GUIDELINES FOR CLINICAL PRACTICE

Current status of radiofrequency ablation of hepatocellular carcinoma

Hyunchul Rhim, Hyo K Lim, Dongil Choi

Hyunchul Rhim, Hyo K Lim, Dongil Choi, Department of Radiology and Center for Imaging Science, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul 135-710, South Korea

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Correspondence to: Hyo K Lim, MD, Department of Radiology and Center for Imaging Science, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul 135-710, South Korea. rfalim@skku.edu

Telephone: +82-2-34102505 Fax: +82-2-34102559

Abstract

Loco-regional treatments for hepatocellular carcinoma (HCC) are important alternatives to curative transplantation or resection. Among them, radiofrequency ablation (RFA) is accepted as the most popular technique showing excellent local tumor control and acceptable morbidity. The current role of RFA is well documented in the evidence-based practice guidelines of European Association of Study of Liver, American Association of Study of the Liver Disease and Japanese academic societies. Several randomized controlled trials have confirmed that RFA is superior to percutaneous ethanol injections in terms of local tumor control and survival. The overall survival after RFA is comparable to after surgical resection in a selected group of patients with smaller (< 3 cm) tumors. Currently, the clinical benefits of combined RFA with transarterial chemoembolization for intermediate stage HCC are increasingly being explored. Here we review the ongoing technical advancements of RFA and future potential.

Key words: Image-guided tumor ablation; Radiofrequency ablation; Hepatocellular carcinoma; Thermal ablation; Loco-regional therapy

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third most frequent cause of death from cancer. Chronic hepatitis B and C viral infections are the predominant factors predisposing patients to HCC in Southeast Asia, Africa, Western countries and Japan. The incidence of HCC is increasing in Western countries and is expected to equal that currently reported in Asian countries[1-3].

Liver transplantation is the best curative option with good survival rates, although its use is restricted by the shortage of donor organs. Surgical resection was accepted as a treatment of choice before the era of transplantation. However, the tumors in most patients are unresectable because of a variety of factors including: poor hepatic reserve, multifocal disease or inability to obtain an optimal tumor free margin[4,5]. Therefore, for the majority of patients with HCC, loco-regional treatment is the only alternative treatment option[6-12].

The image-guided loco-regional treatment for patients with unresectable HCC includes chemical or thermal ablative techniques and catheter-based approaches. Among the ablative techniques, radiofrequency ablation (RFA) has been used as the most popular method for treating early

stage HCC (single or 3 nodules less than 3 cm in diameter). During the past two decades, many clinical studies have confirmed the safety and therapeutic efficacy of RF[13-19]. The purpose of this article is to review and summarize the current status of RFA for HCC. The current and potential roles of RFA in treating HCC will be presented with a review of the evidence of its safety and therapeutic efficacy.

CURRENT ROLE OF RFA IN THE TREATMENT OF HCC

It is difficult to define the current role of RFA in the treatment of HCC because it is still an evolving technique. However, consensus meetings of major scientific societies have presented guidelines for its use. The evidence-based practice guidelines for management of HCC have been proposed by the European Association of Study of Liver (EASL) and the American Association of Study of the Liver Disease (AASLD)[4,20]. In both guidelines, RFA is recommended as a non-surgical technique for the treatment of early stage (Child A or B, solitary HCC or up to 3 nodules < 3 cm in size) HCC.

According to the EASL and AASLD guidelines, local ablation using RFA and percutaneous ethanol injections (PEI), is accepted as a safe and effective therapy for patients that cannot undergo resection or as a bridge to transplantation based on level II (nonrandomized controlled trials, cohort or case-control analytic studies, multiple time series, dramatic uncontrolled experiments) evidence. In addition, RFA is as effective as PEI for smaller (< 2 cm) tumors but clearly superior to PEI for larger tumors based on level I (randomized controlled trial) evidence[4,20].

The barcelona clinic liver cancer staging and treatment assessment system is widely used worldwide. Using this system, RFA is classified as a treatment option for early stage HCC. Patients with early stage disease can be effectively treated by resection, transplantation or percutaneous ablation with the possibility of long-term cure and a 5-year survival rate ranging from 50% to 75%. However, many issues regarding the treatment of choice remain to be resolved by further investigations; currently there are no studies available that have compared treatments considered to be effective for early stage disease (surgical resection, transplantation and percutaneous ablation) or comparing these methods of treatment to no treatment (Figure 1)[4,20,21].

