Laparoscopic Versus Open Resection for Colorectal Liver Metastases

The OSLO-COMET Randomized Controlled Trial

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Objective: To perform the first randomized controlled trial to compare laparoscopic and open liver resection.

Summary Background Data: Laparoscopic liver resection is increasingly used for the surgical treatment of liver tumors. However, high-level evidence to conclude that laparoscopic liver resection is superior to open liver resection is lacking.

Methods: Explanatory, assessor-blinded, single center, randomized superiority trial recruiting patients from Oslo University Hospital, Oslo, Norway from February 2012 to January 2016. A total of 280 patients with resectable liver metastases from colorectal cancer were randomly assigned to undergo laparoscopic (n = 133) or open (n = 147) parenchyma-sparing liver resection. The primary outcome was postoperative complications within 30 days (Accordion grade 2 or higher). Secondary outcomes included cost-effectiveness, postoperative hospital stay, blood loss, operation time, and resection margins.

Results: The postoperative complication rate was 19% in the laparoscopic-surgery group and 31% in the open-surgery group (12 percentage points difference [95% confidence interval 1.67–21.8; $P = 0.021$]). The postoperative hospital stay was shorter for laparoscopic surgery (53 vs 96 hours, $P < 0.001$), whereas there were no differences in blood loss, operation time, and resection margins. Mortality at 90 days did not differ significantly from the laparoscopic group (0 patients) to the open group (1 patient). In a 4-month perspective, the costs were equal, whereas patients in the laparoscopic-surgery group gained 0.011 quality-adjusted life years compared to patients in the open-surgery group ($P = 0.001$).

Conclusions: In patients undergoing parenchyma-sparing liver resection for colorectal metastases, laparoscopic surgery was associated with significantly less postoperative complications compared to open surgery. Laparoscopic resection was cost-effective compared to open resection with a 67% probability. The rate of free resection margins was the same in both groups. Our results support the continued implementation of laparoscopic liver resection.

Keywords: colorectal liver metastases, cost and cost analysis, hepatectomy, laparoscopic, laparoscopy, liver resection, minimally invasive surgery, parenchyma-sparing liver surgery, randomized clinical trial, randomized controlled trial

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LEARNING OBJECTIVES

After participating in this activity, the reader should be better able to:

1. Perform work-up and appropriately select patients for surgical treatment of colorectal liver metastases.
2. Identify patients that are suitable for laparoscopic liver surgery.
3. Select the appropriate and necessary surgical equipment for laparoscopic liver surgery.
4. Describe the costs and effects of open and laparoscopic liver surgery.
5. Explain to patients what to expect in terms of complications and quality of life after open and laparoscopic parenchyma sparing liver resection.

The liver is the most common site for metastatic colorectal cancer (CRC). Despite advances in oncologic treatment, resection of

metastases is still the only curative option, with 5-year survival rates of 40% to 57% after resection of liver metastases.[1–3] The use of neoadjuvant chemotherapy has increased the proportion of patients that can be offered liver resection, whereas advances in surgical techniques and perioperative care has decreased the 30-day mortality of liver surgery from 24% in 1970 to less than 2% today.[4–6]

Although laparoscopic surgery for primary CRC is well documented and widely used,[7] laparoscopic surgery for liver metastasis has been slow to implement.[8] Previous studies have suggested that laparoscopic liver resection is oncologically equivalent to open resection, but with short-term advantages in terms of fewer complications, reduced hospital stay and lower total hospital costs.[9–19] A randomized controlled trial of open and laparoscopic liver resection (Orange II, NCT 00874224) was recently halted after failing to recruit patients.[20] Thus, laparoscopic and open liver resections have never been compared in a randomized controlled trial (RCT). In the Oslo laparoscopic versus open liver resection for colorectal metastases (OSLO-COMET) trial, we report the 30-day complication rate, resection margins and cost-effectiveness for patients randomly assigned to undergo either open or laparoscopic liver resection.

METHODS

Trial Design and Oversight

In this investigator-initiated, open-label, single-center, superiority trial we randomly assigned patients to laparoscopic liver resection (experimental group) or open liver resection (control group). The trial was designed by the protocol committee and conducted at Oslo University Hospital, Oslo, Norway. The trial protocol has been published previously[21] and was approved by the Regional Ethical Committee of South Eastern Norway (REK Sør-Øst B 2011/1285) and the Data Protection Officer of Oslo University Hospital. Data were gathered by the authors, assisted by research assistants who received payment from trial funds. The authors analyzed the data, wrote the manuscript, and vouched for the accuracy of the analyses and the fidelity of the trial to the protocol. The South-Eastern Norway Regional Health Authority sponsored the trial, but had no role in the design, data gathering, data analyses, or writing of the manuscript. (Clinicaltrials.gov identifier NCT01516710).

