

Local ablative treatments for hepatocellular carcinoma: An updated review

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Abstract

Ablative treatments currently represent the first-line option for the treatment of early stage unresectable hepatocellular carcinoma (HCC). Furthermore, they are effective as bridging/downstaging therapies before orthotopic liver transplantation. Contraindications based on size, number, and location of nodules are quite variable in literature and strictly dependent on local expertise. Among ablative therapies, radiofrequency ablation (RFA) has gained a pivotal role due to its efficacy, with a reported 5-year survival rate of 40%-70%, and safety. Although survival outcomes are similar to percutaneous ethanol injection, the lower local recurrence rate stands for a wider application of RFA in hepato-oncology. Moreover, RFA seems to be even more cost-effective than liver resection for very early HCC (single nodule ≤ 2 cm) and in the presence of two or three nodules ≤ 3 cm. There is increasing evidence that combining RFA to transarterial chemoembolization may increase the therapeutic benefit in larger HCCs without increasing the major complication rate, but more robust prospective data is still needed to validate these pivotal findings. Among other thermal treatments, microwave ablation (MWA) uses high frequency electromagnetic energy to induce tissue death *via* coagulation necrosis. In comparison to RFA, MWA has several theoretical advantages such as a broader zone of active heating, higher temperatures within the targeted area in a shorter treatment time and the lack of heat-sink effect. The safety concerns raised on the risks of this procedure, due to the broader and less predictable necrosis areas, have been recently overcome. However, whether MWA ability to generate a larger ablation zone will translate into a survival gain remains unknown. Other treatments, such as high-intensity focused ultrasound ablation, laser ablation, and cryoablation, are less investigated but showed promising results in early HCC patients and could be a valuable therapeutic option in the

next future.

Key words: Liver cancer; Hepatocellular carcinoma; Radiofrequency ablation; Microwave ablation; Radio-frequency ablation

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Core tip: Ablative treatments currently represent the first-line option for the treatment of early stage unresectable hepatocellular carcinoma. Among ablative therapies, radiofrequency ablation has gained a pivotal role due to its efficacy, with a reported 5-year survival rate of 40%-70%, and safety. Among other thermal treatments, microwave ablation, high-intensity focused ultrasound ablation, laser ablation, and cryoablation, are less investigated but showed promising results.

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INTRODUCTION

Hepatocellular carcinoma (HCC) represents a life-threatening condition and constitutes the main cause of death among cirrhotic patients^[1,2]. In the last years, the accurate screening programs and more refined diagnostic imaging have made early HCC diagnosis feasible in 30%-60% of cases^[3].

Local ablation represents the standard of care for patients at early stage, who are not suitable to surgery or orthotopic liver transplantation (OLT). Among ablative treatments, thermal ablative therapies have gained an increasing role in the last decade due to their efficacy in preventing local recurrence as well as in prolonging overall survival (OS). Thermal ablative treatments are classified as hyperthermic, such as radiofrequency ablation (RFA), microwave ablation (MWA), high-intensity focused ultrasound (HIFU) or laser therapy, or hypothermic such as cryoablation.

These procedures are usually performed by means of a percutaneous approach but in particular conditions (for instance in cases of nodules in "at-risk" location) laparoscopic ablation may be recommended.

In this review we aim to provide a comprehensive overview on the main thermal therapies for HCC with the up-to-date data on their efficacy and safety.

INDICATION TO TREATMENT

Thermal ablative treatments represent the standard of care for unresectable HCC in very early/early stage according to Barcelona Clinic Liver Cancer (BCLC)

system^[2,4]. The term "unresectable" covers a broad spectrum of pathological conditions, from single nodule in a deep location (therefore not easy to treat by surgery) to multinodular disease in patients with deteriorated liver function. Therefore, percutaneous therapies are a valuable option in non-optimal candidates to surgery due to tumor size, number, location, liver function, or comorbidities.

Another indication to thermal treatment is the pre-transplant setting, where RFA has been proved to be effective both as downstaging and as bridging therapy^[5-7].

Main absolute and relative contraindications to thermal treatments are described in Table 1. Absolute contraindications, shared with other locoregional treatments, are the presence of extrahepatic liver disease, altered mental status, active infection, tumor abutting a major hepatic duct, impaired liver function (particularly in presence of ascites); relative contraindications are more than 4 nodules or at least one lesion > 5 cm, severe cardiopulmonary disease and refractory coagulopathy^[8].

MECHANISM OF ACTION AND EQUIPMENT OF RFA

The mechanism of action of RFA relies on the destruction of tumoral tissue by the radiofrequency-generated heat. In particular, the injury is due to frictional heat produced by the ionic agitation of particles within tissue as a consequence of the application of alternating current^[9-13].

