Mini-Review

A Recent Advance in Image-Guided Locoregional Therapy for Hepatocellular Carcinoma

Yaoping Shi Bo Zhai

Department of Interventional Oncology, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

Key Words¹²⁵I seed · Ablation · Hepatocellular carcinoma · Image-guided locoregional therapy · Local ablative therapy · Radiofrequency ablation · Transarterial therapy**Abstract**

Background: Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third most common cause of cancer-related deaths. Hepatic resection and liver transplantation are considered to be the preferred treatment for HCC. However, as novel therapeutic options such as image-guided locoregional therapies have emerged and been refined, the manner in which HCC is treated has changed dramatically compared with what it was considered just 2 decades earlier. **Summary:** This study reviews the current results of various image-guided locoregional therapies for treating HCC, especially focusing on thermal ablative and transarterial techniques. **Key Message:** Advances in image-guided locoregional therapies, including local ablative therapy and transarterial therapy, have led to a major breakthrough in the management of HCC. Both survival rates and cure rates of patients with HCC have improved markedly since the introduction of these techniques. **Practical Implications:** Radiofrequency ablation is currently considered as an alternative to surgical resection for patients with early-stage HCC. A newer technique of ablation such as microwave ablation is increasingly being used, especially for large HCC. Transarterial chemoembolization has become a standard care for asymptomatic patients with multinodular tumors in intermediate-stage disease, and transarterial radioembolization has become the method of choice in HCC cases with portal vein thrombosis. Moreover, combination treatment modalities, such as thermal-based ablation combined with transarterial chemoembolization or ¹²⁵I seed implant brachytherapy, may further broaden their clinical indications for HCC. Moreover, use of localized radiation in combination with thermal ablation has been reported to improve tumor control and long-term survival.

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Bo Zhai, MD, PhD
Renji Hospital, Shanghai Jiaotong University School of Medicine
No. 160 Pujian Road
Pudong New District, Shanghai 200127 (China)
E-Mail zhaiboshi@sina.com

Introduction

Major improvements have been made in the management of hepatocellular carcinoma (HCC) during the last several decades. Advances in early detection, imaging techniques, and novel therapies have improved patient selection and enabled evidence-based treatment approaches [1]. Five interventions reach the highest level of evidence, being worldwide accepted recommendations for treating HCC [2]: resection, liver transplantation, percutaneous ablation with radiofrequency, transarterial chemoembolization (TACE), and systematic therapy with sorafenib. Hepatic resection still remains the first-line option for patients with early-stage HCC as defined by the Barcelona Clinic Liver Cancer staging system [3]. However, such surgery requires wide resection margins, and underlying cirrhosis limits the volume of liver that can be resected without causing liver failure [4, 5]. Liver transplantation has been established as an alternative curative treatment for small HCC associated with cirrhosis, offering excellent survival results in patients who met the Milan criteria [6]. Nevertheless, its use has been restricted by the severe shortage of organ donors, which causes longer waiting times and increases dropout rates as a result of tumor progression while waiting for a graft. Conventional chemotherapy was proven ineffective for this malignancy [7] due to the coexistence of liver cirrhosis in most patients, which makes them more susceptible to toxicities associated with drugs, even at early stages of liver failure. The use of image-guided locoregional therapies has developed primarily due to the limited applicability of surgical treatment for HCC. When surgery is precluded, image-guided locoregional therapies, which can be broadly categorized into local ablative therapies and transarterial therapies, are recommended as the most appropriate therapeutic choice to improve the prognosis of patients.

