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Radiofrequency Ablation for 110 Malignant Liver Tumours: Preliminary Results on Percutaneous and Surgical Approaches

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BACKGROUND: Radiofrequency ablation (RFA) has been widely applied for the treatment of hepatocellular carcinoma and liver metastases. The reported mortality and morbidity rates are low. The aim of this study is to evaluate the safety and efficacy of RFA, and compare the results performed percutaneously versus surgically.

PATIENTS AND METHODS: From 2003 to 2006, 79 patients with hepatic malignancies (59 hepatocellular carcinoma, 20 liver metastases) with a total of 110 lesions underwent RFA in our centre. Post-ablation assessment by CT scan was performed in all patients at 1-, 3- and 6-month intervals. Post-procedural complications, recurrence and survival were analysed.

RESULTS: The patients' mean age was 60.0 years. In 46.8% of cases, we used a percutaneous approach; in 53.2% of cases, a surgical approach (8.9% laparoscopic; 44.3% open) was used if percutaneous approach was not feasible. The mean tumour size was 2.4 cm. Within the surgical group, 69% of patients received concomitant operative procedures such as cholecystectomy and hepatectomy. No treatment-related mortality was observed. Immediate complications occurred in five patients (6.3%), including gastric serosal burn ($n=1$), ground pad superficial skin burn ($n=1$), intra-abdominal bleeding ($n=2$) and pleural effusion ($n=1$). All patients except one attended subsequent follow-up, with a mean period of 16 months. Ablation was considered complete in 82.3% of patients (percutaneous approach 81.1%, surgical approach 83.3%, $p=0.72$). Intrahepatic recurrence was observed in 52.3%, the majority of them located away from the RFA site. Extrahepatic recurrences were observed in 16.9% (percutaneous approach 16.7%, surgical approach 17.1%, $p=0.76$). The overall one- and two-year survival rate was 93.7% and 74.4% respectively, and no statistically significant difference was observed between the two approaches.

CONCLUSION: RFA is a safe and effective procedure for treating patients with malignant liver tumours. No difference in short term outcomes was observed between percutaneous and surgical approaches. A more prolonged follow-up study is required to assess longer-term outcomes. [*Asian J Surg* 2009;32(1):13–20]

Key Words: hepatocellular carcinoma, laparoscopic, percutaneous, radiofrequency ablation

Introduction

In recent years, there has been growing interest in radiofrequency ablation (RFA) for treating liver tumours. This has been widely accepted as an effective modality for treating unresectable hepatocellular carcinoma (HCC) and liver secondaries.[1–4] It is a thermoablative technique, based on the conversion of radiofrequency waves into

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heat, and thus generating areas of coagulative necrosis and tissue desiccation.[5] The ablation can be performed percutaneously, laparoscopically, thoracoscopically, or at open surgery.[6] Variable oncological outcomes have been reported by means of different approaches.[7,8] Nowadays, RFA is widely applied to patients with small tumours with encouraging results[9] and its reported mortality and morbidity has been low.[10]

In our locality, where chronic hepatitis B virus (HBV) infection and cirrhosis of liver are commonly seen, the incidence of HCC is particularly high. The prognosis of HCC is generally poor. Liver resection remains the "gold standard" for curative treatment, but is suitable only for minority of patients.[11] Similarly, up to 80% of patients with colorectal liver metastasis are considered not a candidate for surgical treatment.[12] We performed RFA on patients with unresectable disease either percutaneously or surgically. The objective of this study was to evaluate the safety and efficacy of RFA in treating hepatic malignancies. The outcome performed via these two approaches was compared.

Patients and methods

From May 2003 to February 2006, 79 patients (60 men and 19 women) undergoing RFA for malignant liver tumours in our centre were evaluated. Patients' demographics and tumour characteristics are listed in Table 1. The patients' mean age was 60 years (range, 37–93). The nature of malignancy included hepatocellular carcinoma (59 cases) and hepatic metastasis (20 cases). A total of 110 lesions were ablated.

