TOPIC HIGHLIGHT

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Value of radiofrequency ablation in the treatment of hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is a malignant disease that substantially affects public health worldwide. It is especially prevalent in east Asia and sub-Saharan Africa, where the main etiology is the endemic status of chronic hepatitis B. Effective treatments with curative intent for early HCC include liver transplantation, liver resection (LR), and radiofrequency ablation (RFA). RFA has become the most widely used local thermal ablation method in recent years because of its technical ease, safety, satisfactory local tumor control, and minimally invasive nature. This technique has also emerged as an important treatment strategy for HCC in recent years. RFA, liver transplantation, and hepatectomy can be complementary to one another in the treatment of HCC, and the outcome benefits have been demonstrated by numerous clinical studies. As a pretransplantation bridge therapy, RFA extends the average waiting time without increasing the risk of dropout or death. In contrast to LR, RFA causes almost no intraabdominal adhesion, thus producing favorable conditions for subsequent liver transplantation. Many studies have demonstrated mutual interactions between RFA and hepatectomy, effectively expanding the operative indications for patients with HCC and enhancing the efficacy of these approaches. However, treated tumor tissue remains within the body after RFA, and residual tumors or satellite nodules can limit the effectiveness of this treatment. Therefore, future research should focus on this issue.

Core tip: The pivotal role of radiofrequency ablation (RFA) has recently been established among the various treatment strategies for hepatocellular carcinoma (HCC), primarily due to its excellent local tumor control. RFA may be complementary to the other treatments with curative intent for HCC and its beneficial outcomes in patients have been demonstrated in several clinical studies.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most prevalent cancer and the third most frequent cause of cancer-related death worldwide; in 2008 alone, more than 700000 cases of HCC were diagnosed[1]. For most patients HCC develops secondary to hepatic cirrhosis, and is the leading

cause of death among this population[2]. The various geographical incidence of HCC worldwide reflects the presence of different risk factors among different regions. The majority of HCC cases (80%) have occurred in east Asia and sub-Saharan Africa, where the main etiologies are chronic infection with the hepatitis B virus (HBV) and exposure to the fungal aflatoxin B1[1,3]. In particular, the incidence of HCC in China alone accounts for 55% of all cases worldwide[4]. In contrast, hepatitis C virus infection and alcoholism are the major risk factors for HCC in North America, Europe, and Japan[5].

HCC can be cured by liver transplantation, liver resection (LR), or local ablation therapy[6]. Liver transplantation is theoretically the best therapeutic choice for patients who meet the Milan criteria[7]. However, this technique is severely undermined by the shortage of donor organs and hepatectomy remains the first-line treatment for HCC. Nevertheless, only 9% to 29% of patients are able to undergo this procedure because of either poor hepatic reserve secondary to underlying chronic liver disease or a multifocal distribution of tumor nodules[8-10]. Various local ablation techniques have been increasingly applied as alternative HCC treatments to overcome this clinical challenge. Among them, radiofrequency ablation (RFA) is the most widely used method because of its technical ease, safety, cost-effectiveness, and minimal invasiveness[11-15].

Continuous improvements are being made in RFA devices and operation strategies. As a result, the application of RFA has far outreached its original objective as palliative HCC treatment[16] and it has gradually expanded into the therapeutic fields for other diseases[17]. Specifically, RFA demonstrates significant advantages in local tumor control, making it particularly beneficial in the treatment of HCC. As a relatively new technique, few randomized controlled trials evaluating RFA have been reported, highlighting the lack of definitive, good quality data in the publicly available literature. This article reviews the application of RFA in various treatments for HCC.

