

# Efficacy and safety of radiofrequency ablation for perivascular hepatocellular carcinoma without hepatic inflow occlusion

K. K. Ng<sup>1</sup>, R. T. Poon<sup>1</sup>, C. M. Lam<sup>1</sup>, J. Yuen<sup>2</sup>, W. K. Tso<sup>2</sup> and S. T. Fan<sup>1</sup>

Centre for the Study of Liver Disease, Departments of <sup>1</sup>Surgery and <sup>2</sup>Radiology, The University of Hong Kong, Pokfulam, Hong Kong, China

Correspondence to: Dr K. K. Ng, Department of Surgery, The University of Hong Kong, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong, China (e-mail: kcnng66@yahoo.com)

**Background:** The role of radiofrequency ablation (RFA) for perivascular (up to 5 mm from the major intrahepatic portal vein or hepatic vein branches) hepatocellular carcinoma (HCC) is unclear because of possible incomplete tumour ablation and potential vascular damage. This study aimed to evaluate the safety and efficacy of RFA for perivascular HCC without hepatic inflow occlusion.

**Methods:** Between May 2001 and November 2003, RFA using an internally cooled electrode was performed on 52 patients with perivascular HCC (group 1) through open ( $n = 39$ ), percutaneous ( $n = 9$ ), laparoscopic ( $n = 2$ ) and thoracoscopic ( $n = 2$ ) approaches. Hepatic inflow occlusion was not applied during the ablation procedure. The perioperative and postoperative outcomes were compared with those of 90 patients with non-perivascular HCC (group 2) treated by RFA during the same period.

**Results:** The morbidity rate was similar between groups 1 and 2 (25 versus 28 per cent;  $P = 0.844$ ). One patient in group 1 (2 per cent) and two in group 2 (2 per cent) had developed thrombosis of major intrahepatic blood vessels on follow-up computed tomography scan. There were no significant differences between groups 1 and 2 in mortality rate (2 versus 0 per cent;  $P = 0.366$ ), complete ablation rate for small HCC (92 versus 98 per cent;  $P = 0.197$ ), local recurrence rate (11 versus 9 per cent;  $P = 0.762$ ) and overall survival (1-year: 86 versus 87 per cent; 2-year: 75 versus 75 per cent;  $P = 0.741$ ).

**Conclusion:** RFA without hepatic inflow occlusion is a safe and effective treatment for perivascular HCC.

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## Introduction

Radiofrequency ablation (RFA) has been commonly used to treat unresectable primary and secondary liver tumours with low morbidity (4–8.9 per cent) and mortality rates (0–0.5 per cent)<sup>1–3</sup>. Despite its technical simplicity and safety, local recurrence after RFA is common (12–39 per cent)<sup>4–7</sup>. Risk factors for local recurrence at RFA treatment sites include large tumour size<sup>4,5,7–11</sup>, multiple tumour nodules<sup>10</sup>, tumour invasion to major intrahepatic blood vessels<sup>4,11</sup>, percutaneous approach for RFA<sup>9</sup> and colorectal liver metastasis (compared with hepatocellular carcinoma (HCC))<sup>4,8</sup>. In one study, perivascular tumour location was shown to be the only independent risk factor for local recurrence after RFA for 105 primary and secondary liver tumours<sup>12</sup>. This could be partly explained by the ‘heat-sink’ effect of the hepatic blood flow, which protects tumour cells around major

intrahepatic blood vessels from the thermal energy of RFA. On the other hand, portal vein and hepatic vein thromboses have been reported after RFA for perivascular liver tumours<sup>1,13</sup>. However, other researchers have suggested that RFA is safe and effective for liver tumours in the perivascular region, in which complete tumour ablation can be achieved<sup>14–16</sup>. This was also observed in a porcine model using a quantitative method to assess cell viability around intrahepatic blood vessels after RFA<sup>17</sup>. In this controversy, the role of RFA for perivascular liver tumours is yet to be defined regarding its safety and efficacy.

