Minimally invasive image-guided therapies for hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is the fifth most frequently occurring cancer globally and predominantly develops in the setting of various grades of underlying chronic liver disease, which affects management decisions. Image-guided percutaneous ablative or transarterial therapies have acquired wide acceptance in HCC management as a single treatment modality or combined with other treatment options in patients who are not amenable for surgery. Recently, such treatment modalities have also been used for bridging or downsizing before definitive treatment (ie, surgical resection or liver transplantation). This review focuses on the use of minimally invasive image-guided locoregional therapies for HCC. Additionally, it highlights recent advancements in imaging and catheter technology, embolic materials, chemotherapeutic agents, and delivery techniques; all lead to improved patient outcomes, thereby increasing the interest in these invasive techniques.

Keywords: hepatocelleular carcinoma, locoregional therapy, TACE, ablation, ^{90}Y

Introduction

Despite progress in the diagnosis and management of hepatocellular carcinoma (HCC), the incidence and fatality rate are still growing in many countries. Currently, HCC is the fifth most frequently occurring cancer and the third largest contributor to cancer-related mortality worldwide.[1] HCC predominantly develops in the presence of underlying liver cirrhosis rendering its management relatively challenging compared with therapy for other tumors; thus, HCC is managed through a multidisciplinary approach involving various subspecialties including surgery, hepatology, medical oncology, interventional radiology, pathology, and radiation oncology.

Since HCC is considered a two-disease entity because of the presence of HCC tumors and chronic liver disease, all HCC staging systems rely on parameters related to both the tumor stage and the hepatic function. Although many HCC staging systems have been proposed, the Barcelona Clinic Liver Cancer (BCLC) staging system has gained wide acceptance in clinical practice and in many clinical trials. The BCLC system is considered a treatment allocation system; therefore, once the patient has been assigned a BCLC stage, the suitable treatment options are determined. The known factors such as survival predictors, radiologic tumor extension, hepatic functional reserve, and performance status are all included in the BCLC staging system. Hence, patients with BCLC stages A and B are now considered the standard candidate patient population for locoregional HCC therapies.[2] We performed literature search on English language publications in the PubMed database using the terms hepatocellular carcinoma, locoregional therapy,

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TACE, and ablation. This article focuses on minimally invasive image-guided locoregional therapies for HCC. Minimally invasive locoregional therapies (such as percutaneous ablative therapies and transarterial catheter-based techniques) have gained wide acceptance as monotherapy or in combination with other local or systemic treatment modalities in patients who are not surgical candidates or as a bridging or downsizing modality before definitive treatment (ie, surgical resection or liver transplantation).

Percutaneous ablative therapies
Percutaneous chemical ablation

Percutaneous ethanol injection (PEI) is the seminal ablative technique. Absolute ethanol is injected directly in the tumor through a guiding needle, resulting in coagulative necrosis. The best results are achieved in tumors up to 2 cm in diameter.[3–5] The distribution of the ethanol within tumor may be affected by intra-tumoral septae and/or capsule, and this may be responsible for suboptimal response in larger lesions. Currently, PEI should be considered when radiofrequency ablation (RFA) is not feasible as in case of lesions close to important structures that are of concern for damage with thermal ablation.[2]

Percutaneous radiofrequency ablation

Although PEI was first introduced for the management of HCC, current data support using RFA rather than PEI for HCC given the superiority of RFA owing to fewer treatment sessions, shorter hospital stays, better local disease control, higher amounts of tumor necrosis, and improved progression-free survival and overall survival (OS).[6,7] RFA induces coagulative necrosis resulting from the thermal energy created by the delivery of alternating electrical currents through the electrode needle placed in the tumor. The heat generated in the vicinity of the electrode is then conducted to the surrounding environment, not limited by septa or capsulation, resulting in coagulative necrosis of a finite tissue volume. The tissue surrounding the tip of the electrode is destroyed within seconds as the temperature reaches 55°C–60°C, and then the thermal energy disseminates to the surrounding tissue ideally to cover 0.5–1 cm of normal tissue surrounding the tumor.[8]