LIVER TRANSPLANTATION

HCC is the only solid cancer that can be treated by liver transplantation. This surgical approach can simultaneously cure the tumor and underlying cirrhosis, thereby minimizing the chance of recurrence. Moreover, liver transplantation is not affected by the degree of liver function impairment[18]. Mazzaferro *et al*[19] reported a four-year survival rate of 75% and recurrence rate of < 15% after treatment by deceased-donor liver transplantation in patients with one HCC nodule ≤ 5 cm in diameter or up to three nodules ≤ 3 cm in diameter without vascular invasion or extrahepatic spread. The efficacy of the treatment performed in this landmark study was comparable to that of liver transplantation for cirrhosis and initiated the application of liver transplantation for early HCC. These criteria have become known as the Milan criteria and have been adopted as the standard criteria worldwide for

the selection of patients with HCC who are eligible for liver transplantation[6,20-22]. In 2001, investigators from the University of California, San Francisco (UCSF) argued in favor of loosening these criteria to enable greater numbers of patients with HCC to become eligible for liver transplantation[23]. Their study revealed that patients with HCC who met the following criteria achieved treatment efficacy equivalent to patients meeting the Milan criteria (one- and five-year survival rates of 90.0% and 75.2%, respectively): (1) solitary tumor ≤ 6.5 cm in diameter or a maximum of three nodules ≤ 4.5 cm in diameter; and (2) a total tumor diameter ≤ 8 cm. Subsequent studies corroborated the therapeutic outcome of liver transplantation using the two aforementioned sets of criteria[24,25]. In addition, with the development of living-donor liver transplantation, the enlistment criteria for eligible patients were further loosened and impressive treatment results have been demonstrated[26-29].

Despite the successful outcomes of liver transplantation, the insufficient availability of donor organs severely restricts the global application of this technique. Patients with HCC often must wait a long period of time to undergo liver transplantation. During this waiting period, the tumors continue to progress and eventually prevent transplantation[30]. Unfortunately, the average waiting time before cadaveric liver transplantation is more than one year in most countries[31]. The time spent on the transplant waiting list is as long as six to twelve months in Europe and the United States, with dropout rates of 30% to 40% per year[32,33]. Therefore, if the waiting time is more than six months, locoregional strategies [*e.g.*, transarterial chemoembolization (TACE), percutaneous ethanol injection, or RFA] are needed to slow the tumor progression[32]. RFA demonstrates a better effect on local tumor control than TACE, especially for tumors < 3 cm in diameter. As a result, RFA is more frequently used in downsizing therapy prior to liver transplantation.

As early as 2001, RFA was used to delay tumor progression prior to liver transplantation with satisfactory outcomes[34]. Many investigators subsequently reported the use of RFA as a pretransplantation bridge therapy[34-40] (Table 1). According to these studies, preoperative RFA might slow down tumor progression and extend the average waiting time beyond six to ten months. However, as these were retrospective studies with insufficient data, a well-designed randomized trial with sufficient size is necessary for validation. A common belief is that the underestimation of tumor lesions in radiologic studies and the presence of partial tumor necrosis limit the role of RFA as a bridge treatment prior to liver transplantation[41,42]. However, most studies have not supported this conclusion. Brillet *et al*[39] reported that after an average waiting period of 11.9 mo, 76% of preoperative RFA patients were able to undergo liver transplantation regardless of the fact that only 75% of these tumors were completely ablated and that satellite lesions were identified in 44% of the specimens.

The Milan criteria remain a worldwide standard for

Table 1 Characteristics of studies using radiofrequency ablation as a pretransplantation bridge therapy

Ref.	n	Tumor size (cm)	RFA→LT interval (mo)	Dropout	Radiologic response necrosis	Pathologic response necrosis	Satellites found in explants	Follow-up after LT (mo)	Survival 1-yr	Survival 3-yr
Pulvirenti *et al*[34]	14	3.50	8.0	0.0%	90.7%	86.4%	57.0%	16.0	100.0%	100.0%
Fontana *et al*[35]	33	3.60	7.9	21.7%	66.0%	-	-	26.9	85.0%	85.0%
Mazzaferro *et al*[36]	50	2.75	9.5	0.0%	70.0%	55.0%	28.0%	22.0	95.0%	83.0%
Pompili *et al*[37]	40	2.80	8.6	0.0%	75.0%	46.7%	14.0%	34.4	91.9%	85.4%
Lu *et al*[38]	52	2.50	8.7	5.8%	89.6%	70.3%	24.0%	14.9	85.0%	76.0%
Brillet *et al*[39]	21	2.40	11.9	24.0%	76.0%	75.0%	44.0%	25.0	-	-
DuBay *et al*[40]	77	2.50	9.5	21.0%	83.0%	-	-	30.0	-[1]	-[1]