According to the Japanese evidence-based guidelines, if there is only one tumor in a patient with Child A or B disease, hepatectomy is recommended regardless of the diameter of the tumor. However, percutaneous local ablation may also be selected if the severity of liver damage is class B and the diameter of the tumor is not more than 2 cm. If there are 2 or more tumors and their diameters are no more than 3 cm, hepatectomy or ablation is recommended. If there are 2 or 3 tumors and their diameters are 3 cm more, hepatectomy or hepatic artery embolization is recommended. If there are more than 4 tumors, transarterial chemoembolization (TACE) or hepatic arterial infusion chemotherapy is recommended (Figure 2)[22]. Recently, the expert panel of the Japanese

Society of Hepatology established a consensus-based treatment algorithm based on therapeutic protocols used in Japan. This algorithm essentially follows the evidence-based algorithm; however, the treatments widely performed in Japan were included by consensus, even though the evidence was not always present[23].

SAFETY OF RFA

One of the most attractive features of local ablation therapy, including RFA, is that the procedure is minimally invasive compared to curative surgical resection or transplantation. Although RFA is considered to be much safer than surgical treatment, it is not a complication-free procedure. Thus, an operator should be aware of all major complications with the potential morbidity and mortality and should be ready to detect complications as early as possible and manage them appropriately[24-26].
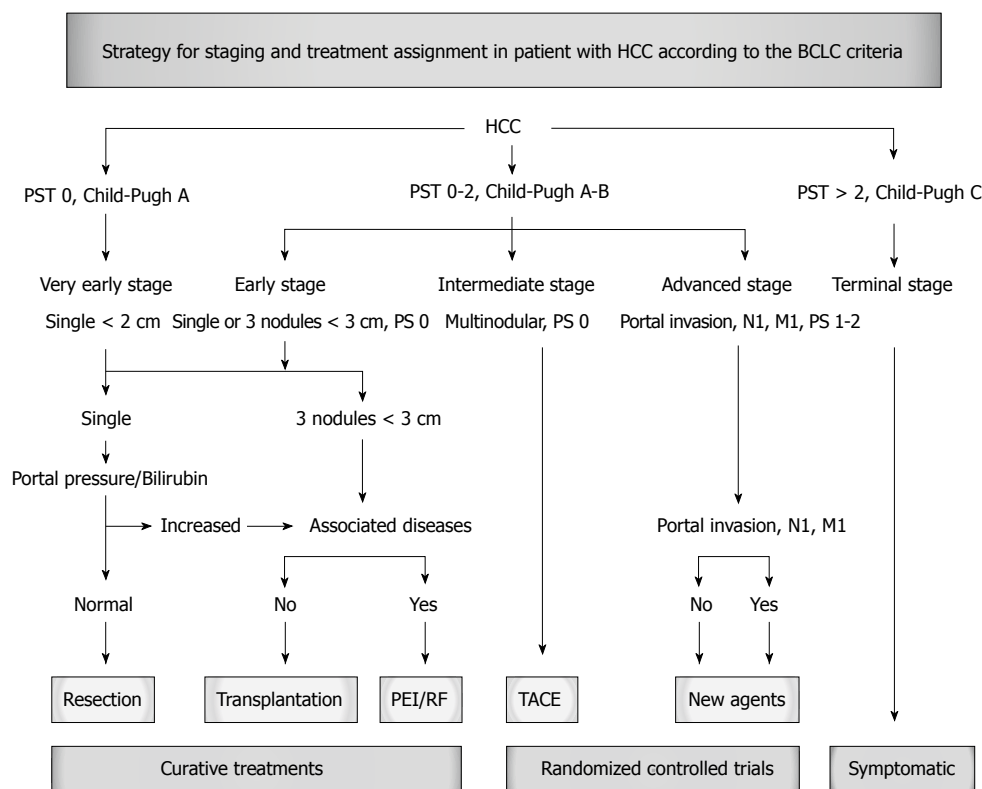
There have been several multicenter studies on the complications in patients after RFA procedures for hepatic tumors. In 2002, the collaborative Italian Group, using the Cool-tip electrode, reported the results of a multicenter study of the complications that occurred in patients after RFA procedures. The mortality, major and minor complication rates were 0.3%, 2.2% and 5% respectively[27]. Another Italian group, using the multi-tined expandable electrodes, reported the complications in 872 patients. The mortality, major and minor complication rates were 0.1%, 3.1% and 6.3% respectively[28]. A Korean multicenter study on complications was performed on 1139 patients treated by RFA. The mortality and major complication rates were 0.1% and 2.4%[29]. A French study with 312 patients reported that the mortality, major and minor complication rates were 1.4%, 10.6% and 6.3% respectively[30].

