Int J Clin Exp Med 2018;11(12):13365-13373
www.ijcem.com /ISSN:1940-5901/IJCEM0082537

Original Article

Contrast enhanced intraoperative ultrasonography-guided radiofrequency ablation of recurrent hepatocellular carcinoma after hepatectomy through percutaneous or open approach: a retrospective cohort study

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Received July 13, 2018; Accepted September 12, 2018; Epub December 15, 2018; Published December 30, 2018

Abstract: Radiofrequency ablation (RFA) is one of the best alternatives for treatment of recurrent hepatocellular carcinoma through percutaneous or an open approach under the guidance of contrast enhanced intraoperative ultrasonography (CE-IOUS). A total of 89 recurrent cases undergoing PRFA or ORFA under the guidance of CE-IOUS were collected in West China Hospital of Sichuan University from 2005 to 2009. Complete ablation was evaluated by CT 1 month after RFA. Abdominal ultrasonographies and alpha fetoprotein were performed every 3 months to demonstrate recurrent sites during the follow-up period. Cumulative overall survival rates, survival rates after RFA, re-recurrent rates, and complications were analyzed between the two approaches. A total of 119 recurrent tumors of 89 patients were ablated in the two approaches (59.7%,71/119 tumors in percutaneous group versus 40.3%, 48/119 tumors in open group). Contrast enhanced CT scans demonstrated that all tumors were completely ablated 1 month after RFA during the follow-up period. Complication rate was 7.4% (4/54) in the percutaneous group, compared to 11.4% (4/35) in the open group (p=0.517). The 1-year, 3-year, and 5-year cumulative overall survival rates were 93%, 37%, and 19%, respectively, and 1-year, 2-year, and 3-year survival rates after RFA were 57%, 31%, and 15%, respectively. Moreover, 27.8% of patients (15/54) had re-recurrence in the percutaneous group, compared to 22.9% of patients (8/35) in the open group (p=0.604). No statistically significant differences were observed between the two approaches. CE-IOUS guided RFA is an effective and safe method of treating recurrent hepatic tumors, achieving complete ablation of all tumors in the present study. PRFA and ORFA have advantages and disadvantages, respectively. Appropriate selection of each is dependent on different situations for recurrent tumors.

Keywords: Contrast enhanced intraoperative ultrasonography (CE-IOUS), percutaneous radiofrequency ablation (PRFA), open radiofrequency ablation (ORFA), recurrence, hepatocellular carcinoma

Introduction

Liver resection and liver transplantation are the best curative treatments for hepatocellular carcinoma, currently. However, only 10-20% of patients undergo resections due to tumor location, multifocality, and severe cirrhosis [1]. In several previous studies, up to 70% of patients that underwent hepatectomy for HCC experienced recurrence in the liver within 5 years after hepatectomies, despite postoperative histological examinations showing negative resected tumor margins [2-5]. If a repeat hepatectomy is feasible, it is still regarded as the gold standard for curative treatment of recurrent HCC [6-8]. Only 10-40% of patients, however, can undergo repeat hepatectomies safely [9-11]. It is nearly impossible to perform resections on patients with multiple tumors or liver dysfunction [12]. Radiofrequency ablation and TACE are possible alternative treatments for them. Lencioni R et al. and Chen MS et al. revealed no significant differences in 3-year or 4-year survival rates for treatment of small HCC between hepatectomies and radiofrequency ablation [13, 14].

There are 3 approaches of radiofrequency ablation, including percutaneous, laparoscopic, and the open approach. The present study focused on the percutaneous and open approach.

