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The current trends of mortality following congenital heart surgery: the Japan Congenital Cardiovascular Surgery Database

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ORIGINAL ARTICLE

Abstract

OBJECTIVES: Whereas surgical outcomes of congenital heart surgery have improved during the past two decades, there are still measurable postoperative mortalities in this field. This study is aimed at evaluating the current situation of mortality following congenital heart surgery.

METHODS: Data on all registered 28 810 patients in The Japan Congenital Cardiovascular Surgery Database (JCCVSD) between 2008 and 2012 were analysed, except for patients with degenerative cardiomyopathy including dilated, restrictive and hypertrophic cardiomyopathy, and pathologically or histologically malignant cardiac tumours. The number of registered cases increased every year, and reached ~9000 cases in 2012. The median age at surgery was 0.8 years (range, 0–82). More than half of the patients (54%) who underwent surgery were <1 year old, and 6.0% of all patients were over 18 years old (adults). In this study, all mortalities within 90 days after the operation and mortality at discharge beyond 90 days of hospitalization were defined as '90-day and in-hospital mortality'.

RESULTS: The 30-, 90-day and in-hospital mortality rates were 2.3, 3.5 and 4.5%, respectively. The mean and median durations from surgery to death were 61 ± 89 and 28 days (range, 0–717), respectively. Whereas 658 mortalities (51%) occurred within 30 days of surgery, 265 (21%) occurred later than 90 days after surgery. A total of 3630 patients (13%) were hospitalized for more than 90 days after the operation; of those, 3365 patients survived at discharge (93%). Cardiac problems were the most frequent causes of death after the surgery at any point in time, and 7.1 per 1000 patients died at over 30 days after the operation due to solely cardiac.

CONCLUSIONS: The investigation of JCCVSD revealed that about a half of mortalities occurred later than 30 days; hence 90-day and in-hospital mortality would be a good discriminator that accurately represented the current situation of mortality after congenital heart surgery. Mortalities long after the operation due to post-cardiotomy heart failure without any other lethal complications were still not rare.

Keywords: Congenital heart disease • Surgery • Database • Extracorporeal membrane oxygenation

INTRODUCTION

Whereas a great improvement in the surgical outcomes of congenital heart surgery has been achieved during the past two decades, there are still measurable postoperative mortalities in this field. In addition, for the further evolution of surgical procedures or treatments for each anatomical group, therapeutic options such as left ventricular assist devices, heart transplantation and cardiac regenerative therapy must be offered to rescue patients falling victim to postoperative heart failure.

The Japan Congenital Cardiovascular Surgery Database (JCCVSD), which is the nationwide congenital heart surgery database registry system, was established in 2008 [1]. The accuracy of follow-up outcomes was confirmed by a site audit [2], and now >90% of congenital heart operations performed in Japan are enrolled in the database. Utilizing this database, we have reviewed the timing, cause and trends of death after congenital heart surgery in Japan in order to assess the current situation and the necessity of further treatment options for post-cardiotomy heart failure.

MATERIALS AND METHODS

Japanese Cardiovascular Surgery Database Organization Committee granted permission to access and analyse the data collected in the JCCVSD with a waiver of informed consent.

Of the patients registered on the JCCVSD between 2008 and 2012, 28 810 patients were selected as study subjects, mainly by fundamental diagnosis (Supplementary material, File S1) [3]. Patients with myocardial degenerative disease including dilated, restrictive and hypertrophic cardiomyopathy, a cardiac tumour or complications after heart transplantation were excluded from this study (Supplementary material, File S2).

The characteristics of the 28 810 enrolled patients are summarized in Table 1. The number of admitted institutions was 17 in 2008, 68 in 2009, 93 in 2010, 102 in 2011 and 111 in 2012; thus, the number of registered cases increased every year and reached ~9000 cases in 2012. The median age at surgery was 0.8 years (range, 0–82). More than half of the patients (54%) who underwent surgery were <1 year old, and 6.0% of all patients were over 18 years old (adults). The surgery was electively scheduled for 84.6% of the patients, 11.3% of the cases were scheduled urgently and 4.1% were emergently performed.

Definitive surgery was defined as the last surgery that was planned according to each anatomical property, and so it included not only complete biventricular repair, but also partial biventricular repair or Fontan operations with or without fenestration. The prevalence rates of the definitive operation with cardiopulmonary bypass (CPB), the palliative operation with CPB, the definitive operation without CPB and the palliative operation without CPB were 64, 13, 7.0 and 15%, respectively.

Prevalence of patients by risk adjustment in the congenital heart surgery system (RACHS) ([4], Supplementary material, File S3) categories were as follows: risk category 1 in 13% of patients, category 2 in 33%, category 3 in 34%, category 4 in 7.7%, category 5 in 0.1% and category 6 in 2.6% of patients.

Table 1: Patient characteristics

Total number of patients (*n*)	28 810	
Male:female (*n*)	14 412:13 105	
Age at operation [mean ± SD, median (range)]	4.4 ± 10.0	0.8 (0–81)
	n	(%)
Generation		
Neonate	4760	(16.5)
Infant	10 778	(37.4)
Child	11 523	(40.0)
Adult	1734	(6.0)
Unknown	15	(0.1)
Year of operation (number of registered institutions)		
2008 (17)	982	(3.4)
2009 (68)	3403	(11.8)
2010 (93)	7051	(24.5)
2011 (102)	8389	(29.1)
2012 (111)	8985	(31.2)
Situation		
Elective	24 360	(84.6)
Urgent	3256	(11.3)
Emergency	1194	(4.1)
Type		
Definitive, with CPB	18 532	(64.3)
Palliative, with CPB	3833	(13.3)
Definitive, without CPB	2019	(7.0)
Palliative, without CPB	4426	(15.4)
RACHS risk category		
1	3454	(12.9)
2	8922	(33.2)
3	9008	(33.5)
4	2078	(7.7)
5	16	(0.1)
6	707	(2.6)
Uncategorized	2689	(10.0)

CPB: cardiopulmonary bypass; RACHS: risk adjustment in congenital heart surgery system.

Definition of 90-day and in-hospital mortality

The database forced medical practitioners to enter the discharge date within 90 days after the last surgery and the life prognosis at postoperative day 90, so that mortality up to and including postoperative day 90 was completely recorded. If patients were in the hospital for more than 90 days after the operation, the entering of the discharge date and life prognosis was voluntary. However, 3616 of 28 810 patients (13%) were in the hospital beyond postoperative day 90, and the life prognoses at discharge were recorded for all patients.

In addition, only 3.1% of all mortalities occurred after discharge. All these patients were discharged within 90 days after the last operation and their death was identified by the confirmation of life prognosis at 90 days after the last surgery. Therefore, in this study, all mortalities within 90 days after the operation and mortality at discharge beyond 90 days of hospitalization were defined as '90-day and in-hospital mortality'.

Definition of the cause of death

The cause of death was determined by the treating physicians according to their clinical impressions when considering the postoperative course, which was objectively assessed according to the clinical chart of the intensive care unit, operative records, echocardiograms, catheterizations and clinical summaries. Then, the principal clinical issue contributing to the patient's death was determined as the cause of death, which was not necessarily the same as the preterminal event occurring immediately before death. Because the identification of the sole cause of death was usually difficult, all possible causes [i.e. (i) cardiac, (ii) lung, (iii) infection, (iv) central nervous system damage, (v) renal and other issues] could be concomitantly recorded.

Post-cardiotomy extracorporeal membrane oxygenation cannulation

Extracorporeal membrane oxygenation (ECMO) cannulation and decannulation have been added as surgical procedures since 2010. During the study period, paediatric left ventricular assist systems were not available, and there had been only 2 donors under 15 years of age for paediatric heart transplantation, nevertheless, the Organ Transplant Law in Japan was revised and enforced in 2010.

Study methods

Evaluated variables in this study were as follows: (a) timing and cause of death after surgery; (b) differences in mortality rates by generation, surgical year, RACHS risk category and operation type; and (c) prognostic outcomes for post-cardiotomy ECMO support.

Preoperative risk factors that were required to be entered into the database are listed in the Supplemental Material. Risk factor analysis was conducted using the Pearson's χ^2 test and data were analysed using the JMP software version 10 (SAS Institute, Cary, NC), USA. Differences were considered statistically significant when the P-value was <0.05.

RESULTS

Timing and cause of death after surgery

Of all the 28 810 patients enrolled in the database, 1293 mortalities (4.5%) were identified (Fig. 1). The 30-day and 90-day mortality rates were 2.3 and 3.5%, respectively. Forty of the mortalities (3.1%) occurred after discharge. The mean and median durations from the last operation to death were 61 ± 89 days and 28 days (range, 0–717), respectively. Whereas 658 mortalities (51%) were observed within 30 days of the last surgery, 352 (27%) were from 30 days to 90 days, and 265 (21%) were observed more than 90 days after the last surgery.

