ORIGINAL ARTICLE

Surgical ablation of hepatocellular carcinoma with 2.45-GHz microwave: a critical appraisal of treatment outcomes

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Objective To evaluate the efficacy and safety of a new generation of 2.45-GHz microwave to ablate hepatocellular carcinoma by surgical approach.

Design Case series with prospective follow-up.

Setting A university teaching hospital in Hong Kong.

Patients From March 2009 to January 2011, 26 consecutive patients (19 men and 7 women) with a median age of 63 (range, 49-79) years with hepatocellular carcinoma were recruited. Five (19%) of the patients had recurrent hepatocellular carcinoma after previous treatment.

Intervention Microwave ablation for hepatocellular carcinomas (one tumour, n=24; two tumours, n=2) using a laparoscopic (n=16) or open approach (n=10).

Main outcome measures Operative mortality and morbidity, rate of incomplete ablation, recurrence rate, and survival rate.

Results The median tumour diameter was 3.8 cm (range, 2.0-6.0 cm). Complications occurred in five (19%) of the patients; only one was ablation-related, and there was no operative mortality. One (4%) of the patients experienced incomplete ablation. Recurrent tumours were noted in 11 (42%) of the patients (5 were local, 2 were remote, and 4 were multifocal) after a median follow-up of 14 (range, 4-26) months. The failure rate for local disease control was 23%, and was 14% if patients with recurrent hepatocellular carcinoma were excluded. All but one patient survived until the time of censorship. The mean survival was 25 (standard deviation, 1) months.

Conclusion This new-generation microwave technique is safe and effective for local ablation of hepatocellular carcinoma. It is a valuable treatment option for patients who are not candidates for hepatectomy.

Key words
Ablation techniques; Carcinoma, hepatocellular; Liver neoplasms; Microwaves

Hong Kong Med J 2012;18:85-91

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New knowledge added by this study

- Local ablation of hepatocellular carcinoma with new-generation microwaves is safe and effective.
- Microwave ablation is at least as effective as radiofrequency ablation, and can achieve a larger ablation zone with shorter treatment time.

Implications for clinical practice or policy

- Microwave ablation should be considered an alternative curative treatment option in selected patients with hepatocellular carcinoma not feasible for partial hepatectomy.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most common cause of cancer death in the world.[1] It is also the third leading cause of cancer deaths in Hong Kong, with more than 1700 new cases presenting per year.[2] Curative treatments for HCC include hepatectomy, liver transplant, and local ablation. Few patients with HCC are candidates for hepatectomy for various reasons (advanced disease, poor liver reserve, or severe co-morbidity). Moreover, liver transplant is a limited treatment option due to the shortage of donor liver grafts. Though previously considered a

使用高頻（2.45GHz）微波外科消融術治療肝細胞癌：對治療結果作批判性評價

目的 評估使用新一代2.45 GHz微波外科消融術治療肝細胞癌的成效及安全性。

設計 病例系列的追踪研究。

安排 香港一所大學教學醫院。

患者 2009年3月至2011年1月期間，連續26位肝細胞癌患者參與本研究。他們年齡介乎49至79歲，中位數為63歲。19男7女中，有5例（19%）為復發性肝細胞癌。

介入治療 通過腹腔鏡（n=16）或開放性（n=10）手術使用微波消融術治療肝細胞癌，患者中的24例有一個腫瘤，另2例同時有兩個腫瘤。

主要結果測量 術後併發症及死亡率、未能完成整個腫瘤消融的比率、復發率及生存率。

結果 腫瘤直徑的中位數為3.8 cm（介乎2.0至6.0 cm）。5例（19%）併發症中，只有1例是與消融術有關。沒有術後死亡的病例。有1例（4%）未能完成整個腫瘤消融。經過中位數為14個月（介乎4至26個月）的跟進期，11例（42%）出現復發性腫瘤，其中5例為局部復發、2例為遠處復發、4例為多灶性復發。未能局部控制率為23%；但如果撇除復發性病例，未能局部控制率則減至14%。研究結束時只有一名病人死亡。患者平均存活期為25個月（標準差：1個月）。

