Review Article

A review on radiofrequency, microwave and high-intensity focused ultrasound ablations for hepatocellular carcinoma with cirrhosis

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Importance: Hepatocellular carcinoma (HCC) is usually accompanied by liver cirrhosis, which makes treatment of this disease challenging. Liver transplantation theoretically provides an ultimate solution to the disease, but the maximal surgical stress and the scarcity of liver graft make this treatment option impossible for some patients. In an ideal situation, a treatment that is safe and effective should provide a better outcome for patients with the dilemma.

Objective: This article aims to give a comprehensive review of various types of loco-ablative treatment for HCC.

Evidence Review: Loco-ablative treatment bridges the gap between surgical resection and transarterial chemotherapy. Various types of ablative therapy have their unique ability, and evidence-based outcome analysis is the most important key to assisting clinicians to choose the most suitable treatment modality for their patients.

Findings: Radiofrequency ablation (RFA) has a relatively longer history and more evidence to support its effectiveness. Microwave ablation (MWA) is gaining momentum because of its shorter ablation time and consistent ablation zone. High-intensity focused ultrasound (HIFU) ablation is a relatively new technology that provides non-invasive treatment for patients with HCC. It has been carried out at centers of excellence and it is a safe and effective treatment option for selected patients with HCC and liver cirrhosis.

Conclusion and Relevance: Selective use of different loco-ablative therapies will enhance clinicians' treatment options for treatment of HCC.

Keywords: High-intensity focused ultrasound (HIFU); hepatocellular carcinoma (HCC); liver cancer; radiofrequency ablation (RFA); microwave ablation (MWA); survival; non-invasive treatment; ablation; cirrhosis; complication

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Introduction

Percutaneous thermal ablation has been one of the treatment options for patients with hepatocellular carcinoma (HCC) and cirrhosis (1,2). Radiofrequency ablation (RFA), high-intensity focused ultrasound (HIFU) ablation and microwave ablation (MWA) are among the popular modes of ablation. According to the Barcelona Clinic Liver Cancer treatment algorithm, ablation is used for HCC of stage 0 and stage 1 only. However, in real-life practice, especially in Asian regions where the Barcelona Clinic Liver Cancer treatment algorithm is not strictly followed, ablative treatment plays an important role in the management of HCC at different stages. This article aims to review the characteristics, advantages and disadvantages of RFA, HIFU and MWA as ablative treatment options for HCC with cirrhosis. We present the following article in accordance with the Narrative Review reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn.2020.03.11/rc).

Working mechanism of RFA and heat-sink effect

Radiofrequency electric current of 400–500 KHz is transmitted to the tumor cell through the distal end of the uninsulated part of the puncturing needle. Frictional heat energy is generated from the vibration of the ionic particles around the needle, and a temperature of 50–100 ℃ is produced. Tumor cells are killed as protein denatures under this high temperature (1). The radiofrequency current is conducted uniformly in a spherical manner if the surrounding tissue is of low impedance. Impedance will increase as tissue chars and vaporized gas accumulated, limiting the spread of heat energy. Most modern multi-array RFA electrodes can achieve an ablation zone of around 5 cm. As a 1-cm ablation margin is recommended, tumors <3 cm should be adequately ablated by RFA. Complete tumor ablation can be achieved in over 80% of cases (2). Since RFA works by inducing heat effect leading to tumor necrosis, when the tumor is located next to a major vessel (i.e., major branch of the portal vein or hepatic vein), the lower temperature of blood "cools down" the tumor abutting the vessel, leading to incomplete ablation. This heat dissipating phenomenon is known as the "heat sink" effect (3).

Comparison of RFA with some other non-surgical treatment modalities

Apart from physical means of ablative therapy, chemical ablation using ethanol, acetic acid (4) and sodium hydroxide (5) has been proposed. Percutaneous ethanol infusion has been the more popular chemical ablation. It works by the dehydrating property of absolute alcohol. After injection of ethanol to the tumor, diffusion of ethanol takes place along the concentration gradient, and tumor cells are killed by denature of protein and tumor vessels are thrombosis (6). Percutaneous ethanol infusion is generally safe and effective for tumors <3 cm although treatment of HCC up to 5 cm has been reported (7-9). When compared to RFA, percutaneous ethanol infusion has inferior survival outcomes as evidenced by many studies including a few meta-analyses (10-13). This is probably related to the presence of intratumoral septa and capsules, leading to uneven distribution of ethanol and hence a higher local recurrence rate.

