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Review Article

Radiofrequency Ablation of Hepatocellular Carcinoma: A Literature Review

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Radiofrequency ablation (RFA) of liver cancers can be performed safely using percutaneous, laparoscopic, or open surgical techniques, and much of the impetus for the use of RFA has come from cohort series that have provided an evidence base for this technique. Here, we give an overview of the current status of radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC), including its physical properties, to assess the characteristics that make this technique applicable in clinical practice. We review the technical development of probe design and summarize current indications and outcomes of reported clinical use. An accurate evaluation of treatment response is very important to secure successful RFA therapy since a sufficient safety margin (at least 0.5 cm) can prevent local tumor recurrences. We also provide a profile of side effects and information on the integration of this technique into the general management of patients with HCC. To minimize complications of RFA, physicians should be familiar with each feature of complication. Appropriate management of complications is essential for successful RFA treatment. Moreover, adjuvant therapy, such as molecular targeted therapies following curative therapy, is expected to further improve survival after RFA.

1. Introduction

Hepatic resection forms part of the conventional treatment for patients with hepatocellular carcinoma (HCC); however, the majority of primary liver cancers are not suitable for curative resection at the time of diagnosis. Difficulties of surgical resection may be related to size, site, and number of tumors, vascular and extrahepatic involvement as well as liver function of the patient [1–4]. There is a need to develop a simple and effective technique for the treatment of unresectable tumors within the liver. Therefore, local ablative techniques (percutaneous ethanol injection (PEI), microwave coagulation therapy (MCT), and radiofrequency ablation (RFA)) have emerged in clinical practice to expand the pool of patients considered for liver-directed therapies [5–8]. Especially, RFA is not associated with some of the side effects of other ablative techniques [9]. Thus, RFA is currently performed widely due to the ease of use, safety, reasonable cost, and applicability to minimally invasive techniques [10].

This paper reviews the evidence supporting the use of RFA for HCC.

2. Background

2.1. Localized Application of Radiofrequency Energy. RFA is a localized thermal treatment technique designed to induce tumor destruction by heating the tumor tissue to temperatures that exceed 60°C [11]. The alternating current of radiofrequency waves passing down from an uninsulated electrode tip into the surrounding tissues generates changes in the direction of ions and creates ionic agitation and frictional heating. This tissue heating then drives extracellular and intracellular water out of the tissue, resulting in tissue destruction by coagulative necrosis [12, 13]. When tumor cells are heated above 45–50°C, intracellular proteins are denatured and cell membranes are destroyed through dissolution and melting of lipid bilayers. As a result, successful ablations usually increase the temperature of the ablated tissue to above 60°C.

Percutaneous RFA under local anesthesia was feasible, although intraoperative RFA under general anesthesia was also performed to prevent severe pain and discomfort during the procedure.

2.2. RFA Electrodes and Generators. Three types of RF electrodes are currently available commercially: two brands of retractable needle electrodes (model 70 and model 90 Starburst XL needles, RITA Medical Systems, Mountain View, CA; LeVeen needle electrode, Boston Scientific, Boston, MA) and an internally cooled electrode (Cool-Tip RF electrode; Radionics, Burlington, MA) [14].

The needle electrodes of RITA consist of a 14-gauge insulated outer needle that houses nine retractable curved electrodes of various lengths. When the electrodes are extended, the device assumes the approximate configuration of a Christmas tree. Nine of the electrodes are hollow and contain thermocouples in their tips in order to measure the temperature of adjacent tissue. The alternating electric current generator comes in a 250 W model at 460 kHz (Model 1500X RF Generator, RITA Medical Systems). The ablation algorithm is based on the temperature at the tips of the electrodes. After the ablation cycle is completed, a temperature reading from the extended electrodes in excess of 50°C at 1 min is considered to indicate satisfactory ablation.

