Efficiency and safety of radiofrequency-assisted hepatectomy for hepatocellular carcinoma with cirrhosis: A single-center retrospective cohort study

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AIM: To assess the efficiency and safety of radiofrequency-assisted hepatectomy in patients with hepatocellular carcinoma (HCC) and cirrhosis.

METHODS: From January 2010 to December 2013, 179 patients with HCC and cirrhosis were recruited for this retrospective study. Of these, 100 patients who received radiofrequency-assisted hepatectomy (RF+ group) were compared to 79 patients who had hepatectomy without ablation (RF- group). The primary endpoint was intraoperative blood loss. The secondary endpoints included liver function, postoperative complications, mortality, and duration of hospital stay.

RESULTS: The characteristics of the two groups were closely matched. The Pringle maneuver was not used in the RF+ group. There was significantly less median intraoperative blood loss in the RF+ group (300 vs 400 mL, P = 0.01). On postoperative days (POD) 1 and 5, median alanine aminotransferase was significantly higher in the RF+ group than in the RF- group (POD 1: 348.5 vs 245.5, P = 0.01; POD 5: 112 vs 82.5, P = 0.00), but there was no significant difference between the two groups on POD 3 (260 vs 220, P = 0.24). The median AST was significantly higher in the RF+ group on POD 1 (446 vs 268, P = 0.00), but there was no significant difference between the two groups on POD 3 and 5 (POD 3: 129.5 vs 125, P = 0.65; POD 5: 52.5 vs 40).

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vs 50, P = 0.10). Overall, the rate of postoperative complications was roughly the same in these two groups (28.0% vs 17.7%, P = 0.11) except that post hepatectomy liver failure was far more common in the RF+ group than in the RF- group (6% vs 0%, P = 0.04).

CONCLUSION: Radiofrequency-assisted hepatectomy can reduce intraoperative blood loss during liver resection effectively. However, this method should be used with caution in patients with concomitant cirrhosis because it may cause severe liver damage and liver failure.

Key words: Hepatocellular carcinoma; Blood loss; Radiofrequency-assisted hepatectomy; Complications; Cirrhosis

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Core tip: The purpose of this study was to assess the efficiency and safety of radiofrequency-assisted hepatectomy in patients with hepatocellular carcinoma and cirrhosis. Radiofrequency-assisted hepatectomy can reduce intraoperative blood loss during liver resection effectively. However, this method should be used with caution in patients with concomitant cirrhosis because it may cause severe liver damage and even liver failure.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignant cancers in the world. It is also a leading cause of cancer-related death[1,2]. Some 80%-90% of HCC patients have cirrhosis, with the majority of these cases occurring in developing countries due to endemic hepatitis B virus and hepatitis C virus[3,4]. Surgery remains the primary curative treatment for cirrhotic patients with HCC. These procedures include liver transplantation, resection, and radiofrequency ablation[5]. Liver transplantation may be the best treatment option for cirrhotic patients with HCC because it involves the simultaneous removal of both the cirrhotic liver and HCC[6]. However, the United Network for Organ Sharing recently reported that only 7.9% of patients in need of liver transplantations receive one, due to organ shortage[7]. Liver resection is the most common treatment for HCC[8]. However, due to poor hepatic reserve, regeneration dysfunction, portal hypertension, and other conditions that patients with concomitant cirrhosis may have, liver resection may involve considerable intraoperative blood loss and the incidence of postoperative complications, thereby affecting the prognosis[9,10]. For this reason, the two main goals regarding liver cirrhosis are the prevention of intraoperative bleeding and the prevention of postoperative complications. In recent years, the continuous use and development of radiofrequency ablation (RFA) in liver surgery have produced satisfactory results in the treatment of small HCC. It can also block small and medium-sized blood vessels in the liver through thermal coagulation, so it has been used in liver resection in order to reduce bleeding[11-13]. Radiofrequency-assisted hepatectomy was first described by Weber et al[12] who used a single needle probe to deploy RFA energy before liver resection, and the mean blood loss during the surgery was only 30 ± 10 mL in 15 patients. Recently, radiofrequency-assisted liver resection has been shown to be effective in reducing intraoperative blood loss; it has been recommended for cirrhotic patients[14,15]. However, the use of this technique remains controversial due to reported perioperative outcomes and complications. Some studies have suggested that radiofrequency-assisted liver resection leads to less blood loss, a lower transfusion rate, and less postoperative morbidity and mortality[13,16,17]. However, some studies have reported that radiofrequency-assisted liver resection causes severe postoperative liver dysfunction, and the incidence of postoperative complications is higher than that of simple hepatectomy[18-20]. The safety of radiofrequency-assisted liver resection is still questioned. Perioperative outcomes after radiofrequency-assisted hepatectomy for HCC in patients with cirrhosis also remain unclear. Here, the efficiency and safety of radiofrequency-assisted hepatectomy were retrospectively assessed in HCC patients with cirrhosis.

