

Incidence of Complication and Tumor Recurrence after Radiofrequency Ablation in High-Risk Location of Hepatocellular Carcinoma Patients

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Objective: To evaluate complication, rate of residual, and tumor recurrence in high-risk location compared to non-high-risk location in hepatocellular carcinoma patients.

Material and Method: Radiofrequency ablation was performed on 409 tumors in Siriraj Hospital between October 2009 and May 2012. Eighty-eight nodules in 78 patients were treated by RF ablation, which divided into high risk and non-high-risk location. Complete ablation rate, residual tumor, recurrent tumor, and complication were retrospectively reviewed.

Results: HCC nodules were in non-high-risk location 34 nodules (38.6%) and in high-risk location 54 nodules (61.4%). Complete tumor ablations were done in 34 nodules (100%) of non-high-risk location group and 50 nodules (92.6%) of high-risk location group. All residual tumors were four nodules (7.2%), which located in subcapsular location. Recurrent tumors were found in six nodules (6.8%), and mean time to recurrence were 210.2 days. Early complication was 10.2% and late complication was 4.5%. The recurrent tumor and complication were not significantly different between two groups.

Conclusion: Radiofrequency ablation is effective treatment of hepatocellular carcinoma in high-risk location tumor. There is no significant difference in complication and tumor recurrent rate between high-risk and non-high-risk group. However, incidence of residual tumor is significantly increased in subcapsular location tumor.

Keywords: Radiofrequency ablation (RFA), Hepatocellular carcinoma (HCC), Complication, High-risk location

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Primary liver cancer is one of the most common malignancy in the world⁽¹⁾ and 75 to 80% are hepatocellular carcinoma (HCC). In Thailand, HCC is the third most common cancer in male and seventh in female⁽²⁾.

For early stage HCC, according to Barcelona Clinic Liver Cancer Staging System 2010, curative aim is considered by hepatic resection, liver transplantation, or radiofrequency ablation (RFA)⁽³⁻⁵⁾. For patients who are not amenable for surgery, RFA proved to be a safe and effective method for selected case. However, tumors in high-risk locations, such as perivascular region, subcapsular region, or adjacent to visceral organs (gall bladder, bowel, kidney, or diaphragm) are difficult to approach and might increase risk of residual tumor and adjacent organ injury.

The tumors located adjacent to large intrahepatic vessels are theoretically prone to have heat sink effect⁽⁶⁾ and may increase risk of residual tumor at RFA margin. The tumors at subcapsular location are not only difficult to place the needle but also increase the risk of subcapsular hemorrhage. In addition, tumor adjacent to visceral organs are at an increased risk of mechanical or thermal injury^(7,8).

The purpose of this study is to evaluate complication and rate of residual and recurrent tumor in high-risk location compared to non-high-risk location in hepatocellular carcinoma patients.

Material and Method

Between October 2009 and May 2012, 320 patients with HCC underwent 409 RFA procedures at Siriraj hospital. The inclusion criteria were 1) patients with three or fewer HCC foci, all of which were less than 5 cm in diameter, 2) No extrahepatic metastasis, and 3) Pre- and post-procedural imaging could accessible evaluation. The patients were excluded if they received prior treatment such as

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surgery, RFA, or transarterial chemoembolization (TACE). Seventy-eight consecutive patients with 88 HCC nodules were included in the study. The 242 patients were excluded due to previous treatment or no available images.

Coagulopathy was corrected in patient who had platelet count less than 50,000 cells/ml or prothrombin time more than 16 seconds.

RFA procedures were performed by three interventional radiologist that had at least three years experience. After local anesthesia with sedation, the expandable RF electrode (Leveen Needle Electrode, Boston Scientific, Marlborough, MA, Starburst Talon or Starburst XL, Angiodynamics, Latham, NY) was inserted under ultrasound or computed tomographic guidance.

