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ORIGINAL ARTICLE

Ultrasound-guided Radiofrequency Ablation for Early Hepatocellular Carcinoma

AKC Cheng, M Cheung, EYL Chu

Department of Radiology, Queen Mary Hospital, Pokfulam, Hong Kong

ABSTRACT

Objectives: *To review the outcome and procedure-related complications of patients who underwent ultrasound-guided percutaneous radiofrequency ablation (RFA) for early hepatocellular carcinoma (HCC).*

Methods: *Medical records of patients who underwent RFA for stage I or IIa solitary HCC between January 2008 and July 2012 were reviewed.*

Results: *17 men and 5 women aged 50 to 95 (mean, 66.3) years were included. The mean time from diagnosis to RFA was 1.8 months. At a mean follow-up of 1.7 months, 20 of 22 patients had complete ablation and no scar recurrence. At a mean follow-up of >8 months, 16 of 22 patients had no scar recurrence. At a mean follow-up of 36 months, 14 of 22 patients had recurrence, six had no recurrence, and two had died. The mean overall survival was 33.0 months. The overall survival at years 1, 2, and 3 were 100%, 86.4%, and 81.8%, respectively. The mean disease-free survival was 19.0 months. The disease-free survival at years 1, 2, and 3 were 54.5%, 44.4%, and 33.3%, respectively. The mean disease-free survival was longer in patients with a smaller tumour (≤1.8 cm) than those with a larger tumour (>1.8 cm) [27.1 vs. 10.9 months, p = 0.01]. None had procedure-related mortality or major complications.*

Conclusion: *Ultrasound-guided percutaneous RFA is a safe and effective primary treatment for early solitary HCC. Larger tumour is associated with a shorter disease-free survival; frequent follow-up is important.*

Key Words: *Carcinoma, hepatocellular; Catheter ablation; Treatment outcome*

中文摘要

早期肝癌的超聲引導射頻消融治療

鄭嘉俊、張皓筠、朱賢麟

目的：回顧接受超聲引導經皮射頻消融（RFA）治療早期肝癌（HCC）的患者的療效和手術相關併發症。

方法：回顧2008年1月至2012年7月期間接受RFA治療I期或IIa期單發HCC患者的病歷。

結果：包括17男和5女，年齡50至95歲（平均66.3歲）。從診斷到RFA的平均時間為1.8個月。在平均隨訪1.7個月後，22例中有20例完全消融及無疤痕復發。在平均隨訪>8個月後，22例中有16例無疤

Correspondence: *Dr AKC Cheng, Flat 7C, Block 2, Academic Terrace, 101 Pok Fu Lam Road, Hong Kong.*
Email: acheng1404@hotmail.com

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痕復發。在平均隨訪36個月後，22例中有14例復發、6例無復發及2例死亡。平均總生存期為33.0個月。1年、2年和3年的總體生存率依次為100%、86.4%和81.8%。平均無病生存期為19.0個月。1年、2年和3年無病生存率依次為54.5%、44.4%和33.3%。腫瘤較小（≤1.8 cm）比腫瘤較大（>1.8 cm）的患者的平均無病生存期更長（27.1對10.9個月，p = 0.0）。無患者出現手術相關死亡或嚴重併發症。

結論：超聲引導經皮RFA能安全有效治療早期單發HCC。較大的腫瘤與較短的無病生存率相關聯；密切隨訪很重要。

INTRODUCTION

Hepatocellular carcinoma (HCC) was the fourth most common cancer and the third major cause of death in Hong Kong in 2012.[1] The Hong Kong Liver Cancer classification system provides treatment guidance for Asian patients with HCC. It recommends ablation therapy, resection, or liver transplantation for early HCC.[2] Liver resection and liver transplantation are the main curative treatments,[3] but only 20% of HCC patients are eligible for hepatic resection[4,5] because of poor liver functional reserve secondary to liver cirrhosis and intrahepatic dissemination.[6-8] The option of liver transplantation is limited by organ donor shortage. Image-guided percutaneous radiofrequency ablation (RFA) is a safe and effective treatment for early HCC. It uses a high-frequency alternating current (460-480 kHz) via electrodes placed within the tissue to cause coagulative necrosis and tissue desiccation in selected regions. This study reviewed the outcome and treatment-related complications of patients who underwent ultrasound-guided RFA for early HCC.

