Laparoscopic parenchyma-sparing surgery in the treatment of colorectal liver metastases

Thesis for the degree of philosophiae doctor (PhD)

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Oslo, June, 2020

Davit L. Aghayan

LIST OF PAPERS

I. Aghayan D L, Pelanis E, Fretland Å A, Kazaryan A M, Sahakyan M A, Røsok B I, Barkhatov L I, Bjørnbeth B A, Elle O J and Edwin, B.

Laparoscopic Parenchyma-Sparing Liver Resection for Colorectal Metastases.

Radiology and Oncology. 2017 Nov 1;52(1):36-41

II. Kazaryan, A M, Aghayan D L, Barkhatov L I, Fretland Å A and Edwin B.

Laparoscopic Multiple Parenchyma-sparing Concomitant Liver Resections for Colorectal Liver Metastases

Surgical laparoscopy, endoscopy & percutaneous techniques. 2019 Jun;29(3):187-193

III. Aghayan D L, Fretland Å A, Kazaryan A M, Sahakyan M A, Dagenborg V J, Bjørnbeth B A, Flatmark K, Kristiansen R, Edwin B.

Laparoscopic versus open liver resection in the posterosuperior segments: a sub-group analysis from the OSLO-COMET randomized controlled trial.

HPB (Oxford). 2019 Nov;21(11):1485-1490

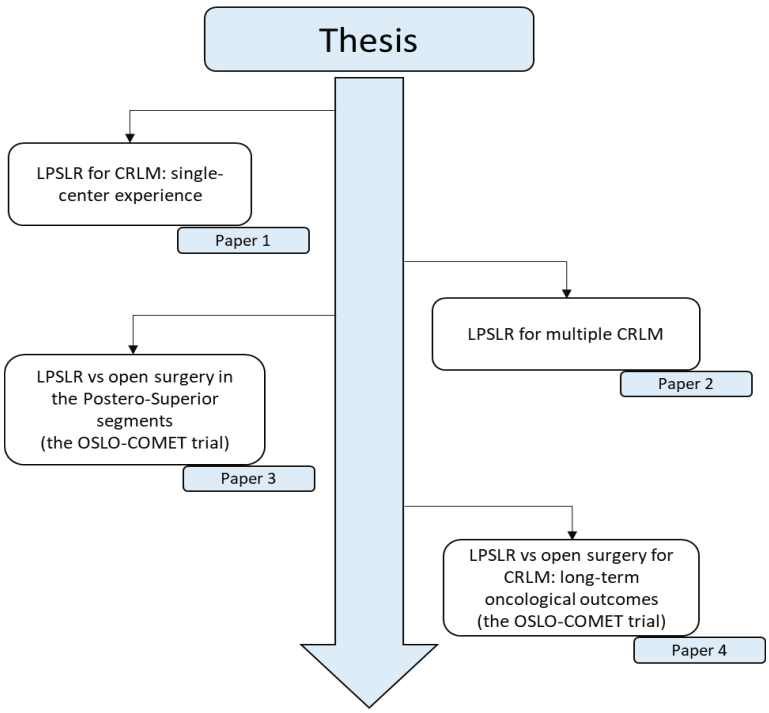
IV. Aghayan D L, Kazaryan A M, Dagenborg V J, Røsok B I, Fagerland M W, Bjørnelv G M, Kristiansen R, Flatmark K, Fretland Å A, Edwin B.

Long-term oncological outcomes after laparoscopic versus open resection for colorectal liver metastases (Submitted to The Lancet)

AIMS OF THE THESIS

General aim

- To investigate and provide high level evidence on the role of laparoscopic parenchyma-sparing liver resection (LPSLR) in the surgical treatment of patients with colorectal liver metastases (CRLM).



