Efficacy of Percutaneous Radiofrequency Ablation of Hepatic Malignant Tumors Using a Perfused-Cooled Electrode

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Objective: *Evaluate the efficacy of percutaneous radiofrequency ablation of hepatic malignant tumors.*
Material and Method: *An ultrasound-guided percutaneous radiofrequency ablation using a 17-gauge single needle perfused-cooled electrode (Cool-tip™) RF ablation system was performed on 30 hepatic tumors in 26 patients between January 2009 and September 2010. The medical records, CT scan, and MRI results were assessed at one and three months after the procedure was completed. Primary technical success, local tumor progression, and complication were also evaluated.*
Results: *Twenty-six hepatic lesions in 23 patients were primarily hepatocellular carcinoma. Only four lesions in three patients were metastasized. Three of them were from colorectal cancer whilst another one was from malignant melanoma. At 1-month follow-up imaging post percutaneous radiofrequency ablation, complete ablation rate was 86.7%. Local tumor progression at 3-month follow-up imaging was 4.2%. The rate for minor complication was 3.8%. No major complication was found. Complete ablation rate was found to increase significantly in tumors size of less than 2 cm compared to those diameter larger than 2 cm ($p < 0.05$).*
Conclusion: *Percutaneous radiofrequency ablation is one of the most effective and invulnerable therapeutic modality in treatment of hepatic malignant tumor. Size is the key factor of technical success as the smaller the size of tumor, the better the outcome achieved.*

Keywords: *Radiofrequency ablation, RFA, Hepatic tumor*

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Malignant hepatic tumor is the one of the most common malignancies with high mortality rate particularly in Southeast Asia. Although surgical hepatic resection remains the gold standard for both primary and metastatic hepatic malignancies, this benefit was restricted to those lesions confined within the liver[1,2]. Nevertheless, most patients presented with either advanced staging with poor hepatic reserve or underlying medical conditions hindering the opportunity of standard surgical therapy.

Regarding to the staging classification of Barcelona-Clinic Liver Cancer (BCLC) and treatment schedule, percutaneous treatments (percutaneous ethanol injection or radiofrequency ablation) are recommended for small non-surgical hepatocellular carcinoma[3].

Despite expensive cost and sophisticated technique, percutaneous radiofrequency ablation (percutaneous RFA) exhibited the remarkable results including complete tumor necrosis, fewer treatment sessions, and high survival rate compared to percutaneous ethanol injection (PEI). To support this, some clinical data confirmed that the rate of complete therapeutic effect of RFA was higher than PEI (91 to 96% vs. 80 to 92%)[4,5].

To date, RFA is the locally controlled therapeutic modality commonly reserved for unresectable primary hepatic malignancies[6]. It has also been suggested that this method might be beneficial, cost-effective, and efficacious in treatment of metastatic tumors originated from colorectum[7]. To address this question, a retrospective study was undertaken to evaluate the efficacy of RFA in hepatic malignant tumors.

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Material and Method

Patient

This retrospective study was approved by the institutional review board. The informed consent was obtained from all patients before the procedure of treatment commenced. Between January 2009 and September 2010, a percutaneous RFA was performed in 38 hepatic tumor lesions in 34 patients at Body Intervention Unit of Diagnostic and Therapeutic Radiology Department, Faculty of Medicine, Ramathibodi Hospital. The eligible criteria were including either single lesions with size was equal or less than 5 cm or those up-to-three intrahepatic lesions with each less than 3 cm, regardless of the primary lesion. For those metastatic lesions with other concurrent extrahepatic metastasis were rejected. Since the patients recruited must not be given prior treatments before receiving RFA, eight patients were excluded since undergoing prior TOCE.

Equipment and procedure

All patients underwent percutaneous RFA using ultrasonographic guidance (US-guide) by an experienced interventional radiologist. Pre-operative analgesia was administered intravenously (20-50 mg of meperidine) with or without sedative drug (5-10 mg of diazepam) depending on patient tolerance. Local anesthesia was also infiltrated with 1% lignocaine at the site of injection.