Cryo-ablation is another physical means of ablative therapy. With sub-zero temperature, crystallization of water at intracellular and extracellular spaces leads to destruction of cellular structures (14). There were a few small series suggesting the effectiveness of cryo-ablation for primary HCC (15,16) and recurrent HCC (17). Nonetheless, the need for laparotomy for probe access, a higher complication rate (16,18-20) and inferior oncological outcomes are unfavorable when compared with RFA (21), and hence cryo-ablation has become obsolete in most centers nowadays.

Efficacy of RFA versus resection in treatment of HCC

Chen *et al.* randomized 180 patients who had HCC ≤5 cm to either percutaneous RFA or resection and saw no significant difference in overall survival or recurrence-free survival between the two treatment arms (22). In a randomized study by Feng *et al.* including patients with HCC <4 cm and ≤2 nodules who received either ablation or resection, again, no survival benefit was demonstrated by either arm (23). Huang *et al.* randomized 230 HCC patients within the Milan criteria (24) to either RFA or resection, and patients who received resection had significantly better 5-year overall survival (76% *vs.* 55%, P=0.001) and recurrence-free survival (55% *vs.* 34%, P=0.017) (25). More recent studies focused on smaller HCCs. Liu *et al.* performed a propensity score matching comparison of these two treatment modalities for HCCs <2 cm and found that resection was a superior treatment approach as shown by the superior 5-year recurrence-free survival (48% *vs.* 18%, P<0.001) and overall survival (80% *vs.* 66%, P=0.034) (26). Another propensity score matching analysis found no difference in overall survival but significant inferiority in recurrence-free survival in the RFA group (HR 1.75; P<0.001) (27). Another recent multi-center study using the Surveillance, Epidemiology, and End Results database suggested that the use of RFA should be limited to HCCs <3 cm and that tumors >3 cm should be treated by resection or transplantation for better oncological outcomes (28). It is difficult to draw a conclusion from these studies as they had different inclusion criteria, and many of these studies did not consider possible confounders such as tumor characteristic, location of tumor, type of electrode (single or cluster needles), and number of ablation cycle used in the RFA group. Further evidence from a multi-center randomized control study with standardized inclusion criteria is needed. It is generally considered that resection produces better oncological outcomes than RFA. Nonetheless, percutaneous RFA has been shown to be associated with better post-treatment quality of life when compared with resection (29), making RFA a reasonable choice for frail patients.

Role of RFA in treating larger HCCs and HCCs in difficult locations

During the process of tumor ablation, charring of tumor tissue increases the impedance of energy transmission and hence limits the size of ablation zone. Although satisfactory survival outcomes have been demonstrated (30,31), RFA for resectable HCCs of over 5 cm is generally not preferred (32-34). Different techniques have been introduced to improve the rate of complete tumor ablation and safety profile. For large tumors, multiple overlapping ablation can be used to increase the effective ablation zone (35). For lesions abutting a vascular structure, application of Pringle maneuver during ablation mitigates the “heat sink” effect (36). For lesions close to the hilum or biliary structure, infusion of chilled saline into the biliary system during ablation can protect the bile duct from heat injury (37,38). A cooled-tip electrode and intermittent energy generator can be used to reduce char formation around the electrode (39). Use of clustered or antenna-like needle configuration can increase the ablation zone to 7 cm (40,41). It has been proposed that sequential use of transarterial chemoembolization (TACE) before RFA can improve the outcomes of HCC treatment (42,43). A recent meta-analysis suggested that combining TACE and RFA could result in superior survival outcomes when compared to using RFA alone in treating large HCCs (44).

Pre-transplant bridging and down-staging therapies using RFA

Due to the scarcity of liver graft, waitlisted HCC patients are expected to have a dropout rate of 20–30% due to disease progression (45-47). Many centers (including ours) offer bridging therapy to HCC patients when the waiting time is expected to be >6 months (48). Some centers used RFA as a bridging therapy and the dropout rate was brought down to <10% (49,50). Furthermore, response to bridging therapy has been shown to be associated with the rate of post-transplant recurrence of HCC. Chan *et al.* found that tumor necrosis of 60% or more was an independent factor associated with a lower rate of post-transplant recurrence (51).

Down-staging therapy with the use of RFA provides the last hope of transplantation for patients who initially presented with beyond-criteria HCC. Several centers practiced down-staging protocols for HCC patients beyond standard criteria, and the rates of successful down-staging and transplantation were 56–90% (52-54) and 44–78% respectively (52-55). Moreover, the long-term oncological outcomes in these patients were not compromised when compared with those in HCC patients within standard criteria at presentation.

Role of RFA in treating ruptured HCCs

RFA has become a treatment of choice for recurrent HCC, with a 5-year overall survival rate of 18–40% (56,57). In a meta-analysis comparing resection, RFA and TACE for recurrent HCC, patients in the RFA group had the best median 5-year overall survival, although the difference did not reach statistical significance (58).