Tissue impedance or internal temperature was monitored by the generator. For larger nodules, overlapping technique was used. No artificial ascites was infused during any RFA procedure. RFA procedures were performed by interventional radiologists (at least 2 years experience in performing ultrasound-guided RFA or CT-guided RFA).

Patients obtained follow-up CT scan or MRI next four weeks after RFA procedures and then every three to six months. Rate of complication, residual and recurrent tumor in both high-risk and non-high-risk locations were collected.

Terminology

Tumors in high-risk locations were classified into two categories. Perivascular tumors locate less than 10 mm from hepatic vein, inferior vena cava (IVC) or first order branch of portal vein. Subcapsular tumors locate less than 10 mm from liver capsule, and included tumors locate less than 10 mm from extrahepatic organs, such as heart, lung, gall bladder, right kidney, or gastrointestinal tract.

Complete ablation was peripheral thin rim arterial enhancement with central hypodensity lesion and no adjacent HCCs characteristic nodule at first follow-up imaging, after procedure four weeks. Residual HCCs was detection of viable HCC abut RFA ablated zone in first follow-up image after procedure. Recurrent HCCs was detection of HCC abut RFA ablated zone during follow-up image with prior evidence of complete ablation.

Complications were categorized according to Society of Interventional Radiology (SIR) Guidelines⁽⁹⁾ Complication occurred within 30 days after RFA procedure define as early complication.

Complication occurred after 30 days define as late complication.

Statistical analysis

The student t-test and Fisher's exact test were used to compare patient characteristic and tumor location. Comparing complication, residual and recurrent tumor in non-high-risk location with high-risk location was performed by Chi-square test. A p-value less than 0.05 by two-tailed analysis was considered to be significant. Local tumor progression curve was plotted using the Kaplan-Meier technique, and differences were tested using the log-rank test. Data analysis was performed using SPSS version 18.

Results

Patient characteristics and locations of HCC nodules

There were 78 patients received RFA treatment in intervention radiology unit. Ten patients had two nodules each; therefore, 88 nodules were included in this study. Age range from 30 to 85 years old (mean age was 63.7±11.6 years). Fifty-three patients were male and 25 patients were female (patients characteristics were shown in Table 1).

Location of HCC nodules were in non-high-risk location 34/88 nodules (38.6%) and in high-risk location 54/88 nodules (61.4%). In high-risk location group, 10 nodules (11.4%) were classified in perivascular tumors (hepatic vein = 2, portal vein = 8), and 44 nodules (50%) were subcapsular tumors. The subcapsular tumors were subcategorized into location adjacent to extrahepatic organ for 13 nodules (heart = 1, lung = 5, gallbladder = 4, right kidney = 2, colon = 1) and subcapsular nodule without adjacent extrahepatic organ for 31 nodules (Table 2) (Fig. 1).

Most RFA procedures were performed under only ultrasound guidance (94.3%). The rest of procedure used combined ultrasound and CT guidance (5.7%). Immediate post RFA CT scan were

Table 1. Patient characteristic and tumor size

Data	Non-high-risk (n = 34)	High-risk (n = 54)	p-value
Sex (%)			0.490
Male	21 (62.0)	32 (59.0)	
Female	13 (38.0)	22 (41.0)	
Mean age, year (SD)	65.9 (11.3)	62.0 (11.6)	0.741
Size, cm (SD)	1.6 (0.5)	1.9 (0.6)	0.083

Table 2. Location of the tumors

Location	Total (n = 88) n (%)
Non high risk location	34 (38.6)
Perivascular tumor	10 (11.4)
Subcapsular tumor	44 (50.0)
Subcapsular only	31 (35.2)
Subcapsular + close to extrahepatic organ	13 (14.7)

performed in 39 patients (50%) to evaluate residual disease or complication.

Success rate

Primary success rate were 95.5%. Four nodules were not completely ablated in first sessions (residual HCC on immediate post RFA CT scan) follow-up period average 571.3±307.3 days, range from 36 days to 1,120 days. Nine patients died during follow-up period but not related to recurrent HCC.

