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Review

Local Ablation for Hepatocellular Carcinoma in Taiwan

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Key Words
Complete ablation · Hepatocellular carcinoma · Local ablation · Local recurrence · Radiofrequency ablation

Abstract
Hepatocellular carcinoma (HCC) is the second commonest cancer in Taiwan. The national surveillance program can detect HCC in its early stages, and various curative modalities (including surgical resection, orthotopic liver transplantation, and local ablation) are employed for the treatment of small HCC. Local ablation therapies are currently advocated for early-stage HCC that is unresectable because of co-morbidities, the need to preserve liver function, or refusal of resection. Among the various local ablation therapies, the most commonly used modalities include percutaneous ethanol injection and radiofrequency ablation (RFA); percutaneous acetic acid injection and microwave ablation are used less often. RFA is more commonly employed than other local ablative modalities in Taiwan because the technique is highly effective, minimally invasive, and requires fewer sessions. RFA is therefore advocated in Taiwan as the first-line curative therapy for unresectable HCC or even for resectable HCC. However, current RFA procedures are less effective against tumors that are in high-risk or difficult-to-ablate locations, are poorly visualized on ultrasonography (US), or are large. Recent advancements in RFA in Taiwan can resolve these issues by the creation of artificial ascites or pleural effusion, application of real-time virtual US assistance, use of combination therapy before RFA, or use of switching RF controllers with multiple electrodes. This review article provides updates on the clinical outcomes and advances in local ablative modalities (mostly RFA) for HCC in Taiwan.

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Overview of Treatment for Early-stage HCC in Taiwan

Hepatocellular carcinoma (HCC) is the second commonest cancer in Taiwan [1]. A national surveillance program has been in operation for several decades and we are able to detect HCC at its early stages [2]. Various curative modalities [including surgical resection, orthotopic liver transplantation (OLT), and local ablation] can achieve overall 5-year survival rates of 50–70% [3, 4]. Because of the resulting reduction in liver function and the shortage of donor livers, resection and OLT are not commonly employed as first-line therapies for small HCC (tumor number ≤ 3, maximum diameter of each ≤ 3 cm) or early-stage HCC (single tumor ≤ 5 cm in diameter, or tumor number ≤ 3, maximum diameter of each ≤ 3 cm) [5–8]. Therefore, nonsurgical curative local ablation therapies are currently advocated for early-stage HCC that is unresectable because of co-morbidities, the desire to preserve liver function, or refusal of surgical treatment. Among the various local ablation therapies, the most commonly used modalities include percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA), whereas percutaneous acetic acid injection (PAI) and microwave ablation (MWA) are less often used [5–9].

Since the introduction of RFA for liver cancer in 1993, numerous groups have reported its use. The technique has gained more attention than other local ablative modalities for the treatment of HCC because the extent of ablation is more predictable and because of its high effectiveness, minimal invasiveness, and the need for fewer treatment sessions [10–14]. RFA also yields survival rates equivalent to those seen with surgical resection for small HCC tumors [15–19]. As a result, RFA has been advocated as a first-line curative therapy for very early stage HCC [i.e., Barcelona Clinical Liver Cancer (BCLC) stage 0] [6] or unresectable early-stage HCC (BCLC stage A) [5–9]. Although RFA is highly effective for treating small HCC tumors, application of the technique is potentially limited for large tumors (diameter >3 cm), for tumors that are poorly visualized on ultrasonography (US), or tumors in high-risk or difficult-to-ablate locations [5–9, 20, 21]. Recent advances such as the artificial instillation of intra-peritoneal or intra-pleural fluid before RFA [22, 23], application of contrast-enhanced US (CE-US) before or after RFA [24, 25], the assistance of real-time virtual sonography (RVS) [26, 27], combination therapy before RFA, or the use of switching RF controllers (SWC) with multiple electrodes [28–30] can resolve these issues. Because RFA is used as a major local ablative therapy worldwide as well as in Taiwan, this review article provides updates on the clinical outcomes and advances in RFA therapies, particularly in the context of the aforementioned issues in Taiwan.

