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**Local ablative treatments for hepatocellular carcinoma: An updated review**

Facciorusso A *et al*. Local ablation in HCC patients

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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; Radiofrequency ablation; Microwave 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 loco-regional 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 RADIOFREQUENCY ABLATION**

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.

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, namelyrecurrence-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 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 surgerystill 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 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 frequency (> 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 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 restrospective 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 RCTenrolling 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/downstaging 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, suchas 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.

**REFERENCES**

1 **El-Serag HB**. Hepatocellular carcinoma. *N Engl J Med* 2011; **365**: 1118-1127 [PMID: 21992124 DOI: 10.1056/NEJMra1001683]

2 **[European Association For The Study Of The Liver](http://www.ncbi.nlm.nih.gov/pubmed/?term=European%20Association%20For%20The%20Study%20Of%20The%20Liver%5BCorporate%20Author%5D)**; [European Organisation For Research And Treatment Of Cancer](http://www.ncbi.nlm.nih.gov/pubmed/?term=European%20Organisation%20For%20Research%20And%20Treatment%20Of%20Cancer%5BCorporate%20Author%5D). EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; **56**: 908-943 [PMID: 22424438 DOI: 10.1016/j.jhep.2011.12.001]

3 **Llovet JM**, Zucman-Rossi J, Pikarsky E, Sangro B, Schwartz M, Sherman M, Gores G. Hepatocellular carcinoma. *Nat Rev Dis Primers* 2016; **2**: 16018 [PMID: 27158749 DOI: 10.1038/nrdp.2016.18]

4 **Bruix J**, Sherman M; [American Association for the Study of Liver Diseases](http://www.ncbi.nlm.nih.gov/pubmed/?term=American%20Association%20for%20the%20Study%20of%20Liver%20Diseases%5BCorporate%20Author%5D). Management of hepatocellular carcinoma: an update. *Hepatology* 2011; **53**: 1020-1022 [PMID: 21374666 DOI: 10.1002/hep.24199]

5 **Mazzaferro V**, Battiston C, Perrone S, Pulvirenti A, Regalia E, Romito R, Sarli D, Schiavo M, Garbagnati F, Marchianò A, Spreafico C, Camerini T, Mariani L, Miceli R, Andreola S. Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: a prospective study. *Ann Surg* 2004; **240**: 900-909 [PMID: 15492574 DOI: 10.1097/01.sla.0000143301.56154.95]

6 **Lu DS**, Yu NC, Raman SS, Lassman C, Tong MJ, Britten C, Durazo F, Saab S, Han S, Finn R, Hiatt JR, Busuttil RW. Percutaneous radiofrequency ablation of hepatocellular carcinoma as a bridge to liver transplantation. *Hepatology* 2005; **41**: 1130-1137 [PMID: 15841454 DOI: 10.1002/hep.20688]

7 **Pompili M**, Mirante VG, Rondinara G, Fassati LR, Piscaglia F, Agnes S, Covino M, Ravaioli M, Fagiuoli S, Gasbarrini G, Rapaccini GL. Percutaneous ablation procedures in cirrhotic patients with hepatocellular carcinoma submitted to liver transplantation: Assessment of efficacy at explant analysis and of safety for tumor recurrence. *Liver Transpl* 2005; **11**: 1117-1126 [PMID: 16123960 DOI: 10.1002/lt.20469]

8 **Lencioni R**, Crocetti L. Local-regional treatment of hepatocellular carcinoma. *Radiology* 2012; **262**: 43-58 [PMID: 22190656 DOI: 10.1148/radiol.11110144.]

9 **Lencioni R**, Cioni D, Crocetti L, Franchini C, Pina CD, Lera J, Bartolozzi C. Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation. *Radiology* 2005; **234**: 961-967 [PMID: 15665226 DOI: 10.1148/radiol.2343040350]

10 **Omata M**, Tateishi R, Yoshida H, Shiina S. Treatment of hepatocellular carcinoma by percutaneous tumor ablation methods: Ethanol injection therapy and radiofrequency ablation. *Gastroenterology* 2004; **127**: S159-S166 [PMID: 15508080 DOI: 10.1053/j.gastro.2004.09.030]

11 **Livraghi T**, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C, Rossi S. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice? *Hepatology* 2008; **47**: 82-89 [PMID: 18008357 DOI: 10.1002/hep.21933]

12 **Pompili M**, Saviano A, de Matthaeis N, Cucchetti A, Ardito F, Federico B, Brunello F, Pinna AD, Giorgio A, Giulini SM, De Sio I, Torzilli G, Fornari F, Capussotti L, Guglielmi A, Piscaglia F, Aldrighetti L, Caturelli E, Calise F, Nuzzo G, Rapaccini GL, Giuliante F. Long-term effectiveness of resection and radiofrequency ablation for single hepatocellular carcinoma ≤3 cm. Results of a multicenter Italian survey. *J Hepatol* 2013; **59**: 89-97 [PMID: 23523578 DOI: 10.1016/j.jhep.2013.03.009]

13 **Chamberlain RS**, Fong Y. Radiofrequency thermal ablation of liver tumors. In: Blumgart LH, Fong Y. Surgery of the liver and biliary tract. 3rd ed. Toronto: W.B. Saunders, 2000: 1589-1595

14 **Jacobs A**. Radiofrequency Ablation for Liver Cancer. *Radiol Technol* 2015; **86**: 645-664; quiz 665-668 [PMID: 26199436]

15 **Facciorusso A**, Del Prete V, Antonino M, Neve V, Amoruso A, Crucinio N, Di Leo A, Barone M. Conditional survival analysis of hepatocellular carcinoma patients treated with radiofrequency ablation. *Hepatol Res* 2015; **45**: E62-E72 [PMID: 25472869 DOI: 10.1111/hepr.12458]

16 **Shiina S**, Tateishi R, Arano T, Uchino K, Enooku K, Nakagawa H, Asaoka Y, Sato T, Masuzaki R, Kondo Y, Goto T, Yoshida H, Omata M, Koike K. Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors. *Am J Gastroenterol* 2012; **107**: 569-577; quiz 578 [PMID: 22158026 DOI: 10.1038/ajg.2011.425]

17 **Kim YS**, Lim HK, Rhim H, Lee MW, Choi D, Lee WJ, Paik SW, Koh KC, Lee JH, Choi MS, Gwak GY, Yoo BC. Ten-year outcomes of percutaneous radiofrequency ablation as first-line therapy of early hepatocellular carcinoma: analysis of prognostic factors. *J Hepatol* 2013; **58**: 89-97 [PMID: 23023009 DOI: 10.1016/j.jhep.2012.09.020]

