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Open versus minimally invasive liver surgery for colorectal liver metastases (LapOpHuva): a prospective randomized controlled trial

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Abstract

Objective To present surgical and oncological outcomes using a prospective and randomized trial (LapOpHuva, NCT02727179) comparing minimally invasive liver resection (LLR) versus open liver resection (OLR) in patients with colorectal liver metastases (CRLM).

Methods Between February 2005 and March 2016, 204 selected patients with CRLM were randomized and 193 were included: LLR ($n=96$) and OLR ($n=97$). The primary endpoint was to compare postoperative morbidity. Other secondary endpoints were oncological outcomes, use of the Pringle maneuver, surgical time, blood losses, transfusions, hospital stay, mortality and OS, and disease-free survival (DFS) at 3, 5, and 7 years.

Results LLR presented with lower global morbidity (11.5% vs. 23.7%, $p=0.025$) but with similar severe complications. Long-term survival outcomes were similar in both groups. The cumulative 1-, 3-, 5-, 7-year OS for LLR and OLR were 92.5%, 71.5%, 49.3%, 35.6% versus 93.6%, 69.7%, 47.4%, 35.5%, respectively (log-rank = 0.047, $p=0.82$). DFS for LLR and OLR was 72.7%, 33.5%, 22.7%, and 20.8% versus 61.6%, 27.2%, 23.9%, and 17.9%, respectively (log-rank = 1.427, $p=0.23$). LLR involved more use of the Pringle maneuver (15.5% vs. 30.2%, $p=0.025$) and a shorter hospital stay (4 vs. 6 days, $p<0.001$). There were no differences regarding surgical time, blood losses, transfusion, and mortality.

Conclusions In selected patients with CRLM, LLR presents similar oncological outcomes with the advantages of the short-term results associated with LLR.

Keywords Minimally invasive liver surgery · Open liver resection · Colorectal cancer · Colorectal liver metastases · Hepatectomy

Open liver resection (OLR) is the "gold standard" treatment for colorectal liver metastases (CRLM) because combined with neoadjuvant/adjuvant chemotherapy [1], a 30–60% overall survival (OS) is achieved at 5 years [1–4].

In 2000, the indications for laparoscopic liver resection (LLR) were published [5], applicable to lesions smaller than 5 cm located in segments II–VI, but no cases of CRLM were included in this series. In the First International Consensus [6], the short-term outcome of LLR in CRLM was analyzed with no serious adverse effects, and in the Second International Consensus [7], short-term and long-term outcomes were presented, but no prospective and randomized studies comparing OLR and LLR had been published. More recently, short-term outcomes have been reported [8–29], showing that LLR results in lower morbidity, fewer blood losses, less transfusion, and a shorter hospital stay. The first randomized trial (OSLO-COMET) [30] also reported shorter hospital stay and lower morbidity in LLR, but only analyzed short-term outcomes. Regarding long-term outcomes, all the published studies had been retrospective, propensity score matching and meta-analyses [9–23], and similar OS and disease-free survival (DFS) had been reported without statistical significance.

The aim of this study was to compare clinical and surgical outcomes between LLR and OLR for CRLM

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performing a prospective and randomized study. We also assessed oncological outcomes for both procedures.

Methods

Trial Design

This was a single-center, prospective and randomized, controlled, open-label, and parallel-group study, in CRLM patients comparing the oncological outcomes of LLR (experimental group) and OLR (control group). The study was conducted between February 2005 and March 2016, and was registered in ClinicalTrial.gov (LapOpHuva, NCT02727179). The protocol was approved by the Clinical Research and Ethics Committee at the Virgen de la Arrixaca Clinic and University Regional Hospital, Murcia, Spain (Internal Protocol Code: *HUVA-0515*). It was performed in accordance with good clinical practice guidelines and following the recommendations of the Declaration of Helsinki.

Participants

Randomization was performed when we had experience of 50 LLR, and so the inclusion criteria were all CRLM patients resectable by laparoscopy following our standardized surgical technique at the beginning of the study. We included wedge resection, segmentectomies 1–8, right posterior sectionectomy, left lateral sectionectomy, and left hepatectomy, which were all performed by two experienced senior surgeons (RR-C and AL-C). All patients were ≥ 18 years old and signed informed consent to participate in the study.

We included in the study patients with simultaneously associated resectable pulmonary metastases, due to the fact that OS at 5 years is similar to patients with only CRLM. Once the patient had recovered from hepatic resection, pulmonary surgery was performed.

