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ORIGINAL ARTICLE

International multicenter propensity score matched study on laparoscopic versus open left lateral sectionectomy

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Abstract

Background: Despite a lack of high-level evidence, current guidelines recommend laparoscopic left lateral sectionectomy (LLLS) as the routine approach over open LLS (OLLS). Randomized studies and propensity score matched studies on LLLS vs OLLS for all indications, including malignancy, are lacking.

Methods: This international multicenter propensity score matched retrospective cohort study included consecutive patients undergoing LLLS or OLLS in six centers from three European countries (January 2000–December 2016). Propensity scores were calculated based on nine preoperative variables and LLLS and OLLS were matched in a 1:1 ratio. Short-term operative outcomes were compared using paired tests.

Results: A total of 560 patients were included. Out of 200 LLLS, 139 could be matched to 139 OLLS. After matching, baseline characteristics were well balanced. LLLS was associated with shorter operative time (144 (110–200) vs 199 (138–283) minutes, $P < 0.001$), less blood loss (100 (50–300) vs 350 (100–750) mL, $P = 0.005$) and a 3-day shorter postoperative hospital stay (4 (3–7) vs 7 (5–9) days, $P < 0.001$).

Conclusion: This international multicenter propensity score matched study confirms the superiority of LLLS over OLLS based on shorter postoperative hospital stay, operative time, and less blood loss thus validating current guideline advice.

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Introduction

Left lateral sectionectomy (LLS) includes resection of Couinaud's[1] liver segments two and three and is considered a minor liver resection.[2] The easy accessibility of these segments, the thin liver parenchyma along the falciform ligament and the absence of any hilar dissection make LLS the ideal procedure for laparoscopy. Multiple authors have published their experiences with overall favorable results compared to open LLS (OLLS),[3–22] leading to the recent guideline statement that LLLS should be a standard procedure for the LLS in all centers.[23] This advice, however, is not based on large comparative studies. Completed randomized studies comparing LLS vs OLLS for all indications, including malignancy, are not available. One randomized trial from Asia

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focused on LLS for intrahepatic stones[24] and the European multicenter randomized ORANGE II trial that did include malignancy was terminated early because of poor accrual.[25]

Since it is highly unlikely that a randomized controlled trial on LLLS for all indications will ever be performed, a multicenter propensity score matched (PSM) study might provide the 'second-best' highest achievable evidence. This propensity score can subsequently be used to match patient cohorts to counter confounding bias, thereby producing estimates that may outperform multivariable regression analyses under specific circumstances.[26,27] Nonetheless, like regression analyses, a propensity score may also not account for all prognostic factors.[28]

A PSM analysis comparing LLLS with OLLS has not been performed yet. The aim of this multicenter study was to provide a PSM comparison of LLLS with OLLS in a large multicenter cohort.

Methods

The present study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[29] It reports on the outcomes of elective LLLS and OLLS performed in six centers in three European countries. All included centers perform more than 60 liver resections annually and have performed more than 50 laparoscopic liver resections. Data were collected retrospectively and registered anonymously, hence there was no additional burden to the patients and the local medical ethics committee of the Amsterdam UMC, location Academic Medical Center, waived the need for written informed consent.

Patients and design

All six participating centers (four from the Netherlands, one from Belgium and one from the United Kingdom) reviewed their surgical databases containing all liver resections performed in the period 2000–2016. All consecutive patients who underwent LLLS or OLLS were included. Patients were excluded when major liver surgery (i.e. resection of 3 or more anatomical segments), emergency surgery or procurement for living donor liver transplantation was performed. Individual patient data were merged after checking all data definitions.

Liver lesions were diagnosed using abdominal computed tomography (CT) scans with triphasic contrast enhancement and/or liver-specific double-contrast magnetic resonance imaging (MRI) in all centers. The results were discussed in a multidisciplinary team meeting with hepato-pancreato-biliary surgeons, radiologists, gastroenterologists, hepatologists, medical oncologists and pathologists attending. A decision regarding the surgical approach was made independently of the indication for surgery.