18 **Facciorusso A**, Del Prete V, Antonino M, Crucinio N, Neve V, Di Leo A, Carr BI, Barone M. Post-recurrence survival in hepatocellular carcinoma after percutaneous radiofrequency ablation. *Dig Liver Dis* 2014; **46**: 1014-1019 [PMID: 25085684 DOI: 10.1016/j.dld.2014.07.012]

19 **N'Kontchou G**, Mahamoudi A, Aout M, Ganne-Carrié N, Grando V, Coderc E, Vicaut E, Trinchet JC, Sellier N, Beaugrand M, Seror O. Radiofrequency ablation of hepatocellular carcinoma: long-term results and prognostic factors in 235 Western patients with cirrhosis. *Hepatology* 2009; **50**: 1475-1483 [PMID: 19731239 DOI: 10.1002/hep.23181]

20 **Facciorusso A**, Del Prete V, Antonino M, Neve V, Crucinio N, Di Leo A, Carr BI, Barone M. Serum ferritin as a new prognostic factor in hepatocellular carcinoma patients treated with radiofrequency ablation. *J Gastroenterol Hepatol* 2014; **29**: 1905-1910 [PMID: 24731153 DOI: 10.1111/jgh.12618]

21 **Lee DH**, Lee JM, Lee JY, Kim SH, Yoon JH, Kim YJ, Han JK, Choi BI. Radiofrequency ablation of hepatocellular carcinoma as first-line treatment: long-term results and prognostic factors in 162 patients with cirrhosis. *Radiology* 2014; **270**: 900-909 [PMID: 24475823 DOI: 10.1148/radiol.13130940]

22 **Ng KK**, Poon RT, Lo CM, Yuen J, Tso WK, Fan ST. Analysis of recurrence pattern and its influence on survival outcome after radiofrequency ablation of hepatocellular carcinoma. *J Gastrointest Surg* 2008; **12**: 183-191 [PMID: 17874276]

23 **Koda M**, Tokunaga S, Okamoto T, Hodozuka M, Miyoshi K, Kishina M, Fujise Y, Kato J, Matono T, Sugihara T, Oyama K, Hosho K, Okano J, Murawaki Y, Kakite S, Yamashita E. Clinical usefulness of the ablative margin assessed by magnetic resonance imaging with Gd-EOB-DTPA for radiofrequency ablation of hepatocellular carcinoma. *J Hepatol* 2015; **63**: 1360-1367 [PMID: 26232269 DOI: 10.1016/j.jhep.2015.07.023]

24 **Kim YS**, Lee WJ, Rhim H, Lim HK, Choi D, Lee JY. The minimal ablative margin of radiofrequency ablation of hepatocellular carcinoma (& gt; 2 and & lt; 5 cm) needed to prevent local tumor progression: 3D quantitative assessment using CT image fusion. *AJR Am J Roentgenol* 2010; **195**: 758-765 [PMID: 20729457 DOI: 10.2214/AJR.09.2954]

25 **Cucchetti A**, Piscaglia F, Caturelli E, Benvegnù L, Vivarelli M, Ercolani G, Cescon M, Ravaioli M, Grazi GL, Bolondi L, Pinna AD. Comparison of recurrence of hepatocellular carcinoma after resection in patients with cirrhosis to its occurrence in a surveilled cirrhotic population. *Ann Surg Oncol* 2009; **16**: 413-422 [PMID: 19034578 DOI: 10.1245/s10434-008-0232-4]

26 **Feng X**, Xu R, Du X, Dou K, Qin X, Xu J, Jia W, Wang Z, Zhao H, Yang S, Guo C, Liu T, Ma K. Combination therapy with sorafenib and radiofrequency ablation for BCLC Stage 0-B1 hepatocellular carcinoma: a multicenter retrospective cohort study. *Am J Gastroenterol* 2014; **109**: 1891-1899 [PMID: 25403366 DOI: 10.1038/ajg.2014.343]

27 **Kan X**, Jing Y, Wan QY, Pan JC, Han M, Yang Y, Zhu M, Wang Q, Liu KH. Sorafenib combined with percutaneous radiofrequency ablation for the treatment of medium-sized hepatocellular carcinoma. *Eur Rev Med Pharmacol Sci* 2015; **19**: 247-255 [PMID: 25683938]

28 **Bruix J**, Takayama T, Mazzaferro V, Chau GY, Yang J, Kudo M, Cai J, Poon RT, Han KH, Tak WY, Lee HC, Song T, Roayaie S, Bolondi L, Lee KS, Makuuchi M, Souza F, Berre MA, Meinhardt G, Llovet JM. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2015; **16**: 1344-1354 [PMID: 26361969 DOI: 10.1016/S1470-2045(15)00198-9]

29 **Mazzaferro V**, Romito R, Schiavo M, Mariani L, Camerini T, Bhoori S, Capussotti L, Calise F, Pellicci R, Belli G, Tagger A, Colombo M, Bonino F, Majno P, Llovet JM. Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. *Hepatology* 2006; **44**: 1543-1554 [PMID: 17133492]

30 **Hsu YC**, Ho HJ, Wu MS, Lin JT, Wu CY. Postoperative peg-interferon plus ribavirin is associated with reduced recurrence of hepatitis C virus-related hepatocellular carcinoma. *Hepatology* 2013; **58**: 150-157 [PMID: 23389758 DOI: 10.1002/hep.26300]

31 **Tamaki Y**, Nakade Y, Yamauchi T, Makino Y, Yokohama S, Okada M, Aso K, Kanamori H, Ohashi T, Sato K, Nakao H, Haneda M, Yoneda M. Angiotensin II type 1 receptor antagonist prevents hepatic carcinoma in rats with nonalcoholic steatohepatitis. *J Gastroenterol* 2013; **48**: 491-503 [PMID: 22886508 DOI: 10.1007/s00535-012-0651-7]

32 **Hirose A**, Ono M, Saibara T, Nozaki Y, Masuda K, Yoshioka A, Takahashi M, Akisawa N, Iwasaki S, Oben JA, Onishi S. Angiotensin II type 1 receptor blocker inhibits fibrosis in rat nonalcoholic steatohepatitis. *Hepatology* 2007; **45**: 1375-1381 [PMID: 17518368]

33 **Yoshiji H**, Noguchi R, Toyohara M, Ikenaka Y, Kitade M, Kaji K, Yamazaki M, Yamao J, Mitoro A, Sawai M, Yoshida M, Fujimoto M, Tsujimoto T, Kawaratani H, Uemura M, Fukui H. Combination of vitamin K2 and angiotensin-converting enzyme inhibitor ameliorates cumulative recurrence of hepatocellular carcinoma. *J Hepatol* 2009; **51**: 315-321 [PMID: 19501932 DOI: 10.1016/j.jhep.2009.04.011]