Patients

Patients were eligible for the trial if diagnosed with CRC liver metastases that could be radically resected by a parenchyma-sparing liver resection, defined as a resection of less than 3 consecutive liver segments. Multiple resections were allowed. Patients with recurrent metastases after previous liver resection (open or laparoscopic) were eligible, as were patients with resectable metastases in lungs or adrenal glands. Patients with other extrahepatic CRC metastases were excluded, as were patients scheduled for concomitant ablation, vascular or biliary reconstruction, or synchronous resection of a primary tumor. A multidisciplinary team decided the eligibility by evaluating the medical history of the patient, an iodine contrast-enhanced computed tomography of the chest and abdomen, and a gadoxetate disodium (Eovist, Bayer HealthCare) contrast-enhanced magnetic resonance imaging of the liver. All patients received written and oral information about the trial from one of the investigators before providing written consent.

The randomization sequence was generated with software created specifically for this trial. The software was both designed and operated by the Department of Information Technology, Oslo University Hospital, and the randomization sequence was stored in a secure database accessible only to the investigators. Allocation to laparoscopic or open procedure was performed approximately 2 weeks before surgery. Participants were not informed of the type of procedure until the day of surgery. Eligible patients were randomly assigned in a 1:1 ratio to undergo laparoscopic liver resection or open liver resection. There was no stratification.

Procedures

Patients received chemotherapy as recommended by the multidisciplinary team meeting, adhering to Norwegian guidelines. When neoadjuvant chemotherapy was recommended, randomization was performed after a radiologic response evaluation. The indication for adjuvant chemotherapy was the same for both groups.

Patients received preoperative information regarding the liver surgery and the trial by the study investigators (Å.A.F. and V.J.D.), and thus standardizing the preoperative management. Patients followed a perioperative fast track protocol that was identical for both groups. The operations were scheduled as part of the departmental routine surgical lists, for which surgeons were scheduled for operations based on the availability of the department and the complexity of the procedure. Patients were given a single dose of intravenous doxycycline (400 mg) and metronidazole (1.5 g) before surgery started. All operations were performed or supervised by consultant hepatopancreato-biliary surgeons skilled in the technique in use. The surgeons could change strategy from parenchyma-sparing resection to hemihepatectomy or ablation during surgery at his/her discretion when needed. The surgical technique was described in the protocol,[21] and the complexity of the procedures was evaluated using modified versions of the Liver Surgery Complexity Score[22] and the Iwate scoring system.[23] The modifications were made in accordance with the authors of each scoring system. The modified score included the score for the most complex resection, with an addition of 1 point for each additional resection that was necessary.

Primary Outcome

Complications were recorded by a blinded assessor who studied the electronic documentation system provided by the nurses. These records did not include information about operative techniques, but rather described the postoperative state of the patient in 3 daily reports. The records also included documentation of the telephone interviews between the nurses and patients at 1, 8, and 28 days after discharge.

Postoperative complications were registered as a dichotomous variable (yes/no) using the Accordion system for grading and definitions.[24] Grade 1 complications are difficult to register consistently, and often have minimal impact on the postoperative course. We, therefore, amended the protocol to specify that the primary outcome was a complication of Accordion grade 2 or higher.

Secondary Outcomes

Complications were also assessed using the Comprehensive Complication Index (CCI), which calculates all the complications that a patient experiences into an index ranging from 0 to 100.[25] The CCI score recorded here was, however, modified compared to the original publication, because grade 1 complications were not registered in our trial, and thus not added to the CCI calculation. Conversions to hand-assisted laparoscopy or laparotomy, intraoperative unfavorable incidents, operation time, blood loss, transfusions, and details about the procedure were recorded on a paper-based case report form. Blood loss was documented by the operating surgeon directly after surgery, based on the amount of blood in the suction canister plus an estimate of blood in the surgical swabs. When patients were transferred to the referring hospital for postoperative care, the recorded length of the postoperative hospital stay included stays at both hospitals.

All resected specimens were sent for biobanking and histopathologic evaluation. Resection margins were evaluated macroscopically and microscopically by pathologists, and the presence of tumor cells within 1 mm from the resection margin was defined as an R1 resection.

Follow-up

Patients were seen in the outpatient clinic by one of the investigators at 1 and 4 months postoperatively. A clinical examination was performed at both visits, and a thoracoabdominal computed tomography was performed at the 4-month visit.

Costs

Costs were estimated in a 4-month health care perspective with a focus on the costs of the operations, cost of the initial hospital stay, and costs due to complications. Resource use was mainly quantified using patient medical records. A microcosting study was conducted to estimate the costs of the operations, and patient questionnaires were used to assess resource use between the 1- and 4-month follow-up. Costs were estimated on a present-value basis as USD 2014, using the mean exchange rate in 2014 (1 USD = 6.3019 NOK). See the Supplementary Appendix for further details, http://links.lww.com/SLA/B261.

