Surg Endosc (2015) 29:458–465
DOI 10.1007/s00464-014-3687-3

Short- and long-term outcomes of laparoscopic versus open hepatectomy for small malignant liver tumors: a single-center experience

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Received: 21 January 2014 / Accepted: 17 June 2014 / Published online: 4 July 2014

Abstract

Background Laparoscopic hepatectomy (Lap-Hx) has been increasingly performed for patients with liver tumors as surgical techniques and devices have progressed. However, the long-term outcomes of Lap-Hx for malignant liver tumors are not oncologically guaranteed. This study compared the short- and long-term outcomes between Lap-Hx and open hepatectomy (Open-Hx) for malignant liver tumors by matched-pair analysis.

Methods The indications for Lap-Hx at our department are a tumor size of <5 cm and fewer than two lesions without macroscopic vascular invasion or the need for biliary reconstruction. In total, 135 patients underwent Lap-Hx for malignant liver tumors through December 2013. We compared the short- and long-term outcomes between Lap-Hx and Open-Hx in patients who met the above-mentioned indications.

Results With respect to short-term outcomes, the operation time, blood loss, postoperative hospital stay, white blood cell count, and C-reactive protein level after Lap-Hx were significantly better than those after Open-Hx in both the patients who underwent partial resection and those who underwent lateral sectionectomy. In patients who underwent partial resection, the incidence of postoperative complications after Lap-Hx was significantly lower than that after Open-Hx; in particular, wound infection and respiratory complications were significantly lower. Furthermore, when the tumor was located in the posterosuperior segments, the operation time for Lap-Hx was not shorter than that for Open-Hx. With respect to long-term outcomes of hepatocellular carcinoma, neither overall nor disease-free survival differed between the two groups. With respect to long-term outcomes of colorectal liver metastases, the disease-free survival rate was similar between Lap-Hx and Open-Hx; however, the overall survival rate was significantly better for Lap-Hx than for Open-Hx.

Conclusions Lap-Hx is a good option for selected patients with malignant liver tumors. The short- and long-term outcomes of Lap-Hx also are considered to be acceptable.

Keywords Laparoscopic hepatectomy · Partial resection · Lateral sectionectomy · Colorectal liver metastases · Hepatocellular carcinoma · Short-term outcome · Long-term outcome

Laparoscopic hepatectomy (Lap-Hx) was reported for the first time by Gagner et al. [1] in 1992. Initially, Lap-Hx for hepatic diseases was limited to centers with experience in laparoscopic surgery because of difficulties with the technique and bleeding control. Previous studies [2, 3] on laparoscopic liver resection demonstrated that the procedure was feasible and safe, and did not increase tumor dissemination. With the progression of surgical techniques and devices, Lap-Hx became a realizable option for patients with liver tumors. Since then, Lap-Hx has been gradually accepted as a treatment of choice for benign and malignant hepatic diseases and has been performed in about 3,000 patients to date. Conversely, open hepatectomy (Open-Hx) is the gold standard treatment for colorectal liver metastasis (CRLM) and hepatocellular carcinoma (HCC) [2–4]. However, the short- and long-term outcomes

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of Lap-Hx for malignant hepatic disease remain unclear. Therefore, in this study, we compared the short- and long-term outcomes between Lap-Hx and Open-Hx for patients with CRLM and HCC by matched-pair analysis.

Materials and methods

Patient selection for laparoscopic hepatectomy

From January 2006 to December 2013, a total of 135 patients underwent Lap-Hx for malignant liver tumors at Osaka Medical College Hospital. The indications for Lap-Hx at our department are a tumor size of <5 cm and fewer than two lesions without macroscopic vascular invasion or the need for biliary reconstruction. There are no limitations regarding tumor location, and liver function requirements are identical to those for Open-Hx. However, even when tumors satisfied the above-mentioned conditions in the present study, the final decision was the surgeon's because performance of the laparoscopic procedure involved a specialized technique.

Two analyses were performed in this study. The first compared the short-term outcomes of Lap-Hx and Open-Hx according to the type of hepatectomy. The second examined the long-term outcomes according to the disease.