The causes of death after surgery were often multifactorial (Table 2). Of all 1293 mortalities, 546 mortalities (42%) were related solely to cardiac issues; thus any other lethal problems such as lung issues, infections, central nervous system damage or renal issues were not related. Solely lung issues was the second most frequent cause of death, which included acute respiratory distress syndrome, pulmonary hypertension crisis or persistent pulmonary hypertension without such problems as left heart issues, pulmonary bleeding or thromboembolism, and so on. Infection was the sole cause of death in 99 patients (7.7%), and central nervous system damage was the sole cause of death in 41 patients (3.2%). Table 2 also demonstrates the different trends in the causes of death by displaying the timing of death. Although cardiac issues were the most common causes of death during the entire period, the prevalence of mortalities caused by cardiac issues decreased as time passed, and mortalities caused by infection increased.

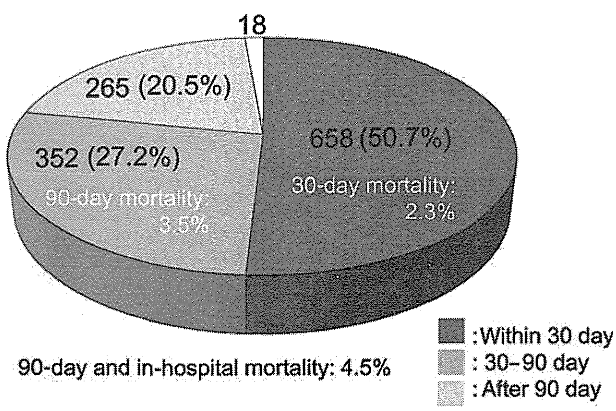

Figure 1: Timing of death after surgery. The areas in red, orange and yellow represent the amount and prevalence of mortality within 30 days after surgery, between 30 and 90 days after surgery, and more than 90 days after surgery, respectively.

Table 2: Causes of death after surgery (multiple reasons allowed)

Mortality	All	Beyond 30 days	Beyond 90 days
N	1293	617	265
Cause of death [*n* (%)]			
Cardiac	776 (60.0)	329 (53.3)	121 (45.7)
Cardiac-only	546 (42.2)	205 (33.2)	72 (27.2)
Lung	376 (29.1)	199 (32.3)	85 (32.1)
Lung-only	169 (13.0)	90 (14.6)	48 (18.1)
Infection	225 (17.4)	155 (25.1)	73 (27.5)
Infection-only	99 (7.7)	62 (10.0)	29 (10.9)
CNS damage	85 (6.6)	31 (5.0)	11 (4.2)
CNS damage-only	41 (3.2)	7 (1.1)	1 (0.4)
Renal	7 (0.5)	6 (1.0)	5 (1.9)
Others	237 (18.3)	142 (23.0)	70 (26.4)

CNS: central nervous system.

Differences in mortality rate by preoperative variables

The differences between the number of patients and mortality rates by generation are shown in Fig. 2A. The postoperative mortality rate of surgery in the neonatal period was 12% (547/4760) and exhibited the highest rate of all four generations ($P < 0.001$). On the other hand, postoperative mortality rates of surgery in children over 1 year of age (1.6%, 188/11 523) and adults over 18 years of age (2.4%, 42/1734) were significantly lower when compared with the other three generations.

The chronological changes of the enrolled patient number and mortality rate by surgical year are shown in Fig. 2B. The number of enrolled patients increased yearly, whereas the mortality rate varied each year varied, ranging from 4.2 to 5.9%. In 2012, 376 of the 9361 patients enrolled were deceased and the mortality rate was 4.2%, which was almost the same trend as in 2011.

The differences between the numbers of patients and the mortality rates by RACHS risk category are shown in Fig. 3. The risk grade category and the mortality rate had a statistically strongly positive, linear correlation ($R^2 = 0.951$, $P < 0.001$), except for risk category 5, where the repair of truncus arteriosus and an interrupted aortic arch was performed. There were only 16 patients who received these procedures during the entire study period.

The differences between the numbers of patients and the mortality rates by surgical situation and type are shown in Fig. 4. Whether CPB was required or not, the mortality rate of palliative surgery was significantly higher than that of definitive surgery (800/8259 = 9.7% vs 493/22 526 = 2.2%, $P < 0.001$). With regard to the former, the mortality rate of palliative surgery with CPB was significantly higher than that of the same surgery without CPB (416/3833 = 10% vs 384/4426 = 8.7%, $P < 0.001$) (Fig. 4A). With regard to surgical situation, emergency surgery resulted in a mortality rate of >20% (255/1194 = 21.4%), while that of elective surgery was 2.8% (682/24 360) (Fig. 4B).

Prognostic outcomes of post-cardiotomy extracorporeal membrane oxygenation cannulation

Between 2010 and 2012, 108 of the registered 24 425 patients (0.4%) required ECMO cannulation during the perioperative period. Of those, 41 patients survived to discharge after successful ECMO decannulation (38.0%). The mean and median durations

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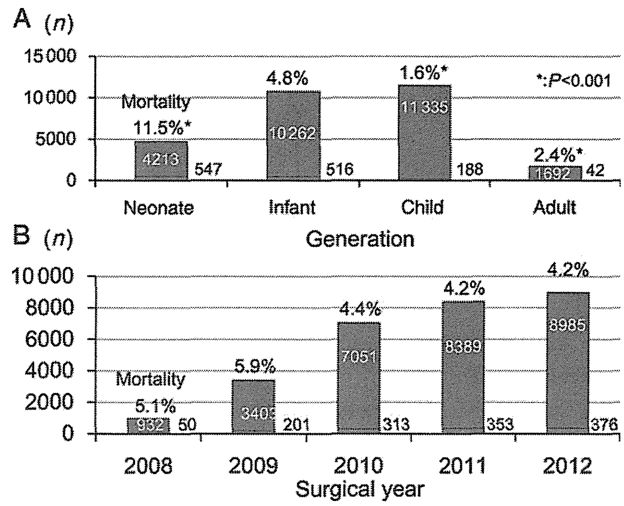

Figure 2: Differences between the number of patients and the mortality rate stratified by generation (**A**), or surgical year (**B**). The blue bar represents the number of surviving patients, and the red bar represents deceased patients. *$P < 0.001$.

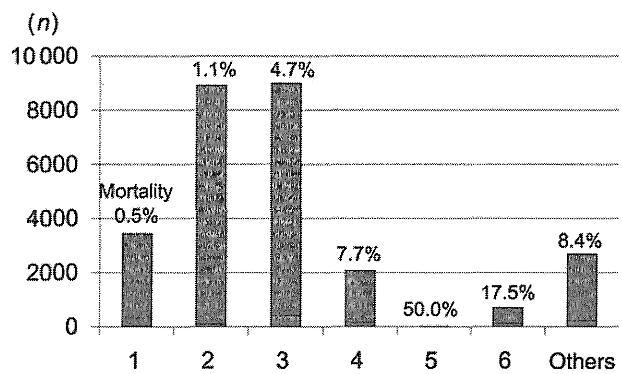

Figure 3: Differences between the number of patients and the mortality rate by risk adjustment in the congenital heart surgery system (RACHS) risk category. The blue bar represents the number of surviving patients, and the red bar represents deceased patients.

from ECMO cannulation to death in the remaining 67 patients were 42.8 ± 66.2 days and 18 days (range, 0–299), respectively.

DISCUSSION

The Japanese Association for Thoracic Surgery Committee has reported the results of thoracic and cardiovascular surgery, including congenital heart surgery, annually since 1986, and is famous for the establishment on a national scale of the annual statistics overview because of the high response rate to the survey [5]. On the other hand, an individual case registration system, according to the authorized nomenclature for the diagnosis and surgical procedure, was mandated to compare the outcomes accurately with other nationwide or international databases [6]. Although each category based on a risk-adjusted tool did not match, 30-day, 90-day, and 90-day and in-hospital mortality rates after congenital heart surgery in Japan were 2.3, 3.5 and 4.5%, respectively, during the past 5 years, which compared favourably with the Congenital Heart Surgery Database of the Society of Thoracic Surgeons, the European Association for Cardio-thoracic Surgery or a combination of the two [7–9]. The number of operations and postoperative mortality rates have currently stabilized at ~9000 cases per year and <5.0% during the last 2 years, respectively.

Two specific medical situations of Japan were demonstrated in this study. First, 111 institutions performed ~7000 congenital open heart surgeries using CPB in 2012. There are <10 institutions in Japan where >200 congenital open heart surgeries were annually performed; thus, the other 5000 cases were carried out at the remaining 100 institutions. Although this database system cannot allow for a more detailed investigation of the relationship between the case volumes, case complexities and mortality rates of each institution, it is noteworthy that the overall nationwide surgical outcomes were acceptable even if such a large amount of small programmes exist [10].