Table 1. Patient demographics and tumor characteristics

	Percutaneous	Laparotomy	p
Number of patients	54	35	
Median age (year)	55 (37-77)	53 (30-78)	
Gender (male:female)	45:9	30:5	
Number of tumors	71	48	
Number of HbsAg (+)	42	25	
Number of cirrhosis	18	11	
Child-Pugh score			
A	49	34	
B	4	2	
Patients' comorbidity	11 (primary hypertension 5, diabetes mellitus 2, primary hypertension + diabetes mellitus 2, gastric ulcer 1, spontaneous peritonitis 1)	8 (primary hypertension 3, diabetes mellitus 2, primary hypertension + diabetes mellitus 1, cerebral atrophy 1, duodenal diverticulum 1)	
Median Size of tumors (cm)	2.8 (0.8-6.0)	3.5 (0.4-5.0)	0.148
Median hospital stays (day)	6 (3-12)	11 (4-28)	0.016
Median follow-up period (month)	26 (4-71)	30 (12-96)	0.224

P, Mann-Whitney test.

Advantages of the percutaneous approach are less invasiveness, less pain after surgery, shorter length of hospital stays, and lower costs, compared to the open approach. It exhibits good visibility and accurate location of tumors in the liver. Small lesions not discovered on ultrasonographies or computerized tomographies, preoperatively, have been shown in intraoperative ultrasonographies. Junji et al. studied the 3 approaches of RFA in treating primary HCC [1], but no prior studies were related to FRA for treatment of recurrent HCC. Recurrence indicates the progression of tumors. Selection of an approach of RFA to treat recurrent tu-mors is still ambiguous. When considering the advantages of the percutaneous and open approach, and whether the survival rates between the two approaches are different or not, no definitive conclusions have been drawn. The present study aimed to examine differences of cumulative overall survival rates, survival rates after RFA, re-recurrent rates, and complication occurrence of the percutaneous approach, compared to the open approach, in the treatment of recurrent HCC.

Intraoperative ultrasound (IOUS) is routinely used in liver surgery to reveal tumor location. However, it's difficult to distinguish malignant nodules from benign nodules in cirrhotic patients with hepatocellular carcinoma because IOUS cannot provide accurate information about tumor vascularity. It has been shown that intravenous ultrasound contrast agents are able to improve nodule characterization, compared to unenhanced ultrasound. Thus, this study evaluated the effects of contrast enhanced intraoperative ultrasound (CE-IOUS) used in radiofrequency ablation of recurrent hepatocellular carcinoma through the percutaneous or open approach.

Patients and methods

From 2005 to 2009, 89 patients (75 male and 14 female) with 119 recurrent hepatic tumors after hepatectomy were collected and analyzed, retrospectively, in West China Hospital of Sichuan University. These tumors were diagnosed as hepatocellular carcinoma by radiological modalities and/or cytohistological examinations, according to EASL 2000. A total of 54 patients underwent radiofrequency ablation percutaneously, while 35 patients were ablated through the open approach. Median follow-up period was 28 months (range, 4-96). Median age was 54 years (range, 30-78). HBsAg (+) was confirmed in 67 patients. Liver function was classified by the Child-Pugh score. It was A in 83 and B in 6, while 29 patients suffered from liver cirrhosis. Eleven patients in the percutaneous group and 8 in the laparotomic group were accompanied with other diseases. The median size of 119 tumors was 3.1 cm (range, 0.8-6.0) and median hospital stay was 8 days (range, 3-28). Detailed information regarding patient demographics and tumor characteristics is listed in **Table 1**.

*Percutaneous radiofrequency ablation, PRFA (**Figure 1C**)*

Percutaneous RFA was performed under general anesthesia. Tumor localization and abla-