Short-term outcomes

Partial resection and lateral sectionectomy were targeted in this study because there were fewer cases of other procedures involving Lap-Hx, such as anterior, posterior, and medial sectionectomy and hemihepatectomy. In total, 117 and 234 patients underwent Lap-Hx and Open-Hx, respectively, under the above-mentioned conditions through December 2013. Of the 117 patients who underwent Lap-Hx, 93 underwent partial resection and 24 underwent lateral sectionectomy. Of the 234 patients who underwent Open-Hx, 200 underwent partial resection and 34 underwent lateral sectionectomy. Perioperative outcomes, including postoperative complications, were compared between these two groups.

Long-term outcomes

From April 2000 to December 2011, 172 patients underwent initial hepatectomy for HCC under the above-mentioned tumor conditions; of these, 37 patients underwent Lap-Hx and 135 underwent Open-Hx. Furthermore, 124 patients underwent initial hepatectomy for CRLM; of these, 46 patients underwent Lap-Hx, and 78 underwent Open-Hx.

Surgical procedure

In general, the minimally invasive approach to hepatectomy can be performed by pure laparoscopy. However, a small-incision approach was very frequently performed in the introductory period of laparoscopic surgery; at that time, tumors were difficult to locate by pure laparoscopy because of the limited visualization and difficulty in controlling bleeding [5]. Thus, we chose the small-incision approach in the present study. For Lap-Hx, each patient was placed in the supine position; when lesions were located in the right lateral sector, patients were placed in the left lateral decubitus position. Trocars were inserted using an open technique, and continuous carbon dioxide pneumoperitoneum was established at a pressure of <12 mmHg to avoid gas embolism. The transection line was determined by intraoperative ultrasonography to evaluate and determine the tumor status. Parenchymal transection was performed using a laparoscopic ultrasonic surgical aspirator and laparoscopic coagulating shears. Hemostasis was performed using monopolar forceps with soft coagulation (VIO System™). The Pringle maneuver using an endoscopic intestinal clip was performed if necessary [6]. Open-Hx was performed following the standard technique as previously described [7]. Although a drain was routinely used until 2006, we thereafter inserted a drain by our previously established standard [8].

Statistical analysis

Actuarial survival rates were calculated using the Kaplan–Meier method. Univariate analyses were performed using the log-rank test. Multivariate analyses were performed by Cox proportional hazards regression. Statistical comparisons were made by Fisher's exact probability test. All analyses were performed using the JMP version 9.0 software package (SAS Institute, Cary, NC, USA) on Mac OS X. Values of $p < 0.05$ were considered statistically significant.

Results

Laparoscopic hepatectomy for malignant liver tumors was performed for 137 patients (including assisted Lap-Hx in 37 patients). Of these, 74 and 61 patients underwent Lap-Hx for CRLM and HCC, respectively. Most Lap-Hx procedures comprised partial Hx (93 patients) and lateral sectionectomy (24 patients). Eleven patients were converted from Lap-Hx to Open-Hx, four underwent conversion because of a high risk of major bleeding, four underwent conversion because of severe adhesion, two underwent conversion because of poor visualization of the

Table 1 Laparoscopic-assisted hepatectomy

Disease	Cases	Conversion
Metastasis liver tumor	74 (22)	3
HCC/CCC	61 (15)	8
Procedure	Cases	
Partial resection	93 (18)	9
Lateral sectionectomy	24 (10)	2
Medial sectionectomy	1 (0)	
Anterior sectionectomy	1 (1)	
Posterior sectionectomy	3 (0)	
Left hemi-hepatectomy	8 (6)	
Right hemi-hepatectomy	5 (2)	
Total	135 (37)	11

transection line, and one was converted to ensure a sufficient oncologic margin (Table 1).