RFA is effective in the treatment of small HCC tumors (<3 cm; very early-stage disease and early-stage disease using the BCLC system). Although according to the BCLC system, resection is the modality of choice in very early-stage disease, there is no clear consensus on whether ablation or surgical resection is better for surgically feasible patients with small HCC tumors. Several nonrandomized and randomized controlled studies have compared ablative therapies with surgical resection for small HCC treatment.[9–15] In a randomized clinical trial including 105 patients with 114 HCC nodules, Lu et al compared surgical resection to percutaneous ablation (RFA and microwave ablation). The investigators concluded that in addition to minimal invasiveness, accessibility, and cost savings, percutaneous ablation achieved a therapeutic effect and 3-year survival outcomes equivalent to those of surgical resection. They suggested that RFA may be considered as one of the first-choice modalities for treating early-stage HCC.[16] In a more recent study, Feng et al reported that in patients with HCC nodules (up to 2) <4 cm (n=168), the therapeutic effectiveness of RFA and surgical resection were similar with no statistical difference in the OS and recurrence-free survival between both the groups.[15] Zhou et al conducted a meta-analysis of 4 randomized controlled trials comparing percutaneous RFA with surgical resection for small HCC reported between 1990 and 2010. The differences in OS between RFA and surgical resection were not statistically significant (P>0.05).[11] In addition, Livraghi et al conducted a cohort study and retrospectively reviewed a prospective multicenter database of 218 patients with a single HCC (<2 cm) treated with RFA. The authors reported that a sustained complete response and the 5-year survival rate were observed in 97.2% and was 68.5%, respectively, comparable to that of surgical resection. The investigators concluded that RFA can be the treatment of choice, even in surgical candidates, whereas surgical resection can be considered in cases not amenable for RFA.[17]

Percutaneous microwave ablation

Microwave ablation is a promising thermal ablation technology that can be used as an alternative to RFA to treat HCC. Multiple microwave ablation systems are currently available in the US market and have been approved for clinical practice. During microwave ablation, coagulative necrosis is induced through the application of electromagnetic waves through the antenna (ie, microwave probe). The transmitted energy induces rapid molecular agitation and friction, leading to a significant increase in the temperature of water and heat conduction to the surrounding target tissue, thereby resulting in cell death and coagulative necrosis.[18] Microwave ablation offers several advantages over other forms of ablation,[19] such as high thermal efficiency resulting in larger ablation volumes, a higher capability of coagulating blood vessels, a faster ablation time, and a less severe heat sink effect.[19]

Poggi et al[20] treated 194 HCC lesions in 144 patients using microwave ablation. The average diameter of the lesions was

2.7 cm (68 lesions >3 cm). Complete response was obtained in 100% of small HCCs and 94.3% of all the lesions. After a median of 19.5-month follow-up, local tumor progression was noted in 5.1% (10 lesions). No major complications occurred, minor complications were reported in 5.1% procedures.[20] Zhang et al[21] evaluated the therapeutic efficacy of percutaneous RFA versus microwave ablation for HCCs measuring up to 5 cm. Complete ablation was achieved in 83.4% (78/93) and 86.7% (91/105) of cases were treated with RFA and microwave ablation, respectively. The tumor progression rate was 11.8% (11/93) in the cases treated with RFA and 10.5% (11/105) in those treated with microwave ablation. There was no statistically significant difference in the OS rates (P=0.780) or the disease-free survival rates (P=0.123) between both the modalities. The authors concluded that RFA and microwave ablation are equally effective in treating HCC, with no significant differences in complete ablation, local tumor progression, and OS.[21]