34 **Yoshiji H**, Noguchi R, Ikenaka Y, Kaji K, Aihara Y, Yamazaki M, Yamao J, Toyohara M, Mitoro A, Sawai M, Yoshida M, Morioka C, Fujimoto M, Uemura M, Fukui H. Combination of branched-chain amino acids and angiotensin-converting enzyme inhibitor suppresses the cumulative recurrence of hepatocellular carcinoma: a randomized control trial. *Oncol Rep* 2011; **26**: 1547-1553 [PMID: 21874260 DOI: 10.3892/or.2011.1433]

35 **Kaibori M**, Ishizaki M, Matsui K, Kitade H, Matsui Y, Kwon AH. Evaluation of metabolic factors on the prognosis of patients undergoing resection of hepatocellular carcinoma. *J Gastroenterol Hepatol* 2011; **26**: 536-543 [PMID: 21332549 DOI: 10.1111/j.1440-1746.2010.06439.x]

36 **Facciorusso A**, Del Prete V, Crucinio N, Muscatiello N, Carr BI, Di Leo A, Barone M. Angiotensin receptor blockers improve survival outcomes after radiofrequency ablation in hepatocarcinoma patients. *J Gastroenterol Hepatol* 2015; **30**: 1643-1650 [PMID: 25974743 DOI: 10.1111/jgh.12988]

37 **Du H**, Liang Z, Zhang Y, Jie F, Li J, Fei Y, Huang Z, Pei N, Wang S, Li A, Chen B, Zhang Y, Sumners C, Li M, Li H. Effects of angiotensin II type 2 receptor overexpression on the growth of hepatocellular carcinoma cells in vitro and in vivo. *PLoS One* 2013; **8**: e83754 [PMID: 24391821 DOI: 10.1371/journal.pone.0083754]

38 **Bertot LC**, Sato M, Tateishi R, Yoshida H, Koike K. Mortality and complication rates of percutaneous ablative techniques for the treatment of liver tumors: a systematic review. *Eur Radiol* 2011; **21**: 2584-2596 [PMID: 21858539 DOI: 10.1007/s00330-011-2222-3]

39 **Kim YS**, Lim HK, Rhim H, Lee MW. Ablation of hepatocellular carcinoma. *Best Pract Res Clin Gastroenterol* 2014; **28**: 897-908 [PMID: 25260316 DOI: 10.1016/j.bpg.2014.08.011]

40 **Brillet PY**, Paradis V, Brancatelli G, Rangheard AS, Consigny Y, Plessier A, Durand F, Belghiti J, Sommacale D, Vilgrain V. Percutaneous radiofrequency ablation for hepatocellular carcinoma before liver transplantation: a prospective study with histopathologic comparison. *AJR Am J Roentgenol* 2006; **186**: S296-S305 [PMID: 16632691]

41 **Rodríguez-Sanjuán JC**, González F, Juanco C, Herrera LA, López-Bautista M, González-Noriega M, García-Somacarrera E, Figols J, Gómez-Fleitas M, Silván M. Radiological and pathological assessment of hepatocellular carcinoma response to radiofrequency. A study on removed liver after transplantation. *World J Surg* 2008; **32**: 1489-1494 [PMID: 18373117 DOI: 10.1007/s00268-008-9559-z]

42 **Majno PE**, Adam R, Bismuth H, Castaing D, Ariche A, Krissat J, Perrin H, Azoulay D. Influence of preoperative transarterial lipiodol chemoembolization on resection and transplantation for hepatocellular carcinoma in patients with cirrhosis. *Ann Surg* 1997; **226**: 688-701; discussion 701-703 [PMID: 9409568]

43 **Golfieri R**, Cappelli A, Cucchetti A, Piscaglia F, Carpenzano M, Peri E, Ravaioli M, D'Errico-Grigioni A, Pinna AD, Bolondi L. Efficacy of selective transarterial chemoembolization in inducing tumor necrosis in small (& lt; 5 cm) hepatocellular carcinomas. *Hepatology* 2011; **53**: 1580-1589 [PMID: 21351114 DOI: 10.1002/hep.24246]

44 **Imamura J**, Tateishi R, Shiina S, Goto E, Sato T, Ohki T, Masuzaki R, Goto T, Yoshida H, Kanai F, Hamamura K, Obi S, Yoshida H, Omata M. Neoplastic seeding after radiofrequency ablation for hepatocellular carcinoma. *Am J Gastroenterol* 2008; **103**: 3057-3062 [PMID: 19086957 DOI: 10.1111/j.1572-0241.2008.02153.x]

45 **Lopez KT**, Kuwada SK, Wong LL. Consequences of needle tract seeding of hepatocellular cancer after liver transplant. *Clin Transplant* 2013; **27**: E400-E406 [PMID: 23837571 DOI: 10.1111/ctr.12160]

46 **Clavien PA**, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A; [OLT for HCC Consensus Group](http://www.ncbi.nlm.nih.gov/pubmed/?term=OLT%20for%20HCC%20Consensus%20Group%5BCorporate%20Author%5D). Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol* 2012; **13**: e11-e22 [PMID: 22047762 DOI: 10.1016/S1470-2045(11)70175-9]

47 **Chen MS**, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, Lin XJ, Lau WY. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg* 2006; **243**: 321-328 [PMID: 16495695]

48 **Huang J**, Yan L, Cheng Z, Wu H, Du L, Wang J, Xu Y, Zeng Y. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. *Ann Surg* 2010; **252**: 903-912 [PMID: 21107100 DOI: 10.1097/SLA.0b013e3181efc656]

49 **Feng K**, Yan J, Li X, Xia F, Ma K, Wang S, Bie P, Dong J. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. *J Hepatol* 2012; **57**: 794-802 [PMID: 22634125 DOI: 10.1016/j.jhep.2012.05.007]

50 **Fang Y**, Chen W, Liang X, Li D, Lou H, Chen R, Wang K, Pan H. Comparison of long-term effectiveness and complications of radiofrequency ablation with hepatectomy for small hepatocellular carcinoma. *J Gastroenterol Hepatol* 2014; **29**: 193-200 [PMID: 24224779 DOI: 10.1111/jgh.12441]

51 **Peng ZW**, Lin XJ, Zhang YJ, Liang HH, Guo RP, Shi M, Chen MS. Radiofrequency ablation versus hepatic resection for the treatment of hepatocellular carcinomas 2 cm or smaller: a retrospective comparative study. *Radiology* 2012; **262**: 1022-1033 [PMID: 22357902 DOI: 10.1148/radiol.11110817]