Short-term outcomes

With respect to partial resection, although the indocyanine green retention rate at 15 min in Open-Hx was higher than that in Lap-Hx, there was no difference in pathological cirrhosis between the two groups. The operation time ($p = 0.0139$) and blood loss ($p < 0.0001$) in Lap-Hx were significantly lower than those in Open-Hx. Furthermore, the incidence of postoperative complications in Lap-Hx was significantly lower than that in Open-Hx; in particular, wound infection ($p = 0.0009$) and respiratory complications ($p = 0.0344$) were significantly lower. The postoperative hospital stay in the Lap-Hx group was shorter than that in the Open-Hx group (10 vs. 16 days, respectively; $p < 0.0001$). The surgical margin in Lap-Hx was more secure than that in Open-Hx (Table 2). The detailed examination according to the tumor location in partial resection revealed a significantly better operation time ($p = 0.0286$), blood loss ($p = 0.0015$), wound infection rate ($p = 0.0007$), respiratory complication rate ($p = 0.0341$), and postoperative hospital stay ($p < 0.0001$) in Lap-Hx than in Open-Hx for tumors of the anterolateral segments. When tumors were located in the posterosuperior segments, partial resection in Lap-Hx was associated with less blood loss ($p = 0.0063$) and a shorter postoperative hospital stay ($p = 0.0027$) than in Open-Hx (Table 3).

With respect to lateral sectionectomy, the operation time ($p = 0.0345$) and blood loss ($p = 0.0002$) in Lap-Hx were significantly lower than those in Open-Hx. The postoperative hospital stay in the Lap-Hx group was shorter than in the Open-Hx group (9 vs. 15 days, respectively; $p = 0.0163$) (Table 2).

In both partial resection and lateral sectionectomy, the postoperative white blood cell count and C-reactive protein level tended to be lower in the Lap-Hx group than in the Open-Hx group (Fig. 1).

Long-term outcomes

With respect to the long-term outcomes of HCC, the 1-, 3-, and 5-year disease-free survival rates were 81, 52, and 52 %, respectively, after Lap-Hx and 81, 54, and 45 %, respectively, after Open-Hx ($p = 0.9373$) (Fig. 2A). Alternatively, the 1-, 3-, and 5-year overall survival rates were 97, 90, and 84 %, respectively, after Lap-Hx and 96, 84, and 67 %, respectively, after Open-Hx ($p = 0.7052$) (Fig. 2B). The two groups did not differ significantly in terms of overall or disease-free survival.

With respect to the long-term outcomes of CRLM, the 1-, 3-, and 5-year disease-free survival rates were 61, 41, and 41 %, respectively, after Lap-Hx. The corresponding rates for Open-Hx were 58, 41, and 38 %, respectively ($p = 0.6591$) (Fig. 3A). On the other hand, the 1-, 3-, and 5-year overall survival rates after Lap-Hx were significantly better than those after Open-Hx (100, 88, and 88 vs. 96, 68, and 53 %, respectively; $p = 0.0042$) (Fig. 3B).

Discussion

This single-institution study compared the short- and long-term outcomes of Lap-Hx with those of Open-Hx under the conditions of a tumor size of <5 cm, fewer than two lesions, and no macroscopic vascular invasion or need for biliary reconstruction. With respect to the short-term outcomes of partial resection and lateral sectionectomy, we found that operation time, blood loss, postoperative early white blood cell count, and C-reactive protein level for Lap-Hx were significantly lower than those for Open-Hx; in addition, the hospital stay for Lap-Hx tended to be shorter than that for Open-Hx. Furthermore, with respect to partial resection, the wound infection and pulmonary complication rates after Lap-Hx were significantly lower than those after Open-Hx. Regarding the long-term outcomes of HCC and CRLM, there were no significant differences in the overall or disease-free survival between the Lap-Hx and Open-Hx groups.

Since the report by Kaneko et al. [9] in 1996, many authors have indicated better results with Lap-Hx than Open-Hx with respect to short-term outcomes [10–20], wound pain [14], operation time [14, 15], blood loss [11, 14–17, 19, 20], postoperative complications [15], postoperative analgesic requirements [15], time to regular diet [11, 14], overall cost [11], postoperative hospital stay [10, 11, 15, 17–20], and other factors. This study also indicated the same benefits as

Table 2 Comparison of clinicopathological factors of laparoscopic and open hepatectomy in partial resection and lateral sectionectomy