Although a case-matched comparison study could not be conducted because of the different definitions of operative mortality, another unique situation in Japan is the long duration from

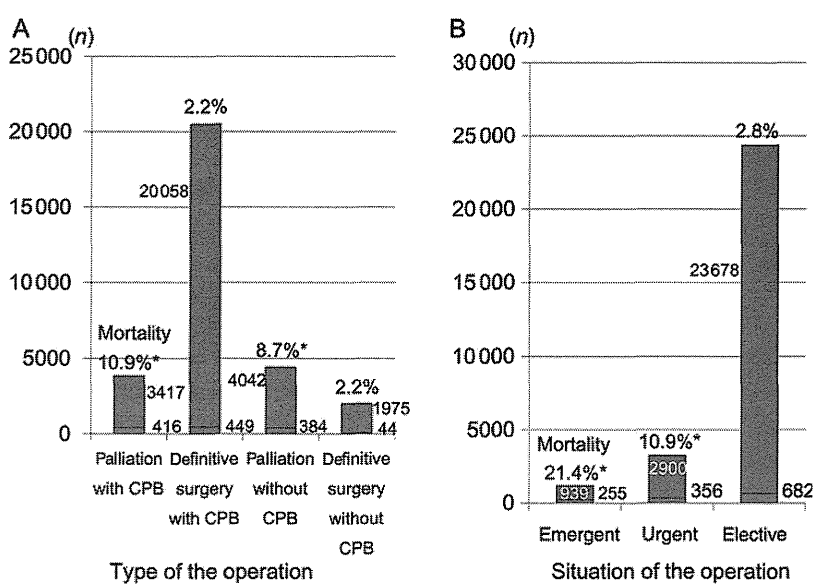

Figure 4: Differences between the number of patients and the mortality rate stratified by type of operation (**A**) and operative situation (**B**). The blue bar represents the number of surviving patients, and the red bar represents deceased patients. CPB: cardiopulmonary bypass. *$P < 0.001$.

operation to death [11–13]. Indeed, half of all mortalities were observed 30 days after surgery, and the median duration from operation to death was 28 days. With full medical cost coverage of patients born with congenital heart disease until 18 years of age, by the support of disabled children from the public health care system in Japan, parents and caregivers can make the greatest efforts possible to cure all children. As a result, extended intensive care continues for patients with post-cardiotomy complications, and a considerable number of patients are finally cured and discharged from the hospital long after surgery. In fact, out of the 3630 patients (13%) hospitalized for more than 90 days after the operation, 3365 patients survived at discharge (93%).

Cardiac problems were the most frequent cause of death after surgery at any point in time, and 7.1 per 1000 patients died after postoperative day 30 due solely to cardiac problems, which means that there are still some patients who died owing to post-cardiotomy heart failure without any other lethal complications after long-term intensive care. Except for some medically developed countries, advanced therapeutic options such as heart transplantation or long-term use of ventricular assistance devices are not available for post-cardiotomy heart failure in the paediatric population [14]. Patients who developed post-cardiotomy heart failure were treated with conventional therapy methods like medication, catheterization or surgical intervention, and temporary extracorporeal membrane oxygenation support with limited therapeutic effects. Finally, the Organ Transplant Law in Japan was revised and enforced in 2010, which legally and ethically allowed for paediatric heart transplantation. Donations from brain-death cadavers under 15 years old are now possible without written declaration of the donors themselves. Although there have only been two donors so far, an increase is expected [15]. In addition, an investigator-initiated trial of the EXCOR® paediatric ventricular assist device (Berlin Heart, Inc., Berlin, Germany) is now ongoing in Japan for bridge-to-heart transplants or recovery use [16, 17].

Study limitations

Limitations of this study were as follows. At first, the number of enrolled institutions significantly increased during the studied 5 years; therefore, only a small percentage of institutions reported their data during a part of the early study period. Even in the later study period, however, ~90% of all congenital heart surgeries was reported to this database. Second, a registry of post-cardiotomy ECMO use after congenital heart surgery should be established [18, 19]. Thirdly, although registration of the cause of death was mandated, cardiac issues included not only ventricular dysfunction, but also arrhythmia, cardiac tamponade, haemodynamic instability caused by unrepaired intracardiac lesions, sudden pulmonary overcirculation after single ventricle palliations, and so on.

With the large number of data in this database system, more detailed information about specific diagnosis/operative procedure is expected to be analysed. Also, further scientific analysis of the discrepancy between 30-day mortality and 90-day and in-hospital mortality by each diagnosis and procedure in addition to the RACHS score is mandatory.

In conclusion, significant discrepancy between 30-day mortality and 90-day and in-hospital mortality was demonstrated from analysis of the JCCSD. Patients who died long after the operation due to post-cardiotomy heart failure without any other complications are not rare.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

Conflict of interest: none declared.

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DOI: 10.1002/jhbp.276

ORIGINAL ARTICLE

Long-term and perioperative outcomes of laparoscopic versus open liver resection for hepatocellular carcinoma with propensity score matching: a multi-institutional Japanese study

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Abstract

Background The aim of this study was to compare the long-term outcomes and perioperative outcomes of laparoscopic liver resection (LLR) with those of open liver resection (OLR) for hepatocellular carcinoma (HCC) between well-matched patient groups.

Methods Hepatocellular carcinoma patients underwent primary liver resection between 2000 and 2010, were collected from 31 participating institutions in Japan and were divided into LLR (n = 436) and OLR (n = 2969) groups. A one-to-one propensity case-matched analysis was used with covariates of baseline characteristics, including tumor characteristics and surgical procedures of hepatic resections. Long-term and short-term outcomes were compared between the matched two groups.

Results The two groups were well balanced by propensity score matching and 387 patients were matched. There were no significant differences in overall survival and disease-free survival between LLR and OLR. The median blood loss (158 g vs. 400 g, $P < 0.001$) was significantly less with LLR, and the median postoperative hospital stay (13 days vs. 16 days, $P < 0.001$) was significantly shorter for LLR. Complication rate (6.7% vs. 13.0%, $P = 0.003$) was significantly less in LLR.

Conclusion Compared with OLR, LLR in selected patients with HCC showed similar long-term outcomes, associated with less blood loss, shorter hospital stay, and fewer postoperative complications.

Keywords Hepatocellular carcinoma · Laparoscopic liver resection · Long-term survival · Open liver resection · Propensity score matched analysis

Introduction

The advancements of laparoscopic procedures in liver surgery have proceeded slowly given the inherent risks for massive bleeding associated with liver resection [1]. The First International Consensus Conference on Laparoscopic Liver Surgery convened in Louisville in 2008 [2], since then, the number of laparoscopic liver resection (LLR) reported has increased steadily worldwide and the greatest diffusion of LLR occurred in East Asia, North America, and Europe [3, 4]. Moreover, the number of hepatocellular carcinoma (HCC) cases to which LLR is applied has increased steeply over the past 5 years, especially in Asia and Europe [5, 6]. However, no randomized controlled trials

(RCTs) have been published and the available data derive from multiple case series, case-control studies, reviews, and meta-analyses published over the last several years.

For new surgical procedures to become widely adopted as standard operations, they should first be compared with established procedures and shown to be superior in at least some respects [7]. Despite its lateness to embrace laparoscopy, liver surgery is now gaining momentum in this paradigm shift. Following improvements in technology and equipment, LLR should now be considered a safe option, if performed by experienced surgeons. Additionally, dramatic improvements in the safety of hepatic resection, based on an increased understanding of liver anatomy and better preoperative radiologic imaging, have facilitated this transition. Thus, adoption of the laparoscopic approach for the surgical treatment of hepatic lesions is now progressively expanding. However, unfortunately, it is impossible to reach an accurate conclusion regarding benefits and risks of LLR over open liver resection (OLR) in the absence of RCTs.

Propensity score matched analysis has become increasingly used in retrospective cohorts to reduce the impact of treatment-selection bias in the comparison of treatment to a non-randomized control using observational data [8, 9]. This type of evaluation has been proven to decrease selection bias in retrospective studies and allows comparison between different surgical procedures. Several studies have demonstrated that LLR for HCC is less invasive and can provide similar disease-free survival (DFS) and overall survival (OS) compared with OLR [10–17]. However, most of these studies were based on retrospective analyses of case-matched studies or meta-analyses of non-randomized studies. The aim of the present study was therefore to compare the long-term oncological outcomes and the perioperative outcomes of LLR with those of OLR for HCC, using propensity score matching (PSM) of relatively large data collected from 31 institutions in Japan.

Patients and methods

This multicenter clinical study was conducted by the "Project Committee of the Endoscopic Surgery" of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. We retrospectively reviewed 3405 patients who underwent primary liver resection for HCC from 2000 to 2010, who were gathered by 31 Japanese institutions in the Endoscopic Liver Surgery Study Group. The patients were divided into LLR (n = 436) and OLR (n = 2969) groups. The diagnosis of HCC was confirmed by histologic examination of resected specimens in all patients.

This study was approved by the ethics committee of the Japanese Society of Hepato-Biliary-Pancreatic Surgery, as well as one from each Institutional Review Board, and conducted in accordance with the mandates of the Helsinki Declaration.