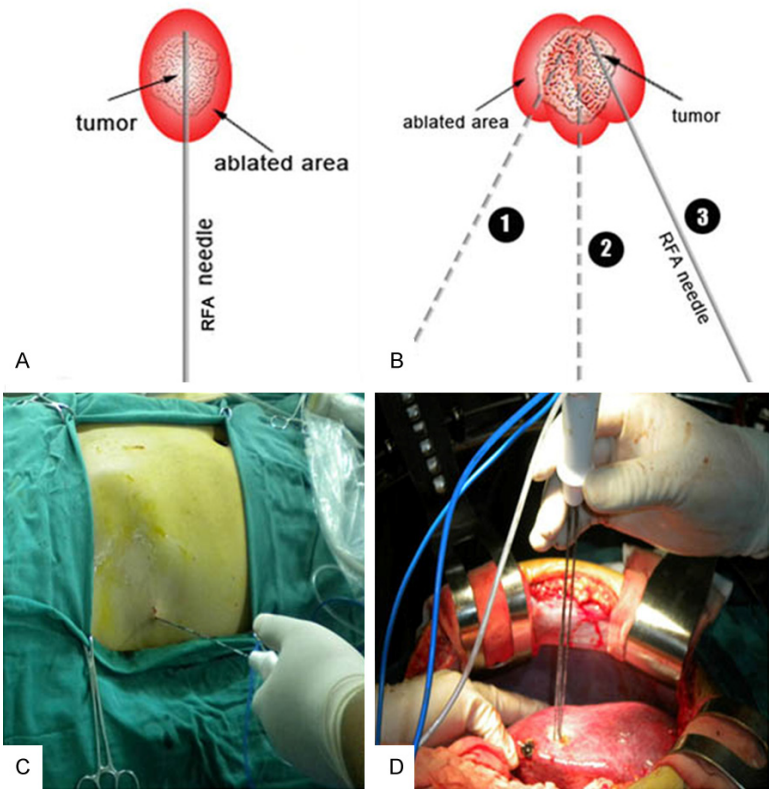

Figure 1. A. Diagram shows the ablated area around the small tumor (smaller than 3 cm); B. Diagram shows multiple overlapping ablated area around big tumor (larger than 3 cm); C. Shows percutaneous radiofrequency ablation (PRFA); D. Shows open radiofrequency ablation (ORFA).

tion were guided by contrast enhanced intraoperative ultrasonography (Vivid4 GE Corp, USA). With the help of contrast (Sono Vue, Italy), tumors were well visualized on ultrasound. Radionics Cool-tip RF System (Tyco Healthcare, USA) was used in all cases and 0.5-1.0 cm around the tumor was ablated in each case. Multiple overlapping ablations were needed to achieve ample coverage with margins (**Figure 1A** and **1B**). Contrast enhanced ultrasonography was used to observe the ablated zone immediately after RFA. If incomplete ablation was obtained, additional FRA would be needed. Ablation time was related to tumor size and proximity to vasculature. The needle track was burned at the end of the procedure before retraction of the needle.

*Open radiofrequency ablation, ORFA (**Figure 1D**)*

Open RFA was administered through a right subcostal incision and general anesthesia. In some cases, mobilization of the liver was needed to expose the tumor. Localization of tumors and ablation processes guided by contrast enhanced intraoperative ultrasonography are like the percutaneous approach, as described above.

Contrast enhanced intraoperative ultrasonography, CE-IOUS

Contrast enhanced intraoperative ultrasonography (CE-IOUS) was carried out to search for lesion characterization and new nodule detection, with the help of IU22 unit (Philips, USA) equipped with a 5-2 MHz convex transducer and a 9-3 MHz linear transducer. The contrast agent used was SonoVue (Bracco Imaging, Milan, Italy) which consisted of sulphur hexafluoride microbubbles stabilized by a phospholipid shell. Next, 4.8 mL SonoVue was injected, intravenously, through a peripheral vein per exploration and a low mechanical index (MI) <0.1 mode was used. Three phases, including arterial (10-20 seconds to 25-35 seconds after injection), portal (30-45 seconds to 120 seconds), and equilibrium (>120 seconds) phases, were recorded and analyzed (**Figure 2A** and **2B**).

Patient follow-up

Results of RFA were checked by enhanced computerized tomography (CT) 1 month after ablation (**Figure 2C** and **2D**) and patients were followed up with alpha fetoprotein (AFP) and ultrasonography every 3 months after RFA. Suspected re-recurrence was confirmed by enhanced computerized tomography (CT) scans and/or hepatic angiography. Chest radiographs or CT scans were used to detect any concurrent extra-hepatic recurrence.

