registered from 239 institutions. Excluded from the analysis were 37 duplications (only one record was removed and the patient remained in the registry), six patients because of insufficient data and 1062 patients with less than 180 days of follow up, leaving 10 280 patients included in the analysis.

Variables

Pathological staging was based on the fifth edition of the TNM classification and the third edition of the General Rule for Clinical and Pathological Studies on Prostate Cancer (2001).[2] For the PSA analysis, only cases measured with the Tandem-R kit PSA assay ($n = 4567$, 44.4%) were included to avoid statistical scatter. The definition of PSA failure was determined based on the clinician's judgement.

Survival data were analyzed according to the main treatment modality and the M stage. The initial main treatment modalities used were categorized into four groups: hormone ablation therapy alone (Hx), radical prostatectomy (RP) with or without neoadjuvant hormone treatment (NHT), radiation therapy (Rx) with or without NHT and watchful waiting (W/W) including active surveillance or palliative observation irrespective of the intent. Characteristics and outcomes from the four treatment groups were analyzed separately.

Analysis of progression-free survival was not possible as a result of difficulties in timing recurrence correctly. In some RP cases, adjuvant therapy was initiated just after the operation on the basis of the pathological findings. In addition, there were substantial differences in how post-Rx PSA failure was defined. For these reasons, the exact timing of recurrence was not able to be determined for a sizable number of patients, whom we consequently described as having "stable disease." Therefore, we had no other choice but to focus on the mortality rate, overall survival (OS) and prostate cancer-specific survival (PCSS).

Statistical methods

For statistical analysis, Student's t-test was used for analysis of intergroup differences in means and the χ^2-test was used for intergroup comparisons. Survival data was analyzed by the Kaplan–Meier method.

Results

Overall data

The registered patients' characteristics including age, PSA, Gleason score and TNM classification were summarized according to the main initial treatment modality (see Table S1, supporting information). In the 10 280 patients, the number of the patients treated by Hx, RP, Rx and W/W was 4934 (49.8%), 3212 (31.5%), 1605 (10.4%) and 485 (4.7%), respectively. The 44 patients were treated by other modalities. There were statistically significant differences among patients in different treatment groups. Patients treated with RP were the youngest (median age 68.0 years), with patients treated with Hx on average approximately 8.5 years older (median age 76.0 years). Overall, median PSA at diagnosis was 13.0 ng/mL, but the median PSA within the W/W group was 7.3 ng/mL, which was the lowest. Median Gleason score was 7 among Hx, RP and Rx groups, and 6 in W/W patients. Approximately 50–60% of each group was staged as T1c or T2 disease. In contrast, 11.5% of patients presented with metastatic disease at the time of diagnosis.

The 5-year OS and PCSS of all 10 280 patients was 98.7% and 94.8%, respectively. Figure 1 shows the Kaplan–Meier curves according to M stage. Bony disease (M1b) comprised the majority of M1 patients. The 5-year OS and PCSS was 61.8% and 66.7%, respectively. In M1 disease, there was a significant correlation between survival and Gleason score ($P < 0.001$).

T1-4N0M0 prostate cancer

There were 8424 patients with T1-4N0M0 prostate cancer. The distribution and proportion of clinical T (cT) stage and age by treatment group are shown in Figure 2. Interestingly, in Japan more than 30% of patients received Hx as the main treatment modality across all cT stages. Even for cT1 or cT2 disease, RP, Hx and Rx were carried out in approximately 50%, 30% and 20% of the cases, respectively. The age distribution differed dramatically across treatment groups. For patients less than 75 years-of-age, RP was widely used. Rx was carried out at similar rates (approximately 20%) in patients up to 80 years-of-age. Hx was the major treatment in patients over 80 years-of-age.

OS and PCSS in T1-4N0M0 disease by treatment group were shown to be 97.6% and 99.6% in RP, 95.6% and 98.5% in Rx, 96.4% and 99.7% in W/W and 88.9% and 97.7% in Hx. Five-year PCSS for patients without metastatic disease was excellent (98.4%).

Distribution of age and PSA in patients with T1-4N0M0 prostate cancer according to treatment was shown in Figure S1. Figure S2 shows cT distribution and the main treatment adopted in these patients. Figure S3 shows overall and prostate cancer-specific survival by main treatment adopted in these patients.

Radical prostatectomy

RP was carried out in 3212 patients (see Table S2, supporting information). Overall, 96.2% of RP patients had radical prostatectomy through the retropubic approach, and 89% had an open procedure. Concerning neurovascular bundle preservation, 70.4% of the patients received RP without nerve preservation. Lymph node dissection was carried out in 91% of the patients with mainly limited obturator lymph node dissection (71.6%).

