Laparoscopic Liver Resection Is a Feasible Treatment for Patients with Hepatocellular Carcinoma and Portal Hypertension

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Abstract. *Aim: To compare outcomes of patients with primary hepatocellular carcinoma (HCC) and portal hypertension (PHT) who underwent laparoscopic liver resection (LLR), open liver resection (OLR) or radiofrequency ablation (RFA). Patients and Methods: We retrospectively reviewed 88 patients with primary HCC and PHT who underwent LLR (n=20), OLR (n=48) or RFA (n=20) and analyzed their outcomes by treatment group. To reduce selection bias, covariate distributions in groups were adjusted using inverse probability treatment weighting (IPTW). Results: Five-year recurrence-free survival (RFS) was significantly better in the LLR and OLR than in the RFA group both before and after IPTW adjustment. The OLR group had significantly more postoperative complications than the RFA group; however, there was no significant difference in the postoperative complication rate between LLR and RFA groups. Conclusion: LLR may be a feasible treatment for patients with Barcelona Clinic Liver Cancer (BCLC) stage 0 or advanced hepatocellular carcinoma (A HCC) and PHT.*

Since the first international consensus conference in 2008 (1), laparoscopic liver resection (LLR) has been increasingly performed, with the technique continuing to evolve worldwide (2-6). However, clinical evidence is lacking in some areas. For example, it has not yet been determined whether LLR is indicated in patients with hepatocellular carcinoma (HCC) and portal hypertension (PHT) (7, 8).

The current guidelines of the Barcelona Clinic Liver Cancer (BCLC) Group (9) and the American Association for the Study of Liver Disease (AASLD) (10) advise that patients with HCC and clinically significant PHT are candidates for radiofrequency ablation (RFA) or liver transplantation and not for open liver resection (OLR). However, this recommendation is questionable because there are no sound data comparing the outcomes of RFA, OLR and LLR or reporting outcomes of LLR in patients with cirrhosis, HCC and PHT.

Clinically significant PHT, defined as a hepatic venous pressure gradient (HVPG) ≥10 mmHg, is reportedly the most powerful predictor of postoperative liver failure and poor long-term survival in patients with Child–Pugh A liver function (11). However, this conclusion was based on a retrospective cohort study of only 77 patients who had undergone open liver resection (OLR). Since preoperative HVPG measurement is invasive, it is not performed routinely in most liver centres. Rather, indirect clinical characteristics, including presence of oesophageal varices (EVs) and/or splenomegaly associated with thrombocytopenia, are used to diagnose PHT (12). Conversely, many studies have reported that OLR improves survival in patients with PHT and that PHT is not an absolute contraindication to hepatectomy in patients with cirrhosis (13, 14). Given the very limited availability of liver transplant donor organs (15), surgical resection may be a better treatment option for some patients with HCC and clinical PHT (16). Moreover, LLR may be safer than OLR in patients with HCC and cirrhosis because postoperative ascites and other complications occur less frequently after the former procedure (17-19).

In this study, we compared the outcomes of patients with BCLC stages 0 and advanced hepatocellular carcinoma (A HCC) and PHT who had undergone LLR, LR or RFA. We

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Key Words: Laparoscopic liver resection, BCLC stage 0 and A, oesophageal varices, splenomegaly.

Table I. *Characteristics of patients with BCLC stage 0 and A HCC and portal hypertension according to treatment group.*

Variables	LLR (n=20)	OLR (n=48)	RFA (n=20)	*p*-Value LLR *vs*. OLR	OLR *vs*. RFA	LLR *vs*. RFA
Age (years)	74±6	70±7	73±9	0.007	0.02	0.64
Gender (% male)	9 (45%)	26 (54%)	11 (55%)	0.48	0.95	0.53
HBsAg positive	2 (10%)	4 (8%)	1 (5%)	0.83	0.63	0.54
Anti-HCVAb positive	15 (75%)	37 (77%)	14 (70%)	0.85	0.54	0.72
Esophageal varices	13 (65%)	36 (75%)	15 (75%)	0.40	1.00	0.49
Splenomegaly	11 (55%)	30 (63%)	15 (75%)	0.56	0.32	0.18
ASA status >3	2 (10%)	7 (15%)	2 (10%)	0.61	0.61	1.00
Serum biochemistry						
Albumin (g/dl)	4.2±0.5	3.8±0.5	3.7±0.4	0.002	0.65	0.003
Total bilirubin (mg/dl)	0.9±0.3	0.8±0.4	1.0±0.5	0.46	0.23	0.70
AST (U/l)	43±16	53±27	48±18	0.73	0.59	0.94
ALT (U/l)	41±17	49±38	44±27	0.16	0.64	0.42
Creatinine (mg/dl)	0.8±0.3	0.8±0.3	0.9±0.8	0.58	0.71	1.00
Prothrombin activity (%)	91±11	86±12	87±13	0.08	0.48	0.60
Platelet count ($\times 10^4$/μl)	12±6	9±3	8±2	0.003	0.46	0.002
ICGR15 (range, %)	26±15	26±13	29±19	0.70	0.83	0.59
Child-Pugh score (points)	5.2±0.4	5.6±0.7	5.5±0.7	0.03	0.44	0.25
AFP (ng/ml)	41±53	135±448	55±68	0.86	0.60	0.53
Maximum tumor						
Diameter (cm)	1.8±0.6	2.3±1.0	1.6±0.6	0.08	0.005	0.31
Number of tumors	1.1±0.2	1.3±0.6	1.1±0.3	0.07	0.20	0.57
Operation time (min)	185±50	232±89	–	0.03	–	–
Blood loss (ml)	241±319	412±431	–	0.02	–	–
Blood transfusion	3 (15%)	14 (29%)	0 (0%)	0.22	0.007	0.07
Postoperative serious complications (Clavien–Dindo ≥III) yes	2 (10%)	8 (16.7%)	1 (5%)	0.48	0.20	0.55

BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; LLR, laparoscopic liver resection; OLR, open liver resection; RFA, radiofrequency ablation; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; ASA, American Society of Anesthesiologists physical status score, AST, aspartate aminotransferase; ALT, alanine aminotransferase; ICGR15, indocyanine green retention test at 15 min; AFP, alpha-fetoprotein. Values are expressed as mean±standard deviation or number (percent).

used inverse probability treatment weighting (IPTW) to reduce patient selection bias. IPTW enhances the validity of comparing non-matched cases by using propensity scores to weight the samples. This minimises the confounding that otherwise frequently occurs in cohort studies of the effects of treatment on outcome. In addition, IPTW enables estimation of marginal or population-average treatment effects (20).