Local Ablative Therapy

Radiofrequency Ablation

Radiofrequency ablation (RFA) is the most common thermal ablation modality worldwide and is currently considered the best therapeutic modality for patients with early-stage HCC who are not candidates for surgical intervention [8, 9]. RFA relies on thermal heat created by an electrical current passing through the electrode embedded in the tumor. Temperatures between 60 and 100°C are generated by the high-frequency alternating current, which induces frictional heating when the ions in the tissue attempt to follow the changing directions of the alternating current [10]. Five randomized controlled trials (RCTs) compared RFA and percutaneous ethanol injection (PEI) for treating early-stage HCC. The results of these investigations consistently showed that RFA is more effective than PEI, leading to better local control of the disease [11–15]. In addition, four independent meta-analyses [16–19] that included all RCTs confirmed that RFA offers a better local control and survival benefit for early-stage HCC in comparison with PEI, thus establishing RFA as the standard percutaneous technique in these patients. An open question is whether RFA can compete with surgical resection as first-line treatment. Head-to-head comparisons between RFA and resection have been conflicting, with one randomized trial [20] demonstrating essentially no difference in overall survival (OS), and the other [9] indicating improved results for surgery over RFA. Similar conflicts are found in two meta-analyses, with one [21] showing equivalent survival rates despite higher rates of local recurrence with RFA, and the other [22] demonstrating better survival rates in surgical patients with tumor sizes ≥ 3 cm in diameter and equivalent rates in smaller tumors.

It has been reported that lesions >3 cm were not as effectively treated at the margins by RFA [23]. The incomplete ablation is largely attributed to the ‘heat sink’ effect, a reduction in

tissue temperature due to the conductive effects of adjacent vessels, typically described as ≥ 3 mm in diameter [24]. Histologic studies performed with liver specimens from patients who underwent RFA as bridge treatment before transplantation showed that the presence of large (≥ 3 mm) abutting vessels results in a decrease of about 50% in the rate of complete tumor necrosis because of the heat loss due to perfusion-mediated tissue cooling in the area to be ablated [25]. The methods to overcome the heat sink effect include pharmacologically decreasing blood flow [26–29], temporary vascular balloon occlusion [30, 31], and intra-arterial embolization [32, 33]. A combination of TACE followed by RFA is the most widely used technique aiming to minimize heat loss due to the heat sink effect, and the effectiveness of this combination treatment has been confirmed by several investigators [34–39]. In theory, the decreased blood flow induced by transarterial embolization reduces heat loss, increasing the ablation volume of the tumor, while the addition of TACE enhances the nearby control of satellite lesions [37, 40]. An RCT [41] compared RFA combined with TACE and RFA alone for treating intermediate-sized (3.1–5.0 cm) HCC. The results of this investigation showed that RFA combined with TACE is more effective than RFA alone for extending the ablated area in fewer treatment sessions and decreasing the local tumor progression rate. Another very recent RCT [42] showed that TACE-RFA was superior to RFA alone in improving survival for patients with HCC < 7 cm. Moreover, several independent meta-analyses [43–46], including the RCTs available for RFA plus TACE compared with RFA alone, confirmed high-quality evidence suggesting that TACE in combination with RFA improved survival outcomes compared with RFA alone for patients with HCC, particularly for tumors > 3 cm in size. An alternative strategy using localized radiation in combination with RFA has also been studied [47]. Results from a recent RCT [48] demonstrated better local and intrahepatic tumor control and long-term survival in combination therapy (^{125}I seed implantation and RFA) compared with RFA alone.

RFA is a safe procedure with a very low death rate of 0.2% and a major complication rate of 2.2%, as reported in a large multicenter study [49]. Clinical experience suggests that RFA of HCC tumors in a subcapsular location or adjacent to extrahepatic organs such as the gastrointestinal wall and gallbladder is associated with an increased risk of major complications due to heat injury [49–51]. The limitations of RFA for such high-risk HCC can be addressed by performing surgically assisted RFA using a laparoscopic approach [52, 53]. The ability to manipulate the perihepatic environment can protect structures such as the colon, stomach, small bowel, and diaphragm from transmitted heat. It also allows for potential removal of the gallbladder prior to RFA, preventing injury and heat sink. Thus, laparoscopic RFA should be recommended for patients with high-risk HCC.