Spontaneous tumor rupture is one of most dreadful complications of HCC and it happens in 3–10% (59,60) of patients. TACE has been the established first-line treatment. However, RFA comes into play when TACE fails to stop bleeding. With regard to the role of RFA in the management of ruptured HCCs, our center has published a 20-year retrospective series. In this study, we found that treating ruptured HCCs with open RFA for hemostasis was an independent factor for better overall survival (HR 0.41, 0.24–0.79) (59).

Complications of RFA as a treatment of HCC

Complications after RFA is uncommon. Most patients can be discharged after overnight observation after percutaneous RFA. The overall complication rate is <10% and the mortality rate is around 0.5% (61-63). Some common non-life-threatening complications are liver abscess, pleural effusion, pneumothorax, and subscapular hematoma. Other rarer life-threatening complications include liver failure, portal vein thrombosis, and bowel perforation. Good patient and operator selection is the only way to avoid mishaps.

Table 1 Treatment outcomes of percutaneous RFA in patients with cirrhosis

Study	Year	No. of patients	Cirrhosis	Tumor size	Complete response	3-year survival	Complication rate
Brunello *et al.* (65)	2008	70	Mainly Child A	<3 cm	95.7%	63%	14.2% (all complications)
Lin *et al.* (66)	2005	62	Mainly Child A	<3 cm	92.8%	74%	4.8% (major complications)
Seror *et al.* (67)	2006	57	Child A only	<3.5 cm	–	91.2% (2-year)	15% (major complications)
Shiina *et al.* (68)	2005	118	Mainly Child A	<3 cm	100%	81%	5.1% (major complications)
Feng *et al.* (23)	2012	84	Mainly Child B	<3 cm	94%	67.2%	9.5% (all complications)
Liu *et al.* (26)	2016	100	Mainly Child A	Milan criteria	–	67.2%	11% (all complications)
Ng *et al.* (69)	2017	109	Mainly Child A	Milan criteria	94.4%	82.3%	4.6% (severe complications)

Limitations of RFA

During RFA treatment, heat energy generated by high-frequency alternating currents (460–480 kHz) targeted at the living tissues causes protein denaturation at a temperature of 60 ℃ through ionic vibration. Coagulative necrosis of the target lesion follows (64). The initial results of percutaneous RFA for small HCCs were encouraging: the complete tumor response rate was high and the complication rate was as low as 5%. *Table 1* lists the outcomes of percutaneous RFA for small HCCs (23,65-69). However, these data can be misleading, as most of the patients did not have decompensation of cirrhosis. Deaths after percutaneous RFA for liver cancer in non-cirrhotic patients have been reported. The reported mortality rate were between 0.3% and 1.6% (70-72). In addition, the efficacy of RFA in treating large tumors is still questionable. Although several reports showed that it was feasible to use RFA with multiple processes and overlapping ablation zones to treat large liver tumors, the high recurrence rates did not favor it as a primary treatment tool for these tumors (41,73,74).

Open RFA may be risky for patients with advanced cirrhosis because of thrombocytopenia and portal hypertension. On the other hand, percutaneous RFA requires a very high level of skill if it is used to treat these tumors: deeply seated tumors, tumors in the caudate lobe, and tumors located at the dome of liver where diaphragmatic injury may result as a collateral damage due to the ablation procedure. Moreover, percutaneous RFA is contraindicated in the presence of ascites because of the increased chance of hemoperitoneum and liver failure.

An effective locoregional treatment with a non-invasive nature could probably bridge the treatment gap between percutaneous RFA and TACE for cirrhotic HCC patients.

History of HIFU treatment

HIFU ablation is a non-invasive treatment modality that uses an extracorporeal source of ultrasound energy focused at a particular point. This technique was first described by Lynn *et al.* in 1942 (75). Clinical use of HIFU started with the concept of utilizing high-energy ultrasound beam to induce hyperthermia and tissue damage as proposed by the Fry brothers in USA in 1950s. The initial experiments were to evaluate this treatment option for patients with Parkinson disease (76,77). With not very successful outcomes, the research interest died down, but the enthusiasm was aroused again in the 1990s when a more powerful output unit was designed. In 1997, Wang made use of the re-designed unit of HIFU machine and demonstrated that effective destruction of liver tissue could be performed in an animal model (78). This report initiated a cascade of clinical studies on the possibility of HIFU treatment for liver tumors.