While contradictive to the adopted guideline statements, OLLS remained to be practiced until 2016 in four centers. The most common reason to opt for OLLS instead of LLLS was the limited availability of experience with laparoscopic liver surgery.

Data collection

Data were collected from electronic patient files that contained daily notes, operative reports, laboratory results, imaging reports, pathology reports, and discharge and follow-up letters in all centers and data were registered anonymously. Baseline characteristics included age, sex, American Society of Anesthesiologists (ASA) classification, preoperative chemotherapy, cirrhosis, previous abdominal surgery (defined as all types of abdominal surgery except hernia surgery), previous liver surgery, indication for surgery (benign/malignant), number of lesions in left lateral segments, size of largest lesion in left lateral segments, distribution of lesions (i.e. uni- or bilobar), additional liver resection, and simultaneous colorectal resection.

The primary study outcome was length of postoperative hospital stay in days. Secondary outcomes included duration of surgery in minutes (measured from the moment of incision until surgical closing), estimated intraoperative blood loss in mL (the amount of blood lost through suction and in compresses), blood transfusion, conversion, intraoperative incidents (Oslo Classification),[30] overall and severe postoperative 90-day morbidity (graded with the Accordion Classification,[31] grade three or higher was considered a severe complication), reoperation and readmission within 90 days (liver and surgery related), resection margins (R0 = tumor free, R1 = microscopic tumor involvement), complication related 90-day or in hospital mortality and incisional herniation at 1-year follow-up.

Operative technique

Both LLLS and OLLS are well known and standardized resections that have been described previously.[6,32] Although uniformity of resection techniques and devices between the centers could not be guaranteed because of the study design, differences were estimated to be minimal.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics for Windows version 24.0 (SPSS Inc., Chicago, IL, USA). Continuous, not normally distributed variables were reported as median with interquartile range (IQR). If variables were normally distributed, these were reported as mean with standard deviation (SD). Mann–Whitney *U* tests were used to compare continuous, not normally distributed variables between groups. Independent samples T-test were applied to compare normally distributed, continuous variables. Categorical variables were reported as proportions and compared between groups using chi-square or Fisher's exact tests.

Propensity score matching

Propensity score matching (PSM) was applied to minimize confounding by indication and is reported according to the recommendations by Lonjon *et al.*[33] PSM was performed using RStudio for Windows version 3.3.3 (RStudio Inc., Boston, MA, USA).

Propensity scores were calculated using a logistic regression model. All available variables were discussed among authors and consensus was reached on which variables to include in the model. The final model included the following variables: age, indication (benign/malignant), preoperative chemotherapy, cirrhosis, previous abdominal surgery, previous liver surgery, size of the primary lesion in the left lateral segments, simultaneous colorectal resection and additional liver resection. Based on this propensity score, LLLS were matched to their nearest neighbor OLLS in a 1:1 ratio with a standard caliper width of 0.2. LLLS were analyzed according to intention-to-treat principle, hence conversions to open surgery were included in the laparoscopic group. The standardized mean differences (SMD) were calculated for each baseline variable before and after matching in order to assess the balance. An SMD between −0.1 or 0.1 and 0 was considered an indicator of optimal balance. After matching, a Wilcoxon signed rank test was used to compare continuous, not normally distributed variables between groups. For normally distributed variables a paired T-test was used, as appropriate. Categorical variables were reported as proportions and were compared between groups using a McNemar test or Wilcoxon signed rank test. A two-tailed *P*-value of <0.05 was considered statistically significant.

Sensitivity analysis

A sensitivity analysis was performed in the matched cohort, excluding all patients who were treated before 2010 or underwent a simultaneous colorectal resection. The remaining patients in both groups were compared using a randomized block design for continuous variables and conditional logistic regression for categorical variables.