[1]No significant difference compared with untreated groups. LT: Liver transplantation; RFA: Radiofrequency ablation.

identifying appropriate candidates for liver transplantation. However, according to the above-mentioned results, patients whose tumors meet these radiographic criteria may have excellent survival outcomes from locoregional therapy alone, while others with similar baseline imaging findings develop distant metastatic disease despite transplantation and have a poor prognosis. These differences occur because of the heterogeneity of HCC[43-48]. Hence, investigators have been dedicated to seeking alternative therapeutics with an efficacy comparable to that of liver transplantation to save precious donor resources. Nkontchou *et al*[49] found no significant difference in prognosis between patients undergoing RFA before salvage liver transplantation with those undergoing liver transplantation before RFA. Thus, the authors proposed a two-step therapeutic strategy for patients eligible for liver transplantation: RFA should be performed first and, if relapse occurs, salvage liver transplantation should then be performed. Although some inadequacies were present in the design and analysis, Nkontchou *et al*[50] did provide a novel concept of the "test of time" using a hypothesis that originated from another UCSF study involving 61 patients who were treated by RFA and/or TACE to downsize tumors. Approximately 30% of these patients were unable to undergo liver transplantation because of tumor progression. The remaining patients successfully underwent liver transplantation after an average waiting period of 8.2 mo and demonstrated a satisfactory four-year survival rate of 69.3% (intention-to-treat analysis). These results suggest that the strategy of "ablation and waiting" potentially facilitates the identification of patients with unfavorable tumor biology who demonstrate progression despite downsizing strategies and who are unlikely to benefit from transplantation. Such a strategy may, to a certain degree, compensate for the inadequacies of the Milan criteria with respect to excessive reliance on imaging examination results. Undoubtedly, the outcome of preoperative RFA is closely related to the complete tumor necrosis rate. Advancement of the modern RFA technique has enabled a one-session complete ablation rate of > 90% for tumors < 5 cm in diameter. Hence, tumors in peculiar locations and small lesions unidentifiable by preoperative imaging severely restrict the efficiency of this technique. Laparoscopic RFA provides an effective solution to these problems[51].

LIVER RESECTION

LR remains the first-line curative treatment for many patients with HCC, especially those in the early stage of the disease. Worldwide, this strategy has achieved a five-year survival rate of > 50% for patients with good hepatic functional reserve and a low operative mortality of 0.0% to 6.4%[52-56]. Unfortunately, only 5% to 15% of patients with malignant liver cancer are eligible for resection because of various contraindications such as multicentric tumor occurrence, unresectable tumor locations, and insufficient hepatic reserve[57]. Therefore, RFA has become a pivotal method for HCC treatment because of its excellent local tumor control and minimal invasiveness.

