Laparoscopic Liver Resection Ameliorates the Postoperative Liver Function Impairment for Hepatocellular Carcinoma Patients

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Abstract: To study whether laparoscopic liver resection (LLR) is able to alleviate the postoperative liver function impairment for hepatocellular carcinoma patients, the clinical data of 103 patients were retrospectively analyzed, including 42 patients who underwent LLR and 61 patients who underwent open liver resection (OLR), during the period spanning from 2012 to 2017. The postoperative peak aspartate aminotransferase and alanine aminotransferase levels in the LLR group were significantly lower than those of the OLR group (209.76 ± 189.516 vs. 262.55 ± 181.19, \( P = 0.046 \); 250.56 ± 200.944 vs. 411.01 ± 412.51, \( P = 0.005 \), for aspartate aminotransferase and alanine aminotransferase, respectively). The recovering of postoperative total protein and albumin in the LLR group was faster than that in the OLR group, and the total protein and albumin levels on the postoperative day-5 were significantly higher in the LLR group than in the OLR group (62.528 ± 9.427 vs. 57.87 ± 6.101, \( P = 0.019 \); 36.456 ± 4.875 vs. 33.653 ± 4.112, \( P = 0.012 \), respectively). In conclusion, these data show that LLR alleviates postoperative liver function impairment and increases liver function recovery.

Key Words: laparoscopic liver resection, open liver resection, aspartate aminotransferase, alanine aminotransferase

(Hepatocellular carcinoma (HCC), which accounts for 70% to 90% of primary liver cancer (PLC) cases, is the third leading cause of cancer-related deaths worldwide. Currently, surgical resection is the recommended treatment method for early-stage HCC. Laparoscopic liver resection (LLR) has been used for HCC patients by Hashizume et al, and, since the Louisville Consensus Conference on Laparoscopic Liver Resection (Morioka, 2014) and the European Guidelines Meeting on Laparoscopic Liver Surgery (Southampton, 2017) state that the outcomes of LLR are not inferior to those of open liver resection (OLR) regarding operative mortality and margin negativity. The Asia Pacific Consensus Statement on Laparoscopic Liver Resection for Hepatocellular Carcinoma (Hong Kong, 2016) reported that LLR produces a better oncological outcome for HCC patients compared with radiofrequency ablation. It is widely regarded that LLR is superior in decreasing postoperative complications, blood loss, and the length of the postoperative hospital stay. We speculated that the superiority of LLR may result from the alleviated impairment of liver function after LLR.

Initially, LLR was applied for tumors located at the lower edge and lateral segments of the liver that could be resected more easily than posterosuperior segments. With the development of technology and the growing experience of hepatobiliary surgeons, LLR has been expanded to major liver resections, anatomic resections, and donor hepatectomies by skilled surgeons. However, due to the concerns over the risk of operative bleeding, tumor seeding, and positive resection margin, the true benefit of LLR remains unclear across the surgical community.

The indications for traditional open hepatectomy are very limited, especially for liver cirrhosis. Nonsurgical ablation or transcatheter arterial chemoembolization is usually applied for these unresectable patients. However, along with the development of the LLR equipment, such as the ultrasonic knife under the endoscope and laparoscopic ultrasonography, the indications for LLR of HCC have expanded. Even for HCC patients having a cirrhotic liver, LLR is a good alternative, safe, and feasible treatment option currently.

The recommendations of the Second International Consensus Conference on Laparoscopic Liver Resection (Morioka, 2014) and the European Guidelines Meeting on Laparoscopic Liver Surgery (Southampton, 2017) state that the outcomes of LLR are not inferior to those of open liver resection (OLR) regarding operative mortality and margin negativity. The Asia Pacific Consensus Statement on Laparoscopic Liver Resection for Hepatocellular Carcinoma (Hong Kong, 2016) reported that LLR produces a better oncological outcome for HCC patients compared with radiofrequency ablation. It is widely regarded that LLR is superior in decreasing postoperative complications, blood loss, and the length of the postoperative hospital stay. We speculated that the superiority of LLR may result from the alleviated impairment of liver function after LLR.

METHODS

Ethical Approval

All procedures involving humans were carried out in accordance with the ethical standards of the 2013 Declaration of Helsinki and were approved by the Institutional Review Board of the Second Affiliated Hospital of Anhui Medical University.

