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Original Article

Microwave-assisted liver resection is safe and effective for selecting patients with BCLC stage B hepatocellular carcinoma

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Abstract: This study aimed to evaluate the feasibility and effectiveness of microwave ablation-assisted liver resection (MW-LR) and clamp-crush liver resection (CC-LR) in Barcelona clinic liver cancer stage B (BCLC-B) hepatocellular carcinoma (HCC). From January 2006 to July 2014, a total of 202 BCLC-B HCC patients who received CC-LR (n=110) or MW-LR (n=92) were retrospectively analyzed. We compared the morbidity, mortality, disease-free survival time, and overall survival time between the CC-LR and MW-LR groups. The 30-day mortality (2.7% vs. 2.2%) and postoperative complication rate (20.9% vs. 22.8%) were both similar in the CC-LR and MW-LR groups, respectively. However, MW-LR provided a survival benefit over CC-LR at one, three, and five years (89.1% vs. 79.2%, 68.2% vs. 49.7%, and 45.8% vs. 30.5%, respectively; P=0.023), as well as disease-free survival benefits at the same period (80.8% vs. 62.2%, 60.0% vs. 42.2%, and 36.4% vs. 25.3%, respectively; P=0.002). Multivariate analysis showed that blood loss (HR=1.832, 95% CI 1.428-2.256, P<0.001) and treatment method (HR=1.733, 95% CI 1.312-2.154, P<0.001) were predictors of overall survival for BCLC-B HCC. MW-LR is a safe and feasible procedure for BCLC-B HCC patients with Child-Pugh liver function grade of A.

Keywords: Hepatocellular carcinoma, microwave ablation, postoperative complication, liver resection, overall survival

Introduction

Hepatocellular carcinoma (HCC) is the sixth most commonly occurring cancer and the third most common cause of death by cancer worldwide [1]. The treatment and prognosis of patients with HCC are related with multiple factors, including tumor burden, functional liver function status, and patients' health status [2]. The Barcelona clinic liver cancer (BCLC) staging system, one of the most acceptable systems for HCC staging system, has taken into account these three variables; this system is also recommended to guide the treatment of HCC in clinics [3, 4].

In BCLC staging system, liver resection (LR) is recommended for BCLC stage A (BCLC-A) HCC (single nodule with diameter <5 cm, or 2-3 mass with diameter <3 cm, no extrahepatic metastasis, no main vascular invasion) [4]. Transarterial chemoembolization (TACE) is recommended for BCLC stage B (BCLC-B) or C (BCLC-C) HCC (single nodule with diameter >5 cm, or 2-3 mass with diameter >3 cm, or >3 mass with any diameter, no extrahepatic metastasis, with or without vascular invasion) [3]. However, treating BCLC-B HCC with LR has attracted controversies [5, 6]. LR is optional and more effective than TACE in treating BCLC-B HCC patients with sufficient liver reservoirs. LR is also effective for large nodular HCC with diameter >5 cm [7]. By contrast, other studies showed that LR for large HCC is dangerous and can result in mortality and serious complication [8].

LR, although considered the curative method for treating HCC, is associated with high recurrence rates [9-11]. Tumor recurrence in HCC is related to vascular invasion, multicentric carci-

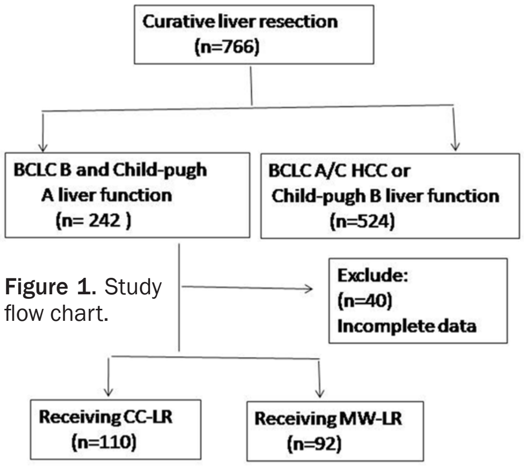

Figure 1. Study flow chart.

nogenesis, and tumor biology [9, 11]. The traditional LR is clamp-crush LR (CC-LR) that is commonly performed using Pringle procedures. CUSA, bipolar diathermy, stapler, and LigaSure are used in assisting LR [2, 12, 13]. Nevertheless, an ideal LR with minimal blood loss, negative resected margin, minimal complication, and without Pringle procedures does not exist.

