

†BCLC criteria for resection include single tumor, normal bilirubin level (<1.5 mg/dL), and absence of significant portal hypertension.

BCLC, Barcelona Clinic for Liver Cancer; HCC, hepatocellular carcinoma; NA, not available; RFA, radiofrequency ablation.

solitary HCC nodules. A RCT comparing resection versus ablation in patients with Child-Pugh class A cirrhosis who have single HCCs 5 cm or less in diameter has failed to show statistically significant differences in overall survival and disease-free survival between the two treatment arms.[37] However, neither overall survival nor disease-free survival were primary endpoints for that study. In addition, the sample size was not powered to show noninferiority, and a non-negligible rate of crossover occurred. Nonetheless, other nonrandomized investigations have suggested that RFA can achieve similar survival rates as surgical resection, particularly in patients bearing small, solitary tumors at the very early stage of the BCLC classification.[38]

Caution is needed when interpreting and generalizing these results, in particular in light of studies that suggest a non-negligible rate of incomplete histopathological response after RFA. Even in small tumors, the ability of RFA to achieve complete tumor eradication appears to be dependent on tumor location. Histological studies performed in liver specimens of patients who underwent RFA as bridge treatment to transplantation showed that the presence of large (≥3 mm) abutting vessels results in a drop of the rate of complete tumor necrosis to <50%, because of the heat loss due to perfusion-mediated tissue cooling within the area to be ablated.[39] Other clinical experiences have suggested that treatment of HCC tumors in subcapsular location or adjacent to the gallbladder is associated with an increased risk of incomplete ablation and local tumor progression.[40,41] Treatment of tumors in such unfavorable locations has also been shown to result in a significant increase of major complications.[42,43] Thus, at this point, there is no unequivocal data to back up RFA as a replacement for resection as first-line treatment for patients with early-stage HCC.

Microwave Ablation. MWA is the term used for all electromagnetic methods of inducing tumor destruction by using devices with frequencies ≥900 kHz. The passage of microwaves into cells results in the rotation of individual molecules. This rapid molecular rotation generates and uniformly distributes heat, which is instantaneous and continuous until the radiation is stopped. Microwave irradiation creates an ablation area around the needle in a column or round shape, depending on the type of needle used and the generating power.

MWA is emerging as a valuable alternative to RFA for thermal ablation of HCC. However, only one RCT has compared the effectiveness of MWA with that of RFA so far.[44] Although no statistically significant differences were observed with respect to the efficacy of the two procedures, a tendency favoring RFA was recognized in that study with respect to local recurrences and complications rates. It has to be pointed out, however, that MWA technology has evolved significantly since the publication of this trial. Newer devices seem to overcome the limitation of the small volume of coagulation that was obtained with a single probe insertion in early experiences.[45] An important advantage of MWA over RFA is that treatment outcome is not affected by vessels located in the proximity of the tumor.

Laser Ablation. The term "laser ablation" should be used for ablation with light energy applied via fibers directly inserted into the tissue. A great variety in laser sources and wavelength are available. In addition, different types of laser fibers, modified tips, and applicators can be used. A spherical volume of coagulative necrosis up to 2 cm in diameter can be produced from a single, bare 400-μm laser fiber. Use of higher power results in charring and vaporization around the fiber tip. Two methods have been developed for producing larger volumes of necrosis. The first consists of firing multiple bare fibers arrayed at 2-cm spacing throughout a target lesion, whereas the second uses cooled-tip diffuser fibers that can deposit up to 30 W over a large surface area, thus diminishing local overheating.[46]

To date, few data are available concerning the clinical efficacy of laser ablation, because the treatment has been adopted by few centers worldwide. In particular, no RCTs to compare laser ablation with any other treatment have been published thus far. In a recent

multicenter retrospective analysis including 432 nonsurgical patients with early-stage HCC, 5-year overall survival was 34% (41% in patients with Child-Pugh class A cirrhosis).[47]

Cryoablation. Cryoablation is a technique in which a cryoprobe cooled with liquid nitrogen is placed into the tumor and an ice ball is created in the target tissue. The technique had limited application in HCC.[48,49] The complication rate is not negligible, particularly because of the risk for "cryoshock", a life-threatening condition resulting in multiorgan failure, severe coagulopathy, and disseminated intravascular coagulation following cryoablation. There are currently no RCTs that support the use of hepatic cryoablation for HCC treatment.

