The Outcome of Radiofrequency Ablation of Metastatic Liver Tumors

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Objective: *To determine outcome of radiofrequency ablation (RFA) in metastatic liver tumor and to evaluate related factors of residual or local tumor recurrences.*

Material and Method: *With Institutional Review Board approval, we retrospectively reviewed RFA procedure between June 2006 and September 2013. Fifty-seven metastatic nodules in 36 patients were treated. The primary tumors were colorectal carcinoma (n = 30), neuroendocrine tumor (n = 2), gallbladder carcinoma (n = 1), adenocarcinoma of head of pancreas (n = 1), and gastrointestinal stromal tumor (n = 2). Tumor characteristics, RFA techniques, success rate, complication, and follow-up imaging were reviewed and recorded. Clinical outcome and overall survival were analyzed.*

Results: *Complete ablation were found in 48/57 nodules (84.2%). The mean follow-up time was 17.9±13.1 months (range, 1 to 47 months). Local tumor recurrence were noted in 12/57 nodules (21.1%), which mean time to recurrence was 8.3±3.8 months (2 to 15 months). Residual tumor was associate with tumor larger than 3 cm (p = 0.009). The 1-, 3-, and 5-year overall survival rates were 93.6%, 56.2%, and 20%, respectively. Median overall survival was 37.8±10.9 months. Major complication rate occurred about 5.3%.*

Conclusion: *Radiofrequency ablation is effective and feasible method to treat small metastatic liver tumor. Tumor size larger than 3 cm is significant risk factor of residual tumor. Tumor in high-risk location is not associated either incomplete ablation or local tumor recurrence.*

Keywords*: Radiofrequency ablation, Liver metastasis*

J Med Assoc Thai 2016; 99 (4): 424-32
Full text. e-Journal: *http://www.jmatonline.com*

The most common liver tumor is metastatic disease. Common primary tumors of liver metastases are breast, lung, and colon cancer[1]. Approximately 10 to 25% of patients with colorectal cancer have liver metastases at the time of diagnosis. About half of patients develop liver metastasis at some point during the course of the disease[1-4]. For the patients with liver-only metastases, surgical resection is a standard treatment and reach 5-year survival rate of 25 to 40%[2,5-7]. Unfortunately, due to many reasons such as inadequate hepatic reserve after resection, anatomical difficulty (tumor close to major vessels or bile ducts), patient's comorbidities, or extrahepatic metastasis, only 8 to 27% of these patients are candidate for curative resection[2,7,8]. Systemic chemotherapy is an alternative treatment for patients who are not candidate for surgical resection. However, response rate is less than 25%[7] and median survival is 10 to 17 months[2].

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In the past decade, local tumor ablative methods have been developed and used as alternative treatment of small liver tumors in patients who were not surgical candidate. Radiofrequency ablation (RFA) is one of tumor ablative methods. It generates an alternating electromagnetic field that produces high temperature around the electrode by frictional heat, resulting in coagulative necrosis of tissue. Currently, RFA is the standard curative treatment of early stage hepatocellular carcinoma (HCC)[9-11]. Previous studies showed no statistically significant difference in overall survival and disease-free survival rates between tumor resection and RFA for small HCC not greater than 5 cm[10]. Furthermore, the use of RFA is applied for the treatment of liver metastasis from colorectal cancer, breast cancer, and pancreatic cancer[2,4,6,8,12-15]. The benefits of RFA for the treatment of liver metastases have been subject of ongoing research. Several studies showed no statistically significant difference in 5-year overall survival and disease free survival rates between tumor resection and RFA[12,16-18]. However, some studies revealed lower 5-year overall survival and disease free survival rates in RFA groups[19-22].

The purpose of the present study was to determine the outcome of RFA performed in metastatic liver tumor and to evaluate related factors of residual and local tumor recurrences.

Material and Method

Subjects

With institutional review board approval, retrospectively review 959 RFA sessions of liver tumors were performed at the interventional radiology unit between June 2006 and September 2013. Ninety-eight metastatic nodules were included. Forty-one nodules were excluded because there was no available preoperative or follow-up imaging study for liver lesions (39 nodules) or patients underwent other locoregional treatments such as transarterial chemoembolization (TACE) or alcohol injection for the liver nodule before RFA session (2 nodules). Fifty-seven nodules in 36 patients (19 men and 17 women) were included in this study. Demographic data were recorded including age, primary tumors, primary tumor staging at presentation, number of liver metastatic nodules, and location and size of each nodule.