Specific aims

- To evaluate the surgical and oncological outcomes of LPSLR in a large cohort of patients with CRLM from a high-volume centre **(Paper 1)**.
- To examine the surgical and oncological outcomes of LPSLR in patients with multiple CRLM **(Paper 2)**
- To compare the surgical outcomes after open and laparoscopic parenchyma-sparing resections in the postero-superior ("difficult") liver segments on a sub-group analysis from a randomized controlled trial **(Paper 3)**.
- To compare the long-term oncological results after open and laparoscopic parenchyma-sparing resections for CRLM through a randomized controlled trial (**Paper 4**).

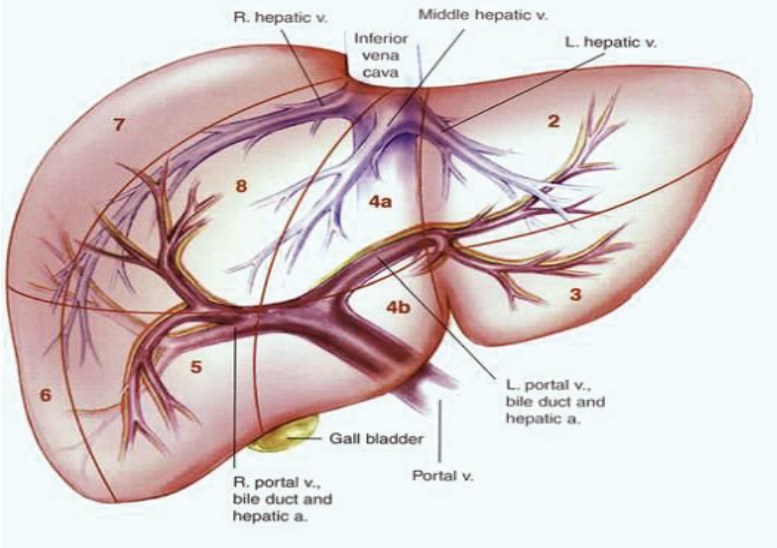
INTRODUCTION

Liver anatomy and surgery

The liver is the largest internal organ in the body. It is located under the diaphragm, in the right upper part of the abdomen. It is a complex parenchymal organ with over 500 essential functions, such as: protein, fat and carbohydrates metabolization; bile production; vitamins and minerals storage; as well as, immunological, hematopoietic, detoxification and other vital functions.

The understanding and description of liver anatomy is challenging. Its blood supply is provided from two sources: the proper hepatic artery (30%) and the portal vein (70%). In the liver hilum, the proper hepatic artery and the portal vein are divided into the right and left branches, which are then subdivided into sectorial and segmental branches. Blood outflow is carried by the hepatic veins (right, middle and left) to the inferior vena cava (the largest vein in the body). The middle hepatic vein divides the liver into right and left lobes (also known as hemilivers).

Figure 1. Vascular anatomy of the liver (from Abdel-Misih et al.[1])



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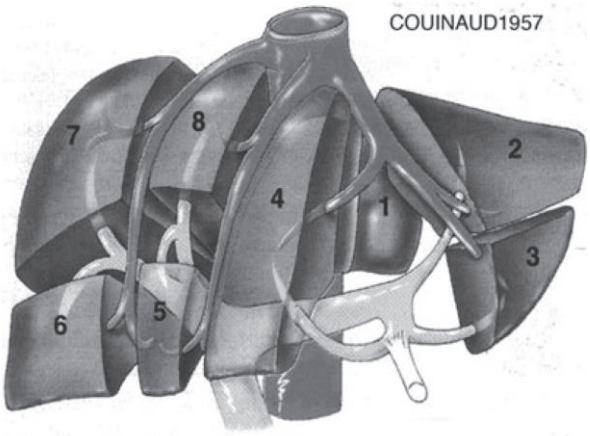
Different definitions and terms have been used throughout history to describe such a complex anatomy. In 1954 Couinaud proposed a division of the liver anatomy based on the portal and hepatic vein distribution (2). Throughout this report and later in his book (3), Couinaud divided the liver into 8 segments. This anatomical model has undergone several modifications and many different terms have been used to describe the liver anatomy making its understanding more difficult (4). Currently, there is general acceptance among surgeons to use the anatomical model proposed by Couinaud as a basis to understand liver anatomy.