52 **Wang JH**, Wang CC, Hung CH, Chen CL, Lu SN. Survival comparison between surgical resection and radiofrequency ablation for patients in BCLC very early/early stage hepatocellular carcinoma. *J Hepatol* 2012; **56**: 412-418 [PMID: 21756858 DOI: 10.1016/j.jhep.2011.05.020]

53 **Hung HH**, Chiou YY, Hsia CY, Su CW, Chou YH, Chiang JH, Kao WY, Huo TI, Huang YH, Su YH, Lin HC, Lee SD, Wu JC. Survival rates are comparable after radiofrequency ablation or surgery in patients with small hepatocellular carcinomas. *Clin Gastroenterol Hepatol* 2011; **9**: 79-86 [PMID: 20831902 DOI: 10.1016/j.cgh.2010.08.018]

54 **Takayama T**, Makuuchi M, Hasegawa K. Single HCC smaller than 2 cm: surgery or ablation?: surgeon's perspective. *J Hepatobiliary Pancreat Sci* 2010; **17**: 422-424 [PMID: 19936598 DOI: 10.1007/s00534-009-0239-7]

55 **Liu PH**, Hsu CY, Hsia CY, Lee YH, Huang YH, Chiou YY, Lin HC, Huo TI. Surgical Resection Versus Radiofrequency Ablation for Single Hepatocellular Carcinoma ≤ 2  cm in a Propensity Score Model. *Ann Surg* 2016; **263**: 538-545 [PMID: 25775062 DOI: 10.1097/SLA.0000000000001178]

56 **Cucchetti A**, Piscaglia F, Cescon M, Ercolani G, Pinna AD. Systematic review of surgical resection vs radiofrequency ablation for hepatocellular carcinoma. *World J Gastroenterol* 2013; **19**: 4106-4118 [PMID: 23864773 DOI: 10.3748/wjg.v19.i26.4106]

57 **Cho YK**, Rhim H, Noh S. Radiofrequency ablation versus surgical resection as primary treatment of hepatocellular carcinoma meeting the Milan criteria: a systematic review. *J Gastroenterol Hepatol* 2011; **26**: 1354-1360 [PMID: 21679247 DOI: 10.1111/j.1440-1746.2011.06812.x]

58 **Wang Y**, Luo Q, Li Y, Deng S, Wei S, Li X. Radiofrequency ablation versus hepatic resection for small hepatocellular carcinomas: a meta-analysis of randomized and nonrandomized controlled trials. *PLoS One* 2014; **9**: e84484 [PMID: 24404166 DOI: 10.1371/journal.pone.0084484]

59 **Cucchetti A**, Piscaglia F, Cescon M, Colecchia A, Ercolani G, Bolondi L, Pinna AD. Cost-effectiveness of hepatic resection versus percutaneous radiofrequency ablation for early hepatocellular carcinoma. *J Hepatol* 2013; **59**: 300-307 [PMID: 23603669 DOI: 10.1016/j.jhep.2013.04.009]

60 **Cucchetti A**, Piscaglia F, Cescon M, Serra C, Colecchia A, Maroni L, Venerandi L, Ercolani G, Pinna AD. An explorative data-analysis to support the choice between hepatic resection and radiofrequency ablation in the treatment of hepatocellular carcinoma. *Dig Liver Dis* 2014; **46**: 257-263 [PMID: 24284006 DOI: 10.1016/j.dld.2013.10.015]

61 **Lencioni R**. Loco-regional treatment of hepatocellular carcinoma. *Hepatology* 2010; **52**: 762-773 [PMID: 20564355 DOI: 10.1002/hep.23725]

62 **Livraghi T**, Bolondi L, Lazzaroni S, Marin G, Morabito A, Rapaccini GL, Salmi A, Torzilli G. Percutaneous ethanol injection in the treatment of hepatocellular carcinoma in cirrhosis. A study on 207 patients. *Cancer* 1992; **69**: 925-929 [PMID: 1310435 DOI: [10.1002/1097-0142(19920215)69:4<925::AID-CNCR2820690415>3.0.CO;2-G](http://dx.doi.org/10.1002/1097-0142(19920215)69:4%3C925::AID-CNCR2820690415%3E3.0.CO;2-G" \t "_blank)]

63 **Livraghi T**, Goldberg SN, Lazzaroni S, Meloni F, Ierace T, Solbiati L, Gazelle GS. Hepatocellular carcinoma: radio-frequency ablation of medium and large lesions. *Radiology* 2000; **214**: 761-768 [PMID: 10715043 DOI: [10.1148/radiology.214.3.r00mr02761](http://dx.doi.org/10.1148/radiology.214.3.r00mr02761" \t "_blank)]

64 **Yang B**, Zan RY, Wang SY, Li XL, Wei ML, Guo WH, You X, Li J, Liao ZY. Radiofrequency ablation versus percutaneous ethanol injection for hepatocellular carcinoma: a meta-analysis of randomized controlled trials. *World J Surg Oncol* 2015; **13**: 96 [PMID: 25889181 DOI: 10.1186/s12957-015-0516-7]

65 **Lin SM**, Lin CJ, Lin CC, Hsu CW, Chen YC. Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma & lt; or =4 cm. *Gastroenterology* 2004; **127**: 1714-1723 [PMID: 15578509 DOI: [10.1053/j.gastro.2004.09.003](http://dx.doi.org/10.1053/j.gastro.2004.09.003" \t "_blank)]

66 **Lin SM**, Lin CJ, Lin CC, Hsu CW, Chen YC. Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. *Gut* 2005; **54**: 1151-1156 [PMID: 16009687 DOI: [10.1136/gut.2004.045203](http://dx.doi.org/10.1136/gut.2004.045203" \t "_blank)]

67 **Shiina S**, Teratani T, Obi S, Sato S, Tateishi R, Fujishima T, Ishikawa T, Koike Y, Yoshida H, Kawabe T, Omata M. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. *Gastroenterology* 2005; **129**: 122-130 [PMID: 16012942 DOI: [10.1053/j.gastro.2005.04.009](http://dx.doi.org/10.1053/j.gastro.2005.04.009" \t "_blank)]

68 **Wang XW**, [Yang](http://xueshu.baidu.com/s?wd=author%3A%28Yang%20sen%29%20&tn=SE_baiduxueshu_c1gjeupa&ie=utf-8&sc_f_para=sc_hilight%3Dperson) S, [Lai](http://xueshu.baidu.com/s?wd=author%3A%28Lai%20zhao%29%20&tn=SE_baiduxueshu_c1gjeupa&ie=utf-8&sc_f_para=sc_hilight%3Dperson) Z. Clinical effect of radiofrequency ablation therapy and percutaneous ethanol injection therapy on small hepatocellular carcinoma. *Med J West China* 2011; **23**: 1671-1673