MATERIALS AND METHODS

Patients
From January 2010 to December 2013, a total of 179 HCC patients with cirrhosis underwent liver resection. Of these cases, 100 patients received radiofrequency-assisted liver resection (RF+ group), and 79 patients had hepatectomy without ablation (RF- group).

The following inclusion criteria were used: (1) consistency with HCC diagnostic criteria issued by the EASL-EORTC Clinical Practice Guidelines[21]; (2) diagnosis of HCC based on cythological evidence collected from liver biopsy specimens and cirrhosis was confirmed in histological examination of non-tumor liver tissue; (3) hepatic function of Child-Pugh class A or B; (4) resectable liver lesion or lesions with adequate (R0) margins; (5) adequate remaining functional liver parenchyma; and (6) no operative
Operative technique

Three expert surgeons with more than 10 years of hepatectomy experience performed the operations. They used the same hepatectomy procedure that they had all agreed upon before the operation to minimize the influence of procedure on outcome. Surgeries were performed under general anesthesia with low central venous pressure (CVP) (0-5 mmHg). The liver was mobilized by division of all the hepatic ligaments. Ultrasonography and intraoperative bimanual liver palpation were then performed to confirm tumor size, location, and adjacent structures.

A HabibTM 4X bipolar radiofrequency device (Generator 1500X, RITA Medical Systems, Inc. CA, United States) was used to deploy the radiofrequency therapy during operation in the RF+ group. These RF-assisted liver resections were performed in three steps. In step 1, the resection was delineated 2 cm from the tumor using an electrosurgical knife. In step 2, the device was introduced into the liver perpendicularly, abutting the transection line for continuous coagulative desiccation and to create a zone of desiccation within the liver parenchyma. Each round of ablation took 1-2 min. The time and duration of radiofrequency ablation were recorded in detail. In step 3, the liver was transected along the necrotic zone with a scalpel. Bleeding from the separated small vessels was stopped using a bipolar device. The Pringle maneuver was not used in the RF+ group.

In the RF- group, parenchyma transection was crushed using a clamp. The Pringle maneuver (15 min clamping and 5 min release) was used to achieve inflow occlusion.

Clips, ligatures, and sutures were used selectively during parenchymal transection with both techniques to ensure hemostasis of the cut surface. Fibrin glue and a thrombin-soaked gelatin foam sheet were used to stop any oozing blood. Drains were placed on the cut surface. During wound closure, layers were matched as closely as possible.

Major hepatectomy was defined as a liver resection of more than 2 segments. The total blood loss including suction volume was estimated after subtraction of rinse fluids. Hemoglobin level < 7 g/dL within 48 h of surgery was the indication for transfusion. Total operative time was recorded from the start of anesthesia to completion of abdominal closure. Radiofrequency-assisted time was the sum of the durations of all radiofrequency ablation procedures. Parenchymal transection time was here defined from the beginning of parenchymal transection to the end. ALT, AST, TBIL, and PT were recorded regularly on POD 1, 3, and 5 to monitor changes in postoperative liver function. If the liver function showed a deteriorating trend, the monitoring continued. Post-hepatectomy liver failure (PHLF) was evaluated based on the 50-50 criteria that were defined as the concomitant presence of prothrombin (PT) < 50% and serum bilirubin > 50 mmol/L on POD 5[22].