Pre-procedural assessment

All patients were assessed clinically and investigated with laboratory tests of liver functions, hepatitis B/C serology, alpha-fetoprotein and carcinoembryonic antigen. Radiologically, they all had a chest X-ray and a trans-abdominal ultrasound, followed by a 3-phase contrast computed tomography (CT) scan. In situations where a malignant nature was uncertain, liver biopsy was performed prior to ablation. Benign conditions were excluded. Standard cardiopulmonary assessments and indocyanine green (ICG) clearance tests were performed if a surgical approach was contemplated.

All RFA procedures were performed either percutaneously or surgically (laparoscopic or open). Parameters taken into consideration when planning the approach included tumour size, number and location, previous operations, general anaesthetic risk as well as the necessity for concomitant operative procedures, such as a cholecystectomy. If feasible, a percutaneous approach remained the first choice of treatment, followed by a laparoscopic approach and open surgery.

Patient selection criteria for RFA followed published recommendations.[6] RFA lesions were deemed unsuitable for curative-intent liver resection due to poor hepatic reserve (i.e. ICG retention at 15 minutes greater than 14%) except in one resectable case, of which the patient refused hepatectomy. The maximum dimension of the tumours was not greater than 5 cm on CT scan measurement. There was no evidence of extrahepatic metastasis upon diagnosis. Subcapsular tumours, perivascular tumours and tumours located too close to major bile ducts were considered unsafe for percutaneous approach, and a surgical approach would be adopted instead.

A laparoscopic approach would be chosen for tumours close to the gallbladder, where a laparoscopic cholecystectomy would be performed in conjunction with the RFA. For tumours located in the posterior aspect of the left lobe, the stomach could be insulated from the RFA site by a wet gauze or cold saline. The whole abdominal cavity could also be carefully inspected to exclude peritoneal metastasis. An open approach would be indicated for patients with previous abdominal surgery, or tumours in close proximity to surrounding organs that required meticulous adhesiolysis. Open approach would be necessary if the tumour was located at the right posterior sector, where full mobilisation of the right lobe was needed. The degree of freedom for introduction of the RFA needle into the target was also taken into consideration.

RFA ablation technique

Percutaneous RF ablations were performed by consultant interventional radiologists. Surgical RFA procedures were performed by the same team of hepato-biliary surgeons. Ablation techniques were standardised according to recommended protocols provided by the manufacturers (Boston Scientific and Tyco Healthcare).

Percutaneous RFA was performed under local anaesthesia with conscious sedation. Para-vertebral block was given in selected cases. Tumour localisation and ablation were guided by abdominal ultrasound or CT scan or by

Table 1. Patient demographics and tumour characteristics

	Percutaneous	Surgical	*p*
Number of patients	37	42	
Sex (M:F)	29:8	31:11	
Age (yr)	63 (37–93)	56 (38–77)	
Diagnosis (HCC:Liver metastases)	27:10	32:10	
Number of tumours	39	71	
Median no. of tumours ablated/patient	1.0 (1.0–2.0)	1.0 (1.0–7.0)	0.005*
Median tumour size (cm)	2.5 (1.3–5.0)	2.0 (0.5–8.0)	0.174
Median hospital stay (d)	4.0 (2.0–8.0)	8.0 (5.0–42.0)	0.001*
Median follow-up period (mo)	13.6 (3.5–26.6)	17.7 (2.1–38.5)	

*$p < 0.05$, Mann-Whitney test. HCC = hepatocellular carcinoma.

both modalities. RF 3000 Radiofrequency Generator with LeVeen needles (Boston Scientific, USA) was used in almost all cases, aiming at a 0.5–1.0 cm margin around the tumour. If the nature of the lesion was not diagnosed radiologically or biochemically, a liver biopsy through a co-access needle system was performed immediately prior to ablation. Only malignant nodules were included in the present study. Multiple overlapping zones of ablation were needed in 50% of cases in order to achieve adequate coverage with margins. The needle track was burned at the end of the procedure.

Laparoscopic RFA procedures were done with a 30° laparoscope with CO_2 pneumoperitoneum. After a full laparoscopy to exclude the presence of peritoneal metastasis, the intrahepatic lesions were localised with intra-operative laparoscopic ultrasound (linear array, Aloka SSD-2000). A Radionics Cool-tip RF System (Tyco Healthcare) was used. Multiple overlapping ablations were performed when necessary to ensure ablation margins, as in the percutaneous group. The needle track was burned at the end of ablation. Two patients in this group also received concomitant laparoscopic cholecystectomy (Table 2).