METHODS

The study was approved by the training supervisor of the Department of Radiology of Queen Mary Hospital and conducted in compliance with Declaration of Helsinki. We retrospectively reviewed the Radiology Information System in Queen Mary Hospital between January 2008 and July 2012 using the key words 'RFA' and 'cooltip'. Patients were included if they (1) had stage I or IIa HCC (no extrahepatic vascular invasion or metastasis, no intrahepatic venous invasion, tumour size ≤5 cm in diameter, ≤3 nodules, liver function of Child-Pugh grade A or B), (2) underwent ultrasound-guided percutaneous RFA, and (3) had no prior treatment for HCC.

Computed tomography (CT), magnetic resonance imaging (MRI) and / or ultrasonography were performed to determine the access route to the tumour. Pre-procedural electrocardiography and chest radiography were also performed. Patients were assessed for hepatitis B surface antigen, antibodies to hepatitis C virus, serum α-fetoprotein, serum albumin, serum total bilirubin, aspartate aminotransferase, alanine aminotransferase, and prothrombin time, as well as the Child-Pugh score. CT or MRI diagnosis of HCC was defined as early-phase arterial enhancement and late-phase contrast washout. Tumour size (maximum diameter) was measured by a single radiologist to minimise inter-observer error.

Ultrasound-guided RFA using the Cool-tip system (Radionics; Burlington [MA], USA) was performed by one of the two interventional radiologists with >10 years of experience. Artificial pleural effusion or ascites were administered for those with tumour sites at high risk of adjacent thermal injury such as in the hepatic dome or gastrointestinal tract (Figure 1). Artificial ascites can improve the sonic window and decrease thermal injury by displacing the liver downward.[3] A single radiofrequency electrode with an exposed length of 3 cm was used. Each ablation cycle lasted for 12 minutes at 60°C. For larger tumours, cluster electrode may be required. Alternatively multiple overlapping ablation zones by a single electrode can be performed. The treatment goal is complete ablation of the tumour plus a 1-cm tumour-free margin to minimise local recurrence.[9] The needle tract was ablated for 30 seconds at the end of the procedure to prevent seeding. Patients' vital signs and serum liver function markers were monitored overnight and they were discharged when clinically stable.

Treatment outcome was assessed using dynamic contrast-enhanced CT. Scar recurrence was defined as any arterial contrast enhancement with portovenous washout in the liver parenchymal tissue at the ablated site. Distant intrahepatic recurrence was defined as any intrahepatic tumour away from the primary ablated