Residual tumor

No residual tumor in non-high-risk group. There were four residual tumors in high-risk group (7.4%), which were located in the subcapsular section. Thus, there was significant difference between non-high-risk and high-risk group (Fig. 2).

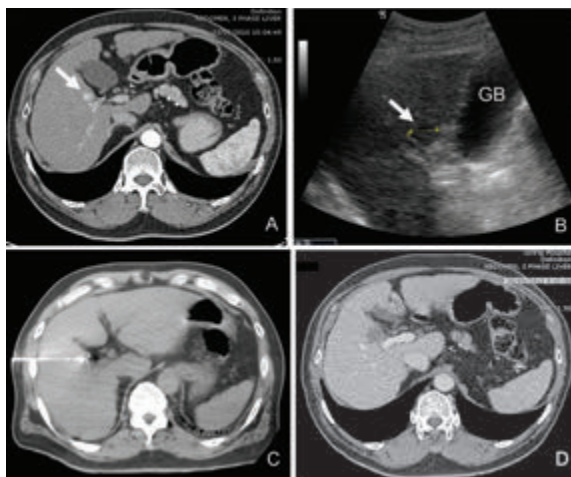


Fig. 1 Image demonstrate complete ablation of tumor in high risk location. (A, B) CT and US show tumor close to gallbladder (arrow). (C) CT confirms expandable RF needle in the tumor. (D) Follow-up CT shows complete post RFA ablation after 1 month.

Three residual tumors were treated by RFA and one by further TACE due to difficult location.

Local recurrent tumor

Six local recurrent HCCs were found (6.8%) and mean time to recurrence were 210.2±146.8 days, range from 32 days to 417 days. Two nodules in non-high-risk group (5.9%), one nodule in perivascular group (10%) and three nodules in subcapsular group (6.8%) were categorized, which was no significant difference (p-value = 0.96) (Fig. 3).

Early complication

Overall, early complications were found in nine patients (10.2%). Eight patients had subcapsular hemorrhage and one patient had colonic injury. No procedural related death was noted. Three patients

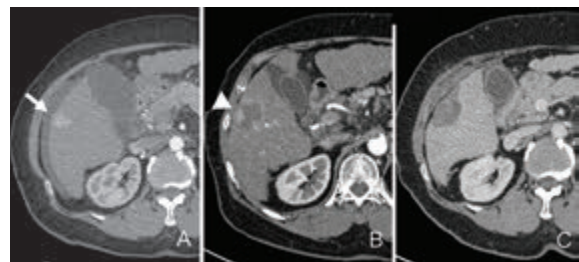


Fig. 2 CT demonstrate residual tumor after RF ablation in high-risk location tumor (A) CT shows arterial enhancing nodule (arrow) at subcapsular location of hepatic segment 5 (B) CT after RF ablation shows residual tumor (arrow head) (C) CT after second RF ablation shows complete tumor ablation.

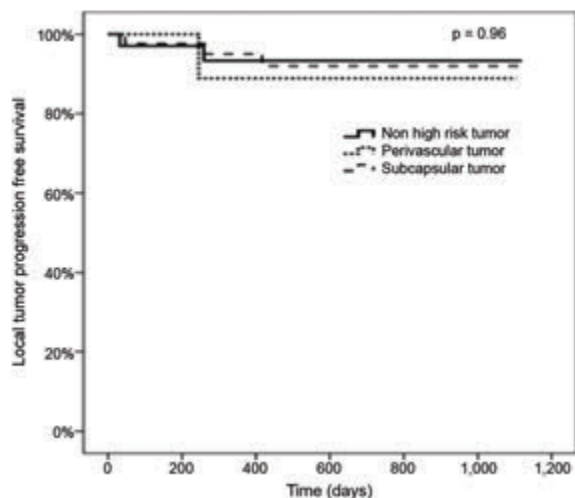


Fig. 3 Local tumor progression free survival of 88 tumor ablations classify by tumor location.

were in non-high-risk group (8.8%). Six patients were in high-risk group (11.1%), four of which were in subcapsular location and two were in perivascular location. However, there was no significant difference (p-value = 0.34) of early complication between two groups.