An extensive meta-analysis of 82 independent reports including 3670 patients, reported by Mulier et al[24], revealed that the overall mortality rate was 0.5%, and the major/minor complication rate was 8.9%. The most common complications were abdominal hemorrhage, abdominal infection (abscess), biliary tract damage, liver failure, pulmonary complications and ground pad burns. The broad spectrum and incidence of major complications are similar to the findings of many single center studies.

There have been many investigations that have focused on methods to minimize the complications associated with RFA procedures[31-38]. The most useful method to prevent collateral thermal injury of abutting organs is the use of artificial fluid or air injected into the peritoneal or pleural spaces. Song et al[38] recently reported the feasibility and efficacy of artificial ascites in 143 patients with HCC abutting the diaphragm or bowel. Artificial ascites separates the organs at risk for damage from the RF ablation zone and improves the sonic window by downward displacement of the liver[31,34,36,38].

THERAPEUTIC EFFICACY OF RFA

It is difficult to objectively review and compare the therapeutic efficacy data of treatment modalities. This is because

Strategy for staging and treatment assignment in patient with HCC according to the BCLC criteria

HCC

PST 0, Child-Pugh A   PST 0-2, Child-Pugh A-B   PST > 2, Child-Pugh C

Very early stage   Early stage   Intermediate stage   Advanced stage   Terminal stage

Single < 2 cm   Single or 3 nodules < 3 cm, PS 0   Multinodular, PS 0   Portal invasion, N1, M1, PS 1-2

Single   3 nodules < 3 cm

Portal pressure/Bilirubin

→ Increased → Associated diseases   Portal invasion, N1, M1

Normal   No   Yes   No   Yes

Resection   Transplantation   PEI/RF   TACE   New agents

Curative treatments   Randomized controlled trials   Symptomatic

Figure 1 Strategy for staging and treatment assignment in patient with hepatocellular carcinoma (HCC) according to the barcelona clinic liver cancer (BCLC) criteria. BCLC staging system was developed based on the collection of data from several independent studies representing different disease stages and/or treatment modalities. It includes variables related to tumor stage, liver functional status, physical status and cancer related symptoms. The main advantage of the BCLC criteria staging system is that it links staging with treatment modalities and with an estimation of life expectancy that is based on published response rates to the various treatments. Early stage disease includes patients with preserved liver function (Child-Pugh Class A and B) with solitary HCC or up to 3 nodules < 3 cm in diameter. These patients can be effectively treated by resection, transplantation or percutaneous ablation with the possibility for long-term survival ranging from 50% to 75%.

there are significant variations among studies in terms of study design and the technical details of treatment. In addition, patient demographics, including etiology and extent of liver disease, as well as tumor features (number, size, location), vary considerably from one study to another[39-41]. Currently, the international working group of image-guided tumor ablation has proposed a "Proposal for Standardization for Terms and Reporting Criteria", which was acknowledged by the society of interventional radiology. The aim of the proposal is to facilitate the effective communication of ideas and appropriate comparisons among treatments[42]. Currently, there are so many non-surgical ablation techniques including radiofrequency, ethanol, microwave, laser, high intensity focused ultrasound, radioembolization and TACE with novel drug eluting beads. However, only RFA and PEI are being widely performed worldwide and accepted as a standard treatment in all the guidelines supported by considerable evidence with many investigations including a randomized controlled study.

