Laparoscopic versus Open Liver Resection in the PosteroSuperior Segments

A sub-group analysis from the OSLO-COMET Randomized Controlled Trial

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Abstract

Background: Laparoscopic liver resection of tumors located in the posterosuperior segments is technically challenging. This study aimed to compare the perioperative outcomes for laparoscopic and open resection of colorectal liver metastases located in the posterosuperior segments.

Methods: This was a subgroup analysis of the OSLO-COMET randomized controlled trial. In OSLO-COMET, 280 patients were randomly assigned to open or laparoscopic parenchyma-sparing liver resections of colorectal liver metastases. Patients with tumors in the posterosuperior segments were identified for the current study. Perioperative and health related quality of life (HRQoL) at the 1- and 4-months after surgery outcomes were compared. The Accordion classification and the Comprehensive Complication Index were used for grading of postoperative complications.

Results: We identified a total of 136 patients included in OSLO-COMET that had lesions in the posterosuperior segments, 62 patients in the laparoscopic group and 74 in the open group. A total of 257 lesions were removed. The postoperative complication rate (Accordion grade 2 or higher) was 26% in the laparoscopic group and 31% in the open group ($P = 0.57$). The blood loss was significantly lower in the open group (500 vs. 250 ml, $P=0.006$), but the perioperative transfusion rate was similar (8 vs. 9, $P=0.52$). The operative time was similar in the two groups, 134 vs. 143 min, while postoperative hospital stay was 2 days in the laparoscopic and 4 days in the open group ($P < 0.001$). HRQoL was significantly better after laparoscopic than open liver resection at 1-month after surgery.

Conclusion: In patients undergoing laparoscopic or open liver resection of colorectal liver metastases in the posterosuperior segments, laparoscopic surgery was associated with a significantly shorter hospital stay and comparable perioperative outcomes Our analysis supports the further development of these technically challenging liver resections.

Introduction

Liver resection remains the only potentially curative treatment for colorectal liver metastases(1, 2). Following technical improvements and accumulated experience, an increasing percentage of liver resection is now performed with a laparoscopic approach (3-5). However, the liver is a complex organ, and the difficulty of laparoscopic liver resection depends on a series of factors, including tumor location.

The classical ‘‘laparoscopic liver segments’’ are the anterolateral segments (2, 3, 4b, 5 and 6), and solitary lesions of less than 5 cm located in these segments were recommended for laparoscopy already in the first Louisville consensus report from 2008(6). In contrast, laparoscopic resection in the posterosuperior segments has always been considered technically challenging, mainly because of limited working space and visualization. This makes it more challenging to evaluate the resection margins and to control bleeding. (3, 7, 8).

Following technical improvements and accumulation of laparoscopic skills, surgeons have increasingly considered lesions in the posterosuperior segments for laparoscopic surgery (9-11). No randomized controlled trial has compared laparoscopic and open resection for liver tumors located in the posterosuperior segments, but matched comparisons have indicated that the usual advantages of laparoscopic surgery could be expected also for these resections (10, 12). OSLO-COMET was the first randomized controlled trial to compare laparoscopic and open liver resection and included tumors in all liver segments. In this subgroup analysis of OSLO-COMET we report surgical outcomes for laparoscopic and open resection of colorectal metastases in the posterosuperior liver segments (13, 14).

Patients and Methods

OSLO-COMET was a single center, open label, randomized controlled trial that was performed at Oslo University Hospital between February 2012 and February 2016. A total of 280 patients were randomly assigned to laparoscopic (n=127) or open (n=143) parenchyma-sparing liver resection. Parenchyma sparing was defined as resections of less than three consecutive liver segments, but multiple resections during the same surgery were allowed. The trial protocol has been published previously (13) 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. The primary endpoint was postoperative complication rate (13, 14). Oslo University Hospital is the tertiary referral center for hepato-pancreato-biliary surgery for South-Eastern Norway, with a population of 3 million.

For the current study, patients with at least one lesion in the posterosuperior segments (1, 4a, 7, and 8) were identified, and data were collected from the prospective trial database.