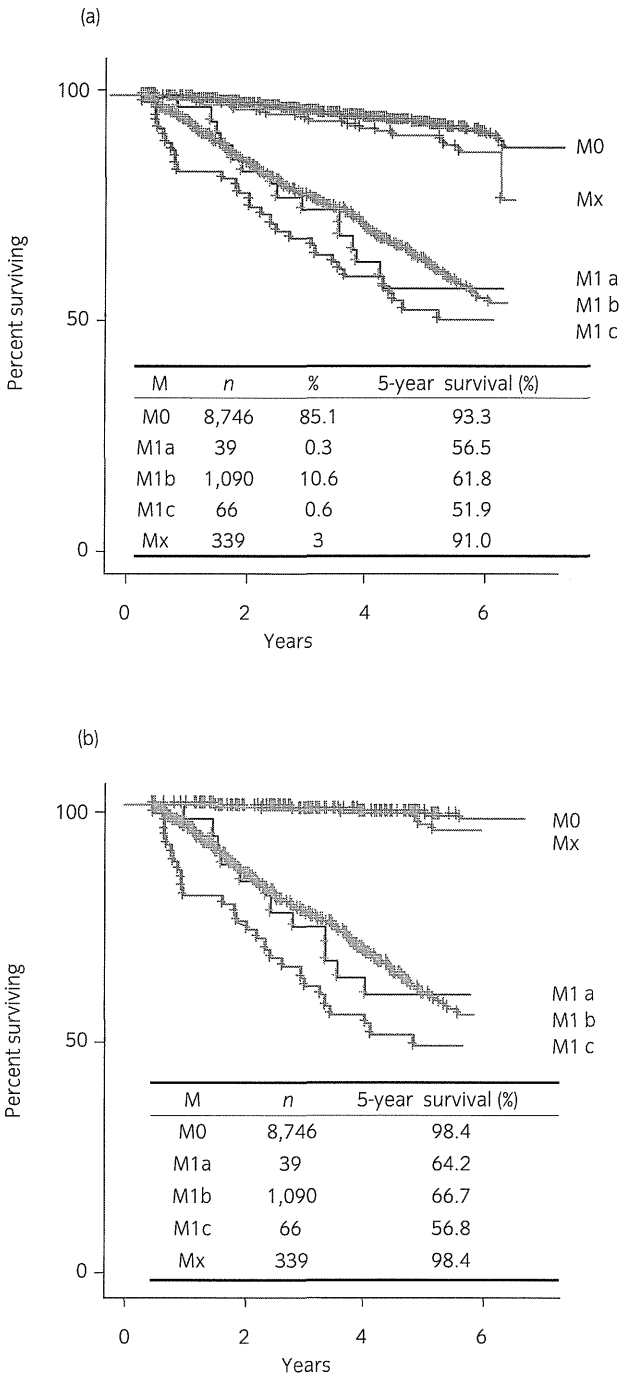

Fig. 1 Kaplan–Meier curves of (a) overall survival and (b) prostate cancer-specific survival according to M stage (n = 10 280).

The outcomes of 3200 RP patients according to NHT duration are summarized (see Table S3, supporting information). Because of uncertain NHT status, 12 patients were excluded. In the RP with NHT group ($n = 1164$), most pathological parameters including node metastasis (pN) and surgical margin status (ew) were better than in those patients without NHT ($n = 2045$; $P < 0.001$), except for seminal vesicle invasion (sv). However, the survival status of RP with NHT group did not differ from the RP without NHT group. The disease-free rate and prostate cancer death rate in the RP group within this observation period of approximately 5 years was approximately 70–75% and less than 1%, respectively.

Hormonal therapy alone

In this registration series, 4934 patients were treated with Hx alone (see Table S4, supporting information). In these patients, 3582 patients (72.6%) had non-metastatic disease (M0) and 1061 patients (21.5%) had bony metastasis (M1b). The combination of luteinizing hormone-releasing hormone (LH-RH) analogs with non-steroidal anti-androgen drugs were used in the majority of the Hx patients (67.4%). In M0 disease, 25% of patients received monotherapy with LH-RH analogs or surgical castration, and 67.4% patients were treated with maximum androgen blockade (MAB). Estrogen or estramustine phosphate therapy as the initial Hx was rare for M0 disease. For M1b disease, 82% of patients received MAB and 14.4% of patients received estrogen or estramustine phosphate as the initial treatment. The 5-year PCSS in patients with M0 disease was 93.3% and in M1b patients, it was 71.2%. In M0 patients, 8.4% of the patients died of other causes, which seemed to be higher when compared with patients treated with other modalities.