Exclusion criteria were as follows: high surgical risk to the patient (ASA score > III, cirrhotic liver, and ECOG performance status > 2); disseminated disease (adrenal metastasis, lymph node metastases, peritoneal implants, high tumor load with multiple and bilobar metastases, huge liver metastases of more than 10 cm, metastases close to major vessels, non-resectable extrahepatic disease); surgical technique not standardized (repeated liver resection, simultaneous resection of the colon and liver metastases, right hepatectomy, extended left/right hepatectomy, two-stage liver resection) (Supplemental Data File 1); participation in another trial interfering with the outcomes of this study; and refusal to participate in the study.

Procedures

Preoperative staging was performed by CEA, Ca 19.9, CT-scan, MRI, and PET-scan. Patients with indicated neoadjuvant chemotherapy were included in the study after radiological response (RECIST criteria), not including patients with disease progression [4].

For liver resection, we used the Brisbane terminology [31], and we considered the resection of 3 or more segments as major liver resections. The Ban et al. [32] Index of Difficulty of the Surgery (IDS) was applied for minimally invasive group and the Lee et al. [33] index for OLR group.

In open surgery, a bilateral subcostal incision was used. Abdominal disease was explored by visual exploration and palpation, and the staging of liver disease was performed by ultrasound probe and palpation. Parenchymal-sparing liver surgery was performed with the objective of achieving a resection margin of at least 1 cm. CUSA® (Cavitron Ultrasonic Surgical Aspirator; Valleylab, Boulder, CO) was used for liver parenchyma division. In the case of segmental resections, left or right lateral sectionectomy or left hepatectomy, we performed an anterior approach. The hepatic vein was divided by applying an endovascular stapler. Hemostasis was achieved by argon-beam coagulation and sutures.

For LLR, the surgical approach has been previously described by our Unit [28]. We used an abdominal CO_2 pressure between 12 and 14 mmHg. Before the beginning of the study, the literature reported that pure laparoscopic staging may cause under-staging due to the suppression of palpation [34]. Therefore, an ultrasound probe and the surgeon's hand were introduced into the abdomen through the handport (Supplemental Data File 2). This is the reason why the abdominal cavity was explored by endoscopic vision and palpation, and liver disease by ultrasound and palpation [35], similar to OLR. The harmonic scalpel (Ethicon Endosurgery, Cincinnati, OH, USA) was used for superficial liver parenchyma division and CUSA® for deep liver parenchymal transection. Hemostasis was achieved by radiofrequency coagulator (TissueLink® TissueLink Medical, Inc., Dover, NH) and sutures.

Primary outcome

1:1 randomization was performed in January 2005, before the beginning of the study, using a computer-generated sequence (Statistical software EPIDAT 3.0). The envelopes about the approach to be taken were kept by the statistician until they were opened in the operating room, before starting the intervention.

The primary endpoint was postoperative morbidity (within the first 90 days). The Clavien–Dindo classification

was used to analyze morbidity [36] (grade ≥ IIIa was considered as severe).

Secondary outcomes

We analyzed overall survival and disease-free survival at 1-, 3-, 5-, and 7 years and also the prognostic factors related with survival outcomes such as neoadjuvant chemotherapy, time between surgery and adjuvant chemotherapy, surgical margin, recurrence of the disease, treatment of the recurrence, patients alive without recurrence, patients alive with recurrence, and patients who died of the disease. R0 resection margin was defined as patients having microscopically more than 1 mm free of the disease. Adjuvant chemotherapy was administered once the patient had recovered, provided there were no contraindications. Other secondary endpoints were surgical time, blood losses, blood transfusion, use of the Pringle maneuver, hospital stay (days), and mortality (postoperative death within the first 90 days).

Follow-up

During the follow-up, the patients were revised by the liver surgeons, performing a CT-scan and tumor marker tests at 3 weeks after surgery. If there were no complications, chemotherapy was then started by oncologists. During the first-year, CT-scan and tumor marker tests were performed every 4 months; in the second year, every 6 months and after the third year, once a year.

Sample size

For the analysis of overall postoperative morbidity, according to the published literature available at the start of the trial, the sample size needed to be calculated with an incidence of 35% for OLR. An estimated reduction in morbidity of 17% in LLR, compared to OLR, was considered clinically relevant. A power of 0.80 and α of 0.05 was used in a two-tailed model. The sample size needed was 92 patients for each arm. Accounting and estimated losses were 10%, and the enrollment of 102 patients in each group was required. Ultimately, 204 patients were enrolled into this study.

