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Original Article

Clinical outcomes of four liver parenchymal transection techniques for hepatocellular carcinoma: a single institution's experience

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Abstract: Background: To evaluate the safety, efficacy and long-term outcomes of the different techniques of parenchymal transection during liver resections. Methods: We analyze the clinical data of 681 HCC patients who received surgical treatment in West China Hospital from June 2008 to February 2010. Among these patients, 115 cases underwent radical hepatic resection using the Clamp-crush technique, 137 cases using the Water-jet dissection, 249 cases using the Cavitron Ultrasonic Surgical Aspirator (CUSA) and 180 cases using the Harmonic Scalpel. The clinical data including intraoperative parameters, postoperative complications, perioperative morbidity and mortality, hospital stay were collected and analyzed. The overall survival (OS) and recurrence-free survival (RFS) were analyzed using the Kaplan-Meier method and compared the groups via the log-rank test. Results: Clamp-crush group has a minimum of operation time (P=0.001), lowest intraoperative estimate blood loss volume (P=0.045) and shortest length of hospitalization (P=0.004). The 1-, 3-, and 5-year overall survival (OS) rates exhibits no significant difference in clamp-crushing group (70.4%, 53.3% and 43.4%), Harmonic scalpel group (79.8%, 59.9% and 41.9%), Water-jet group (77.2%, 57.3% and 37.8%) and CUSA group (81.5%, 51.9% and 38.5%). The 1-, 3-, and 5-year recurrence-free survival (RFS) rates also exerts no significant difference in Clamp-crushing group (68.9%, 34.6% and 20.7%), Harmonic scalpel group (67.1%, 44.3% and 25.8%), Water-jet group (69.4%, 45.1% and 18.1%) and CUSA group (65.6%, 31.8% and 21.7%). Subgroup analysis also suggested no significant difference in the 1-, 3- and 5-year OS or RFS rates. Conclusions: In our study, we believe in that the four techniques for performance of liver parenchymal transection are safe and effective. The Clamp-crush technique should be considered as the first-choice with advantages in less bleeding, short operation time and hospitalization time. And, there is no disadvantageous impact on the OS or RFS for patients with HCC.

Keywords: Hepatocellular carcinoma, hepatectomy, liver parenchymal transection technique, prognosis

Introduction

Hepatocellular carcinoma (HCC) is one of the most frequent causes of cancer-related deaths in the world [1]. Partial hepatectomy (PH) combined with chemotherapy, repeat or staged liver resections after PH improved the long-term prognosis, even achieved radical cure disease [2-4]. Intraoperative blood loss mainly caused by the liver cross section, which is a crucial factor affect the patients' prognosis. Complex or major hepatectomy is commonly associated with substantial blood loss and the subsequent need for transfusion. Intraoperative blood loss has been related to higher mortality and morbidity rates, and shorter overall survival [5-9]. It is learned that several studies [5, 6, 10-11] have proved that transfusion caused by intraoperative excess blood loss had adverse impact on overall and recurrence-free survival rates after liver resection for HCC. Therefore, how to reduce blood loss in the surgery is important. Surgeons consider that improvements in liver parenchymal transection techniques could minimize intraoperative blood loss.

In the past decades, Cavitron ultrasonic aspiration (CUSA), Harmonic Scalpel, Ligasure, Tissue-Link, water-jet dissection and other devices have been accepted and used in different open and minimally invasive surgery. The amounts of

intraoperative and postoperative complications (especially for massive hemorrhage) during hepatectomy have been greatly reduced, and mortality rates are now less than 5% [13].

Meanwhile, the comparisons of the different techniques have been reported. However, the earlier studies [14, 15-19] based on small sample size with short-term case-control data, and paid little attention to oncological outcome and overall survival. Thus, the study focus on the long-term clinical outcomes such as overall survival and HCC recurrence is needed.

We conducted a retrospective study on comparing four different techniques of hepatcetomy. They are Clamp crushing, CUSA, water-jet dissection and Harmonic Scalpel. In this study, we evaluated the short-, long-term clinical outcome of the different techniques after hepatectomy, including safety, efficacy, related complications and patients' self-care ability recovery. Overall survival (OS) and tumor recurrence free survival (RFS) rates were also analyzed.