Statistical analysis

Continuous data are expressed as either mean with standard deviation or median with range depending on the data distribution. The groups were compared using the t test and Mann-Whitney test for continuous variables and the χ² test and Fisher’s exact test for proportions. P < 0.05 was considered significant. Statistical analyses were performed with SPSS (Version 18.0; SPSS, Chicago, IL, United States).

RESULTS

Patients and hepatectomy characteristics

There were no significant differences between the two groups with respect to age, gender, cause of cirrhosis, preoperative liver function (Child-Pugh class, ICG R-15%, Meld score), tumor size, or other parameters (Table 1). A total of 70 (70.0%) minor and 30 (30.0%) major hepatectomies were performed in the RF+ group, and 49 (62.1%) minor and 30 (37.9%) major hepatectomies were performed in the RF- group. There were no statistically significant differences between the two groups.

Intraoperative variables

There was significantly less median intraoperative blood loss in the RF+ group (300 mL vs 400 mL, P = 0.01). Patients in the RF+ group required fewer blood
transfusions than those in the RF- group, though the difference was not statistically significant (17.0% vs 24.1%, P = 0.24) (Table 2). Although the median duration of the parenchymal transection for the RF+ group was shorter than that for the RF- group (30 min vs 54 min, P = 0.03), there was no significant difference between the two groups in the total operation time (230.5 ± 77.93 vs 245.58 ± 75.48 min, P = 0.19). The median radiofrequency-assisted time was 15 min in the RF+ group, but it was not performed in RF- groups (P = 0.00). The Pringle maneuver was only used in the RF- group, and the median duration of portal triad clamping was 15 min (P = 0.00).

Postoperative liver function and complications
In the monitoring of postoperative liver function, on POD 1 and 5, the median ALT was significantly higher in the RF+ group than in the RF- group (POD 1: 348.5 vs 245.5, P = 0.01; POD 5: 112 vs 82.5, P = 0.00), but there was no significant difference on POD 3 (260 vs 220, P = 0.24). The median AST was significantly higher in the RF+ group on POD 1 (446 vs 268, P = 0.00), but there was no significant difference between the two groups on POD 3 and 5 (POD 3: 129.5 vs 125, P = 0.65; POD 5: 52.5 vs 50, P = 0.10). The median total bilirubin and PT showed no significant difference between the two groups on POD 3 and 5 (POD 3: 129.5 vs 125, P = 0.19; POD 5: 52.5 vs 50, P = 0.04). Six patients developed PHLF, as indicated by monitoring biochemical liver function testing. Three patients had recovered liver function after administration of albumin, daily diuretics, and fresh frozen plasma and noninvasive ventilation. However, the others died of unreversed hepatic insufficiency. The first patient showed ALT = 1532 U/L, AST = 6707 U/L, TBIL = 6.95 mg/mL, and PT-INR = 0.03 on day 3 after the surgery. This patient’s liver function subsequently deteriorated further, leading to death. The remaining two patients showed severe postoperative infections, one on day 6 and the other on day 10 after surgery. In both cases, the condition eventually led to liver failure.

Table 1 Patients and hepatectomy characteristics n (%)