結論 新一代微波外科消融術治療局部肝細胞癌是安全及有效的。對於一些不適宜接受肝切除術的病人來說，微波外科消融術是一個重要的治療方法。

palliative treatment, local ablation is now known to have a potential curative role for managing HCC. Radiofrequency ablation (RFA) is currently the most reliable and popular ablative method for targeting liver cancer.[3-6] It involves inserting a needle electrode into the tumour (percutaneously, laparoscopically, or during an open operation). Radio waves generate heat energy, which causes coagulative necrosis of the tumour according to the needle size and treatment duration. In our experience, complete ablation was achieved in 82% of patients (mean tumour diameter, 2.4 cm).[6]

Microwave ablation (MWA) is another local ablation therapy, which has been used for more than 20 years.[7] It has recently attracted considerable attention because of the tremendous progress in microwave technology. Microwaves generate heat by oscillation of dipole water molecules within tissues. Frequencies of 915 MHz and 2.45 GHz are currently used for tissue ablation,[7] with a single, dual, or triple antenna. A Chinese study reported that percutaneous MWA using these two frequencies achieved similar efficacy, but fewer antenna insertions were required with 915 MHz.[8] The advantage of MWA is that the heating is primarily active, and the transmission of microwaves in living tissue is not limited by tissue desiccation and charring.[7,9] In addition, MWA does not require use of earth plates on the patient's body, thus avoiding potential earth plate burn injury that can occur with RFA. In Europe and North America, MWA has been used in many centres.[10-13] The Acculis MTA system (Microsulis Medical Ltd, Denmead, UK) uses a single microwave antenna operating at 2.45 GHz for ablation (Fig 1). With a single application, it can create a 4 × 6 cm ablation in 4 minutes and a 5 × 7 cm ablation in 8 minutes. Compared with RFA, this technique is much faster and creates a larger ablation zone. Here, we report our experience using the Acculis MTA 2.45-GHz system on consecutive patients who underwent MWA for HCC.

Methods

Between March 2009 and January 2011, 26 consecutive patients with a diagnosis of HCC were recruited. The 5-mm diameter microwave applicator was intended for use with the open or laparoscopic approach. The diagnosis was based on histology or typical imaging findings and raised alpha-fetoprotein (AFP) according to the criteria of the European Association for the Study of the Liver. The typical imaging features were for cirrhotic patients with: (1) two imagings showing

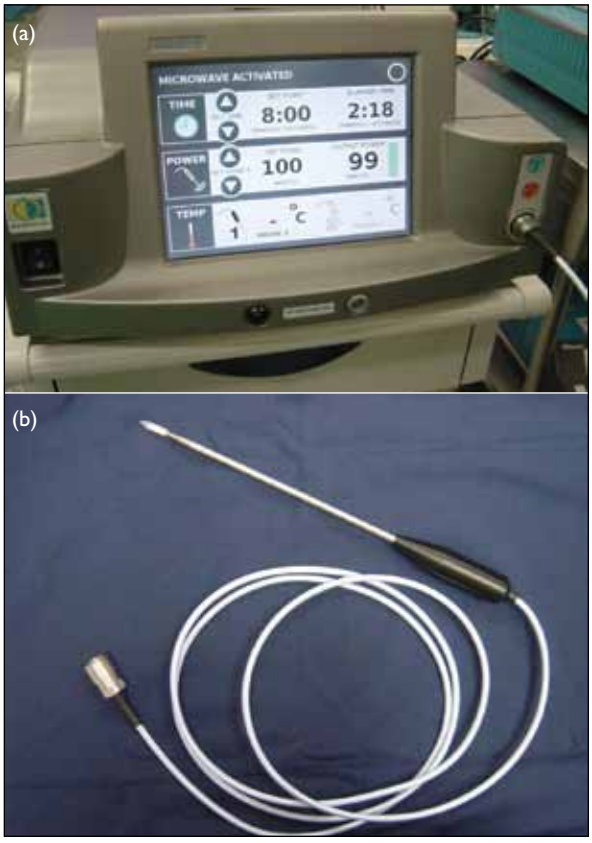

FIG 1. (a) Microwave generator, and (b) microwave applicator

focal lesion of more than 2 cm in diameter and arterial hypervascularisation, or (2) one image with focal lesion of more than 2 cm in diameter and arterial hypervascularisation together with an AFP level of more than 400 mg/mL.[14] Microwave ablation of an HCC was indicated for unresectable tumour, patient preference for local ablation treatment, tumour unsuitable for percutaneous RFA, no macroscopic vascular or bile duct tumour invasion, presence of less than four tumour nodules, and tumours of smaller than 7 cm in diameter. For patients with more than one tumour, the size of the largest tumour was considered when determining the treatment response. Tumour recurrence was not considered a contra-indication for MWA.