Microwave Ablation

Microwave ablation (MWA) is emerging as a valuable alternative to RFA for the thermal destruction of HCC; it employs electromagnetic wavelengths in the frequency range of 900–2,450 MHz. Rapid directional current changes in the microwave electrode cause surrounding water dipoles to oscillate, resulting in heat generation leading to cellular coagulative necrosis [54]. Unlike RFA, MWA is not limited by the conductive property of tissues, and, therefore, a high tissue temperature can be more easily achieved [55], theoretically allowing for an increased efficacy of ablation in comparison to RFA. In addition, MWA is not as influenced by heat sink effects as RFA is [56], and is capable of creating a larger ablation zone [57]. Moreover, because MWA does not depend on the passage of electricity through tissues as RFA does, multiple applicators can be used simultaneously to create larger ablation zones and shorten the procedural time. Faster ablation times, larger ablation zones, and higher intratumoral temperatures have been observed with MWA in ex vivo bovine [58, 59] and in vivo porcine [60] animal models. Given its increased efficacy in ablation and shorter

time to achieve ablations, MWA has increasingly been used in treating HCC [61–67]. Liang et al. [62] evaluated a series of 288 patients with HCC who underwent percutaneous MWA and demonstrated 1-, 2-, 3-, 4-, and 5-year cumulative survival rates of 93, 82, 72, 63, and 51%, respectively. The authors considered a high probability of long-term survival of patients with a single lesion ≤ 4.0 cm in maximum diameter and Child-Pugh class A cirrhosis. Numerous studies have compared MWA with RFA for treating HCC and found similar disease-free survival, cumulative survival, and complication rates in the two groups [68–74]. However, so far, only one RCT [68] has compared the efficacy of MWA with that of RFA, in a series of 72 patients (36 RFA/36 MWA) with equivalent background demographics and mean tumor sizes. Although no statistically significant differences were observed with respect to therapeutic effects, complication rates, and rates of residual untreated disease between the two procedures, a trend favoring RFA was recognized in that study regarding local recurrence and complication rates. It has to be pointed out that the MW technology has improved markedly since this trial [75], and two prospective RCTs (NCT02539212 and NCT01340105) comparing the two techniques (RFA vs. MWA) for HCC are underway, which may obsolete the aforementioned results.

Given that MWA can create a larger ablation zone, MWA alone or combined with TACE has increasingly been used in treating large HCC [76–78]. Abdelaziz et al. [78] recently performed a study to compare the efficacy and safety of percutaneous MWA with TACE for large tumors (5–7 cm) and demonstrated better results for MWA than TACE in managing large HCC lesions. Another retrospective study [77] compared the outcomes of TACE combined with MWA (TACE-MWA) with TACE for treating unresectable large HCC (≥ 5.0 cm in diameter). The results showed that TACE-MWA had advantages in prolonging OS, with satisfying times to progression and improving liver function. However, further prospective studies are required to confirm the findings of these studies. A large multicenter RCT (NCT02630108) is ongoing to compare the efficacy and safety of TACE alone and TACE combined with synchronous multipoint MWA/RFA for large liver tumors.

Cryoablation

Cryoablation, which relies on freezing temperatures to induce tumor cell death, is the oldest local ablative technique for benign or malignant tumors [79]. Percutaneous cryoablation is believed to ablate cancer cells by several mechanisms including direct cell injury, vascular injury and ischemia, apoptosis, and immunomodulation [80, 81]. The advantages of cryoablation, compared with other ablative techniques, are as follows: (1) it allows for visualization of the ‘ice ball’ using noncontrast computed tomography [82], ultrasound [83], or magnetic resonance imaging [84] monitoring, which permits more precise evaluation of the ablated zone in real time; (2) it causes less pain and can be performed under moderate sedation, making it feasible for patients who are poor candidates for anesthesia [85], and (3) it maintains cellular integrity of connective tissue in the vessel walls, or adjacent visceral linings, such as the gallbladder, bowel, and kidney [86]. Despite the technical advantages, cryoablation has a potentially life-threatening complication, cryoshock syndrome, which is characterized by thrombocytopenia, multiorgan failure, and disseminated intravascular coagulopathy, specific for cryotherapy in large HCC [87, 88]. In addition, since cryoablation probes are needle shaped (14 G), large kill zones are not possible with a single probe. Therefore, large masses may require three or four probes. Each additional probe increases procedure time and the risk of organ injury and bleeding [89].