Below, we summarize the current therapeutic efficacy of RFA for treating HCC according to the following categories of treatment: (1) RFA alone; (2) Comparison between RFA and PEI; (3) Comparison between RFA and surgery; and (4) RFA combined with surgery or TACE.

RFA alone
Since 2005, six clinical cohort studies with large series of

patients (more than 200 patients) have been reported in the medical literature. The survival results are summarized in Table 1.

Lencioni *et al*[13] performed a prospective, intention-to-treat clinical trial with 206 patients with early stage unresectable HCC (mean size 2.8 cm). No procedure-related death was observed. Major complications were observed in three (2%) of 187 patients, including two cases of intraperitoneal bleeding and one tumor seeding along the needle track. Overall survival rates were 97%, 67% and 41% at 1, 3 and 5 years respectively. The prognostic factors related to overall survival were Child Class and tumor multiplicity. The 1-, 3- and 5-year local tumor progression rates were 4%, 10% and 10%.

Tateishi *et al*[14] reported therapeutic results of 1000 RFA procedures used to treat 2140 HCC nodules (mean size, 2.6 cm) in 664 patients. Major complications occurred in 4% per treatment and 1.9% per session. The most common complications were tumor seeding along the needle track, hepatic abscess formation requiring drainage and intraperitoneal hemorrhage, in order of decreasing frequency. There were no deaths related to the RFA procedure. The 1-, 3- and 5-year overall survival rates for 319 patients treated, as the first line treatment were 95%, 78% and 54%. Child-Pugh Class, tumor size, and AFP levels were prognostic factors for overall survival.

Chen *et al*[15] reported on the long term outcome of RFA for HCC (mean size 3.8 cm) in 256 patients. Major

Table 1 Summary of therapeutic results of 6 large series cohort studies with percutaneous RFA alone

Year	Author	Patient No.	Size (cm)[1]	FU (mo)[2]	LTP (%)[3]	New recur (%)[4]	Major Cx (%)[5]	Overall survival (%)			Median survival (mo)	Evidence[6]
								1 yr	3 yr	5 yr		
2005	Lencioni *et al*[13]	206	< 5	24	10	49	2.0	97	67	41	57	2
2005	Tateishi *et al*[14]	319	< 5	28	8.7	60	4.0	95	78	54	NA	2
2005	Chen *et al*[15]	256	< 8	2-69	NA	NA	2.4	83	67	41	NA	2
2007	Choi *et al*[16]	570	< 5	30	11.8	52	1.9	95	70	58	77	2
2008	Livraghi *et al*[17]	216	< 2	31	0.9	NA	1.8	NA	76	55	NA	2
2009	N'Kontchou *et al*[18]	235	< 5	27	11.5	42	0.9	NA	60	40	48	

RFA: Radiofrequency ablation; [1]Maximum diameter of tumor; [2]Mean follow-up period; [3]Rate of local tumor progression; [4]Rate of new recurrence including intrahepatic remote and extrahepatic metastasis; [5]Rate of major complications requiring additional hospitalization or therapeutic procedure; [6]Level of evidence.
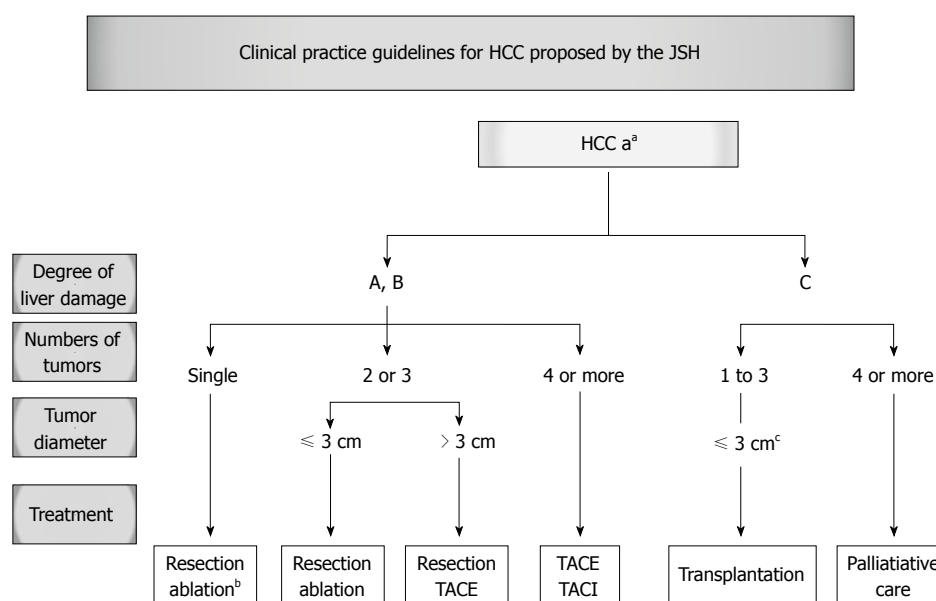
Figure 2 Clinical Practice Guidelines for HCC proposed by the Japan Society of Hepatology. [a]Presence of vascular invasion or extrahepatic metastasis to be indicated separately; [b]Selected when the severity of damage is class B and the tumor diameter is no greater than 3 cm; [c]Tumor diameter should be no greater than 5 cm when there is only one tumor; JSH: Japan society of hepatology.