Materials and methods

Demographic characteristics

Between June 2008 to February 2010, 681 consecutive patients who had undergone partial hepatic resectionat the Department of Liver Surgery, West China Hospital of the Sichuan University, were included. The inclusion criteria were as follows: patients received hepatectomy for initial operation; 18 to 70 years of age, diagnosis of HCC confirmed by postoperative pathological diagnosis, Child-Pugh Class A or B liver function, without extrahepatic metastasis. Exclusion criteria were: patients who had ever received open or laparoscopic surgery and other invasive therapy for HCC were excluded. According to the transection strategies, we divided all include patients into four groups: 115 patients who underwent partial hepatectomy with Clamp crushing technique were divided into Group CC, 180 patients who received operation with Harmonic Scalpel were divided into Group HS, 137 patients who been resected using Water-jet dissection were divided into Group WJ, and the last 249 patients who with CUSA technique were divided into Group CU.

The protocol was approved by the West China Hospital Ethical Committee and written informed consents were obtained from all patients before their operation.

Study methods

According to different liver parenchymal transection techniques which used in the operation, all include patients were divided into four groups: group CC, Clamp-crush technique operation group; group HS, Harmonic scalpel operation group; group WJ, Water-jet dissection operation group; and group CU, CUSA operation group. A retrospective analysis was performed to compare the intraoperative parameters (operation time, blood loss volume and transfusion requirement), postoperative laboratory indexes during hospitalization (liver function was assessed by postoperative aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL) and albumin (ALB) levels, postoperative complications and perioperative mortality), postoperative hospital stay, postoperative long-term outcomes (postoperative 1-, 3-, and 5-year OS and RFS rates) among these four groups.

The operations were performed under general anaesthesia with low central venous pressure (LCVP); the pressure value was controlled less than 5 mmHg. The operations were performed by eight surgeons who were equally skilled in all widely used techniques in our hospital. Major resection was defined as three or more segments were removed according to Couinaud's classification; also included three or more discontinuous segments resected. Minor resection predominantly included non-anatomical wedge resections (≤ two segments) or enucleations and left lateral segmentectomy. According to the surgeons' preference, the different transection techniques; such as (1) clamp-crashing technique; (2) cavitron ultrasonic aspiration (CUSA, Valleylab Corp. Somerville, NJ, US.); (3) water-jet dissection (Jet2, Erbe Corp., Tuebingen, Germany); (4) Harmonic scalpel (Johnson & Johnson Corp. Princeton, NJ, US.); are chosen to perform hepatectomy. Pringle maneuver was used in intermittent or continuous hepatic inflow occlusion.

Definition parameters

We used Clavien-Dindo complications classification system to grade the postoperative complications. An increased INR together with hy-

Table 1. Preoperative Characteristics of HCC Patients

Groups (n)	Clamp-crush (n=115)	Harmonic scalpel (n=180)	Water-jet (n=137)	CUSA (n=249)	*P*-value
Age (years)	49.6±10.8	51.4±11.7	51.0±11.9	51.7±12.3	0.434
Gender (male/female)	94/21	153/27	99/38	198/51	0.043
International Normalized Ratio	1.05±0.1	1.06±0.1	1.06±0.1	1.08±0.1	0.172
Total bilirubin (μmol/L)	15.8±6.9	14.9±7.3	15.6±9.3	16.7±17.4	0.521
Albumin (g/L)	40.5±4.4	41.4±8.4	41.01±10.1	41.5±9.1	0.209
ALT (IU/L)	47.8±41.4	52.3±43.3	49.6±42.1	49.1±34.6	0.779
AST (IU/L)	49.8±36.5	55.9±45.6	51.8±44.6	48.6±31.0	0.273
Creatinine (μmol/L)	76.5±23.5	76.9±14.3	76.5±14.3	79.1±14.5	0.346
Platelets (*10^9/L)	136.2±71.5	146.5±73.9	145.8±71.1	138.4±66.4	0.465
Child-Pugh grade (A/B)	106/9	167/13	133/4	236/13	0.284

HCC = Hepatocellular carcinoma, AST = aspartate aminotransferase, ALT = alanine aminotransferase.

perbilirubinemia (> 28.0 umol/L) on or after postoperative day 5 was defined as post-hepatectomy liver failure, which suggested by international study group of liver surgery in 2011. Perioperative mortality includes death within 30 days after surgery and death after a long hospitalization before discharge. There was a negative correlation between liver biochemical function, patients' self-care ability and hospitalization days.

