REVIEW ARTICLE

Ultrasonography-Guided Radiofrequency Ablation in Hepatocellular Carcinoma: Current Status and Future Perspectives

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Radiofrequency ablation (RFA) is one of the curative treatment modalities for small (diameter, \( \leq 3 \) cm) or early stage (single tumor \( \leq 5 \) cm in diameter or up to three tumors of \( \leq 3 \) cm diameter each) hepatocellular carcinoma (HCC). RFA is more commonly used than other local ablative modalities because the technique is highly effective, minimally invasive, and requires fewer sessions. RFA is advocated as the first-line curative therapy for unresectable or even resectable very early stage or early stage HCC based on a survival rate comparable to that seen with resection. Although RFA is highly effective for local ablation of small HCC tumors, current RFA procedures are less effective against tumors that are in high-risk or difficult-to-ablate locations, are poorly visualized on ultrasonography (US), are associated with major complications, and are large (\( > 3 \) cm in diameter). Recent advances can overcome these issues by creation of artificial ascites or pleural effusion, application of real-time virtual US assistance, incorporation of contrast-enhanced US before or after RFA, use of combination therapy before RFA, or switching RF controller with multiple electrodes. This review article provides updates on the clinical outcomes and advances in RFA in the treatment of HCC, particularly the aforementioned issues.

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Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cancer worldwide [1]. Current diagnostic modalities and surveillance programs can detect HCC at early stages [2], and various curative modalities [including surgical resection, orthotopic liver transplantation (OLT), and local ablation] can achieve 5-year overall survival rates of 50–70% [3–6]. Because of underlying loss of liver function and shortage of donor livers, resection and OLT are uncommonly used as a first-line therapy for small HCC tumors (diameter, ≤3 cm) [3–6]. Therefore, local ablative therapies [including percutaneous ethanol injection (PEI), percutaneous acetic acid injection, radiofrequency ablation (RFA), and microwave ablation (MWA)] have been suggested for the treatment of small HCC tumors [3–7]. Since the introduction of RFA for liver cancer in 1993, numerous groups have reported the use of RFA. The technique has gained more attention than other local ablative modalities for the treatment of HCC because of more predictable ablation extent, high effectiveness, minimal invasiveness, and the need for fewer treatment sessions [8–12]. RFA also provides survival rates equivalent to those seen with surgical resection for small HCC tumors [13–17]. As a result, RFA has been advocated as a first-line curative therapy for very early stage [i.e., Barcelona Clinical Liver Cancer (BCLC) Stage 0] [4] or unresectable early stage (BCLC Stage A) HCC [13–17]. Although RFA is highly effective for treating small HCC tumors, application of the technique is potentially limited for tumors in high-risk or difficult-to-ablate locations, for tumors that are poorly visualized under ultrasonography (US), for HCC with major complications, and for large tumors (diameter, >3 cm) [13–19]. Recent advances can overcome these issues by artificial instillation of intraperitoneal or intrapleural fluid before RFA [20,21], application of contrast-enhanced US before or after RFA [22,23], real-time virtual sonography assistance [24,25], combination therapy before RFA, or switching radiofrequency (RF) controller with multiple electrodes [26–28]. This review article provides updates on the clinical outcomes and advances in RFA therapies, particularly in the context of the aforementioned issues.

Current role of RFA in HCC

Based on the results from several randomized controlled trials and meta-analyses, RFA has been accepted in various HCC guidelines as a first-line curative therapy for small HCC tumors [3–6,29–32]. The high reproducibility of RFA also makes the technique particularly appealing for treatment of intrahepatic recurrences after the application RFA or other ablative therapies [33,34]. Because of extreme shortages of donor livers for OLT, RFA, and transarterial chemoembolization are currently accepted as bridge therapies for early stage HCC patients awaiting liver transplantation [35–37]. It has been shown that tumor progression beyond 12 months increased markedly after RFA for early stage HCC, particularly for patients in whom initial complete ablation failed and who exhibited baseline α-fetoprotein (AFP) above 200 ng/mL and Child–Pugh B status [38]. Therefore, prompt transplantation is required for patients with risk factors in early stage HCC after RFA. We also found that a delay (>5 weeks after diagnosis) in RFA treatment of early stage HCC may impact the survival of patients with HCC detected in a surveillance program [39].