Results

A total of 560 patients met the eligibility criteria, of whom 200 underwent LLLS and 360 OLLS. OLLS was performed in three centers from the beginning of the inclusion period (January 2000), whereas LLLS was adopted by two centers in 2004 and used by five centers in 2016. The median annual volume of LLLS per center was 5 (4–6). Fig. 1 shows the overall use of LLLS and OLLS over time. Of all included patients, 139 LLLS could eventually be matched in a 1:1 ratio to OLLS controls.

Baseline characteristics

Baseline characteristics before and after matching are displayed in Table 1. Patients with previous abdominal surgery, previous liver surgery, malignant disease, bilobar disease distribution, additional liver resections and additional colorectal resection were all more frequently observed in the OLLS group, clearly suggesting the presence of selection bias. Despite these clear imbalances prior to matching, all matching variables were well balanced thereafter. Nearly all other variables were well balanced after matching as well, with the most noticeable remaining imbalance being the distribution of males among the laparoscopic and open groups (59 (42%) vs 73 (53%), SMD −0.20). Bilobar disease distribution was found more frequently in the OLLS group prior to matching (40 (20%) vs 122 (34%), SMD −0.35). This imbalance also remained after matching, though the absolute difference was much less (26 (19%) vs 33 (24%), SMD −0.13).

Operative outcomes

Table 2 displays operative outcomes before and after matching. LLLS was associated with a shorter operating time (144 (110–200) vs 199 (138–283) minutes, $P < 0.001$), less intraoperative blood loss (100 (50–300) vs 350 (100–750) mL, $P < 0.001$) and a 3-day shorter postoperative hospital stay (4 (3–6) vs 7 (4–9) days, $P < 0.001$). Prior to matching, more radical resections for malignant disease were observed in the LLLS group (137 (96%) vs 244 (87%), $P = 0.010$), however this significance disappeared after matching (93 (96%) vs 86 (90%), $P = 0.564$). Conversion to laparotomy occurred in 16 (8%) patients. Reasons for conversion were difficult to reach lesions/slow progression (n = 8), bleeding (n = 4), adhesions (n = 3) and bowel perforation (n = 1). Severe complications occurred in 38 (13%) patients. Most frequent complications were abdominal

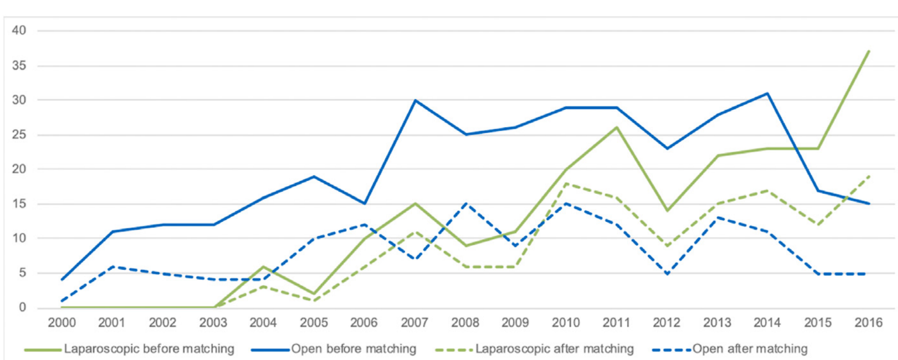

Figure 1 The total number of laparoscopic and open left lateral sectionectomies from 2000 to 2016 and the matched number of laparoscopic and open left lateral sectionectomies from 2000 to 2016

Table 1 Baseline characteristics of patients undergoing laparoscopic and open left lateral sectionectomy, before and after propensity score matching