Follow up

All patients were seen regularly in the out-patient clinic and monitored prospectively by a standard protocol; the follow up program was same as the previously used [20]. HCC recurrence was diagnosed by clinical, laboratory examination and radiological data at each follow-up. They were monitored until June 2015 or their death, and their medical records were retrospectively reviewed.

Statistical analysis

All statistical analyses were performed using the SPSS 19.0 statistical software (SPSS Company, Chicago, IL). Variance analysis was used for numeric continuous variables, and Kruskal Wallis was used for discrete data and non-normal distribution data. The Chi-square test or Fisher's exact test were used to compare categorical variables. The OS and RFS were calculated by the Kaplan-Meier method and were compared between groups using the log-rank test. The patients lost to follow-up were censored. *P* value of < 0.05 was considered as exist statistical significance in this study.

Results

Patients' characteristics

No significant differences in demographics among the groups except gender. Routine preoperative examination suggested that total tumor size and largest single tumor size have no significant differences in groups. The detailed parameters were displayed in **Table 1**.

Intraoperative and postoperative data

The relevant clinical pathologic and laboratory variables of intraoperative and postoperative were analyzed with the statistic method; the detailed data are shown in **Table 2**. The group CC took less operation time (193.5±32.8 minutes, *P*=0.001) and a significantly lower intraoperative estimate blood loss volume (318.2± 298.6 mL, *P*=0.045) than any of the other groups. However, the postoperative blood transfusion were not significantly different among the groups (*P*=0.271). Patients' postoperative recovery and relevant liver function indexes seemed to be no different, except for mean value of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) on postoperative days (POD) 5. Postoperative mean value of ALT and AST in group CC was 174.6±165.1, 119.0±154.4, respectively. The postoperative mean aminotransferase level in group CC were the lowest, with *P* values < 0.001. AST value on PODs 5 in group CC was 129.5±105.4 IU/L; it showed significant lower in the comparison with other three groups on PODs 5, with *P* values of 0.037.

Table 2. Intraoperative parameters and postoperative outcomes

Groups	Clamp-crush (n=115)	Harmonic scalpel (n=180)	Water-jet (n=137)	CUSA (n=249)	*P*-value
ASA grade ≥ III (n; %)	22; 19.1%	48; 26.7%	35; 25.5%	55; 22.1%	0.420
Liver histology (Fibrosis/Cirrhosis)	24/91	43/137	30/107	48/201	0.713
Multiplicity of tumors (single/multiple)	82/33	129/51	96/41	177/72	0.992
Tumor size > 5 cm (Y/N)	64/51	118/62	86/51	149/100	0.352
Macro vascular invasion (Y/N)	13/102	37/143	28/109	38/211	0.115
Major resection (Y/N)	42/73	67/113	53/84	72/177	0.151
Operation time (minute)	193.5±32.8※	213.6±29.9	212.9±29.2	215.0±31.1	0.001
Estimate blood loss (mL)	318.2±298.6※	436.4±351.2	419.1±337.7	463.8±619.9	0.045
Estimate blood loss > 1 litre (Y/N)	8/107	13/167	10/127	23/226	0.818
Postoperative transfusion (Y/N)	8/107	9/171	8/129	24/225	0.271
Albumin* (g/L)	31.3±4.4	30.8±3.9	30.5±4.1	30.7.3±4.0	0.089
Total bilirubin* (μmol/L)	23.7±11.9	26.7±15.5	27.5±20.1	27.4±24.1	0.087
ALT* (IU/L)	174.6±165.1※	299.3±338.6	251.4±287.9	224.3±241.2	< 0.001
AST* (IU/L)	119.0±154.4※	208.1±269.0	187.34±311.5	148.4±219.0	< 0.001
Albumin (g/L) 5 POD	33.3±4.5	32.4±4.3	32.5±4.5	32.9±4.7	0.506
Total bilirubin (μmol/L) 5 POD	22.8±11.7	27.9±16.9	28.1±20.5	27.9±20.5	0.137
ALT (IU/L) 5 POD	129.5±105.4※	166.6±132.5	195.5±180.9	179.4±184.9	0.037
AST (IU/L) 5 POD	57.3±51.7	66.3±70.7	95.6±197.96	72.6±76.7	0.076
Postoperative hospital stay (day)	9.0±2.7※	9.8±5.9	9.8±3.9	10.8±4.7	0.004
Postoperative complications III-V	22; 19.1%	42; 23.3%	38; 27.7%	52; 20.8%	0.343
Perioperative period mortality	1; 0.8%	4; 2.2%	2; 1.4%	9; 3.6%	0.345