Surgical technique and perioperative management have been described previously (13, 14). Modified versions of the Liver Surgery Complexity Score (15) and the Iwate scoring system(16) were used to assess the complexity of the procedures (14).

The Accordion classification (17) and the Comprehensive Complication Index (CCI) (18) were used for grading and definition of postoperative complications. Grade 1 complications (Accordion and Clavien-Dindo) are difficult to register consistently, and often have minimal impact on the postoperative course. We therefore registered only complications grade 2 or higher, and the calculation of CCI scores did not include grade 1 complications.

All resected specimens were evaluated by a pathologist and tissue was collected in a biobank. Resection margins were measured macroscopically and microscopically and the presence of tumor cells within 1mm from the resection margin was defined as an R1 resection.

In this sub-group analysis Health-related quality of life (HRQoL) was analyzed at 1- and 4-months follow-up using the 36-item Medical Outcomes Study Short Form (SF-36, Norwegian version 2.0) as it is described in the OSLO-COMET trial (14).

Outcomes were compared between open and laparoscopic groups. Continuous data were analyzed with a median regression, which provided a 95% CI for the difference between the medians of the groups and a *P*-value for the null hypothesis of equal medians. When the median was not relevant measure to compare the groups, a two-sample t-test was used. Categorical variables were compared using x^2 test or Fisher's exact test, when applicable. Statistical significance was set at $P<.05$. Stata statistical software: Version 15 (StataCorp.2015, College Station, TX: StataCorp LP) and SPSS software: Version 25(IBM SPSS Statistics for Windows, Amonk, NY, USA: IBM Corp.2013), were used for statistical analysis.

Results

We identified 136 patients with at least one lesion in the posterosuperior liver segments. Of the 136 patients included, 62 were assigned to laparoscopic and 74 to open liver resection. The baseline characteristics, including the complexity of procedures, were similar in the two groups (Table 1). A total of 80 patients had lesions located only in the posterosuperior segments, while 56 patients had tumors in both anterolateral and posterosuperior segments. Follow up data was available for all patients.

We found lower blood loss in the open group compared to the laparoscopic (median, 250 vs. 500 ml, $P = .006$). Pringle maneuver was used in two cases (3%) during open and in four cases (6%) during laparoscopic liver resections. There was no difference in transfusion rate or operation time.

Two laparoscopic operations were converted to open surgery (3%), both because of small bowel perforation during adhesiolysis. Both patients had undergone open colon surgery and one also open liver surgery before the current operation. Five procedures were converted to hand-assisted laparoscopy (4%).

The postoperative hospital stay was significantly shorter after laparoscopic liver resection (2 vs. 4 days, $P<.001$). A postoperative complication of grade 2 or higher was experienced by 39 (29%) of the patients, 23 (31%) in the open group and 16 (26%) in the laparoscopic group ($P=.57$).The mean CCI was 10.1 after open surgery and 6.8 after laparoscopic ($P=.18$) (Table 2).There was no 90-days mortality.

A total of 266 specimens were resected. Distribution of performed resections by segments is presented in Table 3. The median number and size of resected lesions, and the R1 resection rates were similar between the two groups (Table 3).

Patients in the laparoscopic group reported significantly higher HRQoL at the 1- month postoperatively compared to the open-surgery group and no significant improvement at 4-months (Table 2).

Discussion

In this sub-group analysis of the OSLO-COMET trial, we report perioperative results and resection margins after laparoscopic and open resection in the posterosuperior liver segments. These are the first data from a randomized trial to compare laparoscopic and open liver resection in the "difficult" segments. We found no difference in complication rate, transfusion rate and operative time, but hospital stay was shorter after laparoscopic surgery and blood loss was lower after open surgery.

In a multicenter propensity score matched-study Scuderi et al (10) reported reduced complication rates in laparoscopic group (Open-group: 24%vs. Laparoscopic-group: 12%; *P* = .039), whereas D'Hondt et al(12) reported complications rates similar to our findings (OLR-group: 31% vs. LLR-group: 26%; *P* = .60) in a multicenter case-matched study.

