



Original Research

Physical recovery after laparoscopic vs. open liver resection – A prospective cohort study

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ABSTRACT

Background: While the number of laparoscopic liver resections (LLRs) is increasing worldwide, its impact on physical recovery remains unclear. We hypothesized that LLR is associated with better physical recovery than open liver resection (OLR). To address this question, we investigated the impact of laparoscopic liver resection compared to open liver resection on physical recovery in a prospective trial.

Methods: Twenty-one patients who underwent LR were included in this study (11 OLR (52.4%) and 10 LLR (47.6%), respectively). Physical recovery was measured by bicycle stress testing at months 1 and 6 after surgery and compared to preoperative stress testing. Standardized performance for bicycle stress testing was calculated based on age, sex, height and weight. Physical recovery was compared between groups as change of performance (%).

Results: Median age was 58 years (Inter Quartile Range (IQR): 44–68), and the main indications for LR were colorectal liver metastases (n = 10; 45%) and hepatocellular carcinoma (n = 6; 27%). The one-month change of performance level was –8% (IQR: -12-1) compared to the preoperative level with no significant difference between open and laparoscopic LR (LLR: -8% (-11 - 1); OLR: -6% (-12 - 4), p = 0.833). Furthermore, 6 months postoperatively, patients in both groups had not reached back their preoperative performance level (LLR: -5.7% (-8.4 - 18.6); OLR -4.8% (-12.6 - 1.9), p = 0.833).

Conclusion: In this study, we report an impaired physical recovery after LR that was not fully restored 6 months after surgery. There was no significant difference between open and laparoscopic LR in terms of bicycle stress testing. Limitations of the study include the limited sample size and differences, albeit non-statistically significant, in the baseline characteristics of the two groups. To rule out a possible role of age or underlying indication for liver resection on physical recovery, future randomized controlled trials need to be performed.

1. Introduction

Relatively low invasive laparoscopic surgery has proven to be equivalent to an open approach regarding outcome in a variety of different types of surgery including colorectal and gastric surgery [1–3]. However, the role of laparoscopic liver surgery still remains unclear, because of a steep learning curve [4,5] and a high technical demand especially within the superior and posterior segments [6–8].

Laparoscopy in liver surgery was primarily used for evaluation of carcinomatosis or peritoneal spread and cyst fenestrations [9,10]. Subsequently the laparoscopic approach was used for malignant lesions and solid tumor resections [11,12]. In 2018, the international consensus conference for laparoscopic liver resection (LLR) in

Southampton recommended that the laparoscopic approach should be considered for selected patients and that these procedures should be performed by an experienced surgical team [13]. Current evidence considering laparoscopic liver resection is largely based on retrospective studies, therefore the evidence in this field is low. Only few prospective trials have been published so far, which is probably attributed to a heterogenous patient population with a large variety of different procedures. However, overall LLR is associated with less postoperative complications and shorter hospitalization [14–16].

Fast physical recovery after liver resection and avoidance of postoperative complications is associated with better clinical outcome, especially in patients with colorectal liver metastasis (CRLM) or cholangiocellular carcinoma, in whom a delay of adjuvant chemotherapy

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initiation has a negative influence on recurrence-free survival [17]. Bicycle stress testing (ergometry) is an established tool to assess preoperative cardiopulmonary fitness and has been used for prediction of postoperative physical recovery [18,19]. We hypothesized that LLR is associated with better physical recovery due to the smaller abdominal wall incision compared to OLR.

The current trial was therefore designed to investigate differences in physical recovery after LLR compared to open liver resection (OLR), in patients requiring liver resection in a prospective controlled pilot study.

2. Material and methods

This study is a prospective single-center trial conducted to test the physical recovery after laparoscopic and open liver resection.

Twenty-one patients between 2016 and 2017 underwent a preoperative ergometry to assess their physical fitness prior to their planned liver resection. Exclusion criteria were: pregnancy, significant traumatic injury within 30 days prior to study enrolment, inability or unwillingness to comply to the protocol or to perform bicycle ergometry.

