

Clinical Value of Trans-parenchymal Compressing Suture to Decrease the Cutting Surface Related Complications after Non-anatomical Liver Resection*

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Summary: Non-anatomical liver resection with appropriate resection margin is regarded as a potential curative treatment for selected major hepatic carcinoma due to preserving maximal normal liver, especially in cirrhotic patients. But occurrence of cutting surface related complications becomes a main challenge. From June 2010 to June 2016, 448 patients with major hepatic carcinoma received non-anatomical liver resection in our liver surgery center. After excluding 66 cases that were incongruent with the purpose of study, 235 patients undergoing trans-parenchymal compressing suture (TCS) to “not good” cutting surface were allocated as study group; 147 patients with exposed surface (ES) were matched as control group. The characteristics of postoperative drainage, postoperative hepatic and renal functions, hospital days, and outcomes were collected retrospectively. We further compared cutting surface related complications under different levels of liver cirrhosis between the two groups. Compared with ES group, patients in TCS group had a decreased incidence of cutting surface related complications (14.3% vs. 6.8%, $P=0.011$) and a decreased probability of interventions for cutting surface related complications (8.2% vs. 3.4%, $P=0.042$). TCS application was much more effective to prevent cutting surface related complications in patients with moderate and severe cirrhosis (5.4% vs. 15.8%, $P=0.003$). Postoperative hepatic and renal function, hospital days and mortality did not differ between the two groups. In conclusion, TCS decreases the probability of cutting surface related complications and postoperative interventions for related complications, especially in patients with moderate and severe cirrhosis.

Key words: liver resection; cutting surface; complication; cirrhosis

Liver resection is considered as the most potentially curative treatment for hepatic carcinoma except liver transplantation. According to the type of liver resection, it is divided into anatomical liver resection and non-anatomical resection. In some specific clinical circumstance, how to select the type of resection is still a controversial issue. Excessive anatomical liver resection is suggested as theoretically more effective for tumor eradication and

supplies a disease free survival benefit. However, in some studies, non-anatomical liver resection with appropriate resection margin reserves more liver parenchyma and gains a similar overall survival rate^[1]. For patients with underlying liver disease, excessive liver resection can result in severe postoperative complications and death^[2]. Most patients with hepatic carcinoma suffers HBV related cirrhosis in China. As a result, non-anatomical liver resection with appropriate resection margin became the optimal surgical strategy in selected patients in China.

Recent advances in surgical procedures have dramatically decreased the risk of bleeding during transection of parenchyma, such as various methods of vascular exclusion and low central venous pressure techniques^[3-7], which ensure the safety of liver resection. But, how to manage the liver cutting surface safely and effectively after liver parenchymal transection is still

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controversial and is a primary concern of hepatobiliary surgeons. Management of the cutting surface is associated with troublesome complications^[8-10], such as bile leakage, postoperative intra-abdominal bleeding, and surgical site infection. Unsatisfactory management of the cutting surfaces results in severe complications and deaths especially in patients with cirrhosis, due to impaired coagulation function^[11]. Because the cutting surface with non-anatomical liver resection is not in the intersegmental plane of the liver^[12], more attention should be paid to decreasing the possibility of postoperative complications.

Currently, a majority of studies investigating cutting surface management are limited to non-surgical treatments, such as the application of hemostasis agents including fibrin sealants, oxidized cellulose, and absorbable gelatin sponge^[13-15]. But there is no consensus regarding the necessity of the hemostatic agent application to the liver cutting surface. Up to date, few studies investigate surgical suture management of the cutting surface in liver resection. We established trans-parenchymal compressing suture (TCS) after “enbloc” resection of tumor and the results were quite encouraging. Here, we compared the cutting-surface related complications between TCS group and “exposed surface” (ES) group based on 6-year clinical data, and further compared the outcomes in patients with different levels of liver cirrhosis between the two groups.