HCC = Hepatocellular carcinoma, AST = aspartate aminotransferase, ALT = alanine aminotransferase, ASA = American Society of Anesthesiologists category, POD = postoperative day. *Mean value of postoperative day 3, 5 and 7; ※existing significant difference versus all other techniques.

Regarding the recovery of patients after operation, group CC had the most favorable postoperative liver function indexes and shortest length of hospitalization. The average duration of hospitalization in group CC was 9.0±2.7 days; it was lowest among the groups, with *P* value of 0.004. The postoperative complications were evaluated through the Clavien-Dindo Classification [21]. The rates of complication with grade III-V were 19.1%, 23.3%, 27.7% and 20.8%, respectively in group CC, group HS, group WJ and group CU. Whereas there were no significant differences among the groups in postoperative complications with grade III-V (*P*=0.343). Sixteen patients died during the perioperative period; one patient (0.8%) died of liver failure in group CC; four patients (2.2%) died in group HS, included two died of liver failure and two died of hemorrhagic shock; two patients (1.4%) died in group WJ, included one liver failure and one septic shock; nine patients (3.6%) died in group CU, included four liver failure, one septic shock, two respiratory failure and two hemorrhagic shock. However, there was no significant difference in hospital mortality among four groups with a *P* value of 0.345.

Postoperative survival and tumor recurrence

The mean follow up time was 38.3±22.4 months (range, 3-70). During the period, 333 patients (48.9%) died and 74 (10.8% censored) were lost to follow up. The OS survival curve contained 681 patients for each groups is shown in **Figure 1**. The 1-, 3-, and 5-year survival rates did not exist significant difference in group CC (70.4%, 53.3% and 43.4%), group HS (79.8%, 59.9% and 41.9%), group WJ (77.2%, 57.3% and 37.8%) and group CU (81.5%, 51.9% and 38.5%), respectively. *P* value of the OS rate comparison among the groups, obtained by log-rank test, was 0.931.

The RFS survival curve contained 681 patients for each groups is shown in **Figure 2**. The 1-, 3-, and 5-year recurrence-free survival rates did not exist significant difference in group CC (68.9%, 34.6% and 20.7%), group HS (67.1%, 44.3% and 25.8%), group WJ (69.4%, 45.1% and 18.1%) and group CU (65.6%, 31.8% and 21.7%), respectively. *P* value of the overall RFS rate comparison among the groups, obtained by log-rank test, was 0.545.