HCC is the most common primary liver cancer. It is closely associated with chronic hepatitis B or C infection and has a high propensity for vascular invasion. Tumours abutting major intrahepatic blood vessels are commonly encountered in clinical practice. For patients with marginal liver functional reserve, surgical resection of the tumour

with an adequate margin including the nearby major blood vessel may require a more extended resection, which could be dangerous because of the high chance of postoperative liver failure. Alternatively, RFA may be curative in such a condition by destroying the tumour while preserving the nearby intrahepatic blood vessel.

The present retrospective study aimed to evaluate the safety and efficacy of RFA in patients with perivascular HCC. The clinical outcomes of these patients were compared with those of patients with non-perivascular HCC who had RFA in the same period.

## Patients and methods

### Patient selection

From May 2001 to November 2003, 159 patients received RFA treatment for HCC at Queen Mary Hospital, University of Hong Kong. Patients with tumour invasion to major intrahepatic blood vessels or with extrahepatic metastases were excluded from the study. Twelve patients received combined treatment of hepatic resection ( $n = 11$ ) or ethanol injection ( $n = 1$ ) with RFA. Five other patients had RFA for haemostasis of ruptured HCC during emergency laparotomy. The clinical details of the remaining 142 patients, who received RFA as the sole treatment for HCC, were analysed. In 84 patients (59.1 per cent), diagnosis of HCC was confirmed by fine-needle (21-gauge) aspiration cytology in those undergoing percutaneous RFA, or by intraoperative core biopsy using an 18-gauge biopsy needle in those undergoing laparoscopic, thoracoscopic or open RFA. For the remaining 58 patients (40.8 per cent), the diagnosis of HCC was based on the radiological features in computed tomography (CT) scan or magnetic resonance imaging and/or raised serum  $\alpha$ -fetoprotein concentration (over 400 ng/ml). Seventy-eight patients (54.9 per cent) had unresectable HCC because of either bilobar disease or poor liver function, whereas 64 patients (45.0 per cent) received RFA as primary treatment for resectable small HCC (up to 5 cm for a solitary tumour, or up to 3 nodules, each up to 3 cm in diameter). Thirty-three patients (23.2 per cent) had previous hepatic resection and received RFA for intrahepatic recurrent tumours. Thirty-four patients (23.9 per cent) had previous transarterial chemoembolization (TACE) for unresectable HCC, and RFA was performed for tumours which did not respond to TACE, the last dose of which was given more than 2 months after RFA. RFA was performed for solitary tumours in 112 patients (78.8 per cent), two tumours in 20 patients (14.0 per cent), three tumours in six patients (4.2 per cent) and four tumours in four patients

(2.8 per cent). A total of 186 tumour nodules were ablated in a single session of RFA.

### Definition of perivascular HCC

A perivascular tumour was defined as a tumour situated within 5 mm from the first- or second- degree branches of the portal and hepatic veins. A tumour was regarded as non-perivascular if the distance between the tumour and the major intrahepatic vessels was more than 5 mm.

### Approaches of radiofrequency ablation

Patients with small HCC (up to 5 cm in diameter) located in the part of liver amenable to percutaneous RFA were treated with this approach. The procedure was performed by interventional radiologists under local anaesthesia and intravenous sedation using midazolam and meperidine in the radiology suite. Transcutaneous ultrasonography or CT scan was used to monitor the ablation process. The patient was kept in the hospital overnight and was discharged the next day if clinically well. RFA through the open approach was considered in the presence of: (1) large tumours (over 5 cm in diameter) that required multiple overlapping ablation zones to cover the entire tumour; (2) tumours located near the dome of the liver, for which percutaneous RFA might cause lung injury; (3) tumours close to visceral organs, such as the gallbladder, small and large bowels and stomach. Laparotomy under general anaesthesia and mobilization of the liver were required in open RFA. In selected patients without previous upper abdominal operation, the laparoscopic approach was adopted if the location of the tumour was favourable. In addition, a thoracoscopic approach was used in some patients with HCC in the dome of the liver. All open, laparoscopic or thoracoscopic ablations were performed by surgeons, and intraoperative or laparoscopic ultrasonography was used to guide the ablation process. Hepatic inflow occlusion (Pringle manoeuvre) was not applied in any patient.