The procedure was performed in the operating theatre under general anaesthesia. Prophylactic antibiotics were routinely administered. Any coagulopathy was corrected before the procedure. If possible, the tumour was ablated via the laparoscopic route (Fig 2); otherwise an open laparotomy via a right subcostal incision with possible upper midline extension was necessary. The peritoneal cavity was thoroughly explored to exclude extrahepatic disease. Operative ultrasound (Aloka, Tokyo, Japan) was used to exclude lesions not detected preoperatively, to guide insertion of the microwave applicator and to monitor the entire ablation process. To prevent thermal injury, surrounding organs were cooled by continuous irrigation with ice-cold saline. Ablation was carried out according to the standard protocol with the aim of creating a 1-cm ablation margin around the tumour nodule. Thereafter, the track was ablated with microwave and in some cases packed with a piece of gelfoam to prevent bleeding. Patients were closely monitored for postoperative complications and discharged when they were mobile and able to take food and fluids orally.

Postoperative follow-up examinations were carried out after 1 month, and then every 3 months during the first 2 years, and every 6 months thereafter. A chest X-ray was performed every 6 months or if indicated. Follow-up contrast computed tomography (CT) of the abdomen was performed for each patient at 1, 3, 6, 12, 18, and 24 months post-ablation. The CT was evaluated by a radiologist experienced in liver tumour ablation. Serum AFP was monitored for disease recurrence, and positron emission tomography scan, bone scan, hepatic angiogram, or liver biopsy were performed if recurrence was suspected. Any intra- or extra-hepatic recurrence was documented and treated.

Survival was calculated from the date of the MWA using the Kaplan-Meier method. The date of disease recurrence was dictated by the first imaging study showing recurrence. Incomplete ablation was defined as the presence of residual disease on CT at 1 month after ablation; subsequent development of disease was regarded as recurrence. Local recurrence was defined as disease occurring adjacent to the ablation site, whereas remote recurrence was defined as tumour occurring at a distant site. Multifocal recurrence was defined as multiple intrahepatic tumours at distant sites. Fisher's exact test was used for comparison of categorical variables. P values of less than 0.05 were considered statistically significant.

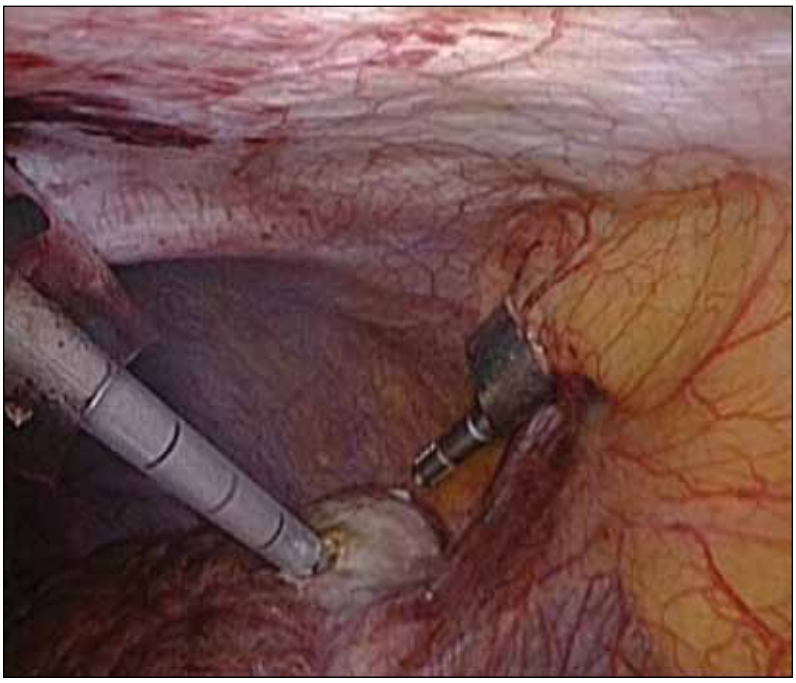

FIG 2. Laparoscopic microwave ablation of a segment-4 hepatocellular carcinoma

A video of surgical ablation of hepatocellular carcinoma with 2.45-GHz microwave is available at <www.hkmj.org>.