Curative radiation for prostate cancer

Rx as a radical treatment was used for 1554 patients. There were 28 patients who received particle radiotherapy and 27 patients were treated by uncertain modality. Excluding these patients, the characteristics of the 1499 patients are summarized (see Table S5, supporting information). Radiation therapy was classified as external beam radiation therapy with Liniac (EBRT; $n = 1241$), brachytherapy (BT; $n = 210$) or a combination (BT + EBRT; $n = 48$). Median age in EBRT was 72.9 years and median PSA was 15.0 ng/mL. In contrast, that in BT was 70.0 years and median PSA was 7.30 ng/mL. When compared with EBRT patients, BT patients were younger and had lower PSA, Gleason scores and earlier stage disease. The median PSA level in patients who received EBRT was 15.0 ng/mL, higher than in RP patients. In 1241 EBRT patients, 88.6% received radiation to the prostate only and the median dose in EBRT was 70 Gy. No cancer deaths were observed in patients who received BT and BT + EBRT. In the EBRT group, 5-year PCSS was 98.3% (see Table S6, supporting information).

Watchful waiting

In this registry, W/W included active surveillance, deferred treatment and palliative observation. At the time of registration, 72.4% of patients were maintained on watchful

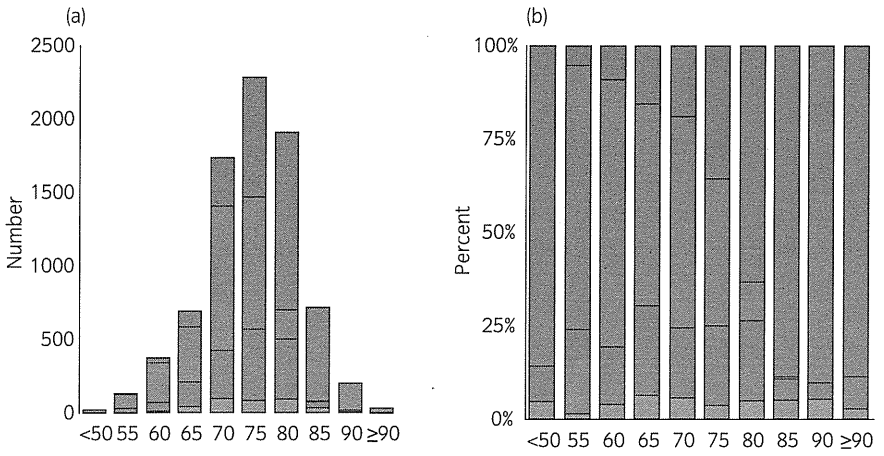

Fig. 2 Age distribution by main treatment modality in patients with T1-4N0M0 prostate cancer ($n = 8424$). (a) Totals and numbers of patients who underwent each treatment modality. (b) Percentages of each treatment by age. Hx, hormone ablation therapy; RP, radical prostatectomy; Rx, radiation therapy; W/W, watchful waiting.

Number of the patients by age and main treatments

	<50	50–55<	55–60<	60–65<	65–70<	70–75<	75–80<	80–85<	85–90<	≥90
Hx	0	7	34	108	329	815	1207	637	184	31
RP	18	94	269	675	982	899	198	4	0	0
Rx	2	30	58	166	326	485	409	41	9	3
W/W	1	2	15	45	100	86	96	37	11	1

waiting. In the W/W group, 0.62% of the patients died of prostate cancer. The incidence was similar to that in the RP patients (see Table S7, supporting information).

Discussion

The present report is the first large-scale study of the characteristics and survival of prostate cancer patients in Japan based on multi-institutional registry data. The estimated number of newly diagnosed prostate cancer patients in Japan in 2005 was 42 997.[3] This registry seems to cover approximately one-quarter of newly diagnosed prostate cancer in Japan. With regard to prostate cancer incidence and mortality, ethnic differences between American or European and Asian men are well known. Understanding the actual situation of Japanese prostate cancer patients is indispensable to addressing many clinical issues regarding prostate cancer treatment.

