Review Article

Percutaneous therapies of hepatocellular carcinoma—an update

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Abstract: Percutaneous image-guided tumor therapies have proved important in the treatment of patients with primary liver cancer. The therapeutic spectrum for the management of this patient group includes ablative techniques such as ethanol ablation and radiofrequency ablation for patients with early-stage disease as well as intra-arterial approaches such as radioembolization and transarterial chemoembolization for patients with intermediate and end-stage disease. The tremendous advantage of such therapies is the reduced systemic toxicity combined with efficient local tumor control. However, specific therapeutic algorithms continue to be highly unstandardized and depend on individual experience of the operator. In this review, we will describe the rationale behind several percutaneous techniques, focusing on intra-arterial therapies of hepatocellular carcinoma (HCC) and review the available clinical evidence. We will also discuss new developments such as the combination of intra-arterial therapies with new systemically applicable drugs.

Keywords: Hepatocellular carcinoma (HCC); intraarterial therapy; sorafenib; deb-tace; radioembolization

Submitted Jul 01, 2013. Accepted for publication Jul 11, 2013.
doi: 10.3978/j.issn.2304-3865.2013.07.04
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Introduction

Hepatocellular carcinoma (HCC) is the sixth most prevalent neoplasm and the third most common cause of cancer-related death in the world. With more than 700,000 diagnosed cases per year, it continues to be the leading cause of death in patients with liver cirrhosis. As Asia continues to be the region with the most cases of HCC, there is an increasing incidence of the disease in Europe and North America (1). Advanced diagnostics and effective early treatment of HCC patients enables a median survival of about 5 years, yet the prognosis remains to be poor for a big number of patients (2). Since the 1980s, percutaneous therapies of primary liver cancer became the most frequently performed locoregional procedures in interventional radiology (IR) (3,4). While significantly contributing to the evolution of interventional oncology and gaining interdisciplinary acceptance as a therapeutic option for the treatment of primary hepatic malignancies, some minimally invasive approaches can also be employed for down-staging prior to orthotopic liver transplantation and resection (5). The management of IR patients with liver cancer requires multidisciplinary cooperation and usually includes hepatologists, surgical oncologists, transplant surgeons, radiation oncologists as well as interventional and diagnostic radiologists (6). While most percutaneous tumor ablation techniques non-selectively target tumor-containing liver tissue, intraarterial therapies of the liver exploit the observation that as opposed to normal liver tissue, most of the liver neoplasms receive their blood supply from arterial blood vessels. This remarkable characteristic allows an operator to use transcatheter intraarterial approaches to deliver high dose treatment selectively to the tumor, while preserving normal hepatic parenchyma (7). Image guidance remains to be a crucial aspect of any percutaneous approach. Several imaging modalities, such as fluoroscopy and cone-beam CT, ultrasound and MR are being used for treatment planning, tumor targeting, treatment monitoring and the assessment of treatment response (8,9). Percutaneous

ablation of small liver tumours in patients with early-stage disease has been a part of IR practice since the early 1980s. It began with the instillation of ethanol (10), which quickly resulted in 5-year survival rates comparable with surgical resection (11). In time, different modalities such as radiofrequency ablation, cryoablation and microwave ablation were developed and new techniques continue to evolve. The initial trials to establish intra-arterial liver therapies dated back to the 1970s and aimed at cutting off the local arterial blood supply of liver tumours in patients with of intermediate- and end-stage disease (12). Although the general principles of intra-arterial therapies remained unchanged, various modifications have been introduced over the course of the last 30 years. The most frequently used image-guided intraarterial liver tumor therapies performed by interventional radiologists include transarterial embolization (TAE), transarterial chemoembolization (TACE) with or without drug-eluting beads (DEBs) and radioembolization using Yttrium-90. While DEB-TACE has been shown to enhance loco-regional drug delivery and to further reduce systemic drug exposure as compared with conventional TACE (13), radioembolization represents an alternative intraarterial method to deliver a high, tumoricidal radiation dose to arterial-fed tumors while sparing healthy liver tissue.