All of the patients with subcapsular hematoma were depicted at the procedural days by immediate CT scan. Only one patient had symptom (abdominal pain, hypotension and decrease hematocrit level) and was subsequently underwent angiography with successful embolization. The rest of them were asymptomatic and no need further treatment.

In case of colonic injury, the HCC nodule located at 1mm from hepatic flexure of colon. CT scan after procedure found bowel wall thickening and some free air adjacent area of injury. The patient got accomplished conservative treatment with total fasting and intravenous antibiotic. After 24 days, the patient was discharged without GI symptoms.

Subgroup analysis about distance of HCC tumors adjacent to liver capsule and extrahepatic organ, the tumor located into less than 5 mm group and 5 to 9.9 mm group, the author found that no complication occurred in group 5 to 9.9 mm from adjacent liver capsule/organ.

For patients with low platelet count (<80,000 cells/mL) and increase prothrombin time value, there was also no significant difference in occurrence of early complication.

Late complication

Late complications were found in four patients (4.5%), which were hepatic infarction in two patients and mild focal intrahepatic duct dilatation in two patients. The tumors located at central location of liver. Mean time to occurrence of late complications were 54.8 ± 42.2 days, range from 32 days to 118 days. Comparison of non-high-risk and high-risk location groups showed no significant difference (non-high-risk = 5.9% and high-risk = 3.7%, p-value = 0.50). All of these complications were treated conservatively.

Discussion

Present study, the authors found no significant difference in early complication, late complication and tumor recurrence, when compared between non-high-risk location group, perivascular and subcapsular group.

Previous study by Teratani et al⁽¹⁰⁾ and Tang et al⁽¹¹⁾ also showed no significant difference in

rate of complication and tumor recurrence between these groups.

Rate of early complication in our study was 10.2%, which was higher than previous study by Teratani et al (4.2%)⁽¹⁰⁾ and Tang et al (2.9%)⁽¹¹⁾. This is because immediate post RFA CT scan were performed in 39 patients (50%) due to interventionist preference even in asymptomatic patient.

In cases of subcapsular hematoma, seven of eight patients were asymptomatic and these complications were detected by immediate post RFA CT scan. However, the other patient had hypotension and abdominal pain, and then immediate abdominal CT and angiography were performed. There was no detectable point of bleeding. However, embolization was done at right hepatic artery that supply ablated area.

Complete ablation rates in our study were 100% in non-high-risk location, 100% in perivascular location and 95.5% in subcapsular location. These results were comparable with previous study by Tang et al, which reported complete ablation rate 87.3% in non-high-risk location and 89% in high-risk location.

In Panikoon et al⁽¹²⁾ reported tumor size larger than 2 cm is associated with incomplete tumor ablation, but in this study found that only subcapsular location tumor has risk of residual tumor. Assumption of residual tumor in subcapsular group is imprecise placement of RFA electrode due to difficult location.

Due to mechanism of heat sink effect, tend to recurrence might be higher in perivascular nodule than non-high-risk nodule. However, rate of local recurrent tumor in this study was not significant difference between non-high-risk and perivascular group, which similar to study by Teratani et al⁽¹⁰⁾.

Conclusion

Radiofrequency ablation is effective treatment of hepatocellular carcinoma even in high-risk location tumor. No significant difference in complication and tumor recurrence rate between high-risk and non-high-risk group are found. However, residual tumor should be concerned in subcapsular location.

What is already known on this topic?

At present, radiofrequency ablation is in the standard treatment guideline of hepatocellular carcinoma (BCLC guideline). Several literatures report high successful treatment rate and low complication in general tumor location.

Some debate about “Should we treat liver tumor in high-risk location with radiofrequency ablation?”.

What this study adds?

The authors do the research about effectiveness of radiofrequency ablation in high-risk location liver tumor, which some institute consider as contraindication.

