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Thermal ablation of hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the fifth most common cause of cancer, and its incidence is increasing worldwide because of the dissemination of hepatitis B and C virus infection. Patients with cirrhosis are at the highest risk of developing HCC and should be monitored every 6 months to diagnose the tumour at an early, asymptomatic stage. Patients with early-stage HCC should be considered for any of the available curative therapies, including surgical resection, liver transplantation and percutaneous image-guided ablation. Liver transplantation is the only option that provides cure of both the tumour and the underlying chronic liver disease. However, the lack of sufficient liver donation greatly limits its applicability. Resection is the treatment of choice for HCC in non-cirrhotic patients, who account for about 5% of the cases in western countries. However, in patients with cirrhosis, candidates for resection have to be carefully selected to reduce the risk of postoperative liver failure. It has been shown that a normal bilirubin concentration and the absence of clinically significant portal hypertension are the best predictors of excellent outcomes after surgery. However, less than 5% of cirrhotic patients with HCC fit these criteria. Image-guided percutaneous ablation is the best therapeutic choice for non-surgical patients with early-stage HCC. While ethanol injection has been the seminal percutaneous technique, radiofrequency ablation has emerged as the most effective method for local tumour destruction and is currently used as the primary ablative modality at most institutions.

Keywords: *Hepatocellular carcinoma; ablation; radiofrequency.*

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cause of cancer, and its incidence is increasing worldwide because of the dissemination of hepatitis B and C virus infection[1−5]. Patients with cirrhosis are at the highest risk of developing HCC and should be monitored every 6 months to diagnose the tumour at an asymptomatic stage[6−8]. In most solid malignancies, tumour stage at presentation determines prognosis and treatment management. Most patients with HCC, however, have two diseases — liver cirrhosis and HCC — and complex interactions between the two have major implications for prognosis and treatment choice[9]. The system that links staging with treatment modalities in HCC is the Barcelona Clinic Liver Cancer (BCLC) staging system[4,5,10] (Table 1). It includes variables related to tumour stage, liver functional status (Child−Pugh classification, Table 2), physical status and cancer related symptoms (World Health Organization performance status, Table 3)[11,12].

Table 1 BCLC staging system in patients diagnosed with HCC [4,5,10]

Very early stage	PS 0, Child−Pugh A, single HCC <2 cm
Early stage	PS 0, Child−Pugh A−B, single HCC or 3 nodules <3 cm
Intermediate stage	PS 0, Child−Pugh A−B, multinodular HCC
Advanced stage	PS 1−2, Child−Pugh A−B, portal neoplastic invasion, nodal metastases, distant metastases
Terminal stage	PS >2, Child−Pugh C

HCC, hepatocellular carcinoma; PS, performance status.

Table 2 Child—Pugh classification of severity of liver disease[11]

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Mild/moderate	Severe/refractory
Bilirubin (mg/dl)	≤2	2–3	>3
Albumin (g/dl)	>3.5	2.8–3.5	<2.8
Prothrombin time			
Seconds over control	<4	4–6	>6
INR	<1.7	1.7–2.3	>2.3
Encephalopathy	None	Mild	Severe

A total score of 5–6 is considered grade A (well-compensated disease); 7–9 is grade B (significant functional compromise); and 10–15 is grade C (decompensated disease).

Table 3 World Health Organization Performance Status grades[12]

Stage 0	Fully active, normal life, no symptoms
Stage 1	Minor symptoms, able to do light activity
Stage 2	Capable of self-care but unable to carry out work activities; up for more than 50% waking hours
Stage 3	Limited self care capacity; confined to bed or chair >50% waking hours
Stage 4	Completely disabled; confined to bed or chair

In the BCLC system, early-stage HCC includes patients with WHO performance status of 0, preserved liver function (Child—Pugh class A or B), and solitary tumour or up to 3 nodules each smaller than 3 cm in size, in the absence of macroscopic vascular invasion and extrahepatic spread. If the patient has Child—Pugh class A cirrhosis and a solitary tumour smaller than 2 cm in size, the stage may be defined as very early. Patients with multinodular HCC with neither vascular invasion nor extrahepatic spread are classified as intermediate-stage according to the BCLC staging system, provided that they have a performance status of 0 and Child—Pugh class A or B cirrhosis[3–5]. Patients with portal vein invasion or extrahepatic disease are classified as advanced stage. The terminal stage includes patients who have either severe hepatic decompensation (Child—Pugh class C) or performance status greater than 2 (Table 1).