complications had an incidence of 2.4% and included track tumor seeding, intraperitoneal hemorrhage and bowel perforation. The overall survival rates were 83% at 1 year, 67% at 3 years and 41% at 5 years.

Choi *et al*[16] evaluated the long-term results and prognostic factors in 570 patients with 674 early stage HCCs. There were no procedure-related deaths. The incidence of major complications was 1.9% per treatment. The cumulative survival rates at 1, 3 and 5 years were 95%, 70% and 58% respectively. The local tumor progression rates at 1, 2 and 3 years were 8%, 11% and 12% respectively. The prognostic factors for survival were Child-Pugh Class, age and pre-treatment AFP levels.

Livraghi *et al*[17] reported on the therapeutic results after RFA procedures for very early HCC in 218 patients. They assessed two primary end points that could be easily compared to surgical resections: (1) the rate of sustained, local and complete response; and (2) the rate of treatment-related complications. The secondary end point was the 5-year survival in 100 patients that had tumors that were considered potentially operable. The sustained complete response rate was 97.2%. The perioperative mortality, major complication rate and 5-year survival were 0%, 1.8% and 69% respectively. They concluded that RFA could be considered the treatment of choice for patients with a single HCC less than 2 cm in diameter, even when surgical resection was possible.

Recently, N'Kontchou *et al*[18] evaluated the long-term results and prognostic factors in 235 consecutive patients with HCC (mean size 2.9 cm). Major complications occurred in three patients (0.9%), including one treatment-related death. The overall 5-year and recurrence-free survival rates were 40% and 17% respectively. However, the overall 5-year survival rate was 76% for operable patients. The prognostic factors associated with overall survival were prothrombin time and serum AFP levels. The tumor size was associated with local tumor progression but not with overall and tumor-free survival.

RFA vs PEI
In addition to the many studies on RFA alone, there have been many comparative studies performed to confirm the therapeutic efficacy of RFA by comparing other ablative techniques (especially PEI). During the past few years, five

Table 2 Summary of 5 randomized controlled studies on comparison between RFA and PEI

Year	Author	Treatment	Patient No.	FU (mo)[1]	Initial CR[2]/Tumor (%)	Initial CR[2]/Patient (%)	Overall survival (%)			Evidence[4]
							1 yr	2 yr	3 yr	
2003	Lencioni et al[43]	RFA	42	23	91	NA[3]	100	98	NA	2
		PEI	44	22	82	NA	96	88	NA	
2004	Lin et al[44]	RFA	52	24	96	96	90	82	74	1
		PEI	105	24	91	91	87	62	48	
2005	Lin et al[45]	RFA	62	28	97	97	93	81	74	1
		PEI	62	26	88	89	81	66	51	
2005	Shiina et al[46]	RFA	118	~4.3 yr	100	97	97	91	81	1
		PEI	187	~4.2 yr	100	91	91	81	67	
2008	Brunello et al[47]	RFA	70	26	NA	96	NA	NA	63	1
		PEI	69	25	NA	66	NA	NA	59	

PEI: Percutaneous ethanol injections; [1]Mean follow-up period; [2]Complete response rate; [3]Not available; [4]Level of evidence.