This study was approved by the local institutional review board (IRB nb 1829/2016) and was performed in accordance with the principles of the Declaration of Helsinki. Informed consent was signed by all patients.

This work has been reported in line with the STROCSS criteria [20].

2.1. Study groups

Bicycle stress testing was performed preoperatively and 1 and 6 months postoperatively. Based on preoperative values (bilirubin, INR, albumine) Child-Pugh score was evaluated [21].

To assess morbidity and mortality (within 30 days), patients were followed up postoperatively and complications were classified according to the Clavien Dindo Classification [22].

2.2. Surgical procedure

Laparoscopic and open liver resection were performed by experienced hepatobiliary surgeons. Open and laparoscopic hepatic resection was performed by using the CUSA (Cavitron ultrasonic surgical aspirator; Valleylab, Boulder, Colorado), Thunderbeat (Olympus Medical Systems, Corporation, Tokyo, Japan) and bipolar forceps. In open LR the incision was an upper midline incision extended to the right at the level of the umbilicus in all patients. Trocar position in the lap LR group varied upon the type of LR and specimen retrieval was performed via a suprapubic Pfannenstiel incision.

2.3. Bicycle stress testing - ergometry

All patients underwent a symptom-limited (acute myocardial infarction, unstable angina, uncontrolled arrhythmia, active endocarditis) [23] bicycle stress testing to the physiological exhaustion on a computer-controlled, electromagnetically braked ergometer (ergometer eBike comfort, GE Medical Systems, Freiburg, Germany) according to the ergometry protocol of the Austrian Society of Cardiology [24]. The testing was done under monitoring of a 12-lead-electrocardiogram (ECG), the workload started with 25 W and increased every 2 min by 25 W and blood pressure was taken at that points of time.

Performance (%) for bicycle stress testing was the primary outcome measure and was calculated on basis of age, sex and body surface corrected set points. Physical recovery was assessed by change of performance (%) at 1 and 6 months postoperatively.

Physicians monitoring the ergometry were not aware of the type of surgery. Outcome assessors and data analysts were also kept blinded to the allocation.

2.4. Study endpoints

The primary endpoint was change in performance after 1 and 6 months postoperatively in comparison to preoperative ergometry. Secondary endpoints included postoperative complications and length of stay. Furthermore, a subgroup analysis investigating patients undergoing minor (≤ 2 liver segments) and major (> 2 liver segments) liver resection was performed [25].

2.5. Statistics

Continuous values were presented as median (IQR) and compared using the Mann-Whitney *U* test. Categorical data were compared using a Fishers-exact test or a chi-square test. A *P*-value < 0.05 was considered statistically significant. For statistical analyses SPSS® version 24.0 software (IBM Inc, Armonk, New York) and for graphic depiction GraphPad Prism, version 8 (GraphPad Prism Software®, La Jolla, CA), was used.

3. Results

3.1. Patient characteristics

All patients completed the full trial. Physiological values like heart rate or blood pressure were stable in all patients and only physiological exhaustion was the reason of ending the examination. No negative effect of testing was reported on intra- and/or postoperative outcome.

At the time of analysis 10 patients were in group LLR (laparoscopic liver resection) and 11 patients in group OLR (open liver resection) (Fig. 1). Patient characteristics are shown in Table 1.

In brief, the median age at surgery was 57.5 years (IQR: 44–68), with no statistical significance between groups (LLR: 49.5 years, 37–66 years; OLR: 64.0, 52–68 years, $p = 0.159$). Overall, indication for partial liver resection were hepatocellular carcinoma (HCC) ($n = 6$, 27%), cholangiocarcinoma ($n = 1$, 5%), colorectal liver metastases (CRLM) ($n = 10$, 45%), Echinococcosis ($n = 2$, 9%), Adenoma ($n = 2$, 9%) and Hemangioma ($n = 1$, 5%). All patients had a preoperative Child-Pugh score A.