New Nonchemical Nonthermal Ablation Techniques

New, nonchemical, nonthermal image-guided ablation techniques are currently undergoing clinical investigation. These include irreversible electroporation (IRE) and light-activated drug therapy. These techniques promise to overcome some of the limitations of chemical and thermal-based techniques in the treatment of HCC.

Irreversible Electroporation. Electroporation is a technique that increases cell membrane permeability by changing the transmembrane potential and subsequently disrupting the lipid bilayer integrity to allow transportation of molecules across the cell membrane via nanosize pores. This process, when used in a reversible fashion, has been used in research for drug or macromolecule delivery into cells. IRE is a method to induce irreversible disruption of cell membrane integrity resulting in cell death without the need for additional pharmacological injury.[50] The IRE system (NanoKnife; AngioDynamics, Queensbury, NY) consists of two major components: a generator and needle-like electrical probes. The generator can deliver up to 3000 V of energy in a maximum of 100 pulses which have a maximum pulse length of 100 μseconds. The electrode probe is 19 gauge in diameter and has an active tip that can be exposed up to 4 cm. Two or more monopolar probes or a single bipolar probe must be used at a time. The number of monopolar probes that are used during an IRE procedure is dependent on the size and shape of the desired zone of tissue ablation. The treatment parameter for voltage is dependent on the distance between probes within the targeted tissue. IRE is administered under general anesthesia with administration of atracurium, cis-atracurium, pancuronium, or an equivalent neuromuscular blocking agent to prevent undesirable muscle contraction.[50]

IRE creates a sharp boundary between the treated and untreated area *in vivo*. This would suggest that IRE has the ability to sharply delineate the treatment area from the nontreated, and that treatment planning can be precisely performed according to mathematical predictions. In addition, IRE can effectively create tissue death in microsecond to millisecond ranges of treatment time compared to thermal ablation techniques, which require at least 20 minutes to hours. Moreover, because IRE is a nonthermal technique, there appears to be complete ablation to the margin of blood vessels without compromising the functionality of the blood vessels. Therefore, issues associated with perfusion-mediated tissue cooling or heating (a significant challenge with thermal methods) are not relevant.

Preclinical investigation of IRE focused on HCC has shown promising results. In a recent study, HCC tumors were grown in 30 Sprague-Dawley rats that were divided into treatment and control groups.[51] For treatment group, IRE electrodes were inserted and eight 100-μsecond, 2500-V pulses were applied to ablate the targeted tumor tissues. Pathology correlation studies documented progression from poorly differentiated viable HCC tissues before treatment to extensive tumor necrosis and full regression in 9 of 10 treated rats 7-15 days after treatment. These findings suggest that IRE can be an effective strategy for targeted ablation of HCC, and have prompted its clinical evaluation.

Light-Activated Drug Therapy. Light-activated drug therapy uses light-emitting diodes to activate talaporfin sodium (Aptocine; Light Sciences Oncology, Bellevue, WA), a small drug molecule which is synthesized from a chlorophyll derivative. Talaporfin sodium has the capacity to concentrate in tumors when administered intravenously. It is then activated by a thin light-emitting activator which is percutaneously inserted intratumorally under imaging guidance. The drug is capable of absorbing long-wavelength light, resulting in singlet oxygen that causes apoptotic cell death through oxidation and permanent tumor blood vessel closure.[50]

The device contains a tiny array of light-emitting diodes at the end of a very narrow (1.2 mm wide) flexible coated microwire. The array is inserted into the target tumor using a biopsy-like procedure requiring only a mild sedation. The device emits red light at a discrete frequency and intensity for a fixed time period. Experimental studies suggest that singlet oxygen causes the destruction of all cells within the kill zone. The size of the kill zone is determined by the fluence level of activating light and the time of illumination. Research has shown that a maximum effective kill

zone of 2.5 cm by 4.5 cm is achieved with a single catheter, although multiple catheters can be used in a single treatment to increase the kill zone. All vasculature within the kill zone is also quickly and permanently occluded by an accumulation of platelet fragments, fibrin deposition, and vascular debris.[52]