	LLLS Before PSM (n = 200)	OLLS Before PSM (n = 360)	SMD Before PSM	LLLS After PSM (n = 139)	OLLS After PSM (n = 139)	SMD After PSM
Patient characteristics						
Age, years, median (IQR)	62 (50–71)	61 (50–68)	0.07	61 (48–70)	61 (48–68)	0.01
Sex, male	89 (45)	191 (53)	−0.17	59 (42)	73 (53)	−0.20
ASA-classification						
Low (ASA 1–2)	158 (79)	275 (76)	0.03	109 (78)	106 (76)	0
High (ASA 3–4)	25 (13)	50 (14)	−0.03	19 (14)	18 (13)	0
Preoperative chemotherapy	50 (25)	81 (23)	0.08	29 (21)	33 (24)	−0.07
Cirrhosis	13 (7)	10 (3)	0.16	6 (4)	8 (6)	−0.07
Previous abdominal surgery	66 (33)	257 (71)	−0.81	60 (43)	64 (46)	−0.06
Previous liver surgery	5 (3)	32 (9)	−0.45	4 (3)	5 (4)	−0.04
Tumor characteristics						
Malignant indication	142 (71)	280 (78)	−0.25	97 (70)	96 (69)	0.02
Number of lesions in left lateral segments						
0	1 (1)	15 (4)	−0.52	0	1 (1)	−0.08
1	170 (85)	280 (78)	0.20	118 (85)	117 (84)	0.02
2	17 (9)	49 (14)	−0.18	11 (8)	16 (12)	−0.13
3	10 (5)	7 (2)	0.14	8 (6)	2 (1)	0.19
≥4	2 (1)	8 (2)	−0.12	2 (1)	3 (2)	−0.07
Largest lesion in left lateral segments, mm, median (IQR)	35 (20–60)	35 (22–60)	−0.03	35 (20–70)	42 (23–65)	−0.04
Distribution of lesions						
Unilobar	160 (80)	237 (66)	0.35	113 (81)	106 (76)	0.13
Bilobar	40 (20)	122 (34)	−0.35	26 (19)	33 (24)	−0.13
Procedure characteristics						
Additional liver resection	28 (14)	122 (34)	−0.65	25 (18)	22 (16)	0.06
Additional colorectal resection	7 (4)	26 (7)	−0.22	6 (4)	6 (4)	0

Values in parentheses are percentages, unless indicated otherwise. Percentages may not add up to 100 due to rounding and/or missing data. LLLS = laparoscopic left lateral sectionectomy, OLLS = open left lateral sectionectomy, PSM = propensity score matching, SMD = standardized mean difference, IQR = interquartile range, ASA = American Society of Anesthesiology.

fluid collections requiring drainage (n = 14), bleeding requiring reoperation (n = 4), respiratory insufficiency (n = 3) and sepsis (n = 3). A total of 6 (1%) patients died within 90 days postoperatively. Causes of death were sepsis (n = 4), liver failure (n = 1), and lung embolism (n = 1). One-year incisional hernia rate was 2 (1%) and 7 (5%) among the groups, respectively ($P = 0.125$).

Sensitivity analysis

After excluding patients who underwent surgery before 2010 or simultaneous colorectal surgery, 101 patients remained in the LLLS group and 63 in the OLLS group. The main imbalances in baseline characteristics include the presence of more males (41 (41%) vs 36 (56%), SMD −0.33), more patients with preoperative chemotherapy (18 (18%) vs 20 (32%), SMD −0.33) and older patients (59 (47–69) vs 63 (54–70), SMD −0.31) in the OLLS group. Operative time (129 (103–201) vs 170 (110–276) minutes, $P = 0.002$) and postoperative hospital stay (4 (3–6) vs 6 (4–8) days, $P = 0.004$) remained significantly shorter in the LLLS group. The reduction in blood loss in the LLLS group was no longer significant (100 (50–300) vs 250 (100–647) mL, $P = 0.097$) (see Supplementary Tables 1, 2).