Results

The study patients included 19 (73%) men and 7 (27%) women with a median age of 63 (range, 49-79) years. The laparoscopic approach was attempted in 16 patients. However, conversion to open surgery was deemed necessary for one patient who had a tumour adherent to the diaphragm. The other 10 patients underwent open ablation. During the operation, liver cirrhosis was detected in 24 (92%) of the patients. Three patients belonged to Child's B staging, while the rest were Child's stage A. Sixteen (62%) of the patients had evidence of portal hypertension. The distribution of American Society of Anesthesiologists (ASA) grades were: 1 (4%), 2 (46%), 3 (46%), and 4 (4%). In all, 21 patients were hepatitis B carriers, and five were hepatitis C carriers. In five (19%) of the patients, the tumours were recurrences (previous hepatectomy, n=2; previous hepatectomy and RFA, n=1; previous transarterial chemoembolisation [TACE], n=1; and previous TACE plus RFA, n=1).

In this series, the median tumour diameter was 3.8 (range, 2.0-6.0) cm; 24 patients had solitary

tumours, and two patients had two tumours (Table 1). In one of these patients (No. 8), a previously undetected 6-mm tumour was identified during the operation by laparoscopic ultrasound, and in the other (No. 17) two tumour nodules were detected preoperatively. The number of MWA applications and the amounts of energy delivered are shown in Table 1. The median number of treatment cycles was 2 (range, 1-4). The median ablation time was 12 (range, 6-28) minutes. Two patients had concomitant procedures: cholecystectomy (n=1), cholecystectomy plus resection of a pelvic tumour (n=1). There was no treatment-related mortality. Complications occurred in five (19%) of the patients; four of whom had early complications (skin bruising; hand cellulitis and atrial fibrillation; adult respiratory distress syndrome [ARDS] and chest infection; intra-abdominal collection drained percutaneously). The patient with ARDS was thought to be allergic to blood products given during the operation. During follow-up, one patient developed an incisional hernia at the umbilical port site. The median blood loss from the procedure was 10 (range, 1-120) mL, and no patient received a blood transfusion. The median duration of the operation was 118 (range, 65-250) minutes, and the median postoperative hospital stay was 6 (range, 2-13) days.

The median follow-up of these 26 patients was 14 (range, 4-26) months, and their treatment outcomes are summarised in Table 2. In one patient (No. 16), CT at the 1-month follow-up revealed incomplete ablation, for which he underwent percutaneous RFA

TABLE 1. Tumour characteristics and treatment

Patient No.	Sex/age (years)	Tumour site(s) (segments)	Tumour diameter (cm)	Approach, concomitant procedure†	Cycle 1 (W×min)‡	Cycle 2 (W×min)	Cycle 3 (W×min)	Cycle 4 (W×min)
1	M/70	5/6	5	O	100×4	100×4	100×4	-
2*	M/51	7	4	O	100×8	100×4	-	-
3	M/58	4a	2.6	L	100×6	-	-	-
4	F/70	5/6	2	L	100×6	100×4	-	-
5	F/79	4b	4.5	L	100×8	70×4	-	-
6*	M/75	5	6	L Cholecystectomy	100×8	100×4	100×4	100×4
7	M/72	8	3	L	100×8	70×4	-	-
8	M/73	8 4b	3.5 0.6	L	100×8, 30×4	100×4	-	-
9	M/50	8	2	L	100×8	-	-	-
10	F/70	8	3.5	O Cholecystectomy, ovarian tumour excision	100×8	-	-	-
11	M/55	7/8	3.2	O	100×8	100×8	-	-
12	M/72	7/8	3.4	L	100×8	100×8	-	-
13	M/62	6/7	3.2	L	100×8	-	-	-
14	F/60	6	4	L	100×8	-	-	-
15*	M/55	4a	4.2	O	100×8	100×8	70×6	70×6
16	M/77	5/8	5	L	70×4	100×4	-	-
17	M/49	7 8	4.2 2.8	O	100×8, 100×4	100×8	-	-
18	F/63	8	3.5	L	100×4	70×4	-	-
19	M/70	6	3	L	100×8	30×4	-	-
20*	M/62	2/3	5.3	O	100×8	100×8	100×8	-
21	F/67	8	4	L converted to O	100×8	100×6	-	-
22	M/58	5	2.5	L	100×8	100×4	-	-
23	M/52	7/8	5.5	O	100×8	100×4	100×4	-
24*	F/60	2	2	L	100×6	70×4	-	-
25	M/57	8	5	O	100×8	100×8	100×8	-
26	M/68	8	4.2	O	100×8	100×8	-	-