Potential advantages of light-activated drug therapy with talaporfin sodium include the accurate prediction of the size of the kill zone by illumination time and fluence, the independency of treatment effect from tumor histotype and tumor location (proximity to large blood vessels or the gastrointestinal tract, for instance, affects neither the production of the primary kill zone nor is it associated with any complications) and the ability to treat large or multiple tumors in a single session requiring only mild sedation. Treatment with talaporfin sodium is generally well tolerated, although cutaneous photosensitivity requires attention and adequate protection. Of interest, findings from animal studies suggest that the production of large apoptotic masses in tumors with light-activated drug therapy yields tumor-specific clones of CD8+ T cells which infiltrate distant, untreated tumors.[53] Talaporfin sodium is currently in a phase 3 clinical trial in HCC.[54]

Image-Guided Transcatheter Tumor Therapy

The term "image-guided transcatheter tumor therapy" is defined as the intravascular delivery of therapeutic agents via selective catheter placement with imaging guidance.[55] Various agents such as chemotherapeutic agents, embolic particles, or radioactive materials can be injected via feeding vessels to tumor(s) in an attempt to achieve cytoreduction by enabling more focused delivery or deposition of higher concentrations within the tumor.[55] Therapeutic material may eventually include drug-eluting microspheres, biologically active agents, chemical mediators of cell function and/or the tumor microenvironment, viral vectors, genetic material, nanoparticles, or other as-yet undescribed agents. The term "transcatheter" aims to distinguish these therapies from direct ablative therapies. The term "image guidance" separates these therapies from chemotherapy administered via an implanted hepatic arterial chemotherapy port. The most common methods of image-guided transcatheter tumor therapy used in HCC treatment are chemoembolization and radioembolization.

Chemoembolization

HCC exhibits intense neoangiogenic activity during its progression. The rationale for TACE is that the intra-arterial infusion of a drug such as doxorubicin or cisplatin with or without a viscous emulsion, followed by embolization of the blood vessel with gelatin sponge particles or other embolic agents, will result in a strong cytotoxic effect combined with ischemia. Although conventional TACE with administration of an anticancer-in-lipiodol emulsion followed by embolic agents has been the most popular technique, the recent introduction of embolic, drug-eluting microspheres has provided a valuable alternative and has replaced conventional regimens at several institutions.

Table 3. Randomized Controlled Trials Comparing TACE or TAE Versus Conservative Management or Suboptimal Therapies for the Treatment of HCC

Author and Year (Reference)	Patients (Number)	Overall Survival (%)		
		1-Year	2-Year	*P*
Lin et al., 1988 (56)				
TAE (gelfoam + ivalon)	21	42	25	NS
TAE + IV 5-fluorouracil	21	20	20	
IV 5-fluorouracil	21	13	13	
Pelletier et al., 1990 (57)				
TACE (doxorubicin, gelfoam)	21	24	NA	NS
Conservative management	21	33	NA	
GETCH*, 1995 (58)				
TACE (cisplatin, gelfoam)	50	62	38	NS
Conservative management)	46	43	26	
Bruix et al., 1998 (59)				
TAE (gelfoam + coils)	40	70	49	NS
Conservative management	40	72	50	
Pelletier et al., 1998 (60)				
TACE (cisplatin, gelfoam) + tamoxifen	37	51	24	NS
Tamoxifen	36	55	26	
Lo et al., 2002 (61)				
TACE (cisplatin, gelfoam)	40	57	31	0.002
Conservative management	39	32	11	
Llovet et al., 2002 (62)				
TACE (doxorubicin, gelfoam)	40	82	63	0.009†
TAE (gelfoam)	37	75	50	
Conservative management	35	63	27	

*Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire.

†Chemoembolization versus conservative management (TAE versus conservative management = NS; TACE versus TAE = NS).

HCC, hepatocellular carcinoma; IV, intravenous; NA, not available; NS, not significant; TACE, transarterial chemoembolization; TAE, transarterial embolization.