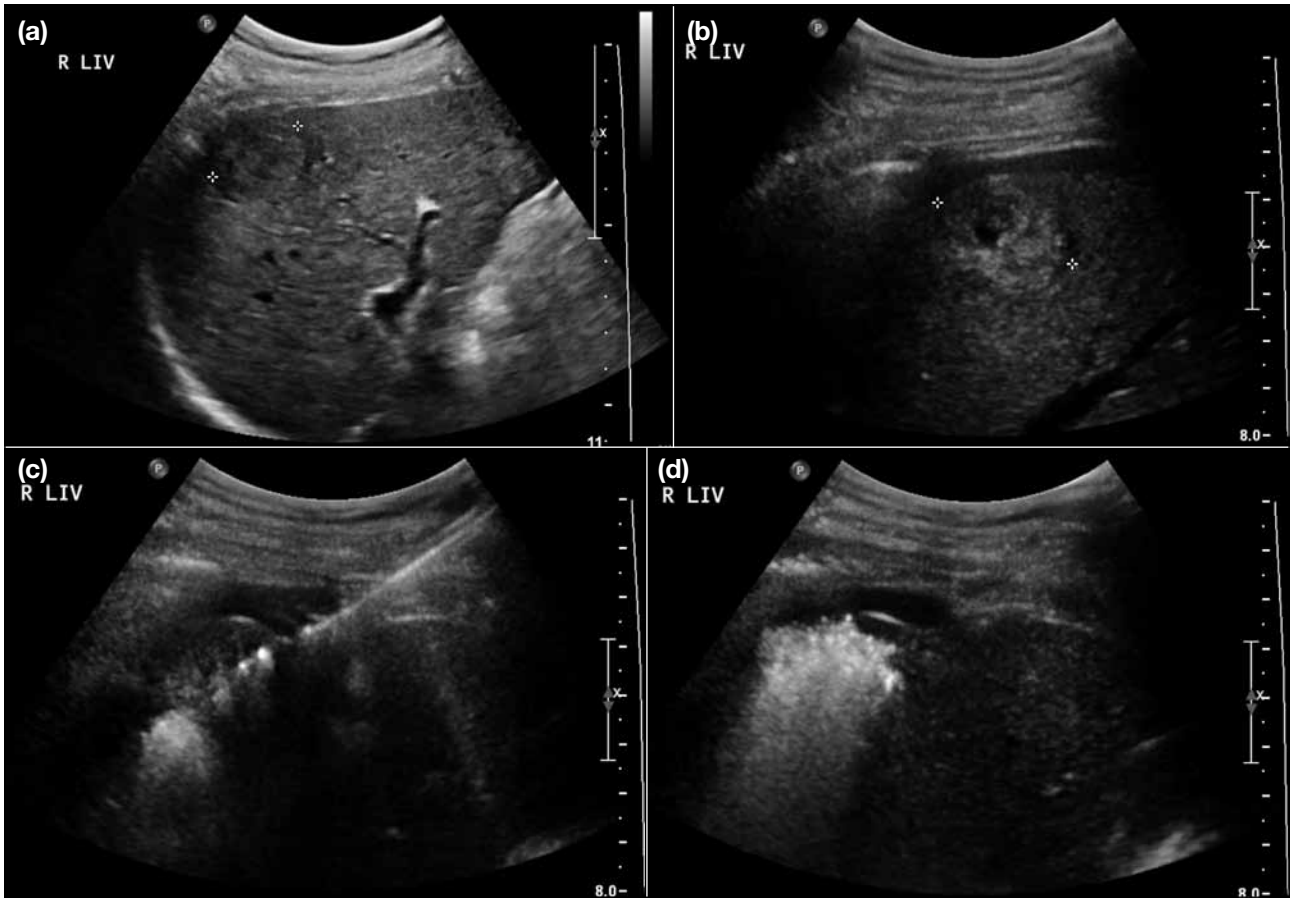

Figure 1. Ultrasonography showing (a) a heterogeneous hypoechoic lesion at segment VI (outlined by calipers), (b) administration of artificial ascites (outlined by calipers), (c) insertion of a cluster Cool-tip probe, and (d) completion of one cycle of radiofrequency ablation.

site. Extrahepatic recurrence was defined as any extrahepatic metastasis. HCC recurrence was defined as any scar recurrence, distant intrahepatic recurrence, or extrahepatic recurrence. Disease-free survival was defined as the time from RFA to HCC recurrence. Overall survival was defined as the time from RFA to death.

The 3-year disease-free survival and overall survival were calculated using the Kaplan-Meier method. Outcomes of different tumour sizes were compared using the log-rank test. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 81 patients with HCC were referred to the Department of Radiology of Queen Mary Hospital between January 2008 and July 2012. 59 of them had recurrent HCC or previous treatment and were excluded. The remaining 17 men and 5 women aged 50 to 95 (mean, 66.3) years were included who underwent one (n = 17) or two (n = 5) cycles of RFA for solitary HCC of ≤1.8 cm (n = 11) or >1.8 cm (n = 11) in diameter (Table 1). The mean time from diagnosis to RFA was 1.8 months.

After a mean follow-up of 1.7 (range, 1-5) months, 20 of 22 patients had complete ablation and no scar recurrence. After a mean follow-up of >8 months, 16 of 22 patients had no scar recurrence. After a mean follow-up of 36 months, 14 of 22 patients had recurrence, six had no recurrence, and two had died (from hepatorenal syndrome or unknown cause). The 14 recurrences included scar recurrence (n = 6), distant intrahepatic recurrence (n = 6), both scar and distant recurrences (n = 1), and intrahepatic and extrahepatic metastases to peritoneum (n = 1) [Table 2]. Three of the six patients with scar recurrence underwent another percutaneous RFA; none had further recurrence within the subsequent 12 months. The other three patients underwent hepatic wedge resection or transarterial chemoembolisation. The six patients with distant intrahepatic recurrence

Table 1. Patient characteristics and outcomes (n = 22).