### Radiofrequency ablation techniques

The Cool-tip<sup>®</sup> radiofrequency system (Radionics, Burlington, Massachusetts, USA) was used in all patients. A single radiofrequency (RF) electrode with an exposed length of 3 cm was used for tumours less than 3 cm in diameter, whereas a clustered electrode (three parallel single electrodes close to each other) with an exposed length of 2.5 cm was used to treat large tumours (over 3 cm in diameter). The RF electrode was of 17 G which contained

internal dual channels for chilled water to be pumped through by a peristaltic pump. The resulting cooling effect around the electrode tip could reduce charring of the surrounding tissue, which might decrease tissue conductivity and block the RF current. Depending on the size and site of the tumour, each ablation cycle lasted for 8–12 min. Multiple overlapping ablation zones were required in large tumours. After the ablation, the needle track was thermocoagulated by continuing the RF current in a manual mode as the electrode was withdrawn slowly. For perivascular tumours, care was taken to avoid thermal injury to the nearby blood vessel by the RF current during each ablation process. Using ultrasonographic or CT guidance, the RF electrode was directed towards the tumour without direct puncture of the nearby blood vessel. In selected patients with tumours close to the portal structures at the liver hilum, the bile duct was irrigated with cold saline through an infant feeding tube, which was inserted via the cystic duct into the common duct after cholecystectomy. The aim was ablation of all liver tumours with curative intent and an ablation margin of 0.5–1 cm in a single session of RFA. Intravenous infusion of 100 ml 20 per cent mannitol was routinely administered during the RFA procedure, and patients were adequately hydrated with intravenous fluid replacement.

#### Data collection and outcome measures

Clinical details of all patients were prospectively collected in a database. The treatment protocol and data collection were approved by the Institutional Review Board of the hospital. The clinical details and outcome measures of the patients with one or more perivascular HCC (group 1) were compared with those of patients without perivascular HCC (group 2). The outcome measures that were compared between groups included post-RFA complication rate, treatment-related mortality, complete ablation rate, local recurrence, distant intrahepatic recurrence, extrahepatic recurrence and survival after RFA. A complication was defined as any adverse event after RFA, excluding pain or transient febrile reaction to the ablation. A urine sample was routinely collected for free haemoglobin analysis after the RFA procedure to detect haemoglobinuria. The patency of nearby intrahepatic blood vessels after RFA in patients with perivascular HCC was studied in a postablation contrast CT scan (Fig. 1). Treatment-related mortality was defined as any death within 30 days of the RFA treatment. Tumour response to the ablation was assessed by CT scan 1 month after RFA. Complete ablation was defined as the absence of contrast enhancement within



**Fig. 1** **a** A 3-cm perivascular hepatocellular carcinoma (black arrow) close to the right posterior segmental portal vein was treated by open radiofrequency ablation. **b** Postablation computed tomography scan showed complete ablation of the tumour and patent portal vein branch (white arrow)

the original tumour. Any contrast-enhancing areas within the target tumour on postablation CT scan indicated incomplete tumour ablation. All patients had monitoring of serum  $\alpha$ -fetoprotein concentration, chest radiograph and CT scan every 3 months to detect intrahepatic and extrahepatic tumour recurrence. Local recurrence was defined as tumour recurrence within or at the periphery of the original ablated lesion in subsequent CT scans after complete ablation was confirmed on the first postablation CT scan. Distant intrahepatic recurrence was defined as any new tumour that occurred in the liver separate from the ablated area. Extrahepatic recurrence referred to any recurrence outside the liver.

## Statistical analysis

Continuous data were expressed as median (range) and were compared between groups using the Mann–Whitney *U* test. Categorical variables were compared using the  $\chi^2$  test (or Fisher's exact test where appropriate). Recurrence risk and overall survival after RFA were calculated by the Kaplan–Meier method and were compared between groups by the log rank test. Treatment mortality was excluded in the analysis of recurrence risk and included in the overall survival analysis. All statistical analyses were done using the SPSS® version 10.0 statistical package for Windows (SPSS, Chicago, Illinois, USA).  $P < 0.050$  was considered statistically significant.