LR using heat coagulative necrosis through microwave (MW) energy or radiofrequency (RF) energy has been widely adopted worldwide. Nevertheless, this method has not been recognized as a primary standard treatment for HCC [14-19]. For BCLC-B HCC, MW ablation could be used for local ablation of two or more mass with diameter less than 3 cm or assisted LR for large mass [15, 16]. In the past 10 years, MW-assisted LR (MW-LR) was performed in some cases of BCLC-B HCC with Child-Pugh liver function A in our unit. This technique results in minimal blood loss and R0 resection margin that favor survival.

In the present study, we retrospectively analyzed the feasibility and effectiveness of MW-LR and CC-LR for BCLC-B HCC, with emphasis on OS and DFS.

Materials and methods

Ethics statement

Written informed consent for data collection and use of devices was obtained from all patients. Patients were well informed of the risks, benefits, and alternatives to hepatic resection. The study protocol followed the ethical guidelines of the 1975 Declaration of Helsinki (as revised in Brazil in 2013). All procedures were approved by the Ethical Committee of Renmin Hospital of Wuhan University.

Patients

From January 2006 to September 2014, a total of 766 HCC patients underwent curative LR at the Hepatobiliary Department of Renmin Hospital of Wuhan University. This population consisted of 500 patients with BCLC-A HCC, 242 patients with BCLC-B HCC, and 24 patients with BCLC-C HCC. Of these patients, only patients with BCLC-B HCC and Child-Pugh A liver function were included in the retrospective analysis (**Figure 1**). Furthermore, we excluded patients who received noncurative LR or only local ablation or incomplete follow-up data. The remaining patients were treated with either CC-LR or MW-ALR. All patients carefully underwent preoperative assessment of their conditions through spiral computed tomography, magnetic resonance imaging, and/or positron emission tomography. Preoperative discussions were conducted for all cases. HCC diagnosis was confirmed after LR by histopathological examination of surgical sample in all patients. We retrospectively analyzed prospectively collected data, which included demographic details, nature and number of tumors, surgical procedures, intraoperative data, postoperative complications, 30-day hospital mortality rates, DFS periods, and overall survival (OS) rates. The criteria for inclusion of operation were as follows: curative intention of resection, without extrahepatic metastasis, Child-Pugh liver function A, and BCLC-B HCC.

Surgical procedure

Surgical procedure was performed in BCLC-B HCC patients with Child-Pugh liver function A. Adequate remnant liver volume, as determined by CT or MRI, was >30% for HCC patients without cirrhosis and >50% for HCC patients with cirrhosis or severe fatty liver. Patients who satisfied the indication for LR received CC-LR, unless the patients requested MW-LR.

CC-LR was performed following the technique described by Zhou [12]. In brief, a modified right or bilateral subcostal incision was performed under general anesthesia. The peritoneal cavity was examined, and an intraopera-