Discussion

In this international multicenter study using PSM, LLLS was associated with significantly reduced operative time, less intraoperative blood loss and a 3-day shorter postoperative hospital stay as compared with OLLS. Postoperative morbidity and mortality rates were comparable. A sensitivity analysis that

Table 2 Operative outcomes of patients undergoing laparoscopic and open left lateral sectionectomy prior and after propensity score matching

	LLLS Before PSM (n = 200)	OLLS Before PSM (n = 360)	*P* value	LLLS After PSM (n = 139)	OLLS After PSM (n = 139)	*P* value
Operating time, min, median (IQR)	140 (101–200)	205 (152–323)	<0.001	144 (110–200)	199 (138–283)	<0.001
Blood loss, mL, median (IQR)	100 (50–300)	400 (150–800)	<0.001	100 (50–300)	350 (100–750)	<0.001
Transfusion requirement	5 (3)	18 (5)	0.124	4 (3)	6 (4)	0.754
Conversion	16 (8)	n/a	n/a	14 (10)	n/a	n/a
Intraoperative incidents, Oslo classification	10 (5)	26 (7)	0.304	7 (5)	10 (7)	0.629
Postoperative complications, Accordion classification						
Overall	42 (21)	85 (24)	0.361	28 (20)	28 (20)	1
Severe	12 (6)	26 (7)	0.586	8 (6)	5 (4)	0.581
Reoperation	5 (3)	6 (2)	0.534	4 (3)	1 (1)	0.375
Readmission	4 (2)	12 (3)	0.364	1 (1)	5 (4)	0.219
Postoperative hospital stay, days, median (IQR)	4 (3–6)	7 (5–9)	<0.001	4 (3–6)	7 (5–9)	<0.001
R0 resection margin for malignant disease	137/142 (96)	244/280 (87)	0.010	93/97 (96)	86/96 (90)	0.564
Pathology			<0.001			0.550
Colorectal liver metastases	77 (39)	222 (62)		51 (37)	72 (52)	
Hepatocellular carcinoma	31 (16)	34 (9)		21 (15)	16 (12)	
Cholangiocarcinoma	4 (2)	8 (2)		4 (3)	3 (2)	
Adenoma	17 (9)	16 (4)		14 (10)	10 (7)	
Cyst	13 (7)	9 (3)		7 (5)	6 (4)	
Focal nodular hyperplasia	13 (7)	10 (3)		12 (9)	8 (6)	
Hemangioma	4 (2)	21 (6)		3 (2)	15 (11)	
Normal liver tissue	1 (1)	3 (1)		0	0	
Other malignant	25 (13)	16 (4)		18 (13)	6 (4)	
Other benign	10 (5)	20 (6)		6 (4)	3 (2)	
In hospital or 90-day mortality	0	7 (2)	0.054	0	1 (1)	>0.999
Incisional hernia within 1-year follow-up	2 (1)	12 (3)	0.073	2 (1)	7 (5)	0.125

Values in parentheses are percentages, unless indicated otherwise. Percentages may not add up to 100 due to rounding and/or missing data. LLLS = laparoscopic left lateral sectionectomy, OLLS = open left lateral sectionectomy, PSM = propensity score matching, IQR = interquartile range, ASA = American Society of Anesthesiology.

excluded patients who were operated before 2010 and who received simultaneous colorectal resection lead to similar results, although the amount of blood loss was comparable between groups. These results provide the required comparative evidence on LLLS vs OLLS which is currently lacking in the guidelines on laparoscopic liver surgery.

The present study is the first to use PSM to compare LLLS and OLLS. PSM minimizes the influence of confounding by indication, which was clearly present prior to matching in the current study as shown by the baseline differences between the groups. Several previous studies have reported benefits of LLLS in terms of operative time, blood loss, postoperative hospital stay or morbidity. However, none of these studies could deal with selection bias properly because they were designed as (meta-analyses of) observational studies.[3–22] Keeping in mind that an additional RCT comparing LLLS with OLLS for benign or malignant disease is highly unlikely to be performed, a comparative analysis using PSM is probably the best way to minimize bias by indication. The use of PSM in the current study resulted in two well balanced groups that made for a fair comparison of the two techniques.