Statistical analysis

Parameters, including tumor size and length of hospital stay, were analyzed. They are express-

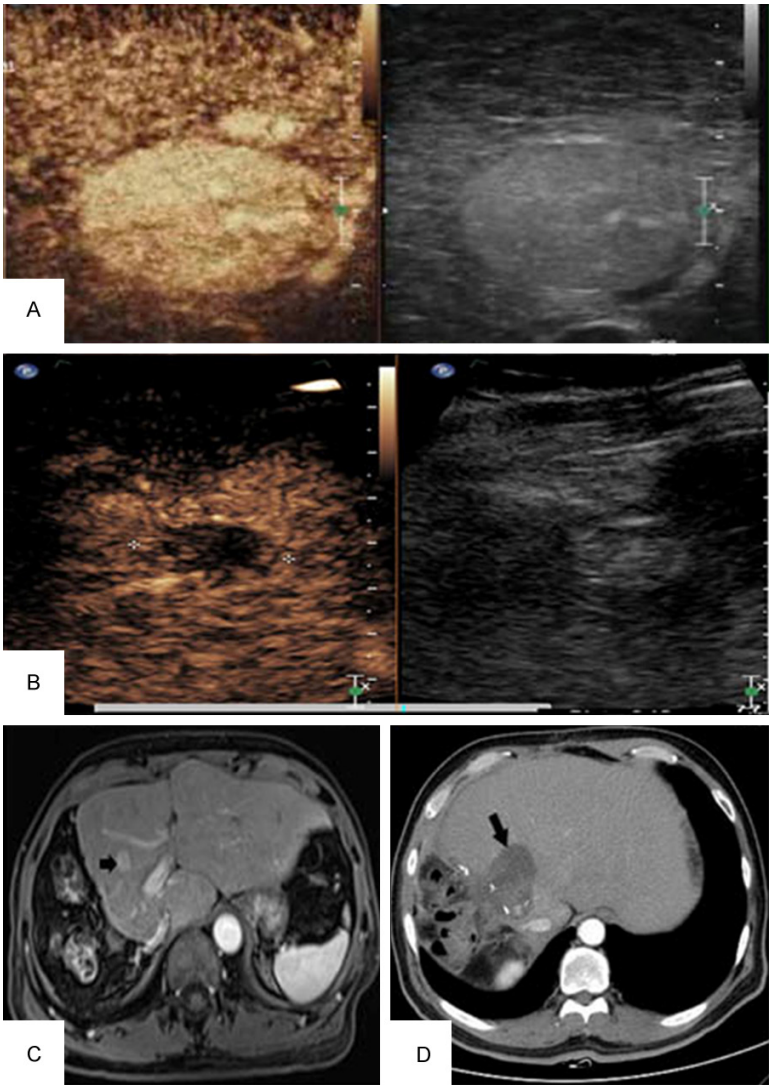

Figure 2. A. Hyperenhancement in arterial phase indicating HCC nodule on CE-IOUS before RFA; B. Hypoenhancement in arterial phase indicating ablated HCC nodule on CE-IOUS after RFA; C. Contrast enhanced CT shows HCC nodule (arrow) in arterial phase; D. Complete ablated region (arrow) 1 month after RFA on contrast enhanced CT during follow-up period.

Table 2. Complications of RFA

Percutaneous approach	Open approach
High fever (n=2)	High fever (n=1)
	Ascites (n=1)
Ascites (n=2)	Atrial fibrillation (n=1)
	Hydrothorax (n=1)

Chi-squared test, P=0.517.

ed as medians (range) and were tested by Mann-Whitney U-test. Chi-Squared test was used on nominal variables. Cumulative analysis of overall and tumor re-recurrence rates was calculated using the Kaplan-Meier method. Statistical comparisons were based on the Log-Rank test. All analyses were performed using SPSS 13.0 and statistical significance is present when *p*-values <0.05.

Results

Characteristics of patients and recurrent tumors undergoing RFA

A total of 119 lesions were ablated in 89 patients. A total of 54 patients (60.7%) underwent radiofrequency ablation percutaneously, while 35 patients (39.3%) were ablated through the open approach. The total number of ablated lesions in the percutaneous group was 71 (59.7%). In the open group, the number was 48 (40.3%). The median size of ablated lesions in the percutaneous group was 2.8 cm (range, 0.8-6.0), compared to 3.5 cm (range, 0.4-5.0) in the open group. Differences were not statistically significant (p= 0.148).