Patients and Methods

Patients and inclusion criteria. This study included 88 consecutively enrolled patients with primary HCC who had undergone LLR, OLR or RFA at the Hiroshima Red Cross and Atomic Bomb Survivors Hospitals between January 2008 and September 2015. All patients had a maximum of three tumours each measuring <3 cm or a solitary tumour <5 cm and had been diagnosed as having PHT, defined as the presence of EVs and/or a platelet count of <100,000/μl in association with splenomegaly. Presence of EVs was determined preoperatively based on upper gastrointestinal endoscopic findings (21). Splenomegaly was diagnosed as present when spleen length exceeded 10 cm on preoperative computed tomography (CT) (12, 22).

Diagnoses of HCC were made by pathological examination in the LLR and OLR groups and by pre-treatment imaging studies, including abdominal contrast-enhanced dynamic CT and gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) enhanced magnetic resonance imaging (MRI), in the RFA group (23, 24). Serious postoperative complications were defined as Clavien-Dindo grade III or higher (25, 26).

Surgical and RFA procedures and basis of treatment decisions. The indications for open and laparoscopic surgery were based on the patient's daily living activities, age and fitness, tumour location, degree of tumour invasion, extent of resection and remnant liver function (27-31), with the choice of these procedures mainly being based on Child-Pugh class and results of indocyanine green retention test at 15 min ($ICGR_{15}$). If their liver function was Child-Pugh class A or B and $ICGR_{15}$ ≤45%, they underwent LLR or OLR. If their $ICGR_{15}$ was greater than 45%, ^{99m}Tc-GSA scintigraphy was performed. If this showed an $ICGR_{15}$ of less than 45%, they underwent partial resection (32). Selection criteria for LLR depended on tumour location (mainly liver wedge and surface) and specific requests from the patient for laparoscopic surgery. The presence of ascites was considered an absolute contraindication to resection. The open hepatectomy procedures performed have been described elsewhere (28, 29). For laparoscopic liver resection, patients were placed in a supine position with the primary surgeon positioned on the right side of the patients and scopist positioned between legs.

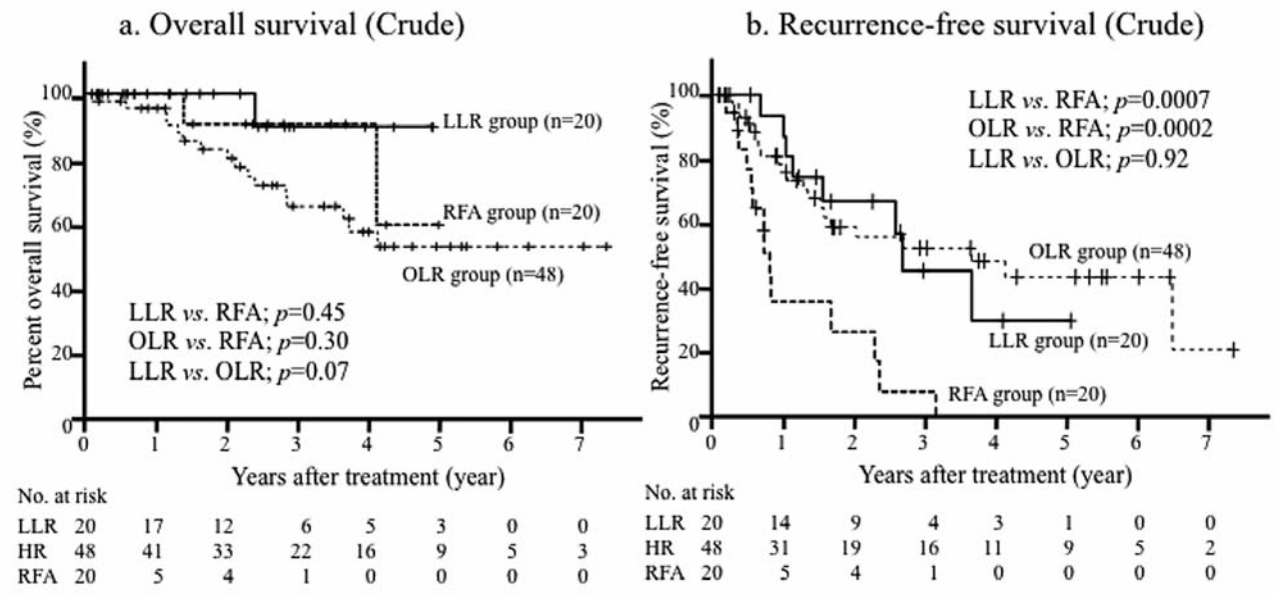


Figure 1. *Prognosis of 88 patients with Barcelona Clinic Liver Cancer (BCLC) stage 0, advanced hepatocellular carcinoma (A HCC) and portal hypertension (PHT) who underwent laparoscopic liver resection (LLR group; n=20), open liver resection (OLR group; n=48) or percutaneous radiofrequency ablation (RFA group; n=20) therapy. a: Unweighted (crude) Kaplan-Meier curve showing the percent overall survival (OS) after treatment. The OS of the LLR group (black line) was comparable to those of OLR (dotted line) and RFA group (small dotted line). b: Unweighted (crude) Kaplan-Meier curve of recurrence-free survival (RFS) after treatment. Five-year RFS was significantly better in the LLR (black line; p=0.0007) and OLR (dotted line; 0.0002) groups than in the RFA group (small dotted line).*

When lesions were located in the right lateral sectors, patients were placed in the left-lateral decubitus position. Trocars were inserted using an open technique. Until 2011, LLR procedures involved inducing a carbon dioxide (CO_2) pneumoperitoneum and performing parenchymal division with a Cavitron Ultrasonic Surgical Aspirator (CUSA) system (Valleylab™ , Boulder, CO, USA) under direct vision through a small laparotomy incision after minimal mobilization of the liver (33). From 2012, pure LLR was introduced in our institution.