Conventional TACE. The survival benefit of arterial embolization or chemoembolization has been the subject of a few RCTs, that provided contradictory results[56-62] (Table 3). A cumulative meta-analysis of these studies, however, has clearly shown that 2-year survival of patients with HCC not suitable for radical therapies who are treated with arterial embolization or chemoembolization is improved compared to conservative management for suboptimal therapies.[63] Sensitivity analysis assessing 323 patients in four studies[58,60-62] showed a significant benefit of chemoembolization with cisplatin or doxorubicin, but no benefit with

embolization alone when 215 patients in three studies were assessed.[56,59,62]

The outcome of the treatment appears to be dependent on careful patient selection. In an RCT that recruited patients with compensated cirrhosis (70% in Child-Pugh A), absence of cancer-related symptoms (81% with Eastern Cooperative Oncology Group [ECOG] performance status of 0), and large or multinodular HCC with neither vascular invasion nor extrahepatic spread, 2-year survival after conventional TACE reached 63%, compared to 27% of the untreated control arm ($P = 0.009$).[62] In contrast, in another RCT, the use of broader enrollment criteria with inclusion of patients with symptoms of limited portal vein invasion resulted in a 2-year survival of only 31%.[61] This figure was still superior to that of the untreated control group (2-year survival, 11%; $P = 0.002$); however, no survival benefit was identified in the subgroup analysis restricted to patients presenting with portal vein invasion.[61]

As a result of these investigations, TACE has been established as the standard of care for patients who meet the criteria for the intermediate stage of the BCLC staging system, i.e., those with multinodular HCC, relatively preserved liver function, absence of cancer-related symptoms, and no evidence of vascular invasion or extrahepatic spread.[7] The recommendations issued on the basis of the mentioned RCTs had a major impact in clinical practice. In an analysis of the management of patients with HCC who were not suitable for curative therapy conducted across several Italian centers, no significant difference in survival between patients treated with TACE and untreated patients was observed in the 1999-2002 period. In contrast, in the 2003-2006 period, a distinct survival benefit ($P < 0.0001$) was shown between TACE-treated and untreated patients, suggesting a better selection of the candidates.[64]

The tolerability of conventional TACE seems to be affected by the type of regimen and the frequency of the treatment. The Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire evaluated a treatment schedule of conventional TACE with cisplatin every 2 months in patients with unresectable HCC but without severe liver disease.[58] This schedule was associated with frequent acute liver failure, with 30 of the 50 treated patients reporting this adverse event. Conversely, Llovet and colleagues evaluated a schedule of conventional TACE treatment with doxorubicin at baseline, 2 months, 6 months, and then every 6 months thereafter, with only 2 of 40 patients submitted to TACE who eventually developed liver failure.[62] However, no RCTs have been designed to fully evaluate the optimum frequency of delivery. There is also a lack of consensus regarding the use and type of chemotherapy agent or embolic material.

TACE with Drug-Eluting Beads. The ideal TACE scheme should allow maximum and sustained concentration of chemotherapeutic drug within the tumor with minimal systemic exposure combined with calibrated tumor vessel obstruction. The recent introduction of embolic microspheres that have the ability to actively sequester doxorubicin hydrochloride from solution and release it in a controlled and sustained fashion has been shown to substantially diminish the amount of chemotherapy that reaches the systemic circulation compared with lipiodol-based regimens, thus significantly increasing the local concentration of the drug and the antitumoral efficacy.[65]

In a multicenter phase 2 RCT that included 201 European patients ("PRECISION V"), use of doxorubicin-eluting beads (DC Bead; Biocompatibles, Surrey, UK) resulted in a marked and statistically significant reduction in liver toxicity and drug-related adverse events compared with conventional TACE with doxorubicin.[66] The mean maximum aspartate aminotransferase increase in the DC Bead group was 50% less than in the conventional TACE group (95% CI, 39%-65%; $P < 0.001$) and 41% less with respect to alanine aminotransferase (95% CI, 46%-76%; $P < 0.001$) (Fig. 1). Because of the improved safety and tolerability profile, high-dose doxorubicin treatment could be applied according to the planned schedule in the whole drug-eluting bead group, regardless of patient baseline characteristics, resulting in consistently high rates of objective response and disease control in all subgroup analyses. Contrary to the observation in the drug-eluting bead arm, the response rates for conventional TACE in the subgroups of patients with more advanced disease were significantly reduced ($P = 0.038$ for objective response; $P = 0.026$ for disease control) (Fig. 2).

