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~ Effective usage of an energy device at hepatectomy ~

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compared to non-coagulation cases. 73 patients diagnosed with cirrhosis via postoperative pathological findings were selected upon reviewing 887 hepatectomy patient files. They were divided into a pre-coagulation group (n=20) and a non-coagulation group (n=53). There were no significant differences in patient and tumor factors between two groups. Pre-coagulation group had significantly less blood loss compared with non-coagulation group [282 vs 563g (p < 0.05)], shorter operative time [214 vs 276min (p = 0.06)], and shorter postoperative hospital stays [14.5 vs 22.5 days (p = 0.12)]. The median recurrence free survival rates time in the pre-coagulation group (733 days) was significantly longer than that in the non-coagulation group (400 days) (p < 0.05). Overall survival rates showed no difference among the two groups (p = 0.62). Pre-coagulation therapy may be one of the preferred treatment application for hepatectomy patients with severe liver fibrosis.
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Abstract

Hepatectomy for liver cirrhosis patients requires skillful surgical technique and careful attention caused by the fibrotic parenchyma, elevated portal pressure, and impaired coagulation. This report evaluated short- and long-term outcomes for liver cirrhosis patients receiving pre-coagulation therapy on the parenchymal transection plane, as compared to non-coagulation cases. 73 patients diagnosed with cirrhosis via post-operative pathological findings were selected upon reviewing 887 hepatectomy patient files. They were divided into a pre-coagulation group (n=20) and a non-coagulation group (n=53). There were no significant differences in patient and tumor factors between two groups. Pre-coagulation group had significantly less blood loss compared with non-coagulation group [282 vs 563g (p < 0.05)], shorter operative time [214 vs 276min (p = 0.06)], and shorter postoperative hospital stays [14.5 vs 22.5 days (p =
The median recurrence free survival rates time in the pre-coagulation group (733 days) was significantly longer than that in the non-coagulation group (400 days) \((p < 0.05)\). Overall survival rates showed no difference among the two groups \((p = 0.62)\). Pre-coagulation therapy may be one of the preferred treatment applications for hepatectomy patients with severe liver fibrosis.

*Key Words*: pre-coagulation therapy - liver cirrhosis - hepatectomy
Introduction

Liver resection remains a primary effective but radical approach in the treatment of liver tumor. However, hepatectomy is associated with high morbidity and mortality, especially for those patients with severe liver fibrosis.1-3 Severe fibrosis cases require skillful surgical technique and careful attention due to the risk caused by the fibrotic parenchyma, elevated portal pressure, and impaired coagulation. It is an indispensable task to shorten the operative time and control the blood loss for cirrhosis patients, in association with post-operative liver failure.

The coagulative tissue generated by thermal energy, a radiofrequency ablation (RFA) or a microwave coagulation therapy (MCT), helps in sealing of the vessels and bile ducts before parenchymal transection.4-8 Some reports have confirmed that liver transection using a coagulative technique decreased both operative blood loss and operation time.9-12 Though heat coagulative technique isn’t generally indicated for the normal liver, there are some severe liver fibrosis cases wherein it is difficult to stop the bleeding by conventional methods. In such cases, pre-coagulation technique reduces intra-operative blood loss on the liver surface prior to transection.13

This study is novel research evaluating short-and long-term outcomes for hepatectomy diagnosed as liver cirrhosis (LC) via post-operative histological findings.
and performing pre-coagulation therapy on the parenchymal transection plane, as compared with non-coagulation cases.

Patients and Methods

Patients

887 patients underwent hepatectomy in our surgical department from January 1994 to December 2018. Of these, 73 patients were diagnosed as LC via post-operative histological findings and accepted to our study. They were then classified into two groups: the first group received pre-coagulation on the transection plane before liver parenchymal transection (Group C; n=20); the second group did not receive the coagulation (Group N; n=53).