PEI and PAI in Taiwan

PEI was the most practical and effective modality of direct ablation therapy for HCC before the introduction of RFA in Taiwan. Although PEI is less effective than RFA, in Taiwan, PEI remains the best choice for 10–15% of small HCC in locations unsuitable for RFA and in institutions where RFA is not yet available. PEI has the advantage that it can be performed at outpatient clinics, whereas RFA is usually performed on inpatients. PEI can also serve as booster treatment for viable tumor in small or medium-sizes HCCs after transarterial chemoembolization (TACE). Moreover, the rate of major complications after PEI is lower than that after RFA in Taiwan [11, 12].

Our unit began to perform PAI in 1996, and in our experience, PAI achieves similar effects to PEI, but requires fewer treatment sessions [12]; however, because of the slightly higher rate of major complications such as liver abscess, cholangitis, and mild renal dysfunction with PAI compared to PEI, currently we rarely employed PAI for small HCC in Taiwan [9].

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Current Status of RFA for HCC in Taiwan

The findings from several randomized controlled trials and meta-analyses have resulted in RFA being accepted in various HCC guidelines as a first-line curative therapy for small HCC [5–8, 31–34]. RFA can also be used for treatment of intra-hepatic recurrences after the initial application of RFA or other ablative therapies [35, 36].

The waiting time for OLT is often prolonged because of shortages of donor livers, but RFA, TACE, or combination therapies with TACE and various local ablations are currently accepted as bridge therapies for early-stage HCC patients awaiting liver transplantation [37–39] in Taiwan. Our recent study showed 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 alfa-fetoprotein (AFP) levels above 200 ng/ml and Child-Pugh B status [40]. Therefore, prompt transplantation is required for early-stage-HCC patients with risk factors after RFA. Another of our studies 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 [41].

Complete Ablation of HCC after RFA by Conventional and Novel RFA in Taiwan

Conventional RFA devices with a single electrode or deployed electrode arrays with a thermal diameter of 3–4 cm provide a complete ablation rate of more than 90% for small tumors, but yield lower rates of 53–61% for medium-sized tumors (diameter 3.1–5 cm), and 20–45% for larger tumors (>5 cm) [42–45]. Therefore, various novel devices, including switching RF controllers with 2–6 unipolar or bipolar electrodes, have been proposed with the aim of producing a larger ablation zone in a shorter time, reducing the number of overlapping ablations, and creating a larger safety margin for HCCs larger than 3 cm. A few preliminary results are available: notably, Lee et al. reported that this unipolar RF electrode device showed a 97% rate of primary technique effectiveness in HCCs 3.1–5 cm in diameter [28–30]. A deployed RF electrode can provide a 5- to 7-cm-diameter ablation zone with a single electrode placement, but the shape of the ablation zone is not circular, and the device's multiple tines have the potential to puncture adjacent vital structures [46]; consequently, the use of this type of device is not common in Taiwan.

Some refined algorithms also can enhance complete ablation. Our study showed that application of an interactive algorithm is superior to the standard algorithm when using a LeVeen deployed electrode, particularly for HCCs larger than 2 cm in diameter [47]. 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 [48]. In addition, the inhibition of angiogenesis (by TACE or medication with thermo-doxorubicin) prior to RFA has been reported (or proposed) to enhance the degree of complete ablation [49–53].

Local Recurrence(LR) of HCC after RFA

In contrast to the anatomical eradication of HCC achieved by resection, LR rates of small HCCs after RFA were 1.3–12% at 1 year, 1.7–24% at 2 years, and 3.2% at both 5 and 10 years [11–14, 54–57](table 1). Factors correlated with LR included larger tumor size (diameter >2 cm or >3 cm), tumor without encapsulation, poorly differentiated HCC, sub-capsular loca-

tion, ablative margin less than 1 cm, a nearby vessel to induce the heat-sink effect, and Edmondson's grade (I, II vs. III, IV, p = 0.013) [11–14, 54–57]. This increase in LR is presumably due to unexplored peri-tumoral satellite nodules, insufficient safety margin, or incomplete ablation [11–14, 54–57]. Newer RF devices or refined algorithms enhancing complete ablation may help to minimize LR.