A 17-gauge straight single needle electrode the Cool-tip™ RF ablation system (Valleylab, Covidien, USA) were applied in all of 32 hepatic lesions. Overlapping ablation zone technique was assured of complete ablation in case of discordance between size of exposure and tumor. The duration of ablation cycle depending on tumor size (six minutes for 1-2 cm and 12 minutes for size larger than 3 cm). This procedure would also be terminated when echogenic cloud presented entirely and the needle track was ablated.

Classification of tumor

The tumor was firstly classified into two groups. The first one (group 1) has diameter ranged from 0.1 to 2.0 cm, whereas those larger than 2.0 cm were defined into group 2.

The location of the tumors is arranged into four categories: intrahepatic parenchymal lesion; subdiaphragmatic; subcapsular and perivascular lesions. Subdiaphragmatic group is the lesions attached to liver capsule below the diaphragm. As connecting to liver capsule without underneath the diaphragm, these lesions are classified as subcapsular group. Those attached to large blood vessels (diameter ≥3 mm) without relating to liver capsule are categorized as the perivascular group. Other incompatible lesions with the above criteria are named the intrahepatic parenchymal group. Another classification of the lesions used in the present study was the Couinaud classification.

Assessment of therapeutic efficacy

For evaluation of tumor response to percutaneous RFA, triple-phase contrast axial CT scan or MRI of the upper abdomen was performed at 1-month after percutaneous RFA. The complete ablation of tumor or primary technical success is defined as no residual unablated tumor found at 1-month follow-up imaging seen entirely area of tumor covered by non-enhancing area of the ablation zone (Fig. 1). However, transient hyperemia or benign periablational enhancement may be found at 1-month post-ablation imaging which can be seen as a clear, smooth and symmetrical enhancing area along margin of the ablation zone[8]. This finding can be seen on both pathological examination and contrast-enhanced imaging suggesting benign physiologic response of thermal injury[9]. The residual unablated tumor is a nodular or asymmetrical enhancing area along the margin of the ablation zone in case of hypervascular tumor (Fig. 2). In case of hypovascular tumor, a residual unablated tumor is a nodular protrusion of a low-enhancing ablation zone with or without a minute difference in attenuation[8].

Local tumor progression is a recurrent tumor in at least 3-month follow-up imaging study. Imaging findings of recurrent tumor was similar to

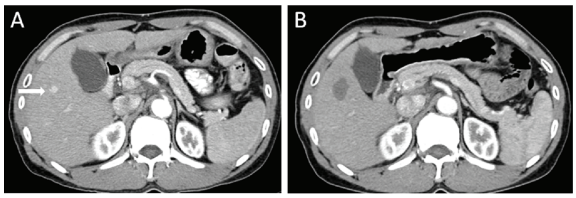

Fig. 1 Typical imaging of complete ablation of post RFA hepatic lesion: (A) Arterial phase of axial CT scan of the liver before RFA showed a small size of arterial enhancing nodule at hepatic segment V (arrow). (B) Arterial phase CT scan obtained 1 month after RFA showed entire area of tumor covered by non-enhancing area of the ablation zone.

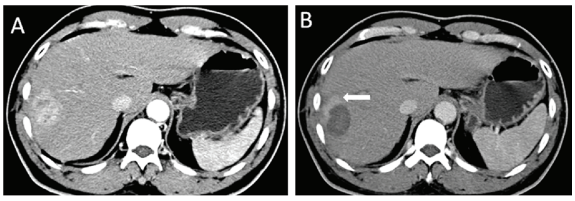

Fig. 2 Typical imaging finding of incomplete ablation tumor: (A) Arterial phase of axial CT scan of the liver before RFA showed a 4.0-cm hepatoma at hepatic segment VII. (B) Arterial phase CT image obtained 1 month after RFA showed enhancing nodular area at margin of ablation zone (arrow), consistent with residual unablated tumor.

aforementioned residual unablated tumor. Subsequent contrast-enhanced CT or MRI of the upper abdomen was followed every three months.

Statistical analysis

Continuous data was represented as mean and SD. Categorical variables were compared using the Chi-square test and Fisher's exact test, which were performed using the SPSS^R version 10.0.5 statistical package for Windows (SPSS, Chicago, Illinois, USA) with $p<0.05$ was considered statistically significant.