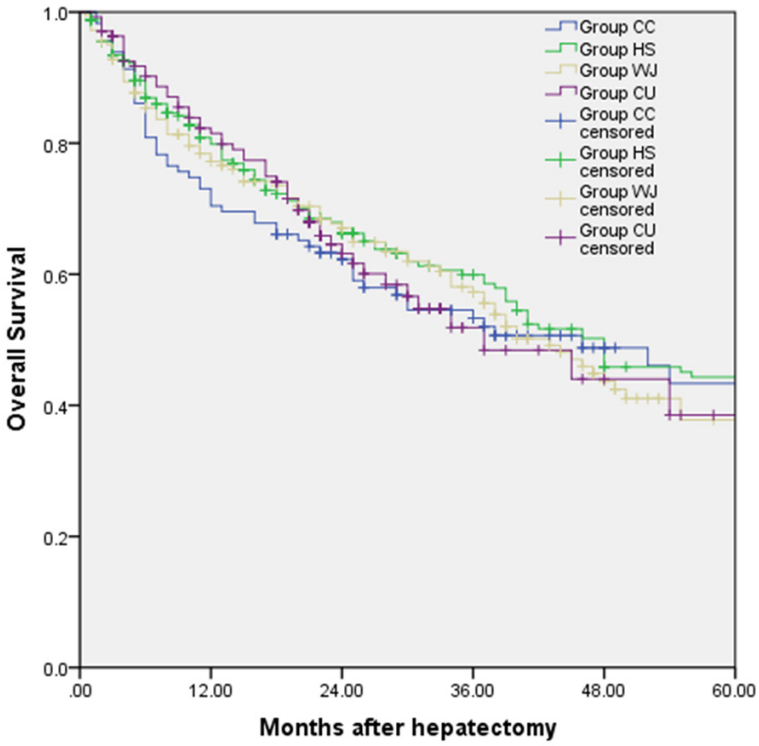

Figure 1. The overall survival rates for all study patients (χ^2=0.362, P=0.931, Log-rank).

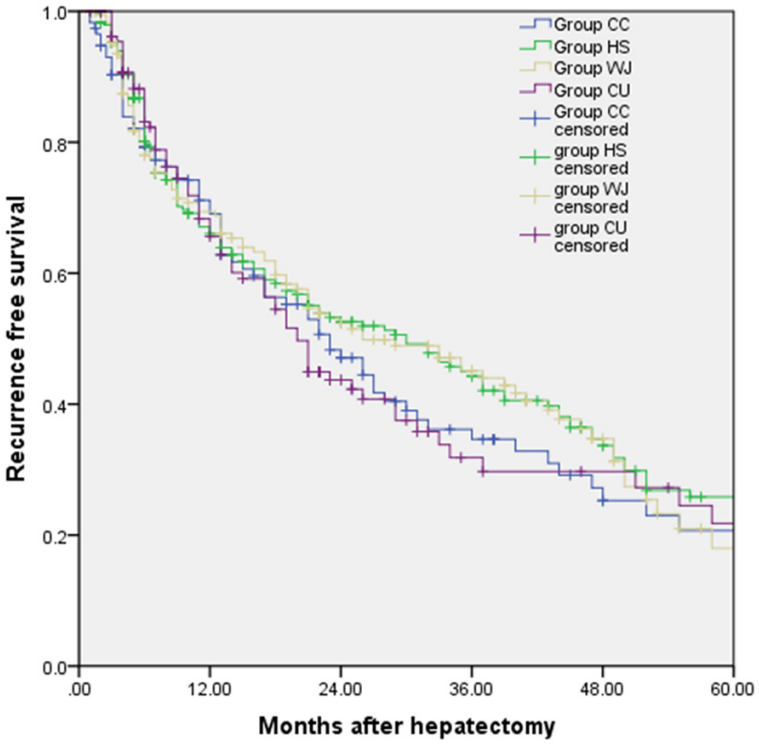

Figure 2. The recurrence-free survival rates for all study patients (χ^2=2.133, P=0.545, log-rank).

Subgroup analysis

Resection scope, pathological parenchyma, tumor size and multiple lesions were important factors that influence the liver cross sectional bleeding. In order to know the above factors whether influence postoperative long-term outcomes in different technique groups. We carried out subgroup analysis on OS and PFS in different technique operation groups; they were major resection (MR group), liver cirrhosis (LC group), single tumor diameter > 5 cm (single > 5 cm group) and multiple nodes (MN group). For example, 234 patients who underwent major resection of liver were divided into MR group *CC/HS/WJ/CU* according to their respective technique operation groups. There was no significant difference found in the 1-, 3- and 5-year OS or RFS rates among the MR group *CC/HS/WJ/CU*. In addition, the OS and RFS rates also had no significant difference been found when comparing the LC group *CC/HS/WJ/CU*, single > 5 cm group *CC/HS/WJ/CU* and MN group *CC/HS/WJ/CU*. Detailed data was displayed in **Tables 3**, **4**.