1 SUBJECTS AND METHODS

1.1 Patients

Between June 2010 and June 2016, 1519 patients with major hepatic carcinoma who underwent open liver resection in our hepatic surgery center were included in this study. In accordance with our research purpose, 382 patients were selected in this study according to the following criteria: (1) tumor size is more than 5 cm and hepatectomy performed involving 3 liver segments or more; (2) the type of liver resection is non-anatomical liver resection; (3) no intravascular infiltration with tumor embolus; (4) no previous liver surgical treatment (e.g. microwave ablation; preoperative transcatheter arterial chemoembolization (TACE); (5) no other concomitant extrahepatic procedures (e.g. splenectomy); (6) no exposed main hepatic veins or (and) retro-hepatic inferior vena cava. As a result, TCS was performed in 235 patients and ES in 147 patients. The process of screening is shown in fig. 1.

One thing to note is that 21 patients who were unable to receive TCS were excluded in this study because of the exposure of main hepatic veins or (and) retro-hepatic inferior vena cava as shown in fig. 2. According to the results of checking for bile and blood staining from cutting surface, we further performed TCS to “not good” cutting surface in hope of decreasing cutting surface related complication.

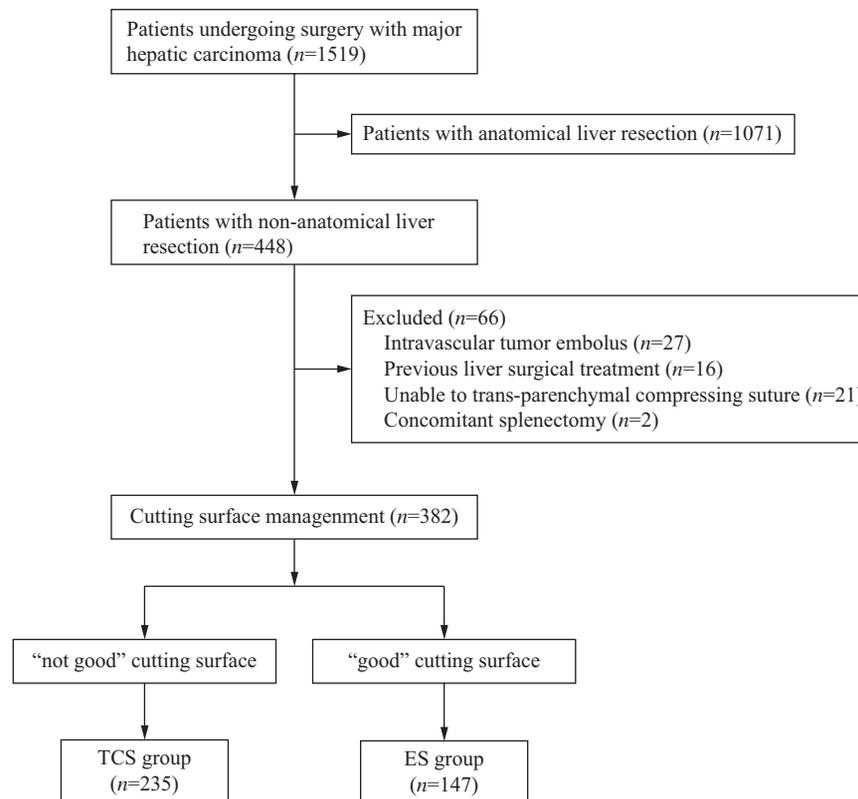


Fig. 1 Flow chart of patients screening

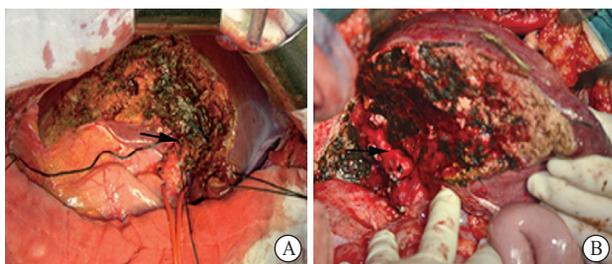


Fig. 2 Representative patients who were unable to perform TCS
 A: One patient with tumor involving IV, V and VIII segment. Hepatic glisson sheath was exposed as indicated by arrow; B: One patient with tumor involving V, VI and VII segment. Retro-hepatic inferior vena cava was exposed as indicated by arrow.