Complete ablation of HCC after RFA

A conventional RFA device with a single electrode or deployed electrode and 3–4 cm thermal diameter placed into the tumor provided a complete ablation rate of over 90% for small tumors (diameter, ≤3 cm), but yielded lower rates of 53–61% for medium-sized tumors (diameter, 3.1–5 cm) and 20–45% for larger tumors (>5 cm) [40–43]. Therefore, various novel devices, including a switching RF controller with two to six unipolar or bipolar electrodes, have been proposed with the aim of providing a larger ablation zone in a shorter time, reducing the number of overlapping ablations required, and creating a larger safety margin for HCC measuring >3 cm. A few preliminary results are available; notably, Lee et al reported that this device showed a 97% rate of complete ablation in HCC of 3.1–5 cm in diameter [26–28]. A deployed RF electrode was reported to provide a 5–7 cm diameter ablation with a single electrode placement, but the shape of the domain ablated by such an electrode was not circular, and the device’s multiple times had the potential to puncture adjacent vital structures [44]; therefore, the use of this device is not common.

Some refined algorithms can also enhance complete ablation or simplify the application of RFA. In our experience, an interactive algorithm was more effective than the standard algorithm when using a LeVeen deployed electrode, particularly for HCC larger than 2 cm in diameter [45]. We also found that combined use of PEI and RFA achieved comparable levels of complete ablation for tumors that were adjacent to a larger vessel (>3 mm in diameter, i.e., vessels expected to induce a heat-sink effect) and for tumors located close to vital structures [46]. In addition, the inhibition of angiogenesis (by transarterial chemoembolization or medication with thermo-doxorubicin) prior to RFA has been reported (or proposed) to enhance the degree of complete ablation [47–51].

Local tumor progression (i.e., local recurrence) of HCC after RFA

In contrast to the efficacy seen with resection, local recurrence (LR) rates of small HCCs after RFA were 1.3–14% at 1 year, 1.7–24% at 2 years, and 3.2% at both 5 and 10 years [9–12,52–59] (Table 1). Factors correlated with LR included larger tumor size (diameter, >2 cm or >3 cm), tumor without encapsulation, poorly differentiated HCC, sub-capsular location, ablative margin <1 cm, or the presence of a structure expected to provide heat-sink effects [9–12,52–55]. This increase in LR is presumably due to unexplored satellite nodules, insufficient safety margin, or incomplete ablation due to limitations of current imaging modalities in detection of tumors [9–12,52–55]. Novel RF devices or refined algorithms enhancing complete ablation may also minimize LR.
Additional new recurrence of HCC after RFA

Because of underlying advanced liver disease in the presence of HCC, additional new recurrence is very common in patients with HCC. A recurrence rate of 81% was reported at 4 years in small HCCs after RFA, a level comparable to that seen after resection [54], but 5- and 10-year recurrence rates of 74.8% and 80.8%, respectively, were reported by Shinya et al in a 10-year follow-up [55]. Recurrence correlated with platelet counts of $<100 \times 10^9$/L, but only in the study by Camma` et al [54]. Some investigators expressed concern that RFA itself might induce the spread of tumors [60]. Our study showed that the occurrence of a popping sound (a possible indication of local pressure) during RFA did not correlate with tumor progression [61]. Nevertheless, if gas is observed spreading into adjacent vessels during RFA, the electrode’s direction and/or position may have to be changed in order to reduce the spread of tissue that may have been incompletely coagulated at an earlier stage of ablation [11]. Further study of the rate of rapid recurrence of HCC and the associated factors or biomarkers might be needed to elucidate the associated risk factors. For HCC in high-risk locations, use of RFA at low RF power ($<120$ W) and maximum power demonstrated that the former resulted in fewer major complications [62].