Figure 2. Liver segments according to Couinaud [3] (from Bismuth et al.[4]).



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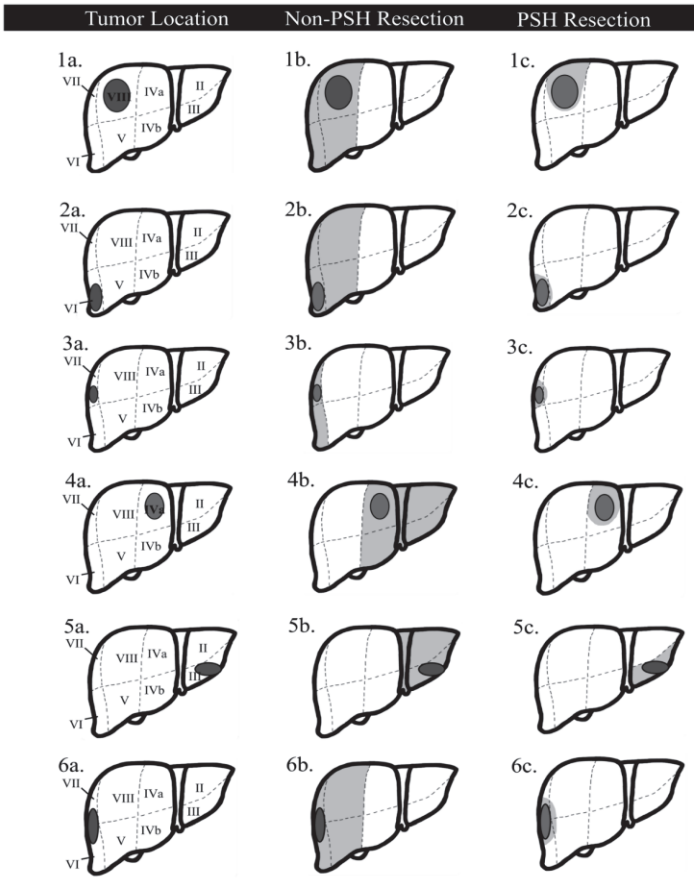
Nowadays, liver resection (removal of a part of the liver) is the most accepted surgical treatment method for various malignant and benign liver tumours (5). Depending on the tumour type, size and localization, different approaches to liver resection (hemihepatectomy (removal of the right or left liver lobe), tri-segmentectomy, bi-segmentectomy, segmentectomy, atypical (non-anatomic) resection) are utilized. Traditionally, anatomical resections (mostly hemihepatectomies) had been considered as a gold standard for resectable malignant liver tumours, however advances in surgical and radiological techniques have changed the strategies of liver resection dramatically (6-8). Parenchyma-sparing liver surgery has become a

preferable alternative to formal hepatectomies, especially in patients with CRLM, owing to the improvement in its multimodal treatment (5, 9, 10). The parenchyma-sparing approach targets only the metastasis and aims to balance two objectives: 1) achieving complete tumour resection with negative margins and 2) sparing as much healthy parenchyma as possible (11). Frequently, patients with CRLM present with multiple tumours, sometimes with bilobar distribution (tumours in the right and left liver lobes), restraining the use of anatomical resections and in these situations, the parenchyma-sparing resection may be the only option for these patients(12).

Figure 3. Different surgical scenarios for parenchyma-sparing and anatomic resections (from Kalil et al.[6]).



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Colorectal liver metastases

Histopathology and Etiology

Colorectal cancer is one of the most common cancers diagnosed worldwide. According to the report of the International Agency for Research on Cancer in 2018, colorectal cancer is the third most commonly diagnosed malignancy and the second leading cause of cancer deaths globally (13). During the disease career, approximately two thirds of the patients develop a distant spread of the disease from its primary location into other organs (metastases). The liver represents the most common target of metastases from colorectal cancer (14). This is due the fact that all the blood from the gastrointestinal tract (except the lower part of the rectum) is delivered to the liver through the portal circulation. Thus, cancer cells escaped from the primary colorectal tumour, can spread hematogenously to the liver, making it the first metastasis site. Once implanted in the liver, metastatic tumours secrete angiogenic factors to induce neovascularisation and supply themselves with blood that helps its cells to survive (15). In contrast to hepatocellular carcinoma, where tumour cells can migrate into intrahepatic portal branches to form secondary liver metastases, some studies have shown that the spread of CRLM tumour cells within the liver occurs through intrahepatic lymphatic invasion (16, 17).