## Results

### Patient characteristics

Group 1 had 52 patients and group 2 had 90. Thirteen patients (25 per cent) in group 1 had non-perivascular

HCC in addition to a perivascular HCC. Among all 186 tumours treated by RFA, 56 (30.1 per cent) were perivascular and the other 130 (69.9 per cent) were non-perivascular. There were 20 tumours close to the portal vein branches and another 36 close to the hepatic vein branches. All patients had underlying cirrhosis due to hepatitis B infection ( $n = 119$ , 83.8 per cent), hepatitis C infection ( $n = 17$ , 12.0 per cent) or chronic alcoholism ( $n = 6$ , 4.2 per cent). *Table 1* shows the baseline characteristics of patients from groups 1 and 2. The two groups were similar in age and sex distribution. There was no difference in the proportions of patients with chronic hepatitis B infection between the two groups. More patients in group 1 (17 per cent) had chronic hepatitis C infection than those in group 2 (9 per cent), although the difference was not statistically significant. Liver function was similar in the two groups in terms of Child–Pugh classification<sup>18</sup>, serum bilirubin concentration, serum albumin concentration, platelet count and indocyanine green retention rate at 15 min. There were no differences

**Table 1** Baseline characteristics of patients with perivascular hepatocellular carcinoma (group 1) and those without perivascular hepatocellular carcinoma (group 2)

|   | Group 1<br>( <i>n</i> = 52) | Group 2<br>( <i>n</i> = 90) | <i>P</i> |
|---|-----------------------------|-----------------------------|----------|
| Age (years)*                                    | 60 (18–79)                  | 63 (42–85)                  | 0.067    |
| Sex ratio (M : F)                               | 42 : 10                     | 69 : 21                     | 0.675    |
| Hepatitis B surface antigen                     | 41 (79)                     | 78 (87)                     | 0.385    |
| Hepatitis C antibody                            | 9 (17)                      | 8 (9)                       | 0.062    |
| Child–Pugh classification                       |                             |                             | 0.405    |
| Class A   | 46 (88)                     | 82 (91)                     |          |
| Class B   | 6 (12)                      | 8 (9)                       |          |
| Serum bilirubin ( $\mu\text{mol/l}$ )*          | 17 (6–63)                   | 14 (6–53)                   | 0.170    |
| Serum albumin (g/l)*                            | 38 (26–47)                  | 40 (18–47)                  | 0.244    |
| Platelet count ( $\times 10^9/\text{l}$ )*      | 119.5 (29–261)              | 127 (39–272)                | 0.473    |
| Indocyanine green retention rate at 15 min (%)* | 18.3 (2.7–60.7)             | 15.3 (3.9–72.9)             | 0.427    |
| Previous hepatic resection                      | 13 (25)                     | 20 (22)                     | 0.837    |
| Previous transarterial chemoembolization        | 12 (23)                     | 22 (24)                     | 1.000    |
| Serum $\alpha$ -fetoprotein (ng/ml)*            | 53 (1–29 860)               | 51 (1–19 350)               | 0.883    |
| Size of largest tumour (cm)*                    | 3.1 (1.3–8)                 | 2.7 (0.5–7)                 | 0.004†   |
| Largest tumour ( $\leq 3$ cm/ $> 3$ cm)         | 25/27                       | 62/28                       | 0.020†   |
| No. of tumours treated (solitary/multiple)      | 37/15                       | 75/15                       | 0.093    |
| One or more subcapsular tumours                 | 31 (60)                     | 48 (53)                     | 0.489    |
| CLIP scoring system                             |                             |                             | 0.244    |
| Score 0   | 24 (46)                     | 53 (59)                     |          |
| Score 1   | 24 (46)                     | 34 (38)                     |          |
| Score 2   | 4 (8)                       | 3 (3)                       |          |
| Patients with biopsy-proven tumours             | 38 (73)                     | 46 (51)                     | 0.013†   |
| Approach of radiofrequency ablation             |                             |                             | <0.001†  |
| Percutaneous                                    | 9 (17)                      | 51 (57)                     |          |
| Laparoscopic                                    | 2 (4)                       | 8 (9)                       |          |
| Thoracoscopic                                   | 2 (4)                       | 0 (0)                       |          |
| Open  | 39 (75)                     | 31 (34)                     |          |