Propensity score analysis

To avoid confounding differences due to baseline varieties between laparoscopic and open approaches, we performed a propensity score-matched subset. Propensity score analysis was used to build a matched group of patients for comparison of oncological and short-term outcomes between LLR and OLR groups. The propensity scores were generated with the preoperative characteristics, including sex, age, underlying liver disease (hepatitis B surface antigen (HBs-Ag) and anti-hepatitis C virus antibody positivity), tumor size, tumor number, serum α-fetoprotein and des-gamma-carboxy prothrombin levels, indocyanine green retention rate at 15 min (ICGR 15 min), extent of liver damage (decide according to the Criteria of the Liver Cancer Study Group of Japan) [18, 19], Child–Pugh score, difficult tumor location (yes, no), and distant metastasis (yes, no). Difficult tumor location was defined as postero-superior segments of the liver (segment 1, 7, 8 and the superior part of segment 4) [20]. Surgical procedures were classified according to the Brisbane 2000 nomenclature of liver resection [21]. In this study, hemihepatectomy, trisectionectomy, central bisectionectomy, right anterior sectionectomy, right posterior sectionectomy, and medial sectionectomy were defined as major hepatectomy, while wedge resection and left lateral sectionectomy were as minor hepatectomy. The wedge resection was only non-anatomical resection. The predicted probability of preprocedural stains was calculated by fitting a logistic regression model, using all preoperative relevant clinical variables as shown in Table 1. PSM was performed using a 1:1 ratio without replacement by caliper-matching on the estimated propensity score. The value of the caliper was calculated by 0.25 × (the standard deviation (SD) of log (the propensity score (PS)/ 1-PS)). Receiver operating characteristic (ROC) curves were used to assess the accuracy of PSM, as a predictor of LLR indicated by a propensity score.

Comparison between the two matched groups

The study criteria for comparing the two matched groups were the following: (i) clinicopathologic data of each matched group; (ii) intraoperative and surgical results. Morbidity was graded according to the Clavien-Dindo classification and Grade IIIa or greater complications were counted between the two matched groups. Further, we investigated each perioperative outcome of patients who underwent major hepatectomy or minor hepatectomy in each matched group; and (iii) long-term oncologic outcomes in aspects of OS and DFS.

Table 1 Comparison of baseline characteristics

Covariates	LLR (n = 436)	OLR (n = 2969)	P	Matched-LLR (n = 387)	Matched-OLR (n = 387)	P
Gender						
Female	142 (32.6%)	644 (21.7%)		125 (32.30%)	126 (32.56%)	
Male	294 (67.4%)	2325 (78.3%)	<0.001	262 (67.70%)	261 (67.44%)	0.939
Age (year)	66.48 ± 9.87	66.68 ± 9.64	0.69	66.42 ± 9.84	66.19 ± 9.96	0.741
Height	160.2 ± 9.12	161.0 ± 8.67	0.073	160 ± 9.19	160.9 ± 8.72	0.21
Weight	59.0 ± 11.25	60.5 ± 11.18	0.012	59.0 ± 10.92	60.0 ± 11.11	0.203
HBV positive	99 (22.7%)	663 (23.1%)	0.886	91 (23.51%)	100 (25.84%)	0.453
HCV positive	222 (51.0%)	1473 (51.3%)	0.932	195 (50.39%)	198 (51.16%)	0.829
Liver damage						
A	347 (80.51%)	2244 (75.94%)		312 (80.62%)	311 (80.36%)	
B	73 (16.94%)	533 (18.04%)		65 (16.80%)	70 (18.09%)	
C	11 (2.55%)	178 (6.02%)	0.009	10 (2.58%)	6 (1.55%)	0.552
Child–Pugh	5.34 ± 0.66	5.34 ± 0.66	0.944	5.33 ± 0.64	5.32 ± 0.61	0.774
ICG R15	15.8 ± 10.9	15.8 ± 9.12	0.949	15.7 ± 11.0	16.5 ± 9.93	0.292
Number	1.16 ± 0.50	1.47 ± 1.09	<0.001	1.17 ± 0.52	1.21 ± 0.54	0.246
Size (mm)	28.7 ± 15.2	40.2 ± 26.0	<0.001	28.8 ± 15.1	28.8 ± 15.0	0.992
Difficult location	96 (22.1%)	1447 (50.2%)	<0.001	82 (21.19%)	80 (20.67%)	0.86
Distant meta	3 (0.69%)	11 (0.37%)	0.332	3 (0.78%)	1 (0.26%)	0.316
AFP (ng/ml)	9.45 (4.35, 65.25)	14.3 (5.1, 133)	0.027	9.3 (4.3, 61.9)	13.5 (5, 100)	0.067
DCP (mAU/ml)	47 (23, 210)	81 (25, 637)	0.206	48 (24, 225)	42 (21, 195.9)	0.206
Major hepatectomy	46 (10.55%)	952 (32.21%)	<0.001	42 (10.85%)	36 (9.30%)	0.474
Minor hepatectomy	341 (78.21%)	1384 (46.82%)	<0.001	299 (77.26%)	305 (78.81%)	0.602

AFP α-fetoprotein, *DCP* des-gamma-carboxy prothrombin, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *ICG* indocyanine green

Statistical analysis

PSM and the other statistical analyses after PSM were performed by Stata 13 (Stata Corporation, College Station, TX, USA). In analyses and comparisons of preoperative covariates and clinical parameters after PSM, Student's t-test or Wilcoxon rank sum test for continuous variables, and χ^2 test or Fisher's exact test for categorical variables were used. All categorical data were expressed as number or frequency (%), and all continuous data were as mean ± standard deviation, or median (25, 75% quartile deviation). The DFS period was calculated from the date of surgery to the recurrence of HCC. Survival rates were estimated using the Kaplan–Meier methods and the log-rank test for the P-value for OS and DFS. The Cox proportional hazards regression was used to calculate the hazard ratio (HR) and 95% confidence interval for univariate and multivariate analyses. A P-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

Table 1 summarizes the baseline characteristics of the overall cohort and that selected after PSM. In the overall cohort, most of the LLR patients were females (32.6% vs. 21.7%), the mean height of the LLR patients was lower than that of the OLR patients, most of the LLR patients had Liver damage A (80.51% vs. 75.94%), the number and size of the tumor in the LLR patients were significantly less and smaller than in the OLR patients, most of the LLR patients had non-difficult location of the tumor (77.9% vs. 49.8%), and minor hepatectomy had been performed in most of the LLR patients (78.21% vs. 46.82%). After PSM both groups were well balanced for all variables, as shown in Table 1. The ROC area under the curve of the propensity score for undergoing LLR was 0.786 (Figs S1,S2).

Clinicopathological outcomes

Between the LLR and OLR groups after PSM, the background of the liver about the staging of the fibrosis according to new Inuyama classification of chronic hepatitis [22], microvascular invasion, positive pathological surgical margin, and the tumor stage according to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer, were almost similar (Table 2).

Table 2 Comparison of clinicopathological outcomes after propensity score matching (PSM)

	Matched–LLR (n = 387)	Matched–OLR (n = 387)	p
Background of liver			
F3–F4	232 (61.7%)	211 (59.6%)	0.562
A2–	90 (33.21%)	99 (43.23%)	0.021
Differentiation			
Well	59 (15.57%)	85 (22.49%)	
Moderately	266 (70.18%)	236 (62.43%)	
Poorly	44 (11.61%)	53 (14.02%)	0.031
Vascular invasion			
va1–va2	4 (1.04%)	1 (0.26%)	0.18
vp1–vp2	48 (12.5%)	58 (15.03%)	
vp3	2 (0.52%)	1 (0.26%)	0.51
vv1–vv2	12 (3.13%)	21 (5.47%)	0.111
b1–b2	3 (0.79%)	1 (0.26%)	0.311
Pathological surgical margin (+)	18 (4.68%)	17 (4.43%)	0.869
TNM classification			
Stage I	97 (25.06%)	96 (24.81%)	
Stage II	227 (58.66%)	210 (54.26%)	
Stage III	55 (14.21%)	73 (18.86%)	
Stage IVa or IVb	8 (2.06%)	8 (2.06%)	0.269

Long-term oncologic outcomes

We performed Kaplan–Meier analyses for OS and DFS curves, as shown in Figures 1 and 2. The median observation period in the LLR group was 46.7 months (25% quartile deviation: 31.4 months, 75%: 60.5 months), and one in the OLR group was 51.7 months (25%: 31.8 months, 75%: 75.8 months). The cumulative 1-, 3- and 5-year OS rates were 95.8, 86.2 and 76.8% in the LLR group, 95.8 and 84.0, and 70.9% in the OLR group. On the other hand, the cumulative 1-, 3- and 5-year DFS rates were 83.7, 58.3 and 40.7% in the LLR group, 79.6 and 50.4, and 39.3% in the OLR group, respectively. There were no significant differences in OS (P = 0.358) and DFS (P = 0.422) between the matched two groups.