Epidemiology and clinical presentation

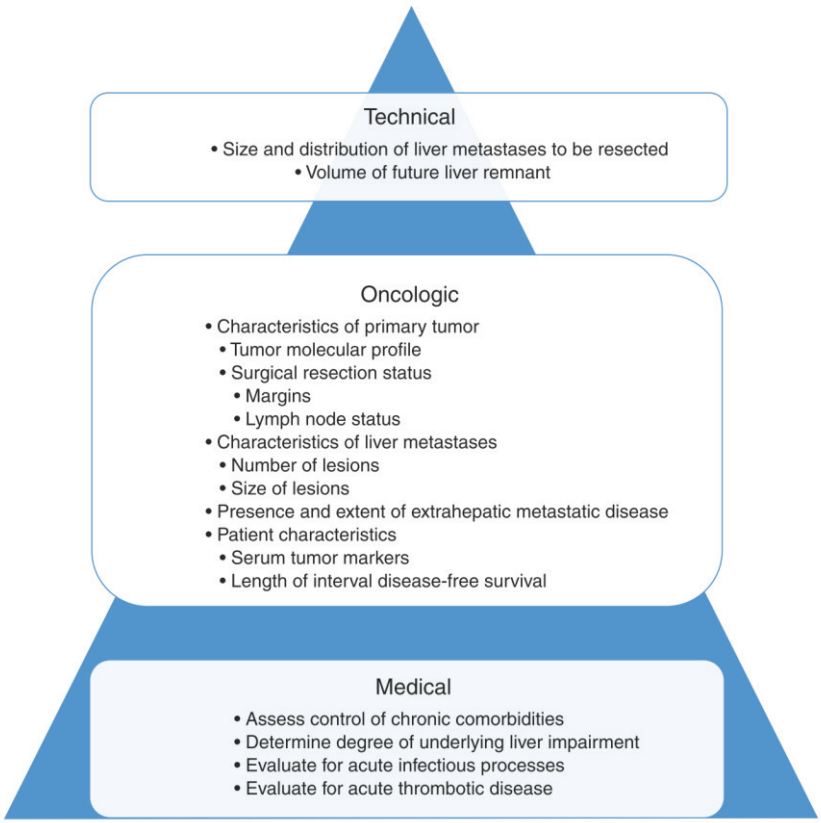
Approximately 15-25% of patients with colorectal cancer have liver metastases at the time of diagnosis (synchronous metastases), while about 18-25% of patients develop liver metastases after diagnosis of the primary tumour (metachronous metastases) (18, 19). However, less than 25% of these patients are eligible for liver resection (20). In fact, for approximately 30% of patients, the liver is the only site of metastatic disease and, if left untreated the majority of patients may die within 1 year (15).

The treatment of patients with CRLM requires a multidisciplinary approach. In the past, the majority of the patients with CRLM were never considered as candidates for resection and were

mostly rendered to palliative care (21, 22). However, thanks to significant improvements in preoperative investigations, surgical techniques, anaesthesia, chemotherapy regimens and the expansion of resectability criteria, nowadays a large portion of patients undergo surgery (9, 23). Surgical resection with and without systematic chemotherapy is the only chance for prolonged survival and potential cure, and depending on selection criteria, 30 to 60% of these patients survive for 5 years after liver resection (24-26).

Selection of patients for surgical treatment and defining the resectability criteria for each patient is of the utmost importance. Three main standpoints should always be considered in a multidisciplinary group: 1) medical, 2) oncological and 3) technical (20).