* Patients with recurrent hepatocellular carcinoma
† O denotes open approach, and L laparoscopic approach
‡ W denotes Watts

TABLE 2. Treatment outcomes (all patients except patient No. 8 were still alive at time of censor)

Patient No.	Pre-op AFP†	Postoperative CT‡						Latest AFP	Site of previous tumour (segment)	Type and site of recurrence (segment)	Treatment for recurrence‖
		1 mo	3 mo	6 mo	12 mo	18 mo	24 mo				
1	12	N	N	N	N	N	N	19	-	-	-
2*	3601	N	N	N	N	N	N	1	-	-	-
3	15	N	N	N	N	N	N	8	-	-	-
4	7	N	N	N	N	N	-	5	-	-	-
5	1145	Y§	N	N	Y	Y	-	535	4b	5, 7, 8 (remote)	TACE
6*	34	N	N	N	Y	Y	-	4	5	5, 8 (local)	Second MWA plus TACE
7	1911	N	N	Y	N	N	-	5	8	6/7 (remote)	Percutaneous RFA
8	3	N	N	Y	Y	-	-	6	8, 4b	6, 7, 8 (multifocal)	TACE
9	15	N	N	N	N	N	-	6	-	-	-
10	9	N	N	N	N	N	-	5	-	-	-
11	199	N	N	N	Y	-	-	644	7/8	5, 6, 7, 8 (multifocal)	TACE
12	6	N	N	N	N	-	-	4	-	-	-
13	1	N	N	Y	N	-	-	1	6/7	6 (local)	TACE
14	7	N	N	N	N	-	-	6	-	-	-
15*	3	N	N	N	Y	-	-	4	4a	4a (local)	TACE
16	6	Y	Y	N	Y	-	-	35	5/8	5/8 (residual) then 2, 3, 4, 7 (multifocal)	Percutaneous RFA, supportive
17	398	N	N	N	N	-	-	2	-	-	-
18	111	N	Y	N	-	-	-	1	8	7/8 (local)	TACE
19	2	N	N	N	-	-	-	2	-	-	-
20*	23 956	N	N	Y	-	-	-	78311	2/3	2/3 (local)	TACE
21	3	N	N	N	-	-	-	4	-	-	-
22	3	N	N	N	-	-	-	2	-	-	-
23	82	N	Y	-	-	-	-	632	7/8	5, 7 (multifocal)	Default TACE
24*	334	N	N	Y	-	-	-	9910	2	2, 6 (multifocal) mesentery, peritoneum	Supportive
25	274	N	N	N	-	-	-	5	-	-	-
26	3	N	N	-	-	-	-	3	-	-	-