The added value of the chemotherapeutic agent over the bland embolic microsphere has been demonstrated by an RCT that compared beads uploaded with doxorubicin versus bland embolization performed with an embolic microsphere with similar characteristics. The rate of tumor progression at 12 months was significantly lower in the drug-eluting bead arm than in the bland embolization arm (46% versus 78%, $P = 0.002$), and time-to-progression increased from 36.2 ± 9.0 weeks to 42.4 ± 9.5 weeks ($P = 0.008$).[67] A recent investigation assessing the degree of necrosis in explanted livers after chemoembolization with epirubicin-loaded DC Bead versus bland

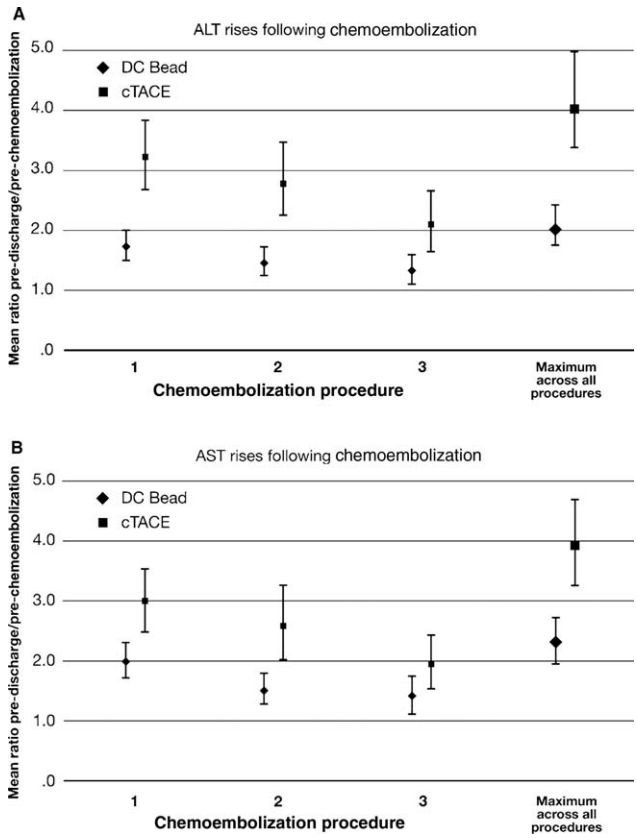

Fig. 1. Randomized trial of conventional TACE with lipiodol and doxorubicin (cTACE) versus doxorubicin-eluting beads (DC Bead). Comparison of treatment groups for fold-changes in liver enzymes by TACE procedure and maximum fold-change across all procedures (mean, 95% confidence interval). Analysis using *t* test for log-transformed data; results back-transformed to ratio scale for presentation. (A) Alanine aminotransferase (ALT): procedures 1 and 2 and maximum across all procedures, $P < 0.001$; procedure 3, $P = 0.004$. (B) Aspartate aminotransferase (AST): procedure 1, $P = 0.001$; procedure 2 and maximum across all procedures, $P < 0.001$; procedure 3, $P = 0.06$. Reprinted from Lammer et al.,[66] with permission.

embolization in patients on a transplant waiting list confirmed that TACE with drug-eluting beads achieved complete necrosis in 77% of lesions, whereas bland embolization achieved complete necrosis in only 27% of lesions ($P = 0.043$).[68]

Radioembolization

The use of conventional external-beam radiation therapy in HCC treatment has been limited by the low radiation tolerance of the cirrhotic liver, that often resulted in radiation-induced liver disease, previously known as radiation-induced hepatitis.[69] Radioembolization is defined as the infusion of radioactive substances including microspheres containing yttrium-90 (^{90}Y), iodine-131 iodized oil, or similar agents into the hepatic artery.[55] Currently, the most popular radioembolization technique uses microspheres coated with ^{90}Y, a beta-emitting isotope. Given the hypervascularity of HCC, microspheres injected intra-arterially will be preferentially delivered to the tumor-bearing area and selectively emit high-energy, low-penetration radiation to the tumor. There are currently two commercially available ^{90}Y microsphere devices: TheraSphere (MDS Nordion, Ottawa, Canada) is made of glass and SIR-Spheres (Sirtex Medical, Sydney, Australia) is made of resin. These two devices are different in a number of important respects.[70] Glass microspheres are a minimally embolic device consisting of particles 20-30 μm in size with higher specific activity (2500 Bq) and lower number of spheres (1.2 million microspheres/3 GBq). Conversely, resin microspheres are moderately embolic, consisting of particles 20-60 μm in size, with lower specific activity (50 Bq) and greater number of spheres (approximately 40-80 million spheres/3 GBq).