Pre-coagulation device

Habib\textsuperscript{TM} 4X (open operative device; Angiodynamics Inc., USA) is a bipolar device and consists of two pairs of opposing electrodes. Two pairs rode can be arranged to 6 or 10 cm in length. The device is connected to a 500-kHz generator which produces up to 250 W of radiofrequency ablation (RFA), with a foot pedal used to turn the energy on and off. It allows measurement of the generator output, tissue impedance, temperature and
time. Habib™ 4X Sealer (laparoscopic operative device; RITA Medical Systems, USA) consists of a $2 \times 2$ array of needles producing bipolar RFA. This device can be introduced via a 12mm laparoscopic port. The total length measures 45cm, including a 5cm electrode needle for RFA. A control button in the handle allows the operator to select the depth of ablation. The most remarkable result of these RFA devices is the coagulation time. Whereas the standard time of other devices requires several minutes, the Habib™ 4X and Habib™ 4X Sealer are able to coagulate in only 4-8 seconds per each action, contributing to shortening of the operative time with prompt hemostasis.

And, the microwave coagulator (Microtaze™; Alfresa-pharma, Japan) consists of one thermal needle which can vary in length from 10 mm to 45 mm, a handpiece, and a microwave generator. The tip angle is able to adjust up to 90 degrees via an attachment piece. This surgical tool produces microwave radiation of tissue with a frequency of 2450 Mhz by the vibration of polar molecules in protein and water. The microwave generator is set at 80W output, 45-seconds duration, and 15-seconds of dissociation.

**Hepatectomy procedure**

Intra-operative ultrasound (IOUS) was performed in order to reveal the device’s positional relation to anatomical landmarks and to detect the presence of new lesions.
prior to liver resection. The resection line was determined using ultrasonography and then marked. After routine scanning for the liver tumor and anatomical landmarks with IOUS, the liver was mobilized. In our department, the pringle maneuver was generally applied to every hepatectomy, except for the cases with severe adhesions or with a hemorrhagic situation. Though modified according to the tumor characteristics and remnant liver function, the resection margin width was typically 10 mm from the tumor’s edge. The liver parenchymal plane was pre-coagulated by repeated insertion of the thermal needle along the resection line. If significant bleeding was seen at the exit point, applying pre-coagulation in different planes away from the bleeding site was found to be effective. According to the information obtained with IOUS, the needles were not inserted near a major vessel or bile duct, in order to avoid heat injury. Next, the pre-coagulated liver parenchymal tissue was transected by the clump crushing method or CUSA. Any major vessels or bile duct larger than 5 mm in diameter were directly ligated or fastened with a clip after encircling the vessel (Fig. 1).

Data collection

We identified patients from prospective databases and retrospectively reviewed office and hospital charts. The patient characteristics, tumor status, operation-related variables,
and short and long-term outcomes were analyzed retrospectively, including age, gender, etiology, blood platelet count (PLT), liver Child-Pugh classification, indocyanine green retention 15 (ICG R15), $^{99}$mTc-galactosyl serum albumin ($^{99}$mTc-GSA), tumor marker (AFP, PIVKA-II), tumor number, maximum tumor diameter, tumor location, operative procedure, operation time, operative blood loss, blood transfusion, surgical margin, tumor staging, post-operative hospital stay, morbidity, mortality, recurrence free survival (RFS) rates and overall survival (OS) rates. Morbidity or mortality were defined as the complications or the deaths during hospitalization or within 30 days following the resection. The median follow-up time from primary surgery was 53.3±110.6 months.

**Statistical analysis**

Statistical analysis was conducted using JMP software (version 14, Inc., SAS Institute). All means were expressed with standard deviation (SD). Univariate associations between potential risk factors and survival were assessed using the log-rank test with two-tailed hypothesis. Survival probabilities were estimated using the Kaplan-Meier method. The significance level of $P < 0.05$ was used in all hypothesis testing.
Results

Patients and Tumor characteristics

The patients in this study were divided according to pre-coagulation on transection plane, group C: pre-coagulation cases (n = 20) and group N: non-coagulation cases (n = 53).