The electrical current in the radiofrequency range (200-1200 MHz) is transmitted by a needle electrode under imaging guidance (usually ultrasonography) and the electrical circuit is completed through grounding pads attached to the thighs or back of the patient. The needle is partially insulated and presents an activated tip that is not insulated. This tip varies in length with the most common size being 3 cm long. Tips may be singular and straight or consisting of an array of expandable tines that form an umbrella fully encompassing the nodule when deployed.

An important aim of the treatment should be to ensure thermal destruction not only of the tumoral nodule but also of a surrounding margin about 1 cm long in order to ablate eventual microsatellites thus preventing local recurrence.

In order to reach this target, multiple electrodes can be applied thus achieving a broader ablation zone and allowing ablation of nodules up to 4-5 cm.

Another aspect to be considered is the "heat-sink effect", namely the dissipation of the thermal output by blood flowing through adjacent vessels thereby decreasing the efficacy of the procedure^[14]. This is the reason why nodules close to major vessel are considered a suboptimal target and constitute a relative contraindication for RFA.

Table 1 Contraindications to thermal ablative treatments

Absolute contraindications
Extrahepatic disease
Altered mental status
Active infection
Tumor abutting a major hepatic duct
Liver decompensation (particularly in presence of ascites)
Relative contraindications
Lesions > 5 cm
More than four lesions
Severe pulmonary or cardiac disease
Refractory coagulopathy

The procedure is usually performed under sedation when the percutaneous approach is preferred. In cases of laparoscopic RFA, to be considered in cases of nodules close to the liver capsule or other organs, general anesthesia is needed^[15].

SURVIVAL OUTCOMES AFTER RFA FOR HCC

A large number of studies have confirmed the efficacy of RFA in early HCC patients suggesting this procedure as viable therapeutic option in unresectable early stage. Considering the state-of-art of the literature, RFA provided 5-year survival rates of 40%-70% and beyond in HCC series^[9,10].

A recent Chinese study reported OS rates of 96.6%, 60.2%, and 27.3% at 1-, 5-, and 10-year^[16], similar to those reported by Kim *et al.*^[17] which were 95.5%, 59.7% and 32.3%, respectively. These results are concordant with other recent Western studies conducted in Milan-in patients (87.0%-99.0% at 1 year, 60.0%-87.4% at 3 years, and 42.3%-74.8% at 5 years)^[18,19].

Several studies pointed out different predictors of survival, such as Child-Pugh (CP) score, initial response, serum ferritin, number or size of nodules and AFP levels^[19-21].

Our group has recently analyzed predictors of post-recurrence survival (PRS) after RFA, namely the survival time elapsed after tumor recurrence^[18]. We found, in line with other studies, baseline CP score, AFP levels and performance status (PS) as predictors of OS in multivariate analysis. However, analysis of PRS showed that in addition to CP score and PS, also tumor burden at the time of recurrence and recurrence pattern significantly influenced PRS^[18]. Interestingly, AFP level, one of the main predictors of survival at baseline, became non-significant when evaluated at tumor relapse, confirming the difference between predictors of OS assessed at baseline and at tumor relapse^[18].

Of note, local recurrence (LR) did not impact significantly on OS in our study^[18] as well as in other reports^[17,21,22], probably due to the frequent multi-focality of distant recurrences that makes more difficult the therapeutic approach, while local recurrences, even when

multifocal, are confined in one liver segment (namely the same as that previously treated) and may be more easily treated with RFA or a single selective transarterial chemoembolization (TACE) session.

Unlike OS, reported rates of LR after RFA are not univocal ranging from 3.2% to 27% at 5 years^[16-21], maybe because of different etiologies of HCC in the published series, different approaches to the problem of insufficient ablative margins, use of combined treatment with TACE and, above all, different definition of radiologic tumor recurrence at imaging. As expected, tumor features such as nodules number, size, histopathological grading, and AFP have been found to be predictors of recurrence^[16-21]. Moreover, an insufficient ablation margin after the treatment appear to be an important prognostic factor for LR^[23,24].

Intrahepatic distant recurrences are common, ranging from 68% to 74% at 5 years^[16-19,21], and are usually associated to poorer prognosis. This type of recurrence is mostly induced by underlying hepatic disease and is often observed after 2 years, which is the time point considered able to differentiate between real recurrences from de novo tumors occurred in the pro-tumorigenic milieu of liver cirrhosis^[25].

Therefore, because of their high frequency and aggressive behavior, distal recurrences are a major determinant of patient survival.

PREVENTION OF RECURRENCE AFTER RFA

The issue of the high rates of post-RFA tumor relapse has recently pushed great efforts in studying adjuvant drugs aimed at decreasing the heavy burden of HCC recurrence after ablation.