Interest in and application of cryoablation for HCC treatment have increased. Although some early review articles reported insufficient data to support or refute cryotherapy for HCC [90], many recent studies have shown that image-guided percutaneous cryoablation is safe and effective for treating HCC [82–84, 91, 92]. A single meta-analysis performed by Huang et

al. [93] investigated the role of cryoablation in comparison to RFA in treating unresectable HCC and showed an advantage for RFA over cryotherapy in terms of complication rates (OR 2.80; 95% CI, 1.54–5.09) and local tumor recurrence (OR 1.96; 95% CI, 1.12–3.42). However, multiple confounders exist in clinical trials, especially the bias in patient selection. A recent study [94], comparing cryoablation with RFA-MWA for treating HCCs sized <5 cm, showed that cryoablation can provide significantly improved local control for HCCs sized >2 cm compared with RFA-MWA. Another multicenter RCT [95] comparing the outcomes of percutaneous cryoablation with RFA for treating HCCs has been published very recently. The authors concluded that in HCC patients with Child-Pugh class A–B cirrhosis, HCC lesions ≤4 cm, and no more than two lesions in total, percutaneous cryoablation and RFA are equally safe and effective ablation treatments. For HCCs sized 3.1–4.0 cm, percutaneous cryoablation is associated with a lower rate of local tumor progression compared with RFA and should be considered one of the standard local ablation modalities.

Other Local Ablative Techniques

Percutaneous Ethanol Injection

PEI is the most common method of chemical ablation. It relies on the dispersion of ethanol within the lesion, which results in coagulation necrosis. PEI is a well-established technique for treating HCC tumors <3 cm in size [96]. Although it is not affected by heat sink, its success is largely limited by the difficulty of obtaining a uniform distillation of ethanol over a large tumor volume. Multiple studies have demonstrated the superiority of RFA to PEI for treating early-stage HCC [11–15]. Hence, PEI has largely been replaced by these modalities in treating HCC. However, owing to its ease of use and cost-effectiveness, PEI remains a viable option in many parts of the world.

Irreversible Electroporation

Irreversible electroporation (IRE) is the newest commercially available percutaneous ablation technique, which uses pulses of a high electrical current to induce irreversible disruption of cell membrane integrity, resulting in cell death via both apoptosis and coagulation necrosis [97, 98]. Two main potential advantages of IRE are that it creates tissue ablation in a manner independent of heat generation and does not affect the extracellular matrix, thus allowing for both a reduction in the heat sink effect and maintenance of structural integrity of the adjacent blood vessels and bile ducts [99, 100]. Several small series have evaluated the safety and efficacy of IRE for hepatic tumors. However, further prospective clinical trials are strongly needed to determine the optimal effectiveness of IRE for treating HCC.

Percutaneous Laser Ablation

Percutaneous laser ablation (PLA), which involves the direct deposition of laser light via fiber-optic applicators to induce tissue hyperthermia in tumors, is a recent technique that has also been proposed as an active treatment for patients with HCC [101–104]. Pacella et al. [105] retrospectively analyzed the use of PLA for treating nonsurgical early HCC and showed an initial complete response in 338 patients (78%) with a median OS of 47 months. A recent prospective randomized study has compared PLA (n = 15) and RFA (n = 15) for treating HCC ≤4 cm in patients with liver cirrhosis. A complete response was obtained in 87% of the lesions treated with PLA and in 93% of the lesions treated with RFA. The overall local recurrence-free survival rates at 3, 6, and 12 months were comparable with a higher rate of recurrence in the PLA group for lesions ≥21 mm. However, currently sufficient prospective data comparing the treatment efficacy in terms of long survival between PLA and other local ablative therapies are lacking.