Length of hospital stay

The median length of hospital stay in the percutaneous group was 6 days (range, 3-12), compared to 11 days (range, 4-28) in the open group. Differences were statistically significant (p=0.016).

Patient follow-up period

In the percutaneous group, the median follow-up period was 26 months (range, 4-71), compared to 30 months (range, 12-96) in the open group. Differences were not statistically significant (p=0.224).

Complication of radiofrequency ablation

Four patients suffered from complications after PRFA, 2 had high fevers with axillary temperatures >39°C, and 2 had ascites. In the open group, complications included ascites (n=1), high fever (n=1), atrial fibrillation (n=1), and

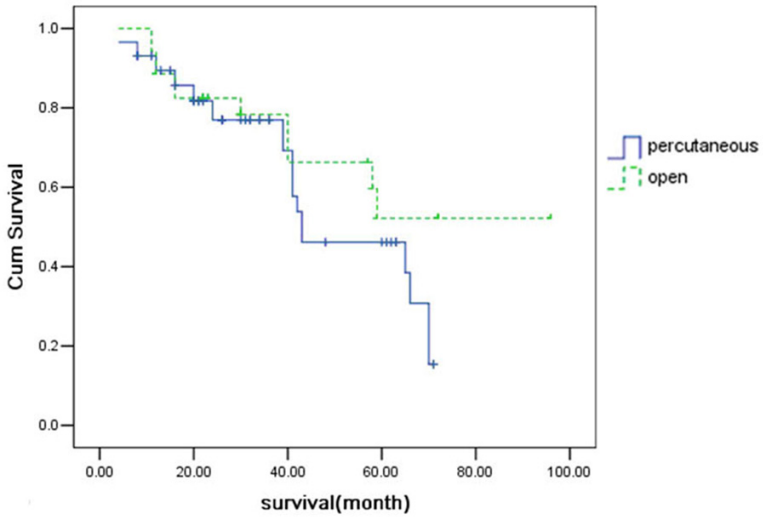

Figure 3. Cumulative overall survival curve of patients after hepatectomy (Log Rank test, P=0.213).

Table 3. Cumulative overall survival rates of the two approaches

Cumulative overall survival rate	Percutaneous	Open	p
1 year (%)	51 (0.94)	32 (0.91)	0.196
3 year (%)	20 (0.37)	13 (0.37)	0.253
5 year (%)	11 (0.20)	6 (0.17)	0.086

P, Mann-Whitney test.

hydrothorax (n=1). No procedure-related mortality occurred in any of the patients and no needle tract seeding was found in the patients during follow-up period. Complications are summarized in **Table 2**. Complication rates were 7.4% (4/54) in the percutaneous group and 11.4% (4/35) in the open group (p=0.517).

Ablation outcomes

Median ablation time per tumor was 13 minutes (range, 6-20) in the percutaneous group and 12 minutes (range, 8-20) in the open group. There was no significant difference between the percutaneous group and open group (p=0.823). Complete ablation was achieved in all cases, according to CT scans 1 month after RFA.

Cumulative overall survival rates

Cumulative overall 1-year survival of the 89 patients with recurrent HCC was 93% (94% in the percutaneous group, 91% in the open group, p=0.196). The 3-year survival was 37% (37% in the percutaneous group, 37% in the open group, p=0.253) and 5-year survival was 19% (20% in the percutaneous group, 17% in the open group, p=0.086). There were no significant differences in terms of survival between the two approaches at 1, 3, and 5 years, respectively. Cumulative overall survival curve is shown in **Figure 3** and 1-year, 3-year, and 5-year survival rates of recurrent HCC patients are listed in **Table 3**.