Health-related Quality of Life

Health-related quality of life (HRQoL) was measured using the 36-item Medical Outcomes Study Short Form (SF-36, Norwegian version 2.0) at baseline, 1- and 4-month follow-up. We calculated the SF-6D by a valuation algorithm from the United Kingdom to estimate the HRQoL of the patients.[26] The SF-6D measures HRQoL on a scale anchored in dead [0] and perfect health [1], and is in combination with time, a measure of patients' quality-adjusted life years (QALYs).

Statistical Analysis

Based on data from our department, we anticipated a complication rate of 27% in the open-surgery group and estimated a potential reduction to 13% in the laparoscopic-surgery group.[1] To show this difference, or a larger one, with a 95% confidence interval (CI) and 80% power of the superiority test, a sample of 254 patients would be needed. We expected a 10% drop-out rate and planned to include 280 patients.

The 30-day complication rate was compared between the 2 treatment groups using Fisher Mid-P test for association. The difference between the treatment group probabilities of having a complication within 30 days (the risk difference) was estimated with a 95% Newcombe hybrid score CI. Intraoperative and postoperative outcomes were analyzed with a median regression, which provided a 95% CI for the difference between the medians of the 2 treatment groups and a P value for the null hypothesis of equal medians. A 2-sample t test was used when the median was not a relevant measure to compare the treatment groups.

Cost differences were tested by a generalized linear model with a log link function and a gamma distribution, and a 95% CI was estimated as the 2.5th and 97.5th percentile using a bootstrap process with 10,000 repetitions. Missing values in the HRQoL were imputed by predictive mean matching using multiple imputations with chained equation.[27] Differences in HRQoL and QALYs were estimated using t tests. QALYs were adjusted for baseline differences.[28] We estimated the incremental cost-effectiveness ratio (ICER) by dividing the cost difference by the effect difference of laparoscopic and open surgery, and used a willingness to pay threshold of $95,000.[29] Uncertainty of the ICER was estimated by bootstrapping with 1000 repetitions. From the bootstrapped sample, for increasing threshold values, we estimated both the probability of laparoscopic liver surgery and open liver surgery to be cost-effective (cost-effectiveness acceptability curves) and the individual expected value of perfect information (EVPI).[30] The EVPI expresses the expected cost of uncertainty, and quantifies the maximum value that society should be willing to pay to eliminate the uncertainty regarding the adaption of the new technology (laparoscopic liver surgery) given current knowledge.[31] We did not discount due to the short time perspective.

Statistical analyses were performed on a modified intention-to-treat basis.[32] Patients who did not undergo any surgical procedures were excluded from this analysis (Fig. 1). Statistical analyses were performed using Stata Statistical Software: Release 14 (StataCorp. 2015, College Station, TX: StataCorp LP).

RESULTS

From February 15, 2012 to January 28, 2016, a total of 280 patients were randomly assigned to laparoscopic (n = 133) or open (n = 147) liver resection. During this period, 308 patients were eligible for randomization. A total of 14 patients were not considered for the trial. Four of these patients had a locally advanced rectal cancer with synchronous liver metastases, and needed liver resection after neoadjuvant radiotherapy, but before definite surgery for the rectal cancer. These patients were fast-tracked to liver surgery outside the trial. The remaining 10 patients were not considered for unknown reasons. Of the 14 patients who were not considered for the trial, 8 had laparoscopic liver resections and 6 had open liver resections. Thus, a total of 294 patients were screened for inclusion (Fig. 1).