Age range from 37 to 80 years old (mean age was 62.3±11.3 years). Primary tumors consist of colorectal cancer in 30 patients (83.3%), neuroendocrine tumor in two patients (5.6%), gastrointestinal stromal tumor in two patients (5.6%), pancreatic cancer in one patient (2.8%), and gallbladder cancer in one patient (2.8%). Stage of primary tumors at the time of diagnosis were stage 1 in one patient (2.8%), stage 2 in 12 patients (33.3%), stage 3 in three patients (8.3%), and stage 4 in 20 patients (55.6%). The demographic data of patients were shown in Table 1.

Mean diameter of metastatic nodules was 2.2±0.9 cm (range, 0.7 to 4.6 cm). Forty-three nodules (75.4%) located in high-risk location consist of tumor close to liver surface in 12 nodules (21.1%), tumor close to extrahepatic organs in 21 nodules (36.8%), and tumor close to large vessels in 12 nodules (21.1%). The characteristic of tumor nodules were shown in Table 2.

RFA procedures

RFA was performed by 2 to 10 years experienced interventional radiologists under local anesthesia and intravenous deep sedation. Two radiofrequency (RF) electrode systems were used in these population (LeVeen electrode from Boston Scientific, Boston, MA and Starburst XL electrode and Talon electrode from Angiodynamics, Queensbury, NY). The RF electrode was percutaneous inserted under ultrasound and/or computed tomography (CT) guidance. Tissue impedance (Boston Scientific "LeVeen" RF ablation system) or internal temperature (Angiodynamics RITA Medical Systems) was monitored during the

Table 1. Patient characteristics

Characteristics	n (%)
Age, mean ± SD (range)	62.3±11.3 (37-80)
Sex	
Male	19 (52.8)
Female	17 (47.2)
Primary tumors	
Colorectal cancer	30 (83.3)
Neuroendocrine tumor	2 (5.6)
GIST	2 (5.6)
Pancreatic cancer	1 (2.8)
Gallbladder cancer	1 (2.8)
Stage of primary tumors at presentation	
Stage 1	1 (2.8)
Stage 2	12 (33.3)
Stage 3	3 (8.3)
Stage 4	20 (55.6)
Number of tumor in each patients, mean ± SD (range)	1.6±1.1 (1-7)
1 nodule	21 (58.3)
2 nodules	13 (36.1)
3 nodules	1 (2.8)
7 nodules	1 (2.8)

GIST = gastrointestinal stromal tumor

Table 2. Nodule characteristics

Characteristics	n (%)
Hepatic segment	
1	1 (1.8)
2	6 (10.5)
3	6 (10.5)
4	5 (8.8)
5	7 (12.3)
6	8 (14.0)
7	12 (21.1)
8	12 (21.1)
Location	
Non-high-risk location	14 (24.6)
High-risk location	
- Close to liver surface	12 (21.1)
- Close to extrahepatic organ	21 (36.8)
- Close to large vessels	12 (21.1)
Size, mean ± SD (range)	2.2±0.9 (0.7-4.6)
≤1.0 cm	4 (7.0)
1.1-2.0 cm	25 (43.9)
2.1-3.0 cm	17 (29.8)
3.1-4.0 cm	8 (14.0)
>4.0 cm	3 (5.3)

procedure. Overlapping technique was used for tumor larger than 3 cm.

Imaging studies and terminology

Preprocedural, periprocedural, and post-procedural images were retrospectively reviewed by two interventional radiologists. Maximum diameter of target lesions were measured in the most recent images either CT scan or magnetic resonance (MR) imaging before the RF procedure. Tumors located less than 10 mm to liver surface, to more than 3 mm vessels (including main portal vein, hepatic vein, and inferior vena cava), and to extrahepatic organ (such as heart, lung, gastrointestinal tract, and kidney) were defined as high-risk tumor location.

Triple-phase CT scan or dynamic contrast-enhanced MR imaging was used for follow-up in four weeks after RF procedures and then every three to six months if there was no residual or recurrent tumor.

Complete ablation was non-enhancing hypodensity/hyposignal intensity area covered the target lesion and no identified tumor nodule adjacent to ablation zone. Primary technique efficacy rate was determined by complete tumor ablation at 1-month follow-up images. Residual tumor was enhancing nodule abut ablation zone at first follow-up images. Local tumor recurrence was new viable tumor adjacent to ablation zone during follow-up images with prior evidence of complete ablation. Intrahepatic recurrence was defined by detection of tumor nodule at any site in liver during follow-up images.