The incidence of metastatic prostate cancer at the initial registration was 11.6% in the present study. In the USA, 6.5% were distant stage according to the report from the 1990–2000 database of the Surveillance, Epidemiology and End Results (SEER) Program[4], suggesting the incidence of metastatic disease is higher in Japan than in the USA. However, the incidence was 21.3% from the Japanese registration data in 2000.[1] Compared with the data from 2000, the ratio of distant disease in 2004 was reduced by half. However, the number of the distant diseases in 2000 ($n = 964$) was almost the same as that in 2004 ($n = 1195$).

In the report derived from the 1973–2000 database of the SEER Program[4], 5- and 10-year PCSS were approximately 99% and 95%, respectively. Two-thirds of patients were diagnosed with well or moderately differentiated localized or regional prostate cancer. Among these patients, 5- and 10-year PCSS were approximately 100%. In the present study, 5-year PCSS was 94.8%, which resembles the SEER data from 1995. The PCSS of localized or regional prostate cancer was 98.4%, similar to the SEER data. Five-year PCSS of patients with bony metastasis in Japan was 66.7%, which was better than the 27–37% 5-year PCSS in the USA[4]. The reason why Japanese patients with bony metastasis showed a longer survival period than American patients is uncertain.

The main treatment used for non-metastatic prostate cancer patients in Japan was quite different from that in the USA. In the USA, approximately half of prostate cancer patients received surgery and more than one-third underwent Rx.[5] In Japan, Hx comprised of 39.9% of the initial main treatment, even for non-metastatic prostate cancer. One of the reasons for the high rate of Hx might be the relatively advanced age at diagnosis. Another reason might be the high rate of health insurance coverage and indifference about erectile dysfunction. In the present study, the most frequent treatment for non-metastatic prostate cancer in patients less than 70-years-old was RP (62.5%). Essentially, for patients younger than 70-years-old, Japanese urologists might choose treatments in agreement with major guidelines published by the National Comprehensive Cancer Network and the European Association of Urology, among others.

Concerning the administration of Hx medications, MAB therapy was recommended for stage D2 prostate cancer.[6] However, in Japan, 65% of patients with non-metastatic disease received MAB therapy and 25% of them received

LH-RH analogs or surgical castration as monotherapy. The 5-year PCSS of non-metastatic prostate cancer patients in Japan showed excellent results, even in the W/W group. The OS of patients with Hx seemed to be lower than that with other modalities. The patients undergoing Hx are relatively older.

In the present series, detailed data on RP was analyzed. In 2004, open retropubic RP (89.6%) with obturator lymph node dissection (71.6%) was the most common procedure. Interestingly, just 20% of patients received nerve-sparing operations in Japan. In high-volume hospitals in the USA, most radical prostatectomy seems to be carried out using the nerve-sparing technique. For most Japanese men, there might be less concern about sexual function when compared with American men.

The pathological results were sorted by NHT duration, because they might be affected by NHT status. Similar to the data from many randomized controlled studies of NHT[7,8] most pathological findings were improved by longer NHT, except for seminal sv and pN. However, there was no remarkable improvement in prognosis despite longer NHT as previously reported. However, these data came from non-randomized, non-historically controlled patients.

Additionally, the present study might be the largest population study of Rx in Japan. In past years, the trends and patterns of Rx in Japan were reported by the patterns of care study (PCS).[9,10] The age, PSA, Gleason score and radiation dose in the EBRT group of the present study were similar to PCS data. The median PSA of 15.0 ng/mL in the EBRT patients was higher than that of the patients treated with RP. Japanese urologists seemed to select EBRT for treating localized advanced disease. The EBRT group in the registry had a disease-free rate of 58% and a stable disease rate of 22.7%. Recently, higher dose radiation has been recognized to contribute to better cancer control. In 2004, 11.0% of the patients received 72 Gy and 11.4% patients received 76 Gy EBRT. Nearly 50% of patients underwent 68 Gy EBRT. Recently, relatively high dose EBRT in combination with NHT was attempted using the intensity modulated radiotherapy technique.

In conclusion, this is the first report of survival data involving one-quarter of newly diagnosed prostate cancer patients in Japan. In Japan, the patient population, survival period with metastatic disease and the ratio of patients receiving Hx differ from Western countries. Also noteworthy is the reduction in the ratio of metastatic prostate cancer at diagnosis, which was 11.6% in 2004, approximately half the rate in 2000. However, the total number of newly diagnosed patients with metastatic prostate cancer in 2004 was almost same as that in 2000. In terms of localized (cT2 or earlier stage) prostate cancer, Hx was used as the main treatment in 36.7% of Japanese patients. The 5-year survival of patients with localized prostate cancer was excellent irrespective of the main treatment used. Five-year OS and PCSS of patients with M1b disease were superior to that in the USA.

