Review

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Percutaneous treatment of hepatocellular carcinoma: State of the art and innovations

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Summary

Percutaneous treatment of hepatocellular carcinoma (HCC) encompasses a vast range of techniques, including monopolar radiofrequency ablation (RFA), multibipolar RFA, microwave ablation, cryoablation and irreversible electroporation. RFA is considered one of the main curative treatments for HCC of less than 5 cm developing on cirrhotic liver, together with surgical resection and liver transplantation. However, controversies exist concerning the respective roles of ablation and liver resection for HCC of less than 3 to 5 cm on cirrhotic liver. In line with the therapeutic algorithm of early HCC, percutaneous ablation could also be used as a bridge to liver transplantation or in a sequence of upfront percutaneous treatment, followed by transplantation if the patient relapses. Moreover, several innovations in ablation methods may help to efficiently treat early HCC, initially considered as "non-ablatable", and might, in some cases, extend ablation criteria beyond early HCC, enabling treatment of more patients with a curative approach.

Keywords: Hepatocellular carcinoma; Radiofrequency ablation; Microwave ablation; Irreversible electroporation; Percutaneous treatment.

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Introduction

Survival of patients with hepatocellular carcinoma (HCC) is poor, with five-year overall survival of around 10 to 15%, mainly explained by diagnosis of the tumour at an advanced stage, which prohibits curative treatment.[1] Ultimately, application of a curative treatment at an early stage is the cornerstone for improving overall survival in patients with cirrhosis and HCC.[2] To achieve this goal, the first step is to identify the "at-risk population", mainly patients with cirrhosis, for whom HCC screening will be cost-effective. The second step is to perform a well-conducted screening program using ultrasonography every six months in patients with cirrhosis.[3] Screening aims to identify patients with HCC, falling within Milan criteria, that can be treated using a curative approach.[4] The final step consists of using curative treatment for all small HCC detected by screening. There are issues in the real-life application of each step that require improvement. In the field of therapeutics, three major types of curative treatment exist in HCC: liver resection, liver transplantation and percutaneous ablation. Each has its limitations that may be partially overcome to provide curative treatment for the highest number of patients and avoid premature use of palliative treatment for small HCC.[5,6] However, the term "curative" treatment for resection or ablation of HCC in patients with cirrhosis is discussed, because the patients are still exposed to *de novo* carcinogenesis. Percutaneous ablation includes a vast range of techniques that have changed over the last 20 years, enabling treatment of an increasing number of patients, with improved efficacy in local control.[7] Moreover, extension of the criteria for borderline HCC treatment using advanced percutaneous techniques, or combinations with endo-arterial approaches, have also been proposed to target larger tumours and augment the number of treatable tumours.[8] Herein, we summarise the different types of percutaneous treatment, discuss their role within the therapeutic algorithm of early HCC, and describe innovations in the field that seek to increase efficacy and extend the boundaries of indications for ablation.

Current indications for percutaneous treatment of small (up to 5 cm) hepatocellular carcinomas

Radiofrequency ablation as standard of care for percutaneous ablation

Classical monopolar percutaneous RFA is based on generation of an electric current (375 to 500 kHz) through a monopolar electrode tip inserted into the HCC that induces a Joule effect by ionic agitation, and thus local heat, reaching a temperature from 60 to 100 °C, which is necessary for coagulation necrosis.[8] The heat propagates in a centrifugal direction from the energy source (electrode tip) in the centre of the tumour to the periphery of the tumour ("centrifugal" ablation) and the temperature decreases, together with the distance from the electrode and when blood flow is present in the vicinity (Fig. 1).[8,9] This phenomenon explains the decrease in local control of a tumour larger than 2 to 3 cm, as well as the decrease in efficacy of the technique when the tumour is localised near a major vessel (the so-called "heat sink effect").[10] To increase the efficacy and size of ablation, new ablation devices have been developed: expandable multi-tined devices, internally cooled electrodes,

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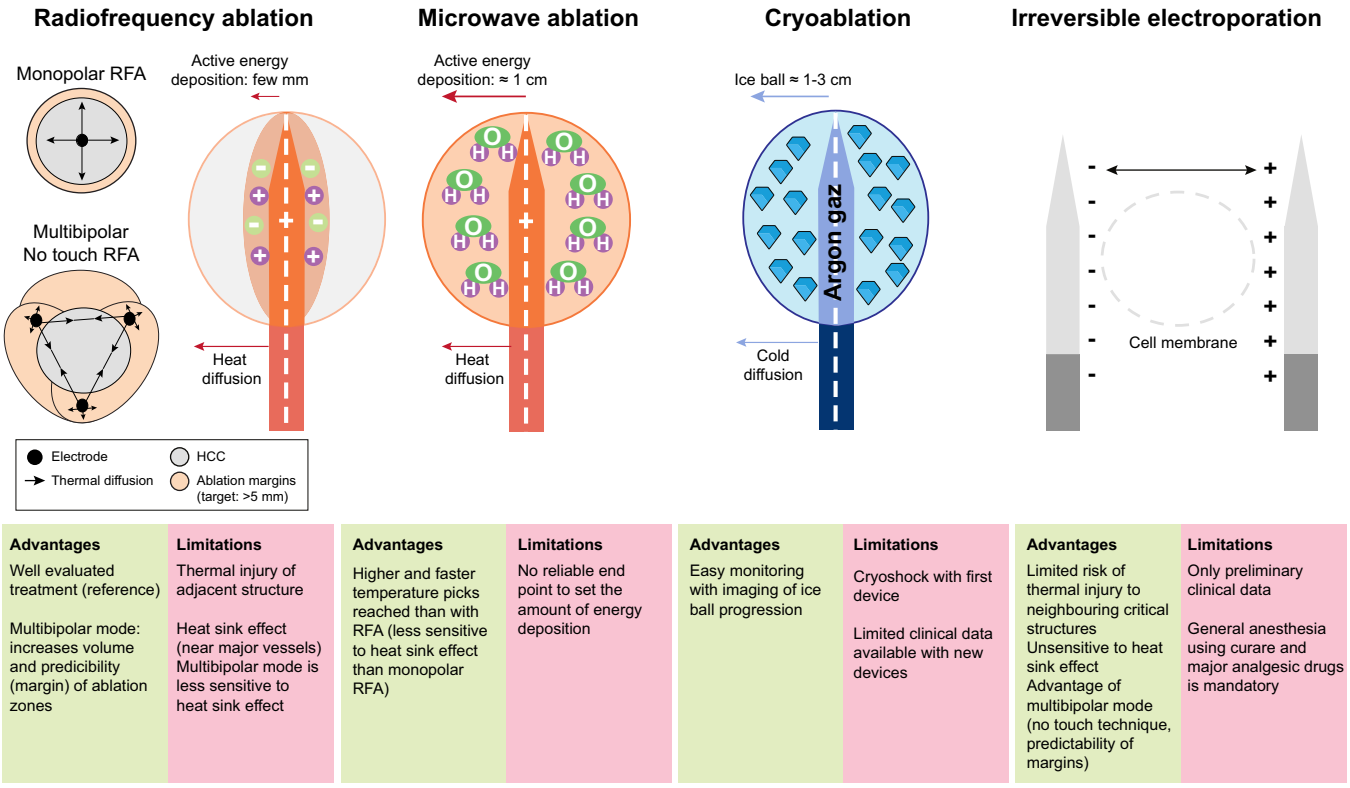

Fig. 1. Description of the different methods of percutaneous ablation. We describe the different methods of percutaneous ablation (thermal and non-thermal), as well as their advantages and limitations. HCC, hepatocellular carcinoma; RFA, radiofrequency ablation.