1.2 Surgery

During surgery, a right subcostal incision was performed. After exploring the abdominal cavity, the liver was mobilized in a standard way according to the location and size of the tumor. Urinary catheters were routinely placed under the portal triad to prepare for clamping. For patients with a high risk of backflow bleeding as shown through the analysis of preoperative imaging and intraoperative ultrasound, the infrahepatic inferior vena cava was also dissected and taped with a vessel loop. Dexamethasone (10 mg) was administered intravenously before vascular clamping. During transection, liver parenchyma and small vessel (<2 mm) were coagulated with irrigated bipolar forceps set at 120 W and sheared directly by tissue scissors, while the larger vascular structures and intrahepatic bile ducts were ligated by silks on the tumor's contralateral side. The vascular clamp was relieved after liver transection.

Oozing from cutting surface was stanchied by coagulation. In order to check for active hemorrhage and visible sites of bile leakage of cutting surface, the raw cutting surface was covered with stainless gauze for 5 min. For patients with any positive findings including bloodstain and (or) bile staining, their cutting surface was recognized as “not good” cutting surface and further TCS was performed, if possible, using a hepatic needle, as shown in fig. 3.

After liver resection, one or two closed suction abdominal drainage tubes were placed routinely to ensure the draining smoothly.

1.3 Data Collection

All data were collected retrospectively. For the comparability of the two groups, preoperative demographic data, severity of cirrhosis, types of resection performed, pathologic diagnosis and other details of the surgical procedure were collected retrospectively. The levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum total bilirubin (TBIL), and creatinine (Cr) were collected on postoperative days 1, 3, 5, and 7. Our postoperative complications collection focused on the detection of

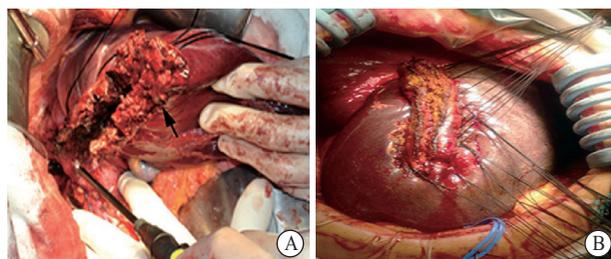


Fig. 3 Representative patients with TCS of liver cutting surface
 A: One patient with tumor involving VI, VII and VIII segment. Cutting surface was effectively compressed by TCS as indicated by arrow; B: One patient with tumor involving IV, V and VIII segment. Cutting surface was closed by trans-parenchymal compressing suture. Adjacent “U” suture was interlocked to make sure the cutting surface compressed effectively or closed. One stitch was about 3–4 cm in length.

cutting surface related complications as well as overall complications of liver surgery. Characteristics and volume of drainage were recorded in detail until the removal of the abdominal drainage tube. Hospital days and mortality were also recorded retrospectively.

1.4 Definition

The abdominal drainage tubes were removed once the discharge became serous, and the volume was lower than 100 mL/day.

Severity of cirrhosis was evaluated based on the diameters of cirrhotic nodules in the liver specimen^[16]: no cirrhosis; mild cirrhosis, nodule diameter <0.4 cm; moderate cirrhosis, 0.4 cm ≤ nodule diameter ≤ 0.8 cm; severe cirrhosis, nodule diameter >0.8 cm.

Bile leakage was diagnosed by one or more of the following findings^[17]: the content of drainage is bile; bilirubin concentration in the drain fluid at least 3 times the serum bilirubin concentration on or after postoperative day 3; and evidence of intra-abdominal collection of bile during percutaneous abdominal paracentesis or reoperation.

Cutting surface bleeding was diagnosed through the following findings^[18]: hematic discharge from the abdominal drainage tube with hemodynamic instability and/or decreased value of serum hemoglobin; and evidence of blood collection during percutaneous abdominal paracentesis or reoperation.