Values are number of patients (percentage) unless stated otherwise. \*Values are median (range). †Statistically significant. CLIP, Cancer of the Liver Italian Program.

between groups in the proportions of patients who had previous hepatic resection and TACE. Despite the similar serum  $\alpha$ -fetoprotein concentration between the two groups, the size of the largest tumour in group 1 was significantly bigger than that in group 2. More patients in group 1 (52 per cent) had larger HCCs (over 3 cm in diameter) than those in group 2 (31 per cent). The proportions of patients who had solitary or multiple tumours were similar between the two groups. There was no difference in the proportion of patients with one or more subcapsular tumours between the two groups. Tumour staging according to the Cancer of the Liver Italian Program (CLIP) scoring system<sup>19</sup> was similar between groups 1 and 2. More patients in group 1 (73 per cent) had biopsy-proven HCC than those in group 2 (51 per cent). A majority of patients in group 1 (75 per cent) underwent RFA through the open approach, whereas only 17 per cent received percutaneous RFA. This was in contrast to patients in group 2, among whom 57 per cent had percutaneous RFA and only 34 per cent underwent open RFA. Significantly more patients in group 2 received laparoscopic RFA, compared with group 1 (9 versus 4 per cent). Thoracoscopic RFA was performed in two patients, and both of them had perivascular HCC.

### Treatment morbidity and mortality

The comparison of treatment-related mortality and morbidity is illustrated in *Table 2*. There was no significant

**Table 2** Treatment-related mortality and morbidity in patients with perivascular hepatocellular carcinoma (group 1) and those without perivascular hepatocellular carcinoma (group 2)

|  | Group 1<br>(n = 52) | Group 2<br>(n = 90) | P     |
|--|---------------------|---------------------|-------|
| RFA-related mortality                              | 1 (2)               | 0 (0)               | 0.366 |
| RFA-related morbidity                              | 13 (25)             | 25 (28)             | 0.844 |
| Haemoglobinuria                                    | 4 (8)               | 3 (3)               |       |
| Thrombosis of portal vein or hepatic vein branches | 1 (2)               | 2 (2)               |       |
| Bile duct stricture                                | 1 (2)               | —                   |       |
| Intrahepatic pseudoaneurysm                        | —                   | 1 (1)               |       |
| Symptomatic pleural effusion                       | 3 (6)               | —                   |       |
| Symptomatic ascites                                | —                   | 2 (2)               |       |
| Chest infection                                    | 1 (2)               | 2 (2)               |       |
| Cardiac arrhythmia                                 | 1 (2)               | 1 (1)               |       |
| Acute myocardial infarction                        | —                   | 1 (1)               |       |
| Wound infection                                    | —                   | 3 (3)               |       |
| Intra-abdominal collection                         | —                   | 1 (1)               |       |
| Sepsis of unknown origin                           | 3 (6)               | 5 (6)               |       |
| Renal failure                                      | 1 (2)               | 1 (1)               |       |

Values are number of patients (percentage). RFA, radiofrequency ablation.

difference in the treatment-related mortality rate between the two groups (2 versus 0 per cent). Among patients in group 1, one patient developed multiorgan failure as a result of severe systemic inflammatory reactions to large-volume RFA (RFA of four intrahepatic recurrent HCCs with the largest tumour 4.9 cm in diameter). This patient died on day 4 after RFA. The overall complication rates were similar between groups 1 (25 per cent) and 2 (28 per cent) ( $P = 0.366$ ). Haemoglobinuria occurred in four patients (8 per cent) of group 1 and three patients (3 per cent) of group 2 ( $P = 0.260$ ). All of them were managed conservatively with adequate hydration by intravenous fluid replacement, and the manifestation of haemoglobinuria resolved spontaneously in these patients within 5 days after RFA. None of them developed renal failure as a result of haemoglobinuria. One patient (2 per cent) in group 1 developed thrombosis of the major portal vein branch, whereas thrombosis of the major portal vein or hepatic vein branches was found in two patients (2 per cent) of group 2 ( $P = 1.000$ ). One patient (2 per cent) in group 1 developed a bile duct stricture close to the RFA treatment site, which was shown on CT scan 3 months after RFA, and this complication was not observed in patients in group 2. Four patients in group 1 underwent cold saline irrigation of the bile duct during the RFA procedure, and none of them developed bile duct stricture during the follow-up period.