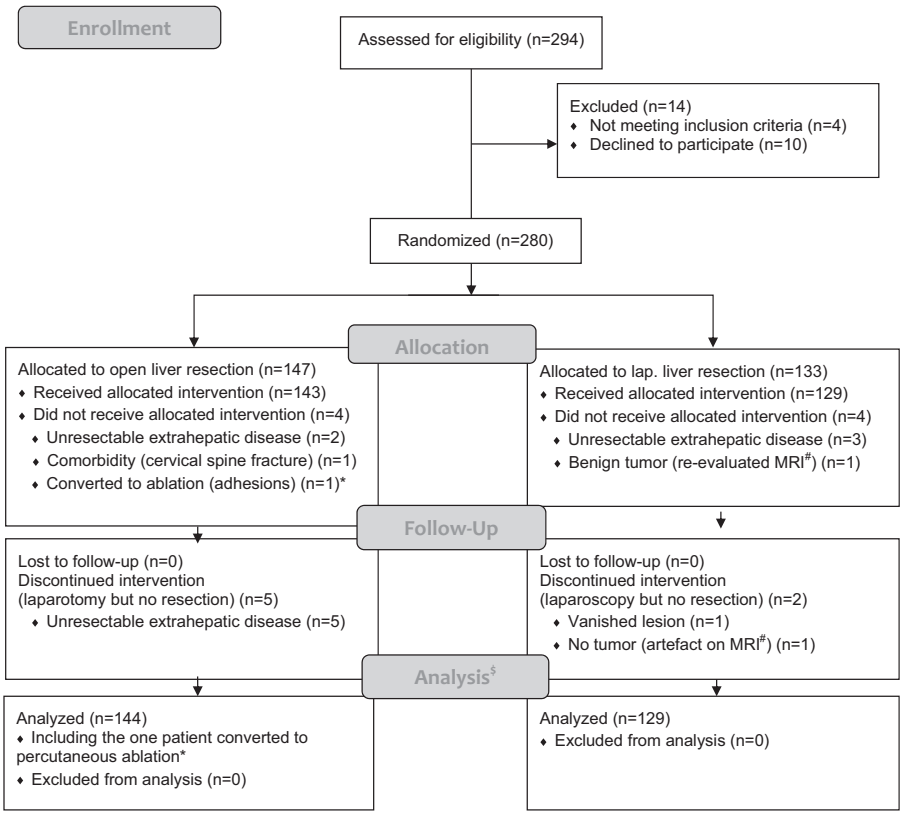
At postoperative day 30, data were available for all patients. The baseline clinical characteristics of the patients are described in Table 1. The groups were similar with 1 exception: More patients in the laparoscopic surgery group had undergone liver resection previously. A total of 10 consultant surgeons performed the procedures, of whom 6 performed laparoscopic operations.

The primary outcome, a complication of Accordion grade 2 or higher, was experienced by 68 of the 273 patients who underwent surgery. In the open-surgery group, 44 patients (31%) experienced a postoperative complication, compared with 24 patients (19%) in the laparoscopic-surgery group, a difference of 12 percentage points (95% CI 1.67–21.8; $P = 0.021$) (Table 2). The mean CCI was 9.3 in the open-surgery group and 5.2 in the laparoscopic-surgery group (difference of 4.1 points, 95% CI 0.6–7.5, $P = 0.021$). One patient in the open-surgery group died on the third postoperative day (Table 3). The patient was a 78-year-old woman with a history of vascular disease, diabetes, and asthma. No certain cause of death was found at the post-mortem examination. Four patients needed intensive care treatment, 3 of whom were in the laparoscopic-surgery group (Tables 2 and 3).

Operation time, blood loss, transfusion rate, and intraoperative unfavorable incidents were similar in the 2 groups, whereas the postoperative hospital stay was significantly shorter after laparoscopic surgery (Table 2). Postoperative pain scores were similar in both groups, but open-surgery patients needed significantly more morphine equivalents.

There was no difference in rates of R0 resection or positive resection margins between the groups. A total of 2 lesions were missed during open operations, and 4 lesions were missed during laparoscopic operations. These patients all underwent repeat operations during which the residual tumors were resected.

The cost of the procedure was significantly higher for laparoscopic liver resections. Patients in the laparoscopic-surgery group, however, had shorter stays in the recovery ward and in the surgical ward, and were less frequently discharged back to the referring hospital.



* This patient was included in the Modified Intention-to-Treat analysis
$ Modified Intention-to-Treat
# MRI denotes Magnetic Resonance Imaging

FIGURE 1. Patient flowchart of the OSLO-COMET trial.

The total costs were equal between the groups (Table 4). Patients in the laparoscopic-surgery group reported significantly higher HRQoL at the 1- and 4-month follow-up compared to the open-surgery group, and consequently had higher QALYs. Given a $95,000 threshold, laparoscopy was cost-effective (ICER ≈ $11,000) with a likelihood of 67% and an individual EVPI of $655 (Figs. 2 and 3). The uncertainty was caused by 4 complicated and resource-demanding patients. When excluding these 4 patients, the likelihood that laparoscopy was cost-effective increased to 100% (Fig. 2). See the supplementary appendix for further details, http://links.lww.com/SLA/B261.

DISCUSSION

This is the first RCT to compare laparoscopic and open liver resection. We found a significantly lower 30-day complication rate in the laparoscopic-surgery group compared to the open-surgery group.

In 2 propensity scored retrospective studies published in 2016, Cipriani et al[10] and Lewin et al[12] reported reduced complication rates from 40% to 23% and from 22% to 13%, respectively, similar to our findings. In the incomplete Orange II trial, no difference could be found between patients randomly assigned to open or laparoscopic left lateral sectionectomy. This trial was, however, stopped prematurely due to slow patient accrual, and results should be interpreted with caution.