Results

Demographic characteristics

Thirty hepatic tumors in 26 patients were included in the present study. Most of them were men (18 patients, 69.2%). Eight of patients were women (30.8%). The age of patient ranged from 48 to 80 years (mean age 62.2 years, SD 8.9 years). Four patients had two hepatic lesions. All patients were Pugh Child class A or B. The follow-up time ranged from one to 15 months (mean 6.7 months, SD 4.5 months)

Characteristics of hepatic tumors

The size of hepatic tumor ranged from 0.9 cm to 4 cm (mean 2.18 cm, SD 0.85 cm). There were 18 intrahepatic parenchymal lesions, two subdiaphragmatic lesions, four perivascular lesions, and six subcapsular lesions. According to Couinaud classification, three lesions were found at hepatic segment II and IV, six lesions at hepatic segment V, one lesion at hepatic segment VI, eight lesions at hepatic segment VII, and nine lesions at hepatic segment VIII. Most of them were located at the right hepatic lobe (80%).

Twenty-six hepatic tumors in 23 patients were suspected HCC. Eight lesions were HCC proven by histological examination. Seventeen hepatic lesions showed typical imaging findings for HCC (arterial enhancing lesion with rapid washout on portovenous phase on contrast enhanced CT or MRI). Only one hepatic lesion showed arterial enhancement and isodense on portovenous phase that was assumed either small HCC or dysplastic nodule. However, there were found a level of alpha-fetoprotein more than 20 ug/L in 15 patients whose HCC lesions have not been proven histologically.

Another four lesions were metastasized with known primary origin. First three lesions in two patients were originally from colorectum whilst another one was malignant melanoma.

Treatment effectiveness

From 30 hepatic lesions, 26 hepatic lesions were completely ablated at 1-month follow-up imaging. As there were four incomplete ablated lesions, the primary success rate was 86.7%. The first partial one was sized approximately 4 cm located in hepatic segment VIII and not adjacent to the liver capsule or the large vessel. The latter two subcapsular lesions sited at segment VII and II and were 3.7 and 3.0 cm on size respectively. The last was a 2.5-cm- perivascular lesion located in hepatic segment VIII.

The size of tumor, and location of tumor (which were divided to subcapsular compared with non-subcapsular group, and perivascular compared with non-perivascular group) were used to correlate with the success of the authors' treatment.

Focusing on size, there was a 100% success rate in the primary technical success of group 1 comparing to 75% in group 2 (Table 1). The likelihood ratio of complete ablation necrosis of group 1 was different significantly compared to group 2 (Fisher's exact, $p = 0.045$).

Moreover, the location of tumor was also considered as a factor of treatment success. Two categories were considered (subcapsular versus non-subcapsular and perivascular versus non-perivascular). Subcapsular group consisted of subcapsular lesion and subdiaphragmatic lesion, whereas the other locations were classified as non-subcapsular group. There were neither significant correlation in technical effectiveness between subcapsular and non-subcapsular lesion and perivascular and non-perivascular lesion (odds ratio = 3.33; 95% CI = 0.39 to 28.96 and odds ratio = 2.56 ; 95% CI = 0.19 to 33.16, respectively).

The result has shown no significant association between the location of tumor (intraparenchyma, subdiaphragmatic, subcapsular and perivascular lesion)

Table 1. Baseline characteristics of tumor between group 1 (0.1-2.0 cm in size) and group 2 (2.1-4.0 cm in size)

Characteristics	Group 1 (0.1-2.0 cm in size) (n = 14)	Group 2 (2.1-4.0 cm in size) (n = 16)	p-value
Type			0.886
HCC[1]	12 (85.71)	14 (87.50)	
Other	2[+] (14.29)	2[#] (12.50)	
Location			0.315
Intraparenchyma	8 (57.14)	10 (62.50)	
Subcapsular	2 (14.29)	4 (25.00)	
Subdiaphragmatic	2 (14.29)	0 (0)	
Perivascular	2 (14.29)	2 (12.50)	
Complete ablation[2]	14 (100)	12 (75.00)	0.045*
Local tumor progression[3]	0 (0)	1 (6.25)	0.257
Complication	1 (7.14)	0 (0)	

Data displayed as number of cases (percent)
[1] Histologic proven or typical imaging finding with alphafetoprotein level >20 ug/L
[2] Complete ablation at 1-month follow up by imaging
[3] Local tumor progression at 3-month follow-up by imaging
[+] Either is metastatic malignant melanoma or metastatic colorectal carcinoma
[#] Both are metastatic colorectal carcinoma
* Statistically significant parameter

and primary technical success (Pearson Chi-square, p = 0.206).