69 **Azab M**, Zaki S, El-Shetey AG, Abdel-Moty MF, Alnoomani NM, Gomaa AA, Abdel-Fatah S, Mohiy S, Atia F. Radiofrequency ablation combined with percutaneous ethanol injection in patients with hepatocellular carcinoma. *Arab J Gastroenterol* 2011; **12**: 113-118 [PMID: 22055587 DOI: 10.1016/j.ajg.2011.07.005]

70 **Giorgio A**, Di Sarno A, De Stefano G, Scognamiglio U, Farella N, Mariniello A, Esposito V, Coppola C, Giorgio V. Percutaneous radiofrequency ablation of hepatocellular carcinoma compared to percutaneous ethanol injection in treatment of cirrhotic patients: an Italian randomized controlled trial. *Anticancer Res* 2011; **31**: 2291-2295 [PMID: 21737654]

71 **Lencioni RA**, Allgaier HP, Cioni D, Olschewski M, Deibert P, Crocetti L, Frings H, Laubenberger J, Zuber I, Blum HE, Bartolozzi C. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. *Radiology* 2003; **228**: 235-240 [PMID: 12759473]

72 **Brunello F**, Veltri A, Carucci P, Pagano E, Ciccone G, Moretto P, Sacchetto P, Gandini G, Rizzetto M. Radiofrequency ablation versus ethanol injection for early hepatocellular carcinoma: A randomized controlled trial. *Scand J Gastroenterol* 2008; **43**: 727-735 [PMID: 18569991 DOI: 10.1080/00365520701885481]

73 **Shen A**, Zhang H, Tang C, Chen Y, Wang Y, Zhang C, Wu Z. Systematic review of radiofrequency ablation versus percutaneous ethanol injection for small hepatocellular carcinoma up to 3 cm. *J Gastroenterol Hepatol* 2013; **28**: 793-800 [PMID: 23432154 DOI: 10.1111/jgh.12162]

74 **Ahrar K**, Newman RA, Pang J, Vijjeswarapu MK, Wallace MJ, Wright KC. 2004 Dr. Gary J. Becker Young Investigator Award: Relative thermosensitivity of cytotoxic drugs used in transcatheter arterial chemoembolization. *J Vasc Interv Radiol* 2004; **15**: 901-905 [PMID: 15361556]

75 **Peng ZW**, Zhang YJ, Liang HH, Lin XJ, Guo RP, Chen MS. Recurrent hepatocellular carcinoma treated with sequential transcatheter arterial chemoembolization and RF ablation versus RF ablation alone: a prospective randomized trial. *Radiology* 2012; **262**: 689-700 [PMID: 22157201 DOI: 10.1148/radiol.11110637]

76 **Cheng BQ**, Jia CQ, Liu CT, Fan W, Wang QL, Zhang ZL, Yi CH. Chemoembolization combined with radiofrequency ablation for patients with hepatocellular carcinoma larger than 3 cm: a randomized controlled trial. *JAMA* 2008; **299**: 1669-1677 [PMID: 18398079 DOI: 10.1001/jama.299.14.1669]

77 **Yang W**, Chen MH, Wang MQ, Cui M, Gao W, Wu W, Wu JY, Dai Y, Yan K. Combination therapy of radiofrequency ablation and transarterial chemoembolization in recurrent hepatocellular carcinoma after hepatectomy compared with single treatment. *Hepatol Res* 2009; **39**: 231-240 [PMID: 19054154 DOI: 10.1111/j.1872-034X.2008.00451.x]

78 **Shibata T**, Isoda H, Hirokawa Y, Arizono S, Shimada K, Togashi K. Small hepatocellular carcinoma: is radiofrequency ablation combined with transcatheter arterial chemoembolization more effective than radiofrequency ablation alone for treatment? *Radiology* 2009; **252**: 905-913 [PMID: 19567647 DOI: 10.1148/radiol.2523081676]

79 **Morimoto M**, Numata K, Kondou M, Nozaki A, Morita S, Tanaka K. Midterm outcomes in patients with intermediate-sized hepatocellular carcinoma: a randomized controlled trial for determining the efficacy of radiofrequency ablation combined with transcatheter arterial chemoembolization. *Cancer* 2010; **116**: 5452-5460 [PMID: 20672352 DOI: 10.1002/cncr.25314]

80 **Kang CB**, Xu HB, Wang SL, Rui B. Treatment of large hepatoma by TACE in combination with RFA. *Zhonghua Gandan Waike Zazhi* 2007; **13**: 828-830

81 **Shen SQ**, Xiang JJ, Xiong CL, Wu SM, Zhu SS. Intraoperative radiofrequency thermal ablation combined with portal vein infusion chemotherapy and transarterial chemoembolization for unresectable HCC. *Hepatogastroenterology* 2005; **52**: 1403-1407 [PMID: 16201083]

82 **Zhang Z**, Wu M, Chen H, Chen D, He J. [Percutaneous radiofrequency ablation combined with transcatheter arterial chemoembolization for hepatocellular carcinoma]. *Zhonghua Waike Zazhi* 2002; **40**: 826-829 [PMID: 12487855]

83 **Ni JY**, Liu SS, Xu LF, Sun HL, Chen YT. Meta-analysis of radiofrequency ablation in combination with transarterial chemoembolization for hepatocellular carcinoma. *World J Gastroenterol* 2013; **19**: 3872-3882 [PMID: 23840128 DOI: 10.3748/wjg.v19.i24.3872]

84 **Iezzi R**, Pompili M, La Torre MF, Campanale MC, Montagna M, Saviano A, Cesario V, Siciliano M, Annicchiarico E, Agnes S, Giuliante F, Grieco A, Rapaccini GL, De Gaetano AM, Gasbarrini A, Bonomo L. Radiofrequency ablation plus drug-eluting beads transcatheter arterial chemoembolization for the treatment of single large hepatocellular carcinoma. *Dig Liver Dis* 2015; **47**: 242-248 [PMID: 25577299 DOI: 10.1016/j.dld.2014.12.007]

85 **Liang P**, Wang Y. Microwave ablation of hepatocellular carcinoma. *Oncology* 2007; **72** Suppl 1: 124-131 [PMID: 18087193 DOI: [10.1159/000111718](http://dx.doi.org/10.1159/000111718" \t "_blank)]

86 **Skinner MG**, Iizuka MN, Kolios MC, Sherar MD. A theoretical comparison of energy sources--microwave, ultrasound and laser--for interstitial thermal therapy. *Phys Med Biol* 1998; **43**: 3535-3547 [PMID: 9869030 DOI: [10.1088/0031-9155/43/12/011](http://dx.doi.org/10.1088/0031-9155/43/12/011" \t "_blank)]