Overall recurrence of HCC after RFA

The overall tumor recurrence rates of small HCCs after RFA were 18–22% at 1 year, 30–48% at 2 years, 44–61% at 3 years, up to 71% at 4 years, and 83% at 5 years [9–12, 54, 56, 57]. Independent factors correlated with higher overall recurrence of HCC included a low platelet count ($<100 \times 10^9$/L), positive status for anti-hepatitis C virus (anti-HCV) antibody, cirrhotic liver, increase in prothrombin time by $>80\%$, multiple tumors, and higher Edmondson’s grade (II or III) [11, 54]. Overall HCC recurrence might be related to LR and tumor recurrence. To increase complete necrosis, reduce LR, and prevent the progression of underlying liver disease using antiviral therapies for chronic hepatitis B or C which may also reduce overall tumor recurrence [3, 4].

Long-term survival of HCC patients after RFA

Data on long-term survival are very limited. A small number of studies reported overall survival rates of 80–100% at 1 year, 63–98% at 2 years, 45–67% at 3 years, 74% at 4 years, 41–60% at 5 years, and 27–60% at 10 years [9–12, 54, 56–59] (Table 1). Longer survival was commonly observed in sub-groups with younger age, hepatitis C virus, early Child-Pugh class, small tumor size, low serum or lectin-reactive AFP level, low des-γ-carboxyprothrombin level, well-differentiated tumors, and solitary tumors [9–12, 54, 56, 57]. Recent studies have showed that RFA can result in good 5-year survival rates (68% as reported by Livraghi et al [8]; 76% as reported by N’Kontchou et al [58]) for very early stage operable HCC. Recent studies also showed similar survival rates in very early stage or early stage HCC when compared to resection [15, 16], and comparable recurrence rates in very early stage HCC for the two treatment modalities [15].

Comparison of RFA with resection

RFA has an efficacy equivalent to that of surgical resection in small HCCs. Therefore, the 2012 European Association for the Study of the Liver HCC guidelines (and some reports) advocate that RFA can also be an option for patients with very early stage (BCLC-0) HCC or BCLC-A-grade resectable