Despite the thorough matching process, it is still possible that some variables potentially determining suitability and likelihood for either approach were not accounted for. One important determinant is technical difficulty. Adequate definition of surgical difficulty for liver resection is challenging. Some difficulty scores have recently been developed and validated.[34,35] The individual variables that are used in these scores were all included in this study, except for the proximity of the tumor to major vessels and the approach to the previous liver resection. The retrospective retrieval of data regarding the proximity of the tumor to major vessels was deemed logistically impossible and its relevance to LLLS is questionable as the resection itself is inherently distant from major vessels. The approach to the previous liver resection is probably more important, as this could influence the formation of adhesions.[36,37] This possible imbalance may have increased the need for adhesiolysis in the open group, which might be a partial explanation why the operative time and blood loss were increased in the open group, even though less than 20% of patients in both groups had undergone previous liver surgery at all.

The randomized ORANGE II trial was set to randomize 110 patients to LLLS or OLLS for all accepted indications based on the hypothesis that LLLS would reduce the time to functional recovery with two days. Unfortunately, the trial was stopped prematurely for slow accrual due to lack of equipoise, having randomized 11 patients in the open arm and 13 patients in the laparoscopic arm. The trial could not determine any significant outcome differences between arms.[25] The intended sample size, although being based on time to functional recovery instead of hospital length of stay, was surpassed by the current cohort. The current multicenter cohort included 278 patients and found that LLLS is associated with a reduction in postoperative hospital stay of three days. Other randomized controlled trials that compare open with laparoscopic liver surgery have been completed; the OSLO-COMET trial and the LapOpHuva trial.[38,39] The Norwegian trial included patients with colorectal cancer metastases receiving parenchyma-preserving liver surgery (a resection of less than 3 segments) in all liver segments. From these patients, 74 (27%) received open resection of segments 2 or 3 and 51 (23%) received laparoscopic resection of segments 2 or 3. The Spanish trial included patients with colorectal cancer metastases receiving a wider variety of liver resections, of which 22 (23%) were open bisegmentectomies and 24 (25%) were laparoscopic bisegmentectomies. In line with the current study, both trials report superior results of laparoscopic liver surgery compared to open liver surgery in terms of hospital stay. However, no differences between arms could be found in terms of operative time and blood loss. In lack of subgroup analyses, the fact that not all included patients received LLS may be a valid explanation for the outcome differences with the current cohort study.

The absolute reduction in operative time with LLLS as compared to OLLS was 55 min, and similarly, a 250 mL reduction in blood loss. Although the clinical relevance of such short-term outcomes may be questioned, it is uncommon for a laparoscopic procedure to have a shorter operative time than its open equivalent. One of the explored long-term outcomes was the one-year incisional hernia rate, with an absolute difference of 4% in favor of LLLS ($P = 0.125$). Lack of statistical significance for this outcome might be explained by the limited follow-up duration and insufficient power for this specific endpoint in this retrospective study design. A larger group of patients, a longer follow-up period and hernia-centered patient examination might have shown differences in incisional herniation between groups. Unlike the current study, a meta-analysis of 12 studies comparing laparoscopic and open colorectal surgery did reveal a significant reduction in incisional hernia rate with laparoscopy (RR 0.58 (0.47–0.72)).[40] A few percent reduction of incisional hernia may indeed be clinically relevant, given the burden to the patient and costs related to incisional hernia repair.[41,42]

The findings of this study should be interpreted in light of some shortcomings. First, PSM may decrease the influence of selection bias but does not correct for unmeasured covariates. Regardless of the comprehensiveness of the matching model, a higher percentage of males and more bilobar disease were observed in the open group. Second, corrections for center effects were not possible. Centers do inherently differ from another, for instance with regards to surgeon proficiency and hospital performance. Moreover, the process of introducing laparoscopic liver surgery was also handled differently between centers, introducing a learning curve effect. Despite their confounding influence, these center differences are part of everyday medical practice and may support external validity.

In conclusion, this study found clear benefits for LLLS in comparison with OLLS. Operative time, intraoperative blood loss and postoperative hospital stay are significantly reduced. As surgeons go through their laparoscopic learning curves the outcomes could further improve.

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Conflict of interest

None to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2020.09.006.