Statistical analysis

The data were analyzed using the SPSS 22.0 statistical package for Windows (SPSS, Chicago, IL). In order to compare quantitative variables in independent samples, we used a combination of Student's *t*-test or the Fisher test depending on whether there was variance or homogeneity between the two groups. To study the relationship between the qualitative variables and to compare the ratios for the independent samples, we conducted an analysis of contingency tables using Pearson's chi-squared test. Categorical variables were compared with the χ^2 test or Fisher's exact test. Normal and non-normal continuous variables were compared using Student's *t*-test and the Mann–Whitney *U* test, respectively. OS and DFS were estimated using Kaplan–Meier's analysis. A 95% confidence interval ($p < 0.05$) was considered for statistically significant differences.

Results

Studied population and surgical procedures

The trial consort [37] flow diagram is shown in Fig. 1. Enrollment was conducted between February 2005 and March 2016. In the same period, 540 patients were operated on for CRLM in our Unit. According to intention-to-treat criteria, 204 patients (38%) were randomly assigned to either OLR (103 patients) or LLR (101 patients). In Supplemental Data File 1, we present the differences between randomized patients and the patients with advanced liver disease excluded of the study (336 patients).

After randomization, 5 patients in the OLR and 4 in the LLR group (1 patient after allocated intervention due to laparotomy conversion) were excluded. Three patients (2 OLR and 1 LLR) were excluded due to a preoperative change in the procedure, where resection was done by right hepatectomy in all cases. In the follow-up, two patients (1 in each group) did not attend the outpatient clinic and were excluded. Finally, 193 selected patients (97 OLR and 96 LLR) were analyzed "per protocol" in the study. There were no statistically significant differences between patients' baseline characteristics and the surgical techniques performed (Table 1).

Total morbidity was statistically significantly lower in LLR (11.5% vs. 23.7%, $p = 0.025$) (Table 2). Morbidity ≥ IIIa was lower in LLR (13.4% vs. 6.2%; $p = 0.095$), but morbidity ≥ IIIb did not differ between the 2 groups. Mortality was similar (1 patient in each arm).

In the LLR, the patient died on the 5th postoperative day due to acute peritonitis secondary to an intestinal injury during the closure of the incision used to take out the specimen. In the OLR group, the patient died on the 25th postoperative day due to an acute necrotizing pancreatitis secondary to an ERCP during the treatment of persistent biliary fistula.

Postoperative outcomes (Table 2)

The Pringle maneuver was used significantly more frequently in LLR, with a higher median occlusion time. Median hospital stay was shorter in laparoscopic surgery (4 days, range 2–6) compared to open surgery (6 days, range 3–54) ($p < 0.001$).