Transarterial Therapy

Transarterial Chemoembolization

TACE is considered first-line therapy for patients with intermediate-stage HCC (multinodular, relatively preserved liver function, absence of cancer-related symptoms, and no evidence of vascular invasion or extrahepatic spread) [8, 106]. The recommendation for TACE as the standard treatment for intermediate-stage HCC is based on the results of two positive RCTs and a meta-analysis, which demonstrated improved survival in patients with HCC treated with TACE compared with best supportive care [7, 107, 108]. TACE also can be used as a bridge therapy before transplantation, by keeping tumors within the size and number required for transplantation [109]. The basis for TACE is the image-guided delivery of chemotherapeutic agents frequently embedded in Lipiodol into the tumor-feeding vessel, followed by embolization of the blood vessel with embolic agents [110–112]. Embolization is feasible and effective in treating HCC primarily based on the dominant arterial vascular supply of HCC compared with the normal liver parenchyma, which is largely supplied by the portal vein [113]. Occlusion of the terminal vasculature feeding the tumor results in ischemia and subsequent coagulation necrosis but typically spares adjacent liver cells as the portal vein remains patent. In addition, the targeted delivery of chemotherapeutic agents would result in high local concentrations, thereby leading to significant antitumor efficacy.

TACE is a highly complex and operator-dependent procedure. Heterogeneity exists in techniques, tumor burden, liver function (Child-Pugh class A or B), and agents used, which might explain the variations in outcomes in patients with HCC treated with TACE [114]. Achieving the best outcomes with TACE relies on appropriate patient selection and an accurate technique. From a technical point of view, more standardization of TACE protocols is still needed. The ideal TACE schedule should achieve a maximal and sustained concentration of the chemotherapeutic drug in the tumor, with minimal systemic exposure combined with the calibrated obstruction of tumor vessels [106].

Drug-eluting bead (DEB)-TACE has shown improved treatment tolerability and efficacy for HCC, as well as facilitated standardization of the procedure due to a high degree of treatment reproducibility. DEBs have the ability to actively sequester a drug from a solution and release it in a controlled and sustained fashion into the tumor vasculature, owing to ion exchange with the surrounding environment [115, 116]. Unlike the rapid release of the drug from Lipiodol in conventional TACE (c-TACE), DEB-TACE can significantly increase the local concentration of the drug and the antitumoral efficacy, with minimal systemic effects [117]. In addition, DEB-TACE has the important advantage of being a more reproducible technique. The results of the randomized phase II PRECISION V trial [118], which aimed to compare the outcomes of DEB-TACE with c-TACE for treating HCC, demonstrated that DEB-TACE with doxorubicin as the chemotherapeutic agent was better tolerated than c-TACE with doxorubicin, owing to a significant reduction in doxorubicin-related adverse events. Moreover, the use of DEBs also significantly improved the objective response rate in patients with Child-Pugh class B bilobar disease and recurrent disease [118]. More recent results of two RCTs have been published, with one trial showing equivalent survival rates [119] and the other demonstrating a better treatment response and delayed tumor progression for DEB-TACE in comparison with c-TACE [120].

Despite the recent advances and technical refinements, the efficacy of TACE is still limited by the dual blood supply of liver tumors, which makes it impossible to achieve sufficient tumor ischemia without irreversible damage to the surrounding normal liver parenchyma. Modified TACE procedures, such as superselective TACE, selective balloon-occluded TACE, and TACE under balloon occlusion of the hepatic vein or the corresponding portal vein branch,

have been developed to obtain a complete necrosis of the tumor [121]. Alternative strategies, including the combination of systemic therapy with TACE, have also been investigated to improve TACE-based regimens. Given that TACE induces a posttreatment surge of VEGF (vascular endothelial growth factor) due to local hypoxia [122, 123], the combination of TACE with anti-VEGF therapy may be an effective strategy to improve outcomes for these patients. A prospective single-center phase II study comparing the advent of sorafenib treatment with placebo 1 week after TACE demonstrated a disease control rate of 95% with manageable toxicity [124]. In contrast, a randomized phase III study with sorafenib beginning 1–3 months after TACE failed to show a survival benefit [125]. The optimal scheduling of antiangiogenic agents with TACE is essential to improve patients' prognosis.

