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

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BACKGROUND: We first performed laparoscopic hepatic resection (Lap-Hx) for hepatocellular carcinoma (HCC) in 1994. Here we review the long-term surgical results of Lap-Hx for HCC in patients with cirrhosis over a 10-year period at a single institution.

STUDY DESIGN: Between January 2000 and December 2013, 99 patients with cirrhosis underwent open hepatic resection (Open-Hx) and 63 underwent Lap-Hx for primary HCC within the Milan criteria. We compared the operative outcomes and patient survival between the 2 groups.

RESULTS: There were no significant differences regarding patient background characteristics or tumor-related factors between the 2 groups. The morbidity rate of the Lap-Hx group was significantly lower than that of the Open-Hx group (26% vs 10%; p = 0.0459), and the complication rate of ascites was significantly lower (7% vs 0%; p = 0.0077). The mean duration of hospital stay of the Lap-Hx group was significantly shorter than that of the Open-Hx group (16 vs 10 days; p = 0.0008). There were no significant between-group differences regarding overall or disease-free survival.

CONCLUSIONS: Laparoscopic-Hx for HCC in patients with cirrhosis is associated with less morbidity and shorter hospital stays, with no compromise in patient survival. It may be time to consider changing the standard operation for primary HCC within the Milan criteria to Lap-Hx in patients with cirrhosis. (J Am Coll Surg 2014;219:1117–1123. © 2014 by the American College of Surgeons)

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, accounting for approximately 6% of all human cancers. The mainstay of curative treatment for HCC is hepatic resection, and the surgical results of hepatic resection for HCC have significantly improved, with the mortality rate nearly reaching zero. However, hepatic resection for HCC remains high risk, especially in patients with cirrhosis. As a less invasive procedure, laparoscopic hepatic resection (Lap-Hx) for HCC has gathered attention in this challenging field.

We first performed Lap-Hx for HCC in patients with cirrhosis in 1994. Until 2007, we selected Lap-Hx for HCC on the left lateral lobe or the peripheral ventral right lobe, and we performed liver parenchymal division through a small laparotomy after mobilization of the liver. We reported favorable short-term surgical results of Lap-Hx for HCC, with less blood loss and shorter hospital stays, with no compromise in patient survival. In June 2008, pure Lap-Hx was introduced in our institution, and Lap-Hx for the posterior segment, anterosuperior segment (S8), and caudate lobe was performed with the patient in the semiprone position.

Several meta-analyses summarized the surgical results of Lap-Hx for HCC as follows: less blood loss, less frequent need for transfusion, less morbidity, a lower complication rate of ascites, a lower complication rate of liver failure,
shorter hospital stays, and no compromise in prognosis. However, long-term (ie, more than 10 years) surgical results of Lap-Hx for HCC in patients with cirrhosis have not yet been reported.

We herein present a retrospective analysis of long-term surgical results including patients’ prognoses after Lap-Hx for HCC within the Milan criteria (ie, ≤5 cm in diameter in single HCC or ≤3 nodules and ≤3 cm in diameter in multiple HCCs) in patients with cirrhosis, over a 10-year period at a single institution.

**METHODS**

**Patient characteristics**
We retrospectively analyzed 653 patients with HCC who underwent hepatic resections at the Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, from January 2000 to December 2013. Among them, 162 patients who underwent curative hepatic resections for primary HCC within the Milan criteria were enrolled in this study. We divided this cohort of 162 patients into 2 groups; the open hepatic resection (Open-Hx) group (n = 99), and the Lap-Hx group (n = 63).

**Surgical procedures and outcomes**
Details of our surgical techniques of Open-Hx and patient selection criteria for hepatic resection for HCC have been reported. Resection volume was decided based on the patients’ indocyanine green dye retention rate at 15 minutes (ICGR-15) in both the Open-Hx and Lap-Hx groups. Patients with an ICGR-15 ≥ 35% were generally selected for limited resection. From 1994 to 2007 in 25 patients (40%), Lap-Hx was done on the principle that parenchymal division would be performed under direct vision through a small laparotomy wound after mobilization of the liver under a carbon dioxide (CO2) pneumoperitoneum. The CUSA system (Valleylab) was used to transect the liver parenchyma.