Although earlier reports showed interesting results^[26,27] and in spite of the theoretical beneficial role of sorafenib (Nexavar®, Bayer, Leverkusen, Germany) as adjuvant therapy, an important multicenter randomised controlled trial (RCT) [Sorafenib as Adjuvant Treatment in the Prevention Of Recurrence of Hepatocellular Carcinoma (STORM)], recruiting 1114 HCC patients after surgery or radiofrequency ablation, failed to meet its primary endpoint, namely recurrence-free survival [hazard ratio (HR): 0.940, 95%CI: 0.78-1.13, $P = 0.26$] and OS (HR: 0.99, 95%CI: 0.76-1.30, $P = 0.48$)^[28]. This daunting finding was at least in part due to the high treatment discontinuation rate (24% vs 7% of placebo) and consent withdrawal (17% vs 6%) in the sorafenib arm, mainly because of severe adverse events^[28].

Similarly, interferon was proven unhelpful as adjuvant treatment because of the high cost and the narrow therapeutic window^[29,30].

Therefore, most of the recent research in this field has focused on other drugs. On the basis of the well-described pro-tumorigenic and pro-fibrogenic properties of angiotensin II, due to the induction of vascular endothelial growth factor and transforming growth

factor-beta 1 release^[31,32], a number of studies have reported significantly reduced HCC relapse rates after RFA when angiotensin converting enzyme inhibitor (ACE I) were used in combination with other agents such as branched-chain amino acids or vitamin K^[33-35]. However, ACE I did not prove effective in monotherapy and, above all, no significant difference in OS was registered as compared to the control arm^[33-35].

Our group has recently published a retrospective report conducted in 153 HCC patients treated with RFA finding a significant benefit both in terms of recurrence and OS in hypertensive subjects in treatment with angiotensin II type 1 receptor blockers (sartans) as compared to those under ACE I therapy and to non-hypertensive subjects^[36]. The apparent superiority of sartans over ACE I may be due to the selective inhibition of angiotensin II receptor 1, responsible of the pro-fibrogenic and pro-angiogenic activity of angiotensin, while pro-apoptotic and anti-tumorigenic activity of receptor 2 is preserved and even enhanced in patients administered sartans unlike ACE I which prevent the binding of angiotensin II to both receptors^[37]. However, these preliminary results still need further confirmation.

In conclusion, in spite of the great amount of published reports and in absence of broad RCTs, clear evidence in favor of an adjuvant treatment after RFA is still lacking.

ADVERSE EVENTS OF RFA

In a recent systematic review of 9531 patients treated with RFA, treatment-related severe adverse events were registered in 4.1% of cases with a mortality rate of 0.15%^[38].

Adverse events include gastrointestinal tract injury with/without perforation (0.06%-0.3%), diaphragm injury (0.03%), pleural effusion (0.2%-2.3%), bile duct stricture (0.06%-0.5%), biloma (0.06%-0.96%), gallbladder injury (0.06%-0.1%), and hepatic infarction (0.03%-0.06%). Other complications, related to direct mechanical injury, are tumor seeding (0.27%), tumor rupture (0.3%), hemoperitoneum (0.3%-1.6%), and hemo/pneumothorax (0.15%-0.8%). Events not related to mechanical or thermal injury to the liver are hepatic abscess (0.1%), grounding pad burn (0.6%), and vasovagal reflex (0.1%)^[39]. However, all these complications are not common and RFA can be considered a safe procedure in high-volume centers when proper indications to treatment are followed.

RFA IN PRE-TRANSPLANT SETTING

RFA has gained increasing interest either as bridging and as downstaging therapy prior to transplantation in hepatocarcinoma patients. A number of papers have reported complete pathological response rates (*i.e.*, complete nodule assessed by the pathologist on the explanted liver) up to 47%-75%^[5-7,40,41].

In particular, this response was observed in 50%-78%

of nodules within 3 cm and between 13% and 43% in larger nodules^[5-7,40,41] vs 27%-57% of TACE in Milan-in patients^[42,43].

Safety concerns previously raised by some authors due to the theoretical risk of tumoral seeding, reported to occur in about 3% of cases^[44], have been recently overcome^[45]. Therefore, although TACE remains the most used treatment before OLT, RFA has to be preferred in cases of single nodules under 3 cm as provides higher complete necrosis rates and lower risk of recurrence after transplantation^[46].

RFA VS LIVER RESECTION FOR HCC

Surgery is the first-line option in very early/early patients not fulfilling transplant criteria^[2-4]. By the way, no more than 10%-35% of patients are actually suitable to surgery due to tumoral burden, inadequate liver reserve, or poor performance status^[2-4]. These patients may be offered RFA as viable option because of its proven efficacy.