### Treatment outcome after RFA

The clinical outcome after RFA treatment is summarized in *Table 3*. The completeness of ablation could not be assessed in one patient of group 1, who died of multiorgan failure after RFA treatment. Overall, complete tumour ablation was achieved in 45 patients (88 per cent) in group 1 and 88 patients (98 per cent) in group 2. Taking into consideration the total number of ablated tumour nodules, the overall complete ablation rate was 84 per cent (47 of 56 tumour nodules) for perivascular HCCs and 96.9 per cent (126 of 130 tumour nodules) for non-perivascular HCC. For patients with tumours up to 3 cm in diameter, the complete ablation rate after a single session of RFA was similar in both groups 1 (22 of 25 patients; 88 per cent) and 2 (59 of 61 patients; 97 per cent) ( $P = 0.145$ ). In contrast, the complete ablation rate after a single session of RFA for patients with large tumours over 3 cm in diameter was significantly lower in group 1 (21 of 26 patients; 81 per cent) than that in group 2 (27 of 28 patients, 96 per cent) ( $P = 0.030$ ). Among 13 patients with residual tumours detected by CT scan 1 month after the first session of RFA, five patients received a second session of

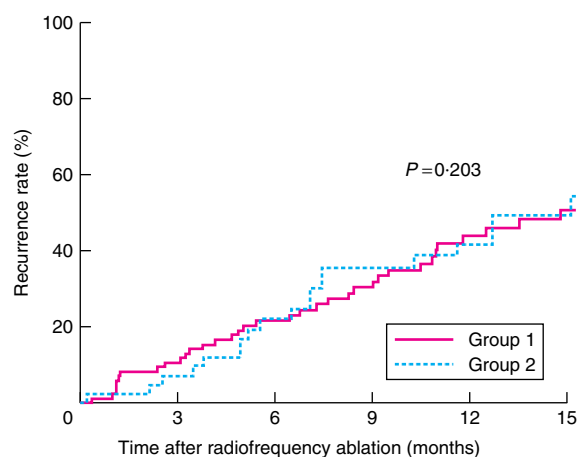
**Table 3** Treatment outcome after RFA in patients with perivascular hepatocellular carcinoma (group 1) and those without perivascular hepatocellular carcinoma (group 2)

|   | Group 1<br>(n = 51)* | Group 2<br>(n = 90) | P      |
|---|----------------------|---------------------|--------|
| Complete ablation after single session of RFA |                      |                     |        |
| Tumour ≤ 3 cm                                 | 22/25 (88)           | 59/62 (97)          | 0.145  |
| Tumour > 3 cm                                 | 21/27 (81)           | 27/28 (96)          | 0.030§ |
| Overall complete ablation†                    |                      |                     |        |
| Tumour ≤ 3 cm                                 | 23/25 (92)           | 61/62 (98)          | 0.197  |
| Tumour > 3 cm                                 | 22/27 (85)           | 27/28 (96)          | 0.101  |
| Local recurrence at ablated site‡             | 5 (11)               | 8 (9)               | 0.762  |
| Distant intrahepatic recurrence‡              | 15 (33)              | 25 (28)             | 0.556  |
| Distant extrahepatic recurrence‡              | 7 (16)               | 7 (8)               | 0.233  |

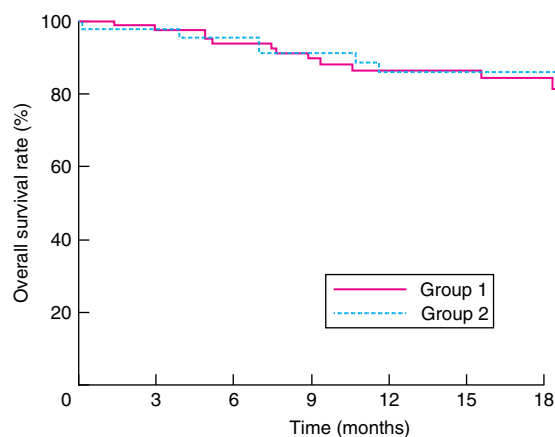
Values are number of patients (percentage). \*One patient who died of multiorgan failure after RFA treatment was excluded from the analysis. †Overall complete ablation refers to the complete ablation rate after a second ablation for residual tumour. A total of four patients had complete tumour ablation after a second ablation by RFA. ‡Local and distant tumour recurrence rates were analysed among patients with overall complete ablation. §Statistically significant. RFA, radiofrequency ablation.