In the recent years, the parenchyma-sparing approach to liver surgery has gained widespread acceptance, especially for colorectal liver metastases. This technique aims to remove the metastasis without compromising cancer-related outcome, sparing as much healthy parenchyma as possible in order to facilitate repeated liver resections in case of recurrence, and to reduce the risk of postoperative liver failure (19-21). Parenchyma-sparing resections in the posterosuperior segments can, however, be at least as challenging as a laparoscopic right hepatectomy. The term "technically major liver resection" has been introduced to describe this (22, 23). During a hemihepatectomy it is usually easier to obtain adequate resection margins, and haemostasis is often better as the vessels are divided in the liver hilum before parenchyma transection (11).The surgical technique for laparoscopic resections in the posterosuperior segments at our institution has been described before, as well the steps facilitating resection of "difficult" segments (8).Based on our experience in laparoscopic liver surgery (more than 1200 procedures) we believe that surgeons should have a wide experience in laparoscopic liver surgery before taking on resections in these segments.

Troisi et al (24)reported tumor in the posterosuperior segments as an independent risk factor for conversion in laparoscopic liver surgery, and bleeding was the main cause of conversion. We report two conversions to laparotomy (3%) in the laparoscopic group, both because of small bowel perforation.

In the current study, we found lower blood loss following open liver resection, but no difference in transfusion rates. However, blood loss in sponges was only visually estimated, not by weight, and this may have caused underestimation of blood loss in the open group. This might be

especially prominent in posterosuperior liver resections, where the surgeon frequently places sponges behind the mobilized liver to facilitate access. The sponges might absorb a significant part of the blood loss, while the blood loss in laparoscopic surgery will be collected in the suction canister. We used intermittent clamping of the hepato-duodenal ligament (Pringle's maneuver) in only 4% of the operations. Pringle's maneuver may in some situations help to limit blood loss during laparoscopic liver surgery in where one in open surgery simply would apply direct manual pressure. After completing this study, we more frequently use Pringle's maneuver for difficult resections, and suggest preparing for Pringle before parenchyma transection during any laparoscopic resection in the posterosuperior segments.

The evaluation of resection margins has also been reported to be more difficult in the posterosuperior segments, mainly because of limited working space and visualization(25, 26). We found a similar rate of resection margins less than 1mm (27% vs 34%, *P*=.46). In our view, several factors are important to achieve free resection margins: Appropriate trocar placement and optimal patient positioning, complete right lobe mobilization from its ligamentous attachments, and the routine use of repeated laparoscopic ultrasound during the parenchyma transection.

Due to difficult access, laparoscopic liver resection of posterosuperior segments is associated with longer operative time than resections in the peripheral segments(26). Scuderi et al. (10)reported significantly longer operation time in laparoscopy (median, 180 vs. 215), while we here report similar operative time (median, 134 vs. 143, *P*=.82).One explanation might be related to the time period, as Scuderi's paper included patients back to 2006, where there still might be some effect of the learning curve for posterosuperior resections. The OSLO-COMET trial was performed between 2012-2016, when both our group and many others had gained a larger experience with these operations. The learning curve for laparoscopic liver resections is long and demanding compared to open. Despite previous studies suggested 20 to 60 cases for minor and 30-60 cases for major resections,(27-30) the expert panel at European Guidelines Meeting on

Laparoscopic Liver Surgery, decided that it is not possible to state a specific number of resections that a surgeon has to perform to reach ‘‘competency’’, and that patient factors must be balanced to the experience of the surgeon and their team. (5) At the same meeting, resections in the postero-superior segments were defined as ‘‘technically major’’ resections. We believe that laparoscopic resections in the posterosuperior segments should be undertaken after having already reached competency with minor resections in antero-lateral segments and studies to investigate the learning curve for these resections are desirable.