All patients scheduled for RFA underwent outpatient abdominal ultrasonography (US) to assess the feasibility of US-guided percutaneous RFA (34). The technique and therapeutic strategy for RFA were the same as previously described (35). RFA treatment was selected for patients with Child-Pugh class A or B, contraindications to surgery or general anaesthesia, and those who requested RFA. Exclusion criteria for RFA comprised segment I tumours, tumours overhanging the liver margin and in close proximity to adjacent organs, such as the gallbladder, stomach or colon, and tumours located near major intrahepatic vessels. Written informed consent was obtained for surgical treatment or RFA therapy from all patients, in accordance with our hospital's guidelines. Decisions regarding treatment modalities were made at a meeting attended by all participating surgeons and gastroenterologists. Our study protocol conforms to the updated ethical guidelines of the 2013 Declaration of Helsinki and was approved by our Institutional Review Board.

Survival and recurrence. Patients underwent blood tests and CT scans every 3 months after LLR, OLR or RFA. Recurrence was diagnosed based on imaging findings. Patients with intrahepatic distant or local recurrence were variously managed with ablative

Table II. *Location in liver, surgical procedure, and resection weight of HCC tumors according to treatment group.*

Variables	LLR (n=20)	OLR (n=48)	RFA (n=20)
Tumor number	21	62	22
Tumor location (in liver segment)			
Segment I	0	2	0
Segment II	3	3	1
Segment III	7	6	0
Segment IV	4	10	1
Segment V	1	5	7
Segment VI	3	15	1
Segment VII	2	12	6
Segment VIII	1	9	6
Surgical procedure			
Partial resection	17	41	-
Segmentectomy	3	4	-
(lateral segment)	(3)	(0)	-
Lobectomy	0	3	-
Resection weight (g, range)	53±57 (8-221)	93±102 (6-452)	-

HCC, Hepatocellular carcinoma; LLR, laparoscopic liver resection; OLR, open liver resection; RFA, radiofrequency ablation. Segment is defined by the Couinaud's nomenclature. Values are expressed as number or mean±standard deviation (range).

Table III. *Univariate and multivariate analyses of overall survival in all HCC patients with portal hypertension.*

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Age (per 1 year)	1.00 (0.94-1.06)	0.94		
Gender: Male/Female	1.72 (0.69-4.65)	0.25		
Treatment (RFA/LLR, OLR)	0.59 (0.09-2.06)	0.45		
Treatment (LLR/RFA, OLR)	0.21 (0.01-1.03)	0.05	0.82 (0.04-9.34)	0.87
Treatment (OLR/LLR, RFA)	3.21 (1.06-13.8)	0.04	2.58 (0.67-17.1)	0.18
HBsAg positive	1.03 (0.16-3.68)	0.96		
Anti-HCVAb positive	1.33 (0.48-4.68)	0.60		
Esophageal varices (yes/no)	3.15 (0.89-20.0)	0.08	3.04 (0.76-20.6)	0.12
Splenomegaly	1.41 (0.56-4.02)	0.48		
ASA status <3 (yes/ no)	1.93 (0.40-34.7)	0.48		
Serum biochemistry				
Albumin (g/dl)	0.54 (0.24-1.27)	0.16		
Total bilirubin (mg/dl)	1.87 (0.71-4.21)	0.19		
AST (U/l)	1.03 (0.07-1.02)	0.98		
ALT (U/l)	0.98 (0.96-1.00)	0.14		
Creatinine (mg/dl)	0.87 (0.16-1.92)	0.82		
Prothrombin activity (%)	0.97 (0.94-1.02)	0.25		
Platelet count ($\times 10^4$/μl)	0.84 (0.71-0.99)	0.03	0.83 (0.64-1.21)	0.046
$ICGR_{15}$	1.03 (0.99-1.05)	0.09	1.02 (0.98-1.05)	0.38
Child-Pugh score (points)	1.61 (0.91-2.76)	0.10	0.99 (0.50-1.92)	0.98
AFP (ng/ml)	1.00 (1.00-1.00)	0.04	1.00 (1.00-1.00)	1.00
Maximum tumor diameter (cm)	1.22 (0.76-1.84)	0.38		
Number of tumors	1.60 (0.52-3.59)	0.36		
Postoperative serious complications (Clavien-Dindo ≥III) yes/no	2.43 (0.78-6.44)	0.11		

HCC, Hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; RFA, radiofrequency ablation; LLR, laparoscopic liver resection; OLR, open liver resection; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; ASA, American Society of Anesthesiologists physical status score; AST, aspartate aminotransferase; ALT, alanine aminotransferase; $ICGR_{15}$, indocyanine green retention test at 15 min; AFP, alpha-fetoprotein.

therapy, transcatheter arterial chemoembolization, surgery, laparoscopic microwave coagulation therapy, radiation or best supportive care. In case of death, survival time after surgery and cause of death were recorded.

Statistical analysis. For continuous variables, the Wilcoxon rank-sum test was used for non-parametric analyses. Categorical variables were compared using the χ^2 test. The Kaplan-Meier method was used to construct overall survival (OS) and recurrence-free survival (RFS) curves. All survival curves were compared using log-rank tests. To identify independent predictors of OS and RFS, factors with *p*-values <0.10 on univariate analysis were subjected to multivariate analysis using a Cox proportional hazards model.

IPTW analysis was used to overcome possible patient selection bias. Using propensity scores from the IPTW analysis, a logistic regression model was used to calculate the probability of each patient receiving LLR, OLR or RFA on the basis of clinicopathological variables. After IPTW balancing of the three groups, differences in OS and RFS rates were tested by Cox regression analyses. Statistical significance was defined as a *p*-value <0.05. Statistical analyses were performed using the R statistical programming environment and JMP 9.0 software (SAS Institute, Cary, NC, USA) (20).