Cutting surface infection diagnosis was based on at least one of the following findings^[19]: the characteristic of drainage is purulent; organisms were isolated from the culture of drainage; and evidence of intra-abdominal collection of purulence during percutaneous abdominal paracentesis or reoperation.

Hepatic insufficiency was defined as follows: the level of prothrombin time was greater than 50% of the normal with inadequate coagulation; the level of serum bilirubin was greater than 50 μmol/L on postoperative day 5 or thereafter^[20].

Mortality was defined as death within 90 days after liver resection.

1.5 Statistical Analysis

Summary statistics were expressed as mean±SD or median (range), as appropriate. Statistical comparisons between the two groups were done using the Student *t* test for continuous data and the Chi-square test (or Fisher exact test where appropriate) for categorical data. All analyses of the data were performed with SPSS 13.0 statistical software. *P* value <0.05 at two-sided was considered to be statistically significantly different.

2 RESULTS

2.1 Comparability of Patients between the Two Groups

The characteristics of the 2 groups are summarized

in table 1. There were no significant differences in the demographic parameters between these 2 groups of patients. Child-Pugh grade and tumor location were evenly distributed in the 2 groups. The severity of cirrhosis was also comparable in the 2 groups.

2.2 Postoperative Drainage and Cutting Surface Related Complications

As shown in table 2, the total volume of drainage during the first 3 postoperative days and the duration of drainage were similar in the two groups. However, the confirmed incidence of non-serous drainage had a statistically significant difference (7.2% vs. 13.6%, *P*=0.041). Among them, the incidence of bile drainage between the two groups also had significant difference (5/235 vs. 10/147, *P*=0.025).

The finding of postoperative drainage is coincident with the outcome of cutting surface related

Table 1 Demographics and clinical characteristics of patients

Parameters	TCS group (n=235)	ES group (n=147)	<i>P</i>
Gender (female/male)	63/172	43/104	0.604
Age (year)	48.9±11.3	49.0±10.0	0.961
HBsAg serology (+/-)	222/13	138/9	0.824
HCV antibody serology (+/-)	4/231	1/146	0.393
Child-Pugh grade			0.719
A	206	127	
B	29	20	
Liver cirrhosis			0.575
No	11	9	
Mild	40	18	
Moderate	134	85	
Severe	50	35	
Segment involved during liver resection			0.332
Segment V, VI, VII, VIII	16	5	
Segment VI, VII, VIII	32	23	
Segment V, VI, VIII	44	29	
Segment II, III, IV	58	33	
Segment IV, V, VIII	25	25	
Segment V, VI, VII	60	32	
Tumor size (cm)			
Operation time (min)	187.8±53.5	178.2±50.6	0.109
Ischemia time (min)	10.2±3.9	10.0±3.7	0.639
Intraoperative blood loss (mL)	514.8±419.5	473.4±334.0	0.312
Number of patients requiring blood transfusion	43 (18.3%)	19 (12.9%)	0.166

Continuous variables are expressed as mean±SEM. The degree of liver cirrhosis was evaluated based on the diameter of cirrhotic nodules.

Table 2 Postoperative drainage and cutting surface related complications

Parameters	TCS group (n=235)	ES group (n=147)	<i>P</i>
Duration of drainage (Days)	6.2±1.7	6.4±2.1	0.433
Volume of drainage (mL)	951.8±477.1	934.7±429.4	0.725
Non-serous drainage	17 (7.2%)	20 (13.6%)	0.041
Bile	5	10	0.025
Hemorrhage	7	7	0.367
Abscess	5	3	0.954
Cutting surface related complications	16 (6.8%)	21 (14.3%)	0.011
Bile leakage	5	11	0.013
Cutting surface bleeding	6	7	0.247
Cutting surface infection	5	3	0.954

complications. Bile leakage was diagnosed in 11 patients in the ES group. Among them, one patient did not show bile drainage due to the biloma. However, only 5 patients were detected with bile leakage in the TCS group, which demonstrates a statistical difference between the two groups (5/235 vs. 11/147, $P=0.022$). Seven patients in the TCS group were detected as having hemorrhagic discharge, but 1 patient's bleeding was from the other surgical site that was confirmed from reoperation. So cutting surface bleeding was observed in 6 patients in TCS group, but 7 patients in ES group, without significant difference. As a composite endpoint patients in the TCS group had less incidence of cutting surface related complications than those in the ES group (6.8% vs. 14.3%, $P=0.011$).