We here present the first data from a RCT to compare laparoscopic and open liver resection in posterosuperior segments. However, it is a subgroup analysis, and thus carries some limitations. If one performs multiple subgroup analyses on one patient cohort, false positive results may occur, because of multiple comparisons. To avoid this problem, we have only undertaken one subgroup analysis from OSLO-COMET. Similarly, false negative results are possible due to inadequate power. For instance, we found a non-significant reduction in complications and non-significant improvement in HRQoL after 4-months in the laparoscopic group, in contrast to the findings in the OSLO-COMET trial. However, the current study is underpowered for this analysis, so results must be interpreted with caution. Despite these limitations, we consider the current analysis justified as laparoscopic resections in the posterosuperior segments are rare and complex.

Conclusions

In this subgroup analysis of posterosuperior resections in the first RCT comparing laparoscopic and open liver surgery (OSLO-COMET), we found shorter hospital stay in the laparoscopic group and less blood loss in the open group. Perioperative outcomes were otherwise similar. Our analysis supports the further development of these technically challenging liver resections.

Disclosures

Authors have no conflicts of interest or financial ties to disclose.

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Figure 1. Patients flowchart of the OSLO-COMET trial

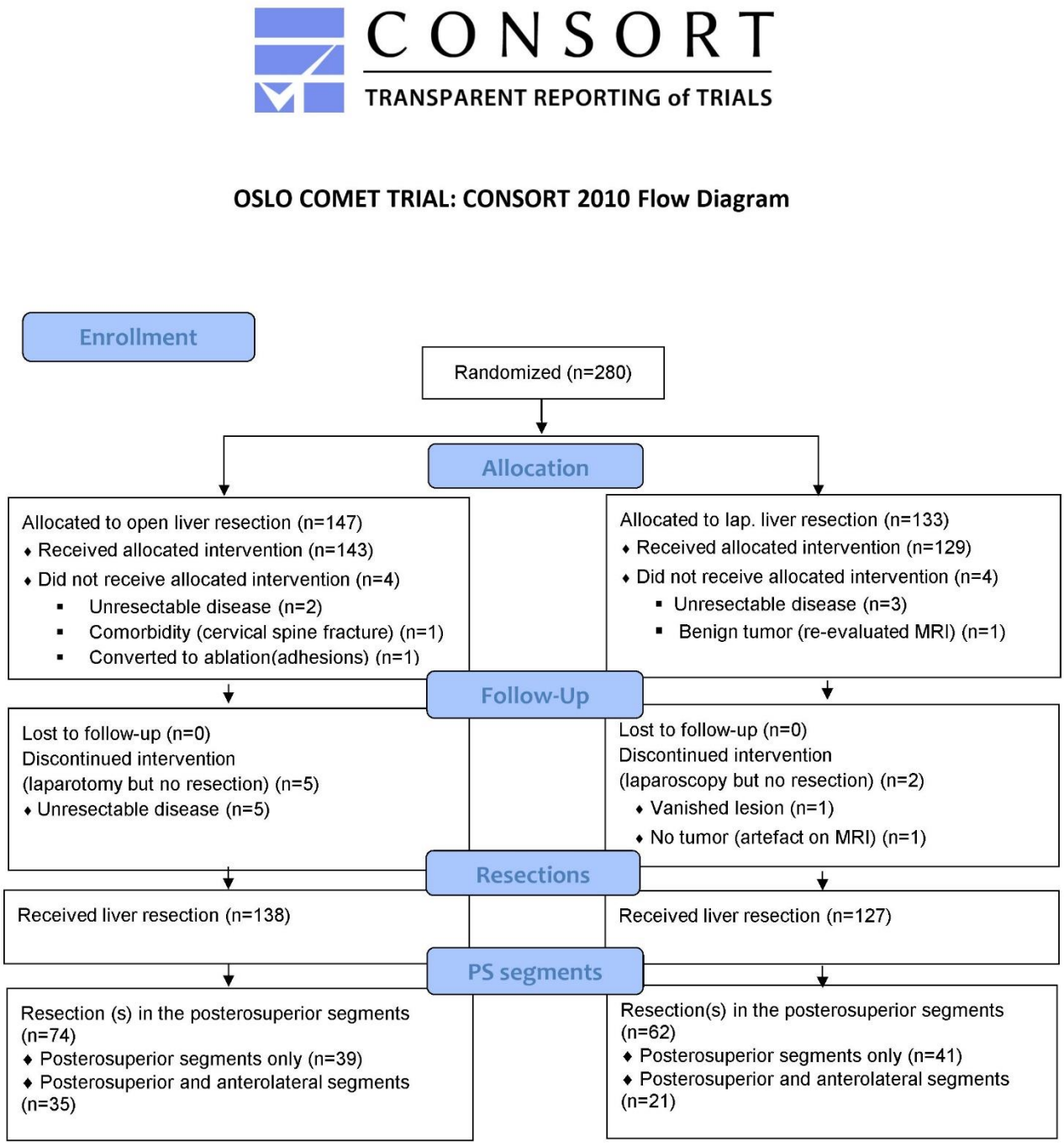

Table 1: Baseline characteristics (n=136)

Variable	OLR (n=74)	LLR (n=62)	*P Value*
Male sex n (%)	48 (65)	31 (50)	.08
Age, mean (SD)	67 (9)	66 (10)	.93
Body mass index, mean (SD)	25.2 (6)	24.7 (4)	.62
ASA score, n (%)			.85
1	4 (6)	7 (11)	
2	46 (62)	30 (49)	
3	24 (32)	25 (40)	
4	-	-	
Synchronous metastases, n (%)	49 (66)	32 (52)	.08
Tumor location, PS/PS+AL, n (%)	39 (53)/35 (47)	41 (66)/21 (34)	.11
