Hybrid-including Endoscopic *versus* Open Hepatic Resection for Patients with Hepatocellular Carcinoma Meeting the Milan Criteria: A Propensity Case-matched Analysis

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Abstract. *Aim: To clarify the surgical outcome of patients who underwent endoscopic hepatectomy (EH) compared to those of conventional open hepatectomy (OH) for hepatocellular carcinoma (HCC). Patients and Methods: Between 1999 and 2011, 269 HCC patients meeting the Milan criteria were divided into EH (n=89) and OH groups (n=180). To equalize the background covariates, a one-to-one propensity case-matched analysis was used. Results: With propensity matching, 52 EH and 52 OH patients showed comparable preoperative clinical characteristics. The operation time (320 min, p=0.049) and the median blood loss (180 g, p<0.001) was significantly lesser with EH, while the median postoperative hospital stay (11 days, p=0.002) was significantly shorter for EH. The cumulative disease-free and overall survival rates were equivalent in both groups. Conclusion: EH for HCC patients meeting the Milan criteria is less invasive and might provide an equivalent disease-free and overall survival when compared to conventional OH.*

Endoscopic hepatectomy (EH) for liver tumors, including laparoscopic and thoracoscopic approach, commenced in the 1990s. Several early reports have described the feasibility and usefulness of this technique (1-4). EH can be performed *via* a pure laparoscopic approach, hand-assisted laparoscopic approach or hybrid technique, as defined in the 2008 Consensus Conference in Louisville, KY, USA (5). The approach used is typically selected on the basis of individual tumor factors and surgeon's preference.

From a global perspective, patients with hepatocellular carcinoma (HCC) cases who meet the Milan criteria are considered appropriate candidates for liver transplantation (6-9). According to the Japanese guidelines for liver cancer, HCC patients meeting the Milan criteria are suitable candidates for hepatic resection (10). EH has been utilized for relatively small tumors, while conventional open hepatectomy (OH) is performed for small to larger tumors. Although there is no conclusive size criterion for EH, a small number of lesions and peripherally-located lesions (≤5 cm) not adjacent to major vessels are most suitable for this method (5). We began performing EH procedures in 1999 and have been refining this therapeutic technique for more than 10 years (11). In Japan, the number of EH procedures being performed has increased dramatically since the social insurance system included EH in April 2010. Certain studies demonstrated good operative and oncological mid-term results using EH for HCC with chronic liver disease (12-16). Recent studies have demonstrated that EH for HCC is less invasive and can provide similar disease-free survival (DFS) and overall survival (OS) compared to OH (17-21). However, most of these findings were based on retrospective analyses of case-matched studies (not propensity-matched studies) or meta-analyses of non-randomized studies. In these investigations, serious selection biases may exist with regard to patients selected for EH. Therefore, we conducted a propensity case-matched analysis. This type of evaluation has been proven to decrease selection bias in retrospective studies and allows for comparison between different therapies (22-24).