Ablative therapies of HCC-technique

Initial experience with one of the first image-guided, percutaneous liver tumor ablations was collected by Livraghi *et al.*, when 12 patients with various primary and secondary liver malignancies were treated with injections of 95% ethyl alcohol (percutaneous ethanol injection, PEI) (10). PEI proved to safely achieve complete necrosis of small liver tumours, even when applied in tumours near sensitive organs. However, the need for multiple treatments and a frequent local tumour recurrence showed significant limitations of the modality (14). radiofrequency ablation (RFA), the first energy-based ablation technique, uses electrical current to cause thermal-based cytotoxicity, producing coagulation necrosis near the electrode (15). Analysis of safety and efficacy in patients treated with RFA shows excellent results for single HCC nodules (5 cm and smaller) as well as for multiple small lesions (each 3 cm or smaller) (16). An important benefit of RFA is the "oven effect", defined as heat retention in nodules surrounded by the tumor capsule and cirrhotic tissue (17) thus causing extensive necrosis. However, a physical limitation of RFA is the "heat sink" effect, defined as the cooling effect of blood flow through large vessels or ascites near the ablation zone (18). This can results in insufficient local tumor response. Microwave ablation (MWA), another ablative technique, appears to be less susceptible to the physical limitations of the "heat-sink" effect (19). This system uses high-frequency electromagnetic energy to rapidly oscillate water molecules, resulting in coagulation necrosis though frictional heat. When compared to RFA, MWA shows higher temperatures and a shorter treatment time. While both, RFA and MWA show similarities for safety and efficacy (20), more studies of MWA effects on long-term survival are needed. Multiple other modalities such as cryoablation, irreversible electroporation as well as image-guided, catheter based high-dose brachytherapy of liver tumours are gaining more attention. However, technical specifics of each method are beyond the scope of this review.

Ablative therapies of HCC—clinical evidence

Multiple studies provide clinical evidence for survival benefits of patients with early stage HCC, treated with ablative techniques. A recently published, retrospective study reported the 20-year clinical outcome of 685 HCC patients, treated with a total of 2,147 ethanol injections. With a median follow-up of 51.6 months, an overall survival rate of 49% and a recurrence rate of 60.8% after 20 years, this analysis confirmed the curative potential of PEI, when used in patients with early-stage HCC and small tumors (2.83±1.47 cm) (21). A prospective trial provided long-term survival rates for early-stage HCC patients treated with RFA. Here, a total of 187 patients were treated and minor complications appeared in only 5% of the patients. In this cohort, the median survival rate was 57 months and an overall survival rate after 5 years was 48%. A local tumor progression was observed in only 10% after 5 years (22), once again proving the efficacy of ablative techniques. A most recent prospective, randomized controlled trial compared the impact of RFA alone versus the combination of TACE with RFA on the overall survival of 189 patients (n=94 received RFA and n=95 received TACE-RFA). The treated collective comprised patients with mostly early-stage and some with intermediate-stage disease, a total of 90 patients in both groups classified as Child-Pugh A. The mean tumor size in each treatment arm was 3.47 and 3.39 cm for the TACE-RFA and the RFA alone group, respectively. In the TACE-RFA group, RFA followed the cTACE treatment within 2 weeks. Patients treated with the

TACE-RFA combination had significant benefits regarding overall survival and recurrence-free survival when compared with the RFA group. Specifically, the 4-year survival rate was reported as 61.8% and 45% for the TACE-RFA and RFA group, respectively (23). The results of this study are encouraging and provide a new perspective for the combination of intra-arterial approaches with ablative techniques in patients with intermediate stage HCC.

Transarterial chemoinfusion and embolization

Systemic chemotherapy remains to be the backbone of multiple anti-cancer treatments since early in the 1940s, yet the primary endpoint of anti-cancer research has experienced a shift from survival towards avoidance of toxicities and recurrence (24). Compared with systemic drug administration, regional chemotherapy of the liver offers the advantage of high selectivity, minimized systemic toxicity and maximized local drug concentration (25). Transarterial chemoinfusion (TACI), historically one of the first loco-regional chemotherapeutic approaches, represents a catheter-based intra-arterial therapy that delivers highly concentrated chemotherapeutic agents to liver tumors. TACI offers a relatively low systemic toxicity profile and a minimal risk of hepatocellular ischemia due to its minimal embolization component. Thus, TACI is very useful for the treatment of patients with borderline hepatic function who are otherwise not eligible for conventional TACE (26,27). TACI remains to be the standard of care in multiple Asian countries (28), yet has become less frequently used by interventional radiologists in the US and Europe.