Study Design

This retrospective case-control study was designed to test the STROBE Statement. Totally, 103 patients who underwent liver resection for HCC were included and retrospectively analyzed in this study during the period spanning from October 1, 2012, to May 31, 2017. All cases of LLR and OLR were performed mostly by a professional hepatobiliary surgeon.
Inclusion and Exclusion Criteria

The cases recruited in both the LLR and OLR groups met the following inclusion criteria: (1) without any surgical contraindication; (2) the diagnosis of HCC was confirmed by the postoperative pathologic evidence; (3) without liver operation history; (4) all the included patients were initially treated for HCC, without previous radiofrequency ablation, microwave treatment, transcatheter arterial chemoembolization, or transcatheter arterial embolization. The exclusion criteria included the following (and they are): (1) mixed HCC with cholangiocarcinoma; (2) ruptured HCC; (3) accompanied by intrahepatic or extrahepatic bile duct stones; and (4) accompanied by other benign liver tumors, such as hemangioma. Some patients refused LLR treatment due to the higher cost and tended to select OLR.

LLR Procedure

General anesthesia was performed routinely. Patients were in the supine position with 15-degree incline. The trocar insertion sites were set depending on the site of the tumor. Five trocars were inserted usually to have optional operative manipulation. A trocar was placed below the umbilicus for pneumoperitoneum creation, and the abdominal pressure was maintained at 12 to 14 mm Hg normally. The site of the liver tumor and its relationship to the vasculature was confirmed using laparoscopic ultrasonography. The line of planned hepatic transection was marked on the liver surface with unipolar electrocaugetation. “Bulldog” was used for Pringle blood blocking. “Hemolock” or “Titanium clip” was used for bleeding vessel occlusion. A laparoscopic harmonic scalpel was applied for liver transection and hepatic pedicle was clipped with a linear cut stapler if necessary. The hepatic cross-section was checked for bleeding or bile leak- ing, and residual fluid was removed by suction. The specimen was removed from the epigastric port wound.

Clinical Outcomes

The first outcomes were the levels of preoperative or postoperative aspartate aminotransferase (ALT), alanine aminotransferase (AST), albumin (ALB), total bilirubin (TB), and total protein (TP). The secondary observations are tumor size, location of the tumor, type of liver resection, operation time, during-operation transfusion rate, R0 resection rate, and blood clamping time. The postoperative hospital stay, complications (including biliary fistula, bleeding, incision infection, ileus, pleural effusion, ascites, and liver failure), and 30-day mobility rate were analyzed.

Statistical Analysis

Baseline variables that were considered clinically relevant with the perioperative outcomes were carefully chosen for inclusion and were analyzed with univariate analysis (Mann-Whitney U for continuous variables or χ² test for categorical variables). Variables that showed a univariate relationship with first outcomes were entered into multivariate analysis. Subgroup analysis was conducted if the interactive factors were shown by multivariate analysis. Statistical analyses were performed with the use of SPSS software, version 19.0. P-value <0.05 was set as a significant difference.

RESULTS

Characteristics of Included Patients

TABLE 1. Characteristics of Included Patients

|              | LLR (N = 41) | OLR (N = 62) | P     |
|--------------|-------------|-------------|-------|
| Age (y)      | 56.29 ± 11.413 | 52.10 ± 11.328 | 0.464 |
| Male/female  | 33/8        | 54/8        |       |
| Weight (kg)  | 64.232 ± 10.871 | 62.673 ± 8.718 | 0.310 |
| AFP (ng/ml)  | 541.51 ± 577.869 | 380.46 ± 517.054 | 0.374 |
| AFP(+)       | 26 (63.4%)  | 37 (59.7%)  | 0.705 |
| Platelet     | 153.15 ± 122.98 | 154.01 ± 79.816 | 0.966 |
| INR          | 1.102 ± 0.098 | 1.049 ± 0.166 | 0.072 |
| HBsAg(+)     | 31 (75.6%)  | 55 (86.7%)  | 0.081 |
| HCV(+)       | 4 (4.9%)    | 7 (3.2%)    | 0.086 |
| Cirrhosis    | 15 (36.5%)  | 29 (46.8%)  | 0.063 |
| Child-Pugh   |             |             | 0.178 |
| classification A | 37 | 49 | |
| B            | 6 (14.6%)   | 17 (27.4%)  | 0.129 |
| Abdominal surgery history |       |       | |
| Alcohol      | 7 (17.1%)   | 14 (22.6%)  | 0.499 |
| No. tumors   | 1.17 ± 0.495 | 1.10 ± 0.349 | 0.476 |
| Diameter of tumor (cm) | 5.341 ± 2.467 | 6.043 ± 3.790 | 0.412 |
| Complete capsule of tumor | 24 (80%) | 55 (93.2%) | 0.063 |