2.3 Postoperative Hepatic and Renal Functions

The postoperative serum transaminases, TBIL, and

Cr levels are summarized in fig. 4. The postoperative hepatic and renal functions were evaluated by the serum bilirubin and Cr levels, respectively. At postoperative 1, 3, 5, and 7 days, there were no differences in the values of serum bilirubin and Cr between the two groups. The peak values of ALT and AST occurred on the first postoperative day, and the levels returned to normal within one week in most patients. In the first few postoperative days, the peak values of ALT were mildly higher in the TCS group than in the ES group, but the difference was not significant. The levels of ALT in the following postoperative days and the levels of AST were also not significantly different between the two groups.

2.4 Postoperative Complications and Hospital Stays

The postoperative outcomes in the two groups are shown in table 3. The overall complications were

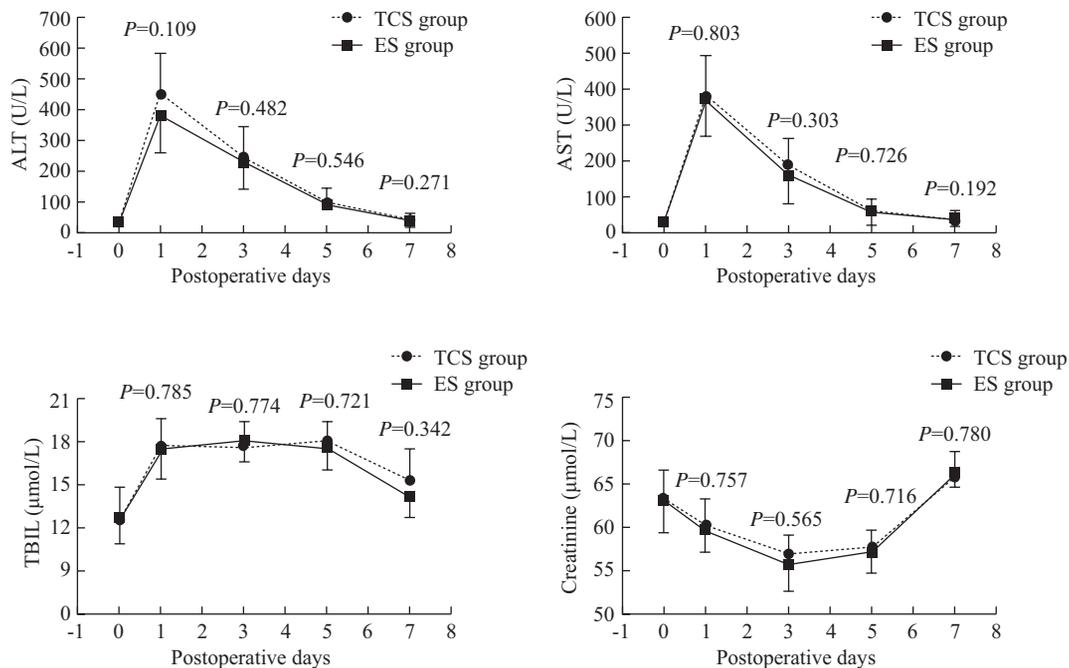


Fig. 4 Postoperative hepatic and renal functions were assessed by serial parameters of the two groups Day 0 refers to the preoperative day. $P<0.05$ was regarded as significant difference between the two groups.