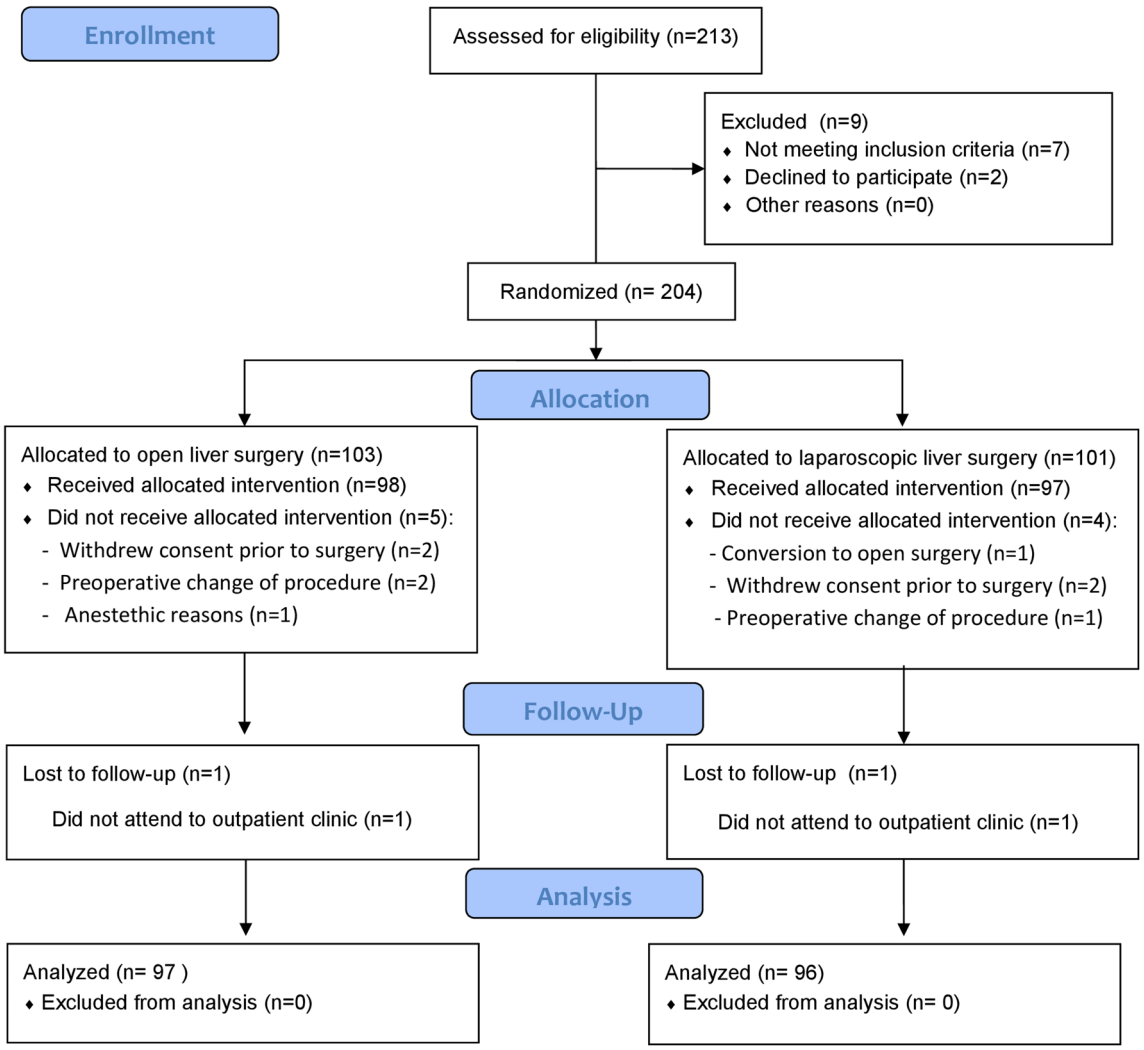

Fig. 1 Study flowchart of the LapOpHuva trial

Oncological outcomes

All patients had atleast 1 year of follow-up. The median length of follow-up (in March 2017), including the patients who died in the postoperative period, was 36 months (range 0–159) and 40 months (range 0–157) for patients undergoing OLR and LLR, respectively. Cumulative 1-, 3-, 5-, and 7-year OS rates in patients undergoing OLR and LLR were 93.6%, 69.7%, 47.4%, and 35.5% versus 92.5%, 71.5%, 49.3%, and 35.6%, respectively (log-rank = 0.047, $p = 0.82$) (Fig. 2). Cumulative 1-, 3-, 5-, and 7-year DFS rates in patients undergoing OLR and LLR were 61.6%, 27.2%, 23.9%, and 17.9% versus 72.7%, 33.5%, 22.7%, and 20.8%, respectively (log-rank = 1.427, $p = 0.23$) (Fig. 2). The results with intention to treat were also similar (Fig. 2).

Sixty-nine patients (71%) in the OLR group presented recurrence of the disease (not statistically significant), compared to LLR (65 patients; 67.7%) (Table 3). Liver and lung recurrence was not significantly different between OLR and LLR. The repeat surgery for the treatment of recurrence was similar, 26 patients (26.8%) for OLR and 32 patients (33.3%) for LLR.

By March 01, 2017, 45 out of 97 patients (46.4%) in the OLR group had died due to disease (Table 2), 12 patients (12.4%) were alive with the disease, and 40 patients (41.2%) were alive but disease-free. In LLR, 49 out of 96 patients (51%) had died, 8 patients (8.3%) were alive with disease, and 39 patients (40.6%) were alive but disease-free.

Discussion

For selected patients with wedge resection, segmentectomies 1–8, right posterior sectionectomy, left lateral sectionectomy, and left hepatectomy operated on by OLR and by LLR (with the same complex surgery in both groups),

Table 1 Demographic and clinical characteristics of randomly assigned patients ($n=193$)