Acknowledgments

These clinicopathological statistics are the results from a number of institutions in Japan (see Appendix I, supporting information). We are grateful for the cooperation of many Japanese urologists. This document was created by the Cancer Registration Committee of the Japanese Urological Association.

Conflict of interest

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Fig. S1 Distribution of age (A) and PSA (B) in patients with T1-4N0M0 prostate cancer ($n = 8424$) according to treatment. RP, radical prostatectomy; Rx, radiation therapy; Hx, hormone ablation therapy; W/W, watchful waiting.
Fig. S2 cT distribution and the main treatment adopted in patients with T1-4N0M0 prostate cancer ($n = 8424$). The graph A shows totals and numbers of patients who underwent each treatment modality. The graph B shows percentages of each treatment by clinical stage. RP, radical prostatectomy; Rx, radiation therapy; Hx, hormone ablation therapy; W/W, watchful waiting.
Fig. S3 Kaplan–Meier curves of overall survival (A) and prostate cancer-specific survival (B) by main treatment adopted in patients with T1-4N0M0 prostate cancer ($n = 8224$). RP, radical prostatectomy; Rx, radiation therapy; Hx, hormone ablation therapy; W/W, watchful waiting.
Table S1 Characteristics of the registered patients.
Table S2 Characteristics of 3212 radical prostatectomy patients.
Table S3 Outcome of 3200 radical prostatectomy cases with or without neoadjuvant hormonal therapy.
Table S4 Outcome of 4934 patients treated with hormone ablation therapy alone.
Table S5 Characteristics of patients treated with radiation therapy as the main treatment.
Table S6 Outcome of patients treated with radiation therapy as the main treatment.
Table S7 Outcome of 485 patients treated with watchful waiting.
Appendix I Statistics from various institutions in Japan.

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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.