Transarterial embolization (TAE) is another variation of loco-regional, catheter-based tumor treatments of the liver. In this procedure, a variety of embolizing agents (e.g., polyvinyl alcohol, gelfoam, acrylic copolymer gelatin particles) can be delivered through the tumor-feeding artery in order to completely occlude the tumor vasculature. Here, the anti-tumor effects are solely based on tumor ischemia as no chemotherapeutic agents are administered (29). The occlusion of more peripheral vessels can cause extensive necrosis. Although TACE is considered the gold standard and TAE has largely been abandoned as a form of effective IA therapy for primary liver cancer, there are a few studies that suggest sufficient anti-tumor effects of TAE (30). A recently presented randomized, single blind controlled trial compared the outcome of TAE and DEB-TACE in a total of 101 patients with unresectable Okuda stage I or II HCC. This study defined the tumor response rate according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria as a primary endpoint, while time to progression (TTP), progression free survival (PFS) and overall survival (OS) were defined as secondary endpoints. As a result, no significant difference between the groups was noted and both groups showed comparable tumor response, PFS and TTP (NCT00539643) (30). The use of very small embolization particles in the TAE group, resulting in a very distal embolization of tumor vessels, should be noticed and could have contributed to the results. However, insufficient treatment response and recurrent disease after TAE is frequently encountered. In fact, recent data suggest that hypoxia, generated by TAE, activates a molecular cascade, leading to compensatory angiogenesis (31). The molecular mechanism behind this reaction will be further discussed.

Conventional transcatheter arterial chemoembolization-technique

The concept of the conventional TACE (cTACE) was originally introduced in 1977 by Yamada *et al.*, who exploited HCC's preferential blood supply from the hepatic artery for the delivery of antitumor therapy (7). The initial rationale for cTACE was to increase the intra-tumoral concentration of the chemotherapeutic agents and to combine its cytotoxic effects with tumor ischemia, while reducing systemic toxicity related to chemotherapy (32). During the cTACE procedure, a mixture of chemotherapeutic agents combined with an oil-based contrast medium (Lipiodol Ultrafluide; Laboratoire Guerbet, France) is selectively delivered to the tumor-feeding artery, followed by temporary or permanent embolization. The mixture of chemotherapeutic agents used for cTACE usually contains cisplatin and adriamycin/doxorubicin (33-35). However, other combinations are possible and often include epirubicin, 5-fluorouracil, or mitomycin C (36). Due to the hypervascularized character of most liver tumors and the absence of Kupffer cells, Lipiodol can persist within tumor nodules for several weeks thus embolizing tumor vasculature up to the capillaries (31,37). A recent pre-clinical study of a rabbit HCC model demonstrated that (when examined in CT) Lipiodol uptake strongly affected liver perfusion. In fact, the uptake of Lipiodol can be used as an imaging biomarker for embolization efficacy (38). The subsequent administration of embolic material [such as gelfoam, polyvinyl alcohol (PA) particles or trisacryl gelatine (TG) microspheres] causes stasis in segmental and sub-segmental arterial branches and prevents washout of the previously deposited drug (39).

Embolization with gelfoam (a biodegradable gelatin sponge, The Upjohn Company, USA) as well as with PA particles has proven safe and effective (40), while the recently introduced, non-biodegradable TG microspheres (Embospheres, Guerbet Bio-medical, France) deserve further studies (41). The overall safety and efficacy of cTACE has been demonstrated in a variety of clinical trials. The adverse systemic effects of cTACE can include nausea, vomiting, bone marrow aplasia, renal failure and potentially cardiac toxicity. The self-limiting post-embolization syndrome (nausea, vomiting, fever, right upper quadrant pain and increased white blood cell count) occurs in approximately 10% percent of the patients and reflects the effects of tumor necrosis, acute cytokine release and systemic exposure to chemotherapeutic agents (42,43). Severe complications, such as post-procedural liver failure, abscess, cholecystitis, biloma and hemorrhage are rare and can be reduced by applying super-selective embolization, which was demonstrated to decrease risks and to improve overall survival when compared with non-selective embolization (44).