	0LR ($n=97$)	LLR ($n=96$)	p
Age, year, median (IQR)	69 (56–76)	66 (58–72)	0.347
Gender; male, *n* (%)	71 (73.2)	61 (63.5)	0.099
BMI (Kg/m^2), median (IQR)	27 (25–29)	27 (25–31)	0.821
ASA, *n* (%)			
I	1 (1)	1 (1)	
II	50 (51.5)	43 (44.8)	
III	46 (47.4)	52 (54.1)	
Charlson comorbidity index, median (IQR)	3 (1–4)	3 (2–4)	0.776
ECOG, *n* (%)			
0	25 (25.7)	26 (27.1)	
1	67 (69.1)	67 (69.8)	
2	5 (5.2)	3 (3.1)	
Hipertensión/diabetes/CVD, *n* (%)	40/21/19 (41.2 /21.6 /19.6)	35/28/16 (36.4 / 29.2/ 16.7)	0.879
Primary tumor, *n* (%)			0.722
Right colon	16 (16.5)	20 (20.8)	
Rest of colon	43 (44.3)	47 (49)	
Rectum	38 (39.2)	28 (29.2)	
Primary tumor approach; *n* (%)			
Open	67 (69)	74 (77)	
Laparoscopic	30 (31)	22 (23)	
T-Stage of the primary tumor, *n* (%)			0.731
T1–T2	14 (14.4)	13 (13.5)	
T3–T4	83 (85.6)	83 (86.5)	
N-stage of the primary tumor, *n* (%)			
N0	15 (36,6)	7 (20,6)	
N1–2	26 (63,4)	27 (79,4)	
Synchronous liver metastases, *n* (%)	35 (36.1)	44 (45.8)	0.347
Bilobar metastases; *n* (%)	18 (19.2)	13 (13.5%)	0.319
Number of lesions, median (IQR)	1 (1–2)	1 (1–2)	0.890
Tumor size (cm), median (IQR)	4 (2–5)	3 (3–4)	0.130
Pulmonary metastases at diagnosis; *n* (%)	7 (7.2)	12 (12.5)	0.168
Neoadjuvant therapy; *n* (%)	32 (33.3)	27 (27.2)	0.091
RECIST criteria			
Complete response	20 (20.6)	18 (18.5)	
Partial response	12 (12.5)	9 (9.2)	
Number of cycles, median (IQR)	6 (5–8)	6 (4–12)	
Number of lines, median (IQR)	1 (1–2)	1 (1–2)	
First-line regimen, *n* (%)			
Oxaliplatin	25 (25.8)	20 (20.8)	
Irinotecan	4 (4.1)	2 (2.1)	
Both	3 (3.1)	1 (1)	
Others	4 (4.1)	1 (1)	
Biological agents, *n* (%)	19 (19.6)	11 (11.5)	
Preoperative CEA level (ng/ml), median (IQR)	8 (3–22)	8 (3–29)	0.120
Segment locations of the nodules, *n* (%)			0.186
Segment 1	2 (1.5)	1 (0.8)	
Segment 2	17 (12.8)	20 (16.2)	
Segment 3	16 (12)	20 (16.1)	
Segment 4a	5 (3.8)	4 (3.2)	

Table 1 (continued)

	0LR ($n=97$)	LLR ($n=96$)	p
Segment 4b	14 (10.6)	10 (8.1)	
Segment 5	20 (15)	17 (13.7)	
Segment 6	26 (19.5)	24 (19.3)	
Segment 7	19 (14.2)	16 (12.9)	
Segment 8	14 (10.6)	12 (9.7)	
Surgical technique performed, *n* (%)			0.337
Left hepatectomy	5 (5.2)	8 (8.3)	
Resection of 3 segments	2 (1.5)	3 (3.1)	
Bisegmentectomy + wedge/es	7 (7.2)	6 (6.2)	
Bisegmentectomy	22 (22.7)	24 (25)	
Segmentectomy + wedge/es	10 (10.3)	4 (4.2)	
Segmentectomy	25 (25.7)	31 (32.3)	
Wedges	12 (12.4)	6 (6.2)	
Wedge	14 (14.4)	14 (14.6)	
Major liver resection, *n* (%)	7 (7.2)	11 (11.5)	0.434
Index of difficulty of the surgery (IDS), median (IQR)	.36 (1.36–7.2)*	6 (2–10)**	***

OLR open liver resection, *LLR* laparoscopic liver resection, *IQR* interquartile range, *BMI* body mass index, *ASA* American Society Anesthesiologists, *ECOG* Eastern Cooperative Oncology Group, *CVD* cardiovascular disease, *CEA* carcinogenic embryonic antigen

*Lee et al. classification34 and **Ban et al. classification33 *** different IDS not comparable

we found lower global morbidity in LLR, but similar severe complications. The long-term outcome was similar in both groups (5-year OS and DFS for OLR was 47.4% and 23.9%, respectively, vs. 49.3% and 22.7% for LLR, respectively). We analyzed OS and DFS with intention to treat and the results were also similar in both groups.