Complications were categorized according to the Society of Interventional Radiology Clinical Practice Guidelines[23]. Early complications were complications occurred within 30 days after RF procedures. Late complications occurred after 30 days RF procedures.

Statistical analysis

Statistical analysis was performed by using SPSS v.18.0 (IBM Corp., Armonk, NY, USA). Demographic data was analyzed using descriptive statistics. Chi-square test was used to test the association between tumor size, high-risk location, and either residual tumor or local tumor recurrences. Kaplan Meier analysis was used to analyze factors affecting local recurrent rate and survival rate. In all analyses, $p<0.05$ was considered statistically significant.

Results

Primary technique efficacy rate was 84.2% (Fig. 1). Residual tumors were noted in nine nodules (15.8%). There was statistically significant difference in occurrence of residual tumors between metastatic nodules larger than 3 cm (5/11 nodules, 45.5%) and nodules smaller than 3 cm (4/46 nodules, 8.7%) ($p = 0.009$). In tumor location aspect, incidence of residual tumors was higher in tumors close to extrahepatic organ group (6/21 nodules, 28.6%), however, there was no statistically significant difference ($p = 0.052$). The mean follow-up time 17.9±13.1 months (range, 1 to 47 months). Local tumor recurrence was found in 12 nodules (21.1%) with mean time to recurrence of 8.8±3.8 months (range, 2.8 to 15.3 months) (Fig. 2). There was no demonstrable correlation between local tumor recurrence and tumor located in any high-risk locations (Table 3). The 1- and 3-year local control rates were 78% and 62%, respectively. There was significant lower local control

Table 3. Residual tumor and local tumor recurrence

	No.	Residual tumor, n (%)	*p*-value	Local recurrence, n (%)	*p*-value
Size (cm)					
≤3	46	4 (8.7)	0.009	10 (21.7)	0.579
>3	11	5 (45.5)		2 (18.2)	
Close to liver surface					
No	45	7 (15.6)	0.614	10 (22.2)	0.511
Yes	12	2 (16.7)		2 (16.7)	
Close to extrahepatic organ					
No	36	3 (8.3)	0.052	6 (16.7)	0.232
Yes	21	6 (28.6)		6 (28.6)	
Close to large vessels					
No	45	8 (17.8)	0.386	9 (20.0)	0.489
Yes	12	1 (8.3)		3 (25.0)	
Total		9 (15.8)		12 (21.1)	

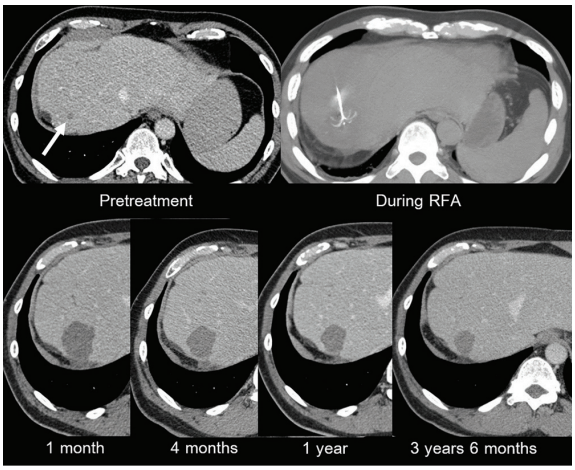

Fig. 1 A 45-year-old man history of colorectal carcinoma with a small liver metastasis at hepatic dome (arrow) was treated by radiofrequency ablation. Complete ablation zone was observed without local recurrent tumor until 3-year and 6-month follow-up.