Factors	Partial resection ($n = 293$)			Lateral sectionectomy ($n = 58$)		
	Lap-Hx ($n = 93$)	Open-Hx ($n = 200$)	p	Lap-Hx ($n = 24$)	Open-Hx ($n = 34$)	p
Background characteristics						
Gender (Male/Female)[a]	58/35	145/55	0.1022	13/11	27/7	0.0495
Age (years)	68 (29–89)	67 (39–89)	0.9679	66 (28–82)	67 (47–87)	0.8278
Virus infection (positive)[b]	30 (32 %)	88 (44 %)	0.0729	9 (38 %)	4 (12 %)	0.0279
Child-Pugh class (B)[b]	8 (8 %)	26 (13 %)	0.3302	2 (8 %)	0 (0 %)	0.2052
Diabetes mellitus[b]	16 (17 %)	31 (16 %)	0.7342	7 (29 %)	5 (15 %)	0.5771
ASA (≥ 3)[b]	3 (3 %)	17 (9 %)	0.1346	5 (7 %)	6 (8 %)	1.0000
ICG R15 (%)	12 (3–72)	18 (2–46)	0.0048	14 (7–28)	10 (3–39)	0.2724
Alb	4.1 (2.9–4.9)	3.9 (2.7–4.9)	0.0544	4.2 (2.9–4.7)	4.1 (2.6–4.7)	0.5800
Surgical factors						
Operation time (min)	220 (50–560)	250 (75–610)	0.0139	200 (50–460)	278 (165–495)	0.0345
Blood loss (ml)	130 (10–1500)	370 (20–7800)	<0.0001	55 (40–1450)	300 (40–1665)	0.0002
Blood transfusion[b]	8 (9 %)	27 (14 %)	0.2484	0 (0 %)	3 (10 %)	0.2453
Resected liver volume (ml)	50 (10–530)	62 (10–470)	0.1243	155 (100–270)	208 (75–350)	0.2024
Surgical margin (mm)	7 (0–25)	5 (0–36)	0.0327	12 (2–30)	5 (0–20)	0.0085
Tumor-related factor						
Location (posterosuperior)[b]	31 (33 %)	75 (39 %)	0.3635	–	–	–
Tumor diameter (cm)	2.5 (0.8–10)	2.5 (0.3–5)	0.2196	2.7 (1–7.5)	2.9(1.0–5.0)	0.5817
Resection number (plural)	20 (22 %)	60 (30 %)	0.1589	–	–	–
Pathological cirrhosis[b]	26 (28 %)	73 (37 %)	0.1848	7 (29 %)	7 (21 %)	0.5393
Outcome						
Complications[b]	17 (18 %)	66 (33 %)	0.0118	3 (13 %)	7 (21 %)	0.4995
Wound infection[b]	3 (3 %)	32 (16 %)	0.0009	0 (0 %)	5 (15 %)	0.0700
Abdominal abscess[b]	4 (4 %)	4 (2 %)	0.2692	1 (4 %)	3 (9 %)	0.6351
Ascites[b]	6 (6 %)	22 (11 %)	0.2869	1 (4 %)	0 (0 %)	0.4138
Respiratory complications[b]	4 (4 %)	25 (13 %)	0.0344	0 (0 %)	0 (0 %)	–
Liver failure[b]	1 (1 %)	3 (1 %)	1.0000	0 (0 %)	0 (0 %)	–
Bile leakage[b]	1 (1 %)	6 (3 %)	0.4377	0 (0 %)	2 (6 %)	0.5064
PHS (days)[b]	10 (3–173)	16 (5–172)	<0.0001	9 (4–37)	15 (7–60)	0.0163

Data are presented as median with range unless otherwise specified

Location (posterosuperior): Posterosuperior is defined as in the posterosuperior segments (segments 4a, 7, and 8 according to the classification of Couinaud)

ASA American Society of Anesthesiologists, *ICG R15* indocyanine green retention rate at 15 min, *Alb* albumin, *PHS* postoperative hospital stay

[a] Number of patients

[b] Number (%) of patients

those described in previous reports; furthermore, new pulmonary complications such as atelectasis or pneumonia were lower in the Lap-Hx group than in the Open-Hx group.