Treatment options for early-stage hepatocellular carcinoma

Patients with early-stage HCC can benefit from curative therapies, including surgical resection, liver transplantation and percutaneous ablation, and have the possibility of long term cure, with 5-year survival figures ranging 50–75%[5].

Resection is the treatment of choice for HCC in non-cirrhotic patients, who account for about 5% of the cases in western countries. However, in patients with cirrhosis, candidates for resection have to be carefully selected to reduce the risk of postoperative liver failure. It has been shown that a normal bilirubin concentration and the absence of clinically significant portal hypertension are the best predictors of excellent outcomes after surgery[13]. In experienced hands, such patients — less than 5% of cirrhotic patients with HCC — have treatment-related mortality of less than 1–3% and may achieve a 5-year survival higher than 70%[13–15]. In contrast, survival drops to less than 50% at 5 years in patients with significant portal hypertension, and to less than 30% at 5 years in those with both adverse factors (portal hypertension and elevated bilirubin)[13].

Liver transplantation is the only option that provides cure of both the tumour and the underlying chronic liver disease. It is recognized as the best treatment for patients with solitary HCC smaller than 5 cm in the setting of decompensated cirrhosis and for those with early multifocal disease (up to 3 lesions, none larger than 3 cm)[1]. The reported outcomes of patients who actually underwent transplantation are better than those of patients submitted to resection, especially if the substantially lower rates of tumour recurrence — less than 10–20% versus more than 70% at 5 years — are considered[13,16]. Overall survival, however, decreases on an intention-to-treat perspective[13,16–18]. In fact, because of the lack of sufficient liver donation, there is always a waiting period between listing and transplantation, during which the tumour may grow and develop contraindications to transplantation (vascular invasion, extrahepatic spread). The rate of dropouts may be as high as 25% if the waiting list is longer than 12 months[19]. This difficulty may be in part overcome by living donation, that, however, has inherent limitations and requires a highly skilled surgical team[16].

Image-guided percutaneous ablation is currently accepted as the best therapeutic choice for non-surgical patients with early-stage HCC[4,5]. Over the past two decades, several methods for chemical ablation or thermal tumour destruction have been developed and clinically tested. These include the injection of ethanol or acetic acid and the administration of localized heating (radiofrequency, microwave, laser ablation) or freezing (cryoablation).