The aforementioned striking results of RFA have recently opened debates on whether RFA can be offered particularly in very early patients (namely, those with a single nodule less than 2 cm) as first-line therapy instead of surgery. To address this point, many research groups have conducted retrospective or randomized controlled studies directly comparing the two treatments.

Table 2 reports the main characteristics of the four RCTs^[47-50] comparing the two treatments published so far. As one can read in Table 2, the available RCTs report discordant results with the sole study by Huang *et al.*^[48] demonstrating a superiority of hepatic resection over RFA. However, the different proportions of nodules larger than 2 cm are likely to be responsible of these discordant results, as RFA is recognized as less effective beyond very early stage.

None of the aforementioned RCTs restricted their analysis to single nodules ≤ 2 cm, while there are five observational studies focused on this specific setting^[51-55]. Unfortunately, most of these retrospective studies suffer from selection bias as RFA patients tended to be older and to present more deteriorated liver function than surgical ones, while larger nodules were more likely to be treated with resection. Therefore, OS and relapse outcomes can be biased by covariate distribution. Two of these studies, which tried to obviate to such a bias through propensity score one-to-one match, reported better DFS in surgical patients ($P = 0.031$ and $P < 0.001$) but discordant results with regard to overall survival ($P = 0.296$ and $P = 0.034$, respectively)^[52,55]. However, several concerns have been raised on the rigorousness of the statistical procedure adopted, hence such findings require further confirmation^[56]. The low level of evidence impairs the findings of several meta-analyses published in this field, which mostly support the superiority of hepatic resection over RFA in early stage without significant differences in single nodules less than 2 cm^[57,58].

An interesting study conducted by the Bologna

Table 2 Randomized controlled trials comparing radiofrequency ablation and surgery in hepatocellular carcinoma patients

Ref.	Liver function	Tumor features	Treatment	3-yr SR	5-yr SR	3-yr DFS	5-yr DFS
Chen <i>et al</i> ^[47]	CP A	Single < 5 cm	HR 90	73.40%	NA	69.00%	NA
	ICG-R15 < 30% PLT > 40000/mm ³		RFA 71	71.40%	NA	64.10%	NA
Huang <i>et al</i> ^[48]	CP A/B	Within MC	HR 115	92.20%	75.70%	60.90%	51.30%
	ICG-R15 < 20% PLT > 50000/mm ³		RFA 115	69.60%	54.80%	46.10%	28.70%
		Single ≤ 3 cm	HR 45	95.60%	82.20%	NA	NA
			RFA 57	77.20%	61.40%	NA	NA
		Single 3-5 cm	HR 44	95.50%	72.30%	NA	NA
			RFA 27	66.70%	51.50%	NA	NA
Feng <i>et al</i> ^[49]		Multifocal < 3 cm	HR 26	80.80%	69.20%	NA	NA
			RFA 31	58.10%	45.20%	NA	NA
	CP A/B	Up to 2 nodules < 4 cm	HR 84	74.80%	NA	61.10%	NA
	ICG-R15 < 30% PLT > 50000 mm ³		RFA 84	67.20%	NA	49.60%	NA
Fang <i>et al</i> ^[50]	CP A/B	Up to 3 nodules ≤ 3 cm	HR 60	77.50%	NA	41.30%	NA
	PLT > 50000 mm ³		RFA 60	82.50%	NA	55.40%	NA

SR: Survival rate; DFS: Disease-free survival; CP: Child-Pugh; ICG-R15: Indocyanin green retention at 15 min; PLT: Platelets; HR: Hepatic resection; RFA: Radiofrequency ablation; NA: Not available; MC: Milan criteria.

group, based on a Markov model and a Monte Carlo probabilistic sensitivity analysis, demonstrated that in a 10-year perspective RFA provided similar life-expectancy and quality-adjusted life-expectancy (QALY) at a lower cost than surgery in very early HCC patients, hence it was the most cost-effective therapeutic strategy for this stage^[59]. In the case of 2 or 3 tumors ≤ 3 cm, life-expectancy and QALY were very similar between surgery and RFA, but cost-effectiveness was again in favor of RFA^[59]. Therefore, the authors concluded that RFA is more cost-effective than surgery in cases of single nodule under 2 cm or 2/3 nodules ≤ 3 cm, while liver surgery still represents the most valuable option for single larger early stage HCCs^[59].

In conclusion, as supported by a decision-making analysis performed by the same group, the superiority or equivalence of a treatment over the other is strictly dependent on the non-linear relationship among tumor number, size and liver function, with RFA to be preferred in cases of smaller tumors and impaired liver function^[60].

RFA VS PERCUTANEOUS ETHANOL INJECTION IN EARLY HCC PATIENTS

Percutaneous ethanol injection (PEI) is a well-established technique for the treatment of small HCCs and induces coagulative necrosis as a result of cellular dehydration and protein denaturation. However, ethanol diffusion is likely to be impaired by intratumoral fibrotic septa in cases of nodules > 2 cm.