Another RFA device (LeVeen Needle Electrode; Radiotherapeutics) has retractable curved electrodes and an insulated 17-gauge outer needle that houses 10 solid retractable curved electrodes that, when deployed, assume the configuration of an umbrella. The electrodes are manufactured in different lengths (2 to 4.0 cm umbrella diameter). The alternating electric current generator is 200 W operated at 480 kHz (RF 3000; Boston Scientific). The ablation algorithm is based on tissue impedance, and ablation is considered successful if the device impedes out.

The third RFA device (Cool-Tip radiofrequency electrode; Radionics) has an insulated hollow 17-gauge needle with an exposed needle tip of variable length (2 or 3 cm). The tip of the needle contains a thermocouple to record the temperature of adjacent tissue. The shaft of the needle has two internal channels that allow the needle to be perfused with chilled water. In an attempt to further increase the size of the ablation area, the manufacturer placed three of the cooled needles in a parallel triangular cluster with a common hub. The generator has a peak power output of 200 W and is operated at 480 kHz (CC-1; Radionics). The ablation algorithm is based on tissue impedance, and ablation is considered successful if the device impedes out. As a result, successful ablations usually increase the temperature of the ablated tissue to above 60°C.

2.3. Treatment Algorithm in Japan and the West. RFA is basically recommended for HCC nodules with a maximum diameter of 3 cm in patients with not more than three tumors who are contraindicated for surgery, although the typical treatment algorithms in Japan, North America, and Europe are each slightly different [35].

One of the major treatment algorithms in Japan is the "consensus-based clinical practice manual for HCC" [14, 36] edited by the Japan Society of Hepatology (JSH). This consensus recommends (1) hepatectomy for a single tumor regardless of tumor size, but local treatment may be selected for a tumor 2 cm or smaller in Child-Pugh B patients; (2) hepatectomy or local treatment when there are 2 or 3 tumors and the tumor size is within 3 cm; (3) liver transplantation for Child-Pugh C patients with 3 or fewer tumors 3 cm or smaller or a single tumor with a tumor size within 5 cm (Milan Criteria); (4) RFA combined with transcatheter arterial chemoembolization (TACE) is recommended for tumors more than 3 cm in diameter. RFA is also recommended for 4 or more nodules where applicable.

In Europe and North America, the algorithm established by the American Association of the Study of the Liver Disease (AASLD) [37] recommends local treatment for 3 or fewer 3 cm or smaller early-stage HCCs and 2-cm or smaller very-early-stage HCCs with complications, such as portal hypertension.

2.4. Assessment of Technical Effectiveness. The assessment of the therapeutic effect of RFA is very important. The technical effectiveness of ablation is commonly assessed by findings on contrast-enhanced CT or MRI. A tumor was considered to have been successfully ablated when there were no longer any enhanced regions within the entire tumor during the arterial phase and at least a 0.5 cm margin of apparently normal hepatic tissue surrounding the tumor during the portal phase [38–40]. Failure to establish a sufficient ablative safety margin was shown to be an independently significant risk factor for local tumor progression on multivariate analysis [41]. Part of the tumor was diagnosed as remaining viable when images of the ablated area showed nodular peripheral enhancement [42].

Basically, the local recurrence rate following a single RFA treatment depends on how strictly the therapeutic effect is assessed. In cases of HCC in which local curative therapy was achieved by securing a safety margin, the 4-year survival rate was relatively high, at 66%–82% (results in Japan) [35, 43].

3. Clinical Outcomes

3.1. Percutaneous Approach

3.1.1. Survival: Comparison with Those after Resection. A randomized control trial (RCT) has shown that RFA achieved survival rates similar to those achieved by resection (Table 1) [15]. Chen et al. conducted RCT on 180 patients with a solitary HCC ≤5 cm indicated to receive either percutaneous RFA or surgical resection [15]. This study showed that percutaneous RFA achieved the same overall and disease-free survival rates as surgical resection for patients with small solitary HCC. The 1- and 4-year overall survival rates after percutaneous RFA and surgery were 95.8%, 67.9% and 93.3%, 64.0%, respectively. The corresponding disease-free survival rates were 85.9%, 46.4% and 86.6%, 51.6%, respectively. Recently, Huang et al. reported an RCT trial in which the 1-, 3-, and 5-year overall survival rates for the RFA group and the RES group were 86.96%, 69.57%, 54.78% and 98.26%, 92.17%, 75.65%, respectively. Overall survival and recurrence-free survival were significantly higher in the

Table 1: Survivals: RFA versus hepatic resection for HCC.