Variables	Value*
Age (years)	66.3 ± 10.9
No. of males:females	17:5
Viral infection	
Hepatitis B surface antigen positive	17 (77.3)
Anti–hepatitis C virus positive	4 (18.2)
Both negative	1 (4.5)
Tumour size (cm)	1.93 ± 0.6
Use of ascites	
None	21 (95.5)
Mild	1 (4.5)
Liver cirrhosis	19 (86.4)
Platelet count (x10^9/l)	132.8 ± 67.3
Prothrombin time (sec)	12.2 ± 1.7
Serum albumin (g/l)	39.9 ± 4.5
Total bilirubin (μmol/l)	12.1 ± 7.1
Serum α-fetoprotein (ng/ml)	
<20	11 (50)
20-200	6 (27.3)
>200	4 (18.2)
Child-Pugh class A	22 (100)
Procedure-related complications	
Serum liver function marker derangement	7 (31.8)
Serum renal function marker derangement	2 (9.1)
Abdominal pain	2 (9.1)
Shock	1 (4.5)
Pleural effusion	0 (0)
Haemorrhage	0 (0)
Bile leak	0 (0)
Subphrenic collection	0 (0)
Infected ascites	0 (0)
Mortality	0 (0)

* Data are presented as mean ± standard deviation or No. (%) of patients.

Table 2. Recurrences at 1, 2, and 3 years.

Recurrence	No. of patients			
	Year 1	Year 2	Year 3	Total
Scar recurrence	5	1	0	6
Distant intrahepatic recurrence	3	1	2	6
Scar and distant intrahepatic recurrences	1	0	0	1
Intrahepatic and extrahepatic metastases	1	0	0	1
Total	10	2	2	14

underwent hepatic wedge resection, laparoscopic RFA, microwave ablation, sorafenib, or high-intensity focused ultrasound. The patient with both scar and distant recurrences underwent transarterial chemoembolisation. The patient with intrahepatic and extrahepatic metastases was given supportive care.

The mean overall survival was 33.0 (95% confidence interval [CI] = 30.2-35.8) months. The overall survival at years 1, 2, and 3 were 100%, 86.4%, and 81.8%, respectively. The mean disease-free survival was 19.0 (95% CI = 12.9-25.1) months. The disease-free survival at years 1, 2, and 3 were 54.5%, 44.4%, and 33.3%, respectively. The mean disease-free survival was longer in patients with a smaller tumour (≤1.8 cm) than with a larger tumour (>1.8 cm) [27.1 vs. 10.9 months, p = 0.01, Figure 2], but the mean overall survival was comparable (34.1 vs. 31.8 months, p = 0.299, Figure 3).

After the RFA procedure, 31.8% of patient had deranged serum liver function markers; 85.7% of them normalised within 2 months. One patient had unexplained shock and another had loss of consciousness shortly after the procedure; both had uncomplicated recovery. None had procedure-related mortality (within 30 days of RFA) or major complications.

DISCUSSION

RFA is a safe and effective treatment for early, small, single HCC of up to 5 cm in diameter, especially in patients with a low serum α-fetoprotein level and well-preserved liver function.[3,4,10] The 1- and 3-year survival rates after RFA are 96.6% and 80.5%, respectively, for patients with HCC of ≤5 cm or <3 tumours of ≤3 cm in diameter.[4] The 5- and 10-year survival rates for primary HCC are 60.2% and 27.3%, respectively.[4] In our study, the 1- and 3-year survival rates were 100% and 81.8%, respectively.

Surgical resection has been the treatment of choice for HCC.[4] In patients with Child-Pugh class A cirrhosis with solitary HCC of ≤3 cm, RFA is comparable with resection in terms of recurrence-free survival.[6] RFA is less invasive and results in a lower morbidity and shorter hospital stay.[11-13] Resection results in a higher morbidity but a lower local recurrence rate.[11,13-15] Two randomised controlled trials have shown no significant difference in survival between RFA and resection.[16,17] In other non-randomised controlled trials, resection is associated with a higher survival.[4,12,13,18] In our hospital, most patients preferred RFA over resection; RFA as the first-line treatment was decided by both patients and surgeons.

Local recurrence of HCC is common after RFA with rates of 12% to 39%.[18-22] This is mainly due to the undetectable micro-satellite lesions.[11] In our study, none of the patients who underwent further RFA for scar recurrence had re-recurrence in subsequent 12 months. Iterative RFA is effective for achieving complete ablation in 87% of cases.[10] Frequent imaging can detect