In fact, the efficacy of such a technique in early stage (namely, multiple nodules or single nodule larger than 2 cm) is considerably inferior as compared to RFA with a complete necrosis rate of 70% in nodules of 2-3 cm and

50% in those between 3 and 5 cm^[61,62]. On the other hand, RFA showed a significantly higher necrosis rate, up to 71% in non-infiltrating medium-size (*i.e.*, between 3 and 5 cm) nodules^[63]. In our recently published experience, overall complete necrosis rate after RFA was 84.4% in a series whose median tumor size was 3 cm^[18,20].

However, if it is widely recognized the superiority of RFA over PEI in medium-size and large nodules, a clear advantage in term of survival in small HCCs (less than 3 cm) is still unclear.

In fact, a recent meta-analysis of 8 RCTs found better survival outcomes (HR: 0.67, 95%CI: 0.51-0.87, $P < 0.001$) and a lower 3-year LR rate [risk ratio (RR): 0.41, 95%CI: 0.30-0.57, $P < 0.01$] after RFA as compared to PEI^[64], but sensitivity analysis confirmed the superiority of RFA only in Asian studies^[65-69] while the three included Italian studies^[70-72] found only a non-significant trend in favor of RFA as for survival (HR: 0.82, 95%CI: 0.56-1.20, $P = 0.30$)^[64]. Table 3 summarizes the main findings of the aforementioned trials. Quite interestingly, RFA provided similar if not better results as compared to PEI requiring a significant lower number of sessions (Table 3). This aspect has to be taken into account since, although a single PEI treatment has significantly lower costs than RFA, the higher number of PEI sessions makes this benefit vanish and increases the risk of tumoral seeding.

The above described results are in keeping with another systematic review of four RCTs comparing the two techniques in small HCCs under 3 cm which, however, found RFA associated to higher major complication rates and to be more costly than PEI^[73].

In conclusion, although whether RFA leads to better survival rates than PEI in small HCCs is still matter of debate, the lower local recurrence rate stands for a wider

Table 3 Randomized controlled trials comparing radiofrequency ablation and percutaneous ethanol injection in hepatocellular carcinoma patients

Ref.	Region	Patients (n)	Nodules n (1/>1)	Tumor size, cm	No. of sessions	Complete response (%)	3-yr survival (%)	3-yr recurrence (%)
Lin <i>et al</i> ^[65]	Taiwan	RFA (52)	38/14	2.9 ± 0.8	1.6 ± 0.4	96.0	74	18.0
		PEI (52)	40/12	2.8 ± 0.8	6.5 ± 1.6	88.0	50	45.0
Lin <i>et al</i> ^[66]	Taiwan	RFA (62)	49/13	2.5 ± 1.0	1.3 ± 0.3	96.1	74	14.0
		PEI (62)	49/13	2.3 ± 0.8	4.9 ± 1.3	88.1	51	34.0
Shiina <i>et al</i> ^[67]	Japan	RFA (118)	72/46	NA	2.1 ± 1.3	100.0	81	1.7
		PEI (114)	60/54	NA	6.4 ± 2.6	100.0	66	11.0
Wang <i>et al</i> ^[68]	China	RFA (49)	NA	2.4 ± 1.2	NA	93.8	NA	NA
		PEI (49)	NA	2.3 ± 1.4	NA	77.5	NA	NA
Azab <i>et al</i> ^[69]	Egypt	RFA (30)	NA	NA	1.45	85.0	NA	NA
		PEI (30)	NA	NA	7.68	75.0	NA	NA
Giorgio <i>et al</i> ^[70]	Italy	RFA (128)	128/0	2.3 ± 0.4	5.00	100.0	83	7.8
		PEI (143)	143/0	2.2 ± 0.5	8.00	100.0	78	9.4
Lencioni <i>et al</i> ^[71]	Italy	RFA (52)	40/12	2.8 ± 0.6	1.1 ± 0.5	91.0	NA	21.0
		PEI (50)	31/19	2.8 ± 0.8	5.4 ± 1.6	82.0	NA	59.0
Brunello <i>et al</i> ^[72]	Italy	RFA (70)	54/16	2.4 ± 0.5	NA	95.7	59	NA
		PEI (69)	54/15	2.2 ± 0.5	NA	65.6	56	NA

RFA: Radiofrequency ablation; PEI: Percutaneous ethanol injection; NA: Not available.

application of RFA in hepato-oncology.

COMBINED TREATMENT

There is increasing evidence that combining RFA to TACE may increase the therapeutic benefit in larger HCCs. In fact, the two techniques may exert a synergistic effect on inducing nodule necrosis: Occlusion of the tumor arterial supply by TACE would increase the area of coagulation necrosis obtained by RFA minimizing heat loss whereas the heating-related reactive hyperemia induced by RFA would concentrate the chemotherapeutic agent released during TACE in the peripheral residual viable neoplastic tissue and would reduce cell resistance to the drug^[74].