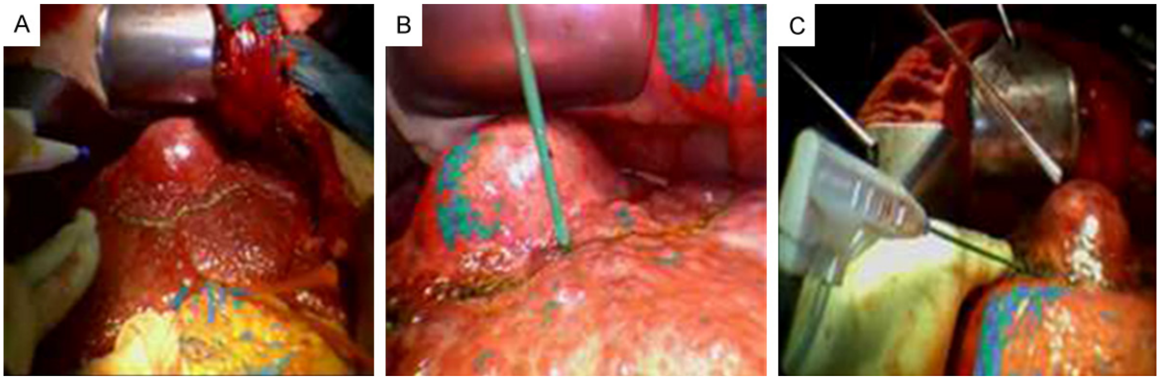

Figure 2. Microwave assisted liver resection procedure. A. The intended line marked 2 cm away from edge of tumor on the liver capsule. B. Ablation produced with microwave probe along intended line before parenchyma transection. C. Additional ablation for deep resection margin.

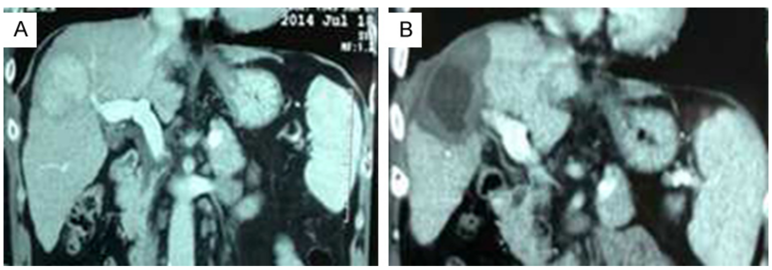

Figure 3. A. Contrast CT scan shown tumor in right liver preoperatively. B. A contrast CT scan shown necrotic area in resection margin of liver parenchyma 1 year postoperatively.

tive ultrasound was performed to reveal any previously undetected lesion. The liver was then mobilized based on the size and sites of lesions. Pringle maneuver was carried out each time for 15 min with five-minute interval. The resection margin was more than 1 cm.

MW-LR was performed following the technique similar to that of Harbib's (**Figure 2A-C**) [14]. In brief, the liver was mobilized as performed in CC-LR procedure, and an intended resection line was marked 2 cm away from the tumor edge on the liver capsule with diathermy. Subsequently, coagulated necrosis was induced along the intended resection line using the MW probe and a 2450 MHZ MW generator (ECO Microwave System Co., Ltd, Nanjing, China). The probe contained 15-cm needle electrodes and two coaxial cannulas through which chilled water was circulated during ablation to prevent tissue carbonization. After complete ablation, the coagulated tissues of the liver overlapped and formed a whole coagulated zone surrounding the tumor. The coagulated liver tissue was easily removed through gentle crushing by forceps or clamp, and the vessels were subsequently separately dissected and ligated. Finally, liver parenchymal transection was completed with a gentle crushing transection along the intended line. The method left a 1-cm size coagulative tissue around the tumor sample and a 1-cm coagulative zone along the LR margin (**Figure 3A**, **3B**). A drain was also placed at the site of resection.

Postoperative complications were graded according to the Clavin-Dindo classification, and complications with grade 2 or above were analyzed [20]. Biliary leakage was defined as either biliary drainage after five-day post-operation or biliary collection confirmed by percutaneous drainage.