### Table 1: Results of radiofrequency ablation (RFA) for early-stage hepatocellular carcinoma.

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. of cases</th>
<th>Maximum tumor size (cm)</th>
<th>Mean follow-up (mo)</th>
<th>Local recurrence (%): 1/2/3/5/10 y</th>
<th>New hepatic or extrahepatic recurrence (%): 1/3/5/10 y</th>
<th>Overall recurrence (%): 1/3/5/10 y</th>
<th>Survival rate (%): 1/3/5/10 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>[9]</td>
<td>52</td>
<td>≤4</td>
<td>25</td>
<td>12/18/18/NA/NA</td>
<td>24/47/NA</td>
<td>NA</td>
<td>90/74/NA/NA</td>
</tr>
<tr>
<td>[11]</td>
<td>118</td>
<td>3</td>
<td>37 (median)</td>
<td>1.3/1.7/1.7/1.7/NA</td>
<td>NA</td>
<td>22/3/61/70</td>
<td>97/81/74/4y/NA</td>
</tr>
<tr>
<td>[56]</td>
<td>87</td>
<td>≤2</td>
<td>27.6 (median)</td>
<td>1.3/2.4/2.4/2.4/NA (total cases)</td>
<td>NA</td>
<td>NA</td>
<td>100/90.8/83.8/NA</td>
</tr>
<tr>
<td></td>
<td>215</td>
<td>2.1–5</td>
<td>27.6 (median)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>93/74.3/45.2/NA</td>
</tr>
<tr>
<td>[57]</td>
<td>206</td>
<td>5</td>
<td>24</td>
<td>12/24/30 (30 mo)/NA/NA</td>
<td>14/49/81</td>
<td>18/55/83</td>
<td>97/67/41/NA</td>
</tr>
<tr>
<td>[54]</td>
<td>202</td>
<td>5</td>
<td>19</td>
<td>12/24/30 (30 mo)/NA/NA</td>
<td>13/30/30 (30 mo)/NA/NA</td>
<td>22/44</td>
<td>80/67/49/30/NA/NA</td>
</tr>
<tr>
<td>[59]</td>
<td>570</td>
<td>5</td>
<td>30</td>
<td>11.8a</td>
<td>52</td>
<td>NA</td>
<td>NA/NA</td>
</tr>
<tr>
<td>[8]</td>
<td>216</td>
<td>2</td>
<td>31</td>
<td>0.9a</td>
<td>NA</td>
<td>NA</td>
<td>NA/76/55/NA</td>
</tr>
<tr>
<td>[58]</td>
<td>235</td>
<td>5</td>
<td>27</td>
<td>11.5</td>
<td>42</td>
<td>NA</td>
<td>NA/60/40/NA</td>
</tr>
<tr>
<td>[55]</td>
<td>1170</td>
<td>&gt;5</td>
<td>38.2</td>
<td>1.4/3.2/3.2/3.2/3.2</td>
<td>25.6/74.8/78.1/80.8/NA</td>
<td>NA</td>
<td>97/82.8/63/48.8/31 (for HCC ≤5 cm)</td>
</tr>
</tbody>
</table>

NA = not available.

*a* Noncumulative rates only; value represents rate in the follow-up period.
HCC that is not suitable for resection. Some randomized or cohort studies (with or without propensity score matching) reported that RFA achieved a good 5-year survival rate for very early stage operable HCC, and provided a survival rate in very early stage or early stage HCC that was comparable to that seen with resection [8,15,16,58,63,64] and comparable recurrence in very early stage HCC [14,15] (Table 2).

Comparison of RFA with PEI and MWA

Among various local modalities, both PEI and RFA are the most widely employed. Several randomized control trials, cohort studies, and meta-analyses have shown that RFA is superior to PEI for small HCCs, in terms of more predictable necrosis in any size of HCC, higher complete ablation, lower LR, and higher overall survival rate [8–11,17,18,29–32]. Conventional MWA provides only a 2 cm diameter thermal ablation per electrode placed into the tumor; however, RFA provides a 2–5 cm diameter thermal ablation per electrode. Thus, RFA is more useful than MWA for the treatment of small HCCs because RFA provides a lower LR rate, yields a higher survival rate, and requires fewer treatment sessions [65–67].

RF electrodes

Various RF electrodes (including deployed electrodes with multiple tines, and internally cooled unipolar or bipolar electrodes) are currently available. Some studies have shown equivalent efficacy (regarding the complete necrosis and local tumor progression) among the various RF electrodes [44,65]. The characteristics of bipolar RF electrodes preclude touching of the tumor when treating smaller tumors; for HCC measuring <3 cm in diameter, the applicator is outside the tumor but for HCC >3 cm in diameter the applicator is inside the tumor, at a interprobe distance [27]. The benefit of no-touch ablation includes prevention of rupture of the tumor capsule, thereby presumably reducing the danger of tumors spreading before ablation and reducing LR. However, no-touch ablation has limitations, including difficulties in probe insertion for tumors at high-risk locations or in narrow spaces. Additionally, this technique may require free-hand insertion of three to six probes [27].

Table 2  Studies comparing radiofrequency ablation and hepatic resection for hepatocellular carcinoma.