Key point

Classical monopolar RFA appears to provide the same long-term results as surgical resection in cases of HCC of less than 2–3 cm developing on cirrhotic liver.

multipolar ablation using bipolar electrodes, microwave ablation (MWA), *etc.*[11–14] RFA has now replaced percutaneous ethanol injection as the most frequently used percutaneous treatment of HCC; indeed, five randomised controlled trials have shown the superiority of percutaneous RFA in local control, with fewer sessions needed to achieve tumour necrosis, and less frequent local tumour recurrence compared to percutaneous ethanol injection[15–19] (Table 1). Meta-analysis was necessary to confirm improvement in overall survival for RFA, since results of individual studies showed discrepancies: three Asian studies showed increased survival in the RFA arm, whereas the two European studies did not.[20,21] Currently, in international guidelines, monopolar RFA is standard of care for percutaneous treatment of HCC[22–24] (Table 2). Moreover, RFA could also be performed alone or in combination with liver resection using a laparoscopic approach or during open surgery.[25,26]

Complications

After RFA of HCC less than 5 cm on cirrhotic liver, morbidity with major complications occurred in 1

Table 1. Randomised controlled trials comparing RFA and percutaneous ethanol injection.

Article	Number of patients per arm	Number of sessions	Complete necrosis after one or more sessions	Local tumour recurrence	Overall survival	Commentaries
Lin S, *et al.* *Gastroenterology* 2014[&,15]	52 RFA *vs.* 105 PEI in HCC <4 cm	1.6 RFA *vs.* 6.5 PEI (p <0.01)	96% RFA *vs.* 88% PEI	18% RFA *vs.* 45% PEI at 3 yr (p = 0.01)	74% RFA *vs.* 50% PEI at 3 yr (p = 0.01)	Two types of PEI: conventional *vs.* high doses
Shiina S, *et al.* *Gastroenterology* 2015[17]	118 RFA *vs.* 114 PEI in HCC <3 cm	2.1 RFA *vs.* 6.4 PEI (p <0.0001)	100% RFA *vs.*100% PEI	1.7% RFA *vs.* 11% PEI at 4 yr (p = 0.003)	74% RFA *vs.* 57% PEI at 4 yr (p = 0.01)	
Lin SM, *et al. Gut* 2005[16]	62 RFA *vs.* 62 PEI in HCC <3 cm	1.3 RFA *vs.* 4.9 PEI (p <0.01)	96% RFA *vs.* 88% PEI	14% RFA *vs.*34.5% PEI at 3 yr (p = 0.01)	74% RFA *vs.* 51% PEI at 3 yr (p = 0.03)	A third arm using PAI was included
Brunello *et al. Scand J Gastro* 2008[19]	70 RFA *vs.* 69 PEI in HCC <3 cm	NA	95.7% RFA *vs.*65.6% PEI	34% RFA *vs.* 64% PEI at 1 yr (p = 0.0005)*	63% RFA *vs.* 59% PEI at 3 yr (p = 0.476)	*Mixture of local failure and local recurrence
Lencioni R, *et al.* *Radiology* 2003[18]	52 RFA *vs.* 50 PEI in HCC <5 cm	1.1 RFA *vs.* 5.4 PEI	91% RFA *vs.* 82% PEI	4% RFA *vs.* 38% PEI at 2 yr (p = 0.002)[$]	98% RFA *vs.* 88% PEI at 2 yr (p = 0.138)	[$]Local tumour-free survival

HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; PAI, percutaneous acetic acid injection.
[&] Percentages were reported as RFA *vs.* conventional PEI.

Table 2. Long-term results of RFA for HCC on cirrhosis.

Article	Number of patients	Complete response	Local recurrence	Distant recurrence	Overall survival	Morbidity/ mortality	Commentaries
Rossi S, *et al. Hepatology* 2011[29]	706 patients 1–2 HCC <35 mm	98.5%	12.1% at 3 yr and 13.2% at 5 yr	58.7% at 3 yr, 68.5% at 5 yr	67% at 3 yr, 40.1% at 5 yr (Child Pugh B)	Major AE 1%, 0% death	Western countries, all cirrhosis, HCV patients
Shiina S, *et al. Am J Gastro* 2012[50]	1,170 patients whatever size and numbers	99.4%	3.2% at 3 yr, 5 yr and 10 yr (serum DCP)	63.3% at 3 yr, 74.8% at 5 yr and 80.8% at 10 yr (HCV, low platelets, HCC >20 mm, multiple HCC, AFP and DCP)	80% at 3 yr, 60% at 5 yr and 27.3% at 10 yr (Age, HCV, Child Pugh B, HCC >20 mm, multiple HCC, DCP and AFPl3)	Major AE 1.5%, 0.03% death	Japan HCV patients Cirrhosis?
Kim YS, *et al. J Hepatology* 2013[51]	1,305 patients HCC in Milan criteria	98.5%	21.4% at 3 yr, 27% at 5 yr and 36.9% at 10 yr (HCC size)	59.5% at 3 yr, 73.1% at 5 yr, 88.5% at 10 yr	77.9% at 3 yr, 59.7% at 5 yr and 32.3% at 10 yr (Age, Child Pugh B, absence of antiviral therapy)	Major AE 2%, 0.01% death	Korea, mainly HBV, 82% cirrhosis
Lencioni R, *et al. Radiology* 2005[42]	206 patients, HCC inside Milan criteria	90%	10% at 3 yr and at 5 yr	49% at 3 yr, 81% at 5 yr	67% at 3 yr, 41% at 5 yr (Child Pugh B, multiple HCC)	Major AE 2%, 0% death	Western patients, all cirrhosis, HBV and HCV
Lee DH, *et al. Radiology* 2013[56]	162 patients, HCC inside Milan criteria	96.7%	14.5% at 3 yr and 5 yr (HCC size)	57.6% at 3 yr, 68.6% at 5 yr	84.1% at 3 yr, 67.9% at 5 yr (Child Pugh B, serum AFP, collateral at CT scan)	Major AE 3.1%, 0% death	Korea, mainly HBV, cirrhosis
Nkontchou G, *et al. Hepatology* 2009[30]	235 patients, HCC inside Milan criteria	94.7%	11.5% at 5 yr	73% at 5 yr	60% at 3 yr, 40% at 5 yr 76% at 5 yr in patients eligible for surgery (prothrombin time, AFP level)	Major AE 0.9%, 0.4% death	Western countries, mainly alcohol, cirrhosis
Francica G, *et al. Dig Liv Dis* 2013[53]	365 patients One HCC <3 cm	n.a.	28.5% at 3 yr, 32.1% at 5 yr	n.a.	80% at 3 yr, 64% at 5 yr (age, Child Pugh B)	Major AE 2.2%, 0% death	Western countries, mainly HCV, cirrhosis
Brunello F, *et al. Eur J gastro Hepatol* 2013[54]	209 patients One HCC <3 cm	95.2%	23.5% at 3 yr and 27.9% at 5 yr	54.2% at 3 yr and 58.3% at 5 yr	62.5% at 3 yr, 44.3% at 5 yr (Child Pugh B, Portal Hypertension)	Major AE 3.4%, 0% death	Western countries, HCV, HBV and alcohol, cirrhosis

Risk factors associated with local recurrence, distant recurrence and overall survival are indicated.
AE, adverse events; AFP, alpha-fetoprotein; CT, computed tomography; DCP, des-gamma-carboxy prothrombin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; RFA, radiofrequency ablation.