Author/Year	Study type	*n* (RFA/resection)	Mean tumor size (cm) (RFA/resection)	Overall survival (%) (RFA versus resection)	*P*
Chen et al. [15], 2006	RCT	90/90	ND/ND	65.9 versus 64.0 (4-year)	NS
Huang et al. [16], 2010	RCT	115/115	ND/ND	54.78 versus 75.65 (5-year)	.001
Vivarelli et al. [17], 2004	Retrospective	79/79	ND/ND	33 versus 65 (3-year)	.002
Montorsi et al. [18], 2005	Prospective	58/40	ND/ND	30 versus 53 (4-year)	.018
Ogihara et al. [19], 2005	Retrospective	40/47	4.6/7.4	39 versus 31 (5-year)	.79
Wakai et al. [20], 2006	Retrospective	64/85	ND/ND	30 versus 53 (10-year)	.012
Guglielmi et al. [21], 2008	Retrospective	23/33	ND/ND	45 versus 55 (5-year)	.7
Abu-Hilal et al. [22], 2008	Retrospective	34/34	3.0/3.8	57 versus 56 (5-year)	.3
Hiraoka et al. [23], 2008	Retrospective	105/59	ND/ND	59.3 versus 59.4 (5-year)	NS
Ueno et al. [24], 2009	Retrospective	123/110	2.0/2.7	63 versus 80 (5-year)	.06
Takayama et al. [25], 2009	Retrospective	1315/1235	1.6/1.8	95 versus 94 (2-year)	.28

HCC: hepatocellular carcinoma; ND: not described; NS: not significant; RFA: radiofrequency ablation.

Table 2: Local tumor progression rates after RFA for HCC.

Author	Year	*n*	Tumor size (mean, cm)	Follow-up period (mean, months)	Local tumor progression rate (%)
Rossi et al. [26]	1996	41	2.3	22.6	5.0
Buscarimi et al. [27]	2001	60	ND	26.8	14
Choi et al. [28]	2004	53	2.1	23	21
Lu et al. [29]	2005	87	2.5	12.7	5.8
Shiina et al. [30]	2005	118	ND	34.8	1.7
Solmi et al. [31]	2006	63	2.8	32.3	41
Hänsler et al. [32]	2007	21	4.2	ND	21
Waki et al. [33]	2010	88	ND	36	4.8
Li et al. [34]	2010	117	2.4	21	9.4

HCC: hepatocellular carcinoma; ND: not described; RFA: radiofrequency ablation.

surgical resection group than in the RFA group ($P = .001$, $P = .017$). However, percutaneous RFA can be expected to have an advantage over liver resection in providing a better short-term postoperative result because local ablative therapy is a less invasive procedure [16–25].

3.1.2. Local Controllability (Local Tumor Progression). The local recurrence rate after RFA for HCC ranged from 1.7% to 41% [26–34] (Table 2). Local tumor progression is related to incomplete tumor ablation. It is often difficult to obtain a specific safety margin in three dimensions all around a large tumor. Some researchers reported that the most important factor associated with failure of local tumor control could be tumor size [8, 36–38]. In Table 2, local tumor progression did not necessarily depend on the tumor size; however, recurrence could occur even after a sufficient margin had been ensured. It is considered that local recurrence appears to arise from residual cancer after RFA while recurrence from a microsatellite or by microvascular invasion other than the main nodule may also appear as a late local recurrence. The local tumor progression rate can differ markedly depending on whether or not a 5 mm circumferential safety margin has been secured. Nishijima et al. categorized the presence of no margin, a partially lacking margin, margin narrower than 5 mm, and complete margin wider than 5 mm as R0, R1, R2, and R3 on the assessment of the therapeutic effect of RFA, respectively, and found significant differences in the local recurrence rate between R0 and R1 and between R2 and R3. The local recurrence rate significantly differed between patients with and without a sufficient safety margin [44].