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study design</th>
<th>Treatment method</th>
<th>No. of patients</th>
<th>Max size (cm)/no. of tumor(s)</th>
<th>Overall survival rate (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>[63]</td>
<td>Cohort</td>
<td>RFA C-P A: 43</td>
<td>NA</td>
<td>82</td>
<td>NA 43</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>C-P A: 70</td>
<td>NA</td>
<td>88</td>
<td>NA 71</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>RFA</td>
<td>C-P B: 36</td>
<td>NA</td>
<td>74</td>
<td>NA 25</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>C-P B: 9</td>
<td>NA</td>
<td>52</td>
<td>NA 19</td>
<td>0.036</td>
</tr>
<tr>
<td>[14]</td>
<td>RCT</td>
<td>RFAa C-P A: 71</td>
<td>5/1</td>
<td>95.8</td>
<td>82.1 71.4</td>
<td>67.9b NS</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>C-P A: 90</td>
<td>5/1</td>
<td>93.3</td>
<td>82.3 73.4</td>
<td>64.0b NS</td>
</tr>
<tr>
<td>[15]</td>
<td>Propensity</td>
<td>RFAa 66</td>
<td>2/1</td>
<td>98.3</td>
<td>94.9 86.4</td>
<td>77.8 NS</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>C-P A: 50</td>
<td>2/1</td>
<td>100</td>
<td>95.9 91.1</td>
<td>84.6</td>
</tr>
<tr>
<td>[16]</td>
<td>Cohort</td>
<td>RFA 91</td>
<td>2/1</td>
<td>96.7</td>
<td>NA 80.3 72</td>
<td>0.073</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>52</td>
<td>2/1</td>
<td>98</td>
<td>NA 98 91.5</td>
<td>0.0003</td>
</tr>
<tr>
<td>[16]</td>
<td>RFA 254</td>
<td>3/3, 5/1</td>
<td>91.6</td>
<td>NA 73.5</td>
<td>57.4 0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR 208</td>
<td>96.1</td>
<td>87.8</td>
<td>71.2</td>
<td>0.342</td>
<td></td>
</tr>
<tr>
<td>[64]</td>
<td>RCT</td>
<td>RFAa 84</td>
<td>4/2</td>
<td>93.1</td>
<td>83.1 67.2</td>
<td>NA 0.342</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>84</td>
<td></td>
<td>96</td>
<td>87.6 74.8</td>
<td>0.034</td>
</tr>
</tbody>
</table>

C-P = Child–Pugh class; HCC = hepatocellular carcinoma; HR = hepatic resection; NA = not available; NS = not significant; RCT = randomized controlled trial; RFA = radiofrequency ablation.

a Additional treatment with ethanol injection or chemoembolization.

b 4-year survival rate.

RFA for HCC in difficult-to-treat or high-risk locations

RFA for HCC in difficult-to-treat or high-risk locations is a challenge; spatial challenges can make it difficult to achieve complete necrosis [18,46,68]. A “difficult-to-treat” tumor is generally defined as a tumor located within 1 cm of a vital structure, such as the GI tract, gallbladder, visible intrahepatic bile duct, or vessel, particularly vessels >3 mm in diameter [18,46,52,68]. Several strategies have been developed to counter these problems. Combined use of ethanol injection and RFA achieves a higher rate of complete necrosis than RFA monotherapy in HCC in a high-risk location [46]. In addition, we observed comparable clinical outcomes using RFA at low RF power (≤120 W) and maximum RF power (>120 W), with considerably fewer adverse effects encountered in the low-power group, particularly in difficult-to-treat HCC [62]. Artificial ascites or artificial pleural effusion has also been employed as an adjunct to percutaneous RFA for tumors in problematic locations. The safety and efficacy of artificial ascites or artificial pleural creation has been evaluated at several sites [20,21,69,70]. Ultimately, open or laparoscopic RFA is also recommended as an alternative, but both of these techniques are more invasive and require a technically demanding approach to electrode placement due to limited access [71–73].
RFA with switching RF controller and multiple RF electrodes