| Variable                        | RF(-) group (n = 79) | RF(+) group (n = 100) | P value |
|--------------------------------|----------------------|-----------------------|---------|
| Age (yr)                       | 50.27 ± 8.30         | 47.77 ± 8.96          | 0.06    |
| Gender (male: female)          | 71.8                 | 84.16                 | 0.25    |
| Cause of cirrhosis             | 0.92                 |                       |         |
| Hepatitis B                    | 70 (88.6)            | 90 (90.0)             |         |
| Hepatitis C                    | 3 (3.8)              | 4 (4.0)               |         |
| Alcohol abuse                  | 0                    | 1 (1.0)               |         |
| Unknown                        | 6 (7.6)              | 5 (5.0)               | 0.79    |
| Child-Pugh class               |                      |                       |         |
| A                              | 76 (96.2)            | 98 (98.0)             |         |
| B                              | 3 (3.8)              | 2 (2.0)               |         |
| ICG R-15%                      | 5 (1.5-20.5)         | 4.2 (0.2-17.3)        | 0.16    |
| TBIL (mg/dL)                   | 0.99 (0.35-5.14)     | 0.94 (0.29-4.3)       | 0.26    |
| ALT (U/L)                      | 39 (11-227)          | 35 (14-212)           | 0.83    |
| PT-INR                         | 1.07 ± 0.09          | 1.06 ± 0.08           | 0.45    |
| Platelets (× 10³/L)            | 69.2 ± 17.2          | 72.3 ± 23.4           | 0.37    |
| MELD Score                     | 4.8 ± 2.37           | 4.12 ± 2.41           | 0.06    |
| Dimensions of tumor (cm)       |                      |                       | 0.62    |
| ≤ 5                            | 13 (16.5)            | 19 (19.0)             |         |
| > 5 and ≤ 10                   | 57 (72.2)            | 71 (71.0)             |         |
| > 10                           | 9 (11.3)             | 10 (10.0)             |         |
| Number of tumors               |                      |                       | 0.19    |
| Single                         | 69 (87.3)            | 80 (80.0)             |         |
| Multiple                       | 10 (12.7)            | 20 (20.0)             |         |
| Type of resection              |                      |                       | 0.26    |
| Minor resection                | 49 (62.1)            | 70 (70.0)             |         |
| Major resection                | 30 (37.9)            | 30 (30.0)             |         |

Table 2 Intraoperative variables

| Variable                        | RF(-) group (n = 79) | RF(+) group (n = 100) | P value |
|--------------------------------|----------------------|-----------------------|---------|
| Blood loss (mL)                 | 400 (50-1500)        | 300 (100-1400)        | 0.01    |
| Transfusion requirement, n (%)  | 19 (24.1)            | 19 (17.0)             | 0.24    |
| Total operative time (min)      | 245.58 ± 75.48       | 230.5 ± 77.93         | 0.19    |
| Parenchymal transection time (min) | 54 (15-130)       | 30 (10-108)           | 0.03    |
| Radiofrequency-assisted time (min) | 0                   | 15 (5-60)             | 0.00    |
| Pringle clamping time (min)     | 15 (0-97)            | 0                     | 0.00    |

1Non-normally distributed data analyzed with the Mann-Whitney test.

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and death. No patients died in the RF- group. The 30-d mortality and hospital stays showed no statistically significant differences between the two groups.

**DISCUSSION**

Radiofrequency ablation is currently one of the most commonly used technologies in the clinical treatment of HCC. Its efficacy in the treatment of small HCC is comparable to that of surgical resection. Radiofrequency ablation can not only resect the tumor itself but is also effective in sealing vessels and bile ducts, which can facilitate nearly bloodless liver resection. The use of RFA devices to perform liver resection was described in 2002 by Weber et al. Later, a bipolar, handheld disposable RFA device (HabibTM 4x) was developed especially for liver resection. Then a series of studies by different groups confirmed the benefits of radiofrequency-assisted hepatectomy in reducing blood loss. Recently, this technique has been recommended for patients with cirrhosis by Curro et al. because it is believed to be safe and effective. A randomized clinical trial (RCT) comparing radiofrequency-assisted parenchyma transection (RF-PT) to clamp-crushing parenchyma transection (CC-PT) showed RF-PT to be the superior procedure in HCC with cirrhosis due to the lower amount of blood loss and mobility. However, a few controversial studies maintain that this technique is not completely safe in patients with poor hepatic function reserve or liver cirrhosis. Mitsuo asserts that RF-assisted hepatectomy may be problematic for patients with poor hepatic function. A RCT comparing RF-PT to traditional CC-PT revealed there to be no priority for RF-PT due to its higher rate of postoperative complications.