Follow-up examinations

Follow-up examinations consisted of ultrasonography and/or helical CT of the liver and serial check-up of AFP levels one month after surgery and then every three months in the first two years and every six months thereafter. Diagnosis of tumor recurrence and distant metastasis were based on cytohistology or non-invasive diagnostic criteria for HCC used by European association for the study of liver. All recurrence and metastasis were evaluated for new treatment. Patients with recurrence were treated with LR, RF or MW ablation, TACE, and

Table 1. Comparison of clinicopathologic features between MW-LR and CC-LR groups

	CC-LR (N=110)	MW-LR (N=92)	*P*
Gender (M/F), n	88/22	77/15	0.342
Age (Yr)	52.1±12.8	53.4±14.7	0.241
Tumor size, cm	8.9±4.0	8.2±3.5	0.231
Cirrhosis (Yes/no), n	68/42	57/35	0-762
Tumor number, n			0.133
Uninodular	72	67	
Multinodular	38	25	
Etiology, n			0.235
HBV	90	80	
HCV	20	12	
Albumin (g/L)	39±5.1	38±4.3	0.254
Alpha fetoprotein			0.134
>400 ng/mL	67	52	
<400 ng/mL	37	40	
Platelet (10^9/L)	193.4±73.3	154.6±63.6	0.422
Edmondson grade, n			0.342
I-II	63	52	
III-IV	47	40	
Alamine aminotransferase (U/L)	56.2±36.6	62.5±51.3	0.393
Total bilirubin (μmol/L)	13.5±6.7	14.2±8.2	0.233
Prothrombin time, s	13.1±2.2	14.3±2.7	0.765

Values with "±" are written as mean ± SD. HBV, Hepatitis B Virus; HCV, Hepatitis C virus.

Table 2. Comparison of operative variable and postoperative outcome between MW-LR and CC-LR group

	CC-LR (N=110)	MW-LR (N=92)	*P*
Blood loss, mL	850±1100.2	320±330.6	<0.001
Blood transfusion, n	56	21	<0.001
Operative time, min	258±85.0	270±96.2	0.342
Pringle manoeuvre	110	23	
Pringle time, min			
Complications*			0.542
Class II	9	10	0.342
Class III	8	7	0.435
Class IV-V	6	4	0.129
Abdominal abscess	3	8	0.032
Bile leakage	3	6	0.024
Surgical wound infection	5	2	0.102
Pleural effusion	3	3	0.768
Uncontrolled ascites	3	3	0.563
Postoperative bleeding	3	3	0.654
30-Day mortality, No	3	2	0.267

*Postoperative complications were graded as according to the Clavin-Dindo classification. Values with "±" are written as mean ± SD.

chemotherapy. Therapy was decided based on the number and location of tumor, hepatic function, general health, and economical status.

Study objective

The total survival time was the primary objective of this study. Survival time was defined as the time between the date of surgery and the date of death. Patients who were alive at the end of follow-up were censored. The second objective of the study was the DFS time, which was defined as the time between the date of surgery and the date of recurrence.

Statistical analysis

Continuous variables were expressed as mean ± SD and compared using Student's *t*-test. Categorical variables were compared using χ^2, Fisher's exact, and Mann-Whitney U tests, as deemed appropriate. All statistical tests were two-sided, and a difference was considered statistically significant when $P<0.05$. Significant factors obtained using univariate analysis were subjected to multivariate Cox regression analysis to determine hazard ratios. OS and DFS rates were calculated using the Kaplan-Meier method. Statistical analyses were performed using SPSS 19.0 statistical software for Windows (SPSS, Chicago, IL, USA).

Results

Study population

During the study period, a total of 766 consecutive patients with HCC underwent curative LR and were enrolled in the database. Of these, 242 patients exhibited BCLC-B HCC with Child-Pugh liver function grade A. We excluded 25 patients (10.3%) who received local ablation or noncurative resection and 15 other patients (6.2%) because of incomplete data. The remaining 240 pati-