3.2. Morbidity and mortality

Six months-overall survival was 100% for all patients. Besides, there was one grade IIIa complication in the LLR group and one grade II complication in the OLR group (Table 2). Mean time of operation ($p = 0.254$) and mean time of hospitalization ($p = 0.159$) was not statistically different between the two cohorts.

3.3. Ergometry

Median overall performance (on basis of age, sex and body surface corrected set point) was 83% (IQR: 75–91) preoperatively and significantly decreased to 76% (67–86) at 1 month after LR. Six months after LR, physical fitness was restored to values measured preoperatively in most patients (82% (67–88) (Fig. 2). When analyzing open and laparoscopic LR, no statistical significant difference could be found between the groups: preoperative (LLR: 85% (79–96) vs. OLR: 80% (74–90), $p = 0.314$), 1 month postoperative (LLR: 80% (67–88) vs. OLR: 72% (60–86), $p = 0.512$) or 6 months postoperative (LLR: 84% (73–85) vs. OLR: 76% (61–92), $p = 0.833$). Analyzing the recovery rate, 1-month postoperative performance levels were -8% ($-12 - 1$) (LLR: -8% ($-11 - 1$) vs. OLR: -6% ($-12 - 4$); $p = 0.833$) compared to the preoperative level. Furthermore, 6 months postoperatively, patients in both groups could not reach their preoperative performance level, LLR: -5.7% ($-8.4 - 18.6$) vs. OLR: -4.8% ($-12.6 - 1.9$), $p = 0.833$).

A subgroup analysis of minor and major liver resections revealed that a significantly lesser drop of performance 1 month postoperatively

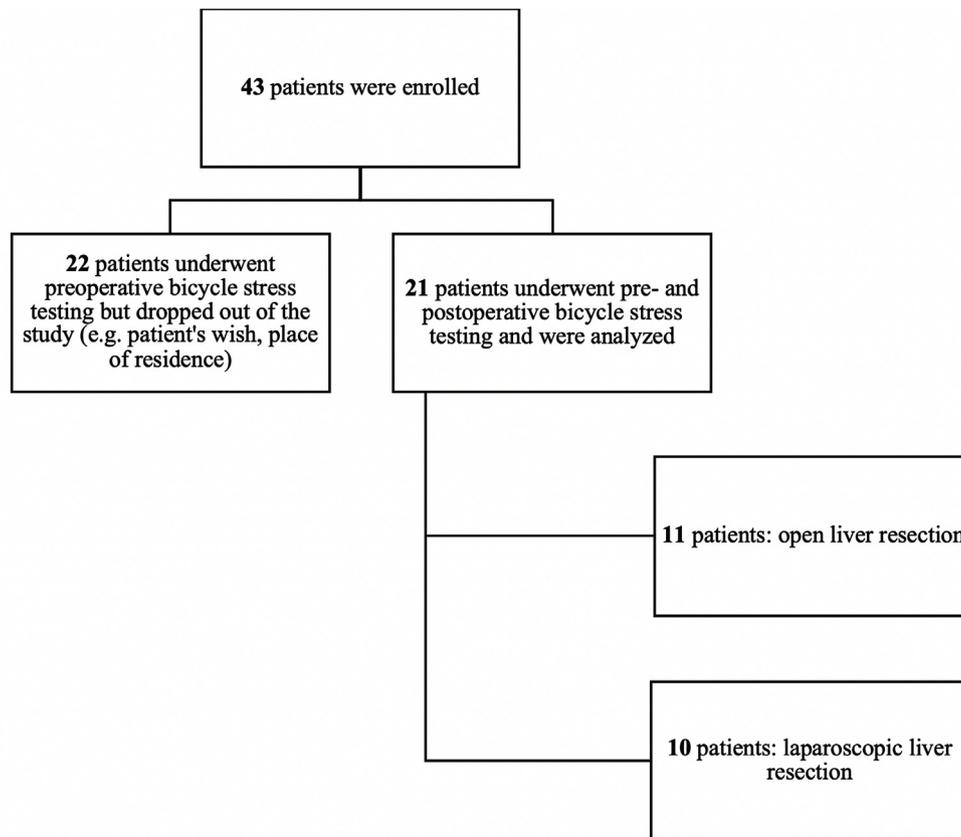


Fig. 1. Flowchart. Patient enrollment

Table 1 Patient characteristics.