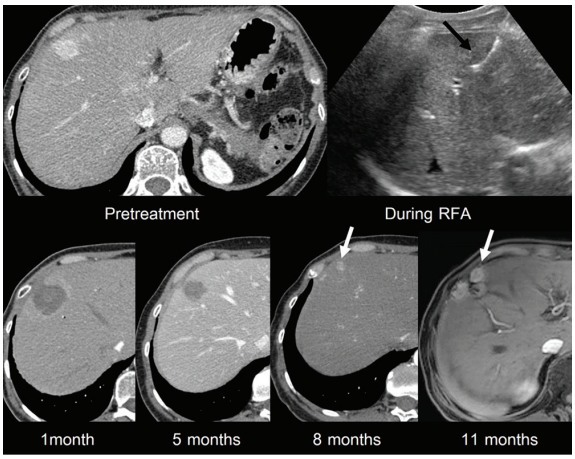

Fig. 2 A 59-year-old woman with pancreatic neuroendocrine tumor with liver metastasis was treated by RFA (black arrow). CT scan at 1 and 5 months revealed complete tumor ablation with no residual or recurrent tumor. The follow-up images at 8 and 11 months showed local recurrent tumor adjacent to ablation zone (white arrow).

rate in tumor nodule larger than 3 cm (median survival 7.4 months, $p = 0.036$) (Fig. 3), but no significant difference of local control rate between non-high-risk and high-risk locations ($p = 0.19$) (Fig. 4).

Median time to intrahepatic metastasis was 11.8±2.4 months (range, 1 to 53.9 months). The 1-, 3-, and 5-year overall survival rates were 93.6%, 56.2%, and 20%, respectively. Median overall survival

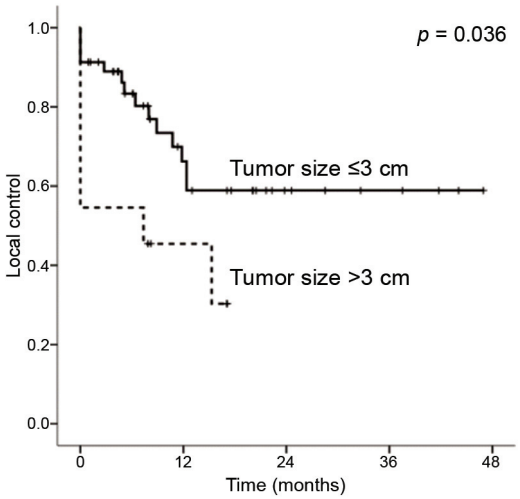

Fig. 3 Local tumor control rate based on tumor size.

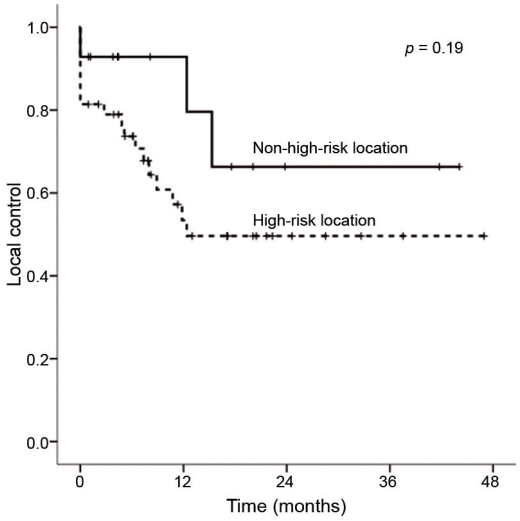

Fig. 4 Local tumor control rate stratified by tumor location.

was 37.8±10.9 months (Fig. 5). In subgroup analysis, 1-, 3-, and 5-year overall survival rates in patient with colorectal carcinoma were 92.3%, 46.5%, and 20.7%, respectively. Median overall survival in these patients was 37.8±8.1 months (Fig. 6).

There was no procedure related death in the present study. We found major complications in two patients (3 nodules, 5.3%). All of these were liver abscess after RFA treatment of colonic liver metastatic nodules. One patient was treated by percutaneous drainage with intravenous antibiotics. The other patient was treated by intravenous antibiotic only.

Minor complications were found in the present study including first-degree skin burn at

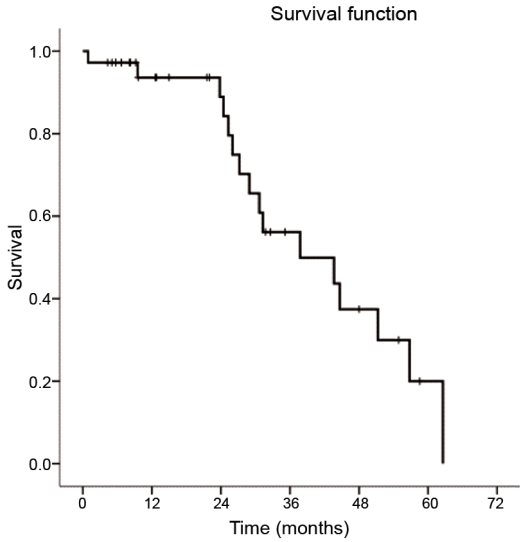

Fig. 5 Overall survival rate (median survival = 37.8±10.9 months).