Perioperative outcomes

In the LLR group after PSM, the median blood loss (158 g) was significantly less ($P < 0.001$) than in the OLR group (400 g), and the median postoperative hospital stay (13 days) for the LLR patients was significantly shorter ($P < 0.001$) than for the OLR patients (16 days), while the operation time in the LLR group (294.4 ± 158.8 min) was significantly longer than in the OLR group (271.0 ± 130.0) (P = 0.025). Conversion

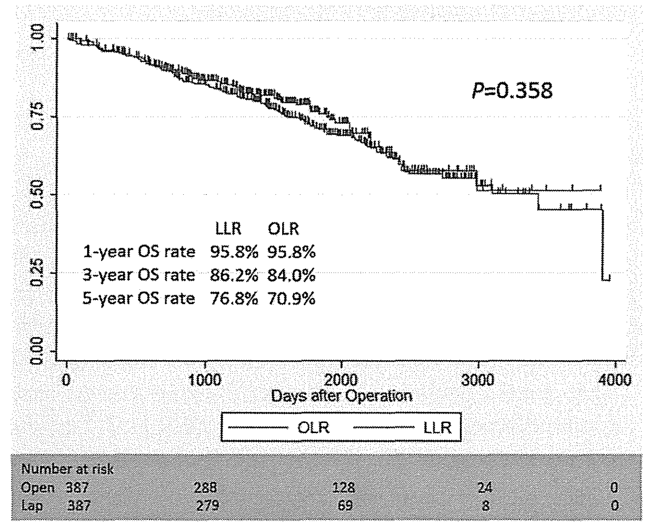

Fig. 1 Kaplan–Meier survival curve comparing overall survival (OS) in the propensity score matching (PSM) cohort

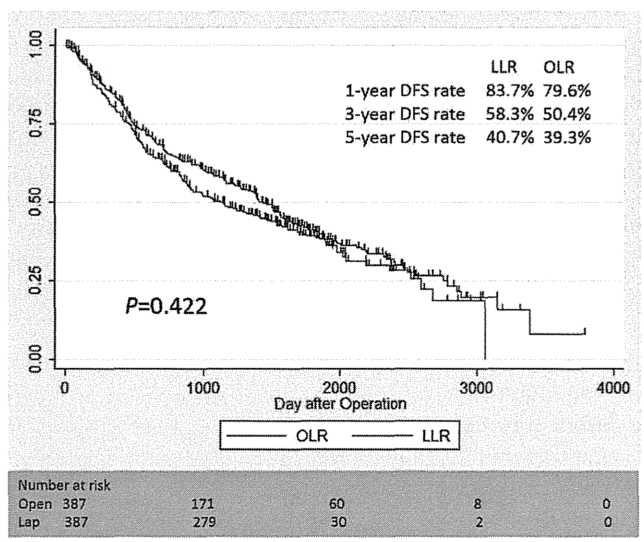

Fig. 2 Kaplan–Meier survival curve comparing disease-free survival (DFS) in the propensity score matching (PSM) cohort

from LLR to OLR or Hybrid or hand-assisted laparoscopic surgery occurred in 25 patients (6.5%). Complications over Grade IIIa according to the Clavien-Dindo classification after LLR included ascites (n = 7), intraperitoneal abscess (n = 4), pleural effusion (n = 2), bile leak (n = 5), and liver failure (n = 2), while ones after OLR included ascites (n = 12), intraperitoneal abscess (n = 4), pleural effusion (n = 5), bile leak (n = 9), and liver failure (n = 7). Postoperative complication rates in the LLR group were significantly lower than in the OLR group (6.7% vs. 13.0%, P = 0.003). The frequency of intraoperative accident was almost the same between the two groups. Mortality at 30 postoperative days was none, at 90 days was 0.26% (n = 1) in the LLR group, while at 30 days it was 0.26% (n = 1), and at 90 days it was 1.03% (n = 4) in the OLR group (Table 3).

Discussion

A comprehensive meta-analysis of 26 studies comparing LLR with OLR revealed that there were advantages associated with LLR, such as reduced blood loss, decreases in overall and liver-specific complications, and shorter postoperative hospital stays, although LLR procedures were associated with longer operating time, and moreover, it found that the oncological outcomes were not different from OLR [23]. Likewise the large study analyzing 31 papers comparing LLR (1146 patients) to OLR (1327 patients) came to the same conclusions for benefits of LLR over OLR, with equivalent cancer outcomes [24]. Another meta-analysis about surgical and oncological outcomes following LLR versus OLR for HCC included 10 studies comprising 627 patients [25]. The 10 studies were six case-control and four retrospective analyses; no RCTs were included. The laparoscopic group had significantly less blood loss by 223.17 ml ($P < 0.001$), less need for transfusions ($P = 0.007$), shorter hospital stay by 5.05 days ($P < 0.001$) and fewer postoperative complications ($P = 0.002$). However, these results were not produced by RCTs and were affected more or less by the selection-bias of LLR. To date, several reports have been published using PSM, confirming short-term advantages and comparable oncological outcomes in LLR patients compared with OLR patients for HCC. Common short-term advantages by LLR were less intraoperative blood loss and a shorter hospital stay [26, 27]. However, these studies included a relatively small number of patients after PSM.

Table 3 Comparison of perioperative outcomes after propensity score matching (PSM)

	Matched–LLR (n = 387)	Matched–OLR (n = 387)	P
Blood loss (ml)	158 (50, 450%)	400 (170, 675%)	<0.001
RCC transfusion	28 (7.24%)	38 (9.82%)	0.198
FFP transfusion	17 (4.44%)	30 (7.85%)	0.049
Operation time (min)	294.4 ± 158.8	271.0 ± 130.0	0.025
Hospital stay (days)	13 (9, 18)	16 (11, 25)	<0.001
Conversion			
Pure → Hybrid or HALS	7 (1.81%)	–	
Pure → Open	7 (1.81%)	–	
Hybrid or HALS → Open	11 (2.84%)	–	
Accident			
Bleeding	9 (2.33%)	14 (3.79%)	
Injury of other organs	0	0	
Others	1 (0.26%)	0	0.313
Complications	26 (6.72%)	50 (12.99%)	0.003
Ascites	7	12	
Intraperitoneal abscess	4	4	
Pleural effusion	2	5	
Bile leak	5	9	
Liver failure	2	7	
Wound infection	1	4	
Bleeding	1	1	
Others	4	8	
30 days mortality	0	1 (0.26%)	0.317
90 days mortality	1 (0.26%)	4 (1.03%)	0.178

FFP fresh frozen plasma, *HALS* hand-assisted laparoscopic surgery, *RCC* red cell concentration

Although we can easily assess the malignancy of HCC using tumor size, number, and the levels of serum tumor markers, and the liver functional reserve examining the extent of liver damage and Child–Pugh score, it is difficult to evaluate the complexity of the hepatic resection. We evaluated the difficulty of hepatic resection by finding difficult tumor locations for LLR demonstrated by Cho et al. [20], and additionally we divided the hepatic resection into the major hepatectomy, minor hepatectomy and others. Practically in the overall cohort, there were significant differences not only in tumor size and tumor number but also in the difficult location and in the frequency of the major or minor hepatectomy between LLR and OLR for HCC (Fig. S3).

In each institution there are various selection criteria of LLR for HCC, and the criteria might be affected by the learning curve of the surgical skill of LLR. And so, we intend to treat all preoperative relevant clinical variables as the covariates to build the propensity score. Forty-nine LLR patients were not matched because PSM was statistically performed using a 1:1 ratio on the estimated propensity score. Nevertheless, our study includes the large number of 387 patients and 387 patients for HCC in LLR and OLR, respectively, after the background characteristics of each patient were almost identical.

Regarding the long-term survival of two matched groups, median observation periods were not comparable between the two groups because the timing that LLR had been introduced was different in each institution. Regarding the histopathological outcomes, the degree of inflammation of the background liver and the differentiation of the tumor in the matched-open group were worse than those in the matched-lap group. These results were limitations in our retrospective study. However, it is difficult to assess the impact of primary hepatic resection on the OS in HCC treatment. The result that DFS as well as OS in the well-matched groups was statistically even in the comparison of the oncological outcomes, was noteworthy.

Further, in regard to the perioperative outcomes between the well-matched groups, the LLR patients had less blood loss, shorter hospital stay, and less morbidity than the OLR patients as shown in Table 3. These results are consistent with the recommendations in the 2nd International Consensus Conference on LLR held in Morioka, Japan, from 4 to 6 October 2014 [28]. However, in the subgroup analysis, major LLR failed to show less blood loss, although it still had shorter hospital stay and less morbidity (Table S1). These significances cannot be blindly accepted as the patient number of each matched group was small. It is also likely that major LLR was in an introduction phase and the learning curve must have an impact during our study period.

With respect to the contents of the complications, the frequency of the liver failure after LLR was lower than after OLR. This result might be explained by less destruction of the collateral blood/lymphatic flow by LLR during mobilization of the liver. Reduction of surgery-induced injury with LLR may lower the risk of liver failure after LLR for HCC patients with severe cirrhosis [29, 30].

In conclusion, compared with OLR, LLR in selected patients with HCC showed similar long-term outcomes, associated with less blood loss, shorter hospital stay, and fewer postoperative complications. Especially, the minor LLR in selected patients is confirmed to be one good option as a standard practice for the treatment of HCC.

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Conflict of interest None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Comparison of perioperative outcomes according to the surgical procedure.
Fig. S1 Receiver operating characteristics (ROC) curve.
Fig. S2 Histogram of propensity score before and after PSM.
Fig. S3 Standardized differences before and after PSM.