	Laparoscopic Resection		Open Resection	
	n	(%)	n	(%)
Number of patients	n = 10		n = 11	
Sex [male]	6	(60)	10	(83)
Age [years], median (IQR)	49.5 (37–66)		64.0 (52–68)	
BMI, median (IQR)	24.3 (22–27)		28.4 (24–32)	
Sports: ≥ 2 h/week	8	(80)	9	(75)
Child-Pugh Score				
Child A	10	(100)	11	(100)
Child B	0	(0)	0	(0)
Child C	0	(0)	0	(0)
Indication:				
HCC	4	(40)	2	(17)
Cholangiocarcinoma	–		1	(8)
CRLM	1	(10)	9	(75)
Echinococcosis	2	(20)	–	
Adenoma	2	(20)	–	
Hemangioma	1	(10)	–	
Type of liver resection:				
minor (≤2 segments)	7	(70)	8	(67)
major (≥3 segments)	3	(30)	4	(33)

BMI. body mass index.
 CRLM. colorectal liver metastases.
 HCC. hepatocellular carcinoma.
 IQR. Interquartile range.

in comparison to preoperative values could be seen in minor liver resections compared to major liver resections (minor LR: -5% (-8 – 5) vs. major LR -12% (-25 to -10); p = 0.001) (Fig. 3).

Table 2 Morbidity and mortality.

	Laparoscopic Resection		Open Resection	
	n	(%)	n	(%)
Number of patients	n = 10		n = 11	
Mortality	0	(0)	0	(0)
Morbidity				
Clavien Dindo Class.				
Clavien Dindo 0	9	(90)	10	(91)
Clavien Dindo II	0		1	(9)
Clavien Dindo IIIa	1	(10)	0	(0)
Clavien Dindo IIIb	0	(0)	0	(0)
Clavien Dindo IVa	0	(0)	0	(0)
Clavien Dindo IVb	0	(0)	0	(0)
Clavien Dindo V	0	(0)	0	(0)
ISGLS				
A	9	(90)	10	(91)
B	1	(10)	1	(9)
C	0	(0)	0	(0)
Hospitalization, median (IQR)	5 (5–7)		9 (5–12)	
Operation time, median (IQR)	155 (64–238)		210 (154–248)	

ISGLS. International Study Group of Liver Surgery: Posthepatectomy liver failure.

4. Discussion

The real benefit of laparoscopic liver resection still remains to be determined. In our prospective study assessing physical recovery after liver resection, a significant decrease of physical fitness could be found shortly after surgery that was more pronounced in patients undergoing major LR. After 6 months, physical fitness had not recovered to preoperative levels. Although no significant difference between LLR and OLR could be observed, there was a trend towards a lesser drop of