This was a trial of parenchyma-sparing resection of colorectal liver metastases. This technique aims to spare healthy liver parenchyma in order to facilitate repeated liver resections in case of recurrence, and to reduce the risk of posthepatectomy liver failure. Parenchyma sparing techniques have been used since the early 2000s, and their oncologic safety has been validated.[33–37] An optimal result after liver resection is achieved with free resection margins.[38] The rate of free resection margins in this trial was not significantly different between the groups, and was comparable to data from open liver resection.[38] We missed a total of 6 lesions during these 273 operations, 2 during open and 4 during laparoscopic operations. Small liver metastases can be hard to identify, and the liver surgeon needs to have a thorough understanding of the radiology and anatomy, and must be confident in the use of intraoperative ultrasound. In experienced hands, intraoperative ultrasound may be even more sensitive than palpation. Despite this, our experience is that small lesions sometimes are missed, during both parenchyma-sparing resections and hemihepatectomies. Although this obviously is an unfavorable outcome of an operation, patients with colorectal liver metastases undergo close surveillance postoperatively, and in selected cases in which the tumor is very small and difficult to locate, observation can be chosen before immediate repeated liver resection. In most cases of missed lesions, however, it is reasonable to perform an early repeated liver resection.

Liver resections are difficult to compare, because each procedure must be tailored to the patient. When comparing the complexity of the procedures, we found no difference between the groups. The complexity scoring systems for liver surgery, however, do not include a quantification of adhesions after previous operations, and especially not regarding details on previous liver surgery.[22,23] Previous open liver surgery has been shown to increase the complexity of liver resection.[39] In our trial, more patients in the laparoscopic-surgery group had

TABLE 1. Baseline Characteristics of the Intention-to-Treat Population (n = 280)

Characteristic	Open (n = 147)	Laparoscopic (n = 133)
Male sex	87 (54%)	77 (65%)
Age, mean (SD)	66 (10)	67 (8)
Body mass index, mean (SD)	25 (4)	26 (5)
ECOG score		
0	111 (82%)	111 (85%)
1	23 (17%)	18 (14%)
2	2 (1%)	1 (1%)
ASA score		
1	20 (15%)	11 (9%)
2	73 (53%)	59 (48%)
3	44 (32%)	51 (42%)
4		1 (1%)
Number of metastases, mean (SD)	1.6 (1.1)	1.5 (1.1)
Primary tumor rectum	64 (54%)	50 (38%)
Synchronous metastases	91 (62%)	75 (56%)
Chemotherapy before surgery	99 (69%)	77 (60%)
CEA, median (IQR)	4 (1–128)	4 (1–200)
Previous liver resection	13 (9%)	23 (18%)
Clinical Risk Score, median (IQR)	2 (1–2)	2 (1–2)
Basingstoke Predictive Index, median (IQR)	5 (2–12)	5 (3–12)
Modified Iwate complexity score,[23] median (IQR)	6 (2–11)	6 (2–11)
Modified Liver surgery complexity score,[22] median (IQR)	1.36 (1.36–7.36)	1.99 (1.3–6.75)
Pathology weight of resected specimen, median (IQR)	64 (31–204)	83 (38–185)
Tumor location		
Segment 1	4 (2%)	1 (0.5%)
Segment 2	42 (15%)	27 (12%)
Segment 3	32 (12%)	24 (11%)
Segment 4a	28 (10%)	14 (6%)
Segment 4b	19 (7%)	13 (6%)
Segment 5	42 (15%)	29 (13%)
Segment 6	29 (11%)	41 (19%)
Segment 7	44 (16%)	40 (18%)
Segment 8	34 (12%)	33 (15%)

Unless otherwise stated, numbers are n (%).
ASA indicates American Society of Anesthesiologists; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; SD, standard deviation.

TABLE 2. Operative Results (Modified Intention-to-treat, n = 273)