The seminal technique used for local ablation of HCC is percutaneous ethanol injection (PEI). Ethanol induces coagulation necrosis of the lesion as a result of cellular dehydration, protein denaturation, and chemical occlusion of small tumour vessels. PEI is a well-established technique for the treatment of nodular-type HCC. HCC nodules have a soft consistency and are surrounded by a firm cirrhotic liver. Consequently, injected ethanol diffuses within them easily and selectively, leading to complete necrosis of about 70% of small lesions[20]. Although there have not been any RCT comparing PEI and best supportive care or PEI and surgical resection, several retrospective studies have provided indirect evidence that PEI improves the natural history of HCC: the
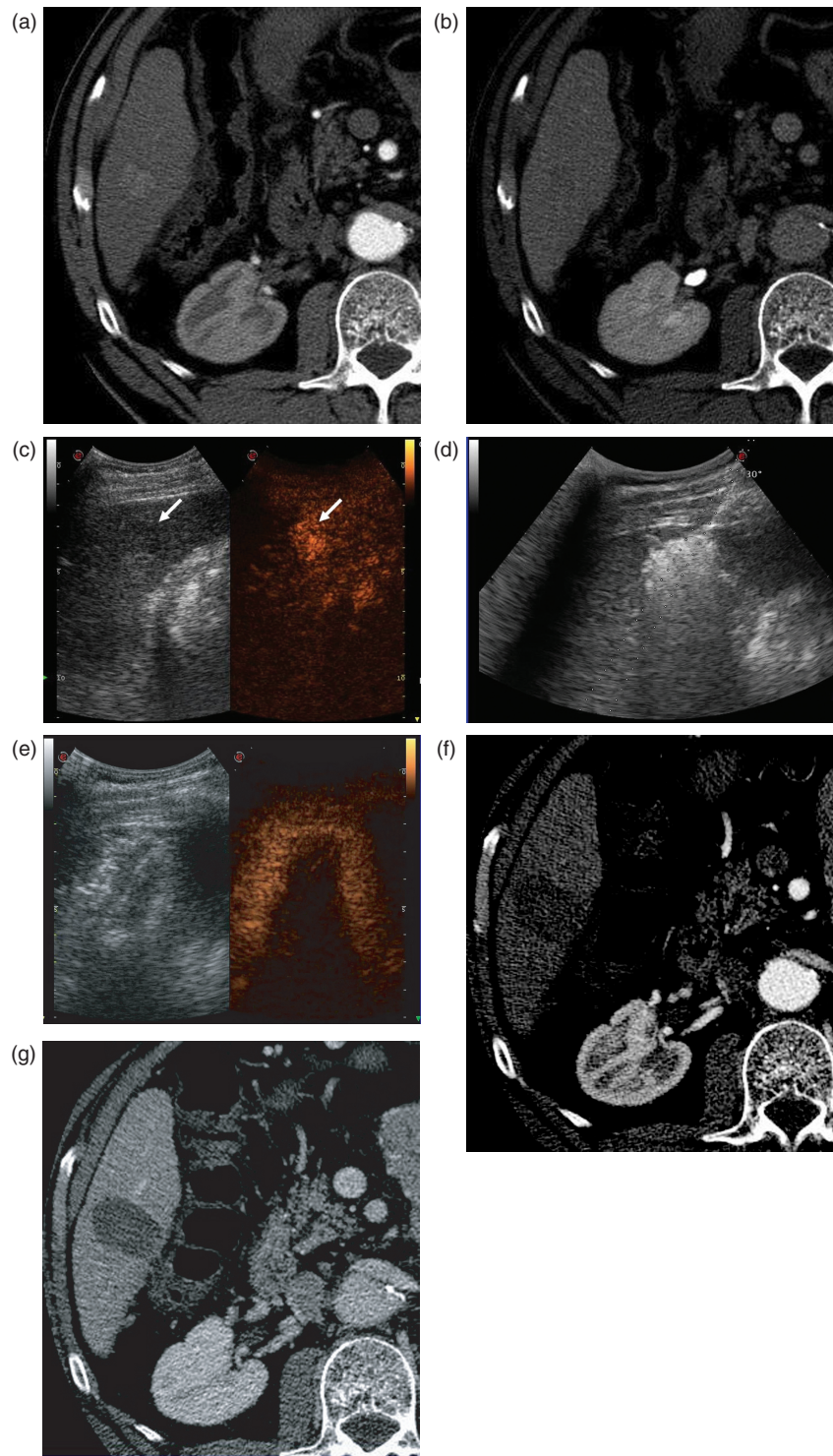
Figure 1 **Complete response of hepatocellular carcinoma treated with radiofrequency ablation. Pre-treatment CT obtained in the arterial (a) and the delayed phase (b) shows the lesion as a small hypervascular nodule (a). Injection of an ultrasound contrast agent confirms arterial-phase enhancing tumour (arrow, c). B-mode low-mechanical index image is shown in the left side of the image; the contrast-specific mode during the arterial phase is shown in the right side. The tumour is treated with RF ablation under US guidance. At the end of the procedure, a large hyperechoic cloud covering the tumour as well as a cuff of surrounding liver parenchyma is seen on US (d). Contrast-enhanced ultrasound study performed at the end of the procedure shows the ablation zone as an unenhanced area completely covering the tumour. Peri-ablation enhancement is also seen, representing reactive hyperaemia (e). On CT images obtained in the arterial (f) and the portal venous phase (g) 1 month after treatment, the tumour is replaced by a non-enhancing ablation zone. The findings are consistent with complete response.**

long-term outcomes of patients with small tumours who were treated with PEI were similar to those reported in surgical series, with 5-year survival rates ranging 41–60% in Child A patients[20–25]. Of importance, two cohort studies and one retrospective case–control study comparing surgical resection and PEI failed to identify any difference in survival, despite the fact that the patients in PEI groups had poorer liver function[26–28].

The major limitation of PEI is the high local recurrence rate, which may reach 33% in lesions smaller than 3 cm and 43% in lesions exceeding 3 cm[29,30]. The injected ethanol does not always accomplish complete tumour necrosis because of its inhomogeneous distribution within the lesion — especially in the presence of intratumoural septa — and the limited effect on extracapsular cancerous spread. Moreover, PEI is unable to create a safety margin of ablation in the liver parenchyma surrounding the nodule, and therefore may not destroy tiny satellite lesions that — even in small tumours — may be located in close proximity to the main nodule.