Regarding short-term results, the randomized study OSLO-COMET [30], which includes 280 patients who underwent surgery for CRLM, shows a shorter hospital stay and lower morbidity with LLR than with OLR, similar to results obtained by Zhang [38]. The short-term results of the present study coincide exactly with the Norwegian Trial, with no differences in surgical time, blood loss, transfusion, or mortality. Intraoperative hemorrhage is the most feared complication during LLR, which could be related to the inability to carry out compression, since it could be associated with greater morbidity. In case of hemorrhage, we increased the abdominal pressure to 16 mmHg, we tried to occlude the vessel using a forceps, and we introduced a gauze to compress the hemorrhage site. In cases of failure, hilar clamping is indicated before conversion. To perform the Pringle maneuver, in minimally invasive surgery, we used a laparoscopic vascular clamp introduced through a trocar placed on the left flank middle axillary line, as we previously described [28].

The first prospective and non-randomized study was performed by the Oslo University Hospital group in 2002 [8] comparing LLR ($n=13$) and OLR ($n=14$) in CRLM, with a very short follow-up period. When our randomized study was started in 2005, the worldwide experience with LLR in CRLM was limited. In fact, in the series by Cherqui et al. [5], there were no cases of CRLM and only a few patients were included in the prospective study by Mala et al. [8] The first homogenized comparative study that obtained a similar OS rate at 5 years was published by Castaing et al. [9] including 60 patients per group, but with a longer follow-up (30 for LLR versus 33 months for OLR). After this paper, several authors reported similar survival rates using retrospective studies including propensity score matching (PSM) [8–20].

A recent meta-analysis [38] analyzed 10 previously published PSM studies and no differences were found regarding DFS and 5-year OS, but they found that laparoscopic surgery had better 3-year OS than open surgery (a surprising result not previously described). These authors report that a lower recurrence rate and better OS were obtained than those previously published in some series [39]. However, the LapOpHuva study confirms that LLR has the same OS and DFS rates as OLR, in line with results in the reviewed literature (Supplemental Data File 3) and meta-analysis [40–46].

As liver palpation is lost in the pure laparoscopic approach, it may be necessary to perform repeat ultrasounds to obtain adequate surgical margins. So, no differences in R0 resections were achieved in most of the series [11, 12, 15–17, 19–22], but in some series, a higher R0 resection rate was obtained by laparoscopy [9, 10]. In this study, there were no differences in R0 resection (95.8% in LLR vs. 88.6%

Table 2 Intraoperative and postoperative outcome of the patients

	OLR ($n=97$)	LLR ($n=96$)	p
Operative time (min), median (IQR)	120 (110–165)	120 (90–180)	0.953
Blood loss (ml), median (IQR)	200 (100–300)	100 (50–300)	0.181
Blood transfusion, *n* (%)	8 (8.2)	4 (4.2)	0.240
Pringle maneuver, *n* (%)	15 (15.5)	29 (30.2)	0.025
Clamping time (min), median (IQR)	10 (8–15)	15 (8–20)	0.156
Associated cholecystectomy, *n* (%)	33 (34)	19 (19.8)	0.026
Other resections, *n* (%)			0.153
Diaphragm	4 (4.1)	1 (1)	
Omental nodule	1 (1)	1 (1)	
Drainage	75 (77.3)	74 (77.1)	0.969
Global morbidity (*n*, %)	23 (23.7)	11 (11.5)	0.025
Clavien–Dindo; *n* (%)			
Grade I–II	10 (10.3)	5 (5.2)	
Grade IIIa	11 (11.3)	5 (5.2)	
Grade IIIb	1 (1)	0	
Grade IV	0	0	
Grade V	1 (1)	1 (1)	
Clavien–Dindo ≥ IIIa, *n* (%)	13 (13.4)	6 (6.25)	0.095
Type of morbidity, *n* (%)			
Deep surgical site infection	10 (10.3)	6 (6.25)	
Surgical wound infection	2 (2.1)	0	
Anemia severe	2 (2.1)	0	
Acute urinary retention	2 (2.1)	0	
Fascia dehiscence	1 (1)	0	
Pleural effusion	1 (1)	0	
Ileus	1 (1)	0	
Acute necrotizing pancreatitis	1 (1)	0	
Bile leak	1 (1)	1 (1)	
Ascites	1 (1)	1 (1)	
Peritonitis	0	1 (1)	
Pneumothorax	0	1 (1)	
Urinary tract infection	0	1 (1)	
Reoperations within 90 days, *n* (%)	1 (1)	1 (1)	0.973
Postoperative length of stay (days), median (IQR)	6 (5–8)	4 (4–5)	0.001
R0 resection margin, *n* (%)	86 (88.6)	92 (95.8)	0.132
Pathologic weight of the specimen (g), median (IQR)	92 (73–126)	89 (67–138)	0.732
Late incisional hernias, *n* (%)	4 (4.1)	2 (2)	0.351

OLR open liver resection, *LLR* laparoscopic liver resection; *g* grams, *IQR* interquartile range

in OLR) or recurrence of the disease (67.7% in LLR vs. 71% in the OLR).