Drug-eluting beads chemoembolization-technique

The advent of new drug delivery systems such as drug-eluting microspheres (drug-eluting beads, DEBs) enabled a new transarterial approach, the DEB-TACE. This system combines enhanced local delivery of greater concentrations of drugs to the tumor with a reduced systemic drug exposure and has led to a shift away from conventional TACE towards DEB-TACE in the treatment of patients with HCC especially in the US and Europe (13,45). Several drug-eluting microsphere systems have been tested for intratumoral drug delivery. Currently, there are 2 types of microspheres approved for clinical use: superabsorbent polymer (SAP)-based Quadsphere/ Hepasphere microspheres (Biosphere Medical Inc., USA) and the DC Bead microspheres (Biocompatibles, UK). The SAP microspheres are non-biodegradable and have the ability to absorb fluids and thus to expand their volume to a size of up to 800 µm. Initial studies with this system show encouraging results in combination with doxorubicin or cisplatin (46). The DC beads are non-biodegradable, can be loaded with doxorubicin or irinotecan and range in size from 100 to up to 900 µm, whereas smaller bead diameters achieve a more distal embolization and a more extensive necrosis as compared with larger beads (47). Studies of pharmacokinetics show that drug elution occurs gradually and only in an ionic environment once the microspheres are delivered to the tumor. Several *in vitro* as well as animal experiments demonstrated the continuous release of doxorubicin from DC beads to the tissue (48,49). Furthermore, a histopathological study described the high efficiency of DEB-mediated drug delivery and release to the tumor tissue, thus causing local coagulative necrosis and an inflammatory-fibrotic tissue (50). The enhanced systemic pharmacokinetics of drug-eluting beads in TACE have been observed when peak plasma concentrations of doxorubicin were measured for DEB-TACE and compared with conventional TACE, showing significantly lower peak plasma levels of the chemotherapeutic for DEB-TACE in animal models (49) as well as in patients (51). The systemic side effects of doxorubicin and related drugs used in DC Beads can range from alopecia and skin discoloration to mucositis and bone marrow suppression. In a multicenter, randomized, prospective phase II study, that compared the safety and toxicity of DEB-TACE and cTACE in HCC patients, significant toxicity profile benefits were shown for DC Beads over cTACE. The overall frequency of treatment-related adverse effects was lower in the DEB-TACE group as were the toxicity grades and the severe adverse effects. The post hoc analysis of true toxicity incidence in DEB-TACE and cTACE has shown significant events in 11.8% patients *vs.* 25.9% patients, respectively. Alopecia as the most common event in patients treated with doxorubicin was almost absent in the DEB-TACE group with 1 *vs.* 23 events, respectively. Furthermore, major liver toxicities were also lower in DEB-TACE as compared to cTACE (13). In conclusion, DEB-TACE can be viewed as a safe, tolerable and effective technique and thus represents a reliable method of selective locoregional drug delivery to hepatic tumors.

Transarterial chemoembolization—clinical evidence

A retrospective, single-center study, designed to assess treatment response and long-term survival outcomes after cTACE, included a total of 172, mainly cirrhotic (91%) patients that received treatment over the course of 9 years (between 2000-2008). According to EASL criteria, 64% of the treated tumors showed response with 23% showing complete response. With a median overall survival of 40.0 months for patients classified as BCLC A (for BCLC B and C 17.4 and 6.3 months, respectively), this study confirmed the efficacy and the survival benefits

previously seen in similar patient cohorts months (52). Another, recently published retrospective multi-center study confirmed the effects of highly selective Lipiodol-based TACE. Here, a total of 199 patients were treated and followed over the course of 10 years. The median overall survival was 3.8 years with a 5- and 10-year survival of 38.8% and 9.4% respectively. However, local recurrence rates for all 199 patients were described as 46%, 58% and 62% after 2, 3 and 5 years of follow up, respectively (53). A most recently published study assessed response rates and the clinical outcome of cTACE, performed "on demand" in 151 consecutive HCC patients. CR was observed in 48% of the treated patients after the first cTACE procedure. While the CR-rate was slightly increased after the second and third procedure, the recurrence rates at 6 and 12 months of follow up continued to be relatively high with 37% and 61% respectively. The median overall survival in non-resected and non-transplanted patients was 25.0 months (54).