Therefore, ensuring a safety margin in RFA is important for not only the simultaneous treatment of microsatellite lesions, but also to ensure sufficient tumor ablation on the assumption of a partial volume effect-associated limitation on evaluation of the therapeutic effect by imaging.

3.1.3. Advances of Techniques: Large HCC. Tumor size is an important factor influencing the local recurrence rate after RFA [45]. To increase the size of the coagulation zone in RFA, physicians have tried using vascular occlusion during RFA because vascular occlusion reduces heat dispersion. It was shown in the consensus meeting "HCC Treatment" at the 45th Annual Meeting of the JSH in Kobe in 2009 [46] that about 90% of physicians performing RFA employ lipiodol TACE-preceded RFA for 3 cm or larger HCCs. Lipiodol TACE-preceded RFA is relatively curative and can be readily performed for the following reasons: (1) lipiodol regurgitates into the portal branches via the peribiliary venous plexus, causing a transient state of liver infarction, which reduces the cooling effect, expanding the ablative area, and resulting in (2) coagulation of satellite lesions [43]. Peng et al. reported a series of 120 patients with HCC, and the 1-, 3-, 5-year overall survival rates for TACE-preceded RFA and RFA groups were 93%, 75%, 50%, and 89%, 64%, 42%, respectively ($P = .045$) [47]. Yamakado et al. reported that the survival rates of large HCC cases treated with resection and lipiodol TACE-preceded RFA were almost equivalent [48]. TACE combined with RFA therapy might improve the overall survival status for patients with large HCCs (Table 3) [47, 49–52].

3.1.4. Advanced Techniques: Tumors Abutting the Diaphragm and Gastrointestinal Tract. Ultrasound- (US-) guided procedures are necessary but limited for tumors located under the diaphragm. However, saline solution injection into the pleural cavity can separate the lung and liver on B-mode US, that is, artificial pleural effusion acts as an acoustic window. There are reports on the feasibility and safety of RFA with artificially induced pleural effusion for HCC located in the right subphrenic region [53–56]. In a series of 24 patients with HCC located in the hepatic dome, 200–1100 mL of 5% glucose solution was infused intrathoracically to separate the lung and liver, thus, complete tumor necrosis in a single session was achieved in 96.4% [56].

Artificial preparation of a space between the intestine and nodule by infusing normal saline or 5% glucose (artificial ascites method) for treatment has recently become possible [57, 58]. These techniques markedly expanded the indication for RFA. Laparoscopic resection or laparotomic RFA had to be inevitably performed in patients with HCC nodules <2.0 cm in diameter before the introduction of artificial ascites, but more than 90% of cases are now treatable by the "artificial ascites method".

3.1.5. Advanced Techniques: Cases That Are Unclear on B-Mode US. Multiple RFA sessions for HCCs were frequently required because of HCC nodules that are unclear on B-mode US. Under CT fluoroscopy using either CT arteriography or iodized oil injection, we can target and puncture hepatic malignancies using a percutaneous ethanol injection needle. Real-time CT fluoroscopy is useful to guide the needle puncture and to monitor ethanol injection in small hepatic malignancies [67]. Another merit is that the efficacy of treatment can be evaluated using contrast enhanced CT immediately after treatment.

Contrast enhanced harmonic US imaging is able to evaluate small hypervascular HCCs even when B-mode US cannot adequately characterize the tumors [68–72]. The microbubbles of these contrast agents provide stable nonlinear oscillation in a low-power acoustic field because of the hard shells of these bubbles, producing great detail in the harmonic signals in real time [71–73]. It has been reported that contrast harmonic sonography-guided RFA is an efficient approach for guiding further ablation of hepatic malignancies that are not clearly demarcated by B-mode US [74–78].