The patients and tumor characteristics for all patients were analyzed and summarized in Table 1, including gender, age, liver disease, cirrhosis etiology, blood platelet count (PLT), prothrombin time (PT), blood albumin (Alb), liver functional status (liver Child-Pugh classification), indocyanine green retention 15 (ICG R15), $^{99}$mTc-galactosyl serum albumin ($^{99}$mTc-GSA), Tumor marker (CEA, AFP, PIVKA- II level), tumor location in liver, tumor number, and maximum tumor diameter. There weren’t significant differences in patient and tumor factor between the each groups. All cases in the pre-coagulation group were hepatocellular carcinoma (HCC; 100%), compared to the non-coagulation group (HCC 91%, CCC 5%, Other 4%). Segment 6 (S6) was the most common site for tumor location (group C: 25%, group N: 24.3%), next in frequency were S5 and S8. The maximum tumor diameter was the same size between the two groups (group C: 29.8 vs group N: 30.5mm).
Operative details and outcome

Operation type, operative blood loss, perioperative transfusion, and surgical margin (SM) were analyzed and summarized in Table 2. Partial resection (Hr0) was the most frequently performed surgical procedure in both groups (group C: 70.0% vs group N: 55.8%; p = 0.27). Operative time for the pre-coagulation group didn’t find any significant difference as compared to the non-coagulation group (group C: 214±271 vs group N: 276±324 min; p = 0.06), operation blood loss was significantly less for the coagulation group (group C: 282±1188 vs group N: 563±1342 g; p < 0.05). Blood transfusions for group C was not required in all cases (5.6%), compared with 5.9% for group N (p=0.96).

Peri-operative morbidity, mortality, and hospital stay

Complications in group C included liver-related events: 2 (post-operative bleeding 1, perihepatic abscess 1) and general:2 (ascites 1, pneumonia 1) (Table 3). One case showed complications of grade-IIIa and over (Clavien-Dindo classification), namely perihepatic abscess (n=1). There was no liver failure or mortality case in group C. The pre-coagulation group had significantly shorter postoperative hospital stays (group C: 14.6±18.4 vs group N: 22.5±106.5 days; p = 0.12).
Recurrence-free survival and Overall survival

RFS rates of group C were significantly better than that of group N (1-, 3-, and 5-year recurrence-free survival rates of group C: 88.9%, 48.9%, and 42.8%, respectively vs group N: 56.0%, 28.0%, and 9.3%, respectively; p <0.05) (Fig. 2).

OS rates showed no difference among the two groups (1-, 3-, and 5-year overall survival rate of group C: 100%, 77.8%, and 65.0%, respectively vs group N: 84.7%, 75.0%, and 60.5%, respectively; p = 0.62) (Fig. 3).

Discussion

Hepatectomy with LC requires skillful surgical technique and careful attention due to the fibrotic parenchyma, elevated portal pressure, and impaired coagulation. Minimizing operative blood loss and shortening the operative time of the intervention are important objectives.\(^{14,15}\) In fact, it is reported that liver resection with coagulation are availability at the point of operative blood loss and operative time.\(^{8,16,17}\) A systematic review was reported for the outcomes of liver resection with radiofrequency energy devices in comparison to the clamp-crush technique by Kumar et al,\(^{18}\) and a systematic review was reported for the operative effects of radiofrequency energy devices in laparoscopic
hepatectomy by Isabella et al.\textsuperscript{19} Coagulation technique has been shown to reduce intra-operative blood loss on the liver parenchymal plane prior to transection.\textsuperscript{13} This technique is not generally indicated for the normal liver. However, the presence of cirrhosis is associated with a high risk of hemorrhage caused by the fibrotic parenchyma, elevated portal pressure, and impaired coagulation. Minimizing operative blood loss is an indispensable goal of the highest priority. As the result of our comparative study focused on the pre-coagulation cases with pathologically severe liver fibrosis, intra-operative blood loss was significantly decreased in the pre-coagulation group and operative time was shorter as compared to the non-coagulation group.