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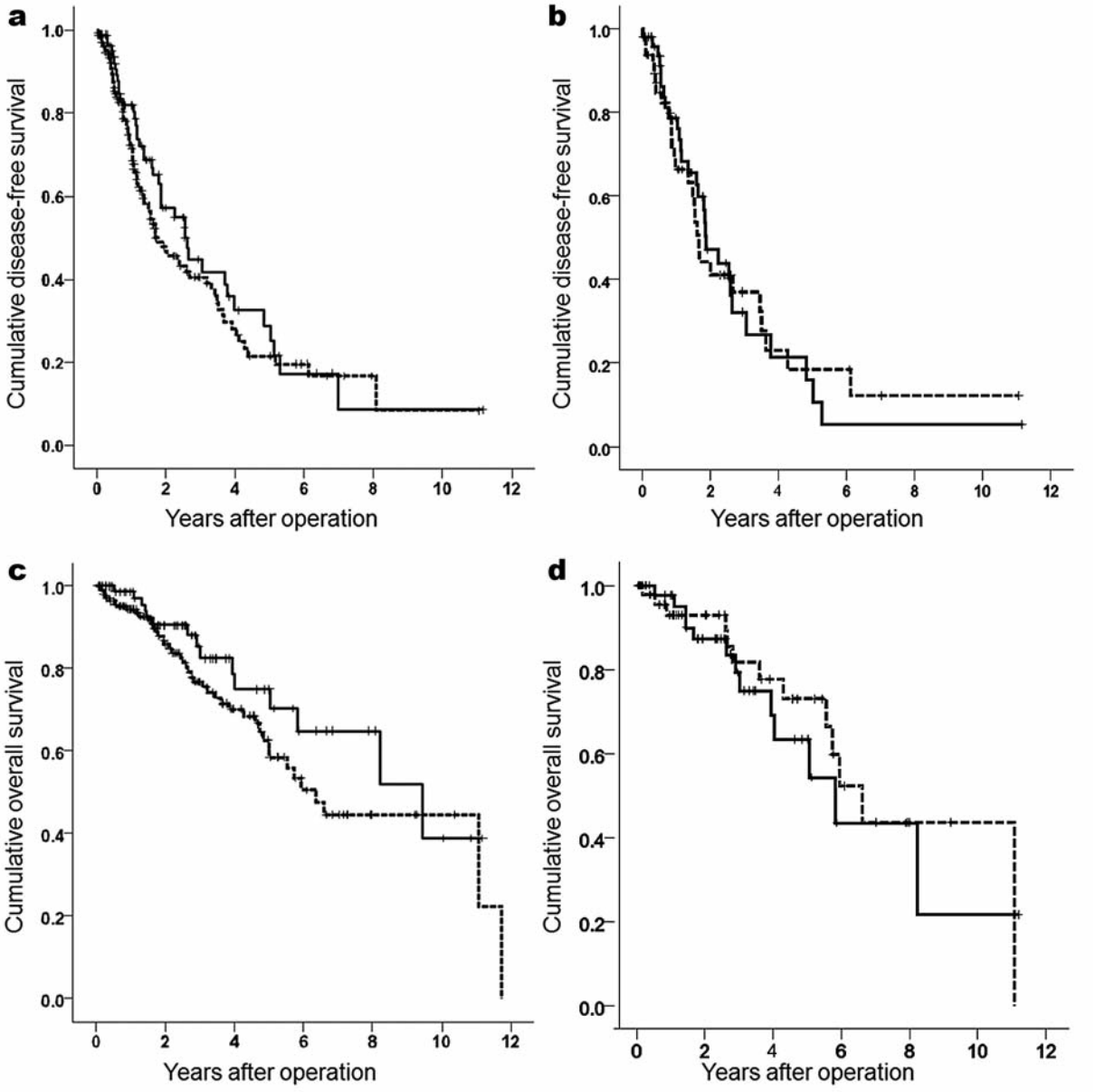

Figure 1. *Kaplan-Meier survival curves comparing disease-free survival (DFS) and overall survival (OS) in the overall and propensity-matched cohorts. a. DFS in overall cohort, b. DFS in propensity-matched cohort, c. OS in overall cohort, d. OS in propensity-matched cohort. Solid line, EH; Dotted line, OH.*

We hypothesized that patients with HCC who meet the Milan criteria are suitable candidates for EH. This study was undertaken to determine the surgical outcome and long-term prognosis of EH in comparison to those of conventional OH for HCC patients who met the Milan criteria.

Patients and Methods

From January 1999 to October 2011, a prospective database of 269 hepatectomized HCC patients meeting the Milan criteria (6) was analyzed. All patients were treated by limited hepatectomy that was equal to or smaller than sectionectomy (25) at the Department of Gastroenterological Surgery, Kumamoto University Hospital. The diagnosis of HCC in all patients was confirmed by histopathological examination of resected specimens. The patients were divided into two groups: an EH group (n=89) and an OH group (n=180). Mean age, gender, etiology of liver background disease, liver damage grade, alpha-fetoprotein (AFP) and des-gamma-carboxyl prothrombin (DCP) levels, tumor size, tumor number and tumor location were investigated before surgery. "Liver damage grade" was decided according to the Criteria of the Liver Cancer

Table I. *Clinical characteristics of HCC patients who underwent EH and OH: overall patient cohort versus one-to-one propensity-score-matched pairs.*