* Patients with recurrent hepatocellular carcinoma
† AFP denotes alpha-fetoprotein
‡ CT denotes computed tomography; N = no evidence of recurrence on CT, and Y = evidence of recurrence on CT
§ Initial recurrence on 1-month CT in patient No. 5 was a synchronous lesion present before ablation that escaped preoperative detection
‖ TACE denotes transarterial chemoembolisation, MWA microwave ablation, and RFA radiofrequency ablation

of the residual tumour. However, he later developed bilobar multifocal recurrences for which no specific treatment was offered due to his concurrent medical condition. Another patient (No. 5) was noted to have another focus of HCC on the postoperative CT at 1 month that was also present on the preoperative CT image but had escaped detection. Eleven (42%) of the patients developed recurrent disease during follow-up, despite no residual tumour being evident in the early postoperative CTs; five had local recurrences, two had remote recurrences, and four developed multifocal recurrences in the liver. One of the latter patients also experienced extrahepatic recurrences (in the omentum and peritoneum). Most patients underwent TACE for recurrent HCC, but one was treated with MWA for the second time plus TACE, and another underwent percutaneous RFA. Three of these nine patients were disease-free after repeated ablative or transarterial treatments (TACE, n=2; percutaneous RFA, n=1). Except for one patient who died of recurrent multifocal disease and liver failure 13 months after tumour ablation, all of them were alive at the time outcomes for this study were censored. At that time, 17 (65%) were disease-free. The estimated mean survival was 25 (standard deviation, 1) months. Interestingly, all except one patient with recurrent HCC who received MWA had further recurrences (Table 2).

Discussion

We selected patients with HCC who were not candidates for liver resection or refused hepatectomy. More than 90% of them had underlying cirrhosis, and almost one-fifth had recurrence of their HCC after previous treatments. The median patient age was 63 years, and most had ASA grade 2 or 3 status. The patients appeared to tolerate the ablation procedure well and could be discharged early after the operation (median, 6 days). There was no procedure-related mortality, with only one ablation-related complication (intra-abdominal collection).

Like other local ablation techniques, local control of the disease is an important measure of MWA efficacy. Local recurrence represents treatment failure; however, local ablation alone cannot prevent remote or multifocal recurrence. The incomplete ablation rate of 4% in this series was comparable to that reported in other studies using MWA[13,15] and RFA.[3-6] Although our local recurrence rate (5/26, 19%) appears high, it is within the reported range of local recurrence rates after RFA (6-39%).[5] Local recurrence rates after MWA have been reported to be between 2% and 12%.[10,12,13,15] It should be noted, however, that many of the series from western countries primarily dealt with colorectal liver metastasis, and that the highest local recurrence rate was from a series of patients with HCC only.[15] Furthermore, treatment results are affected by tumour heterogeneity, tumour size, the proportion with recurrent tumour, and the length of follow-up. When we excluded the five patients with recurrent HCC, the local recurrence rate was down to 2/21 (10%). If we accept that residual tumour also represents failure of local control, the overall local disease control failure rate after MVA was 3/21 (14%).

A meta-analysis of RFA (5224 liver tumours) revealed an overall local recurrence rate of 12.4%.[16] Results of multivariate analysis showed that the local recurrence rate was significantly lower with smaller tumours and with a surgical (vs percutaneous) approach. For the subgroup of patients with 3- to 5-cm diameter tumours treated surgically (ie tumour size and treatment approach similar to ours), the local recurrence rate was 22%.[16] A systematic review of MWA for HCC revealed that the rate of complete ablation ranged from 88 to 100%, and the local recurrence rate ranged from 0 to 50%; most studies reported a rate of approximately 10%.[9] After adjusting for tumour size, local control of HCC with MWA appeared superior to RFA.

When we compared our patients with tumour diameters exceeding 3 cm to those equal to or less than 3 cm, there was no significant difference in the local recurrence rate (5/19 vs 0/7, respectively; P=0.28). Besides, there was no significant difference in local recurrence rates between those having laparoscopic or open ablation (3/15 vs 2/11, respectively; P<0.99). Our sample size, however, was too small to make any definitive inferences. The only significant risk factor we could identify was recurrent HCC (3/5 vs 2/21, P=0.03), which was associated with a higher local recurrence.

Our results show that local recurrence can occur up to 1 year after ablation. However, many previous studies assessing local ablation of liver tumours reported a median follow-up of less than 1 year,[16] which may therefore have underestimated local recurrence rates. Notably, recurrence after local ablation may be amenable to further treatment. In our series, three patients (No. 7, 13, and 18) were disease-free after additional treatment with percutaneous RFA or TACE (Table 2).