87 **McWilliams JP**, Yamamoto S, Raman SS, Loh CT, Lee EW, Liu DM, Kee ST. Percutaneous ablation of hepatocellular carcinoma: current status. *J Vasc Interv Radiol* 2010; **21**: S204-S213 [PMID: 20656230 DOI: 10.1016/j.jvir.2009.11.025]

88 **Dong B**, Liang P, Yu X, Su L, Yu D, Cheng Z, Zhang J. Percutaneous sonographically guided microwave coagulation therapy for hepatocellular carcinoma: results in 234 patients. *AJR Am J Roentgenol* 2003; **180**: 1547-1555 [PMID: 12760916 DOI: [10.2214/ajr.180.6.1801547](http://dx.doi.org/10.2214/ajr.180.6.1801547" \t "_blank)]

89 **Liang P**, Dong B, Yu X, Yu D, Wang Y, Feng L, Xiao Q. Prognostic factors for survival in patients with hepatocellular carcinoma after percutaneous microwave ablation. *Radiology* 2005; **235**: 299-307 [PMID: 15731369 DOI: [10.1148/radiol.2351031944](http://dx.doi.org/10.1148/radiol.2351031944" \t "_blank)]

90 **Lu MD**, Chen JW, Xie XY, Liu L, Huang XQ, Liang LJ, Huang JF. Hepatocellular carcinoma: US-guided percutaneous microwave coagulation therapy. *Radiology* 2001; **221**: 167-172 [PMID: 11568335 DOI: [10.1148/radiol.2211001783](http://dx.doi.org/10.1148/radiol.2211001783" \t "_blank)]

91 **Livraghi T**, Meloni F, Solbiati L, Zanus G; [Collaborative Italian Group using AMICA system](http://www.ncbi.nlm.nih.gov/pubmed/?term=Collaborative%20Italian%20Group%20using%20AMICA%20system%5BCorporate%20Author%5D). Complications of microwave ablation for liver tumors: results of a multicenter study. *Cardiovasc Intervent Radiol* 2012; **35**: 868-874 [PMID: 21833809 DOI: 10.1007/s00270-011-0241-8]

92 **Shibata T**, Iimuro Y, Yamamoto Y, Maetani Y, Ametani F, Itoh K, Konishi J. Small hepatocellular carcinoma: comparison of radio-frequency ablation and percutaneous microwave coagulation therapy. *Radiology* 2002; **223**: 331-337 [PMID: 11997534]

93 **Lu MD**, Xu HX, Xie XY, Yin XY, Chen JW, Kuang M, Xu ZF, Liu GJ, Zheng YL. Percutaneous microwave and radiofrequency ablation for hepatocellular carcinoma: a retrospective comparative study. *J Gastroenterol* 2005; **40**: 1054-1060 [PMID: 16322950]

94 **Ohmoto K**, Yoshioka N, Tomiyama Y, Shibata N, Kawase T, Yoshida K, Kuboki M, Yamamoto S. Comparison of therapeutic effects between radiofrequency ablation and percutaneous microwave coagulation therapy for small hepatocellular carcinomas. *J Gastroenterol Hepatol* 2009; **24**: 223-227 [PMID: 18823439 DOI: 10.1111/j.1440-1746.2008.05596.x]

95 **Ding J**, Jing X, Liu J, Wang Y, Wang F, Wang Y, Du Z. Comparison of two different thermal techniques for the treatment of hepatocellular carcinoma. *Eur J Radiol* 2013; **82**: 1379-1384 [PMID: 23726122 DOI: 10.1016/j.ejrad.2013.04.025]

96 **Zhang L**, Wang N, Shen Q, Cheng W, Qian GJ. Therapeutic efficacy of percutaneous radiofrequency ablation versus microwave ablation for hepatocellular carcinoma. *PLoS One* 2013; **8**: e76119 [PMID: 24146824 DOI: 10.1371/journal.pone.0076119]

97 **Abdelaziz A**, Elbaz T, Shousha HI, Mahmoud S, Ibrahim M, Abdelmaksoud A, Nabeel M. Efficacy and survival analysis of percutaneous radiofrequency versus microwave ablation for hepatocellular carcinoma: an Egyptian multidisciplinary clinic experience. *Surg Endosc* 2014; **28**: 3429-3434 [PMID: 24935203 DOI: 10.1007/s00464-014-3617-4]

98 **Vogl TJ**, Farshid P, Naguib NN, Zangos S, Bodelle B, Paul J, Mbalisike EC, Beeres M, Nour-Eldin NE. Ablation therapy of hepatocellular carcinoma: a comparative study between radiofrequency and microwave ablation. *Abdom Imaging* 2015; **40**: 1829-1837 [PMID: 25601438 DOI: 10.1007/s00261-015-0355-6]

99 **Chinnaratha MA**, Chuang MY, Fraser RJ, Woodman RJ, Wigg AJ. Percutaneous thermal ablation for primary hepatocellular carcinoma: A systematic review and meta-analysis. *J Gastroenterol Hepatol* 2016; **31**: 294-301 [PMID: 26114968 DOI: 10.1111/jgh.13028]

100 **Facciorusso A**, Di Maso M, Muscatiello N. Microwave ablation versus radiofrequency ablation for the treatment of hepatocellular carcinoma: A systematic review and meta-analysis. *Int J Hyperthermia* 2016; In press

101 **Quesson B**, Merle M, Köhler MO, Mougenot C, Roujol S, de Senneville BD, Moonen CT. A method for MRI guidance of intercostal high intensity focused ultrasound ablation in the liver. *Med Phys* 2010; **37**: 2533-2540 [PMID: 20632565]

102 **Chan AC**, Cheung TT, Fan ST, Chok KS, Chan SC, Poon RT, Lo CM. Survival analysis of high-intensity focused ultrasound therapy versus radiofrequency ablation in the treatment of recurrent hepatocellular carcinoma. *Ann Surg* 2013; **257**: 686-692 [PMID: 23426335 DOI: 10.1097/SLA.0b013e3182822c02]

103 **Chok KS**, Cheung TT, Lo RC, Chu FS, Tsang SH, Chan AC, Sharr WW, Fung JY, Dai WC, Chan SC, Fan ST, Lo CM. Pilot study of high-intensity focused ultrasound ablation as a bridging therapy for hepatocellular carcinoma patients wait-listed for liver transplantation. *Liver Transpl* 2014; **20**: 912-921 [PMID: 24753206 DOI: 10.1002/lt.23892]