Physical properties of HIFU treatment

The modern HIFU treatment unit has a significantly higher time-averaged intensity in the focal region of the ultrasound transducer, when compared with typical diagnostic ultrasound. HIFU ablation utilizes a unique frequency of ultrasound wave of 0.8–3.5 MHz, which can be focused at a distance from the therapeutic transducer. This causes vibration of the particles inside the cells, and the heat generated as a result raises the temperature in the tissue rapidly to 60 ℃ or higher, causing coagulative necrosis within a few seconds. Energy-focusing results in high intensity at a specific location and over a small volume. Temperature outside the focus point remains static as particle oscillation remains minimal. In addition to thermal effects, cavitation effects, microstreaming and radiation forces all contribute to cell death. At high intensity, ultrasound can result in tissue heating and necrosis, cell apoptosis, and cell lysis. Cavitation, as a cause of tissue damage, is a result of the presence of small gaseous nuclei existing in subcellular organelles and fluid in tissue that can expand and contract under the influence of the acoustic pressure. Gas is drawn out of the solution during rarefaction, creating bubbles. These bubbles may remain relatively stable and simply oscillate or they may collapse spontaneously, causing mechanical stresses and generating heat in the environment (79). There are different treatment machines manufactured by different companies. In general, a HIFU treatment unit is composed of an ablation unit, an energy-generating unit, and a monitoring unit for the change in ablation. HIFU treatment machines can be classified into MRI-guided HIFU (MRgHF) and ultrasound-guided HIFU (USgHF) according to the monitoring modality. Currently, USgHIFU is approved for use in Bulgaria, Italy, Japan, South Korea, Malaysia, Mexico, the UK, Russia, Romania, Spain and China (including the Hong Kong SAR) for the treatment of uterine fibroids and cancers of the brain, breast, liver, bone and prostate. On the other hand, MRgHIFU is an approved therapeutic procedure for treating uterine fibroids in Asia, Europe, Australia, Israel, Canada and the USA (approved by U.S. Food and Drug Administration).

As ultrasound energy travels much better in water than in air, the presence of ascites in HCC patients actually facilitates energy propagation to the targeted tumor.

HIFU for small HCCs

In 2001, Wu *et al.* reported that effective destruction of tumor cells was achieved in a group of HCC patients who received HIFU two weeks before resection. In the treated areas, irreversible cell death (nuclear pyknosis, debris, and dissolution) was observed. Blood sinusoids collapsed with endothelial cell damage. Electronic microscopic examination showed that there were distorted tumor cells with severe destruction of cell organelles and nuclei in the treated area. Disintegration of cell membrane and nuclear membrane, as well as nucleus disruption, was generally observed (80). Studies reporting successful HIFU ablation in patients with non-resectable small HCCs began to appear. Ng *et al.* demonstrated that the initial treatment response in patients with HCCs with a median tumor size of 2.2 cm was promising. The primary complete ablation rate was 79.5%. It increased from 66.6% in the initial series to 89.2% in the last 28 patients. The primary technique effectiveness for tumors <3.0 cm was 90.6%, whereas that for tumors ≥3.0 cm was 58.8% (81). Xu *et al.* in a clinical study involving 145 patients demonstrated that HIFU ablation was an effective treatment for HCC. The 2-year survival rates in patients with stage-I, stage-II and stage-III HCC were 80%, 51.4% and 46.5% respectively (82). Cheung *et al.* demonstrated that HIFU ablation was an effective alternative to percutaneous RFA for small HCCs. In the HIFU group, there were significantly more patients with Child-B cirrhosis (35%). In patients with HCCs <3 cm, the 1 and 3-year survival rates after HIFU treatment were 81.2% and 79.8% respectively. The 1- and 3-year disease-free survival rates were 62.4% and 34.1% respectively (83).