RFA treatment. Complete tumour ablation was eventually achieved in two patients in each group and the remaining patient needed TACE to control the residual tumour at the RFA site. In addition, TACE and percutaneous ethanol injection were given as salvage treatment for residual tumours after RFA to four patients (two in each group) and one patient (group 1) respectively. One patient underwent curative hepatic resection for residual tumour and remained disease-free 18 months after the operation. Two patients were offered conservative treatment for malignancy because of poor liver functional reserve.

All patients were followed up for at least 12 months after RFA. Excluding one patient who died after RFA, the median (range) follow-up of the remaining 141 patients was 13 (13–35) months. Among patients with overall complete tumour ablation, the overall local recurrence rate was 9.8 per cent (13 of 133 patients). There was no significant difference in the local recurrence rate between groups 1 (11 per cent) and 2 (9 per cent) ( $P = 0.762$ ). When the total number of ablated tumour nodules was taken into consideration, the local recurrence rate was 9 per cent (five of 56 nodules) for perivascular HCC and 6.2 per cent (eight of 130 nodules) for non-perivascular HCC ( $P = 0.496$ ). The local tumour recurrence rate was similar between patients with biopsy-proven HCC (nine of 75 patients, 12 per cent) and those without biopsy-proven tumours (four of 54 patients, 7 per cent) ( $P = 0.556$ ). There was no significant difference between the two groups in the incidence of distant intrahepatic recurrence and



| No. at risk | 3  | 6  | 9  | 12 | 15 |    |
|-------------|----|----|----|----|----|----|
| Group 1     | 45 | 39 | 29 | 22 | 16 | 10 |
| Group 2     | 88 | 73 | 56 | 43 | 27 | 20 |

**Fig. 2** Cumulative recurrence rates of patients with perivascular hepatocellular carcinoma (group 1;  $n = 51$ ) and those without perivascular hepatocellular carcinoma (group 2;  $n = 90$ ) ( $P = 0.203$ ; log rank test)

| No. at risk | 3  | 6  | 9  | 12 | 15 | 18 |    |
|-------------|----|----|----|----|----|----|----|
| Group 1     | 52 | 50 | 43 | 38 | 28 | 19 | 12 |
| Group 2     | 89 | 82 | 70 | 60 | 47 | 38 | 27 |

**Fig. 3** Cumulative overall survival curves of patients with perivascular hepatocellular carcinoma (group 1;  $n = 52$ ) and those without perivascular hepatocellular carcinoma (group 2;  $n = 90$ ) ( $P = 0.741$ ; log rank test)

extrahepatic recurrence. During the follow-up period, the cumulative recurrence rates at 1 and 2 years in group 1 were 52 and 75 per cent respectively, which were similar to those in group 2 (1 year: 45 per cent; 2 years: 61 per cent) ( $P = 0.203$ ) (Fig. 2). The cumulative 1-year and 2-year overall survival rates were 86 and 75 per cent respectively for group 1 and 87 and 75 per cent respectively for group 2

(Fig. 3), showing no statistically significant difference between the two groups ( $P = 0.741$ ).

## Discussion

Treatment of liver tumours close to major intrahepatic blood vessels by RFA poses a great challenge to clinicians. Because of the possible 'heat-sink' effect of intrahepatic blood flow, there may be a high chance that ablation of the perivascular tumour is incomplete. This hypothesis was supported by a study conducted by Lu *et al.*<sup>12</sup>, in which perivascular tumour location was the independent and dominant predictor of treatment outcome of RFA in terms of completeness of ablation and local tumour recurrence. In their study, the overall local recurrence rate was 19 per cent in 105 primary and secondary liver tumours. Up to 48 per cent of perivascular tumours recurred locally at previous ablated sites, whereas only 7 per cent of non-perivascular tumours had local recurrence after RFA. As HCC has a high propensity for intrahepatic vascular invasion, a large-scale study will be needed to clarify the role of RFA for perivascular HCC. To our knowledge, this is the first study investigating the efficacy and safety of RFA for perivascular HCC in a single institution.