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ORIGINAL ARTICLE

Long-term and perioperative outcomes of laparoscopic versus open liver resection for colorectal liver metastases with propensity score matching: a multi-institutional Japanese study

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Abstract

Background The aim of the present study was to clarify the surgical outcome and long-term prognosis of laparoscopic liver resection (LLR) compared with conventional open liver resection (OLR) in patients with colorectal liver metastases (CRLM).
Methods A one-to-two propensity score matching (PSM) analysis was applied. Covariates ($P < 0.2$) used for PSM estimation included preoperative levels of CEA and CA19-9; primary tumor differentiation; primary pathological lymph node metastasis; number, size, location, and distribution of CRLM; existence of extrahepatic metastasis; extent of hepatic resection; total bilirubin and prothrombin activity levels; and preoperative chemotherapy. Perioperative data and long-term survival were compared.
Results From 2005 to 2010, 1,331 patients with hepatic resection for CRLM were enrolled. By PSM, 171 LLR and 342 OLR patients showed similar preoperative clinical characteristics. Median estimated blood loss (163 g vs 415 g, $P < 0.001$) and median postoperative hospital stay (12 days vs 14 days; $P < 0.001$) were significantly reduced in the LLR group. Morbidity and mortality were similar. Five-year rates of recurrence-free, overall, and disease-specific survival did not differ significantly. The R0 resection rate was similar.
Conclusions In selected CRLM patients, LLR is strongly associated with lower blood loss and shorter hospital stay and has equivalent long-term survival comparable with OLR.

Keywords Colorectal liver metastases · Laparoscopic liver resection · Open liver resection · Propensity score matched analysis

Introduction

Hepatic resection is a highly curative treatment for colorectal liver metastases (CRLM) usually providing excellent long-term survival, with 5- and 10-year overall survival (OS) rates being 33%–58% and 23%–39%, respectively [1–5]. Recent data demonstrated the superiority of hepatic resection to thermal ablation for CRLM [6, 7]. Advances in chemotherapy and targeted therapy may render initially unresectable CRLM patients eligible for hepatic resection and may improve prognosis, particularly in those patients who respond to induction therapy [8, 9]. CRLM may often recur even after curative resection, and repeated hepatectomy is obviously useful for such patients [10, 11]. Based on a worldwide survey, the long-term survival after the first to the fourth hepatic resection for patients with CRLM is almost similar [11].

Laparoscopic liver resection (LLR) was initially applied only to limited resections, including partial resection or left lateral sectionectomy. The pure laparoscopic approach (Pure), the hand-assisted laparoscopic approach (HALS), and the hybrid technique (Hybrid) were defined in the 2008 1st International Consensus Conference on Laparoscopic Liver Resection (ICCLLR) in Louisville, KY, USA [12]. These approaches are typically selected based on individual tumor size and location, background liver factors, and individual preference of the surgical team. Nowadays, the indication of LLR for CRLM has expanded from metastases located in anterolateral positions to those located in posterosuperior positions [13]. Hemihepatectomy or anatomic resection of the segment and sector can also be used for CRLM patients according to the 2014 2nd ICCLLR in Morioka, Iwate, Japan [14].

Several studies have demonstrated that LLR is associated with better short-term outcomes, including reduced intraoperative bleeding, a lower morbidity rate, and a shorter hospital stay compared with conventional open liver resection (OLR) [15–18]. Additional advantages include reduction of tissue damage, surgical stress, and overall costs [19, 20]. Several articles have focused on the better oncological and surgical results enabled by LLR [21–30]. However, most of these findings were based on retrospective analyses of case-matched studies or meta-analyses of non-randomized studies. Recently, a small-size propensity score matching (PSM) study of CRLM patients reported that LLR results in significantly lower blood loss, lower morbidity, and shorter hospital stay [31–33].

Multiple selection biases exist with regard to allocating patients for LLR. To obtain enough numbers of CRLM patients undergoing hepatectomy for analysis, we conducted a multicenter study involving Japanese specialized centers for both hepatobiliary and endoscopic surgery. In addition, we performed a PSM analysis, which enables comparison between different therapies with reduced selection bias in retrospective studies [34–36]. Recently, it was reported that there is no statistically significant difference with regard to treatment effect between non-randomized studies involving suitable PSM analysis and randomized controlled trials (RCT) [37]. This study was undertaken to determine the surgical outcome and long-term prognosis of LLR in comparison with those of conventional OLR for CRLM patients.

Methods

This clinical study was performed by the "Project Committee of the Endoscopic Surgery" of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. From January 2005 to December 2010, practically all patients with CRLM treated with initial hepatic resection were enrolled. Patients had a histologically proven diagnosis of colorectal cancer with synchronous or metachronous liver metastases. Perioperative chemotherapy was performed based on the policy of each individual institution. Hepatic resection modality was recorded in accordance with the terms established by the International Hepato-Pancreato-Biliary Association, Brisbane, Australia, 2000 [38]. Liver resection of three segments or more was defined as major liver resection. Difficult tumor location was defined as tumors situated in the posterosuperior segments of the liver (segments 1, 7, and 8) [13]. Gender (female, male), age (≤70, >70), body mass index (BMI) (≤25, >25), hepatitis B surface antigen (HBs-Ag; negative, positive), hepatitis C antibody (HCV-Ab; negative, positive), American Society of Anesthesiologists (ASA) physical status classification (1–2, ≥3), disease-free interval (DFI) between primary tumor and liver metastases (≤1 year, >1 year), preoperative levels of carcinoembryonic antigen (CEA; ≤100 ng/ml, >100 ng/ml) and carbohydrate antigen 19-9 (CA19-9; ≤100 U/ml, >100 U/ml), primary tumor differentiation (well, moderately, poorly, and mucinous), vessel invasion and lymphatic invasion of the primary tumor (negative, positive), primary pathological lymph node (LN) metastasis (negative, positive), location of primary sites (colon, rectum), timing of liver metastases (synchronous, metachronous), tumor number (1, 2–4, ≥5) [39], tumor size (≤5 cm, >5 cm), tumor location (difficult, non-difficult), tumor distribution (unilobar, bilobar), existence of extrahepatic metastasis (yes, no), hilar lymph node metastasis (yes, no), coexistence of radiofrequency ablation (RFA; yes, no), extent of hepatic resection (major, minor) were investigated prior to surgery. All patients also underwent preoperative liver function tests, including those measuring total bilirubin (≤2 mg/ml, >2 mg/ml) and albumin (≥3.5 g/dl, <3.5 g/dl) levels, prothrombin activity (≥80%, <80%), 15-min indocyanine retention rate (ICG R15; ≤15%, >15%), and Child–Pugh score (A, B). The presence or absence of pre- and postoperative chemotherapy (yes, no) was recorded. All data were collected retrospectively in 2014 using a shared database for CRLM produced by the Japanese Society of Hepato-Biliary-Pancreatic Surgery and the Japanese Society for Cancer of the Colon and Rectum. This study was approved by the institutional review board (IRB) (approval number, 798; Kumamoto University) and the ethics committee of the Japanese Society of Hepato-Biliary-Pancreatic Surgery and conducted in accordance with the mandates of the Helsinki Declaration 2013.

Operative procedure

Selection of LLR vs OLR was based on individual institutional strategies according to tumor size and location, liver function, and the volume of the future remnant liver [40]. Similarly, LLR operative procedures were selected by surgeons depending on their familiarity with and understanding of the instruments and individual procedures [41]. LLR can be performed using a Pure, HALS, or Hybrid approach as defined by the 2008 Consensus Conference [12].

Intraoperative and postoperative parameters

Intraoperative blood loss, operative time, and frequency of red cell concentrate (RCC) administration were recorded. Morbidity was graded according to the Clavien–Dindo classification [42], and adverse events of grade IIIA or more were defined as morbidity.

Surgical site infection (SSI), bile leakage, pleural effusion/ascites, postoperative intra-abdominal bleeding, ileus, and high bilirubinemia were registered. SSI included superficial and deep incisional SSI. Other morbidities were recorded separately. Moreover, 1- and 3-month mortality was evaluated. Final curability (R0, R1, R2) was assessed by histological investigation of resected specimens. Surgical margins were measured at the cutting surfaces of resected specimens. The number of postoperative hospital days was assessed for each patient.

Recurrence and survival

The starting point was the day of initial hepatic resection. Causes of death were recorded as either colorectal cancer-related or related to other causes. All deaths and recurrences of colorectal cancer were estimated for calculation of recurrence-free survival (RFS). OS and disease-specific survival (DSS) were calculated using the overall number of deaths and deaths specifically due to colorectal cancer, respectively. Size, number, and location of the initial recurrent tumor and the time to the first recurrence were recorded. The initial recurrence pattern was characterized as being intrahepatic only, extrahepatic only, or both intra- and extrahepatic. The number of patients who exhibited recurrence at the cutting surface of the liver was recorded.

Statistical analyses

A PSM analysis [34–36] was used to build a matched group of patients for comparison of clinical and survival outcomes between the LLR and OLR groups. In the overall sample, the patients' characteristics listed in Table 1 (30 variables in total) were compared between LLR and OLR using the Fisher's exact test for categorical variables and Wilcoxon rank-sum (Mann–Whitney) test for continuous variables. Possible confounders were chosen for their potential association with the outcome of interest based on clinical knowledge. The PS model was estimated using a logistic regression model that adjusted for the variables that had $P < 0.20$ in Table 1 (13 variables in total) and ensuring that the proportion of missing data was below 25%. Each LLR patient was matched to an OLR patient using 1-to-2 optimal data matching by Mahalanobis Distance within Propensity Score Calipers in random order without replacement [35]. Propensity scores were matched using a caliper width 1.0 logit of the SD to achieve a good covariate balance. The standardized differences were used to measure covariate balance, whereby an absolute standardized difference above 10% represents meaningful imbalance. Of patients who underwent LLR, 81.4% (171 out of 210) were matched to similar patients who underwent OLR. The covariate balance in the matched cohort was considerably improved.