to 5% of patients, with mortality estimated at around 0% to 0.3%.[27–30] Morbidity and mortality is clearly lower than that observed following liver resection for HCC in patients with cirrhosis.[31] However, the rate of complications increased with more aggressive treatment, performed to ablate larger tumours, and severity of underlying liver disease.[32–35] Post-ablation syndrome causes pain and fever, and is not considered a complication *per se* if the duration of this syndrome remains short and easily manageable with symptomatic treatment.[36] The main complications of percutaneous ablation include pleural effusion, pneumothorax, liver haematoma or haemoperitoneum, haemobilia ascites, liver failure, liver abscess, gall bladder injury, bile duct stricture, colon or stomach perforation, diaphragm injury and tumour seeding.[27,32] Knowledge of each risk factor linked to each complication helps to prevent the occurrence of these events after ablation (Fig. 2). Tumour seeding is observed in 0.5 to 3% of RFA and is fostered by direct puncture of subcapsular HCC.[37,38] The risk of developing ascites and liver failure depends on both the size of the ablation and the underlying liver function. The risk of pleural effusion, diaphragm injury or organ perforation is related to the position of the tumour relative to the diaphragm or colon/stomach, respectively.[39] The risk of biliary tract injury is considerably increased in central HCC abutting the primary bile duct, and is still considered a definitive contraindication for thermal ablation, like RFA, cryoablation or microwave.[40] A history of sphincterotomy or bilio-enteric anastomosis predisposes patients to the occurrence of liver abscess.[41] Procedures have been developed to decrease the risk of complications in HCC situated in the so-called "at-risk localisation" (see "How to manage at-risk localisation…").

Long-term results of RFA for small HCC

Percutaneous monopolar RFA leads to complete ablation (defined by the absence of residual enhancement on contrast-enhanced CT or MRI imaging) of HCC of less than 5 cm in over 95% of cases.[15–19,21,42] Despite the imperfect sensitivity of imaging for detecting residual viable tumour, obtaining a complete radiological response is the primary goal of ablative techniques, since complete ablation has been associated with prolonged

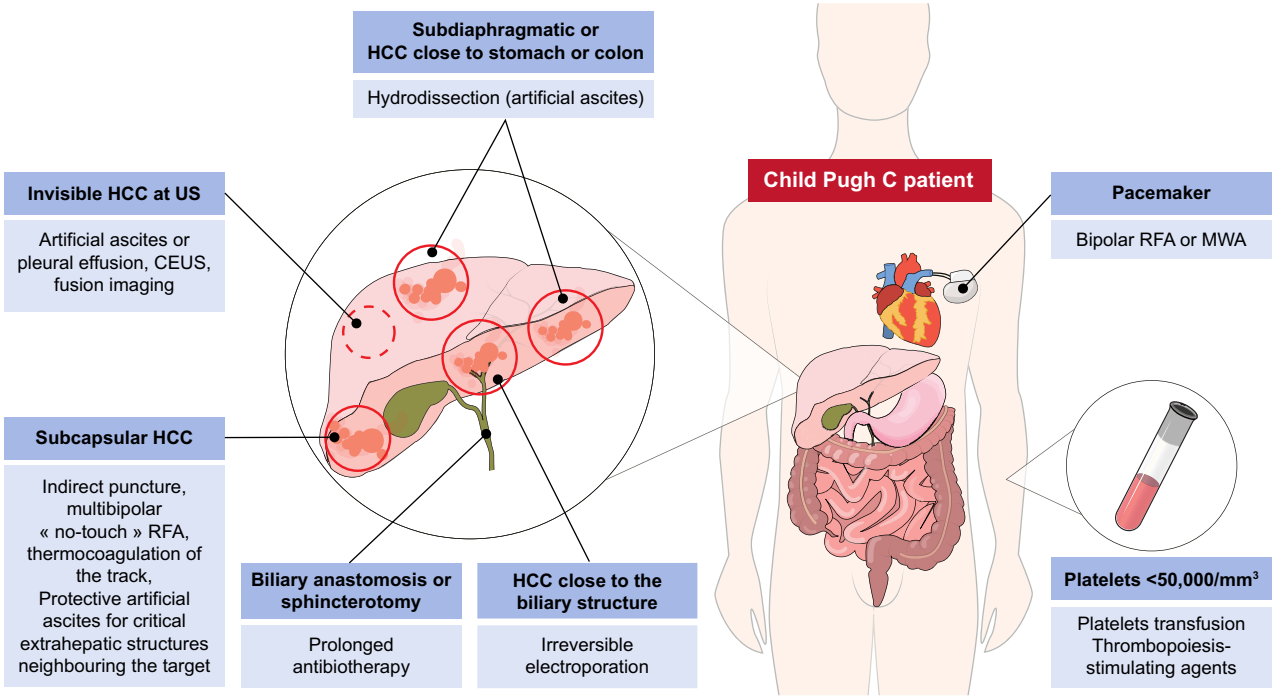

Fig. 2. How to manage at-risk localisation and at-risk patients. In light red, we present relative contraindications to percutaneous ablation; in dark red, absolute contraindications. In blue, we show the method for safely bypassing each relative contraindication. CEUS, contrast-enhanced US; HCC, hepatocellular carcinoma; MWA, microwave ablation; RFA, radiofrequency ablation; US, ultrasound.

overall survival.[43,44] Overall, the pathological response (% of necrosis) is less impressive, varying from 63 to 83% with classical monopolar RFA, but climbing to 90% using the multipolar mode.[12,45,46] In clinical practice, most patients with HCC treated by ablation will never undergo resection or transplantation. Therefore the suboptimal sensitivity of imaging for the assessment of response is an obvious limitation of these techniques both for individual management and for comparative appraisal of the effectiveness of each method.

Otherwise, the % necrosis observed from explant liver depends on the time from RFA to liver transplantation.[46] The incomplete necrosis observed in liver explants probably explains the local tumour recurrence rate of 10 to 30% after percutaneous monopolar RFA of HCC within Milan criteria.[15–19,21,47] In general, local tumour recurrence was treated efficiently and safely with repeated sessions of ablation.[29,48] The rate of distant tumour recurrence at three, five and 10 years was 49 to 63%, 58 to 81% and 80 to 88%, respectively. These recurrences were frequently treatable by repeated RFA sessions.[49] Overall survival was 60 to 84% at three years, 40 to 68% at five years and 27 to 32% at 10 years after RFA for HCC within Milan criteria[29,30,50–54] (Table 2). Prognostic factors associated with overall survival in the literature were age, liver failure (Child Pugh B), presence of portal hypertension, tumour features (high alpha-fetoprotein [AFP], multiple HCC, tumour size) and aetiology of liver disease.[29,30,50–54]

Key point

While local recurrence may be efficiently controlled by additional percutaneous approaches, long-term results are impaired by a high rate of distant tumour recurrence.

Pattern of tumour relapse after RFA: clinical and biological implications

Different types of recurrence have been described based on temporal and spatial distribution of tumour relapse (Fig. 3).[8,55] In terms of localisation of recurrence, local relapse occurred near the ablation area and was linked to insufficient ablation or aggressive tumour features. Size of the tumours (>2–3 cm) and the presence of a major vessel in the vicinity are the two main risk factors for local tumour relapse identified in the literature.[51,56] A margin ablation of at least 0.5 cm to 1 cm, 360 degrees around the tumour, has been advocated to treat microvascular invasion and satellite nodules and decrease the risk of local tumour progression.[12,57,58] Some preclinical studies suggested that incomplete ablation might promote tumour aggressiveness through epithelial-mesenchymal transition, but the link between incomplete ablation and its relation to tumour aggressiveness remains to be proven in clinical practice.[59–61] Interestingly, aggressive intrasegmental tumour recurrences have also been described, and were linked to the periportal location of the tumours, possibly responsible for incomplete ablation and tumour spread through the portal system.[10] In contrast, distant relapse is due to a combination of tumour metastasis related to tumour features (size and number of tumours, AFP level,) and *de novo* carcinogenesis in cirrhosis (with risk factors such as non–hypervascular hypointense nodules at the hepatobiliary phase on gadoxetic acid-enhanced MRI and severity and aetiology of liver

disease, such as the presence of portal hypertension and HCV-related cirrhosis) (Fig. 3).[50,62]

The temporal distribution of tumour relapse has been described following surgical resection of HCC.[63] Early relapse occurred within two to three years following surgery and was related to tumour features, whereas late relapse occurred two to three years after surgery and was related to *de novo* carcinogenesis in cirrhosis (Fig. 3).[63] However, risk factors linked to temporal tumour recurrence have been poorly studied for HCC, in cirrhotic livers treated by RFA.