Our experience shows that MWA can create a larger zone of ablation entailing shorter durations of

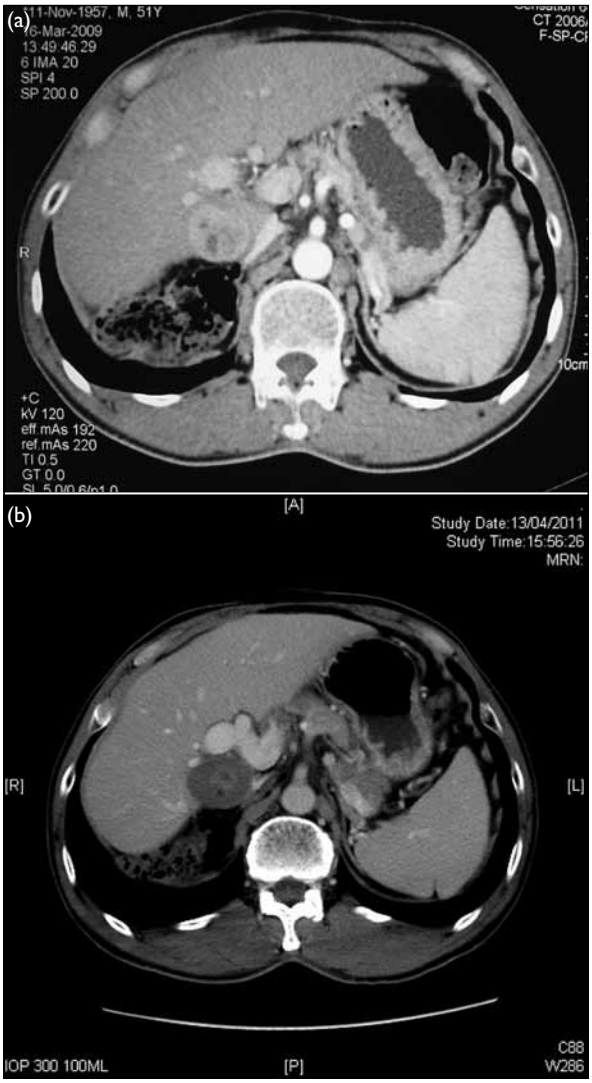

FIG 3. (a) Recurrent hepatocellular carcinoma between portal vein (front) and inferior vena cava (behind). (b) Post-ablation appearance of the same tumour on computed tomography

treatment than with RFA. It can also treat tumours of up to 4 cm in diameter with just a single insertion of the applicator, whereas some RFA applicators require the simultaneous insertion of three needles (cluster needles) to achieve an ablation zone with a 5-cm diameter. The insertion of a single MWA applicator for large tumours makes the laparoscopic approach more feasible. Another theoretical advantage of MWA over RFA is the lower potential for a heat-sink effect when treating tumours close to large vessels,[7,17] as noted with patient No. 2, who experienced tumour recurrence between the portal vein and inferior vena cava after a previous right posterior sectionectomy (Fig 3a). In this patient, no recurrence was detected up to 2 years after MWA (Fig 3b).

The disadvantage of the MWA system used in this series was the large size of the applicator, which made it unsuitable for percutaneous use. Moreover, puncture of the tumour with a large applicator may increase the risk of bleeding and tumour seeding. The fine bore 1.8-mm percutaneous applicators with a shaft cooling system introduced by the same company last year may therefore replace the old applicator entirely, so long as it can be shown to have the same or superior efficacy. The cost of the MWA applicator is approximately 2 to 3 times that of the RFA applicator; however, widespread use of this new local ablation technique may reduce its cost.

Conclusion

Our initial results show that MWA is safe and effective for HCC treatment, and achieves a low frequency of residual tumour and an acceptable recurrence rate. Longer follow-up is required to determine the long-term outcome of this new treatment modality. With rapid improvements in MWA technology, it may play an increasingly important role in HCC treatment, alone or combined with other therapies.

Acknowledgements

We would like to thank The Shun Tak District Min Yuen Tong of Hong Kong for providing funding for the purchase of MWA applicators used in this study. We would also like to thank Mr Philip Ip for his assistance in data processing and statistical analysis.

Declaration

No conflicts of interest were declared by the authors.

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