	Overall patient cohort (n=269)			Propensity-matched patients (n=104)		
	EH (n=89)	OH(n=180)	*p*	EH (n=52)	OH (n=52)	*p*
Gender						
Female	29	34		16	14	
Male	60	146	**0.015**	36	38	0.829
Anatomic						
No						
Yes	69	125		40	42	
	20	55	0.194	12	10	0.811
Initial treatment						
No	22	63		15	12	
Yes	67	117	0.096	37	40	0.655
HBs-Ag						
(-)	61	143		40	43	
(+)	28	37	**0.015**	12	9	0.626
HCV-Ab						
(-)	45	68		24	17	
(+)	44	112	0.050	28	35	0.228
Liver damage grade						
A	82	159		47	47	
B	7	21	0.401	5	5	1.000
Difficult tumor location						
No	69	110		37	40	
Yes	20	70	**0.009**	15	12	0.655
Superficial location						
No	34	93		26	22	
Yes	55	87	**0.0499**	26	30	0.555
Vascular proximity						
No	84	150		47	44	
Yes	5	30	**0.012**	5	8	0.555
Age (year), median (range)	67(36-83)	68(36-86)	0.220	69(38-83)	67(36-81)	0.750
AFP (ng/ml), median (range)	9.5(1-3689)	10.3(1-32048)	0.724	8.8(2-2821)	10.0(1-32048)	0.993
DCP (mAU/ml), median (range)	28(11-27802)	44(1-23461)	0.023	31(13-27802)	45(12-11043)	0.307
Tumor Size (mm), median (range)	22(2-50)	30 (8-50)	**<.001**	25(12-55)	27(12-50)	0.326
Tumor Number, median (range)	1 (1-3)	1 (1-3)	0.478	1(1-5)	1(1-3)	0.574

Bold values show significant statistical levels ($p<0.05$). HBs-Ag, Hepatitis B surface antigen; HCV-Ab, anti-hepatitis C antibody; AFP, alpha-fetoprotein; DCP, des-gamma-carboxyl prothrombin. Clinical parameters were compared with the Mann-Whitney *U* test for ordinal and Fisher's exact test for categorical data.

Study Group of Japan (26). "Difficult tumor location" was defined as posterosuperior segments of the liver (segments 1, 7 and 8 and the superior part of segment 4) (27). "Superficial location" and "vascular proximity" was defined as tumor detected on the liver surface and tumor in contact with the remaining major vessels, respectively. All patients also underwent preoperative liver function tests, including those for measuring bilirubin and albumin levels, prothrombin activity and international normalized ratio (PT-INR), as well as indocyanine retention rate at 15 min to classify liver damage, and 99mTc-galactocyl human serum albumin scintigraphy single-photon emission computed tomography (CT) imaging (28). Intraoperative blood loss, operative time, frequency of red cell concentrate (RCC) and fresh-frozen plasma administration were prospectively recorded. Morbidity was graded according to the Clavien-Dindo classification (29) and 3-month mortality was evaluated. Grade IIIA or greater complications were considered morbidities. The Institutional Review Board of the Kumamoto University Hospital approved this study and written informed consent was obtained from all patients prior to study initiation.

Selection of EH or OH. The operative indications for EH and OH were decided on the basis of liver functional reserve and volume of future remnant liver (28, 30). Contraindications included uncontrollable ascites, total bilirubin levels of >2 mg/dl, prothrombin activity of ≤40% (PT-INR≥ 1.79), platelet count of ≤30,000/μl and inability to receive general anesthesia. EH was our initial preference; however, we performed OH in patients who requested it, patients unfit for pneumoperitoneum or patients with complicated tumor locations.

Operative procedure. All procedures were performed by the same surgical team. A CUSA™ aspiration system (Valley Lab, address)

Table II. *Perioperative course of HCC patients who underwent EH and OH: Data are reported from the whole study series and for one-to-one propensity-score matched pairs.*

	Overall patient cohort (n=269)			Propensity-matched patients (n=104)		
	EH (n=89)	OH (n=180)	*p*	EH (n=52)	OH (n=52)	*p*
Operation time (min) median (range)	310 (182-587)	355 (165-725)	**<.001**	320 (182-580)	345 (184-653)	0.049
Blood loss (g), median (range)	130 (5-3327)	408 (20-6000)	**<.001**	180 (5-3327)	473 (20-3404)	<.001
RCC administration (%)	2 (2.2)	12 (6.7)	0.153	2 (3.8)	2 (3.8)	>.999
FFP administration (%)	4 (4.5)	15 (8.3)	0.317	4 (7.7)	4 (7.7)	>.999
Morbidity (%)	6 (6.7)	39 (21.7)	**0.002**	4 (7.7)	11 (21.2)	0.092
Mortality (%)	0 (0.0)	3 (1.7)	0.553	0 (0.0)	0 (0.0)	-
Postoperative hospitalization (days), median (range)	10 (6-46)	14.5 (7-87)	**<.001**	11 (6-46)	14 (8-87)	0.002