In almost all of the hepatic resections, the Pringle’s maneuver, consisting of clamping the portal triad for 15 minutes and then releasing the clamp at 5-minute intervals, was applied; alternatively, hemivascular occlusion was performed. From June 2008 in 38 patients (60%), pure Lap-Hx was introduced in our institution, and Lap-Hx for the posterior segment, anterosuperior segment (S8), and caudate lobe was performed with the patient in the semiprone position. In patients who underwent the Lap-Hx, bipolar scissors or a Biclamp under the VIO soft-coagulation system (ERBE Elektromedizin) fitted with a silicon tube dropping saline to the tip was used to transect the liver parenchyma. If transection of the liver parenchyma of S7, S8, or the right superior portion of S1 was needed in the Lap-Hx patients, an intracostal port with a balloon was placed under left-lung ventilation. Types of hepatic resections in both the Open-Hx group and the Lap-Hx group are summarized in Table 1. There were no patients who underwent lobectomy or more for HCC within the Milan criteria in our series. The majority of operations performed were partial hepatic resections: 71 patients (71.7%) in the Open-Hx group and 36 patients (57.1%) in the Lap-Hx group.

Any death that occurred in the hospital after hepatic resection was recorded as a mortality. Complications were evaluated by Clavien’s classification of surgical complications, and the complications with a score of grade II or more were defined as positive.

**Follow-up and treatment strategy for recurrent hepatocellular carcinoma**
After discharge, all patients were examined for recurrence by ultrasonography and tumor markers such as α-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) every month and by dynamic CT every 3

### Table 1. Types of Hepatic Resection

<table>
<thead>
<tr>
<th>Operative procedures</th>
<th>Open (n = 99)</th>
<th>Laparoscopic (n = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobectomy or more</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right liver</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Left liver</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Segmentectomy or more</td>
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<td></td>
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<tr>
<td>Left lateral</td>
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</tr>
<tr>
<td>Medial</td>
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<td>1</td>
</tr>
<tr>
<td>Anterior</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Posterior</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Subsegmentectomy or more*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S2</td>
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<td>2</td>
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<td>S3</td>
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<td>S5</td>
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<td>1</td>
</tr>
<tr>
<td>S6</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>S7</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>S8</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>S5 + 6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Partial</td>
<td>71</td>
<td>36</td>
</tr>
</tbody>
</table>

*S, segment defined by the Couinaud’s nomenclature.
months. The mean follow-up period after hepatic resection was 4.2 years (range 0.3 to 13.7 years) in the Open-Hx group, and 3.4 years (range 0.2 to 13.4 years) in the Lap-Hx group. When recurrence was suspected, we treated the recurrent HCC by repeat hepatic resection at any times of recurrence, with ablation therapy or iodolization.

Statistics
Continuous variables are expressed as the mean ± standard deviation (SD) and were compared using Student’s t-test. Categorical variables were compared using the chi-square test. Survival curves were generated by the Kaplan-Meier method and compared using the log-rank test. All analyses were performed with JMP Pro 9.0.2 (SAS Institute Inc). Values of p < 0.05 were considered significant.

RESULTS
Patients’ background characteristics
The patients’ background characteristics are summarized in Table 2. There are no significant differences in the patient characteristics between the Open-Hx and the Lap-Hx groups, including mean age (65.2 vs 67.5 years; p = 0.1483), the positive rate of diabetes mellitus (24% vs 32%; p = 0.2977), hepatitis B surface antigen (17% vs 16%; p = 0.3813), and hepatitis C virus antibody (68% vs 63%; p = 0.4952), respectively. Concerning liver function, such as the serum level of albumin (3.99 vs 3.93 g/dL; p = 0.3266) and total bilirubin (0.82 vs 0.86 mg/dL; p = 0.1263), ICGR-15 (16.1% vs 16.3%; p = 0.8590), the ratio of Child A/B (96/3 vs 59/4; p = 0.3187) and Liver damage A/B (76/23 vs 44/19; p = 0.3293), respectively, there were also no significant differences between the 2 groups.

Short-term surgical outcomes
The patients’ short-term surgical outcomes are summarized in Table 3. The mean resected liver volume in the Lap-Hx group (112.2 ± 97.3 g) was significantly larger than that in the Open-Hx group (81.2 ± 65.3 g; p = 0.0165). There were no deaths in either group, and the morbidity rate in the Lap-Hx group (10%) was significantly lower than that in the Open-Hx group (26%; p = 0.0459). Concerning the breakdown of morbidity, the positive rate of ascites in the Lap-Hx group (0%) was significantly lower than that in the Open-Hx group (7%; p = 0.0077). The duration of hospital stay in the Lap-Hx group (10.3 ± 4.4 days) was significantly shorter than that in the Open-Hx group (16.2 ± 13.4 days; p = 0.0008).