The Kaplan–Meier method was used to calculate 5-year survival rates, the log-rank test for calculating *P*-values for the overall cohort, and the stratified Cox proportional hazard regression model for the matched cohort for RFS, OS, and DSS. Other paired comparisons were performed using conditional logistic regression analysis for categorical variables and Wilcoxon signed rank test for continuous variables [35]. Binomial exact was used to calculate 95% confidence interval for median observation period unless otherwise indicated. A *P*-value of <0.05 was considered statistically significant. Statistical analyses were performed using the Stata Statistical Software: Release 13.1 (StataCorp LP, College Station, TX, USA), and the NCSS 10 Statistical Software (2015) (Kaysville, UT, USA).

Results

A total of 1,331 CRLM patients undergoing laparoscopic or open liver resection were evaluated, and they were divided into two groups: the LLR group ($n = 210$) and the OLR group ($n = 1{,}121$). The proportion of LLR was 15.8%. The ratio of LLR was 6.2% in the first half (2005 to 2007) and 23.1% in the second half (2008 to 2010) of the study. In the overall cohort, LLR involved the Pure (62%), the HALS (9%), and the Hybrid (29%) approaches. Partial hepatectomy, segmentectomy or sectionectomy and hemihepatectomy were selected in 71.1%, 24.2%, and 5.8% in the LLR group and 64.6%, 25.7%, and 9.7% in the OLR group. In overall cohort, univariate analysis revealed the following 13 positively related factors ($P < 0.2$) among the 30 factors: serum levels of CEA and CA19-9; primary tumor differentiation; pathological LN metastasis; number, size, location and distribution of CRLM; extrahepatic metastasis; extent of hepatic resection; total bilirubin and prothrombin activity; and postoperative chemotherapy.

After one-to-two case propensity matching, a total of 171 LLR and 342 OLR patients were subjected to further analysis. Patient characteristics of the overall cohort and PSM cohort are displayed in Table 1. All baseline characteristics in the PSM cohort except timing of liver metastases were comparable between the two groups, and the proportion of synchronous

Table 1 Patients' characteristics underwent laparoscopic liver resection (LLR) and open liver resection (OLR): the overall cohort and propensity score matching (PSM) cohort

	Overall cohort ($n = 1{,}331$)			PSM cohort ($n = 513$)		
	LLR ($n = 210$)	OLR ($n = 1{,}121$)	P-value	LLR ($n = 171$)	OLR ($n = 342$)	P-value
Patient factors						
Age (≤70, >70)	142: 68	800: 320	0.282	110: 61	239: 103	0.356
Gender (male, female)	134: 76	721: 395	0.814	107: 64	215: 126	0.816
BMI (≤25, >25)	164: 46	844: 277	0.430	131: 40	261: 81	0.940
HCV-Ab (yes, no)	5: 198	34: 925	0.526	5: 161	8: 323	0.811
HBs-Ag (yes, no)	3: 200	20: 938	0.783	1: 165	6: 324	0.344
ASA (1-2, 3≤)	187: 7	911: 42	0.845	161: 5	288: 10	0.965
DFI (≤1 year, >1 year)	139: 71	784: 337	0.290	119: 52	231: 111	0.536
CEA levels (≤100 ng/ml, >100 ng/ml)	191: 8	776: 95	0.002	165: 6	330: 12	0.968
CA19-9 levels (≤100 IU/ml, >100 IU/ml)	177: 19	697: 152	0.005	157: 14	309: 33	0.865
Total bilirubin (≤2 mg/dl, >2 mg/dl)	205: 5	968: 153	<.001	170: 1	340: 2	>.999
Albumin (≥3.5 g/dl, <3.5 g/dl)	22: 188	111: 1010	0.802	19: 152	22: 320	0.083
Prothrombin activity (≥80%, <80%)	11: 199	108: 1013	0.047	8: 163	14: 328	0.730
ICG R15 (≤15%, >15%)	141: 69	731: 390	0.635	116: 55	256: 86	0.081
Child–Pugh score (A, B)	209: 1	1095: 26	0.107	171: 0	339: 3	-
Pre-operative chemotherapy (yes, no)	38: 172	245: 876	0.234	30: 141	67: 275	0.801
Postoperative chemotherapy (yes, no)	108: 102	633: 488	0.198	87: 84	195: 147	0.638
Primary lesion factors						
Tumor differentiation (well/moderately/poorly and mucinous)	53: 137: 10	315: 585: 50	0.172	42: 120: 9	90: 241: 11	0.719
Vessel invasion (negative, positive)	46: 147	218: 705	0.926	37: 128	89: 242	0.236
Lymphatic invasion (negative, positive)	51: 143	227: 714	0.522	45: 121	96: 237	0.556
Primary pathological lymph node (negative, positive)	81: 109	297: 513	0.135	75: 96	134: 208	0.517
Location of primary sites (colon or rectum)	106: 84	547: 379	0.419	90: 70	173: 142	0.667
Liver metastases factors						
Timing of liver metastases (synchronous, metachronous)	83: 127	474: 647	0.493	69: 102	107: 235	0.015
Tumor number (1, 2-4, ≥5)	149: 52: 2	570: 400: 96	<.001	127: 43: 1	251: 89: 2	0.251
Tumor size (≤5 cm, >5 cm)	202: 6	1018: 82	0.015	167: 4	334: 8	0.924
Tumor location (difficult, non-difficult)	80: 130	645: 470	<.001	68: 103	154: 188	0.968
Tumor distribution (unilobar, bilobar)	174: 36	762: 353	<.001	143: 28	283: 59	0.566
Extrahepatic metastasis (yes, no)	9: 201	89: 1025	0.062	7: 164	13: 329	0.690
Hilar lymph node metastasis (yes, no)	0: 101	11: 720	0.378	0: 78	3: 204	0.992
Coexistence of RFA (yes, no)	5: 205	40: 1081	0.532	5: 166	8: 334	0.445
Extent of hepatic resection (major, minor)	12: 198	103: 1018	0.109	10: 161	20: 322	0.682

ASA American Society of Anesthesiologists, *BMI* body mass index, *CA19-9* carbohydrate antigen 19-9, *CEA* carcinoembryonic antigen, *DFI* disease-free interval, *HBs-Ag* hepatitis B surface antigen, *HCV-Ab* anti-hepatitis C antibody, *ICG R15* indocyanine green retention rate at 15 min, *RFA* radio-frequency ablation

Clinical parameters were compared with Fisher's exact test for overall cohort, and 5-stratified conditional logistic regression for PSM cohort

CRLM was larger in LLR patients. Patients' continuous factors were listed as median value with range (Table S1). In the PSM cohort, LLR was applied for selected CRLM patients with one metastasis (max, 5), 2.2 cm in diameter (max, 8.4 cm) and slightly elevated CEA level of 7.1 ng/ml and normal CA19-9 level of 16.2 IU/ml. Percentage of patients with a difficult tumor location was 39.8%. Our initial study with $P < 0.05$ yielded eight factors, which reduced to five after stepwise logistic regression. We set the cutoff level to $P < 0.20$ with the proceeding logistics without stepwise analyses to cover more factors in clinical aspects. Standardized differences before and after PSM are demonstrated (Fig. S1). Imbalances were defined as an absolute value greater than 10%. The receiver operating characteristic (ROC) curves were used to evaluate the accuracy of PSM. The area under the curve of the propensity score for LLR was 0.693.