Table 3 Summary of 6 clinical studies on comparison between RFA and surgical resection

Year	Author	Study	Treatment	Patient No.	FU (mo)[1]	Tumor size (cm)	Overall survival (%)					*P*-value	Evidence[3]
							1 yr	2 yr	3 yr	4 yr	5 yr		
2004	Vivarelli et al[51]	NR[4]	RFA	79	29	< 5	78	NA	33	NA	NA	0.020	2
			Resection	79			88	NA	65	NA	NA		
2005	Montorsi et al[52]	NR	RFA	58	NA[2]	< 5	85	75	61	45	NA	0.139	2
			Resection	48			84	79	73	61	NA		
2005	Hong et al[53]	NR	RFA	55	35	< 5	100	NA	74	NA	NA	0.240	2
			Resection	93			98	NA	84	NA	NA		
2005	Chen et al[54]	R[5]	RFA	47	36	< 5	93	82	64	NA	NA	0.753	1
			Resection	65			93	86	67	NA	NA		
2006	Lü et al[55]	R	RFA	51	NA	< 5	94	87	87	NA	NA	0.808	1
			Resection	54			91	86	86	NA	NA		
2009	Ueno et al[56]	NR	RFA	110	36	< 5	98	NA	92	NA	63	0.060	2
			Resection	123			99	NA	92	NA	80		

[1]Mean follow-up period; [2]Not available; [3]Level of evidence; [4]Non-randomized study; [5]Randomized controlled study.

randomized clinical trials and three meta-analysis studies on the therapeutic efficacy of RFA *vs* PEI have been published[43-50]. The data of seven studies are summarized in Table 2.

The key points from the five randomized controlled trials and three meta-analysis studies are that PEI and RFA are equally effective for tumors less than 2 cm. However, the necrotic effect of RFA is more predictable for all tumor sizes and its efficacy is clearly superior to that of PEI in larger tumors (level I)[4,20,43-50]. Overall, RFA demonstrated superior efficacy in regard to lower local tumor progression and a longer disease-free survival. The local tumor control rate was reported to range between 91% and 96% for RFA and between 65% and 88% for PEI. Both treatment groups presented similar adverse events; only one study found RFA associated with more major complications[43].

RFA vs surgical resection
After the introduction of percutaneous ablation therapy, the efficacy compared with curative treatment, namely surgical resection, for the treatment of small HCC has been debated[51-57]. The therapeutic efficacy reported by these comparative studies of RFA and surgical resection are summarized in Table 3.

Several non-randomized studies have demonstrated equivalent outcomes for RFA and surgery. Montorsi *et al*[52] performed a prospective nonrandomized trial comparing RFA (58 patients) with surgery (40 patients) in 98 patients with a single HCC less than 5 cm in diameter. While long-term (up to 4 years) survival was equivalent in both treatment groups, RFA resulted in significantly higher rates of intrahepatic recurrence compared to the surgical resection group. Another nonrandomized comparative study reported by Hong *et al*[53] demonstrated that RFA was as effective as surgical resection for single small (< 5 cm) HCC in patients with Child A disease, similar to the results reported by Montorsi *et al*[52]. A large Japanese prospective study with 7185 patients with small HCC demonstrated no significant difference in overall survival for hepatic resection *vs* RFA *vs* PEI group, although the time-to-recurrence rates were better for the hepatic resection group[57]. Ueno *et al*[56] performed a retrospective study on 278 consecutive patients with HCC classified by the Milan criteria that were treated by surgical resection (123 patients) and RFA (155 patients). The overall survival and disease-free survival was significantly better in the surgical resection group than in the RFA group, although differences in liver function reserve existed. A recent study by Livraghi *et al*[17] focused on early stage disease and

demonstrated a sustained local complete response after RFA comparable with that of hepatic resection.

Two randomized controlled trials compared RFA to hepatic resection in patients with early HCC. Chen *et al*[54] reported a randomized controlled trial in 112 patients with a single HCC less than 5 cm that received either resection (65 patients) or percutaneous RFA (47 patients). No significant differences in local recurrence, overall survival or disease-free survival were detected between the two groups. Most clinical trials, including randomized controlled trials, have shown that RFA is comparable to surgical resection in terms of overall survival; in addition, it is less invasive and associated with lower complication rates and lower costs[51-57].