Virtual CT sonography using magnetic navigation (Real-time Virtual Sonography (RVS); HITACHI Medico, Tokyo, Japan) provides cross sectional images of CT volume data corresponding to the angle of the transducer in the magnetic field in real-time. This imaging technique displays a real-time synchronized multiplanar CT image in precisely the same slice of the US plane. Thus, RVS can be used for real-time needle insertion guidance, especially for nodules demonstrated on CT, but not on US [79, 80].

3.2. Laparoscopic/Open Surgical Approach. The use of a laparoscopic or open approach allows repeated placement of RFA electrodes at multiple sites to ablate larger tumors [59–66] (Table 4). Moreover, a hand-assisted technique can be applied safely and effectively to laparoscopic liver surgery and offers the advantages of intraoperative US, which provides better resolution of the number and location of liver tumors. The postoperative recovery of patients was shorter compared with that after an open surgical approach. Ishiko et al. reported that the surgical procedures consisted of 5 RFA sessions for tumors in the caudate lobe with hand-assisted laparoscopic surgery (HALS) and a postoperative CT scan demonstrated sufficient ablation in all patients and there was no surgical mortality [63]. The HALS approach has several advantages; it facilitates and expedites the procedure, reduces the stress factor on the surgeon, greatly improves exposure, and facilitates immediate and efficient control of bleeding vessels with the internal hand. However, the local treatment failure rate of the laparoscopic approach was higher in patients with HCC nodules situated deep within the liver and measuring 4 cm or more in diameter [81]. Great difficulty can be encountered during treatment of lesions in contact with the diaphragm.

Although more invasive, open RFA can be performed more easily, and the puncture course of RF needle can be more widely selected than that during laparoscopic approach. Some have reported that patients undergoing radical open RFA demonstrated few ablation site recurrences even though the nodules measured more than 4 cm in diameter and/or there were more than three nodules [59, 62, 65].

3.3. Complications. A recent review indicated that complication rates for percutaneous, laparoscopic, and open RFA of hepatic tumors in 3670 patients were 7.2%, 9.5%, and

Table 3: Survivals: RFA combined with TACE versus RFA alone for HCC.

Author/year	*n* (TACE+RFA/RFA)	Tumor size (mean, cm) (TACE+RFA/RFA)	Overall survival (%) (TACE+RFA/RFA)	*P*
Kitamoto et al. [49]/2003	10/16	3.9/3.4	ND	
Wang et al. [50]/2007	43/40	ND	68.3/57.6 (1-year)	<.05
Shibata et al. [51]/2009	46/43	ND	84.8/84.5 (3-year)	.515
Morimoto et al. [52]/2010	19/18	3.6/3.7	93/80 (3-year)	.369
Peng et al. [47]/2010	120/120	ND	50/42 (5-year)	.045

HCC: hepatocellular carcinoma; ND: not described; RFA: radiofrequency ablation, TACE: trans catheter arterial chemoembolization.

Table 4: Laparoscopic/open RFA for liver malignancies: local tumor progressions and survivals.

Author/year	Arms	*n*	Tumor size (mean, cm)	Follow-up period (mean, months)	Local tumor progression	Survival (%)
Topal et al. [59]/2003	LS/open	9/9	3.8/3.5	12.2	1/9, 0/9	ND
Berber et al. [60]/2005	LS	66	4.1	25.3	ND	38% (3-year)
Hildebrand et al. [61]/2007	LS	14	ND	23.2	1/14	ND
Minami et al. [62]/2007	open	30	3.2	18.9	1/30	71.6% (3-year)
Ishiko et al. [63]/2008	HALS	5	ND	32.2	1/5	ND
Ballem et al. [64]/2008	LS	104	3.5	23	ND	21% (3-year)
Tanaka et al. [65]/2009	open	26	ND	ND	1/26	ND
Salama et al. [66]/2010	LS	72	ND	14.3	2/72	ND

HALS: hand-assisted laparoscopic surgery; LS: laparoscopy; ND: not described; RFA: radiofrequency ablation.