RFA vs LR

Comparison between the efficacy of RFA and that of LR has been a source of long-standing controversy, especially in the treatment of small HCC. Anatomic resection of centrally situated small HCC sacrifices a large volume of functional liver parenchyma, contributing to a high rate of complications and surgical mortality[58-60]. However, RFA provides excellent local control and has achieved an efficacy equivalent to that of surgical resection in the treatment of small HCC[13,57,61]. Moreover, RFA requires a shorter hospitalization, fewer blood transfusions, and has a lower rate (0.0% to 8.5%) of major complications, including gastrointestinal bleeding or perforation, serious infection, biliary duct injury, persistent jaundice, hepatic failure and death[61-65]. RFA has been written into the international liver cancer treatment guidelines established by the American Association for the Study of Liver Diseases as a curative treatment for early HCC[6]. However, Imai *et al*[66] proposed that surgical resection is superior to RFA for the treatment of small solitary HCC, as demonstrated by increased five-year overall (87.5% *vs* 59%) and disease-free survival rates (46.8% *vs* 23.9%) for tumors with a diameter of 2 to 3 cm. Though Peng *et al*[67] argued that RFA should be the first choice for early HCC tumors ⩽ 3 cm in diameter, reporting one-, three- and five-year overall survival rates of 94.2%, 82.6% and 67.5% compared to 90.1%, 65.0% and 55.1%, respectively, for resection. In addition, they report corresponding RFA-associated recurrence-free survival rates of 85.5%, 69.1% and 40.7%, compared to resection-associated rates of

Tumors (*n*)	Tumor size (cm)	Child-Pugh class	Tumor characteristics	Recommended strategy
1	⩽ 2	A	M0, subcapsular, adjacent to intrahepatic vessel trunk or extrahepatic organs	LR
		B	M0, central location	RFA
	> 2 to ⩽ 4	A	M0	LR or RFA
			M0, subcapsular, adjacent to intrahepatic vessel trunk or extrahepatic organs	LR
		B	M0, central location	RFA
	> 4	A	M0	LR
2-3	⩽ 3	A	M0, bilobar disease	LR and/or RFA
			M0, unilobar disease	LR
		B	M0	RFA

Table 2 Recommended treatment strategies with curative intent for patients with early-stage hepatocellular carcinoma

HCC: Hepatocellular carcinoma; LR: Liver resection; M: Metastasis classification; RFA: Radiofrequency ablation.

82.2%, 40.1% and 31.8%, respectively, especially for tumors located in the central liver parenchyma.

Advancements in RFA ablation devices and technologies, particularly secondary to the emergence of various radiofrequency electrodes, have made it feasible to use a single probe to achieve greater necrosis in a large area. As a result, RFA has been used to treat tumor nodules of greater sizes. Many scientists have attempted to expand the treatment indications for RFA by conducting numerous clinical studies, although the conclusions have often been inconsistent and occasionally conflicting[68-72]. Most of these were retrospective studies with insufficient probative value of evidence-based medicine. From this viewpoint, it is also important to consider three recently published randomized controlled trials. One of these trials, performed by Chen *et al*[61], showed for the first time that RFA and surgical resection demonstrate indistinguishable efficacy for single-nodule HCC < 5 cm in diameter. However, in a study examining patients who met the Milan criteria, Huang *et al*[65] discovered that hepatectomy is superior to RFA in terms of both postoperative survival and disease-free survival. Given that these two contradictory studies were each characterized by an evidence level of I, it is difficult to draw a firm conclusion regarding surgical treatment versus RFA for patients with HCC. Although these two reports had different inclusion criteria, the conclusion obtained by Huang *et al*[65] was opposite that obtained by Chen *et al*[61] from the analyses of patients with single tumor nodules. In this regard, many retrospective analyses tend to support the finding that RFA yields a significantly higher postoperative recurrence rate than LR. This is particularly true with respect to the short-term postoperative recurrence rate, whereas the long-term rate varies considerably. Interestingly, a recent meta-analysis revealed that RFA generates a higher recurrence rate in the previous site than does surgical resection, whereas surgical resection generates a higher recurrence rate in new areas[69]. In addition, two randomized controlled trials showed that RFA produced complete tumor necrosis rates of 91.5% and 100.0% based on post-RFA imaging examination results[61,65]. In comparison, only approximately 70% of tumors were completely ablated in explants from post-RFA liver transplantation patients, and the occurrence rate of satellite lesions was

as high as 44%. Whether the post-RFA recurrence is relapse or simply the regrowth of residual tumors from the previous operation remains unclear. To address this question, we used the ratio change of *Lens culinaris* agglutinin-reactive alpha-fetoprotein to identify all possible patients with postoperative residual tumors. This strategy allowed us to minimize the skewing of experimental results by this factor. Our results showed that when small HCC tumors were completely ablated, neither RFA nor LR showed significant differences in postoperative recurrence or overall survival[73]. Moreover, even in cases of short-term postoperative recurrence involving residual tumors, no significant difference was found in the three-year survival rate between the two strategies. These findings suggest that proactive therapeutic measures after recurrence may avoid reductions in post-RFA survival. Although this controversy has not been settled, the results of most studies on this issue are summarized along with some recommendations in Table 2.

