REVIEW

Radiofrequency Ablation of Hepatocellular Carcinoma: Pros and Cons

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Among locoregional treatments for hepatocellular carcinoma (HCC), radiofrequency ablation (RFA) has been accepted as the most popular alternative to curative transplantation or resection, and it shows an excellent local tumor control rate and acceptable morbidity. The benefits of RFA have been universally validated by the practice guidelines of international societies of hepatology. The main advantages of RFA include 1) it is minimally invasive with acceptable morbidity, 2) it enables excellent local tumor control, 3) it has promising long-term survival, and 4) it is a multimodal approach. Based on these pros, RFA will play an important role in managing the patient with early HCC (smaller than 3 cm with fewer than four tumors). The main limitations of current RFA technology in hepatic ablation include 1) limitation of ablation volume, 2) technically infeasible in some tumors due to conspicuity and dangerous location, and 3) the heat-sink effect. Many technical approaches have been introduced to overcome those limitations, including a novel guiding modality, use of artificial fluid or air, and combined treatment strategies. RFA will continue to play a role as a representative ablative modality in the management of HCC, even in the era of targeted agents. **(Gut Liver 2010;4(Suppl. 1):S113-118)**

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

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third most common cause of death of cancer worldwide.[1-3] The curative treatment of HCC is transplantation or surgical resection. However, most of patients with HCC could not be a candidate for those curative options because of the shortage of donor organs, poor hepatic reserve, or multifocal diseases.[3-9] For those patients with unrectable HCCs, there are many non-surgical treatments introduced.[10-19] The image-guided loco-regional treatment for patients with unresectable HCC includes chemical or thermal ablative techniques and catheter-based treatments. Among the ablative techniques, radiofrequency ablation (RFA) has been used as the most popular method for treating early stage HCC. During the past two decades, many clinical studies have confirmed the safety and therapeutic efficacy of RFA.[20-29] The purpose of this article is to review the current status of RFA for HCC by presenting the pros and cons. The current and potential roles and limitation of RFA in treating HCC will be addressed.

PROS OF RFA FOR HCC

As RFA is still an evolving technique, it is difficult to define the current role of RFA in the treatment of HCC. However, RFA is widely accepted as the most important ablative modality from the major academic societies (European Association of Study of Liver [EASL], American Association of Study of the Liver Disease [AASLD], Japanese Society of Hepatology).[3,6,9,10] In the guidelines proposed by EASL and AASLD, 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 (Fig. 1). Since the introduction of RF technology in the field of interventional oncology, RFA is get-

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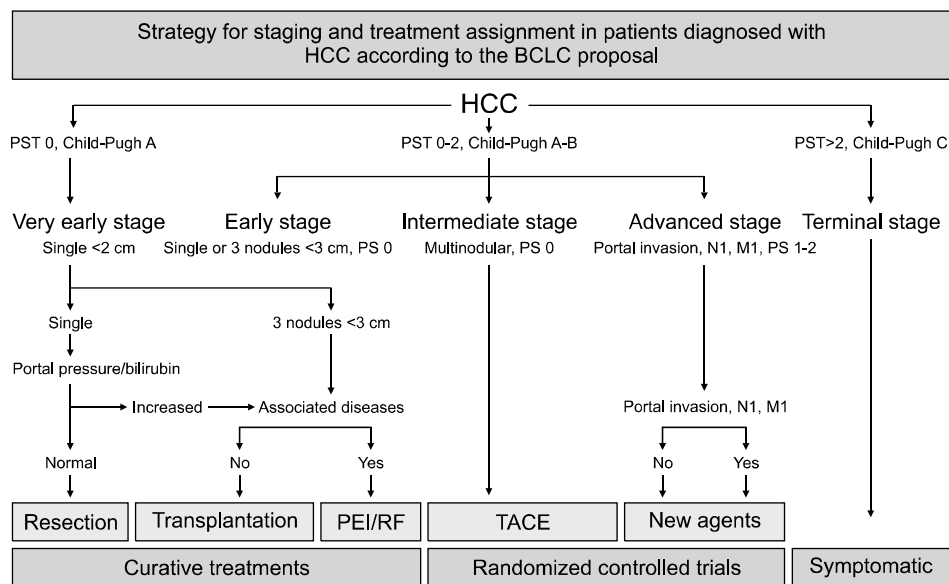   Tel: +82-2-3410-2507, Fax: +82-2-3410-2559, E-mail: rhimhc@skku.edu

Fig. 1. Strategy for staging and treatment assignment in patient with hepatocellular carcinoma (HCC) according to the 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%.

ting a consensus of the most valuable ablative method for unresectable HCC because of the following reasons: i) Minimally invasiveness with acceptable morbidity, ii) excellent local tumor control power, iii) favorable overall survival gain, iv) potential to be one of multimodality treatment.