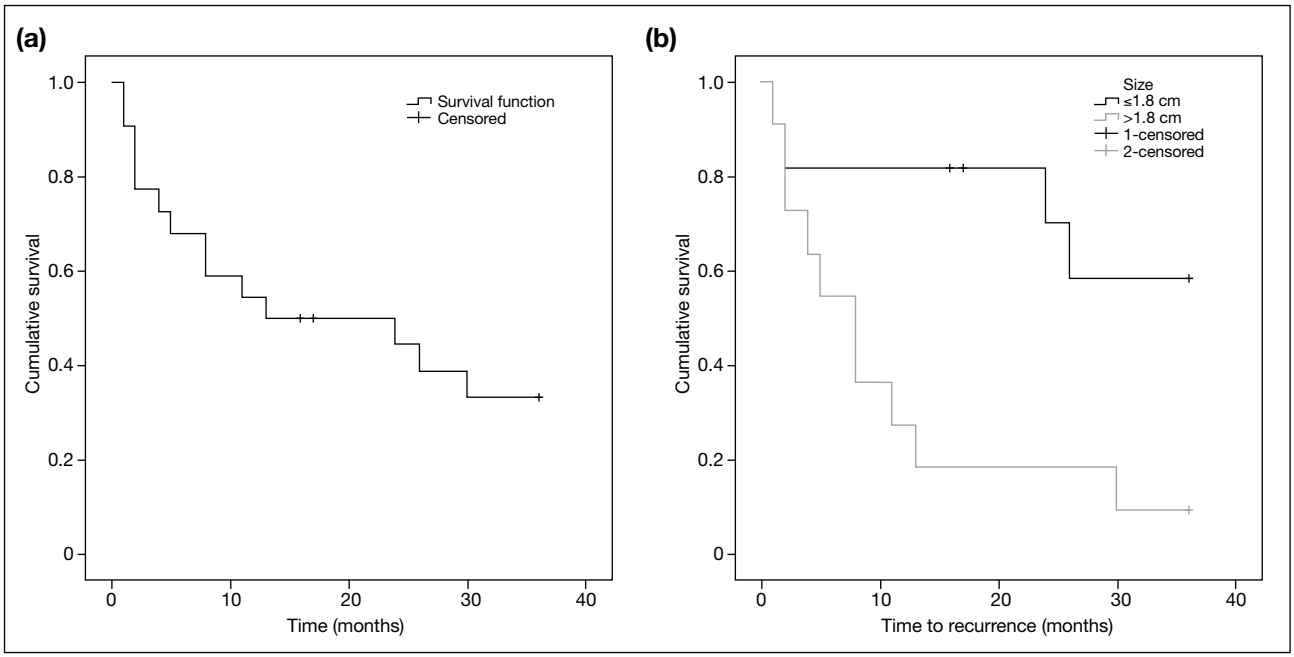

Figure 2. Kaplan-Meier curves showing the mean disease-free survival rates (a) at 1, 2, and 3 years and (b) in patients with a large (>1.8 cm) or small (≤1.8 cm) tumour.