Figure 7. Core components to the stepwise evaluation of resectability in patients with CRLM (from R. K. Marcus and T. A. Aloia [20]).



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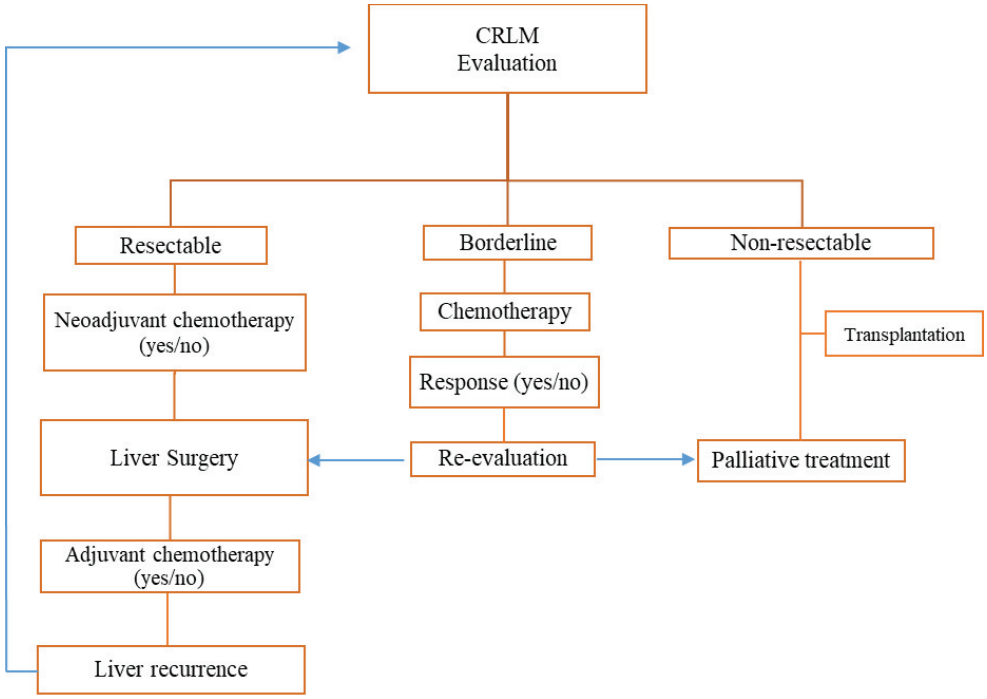
The first steps to evaluate a patient by a multidisciplinary group, consist of assessing both the patient's ability to undergo surgery and the oncological expediency of the surgical process. After confirming medical and oncological resectability, the surgeons evaluate the technical feasibility of the surgery considering size, location and distribution of liver metastases, and the volume of functional liver remnant after the removal of all metastases with negative microscopic margin.

The concept of resectability of CRLM has changed significantly. Although not long ago, mainly patients with solitary metastasis were considered for liver resection (mostly formal hemihepatectomies), nowadays, surgical treatment is considered regardless of tumour size and number, provided that the remaining functional liver parenchyma is enough to prevent postoperative liver failure (27).

With the introduction of parenchyma-sparing liver surgery, resectability criteria were expanded and more patients with CRLM became eligible for surgical resection (9). The primary goal of this strategy is to spare as much healthy liver parenchyma as possible without jeopardizing oncological outcomes. The parenchyma-sparing strategy has been proven to reduce the risk of postoperative complications and mortality (28) and may at the same time provide improved long-term survival, by increasing the chance for re-do liver resections in case of liver recurrence (salvage surgery) (9, 29). Another advantage of parenchyma-sparing liver surgery can be seen in patients with bilobar metastases, a condition, where the surgical treatment might appear to be inappropriate (30).

This method has been accepted as a preferable alternative to anatomical liver resections, both for laparoscopic and open liver surgery (12, 31, 32). Today, parenchyma-sparing liver resection has become a first line surgical treatment method for patients with CRLM in our centre, as well as in many specialized centres worldwide (33, 34).