Open RFA procedures were performed via a right subcostal incision. After adequate mobilisation, tumour localisation and electrode placement was guided by intra-operative ultrasound (T-probe, Aloka SSD-2000). Ablation was performed as described above. Both the Radionics Cool-tip RF System (Tyco Healthcare) and RF 3000 Radiofrequency Generator (Boston Scientific, USA) systems were used, whichever more applicable. In general, LeVeen needles (Boston Scientific, USA) were avoided in lesions located peripherally. The Pringle manoeuvre was not applied for all cases. Concomitant surgical procedures were listed in Table 2.

Table 2. Concomitant surgical procedures during RFA (laparoscopic and open)

Type of surgery	Number of patients
Laparoscopic group	7
Cholecystectomy	2
Open group	35
Hepatectomy only	5
Cholecystectomy only	11
Hepatectomy & cholecystectomy	4
Excision of peritoneal nodules	2
Colectomy	1
Excision of liver haemangioma	1
Right adrenalectomy	1
Hernioplasty (Inguinal & paraumbilical)	1
Celiac lymph node dissection	1

Patients' follow-up

All patients except one from the surgical group attended subsequent follow-up visits, with a mean follow-up period of 16 months (range, 2.1–38.5). Patients were assessed by contrast-enhanced CT scans 1, 3 and 6 months after RFA. The ablation response was defined as "incomplete" if there was existence of arterial enhanced areas on the first set of post-ablation imaging. For the completely ablated cases, the presence of enhanced appearance on subsequent scans was defined as "recurrence". Intrahepatic recurrence could be at the previously ablated sites or at distant sites. Extrahepatic recurrences were detected by CT scans, chest

Table 3. Complications of RFA

	Percutaneous	Surgical	
Immediate	Perihepatic bleeding ($n=1$) Pleural effusion ($n=1$)	Right adrenal haemorrhage ($n=1$) Superficial skin burn ($n=1$) Gastric serosal burn ($n=1$)	n.s.
Early	Nil	Chest infection ($n=1$) Wound infection ($n=1$) Ascites ($n=1$) Atrial fibrillation ($n=1$) Supra-ventricular tachycardia ($n=1$)	$p=0.057$
Delay	Needle-track seeding ($n=1$)	Nil	n.s.

Fisher's exact test. n.s. = not significant.

X-rays, bone scans, PET scans or tissue histology in individual cases. All patients on subsequent follow-up visits had a clinical assessment by the surgical team with documentation of all complications.

Statistical analysis

Parameters including tumour number, tumour size, length of hospital stay, procedure-related complications and treatment outcome were analysed and data compared between the percutaneous and surgical groups. Data were expressed as mean ± SD. Non-parametric data were expressed as median (range) and tested by the Mann-Whitney test. Survival data and tumour recurrence rates were calculated using the Kaplan-Meier method and were compared by the log rank test. The level of significance was set at 0.05 for all tests.

Results

Tumour number and RFA approach

A total of 110 lesions were ablated in 79 patients. A percutaneous approach was applicable in 46.8% of cases, a laparoscopic approach in 8.9% and an open approach in 44.3% (surgical approach = 8.9% + 44.3% = 53.2%). The total number of ablated lesions in the percutaneous group was 39, and for the surgical group the number was 71. The median number of ablated lesions per patient in the percutaneous group was 1.0 (range, 1.0–2.0), as compared to 1.0 (range, 1.0–7.0) in the surgical group.

Tumour size

The median tumour size was 2.5 cm (range, 1.3–5.0) in the percutaneous group; and 2.0 cm (range, 0.5–8.0) in the surgical group. The difference was not statistically significant ($p=0.174$).

Length of hospital stay

The median length of hospital stay in the percutaneous group was 4 days (range, 2–8); compared to 8 days (range, 5–42) in the surgical group, and the difference was statistically significant ($p=0.001$).