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AFP indicates alpha-fetoprotein; HBsAg, hepatitis B surface antigen; HCV, Hepatitis C virus; INR, international normalization ratio; LLR, laparoscopic liver resection; OLR, open liver resection. Analysis. The characteristics of the included patients are shown in Table 1. There was no significant difference with regard to the age, weight, alpha-fetoprotein, the diameter of the tumor, nodes of tumors, liver cirrhosis, hepatitis B virus-infection, hypertension, and diabetes.

Perioperative Outcomes After Liver Resection

The types of liver resection in LLR and OLR groups are shown in Table 2. The operation time for LLR is longer than that for OLR (222.89 ± 85.585 vs. 202.65 ± 79.894 min, P = 0.196) without significant difference. The R0 resection rate in the OLR group is higher than that in the LLR group (95.1% vs. 90.2%, P = 0.286). The length of hospital stay after OLR is significantly longer than that after LLR (10.73 ± 3.220 vs. 7.90 ± 5.638, P <0.005). The intraoperative transfusion rate is a little higher in the OLR group than in the LLR group (8.1% vs. 7.3%, P = 0.890). There was no significance in the intraoperative clamping rate. A total of 7 cases (17.1%) in the LLR group and 20 cases (32.3%) in the OLR group showed postoperative complications, and subgroup analysis showed that there was no significant difference with regard to the occurrence of bile leakage, postoperative bleeding drainage tube, wound infection, and ascites. No mortality was observed in both groups. No trocar metastasis was observed in the LLR group and no incisional hernia in both groups.

Levels of the Perioperative Liver Function Markers

The levels of perioperative liver function markers are shown in Table 3. Plasma ALT, AST, TB, TP, and ALB levels before and after operation were measured and analyzed. The results show that there was no significant difference with regard to the levels of ALT, AST, TB, TP, and ALB between the LLR and OLR groups before the operation. The AST and ALT levels were increased on postoperative day-1 in both the LLR and OLR groups, but patients who underwent LLR had lower
plasma AST and ALT levels than those who underwent OLR (ALT: 209.76 ± 189.516 vs. 262.55 ± 181.19, P = 0.046; AST: 411.01 ± 412.51 vs. 250.56 ± 200.944, P = 0.005).

Along with the postoperative liver function recovery, plasma ALT and AST levels decreased in both groups. However, levels of AST and ALT after OLR were still higher than those in the LLR group on postoperative day-3 (ALT: 242.50 ± 233.34 vs. 109.36 ± 114.43, P = 0.057; AST: 45.0 ± 26.843 vs. 46.12 ± 29.290, P = 0.915).

Furthermore, there was no significant difference in plasma TB during the perioperative period. Interestingly, our analysis also shows that the increase of TP and ALB after LLR is faster than that observed after OLR. On day-5 after liver resection, the values of TP and ALB of the forth day after LLR were significantly higher than that in the LLR than in OLR group (TP: 64.69 ± 110.45 vs. 68.32 ± 6.672, P = 0.005; ALB: 38.90 ± 5.686 vs. 38.56 ± 5.686, P = 0.681).

Tumor Size Is Relevant to the Postoperative Liver Function Markers

Several clinically relevant factors were selected in the multivariate analysis: international normalization ratio, Child-grade, tumor size, clamping time, and platelet count. A multivariate analysis identified that tumor size was significantly associated with postoperative AST, ALT, or ALB levels (Supplement Table 1, Supplemental Digital Content 1, http://links.lww.com/SLE/A230). Therefore, the subgroup analysis was conducted to identify the correlation with the tumor size and postoperative clinical outcomes (Table 4). The subgroup analysis showed that, for the tumors that were <5 or >10 cm, there was no significant difference in postoperative serum ALT, AST, and ALB levels in both the LLR and the OLR groups. However, for the tumors between 5 and 10 cm, the most common size (50% in this study), the postoperative AST and ALT levels were significantly decreased in the LLR group than in the OLR group, as shown in Table 4.