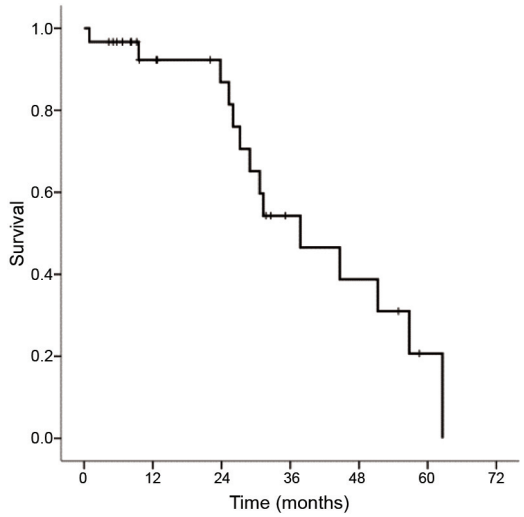

Fig. 6 Overall survival rate in group of colorectal carcinoma patients and liver metastases (median survival = 37.8±8.1 months).

Table 4. Complication according to SIR guideline[23]

Complication	Grade	n (%)
Major complication		
Liver abscesses	C, D	3 (5.3)
Minor complication		
Biloma	B	4 (7.0)
Mild IHD dilatation	A	4 (7.0)
Minimal pneumothorax	B	1 (1.8)
Hepatic vein thrombosis	A	1 (1.8)
1st degree skin burn at puncture site	B	1 (1.8)

SIR = Society of Interventional Radiology; IHD = intrahepatic duct

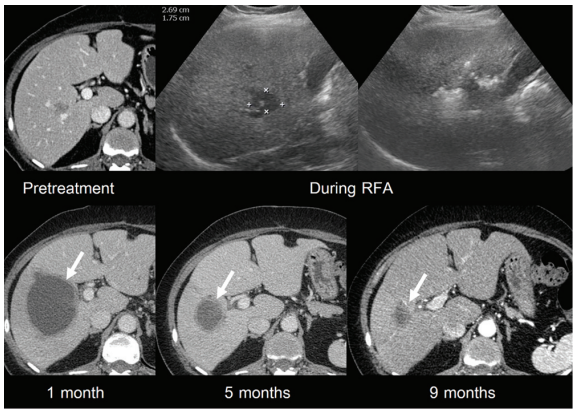

Fig. 7 A 68-year-old woman with colonic cancer and liver metastasis underwent RFA. Follow-up CT scan at 1 month after the procedure revealed complete ablation zone with large biloma (arrow). She had no clinical symptom. Follow-up CT scan at 5 and 9 months showed spontaneous resolving of the biloma.

punctured site (1 nodules), mild intrahepatic bile duct dilatation (4 nodules), biloma (4 nodules) (Fig. 7), minimal pneumothorax (1 nodule), and hepatic vein branch thrombosis (1 nodule).

Discussion

The primary efficacy after RFA of metastatic liver lesion have been reported at 58 to 98% and local tumor recurrence rates at 5 to 39%[2,7]. Similarly to our study, primary efficacy and local tumor recurrence were 84.2% and 21.1%, respectively (Table 5).

Solbiati et al[14,29] studied in related factors of complete ablation rates and local tumor recurrence. RFA in the small tumors smaller than 3 cm had high complete ablation rate, 95.1% in smaller than 2 cm tumors, 80.9% in 2.1 to 3.0 cm tumors, and 54.5% in larger than 3 cm tumors, $p<0.001$. Similarly, our study found significant higher complete ablation rates in smaller tumor (91.3% in smaller than 3 cm tumors vs. 54.5% in larger than 3 cm tumors, $p = 0.009$). For the local tumor recurrence, there was reporting of a significant difference in local tumor recurrence comparing tumor smaller than 3 cm (16.5%) and those larger than 3 cm (56.1%). In our study, there was no significant difference of local recurrence rates among the lesions smaller than 3 cm tumors and those larger than 3 cm. However, we found significant higher local control rate in smaller tumors group ($p = 0.036$) (Fig. 2).