A recent meta-analysis of eight RCTs^[75-82] including 598 patients indicated that RFA plus TACE determines a significantly higher 3-year OS rate [odds ratio (OR): 2.65, 95%CI: 1.81-3.86, $P < 0.001$] and 3-year RFS rate (OR: 3.00, 95%CI: 1.75-5.13, $P < 0.001$) than RFA alone, with no difference in major complications (OR: 1.20, 95%CI: 0.31-4.62, $P = 0.79$)^[83]. Subgroups analysis revealed that most of this benefit was obtained in patients with intermediate- and large-size HCCs, which are likely to be the optimal setting for the combined treatment^[83]. These results should be considered with caution as all the included studies had been conducted in Asia with conventional TACE (Table 4), hence the applicability of such findings in the West is still unclear, although a recent small Italian retrospective report confirmed the superiority of RFA combined to drug-eluting beads TACE over RFA alone in single HCCs beyond 3 cm^[84].

OTHER THERMAL ABLATION TECHNIQUES

Microwave ablation

MWA aims to induce tumor necrosis by using high fre-

quency (> 900 MHz, usually 2450 MHz) electromagnetic energy which determines continuous rotation of dipole molecules in the microwave's oscillating electric field. This vigorous movement of dipoles (mainly water molecules) generates friction and heat, thus inducing tissue death *via* coagulation necrosis^[85].

In comparison to RFA, MWA has several theoretical advantages: It induces a wider area of active heating and warmer temperatures into the target zone in a shorter treatment time as it is not impaired by tissue desiccation and charring^[86]; its efficacy is less impaired by heat-sink effect, due to the more pronounced cooling effect of blood flow and the conductive rather than active nature of heating^[87]; multiple antennae can be simultaneously activated without the electrical interference phenomena observed in RFA, thus allowing more rapid treatment of large or multifocal tumours^[87]. On these premises, MWA mostly shares the applications of RFA, with the above cited advantages in larger nodules and/or close to blood vessel.

Complete ablation rates of 89%-94% and 5-year survival rates of 51%-57% are reported in 3 retrospective studies enrolling mainly CP B patients^[88-90].

The safety concerns raised on the risks of the procedure, due to the broader and less predictable necrosis areas induced by MWA, have been recently overcome by a large multicenter Italian study conducted in a series of 736 patients, of which 522 with HCC, where MWA determined a major complication rate of 2.9% with a peri-procedural mortality rate of < 0.01%^[91].

There are actually 7 studies (of which one RCT) directly comparing MWA and RFA in HCC patients^[92-98] (Table 5). Unfortunately, the sole RCT published did not report long-term survival data but only complete necrosis rates, which were similar in the two treatment groups (89% for MWA vs 96% for RFA)^[92]. Retrospective studies reported heterogeneous results, particularly with regard

Table 4 Randomized controlled trials comparing transarterial chemoembolization combined to radiofrequency ablation *vs* radiofrequency ablation alone in hepatocellular carcinoma patients

Ref.	Region	Patients (n)	Tumor size, cm	CP A/B/C	3-yr survival (%)	3-yr recurrence (%)
Peng <i>et al</i> ^[75]	China	TACE + RFA (69)	≤ 5.01	60/9/0	69.0	45.0
		RFA (70)	-	59/11/0	47.0	18.0
Cheng <i>et al</i> ^[76]	China	TACE + RFA (96)	≤ 7.5	NA	55.0	NA
		RFA (100)	-	NA	32.0	NA
Yang <i>et al</i> ^[77]	China	TACE + RFA (24)	6.6 ± 0.6	NA	NA	NA
		RFA (12)	5.2 ± 0.4	NA	NA	NA
Shibata <i>et al</i> ^[78]	Japan	TACE + RFA (46)	1.7 ± 0.6	32/14/0	84.8	48.8
		RFA (43)	1.6 ± 0.5	33/10/0	84.5	29.7
Morimoto <i>et al</i> ^[79]	Japan	TACE + RFA (19)	3.6 ± 0.7	12/7/0	93.0	NA
		RFA (18)	3.7 ± 0.6	16/2/0	80.0	28.0
Kang <i>et al</i> ^[80]	China	TACE + RFA (19)	6.7 ± 1.1	12/7/0	36.8	NA
		RFA (18)	6.2 ± 1.2	12/6/0	16.7	NA
Shen <i>et al</i> ^[81]	China	TACE + RFA (18)	5.6 (2.2-15.8)	4/14/0	73.3	50.0
		RFA (16)	5.0 (2.3-12.3)	6/10/0	20.4	18.7
Zhang <i>et al</i> ^[82]	China	TACE + RFA (15)	4.6 (2.3-7.1)	NA	NA	NA
		RFA (15)	4.1 (2.4-6.0)	NA	NA	NA

CP: Child-Pugh; TACE: Transarterial chemoembolization; RFA: Radiofrequency ablation; NA: Not available.