After 3-months, there were only two patients with complete ablation losing follow-up. Only one of 24 lesions, a 2.1 cm subcapsular lesion at segment VII was recurrent locally at the RFA site, which was 4.2%.

Procedure safety

Although there was no major complication observed, the minor complications of right pleural effusion and trivial perihepatic fluid without necessary further management was found in one subdiaphragmatic tumor, which is only 3.8%.

Discussion

Although the proven curative treatment for HCC is currently limited to surgical resection, only 10 to 37% of the patients were suitable for surgery[10]. Numerous data have been shown that ablation therapy including chemical (ethanol injection) and thermal (RFA) ablation were alternative treatment in those unfit for surgical management. In addition, it is suggested that RFA has been found to be more practicable than PEI in both effective locally control and frequency of ablative session[4,5]. To confirm the efficacy and investigate the factor associated with therapeutic efficacy of percutaneous RFA for treatment of hepatic tumor, the present study was undertaken at the faculty of medicine, Ramathibodi hospital.

In consistent with a previous study[10-16], the primary technical success of percutaneous RFA of hepatic tumors was found 86.7% (26 of 30). Four tumor with partially ablated were larger than 2 cm. There were a remarkably significant difference of primary technical success in tumor size larger than 2 cm compared to those size equal or smaller than 2 cm (100% vs. 75%; Likelihood ratio = 7.16; p = 0.018), which is concordant with a previous study by Head et al that reported a high complete ablation rate in tumor size less than 3 cm compared to the larger one (87.5% vs. 29.4%)[11]. This result has established a strong relationship between size of tumor and primary technical success.

Minimal right pleural and perihepatic effusion with subsequently spontaneous resolutions, which are regarded as minor complications, occurred in one case located at subdiaphragmatic area. These damages were thought to be iatrogenic thermal injury, which is commonly seen in this location. As Head HW et al reported a frequency of diaphragmatic injury after performing percutaneous RFA adjacent to the diaphragm[11]; new pleural effusion was noticed approximately 20%, whereas adjacent fluid collection was found up to 41%. Subsequent benign diaphragmatic thickening was detected approximately half of all cases. The artificial ascites has also been demonstrated to minimize diaphragmatic thermal injury with no heat-sink effect on the volume of ablation zone[13].

Whilst the primary technical success and location of tumor categorized as intraparenchyma, subdiaphragmatic, subcapsular, and perivascular lesion were investigated and minor complication was detected, there was shown no significant correlation in this study (Pearson Chi-square 8.458, p = 0.206). Furthermore, there were two from four incomplete ablated lesions located in subcapsular region. There was no significant difference of primary technical success between the subcapsular and non-subcapsular group.

Some previous data suggested that perivascular location was a predictor for incomplete ablation and temporary hepatic inflow occlusion was a useful technique for decreasing perivascular heat-sink effect[12]. On the other hand, a recent study by Ng KK et al has demonstrated that this technique might not be desirably benefit for complete ablation rate and local recurrence rate in both perivascular and non-perivascular HCC[14]. In consistent with a later study, only one of four perivascular lesions has been partially ablated with no statistically significant differences of primary technical success in perivascular compared to non-perivascular lesions.

It has been demonstrated that local tumor progression followed RFA ranged from 7.5 to 11%[12,15,17], whereas there was a lower recurrent rate at three months noticed in the present study (4.2%). This higher curative rate achieved might be from succeeding ablative margin because of effective correspondence of a three-dimensional tumor configuration with either ablative zone of electrode or the electrode path. It has been exhibited that the ablative margin approximately 1 cm surrounding the tumor mass yielded a lower recurrent rate[18].