Few previous studies reported correlation of subcapsular location or tumor adjacent extrahepatic

organs related with incidence of major complications[30-32]. Conversely, some investigators reported no significant difference of incidence of major complication between subcapsular and non-subcapsular tumors[33, 34]. Tumor located adjacent to large vessels is also included in high-risk tumor location. Blood vessel size 3 mm or larger can cause disturbance of temperature (heat-sink effect) and may limit the effectiveness of all thermal ablation methods[35,36]. However, Thanos et al[37] reported effectiveness and low local tumor progression rate of RFA of tumor located adjacent to large vessels. In this study, we analyzed primary efficacy rates and local recurrence rates among tumor located in non-high-risk location and those located in high-risk location (close to liver surface, extrahepatic organ, or large vessels) but there was no significant difference in both primary efficacy rate and local recurrence rate among those two groups (Table 3). Kaplan-Meier curve analysis also demonstrated no significant difference of local control rate between non-high-risk and high-risk location (Fig. 3). Recent prior study also reported no statistically significant difference in local tumor progression rate between HCC nodules in high-risk and non-high-risk location (p = 0.275). Thus, high-risk location should not be limitation of RFA of liver tumor[38].

Previous studies showed 3- and 5-year overall survival rate were 26% to 67% and 0% to 48.5%, respectively[12]. The 1-, 3-, and 5-year overall survival rates in our study were 93.6%, 56.2%, and 20%, respectively (median overall survival 37.8±10.9 months), which were comparable to the previous studies. In subgroup analysis of patient with colorectal carcinoma, 1-, 3-, and 5-year overall survival rates were 92.3%, 46.5%, and 20.7%, respectively (median overall survival 37.8±8.1 months). There was slightly decreased of 3-year overall survival rate in the present group, which could be due to the majority of colorectal cancer patients in this study were stage 4 disease at the time of diagnosis (Table 6).

Surgical resection is a standard treatment for patient with liver-only metastases which has produced 5-year survival rate of 25 to 40%. Several studies showed no statistically significant difference in 5-year overall survival rates and disease free survival rates between tumor resection and RFA[12,16-18]. Aloia et al[19] reported lower 5-year overall survival rates and disease free survival rates in RFA groups (5-year OS 27% of RFA group vs. 71% of resection group, p<0.001, and 5-year DFS 0% of RFA group vs. 50% of resection group, p = 0.01). Kim et al[20] revealed no significant difference of 5-year overall survival rate between RFA

Table 5. Results of radiofrequency ablation of metastatic liver tumors

Author, year	No. of patients	Mean follow-up (months)	Complete ablation (%)	Local recurrence (%)
Rossi et al.[24], 1996	11	11	73	15
Rossi et al.[25], 1998	14	12	93	9
Solbiati et al.[26], 1997	29	10	66	34
Siperstein et al.[27], 2000	-	13.9	98	12
Livraghi[28], 2001	24	19	92	8
Present study	36	18	84.2	21.1

Table 6. Results of radiofrequency ablation of metastatic liver tumors

Author, year	No. of patients	Median follow-up (months)	3-year overall survival (%)	5-year overall survival (%)
Aloia et al.[19], 2006	30	31.3	57	27
White et al.[39], 2007	22	17	26	0
Lee et al.[17], 2008	37	-	43	48.5
Berber et al.[16], 2008	68	27	35	30
Hur et al.[40], 2009	25	42	60	26
Otto et al.[18], 2010	28	26.74	67	48
Kim et al.[20], 2011	99	-	50.3	31.2
Present study: all	36	17.08	56.2	20
Present study: colorectal cancer	36	17.88	46.5	20.7

and resection group in tumor less than 3 cm (33.6% vs. 31.6%). However, in tumor larger than 3 cm, the 5-year overall survival rate in RFA group was significant lower than that in resection group (23.1% vs. 36.6%, $p = 0.01$). In patient with multiple liver metastases, 5-year overall survival rate in RFA group was also significant lower than resection group (6.4% vs. 16.2%).

Limitations of the present study included: 1) a retrospective review and no comparison to standard treatment (tumor resection), 2) small sample size, and 3) heterogeneous characteristics of the primary tumors and other treatments, which may affect outcome and survival.

Conclusion

Radiofrequency ablation is effective and feasible method to treat metastatic liver tumor. Residual tumor is associate with tumor size larger than 3 cm. High-risk location of the tumor is not related to incomplete ablation and local tumor recurrence.

What is already known on this topic?

Radiofrequency ablation is an effective method in the treatment of metastatic liver tumor especially in small tumor less than 3 cm.