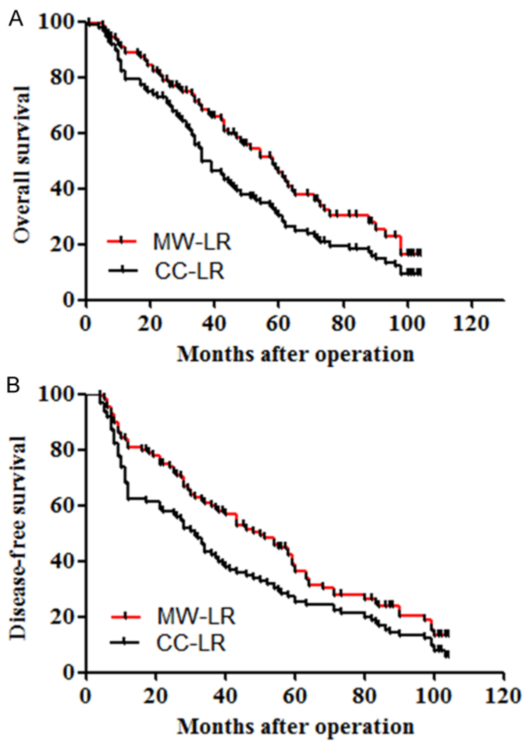

Figure 4. Overall survival and disease-free survival curves of patients in MW-LR and CC-LR groups. A. MW-LR provided a survival benefit over CC-LR at 1, 3, and 5 years (89.1% vs. 79.2%, 68.2% vs. 49.7%, and 45.8% vs. 30.5%, respectively; P=0.023). B. MW-LR provided a disease-free survival benefit over CC-LR at 1, 3, and 5 years (80.8% vs. 62.2%, 60.0% vs. 42.2%, and 36.4% vs. 25.3%, respectively; P=0.002).

ents (91.6%) were enrolled in this study, among which 110 (45.5%) received CC-LR, and 92 (38.0%) received MW-LR (**Figure 1**).

Clinicopathological data

Demographics and clinicopathological data of the 202 HCC patients are listed in **Table 1**. All clinical characteristics were similar between the two groups at baseline (**Table 1**). Age, gender composition, tumor number, tumor size, tumor etiology, prothrombin time, Edmondson grade, total bilirubin, and the level of AFP, albumin, and alamine aminotransferase showed no significant differences.

Mortality and morbidity

The 30-day mortality (2.7% vs. 2.2%) and postoperative complication rate (20.9% vs. 22.8%) were both similar in the CC-LR and MW-LR (2.2%) groups, respectively (**Table 2**). However, the abdominal abscess rate was higher in MW-LR group (8.7%) than that in CC-LR group (2.7%, P=0.002). The biliary fistula rate was also higher in MW-LR group (6.5%) than in CC-LR group (2.7%, P=0.024). The blood loss volume was significantly higher in CC-LR group (mean 320 ml) than in MW-LR group (mean 850 ml, P<0.001). The Pringle maneuver was also significantly less used in the MW-LR group (25%) than in the CC-LR group (100%, P<0.001). Blood transfusion was also significantly less in the MW-LR group (22.8%) than in the CC-LR group (50.9%, P<0.001).

OS analysis

The OS rate was significantly better in the MW-LR group than that in the CC-LR group (**Figure 4A**). The one-, three-, and five-year OS rates of patients in the MW-LR group were 89.1%, 68.2%, and 45.8%, and the corresponding rates in the CC-LR group were 79.2%, 49.7%, and 30.5%, respectively (P=0.023). The median survival time was 49.9 and 36.0 months in the MW-LR and CC-LR groups, respectively.

DFS time

The DFS rate was significantly better in the MW-LR group than in the CC-LR group (**Figure 4B**). The one-, three-, and five-year DFS rates of patients in the MW-LR group were 80.8%, 60.0%, and 36.4%, and the corresponding rates in the CC-LR group were 62.2%, 42.2%, and 25.3% (P=0.002), respectively.