In addition to postoperative recurrence and survival rates, the potential differences between these approaches (with respect to their other aspects) have been compared. Given the prominent feature of minimal invasiveness, RFA is associated with a markedly lower rate of postoperative complications and a better economic benefit than LR[74]. It is also well established that HBV reactivation is an independent risk factor for postoperative HCC recurrence. A study by Dan *et al*[75] reported that LR is more likely to cause postoperative HBV reactivation than RFA. Meredith *et al*[76] performed a study using a mouse model and revealed that LR led to increased secretion of hepatocyte growth factor and basic fibroblast growth factor, thereby promoting tumor growth. However, the levels of these two factors decreased after RFA. In contrast to LR, RFA leaves the treated tumor tissue in the body instead of removing it from the body, which may induce innate and adaptive immune responses[77-79]. Zerbini *et al*[80,81] recently demonstrated that RFA can activate tumor-specific T cells and enhance the ability of natural killer cells to kill HCC cells. Many other important aspects of the influence of RFA on the tumor biology of HCC are also evident. For example, residual tumors display markedly enhanced growth and invasive ability after RFA. This likely occurs because the RFA transition zone provides

a special microenvironment for the locally remaining tumor cells[82-85]. In this type of secondary persistent anoxic environment, tumor cells undergo heat shock-resistant apoptosis and upregulate the expression of various cytokines (*e.g.*, proliferating cell nuclear antigen, matrix metalloproteinase 9, vascular endothelial growth factor, hepatocyte growth factor, interleukin 6, *etc.*), resulting in increased proliferation and invasiveness of the tumor cells[86]. Moreover, Cheng *et al*[87] reported that sublethal heat can stimulate the transition of hepatoma cells into epithelial mesenchymal-like cells and augment their invasive capacity.

Taken together, the evidence suggests that improved therapeutic efficacy of HCC treatment, either by LR or RFA, principally requires minimizing residual tumors during the procedure, close follow-up, and active treatment once recurrence develops. In addition, complete removal of HCC tissue comprising more than two nodules does not guarantee curative resection because of the multicentric nature of HCC. Surgical resection of single-nodule HCC tissue without vascular invasion results in an excellent prognosis even if the nodule is larger than that recommended in the Milan criteria[88]. Therefore, the Milan criteria, which are mainly based on preoperative imaging analyses, cannot precisely determine whether patients with similar baseline imaging findings will develop distant metastatic disease. Such patients often cannot benefit from LR, RFA, or even liver transplantation.

RFA combined with LR
The presence of multicentric tumor lesions is a key factor that limits the efficacy of surgical treatment for HCC. Hepatectomy cannot remove all tumor lesions due to cirrhotic impairment of the functional reserve, as is particularly evident for small HCC foci situated deep in the liver parenchyma. Elias *et al*[89,90] used RFA to ablate microscopic lesions outside of the main tumor tissue during hepatectomy and achieved excellent outcomes. In addition, Choi *et al*[91] reported that the combination of RFA and LR to treat multifocal HCC yielded one-, three- and five-year survival rates of 87%, 80% and 55%, respectively, which were comparable to rates from simple surgical removal. Interestingly, these authors also revealed that the resected tumor size was a significant prognostic predictor of long-term survival. Cheung *et al*[92] found that a combined surgery group had one- and three-year survival rates of 88.8% and 62.6%, respectively, compared to 88.9% and 51.8%, respectively, in a simple surgery group. Moreover, the postoperative recurrence rate in the combined surgery group was higher than that in the simple surgery group (63.2% *vs* 50.0%), though this difference was not statistically significant. No operative deaths occurred in these studies, as individuals with relatively good hepatic functional reserve were recruited. Although RFA has a far lower probability of causing liver failure than does extended hepatectomy, RFA in patients with multiple tumor nodules may result in morbidity[91,93]. Therefore, suitable patients should be carefully selected.