Figure 8. General aspects of the multimodal treatment for CRLM



Laparoscopic liver surgery

Laparoscopic surgery is a type of minimally-invasive endoscopic technique, in which surgery is performed through small incisions (usually 0.5-1.5 cm) on the abdominal wall, as opposed to the large incisions used in open surgery.

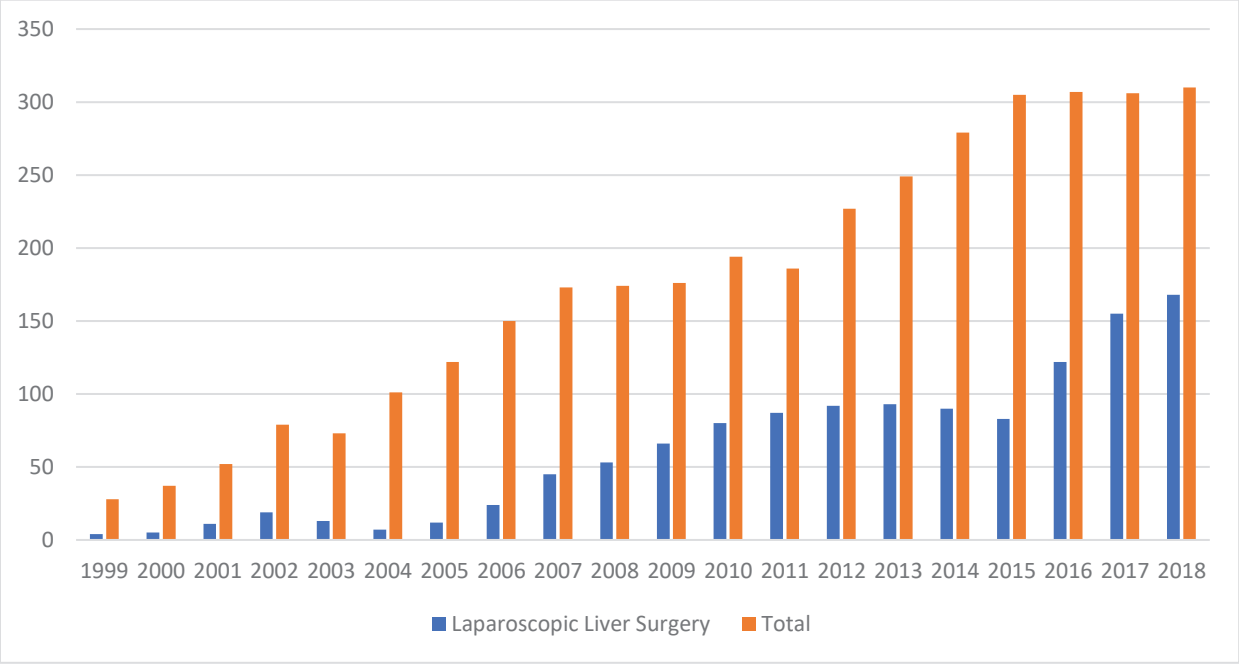
This minimally-invasive technique is based on the use of a laparoscope - a fiber-optic instrument or an imaging sensor on the tip of instrument (or chip-on-the-tip technology) with a light source which provides a view of the structures within the abdomen and pelvis. To allow for visualization of the abdominal organs, prior to laparoscopy, the abdominal cavity is insufflated with carbon dioxide gas (a process known as pneumoperitoneum or carboxy-peritoneum). This helps to elevate the abdominal wall above the internal organs and creates a working and viewing space.

Laparoscopic surgery has dramatically changed surgical practice in the last 2-3 decades and has replaced open surgery in many surgical subspecialties. It provides advantages over open surgery in terms of postoperative pain, length of hospitalization, and aesthetic results (35, 36).