Percutaneous cryoablation

During cryoablation, a probe is inserted directly into the target lesion to reduce its temperature (–20°C to –40°C), creating an ice ball that can be monitored by imaging. The resultant low temperature in the target tissue is lethal and causes cell death. In addition, alternating cooling and thawing add more cytotoxic effects through different mechanisms. Cryoablation has limited application in HCC. Lee et al[22] studied percutaneous cryoablation for 20 HCCs (<3 cm) in 20 patients who were not surgical candidates. Technical success was achieved in all the procedures, and no complications were reported. At 1-month follow-up, computed tomography revealed complete response, partial response, stable disease in 13, 4, and 3 patients, respectively. None of the patients had progressive disease. After a mean of 20.7-month follow-up (6–30 months), one of the 13 lesions (8%) developed local recurrence.[22] Nevertheless, the potential serious complications following cryoablation cannot be neglected, such as "cryoshock," a systemic inflammatory response resulting in multiorgan failure.[23–25]

Percutaneous transarterial therapies

HCCs derive most of their vascular supply from the hepatic artery, contrary to most of the normal liver, which derives blood supply from the portal vein. This is the rationale behind the transarterial therapies during which the delivery of therapeutic agents and/or the blockage of the supplying vessels is attempted.

Transarterial chemoembolization

For conventional transarterial chemoembolization (cTACE), one or more chemotherapeutic drugs, most commonly doxorubicin and cisplatin, are added to lipiodol and delivered to the feeding arteries of the tumor. Following this, an embolic agent is administered in the feeding arteries to minimize the tumor washout of the chemotherapeutic mixture and induce ischemic necrosis.

Recently, the use of calibrated microspheres loaded with chemotherapeutic agents has gained wide acceptance. During TACE with drug-eluting beads (DEB-TACE), the microspheres deposited within the tumor elute the loaded drug over time, resulting in very low levels of the chemotherapeutic agent in the systemic circulation and conveyance of high-dose chemotherapy to the tumor with more definite distal blockage of small vessels.[26,27]

According to BCLC guidelines, TACE is considered the treatment of choice for intermediate stage disease (stage B). In a meta-analysis of randomized clinical trials of unresectable HCC, Llovet et al showed that TACE improved survival compared with the best supportive care.[28] In a study published by Burrel et al, patients classified as BCLC-B who underwent DEB-TACE had a median survival of 42.8 months after censoring follow-up at the time of liver transplantation, chemotherapy treatment (sorafenib), and radioembolization.[29] More recently, TACE has also been used for bridging and downstaging in HCC patients prior to liver transplantation. Bridging refers to the use of TACE for patients who meet transplantation criteria and are on the transplant list. In a multicenter study evaluating the impact of preoperative locoregional treatments on recurrence-free survival following hepatic transplantation for HCC, the 5-year recurrence-free survival rate in the subgroup with pathologic T2 or T3 HCC was 93.8% and 80.6% in patients who underwent locoregional therapy and in patients who did not receive any treatment, respectively.[30]

Downstaging refers to patients who do not meet the criteria for orthotopic liver transplantation owing to the extent of disease according to the current including criteria and receive any locoregional therapy in an attempt to reduce the extent of the disease, ultimately becoming eligible for the liver transplantation. In a prospective study investigating the use of locoregional therapy to downstage HCC prior to liver transplantation, Yao et al revealed that downstaging was achieved in 70% of patients who subsequently underwent liver transplantation.[31]

Transarterial bland embolization

Transarterial catheter-based therapy includes delivery of embolic agent with (TACE) or without (transarterial embolization [TAE]) chemotherapeutic drugs.[32] In a case–control study including 25 and 50 patients who underwent TAE and TACE,

respectively, prior to liver transplantation, complete necrosis was achieved in 36% of the TAE patients and in 26% of the TACE patients. There was no significant differences between both the groups in the 3-year OS rates (P=0.66) and the 3-year recurrence-free survival rates (P=0.67). The investigators concluded that no significant differences were noted in wait-list dropout or in OS or recurrence-free survival between HCC patients undergoing either TAE or TACE before transplantation.[33] In a more recent single-center randomized phase II trial that included 101 patients, Brown et al[34] investigated the differences in response (using Response Evaluation Criteria in Solid Tumors criteria) as a primary point between patients who underwent TAE (n=50) and the patients who underwent TACE (n=51). Other secondary assessment points included safety and tolerability, time to progression (TTP), progression-free survival, and OS. The investigators concluded that no apparent differences were noted between both the groups.[34]