Those with < 10% indocyanine green retention at 15 min are good candidates for lobectomy[94].

Repeat hepatectomy to treat recurrent HCC reportedly yields three- and five-year survival rates of 56% to 83% and 40% to 52%, respectively[95-98]. However, repeat hepatectomy is not feasible in a majority of patients because of substantial hepatic dysfunction or multiplicity of recurrent HCC. In the past, patients with recurrence who were intolerant to repeat hepatectomy were mainly treated by TACE and ethanol ablation[99]. In contrast, RFA is now more often performed to treat recurrent tumors in the remnant liver after hepatectomy and has shown good outcomes (Table 3)[100-108]. A recent report showed that three- and five-year survival rates reached satisfactory levels of 65.7% and 51.6%, respectively, which are very similar to those of repeat hepatectomy[105]. Such impressive advances in efficacy may be closely associated with the tremendous innovations in RFA devices and operation strategies. Figure 1 shows the results of RFA combined with hemihepatectomy for the treatment of multifocal HCC in a 69-year-old woman.

Radiofrequency-assisted hepatectomy
The heat generated by RFA may result in coagulative necrosis of liver tissues, in turn clogging the sinusoids and bile duct. Therefore, Weber *et al*[109] creatively introduced RFA to the hepatectomy approach in 2002. This modification markedly reduced surgical blood loss, decreased the number of portal triad clampings, and achieved excellent efficacy. Subsequently, this approach was adopted for LR by many groups and gave rise to the concept of "bloodless LR"[110-116]. However, this method is still accompanied by operative death and severe postoperative complications, mainly liver failure, bile leakage, and intraperitoneal bile collection[117]. The standard procedure of this technique is to use a bipolar radiofrequency electrode to burn two continuous ablation zones, 1 to 2 cm in width, flanking the predetermined resection line on the liver surface; this is followed by severance of the liver parenchyma (Figure 2)[118]. However, such an approach may damage a considerable number of functional hepatocytes, particularly in cirrhotic livers, and significantly increase the likelihood of liver failure. Such an ablation strategy undoubtedly elevates the occurrence of liver failure in patients with concurrent HCC and liver cirrhosis, especially for patients in Asian and South African regions[119]. Therefore, adjustments and alterations of this operative technique are necessary to minimize the loss of functional liver parenchyma.

CONCLUSION
Advantages of RFA over LR include minimal invasiveness and almost no postoperative intra-abdominal adhesion. These factors produce favorable conditions for subsequent liver transplantation. Patients in the waiting period can receive the most suitable treatment *via* an extended "test time." This strategy not only provides

Table 3 Characteristics of studies involving treatment of recurrent hepatocellular carcinoma by radiofrequency ablation