Current RFA devices are more effective in HCC >3 cm in diameter [18]. Recently, application of a switching RF controller with simultaneous placement of unipolar or bipolar RF electrodes has been reported to create a larger ablation in a shorter time [26–28]. Very limited but promising preliminary results have been reported for treatment of HCC with RFA administered via simultaneous use of two or three RF electrodes and a switching RF generator [26–28]. In our center, we enrolled 70 patients with at least one index HCC tumor >3.0 cm in diameter for treatment (between 1 January 2009 and 31 December 2011) using a switch-control RFA with 2–3 RF electrodes. Fifty-three (75.7%) patients had a total of 58 index tumors of medium size (3.0–4.9 cm in diameter), and the remaining patients had a total of 17 large tumors (5.0–7.0 cm in diameter). The mean diameters of the index tumors were 3.7 ± 0.5 cm and 5.7 ± 0.6 cm, respectively. The rates of complete ablation after the first session were 79.3% (46/58) and 82.4% (14/17), respectively. After an additional one or two RFA sessions for each patient, the rate of primary technique effectiveness was scored as 91.4% (medium-size tumors) and 94.1% (large tumors). After a mean follow-up of 21.0 ± 10.2 months, 12 (18.8%) patients exhibited local tumor progression and 10 (14.3%) patients had died. Estimated cumulative overall survival rates and local tumor progression rates were 93.9% and 84.6% (1 year), 81.3% and 10.7% (2 years), and 17.2% and 32.8% (3 years), respectively. Comparing conventional RFA with single RF electrode and sequential ablation, the rate of complete ablation was 53–61% in medium-sized HCC and 20–45% in large HCC. Seror et al used switching RFA and showed 81% of complete ablation in HCC >5 cm [27], and Lee et al showed 97% in HCC of 3.1–5 cm [28]. Therefore, RFA with two or three electrodes and a switching RF generator achieved a high rate (>90%) of complete ablation for medium-size and large HCC.

Moreover, RFA with multiple bipolar RF electrodes connected via a switching RF generator could create a larger coagulation necrosis by enabling placement of RFA electrodes with interelectrode distances as great as 3 cm [27]. This method may reduce the risk of tumor spreading in small HCC, since this technique permits the use of no-touch RFA for tumors >3 cm in diameter. From November 2010 to April 2011, we enrolled six patients with solitary HCC >2.5 cm in diameter. Three bipolar RFA electrodes were placed just outside the margin of the tumor, and the procedure was conducted using a switching RF generator. The results showed that the mean lengths of the three dimensions of the tumors were 1.6 ± 0.3 cm, 1.6 ± 0.4 cm, and 2.1 ± 0.4 cm before RFA and 3.8 ± 0.4 cm, 3.2 ± 0.6 cm, and 3.9 ± 0.6 cm after RFA (all p < 0.05). The total tumor volume before and after RFA were 3.0 ± 1.4 cm³ and 24.5 ± 6.0 cm³ (p < 0.001). Transient postablative pain or fever (Grade 1–2) was reported. No LR has been observed at >6 months of follow-up after RFA (median follow-up, 10.2 ± 2.5 months). These results suggest that RFA using a switching RF generator, multiple bipolar RF electrodes, and a no-touch method may effectively ablate HCCs >3 cm in diameter with sufficient safety margin and minimal risk of tumor spread. A larger sample size and a longer observation period are required to confirm potential clinical efficacy.

Future perspectives

Recent advances in RFA include application of switching RFA with several RF electrodes in the treatment of large HCC with higher complete ablation rate and fewer ablation sessions. However, further experimentation is required to confirm the benefit(s) of switching RFA, particularly in comparison to switching MWA, cryoablation, high-intensity focused US, and electroporation. Additionally, the benefit(s) of combination therapies using RFA with chemembolization or other medications requires confirmation by randomized or comparative studies. The assessment of the efficacy of RFA may also be improved by using contrast enhanced-US, with or without three-dimensional sonography or real-time virtual sonography assistance.

References