Intra-hepatic 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 for small HCCs after RFA, a level comparable to that seen after resection [56], but 5- and 10-year recurrence rates of 74.8% (95% CI, 71.8–77.8%) and 80.8% (95% CI, 77.4–84.3%) were reported by Shiina et al. in a 10-year follow-up [57]. Some investigators expressed concern that RFA might induce the spread of tumors [58]. Our study showed that the occurrence of a popping sound (a possible indication of local pressure) during RFA did not correlate with tumor progression [59]. Nevertheless, if gas is observed spreading into adjacent vessels during RFA, we change the electrode direction and/or position to reduce the spread of tissue that may have been incompletely coagulated at an earlier stage of ablation [13]. Further study of the rate of rapid recurrence of HCC and associated factors or biomarkers is needed to elucidate the risk factors. For HCC in high-risk locations, our recent study showed that use of RFA at low RF power (<120 W) and maximum power demonstrated equivalent effectiveness, but the use of low power resulting in fewer major complications [60].

Overall Recurrence of HCC after RFA

The overall tumor recurrence rates of small HCC 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 [11–14, 56, 61, 62]. Independent factors that correlated with higher overall recurrence of HCC included a low platelet count (≤ 100,000/ml), 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) [13, 56]. Overall HCC recurrence might be related to LR and tumor recurrence. Increasing the rate of complete necrosis, reducing LR, and preventing the progression of underlying liver disease using antiviral therapies for chronic hepatitis B or C might reduce overall tumor recurrence [5, 6].

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 [11–14, 56, 61, 62–64](table 1). Longer survival was commonly observed in sub-groups with lower ages, HCV, early Child Pugh Class (C-P), small tumor size, low serum AFP or lectin-reactive AFP (AFP-L3) levels, low des-γ-carboxyprothrombin level, well-differentiated tumors, and solitary tumors [11–14, 56, 61, 62]. Recent studies have shown that RFA can result in good 5-year survival rates

Table 1. Outcomes of RFA for early-stage HCC

Authors (year)	No. of cases	Maximum tumor size (cm)	Mean Follow-up (months)	Local recurrence (%): 1/2/3/5/10 years	New hepatic or extra-hepatic recurrence (%): 1/3/5/10 years	Overall recurrence (%): 1/3/5/10 years	Survival rate (%): 1/3/5/10 years
Lin et al. (2004) [11]	52	≤ 4	25	12/18/18/NA/NA	24/47/NA	NA	90/74/NA/NA
Shiina (2005) [13]	118	3	37 (median)	1.3/1.7/1.7/1.7/NA	NA	22/3/61/70 (4 year)	97/81/74 (4 years)/NA
Tateishi (2005) [61]	87	≤ 2	27.6 (median)	1.3/2.4/2.4/2.4/NA (total cases)	NA	NA	100/90.8/83.8/NA
	215	2.1–5	27.6 (median)		NA	NA	93/74.3/45.2/NA
Lencioni (2005) [62]	206	5	24		14/49/81	18//55/83	97/67/41/NA
Camma (2005) [56]	202	5	19	12/24/30 (30M)/NA/NA	13/30 (30M)//NA	22/ 44 (30M)/NA	80/49 (30M)/NA/NA
Choi (2007) [64]	570	5	30	11.8*	52	NA	
Livraghi (2008) [10]	216	2	31	0.9*	NA	NA	NA/76/55/NA
N'Kontchou (2009) [63]	235	5	27	11.5*	42	NA	NA/60/40/NA
Shiina (2012) [57]	1170	> 5	38.2	1.4/3.2/3.2/3.2	25.6/74.8/78.1/ 80.8	NA	97/82.8/63.8/48.8 (31 for HCC ≤ 5 cm)

* Non-cumulative rates only (value represents rate in the follow-up period). NA=not available; 30M=data of 30 months only.

(68% as reported by Livraghi et al. [10]; 76% as reported by N'Kontchou et al. [63]) for very early stage operable HCC.