9.9%, respectively [82]. Overall, the frequency of major complications of percutaneous RFA ranged from 0.6%–8.9%, which was higher than that of PEI, but generally less than that of MCT [43]. Complications of percutaneous RFA reported in 2320 patients treated at 41 different hospitals in Italy indicate that the mortality rate was 0.3% with an overall complication rate of 7.1% [83, 84]. The authors described major complications (2.4% incidence) including death, hemorrhage, RFA needle-track seeding, RFA lesion abscess, perforation of gastrointestinal viscus, liver failure, biloma, biliary stricture, portal vein thrombosis, and hemothorax or pneumothorax requiring drainage, and minor complications (4.7% incidence) including pain, fever, and asymptomatic pleural effusion. Although Llovet et al. [85] reported that dissemination along puncture route was observed in 12.5% of their patients, dissemination might not occur at such a high frequency. This complication was almost absent in many reports from Japan [43].

Theoretically, a tumor that is contiguous to a large vessel is more likely to have some viable tumor cells following local thermal therapy because there is a significant tissue cooling effect caused by blood circulation of normal body temperature. Thus, the effort to thoroughly ablate the lesion with a safety margin under such conditions increases the total number of electrode insertions, and this may increase the risk of complications. Some investigators have suggested that tumor location is closely related to the risk of major complications. Central tumors close to the hepatic hilum were reported to be unsuitable for percutaneous RFA because of the risk of injuring adjacent bile ducts [7]. Moreover, peripheral tumors adjacent to extrahepatic organs were also suggested to be unsuitable because of the risk of heat injuries, such as intestinal perforation and pleural effusion [84, 86]. However, Teratani et al. reported that there was no difference in early complication rates according to tumor location [87]. The effort to achieve thorough ablation increased the total number of electrode insertions, and this may have led to an increase in complications.

Not only elevating the survival rate and reducing the incidence of local recurrence but also avoiding complications as much as possible are major tasks. To minimize complications of RFA, knowledge of risk factors and prevention methods is required. In addition, because early and accurate diagnosis is necessary for the appropriate management of complications, physicians should be familiar with all features of complication.

4. Future Perspective

Currently, a multicenter randomized controlled study (prospective randomized study of surgery or RFA for early HCC: SURF Trial) is underway in Japan, involving patients with 3 or fewer tumors 3 cm or smaller for which both hepatectomy and RFA are applicable [88], and a large global study is currently underway (the Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of HepatocellularCarcinoma

(STORM) trial), looking at the efficacy of sorafenib therapy after potentially curative treatment with liver resection or RFA.

5. Conclusion

Here, we have assessed the role of RFA in the overall therapeutic strategy for patients with HCC and highlighted deficiencies in current knowledge. We intend to strive for a balanced discussion between the tendency to overemphasize the potential advantages of RFA and the tendency to understate a potentially useful treatment. Percutaneous RFA can achieve the same overall and disease-free survival rates as surgical resection for patients with small HCC, while causing few side effects. Percutaneous RFA combined with TACE will make the treatment of larger tumors a clinically viable treatment alternative. The use of a laparoscopic or open approach allows repeated placement of RFA electrodes at multiple sites to ablate larger tumors. In addition, an accurate evaluation of treatment response is very important to secure successful RFA therapy since a sufficient safety margin (at least 0.5 cm) can prevent local tumor recurrence. Adjuvant therapy, such as molecular targeted therapies following curative therapy, is expected to further improve survival after RFA.

Authors' Contributions

Y. Minami drafted the paper and wrote the final version of the paper. M. Kudo reviewed and approved the final version of the paper.

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