Liver resection using combined pre-coagulation devices contribute to less operative bleeding and shorter operative time. However, this thermal technique is not widely accepted as an effective method. The main reasons for this are considered to be the potential risk for bile duct thermal injury, thrombogenesis in the vessel, and toxicity of remnant necrosis on the transection plane. Some reports found that transection near the hepatic hilar with these devices occasionally caused an increased risk of thermal injury and abdominal abscess.\textsuperscript{20-25} Alternatively, several studies reported the safety of liver resection with pre-coagulation, including hepatic hilar dissection cases.\textsuperscript{26-28} In our 20 cases, there were no biliary leakage cases. Although there was one case with a
perihepatic abscess, it is unclear whether the abscess was a result of remnant necrotic tissue. As almost all heptatectomies for the normal liver are able to be safety performed by the conventional operative method, it is necessary to ascertain surgical indication carefully, especially, the utilization at the deep parenchymal tissue, considering account of their cost-effectiveness.

Recently, Qiu et al.\textsuperscript{29} demonstrated improved survival rates for the surgical resection of liver tumor with coagulation. Huang et al.\textsuperscript{30} reported that liver resection with a coagulation device had better oncological outcomes in comparison to CUSA and showed the possibility of the systemic and local immunomodulatory effect involving induction of kupffer cells and effector CD-8 T cells, further improving oncological outcomes. It was suggested that necrotic tissue contained a portion of tumor on the transection plane affected as the trigger and can activate immunocyte cells. In fact, in this study, recurrence-free survival rates of the cases with pre-coagulation therapy were significantly lower than that of the non-coagulation therapy patients. However, RCTs and larger series are needed to better understand the potential advantages of the cases with pre-coagulation therapy recurrence free-survival rates.

The availability of pre-coagulation therapy for liver cirrhosis cases was analyzed in our comparative study. It was demonstrated that the pre-coagulation therapy was
occasionally an effective method to reduce bleeding, shorten operative time, and contribute to the prevention of recurrence. The pre-coagulation therapy may be a preferred choice of therapy as a countermeasure for hepatectomy patients with severe liver fibrosis.

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Informed Consent Policy

The present study was approved by the local institutional ethics committee of Showa University Hospital. All patients provided a written informed consent prior to the procedure.
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Figure with Legends

Fig. 1  The resection line was determined using ultrasonography and marked. Initially, the liver parenchymal plane was pre-coagulated by repeated insertion of the thermal device needles along the intended resection line. Then, the pre-coagulated liver parenchymal tissue was transected using the clump crushing method or CUSA.

Fig. 2  Recurrence-free survival (RFS). Median RFS time in the pre-coagulation group (733 days) was significantly longer than that in the non-coagulation group (400 days) (p=0.132).

Fig. 3  Overall survival (OS). There was no difference between the two groups (p = 0.62).
1\textsuperscript{st}-step: Pre-coagulation