Thermal ablation

Application of localized heating or freezing enables in situ destruction of malignant liver tumours preserving normal liver parenchyma. The thermal ablative therapies involved in clinical practice can be classified as either hepatic hyperthermic treatments — including radiofrequency (RF) ablation, microwave ablation, and laser ablation — or hepatic cryotherapy. Hepatic hyperthermic treatments are mostly performed via a percutaneous approach; until recently, an open or laparoscopic approach was widely adopted for hepatic cryotherapy.

The thermal damage caused by heating is dependent on both the tissue temperature achieved and the duration of heating. Heating of tissue at 50–55°C for 4–6 min produces irreversible cellular damage. At temperatures between 60°C and 100°C near immediate coagulation of tissue is induced, with irreversible damage to mitochondrial and cytosolic enzymes of the cells. At more than 100–110°C, tissue vaporizes and carbonizes[31]. For adequate destruction of tumour tissue, the entire target volume must be subjected to cytotoxic temperatures. Different physical mechanisms are involved in the hepatic hyperthermic treatments in order to generate a lethal temperature. A common important factor that affects the success of thermal ablation is the ability to ablate all viable tumour tissue and possibly an adequate tumour-free margin. Ideally, a 360°, 0.5–1-cm-thick ablative margin should be produced around the tumour[31]. This cuff would ensure that microscopic invasions around the periphery of a tumour have been eradicated. Thus, the target diameter of an ablation, or of overlapping ablations, must be larger than the diameter of the tumour undergoing treatment[32].

Thermal ablation is usually performed under intravenous sedation with standard cardiac, pressure, and oxygen monitoring. Targeting of the lesion can be performed with ultrasound, computed tomography (CT), or magnetic resonance (MR) imaging. The guidance system is chosen largely on the basis of operator preference and local availability of dedicated equipment such as CT fluoroscopy or open MR systems. Real-time ultrasound/CT (or ultrasound/MR imaging) fusion imaging substantially improves the ability to guide and monitor liver tumour ablation procedures. Current virtual navigation systems can help to define the extent of the liver tumour burden, plan and simulate the insertion of the needle, and predict the amount of the induced necrosis. During the procedure, important aspects to be monitored include how well the tumour is being covered and whether any adjacent normal structures are being affected at the same time. While the transient hyperechoic zone that is seen at ultrasound within and surrounding a tumour during and immediately after RF ablation can be used only as a rough guide to the extent of tumour destruction, MR is currently the only imaging modality with validated techniques for real-time temperature monitoring. At the end of the procedure, the needle track can be ablated in most systems, aimed at preventing any tumour cell dissemination. Contrast-enhanced ultrasound performed at the end of the procedure may allow an initial evaluation of the effect of the treatment. However, contrast-enhanced CT and MR imaging are recognized as the standard modalities to assess treatment outcome. CT and MR images obtained after treatment show successful ablation as a non-enhancing area with or without a peripheral enhancing rim. The enhancing rim that may be observed along the periphery of the ablation zone appears a relatively concentric, symmetric area, with smooth inner margins. This is a transient finding that represents a benign physiologic response to thermal injury (initially, reactive hyperaemia; subsequently, fibrosis and giant cell reaction). Benign peri-ablational enhancement needs to be differentiated from irregular peripheral enhancement due to residual tumour that occurs at the treatment margin. In contrast to benign peri-ablational enhancement, residual unablated tumour often grows in scattered, nodular, or eccentric patterns[33]. Later follow-up imaging studies should be aimed at detecting the recurrence of the treated lesion (i.e. local tumour progression), the development of new hepatic lesions, or the emergence of extrahepatic disease.

Radiofrequency ablation

The goal of RF ablation is to induce thermal injury to the tissue through electromagnetic energy deposition. The patient is part of a closed-loop circuit, that includes an RF generator, an electrode needle, and a large dispersive electrode (ground pads). An alternating electric field is created within the tissue of the patient. Because of the relatively high electrical resistance of tissue in comparison with the metal electrodes, there is marked agitation of the ions present in the target tissue that surrounds the

electrode, since the tissue ions attempt to follow the changes in direction of alternating electric current. The agitation results in frictional heat around the electrode. The discrepancy between the small surface area of the needle electrode and the large area of the ground pads causes the generated heat to be focused and concentrated around the needle electrode. Several electrode types are available for clinical RF ablation, including internally cooled electrodes and multitined expandable electrodes with or without perfusion[33].