Bold values show significant statistical levels ($p<0.05$). RCC, red cell concentrate; FFP, fresh frozen plasma. Clinical parameters were compared with the Mann-Whitney *U* test for ordinal and Fisher's exact test for categorical data.

and coagulating devices were used as part of the standard technique for liver transection (30). Intraoperative ultrasonography was performed routinely. During OH, a pair of bipolar forceps with electrical coagulation or VIO soft coagulation system (VIO 300D BiClamp model; ERBE, Elektromedizin, GmbH, City, Germany) were initially used to prevent parenchymal oozing while performing hepatic transection. In the EH group, we used various precoagulation techniques, including microwave coagulation, radiofrequency ablation or the use of soft coagulation devices in combination with the transection of liver parenchyma mainly by CUSA (31). If necessary, intermittent cessation of hepatic flow was achieved with the Pringle maneuver (30) in both groups. In EH patients, the pressure of pneumoperitoneum was set as 8 to 10 mmHg during laparoscopic procedure and the pressure was increased to 12 mmHg as an upper limit during hepatic transection. For the limited number of patients with HCC tumors located in the hepatic dome, we selected a thoracoscopic approach for EH (11). In the hybrid approach, we created an upper abdominal midline incision of 8-10 cm for left-side tumor and 10-12 cm for right-side subcostal incision for right-side tumor (32, 33).

Follow-up. All patients underwent regular postoperative follow-up. Serum AFP and DCP levels were measured every 1 to 2 months and abdominal ultrasound and enhanced CT or magnetic resonance imaging were performed every 3 to 4 months to detect any recurrences as described previously (34). When tumor recurrence was confirmed, suitable therapeutic modalities were selected.

Propensity score analysis. A propensity score analysis (22-24) was used to build a matched group of patients for comparison of clinical outcomes and long-term survival between EH and OH. The following clinical variables were included for propensity score generation: gender, age, hepatitis B surface antigen (HBs-Ag) positivity, anti-hepatitis C virus antibody positivity, tumor size, tumor number, serum AFP and DCP levels, extent of liver damage (grade A, B), use of anatomic resection (yes, no), history of initial treatment (yes, no), difficult tumor location (yes, no), superficial location (yes, no) and vascular proximity (yes, no). Logistic regression was applied to generate a continuous propensity score ranging from 0 to 1. One-to-one matching without replacement, as performed by 0.01 caliper-matching on the estimated propensity score, generated 52+52 matched EH and OH units.

Statistical analyses. Clinical parameters were compared using the Mann-Whitney *U* test for ordinal data and the Fisher's exact test for categorical data. The 95% confidence intervals (CIs) for medians were estimated using the bootstrap method. The DFS period was calculated from the date of surgery to the date of recurrence or last follow-up. The Kaplan-Meier method was used to calculate the 5-year survival rate and the log-rank test for the p value for DFS and OS, unless otherwise noted. The Cox proportional hazards regression was used to calculate the hazard ratio (HR) and 95% CI for univariate and multivariate analyses. All variables showing significance in univariate analysis were included in multivariate analysis. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using the statistical package SPSS, release 20.0 (IBM Corporation, Armonk, NY, USA).

Results

The characteristics of the overall cohort and that used for propensity score matching are presented in Table I. In the overall cohort, most of EH patients were females (33% *versus* 19%), HBs-Ag-positive (31% *versus* 21%), had non-difficult tumor location (77% *versus* 61%), superficial location (62% *versus* 48%), non-vascular proximity (94% *versus* 83%) and smaller tumors (22 *versus* 30 mm). EH procedures were performed using the pure laparoscopic approach (n=6), hand-assisted laparoscopic approach (n=30), hybrid technique (n=51) or thoracoscopic approach (n=2). Partial resection, segmentectomy and sectionectomy were performed in 68 and 125, 1 and 27 and 20 and 28 EH and OH patients, respectively. Left lateral sectionectomy was included 11/89 (12.3%) in EH and 5/180 (2.8%) in OH. After one-to-one case

propensity matching, a total of 52 EH and 52 OH cases were subjected to further analysis. All baseline characteristics were comparable between the two groups. Moreover, standardized differences between pre- and post-matching showed a large decrease as shown in Table II. Additionally, preoperative liver function-related factors (indocyanine green retention rate at 15 min (ICG R15) value, uptake ratio of the liver to the liver plus heart at 15 min (LHL15), total bilirubin, serum albumin, aspartate aminotransferase (AST) /alanine aminotransferase (ALT) and platelet counts) were not significantly different in the novel propensity-matched two groups.