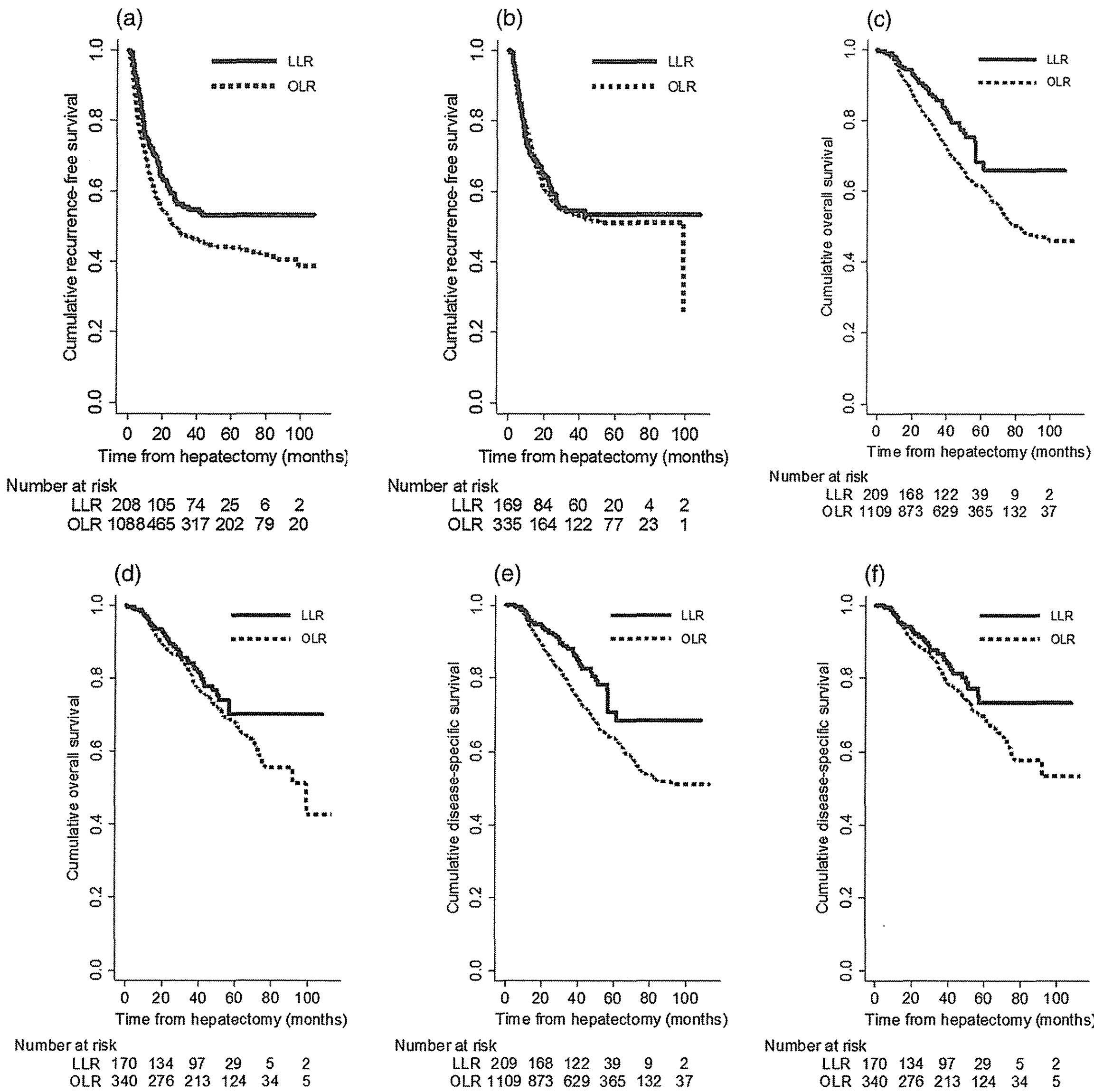

Fig. 1 Kaplan–Meier survival curves comparing recurrence-free survival (RFS), overall survival (OS), and disease-specific survival (DSS) in the overall ($n = 1{,}331$) and propensity score matching (PSM) cohorts ($n = 513$). (**a**) RFS in the overall cohort; (**b**) RFS in the PSM cohort; (**c**) OS in the overall cohort; (**d**) OS in the PSM cohort; (**e**) DSS in the overall cohort; (**f**) DSS in the PSM cohort. Solid line, laparoscopic liver resection (LLR); dotted line, open liver resection (OLR). Standardized differences before and after PSM. Open circle, before propensity matching; closed triangle, after propensity matching

Intraoperative parameters

In the PSM cohort, the median operative time (282 min vs 277 min, $P = 0.130$) was comparable, and median blood loss (163 g vs 415 g, $P < 0.001$) and the ratio of blood loss larger than 1,000 mL (6.5% vs 16.5%, $P = 0.004$) were significantly lower in the LLR group than in the OLR group (Table 2). The frequency of RCC transfusion did not differ significantly across the two groups (8.4% vs 4.4%, $P = 0.148$). R0, R1, and R2 resection was performed for 92.2%, 5.4%, and 3.0% patients in the LLR group and in 95.5%, 2.4%, and 2.1% in the OLR group. R2 resection included resection with ablation (four patients in the LLR group and six in the OLR group). Curability was similar across the two groups. The median pathological surgical margin was comparable ($P = 0.963$), namely 5 (0–40) mm and 5 (0–45) mm by LLR and OLR, respectively.

Postoperative morbidity and mortality

In the PSM cohort, postoperative complication rates (14.1% vs 12.7%, $P = 0.631$), and the level of morbidity were comparable across the two groups (Table 2). Postoperative complications following LLR in the PSM cohort included incisional SSI (3.5%), bile leakage (2.9%), ascites and pleural effusion (1.2%), and intra-abdominal hemorrhage (0.6%); in addition, leakage of

Table 2 Perioperative outcome of colorectal liver metastases (CRLM) patients who underwent laparoscopic liver resection (LLR) and open liver resection (OLR): the overall cohort and propensity score matching (PSM) cohort

	Overall cohort ($n=1,331$)			PSM cohort ($n=513$)		
	LLR ($n=210$)	OLR ($n=1,121$)	*P*-value	LLR ($n=171$)	OLR ($n=342$)	*P*-value
Operation time (min) median (range)	281 (60-1120)	312 (39-3350)	0.020	282 (60-1120)	277 (40-1343)	0.130
Blood loss (g), median (range)	160 (0-3355)	500 (0-11240)	<0.001	163 (0-3355)	405 (0-11240)	<0.001
Blood loss ≥ 1,000 (g) (yes, no)	15: 192	211: 813	<0.001	11: 159	55: 278	0.004
pRBC administration (%)	8.7	16.6	0.004	8.4	12.8	0.148
R0	190	929		154	315	
R1	9	60		9	8	
			0.899			0.120
R2	1	7		1	1	
R0+ablation	4	26		4	6	
Pathological surgical margin (mm), median (range)	5 (0-40)	5 (0-50)	0.203	5 (0-40)	5 (0-45)	0.963
Morbidity (%)	13.0	13.4	>0.999	14.1	12.7	0.631
Mortality (%) within 1 month	0.0	0.1	>0.999	0.0	0.0	N.A.
within 3 months	0.0	0.5	>0.999	0.0	0.6	N.A.
Postoperative hospitalization (days), median (range)	12 (1-192)	16 (2-745)	<0.001	12 (3-192)	14 (4-174)	<0.001

N.A. not applicable, *pRBC* packed red blood cell
Clinical parameters were compared with; Overall cohort: Wilcoxon rank-sum (Mann–Whitney) test for ordinal, and Fisher's exact test for categorical data. PSM cohort: 5-stratified conditional logistic regression for ordinal, and 5-stratified conditional logistic regression for categorical

intestinal anastomosis (3.5%) and organ/space SSI (3.5%) were seen. No patients experienced intestinal bleeding, intestinal obstruction, or hyperbilirubinemia. No patients experienced port site recurrence or dissemination, even in the overall cohort and one patient experienced port site hernia. In the PSM cohort, no fatalities were observed in the LLR group within 3 months, while there were two fatalities within 3 months in the OLR group.

Postoperative hospital stay

Median postoperative hospital stay was significantly shorter for LLR patients than for OLR patients [12 days (range, 3–192 days) vs 14 days (range, 4–174 days), $P<0.001$; Table 2].

Postoperative survival and recurrence

In the overall cohort, RFS, OS, and DSS curves were significantly superior for LLR patients compared with those for OLR patients (Fig. 1a,c,e): RFS ($P=0.013$), OS ($P=0.004$), or DSS ($P=0.004$). In the propensity-matched cohort, median observation periods were different between the two procedures (LLR, 41.7 months; 95% CI, 39.5–44.2; OLR, 49.1 months; 95% CI, 44.4–52.4). The cumulative 1-, 3-, and 5-year RFS rates were 70.7%, 54.5%, and 53.4%, respectively, for the LLR group and 73.4%, 53.5%, and 51.2%, respectively, for the OLR group (Fig. 1b). The cumulative 1-, 3-, and 5-year OS rates were 96.3%, 84.2%, and 70.1%, respectively, for the LLR group and 96.0%, 80.8%, and 68.0%, respectively, for the OLR group (Fig. 1d). The cumulative 1-, 3-, and 5-year DSS rates were 96.8%, 86.8%, and 73.2%, respectively, for LLR patients and 96.6%, 82.2%, and 69.8%, respectively, for OLR patients (Fig. 1f). No significant differences in RFS ($P=0.953$), OS ($P=0.299$), or DSS ($P=0.218$) were observed between the two groups. Recurrence at the cutting line was encountered in 3.5% by LLR and 3.5% by OLR, and the ratios were considered similar in the two groups ($P=0.890$). The initial recurrence patterns were assessed, and recurrence classified as "intrahepatic only" was similar (22.0% vs 19.5%, $P=0.370$), "extrahepatic only" was significantly less commonly observed in the LLR group than in the OLR group (19.0% vs 33.0%, $P=0.001$), and "intra- and extrahepatic recurrence" was significantly more in the LLR group than in the OLR group (15.7% vs 7.2%, $P=0.003$). As intrahepatic recurrences, the largest tumor diameters at first recurrence were considered marginally smaller in the LLR group ($P=0.058$); 17 (1–60) mm in the LLR group and 20 (2–70) mm in the OLR group. The frequency of solitary recurrences was similarly observed (55.9% vs 56.8%; $P=0.812$). The time elapsed to the first recurrence was comparable ($P=0.145$); 9.1 (0.9–95.6) months in the LLR group and 12.7 (0.9–110.2) months in the OLR group.

Discussion

A web-based international survey of the global application of LLR was reported prior to the 2nd ICCLLR in Iwate, Japan