RF ablation has been the most widely assessed alternative to PEI for local ablation of HCC[34]. Histologic data from explanted liver specimens in patients who underwent RF ablation showed that tumour size and the presence of large (3 mm or more) abutting vessels significantly affect the local treatment effect. Complete tumour necrosis was pathologically shown in 83% of tumours less than 3 cm and 88% of tumours in a non-perivascular location[35]. Three RCTs compared RF ablation versus PEI for the treatment of early-stage HCC[36–38]. The first trial, performed in European centres, failed to show a statistically significant difference in overall survival between patients who received RF ablation and those treated with PEI[36]. However, survival advantages were identified in a subgroup analysis of a trial coming from Taiwan[37] and in a Japanese study, although in the latter the survival benefit was not confirmed in the subgroup analysis of patients with solitary tumours[38]. All three investigations showed that RF ablation had a higher local anticancer effect than PEI, leading to better local control of the disease. Therefore, RF ablation appears as the preferred percutaneous treatment for patients with early-stage HCC on the basis of more consistent local tumour control.

Recently, the long-term survival outcomes of RF ablation-treated patients were reported (Table 4). In the first published report, 206 patients with early-stage HCC who were not candidates for resection or transplantation were enrolled in a prospective, intention-to-treat clinical trial[39]. RF ablation was considered as the first-line non-surgical treatment and was actually performed in 187 (91%) of 206 patients. Nineteen (9%) of 206 patients had to be excluded from RF treatment because of the unfavourable location of the tumour. In patients who underwent RF ablation, survival depended on the severity of the underlying cirrhosis and the tumour multiplicity. Patients in Child class A with solitary HCC had a 5-year survival rate of 61%. Three other studies confirmed that the survival of naive patients (i.e. patients who received radiofrequency ablation as primary treatment) with well-compensated cirrhosis bearing early-stage HCC ranged from 43% to 64%[40–42] (Table 4). Of interest, in a randomized trial of RF ablation versus surgical resection in patients with solitary HCC less than 5 cm in diameter, no differences in overall survival rates and cumulative recurrence-free survival rates were observed[43].

RF ablation of HCC is associated with very low mortality rates and acceptable morbidity. Recently, three separate multicentre surveys have reported mortality rates ranging from 0.1% to 0.5%, major complication rates ranging from 2.2% to 3.1%, and minor complication rates ranging from 5% to 8.9%[44]. The most common causes of death were sepsis, hepatic failure, colon perforation, and portal vein thrombosis, while the most common complications were intraperitoneal bleeding, hepatic abscess, bile duct injury, hepatic decompensation, and grounding pad burns[45–47]. Minor complications and side effects were usually transient and self-limiting. An uncommon late complication of RF ablation is tumour seeding along the needle track. In patients with HCC, tumour seeding occurred in 8 (0.5%) of 1610 cases in a multicentre survey[45] and in 1 (0.5%) of 187 cases in a single-institution series[39]. Lesions with subcapsular location and an invasive tumoural pattern, as shown by a poor degree of differentiation, seem to be at higher risk for such a complication[48]. While these data indicate that RF ablation is a relatively safe procedure, a careful assessment of the risks and benefits associated with the treatment has to be made in each individual patient by a multidisciplinary team.

Table 4 *Studies reporting long-term survival outcomes of patients with early-stage hepatocellular carcinoma who underwent percutaneous radiofrequency ablation*

Author and year		No. patients	Survival rates (%)		
			1 year	3 years	5 years
Lencioni *et al*., 2005[39]	Child A, 1 HCC <5 cm or 3 <3 cm	144	100	76	51
	1 HCC <5 cm	116	100	89	61
	Child B, 1 HCC <5 cm or 3 <3 cm	43	89	46	31
Tateishi *et al*., 2005[40]	Naive patients[a]	319	95	78	54
	Non-naive patients[b]	345	92	62	38
Cabassa *et al*., 2006[41]		59	94	65	43
Choi *et al*., 2007[42]	Child A, 1 HCC <5 cm or 3 <3 cm	359	NA	78	64
	Child B, 1 HCC <5 cm or 3 <3 cm	160	NA	49	38

HCC, hepatocellular carcinoma.
[a]Patients who received radiofrequency ablation as primary treatment.
[b]Patients who received radiofrequency ablation for recurrent tumour after previous treatment including resection, ethanol injection, microwave ablation, and transarterial embolization.