HIFU for large HCCs

The prognosis for larger unresectable HCCs is very poor (84,85), and TACE has been a suggested treatment for this group of patients (86-88). However, the median patient survival after TACE has not been very satisfactory. The 3-year survival rate after TACE in patients with HCCs >5 cm was reported to be <31% (89). RFA is considered not suitable for patients who have large HCCs, especially if they also have advanced cirrhosis. The non-invasive nature of HIFU is an advantage for patients with advanced cirrhosis. Research has been carried out to investigate whether HIFU ablation is a suitable treatment for large HCCs in the presence of cirrhosis. Wu *et al.* reported that HIFU could be safely used in cirrhotic patients with advanced HCC. In a study involving 55 patients with a median tumor size of 8.1 cm (4–14 cm), the overall survival rates at 6, 12 and 18 months were 86.1%, 61.5% and 35.3% respectively. No severe complications were reported (90). In a study involving 151 patients with advanced HCC, the complete response and partial response rates for HIFU treatment were 28.5% and 60.3% respectively in patients with advanced HCC. The 1-year and 2-year survival rates were 50% and 30.9% respectively in these patients and 3.4% and 0% respectively in patients who received maximal conservative treatment only (91). Cheung *et al.* reported that the complete response rate of tumors >5 cm was 50%, and the 1-, 3- and 5-year survival rates were 84.6%, 49.2% and 32.3% respectively (92). Incomplete ablation likely happens with larger tumors. In order to improve the survival of patients with larger tumors, clinicians have tried to combine TACE and HIFU ablation. Wu *et al.* randomized 50 patients with HCCs >10 cm to two treatment groups: TACE alone and TACE with HIFU. A survival benefit was seen in the latter group. Patients with stage-IV HCC in this group had a 1-year survival rate of 42.9%, versus 0% in their counterparts (93). Li *et al.* also compared these two modalities (TACE alone and TACE with HIFU) for unresectable large HCCs. They randomized 89 patients with unrespectable large HCCs to these two treatment groups. A significantly higher tumor response rate and a survival benefit were seen in the group having combined treatment. The 1-, 2- and 3-year overall survival rates in this group were 72.7%, 50.0% and 31.8% respectively, versus 47.2%, 16.7% and 2.8% respectively in their counterparts (94).

HIFU for tumors in difficult positions

Proximity of tumor to large blood vessels plays a significant role in heat transmission. Blood flow protects the vessel wall from damage, but it also acts as a "heat sink" and cools nearby tissue, limiting coagulative potential (95). The potential heat-sink effect of HIFU has been investigated. In a study involving 39 patients with 42 tumors (1.5–22 cm; median, 7.4 cm) close to major hepatic vessels, patients with smaller tumors had better tumor response to HIFU treatment. The complete response rate was 50% and the partial response rate was 50% (96). The heat-sink effect was minimal due to the extracorporeal mode of energy delivery. Unlike percutaneous RFA where heat energy dissipates from the radius of the active treatment electrode, HIFU delivers heat energy at a precise focus point of around 1cm in diameter. HIFU can theoretically ablate tumors in difficult locations. With the aid of artificial pleural effusion with normal saline, effective ablation can be achieved near the diaphragm or the heart where percutaneous RFA is technically impossible (97,98).

HIFU ablation as a bridging therapy

Patients awaiting liver transplantation in general have relatively poor liver function. They may present with gross ascites and hyperbilirubinemia, which are contraindications to TACE. Since the liver donation rate is very low in most Asian regions, these patients need an effective bridging therapy to prevent the progression of HCC and dropping out while waiting for a liver graft. HIFU ablation can potentially provide a suitable bridge in this context. HIFU ablation is well tolerated in cirrhotic HCC patients. After the first report of successful HIFU ablation as a bridging therapy for patients awaiting transplantation (97), the Hong Kong group started using it as a treatment modality for waitlisted HCC patients (99). The interim results with a small sample number showed that HIFU ablation is a safe and promising treatment in waitlisted patients. None of the patients developed liver failure after treatment. The treatment can potentially reduce the dropout rate in areas where the liver donation rate is low.

Complications of HIFU ablation

Complications of HIFU ablation are mainly related to the thermal injury resulting from the focused ultrasound. It can cause damage to internal organs if the focus point is misplaced or it can cause damage to the tissue along the pathway of the HIFU energy penetration. Most patients may experience first-degree skin burn and pain after treatment but most of these conditions are self-limiting. However, severe complications, including ablation of the small bowel in the surrounding area requiring laparotomy, have been reported (100). Xu *et al.* showed that HIFU treatment was a well-tolerated treatment option for cirrhotic HCC patients. First-degree skin burn occurred in 37.2% of the patients, second-degree skin burn occurred in 31.7% of the patients and third-degree skin burn occurred in 2.1% of the patients. No complication related to liver function decompensation was reported (82). Cheung *et al.* reported that 13 patients developed complications after HIFU treatment for HCC. Most of the complications were associated with skin injuries. One patient developed transient hyperbilirubinemia and one patient developed liver abscess that did not require drainage. More than one-third of patients had Child-B cirrhosis. There was no mortality reported (101). *Table 2* summarizes the results of HIFU treatment in cirrhotic HCC patients.