Radiofrequency ablation in the therapeutic algorithm

For some time, percutaneous RFA was the curative treatment performed when upfront liver transplantation or liver resection was not possible, and it is still the recommended method when the patient is not transplantable because of age or co-morbidity, or when the patient is not resectable because of liver failure, significant portal hypertension or co-morbidity.[5,64] This situation led to selection of patients with more severe natural histories, and consequently, a direct comparison of RFA with other curative treatments has been biased.[65] This has created controversy concerning the comparison between percutaneous RFA and liver resection for small HCC developing in the context of cirrhosis.[66] Although liver resection for HCC >2 to 3 cm appears to be a better treatment than monopolar RFA because of the higher rate of local control and less frequent tumour recurrence, the same assumption is subject to discussion in the case of small HCC less than 2 to 3 cm.[5] Cohort studies alone, or using a Markov model or matched propensity score, have proposed that RFA can compete with liver resection in this clinical scenario.[65,67–70] In our experience, five-year overall survival of selected patients with HCC "eligible for surgery" but treated by RFA was comparable to resection, reaching 76%.[30] Moreover, several studies suggested that RFA may be associated with less morbidity and a better quality of life, and appears to be more cost-effective than surgery.[70–73] This seems to be the case, particularly for patients in whom small HCC was detected during screening, as suggested by a recent cost-effective analysis.[74] Three randomised controlled trials have been performed in an Asian population mainly composed of patients with HBV; they showed either no differences (two RCTs)[31,75] or the superiority of liver resection (one RCT)[76] (Table 3). However, those studies were criticised for their methodology: lack of power in showing differences and equivalences, mixing cirrhotic and non-cirrhotic patients, high rate of loss to follow-up or consent withdrawal, and a high percentage of HCC of over 3 cm. It is highly probable that we will not be able to perform a well-designed randomised controlled trial with sufficient power to show a difference, owing to the high number of patients that would be required.[66,68] Currently, RFA and liver resection can be performed for a small HCC of less than 2–3 cm, and the choice between these two techniques should be based on tumour size, number, liver function, portal hypertension, local technical skills and/or localisation of the lesion. Classically, central HCC is a good candidate for ablation, whereas peripheral lesions are candidates for liver resection.[5,77]

Transarterial chemo-embolisation (TACE), RFA and liver resection are the main treatments used as bridges to liver transplantation.[78] TACE is frequently used as a treatment for patients on the waiting list for transplantation because it enables treatment of multiple lesions, and possibly avoids the risk of tumour seeding associated with RFA.[79] However, several cohort studies of patients treated by RFA prior to transplantation, or of patients with tumour biopsy before transplantation, have shown

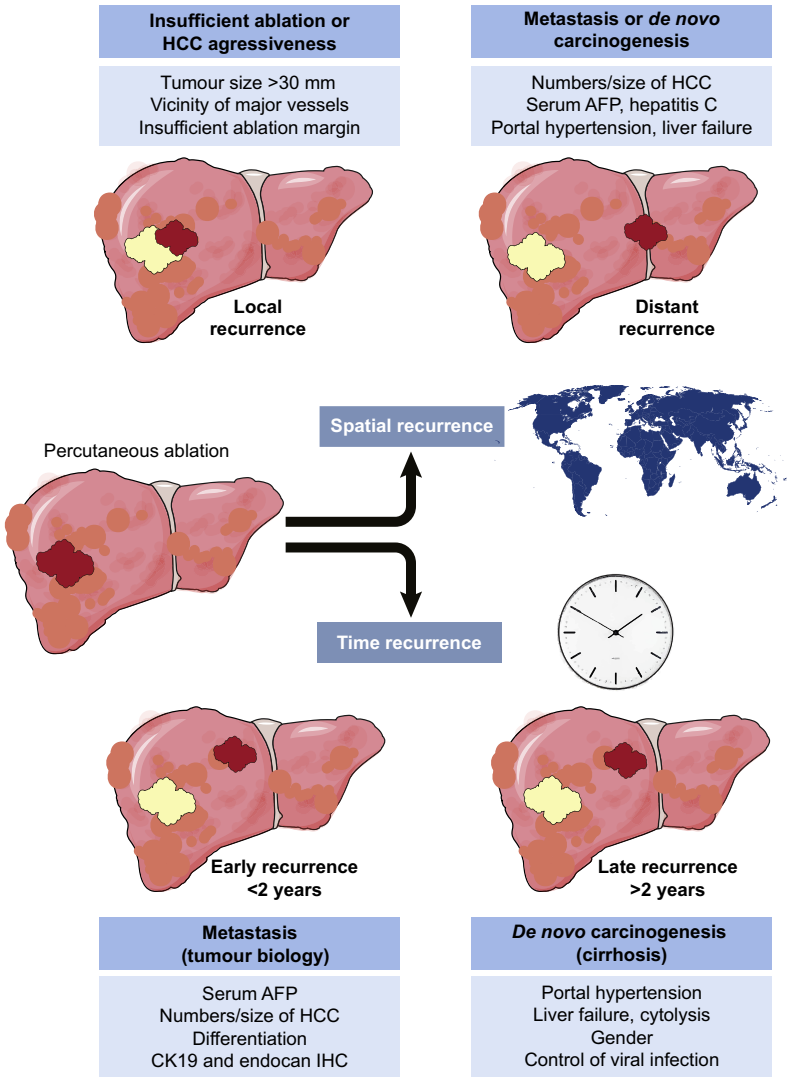

Fig. 3. Risk factors according to the pattern of tumour recurrence. Tumour recurrence was divided into time-related recurrence ("early", two years after ablation; "late", after two years) and spatial recurrence ("local", in the vicinity of the ablation area; and "distant" for other types of recurrences). Risk factors linked to each type of recurrence are also reported. AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma.

Key point

Morbidity and mortality rates for percutaneous ablation of HCC on cirrhotic livers are low.

Table 3. Randomised controlled trials comparing RFA and surgical resection.