104 **Jacques SL**. Laser-tissue interactions. Photochemical, photothermal, and photomechanical. *Surg Clin North Am* 1992; **72**: 531-558 [PMID: 1589829]

105 **Giorgio A**, Tarantino L, de Stefano G N, Catalano O, Cusati B, Del Viscovo L A, Caturelli E. Interstitial laser photocoagulation under ultrasound guidance of liver tumors: results in 104 treated patients. *Eur J Ultrasound* 2000; **11**: 181-188 [PMID: 10874193 DOI: [10.1016/S0929-8266(00)00086-0](http://dx.doi.org/10.1016/S0929-8266(00)00086-0" \t "_blank)]

106 **Pacella CM**, Bizzarri G, Francica G, Bianchini A, De Nuntis S, Pacella S, Crescenzi A, Taccogna S, Forlini G, Rossi Z, Osborn J, Stasi R. Percutaneous laser ablation in the treatment of hepatocellular carcinoma with small tumors: analysis of factors affecting the achievement of tumor necrosis. *J Vasc Interv Radiol* 2005; **16**: 1447-1457 [PMID: 16319150 DOI: [10.1097/01.RVI.90000172121.82299.38](http://dx.doi.org/10.1097/01.RVI.90000172121.82299.38" \t "_blank)]

107 **Francica G**, Iodice G, Delle Cave M, Sarrantonio R, Lapiccirella G, Molese V, Smeraldo D, Scarano F, De Marino F. Factors predicting complete necrosis rate after ultrasound-guided percutaneous laser thermoablation of small hepatocellular carcinoma tumors in cirrhotic patients: a multivariate analysis. *Acta Radiol* 2007; **48**: 514-519 [PMID: 17520427 DOI: [10.1080/02841850701199942](http://dx.doi.org/10.1080/02841850701199942" \t "_blank)]

108 **Pacella CM**, Bizzarri G, Magnolfi F, Cecconi P, Caspani B, Anelli V, Bianchini A, Valle D, Pacella S, Manenti G, Rossi Z. Laser thermal ablation in the treatment of small hepatocellular carcinoma: results in 74 patients. *Radiology* 2001; **221**: 712-720 [PMID: 11719667 DOI: [10.1148/radiol.2213001501](http://dx.doi.org/10.1148/radiol.2213001501" \t "_blank)]

109 **Pacella CM**, Francica G, Di Lascio FM, Arienti V, Antico E, Caspani B, Magnolfi F, Megna AS, Pretolani S, Regine R, Sponza M, Stasi R. Long-term outcome of cirrhotic patients with early hepatocellular carcinoma treated with ultrasound-guided percutaneous laser ablation: a retrospective analysis. *J Clin Oncol* 2009; **27**: 2615-2621 [PMID: 19332729 DOI: 10.1200/JCO.2008.19.0082]

110 **Di Costanzo GG**, Tortora R, D'Adamo G, De Luca M, Lampasi F, Addario L, Galeota Lanza A, Picciotto FP, Tartaglione MT, Cordone G, Imparato M, Mattera S, Pacella CM. Radiofrequency ablation versus laser ablation for the treatment of small hepatocellular carcinoma in cirrhosis: a randomized trial. *J Gastroenterol Hepatol* 2015; **30**: 559-565 [PMID: 25251043 DOI: 10.1111/jgh.12791]

111 **Hutchinson M**, Shyn P, Silverman S. Cryoablation of Liver Tumors. In: Dupuy DE, Fong Y, McMullen WN, editors. Image-Guided Cancer Therapy. New York: Springer Inc., 2013: 491-503

112 **Hu KQ**. Advances in clinical application of cryoablation therapy for hepatocellular carcinoma and metastatic liver tumor. *J Clin Gastroenterol* 2014; **48**: 830-836 [PMID: 25148553 DOI: 10.1097/MCG.0000000000000201]

113 **Mala T**, Samset E, Aurdal L, Gladhaug I, Edwin B, Søreide O. Magnetic resonance imaging-estimated three-dimensional temperature distribution in liver cryolesions: a study of cryolesion characteristics assumed necessary for tumor ablation. *Cryobiology* 2001; **43**: 268-275 [PMID: 11888220]

114 **Sheen AJ**, Siriwardena AK. The end of cryotherapy for the treatment of nonresectable hepatic tumors? *Ann Surg Oncol* 2005; **12**: 202-204 [PMID: 15827810]

115 **Rong G**, Bai W, Dong Z, Wang C, Lu Y, Zeng Z, Qu J, Lou M, Wang H, Gao X, Chang X, An L, Li H, Chen Y, Hu KQ, Yang Y. Long-term outcomes of percutaneous cryoablation for patients with hepatocellular carcinoma within Milan criteria. *PLoS One* 2015; **10**: e0123065 [PMID: 25849963 DOI: 10.1371/journal.pone.0123065]

116 **Wu S**, Hou J, Ding Y, Wu F, Hu Y, Jiang Q, Mao P, Yang Y. Cryoablation Versus Radiofrequency Ablation for Hepatic Malignancies: A Systematic Review and Literature-Based Analysis. *Medicine* (Baltimore) 2015; **94**: e2252 [PMID: 26656371 DOI: 10.1097/MD.0000000000002252]

117 **Wang C**, Wang H, Yang W, Hu K, Xie H, Hu KQ, Bai W, Dong Z, Lu Y, Zeng Z, Lou M, Wang H, Gao X, Chang X, An L, Qu J, Li J, Yang Y. Multicenter randomized controlled trial of percutaneous cryoablation versus radiofrequency ablation in hepatocellular carcinoma. *Hepatology* 2015; **61**: 1579-1590 [PMID: 25284802 DOI: 10.1002/hep.27548]

118 **Ei S**, Hibi T, Tanabe M, Itano O, Shinoda M, Kitago M, Abe Y, Yagi H, Okabayashi K, Sugiyama D, Wakabayashi G, Kitagawa Y. Cryoablation provides superior local control of primary hepatocellular carcinomas of & gt; 2 cm compared with radiofrequency ablation and microwave coagulation therapy: an underestimated tool in the toolbox. *Ann Surg Oncol* 2015; **22**: 1294-1300 [PMID: 25287439 DOI: 10.1245/s10434-014-4114-7]

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**S- Editor:** Gong XM **L- Editor:** **E- Editor:**