Result	Open (n = 144)	Laparoscopic (n = 129)	*P*
Postoperative complications, Accordion grade 2 or higher	44 (31%)	24 (19%)	0.021
Comprehensive Complication Index,[25] mean (95% CI)	9.3 (6.6–12.0)	5.2 (3.1–7.3)	0.021
Operation time (minutes), median (95% CI)	120 (106–134)	123 (108–138)	0.76
Blood loss (mL), median (95% CI)	200 (126–273)	300 (224–375)	0.062
Unfavorable peroperative incidents	9 (6%)	14 (11%)	0.16
Conversion to laparotomy/hand assisted	–	2 (2%)/7 (5%)	
Postoperative analgesia, PCA/EDA/none (n)	67/76/1	129/0/0	
Postoperative hospital stay (h), median (95% CI)	96 (89–103)	53 (45–61)	<0.001
Transfusion during hospital stay	15 (10%)	13 (10%)	0.91
Postoperative morphine equivalents, median (95% CI)	170 (149–191)	52 (29–74)	<0.001
Stay in recovery ward (h), median (95% CI)	4.27 (3.91–4.63)	3.67 (3.29–4.05)	0.024
Discharge to referring hospital	30 (21%)	15 (11%)	0.042
Intensive care treatment	1 (1%)	3 (2%)	0.24
Readmissions within 30 days	12 (8%)	13 (10%)	0.60
Reoperations within 30 days	6 (4%)	5 (4%)	0.88
Resection margin >1 mm	102 (71%)	92 (71%)	0.83
Resection margin <1 mm but not involved	32 (22%)	29 (22%)	0.94
Involved resection margin	10 (7%)	8 (6%)	0.88
Missed lesion	2 (1%)	4 (3%)	0.32
Changes from initial strategy			
No (parenchyma-sparing resection performed as planned)	137	124	
Converted to ablation only	1	0	
Converted to hemihepatectomy	1	2	
Exploration only	3	2	
Converted to resection + ablation	1	1	
Need for vascular reconstruction	1	0	

Unless otherwise stated, numbers are n (%).
CI indicates confidence interval; EDA, epidural analgesia; PCA, patient-controlled analgesia.

TABLE 3. Postoperative Complications Within 30 Days (Modified Intention-to-treat, n = 273)

Open liver resection (n = 144)		Laparoscopic liver resection (n = 129)		Definitions[24]
Accordion grade 2	**24**	**Accordion grade 2**	**10**	Pharmacological treatment, transfusion, or total parenteral nutrition. (similar to Clavien-Dindo grade II)
Atrial fibrillation	1	Atrial fibrillation	2	
Hemorrhage	3	Hemorrhage	4	
Hypertension	1			
Infected fluid collection	2			
Other	3	Other	1	
Pneumonia	1			
Sepsis	1			
Urinary tract infection	3	Urinary tract infection	2	
Wound hemorrhage	3	Wound hemorrhage	1	
Wound infection (antibiotics)	6			
Accordion grade 3	**10**	**Accordion grade 3**	**10**	Management by an endoscopic procedure, interventional procedure, or reoperation without general anesthesia (similar to Clavien-Dindo grade IIIa)
Bile leak	0	Bile leak	1	
Gastric ulcer	2	Duodenal ulcer	1	
Infected fluid collection	3	Infected fluid collection	4	
Pleural effusion	2	Pleural effusion	1	
Pneumothorax	3	Pneumothorax	3	
Accordion grade 4	**8**	**Accordion grade 4**	**1**	Management in general anesthesia, or single-organ failure (similar to Clavien-Dindo grade IIIb or IVa)
Suspected bowel perforation	1	Intra-abdominal abscess	1	
Cardiac arrest (resuscitated)	1			
Fascia dehiscence	2			
Intra-abdominal hemorrhage	1			
Small bowel obstruction	2			
Stroke	1			
Accordion grade 5	**1**	**Accordion grade 5**	**3**	Management in general anesthesia and single organ failure, or multisystem organ failure (2-organ systems) (similar to Clavien-Dindo grade IV b)
Pulmonary embolism	1	Retroperitoneal hemorrhage	1	
		Small bowel perforation	2	
Accordion grade 6	**1**	**Accordion grade 6**	**0**	Death (similar to Clavien-Dindo grade V)
Sudden death	1			

TABLE 4. The Cost, Health-related Quality of Life and Incremental Cost-effectiveness Ratio of Laparoscopic and Open Surgery