DISCUSSION

To the best of our knowledge, this study reports the investigated benefits of LLR on the postoperative liver function recovery for HCC patients for the first time. The results show that LLR alleviates the hepatic injury and improves the liver function recovery after liver resection compared with traditional open surgery.

Since the first LLR was reported by Hashizume et al, LLR experienced rapid development in the last 2 decades. Early in 2009, a comprehensive “Louisville statement” was published and reported the clinical benefits of LLR, such as shorter hospital stay, less pain, and better cosmesis, especially for patients who underwent laparoscopic major liver resection. In 2017, de’Angelis et al reported that early discharge (within 24 h) after minor LLR can be successfully achieved for highly selected patients. The faster liver function recovery after liver resection results in a shorter hospital stay and faster physical function recovery.

Plasma transaminase levels (aspartate transaminase, AST, and ALT, ALB) and plasma bilirubin levels are clinically

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correlated with the postoperative outcomes and are measured routinely after liver resection to access the hepatocellular injury after liver resection. Olthof et al reported that the peak AST and ALT levels are predictors of both postoperative morbidity and mortality. On the basis of our analysis in this study, the postoperative peak results of plasma AST and ALT after LLR

**FIGURE 1.** The changes in liver function plasma markers after LLR and OLR. A and B, The changes in the plasma ALT and AST levels of HCC patients who underwent LLR and OLR. C and D, The changes in the plasma TP and ALB levels. P0: the measurement of liver functions before liver resection; P1, 3, 5: the 1, 3, 5 days after liver resection. *P < 0.05, **P < 0.01, ***P < 0.001. ALB indicates albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; LLR, laparoscopic liver resection; OLR, open liver resection; TP, total protein.

**TABLE 4.** The Level of Plasma Liver Function Markers After Liver Resection in Different Tumor Size Groups

| Diameter of Tumor | Postoperative day-1 | Postoperative day-3 | Postoperative day-5 |
|-------------------|---------------------|---------------------|---------------------|
| D < 5 cm          | LLR (N = 11)        | OLR (N = 20)        | P                   |
|                   | 162.7 ± 46.6        | 238.6 ± 171.9       | 0.148               |
| ALT               | 211.1 ± 116.4       | 359.8 ± 365.2       | 0.184               |
| AST               | 36.3 ± 50.8         | 22.0 ± 11.4         | 0.245               |
| TB                | 55.2 ± 6.8          | 55.9 ± 6.3          | 0.767               |
| TP                | 32.3 ± 6.1          | 32.6 ± 4.6          | 0.897               |
| ALB               | 155.9 ± 124.7       | 257.5 ± 312.4       | 0.313               |
| Postoperative day-3 | LLR (N = 24)        | OLR (N = 29)        | 0.031               |
|                   | 162.7 ± 46.6        | 238.7 ± 171.9       | 0.326               |
| ALT               | 116.4 ± 33.6        | 359.8 ± 365.2       | 0.031               |
| AST               | 36.3 ± 50.8         | 22.1 ± 11.4         | 0.218               |
| TB                | 55.2 ± 6.8          | 55.9 ± 6.3          | 0.807               |
| TP                | 32.3 ± 6.1          | 32.6 ± 4.6          | 0.625               |
| ALB               | 164.7 ± 149.8       | 257.6 ± 312.4       | 0.015               |
| Postoperative day-5 | LLR (N = 6)         | OLR (N = 13)        | 0.002               |
|                   | 64.8 ± 45.5         | 130.5 ± 146.8       | 0.426               |
| ALT               | 37.4 ± 22.2         | 34.4 ± 19.4         | 0.706               |
| AST               | 13.2 ± 5.5          | 19.3 ± 6.3          | 0.015               |
| TB                | 36.0 ± 11.8         | 33.8 ± 3.4          | 0.127               |

Bold values indicate statistically significant (P < 0.05). ALB indicates albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D, diameter of liver tumor; LLR, laparoscopic liver resection; OLR, open liver resection; TP, total protein.
were significantly lower than those observed after OLR, which may be the reason to explain the fewer postoperative complications in the LLR group and to answer why LLR significantly accelerates the impairment of liver function.

In addition, postoperative AST and ALT levels are associated with hepatic ischemia reperfusion, which means that the less bleeding and fewer instances of ischemia-reperfusion under LLR bring out the lower peak postoperative AST and ALT levels. Other factors may determine peak transaminase levels, such as duration of the liver resection and blood transfusion, but the vascular inflow occlusion is not associated with the peak levels of AST and ALT. In this study, there was no significant difference between factors such as the operation time and the transfusion rate.