As new DEBs became available, more studies to describe clinical outcomes of DEB-TACE evolved. In a first experience with DEB-TACE in the US, a prospective phase II pilot study evaluated safety, efficacy as well as progression-free and overall survival in 20 mostly cirrhotic (80%) patients with unresectable HCC. 75% of the patients were staged as Child-Pugh A, while 60% of the patients were classified as BCLC stage C. After 34 sessions and an overall modest toxicity, 64% were classified as responders according to EASL criteria and 30% achieved CR. After 6 months, only 1 patient showed disease progression according to RECIST. The median overall survival of 26 months confirmed the potential of DEB-TACE in the treatment of patients with intermediate and end-stage HCC (45). In a first international, multicenter, prospective, randomized phase II trial the authors compared the safety and efficacy of cTACE *vs.* DEB-TACE. Here, a total of 212 patients were 1:1 randomized and 201 patients received the treatment according to standardized protocols. The two groups were stratified according to ECOG performance status, and the Child-Pugh class. As a result, patients who received DEB-TACE showed a better imaging-based response according to EASL criteria. In a follow-up 6 months after the first treatment, 26.6% and 22.2% achieved complete response in DEB-TACE and cTACE, respectively. Progressive disease was observed in 32.3% *vs.* 40.7% in DEB-TACE *vs.* cTACE (13). Another, prospective, multi-center study enrolled 173 patients with unresectable HCC into a DEB-TACE treatment protocol. Designed to assess long-term clinical outcome of patients treated with DEB-TACE, the results of this study shows a 5-year survival of 29.4% and 12.8% for Child-Pugh class A and B, respectively (55). In conclusion, these results show the feasibility and rationale of DEB-TACE in the treatment of unresectable HCC

Combination of TACE with systemic chemotherapy

The main anti-cancer effects of chemoembolization are a combination of ischemia and direct chemotherapy-induced cytotoxicity to the cancer cells. Although chemoembolization can cause massive tumor destruction, tumor recurrence is frequently encountered (56,57). It has been postulated that the reason for tumor recurrence is the stimulation of neo-angiogenic pathways that have been shown to be significantly up-regulated within 36 hours of TACE presumably as a result of the hypoxia caused by embolization within the tumor. Indeed, surrogate markers of tumor hypoxia including the Hypoxia-inducible Factor 1 alpha (HIF-1alpha) as well as the Vascular Endothelial Growth Factor (VEGF) are directly up-regulated after TACE procedures, suggesting direct stimulation of angiogenesis (58,59). Thus, as a result, disturbing the angiogenic pathway during planned treatment with TACE is extremely appealing. One such approach consists of using sorafenib, a multikinase inhibitor with strong antiangiogenic properties, in combination with TACE. In this way, the negative hypoxic changes induced by TACE within the tumor would possibly be counterbalanced by sorafenib (60). Sorafenib had previously been shown to significantly prolong survival over placebo in a randomized trial that led to the approval of the drug for patients with HCC (61). Here, we will review the latest data on the use of combination TACE and sorafenib for patients with HCC.

A single-center prospective Phase II trial designed to evaluate the safety and efficacy of concurrent sorafenib and DEB-TACE therapy (n=35 patients with unresectable HCC) included patients with ECOG performance status of 0 to 1, Child-Pugh liver function up to B7, and segmental portal vein thrombosis (BCLC C). Patients were treated on a 6-week cycle regimen, in which one cycle consisted of 400 mg sorafenib twice daily, initiated 1 week before DEB-TACE. The 35 patients were treated with a total of 128 cycles of therapy. All patients received DEB-TACE (mean dose of doxorubicin decreased over time; cycle one: 75 mg; two: 60 mg; three: 49 mg). The primary end points of the

study were safety and toxicity, the secondary end point was efficacy. All patients experienced at least one treatment-related toxicity during cycle one. However, most toxicities were minor (only 17% of all toxicities were grade 3 to 4). Using EASL criteria, the objective tumor response rate to treatment was 58% and the disease control rate was 100%. This study was truly the first to confirm the safety profile of the DEB-TACE sorafenib combination (60).