Article	Number of patients	Population description	Primary endpoint	Complications	Secondary endpoint	Commentaries
Feng K, *et al.*[31] *J Hepatology* 2012	84 RFA *vs.* 84 LR	60% cirrhosis 64% HCC between 2 to 4 cm Asian, HBV	OS at 3 yr 74.8% for LR *vs.* 67.2% for RFA ($p = 0.342$)	9.5% in RFA *vs.* 21.4% in LR ($p = 0.017$) 0% death	Recurrence at 3 yr: 37.7% in LR *vs.* 49.6% in RFA ($p = 0.119$)	Increased local recurrence in RFA group
Huang J, *et al.* *Ann Surg* 2010[76]	115 RFA *vs.*115 LR	70% cirrhosis 50% HCC between 3 to 5 cm Asian, HBV	OS at 3 yr and 5 yr: 76% and 55% in RFA *vs.* 92% and 76% in LR ($p = 0.0001$)	4% in RFA *vs.* 28% in LR ($p < 0.05$) 0% death	Recurrence at 3 and 5 yr: 49% and 63% in RFA *vs.* 34% and 42% in LR ($p = 0.024$)	Larger HCC in RFA group Patients switch from RFA to LR (6%) High rate of lost-to-follow-up in LR (16%)
Chen MS, *et al.* *Ann Surg* 2006[75]	90 RFA *vs.* 90 LR	Cirrhosis? 50% HCC between 3 to 5 cm Asian, HBV	OS at 3 and 4 yr: 69% and 66% in RFA *vs.*73% and 64% in LR	4% in RFA *vs.* 55% in LR ($p < 0.05$) 1.1% deaths in LR *vs.* 0% in RFA	Disease-free survival at 3 and 4 yr: 60% and 48% in RFA *vs.* 69% and 52% in LR (p = ns)	High rate of consent withdrawal in RFA (21%)

AE, adverse events; AFP, alpha-fetoprotein; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LR, liver resection; OS, overall survival; RFA, radiofrequency ablation.

Key point

Percutaneous ablation could be used as a bridge to transplantation, or as a sequence of ablation first followed by salvage liver transplantation if the tumour recurs.

that tumour seeding is very rare and should not be an obstacle to RFA as a bridge to transplantation.[80,81] Moreover, RFA has been associated with a low dropout rate and high intention-to-treat overall survival for such patients, without the increased risk of tumour seeding.[46,81–84] Consequently, RFA is efficient and safe as bridge therapy for transplantation, with the advantage of providing a potentially curative treatment during the waiting period.

Finally, liver transplantation is often considered the best treatment for eligible patients, but organ shortage is the main limitation, with new therapeutic strategies required to save grafts.[85] A therapeutic sequence with liver resection, followed by salvage liver transplantation after tumour relapse, was considered an alternative to liver transplantation as a first-line treatment, and has the advantage of reducing the number of grafts used.[86,87] We reported the same therapeutic algorithm with ablation of HCC as a first-line treatment in transplantable patients, followed by salvage transplantation if tumours recurred. The intention-to-treat overall survival was 74% at five years, with only 31% of patients transplanted, leading to 69% of patients being considered "tumour-free" at the end of follow-up.[88] Additional studies are required to validate and refine the selection of patients who might benefit from this strategy without their chance of survival being reduced. In France, an expert consensus and regulatory agencies have decided that RFA or liver resection should be proposed, if technically possible, in first-line treatment before liver transplantation; patients would have access to transplantation only after tumour recurrence.

Key point

Up to 30% of small HCCs were classically considered as non-ablatable owing to high-risk location or at-risk patients, but several techniques are now available to efficiently and safely treat these patients.

Innovations

New paradigms

Prognostic tissue and serum biomarkers

In RFA, the main prognostic pathological features (satellite nodules, microvascular invasion) could not be identified on tumour biopsy and, in this setting, identification of new prognostic tumour biomarkers is important in clinical practice. Some authors suggested performing resection rather than RFA to have a full pathological analysis that would help to select patients at a high risk of recurrence, based on histological features, that require liver transplantation "*ab initio*" before tumour recurrence.[89,90] Elsewhere, several studies tested serum and tissue biomarkers to predict the prognosis of patients treated by RFA for HCC. High serum AFP, DCP, AFP-L3 and VEGF levels before RFA have been associated with a greater risk of tumour recurrence.[91] Tissue biomarkers based on tumour biopsy could also be used to predict tumour recurrence and survival. Tumour positivity for CK19, a stem cell marker, glutamine synthase, a target gene of the Wnt/β-catenin pathway and positive immunostaining of tumour endothelial cells by endocan, a surrogate marker of endothelial activation and microvascular invasion, have been shown to predict prognosis after RFA for HCC.[92–94] A molecular signature based on gene expression from tumour analysis could predict early tumour recurrence, while a molecular signature derived from non-tumour liver could predict late recurrence due to *de novo* carcinogenesis on cirrhotic liver.[95,96] However, these molecular signatures have not been validated on tumour and non-tumour biopsies of patients with cirrhosis treated by RFA for HCC.

How to manage at-risk localisation, tumour invisibility and at-risk patients

Studies have shown that, in real life, up to 36% of early HCC received suboptimal palliative treatment (mainly TACE) instead of curative treatments like percutaneous ablation, liver resection or liver transplantation.[97–99] However, even for RFA, around 30% of HCC patients referred for such treatment ablation were regarded as non-feasible because of an at-risk location, an at-risk patient profile or undetectable nodules on ultrasonography.[51] However, several techniques have been developed to safely and efficiently treat these patients and avoid the drift to palliative treatments (Fig. 2). Subcapsular or subdiaphragmatic localisation near the colon or gall bladder were considered at-risk locations. Subcapsular localisation could be treated by indirect puncture, while

subdiaphragramatic localisation or HCC close to the stomach or colon could be treated by hydrodissection using artificial ascites.[100,101] These different approaches enable safe treatment of these patients, and some studies have shown that treatment of at-risk localisation was not associated with decreased efficacy compared to ablation of non-at-risk localisation.[100,102] For example, subcapsular localisation is classically proposed for surgery, but patients treated by RFA in this situation have the same outcome in terms of local recurrence, distant recurrence and overall survival compared to RFA for HCC situated in a non-subcapsular localisation, suggesting that treatment of subcapsular HCC could be safely performed by percutaneous ablation with satisfactory long-term results.[103] Thermocoagulation of the puncture tract and interposition of non-tumour liver during RFA decreases the risk of tumour seeding to less than 1%.[37] Moreover, multibipolar RFA enables easy performing of "no-touch" ablations of subcapsular tumours, even exophytic, without tumour puncture.[40] A pacemaker is a contraindication for monopolar RFA, but not for bipolar RFA or MWA.

Severe thrombocytopenia (<50,000/mm^3) or a history of biliary anastomosis or sphincterotomy were previously considered contraindications because of the risk of bleeding or liver abscesses, respectively. However, thrombocytopenia could be treated by platelet transfusion before treatment, together with thermocoagulation of the puncture track to avoid bleeding.[41] Moreover, thrombopoiesis-stimulating agents were shown to reduce the need for platelet transfusions in patients with cirrhosis and thrombocytopenia who were undergoing elective invasive procedures.[104] However, an increased incidence of portal vein thrombosis has been observed with eltrombopag.[104] Wide-spectrum antibiotherapy prevents liver abscesses in patients with sphincterotomy or bilio-enteric anastomosis.[105] Moreover, HCC situated near the gall bladder or biliary structure can be treated by a non-thermal method of ablation, such as electroporation (see Technological advances).

Tumour invisibility at ultrasonography is one of the main limitations of percutaneous ablation. However, several methods have been proposed to overcome this limitation. Firstly, creation of artificial ascites or artificial pleural effusion could help to treat these patients.[106] Several teams used contrast-enhanced ultrasonography to better delineate the target of ablation.[107] Moreover, fusion imaging between pretherapeutic CT or MRI with ultrasonography has been associated with a high rate of success in ablation of HCC that is invisible or poorly visible with ultrasonography alone.[108] More recently, a new fusion image technology, fluoroscopic real-time guidance was used to place applicators inside or around the overlay of tumours previously segmented, by pre-ablative enhanced 3D cone beam CT acquisition, allowing successful ablations of targets poorly visible with ultrasonography. Finally, one of the main limitations in the treatment of patients with HCC is impairment of liver function. Treatment of Child Pugh C patients with percutaneous ablation seems useless, since patients will die from liver failure and not from HCC progression and because of the risk of worsening of liver failure after ablation.[109] The role of percutaneous ablation in Child Pugh B patients is subject to serious discussion; these patients have been safely treated in several series published worldwide, but have also been systematically associated with decreased overall survival; thus, the balance between risk of death due to liver failure and HCC progression sometimes remains difficult to assess in this heterogeneous population.[30,50]

Key point

Several new methods of percutaneous ablation (multi-bipolar no-touch RFA, microwave, irreversible electroporation, cryoablation, etc.) seek to increase the safety and efficacy of these treatments and to extend their indications into the algorithm of HCC treatment.