MWA—aim of the treatment

The ultimate mechanism of tumor destruction by MWA is thermally induced coagulative necrosis. Heat is generated by high-frequency (>900 MHz) electromagnetic energy via interaction with protons predominately residing within water molecules, which causes them to flip their electrical charge (hydrogen has a positive charge and oxygen

Table 2 Summary of HIFU treatment in patients with HCC and cirrhosis

Study	Treatment	Year	No. of patients	Cirrhosis	Tumor size	Complete response	Survival	Complication rate
Xu *et al.* (82)	HIFU	2011	145	44% Child B or above	<2, 2–5, >5 cm	–	80% (2 years), 51.4%, 46.5%	2.1% (major complications)
Cheung *et al.* (97)	HIFU	2012	47	34% Child B or above	<3 cm	90%	79.8% (3 years)	6.3% (major complications)
Wu *et al.* (90)	HIFU	2004	55	Child A and B	>8 cm	3.6% (90% partial response)	35.3% (18 months)	23.6% (minor complications) no major complication
Li *et al.* (91)	HIFU	2007	151	51% Child B or above	>5 cm	28.5% (60.3% partial response)	30.9% (2 years)	15% (major complications)
Cheung *et al.* (92)	HIFU	2014	26	34% Child B or above	>3 cm	50%	49.2% (3 years)	56% (minor complications), no major complication
Wu *et al.* (93)	HIFU + TACE	2005	24	Mainly Child A	50% >10 cm	64% partial response	42.9% (1 year)	25% (minor complications) no major complication
Li *et al.* (94)	HIFU + TACE	2010	44	22.7% Child B or above	Mainly >5 cm	27.3% (45.5% partial response)	50% (1 year)	29.6% (minor complications), no major complication

negative) 2–5 billion times/s, thereby generating friction and heat (102).

MWA can be performed in open or laparoscopic approach or percutaneously under the guidance of ultrasound or computed tomographic scan. It allows broader fields of power density, and is able to create more uniform and larger ablation zones, thereby reducing or eliminating the heat-sink effect (especially when adjacent to large vessels). It has several technical advantages over RFA, including predictable ablation zone, faster ablative time, and non-susceptibility to current and thermal "heat sinks" within the ablation field (103).

Microwave coagulation therapy was first introduced as a treatment modality in Japan (104-106) and was used mainly for hemostasis or coagulation during liver resection (107,108). The advantages of MWA include larger volume of cellular necrosis, reduced procedure time, higher temperature delivered to the target lesion, possibility of simultaneous use of multiple antennae, fewer intraprocedural complications, and efficacy on lesions with a cystic component and/or in proximity to vascular structures with reduced heat-sink effect (102,109,110).

Physical properties of MWA

This surgical tool is based on the principle that microwave irradiation of tissue with a frequency of 2,450 MHz (corresponding wavelength of 12 cm) via a monopolar antenna produces heat due to energy produced by the vibration of polar molecules in protein and water (107,108,111). The generation of heat is limited to the electromagnetic field around the antenna, and the coagulation field is determined by the relationship between antenna length and tissue permittivity. Each coagulation session consists of 30–45 s of coagulation and 5 s of dissociation.

Microwave tissue coagulator

The microwave tissue coagulator system consists of a microwave generator [which generates the power required and monitors energy delivery to the patient (112,113)], a hand piece, and a reusable needle antenna that can be adjusted in length (10–45 mm). There is an attached device that can change the antenna angle in 90°, usually a semi-rigid coaxial cable that emits microwave radiation from its exposed (uncovered by the outer conductor) distal end, embedded into a needle-like device. There is also a power transmission line linking the energy source output ports to the antennae.

MWA for small HCCs

Early-stage HCC is defined as a single HCC lesion ≤5 cm in diameter or three nodules ≤3 cm in diameter, according to the Barcelona Clinic Liver Cancer staging system (114). For early HCC, thermal ablation has been gaining acceptance (22,115-118), and RFA and resection achieve similar treatment outcomes (22,116-118). For HCC <2 cm, RFA can achieve a comparable 5-year survival rate of 70% (26,32,119-123).

MWA has also been used for early or very early HCC. Xu *et al.* reported non-inferior treatment results of MWA when compared to RFA in treating very early HCC, with a 5-year survival rate of 78.3% *vs.* 73.3% (124). Similar outcomes were also observed in treating early HCC with MWA versus RFA, although further subgroup analysis showed that MWA had better outcomes in treating HCCs >3.5 cm (125). The additional use of laparoscopic thermal ablation might allow precise localization and benefit from the laparoscopic surgical approach, while similar survival was achieved in treating tumors ≤3 cm with MWA versus RFA (126). Unfortunately, the use of the thermal ablative modality, unlike surgical resection, is associated with a higher rate of early recurrence, particularly in patients having percutaneous ablation (127).

MWA for large HCCs

It is possible to consider microwave treatment as a curative therapy rather than a palliative treatment for large lesions because of its large ablative zone (128). In a study of MWA for HCCs 5–8 cm, complete ablation rates from 73.1% to 87.5% were achieved (129). In another study of MWA for HCCs 3–7 cm, higher complete ablation rates up to 92.6% were reported (130), despite the fact that 22.2% of the patients developed local recurrence, which is a common phenomenon in ablative therapy (130,131). MWA can be an alternative treatment modality, especially for patients who are not fit for resection or transplantation, or when the tumor location is not ideal for RFA.