Thus, clinicians should be aware of the higher risk of postoperative pulmonary complications in patients undergoing hepatectomy, especially because pulmonary complications are associated with a worse prognosis in elderly patients than in younger patients [21–23]. Recent reports suggest that the rate of pulmonary complications may be lower with laparoscopic surgery than with open surgery [24], and this strategy will likely be the subject of future investigation. With respect to patients with cirrhosis, although there was no significant difference in the rate of intractable ascites and liver failure between the two groups in the present study, Kanazawa et al. [15] reported that Lap-Hx decreased the incidence of intractable ascites because this procedure minimizes blockage of the collateral circulation around the liver and abdominal wall, thus preventing lymphatic flow disturbance and postoperative portal hypertension, and minimizes parenchymal damage

Table 3 Comparison of clinicopathological factors according to tumor location in partial hepatectomy

Factors	Anterolateral location (n = 179)			Posterosuperior location (n = 106)		
	Lap-Hx (n = 62)	Open-Hx (n = 117)	p	Lap-Hx (n = 31)	Open-Hx (n = 75)	p
Child-Pugh class (B)[a]	5 (7 %)	14 (12 %)	0.6108	3 (10 %)	11 (15 %)	0.7533
Operation time (min)	193 (50–455)	245 (90–600)	0.0286	245 (95–560)	258 (130–610)	0.6602
Blood loss (ml)	8115(10–950)	300 (20–5040)	0.0015	130 (50–1500)	483 (30–7800)	0.0063
Pathological cirrhosis[a]	19 (31 %)	43 (37 %)	0.5096	7 (22 %)	26 (35 %)	0.2563
Wound infection[a]	1 (2 %)	22 (19 %)	0.0007	2 (6 %)	9 (12 %)	0.5026
Respiratory complications[a]	2 (3 %)	15 (12 %)	0.0341	2 (6 %)	10 (13 %)	0.5023
PHS (days)	10 (3–173)	16 (5–172)	<0.0001	11 (5–29)	17 (6–82)	0.0027

Data are presented as median with range unless otherwise specified

Anterolateral location: in the anterolateral segments (segments 2, 3, 5, and 6 and the inferior part of 4 according to the classification of Couinaud)

Posterosuperior location: in the posterosuperior segments (segments 4a, 7, and 8 according to the classification of Couinaud)

PHS postoperative hospital stay

[a] Number (%) of patients

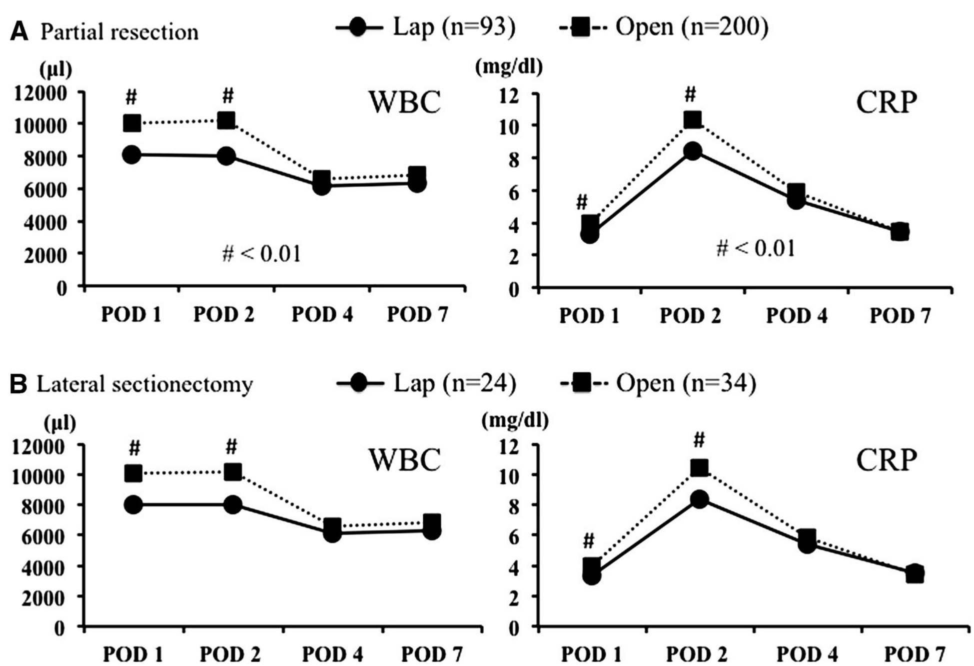

Fig. 1 Postoperative white blood cell count and C-reactive protein level. Data for Lap-Hx are shown by a thick line, and data for Open-Hx are shown by a dotted line. **A** Partial resection: The postoperative white blood cell count and C-reactive protein level tended to be lower after Lap-Hx than after Open-Hx. **B** Lateral sectionectomy: The postoperative white blood cell count and C-reactive protein level tended to be lower after Lap-Hx than after Open-Hx

in comparison with Open-Hx. Lap-Hx is therefore a more useful procedure than Open-Hx for patients with poor liver function.