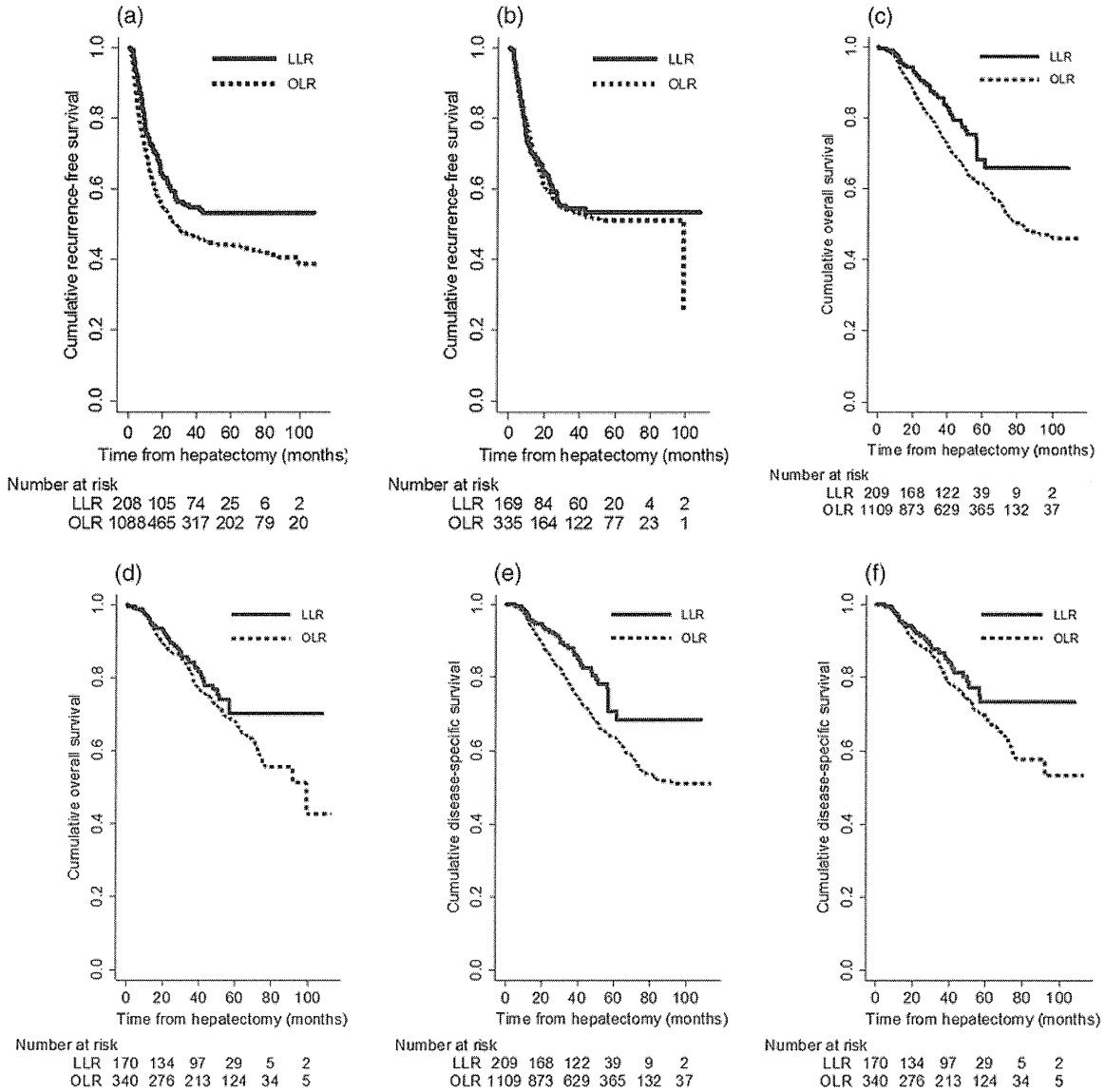

Fig. 1 Kaplan–Meier survival curves comparing recurrence-free survival (RFS), overall survival (OS), and disease-specific survival (DSS) in the overall ($n = 1,331$) and propensity score matching (PSM) cohorts ($n = 513$). (**a**) RFS in the overall cohort; (**b**) RFS in the PSM cohort; (**c**) OS in 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

[43]. Surgeons performing LLR were typically in their 40s. In North America and Europe, LLR was mostly performed at academic medical centers and has undergone global diffusion after the 1st ICCLLR in 2008 [12]. Meanwhile, in Japan, the majority of surgeons performing LLR belonged to middle-tier regional hospitals, where LLR has been increasingly used since its implementation in 2009 or later, comprising up to 40% of all liver resections. The Japanese social insurance system approved LLR including partial hepatectomy and left lateral sectionectomy in April 2010. In the current study, we collected data from 1,331 patients between 2005 and 2010 from 32 institutions representative of the "Endoscopic Liver Surgery Study Group." Surgeons participating were experienced in both liver surgery and laparoscopic surgery. In Japan, modern chemotherapy consists of oxaliplatin or irinotecan was introduced in 2005 [9]. It has been reported that administrative databases are not designed to resolve a specific scientific question and important true confounders may not be systematically recorded [36]. Therefore, we recently developed a unified database for CRLM produced by the Japanese Society of Hepato-Biliary Pancreatic Surgery and the Japanese Society of Cancer of the Colon and Rectum. We have access not only to the contents of operative data and accurate outcomes but also to information on perioperative non-surgical therapy, including chemotherapy, radiotherapy, or ablation therapy. This database can be applied also to those situations where the patients wish to change hospitals or change the treatment concept according to a personal anonymized number. We believe that this study reveals precise results on the emerging use of LLR for CRLM in Japan.

Laparoscopic liver resection may theoretically be superior to OLR in terms of good visibility of the operative field because of the magnifying effect and reduced blood loss from the hepatic vein due to pneumoperitoneum pressure [44]. On the other hand, some weak points remain, including the lack of sensation, limitation of the two-dimensional field of view and the difficulty to use long forceps or intraoperative ultrasonography. For several reasons (ethical, learning curve, lack of standardized techniques, benefits of laparoscopy across the field of surgery, etc.), its oncological value has not yet been determined by RCT [37]. Another major hurdle to designing a RCT is that patients may not be willing to be randomized into the OLR group [31]. As far as we know, two RCTs are in progress comparing LLR and OLR; the ORANGE II PLUS trial (http://clinicaltrials.gov/ct2/show/record/NCT01441856) and the OSLO CoMet study (http://clinicaltrials.gov/ct2/show/NCT01516710) [14]. The latter is the RCT comparing LLR and OLR for CRLM, but data are not available yet.