2\textsuperscript{nd}-step: parenchymal transection

Coagulation device

Clamp-crashing / CUSA
Figure 3

A Kaplan-Meier survival curve showing overall survival over time. The curve for the H group has a median of 2063 days, and the curve for the N group has a median of 2101 days. The p-value for the comparison is 0.625.
| Characteristics                  | Group C: pre-coagulation (+) (n = 20) | Group N: pre-coagulation (-) (n = 53) | P value |
|---------------------------------|--------------------------------------|-------------------------------------|---------|
| a) Patient Factor               |                                       |                                     |         |
| Gender (M/F)                    | 12 / 8                               | 36 / 17                             | 0.68    |
| Age (y)                         | 66.7 (52-79)                         | 67.2 (46-85)                        | 0.83    |
| Liver disease                   |                                       |                                     | 0.48    |
| HCC                             | 20 (100%)                            | 48 (90.6%)                          |         |
| CRLM                            | 0 (0%)                               | 0 (0%)                              |         |
| CCC                             | 0 (0%)                               | 3 (5.7%)                            |         |
| Others                          | 0 (0%)                               | 2 (3.7%)                            |         |
| Cirrhosis etiology              |                                       |                                     | 0.16    |
| HCV                             | 8 (40%)                              | 35 (66%)                            |         |
| HBV                             | 5 (25%)                              | 9 (17%)                             |         |
| Alcohol                         | 2 (10%)                              | 2 (3.8%)                            |         |
| NAFLD                           | 4 (20%)                              | 3 (5.7%)                            |         |
| Others                          | 1 (5%)                               | 4 (7.5%)                            |         |
| PLT (×10,000/μl)                | 12.5 (6.7-21.1)                      | 13.1 (4-31.9)                       | 0.66    |
| PT (%)                          | 80.1 (63-100)                        | 83.8 (57-100)                       | 0.20    |
| Alb (g/dl)                      | 3.8 (2.8-4.6)                        | 3.6 (2.7-4.5)                       | 0.20    |
| Child-Pugh classification       | 5.5 (5-7)                            | 5.3 (5-8)                           | 0.29    |
| ICG 15 (%)                      | 21.8 (6-47)                          | 19.3 (6-56)                         | 0.45    |
| 99mTc-GSA (LHL15)               | 0.79 (0.57-0.96)                     | 0.81 (0.56-0.93)                    | 0.61    |
| Tumor maker                     |                                       |                                     |         |
| AFP (ng/ml)                     | 125.6 (2-1417)                       | 338.0 (2-3066)                      | 0.21    |
| PIVKA-II (mAU/m)                | 234.0 (11-1783)                      | 326.4 (6-4330)                      | 0.64    |
| b) Tumor Factor                 |                                       |                                     |         |
| Number                          | 1.3 (1-3)                            | 1.4 (1-7)                           | 0.82    |
| Tumor Diameter (mm)             | 29.8 (11-90)                         | 30.5 (7-70)                         | 0.87    |
| Location                        |                                       |                                     | 0.68    |
| S1                              | 0 (0%)                               | 1 (1.9%)                            |         |
| S2                              | 0 (0%)                               | 3 (5.7%)                            |         |
|    | S3  |     | S4  |     | S5  |     | S6  |     | S7  |     | S8  |     |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|    | 2 (10%) | 3 (5.7%) | 3 (15%) | 5 (9.4%) | 5 (25%) | 5 (9.4%) | 5 (25%) | 9 (16.9%) | 1 (5%) | 4 (7.5%) | 3 (15%) | 7 (13.2%) |

HCC: hepatocellular carcinoma  
CCC: cholangiocellular carcinoma  
CRLM: colorectal liver metastasis  
NAFLD: non-alcoholic fatty liver disease  
99mTc-GSA (LHL15): 99mTc-galactosyl serum albumin (uptake ratio of the liver to the liver plus heart at 15 minutes)
| Characteristics          | Group C : pre-coagulation (+) (n = 20) | Group N : pre-coagulation (-) (n = 53) | P value |
|-------------------------|--------------------------------------|---------------------------------------|---------|
| Operation Procedure     |                                      |                                       | 0.27    |
| Hr0                     | 14 (70%)                             | 29 (55.8%)                            |         |
| >Hr0                    | 6 (30%)                              | 23 (44.2%)                            |         |
| Operative Time (min)    | 214 (55-485)                         | 276 (96-600)                          | 0.06    |
| Blood loss (g)          | 282 (5-1470)                         | 563 (5-2195)                          | <0.05   |
| Blood transfusion       | 1 (5.6%)                             | 2 (5.9%)                              | 0.96    |
| Characteristics                  | Group C: pre-coagulation (+) | Group N: pre-coagulation (-) | P value |
|----------------------------------|------------------------------|------------------------------|---------|
|                                  | (n = 20)                     | (n = 53)                     |         |
| Morbidity                        |                              |                              | 0.76    |
| postoperative bleeding           | 1 (5%)                       | 1 (2%)                       |         |
| bile leak                        | 0                            | 0                            |         |
| perihepatic abscess             | 1 (5%)                       | 0                            |         |
| liver failure                    | 0                            | 0                            |         |
| ascites                          | 1 (5%)                       | 4 (8%)                       |         |
| SSI                              | 0                            | 0                            |         |
| pneumonia                        | 1 (5%)                       | 1 (2%)                       |         |
| other                            | 0                            | 4 (8%)                       |         |
| Mortality                        | 0 (0%)                       | 0 (0%)                       | 0.38    |
| Hospital stay (day)              | 14.6 (7-33)                  | 20.5 (3-89)                  | 0.12    |

SSI: surgical site infection