By using a 2-cm-exposure needle, the ablation of one of two histologically proven HCC lesions, with a diameter approximately 2.1 cm, was unsuccessful due to improper size of needle exposure has been selected. The remaining one in the same patient with size 0.9 cm, however, was totally ablated without local recurrence by using the same needle exposure at first attempt.

This current study has confirmed the efficacy and effectiveness in treatment of hepatic tumor with size less than 2 cm. Since the data were collected retrospectively, the information on tumor location and duration of tumor progression evaluation were restricted. The tumor locations allocated were not effectively distributed causing a limitation of power of calculation distinguishing the significant differences. The local tumor progression evaluation time is also limited at three months. The contributive factors including size of needle exposure, location of tumor and long-term evaluation have therefore yet to be further investigated prospectively.

Conclusion

Percutaneous RFA was safe and effective for treatment of primary and metastatic hepatic tumors in patients unsuited for surgery. It has been represented that the important factor of primary technical success was the tumor size in which less than 2 cm has a higher curative rate.

Potential conflicts of interest

None.

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การศึกษาผลการรักษาเนื้องอกตับโดยการจี้เผาด้วยความร้อนจากคลื่นวิทยุความถี่สูง

ธนพงศ์ พันธุ์พิกุล, ธรินธร ตรีสิทธิ์, เจียมจิตร ตปนียากร, บรรจงศักดิ์ เวชศาสตร์, ฐานิภา อินมั่น

วัตถุประสงค์: *เพื่อศึกษาผลการรักษาและภาวะแทรกซ้อนจากการรักษาเนื้องอกตับโดยการจี้เผาด้วยความร้อนจากคลื่นวิทยุความถี่สูง (Radiofrequency ablation; RFA)*

วัสดุและวิธีการ: *เก็บข้อมูลย้อนหลังของผู้ป่วยเนื้องอกตับที่ได้รับการรักษาโดยการจี้เผาด้วยความร้อนจากคลื่นวิทยุความถี่สูงด้วยเข็มจี้ชนิดตรง ขนาด 17G ระหว่าง เดือนมกราคม พ.ศ. 2552 ถึง กันยายน พ.ศ. 2553 โดยศึกษาผลการรักษาที่หายขาดภายหลังจากการรักษาครั้งแรก (primary technical success), การกลับเป็นซ้ำของเนื้องอกภายหลังจากการรักษาครั้งแรก (local tumor progession) รวมถึงภาวะแทรกซ้อนที่เกิดขึ้น*

ผลการศึกษา: *ก้อนเนื้องอกตับ 30 ก้อน ในผู้ป่วย 26 ราย เป็นมะเร็งตับ (Hepatocellular carcinoma) 26 ก้อน และเป็นมะเร็งที่แพร่กระจายมาที่ตับ (metastasis) 4 ก้อน ที่ 1 เดือนหลังการรักษามี primary technical effectiveness 86.7%, ที่ 3 เดือนหลังการรักษามี local tumor progession 4.2% ไม่มีภาวะแทรกซ้อนที่รุนแรง พบภาวะแทรกซ้อนที่ไม่รุนแรง คือ น้ำในช่องปอดปริมาณเล็กน้อย (minimal pleural effusion) 3.8% ก้อนเนื้องอกขนาดเล็กกว่า 2 ซม. มี primary technical effectiveness สูงกว่าก้อนเนื้องอกขนาดใหญ่กว่า 2 ซม. อย่างมีนัยสำคัญ*

สรุป: *การรักษาเนื้องอกตับโดยการจี้เผาด้วยความร้อนจากคลื่นวิทยุความถี่สูง (Radiofrequency ablation; RFA) ให้ผลการรักษาที่ดีและไม่มีภาวะแทรกซ้อนที่รุนแรง ขนาดของก้อนเป็นปัจจัยสำคัญที่มีผลต่อการรักษา โดยที่ก้อนขนาดเล็กมีโอกาสหายขาดภายหลังจากการรักษาสูงกว่าก้อนขนาดใหญ่*