Complications (Table 3)

Five patients (6.3%) suffered from immediate procedural-related complications (Table 3). In the percutaneous group, one patient developed mild perihepatic bleeding and one patient had pleural effusion, both resolved on conservative management. In the surgical group, immediate complications included superficial skin burns at the ground pad site ($n=1$), bleeding from the right adrenal ($n=1$) and serosal burns of the anterior wall of the stomach ($n=1$). These were all identified intra-operatively. No treatment-related mortality was documented in any of the patients.

Post-ablation fever was noted in 20.3% of the overall patients. The majority of them responded well to a course of non-steroidal anti-inflammatory drugs. Prescription of antibiotics was restricted to those with evidence of leukocytosis or clinical signs of sepsis. Needle-track seeding was identified in one patient 9 months after percutaneous RFA. All complications were summarised in Table 3.

Treatment outcome (Tables 4 and 5)

Complete ablation, as defined by no viable tumour detectable on the first set of CT scans 1 month after ablation, was achieved in 82.3%. There was no significant difference between the percutaneous (81.1%) and the surgical group

Table 4. Summary of RFA treatment outcome

	Percutaneous	Surgical	*p*
Complete ablation (%)	81.1	83.3	0.717
HCC	81.5	84.4	
Liver metastases	80.0	80.0	
Intrahepatic recurrence (%)			
RFA site	10.0	2.9	0.195
Distant site	43.3	54.3	0.918
Extrahepatic recurrence (%)	16.7	17.1	0.756
1-year survival (%)	97.3	90.5	
2-year survival (%)	79.8	70.8	

HCC = hepatocellular carcinoma.

Table 5. Survival of HCC and liver metastases patients treated by percutaneous and surgical approach

	Percutaneous	Surgical
HCC	($n=27$)	($n=32$)
1-year survival (%)	96.3	87.5
2-year survival (%)	96.3	66.0
Liver metastases	($n=10$)	($n=10$)
1-year survival (%)	100.0	100.0
2-year survival (%)	42.9	85.7

HCC = hepatocellular carcinoma.

Table 6. Sites of extrahepatic recurrence in the 11 patients

Sites	Number of patients (%)
Lung	6 (54.5)
Bone	3 (27.3)
Adrenal	2 (18.2)
Skin	2 (18.2)
Peritoneum	2 (18.2)
Mesocolon	2 (18.2)
Lymph nodes	1 (9.1)
Spleen	1 (9.1)
Omentum	1 (9.1)
Kidney	1 (9.1)
Small bowel mesentery	1 (9.1)

(83.3%) ($p=0.717$). Subgroup analysis demonstrated no difference in outcome with regard to the primary pathology (i.e. HCC or liver metastasis).

The overall intrahepatic recurrence rate was 52.3%. Only a minority occurred at the previous RFA site (percutaneous approach 10.0%, surgical approach 2.9%, $p=0.195$); while the majority occurred at a distant site (percutaneous approach 43.3%, surgical approach 54.3%, $p=0.918$).

Extrahepatic recurrence was documented in 16.9% of all patients in this series (Table 6). Again, there was no significant difference between the two groups (percutaneous approach 16.7%; surgical approach 17.1%, $p=0.756$).

Overall, patients had a median follow-up period of 14.3 months (range, 2.1–38.5) after RFA (percutaneous group 13.6 months, range, 3.5–26.6; surgical group 17.7 months, range, 2.1–38.5). Survival curves were shown in Figure. The overall 1-year survival was 93.7%, (97.3% in the percutaneous group, 90.5% in the surgical group). The overall 2-year survival was 74.4%, (79.8% in the percutaneous group, 70.8% in the surgical group). There was no significant difference in terms of survival between the two approaches ($p=0.644$). One- and 2-year survival rates of HCC patients and liver metastasis patients after RFA are listed in Table 5. The number of patients in each subgroup was too small for meaningful survival analysis and comparison.