1. Minimally invasiveness with acceptable morbidity

Minimally invasiveness of RFA procedure is the most important advantages compared to surgical resection especially for the patients with poor liver function. Most procedure can be performed under local and conscious sedation and on the out-patient or 2-3 days hospitalization basis. Several multicenter studies on the complications in patients after RFA procedures for hepatic tumors have proven the safety of RFA procedure.[21-27] An extensive meta-analysis of 82 independent reports including 3,670 patients, reported by Mulier et al., revealed that the overall mortality rate was 0.5%, and 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. Two multicenter studies from Italy and Korea showed similar mortality and morbidity. Many large-series studies demonstrated that RFA is a safe procedure showing acceptable morbidity and mortality (Table 1). 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 mange them appropriately.

2. Excellent local tumor control

The local tumor control is the primary goal of ablative therapy. RFA can make a reproducible ablation zones within 10-15 minutes. The average ablation zones by currently available RF electrodes are 3-4 cm in maximum diameter depending on the devices and ablation parameters. However, there are insufficient data and experiences to prove which energy or device is superior or inferior. Superior results can be due to ablation technique and/or tumor biology in the study group. The difference of the results is modest, and it can be overcome by technique.

Many meta-analysis studies demonstrated that RFA is superior to PEI in terms of local tumor control and the

Table 1. Summary of Therapeutic Results of 6 Large Series Cohort Studies with Percutaneous RFA Alone

Year	Author	No. of patients	Size, cm*	FU, mo[†]	LTP, %[‡]	New recur, %[§]	Major Cx, %[‖]	Overall survival, %			Median survival, mo	Evidence[¶]
								1 yr	3 yr	5 yr		
2005	Lencioni	206	<5	24	10	49	2.0	97	67	41	57	2
2005	Tateishi	319	<5	28	8.7	60	4.0	95	78	54	NA	2
2006	Chen	256	<8	2-69	NA	NA	2.4	83	67	41	NA	2
2007	Choi	570	<5	30	11.8	52	1.9	95	70	58	77	2
2008	Livraghi	216	<2	31	0.9	NA	1.8	NA	76	55	NA	2
2009	N'Kontchou	235	<5	27	11.5	42	0.9	NA	60	40	48	

RFA, radiofrequency ablation.
*Maximum diameter of tumor; [†]Mean follow-up period; [‡]Rate of local tumor progression; [§]Rate of new recurrence including intrahepatic remote and extrahepatic metastasis; [‖]Rate of major complications requiring additional hospitalization or therapeutic procedure; [¶]Level of evidence.

Table 2. Summary of 6 Clinical Studies on Comparison between RFA and Surgical Resection

Year	Author	Study	Treatment	No. of patients	FU, mo*	Tumor size, cm	Overall survival, %					p-value	Evidence[†]
							1 yr	2 yr	3 yr	4 yr	5 yr		
2004	Vivarelli	NR	RFA	79	29	<5	78	NA	33	NA	NA	0.020	2
			Resection	79			88	NA	65	NA	NA		
2005	Montorsi	NR	RFA	58	NA[†]	<5	85	75	61	45	NA	0.139	2
			Resection	48			84	79	73	61	NA		
2005	Hong	NR	RFA	55	35	<5	100	NA	74	NA	NA	0.240	2
			Resection	93			98	NA	84	NA	NA		
2005	Chen	R	RFA	47	36	<5	93	82	64	NA	NA	0.753	1
			Resection	65			93	86	67	NA	NA		
2008	Lu	R	RFA	51	NA	<5	94	87	87	NA	NA	0.808	1
			Resection	54			91	86	86	NA	NA		
2009	Ueno	NR	RFA	110	36	<5	98	NA	92	NA	63	0.060	2
			Resection	123			99	NA	92	NA	80		

RFA, radiofrequency ablation; R, randomized; NR, non-randomized.
*Mean follow-up period; [†]Level of evidence; [‡]Not available.

guideline proposed by major scientific societies approved the superiority of RFA over PEI.[30-36] The local tumor progression rate after RFA ranged from 0.9% to 11.8% (Table 1).[14-19] The prognostic factors on local tumor progression are the size of tumor, tumor abutting the larger vessel. The tumor size is the main factor for successful local tumor control. Thus, combined treatment with TACE or novel thermosensitive drug may be a good alternative for the large tumors more than 3 cm in diameter.