Survival rates of recurrent HCC patients after treatment of FRA

Survival of the 89 recurrent patients from the time of hepatic resection was 57%, 31%, and 15%, respectively, at 1, 2, and 3 years. The survival curve is shown in **Figure 4**. The 1-year survival rate after RFA was 61% in the percutaneous group, compared to 51% in the open group, p=0.087. Two-year survival rate was 31% in the percutaneous group, compared to 31% in the open group, p=0.309. Three-year survival rate was 15% in the percutaneous group, compared to 14% in the open group, p=0.264. The 1-year, 2-year, and 3-year survival rates of recurrent HCC patients after treatment of RFA are listed in **Table 4**.

Re-recurrent rates

The overall re-recurrent rate was 25.8% (percutaneous approach 27.8%, 15/54; open approach 22.9%, 8/35, p=0.604). Re-recurrence was classified as intrahepatic re-recurrence, including previous RFA site and distant site, and extrahepatic re-recurrence, which may associate with pulmonary, vertebral, and adrenal metastasis. Extrahepatic re-recurrence was documented in 10.1% (9/89) of all patients (**Table 5**). Median re-recurrent interval after RFA was 17 months (range, 2-50) in the percutaneous group and 19 months (range, 3-48) in the open group, p=0.253.

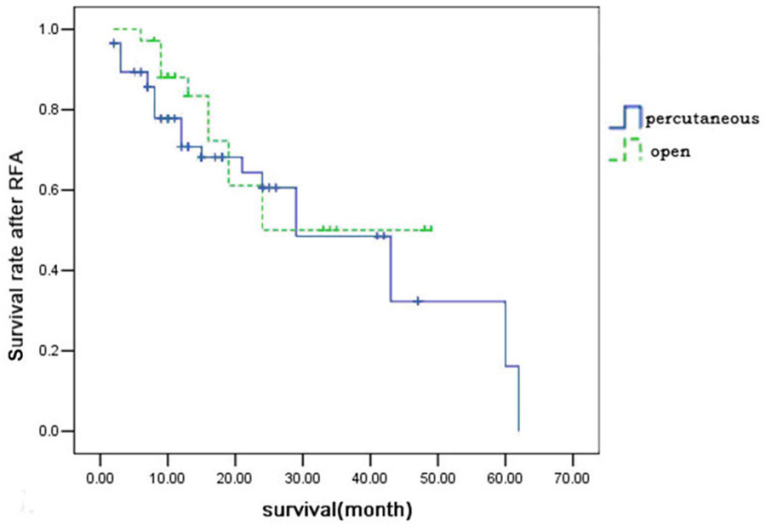

Figure 4. Survival curve of patients after RFA (Log Rank test, P=0.355).

Table 4. Survival rates after RFA in PRFA and ORFA

Survival rate after FRA	Percutaneous	Open	p
1 year (%)	33 (0.61)	18 (0.51)	0.087
2 year (%)	17 (0.31)	11 (0.31)	0.309
3 year (%)	8 (0.15)	5 (0.14)	0.264

Table 5. Re-recurrent sites after RFA

	Percutaneous	Open
Intrahepatic		
RFA site	0	0
Distant site	8	6
Extrahepatic		
Lung	4	1
Vertebra	2	1
Adrenal gland	1	0

Chi-squared test, p=0.604.

Discussion

Surgical resection remains the best treatment for primary HCC or recurrent HCC. However, only a small proportion of patients are suitable to undergo radical hepatectomy due to poor liver reserves, extrahepatic recurrence, patient comorbidity, and the number and location of tumors [15]. Currently, there are several kinds of alternative local therapeutic modalities, including radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), cryoablation, microwave, high intensity focused ultrasound (HIFU), and chemoembolization. RFA has become one of the best alternatives in treating patients that are not candidates for curative hepatectomy. Sutherland et al. concluded that RFA generally resulted in larger and more complete areas of ablation and that RFA may also be associated with higher survival rates than other ablative techniques [16-18]. RFA can be performed by percutaneous, laparoscopic, and open approaches, as well as a combination of approaches. The objective of this study was to analyze the safety and efficacy of FRA performed in the percutaneous and open approach. Selection from the two approaches requires a careful discussion because of their advantages and disadvantages.