In terms of blood loss, most reports on Lap-Hx have shown lower bleeding volumes than those on Open-Hx [11, 14–17, 19, 20]. However, whether bleeding from small vessels can be better prevented by continuous abdominal pressure or the use of new coagulation and transection devices remains unclear. Conversely, it was found that the operation time was prolonged by inexperience with laparoscopic surgery. However, the operation time was not longer for Lap-Hx than for Open-Hx; rather, the operation time for laparoscopic lateral sectionectomy and partial resection of peripheral lesions was significantly shorter than that for Open-Hx [25, 26]. On the contrary, when the tumor was located in the posterosuperior segments (segments 4a, 7, and 8), partial resection in Lap-Hx was associated with lower blood loss volumes, but not shorter operation times, compared with Open-Hx. In previous reports, most surgeons have considered that Lap-Hx for lesions located in the posterosuperior segments is not appropriate because of the limited visualization and difficult control of bleeding. On the contrary, some recent reports have proposed the use of Lap-Hx for lesions located in the posterosuperior segments [16, 27–30]. In this study, the operation time gradually decreased to 222 min in the

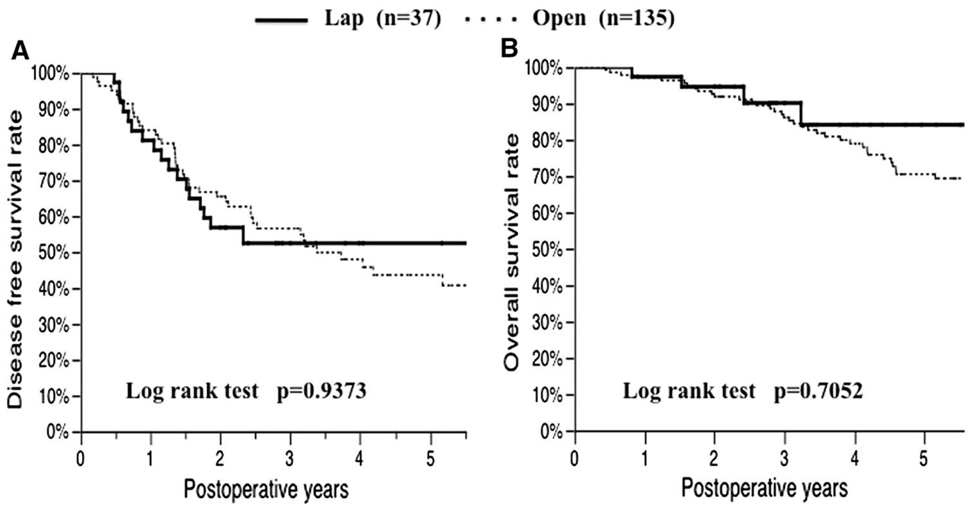

Fig. 2 Disease-free (**A**) and overall (**B**) survival curves after hepatectomy for small (≤5 cm) HCC without macroscopic vascular invasion in laparoscopic hepatectomy (Lap-Hx) and open hepatectomy (Open-Hx). Data for Lap-Hx ($n = 37$) are shown by a *thick line*, and data for Open-Hx ($n = 135$) are shown by a *dotted line*. **A** There were no significant differences in disease-free survival between the two groups. **B** The overall survival curves were very similar between the two groups, and there were no significant differences between them