Despite the many published reports, some questions concerning image-guided RF ablation in HCC treatment are still unanswered. Some authors have reported that RF ablation may be a safe and effective bridge to liver transplantation[49–52]. However, randomized studies would be needed to determine the advantages and disadvantages of RF ablation with respect to transarterial chemoembolization (TACE) for HCC patients awaiting transplantation. Recent studies have reported encouraging initial results in the treatment of intermediate-size HCC lesions with a combination of RF ablation and balloon catheter occlusion of the tumour arterial supply or prior TACE[53–57]. However, further clinical trials are warranted to determine the survival benefit associated with this approach.

Microwave ablation

Microwave ablation is the term used for all electromagnetic methods of inducing tumour destruction by using devices with frequencies greater than or equal to 900 kHz. The passage of microwaves into cells or other materials containing water results in the rotation of individual molecules. This rapid molecular rotation generates and uniformly distributes heat, which is instantaneous and continuous until the radiation is stopped. Microwave irradiation creates an ablation area around the needle in a column or round shape, depending on the type of needle used and the generating power[58].

The local effect of treatment in HCC was assessed by examining the histological changes of the tumour after microwave ablation[59,60]. In one study, 89% of 18 small tumours were ablated completely[59]. Coagulative necrosis with faded nuclei and eosinophilic cytoplasm were the predominant findings in the ablated areas. There were also areas in which the tumours maintained their native morphological features as if the area was fixed, but their cellular activity was destroyed as demonstrated by succinic dehydrogenase stain. One study compared microwave ablation and PEI in a retrospective evaluation of 90 patients with small HCC[61]. The overall 5-year survival rates for patients with well-differentiated HCC treated with microwave ablation and PEI were not significantly different. However, among the patients with moderately or poorly differentiated HCC, overall survival with microwave ablation was significantly better than with PEI. In a large series including 234 patients, the 3- and 5-year survival rates were 73% and 57%, respectively[62]. At a multivariate analysis, tumour size, number of nodules, and Child–Pugh classification had a significant effect on survival[63]. Only one randomized trial compared the effectiveness of microwave ablation with that of RF ablation[64]. Seventy-two patients with 94 HCC nodules were randomly assigned to RF ablation and microwave ablation groups. Unfortunately, in this study the data were analyzed with respect to lesions and not to patients. Although no statistically significant differences were observed with respect to the efficacy of

the two procedures, a tendency favouring RF ablation was recognized with respect to local recurrences and complications rates.

Laser ablation

The term laser ablation should be used for ablation with light energy applied via fibres directly inserted into the tissue. A great variety of laser sources and wavelengths are available. In addition, different types of laser fibres, modified tips, and single or multiple laser applicators can be used. From a single, bare 400-µm laser fibre, a spherical volume of coagulative necrosis up to 2 cm in diameter can be produced. Use of higher power results in charring and vaporization around the fibre tip. Two methods have been developed for producing larger volumes of necrosis. The first consists of firing multiple bare fibres arrayed at 2-cm spacing throughout a target lesion; the second uses cooled-tip diffuser fibres that can deposit up to 30 W over a large surface area, thus diminishing local overheating[65].

To date, few data are available concerning the clinical efficacy of laser ablation. No randomized trials to compare laser ablation with any other treatment have been published thus far. In one study including 74 patients with early-stage HCC, overall survival rates were 68% at 3 years and 15% at 5 years, respectively[66]. Laser ablation appears to be relatively safe, with a major complication rate less than 2%[67]. The major drawback of current laser technology appears to be the small volume of ablation that can be created with a single-probe insertion. Insertion of multiple fibres is technically cumbersome and may not be feasible in lesions that are not conveniently located. New devices could overcome this limitation.

Conclusions

Several image-guided ablation techniques have been developed to treat non-surgical patients with HCC. These minimally invasive procedures can achieve effective and reproducible tumour destruction with low morbidity. Percutaneous ablation is accepted as the best therapeutic choice for patients with early-stage HCC when resection or transplantation are precluded. On the basis of the current evidence, RF ablation seems to offer higher cumulative survival and recurrence-free survival rates compared with other image-guided treatments and is accepted as the primary ablative modality at most institutions. Further trials are needed to establish the clinical value of image-guided ablation in combination with intra-arterial treatments[68].

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