Table 3 Postoperative outcomes

Outcomes	TCS group (n=235)	ES group (n=147)	P
Overall complications according to Clavain-Dindo classification grade	59 (25.1%)	43 (29.3%)	0.373
Grade 1	7	4	
Grade 2	32	21	
Grade 3	14	16	
Grade 4	5	2	
Grade 5	1	0	
Intervention for cutting surface related complications	8 (3.4%)	12 (8.2%)	0.042
Surgical intervention	5	8	
Radiological intervention	2	3	
Reoperation	1	1	
Hospital days	13.0±3.1	12.8±3.2	0.599
Mortality	1	0	0.428

Complications were collected according to Clavain-Dindo classification of surgical complications. Only the highest degree of complication in each patient was listed.

Table 4 Cutting-surface related complications under different levels of liver cirrhosis (n or %)

	No and mild liver cirrhosis			Moderate and severe liver cirrhosis		
	Complications	No complications	Incidence	Complications	No complications	Incidence
TCS	4	47	7.8%	10	174	5.4%
ES	2	25	7.4%	19	101	15.8%
<i>P</i>			0.945			0.003

collected according to the classification of surgical complications reported by Dindo *et al*^[21]. The incidence of overall complications was 25.1% and 29.3%, respectively ($P>0.05$). However, the patients in the ES group had a higher incidence of intervention for cutting surface related complications than those in the TCS group (8.2% vs. 3.4%, $P=0.042$). In detail, cutting surface related complications which required percutaneous drainage under ultrasound guidance occurred in 5 patients in the TCS group and 8 patients in the ES group. Two patients (one patient in each group) underwent reoperation and 5 patients received transcatheter arterial embolization (2 patients in the TCS group and 3 patients in the ES group) due to intra-abdominal bleeding.

The overall hospital stay (14.0 days vs. 13.9 days, $P=0.842$) and mortality rate were not significantly different between the two groups.

2.5 Comparison of Cutting Surface Related Complications between Two Groups with Different Levels of Liver Cirrhosis

Due to the influence of liver texture on the suture, further statistical analyses were performed for the subgroups of patients with different levels of liver cirrhosis. The distribution of liver cirrhosis severity is detailed in table 1. There was no difference in the distribution of liver cirrhosis between the two groups. Further subgroup analysis is shown in table 4. Among patients with mild cirrhosis or no cirrhosis, 10 patients in the TCS group suffered cutting surface related complications, compared with 5 patients in the ES group. There was no significant difference between these two subgroups (7.8% vs. 7.4%, $P=0.945$). For patients with moderate and severe cirrhosis, 6 patients in the TCS group suffered from cutting surface related complications, while 16 patients in the ES group suffered from cutting surface related complications. The difference was significant (5.4% vs. 15.8%, $P=0.003$). Accordingly, TCS may be more effective in decreasing the incidence of cutting surface related complications in patients with moderate and severe liver cirrhosis than in those with no or mild cirrhosis.

3 DISCUSSION

Hepatic resection is now firmly considered to be the most effective treatment for hepatic neoplasm. Indication of hepatectomy has been broadened in

patients with normal liver, even in patients with liver cirrhosis^[22]. Non-anatomical liver resection with appropriate resection margin became the optimal surgical strategy for patients with major hepatic carcinoma to prevent liver failure resulting from excessive liver resection, especially in patients with moderate or severe cirrhosis. In this study, 79.2% (304/384) patients had moderate or severe cirrhosis. During surgery, a better understanding of hepatic anatomy and a refined surgical technique control for inflow and outflow are crucial for successful hepatic resection, which have a beneficial effect to reduce the intraoperative blood loss and blood transfusion^[23, 24]. It has been shown that less intraoperative blood loss, along with fewer blood transfusions, decreased the postoperative morbidity and mortality^[25]. However, due to the impairment of hepatic function and lowered immunity after hepatectomy, primary complications occurring after hepatic resection, such as the postoperative bile leakage, bleeding from the remnant liver resection surface and infection at surgical site, are still a formidable problem^[26, 27]. These cutting surface related complications not only prolong hospital stays and result in exorbitant hospital costs, but they may also induce hepatic failure.