Previous liver resection, n (%)	9 (12)	13 (21)	.16
- open/laparoscopic	7 / 2	11 / 2	
Modified Iwate complexity score, mean (IQR)	7.3 (6.7-7.8)	7.4 (6.8-8)	.66
Modified Liver surgery complexity score, mean (IQR)	2.9 (2.4-3.3)	3.2 (2.6-3.7)	.42

Abbreviations: SD, standard deviation; ASA, American Society of Anesthesiologists; PS, posterosuperior; AL, anterolateral; IQR, interquartile range

Table 2: Perioperative outcomes, postoperative complications and descriptive statistics of HRQoL

Variable	OLR (n=74)	LLR (n=62)	*P Value*
Operation time(minutes), median (95% CI)	134(118-150)	143(125-160)	.45
Blood loss(mL), median (95% CI)	250(132-368)	500(371-629)	.006
Pringle maneuver, n (%)	2(3)	4(6)	.41
Perioperative transfusion, n (%)	8 (11)	9(14)	.52
Conversion, n (%)	-	2 (3)	-
Postoperative stay (days), median (95% CI)	4(3.5-4.5)	2(1.5-2.5)	<.001
Accordion grade 2 or higher, n (%)	23(31)	16(26)	.57
Accordion grade 3 or higher, n (%)	11(15)	9(14)	.95
CCI, mean (95% CI)	10.1(6.2-13.9)	6.8(3.6-10)	.18
HRQoL (SF-6D)			
1 month (s.e.)	.67(.012)	.72(.016)	.011
4 months(s.e.)	.72(.015)	.74(.015)	.315

Abbreviations: CI, confidence interval; CCI, comprehensive complication index; HRQoL, health related quality of life; s.e., standard error

Table 3: Resected segments and histopathologic data			
Variable	**OLR (n=74)**	**LLR (=62)**	***P Value***
Total number of resected specimen	156	110	.04
Resections in PS segments	104	79	.29
By segments			
1	4	0	
1 + AL	1	0	
4a	10	6	
4a+AL	13	8	
7	25	26	
7+AL	20	11	
8	16	18	
8+AL	15	10	
Pathology weight of resected specimen (g), median (IQR)	47(24-95)	68 (35-132)	.07
Number of removed lesions, mean (SD)	2 (1.2)	1.8 (1.2)	.21
Biggest size of lesions (mm), median (IQR)	22 (15-34)	23 (14-35)	.78
R1 (<1mm) resection margin, n (%)	25 (34)	17 (27)	.46
Involved resection margin, n (%)	7 (9)	3 (5)	.34

Abbreviations: PS, posterosuperior; AL, anterolateral; IQR, interquartile range; SD, standard deviation