To date, numerous retrospective, comparative studies and meta-analyses of non-RCTs have been published [15–30]. These papers tend to demonstrate longer operative time, lower estimated blood loss, and a shorter hospital stay in LLR patients compared with OLR patients. In comparison with synchronous hepatectomy and colectomy, the laparoscopic approach was associated with shorter hospitalization durations than the open approach [29]. Overall morbidity and mortality were comparable. The LLR did not affect RFS and OS for CRLM; however, one study showed better OS for LLR patients [30]. However, comparison of surgical outcomes between LLR and OLR using all patients enrolled could be considered quite unfair, because there is serious selection bias in preoperative background factors. In the current study, after PSM matching, almost all collaborates were turned to within the range of standardized difference almost 10% differences. Recently, it was reported that there is no statistically significant difference in treatment effect between non-randomized studies with appropriate PSM analysis and RCT [37]. The PSM design might be considered the best level of evidence available, especially if based on a prospectively maintained database and carried out with an intention-to-treat analysis [32].

To date, three documents have been published using PSM, confirming short-term advantages and comparable survival outcomes in LLR patients compared with OLR patients for CRLM [31–33] (Table 3). Common short-term advantages by LLR included reduced blood loss and a shorter hospital stay. One study demonstrated lower morbidity [31] and another study showed longer operating time in LLR [33]. However, in these studies, the number of CRLM patients

Table 3 Outcomes in colorectal liver metastases (CRLM) patients who underwent laparoscopic liver resection (LLR) and open liver resection (OLR) in the papers using propensity score matching

Reference number	Patients' number LLR/OLR	Operation time	Blood loss	Morbidity	Mortality	Hospital stay	RFS/DFS	OS/DSS
[31]	35 / 140	Equal	LLR lesser	LLR lesser	Equal	LLR shorter	Equal (DFS)	Equal (OS)
[32]	52 / 52	Equal	LLR lesser	Equal	Equal	LLR shorter	Equal (DFS)	Equal (OS)
[33]	36 / 36	LLR longer	LLR lesser	Equal	Equal	LLR shorter	Equal (DFS)	Equal (OS)
This paper	171 / 342	Equal	LLR lesser	Equal	Equal	LLR shorter	Equal (RFS)	Equal (OS) (DSS)

DFS disease-free survival, *DSS* disease-specific survival, *LLR* laparoscopic liver resection, *OLR* open liver resection, *OS* overall survival, *RFS* recurrence-free survival

undergoing LLR was small (35 to 52 patients), and several heterogeneous background factors existed. In the current study, the number of PSM-patients with CRLM undergoing LLR was 171, and the majority of background factors were matched. PSM matching was performed for the patients in the same period (2005 to 2011), and the survival data were calculated more than 3 years after hepatic resection. We clearly demonstrated lower intraoperative blood loss (163 g vs 415 g, $P < 0.001$) and a smaller ratio of massive bleeding larger than 1,000 mL (6.4% vs 17.6%, $P < 0.001$). It is essential for CRLM patients undergoing hepatectomy to minimize blood loss. We have reported that substantial intraoperative blood loss can worsen OS for liver cancer patients after hepatectomy [45]. The CO2 pneumoperitoneum is generally established at 10–14 mmHg, and this provides a fairly good control of back-bleeding during liver transection. Low central venous pressure (<5 mm Hg) should be used during LLR, as in open surgery [14]. Among other perioperative findings, we observed a shorter hospital stay (12 days vs 14 days, $P < 0.001$) and equivalent operation time, complication rate, transfusion rate, and R0 operation rate in LLR compared with OLR. Furthermore long-term RFS, OS, and DSS were comparable, and these results add support to previous reports.

Laparoscopic liver resection has been widely used for the treatment of malignant liver tumors instead of OLR [24]. Although we can assess the malignancy of CRLM using tumor size, tumor number, and the levels of serum tumor markers, it is difficult to evaluate the complexity of hepatic resection. Han and coworkers [13] demonstrated difficult tumor locations for LLR, and therefore we assessed this item in the present study. Practically, this variable was significantly different in the two groups, equaling however after PSM. In fact, the median operative time and the amount of intraoperative bleeding were significantly greater in the posterosuperior group than in the anterolateral group (data not shown). We have already identified important factors related to the complexity of hepatic resection, namely deep location and vascular proximity [46], but unfortunately data on these factors were not included in the current database. Lately, a novel difficulty scoring system for LLR was introduced [47]. This scoring system can be used to predict the difficulty of LLR from preoperative factors and to properly select patients according to the skill level of the surgeon.