MWA for tumors in high-risk locations

High-risk locations are areas close (<5 mm) to the gallbladder, the gastrointestinal tract, the second bile duct or the third bile duct. The major complication rate resulting from RFA can be as high as 4.1% (132), including bile duct injury, biliary stricture, biloma, bilioperitoneum or biliopleural fistula in up to 12% of patients (133). While perforation of the gastrointestinal tract has been reported, the overall incidence was around 0.1–0.3% (134). The temperature dispersed from MWA can be set at as high as 60 ℃ for the gallbladder and bile duct and 55 ℃ in areas close to the gastrointestinal tract. In a recent study, the complete ablation rate was 98.2% but some patients required more than one session to get complete ablation (135).

For tumors at the liver dome, thermal ablative therapy may be difficult because of potential complications; phrenic nerve/diaphragmatic injury, pneumothorax or peritoneal burn may occur if the tumor is close to the diaphragm, peritoneum or lung. Moreover, using ultrasound to localize tumors in this region may be difficult because of poor acoustic penetration due to overlying lung tissue (136). For these tumors, MWA guided by computed tomography is feasible, with the aid of artificial ascites to displace the liver dome from the right hemi-diaphragm (137).

HCC may present as exophytic tumor, in which a portion of the tumor goes beyond the margin of the liver and extrudes into the abdominal cavity. With insufficient normal liver parenchyma to surround it, it has the risks of rupture, seeding and hemorrhage when treated with thermal ablation (138). To minimize the complication risk, an antenna is inserted into the normal liver tissue and the vessel feeding the tumor, which should be ablated first so as to reduce the blood flow to the tumor before ablation of the main tumor bulk (139). Furthermore, the use of artificial pleural effusion or ascites can help to prevent adjacent viscera from heat injury (140,141). With these measures, exophytic HCCs can be safely ablated by MWA.

MWA as a bridging therapy

Patients awaiting liver transplantation in general have relatively poor liver function. They may present with gross ascites and hyperbilirubinemia, which are contraindications to TACE. Since the liver donation rate is very low in most Asian regions, these patients need an effective bridging therapy to prevent the progression of HCC and dropping out while waiting for a liver graft. TACE and percutaneous thermal ablation have been successful at prolonging survival of HCC patients and at bridging patients to transplantation (142-145). Microwave can be used in bridging therapy in this context. In a study by Zanus *et al.*, six patients who had HCC (from single nodule to multifocal HCC) underwent MWA as a bridging therapy before transplantation. These patients did not have evidence of peritoneal or nodal HCC or histological signs of active neoplastic disease in the treated nodules. One patient died 15 days after transplantation due to sepsis and five patients were alive one year after transplantation without evidence of recurrence (146). Combination of treatment modalities have also been advocated (TACE with RFA or TACE with MWA). In a study by Vasnani *et al.*, >90.5% tumor coagulation was noted in excised livers treated by TACE with MWA, and complete tumor coagulation was noted in 53% of patients. The group having TACE with RFA had similar results (147). Combination therapy is safe and may offer further advantages such as control of micro-metastasis and more uniform ablation zones by MWA (44,148). Studies involving more patients are needed to confirm the usefulness of MWA as a bridging therapy on its own or as a component in a combination bridging therapy. However, the reported explant histology showed a promising result. Further study is needed for confirmation.

Complications of MWA

Complications of MWA mainly arise from heat damage. A complication rate lower than RFA has been reported (149). Thermal injury to the bile duct may result in acute cholangitis or liver abscess formation. Insertion of antenna may result in intraperitoneal bleeding and liver hematoma formation. Liver decompensation is rarely seen, and the incidence can be reduced with better patient selection (149-154). *Table 3* summarizes the outcomes of MWA in HCC patients.