Comparison of RFA with Resection

RFA has an efficacy equivalent to that of surgical resection for small HCCs. Therefore, the 2012 EASL HCC guidelines (and some reports) advocate that RFA is also an option in patients with very early stage (BCLC-0) HCC or BCLC-A-grade resectable HCC that is not suitable for resection. Some randomized or cohort studies, including some studies from Taiwan (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 for very early stage or early-stage HCC that was comparable to that seen with resection [10, 17, 18, 63, 65, 66] with comparable recurrence rates for very early stage HCC [17](table 2).

Comparison of RFA with PEI and MWA

Among various local modalities, both PEI and RFA are the most widely employed. Several randomized controlled trials, cohort studies, and meta-analyses have shown that RFA is superior to PEI for small HCC in terms of the more predictable necrosis for any size of HCC, higher complete ablation rates, lower LR, and higher overall survival rate [10–13, 19, 20, 31–34]. Conventional MWA provides only a 2-cm-diameter thermal ablation zone per electrode placed into the tumor; however, RFA provides a 2- to 5-cm-diameter thermal ablation zone 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 [67–69]. In Taiwan, conventional MWA was used in some centers; however, novel MWA with cool-shaft and multiple antennas is now available in Taiwan.

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 complete necrosis and local tumor progression) among the various RF electrode types [46, 67]. The characteristics of bipolar RF electrodes preclude touching of the tumor when treating smaller tumors. For HCCs measuring greater than 3 cm in diameter, the applicator remains outside the tumor, but for HCCs larger than 3 cm, the applicator is placed inside the tumor but the inter-probe distance must not be more than 3 cm [29]. The benefit of no-touch ablation includes prevention of rupture of the tumor capsule, thereby presumably reducing the danger of tumors spreading before ablation, leading to reduced LR. However, no-touch ablation has its limitations, including difficulties in probe insertion for tumors at high-risk locations or in narrow spaces. Additionally, this technique is best carried out by the free-hand insertion of 3–6 probes [29].

Table 2. Studies comparing RFA and surgical resection for HCC: randomized or cohort studies with and without propensity score matching

Authors (year)	Study design	Treatment method	No. of patients	Max size (cm)/ No. of tumor (s)	Overall Survival Rate (%)				p value
					1-year	2-year	3-year	5-year	
Vivarelli et al. (2004) [65]	Cohort	RFA	C-P A: 43	NA	82	NA	43	NA	0.02
		HR	C-P A: 70	NA	88	NA	71	NA	
		RFA	C-P B: 36	NA	74	NA	25	NA	NS
		HR	C-P B: 9	NA	52	NA	19	NA	
Chen et al. (2006) [16]	RCT	RFA[a]	C-P A: 71	5/1	95.8	82.1	71.4	67.9[b]	NS
		HR	C-P A: 90	5/1	93.3	82.3	73.4	64.0[b]	
Hung et al. (2011) [17]	Propensity	RFA	66	2/1	98.3	94.9	86.4	77.8	NS
		HR	50	2/1	100	95.9	91.1	84.6	
Wang et al. (2012) [18]	Cohort	RFA	91	2/1	96.7	NA	80.3	72	0.073
		HR	52		98	NA	98	91.5	
Wang et al. (2012) [18]		RFA	254	3/3, 5/1	91.6	NA	73.5	57.4	0.001
		HR	208		96.1	NA	87.8	71.2	
Feng et al. (2012) [66]	RCT	RFA	84	4/2	93.1	83.1	67.2	NA	0.342
		HR	84		96	87.6	74.8	NA	

a=Additional treatment with ethanol injection or chemoembolization; b=Four-year survival rate; HR=hepatic resection; RCT=randomized cotrol trial; NS=not significant.