Furthermore, the increase of postoperative TP and ALB after LLR is faster than that observed after OLR (Fig. 1), which also indicates the enhanced liver function recovery. Combined with the lower peak ALT and AST, these may be the reason for the shorter postoperative hospital stay after LLR. Moreover, LLR is also a part of the enhanced recovery after operation (ERAS) recommendations in hepatic surgery. The findings of this study enhance that LLR is beneficial for postoperative ERAS by improving liver function recovery.

Limitation of This Study

It is important to consider these findings in the context of the strengths and limitations of this study. The major limitation of this study is its single-center retrospective study design. Therefore, we have registered and are carrying out the prospective randomized controlled trial in relation to this issue (NCT03672357, https://register.clinicaltrials.gov).

REFERENCES

1. Venook AP, Papandreou C, Furuse J, et al. The incidence and epidemiology of hepatocellular carcinoma: a global and regional perspective. Oncologist. 2010;15(suppl 4):5–13.
2. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65:87–108.
3. Bruix J, Reig M, Sherman M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. Gastroenterology. 2016;150:835–853.
4. Hashizume M, Takenaka K, Yanaga K, et al. Laparoscopic hepatic resection for hepatocellular carcinoma. Surg Endosc. 1995;9:1289–1291.
5. He J, Amini N, Spolverato G, et al. National trends with a laparoscopic liver resection: results from a population-based analysis. HPB (Oxford). 2015;17:919–926.
6. Ikeda T, Toshima T, Harimoto N, et al. Laparoscopic liver resection in the semiprone position for tumors in the anteroinferior and posterior segments, using a novel dual-handling technique and bipolar irrigation system. Surg Endosc. 2014;28:2484–2492.
7. Coelho FF, Kruger JAP, Fonseca GM, et al. Laparoscopic liver resection: experience based guidelines. World J Gastrointest Surg. 2016;8:5–26.
8. Wakabayashi G, Cherqui D, Geller DA, et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. Ann Surg. 2015;261:619–629.
9. Hu B-S, Chen K, Tan H-M, et al. Comparison of laparoscopic vs open liver lobectomy (segmentectomy) for hepatocellular carcinoma. World J Gastroenterol. 2011;17:4725–4728.
10. Balzan S, Belgitti J, Farges O, et al. The “50-50 criteria” on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. Ann Surg. 2005;242:824–828; discussion 828–829.
11. Abu Hilal M, Aldrighetti L, Dagher I, et al. The Southampton Consensus Guidelines for Laparoscopic Liver Surgery: From Indication to Implementation. Ann Surg. 2018;268:11–18.
12. Cheung TT, Han HS, She WH, et al. The Asia Pacific Consensus Statement on Laparoscopic Liver Resection for Hepatocellular Carcinoma: A Report from the 7th Asia-Pacific Primary Liver Cancer Expert Meeting Held in Hong Kong. Liver Cancer. 2018;7:28–39.
13. de’Angelis N, Menahem B, Compagnon P, et al. Minor laparoscopic liver resection: toward 1-day surgery? Surg Endosc. 2017;31:4458–4465.
14. Othof PB, Huiskens J, Schulte NR, et al. Postoperative peak transaminases correlate with morbidity and mortality after liver resection. HPB (Oxford). 2016;18:915–921.
15. Scatton O, Zalinski S, Jegou D, et al. Randomized clinical trial of ischaemic preconditioning in major liver resection with intermittent Pringle manoeuvre. Br J Surg. 2011;98:1236–1243.
16. Clavien PA, Selzner M, Rudiger HA, et al. A prospective randomized study in 100 consecutive patients undergoing major liver resection with versus without ischemic preconditioning. Ann Surg. 2003;238:843–850; discussion 851-842.
17. Boleslawski E, Vibert E, Pruvot FR, et al. Relevance of postoperative peak transaminase after elective hepatectomy. Ann Surg. 2014;260:815–820; discussion 820-811.
18. Melloul E, Hubner M, Scott M, et al. Guidelines for Perioperative Care for Liver Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. World J Surg. 2016;40:2425–2440.
19. Song W, Wang K, Zhang RJ, et al. The enhanced recovery after surgery (ERAS) program in liver surgery: a meta-analysis of randomized controlled trials. Springerplus. 2016;5:207.