Direct comparison by a well designed randomized controlled trial is the only way to assess whether RFA might replace surgical resection for treating early stage, resectable HCC. The difference in survival between the two treatments appears to be fairly small, based on the currently available data. The sample size required to ensure meaningful conclusions should be quite large. Thus, this kind of randomized controlled study may be not feasible[17].

RFA combined with other treatments (surgery or TACE)

RFA combined with surgery: RFA can be used as one complimentary method for multifocal or larger tumors. In patients with multifocal HCCs that are not feasible for hepatic resection, resection of the dominant tumors can be performed first and then the remaining small tumors can be simultaneously ablated by RFA. Using this approach, more patients previously considered inoperable become eligible for a curative resection[58-61]. Choi *et al*[62] reported acceptable perioperative morbidity and long-term survival in a series of 53 patients that had combined hepatectomy and RFA for multifocal HCCs. They confirmed an important role for RFA in increasing the chance of curative treatment for patients with multifocal tumors that might be traditionally considered unresectable. However, further investigation is needed to compare the outcome of hepatectomy plus RFA with that of hepatectomy alone to assess whether the survival results are truly comparable[58,59].

RFA combined with TACE: Another promising role of RFA is combined treatment with TACE for intermediate to large tumors. Although RFA shows excellent local tumor control for small tumors less than 3 cm, the limited size of the ablation zone usually fails to achieve complete ablation of large HCC greater than 5 cm[12-18,63]. To obtain a large coagulation area, various techniques including multiple overlapping ablations[64-67], saline-enhanced ablation to reduce the tissue impedance[68,69] and temporary occlusion of tumor blood supply have been attempted[64,70-73]. The combination of TACE with RFA has two theoretical merits: (1) Occlusion of hepatic arterial flow by means of embolization may contribute to the decrease in the heat-sink effects during RFA and increase the ablation volume by RFA; and (2) Combined treatment may have the effect of anticancer agents on cancer cells, which is enhanced by the hyperthermia.

Yamakado *et al*[74] compared the therapeutic efficacy of combined TACE plus RFA and Surgical resection in 142 patients with HCC (< 5 cm, up to 3 in number). The 1-, 3- and 5-year overall survival rate after TACE followed by RFA (98%, 94% and 75%) were similar to surgical resection (97%, 93% and 81%)[75]. In addition, they reported another study with 20 patients with HCC larger than 5 cm. The overall and recurrence-free survival rates were 100% and 71% at 1 year, 62% and 28% at 3 years and 41% and 14% at 5 years. Recently, Shibata *et al*[76] reported a prospective study comparing the therapeutic efficacy of a combined TACE and RFA group (46 patients) with a RFA alone group (43 patients). They concluded that combined TACE with RFA had equivalent effectiveness for the treatment of small (< 3 cm) HCCs; therefore, combined treatment may not be necessary for small tumors.

PERSPECTIVE ON RFA

Based on current evidence, RFA will remain the mainstay of local treatment for early stage HCC because of its excellent local tumor control and minimal morbidity. The therapeutic efficacy of RFA will continue to be refined with advancements in technology in terms of planning, targeting, monitoring, controlling and assessment of therapeutic efficacy. The technical advancements will include novel guiding modalities (CE-US, fusion imaging or robotic guidance)[77-81], more powerful ablation strategies (multiple applicators) and combined treatment with adjuvant therapy such as thermo-sensitive drugs or targeted agents such as sorafenib[22,82-84]. However, RFA technology will be challenged by other ablative techniques including novel microwave or cryosurgery technologies as well as non-invasive emerging techniques such as high intensity focused ultrasound treatment and irreversible electroporation in the near future[85-90].

CONCLUSION

RFA is the most popular non-surgical technique for treating early stage unresectable HCC because of its excellent local tumor control and acceptable morbidity. RFA is superior to PEI in terms of local tumor control and survival. Overall survival of RFA is comparable to surgical resection in a selected group of patients with smaller tumors. Currently, combined RFA with TACE is increasingly being investigated for the treatment of intermediate stage HCC. Considering the ongoing technical advances, RFA remains an attractive technique with additional potential to be explored by further investigations.

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