Regarding the management of the liver cutting surface, many published papers are restricted to non-surgical management. Various hemostatic agents are generally used to promote the hemostasis of the liver's raw cutting surface and some are even applied prophylactically to decrease the postoperative cutting surface related complications^[28, 29]. However, some studies have shown that application of hemostatic agents is cost wasting and ineffective in avoiding postoperative blood and bile leakage^[30-33]. Some surgeons also used omentum wrapping to pack the dead space around the raw cutting surface in order to prevent the occurrence of cutting surface related complications, but the efficacy of this is also doubtful^[34]. This current retrospective study evaluated the TCS of liver cutting surface for the first time.

TCS using a hepatic needle was initially performed to simplify the hemorrhage control procedures and facilitate hepatic resection^[35-37]. Two rows of interlocking sutures placed along the transection plane may reduce the oozing of blood and bile from the cutting surface^[38]. The value of controlling bleeding during liver transection has long been ignored due to

the improvement of various coagulation devices and hepatic vascular occlusion techniques^[39, 40]. In our hepatic surgery center, we performed TCS after liver transection with an expectation of decreasing cutting surface related complications. Because most hepatic carcinoma cases in China are associated with the HBV carrier status, most patients suffering hepatic carcinoma had some degree of liver cirrhosis^[41]. In this research cohort, out of the 382 patients suffering primary hepatic carcinoma, 276 patients had various degree of liver cirrhosis. For major liver resection on patients with cirrhosis, non-anatomical liver resection was used to prevent postoperative liver failure due to the maximum reservation of non-tumor liver parenchyma. Unlike the cutting surface after anatomical liver resection, the cutting surface after non-anatomical liver resection doesn't lie in the inter-segmental plane. Thus, TCS is applicable in the non-anatomical liver resection with cirrhosis.

According to the results of this retrospective study, patients with TCS have less incidence of cutting surface related postoperative complications than patients with exposed cutting surface. Due to the favorable comparability between the two groups, the demonstrated significant difference can be attributed to the efficacy of TCS. Another important finding in this study is that the efficacy of TCS is more pronounced in patients with moderate and severe liver cirrhosis. One reasonable explanation may be that the compression of liver parenchyma exerted by mattress suturing blocks the oozing of bile and blood from cutting surface more easily in cirrhotic liver. But in the normal liver, the fragile liver tissue is not as much applicable for TCS as the cirrhotic liver, so the efficacy to prevent postoperative complications can be easily shown in patients with cirrhosis. In order to better evaluate the efficacy of TCS, we further divided cutting surface related complications into bile leakage, cutting surface bleeding and cutting surface infection to make sub-item analysis. It is more interesting that TCS shows significant benefit to reduce the incidence of bile leakage. Patients in ES group has 7.5% (11/147) incidence of bile leakage, which is similar to other related report about incidence of bile leakage (4.0%-9.8%) after liver resection^[42]. However, patients in TCS group has only 2.1% (5/235) incidence of bile leakage. We can see that prevention of bile leakage of cutting surface by TCS may be the dominant contribution for its role of decreasing cutting surface related complications.

A potential concern with patients undergoing TCS is the vitality of liver tissue around the cutting surface after suturing. In this study, we demonstrated that patients in each group had similar recovery rates for hepatic function, and that the rate of infection at the surgical site was also not significantly different

between the two groups. The other point is that 21 patients (21/403, 5.2%) with non-anatomical liver resection were excluded from this study due to being unable to perform safe TCS. This particular situation was experienced in 14 patients with tumor involving IV, V, VIII because of possibility of compressing of liver Glisson sheath, and 7 patients with tumor involving VI, VII because of possibility of compressing of liver hepatic veins or retro-hepatic inferior vena cava. Generally, TCS can be feasible and safe to be performed in selected patients with non-anatomical liver resection.

Although this study is not a random controlled trial (RCT), this comparable cohort study confirms the potential clinical value of TCS in patients undergoing non-anatomical liver resection in order to preserving maximal normal liver tissue.

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