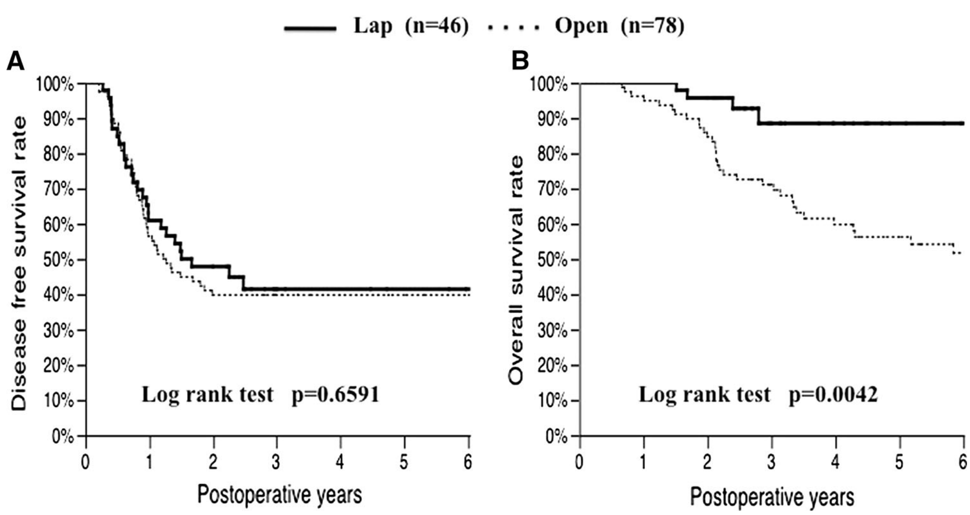

Fig. 3 Disease-free (**A**) and overall (**B**) survival curves after hepatectomy for small (≤5 cm) CRLM of fewer than two lesions without macroscopic vascular invasion in laparoscopic hepatectomy (Lap-Hx) and open hepatectomy (Open-Hx). Data for Lap-Hx ($n = 37$) are shown by a *thick line*, and data for Open-Hx ($n = 135$) are shown by a *dotted line*. **A** There was no significant difference in disease-free survival between the two groups. **B** The overall survival curve of Lap-Hx was significantly better than that of Open-Hx (100, 88, and 88 vs. 96, 68, and 53 %, respectively; $p = 0.0042$)

later period from 298 min in the early period with improvements in surgical techniques such as the insertion of intercostal ports and the use of the semi-prone position (data not shown) [31]. This will be further improved as the learning curve improves in the future.

With respect to long-term outcomes, although previous reports on Lap-Hx described fewer patients and shorter observation periods, the overall and disease-free survival rates were similar between Lap-Hx and Open-Hx for both CRLM [19, 32] and HCC [33, 34]. The overall and disease-free survival rates of patients with HCC with a tumor size of ≤5 cm and without macroscopic vascular invasion were similar between the Lap-Hx and Open-Hx groups in the present study. Although whether anatomical resection is necessary for small HCC remains controversial, a previous report showed that nonanatomical resection is more useful than anatomical resection for HCC under the above-mentioned tumor conditions [35].

In patients with CRLM, the disease-free survival rate was similar between the Lap-Hx and Open-Hx groups;

however, the overall survival rate in the Lap-Hx group was better than that in the Open-Hx group in this study. Furthermore, we re-examined overall survival after adjustment for tumor background because local development of the original tumor has an influence on the overall survival; however, the overall survival after Lap-Hx was better than that after Open-Hx even with this adjustment. We speculate that this may have been associated with the fact that Lap-Hx was performed with the administration of a new anticancer agent, such as FOLFOX, at the time of recurrence in contrast to Open-Hx, which was performed with the administration of more outdated anticancer agents, and with the fact that the observation periods for Lap-Hx were shorter than these for Open-Hx.

In conclusion, regardless of the presence of HCC or CRLM, Lap-Hx is the better option for patients with a tumor size of <5 cm, fewer than two lesions, and no macroscopic vascular invasion. However, a study involving a larger number of patients is necessary to obtain definitive conclusions. Furthermore, it is necessary to establish the Lap-Hx technique for tumors located in the posterosuperior segment to ensure that the performance of Lap-Hx becomes more widespread.

Disclosures Drs. Fumitoshi Hirokawa, Michihiro Hayashi, Yoshiharu Miyamoto, Mitsuhiro Asakuma, Tetsunosuke Shimizu, Koji Komeda, Yoshihiro Inoue, and Kazuhisa Uchiyama have no conflict of interests or financial ties to disclose.

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