The result shows safety of radiofrequency ablation in high-risk located liver tumor with no increased risk of complication or recurrent tumor. However, there would still be residual tumor after treatment at subcapsular tumor location.

Potential conflicts of interest

None.

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อุบัติการณ์การเกิดภาวะแทรกซ้อนและการกลับเป็นซ้ำของก้อนเนื้ออกมะเร็งตับที่อยู่ในตำแหน่งเสี่ยงสูงหลังการรักษาด้วยเข็มให้ความร้อนจากคลื่นวิทยุ

สมราช ธรรมธวัฒน์, ปณิดา ลิ้มสุวรรณ, ตรงธรรม ทองดี, วลัยลักษณ์ ชัยสูตร, ทนงชัย สิริอภิสิทธิ์

วัตถุประสงค์: เพื่อศึกษาอุบัติการณ์การเกิดภาวะแทรกซ้อน ผลสำเร็จ และการกลับเป็นซ้ำหลังจากการรักษาด้วยเข็มให้ความร้อนจากคลื่นวิทยุ radiofrequency ablation (RFA) ของก้อนเนื้ออกมะเร็งตับในตำแหน่งที่มีความเสี่ยงสูงเทียบกับในตำแหน่งทั่วไป

วัสดุและวิธีการ: ศึกษาโดยการเก็บข้อมูลย้อนหลังของผู้ป่วยที่ได้รับการรักษา มะเร็งตับด้วยเข็มให้ความร้อนจากคลื่นวิทยุในโรงพยาบาลศิริราช ระหว่างเดือนตุลาคม พ.ศ. 2552 ถึง เดือนพฤษภาคม พ.ศ. 2555 โดยแบ่ง ก้อนเนื้ออกเป็นสองกลุ่ม คือ กลุ่มที่ก้อนเนื้ออกอยู่ในตำแหน่งเสี่ยงสูง และกลุ่มที่เนื้ออกอยู่ในตำแหน่งทั่วไป ศึกษาผลสำเร็จของการจัดด้วยเข็มให้ความร้อนภาวะแทรกซ้อนและอัตราการกลับเป็นซ้ำ

ผลการศึกษา: ก้อนเนื้ออกมะเร็งตับ 34 ก้อน อยู่ในตำแหน่งทั่วไป และ 54 ก้อน อยู่ในตำแหน่งที่มีความเสี่ยงสูง ผลการรักษาพบการจี้ความร้อนสมบูรณ์ 34 ก้อน (100%) ของเนื้ออกตำแหน่งทั่วไป และ 50 ก้อน (92.6%) ของเนื้ออกในตำแหน่งที่มีความเสี่ยงสูง มีก้อนเหลือจากการจี้ความร้อน 4 ก้อน (7.2%) ซึ่งทั้งหมดอยู่ในตำแหน่งพิวตัม การกลับเป็นซ้ำของก้อนเนื้ออกในตำแหน่งเดิม 6 ก้อน (6.8%) โดยระยะเวลาเฉลี่ยของการกลับเป็นซ้ำคือ 210.2 วัน ภาวะแทรกซ้อนในระยะแรกคือ 10.2% และในระยะหลัง 4.5% ไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติ ระหว่างการกลับเป็นซ้ำและการเกิดภาวะแทรกซ้อนของเนื้ออกทั้งสองกลุ่ม

สรุป: การรักษาเนื้ออกมะเร็งตับด้วยเข็มให้ความร้อนจากคลื่นวิทยุมีความปลอดภัยและให้ผลการรักษาที่ดี และไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติของการเกิดภาวะแทรกซ้อนและการกลับเป็นซ้ำของเนื้ออกระหว่างก้อนเนื้ออกในตำแหน่งปกติและตำแหน่งที่มีความเสี่ยงสูง แต่สามารถพบก้อนเหลือจากการจี้ความร้อนเพิ่มขึ้นในก้อนเนื้ออกที่อยู่ตำแหน่งพิวตัม