Transarterial radioembolization

During transarterial radioembolization (TARE), a B-emitter radioactive isotope, yttrium-90 (^{90}Y), is loaded on microspheres. Like other transcatheter-based treatments, TARE depends on the preferential flow of blood to the hepatic tumors. Thus, compared with traditional external radiation, TARE permits the delivery of a significantly higher radiation dose to the tumor with minimal irradiation to the normal liver parenchyma, thereby minimizing the risk of radiation hepatitis.[35,36]

In the United States, Food and Drug Administration (FDA) has approved two ^{90}Y microsphere products for clinical treatment: TheraSphere (MDS Nordion Inc., Kanata, Ontario, Canada) and SIR-Spheres (SIRTeX Medical Ltd., Sydney, New South Wales, Australia). TheraSphere, consists of glass ^{90}Y microspheres , was approved in the United States for the treatment of patients with HCC. SIR-Spheres, the resin ^{90}Y microspheres, have approval for the treatment of hepatic colorectal metastasis with adjuvant hepatic arterial infusion of floxuridine. However, worldwide, the clinical use of both the ^{90}Y microspheres is more generic, and both are used for HCC therapy.

Although not specified on the BCLC staging and treatment algorithm, TARE is used for intermediate and advanced stage HCC. A recent phase II study investigated the efficacy of TARE (lobar delivery of 120 Gy) on patients with intermediate (n=17) and advanced (n=35) HCC. The study included primary endpoint; TTP and secondary endpoints; and tumor response, safety, and OS. After a median of 36 months of follow-up in 52 patients who received 58 treatments, there was no significant difference in TTP between patients with portal vein thrombosis (PVT) and those without PVT (7 vs 13 months).

The median OS was 18 and 13 months in non-PVT and PVT patients, respectively, with an insignificant tendency in favor of non-PVT patients. The authors concluded that TARE is effective for treating intermediate to advanced HCC, particularly for patients with PVT.[37]

In a single-center prospective cohort study, Salem et al[38] administered ^{90}Y treatments to 291 patients with HCC (52% BCLC-C). The response rates were based on World Health Organization (42%) and European Association for the Study of Liver criteria (57%). The overall TTP was 7.9 months. The median survival time was 17.2 months in patients with Child–Pugh A and 7.7 months in patients with Child –Pugh B disease (P=0.002). Child–Pugh B patients with PVT survived a median of 5.6 months (95% confidence interval [CI], 4.5–6.7).[38]

Combined therapies

Although not described in the HCC treatment algorithm, combined local therapies or combined local and systemic therapies have gained wide recognition in many institutions.

Combined local therapies

Given the suboptimal response of larger tumors to ablative therapies, several studies have evaluated the combination of ablative therapies with TACE for lesions measuring 3–5 cm.[39–42] The combination of TACE and RFA is the most studied combination used for HCC treatment. Two techniques were used: 1) RFA followed by TACE and 2) TACE followed by RFA. The concept behind the former technique is increased delivery of the chemoembolic agent in the ablated tumor periphery, the most common zone for tumor recurrence.[43] Lencioni et al[43] studied this concept in 20 patients with a single HCC measuring 33–70 mm. DEB-TACE was then performed (50–125 mg doxorubicin), and patients were monitored for 6–20 months (mean of 12 months). The volume of treatment-induced necrosis was calculated through imaging. Complete response was achieved after the combined therapy in 60% of patients, and the volume of necrosis was increased from 48.1 cm^3 after RFA to 75.5 cm^3 after DEB-TACE, with mean increase of 60.9%.[43]

The rationale for the use of TACE preceding RFA is the occlusion of the tumor-supplying vessels decreasing perfusion-mediated tissue cooling classically associated with the heat sink effect in hypervascular tumors. Several studies validated this approach and demonstrated increased therapeutic effect when RFA was performed after TAE or TACE.[39,40,44] Veltri et al[39] used this approach to treat 51 HCC lesions (mean 4.89 cm) in 46 patients. On the first follow-up CT, complete response was achieved in 85.2% of the patients (23/27) and partial response was achieved in 14.8% (4/7 patients

in lesions <5 cm. In lesions >5 cm, complete response was achieved in 45.8% (11/24 patients) and partial response in 54.2% (11/24 patients). The investigators concluded that combined treatment for non-early HCC yielded a high rate of complete response (particularly in lesions <5 cm).[39]