Results

Clinicopathological characteristics of patients with BCLC stage 0 and A HCC and PHT according to treatment group. The preoperative background characteristics of the study patients according to treatment group are summarized in Table I. Compared to the OLR group, the LLR group had a greater mean age (74 *vs*. 70 years, $p=0.007$), mean serum albumin concentration (4.2 *vs*. 3.8 mg/dl, $p=0.027$) and mean platelet count (12 *vs*. 9×10^4/μl, $p=0.003$), lower Child-Pugh score (5.2 *vs*. 5.6 points, $p=0.03$), shorter mean operation time (185 *vs*. 232 minutes, $p=0.03$) and less mean blood loss (241 *vs*. 412 ml, $p=0.02$). Compared to the RFA group, the OLR group had a lower mean age (70 *vs*. 73 years, $p=0.02$). Compared to the RFA group, the LLR group had a greater mean serum albumin (4.2 *vs*. 3.7 mg/dl, $p=0.003$) and greater mean platelet count (12 *vs*. 8×10^4/μl, $p=0.003$). Table II shows tumour numbers, locations and weights, as well as surgical procedures performed according to treatment group. The mean resection weights were 53 and 93 g in the LLR and OLR groups, respectively ($p=0.08$, Table II).

Table IV. *Univariate and multivariate analyses of recurrence-free survival in all HCC patients with portal hypertension.*

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Age (per 1 year)	1.01 (0.97-1.06)	0.54		
Sex: Male/Female	0.97 (0.53-1.79)	0.91		
Treatment (RFA/LLR, OLR)	3.95 (1.97-7.64)	0.0002	3.02 (1.23-7.92)	0.02
Treatment (LLR/RFA, OLR)	0.72 (0.31-1.49)	0.40		
Treatment (OLR/LLR, RFA)	0.51 (0.27-0.95)	0.03	0.82 (0.36-2.03)	0.65
HBsAg positive	1.04 (0.31-2.59)	0.95		
Anti-HCVAb positive	0.71 (0.38-1.41)	0.31		
Esophageal varices (yes/ no)	1.64 (0.80-3.82)	0.19		
Splenomegaly	1.01 (0.55-1.90)	0.98		
ASA status <3 (yes/ no)	1.58 (0.57-6.56)	0.42		
Serum biochemistry				
Albumin (g/dl)	1.04 (0.57-1.96)	0.91		
Total bilirubin (mg/dl)	2.12 (1.00-4.15)	0.048	1.68 (0.83-3.21)	0.14
AST (U/l)	1.00 (0.98-1.01)	0.69		
ALT (U/l)	1.00 (0.99-1.00)	0.43		
Creatinine (mg/dl)	1.13 (0.56-1.74)	0.68		
Prothrombin activity (%)	1.00 (0.97-1.03)	0.97		
Platelet count ($\times 10^4/\mu l$)	0.93 (0.84-1.00)	0.06	0.94 (0.85-1.02)	0.13
$ICGR_{15}$	1.00 (0.98-1.02)	0.75		
Child-Pugh score (points)	1.10 (0.69-1.68)	0.67		
AFP (ng/ ml)	1.00 (1.00-1.00)	0.13		
Maximum tumor diameter (cm)	1.02 (0.72-1.39)	0.90		
Number of tumors	1.80 (0.80-3.51)	0.14		
Postoperative serious complications (Clavien-Dindo ≥III) yes/no	20.80 (0.27-1.86)	0.63		

HCC, Hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; RFA, radiofrequency ablation; LLR, laparoscopic liver resection; OLR, open liver resection; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; ASA, American Society of Anesthesiologists physical status score; AST, aspartate aminotransferase; ALT, alanine aminotransferase; $ICGR_{15}$, indocyanine green retention test at 15 min; AFP, alpha-fetoprotein.

Crude OS and RFS (before IPTW adjustment). The median duration of follow-up after surgery was 29.3 months (range=0.3-89.2). There were no significant differences in OS between the LLR, OLR and RFA groups (Figure 1a). By contrast, RFS at 1, 3 and 5 years was significantly better in the LLR than in the RFA group ($p<0.0007$): 81.3%, 46.3% and 30.9% *vs*. 36.8%, 9.2% and 0%, respectively (Figure 1b). RFS at 1, 3 and 5 years was also significantly better in the OLR than in the RFA group ($p<0.0002$): 76.4%, 53.2% and 44.2% *vs*. 36.8%, 9.2% and 0%, respectively (Figure 1b).

The clinicopathological factors were evaluated to identify those associated with worse OS (Table III). In univariate analyses, *p*-values for treatment with LLR or OLR, presence of oesophageal varices, platelet count, $ICGR_{15}$, Child-Pugh score and α-fetoprotein (AFP) were all <0.10. The inclusion of these seven variables in a multivariate Cox proportional hazards analysis showed that platelet count ($p=0.046$; hazard ratio (HR)=0.83; 95% confidence interval (CI)=0.64-0.99) was the only independent predictor of worse OS.

The clinicopathological factors were also evaluated to identify those associated with worse RFS (Table IV). In univariate analyses, *p*-values for treatment with RFA or OLR, serum total bilirubin and platelet count were all <0.10. The inclusion of these four variables in a multivariate Cox proportional hazards analysis showed that RFA ($p=0.02$; HR=3.02; 95% CI=1.53-4.29) was the only independent predictor of worse RFS.

Postoperative complications, hospital stay and recurrence pattern. In the OLR group, one in-hospital death secondary to sepsis occurred. This group had a significantly higher rate of postoperative complications than the RFA group (47.9 *vs*. 20%; $p=0.032$, Table V). There were no significant differences in overall postoperative or serious postoperative complications between the LLR and RFA groups. The OLR group had a significantly higher rate of postoperative ascites and pleural effusion than the LLR group (18.8 *vs*. 0%; $p=0.038$).