Discussion

The two most commonly encountered liver malignancies in our locality are hepatocellular carcinoma and colorectal liver metastases. While surgical resection remains the "gold standard" for treating both conditions, only a small proportion of patients are suitable candidates for curative-intent hepatectomy.[11] This may be due to patient's comorbidity, poor liver reserve, presence of extrahepatic disease, or it may be related to the number and anatomical location of the tumours. Radiofrequency ablation has become one of the best alternatives in treating these patients who

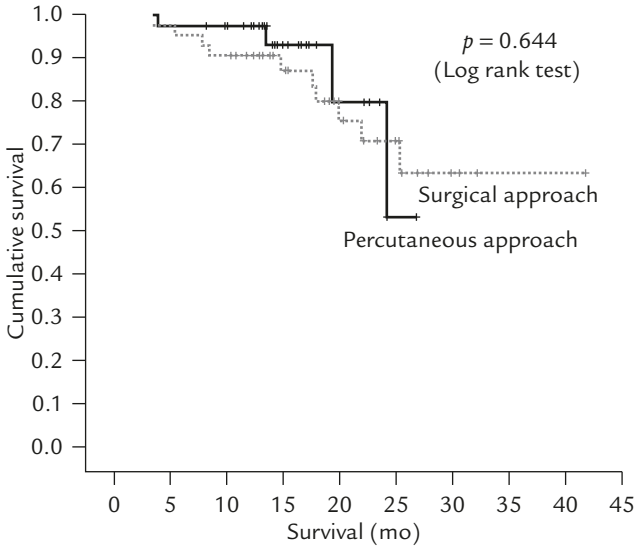

Figure. Cumulative overall survival of patients after RFA.

are not candidates for curative hepatectomy. A recent systematic review by Sutherland et al concluded that RFA generally resulted in larger and more complete areas of ablation, and RFA may also be associated with higher survival rates than the other ablative techniques being assessed.[1,13,14] The objective of this study is to evaluate the safety and efficacy of RFA performed in our centre. The results performed percutaneously and surgically were analysed.

The choice between percutaneous and surgical (open or laparoscopic) approaches deserves a careful discussion. The percutaneous approach obviously has the advantage of avoiding general anaesthesia and a surgical wound. It can also be applied repeatedly to treat recurrent tumours. Moderate to severe pain during the procedure was commonly encountered, but we have overcome this problem by the addition of a para-vertebral block immediately prior to the procedure. The percutaneous approach is less invasive and the patients' length of hospital stay was significantly shorter in our study. A very similar result was demonstrated in the Italian group.[15] The procedure may be guided by a transabdominal ultrasound or CT scan, and in majority of cases, we used both modalities simultaneously to maximise the accuracy in tumour localisation.

Nevertheless, certain limitations prevent interventional radiologists applying the RFA electrode and target at the lesion through the percutaneous route. These include tumours that lie too peripherally and too close to the diaphragm, major blood vessels or hollow organs such as the bowel or gallbladder.[16] Under these circumstances, open surgical approach allows greater flexibility, both in the placement of an intra-operative ultrasound transducer as well as the RFA electrode. The laparoscopic RFA technique offers certain advantages over both percutaneous and open RFA.[16] However, this minimally invasive approach is more technically demanding, especially during tumour localisation by the laparoscopic ultrasound and insertion of the RFA electrode.

Another advantage of the surgical approach is that concomitant procedures can be performed during RFA. In the present series, a majority of the procedures were cholecystectomies ($n = 17$) and liver resections ($n = 9$). The gallbladders were removed not merely for those who had concurrent symptomatic gallstones; this also facilitates ablation of liver tumours located near to the gallbladder bed. A combined approach using RFA with liver resections has been reported with encouraging results.[17,18] We find this approach particularly useful for bilobar lesions located in the peripheral segments. The prolonged hospital stay in the surgical group (8 days) can be accountable by the longer surgical wound and a greater magnitude of surgery, as compared to the percutaneous group (4 days).

There have been postulations that the Pringle manoeuvre during surgical RFA prevents dissipation of heat from a vascular tumour and thus improves the likelihood of complete ablation.[16] However, using a pig model, Shen et al demonstrated that laparoscopic RFA with the Pringle manoeuvre in proximity to major vascular structures did not significantly increase ablation size, or cause vascular injury.[19] In our series, the Pringle manoeuvre was not performed in all cases.