Combined local and systemic therapies

Sorafenib, a multikinase inhibitor was approved by the US FDA in 2007 for unresectable or untransplantable HCC with Child–Pugh class A or B. As recommended in the BCLC guidelines, sorafenib is the mainstay for advanced stage HCC (ie, patients who have a branch vein tumoral invasion with or without minimal extra-hepatic disease and a performance status of 1–2). The impact of sorafenib on the OS and TTP was revealed in two randomized control trials.[45,46] Although not outlined in the BCLC guidelines, several studies have investigated the effectiveness of combining sorafenib with locoregional treatment (TACE or TARE) in intermediate and advanced HCC.[47–51] A prospective, single-arm, phase II study evaluated the safety of combined TACE and sorafenib on the TTP in 50 patients (BCLC stage B [82%] and BCLC stage C [18%]). Sorafenib was given for 24 consecutive weeks starting 3 days after TACE was administered. Evaluation of the tumor response was performed every 8 weeks. The overall median TTP was 7.1 months (95% CI, BCLC stage B [7.3 months] and BCLC stage C [5 months]). The progression-free survival rate at 6 months was 52% and the median OS was 20.8 months.[49]

Another prospective single-center phase II study evaluated the safety of and response to combined DEB-TACE and sorafenib in unresectable HCC patients (64% BCLC stage C). The authors concluded that the sorafenib and DEB-TACE combined therapy in patients with unresectable HCC is safe and well tolerated, with most adverse effects from sorafenib. Most adverse effects were minor (grade 1–2 in 83% versus grade 3–4 in 17%) and manageable with adjustments in the sorafenib dose.[48]

A recent study by Mahvash et al investigated therapy effectiveness, TTP, and survival in 19 patients who received TARE and sorafenib. The median OS was 19.52 and OS rates were 62.3% and 31.7% at 1 and 2 years, respectively. The investigators concluded that local response (partial response/ stable disease) was obtained in 100% of the patients with an increase in the survival when compared with available studies evaluating sorafenib alone in similar patient populations.[52]

Future directions

Tumor recurrence is a major challenge in the treatment of early-stage HCC. Effective preventive measures in the form of better single locoregional therapy or combined therapies are crucial.

Irreversible electroporation (IRE) is a novel technique for nonthermal ablation based on the electroporation phenomenon. The delivery of direct electric current into cells using short pulses for microseconds results in the disruption of cell membrane integrity and creation of nanopores, which can be temporary (reversible electroporation) or permanent (IRE). The permanent nanopores result in the loss of cells' homeostatic mechanisms, thereby inducing cell death.[53–56] Some investigators have evaluated IRE ablation in the liver, lung, prostate, and kidney.[57–61] Interestingly, several unique characteristics of IRE ablation have been reported, including its capability of preserving the integrity of adjacent nearby structures and lack of a heat sink effect.[59,60] Needless to say, these alluring advantages make IRE a potential choice for tumor ablation near vascular structures or thermally sensitive areas.

Another alternative treatment modality under investigation is light-activated drug therapy; activating talaporfin sodium that has the ability to concentrate in tumors following intravenous administration. Upon the activation of talaporfin sodium, through a percutaneously inserted light-emitting activator inside the tumor under imaging guidance, singlet oxygen is produced which causes oxidation and tumor blood vessel occlusion, resulting in cell death.[62]

In conclusion, the image-guided locoregional therapies have a key role in HCC management. Nowadays, these therapies are more frequently used with curative intent in surgical candidates (as a bridge before surgical resection or liver transplantation) or for nonsurgical candidates, as monotherapy or in combination with other therapies.

Finally, continuous clinical and translational research is of the utmost importance to better outline the indications and outcomes of monotherapy or combined therapy aiming to increase disease control and improve survival.

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Disclosure

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