RFA for HCC in Difficult-to-treat or High-risk Locations

RFA for HCC in difficult-to-treat or high-risk locations is not easy; spatial challenges can make it difficult to achieve complete necrosis [20, 48, 70]. A “difficult-to-treat” tumor is generally defined as a tumor located within 1 cm of a vital structure, such as the gastrointestinal tract, gallbladder, diaphragm, visible intra-hepatic bile duct, or vessel (particularly vessels >3 mm in diameter) [20, 48, 54, 70]. Several strategies have been developed to counter these problems. The combined use of ethanol injection and RFA achieves a higher rate of complete necrosis than does RFA monotherapy for HCC in high-risk locations [48]. In addition, we observed comparable clinical outcomes using RFA at low RF power (≤ 120W) and maximum RF power (> 120W), with considerably fewer adverse effects encountered in the low-power group, particularly for difficult-to-treat HCC [60]. Artificial ascites or artificial pleural effusion (AAAP) also has been employed as an adjunct to percutaneous RFA for tumors in problematic locations. The safety and efficacy of AAAP creation has been evaluated at several sites [22, 23, 71, 72]. Ultimately, open or laparoscopic RFA is recommended as an alternative approach, but both of these techniques are more invasive and require a technically demanding approach to electrode placement due to limited access [73–75].

RFA with Switching RF Controllerand Multiple RF Electrodes

Current RFA devices are more effective in HCCs smaller than 3 cm in diameter [20]. Recently, application of a switching RF controller with the simultaneous placement of multiple unipolar or bipolar RF electrodes has been reported to create a larger ablation zone in a shorter time [28–30]. 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 [28–30]. In our center, we enrolled 70 patients with at least one index HCC tumor greater than or equal to 3.0 cm in diameter for treatment (between 1 January 2009 and 31 December 2011) using switch-control RFA with tow or three 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 to 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, 10 (14.3%) patients had died; another 12 (18.8%) patients exhibited local tumor progression. Estimated cumulative overall survival rates and local tumor progression rates were 93.9 and 10.7% (1 year), 84.6 and 17.2% (2 years), and 81.3 and 32.8% (3 years), respectively. In comparison, conventional RFA with a single RF electrode and sequential ablation achieved complete ablation rates of 53–61% for medium-sized HCC and 20–45% for large HCC. Seror et al. used SWC RFA and achieved 81% complete ablation in HCC greater than 5 cm [29], and Lee et al. showed 97% complete ablation in HCC of 3.1–5 cm [30]. Therefore, RFA with two or three electrodes and a switch RF generator achieved a high rate (>90%) of complete ablation for medium-sized and large HCCs.

Moreover, RFA with multiple bipolar RF electrodes connected via a switching RF generator can create larger coagulation necrosis by enabling placement of RFA electrodes with inter-electrode distances as long as 3 cm [29]. This method may reduce the risk of tumor spread in small HCCs, since the technique permits the use of no-touch RFA for tumors smaller than 3 cm in diameter. From November 2010 to April 2011, we enrolled six patients with solitary HCC less than 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 SWC RF generator. 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 volumes before and after RFA were 3.0 ± 1.4 cm^3 and 24.5± 6.0 cm^3($p < 0.001$). Transient post-ablative pain or fever (grade 1–2) was reported. No LR has been observed at more than 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 the no-touch method may effectively ablate HCCs smaller than 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 the potential clinical efficacy of this approach.

Microwave Ablation (MWA)

Because of the smaller volume of thermal ablation generated by previous-generation MWA antennas (i.e., an ablation zone of 2 cm diameter), MWA is optimally applied to HCC of less than 2 cm in diameter [68, 69]. Multiple overlapping electrode insertion should be

performed for tumors larger than 2 cm. Nowadays RFA is gradually replacing MWA for HCC treatment owing to a wider range of target thermal sizes in Taiwan [9]. However, novel MWA techniques with multiple cool-shaft antennas are also employed for ablation of small HCC in Taiwan. The thermal diameter can also encompass 5 cm by the use of a switching controller and two or three antennas in a relatively short time compared with older MWA antennas and multiple sequential ablation [76, 77].

Future Advances in Local Ablation in Taiwan

Recent advances in local ablation in Taiwan include SWC RFA with several RF electrodes and SWC MWA with multiple cool-shaft antennas to treat large HCC; these techniques achieve higher complete ablation rates and require fewer ablation sessions. Assessment of the efficacy of RFA may be improved by using CE-US, with or without three-dimensional sonography or RVS assistance; these approaches are not commonly employed at present.

Conflict of Interest

none.

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