Adjuvant chemotherapy after liver surgery is recommended to be started within the first 8 weeks. In a recent PSM study [47], LLR involved an earlier start of adjuvant chemotherapy than OLR (43 vs. 55 days, $p=0.012$). Other authors [48] found that LLR had an earlier start of chemotherapy than OLR and the patients who initiated chemotherapy before 60 days had better median survival (29 months vs. 14 months, $p=0.05$). These results could be related to an improvement in long-term survival due to the lower surgical aggressiveness, morbidity, and immunosuppression [49] of the LLR.

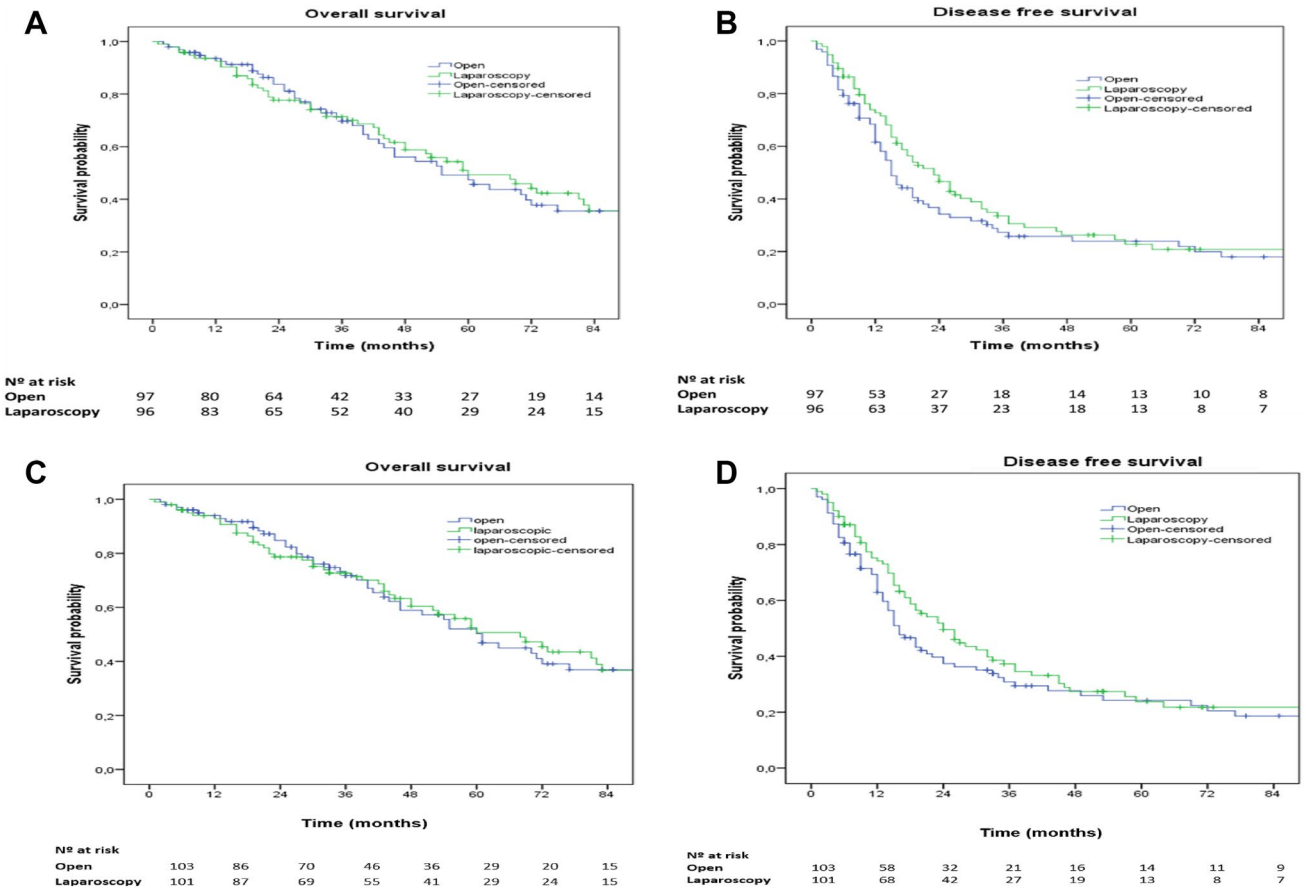

Fig. 2 Overall and disease-free survival in open liver resection and laparoscopic liver resection groups: per-protocol (**a** and **b**) and intention to treat (**c** and **d**)