Perioperative parameters. Conversion from EH to OH occurred in 2/89 (2.2%) patients in the overall cohort. In the cohort used for propensity matching, the median operative time (320 min *versus* 345 min, $p=0.049$) and the median blood loss (180 g *versus* 473 g, $p<0.001$) were significantly less with EH than with OH (Table II). Before matching, the postoperative complication rates were significantly lower in the EH group than in the OH group (6.7% *versus* 21.7%, $p=0.002$) (Table II). Complications after EH included surgical site infection (n=2), renal failure (n=1), bile leakage (n=1), portal vein thrombus (n=1) and bronchial plexus nerve disorder (n=1). There was no patient of port site recurrence or dissemination. In contrast, after propensity matching, the morbidity rates were similar between the two groups (7.7% for EH and 21.2% for OH), while mortality at 3 months was nil in both groups. However, median postoperative hospital stay was significantly shorter for EH patients than for OH patients (11 days *versus* 14 days, $p=0.002$; Table II).

Survival and recurrence data. Similar DFS and OS curves were observed for the overall cohort (Figure 1a, c). In the propensity-matched cohort, median observation periods were comparable between the two procedures (EH: 29.0 months; 95% CI=19.9-35.5; OH: 29.9 months; 95% CI=12.9-43.9; $p=0.878$). For EH, the cumulative 3-, 5- and 10-year DFS rates were 32.2%, 16.1% and 5.4%, respectively, and 37.0%, 18.5% and 12.3% for OH, respectively (Figure 1b). The median DFS period for EH and OH was 22.4 months (95% CI=15.8-29.1) and 20.2 months (95% CI=17.9-22.4), respectively. Cumulative 3-, 5- and 10-year OS rates were 79.3%, 63.4% and 21.7%, respectively, for EH and 81.8%, 73.1% and 43.6%, respectively, for OH (Figure 1d). The median survival time for EH and OH was 69.8 months (95% CI=40.7-99.0) and 79.3 months (95% CI=63.1-95.5), respectively. There were no significant differences in DFS ($p=0.978$) and OS ($p=0.614$) between the two groups.

Discussion

According to a recent randomized trial of surgical treatments other than transplantation for patients meeting the Milan criteria, surgical resection provides better survival and lower recurrence rates compared to radiofrequency ablation (35). Therefore, hepatic resection should be initially performed for HCC patients meeting the Milan criteria with sufficient liver function. In the current study, we selected HCC patients who met the Milan criteria to determine whether EH could provide clinical advantages compared to conventional OH. A simple comparison of surgical outcomes between EH and OH patients is quite difficult because there is considerable selection bias in terms of preoperative background factors. The EH group included a greater number of female and HBs-Ag-positive patients, as well as patients with a smaller tumor size. These parameters have been reported to be good prognostic factors for patients who have undergone HCC resection (36, 37). Therefore, we created a propensity case-matched cohort of EH and OH patients with equivalent preoperative background factors to compare the procedures on a more actuarial basis.

Numerous reports on the clinical advantages of EH over conventional OH for liver tumors have been published. No randomized control trial (RCT) comparing EH and OH has been published till date. According to these reports, EH may decrease intraoperative blood loss, surgical stress and postoperative hospital stay while providing a lower rate of postoperative intra-abdominal adhesions (13, 14, 38-42). However, these studies were mostly systematic reviews or meta-analyses of non-randomized studies. Lately, it was reported that EH was technically feasible for HCC in selected patients and could provide similar perioperative and long-term oncological outcomes when compared to OH using propensity score matching (43). However, the study included relatively small number of patients; 29 and 29 patients in EH and OH, respectively, and there were significantly more non-anatomical resections in EH. Our study included 52 and 52 patients in EH and OH, respectively, while the background factors were identical.