Extension of ablation criteria to hepatocellular carcinoma

Size: Extension of criteria for liver transplantation and liver resection has already been proposed in the literature, with different goals according to the situation: i) for liver transplantation the goal is to reduce tumour recurrence and maintain overall survival compared to patients within the classical criteria; ii) for liver resection the goal is to limit the morbidity and improve survival in patients receiving palliative treatment. For percutaneous ablation, extension of criteria should be proposed to non-resectable patients based on technical feasibility and safety, and with the aim of achieving better overall survival than palliative treatments and, in the best scenario, the same overall survival as liver resection.[110] Classically, RFA has been proposed for tumours of less than 5 cm. However, several groups from both the East and West have reported series of patients, potentially with HCC between 5 to 10 cm, and potentially treatable by multipolar RFA or MWA performed alone, with complete ablation obtained in 80 to 87% of cases and one- and three-year overall survival of 68 to 94% and 70 to 81%, respectively (Fig. 4).[33,111–114] These results were obtained mainly in non-resectable patients and with acceptable increased morbidity compared to RFA of small tumours. Combinations of TACE and RFA have also been proposed to treat large HCC (see TACE and RFA chapter).

Numbers: Guidelines have been proposed for using RFA to treat bi- or trifocal HCC of less than 3 cm not amenable to liver transplantation. A multinodular form was associated with higher tumour recurrence in most clinical studies and with decreased overall survival in some of them.[50,115,116] Some authors increased the number of tumours beyond guidelines, with more than three HCC treated by RFA or MWA, and satisfactory long-term survival.[50,114,115,117] However, the increase in the number of lesions ablated is limited by the time of the procedure and the risk of liver failure induced by multiple ablations.

Key point

Ablation therapies combined with transarterial chemo-embolisation may improve sustained local control of tumours of over 3 cm in diameter compared to monopolar RFA.

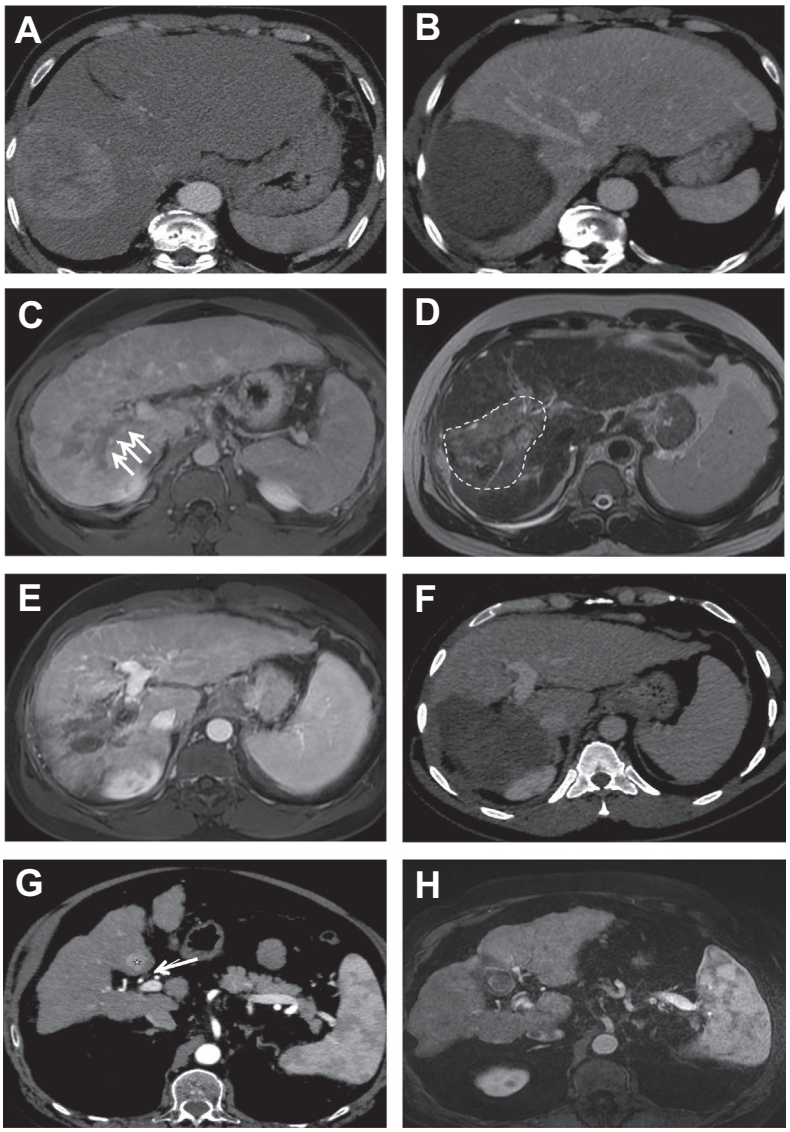

Fig. 4. Examples of extension of ablation criteria. *Case 1*: Large single 8.5 cm HCC in the right hepatic lobe in a 50-year-old man with hepatitis B cirrhosis (A). Surgical resection was contraindicated because of severe portal hypertension. The patient was finally treated with multibipolar RFA. Portal phase CT images after two multibipolar RFA sessions showed complete ablation with a large necrotic unenhanced area encompassing the targeted tumour (B). *Case 2*: Infiltrative HCC and vascular invasion in a 42-year old man with hepatitis B cirrhosis (BCLC C). MR images showed an infiltrative pattern of the right liver with tissular hypervascular tumour thrombus (arrows) in the right portal branches (C). Note that the head of the thrombus is located at the ostium of the right portal branch. Irreversible electroporation (IRE) of the head of the thrombus was performed first in order to stop vascular invasion and to avoid contralateral tumour dissemination. One-month post-IRE, MR images showed the electroporated area (dotted lines) with T2 hyperintensity (D). Note devascularisation of tumour thrombus on contrast-enhanced MR images (E). Large multibipolar RFA of the remnant right liver was subsequently performed. Follow-up CT images (F) showed complete destruction of the right liver, with patency of the main and left portal veins. More than 1 year after the first IRE, the patient was alive without a detectable tumour. *Case 3*: A 71-year-old man with alcoholic cirrhosis and 2 cm typical HCC at the arterial phase of the CT scan (star) (G). The lesion was located at the hilar side of segment IV, in contact with the main bile duct (arrow), the reason for choosing IRE in this case, which is a contraindication for thermal ablation. One month post-IRE, MR images showed T1 hyperintensity of the treated tumour, without residual arterial enhancement (H), along with T2 hypo-intensity indicating complete treatment. After 20 months of follow-up, the patient was tumour-free and the main bile duct was not enlarged or narrowed. CT, computed tomography; HCC, hepatocellular carcinoma; IRE, irreversible electroporation; MR, magnetic resonance; RFA, radiofrequency ablation.