| Ref.	n	Tumors (n)	Tumor size (cm)	Radiologic response necrosis	PLR→RFA interval (mo)	Follow-up after RFA (mo)	Overall survival			Disease-free survival			Main findings
							1-yr	3-yr	5-yr	1-yr	3-yr	5-yr	
Nicoli *et al*[100]	5	-	-	-	43 (31.0-61.0)	25.5 (-)	-	60.0%	-	-	20.0%	-	RFTA is the first-choice treatment in the management of intrahepatic recurrence
Choi *et al*[101]	45	53	2.1 (0.8-4.0)	87.0% (46.0/53.0)	23 (10.0-40.0)	18.0 (2.0-47.0)	82.0%	54.0%	-	57.0%	34.0%	-	Percutaneous RFA is effective and safe for intrahepatic recurrent HCC after hepatectomy. Serum alpha-fetoprotein level before RFA and resected tumor size were significant prognostic predictors of long-term survival
Lu *et al*[102]	72	124	2.4 (0.9-7.0)	96.0% (119.0/124.0)	27.9 (2.0-75.9)	21.0 (1.0-215.2)	70.0%	55.0%	28.0%	22.0%	95.0%	83.0%	Percutaneous thermal ablative therapies were particularly suitable for recurrent HCC and improved long-term survival
Schindera *et al*[103]	35	61	1.7 (0.5-5.3)	85.5% (54.0/61.0)	18 (1.0-65.0)	-	76.0%	45.0%	-	-	-	-	Percutaneous RFA is effective and safe for recurrent HCC after hepatectomy, with a good overall patient survival rate
Yang *et al*[104]	41	76	3.8 (2.0-6.6)	93.4% (71.0/76.0)	-	24.5 (1.0-96.0)	73.0%	41.0%	-	46.0%	24.0%	-	Percutaneous RFA is effective and safe for recurrent hepatic tumors after previous partial hepatectomy
Choi *et al*[105]	102	119	2.0 (0.8-5.0)	93.3% (111.0/119.0)	35.6 (7.0-83.0)	22.3 (1.3-125.7)	93.9%	65.7%	51.6%	52.2%	21.3%	7.2%	RFA is effective and safe for recurrent HCC after hepatectomy and is more effective in late than in early recurrence
Liang *et al*[106]	66	88	-	93.9% (62.0/66.0)	21.1 (2.4-69.4)	-	76.6%	48.6%	39.9%	-	-	-	Percutaneous RFA is as effective as repeat hepatectomy for recurrent small HCC. Percutaneous RFA has an advantage over repeat hepatectomy in terms of being less invasive
Chan *et al*[107]	45	-	2.2 (0.8-6.0)	87.0% (46.0/53.0)	35.6 (7.0-83.0)	-	83.7%	43.1%	29.1%	32.2%	12.4%	9.3%	Repeat resection and RFA attained similar survival benefits in the management of recurrent HCC after hepatectomy. The high repeatability of RFA and its ability to be delivered percutaneously render it a preferred treatment option for selected patients
Eisele *et al*[108]	27	-	2.8 (-)	-	-	21.0 (-)	96.0%	62.0%	32.0%	51.0%	30.0%	11.0%	Overall survival and disease-free survival were not significantly different between patients treated by RFA and repeat resection. There was, however, a tendency toward longer tumor-free survival in the resected patients

HCC: Hepatocellular carcinoma; PLR: Previous liver resection; RFA: Radiofrequency ablation; RFTA: Radiofrequency thermal ablation.

patients with therapeutic benefits, but also saves precious donor resources. Studies demonstrating mutual interactions between RFA and hepatectomy have expanded the operative indications for patients with HCC and have enhanced the efficacy of these approaches. Nevertheless, the novel strategy of radiofrequency-assisted LR requires strict adherence to individual patient-specific indications to avoid the occurrence of severe complications. Most