	Open (n = 144)	Laparoscopic (n = 129)	Difference	P^*
Operation				
Personnel, mean (SD), $	2,298 (547)	2,333 (609)	35	0.616
Disposable equipment, mean (SD), $	1,501 (332)	2,156 (930)	655	<0.001
Operation room, mean (SD), $	964 (442)	984 (467)	21	0.709
Sum operation, mean (SD), $	**4,762 (1,158)**	**5,472 (1,926)**	710	**0.000**
Peroperative transfusion, mean (SD), $	37 (140)	45 (175)	8	0.674
Postoperative ward, mean (SD), $	1,278 (1,120)	1,044 (844)	-235	0.048
Surgical ward, mean (SD), $	5,371 (2,855)	3,973 (3,725)	-1,398	0.001
Intensive care unit, mean (SD), $	1,358 (16,296)	2,441 (17,445)	1,083	0.629
Physiotherapy, mean (SD), $	78 (0)	0 (0)	-78	n.e.¶
Complications,† mean (SD), $	262 (1,055)	341 (1,640)	78	0.637
Imaging, mean (SD), $	814 (1,407)	811 (2,942)	-2	0.994
Sum initial hospital stay, mean (SD), $	**13,961 (18,393)**	**14,127 (23,549)**	**167**	**0.968**
Other hospital (direct), mean (SD), $	928 (2,729)	931 (5,247)	3	0.995
Other hospital (direct), mean (SD), $ (n = 15 LLR/ 30 OLR)	4,454 (13,821)	8,005 (4,525)	3,551	0.151
Sum initial treatment, mean (SD), $	**14,888 (20,316)**	**15,058 (27,287)**	**169**	**0.954**
Complications,‡ mean (SD), $	419 (1,603)	735 (3,491)	316	0.280
Complications,‡ mean (SD), $ (n =14 LLR/ n=19 OLR)	3,174 (3,345)	6,771 (8,716)	3,597	0.280
Sum treatment up to 1 month, mean (SD), $	**15,307 (20,354)**	**15,793 (27,475)**	**486**	**0.867**
Treatment 1 to 4 months				
Readmission hospital, mean (SD), $ (n = 45 LLR/ 51 OLR)	1,960 (7,244)	1,824 (4,709)	−135	0.914
Outpatient chemotherapy, mean (SD), $ (n = 42 LLR/ 47 OLR)	1,378 (1,885)	1,176 (1,815)	−203	0.606
Outpatient other, mean (SD), $ (n = 41 LLR/ 47 OLR)	157 (371)	144 (334)	−13	0.863
General practitioner, mean (SD), $ (n = 43 LLR/ 48 OLR)	74 (86)	63 (59)	−12	0.451
Sum treatment 1to 4 months, mean (SD), $	**3,569 (4,621)**	**3,207 (3,074)**	−363	**0.442**
Sum health care costs, mean (SD)	**18,877 (21,959)**	**19,000 (27,565)**	123	**0.967**
HRQoL 1 month, mean (SE)	0.665 (0.01)	0.713 (0.01)	0.047	0.001
HRQoL 4 month, mean (SE)	0.711 (0.01)	0.755 (0.01)	0.044	0.008
QALYs, mean (SE)	0.229 (0.00)	0.243 (0.00)	0.014	0.001
QALYs baseline adjusted, mean (SE)	n.e.¶	n.e.¶	0.011	0.001
Cost-effectiveness analysis				
ICER,§ $	**8,786**			
ICER§ baseline adjusted, $	**11,182**			

*P values estimated using the generalized linear model with a log link function and a gamma distribution.

†Complications during initial hospital stay.

‡Complications after initial hospital stay and up until 1 month after surgery.

§ICER estimated as the cost difference divided by the effect difference.

¶n.e. = not estimated.

HRQoL indicates health related quality of live; ICER, incremental cost-effectiveness ratio; LLR, laparoscopic liver resection; OLR, open liver resection; QALYs, quality adjusted life years; SD, standard deviation; SE, standard error.

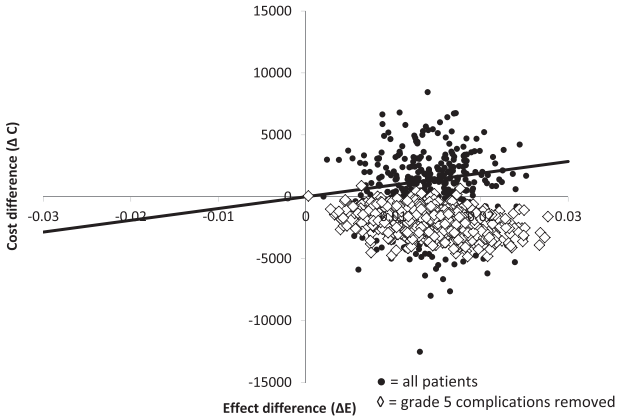


FIGURE 2. The cost effectiveness plane displaying the bootstrapped total cost differences and QALY differences between laparoscopic liver resection and open liver resection, with a willingness to pay threshold $95,000.[29,30]

previously undergone liver surgery. Three of the 4 patients who needed intensive care treatment for grade 5 complications had previously undergone liver surgery.

A theoretical advantage for laparoscopic liver resection is reduced blood loss due to the increased intra-abdominal pressure counteracting venous bleeding from the liver.[40] Previous studies reported blood loss ranging from 210 to 700 mL after open liver resection and from 127 to 450 mL after laparoscopic liver resection.[10,12,13] We found blood loss in the lower range of this spectrum, with no difference between the groups. A limitation of our study is that the protocol did not contain a specific instruction to weigh the surgical swabs and, thus, the blood loss in swabs might have been underestimated. This mostly affected the open-surgery group, as most of the blood loss during laparoscopic surgery is collected in a suction canister.