Transarterial Radioembolization

Radioembolization, which refers to the intra-arterial administration of ^{90}Y -loaded beads that lodge in the arteriolar circulation supplying tumors and deliver tumoricidal radiation, has emerged as a potential option in patients with limited hepatic reserve. It evolved out of the inability of external beam radiation to deliver high doses without causing radiation hepatitis [126]. In contrast to external beam radiation, which can only deliver 30–35 Gy of radiation before causing clinically significant hepatotoxicity, intra-arterial ^{90}Y can deliver up to 150 Gy [127, 128]. Moreover, ^{90}Y beads lodge preferentially in the tumor vasculature and have a limited treatment zone, thus maximizing radiation to the tumor and minimizing it to the hepatic parenchyma. The safety and efficacy of ^{90}Y radioembolization have been demonstrated in a number of studies [129–132]. In 2011, Salem et al. [133] performed a retrospective study comparing the outcomes of radioembolization and TACE. Although no significant difference in survival time was observed, radioembolization resulted in a longer time to progression and produced less toxicity than TACE. Moreover, compared with TACE, radioembolization is safe for use in patients with portal vein thrombosis, due to its minimal embolic effect [134]. Despite the antitumor activity and promising survival results of radioembolization, further prospective studies, especially RCTs, are needed to provide the highest level of evidence.

Image-Guided ^{125}I Seed Implant Brachytherapy

Iodine-125 (^{125}I) is a nuclide that emits gamma rays with a very low average energy, a long half-life of 60 days, and a radiation diameter of 2 cm for tissue and 0.025 mm for lead [135]. Image-guided ^{125}I seed implant brachytherapy can achieve a necrotizing dose irradiation within the target volumes with a very sharp falloff outside the implanted area, thus sparing the normal tissues around the lesion. It has been widely used for a variety of tumors, including prostatic cancer [136], pancreatic cancer [137], pulmonary cancer [138], and head and neck cancers [139]. More importantly, based on its favorable therapeutic efficacy [140], ^{125}I seed implant brachytherapy is now recognized as a standard treatment for patients with localized low-risk prostate cancer. In terms of HCC, a recent study has evaluated the feasibility and therapeutic efficacy of 1.5-tesla conventional magnetic resonance-guided percutaneous interstitial ^{125}I seed implant brachytherapy [141]. However, strong evidence which would justify the use of ^{125}I seed implant brachytherapy alone for HCC is still insufficient. ^{125}I seed implant brachytherapy might be indicated in highly selected patients with high-risk, localized HCCs, such as those adjacent to large vessels being susceptible to a heat sink effect. Moreover, ^{125}I seed implant brachytherapy in combination with other locoregional therapy may lead to better control of HCC.

Conclusion and Future Directions

Image-guided locoregional therapies for HCC with both local ablative and transarterial therapeutic techniques have become common since the advent of modern imaging. Impressive progress in locoregional therapies has been made with a parallel continuous advance in technical developments. For example, energy-based techniques such as RFA and MWA, which were historically limited to lesions <3 cm, have benefited from recent advances in technology that have expanded their capability to up to 5 cm. Likewise, transarterial therapy, which was historically limited to intermediate-stage HCC, has expanded its role in treating HCC with portal vein thrombosis after introduction of transarterial radioembolization. Moreover, combination treatment modalities (thermal-based ablation and TACE) have shown promising results compared with single-therapy treatment for large tumors (<7 cm), which have consequently broadened their clinical indications.

Despite significant improvement, long-term survival outcomes in patients treated with these techniques are still not fully satisfactory, due to the high rates of tumor recurrence. The use of localized radiation in combination with thermal ablation is of particular interest for future investigation, as both improved local and intrahepatic tumor control and long-term survival have been demonstrated in a recent RCT. Tumor-specific immune responses have been reported to be activated after thermal ablative therapies, and, therefore, they represent potential interesting combination partners for thermal-based ablative approaches in HCC. Finally, tumor-targeting gene therapy may offer an intriguing area of future research. Intra-arterial delivery of both viral and nonviral vectors (nanocomposites or iodized oil) may improve, respectively, the safety profile of and concentrations usable in these two approaches.

Disclosure Statement

No potential conflicts of interest are disclosed.

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