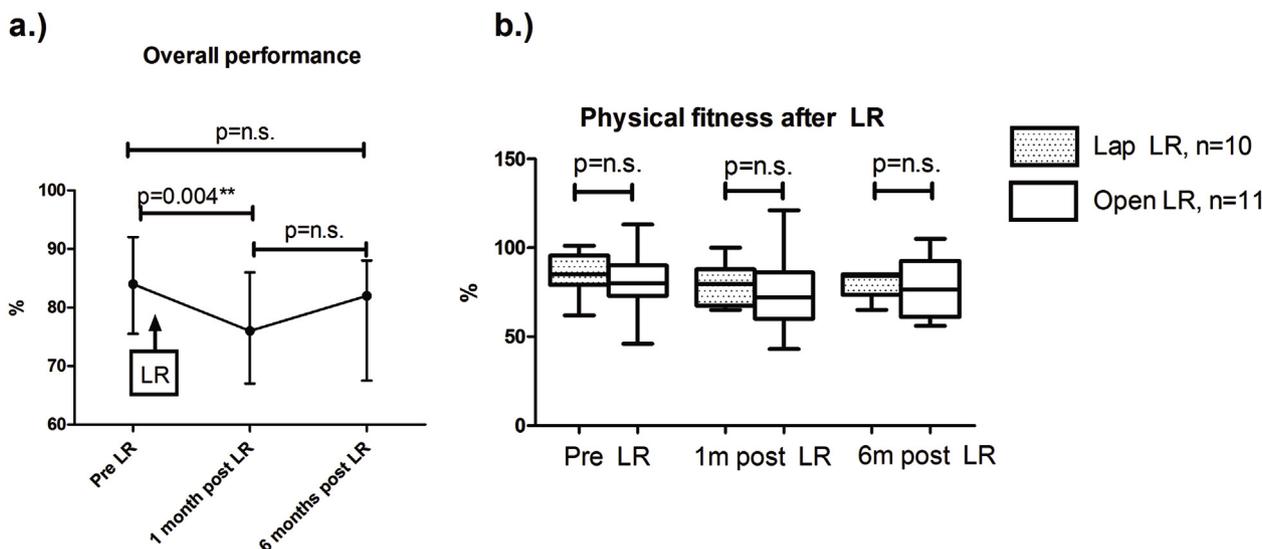


Fig. 2. Performance . a) Overall performance; b) Physical fitness after liver resection

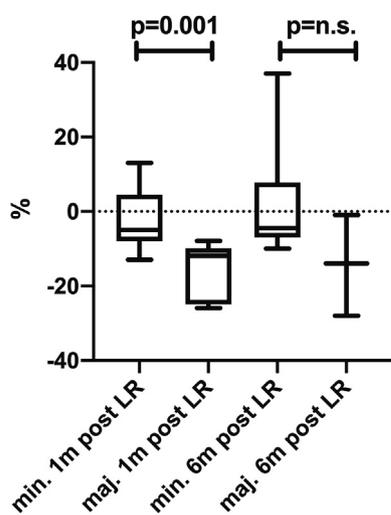


Fig. 3. Subgroup analysis of minor and major liver resections.

performance 1 month postoperatively in major LLR.

The goal of the Orange II trial was to evaluate for the first time functional recovery in patients after either OLR or LLR in an international multicenter randomized controlled trial [14]. Only patients undergoing left lateral sectionectomies were included with the primary endpoint of functional recovery defined as an adequate pain control, restoration of mobility, absence of intravenous fluid administration, ability to eat solid foods as well as normal or decreasing serum bilirubin levels. However, due to low patient recruitment the trial was terminated by the monitoring board. From the included 24 patients in the randomized part of the study, no significant differences in all primary and secondary end points could be reached [26].

In a recently published RCT, Fretland et al. analyzed the impact of LLR in patients with CRLM (Oslo CoMet Trial). There was a significantly lower rate of postoperative complications within 30 days of 19% in the LLR group compared to 31% in OLR group ($p = 0.021$), without difference in the rates of clear resection margins [16]. Furthermore, in a sub-analysis of inflammatory markers within the Oslo CoMet Trial revealed higher levels of pro-inflammatory markers (HMGB-1, cfDNA, IL-6, C reactive protein and macrophage inflammatory protein -1beta) in the OLR group [27].

In a prospective randomized trial, Han et al. investigated the short- and long-term clinical outcome in 88 patients with HCC and found a

significantly shorter hospital stay and lower postoperative morbidity rate in patients undergoing LLR, but could not demonstrate a difference in 1-, 3- or 5-year overall survival rate between LLR and OLR. A Chinese trial (NCT01768741) is still recruiting patients until 12/01/2021 to investigate the total survival time and disease-free survival time in planned 500 patients.

Our prospective evaluation of patients who underwent planned liver resections due to different pathologies showed no differences in regards to morbidity and mortality or length of hospital stay between LLR and OLR, which was not expected and might be explained by the limited sample size.