Table 5 Studies comparing radiofrequency ablation and microwave ablation in hepatocellular carcinoma patients

Ref.	Arm (n)	Study design	Region	CP (A/B/C)	Tumor size (cm)	Number nodules	3-yr survival (%)	Local tumor recurrence (%)
Shibata <i>et al</i> ^[92]	RFA (36)	RCT	Japan	21/15/0	1.6 (0.7-2)	1.08	NA	8.3
	MWA (36)			19/17/0	1.7 (0.8-2)	1.14	NA	17.4
Lu <i>et al</i> ^[93]	RFA (53)	R	China	49/4/0	2.6 (1-6.1)	1.35	37.6	20.9
	MWA (49)			39/10/0	2.5 (0.9-7.2)	2.00	50.5	11.8
Ohmoto <i>et al</i> ^[94]	RFA (34)	R	Japan	20/11/3	1.6 (0.7-2)	1.08	49.0	9.0
	MWA (49)			31/14/4	1.7 (0.8-2)	1.14	70.0	19.0
Ding <i>et al</i> ^[95]	RFA (85)	R	China	49/36/0	2.38 (1-4.8)	1.15	77.6	5.2
	MWA (113)			75/38/0	2.55 (0.8-5)	1.15	82.7	10.9
Zhang <i>et al</i> ^[96]	RFA (78)	R	China	78/0/0	NA	1.24	64.1	11.8
	MWA (77)			77/0/0	NA	1.36	51.7	10.5
Abdelaziz <i>et al</i> ^[97]	RFA (45)	R	Egypt	24/21/0	2.95 ± 1.03+	1.00	NA	13.5
	MWA (66)			25/41/0	2.9 ± 0.97	1.00	NA	3.9
Vogl <i>et al</i> ^[98]	RFA (25)	R	Germany	NA	NA	1.28	72.0	9.4
	MWA (28)			NA	NA	1.28	79.0	8.3

CP: Child-Pugh; RFA: Radiofrequency ablation; MWA: Microwave ablation; RCT: Randomized controlled trial; R: Retrospective.

to local recurrence probably because of different follow-up time length or radiologic criteria adopted (Table 5).

The two meta-analysis published so far in this field reported no difference 3-year OS with MWA outperforming RFA in terms of LR for treatment of larger tumours^[99,100]. However, further RCTs are needed to verify whether MWA efficacy in determining broader ablation areas will translate into a real survival benefit.

HIFU ablation

HIFU ablation aims to elevate tissue temperature by focusing high energy ultrasound (US) waves into one small spot^[39]. The main advantage of HIFU ablation is the safety and the less invasiveness with, on the other hand, the limitation of a longer procedure time and acoustic shadowing by the rib cage, which may also cause thermal injury of the overlying soft tissue as a result of high US absorption by the bony cortex^[39]. This drawback has been

partially overcome by novel equipment using a larger transducer to spread the US beams out, thus decreasing the superficial energy wasting, or a multi-element phased-array transducer able to selectively activate only elements corresponding to the intercostal spaces^[101]. There are actually few studies on HIFU, mainly conducted in advanced or recurrent cases for palliative purposes. A retrospective study by Chan *et al*^[102] did not find any difference in terms of 3-year survival between HIFU and RFA for recurrent HCCs (69.8% vs 64.2%, $P = 0.19$). The same group compared the outcomes of HIFU ablation to those of TACE as bridging therapy before OLT and found similar results as for tumor necrosis in explanted livers ($P = 0.35$)^[103]. The authors concluded that HIFU ablation was safe even for CP C patients and increased the number of subject receiving bridging therapy from 39.2% to 80.4%^[103].

In our opinion, because of the scarce data currently

available and in attendance of further reliable results in the clinical setting, HIFU represents a promising option to be performed in highly-experienced centers and in selected cases.

LA

LA is one of the least investigated ablative treatments.

In this case, ablation is induced by the interaction of light energy (derived by electrical energy) and tissue^[104]. Because laser light is coherent and monochromatic, it can be selectively collimated and focused and large amounts of energy can be transmitted over long distances without significant losses. Light is delivered *via* multiple flexible quartz fibers which have flat or cylindrical diffusing tips. The use of water-cooled laser application sheaths enables a higher laser power output (up to 50 W compared with 5 W of previous devices) while preventing carbonization, thus allowing ablative zones of up to 80 mm diameter^[105].