Patients in the OLR group also had a significantly longer postoperative hospital stay (median=15 days; range=7-66)

Table V. *Complications and mortality of HCC patients with portal hypertension according to treatment group*

Variables	LLR (n=20)	OLR (n=48)	RFA (n=20)
Complications	6 (30%)	23 (47.9%)	4 (20%)
Clavien–Dindo classification			
Grade I			
Shoulder pain	0 (0%)	0 (0%)	1 (5%)
Ascites (treated with diuretics)	0 (0%)	8 (16.7%)	0 (0%)
Grade II			
Superficial surgical site infection	1 (5%)	3 (6.3%)	0 (0%)
Colitis	1 (5%)	0 (0%)	0 (0%)
Cholangitis	0 (0%)	0 (0%)	3 (15%)
Delirium	2 (10%)	2 (4.2%)	0 (0%)
Pneumonia	0 (0%)	2 (4.2%)	0 (0%)
Grade IIIa			
Pleural effusion (requiring drainage)	0 (0%)	1 (2.1%)	1 (5%)
Ileus (requiring drainage)	1 (5%)	0 (0%)	0 (0%)
Deep surgical site infection	0 (0%)	2 (4.2%)	0 (0%)
Bile leakage (requiring drainage)	0 (0%)	2 (4.2%)	0 (0%)
Grade IVa			
Liver failure	1 (5%)	2 (4.2%)	0 (0%)
Grade V			
Sepsis	0 (0%)	1 (2.1%)	0 (0%)
Postoperative serious complications (Clavien–Dindo grade III or higher)	2 (10%)	8 (16.7%)	1 (5%)
Mortality	0 (0%)	1 (2.1%)	0 (0%)

HCC, Hepatocellular carcinoma; LLR, laparoscopic liver resection; OLR, open liver resection; RFA, radiofrequency ablation.

than the RFA group (median=8 days; range=2-14, $p<0.0001$). There was no significant difference in postoperative hospital stay between the LLR (median=9 days; range=7-14) and RFA groups.

At the time of data collection, tumour recurrence had developed in 8/20 patients in the LLR group, all of which (100%) were intrahepatic distant recurrences. In the OLR group, tumour recurrence had developed in 21/48 patients: 20 (95.2%) being intrahepatic distant and one (4.8%) local recurrence, whereas in the RFA group in 13/20 patients had developed recurrences: 9 (69.2%) intrahepatic distant and four (30.8%) local recurrences. The frequencies of intrahepatic distant and local recurrence differed significantly between the OLR and RFA groups ($p=0.038$).

OS and RFS after IPTW adjustment. Among the 20 clinicopathological variables (age, sex, hepatitis B surface antigen (HBsAg)-positive, anti-hepatitis C virus (HCV) antibody, oesophageal varices, splenomegaly, ASA status, albumin, total bilirubin, aspartate transaminase, alanine transaminase, creatinine, prothrombin activity, platelet count, $ICGR_{15}$, Child-Pugh score, AFP, maximum tumour diameter, number of tumours and blood transfusion), the distributive covariates that differed between the LLR and RFA groups were serum albumin concentration and platelet count (Table I). After IPTW adjustment of these two covariates, the weighted RFS of the LLR group remained significantly higher than that of the RFA group ($p=0.049$; adjusted HR= 0.39; 95% CI=0.12-1.24; Figure 2a). However, there was no significant difference between the weighted OS of the LLR and RFA groups ($p=0.70$, adjusted HR=0.61; 95% CI=0.05-7.63).

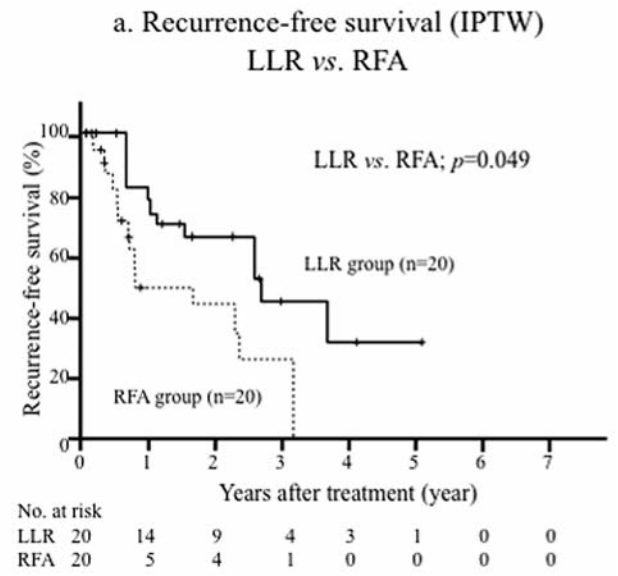
The distributive covariates that differed between the OLR and RFA groups were age, maximum tumour diameter and blood transfusion (Table I). After IPTW adjustment of these covariates, the weighted RFS of the OLR group remained significantly higher than that of the RFA group ($p=0.004$, adjusted HR=0.24; 95% CI=0.12-0.47; Figure 2b), whereas there was no significant difference between the weighted OS of the OLR and RFA groups ($p=0.60$, adjusted HR=1.34; 95% CI=0.39-4.64).

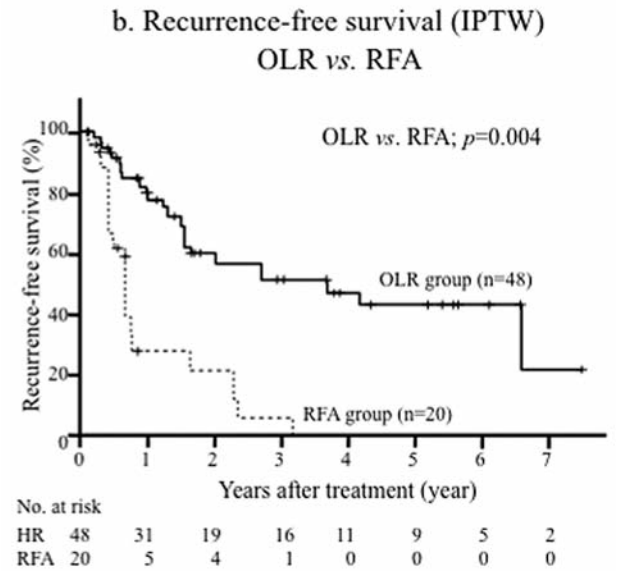
By contrast, there was no significant difference between the weighted OS and RFS of the LLR and OLR groups ($p=0.11$, adjusted HR=0.30; 95% CI=0.04-2.16 and $p=0.88$, adjusted HR=1.07; 95% CI=0.43-2.68, respectively; Figure 2c), considering the distributive covariates that differed between the LLR and OLR groups were age, serum albumin concentration, Child-Pugh score, operation time and blood loss (Table I).