Discussion

Protecting anatomical structure is closely related to the blood loss during hepatectomy [22]. In 1974, Clamp-crush technique was first reported, and it still remains the standard technique of hepatectomy [23]. Decades later, several different kind of techniques were recommend and popularised. They combined with the perioperative management greatly reduced the postopera-

Table 3. Overall survival analysis of different technique operation groups and subgroups

Groups/Subgroups	Patients (n)	1-year survival rate (%)	3-year survival rate (%)	5-year survival rate (%)	*P* value of the OS rate		
Group CC (Clamp-crush)	115	70.4	53.3	43.4	0.931		
Group HS (Harmonic Scalpel)	180	79.8	59.9	41.9		CC vs. HS	0.287
Group WJ (Water-jet)	137	77.2	57.3	37.8		HS vs. WJ	0.758
Group CU (CUSA)	249	81.5	51.9	38.5		WJ vs. CU	0.892
Major resection (Group *CC/HS/WJ/CU*)	42/67/53/72	80.4/78.4/76.7/75.9	53.4/53.1/49.9/49.5	31.9/34.3/35.8/39.4	0.879		
						CC vs. HS	0.582
						HS vs. WJ	0.889
						WJ vs. CU	0.846
Liver cirrhosis (Group *CC/HS/WJ/CU*)	91/137/107/201	69.2/71.6/78.5/68.6	43.1/46.7/37.7/40.7	14.9/27.9/23.9/30.6	0.947		
						CC vs. HS	0.451
						HS vs. WJ	0.698
						WJ vs. CU	0.546
Single ≥ 5 cm (Group *CC/HS/WJ/CU*)	37/53/49/93	68.3/61.9/71.9/66.3	51.5/40.9/57.3/51.6	36.1/28.6/21.8/33.8	0.783		
						CC vs. HS	0.562
						HS vs. WJ	0.325
						WJ vs. CU	0.495
Multiple nodes (Group *CC/HS/WJ/CU*)	33/51/41/72	72.7/73.5/84.6/71.6	53.4/50.8/52.5/47.7	41.3/36.3/42.0/40.7	0.803		
						CC vs. HS	0.562
						HS vs. WJ	0.542
						WJ vs. CU	0.425

Table 4. Recurrence-free survival analysis of different technique operation groups and subgroups

Groups/Subgroups	Patients (n)	1-year RFS rate (%)	3-year RFS rate(%)	5-year RFS rate (%)	*P* value of the overall RFS rate		
Group CC (Clamp-crush)	115	68.9	34.6	20.7	0.545		
Group HS (Harmonic Scalpel)	180	67.1	44.3	25.8		CC vs. HS	0.259
Group WJ (Water-jet)	137	69.4	45.1	18.1		HS vs. WJ	0.697
Group CU (CUSA)	249	65.6	31.8	21.7		WJ vs. CU	0.509
Major resection (Group *CC/HS/WJ/CU*)	42/67/53/72	81.5/79.5/78.5/80.4	36.7/35.5/46.7/38.3	18.4/14.8/19.9/21.1	0.406		
						CC vs. HS	0.979
						HS vs. WJ	0.401
						WJ vs. CU	0.493
Liver cirrhosis (Group *CC/HS/WJ/CU*)	91/137/107/201	68.9/65.6/64.5/67.3	38.6/43.8/31.5/43.3	20.5/17.6/22.9/22.6	0.688		
						CC vs. HS	0.872
						HS vs. WJ	0.686
						WJ vs. CU	0.499
Single ≥ 5 cm (Group *CC/HS/WJ/CU*)	37/53/49/93	62.2/60.9/72.5/70.4	15.5/26.4/22.9/27.3	7.8/17.6/8.6/13.6	0.692		
						CC vs. HS	0.721
						HS vs. WJ	0.649
						WJ vs. CU	0.774
Multiple nodes (Group *CC/HS/WJ/CU*)	33/51/41/72	65.1/62.2/73.8/61.5	40.8/38.5/37.3/39.9	35.0/22.8/19.9/25.4	0.93		
						CC vs. HS	0.587
						HS vs. WJ	0.867
						WJ vs. CU	0.612

tive morbidity and mortality, whilst shorten the hospital stay.