Tumor-related factors
Tumor-related factors are summarized in Table 4. There were no significant differences in tumor-related factors between the 2 groups, including the maximum tumor diameter (2.6 vs 2.5 cm; p = 0.5106), the positive rate of solitary tumor (84% vs 89%; p = 0.4593), poorly differentiated HCC (20% vs 19%; p = 0.8570), pathologic portal vein infiltration and/or intrahepatic metastasis (27% vs 19%; p = 0.4952), and stages III/IV-A (13% vs 10%; p = 0.4814), respectively. There were also no significant differences between the 2 groups regarding the tumor markers: serum levels of AFP (262.5 vs 593.4 ng/mL; p = 0.3128) and DCP (183.3 vs 127.1 mAU/mL; p = 0.1831), respectively.

Survival after hepatic resections for hepatocellular carcinoma
Disease-free survival and overall survival curves are provided in Figure 1. There were no significant differences in disease-free survival (p = 0.5196) or overall survival

Table 2. Comparisons of Patient Background Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Open (n = 99)</th>
<th>Laparoscopic (n = 63)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65.2 ± 10.1</td>
<td>67.5 ± 9.5</td>
<td>0.1483</td>
</tr>
<tr>
<td>Male/female, n</td>
<td>74/25</td>
<td>48/15</td>
<td>0.8353</td>
</tr>
<tr>
<td>DM (+), n (%)</td>
<td>24 (24)</td>
<td>20 (32)</td>
<td>0.2977</td>
</tr>
<tr>
<td>HBs-Ag (+), n (%)</td>
<td>17 (17)</td>
<td>10 (16)</td>
<td>0.3813</td>
</tr>
<tr>
<td>HCV-Ab (+), n (%)</td>
<td>68 (68)</td>
<td>40 (63)</td>
<td>0.4952</td>
</tr>
<tr>
<td>Alb, g/dL, mean ± SD</td>
<td>3.99 ± 0.38</td>
<td>3.93 ± 0.40</td>
<td>0.3266</td>
</tr>
<tr>
<td>T-bil, mg/dL, mean ± SD</td>
<td>0.82 ± 0.32</td>
<td>0.86 ± 0.39</td>
<td>0.1263</td>
</tr>
<tr>
<td>ICGR-15, %, mean ± SD</td>
<td>16.1 ± 8.1</td>
<td>16.3 ± 8.3</td>
<td>0.9059</td>
</tr>
<tr>
<td>Child A/B, n</td>
<td>96/3</td>
<td>59/4</td>
<td>0.3187</td>
</tr>
<tr>
<td>Liver damage A/B, n</td>
<td>76/23</td>
<td>44/19</td>
<td>0.3293</td>
</tr>
</tbody>
</table>

Alb, albumin; DM, diabetes mellitus; HBs-Ag, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; ICGR15, indocyanin green retention rate at 15 min; T-bil, total bilirubin.
(p = 0.6791) between the 2 groups. The 2-year and 5-year disease-free survival rates were 70% and 41% in the Open-Hx group, and 68% and 33% in the Lap-Hx group, respectively. The 5-year and 10-year overall survival rates were 77% and 57% in the Open-Hx group, and 78% and 69% in the Lap-Hx group, respectively. There were no port site recurrences or peritoneal seeding of HCC in the Lap-Hx group.

**DISCUSSION**

With advances and improvements in instruments and surgical experiences for laparoscopic surgery, there are increasing interests and options for Lap-Hx for HCC in patients with cirrhosis. The Louisville consensus statement concluded that laparoscopic left lateral sectionectomy should be considered standard practice, and it described the currently acceptable indications for Lap-Hx as patients with a solitary lesion, 5 cm or less, located in liver segment 2–6. Several recent studies have reported their comparative results of Lap-Hx vs Open-Hx for HCC, and several meta-analyses summarized the surgical and oncologic outcomes of Lap-Hx as follows: less blood loss, less frequent need for transfusion, less morbidity, a lower complication rate of ascites, a lower complication rate of liver failure, shorter hospital stays, and no compromise in prognosis.9-13 However, in our study, the intraoperative blood loss of the Lap-Hx group (455.7 ± 741.9 g) did not significantly differ from that of the Open-Hx group (436.6 ± 320.7 g; p = 0.8221). Therefore, regarding the need for transfusion, there is no significant difference between the 2 groups (2% vs 6%; p = 0.1612). High intraperitoneal pressure caused by CO2 pneumoperitoneum is considered to be one of the major reasons for reduced blood loss in Lap-Hx for HCC. However, generally speaking, Lap-Hx tends to be applied for limited resection to peripheral ventral small HCCs, in which hepatic resections are relatively easy to perform.9-13 These “selection biases” were one of the potential causes of the smaller blood loss in Lap-Hx for HCC in other studies.9,11-13 However, in our study, the resected liver volume of the Lap-Hx group (112.2 ± 97.3 g) was significantly larger than that of the Open-Hx group (81.2 ± 65.3 g; p = 0.0165), and the
rate of anatomic resection was also higher (43% vs 28%; p = 0.0516). Hepatic resections of segments 1, 7, and 8, where Lap-Hx is considered to be difficult to perform, reached up to 17 cases (27%) in our Lap-Hx group using the semiprone position. Therefore, the selection biases in HCC location indicated for Lap-Hx in our study would be smaller than those of the previous studies.