The single-center design is a limitation of our trial, and may affect the external validity. All patients in South East Norway (population of 3 million) who need liver surgery are treated at our institution, limiting selection bias based on referral patterns. The single-center design allowed for a high degree of standardization of diagnostics, patient selection, operative techniques, and postoperative care. As the technique and learning curve is different for laparoscopic and open liver surgery, and as open liver surgery has been performed for a longer time, there were more surgeons trained for open resections. For both techniques, surgeons were allowed to operate only after completing the learning curve. More than 400 laparoscopic liver resections had been performed in our center before the trial started. Therefore, this must be considered an expert trial, and the results might only be applicable to other high-volume hepatobiliary centers with extensive laparoscopic experience.

A double-blind trial is the criterion standard in trial design, but difficult to perform in a surgical setting.[41] In the present trial, the primary outcome was scored by a blinded assessor, limiting observer bias to the greatest extent possible. The patients and caregivers were not blinded, and this may have introduced treatment bias. A strict, fast-track protocol for perioperative care was developed to compensate this. A postoperative hospital stay of only 96 hours in the open-surgery group indicates a high degree of adhesion to the fast-track protocol.

Another limitation of our trial is that the margin of the statistical significance is small. If we had found only 3 fewer complications in the open group, the primary endpoint would lose its statistical significance. This underlines the need for rigid follow-up of the patients, because some complications were diagnosed and treated after discharge from hospital, and then found at the 30-day follow-up.

The increasing cost of medical treatment is a concern to governments worldwide, and the cost of laparoscopy equipment

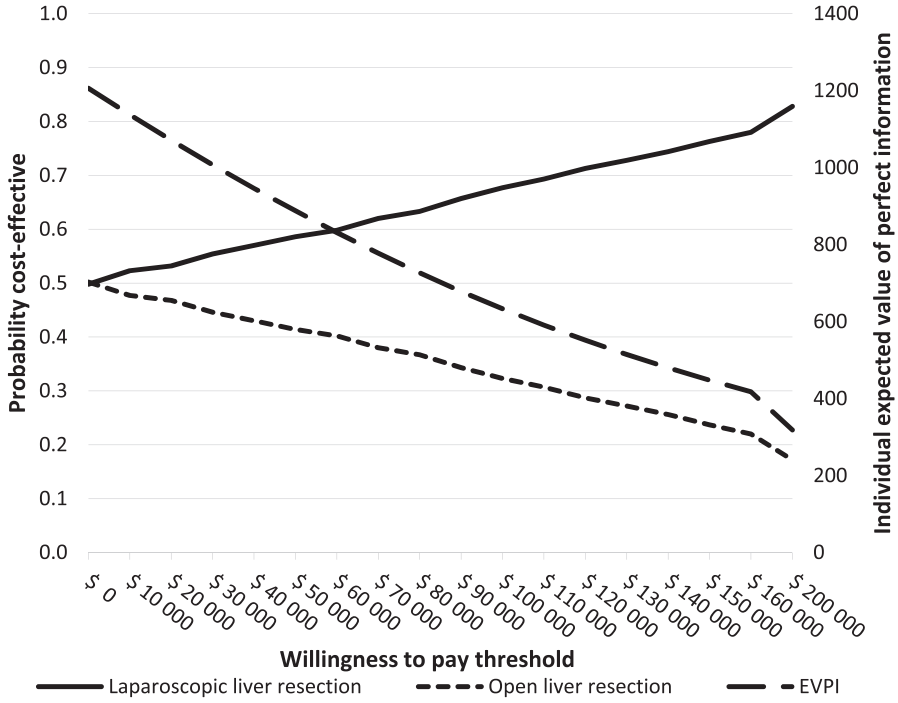


FIGURE 3. The cost-effectiveness acceptability curves and the corresponding individual expected value of perfect information given different willingness to pay thresholds.

may impair the transition from open to laparoscopic techniques. In our trial, we found that laparoscopic liver resection was cost effective, with similar costs but higher QALYs than open liver resection. The uncertainty regarding the cost-effectiveness was driven by the high cost of the intensive care treatment of 4 patients with grade 5 complications, 3 of whom were in the laparoscopic-surgery group. It is impossible to say if this was by chance. In a comparison of 146 laparoscopic and 138 open liver resections, Lewin et al[12] reported 4 Accordion grade 5 complications in the open-surgery group and 2 in the laparoscopic-surgery group. Results from the ongoing Orange II plus trial (NCT01441856) will give more insight into the pattern of complications after laparoscopic and open liver surgery.

CONCLUSIONS

Laparoscopic liver resection significantly reduced the postoperative complication rate, had comparable resection margins, and was cost-effective, compared to open liver resection.

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