We used ergometry to define physical fitness, which has shown a high grade of reproducibility and objectivity in different specialties [18,28,29]. Forty-three patients were enrolled and underwent pre-operative bicycle stress testing, however twenty-two patients dropped out of the study, due to place of residence or patients wish. Twenty-one patients underwent pre- and postoperative stress testing and were analyzed. Although there was a wide variety of performance levels among patients (on basis of age, sex and body surface corrected set points), no negative effect of testing was seen on patient's outcome and only physiological exhaustion was the reason to end the examination. Dunne et al. showed in a study of cardiopulmonary exercise testing before liver resection that a lower fitness levels should not be used as a barrier to surgical intervention [30]. However, they did not report on the recovery rate or ergometry results after the planned resection. Fast physical recovery after general surgery is essential to quickly restore patient's quality of life and to allow patients to undergo adjuvant chemotherapy. A previous study showed that a delay of initiation chemotherapy has a negative effect on clinical outcome in patients with CRLM [17].

The limitations to this study are the non-randomized character and the limited number of cases. However, a detailed follow up and a relatively long observation period may outweigh the latter restrictions. There were some, albeit non-statistically significant differences in the baseline characteristics of the two groups that could, theoretically, have an impact on physical recovery. We tried to minimize confounders by primarily analyzing the intra-individual change in post-operative fitness. However, to rule out a possible role of age or underlying indication for liver resection on physical fitness after open or laparoscopic liver resection future randomized controlled trials need to be performed.

5. Conclusion

Herein we could show for the first time that physical recovery after laparoscopic vs. open surgery did not demonstrate significantly different results. Patients with major laparoscopic liver resections tended to have better physical performance 1 month after LLR, and therefore faster recovery, which could be an advantage for patients with metastatic disease awaiting postoperative chemotherapy.

Ethical approval

This study was approved by the institutional review board of the Medical University of Vienna (IRB number 1829/2016) and was performed in accordance with the principles of the Declaration of Helsinki.

Sources of funding

No funding was received.

Author contribution

S. Kampf: patient recruitment, data acquisition, analysis, interpretation of data, drafting the article.

M. Sponder: Ergometry testing, data acquisition, analysis, interpretation of data.

J. Bergler-Klein: Ergometry testing, data acquisition, analysis, interpretation of data.

C. Sandurkov: acquisition of data.

F. Fitschek: acquisition of data.

M. Bodingbauer: revising manuscript.

S. Stremitzer: conception and design of the study, revising the manuscript.

K. Kaczirek: conception and design of the study, revising the manuscript.

C. Schwarz: conception and design of the study, revising the manuscript.

Trial registry number

1. Name of the registry: [Clinicaltrials.gov](https://clinicaltrials.gov)
2. Unique Identifying number or registration ID: NCT04067349
3. Hyperlink to the registration (must be publicly accessible): <https://clinicaltrials.gov/ct2/results?cond=&term=NCT04067349&cntry=&state=&city=&dist=>

Guarantor

K.Kaczirek.

C. Schwarz.

S. Kampf.

Data statement

Due to the sensitive nature of the parameters collected in this study, participants were assured raw data would remain confidential and would not be shared.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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CRedit authorship contribution statement

S. Kampf: Conceptualization, Validation, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **M. Sponder:** Validation, Investigation, Resources, Writing - review & editing, Project administration. **J. Bergler-Klein:** Investigation, Resources, Writing - review & editing, Supervision. **C. Sandurkov:** Investigation, Writing - review & editing. **F. Fitschek:** Investigation, Writing - review & editing. **M. Bodingbauer:** Investigation, Writing - review & editing. **S. Stremitzer:** Methodology, Validation, Writing - review & editing. **K. Kaczirek:** Conceptualization, Methodology, Validation, Formal analysis, Writing - review & editing, Supervision. **C. Schwarz:** Conceptualization, Methodology, Validation, Formal analysis, Writing - review & editing.

Declaration of competing interest

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijssu.2019.10.040>.

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