Advantages of percutaneous RFA include less invasiveness and shorter length of hospital stay. In the present study, median hospital stay was 6 days in the percutaneous group and 11 days in the open group (p=0.016). Patient satisfaction and acceptability are high, with quick recovery periods and minimal postoperative pain. Disadvantages of PRFA include less accuracy in localization with the possibility of missing small or occult tumors and the presence of ultrasonically inaccessible areas in certain patients, usually small tumors in segment VII or VIII that are not visible due to the interference of lungs. However, with the help of artificial hydrothorax or ascites, PRFA can be done successfully [19, 20]. Certain limitations, such as tumors that lie too close to major vessels, diaphragm, hollow organs, or the surface of liver, can prevent the availability of PRFA [19]. Under these conditions, the open approach allows greater flexibility and concomitant surgeries, like hepatic resection or other organ (e.g, gallbladder) resections, could be achieved in ORFA. Further advantages of the open approach include better localization of tumors with intraoperative ultrasound, accessibility to tumors in all areas of the liver, and the ability to perform the Pringle maneuver, which can reduce heat-sink effects.

The main disadvantages of ORFA are its invasiveness, along with with increased surgical risks and longer hospital stays and recovery times.

Complications of RFA are rare. A multicenter survey on 582 hepatic tumors reported major and minor complication rates to be 5.7% and 6.3% respectively [21]. In the present study, 7.4% (4/54) of patients developed complications in the PRFA group, compared to 11.4% (4/35) in the ORFA group, P=0.517. They were resolved with conservative management and no procedure related mortality was observed. Occurrence of complications may be associated with hepatic reserves, surgical approach, tumor size, and lack of experience.

CE-IOUS is a new technology used in the detection of tumors. It appears to be an exciting and promising new application, helping differentiate nodules detected by IOUS in cirrhotic livers and finding isoechoic nodules which cannot be shown on IOUS [22-24]. Lu et al. reported that CE-IOUS changed the surgical strategy in 35% (7/20) of patients and avoided unnecessary intervention in 30% (6/20) of patients [25]. CE-IOUS makes operations more accurate, enhancing the impact of this technique on operative decision-making for liver tumors. Sensitivity and specificity of CE-IOUS in detecting HCC nodules were 100% [26]. This study performed CE-IOUS before FRA to accurately localize tumors or detect susceptible tumors not shown on contrast ultrasound or CT. With the guidance of CE-IOUS, RFA was performed perfectly. There was no enhancement of ablated lesions on CE-IOUS, postoperatively, and no enhancement was observed 1 month after FRA during follow-ups. Therefore, in this study, 100% complete ablation was achieved in both percutaneous and open groups.

A total of 15 patients (27.8%) re-recurred in the percutaneous group, compared to 8 patients (22.9%) in the open group, during follow-up time (p=0.604). No RFA site re-recurrence was found in either approach. CE-IOUS played an important role in complete ablation of RFA site. The re-recurrent rate was relatively lower than in other studies (ranging from 50% to 60%) [27]. Recurrence at extrahepatic sites, as well as intrahepatic distant sites, was more determined by tumor biology and natural history of the disease. In terms of survival, there were no differences in cumulative overall survival rates and survival rates after RFA, respectively, between the percutaneous and open approach. These figures are similar to survival data reported by Rossi et al. [28].

In conclusion, RFA is a safe and effective method of treating recurrent hepatic tumors. CE-IOUS plays a very important role in detecting and differentiating tumors. No FRA site recurrence was observed from CE-IOUS. This study did not observe any significant differences in terms of recurrence rates or survival rates between percutaneous and open groups. This study also discussed advantages and disadvantages of the two approaches. Appropriate selection of an approach depends on different situations for recurrent tumors.

Acknowledgements

This research was funded by the Chinese Foundation for Hepatitis Prevention and Control-TianQing Liver Disease Research Fund Subject (TQGB20170067), Scientific Research Starting Foundation for Youths of Sichuan University (2015SCU11999-9), and the Science and Technology Support Program of Sichuan Province (2017KZ0019).

Disclosure of conflict of interest

None.

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