**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 |

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

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Liver function** | **Tumor features** | **Treatment** | **3-yr SR** | **5-yr SR** | **3-yr DFS** | **5-yr DFS** |
| Chen *et al*[47] | CP A  ICG-R15 < 30%  PLT > 40000/mm3 | Single < 5 cm | HR 90  RFA 71 | 73.4%  71.4% | NA  NA | 69%  64.1% | NA  NA |
| Huang *et al*[48] | CP A/B  ICG-R15 < 20%  PLT > 50000/mm3 | Within MC  Single ≤ 3 cm  Single 3-5 cm  Multifocal < 3 cm | HR 115  RFA 115  HR 45  RFA 57  HR 44  RFA 27  HR 26  RFA 31 | 92.2%  69.6%  95.6%  77.2%  95.5%  66.7%  80.8%  58.1% | 75.7%  54.8%  82.2%  61.4%  72.3%  51.5%  69.2%  45.2% | 60.9%  46.1%  NA  NA  NA  NA  NA  NA | 51.3%  28.7%  NA  NA  NA  NA  NA  NA |
| Feng *et al*[49] | CP A/B  ICG-R15 < 30%  PLT > 50000 mm3 | Up to 2 nodules < 4 cm | HR 84  RFA 84 | 74.8%  67.2% | NA  NA | 61.1%  49.6% | NA  NA |
| Fang *et al* [50] | CP A/B  PLT > 50000 mm3 | Up to 3 nodules ≤ 3 cm | HR 60  RFA 60 | 77.5%  82.5% | NA  NA | 41.3%  55.4% | NA  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.

**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** | **Number of sessions** | **Complete response (%)** | **3-yr Survival (%)** | **3-yr Recurrence (%)** |
| Lin *et al*[65] | Taiwan | RFA (52)  PEI (52) | 38/14  40/12 | 2.9 ±0.8  2.8 ± 0.8 | 1.6 ± 0.4  6.5 ± 1.6 | 96.0  88.0 | 74  50 | 18  45 |
| Lin *et al*[66] | Taiwan | RFA (62)  PEI (62) | 49/13  49/13 | 2.5 ± 1.0  2.3 ± 0.8 | 1.3 ± 0.3  4.9 ± 1.3 | 96.1  88.1 | 74  51 | 14  34 |
| Shiina *et al* [67] | Japan | RFA (118)  PEI (114) | 72/46  60/54 | NA  NA | 2.1 ± 1.3  6.4 ± 2.6 | 100.0  100.0 | 81  66 | 1.7  11 |
| Wang *et al* [68] | China | RFA (49)  PEI (49) | NA  NA | 2.4 ± 1.2  2.3 ± 1.4 | NA  NA | 93.8  77.5 | NA  NA | NA  NA |
| Azab *et al* [69] | Egypt | RFA (30)  PEI (30) | NA  NA | NA  NA | 1.45  7.68 | 85.0  75.0 | NA  NA | NA  NA |
| Giorgio *et al* [70] | Italy | RFA (128)  PEI (143) | 128/0  143/0 | 2.3 ± 0.4  2.2 ± 0.5 | 5  8 | 100.0  100.0 | 83  78 | 7.8  9.4 |
| Lencioni *et al*[71] | Italy | RFA (52)  PEI (50) | 40/12  31/19 | 2.8 ± 0.6  2.8 ± 0.8 | 1.1 ± 0.5  5.4 ± 1.6 | 91.0  82.0 | NA  NA | 21  59 |
| Brunello *et al*[72] | Italy | RFA (70)  PEI (69) | 54/16  54/15 | 2.4 ± 0.5  2.2 ± 0.5 | NA  NA | 95.7  65.6 | 59  56 | NA  NA |

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

**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 *et al*[75] | China | TACE + RFA (69)  RFA (70) | ≤ 5.01  - | 60/9/0  59/11/0 | 69  47 | 45  18 |
| Cheng *et al* [76] | China | TACE + RFA (96)  RFA (100) | ≤ 7.5  - | NA  NA | 55  32 | NA  NA |
| Yang *et al* [77] | China | TACE + RFA (24)  RFA (12) | 6.6 ± 0.6  5.2 ± 0.4 | NA  NA | NA  NA | NA  NA |
| Shibata *et al* [78] | Japan | TACE + RFA (46)  RFA (43) | 1.7 ± 0.6  1.6 ± 0.5 | 32/14/0  33/10/0 | 84.8  84.5 | 48.8  29.7 |
| Morimoto *et al* [79] | Japan | TACE + RFA (19)  RFA (18) | 3.6 ± 0.7  3.7 ± 0.6 | 12/7/0  16/2/0 | 93  80 | NA  28 |
| Kang *et al*[80] | China | TACE + RFA (19)  RFA (18) | 6.7 ± 1.1  6.2 ± 1.2 | 12/7/0  12/6/0 | 36.8  16.7 | NA  NA |
| Shen *et al*[81] | China | TACE + RFA (18)  RFA (16) | 5.6 (2.2-15.8)  5 (2.3-12.3) | 4/14/0  6/10/0 | 73.3  20.4 | 50  18.7 |
| Zhang *et al*[82] | China | TACE + RFA (15)  RFA (15) | 4.6 (2.3-7.1)  4.1 (2.4-6) | NA  NA | NA  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) | Numbernodules | 3-yr Survival (%) | Local tumor recurrence (%) |
| Shibata *et al*[92] | RFA (36)  MWA (36) | RCT | Japan | 21/15/0  19/17/0 | 1.6 (0.7-2)  1.7 (0.8-2) | 1.08  1.14 | NA  NA | 8.3  17.4 |
| Lu *et al* [93] | RFA (53)  MWA (49) | R | China | 49/4/0  39/10/0 | 2.6 (1-6.1)  2.5 (0.9-7.2) | 1.35  2 | 37.6  50.5 | 20.9  11.8 |
| Ohmoto *et al*[94] | RFA (34)  MWA (49) | R | Japan | 20/11/3  31/14/4 | 1.6 (0.7-2)  1.7 (0.8-2) | 1.08  1.14 | 49  70 | 9  19 |
| Ding *et al*[95] | RFA (85)  MWA (113) | R | China | 49/36/0  75/38/0 | 2.38 (1-4.8)  2.55 (0.8-5) | 1.15  1.15 | 77.6  82.7 | 5.2  10.9 |
| Zhang *et al*[96] | RFA (78)  MWA (77) | R | China | 78/0/0  77/0/0 | NA  NA | 1.24  1.36 | 64.1  51.7 | 11.8  10.5 |
| Abdelaziz *et al*[97] | RFA (45)  MWA (66) | R | Egypt | 24/21/0  25/41/0 | 2.95 ± 1.03+  2.9 ± 0.97 | 1  1 | NA  NA | 13.5  3.9 |
| Vogl *et al*[98] | RFA (25)  MWA (28) | R | Germany | NA  NA | NA  NA | 1.28  1.28 | 72  79 | 9.4  8.3 |

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