In the study, we made a comparison among four widely used liver parenchymal transection techniques. As shown in **Table 1**, we found that patients did not show any significant baseline differences in age, tumor size and number, serum biochemistry, routine blood test and liver function.

Clamp-crush technique was shown to be superior to other technologies in terms of operation time (especially for liver cross-section cutting speed) and intraoperative estimate blood loss. The relevant studies [19, 24] have proved that Clamp-crush technique was quicker than most other techniques (particularly in terms of the parenchyma transection speed). Although the intraoperative blood loss in the clamp-crush group was less than other three techniques, however no significant difference was found in the intraoperative or postoperative transfusion. The trials [17, 19, 25] which compared clamp-crush technique with other techniques did not report the difference in blood transfusion requirements. In our study, hepatic inflow occlusion was performed in all kinds of technique. Hepatic inflow occlusion could minimize intraoperative blood loss and decrease transfusion. On the other hand, surgeons could quickly handle the bleeding by suturing the parenchyma and ligaturing the vessels after parenchyma transection. So, the decrease of blood loss might befit from liver parenchyma transection speed. As the cross-sectional bleeding time decrease, the total bleeding would be reduced.

In order to compare the postoperative liver function injury and recovery, we investigated the value of ALT, AST, ALB and TBIL on postoperative day (POD) 5; and their mean value on PODs 3, 5 and 7. The patients had lower mean AST and ALT levels in clamp-crush technique group and CUSA group than others. Three unfavorable factors aggravated hepatocyte injury during the parenchyma transection. First, liver cells were damaged in the process of parenchymal transection, and then transaminases were released into the blood, and elevated the serum transaminase level. Second, due to the different mechanical principles, harmonic scalpel and water-jet technique might cause more side injury in liver parenchyma, more liver cells were injured. Thirdly, harmonic scalpel technique would release a lot of heat and its electric effect in process of parenchyma transection. Clavien with colleagues have proved that ischemic time less than 30 minutes would not cause the reperfusion injury of cell in hepatectomy [26]. In our hospital, the criterion, the time of one continuous hepatic inflow occlusion was no more than 15 minute, was strictly implemented. It avoided unnecessary reperfusion injury and made postoperative AST or ALT at a lower level.

In our study, the incidence of complications grade III-V has no significant difference among the groups. The rate of secondary operation and perioperative mortality also has no significant difference, irrespective of which kind of technique was used for hepatectomy. Similar results had been reported in the literature, including several retrospective, randomized control trials [17-19, 24, 25] and a meta-analysis [27]. Nevertheless, whether different techniques would affect the overall survival and recurrence free survival? Our results found that the technique of parenchyma transection did not impact OS or RFS. In addition, subgroup analysis were performed on patients with single tumor (single tumor diameter more than 5 cm), patients with liver cirrhosis, patients with multiple nodes and patients underwent major hepatectomy. There were no significant differences were found among the subgroups on the 1-, 3- and 5-year OS or RFS rates.

One of the major limitations is its retrospective design, which probably leads to potential selection bias. A single center non-randomized study has resulted in limitation and regional difference. These deficiencies would be improved and solved in further research.

This study, as we known, represents the first and largest cohort to compare short- and long-term clinical outcomes for HCC patients who underwent hepatectomy with different kinds of technique. The results suggested that clamp crushing technique offers several advantages over others, involving shorter operation time, hospital stay and less intraoperative blood loss. Furthermore, we found that the clamp crushing technique is cost-efficient device through a portion of hospitalization costs data analysis. Based on these advantages, Clamp-crush technique should be advocated to as a safe and cost-effective technique of liver par-

enchymal transection for HCC needing hepatectomy.

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Disclosure of conflict of interest

None.

Abbreviations

HCC, Hepatocellular carcinoma; CUSA, Cavitron ultrasonic aspiration; OS, overall survival; RFS, recurrence free survival; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBIL, total bilirubin; ALB, albumin; LCVP, low central venous pressure; POD, on postoperative day.

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