Discussion

Treatment of patients with cirrhosis, HCC and PHT is currently hampered by a shortage of liver graft donors (15). According to the BCLC and AASLD guidelines, RFA is a valid option for the treatment of such patients; however, RFA has high local recurrence rates and there are some technical problems, such as locating tumours (19, 35, 36). We have reported that OLR may be an appropriate treatment option for patients with BCLC stage 0 or A HCC and PHT (36). However, in that study, RFA treatment was associated with fewer postoperative complications than OLR (36). We, therefore, decided to investigate the usefulness of treatment with the minimally invasive procedure of LLR in patients with cirrhosis, HCC and PHT postulating that this might further reduce the incidence of postoperative complications. In this study, we demonstrated that, in patients with primary HCC of BCLC stages 0 and A, the outcomes of the LLR group were better than those of the RFA group. Additionally, there was no significant difference in rate of postoperative complications between the LLR and RFA groups. To the best of our knowledge, this is the first study to report the feasibility of LLR treatment in cirrhotic patients with HCC and PHT.

Being a minimally invasive procedure, LLR results in less disturbance of collateral blood and lymphatic flow and, therefore, less bleeding, postoperative ascites and mesenchymal injury caused by compression of the liver than





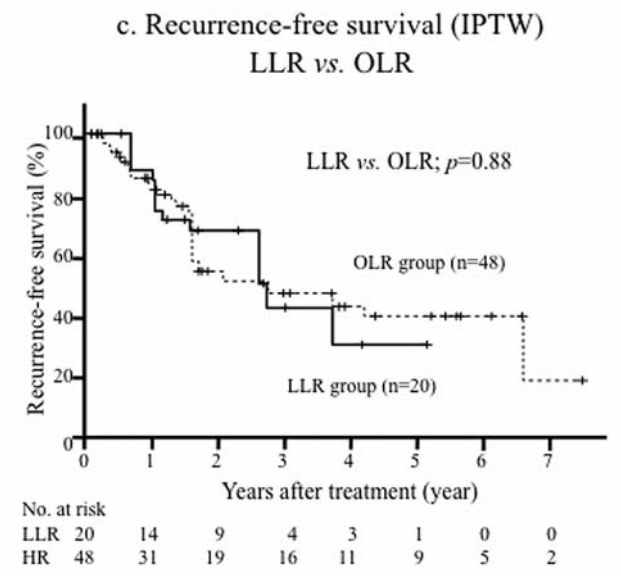


Figure 2. *Kaplan–Meier curve after inverse probability treatment weighting (IPTW) showing recurrence-free survival (RFS) after treatment. a: The RFS (%) of the laparoscopic liver resection (LLR) group (black line) was significantly better than that of the RFA group (dotted line, p=0.049). b: The RFS of the open liver resection (OLR) group (black line) was significantly better than that of the RFA group (dotted line, p=0.004). c: The RFS of the LLR (black line) and OLR (dotted line) groups were comparable (p=0.88).*

does laparotomy, which involves liver mobilization (37). During laparotomy, mobilization and detachment of the liver can result in massive postoperative ascites, pleural effusion and bleeding, especially in patients with PHT because collateral veins and lymphatic vessels have developed around the liver and peritoneum. Such complications, which can lead to severe postoperative liver failure, are less frequent and severe after LLR than after OLR, partly because the small incision of LLR limits evacuation of ascites, thereby reducing the risk of infection with the dual benefits of less need for fluid infusion and improved reabsorption of ascites.

In our study, the reasons for better RFS of the LLR and OLR groups than the RFA group are not clear; however, at least in theory, LLR and OLR have the advantage of offering better local control of HCC because of complete resection of HCCs, whereas RFA carries a potential risk of local recurrence associated with insufficient ablation (38).

Moreover, despite significant differences in recurrence rates, survival rates were similar in the LLR, OLR and RFA groups. Patients were followed up every 3 or 4 months after RFA treatment, enabling early detection of recurrence and more rapid and appropriate treatment with surgical or interventional methods, which may explain why the high HCC recurrence rate in the RFA group was not associated with a detectably higher death rate.

There are several technical aspects to performing LLR in patients with cirrhosis, HCC and PHT. When the five or six surgical trocars are inserted into the abdominal wall, care must be taken to avoid injuring the collateral veins that have developed in the abdominal wall. Since these patients often have thrombocytopenia, injury to vessels in the abdominal wall by insertion of trocars is one of the major causes of postoperative bleeding. In this study, none of the tumours were located in Segment I in the liver; however, we believe that LLR is indicated for all HCCs, regardless of their locations in the liver. In general, it is technically difficult to resect tumours located in Segment VII and VIII by LLR;

however, resection of tumours in these locations can be facilitated by placing the patient in a semi-prone position and using a transthoracic trocar (39). On the other hand, since this approach requires only a small incision, LLR has a technical advantage over OLR when resecting tumours located on the edge and surface of liver in Segment II-VI. However, central lesions in patients with cirrhosis, HCC and PHT that would require massive hepatectomy may be better treated by RFA to minimize the risk of postoperative liver failure. To prevent intraoperative bleeding during hepatectomy by LLR, it may be necessary to implement both Pringle's manoeuvre (40) and precoagulation methods (41) to achieve hemostasis during liver parenchyma transection before hepatectomy. These techniques may make the LLR in patients with cirrhosis, HCC and PHT more feasible and effective in the future.

Our study had several limitations. First, the sample was relatively small, which made it difficult to evaluate the outcomes of HCC patients with BCLC stage 0 and A disease and PHT who underwent LLR, OLR or RFA. However, no previous study has compared these three treatment groups. Second, our findings may not be applicable in other centres because this was a single-centre retrospective study and not a randomized controlled trial, which is why we used IPTW to adjust for selection bias. Additionally, LLR in patients with PHT is a technically challenging procedure. Technological advances and accumulation of experience may make LLR in such patients safer and more effective and, thus, achieve better OS than OLR and RFA. In the future, more favourable outcomes may be achieved in carefully selected patients in high volume centres.

In conclusion, our findings that the RFS of the LLR group was significantly better than that of the RFA group and also the fact that there was no significant difference in incidence of postoperative complications between the LLR and RFA groups indicate that LLR may be a feasible treatment option for patients with BCLC stage 0 or A HCC and PHT. Good candidates for LLR include patients with tumours on the liver edge or surface and in whom ablation therapy would be difficult.