Table 3 Summary of microwave ablation in patients with HCC and cirrhosis

Study	Year	No. of patients	Cirrhosis	Tumor size	Tumor location	Complete response	Survival	Complication rate
Seki *et al.* (150)	1999	48	56.3% A, 41.7% B, 2.1% C	1.83±0.23 cm	NS	NS	78% (5 years)	
Ohmoto *et al.* (153)	2009	49	63.3% A, 28.6% B, 8.2% C	1.7 (0.8–2.0) cm	NS	NS	39% (4 years)	14% (major complications)
Ding *et al.* (154)	2013	113	66.4% A, 33.6% B	2.55±0.89 cm	7 near major vessels, 4 near gallbladder, 23 near diaphragm, 8 near gastrointestinal tract	98.5%	77.6% (3 years), 45.34±2.28 months	2.7% (major complications)
Liu *et al.* (131)	2013	80	85% A, 15% B	3–8 cm	19 near bile duct	87.5%	34.6% (5 years)	7.5% (major complications)
Zhang *et al.* (145)	2013	77	100% A	up to 5 cm	NS	86.7%	38.5% (5 years)	2.6% (major complications)
Groeschi *et al.* (127)	2014	139	NS	2.6 (0.7–6.0) cm	NS	94.1%	19% (5 years)	NS
Abdelaziz *et al.* (149)	2014	66	37.9% A, 62.1% B	2.9±0.97 cm	93.9% right lobe, 6.1% left lobe	96.1%	62% (2 years)	3.2% (minor complications); no major complication
Medhat *et al.* (129)	2015	26	73.1% A, 27.9% B	5.57±0.73 cm	NS	73.1%	Median 21.5 months	No major complication
Asvadi *et al.* (137)	2016	48	NS	2.4 (0.9–5.2) cm	Liver dome	85%	73.9% (2 years)	No major complication
Lee *et al.* (125)	2017	26	88.5% A, 11.5% B	3.75 (2.0–6.0) cm	NS	NS	70% (3 years)	15.4% (minor complications)
Xu *et al.* (124)	2017	301	92.4% A, 7.6% B	1.7±0.3 cm	NS	98.3%	78.3% (5 years)	0.7% (major complications)
Santambrogio *et al.* (126)	2017	60	100% A	2.15±0.53 cm	62% at deep intrahepatic location, 37% adjacent to hepatic structures or other viscera, 7% adjacent to major vessels	95%	37% (5 years)	23% (minor complications); <2% (major complications)
Ding *et al.* (139)	2017	132	91% A, 9% B	2.52±0.83 cm	71 exophytic growths	96.6%	61.5% (5 years)	No major complication

NS, not specified.

Table 4 Comparison of RFA, HIFU and MWA

	RFA	HIFU	MWA
Physics	Electric current	Ultrasound	Electromagnetic
Frequency of vibration	400–500 KHz	0.8–3.5 MHz	>900 MHz
Temperature of ablation (degree Celsius)	50–70	~60	Up to 120–150
Need of ground pad	Yes	No	No
Heat Sink effect	Yes	Minimal	Minimal
Homogeneity of heat distribution	Uneven due to charring effect	Focused ablation	Even distribution of heat energy
Size limit	3–4 cm	3 cm	5 cm
Procedure time	Medium (12 mins/cycle)	Long (1–2 hours per tumor)	Short (few minutes)
Mode of anesthesia	LA/GA	Only GA	LA/GA
Ascites	Contraindicated	Not contraindicated	contraindicated
Specific complication	Bile duct injury	Skin necrosis	Similar to RFA
	Diaphragmatic injury	Pleuritic	
	Visceral injury	Pleural effusion	
	Hepatic hematoma	Rib fracture	
	Liver abscess	Hepatic hematoma	
Machine cost	Moderate	High	Moderate

GA, general anesthesia; LA, local anesthesia.

Summary and conclusions

RFA is an indispensable part of the armamentarium for HCC treatment. It remains the most reliable means of ablative therapy. It represents an ideal alternative to hepatectomy in treating HCCs <2–3 cm and a reasonable second choice in treating larger tumors. It plays an important role in bridging and down-staging therapies before transplantation. RFA will continue to be a popular treatment for both fit and frail patients, judging from its high safety profile and good post-treatment quality of life.

HIFU therapy is an emerging loco-ablative treatment option. It is an effective and safe treatment for cirrhotic HCC patients. As with other loco-ablative treatments, smaller HCCs usually have a better complete ablation rate. The combination of HIFU and TACE may provide good survival outcomes in patients with larger unresectable tumors, for which RFA is considered dangerous. On liver transplant waiting lists, HCC patients compete with liver failure patients. Their priority is inevitably lower than that of patients having high Model for End-Stage Liver Disease scores. Since HIFU has been shown to be well tolerated in patients with advanced cirrhosis, the use of HIFU as a bridging therapy is worth further evaluation.

MWA is a promising and emerging loco-ablative treatment option. It is an effective and safe treatment option for cirrhotic HCC patients. In general, small HCCs have higher response and complete ablation rates. With a more uniform ablative zone and no heat-sink effect, it may potentially offer advantages over RFA.

A comparison of these three modes of ablation is also shown in *Table 4*. Selective use of different loco-ablative therapies will enhance clinicians' treatment options for treatment of HCC.

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Footnote

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