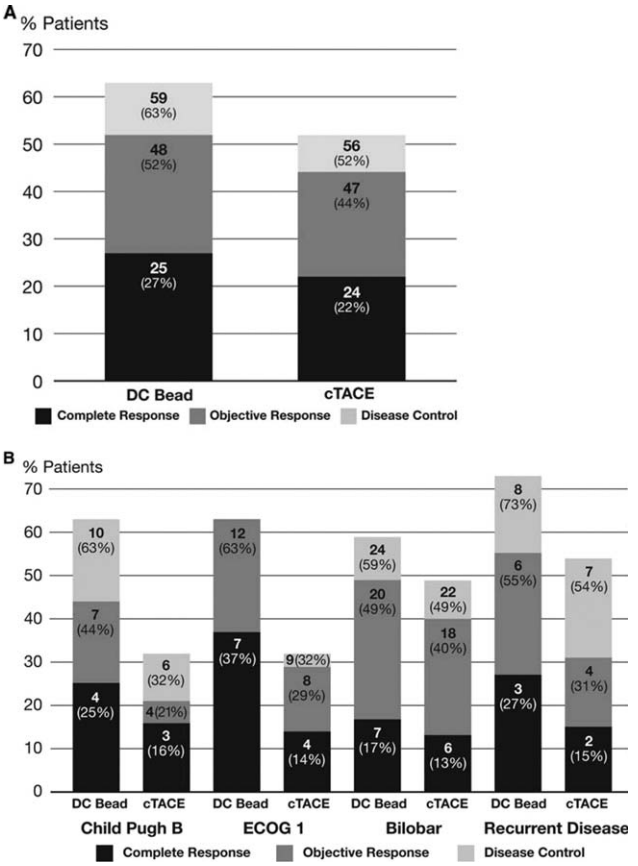

Fig. 2. Randomized trial of conventional TACE with lipiodol and doxorubicin (cTACE) versus doxorubicin-eluting beads (DC Bead). (A). Comparison of complete response, objective response, and disease control rate (cumulative number [percent] of patients) of all patients at 6 months. (B). Complete response, objective response, and disease control rate (cumulative number [percent] of patients) of patients by stratification factors for advanced disease (Child-Pugh class B, ECOG performance status 1, bilobar tumor, recurrent tumor) at baseline. Reprinted from Lammer et al.,[66] with permission.

The safety of ^{90}Y radioembolization has been documented in several phase 1 and 2 clinical investigations.[71-73] Because of the minimally embolic effect of ^{90}Y microspheres, treatment can be safely used in patients with portal vein thrombosis.[74] Two absolute contraindications exist for the use of ^{90}Y microsphere treatment. The first includes a pretreatment ^{99m}Tc macro-aggregated albumin scan demonstrating significant hepatopulmonary shunting that would result in >30 Gy being delivered to the lungs with a single infusion or as much as 50 Gy for multiple infusions. The second includes the inability to prevent deposition of microspheres to the gastrointestinal tract with modern catheter techniques. Serious complications have been reported as a result of untargeted radiation, including cholecystitis, gastric ulceration, gastroduodenitis, pancreatitis, and radiation pneumonitis.

A number of cohort studies and retrospective analyses have reported the efficacy of radioembolization in the treatment of HCC. In a study that reported the correlation between radiologic and pathologic findings in patients with HCC who underwent radioembolization with ^{90}Y microspheres prior to transplantation, all target lesions demonstrated some degree of histologic necrosis and 23 of 38 (61%) showed complete pathologic necrosis.[75] In a recently published article, the long-term outcomes of patients with HCC (n = 291) who were treated with ^{90}Y as part of a single-center, prospective, longitudinal cohort study were reported.[76] Toxicities included fatigue (57%), pain (23%), and nausea/vomiting (20%); 19% exhibited grade 3/4 bilirubin toxicity. The 30-day mortality rate was 3%. Survival times differed between patients with Child-Pugh class A and B disease (class A = 17.2 months; class B = 7.7 months; $P = 0.002$).