Cox model

Several factors link to OS were considered in the survival analysis (**Table 3**). Univariate analysis showed that tumor size, serum AFP level (>400 μg/ml), blood loss, Edmondson grade, and treatment method (MW-LR) were predictors of OS in total study population. Multivariate analysis showed that blood loss (HR=1.832, 95% CI 1.428-2.256, P<0.001) and treatment method (HR=1.733, 95% CI 1.312-2.154, P< 0.001) were predictors of OS (**Table 3**).

Discussion

On the basis of the guidelines of American Association for the Study of Liver Disease [21] and European Association for the Study of Liver [22], LR is recommended for patients with

Table 3. Prognostic factor related to survival determined by univariate and multivariate analysis using the cox proportional hazard model

	Hazard ratio	95% CI	*P*
Univariate			
Age	0.863	0.981-1.123	0.324
Gender	1.328	0.786-2.086	0.426
Tumor size	1.123	1.092-1.152	0.003
Tumor number	0.789	0.578-1.184	0.356
AFP	1.524	1.076-1.925	0.007
PT	1.056	0.926-1.168	0.425
Treatment method	1.672	1.318-2.023	<0.001
Blood loss	1.725	1.325-2.012	<0.001
Edmondson grade	1.125	0.972-1.198	0.033
Blood transfusion (yes/no)	3/17	2/48	0.109
Gentle crushing (yes/no)	8/16	36/12	0.256
Multivariate			
Tumor size	1.086	0.956-1.158	0.356
AFP	1.026	0.987-1.102	0.245
Blood loss	1.832	1.428-2.256	<0.001
Treatment method	1.733	1.312-2.154	<0.001

AFP: alpha fetoprotein. PT, prothrombin time.

BCLC-A HCC, and TACE is recommended for BCLC-B/C HCC. Recently, LR is also recommended effective for BCLC-B/C HCC if the patients present sufficient residual liver volume and liver function, irrespective of tumor size [23-25]. The present study showed that the one-, three-, and five-year OS rates of patients in the MW-LR group were 89.1%, 68.2%, and 45.8%, and the corresponding rates in the CC-LR group were 79.2%, 49.7%, and 30.5%, respectively. Our results was consistent with those of other studies, where the three- and five-year OS rates of LR for BCLC-B/C HCC patients were in the range 50%-71% and 39%-57%, respectively [26-28].

Although LR is effective for BCLC-B HCC, the mortality and morbidity are remarkable postoperatively. In this study, BCLC-B HCC patients presented a mortality of 3.1% and 2.1% and morbidity of 21.8% and 28.7% in CC-LR and in MW-LR groups, respectively. Our mortality and morbidity were compared with those of other studies, where morbidity and mortality rates varied in the range of 10.9%-42% and 0%-8%, respectively [7, 29, 30].

Blood transfusion and inflow vascular clamping are risk factors for postoperative liver insufficiency with subsequent high morbidity and mortality rates [10, 31, 32]. Moreover, intraoperative blood loss affects long-term survival in HCC [10, 31]. Thus, a LR method with minimal blood loss without any form of inflow vascular occlusion or dissection of the hepatic pedicle would considerably increase the survival of HCC patients. In this study, less blood loss, transfusion number, and Pringle number were observed in MW-LR group than those in CC-LR group (P<0.05). Our results were consistent with those of other reports about precoagulated LR using RF or MW energy [14-19]. Pai et al. reported about RF-assisted LRs with a mean blood loss of 305 ml in 384 consecutive LRs [17]. Sasaki et al. reported that they used a MW tissue coagulator to perform LR and obtained a mean blood loss of 250 ml in 1118 cases of HCC [15]. Therefore, MW-assisted LR with minimal blood loss is a safe procedure for HCC patients with BCLC type B disease.