3. Promising long-term survival gain

Many clinical studies regarding the long-term results showed that RFA provided the favorable long-term survival gain for the patients with HCC. Since 2005, six clinical cohort studies with large series of patients (more than 200 patients) have been reported in the medical literature.[14-19] The survival results are summarized in Table 1. The 5 year survival rates are reported from 41% to 68% depending on the tumor size, which are quite comparable to those of surgical resection. Based on the recent data, RFA is considered as one of curative option especially for the small sized single HCC (<2 cm) in the many scientific societies. The proven prognostic factors in the literatures are Child-Pugh class, Pre-procedural AFP level, age, etc. After introduction of percutaneous ablation therapy, the efficacy compared with curative treatment, namely, surgical resection, for the treatment of small HCC has been debated. The therapeutic efficacy reported by these comparative studies of RFA and surgical resection are summarized in Table 2.[37-42] 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.

4. One of multi-modality approach

HCC is not a tumor which can be controlled completely by single treatment even if using transplantation. Hence, we should be wise to take a multi-modality treatment strategies. Given that context, RFA is a good therapeutic modality to provide a promising local tumor control. If a patient has a bilobar tumors, we can take the one lobe with major tumor and simultaneously ablation the remained minor tumor in the contralateral lobe in the same operating fields. If the tumor size is over than 5 cm, we can combine TACE with RFA to achieve complete local tumor control. For the recurrent tumor after the curative surgical resection or transplantation, we can control the tumor successfully with minimal morbidity.[43-45]

CONS OF RFA FOR HCC

Although RFA has many pros for treating the patient with HCC, RFA has several limitations and pitfalls to be overcome. They include i) limited ablation volume, ii) technically difficult tumors, iii) heat-sink effect, iv) miscellaneous, etc.

1. Limited ablation volume

Even using the currently available RF technology, the ablation zone is limited upto 4-5 cm in maximum diameter. Unfortunately, the ablation zone at in-vivo condition usually decreases due to tissue mediated perfusion.[46-49] Furthermore, the incidence of micro-satellite nodules around the main tumor tends to be increase as the tumor size increases. Thus, we need to use multiple electrodes or overlapping ablations with single electrode for achieving enough (5-10 mm) ablative margin surrounding the index tumor. Both solutions has a cost-effectiveness for multiple electrodes and a technically difficulty due to worsening sonic window for overlapping ablations.

2. Technically infeasible tumors

There are many conditions to be technically infeasible for successful ablation.[50-57] The tumor with poor conspicuity is the most common cause of technically infeasible tumor if we use ultrasound as a guiding modality. In this case, we can use contrast-enhanced ultrasound to enhance the conspicuity of index tumor or use CT or MR guidance. If the tumor is located close to the organ, the collateral thermal injury can develop. Most vulnerable organ is the colon, diaphragm, gallbladder, main

bile duct. For minimizing thermal injury to the gastro-intestinal tract and diaphragm, we can use artificial fluid or air to separate the dangerous organ from the ablation zone. Artificial ascites assisted RFA is getting popular in treating the tumor located at the hepatic dome as artificial ascites can improve the sonic window as well as decrease the thermal injury by displacing the liver downward. To minimize thermal injury to the main bile duct, we can use biliary cooling through a naso-biliary catherter during ablation. If the tumor is too exophytic, it is hard to find normal hepatic parenchyma for RF electrode path. It is better to take another alternative such as TACE because the direct puncture of exophytic tumor can increase the possibility of tumor seeding.

3. Heat sink effect

Heat sink effect is a well known phenomenon affecting the negative effect on thermal ablation.[55-57] The convected heat from the adjacent large vessel can decrease the ablation effect which finally resulting in local tumor progression during the follow-up. There are several tips introduced in the literatures. Pringle's maneuver is an established method to minimize the heat-sink effect when we treat the tumor abutting the large vessel. However, open laparotomy is required for this technique. Angiographic technique using balloon catheter has been introduced, but is not popularized. Combined PEI can be an alternative especially for the perivascular site of tumor.

4. Miscellaneous

Needle track seeding is a well known complication of RFA.[22-28] However, it can be decrease if we traverse the normal parenchyma and coagulate the tract enough when removing the electrode. The one of the remaining cons is intravascular spreading of tumor by increasing intratumoral pressure during ablation. When using multi-tined electrode, stepwise deployment of internal prongs can decrease the intratumoral pressure increasement.

SUMMARY

Radiofrequency ablation is the most popular non-surgical technique for treating early stage unresectable HCC because of its excellent local tumor control and acceptable morbidity. Radiofrequency ablation is superior to PEI in terms of local tumor control and survival. Overall survival of radiofrequency ablation is comparable to surgical resection in a selected group of patients with smaller tumors. The most important advantages of RFA is the minimal invasiveness, favorable local tumor control power, promising long-term survival gain, and one of multi-

modality treatment. The cons to be overcome includes the limited ablation volume using current RF technology, substantial proportion of technically infeasible tumors, and heat-sink effect. In conclusion, RFA will play a role of main stream as a local ablative technique in the era of multi-modality treatment of HCC.

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