Despite the amount of data, no RCTs have been published so far that prove the clinical benefit of radioembolization with respect to the established treatment options for the patient populations that are targeted by radioembolization, i.e., TACE for noninvasive multinodular tumors at the intermediate stage of the BCLC classification, and sorafenib for advanced HCC showing vascular invasion. Two recent studies have reported a nonrandomized comparison of radioembolization and conventional TACE. In a North American two-cohort experience, 99 patients with HCC not suitable for curative treatments received a single dose of ^{90}Y, and 691 patients who had similar treatment criteria received repetitive, cisplatin-based TACE: overall survival was slightly better in the ^{90}Y group compared with the TACE group (median survival, 11.5 months versus 8.5 months). However, the selection criteria indicated a significant bias toward milder disease in the ^{90}Y group.[77] In another study, outcomes from patients who underwent radioembolization (n = 44) or conventional TACE (n = 27) as the only treatment were compared, and no difference in median overall survival was observed.[78] These data can be used to describe ^{90}Y as a potential treatment option for patients with HCC and to design future RCTs.

Synergies and Combination Strategies

Image-guided loco-regional therapies have long been used in the setting of combined treatment strategies. An accepted indication is the use of interventional treatment in patients awaiting transplantation to prevent tumor progression when the waiting time exceeds 6 months.[7,79] The combined use of transcatheter treatments and tumor ablation techniques is very popular in the treatment of HCC tumors of intermediate (3-7 cm) size. A combination of TACE followed by RFA has been used to minimize heat loss due to perfusion-mediated tissue cooling and increase the therapeutic effect of RFA.[80-83] On the other hand, TACE with drug-eluting beads has been performed after an RFA procedure to increase tumor necrosis by exposing the peripheral part of the tumor, where only sublethal temperatures may be achieved in a standard RFA treatment, to high drug concentration.[84] Unfortunately, despite several investigations that reported promising results, no definitive proof of clinical efficacy was reached, because no robust RCT comparing the efficacy of the combined use of transcatheter treatments and tumor ablation techniques over the one obtained with either therapy alone has been completed so far.

An important limitation of any loco-regional treatment is the high rate of tumor recurrence. After local ablation of early-stage HCC, tumor recurrence rate exceeds 80% at 5 years, similar to postresection figures.[29] Molecular studies have shown that early recurrences, occurring within the first 2 years after curative treatment, are mainly due to the spread of the original tumor, whereas late recurrences are more frequently due to the development of metachronous tumors independent of the previous cancer. On the other hand, in patients with large or multinodular tumors at the intermediate-stage HCC who received TACE, tumor recurrence or progression is almost inevitable. In RCTs, a sustained response lasting more than 3-6 months was observed in only 28%-35% of the cases, and in nonresponders, no survival benefit was identified compared to best supportive care.[61,62] Even in those patients in whom initial response was achieved, the 3-year

cumulative rate of intrahepatic recurrence reached 65%, with recurrent tumor showing significantly shorter median doubling time.[85] As a result, the 3-year survival rate of TACE-treated patients did not exceed 26%-29% even in the two positive RCTs.[61,62]

Increased understanding of the molecular signaling pathways involved in HCC has led to the development of molecular targeted therapies aimed at inhibiting tumor cell proliferation and angiogenesis. Sorafenib, a multikinase inhibitor with antiangiogenic and antiproliferative properties, has been shown to prolong median overall survival and median time to radiological progression compared to placebo in RCTs and has become the current standard of care for patients with advanced-stage tumors not suitable for surgical or loco-regional therapies.[86,87] To date, studies of sorafenib have demonstrated its efficacy in advanced HCC; however, there may also be a role for this agent, or other molecular targeted drugs, in earlier-stage disease, either as adjuvant treatment after curative therapy or in combination with TACE.

Tumor recurrence following TACE, in particular, is characterized by increased vascular endothelial growth factor production and subsequent angiogenesis. Moreover, TACE increases vascular endothelial growth factor expression in the residual surviving cancerous tissue[88] and induces expression of other proangiogenic factors, such as hypoxia-inducible factor 1 alpha.[89] Based on these findings, combination of TACE with agents with antiangiogenic properties would appear to be a rational approach. The availability of drug-eluting beads, which ensure a minimal systemic exposure to the chemotherapeutic agent at the time of the TACE, is very appealing for combination regimens including transcatheter treatment in association with a systemically active drug.

The first large studies in which an interventional loco-regional treatment is evaluated in combination with a systemically active molecular targeted drug are already ongoing. Undertaking these studies has required an extraordinary effort, due to the need to go beyond the boundaries of each discipline and to develop a common framework for the design of clinical trials to facilitate comparability of the results.[13,90] The outcomes of these trials are eagerly awaited, because they have the potential to revolutionize the treatment of HCC.

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