Conflicts of Interest

The Authors declare that they have no conflict of interest.

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References

1 Buell JF, Cherqui D, Geller DA, O'Rourke N, Iannitti D, Dagher I, Koffron AJ, Thomas M, Gayet B, Han HS, Wakabayashi G, Belli G, Kaneko H, Ker CG, Scatton O, Laurent A, Abdalla EK, Chaudhury P, Dutson E, Gamblin C, D'Angelica M, Nagorney D, Testa G, Labow D, Manas D, Poon RT, Nelson H, Martin R, Clary B, Pinson WC, Martinie J, Vauthey JN, Goldstein R, Roayaie S, Barlet D, Espat J, Abecassis M, Rees M, Fong Y, McMasters KM, Broelsch C, Busuttil R, Belghiti J, Strasberg S and Chari RS: The international position on laparoscopic liver surgery. Ann Surg *250*: 825-830, 2009.

2 Nguyen KT, Gamblin TC and Geller DA: World review of laparoscopic liver resection-2804 patients. Ann Surg *250*: 831-841, 2009.

3 Bryant R, Laurent A, Tayar C and Cherqui D: Laparoscopic liver resection-understanding its role in current practice: the Henri Mondor Hospital experience. Ann Surg *250*: 103-111, 2009.

4 Sasaki A, Nitta H, Otsuka K, Takahara T, Nishizuka S and Wakabayashi G: Ten-year experience of totally laparoscopic liver resection in a single institution. Br J Surg *96*: 274-279, 2009.

5 Dagher I, O'Rourke N, Geller DA, Cherqui D, Belli G, Gamblin TC, Lainas P, Laurent A, Nguyen KT, Marvin MR, Thomas M, Ravindra K, Fielding G, Franco D and Buell JF: Laparoscopic major hepatectomy: an evolution in standard of care. Ann Surg *250*: 856-860, 2009.

6 Lin NC, Nitta H and Wakabayashi G: Laparoscopic major hepatectomy: a systematic literature review and comparison of 3 techniques. Ann Surg *257*: 205-213, 2013.

7 Hibi T, Cherqui D, Geller DA, Itano O, Kitagawa Y and Wakabayashi G: Expanding indications and regional diversity in laparoscopic liver resection unveiled by the International Survey on Technical Aspects of Laparoscopic Liver Resection (INSTALL) study. Surg Endosc Oct 20, 2015.

8 Makuuchi M, Kosuge T, Takayama T, Yamazaki S, Kakazu T, Miyagawa S and Kawasaki S: Surgery for small liver cancers. Semin Surg Oncol *9*: 298-304, 1993.

9 Forner A, Reig ME, de Lope CR and Bruix J: Current strategy for staging and treatment. Semin Liver Dis *30*: 61-74, 2010.

10 Bruix J and Sherman M: Management of hepatocellular carcinoma: an update. Hepatology *53*: 1020-1022, 2011.

11 Bruix J, Castells A, Bosch J, Feu F, Fuster J, Garcia-Pagan JC, Visa J, Bru C and Rodés J: Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology *111*: 1018-1022, 1996.

12 Ishizawa T, Hasegawa K, Aoki T, Takahashi M, Inoue Y, Sano K, Imamura H, Sugawara Y, Kokudo N and Makuuchi M: Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. Gastroenterology *134*: 1908-1916, 2008.

13 Cucchetti A, Ercolani G, Vivarelli M, Cescon M, Ravaioli M, Ramacciato G, Grazi GL and Pinna AD: Is portal hypertension a contraindication to hepatic resection? Ann Surg *250*: 922-928, 2009.

14 Capussotti L, Ferrero A, Viganò L, Muratore A, Polastri R and Bouzari H: Portal hypertension: contraindication to liver surgery? World J Surg *30*: 992-999, 2006.

15 Dutkowski P, Linecker M, DeOliveira ML, Müllhaupt B and Clavien PA. Challenges to liver transplantation and strategies to improve outcomes. Gastroenterology *148*: 307-323, 2015.

16 Harada N, Shirabe K, Maeda T, Kayashima H, Ishida T and Maehara Y: Surgical resection for hepatocellular carcinoma with concomitant esophageal varices. World J Surg *39*: 2510-2518, 2015.

17 Takahara T, Wakabayashi G, Beppu T, Aihara A, Hasegawa K, Gotohda N, Hatano E, Tanahashi Y, Mizuguchi T, Kamiyama T, Ikeda T, Tanaka S, Taniai N, Baba H, Tanabe M, Kokudo N, Konishi M, Uemoto S, Sugioka A, Hirata K, Taketomi A, Maehara Y, Kubo S, Uchida E, Miyata H, Nakamura M, Kaneko