Metastases: In general, metastases of HCC are not amenable to percutaneous ablation because of their multiplicity and rapid growth or concomitant intrahepatic multifocal progression. When confronted with oligo-metastasis, several authors have shown the feasibility and safety of percutaneous ablation of lung, adrenal, bone or even lymph node metastasis of HCC.[118–122] The best clinical scenario for proposing such treatment is a single metastasis that could be safely ablated in a patient without intrahepatic disease, or with limited controllable intrahepatic disease.[120] However, it is not clear whether such an approach leads to a benefit for patients compared to systemic therapy alone.[123,124]

Portal venous thrombosis and infiltrative tumours: Infiltrative HCC and HCC with portal vein thrombosis are classically treated either by radio-embolisation or systemic treatment. Some preliminary reports have shown the possibility of treatment using percutaneous ablation on selected patients with localised infiltrative HCC, or HCC with portal tumour thrombosis, with complete ablation in 74 to 82% of cases, but a high rate of tumour recurrence and poor overall survival (Fig. 4).[125–128] Currently, insufficient data are available and more studies are required to validate such aggressive percutaneous approaches.

Technological advances

No-touch multibipolar radiofrequency ablation

No-touch multibipolar RFA is based on sequential activation of two separate electrodes that lead to centripetal diffusion of heat, in contrast to monopolar devices that lead to centrifugal diffusion of heat (Fig. 1).[8] Multibipolar RFA helps to control the extent and shape of the ablation area; the no-touch concept seeks to place the electrode outside the tumour to avoid puncture of the tumour in order to decrease the risk of tumour seeding and to increase the ablation margin around the HCC.[129] This technique efficiently ablates larger tumours between 3 and 5 cm. In the first retrospective cohorts of HCC of less than 5 cm, treated by multibipolar RFA, HCCs larger than 3 cm or in the vicinity of large vessels were no longer predictive factors in local tumour progression.[130,131] Moreover, liver explants revealed a higher rate of complete tumour necrosis after multibipolar no-touch RFA (90%) compared to monopolar RFA (50%).[12] The no-touch strategy is also useful for safely treating subcapsular HCC and exophytic HCC.[132] Multibipolar no-touch RFA would appear be a potential competitor to liver resection in HCC between 3 and 5 cm, but no direct comparison has yet been performed. A retrospective multicentric study compared monopolar RFA with multibipolar no-touch RFA and concluded that multibipolar no-touch RFA

was associated with a lower rate of local tumour recurrence, even in cases of small HCC <3 cm.[133] A multicentric randomised controlled study comparing classical RFA with multibipolar no-touch RFA is ongoing (ARCEMVIN trial, NCT01008657).

Microwave ablation

MWA is a thermal technique that creates an electromagnetic field around a monopolar electrode (centrifugal ablation), inducing homogeneous heating and coagulation necrosis (Fig. 1). MWA heats up more rapidly, reaching a higher temperature than RFA, and consequently has the potential advantage of simultaneously treating more lesions in a shorter time than RFA. Theoretically, MWA leads to a larger ablation area compared to monopolar RFA and has been used to treat lesions sometimes larger than 5 cm.[113] However, in the first retrospective series published on first-generation devices, it was not clear whether MWA was superior, or even equivalent to RFA.[134–136] The only randomised controlled trial comparing monopolar RFA with a first-generation device of MWA failed to show the superiority of MWA, with a trend toward superiority for RFA, with fewer sessions required to achieve complete ablation (Table 4).[137] Recently, results using next-generation devices of MWA have been reported, with complete ablation in 95 to 100% of cases, with local recurrence varying from 10 to 13% at three years, distant recurrence from 27% to 59% at three years and overall survival from 52 to 86% at three years (Table 4).[117,138–141] Morbidity and mortality were similar to RFA.[142] Interestingly, one study suggested that MWA could treat HCC adjacent to large vessels without increasing the risk of local progression.[14] Currently, MWA seems to be an alternative to monopolar RFA in HCC less than 3 cm (especially multiple HCC, since MWA helps to quickly treat multifocal disease), whereas no strong evidence indicates the superiority of MWA compared to RFA in treating HCC of 3 to 5 cm.

Irreversible electroporation (IRE)

IRE is a non-thermal ablative method that delivers short electric pulses of high power and intensity between two electrodes (convergent centripetal technique) and induces definitive pores across the cellular bilipid membrane, leading to cell death, mainly by apoptosis due to loss of cell homeostasis (Fig. 1).[8] General anaesthesia is required, with muscular blockade in patients with sinusoidal cardiac rhythm, since IRE is synchronised with the heartbeat to avoid cardiac arrhythmia.[8] Accordingly, contraindications to IRE are cardiac arrhythmia and pace-makers. The absence of heat reduces the risk of thermal injury of the adjacent structure. Thus, the efficacy of IRE ablation is no longer affected by the heat sink effect. One of the main advantages of IRE is the ability to treat HCC situated at at-risk localisations, such as biliary structures that classically preclude thermal ablation (Fig. 4).[143] The rare cases of liver explant analysed post-IRE showed complete tumour necrosis and preservation of the skeleton of connective tissue, vessels and bile ducts.[144] Most series that described IRE treatment of liver tumours mixed primary liver tumours (HCC, cholangiocarcinoma) and liver metastasis, or else analysed only a small number of patients with HCC, with short follow-up.[143,145–147] We described IRE for HCC in 58 patients that were not treatable by thermal techniques, with complete ablation observed in 92% of cases, and 70% local tumour progression-free survival at one year, alongside a good safety profile (Table 4).[139] Moreover, some authors suggested that IRE leads to less frequent liver failure than thermal ablation, and enables treatment of a larger number of Child Pugh B patients.[148,149] Overall, it seems that IRE could be indicated for HCC not amenable to thermal techniques, such as RFA or MWA, due to tumour localisation or liver failure. Larger series of patients with longer follow-up are required to assess the long-term efficacy of this method.

Cryoablation

Cryoablation is a thermal percutaneous technique that uses a device with argon or helium gas to decrease the temperature by the Thomson effect around the needle and induce tissue freezing and vascular injury (Fig. 1).[150] Interestingly, an ice ball can be visualised with US, CT or MRI during ablation and helps to monitor treatment and control the ablative margin. Initial studies reported an increased rate of adverse events after cryoablation, including cryoshock leading to multiorgan failure, and decreased efficacy compared to RFA.[151–154] However, these data were reported in first-generation cryoablation devices (using liquid nitrogen or cryogen) that mixed HCC with metastasis, and percutaneous ablation mixed with laparoscopic cryoablation.[152–154] A recent monocentric study that included a high number of patients has provided data on the safety and efficacy of cryoablation for HCC (Table 4).[155] Finally, one randomised controlled trial showed a slight decrease in local relapse after cryoablation compared to RFA for HCC of less than 4 cm (Table 4).[156]

Role of combined treatment

Percutaneous treatment is associated with a high risk of local (up to 30%) and distant (up to 80%) tumour recurrence at five years; different combinations of treatments have been tested to increase local control and decrease distant recurrence.

TACE and RFA

The combination of TACE with percutaneous RFA has been proposed to increase local control. Several retrospective series showed that this combination is feasible and safe. The main target of the combination of TACE and RFA is HCC over 3 cm,

Table 4. Retrospective and randomised controlled studies of electroporation, microwave ablation and cryoablation.