It has been recommended that the efficacy of percutaneous ablation should be assessed by a contrasting CT scan 1 month after therapy.[20] Although not entirely accurate, the absence of a contrasting uptake inside the tumour reflects tumour necrosis, while the persistence of a contrasting uptake indicates viable tumours and incomplete ablation. We assessed the efficacy of RFA by contrasting CT scans performed at 1-, 3-, and 6-months after the procedure, in order to examine a more prolonged outcome. Thereafter, patients were assessed by a contrasting CT scan at a 6-month interval. Similar protocols for post-ablation assessment have been followed in previous studies.[21]

Complications from RF ablation are not uncommon. Mulier et al reviewed 3,670 patients after RFA; mortality

and morbidity rates were 0.5% and 8.9%, respectively.[10] Another multicentre survey on 582 hepatic tumours over a 5-year period reported the mortality, major and minor complication rates to be 1.4%, 5.7% and 6.3%, respectively.[22] Significant risk factors associated with treatment morbidity included hyperbilirubinaemia (> 20 μmol/L), multiple tumour nodules, surgical approach, and early experience (< 50 cases).[23] In the present study, we did not observe procedure-related mortality. The immediate morbidity rate was 6.3% (5/79). In the percutaneous group, one patient developed a subcapsular haematoma and another patient developed a sympathetic right pleural effusion. Both situations resolved on conservative management. In the surgical group, one patient had minor bleeding from the right adrenal bed and managed by plication. Another patient developed a superficial gastric serosal burn after laparoscopic ablation of a left lateral segment tumour, which was identified at the end of procedure and repaired. There was a single case of a 1° skin burn from the ground-pad.

Needle track seeding in patients treated with percutaneous RFA has raised a great deal of concern. Bonatti et al reported a case of skin implant metastasis after percutaneous RFA for colorectal liver metastasis.[24] Seeding has also been described after percutaneous RFA for hepatocellular carcinoma performed with a single cooled-tip electrode.[25] There are several postulations for this phenomenon: dissemination of tumour cells on retraction of the radiofrequency electrode, tumour cell spread from needle track haemorrhage and cells extruded by an increased intratumoural pressure during RFA.[16] One patient in our series suffered from needle track metastasis 9 months after percutaneous RFA for her colorectal liver secondaries. She subsequently died of carcinomatosis. Our practice to minimise this complication was to burn the track within the liver parenchyma during withdrawal of the electrode under all circumstances, and to discourage the use of percutaneous RFA for subcapsular lesions.

With regard to RFA treatment responses and outcome, the follow-up period of this study was similar to previous reports.[2,21,26,27] Complete ablation was achieved in 81.1% (percutaneous) and 83.3% (surgical), without a significant difference between the two approaches. This result is comparable to international figures, in the region of 80%.[16,21] Some authors quoted a higher rate of complete ablation by the open surgical approach than by the percutaneous approach,[21,26] possibly related to longer ablation times with better pain tolerances under general anaesthesia in the surgical group. Being unable to achieve a complete ablation is usually related to a failure in the RFA technique. Larger tumours need multiple overlapping zones to cover adequate ablation margins in 3 dimensions. We collaborated with senior radiologists in the intraoperative tumour localisation until our technique matured.

Recurrence at extrahepatic sites (as well as distant site intrahepatic recurrence), on the other hand, is more determined by the tumour biology and the natural history of the disease. The incidence varies among individual studies.[6,27] This illustrates the inability of local ablative therapy in controlling the disease progression as a whole. Again, we observed no significant difference in both approaches (16.7% percutaneous *vs.* 17.1% surgical). In terms of survival, 1-year and 2-year survival rates were 93.7% and 74.4%, respectively. These figures were similar to the survival data reported by Rossi et al.[28] Data on longer-term outcome and survival are still lacking.

In conclusion, this study demonstrated that RFA is a safe and effective procedure for treating unresectable primary or secondary liver malignancies. We did not observe any significant difference in terms of recurrence rate or survival outcome between the percutaneous and surgical groups, although the two groups were not totally comparable. The length of hospital stay is significantly shorter in the percutaneous group, but concomitant operations can be performed in the surgical group. A more prolonged follow-up study is required to assess the longer-term outcomes.

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