H, Yamaue H, Miyazaki M and Takada T: Long-term and perioperative outcomes of laparoscopic *versus* open liver resection for hepatocellular carcinoma with propensity score matching: a multi-institutional Japanese study. J Hepatobiliary Pancreat Sci *22*: 721-727, 2015.
18 Kanazawa A, Tsukamoto T, Shimizu S, Kodai S, Yamazoe S, Yamamoto S and Kubo S: Impact of laparoscopic liver resection for hepatocellular carcinoma with F4-liver cirrhosis. Surg Endosc *27*: 2592-2597, 2013.
19 Vitali GC, Laurent A, Terraz S, Majno P, Buchs NC, Rubbia-Brandt L, Luciani A, Calderaro J, Morel P, Azoulay D and Toso C: Minimally invasive surgery *versus* percutaneous radio frequency ablation for the treatment of single small (≤3 cm) hepatocellular carcinoma: a case-control study. Surg Endosc Nov 3, 2015. doi: 10.1007/s00464-015-4295-6. [Epub ahead of print]
20 Austin PC: The performance of different propensity score methods for estimating marginal hazard ratios. Stat Med *32*: 2837-2849, 2013.
21 Tajiri T, Yoshida H, Obara K, Onji M, Kage M, Kitano S, Kokudo N, Kokubu S, Sakaida I, Sata M, Tajiri H, Tsukada K, Nonami T, Hashizume M, Hirota S, Murashima N, Moriyasu F, Saigenji K, Makuuchi H, Oho K, Yoshida T, Suzuki H, Hasumi A, Okita K, Futagawa S and Idezuki Y: General rules for recording endoscopic findings of esophagogastric varices (2nd edition). Dig Endosc *22*: 1-9, 2010.
22 Bezerra AS, D'Ippolito G, Faintuch S, Szejnfeld J and Ahmed M: Determination of splenomegaly by CT: is there a place for a single measurement? Am J Roentgenol *184*: 1510-1513, 2005.
23 Bruix J and Sherman M: Management of hepatocellular carcinoma. Hepatology *42*: 1208-1236, 2005.
24 Maiwald B, Lobsien D, Kahn T and Stumpp P: Is 3-Tesla Gd-EOB-DTPA-enhanced MRI with diffusion-weighted imaging superior to 64-slice contrast-enhanced CT for the diagnosis of hepatocellular carcinoma? PLoS One *9*: e111935, 2014.
25 Dindo D, Demartines N and Clavien PA: Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg *240*: 205-213, 2004.
26 Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, Koch M, Makuuchi M, Dematteo RP, Christophi C, Banting S, Usatoff V, Nagino M, Maddern G, Hugh TJ, Vauthey JN, Greig P, Rees M, Yokoyama Y, Fan ST, Nimura Y, Figueras J, Capussotti L, Büchler MW and Weitz J. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery *149*: 713-724, 2011.
27 Shirabe K, Takeishi K, Taketomi A, Uchiyama H, Kayashima H and Maehara Y: Improvement of long-term outcomes in hepatitis C virus antibody-positive patients with hepatocellular carcinoma after hepatectomy in the modern era. World J Surg *35*: 1072-1084, 2011.
28 Yamashita Y, Tsuijita E, Takeishi K, Ishida T, Ikegami T, Ezaki T, Maeda T, Utsunomiya T, Nagasue N, Shirabe K and Maehara Y: Trends in surgical results of hepatic resection for hepatocellular carcinoma: 1,000 consecutive cases over 20 years in a single institution. Am J Surg *207*: 890-896, 2014.
29 Takeishi K, Shirabe K, Muto J, Toshima T, Taketomi A and Maehara Y: Clinicopathological features and outcomes of young patients with hepatocellular carcinoma after hepatectomy. World J Surg *35*: 1063-1071, 2011.
30 Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC and Williams R: Transection of the oesophagus for bleeding oesophageal varices. Br J Surg *60*: 646-649, 1973.
31 Chau GY, Lui WY, King KL and Wu CW: Evaluation of effect of hemihepatic vascular occlusion and the Pringle maneuver during hepatic resection for patients with hepatocellular carcinoma and impaired liver function. World J Surg *29*: 1374-1383, 2005.
32 Kawamura H, Kamiyama T, Nakagawa T, Nakanishi K, Yokoo H, Tahara M, Kamachi H, Toi H, Matsushita M and Todo S: Preoperative evaluation of hepatic functional reserve by converted $ICGR_{15}$ calculated from Tc-GSA scintigraphy. J Gastroenterol Hepatol *23*: 1235-1241, 2008.
33 Yamashita Y, Ikeda T, Kurihara T, Yoshida Y, Takeishi K, Itoh S, Harimoto N, Kawanaka H, Shirabe K and Maehara Y: Long-term favorable surgical results of laparoscopic hepatic resection for hepatocellular carcinoma in patients with cirrhosis: a single-center experience over a 10-year period. J Am Coll Surg *219*: 1117-1123, 2014.
34 Rhim H, Choi D, Kim YS, Lim HK and Choe BK: Ultrasonography-guided percutaneous radiofrequency ablation of hepatocellular carcinomas: a feasibility scoring system for planning sonography. Eur J Radiol *75*: 253-258, 2010.
35 Waki K, Aikata H, Katamura Y, Kawaoka T, Takaki S, Hiramatsu A, Takahashi S, Toyota N, Ito K and Chayama K: Percutaneous radiofrequency ablation as first-line treatment for small hepatocellular carcinoma: results and prognostic factors on long-term follow up. J Gastroenterol Hepatol *25*: 597-604, 2010.
36 Harada N, Shirabe K, Maeda T, Kayashima H, Takaki S and Maehara Y: Comparison of the Outcomes of Patients with Hepatocellular Carcinoma and Portal Hypertension After Liver Resection *vs*. Radiofrequency Ablation. World J Surg Feb 24, 2016.
37 Morise Z, Sugioka A, Kawabe N, Umemoto S, Nagata H, Ohshima H, Kawase J, Arakawa S and Yoshida R: Pure laparoscopic hepatectomy for hepatocellular carcinoma patients with severe liver cirrhosis. Asian J Endosc Surg *4*: 143-146, 2011.
38 Cammà C, Di Marco V, Orlando A, Sandonato L, Casaril A, Parisi P, Alizzi S, Sciarrino E, Virdone R, Pardo S, Di Bona D, Licata A, Latteri F, Cabibbo G, Montalto G, Latteri MA, Nicoli N and Craxì A: Treatment of hepatocellular carcinoma in compensated cirrhosis with radio-frequency thermal ablation (RFTA): a prospective study. J Hepatol *42*: 535-540, 2005.
39 Ikeda T, Yonemura Y, Ueda N, Kabashima A, Shirabe K, Taketomi A, Yoshizumi T, Uchiyama H, Harada N, Ijichi H, Kakeji Y, Morita M, Tsujitani S and Maehara Y: Pure laparoscopic right hepatectomy in the semi-prone position using the intrahepatic Glissonian approach and a modified hanging maneuver to minimize intraoperative bleeding. Surg Today *41*: 1592-1598, 2011.
40 Pringle JH. V. Notes on the Arrest of Hepatic Hemorrhage Due to Trauma. Ann Surg *48*: 541-549, 1908.
41 Itano O, Ikoma N, Takei H, Oshima G and Kitagawa Y: The superficial precoagulation, sealing, and transection method: a "bloodless" and "ecofriendly" laparoscopic liver transection technique. Surg Laparosc Endosc Percutan Tech *25*: e33-36, 2015.

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