Postoperative bile complications remain controversial in the performance of precoagulated LR [15, 17-19]. The rate of bile leakage varies from 4.1% to 16% in some studies [15, 17-19]. Another issue associated with coagulated-assisted LR is the complication caused by infection. The rate of infected abdominal collections varies from 1.8% to 16.9% [15, 17-19]. In our study, the rate of biliary leakage was 5.5%, and the rate of abdominal abscess was 5.5%. Each vessel across transection plane was separately exposed and ligated because the coagulated liver tissue was fragile and can be easily removed through gentle crushing by forceps or clamp. Our gentle crushing method was different from other precoagulated LR methods utilizing MW energy or RF energy, where the transection of liver parenchyma involves cutting with a scalpel after precoagulation but without ligation of the vessels across the coagulated plane [14, 15, 17-19]. The coagulated biliary branch, if without ligation, may reopen postoperatively and cause biliary fistula, which will significantly increase the chances of abscess leakage originating from the necrotic liver tissue.

The causes of recurrence of HCC after LR are related to micrometastasis through portal system and/or multicentric carcinogenesis, especially in the patients with hepatitis background [2, 9, 11, 13, 33, 34]. The width of surgical margin in HCC is controversial [2, 9, 11, 13, 33, 34]. Poon et al. [34] found that both wide and narrow-resection margin groups in HCC exhibit similar recurrence rates occurring in the liver remnant at a distal segment or multiple segments. Most of the recurrences occur within one year after hepatectomy in both groups, thereby suggesting that most recurrences are probably caused by intrahepatic metastasis. However, Shi et al. [33] discovered that a wide resection margin (2 cm) significantly decreases postoperative recurrence rates and improves survival outcomes more than that of narrow resection margin (1 cm). They also reported that a tumor resection margin of 1 cm removes majority of the micrometastasis when the tumor diameter is approximately 3 cm.

In this study, MW-LR provided a survival (89.1% vs. 79.2%, 68.2% vs. 49.7%, and 45.8% vs. 30.5%, respectively; P=0.023) and DFS (80.8% vs. 62.2%, 60.0% vs. 42.2%, and 36.4% vs. 25.3%, respectively; P=0.002) benefits over CC-LR at one, three, and five years. Our results were consistent with those of Sasaki et al. that used MW-LC in a study of 1,118 HCC patients; they found that one-, three-, and five-year recurrence-free survival rates are 84%, 56%, and 40%, and the 3-, 5-, and 10-year OS rates are 88%, 78%, and 49%, respectively [15]. Several reasons account for the differences of survival between CC-LR and MW-LR. First, multiple studies have shown that blood loss and blood transfusion are significantly related to tumor recurrence and OS of HCC patients [9-11, 31]. Hence, MW-LR can decrease the recurrence rate of HCC because of minimal intraoperative blood loss. Second, in CC-LR group, rotating, lifting, and stretching of liver parenchyma around the tumor increase the chances of developing distant metastasis of tumor through portal system [2, 13]. In addition, MW-LR needs no complete liver mobilization and Pringle maneuver. Consequently, MW-LR is considerably in accordance with the no-touch principle of oncologic surgery than CC-LR. Finally, positive resection margin accounts for some recurrences of HCC, especially when tumor is adjacent to the large branch of the hepatic vascular system [2, 13]. As shown in postoperative CT scan (**Figure 3B**), MW-LR produced a 1 cm necrotic area at the resection margin after transection of liver parenchyma. Consequently, the rate of positive surgical margin in HCC decreased.

Some limitations of this study must also be addressed. First, this study was retrospectively designed and probably with selection bias. In the future, multicentric, randomized, and controlled clinical studies with long follow-up periods should be carried out to prove the feasibility of using MW-LR for HCC. Second, this technique was primitive and time consuming because it required a series of applications to achieve a zone of coagulated necrosis along the intended line of transection. The probe was a needle electrode, which when inserted into the vessels, might cause bleeding. We expect further improvement of this method in the future.

Conclusions

Our data showed that MW-LR was a safe and feasible procedure for BCLC-B HCC. We believe that further technical advances will improve the safety and rate of this technique for LR.

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Disclosure of conflict of interest

None.

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