Compared with the study by Lu *et al.*<sup>12</sup>, the overall local tumour recurrence rate was much lower (9.8 per cent) in this study. In addition, there was no difference in local recurrence rates between patients with and without perivascular HCC (11 *versus* 9 per cent). This finding could be related to the choice of RFA approaches in this study. RFA through the open approach was performed in 75 per cent of patients with perivascular HCC, whereas only 34 per cent of patients with non-perivascular HCC received open RFA. Most patients with non-perivascular HCC (57 per cent) were treated with percutaneous RFA. During laparotomy, there were more degrees of freedom for the introduction of the RF electrode into the tumour, and the aim was ablation of all tumour nodules with at least a 0.5-cm ablation margin. In fact, open RFA was associated with a higher complete ablation rate than percutaneous RFA by a multivariate analysis in a previous study<sup>2</sup>. As far as complete ablation rate was concerned, tumour size as well as perivascular tumour location were important contributing factors in this study. The complete ablation rates were similar between patients with small perivascular HCC and those with small non-perivascular HCC. However, patients with large perivascular HCCs (over 3 cm in diameter) had a significantly lower complete ablation rate after a single session of RFA than those with non-perivascular HCC of similar tumour size (81 *versus* 96 per cent). With repeated RFA for patients with

residual tumours in the large perivascular HCC group, the overall complete ablation rates were similar between the two groups (85 *versus* 96 per cent). This signifies the importance of an aggressive RFA approach for liver tumours which failed the initial session of RFA.

This study is unique in providing the clinical evidence that RFA is feasible and effective for perivascular HCC, in terms of a high complete ablation rate (over 95 per cent) and low rate of local recurrence (9 per cent). This phenomenon of perivascular cellular destruction by RFA has been investigated experimentally in the authors' previous study<sup>17</sup>. We postulated that, without direct puncture of nearby blood vessels, the intact RF current could be propagated to the region around the blood vessels, causing lethal energy to ablate the tissue.

The safety of RFA for perivascular HCC has been well illustrated in this study. The morbidity and mortality rates were comparable between the perivascular HCC and non-perivascular HCC groups. There was no significant difference between the two groups in the incidence of potential complications after RFA for perivascular tumours, which included haemoglobinuria, blood vessel thrombosis and bile duct stricture. The presence of haemoglobinuria is believed to be caused by intravascular haemolysis as a result of RFA near major intrahepatic blood vessels<sup>20</sup>. Of seven patients who had haemoglobinuria after RFA, none developed renal impairment subsequently. This could be attributed to the vigilant management strategy during surgery, when patients received intravenous mannitol and adequate fluid replacement to ensure sufficient fluid load of the kidney.

Patency of nearby intrahepatic blood vessels after RFA was observed in 98 per cent of patients in the perivascular HCC group. During the RFA procedure in all patients, special care was taken to avoid direct puncture of blood vessels by the RF electrode, and this might have contributed to the low incidence of thrombosis in the present study. In addition, it is routine practice to perform RFA without the application of hepatic inflow occlusion, and the resulting hepatic blood flow might help to protect the blood vessel by the 'heat-sink' effect against thermal injury of RFA. Such a hypothesis was supported by the authors' experimental study using a porcine liver model<sup>17</sup>.

A drawback in this study was that the outcomes of patients with liver tumours close to the portal vein branch were analysed with the outcomes of those with tumours close to the hepatic vein branch. The haemodynamics of the portal vein are different from those of the hepatic vein, so the effects of portal vein and hepatic vein blood flow on the thermal injury of RFA may differ. Comparison of the local effect of RFA on portal vein and hepatic vein branches

needs to be investigated further in future experimental and clinical studies.

The present study shows that RFA without hepatic inflow occlusion is a safe and effective treatment modality for perivascular HCC. With meticulous RFA techniques, potential complications associated with RFA at the perivascular region could be minimized.

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