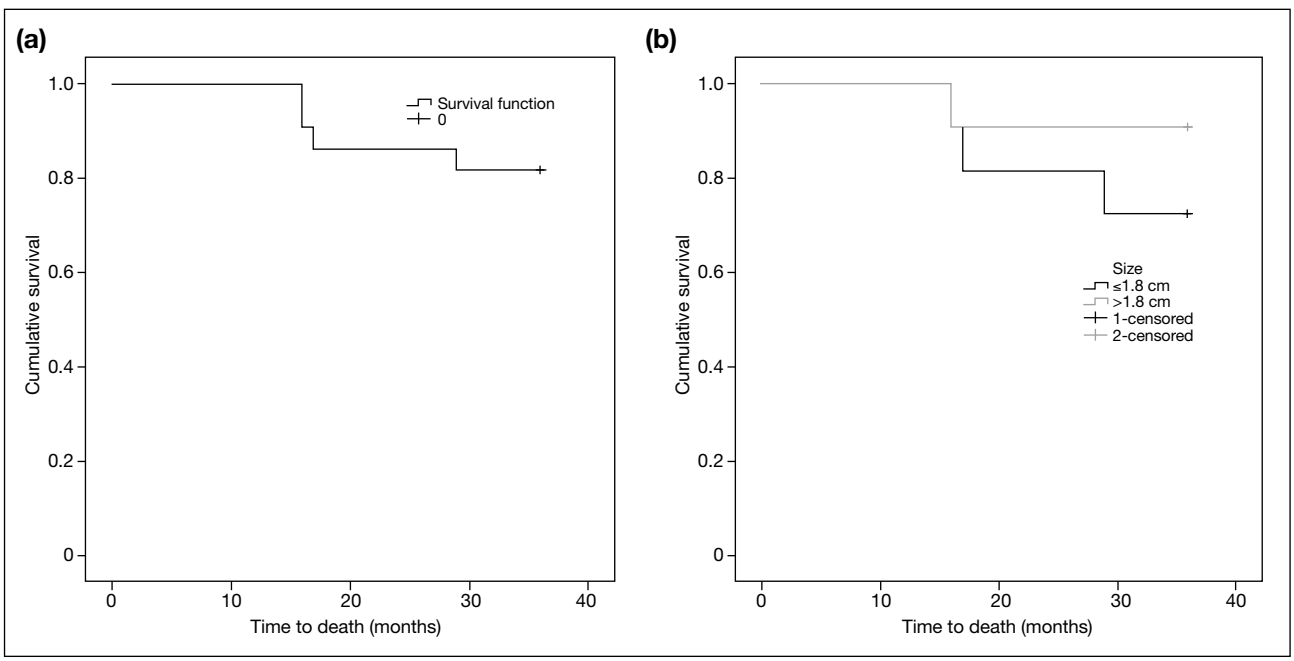

Figure 3. Kaplan-Meier curves showing the mean overall survival rates (a) at 1, 2, and 3 years and (b) in patients with a large (>1.8 cm) or small (≤1.8 cm) tumour.

recurrence early. In our hospital, multiphase contrast-enhanced CT within 1 month of RFA is used for follow-up.

RFA uses a Cool-tip electrode needle and single coagulation to necrotise a sphere of 3 cm in diameter.[6,23] In our study, tumour size was a predictor of disease-free survival but not overall survival, because complete ablation is affected by the tumour size.[24-26] The micro-satellite nodules around the main tumour tend to

increase as the tumour size increases.[3] The risk of left-behind tumour cells increases in larger lesions after RFA ablation.[9] In our study, RFA resulted in a lower complete ablation rate among patients with a larger lesion, and thus recurrence in those with a larger tumour was earlier. Nonetheless, most recurrences were detected and re-treated promptly. Therefore, the tumour size did not affect the overall survival. This highlights the importance of frequent follow-up for prompt re-treatment.

The complication rate of RFA has been reported to be 0.6% to 8.9%,[27-34] and the mortality rate to be 0 to 1.2%.[35] The most common complications are abdominal haemorrhage, abscess, biliary tract damage, liver failure, pulmonary complications, and ground pad burns.[3] In our study, no patient had procedure-related mortality or major complications.

From our experience, about 5.1% of HCC could be detected by CT or MRI but not by ultrasonography, and thus ultrasound-guided RFA could not be performed. About 30% of small HCCs referred for percutaneous RFA are not identifiable on ultrasonography and thus are excluded from ultrasound-guided ablation.[35] Nonetheless, about 78.5% of small (≤3 cm) HCCs are visible on targeted ultrasonography with reference to prior CT or MRI.[36] The two independent predictors of lesion invisibility on targeted ultrasonography are small size and subphrenic location.

Compared with traditional ultrasonography, contrast-enhanced ultrasound-guided RFA improves treatment outcome and reduces recurrence by improving detection and localisation of the target lesion with an indistinct border.[37,38] Contrast-enhanced ultrasonography is sensitive in detecting small metastatic liver carcinoma and provides information such as size, number, location, focal infiltration, central necrosis, and blood supply.[39] It is useful for selecting candidates and planning the protocol. Further evaluation of the treatment outcome of contrast-enhanced ultrasound-guided RFA is warranted.

For HCCs of >3 cm, a combination of transcatheter arterial chemoembolisation and RFA achieves higher survival rates at 1, 3, and 5 years than RFA alone, but for HCCs of <3 cm, the outcome is comparable.[40-42] RFA is comparable with microwave ablation in terms of complete ablation, residual foci of untreated disease, and recurrence.[43] CT is as sensitive as MRI in detecting residual or recurrent tumour at a lower cost; both are useful to evaluate the post-interventional ablation zone and local recurrence.[44,45]

To minimise complications and improve outcome, a multidisciplinary approach, securing a safety margin around the tumour, vigilant monitoring of treatment response and recurrence, and prompt treatment are essential.

There were limitations to our study. The study was retrospective and the sample was small; the results might not be reproducible. There was selection bias, as only patients with solitary HCC were included; the findings might not be applicable to patients with multifocal HCCs.

CONCLUSION

Ultrasound-guided percutaneous RFA is a safe and effective primary treatment for early solitary HCC. Larger tumour is associated with a shorter disease-free survival; frequent follow-up is important.

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