The results of the current work demonstrated that there was less blood loss in the RF+ group than in the RF- group (300 mL vs 400 mL). Patients in the RF+ group required fewer blood transfusions (17.0% vs 24.1%), because small vessels in the section line that would ordinarily bleed in conventional hepatectomy were cauterized with RF waves and did not bleed during the liver resection. As in other works, RF-assisted liver resection was found to reduce the amount of intraoperative blood loss and the number of intraoperative blood transfusion procedures required effectively.

ALT and AST levels were measured on postoperative days to assess the extent of hepatocellular damage to the remaining liver. They were significantly higher in the RF+ group than in the RF- group on POD 1, and ALT levels were significantly higher on day 5. On day 3, they did not differ significantly between the two groups. This may be because, in the presence of cirrhosis, liver function reserve is very low, and liver resection can damage the liver further. On POD 1, the RF+ group showed severely compromised liver function. This was because radiofrequency cauterization affected the remaining liver tissues, which caused rapid necrosis of many liver cells and a sharp rise in ALT and AST, which were higher than those in the RF- group. In the RF- group, the damaged liver cells suffered progressive necrosis on day 3. This caused an increase in transient ALT and AST, and their levels became similar to those of the RF+ group. The two groups did not differ significantly. On day 5, during the recovery of liver function, the two groups differed significantly in ALT. This suggested that thermal damage to the residual cirrhotic liver tissues lasted a long time in the RF+ group. This was consistent with the results of other reports. In Mitsuo’s work, the RF waves caused ALT to increase to over 1000 on the first postoperative day in three patients with both HCC and liver cirrhosis. In a study by Chen et al., the RF-assisted liver resection group showed significantly higher serum AST levels than the CUSA group. Other studies have suggested that radiofrequency-assisted hepatectomy without inflow occlusion can prevent ischemia-reperfusion injury of the remnant of the cirrhotic liver and cause only minor liver injury. However, the results of the present study indicate that, during liver resection in patients with cirrhosis, radiofrequency ablation involves more damage to the liver function than the Pringle maneuver. It is here asserted that radiofrequency-assisted hepatectomy produces substantial damage to postoperative liver function in patients with cirrhosis, and should be used with caution.

In PHLF, marked elevations of ALT and AST are signs that the RF waves have destroyed some cells in the remaining liver, and they also suggest decreased liver reserve capacity. This is associated with an increased risk of failure. However, due to the surgical learning curve, each round of radiofrequency of cirrhotic liver tissue took 1-2 min in our center. In contrast, in Habib surgery, each round of treatment lasts less than 1 minute in normal liver. The more time required for radiofrequency, the more severe the postoperative injury to the remaining liver tissue, leading to postoperative liver failure.

There is another issue associated with this procedure: PHLF due to necrotic remnant tissue on the surface of the resected area. This necrotic tissue might facilitate the growth of microbes and lead to infection. Two patients experienced severe postoperative infections, one on day 6 and the other on day 10; both cases ultimately led to liver failure and death. These two patients did not show signs of infection early after surgery, but later both showed fever, increased blood cell counts, and elevated transaminase and bilirubin (one on day 6 and the other on day 10). Upper abdominal CT revealed diffuse patchy and spotty necrosis in liver section and liver tissues. This might be because the tissues subjected to coagulative necrosis remaining on the liver sections are prone to infection, resulting in acute inflammation of remnant liver tissues, which then leads to damage and necrosis.

The present study has several limitations. Although
the results suggest that patients with cirrhosis in the RF+ group sustained severe liver damage and had a relatively high incidence of liver failure, they were not graded for severity of cirrhosis, which would have facilitated systematic assessment of the effect of liver cirrhosis on the outcome. This may be suitable for further study.

In this paper, although possible factors that may lead to liver failure are discussed, no statistical analysis was performed on preoperative or intraoperative factors that could affect the occurrence of complications among patients who underwent RFA. Factors that contribute to liver failure merit particular attention.

In conclusion, radiofrequency-assisted hepatectomy can reduce intraoperative blood loss during liver resection effectively. However, it should be used with caution in patients with cirrhosis because it may cause severe liver damage and liver failure in these patients.

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