Figure 1 Radiofrequency ablation combined with right hemihepatectomy for multifocal hepatocellular carcinoma in a 69-year-old woman. A: Preoperative contrast-enhanced transverse helical computed tomography (CT) scan obtained during the venous phase shows one small hepatocellular carcinoma (HCC) 1.4 cm diameter in the left hepatic lobe (black arrow); B: An HCC 7.0 cm in diameter (black arrow) is present in the right hepatic lobe; C: Contrast-enhanced CT showed round ablation zones (white arrow) 6 mo after resection of the large tumor and concurrent radiofrequency ablation for the small tumor. Tumor recurrence was not found in the remnant liver.
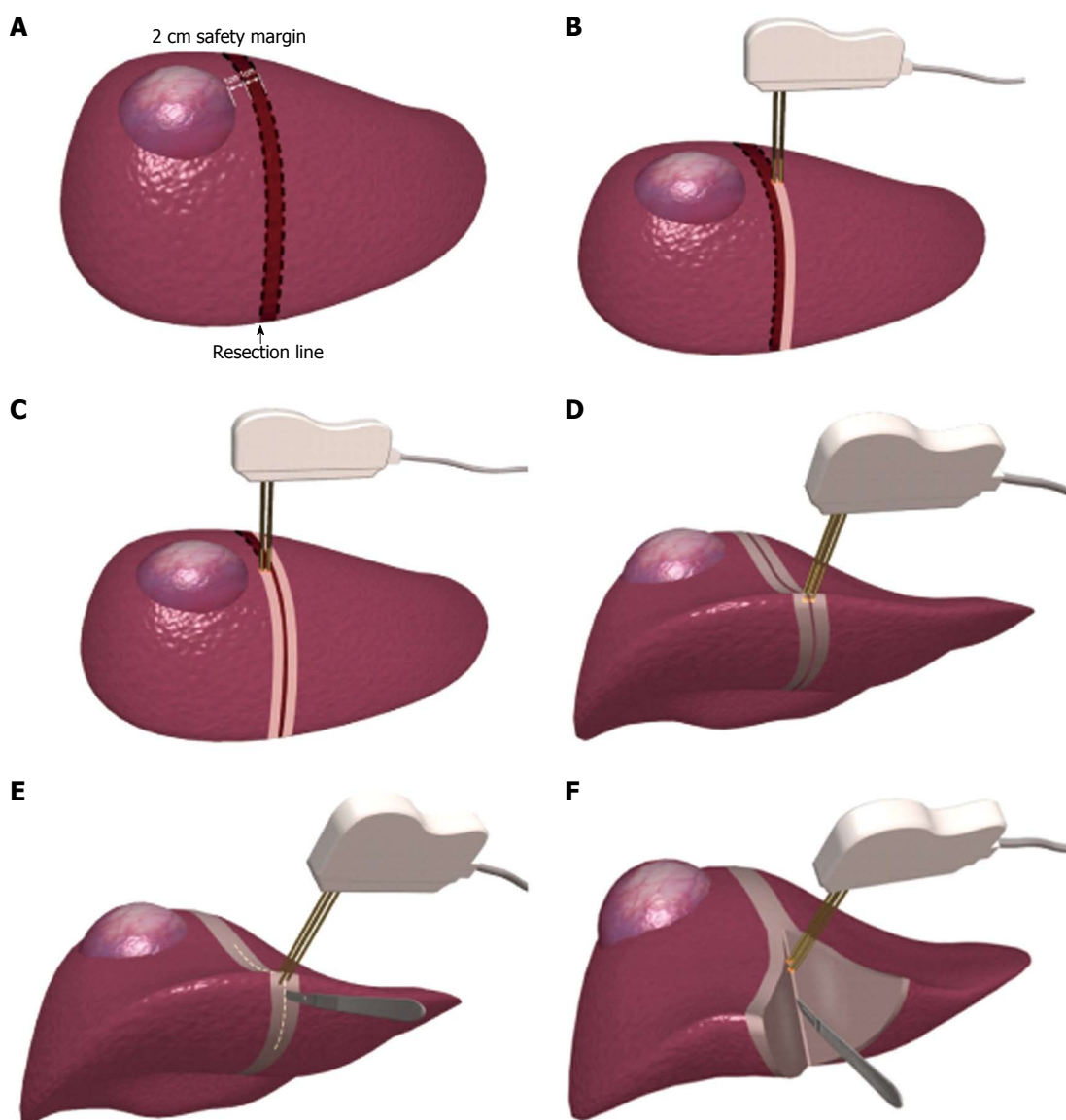
Figure 2 Classic operative technique using a bipolar radiofrequency device for hepatectomy (A-F).

importantly, the outcome of RFA in HCC treatment is inevitably linked to the development of residual tumors. Therefore, the goal of future research is to minimize residual tumors and suppress their growth.

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