Concerning short-term surgical results, also in our study, less Clavien II or more morbidity (26% vs 10%; p = 0.0459), a lower complication rate of ascites (7% vs 0%; p = 0.0077), and shorter hospital stays (16 vs 10 days; p = 0.0008) of the Lap-Hx group were confirmed. The reduced morbidity of laparoscopic surgery in patients with cancer has been already reported in colorectal and gastric cancer, so laparoscopic procedures are regarded as “minimally invasive.” In addition, Lap-Hx for HCC in patients with cirrhosis should be minimally invasive compared with Open-Hx because there is less tissue destruction of the abdominal wall with small incisions and/or less mobilization and manipulation of the liver.

A CO₂ pneumoperitoneum is known to reduce local immune responses such as the secretion of tumor necrosis factor-α (TNF-α) or nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) from peritoneal macrophages against surgical stress. Less destruction of intra-abdominal tissues and the favorable effects of a CO₂ pneumoperitoneum in Lap-Hx would lead to a lower rate of postoperative ascites. The minimal invasiveness of Lap-Hx improves the postoperative quality of life and reduces surgical morbidities. In this study, we found that the duration of hospital stay in cirrhotic patients with HCC who underwent Lap-Hx was significantly shortened compared with that of the Open-Hx patients.

Concerning patient prognoses, several meta-analyses reported that no compromise in prognosis was linked to the Lap-Hx procedure. Our study is first to report the long-term (more than 10 years) favorable results of Lap-Hx for HCC in patients with cirrhosis. The 5- and 10-year survival rates of cirrhotic HCC patients who underwent Lap-Hx were 78% and 69%, respectively. In addition, in laparoscopic surgery for colorectal and gastric cancers, no compromise in prognosis was found by a meta-analysis including several randomized control trials.

Despite the comparable oncologic outcomes and some advantages of Lap-Hx for HCC, port-site recurrence has remained a concern. We routinely use the surgical porch to retract the resected liver specimen including the HCC from the port site in Lap-Hx, and we have had no patients with port site recurrences or related peritoneal seeding of HCC. The negative impact of surgical morbidity on the recurrence rate and long-term outcomes has been reported in patients with colorectal liver metastasis, colorectal cancer, gastric cancer, and esophageal cancer. Reduction of surgical morbidity such as postoperative ascites by the less invasiveness of Lap-Hx for HCC could lead to a survival impact for better prognosis after curative hepatic resection for HCC in patients with cirrhosis in further study.

There have been no reported prospective randomized controlled studies of Lap-Hx vs Open-Hx for HCC, and only 1 trial is currently underway in Korea (www.ClinicalTrials.gov Identifier NCT00606385). To minimize the selection biases of Lap-Hx, a case-controlled study with propensity score matching for long-term outcomes of Lap-Hx for HCC was reported. However, in this study, there were originally no significant differences in the patients’ background characteristics, operation time, intraoperative blood loss, need for transfusion, or tumor-related factors that could affect the patient prognoses between the 2 groups. Based on our encouraging
short-term and long-term results of Lap-Hx for primary HCC within the Milan criteria irrespective of the HCC location in patients with cirrhosis, well-conducted prospective randomized controlled trials with large numbers of patients are needed to confirm our favorable results. The next challenge of Lap-Hx for HCC should be against huge HCCs and laparoscopic resections. The feasibility and safety of Lap-Hx for HCC with a tumor size of 5 to 10 cm\textsuperscript{15} and laparoscopic re-resection for recurrent HCC\textsuperscript{15} have been reported, and we are now expanding the indication of Lap-Hx for repeat resections for recurrent HCC.

CONCLUSIONS
In conclusion, Lap-Hx for HCC in patients with cirrhosis is associated with less morbidity and shorter hospital stays, with no compromise in patient survival. It may be time to consider changing the standard operation to Lap-Hx for primary HCC within the Milan criteria in patients with cirrhosis.

Author Contributions
Study conception and design: Yamashita, Ikeda, Kawanaka, Shirabe, Maehara
Acquisition of data: Yamashita, Kurihara, Yoshida, Analysis and interpretation of data: Yamashita, Takeishi, Itoh, Harimoto
Drafting of manuscript: Yamashita, Ikeda, Shirabe
Critical revision: Maehara

REFERENCES