The first global trial on the use of DEB-TACE with sorafenib, which was recently presented, is a Phase II randomised, double-blind, placebo-controlled SPACE study (sorafenib or Placebo in Combination with DEB-TACE for Intermediate-Stage HCC), that enrolled patients across 85 centres in Europe, North America and Asia. A total of 307 eligible patients were randomised to either sorafenib (n=154) or placebo (n=153) in addition to DEB-TACE. The patients received a dose of 400 mg sorafenib twice daily or a matching placebo continuously at a cycle duration of 4 weeks. DEB-TACE was used in all patients within the first 3-7 days after the first dose of sorafenib or placebo and subsequently on day 1 of cycle 3, 7 and 13 respectively. The primary end points of that study were efficacy [time to tumor progression (TTP) according to RECIST] and safety. Overall survival, time to vascular invasion and other surrogate markers of progression were defined as secondary end points. Median TTP was 169 days in the sorafenib group and 166 days in the placebo group. TTP at the 25th and 75th percentile was 112/88 days and 285/224 days in the sorafenib and placebo groups, respectively. The overall preliminary results appear to be disappointing showing no statistically significant benefits regarding overall survival and TTP (62). This trend confirms the negative results of a phase III study in Japanese and Korean patients, where a total of 458 patients were randomized to receive TACE with or without Sorafenib. In this trial, sorafenib failed to significantly prolong TTP in patients with tumor response to treatment (63).

Multiple trials investigating the outcome of conventional TACE in combination with sorafenib are also available. In particular, a South Korean non-randomized prospective single-arm Phase II study investigating the Combination of Transcatheter Arterial Chemoembolization and sorafenib for Patients with Unresectable Hepatocellular Carcinoma (COTSUN) focused specifically on safety and tolerability. The initial results appear to be promising with a median TTP of 7.1 months (7.3 months in BCLC stage B; 5.0 months in BCLC stage C), while the 6-month progression-free survival rate was 52% and the safety profile appeared to be manageable (64). Other ongoing studies should shed even more light as to the potential benefit of this combination therapy. An example is the multi-center Study in Asia of the combination of conventional TACE with sorafenib in patients with Hepatocellular Carcinoma Trial (START) which should provide further insight into progression-free survival (PFS) and TTP hopefully in the next year (65). As already mentioned, other trials are under way, among them a phase III randomized, double-blind, controlled multicenter trial, using the E1208 study protocol. This trial will compare the outcomes of TACE with or without Sorafenib in HCC patients with or without vascular invasion (NCT01004978). Another ongoing phase III randomized trial from the United Kingdom will provide more data on the combination of sorafenib and TACE while comparing the outcome with TACE alone (TACE-2, EudraCT2008-005073-36). The results of both trials should be available at the end of 2014.

Yttrium-90 (Y90) radioembolization-technique

Historically, whole-liver external beam radiation therapy of primary and metastatic liver cancer has been of limited use. Patients with preserved liver-function can tolerate a cumulative dose of up to 40 Gy, yet the incidence of radiation induced liver disease is as high as 50% (66,67). Given the high toxicity profile of external beam irradiation in patients with HCC (68), new intra-arterial approaches to deliver a high dose of radiation directly to the tumors were developed. The infusion of small embolic particles loaded with the radioisotope ^{90}Yttrium (Y90) is a suitable technique to achieve tumoricidal effects while preserving healthy liver tissue and reducing systemic toxicities of external beam radiation (69). Currently, there are two embolization agents available for clinical use: the resin-based SIR-Spheres (Sirtex Medical Ltd., Australia) and the glass-based TheraSpheres (MDS Nordion, Canada) (70). The 20-30 μm sized TheraSpheres show a high activity (2,500 Bq/Sphere) and are approved for radioembolization of HCC. The slightly bigger, 20-60 μm sized SIR-Spheres show a lower activity (50 Bq/Sphere) and can be used for the treatment of colorectal metastases to the liver. Both glass and resin microspheres deliver high cumulative doses to the tumor, which can vary from 100 Gy to more than 3,000 Gy. Because of the extremely small size of the microspheres and their highly aggressive content, radioembolization bears the risk of systemic distribution of radioactive isotopes via pulmonary shunts or non-target delivery of Y90 to the

gastrointestinal tract (71). Thus, it is recommended to subject all patients to careful angiographic evaluation as well as to a test injection of ^{99m}Tc-labeled macro-aggregated albumin prior to the procedure. This happens in order to evaluate vessel anatomy, to exclude a high shunting fraction and to estimate the dose delivered to the tumor (72). The incidence of adverse effects, such as fatigue, vomiting, anorexia, fever and abdominal pain after radioembolization ranges from 20% to 50% (73), yet there is evidence that the degree of symptoms and the post-procedural quality of life is increased if compared with cTACE (74).