Although OLR has been the golden standard procedure for CRLM, LLR has not proved to be a comparable surgical intervention. Specific concerns about the oncologic adequacy of laparoscopy in general include port site metastases, the trophic effect of pneumoperitoneum on malignant cells, and the inability to inspect the peritoneal cavity adequately when inspecting the liver [31, 48–51]. Therefore, we analyzed details of complications and postoperative recurrence. Morbidity rates and levels of complication were similar including no port site recurrences or seeding of malignant cells. We observed no specific disadvantages regarding recurrence in LLR patients when we analyzed recurrence-free time from initial hepatic resection, and the number and size of initial recurrences. LLR included the Pure, HALS, and the Hybrid technique [12]. The independent role of these three approaches is not well known. A recent literature review demonstrated that there is insufficient evidence to conclude that any single approach is superior to the others, although HALS and the Hybrid technique are useful when dealing with difficulties associated with Pure LLR. Conversely, the need for these two methods, which can function as a bridge to Pure LLR, may be overcome with appropriate training [47, 52].

A problematic limitation was that this study was not an RCT. Although a well-designed PSM analysis was reported to be as accurate as an RCT [36], probable minimal confounding factors could have affected the results. Second, this study was investigated in the initial period of LLR usage for CRLM in Japan. The LLR to OLR ratio was 1: 5.3. The ratio of the Pure, HALS, and Hybrid approaches were 62%: 9%: 29%. The percent increase in LLR, was 16.9% between the first half and second half. The results might be modified with an increased number of LLR. Finally, in the propensity-matched cohort, median observation periods were different between the two procedures (LLR, 41.7 months vs OLR, 49.1 months). The sample size decreased after PSM, which could have affected the accuracy of recurrence and survival-estimated data. A total of 1,121 OLR patients were reduced to 513 patients after the PSM, which is caused by the small sample size of LLR group. One fifth of the LLR patients were excluded from the final analysis that might account for PSM selection bias. We can conclude from this PSM study that LLR can provide excellent perioperative benefits without compromising oncologic outcomes or long-term survival for patients with relatively early stage of CRLM. LLR should be considered to be a standard practice for selected patients with CRLM.

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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 continuous background factors for LLR and OLR before and after PSM matching.

Fig. S1 Standardized differences before and after PSM. Open circle, before propensity matching; closed triangle, after propensity matching.

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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

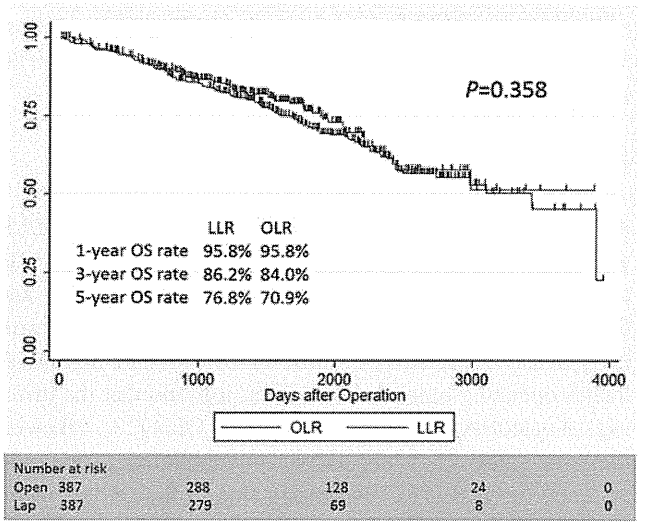

Fig. 1 Kaplan–Meier survival curve comparing overall survival (OS) in the propensity score matching (PSM) cohort

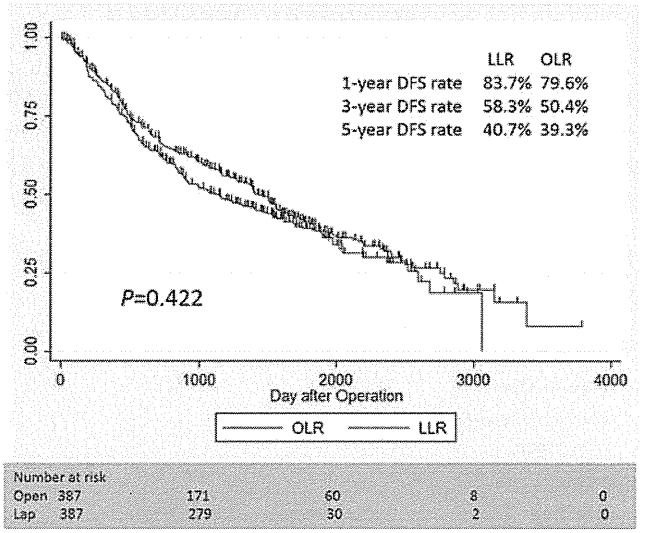

Fig. 2 Kaplan–Meier survival curve comparing disease-free survival (DFS) in the propensity score matching (PSM) cohort

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 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.