The single-center design of this study could be a limitation, although it provides some advantages such as a better standardization of diagnosis, patient selection, surgical technique, and postoperative care. The learning curve period is different for OLR and LLR, which could affect external validation. For laparoscopic surgery, in 2009, Viganó et al. [50] believed that after a case-mix adjustment, the cumulative sum analysis demonstrated a learning curve for laparoscopic hepatectomies of 60 cases. To prevent surgical bias, our study began when we had already performed 50 LLR and standardized the surgical techniques that we considered as inclusion criteria, and during the study, 260 LLR were performed in our unit. This trial was performed over 11 years, a very long period of time. The reason for the prolonged recruitment of patients was due to the fact that our Liver Unit is a regional reference center in which most of the hepatectomies are highly complex. This is the reason why only 38% of the patients operated on for CRLM in the period of study could be included in the trial.

Conclusions

The results of this trial might have important clinical implications because together with the advantages of the short-term results associated with LLR (lower hospital stay and less morbidity), it offers similar oncological outcomes to OLR.

Table 3 Adjuvant chemotherapy, recurrence of the disease, and patients alive at the time of the last review

	0LR ($n=97$)	LLR ($n=96$)	p
Adjuvant therapy, *n* (%)	79 (81.4)	77 (80,2)	0.945
Number of cycles, median (IQR)	12 (6–17)	19 (6–16)	0.36
Number of lines, median (IQR)	1 (1–2)	1 (1–2)	0.201
First-line regimen, *n* (%)			
Oxaliplatin	38 (39.1)	39 (40.6)	
Irinotecan	19 (19.5)	16 (16.6)	
Both	1 (1)	0	
Others	21 (21.6)	22 (22.9)	
Second-line regimen, *n* (%)			
Oxaliplatin	4 (4.1)	6 (6.2)	
Irinotecan	10 (10.3)	12 (12.5)	
Both	0	0	
Others	12 (12.3)	16 (16.6)	
Third-line regimen, *n* (%)			
Oxaliplatin	3 (3.1)	2 (2.1)	
Irinotecan	0	4 (4.2)	
Both	0	0	
Others	13 (13.4)	14 (14.6)	
Fourth-line regimen, *n* (%)			
Oxaliplatin	3 (3.1)	3 (3.1)	
Irinotecan	1 (1)	1 (1)	
Both	0	0	
Others	3 (3.1)	6 (6.25)	
Fifth-line regimen, *n* (%)			
Oxaliplatin	1 (1)	1 (1)	
Irinotecan	0	1 (1)	
Both	0	0	
Others	2 (2.1)	2 (2.1)	
Biological agents, *n* (%)	37 (38.1)	35 (36.5)	0.515
Time between surgery and adjuvant chemotherapy (days), median (IQR)	42 (31–61)	35 (30–60)	0.395
Recurrence, *n* (%)	69 (71.1)	65 (67.7)	0.606
First recurrence (single or multiple sites), *n* (%)			
Single site	50 (51.5)	34 (35.1)	
Liver	18 (18.5)	15 (15.6)	
Lung	21 (21.64)	16 (16.6)	
Other	11 (11.3)	3 (3.1)	
Multiples sites	19 (19.6)	31 (32.2)	
Liver + lung	9 (9.3)	11 (11.4)	
Liver + other	3 (3.1)	7 (7.3)	
Lung + other	4 (4.1)	3 (3.1)	
Liver + lung + other	3 (3.1)	2 (2.1)	
Repeat surgery for recurrence, *n* (%)	26 (26.8)	32 (33.3)	0.323
Hepatic recurrence	16 (16.5)	19 (19.7)	
Extrahepatic recurrence	10 (10.3)	13 (13.5)	
Patients alive with disease, *n* (%)	12 (12.3)	8 (8.3)	0.357
Patients alive without disease, *n* (%)	40 (41.2)	39 (40.6)	0.931

OLR open liver resection, *LLR* laparoscopic liver resection, *IQR* interquartile range

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Compliance with ethical standards

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