Yttrium-90 (Y90) radioembolization—clinical evidence

In a multi-center trial designed to evaluate the safety and survival of HCC patients treated with Radioembolization, a total of 80 patients was enrolled into the study. Patients with unresectable non-infiltrative HCC, an ECOG performance status of 0-2 and adequate liver, pulmonary, renal and bone marrow function were evaluated for treatment and treated with TheraSpheres. 44% of the Patients showed bilobar disease (47% right lobe, 9% left lobe) and 90% of the patients were staged as Child Pugh A. 27 patients received multiple treatments with 1 patient receiving a maximum of 4 procedures. 28% of the patients showed adverse events with 8 patients showing life-threatening and 1 patient a fatal event. Regarding the overall survival, Child-Pugh A patients showed a median overall survival of 18.6 months while Child-Pugh B patients achieved only a median of 8.04 months (69). This study was one of the first survival analyses for the use of Radioembolization in HCC and multiple studies followed. In a prospective, single-center study designed to validate safety and efficacy of Radioembolization in HCC patients not eligible for TACE, a total of 108 patients were treated with TheraSpheres. 51% of the patients were classified as Barcelona Clinic Liver Cancer (BCLC) stage C and 77% were staged as Child-Pugh A. According to mRECIST 90 days after treatment, 6% of the patients showed complete response (CR), while 35% and 48% showed partial response (PR) and stable disease (SD), respectively and 10% showed progressive disease (PD). The overall survival rate for the entire patient collective after 2 years of follow-up was 16.4 months, again showing significant differences for Child Pugh A *vs.* B (75). In a prospective, longitudinal cohort study designed to show long-term outcomes after radioembolization, a total of 291 patients were treated with TheraSpheres in 526 sessions over the course of 5 years. 45% of the patient collective was staged as Child-Pugh A (52% as Child-Pugh B) and 52% of the patients were classified as BCLC stage C (BCLC A 17%, BCLC B 28%). Using EASL criteria, the overall response rate was reported as 57% (CR 23%, PR 34%), while stratified response rates were significantly better for Child-Pugh A patients (EASL 66%) when compared to Child-Pugh B patients (EASL 51%). The time to progression for the entire cohort was 7.9 months. The median overall survival was 17.2 months for Child-Pugh A patients and 7.7 months for Child-Pugh B patients (76). This study underlines the potential of radioembolization in the treatment of unresectable HCC Patients, specifically emphasizing the benefits of patients staged as Child-Pugh A.

Commentary

After decades of development and research, reduced systemic toxicity combined with efficient local tumor response continue to be the paramount advantages of image-guided, percutaneous therapies of primary liver cancer. Multiple studies demonstrate the advantages of ablative techniques for patients with early-stage liver tumours, showing prolonged overall survival and even curative potential of these modalities. Due to the lack of standardized treatment protocols and the absence of categorical guidelines, no definitive recommendation for the use of one or another modality in patients with end-stage disease can be stated. Trials are needed to evaluate survival benefits of each modality in matched patient cohorts. Currently, different tumor response criteria (RECIST, mRECIST, EASL, WHO) and multiple surrogate markers of survival can be applied to assess tumor response to treatment. Hence, the obvious drawback is the lack of standardization making a comparison between different modalities very difficult and leaving room for interpretation according to individual preferences and center expertise. In summary, further comparative investigation of the available intra-arterial techniques and standardized methods of reporting clinical results are needed to answer the innumerable open questions.

The near future of intra-arterial therapies is promising with multiple innovative technologies, new agents and combination treatments to appear on the horizon. New concepts include molecular targeted treatment of liver cancer metabolism (77) as well as oncolytic immunotherapy (78). The use of new, imageable carrier systems for intra-arterial drug delivery and embolization will provide intraprocedural

identification of undertreated tumor areas (79), while the introduction of advanced intraprocedural imaging, such as dual-phase cone-beam CT will help predicting tumor response immediately after treatment (9). As mentioned before, multiple trials are investigating the outcome of cTACE, DEB-TACE and most recently Radioembolization in combination with systemic chemotherapy with sorafenib (80) and will hopefully contribute to prolonged survival for liver cancer patients treated by interventional radiologists.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Chapiro J, Geschwind JF. Percutaneous therapies of hepatocellular carcinoma—an update. Chin Clin Oncol 2013;2(4):36. doi: 10.3978/j.issn.2304-3865.2013.07.04

