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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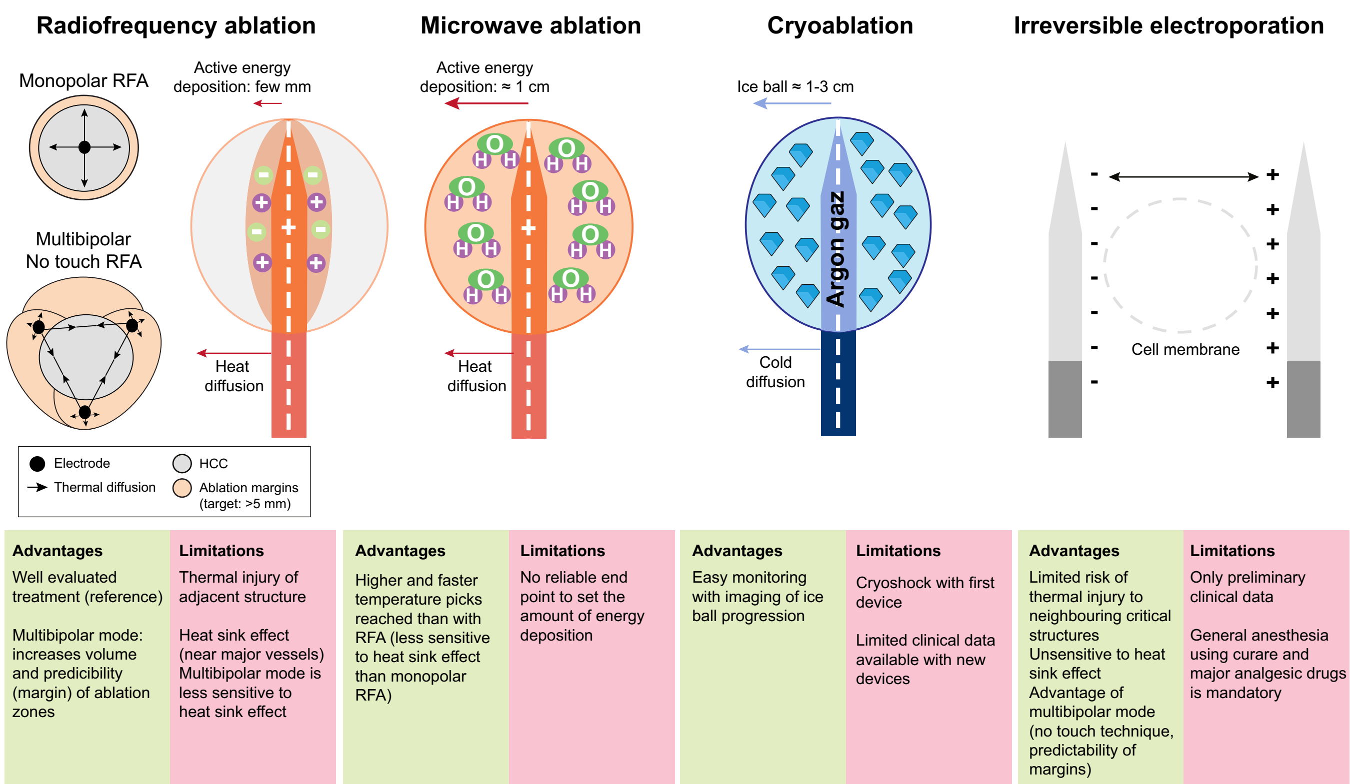

Fig. 1. Description of the different methods of percutaneous ablation. We describe the different methods of percutaneous ablation (thermal and non-thermal), as well as their advantages and limitations. HCC, hepatocellular carcinoma; RFA, radiofrequency ablation.

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.