Article	Number of patients per arm	Number of sessions	Complete necrosis after ≥1 session	Local tumour recurrence	Overall survival	Commentaries
Randomised controlled trial						
Wang C, *et al.* *Hepatology* 2014[156]	180 RFA *vs.* 180 cryo 1 to 2 HCC <5 cm	2 RFA *vs.* 2 cryo	95.6% RFA *vs.* 98.3% cryo ($p = 0.126$)	11% in RFA *vs.* 7% at 3 yr ($p = 0.043$)	66% at 3 yr, 38% at 5 yr *vs.* 67% at 3 yr, 40% at 5 yr ($p = 0.747$)	Same rate of major AE (4%)
Shibata T, *et al.* *Radiology* 2002[137]	36 RFA *vs.* 36 MWA	1.1 RFA *vs.* 2.4 MWA ($p < 0.001$)	96% in RFA *vs.* 89% in MWA ($p = 0.26$)	10% in RFA *vs.* 24% in MWA at 2 yr ($p = 0.20$)	Not reported	MWA device of first generation Low numbers of patients
Article	**Number of patients**	**Complete response**	**Local**	**Distant**	**Overall survival**	**Morbidity, mortality**
Cryowave ablation						
Rong G, *et al.* *PLoS One* 2015[155]	866 cryo HCC in Milan criteria	96.1%	22.1% at 3 yr, 24.2% at 5 yr (multiple tumours, HCC >30 mm)	48.6% at 3 yr, 64.9% at 5 yr (multiple tumours, HCC >30 mm, low platelets)	80.6% at 3 yr and 60.3% at 5 yr (age, HCC family history, high HBV DNA, multiple HCC)	Major AE, 2.4% 0% death
Irreversible electroporation						
Sutter O, *et al.* *Radiology* 2017[149]	58 IRE HCC whatever the size	92%	20% at 1 yr (AFP >200)	21% at 1 yr	96% at 1 yr	Major AE 5%, 1.8% death
Microwave ablation						
Dong B, *et al.* *AJR* 2002[134]	234 MWA HCC whatever the size and numbers. First generation device	89%	17% of local recurrence (follow-up?)	24% of distant recurrence (follow-up?)	73% at 3 yr and 57% at 5 yr	Major AE 0%, 0% death
Lu MD, *et al.* *J Gastro* 2005[136]	49 MWA HCC within Milan criteria First generation device	94.9%	11.8% at 3 yr	69.4% at 4 yr	50.5% at 3 yr, 36.8% at 4 yr	Major AE 4% 0% death
Ohmoto K, *et al. J Gastro Hepatol* 2009[135]	40 MWA HCC within Milan criteria	NA	9% at 3 yr, 19% at 4 yr	72% at 3 yr, 78% at 4 yr	49% at 3 yr, 39% at 4 yr	Major AE 8%, 0% death
Zhang L, *et al.* *PLoS One* 2013[140]	77 MWA HCC within Milan criteria	100%	10.5% at 5 yr	80.5% at 5 yr	51.7% at 3 yr, 38.5% at 5 yr	Major AE 2.6% 0% death
Ding J, *et al.* *Eur J Radiology* 2013[141]	113 MWA HCC within Milan criteria	100%	10.9% at 3 yr	26.5% at 3 yr	77.6% at 3 yr	Major AE 2.7% 0% death
Abdelaziz A, *et al. Surg Endosc* 2014[138]	66 MWA HCC within Milan criteria	96%	3.9% at 2 yr	13.6% at 2 yr	86.1% at 2 yr	Major AE 3.2%,0% death
Ma S, *et al.* *J Cancer Res Clin Oncol* 2016[117]	433 MWA HCC whatever the size and number	94.9%	12.9% at 3 yr	58.9% at 3 yr	58.7% at 3 yr (HCC >50 mm, high AFP)	Major AE 5.3%, 0% death

AE, adverse events; AFP, alpha-fetoprotein; cryo, cryoablation; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IRE, irreversible electroporation; MWA, microwave ablation; RFA, radiofrequency ablation.

where tumour ablation using monopolar RFA is frequently incomplete and is associated with a higher rate of local recurrence.[157] Several retrospective studies have suggested that a combination of TACE and RFA in HCC between 3 to 5 cm increased local control compared to monopolar RFA alone.[158–161] In contrast, in small HCC of less than 3 cm, combination therapy seems ineffective, mainly due to the high rate of complete necrosis after RFA alone.[162,163] Randomised controlled trials showed better recurrence-free survival and overall survival for RFA + TACE compared to RFA alone, mainly in large HCC.[159,162,164] However, these randomised controlled trials had several biases, were mostly monocentric Asian heterogeneous studies, often with a small number of patients, and included HCC of up to 7 cm.[159] Therefore, the validity of these results in a Western cirrhotic population with HCC between 3 and 5 cm remains controversial.

Systemic and percutaneous treatment combination

The combination of systemic therapy with percutaneous ablation aimed to reduce the incidence of distant tumour recurrence related both to intrahepatic metastasis from the initial tumour and *de novo* carcinogenesis in cirrhotic liver. The STORM trial compared sorafenib *vs.* placebo in the adjuvant setting of 1,114 patients treated curatively by resection or RFA, but failed to improve

recurrence-free survival.[165] Only 214 patients in this trial were treated by RFA but, in this subgroup, sorafenib failed to show efficacy as an adjuvant treatment. The advent of immunotherapy targeting immune checkpoints, such as CTLA4 or PD1/PDL1 antibody, has improved survival in advanced stages of several types of solid cancer.[166] The rationale for combining RFA and immunotherapy is based on boosting the immune response that is triggered by necrosis resulting from percutaneous treatment. A combination of RFA with [131I] metuximab, a radioimmunoconjugate labelling metuximab directed against CD147 with iodine-131, reduced time to recurrence, compared to RFA alone, in a monocentric randomised controlled study.[167] A pilot study combined antibody against CTLA4 with RFA and showed an accumulation of CD8 cells in the tumour and a signal for efficacy in terms of radiological response.[168] However, additional trials are required to confirm these interesting results.

Conclusion

Percutaneous treatments are approaching the age of maturity for the treatment of HCC. Monopolar RFA is still impaired by local and distant tumour recurrence, and several new ablation techniques, as well as new combinations of treatments, have been proposed to improve prognosis; however, they need to be rigorously studied in randomised controlled trials *vs.* the treatment of reference. However, randomised controlled trials are difficult to perform in such a rapidly moving field. For ablative techniques, completeness of tumour control appears to be the most relevant primary endpoint of efficacy, with the rate of local recurrence and overall recurrence as secondary endpoints. We are no longer simply dealing with one technique of percutaneous ablation (monopolar RFA), but we now have a wide choice of techniques (monopolar RFA, multibipolar RFA, IRE, MWA, cryoablation, *etc.*) that increase the armamentarium available to curatively treat the maximum number of patients with HCC within Milan criteria. Consequently, a large range of percutaneous ablative technologies needs to be available in each centre dealing with HCC. This increased ability to safely ablate a larger number of patients will avoid the drift from curative to palliative treatment observed in a percentage of patients with HCC within Milan criteria. Moreover, we are also observing a changing paradigm in the role of ablation in the complex discussion of curative treatment. Overall, the question of liver resection, percutaneous ablation and liver transplantation should not be seen as a cause for disagreement, but rather, as a puzzle for a multidisciplinary tumour board, that will lead to propositions for safe curative treatment for a large number of patients while preserving the number of grafts used. Moreover, treatment of larger tumours, sometimes with metastases or portal vein thrombosis, pushes the concept of curative ablation into a grey zone between curative and palliative percutaneous treatment. Finally, hepatobiliary surgeons are implementing training in liver surgery in order to propagate worldwide surgical techniques for safely treating patients with HCC. The same principle should be applied to percutaneous interventional radiology, to train young interventional radiologists, and to test and disseminate new ablation techniques at centres throughout the world.

Conflict of interest

O Seror received personal fees and non-financial support from Angiodynamics, Olympus, and Bayer Schering Pharma and received personal fees from GE as a consultant. N Ganne and P Nahon received personal fees from Bayer Schering Pharma. JC Nault and O Sutter has no conflict of interest to declare.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Writing and approval of this review (JCN, OSu, PN, NGC, OSe).

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