What this study adds?

In the present knowledge, tumors located in high-risk location are susceptible to have higher incidence of residual and recurrent diseases. However, some studies showed no significant higher local tumor progression rate in tumors located in high-risk location.

The result showed no significant difference in complete ablation and local tumor recurrence between tumor located in high-risk locations and those elsewhere.

Potential conflicts of interest

None.

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ผลการรักษาด้วยวิธีการใช้เข็มความร้อนในผู้ป่วยที่เป็นมะเร็งกระจายที่ตับ

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วัตถุประสงค์: *เพื่อศึกษาผลของการรักษาด้วยวิธีการใช้เข็มความร้อน (radiofrequency ablation: RFA) ในผู้ป่วยที่เป็นมะเร็งกระจายที่ตับรวมทั้งหาปัจจัยที่มีผลต่อการเกิดการหลงเหลือ (residual tumor) และการกลับเป็นซ้ำ (recurrent tumor) ของมะเร็งหลังการรักษา*

วัสดุและวิธีการ: *ทำการศึกษาโดยการเก็บข้อมูลย้อนหลังของผู้ป่วยที่ได้รับการรักษาด้วยวิธีการใช้เข็มความร้อนทั้งหมดที่หน่วยรังสีร่วมรักษา ระหว่างเดือนมิถุนายน พ.ศ. 2549 ถึง กันยายน พ.ศ. 2556 มะเร็งกระจายที่ตับที่ได้รับการรักษาด้วยวิธีการใช้เข็มความร้อนในช่วงเวลาทั้งหมด 57 ก้อน ในผู้ป่วย 36 ราย โดยมะเร็งปฐมภูมิ ได้แก่ มะเร็งลำไส้ใหญ่ (colorectal carcinoma) 30 ราย มะเร็งนิวโรเอ็นโดคริน (neuroendocrine tumor) 2 ราย มะเร็งถุงน้ำดี (gallbladder carcinoma) 1 ราย มะเร็งตับอ่อน (adenocarcinoma of head of pancreas) 1 ราย และมะเร็งเนื้อเยื่อในระบบทางเดินอาหาร (gastrointestinal stromal tumor) 2 ราย โดยเก็บข้อมูลเกี่ยวกับลักษณะของก้อนมะเร็ง เทคนิคการใช้เข็มความร้อน อัตราความสำเร็จ ผลข้างเคียง การกลับเป็นซ้ำ รวมถึงภาพการตรวจหลังการรักษา นำมาวิเคราะห์ข้อมูลเพื่อหาผลของการรักษาและอัตราการมีชีวิตรอดของผู้ป่วยหลังการรักษา*

ผลการรักษา: *จากผลการศึกษาพบการจี้โดยสมบูรณ์ (complete ablation) ทั้งหมด 48 ก้อน (ร้อยละ 84.2) มีการกลับเป็นซ้ำของมะเร็ง ณ ตำแหน่งเดิม 12 ก้อน (ร้อยละ 21.1) โดยมีค่าเฉลี่ยของระยะเวลาในการกลับเป็นซ้ำเท่ากับ 8.3±3.8 เดือน (2-15 เดือน) และจากการศึกษาพบว่าการหลงเหลือของมะเร็งหลังการรักษามีส่วนเกี่ยวข้องกับขนาดของมะเร็งที่มากกว่า 3 เซนติเมตร อัตราการมีชีวิตรอดของผู้ป่วยที่ 3 ปี และ 5 ปี เท่ากับร้อยละ 56.2 และ 20 ตามลำดับ ค่าเฉลี่ยของการมีชีวิตรอดเท่ากับ 37.8±10.9 เดือน และอัตราการเกิดภาวะแทรกซ้อนรุนแรงเท่ากับร้อยละ 5.3*

สรุป: *การรักษาด้วยวิธีการใช้เข็มความร้อนเป็นการรักษาที่ดีและมีประสิทธิภาพในการรักษามะเร็งกระจายที่ตับ โดยการหลงเหลือของมะเร็งหลังการรักษามีส่วนเกี่ยวข้องกับขนาดของมะเร็งที่มากกว่า 3 เซนติเมตร และมะเร็งที่อยู่ในตำแหน่งที่มีความเสี่ยงสูงไม่มีความสัมพันธ์กับการหลงเหลือและการกลับเป็นซ้ำของมะเร็งหลังการรักษา*