The largest meta-analysis ever of 10 articles comprising 627 HCC patients (15) described that surgical and oncological outcomes were better with EH than with OH. However, the 10 articles included six case-control and four retrospective analyses; no RCT was included. The overall conversion rate to open surgery was 6.6%. The laparoscopic group exhibited significantly less blood loss by 223 mL ($p<0.0001$), fewer requirements for RCC transfusions (HR, 0.42; $p=0.007$), shorter hospital stay by 5.05 days ($p=0.0004$) and fewer postoperative complications (odds ratio, 0.50; $p=0.002$). The analysis of our propensity case-matched cohort of 104 patients confirmed the advantages of EH over OH as the median operative time and blood loss were significantly less with EH than with OH (Table II), while laparotomy and abdominal wall closure times were also shorter during EH than during OH. More delicate surgery can decrease operative time and intraoperative blood

loss with a magnification effect and higher intra-abdominal pressure due to carbon dioxide (44). Furthermore, pre-coagulation using soft coagulation, with a ball-electrode or radiofrequency or microwave ablation, can minimize blood loss during hepatic transection (31). Large amount of intraoperative bleeding and RCC transfusion has been described as a poor prognostic factor (45, 46). In our study, the rate of RCC or fresh frozen plasma transfusion was low in both groups. Although analysis of the overall patient cohort confirmed a significantly lower morbidity rate in the EH group (6.7%) than in the OH group (21.7%), analysis of the propensity-matched cohort demonstrated a similar morbidity rate with no significant difference between the two groups (EH: 7.7% and OH: 21.2%). It was speculated that OH was mainly performed for patients presenting greater operative difficulties; complicated tumor location to resect or larger tumor. Actually, the rate of difficult tumor location, deep location and vascular proximity was significantly greater in OH patients compared to EH patients. In the present study, difficult tumor location was defined as posterosuperior segments of the liver (segments 1, 7 and 8 and the superior part of segment 4) (26). In fact, the mean operative time and the amount of intraoperative blood loss were significantly greater in the posterosuperior group than in the anterolateral group (data not shown). We believe that propensity-matching can also minimize the bias of operative difficulties. The 3-month mortality rate was nil in the EH group. The lesser invasiveness and lower morbidity may have been responsible for the shorter postoperative stay in the EH group (11days) and, consequently, the selection of EH might increase in the treatment strategies for HCC.

A worldwide review of laparoscopic liver resections in 2,804 patients (38), 50% of whom had malignant tumors, included EH performed using the genuine laparoscopic (75%) approach, the hand-assisted (17%) laparoscopic approach or the hybrid technique (2%). However, a comparison of the different EH procedures was not well discussed. Even in our study, EH was essentially performed using one of these three approaches. The advantage of laparoscopic-assisted hepatic resection has been previously discussed in comparison with open resection (39). The laparoscopic-assisted hepatic resection involved hand-assisted mobilization of the liver and parenchymal dissection through the hand port incision and is one of the hybrid techniques. Although decreased surgical pain, improved esthetics and shorter hospital stay were demonstrated in the laparoscopic-assisted hepatic resection group, the mean operative time and lesion size were similar between the two groups. In the general hybrid approach, we used an upper abdominal midline incision of 8-10 cm or 10-12 cm for right-side subcostal incision in accordance with previous reports (32, 33) or ongoing multicenter clinical trial "Laparoscopy-assisted hepatectomy using the radiofrequency ablation system (UMIN000010731)". Hybrid hepatectomy can shorten the duration of hospitalization (47) and improve the postoperative quality of life (QOL) of living donors (32).

We emphasize that while there exist few oncological disadvantages associated with EH compared to conventional OH, we encountered no complications of port-site recurrence or intra-abdominal seeding. In addition, compared to endoscopic ablation for HCC, EH has some distinct advantages, namely a lower rate of recurrence at the therapeutic sites or a lower rate of intraperitoneal implantation of tumor cells. It also provides the possibility of histopathological examination of resected specimens (11). Lesser invasive surgery with minimal blood loss, no RCC transfusion and no postoperative complications are recommended for a good prognosis. Actually, the long-term DFS and OS for EH were quite good and comparable to those of conventional OH (Figure 1).

This is the first report, to the best of our knowledge, to focus on HCC patients meeting the Milan criteria who were treated with EH. However, this study has certain limitations, with the most important being that this was not an RCT. Confounding factors may have been minimal but could have affected the results. Secondly, this study included 51 (57%) patients treated with hybrid hepatectomy that may account for the results obtained in contradistinction to genuine laparoscopic hepatectomy. The sample size decreased after matching, which could have affected the accuracy of survival-estimated values. The number of 89 EH patients was reduced to 52 due to caliper-matching, which is caused by the small sample size of OH group. Finally, the number of excluded patients from the final analysis (one third of the EH group) might account for the selection bias of the propensity score analysis.

In conclusion, compared to the OH approach, EH is a safe and less invasive procedure for HCC patients and might provide similar perioperative and long-term outcomes for selected patients meeting the Milan criteria. A prospective RCT comparing EH and OH should be performed to confirm these results.

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