Several retrospective cohort studies have shown that LA is a safe and feasible procedure for the treatment of HCC with a complete response rate ranging from 82% to 97%^[105-108].

In an Italian multicenter retrospective study, 5-year cumulative survival was 41%, median survival times were 65 and 68 mo in patients with tumor size ≤ 3 cm and ≤ 2 cm, respectively, while median time to recurrence was 24 mo^[109].

In a recent RCT with 140 Milan-in patients, complete response was observed in 97.4% of patients treated with RFA and 95.7% with LA and mean time-to local progression and overall survival were comparable between the two study groups ($P = 0.129$ and 0.693 , respectively)^[110]. The authors concluded that LA resulted non-inferior to RFA and therefore it should be considered as a valuable alternative for thermal ablation of small HCC in cirrhotic patients^[110].

However, in spite of the apparently excellent results in terms of safety and of the described efficacy of LA, the low experience available worldwide currently restricts its application to a limited number of high-volume centers.

CRYOABLATION

Cryoablation induces cytotoxicity based on cyclic applications of extremely low temperatures (-20°C to -40°C) within the tumour^[39]. Multiple cryoprobes of 2-3 mm in diameter are inserted into the target lesion *via* a dilation catheter to ensure the rapid freezing of the nodule. Cryotherapy is delivered by means of multiple cycles and between two consecutive cycles the cryoprobes are rewarmed by an heating system.

Despite being widely used in various other cancers, the application of percutaneous cryoablation in HCC was sparsely reported. Compared to RFA, cryoablation endows several unique advantages including larger ablative zones, more clearly discernible treatment margin, less pain and

good visualization by imaging^[111,112]. Main drawbacks are: (1) smaller ablation areas generated by each single probe, hence multiple cryoprobes applications are needed; (2) unpredictable area of ablation (4-10 mm or more); and (3) concerns on the risk of complications such as massive haemorrhage due to ice ball fracture, cold injury to adjacent organs, and cryoshock syndrome^[113,114].

Nevertheless, with the recent improvements in technology and the increasing experience acquired worldwide, cryoablation represents a promising therapeutic tool in the field of HCC ablation.

An Asian series of 866 patients within Milan criteria who underwent percutaneous cryoablation was recently analyzed: Complete response was achieved in 96.1% of patients with a major complication rate of 2.8% and no treatment-related mortality^[115]. Five-year local tumor recurrence rate was 24.2% and 5-year survival rate was 59.5%^[115].

A recent meta-analysis including 4 retrospective studies comparing the effect of cryoablation and RFA on hepatic neoplastic lesions concluded that RFA was significantly superior in terms of safety and local recurrence^[116]. However, these studies referred not only to HCC but also to other liver malignancies, used several different equipments as laparoscopic or even surgical cryoablation^[116] and were mostly conducted several years ago when experience with cryoablation was still low. In a multicenter Asian RCT enrolling 360 patients with one or two HCC lesions ≤ 4 cm, cryoablation proved superior to RFA according to 3-year local tumor progression (7% vs 11%, $P = 0.043$) while 5-year overall survival was similar between the two groups (40% vs 38%, $P = 0.747$)^[117]. Major complications occurred in seven patients (3.9%) following cryoablation and in six patients (3.3%) following RFA ($P = 0.776$)^[117]. These results have been confirmed in an interesting retrospective study comparing cryoablation and RFA combined to microwave coagulation therapy, where hypothermal therapy proved superior to combined regimen as for 2-year local recurrence-free survival (HR: 0.3, 95%CI: 0.1-0.9; $P = 0.02$) with no difference in safety outcomes^[118].

Although further RCTs are needed in order to confirm these promising results, appropriate use of cryoablation could represent a valuable therapeutic option in early stage HCC patients.

CONCLUSION

Ablative treatments, particularly RFA, currently represent the first-line option for early stage unresectable HCC patients. Main indications to ablative treatments are BCLC 0/A patients not suitable to surgical therapies, namely liver resection and OLT, and bridging/down-staging setting before transplantation. Considering the state-of-art of the literature, RFA provided 5-year survival rates of 40%-70% and beyond in HCC series and, although survival rates are similar to PEI, the lower local recurrence rate stands for a wider application of RFA in

hepato-oncology.

In comparison to RFA, MWA has several theoretical advantages such as a wider ablation area, warmer temperatures into the target area in a shorter treatment time and it is not impaired by heat-sink effect. The safety concerns raised on the risks of this procedure, due to the broader and less predictable necrosis areas, have been recently overcome. However, whether MWA ability to induce a broader ablation zone will lead to a real survival benefit is still unclear.

Other treatments, such as HIFU, LA and cryoablation, are less investigated but showed promising results in early HCC patients and could be a valuable therapeutic option in the next future.

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