History and current status

At the end of the last century, the widespread interest in laparoscopic surgery reached the hepatobiliary field and the first laparoscopic liver resections (LLR) were reported in 1991 by Reich et al. (37) and in 1992 by Gagner et al. (38). The first reports concerned technically relatively minor resections for benign tumours. Later, case series showed the feasibility and safety of LLRs for benign and malignant liver tumours (39, 40). The first LLR in Norway was performed by Bjørn Edwin in 1998, which was followed by the first Norwegian report of this procedure in 2001 including 11 LLRs (8). Nowadays, almost 60% of all liver resections at the Oslo University Hospital, are performed by laparoscopic approach.

Figure 4. Annual number of liver resection procedures from January 1999 to December 2018 at the Oslo University Hospital



Despite advances in laparoscopic surgical technique, imaging and instrument technology, the spread of laparoscopic liver surgery, particularly for liver malignancies, has been hindered by concerns regarding the resection margin, the risk of dissemination (implantation metastases) during surgery, as well as difficulties in detecting small metastases during the intraoperative revision. Later studies, in the early 2000s, proved the safety of this approach for both primary and metastatic liver tumours (41, 42). Thereafter, a consensus started to grow among surgeons, perceiving that this technique is a valid alternative to open surgery.

In spite of the relatively slow spread and implementation of LLRs, the number of patients and the range of its indications has started to grow. In 2009, 2804 patients were reported in the first world review of laparoscopic liver surgery (43). In a successive review of LLRs, in 2016, the number of LLRs increased to a total of 9000 (44).

Figure 5. Number and indications of LLRs reported worldwide from 2002 to 2008 (from Nguyen et al. [43]).

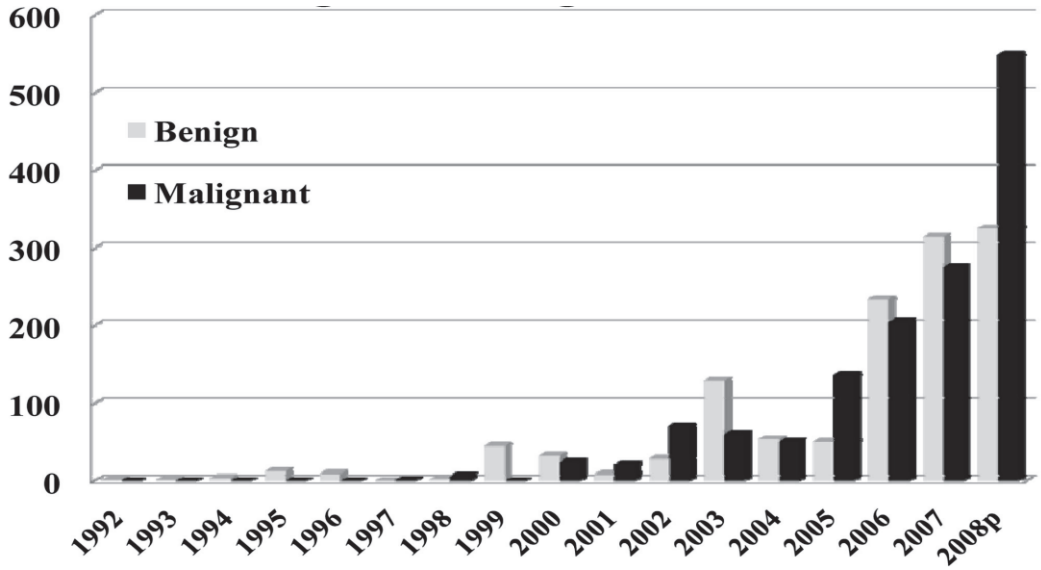


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Figure 6. Number and type of LLRs from 1996 to 2014 (from Ciria et al. [44]).

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To date, 2 consensus (45, 46) and 1 guidelines (47) meetings have been held at which leading experts have determined the optimal indications and conditions for performing LLRs, as well as provided recommendations on the further development and implementation of minimally invasive technologies in the practice of hepato-biliary surgery.

In the first consensus meeting in 2008 (Louisville, USA), experts reviewed the feasibility, safety and perspectives of LLRs (45). For the first time, a classification of laparoscopic liver interventions was provided (this included pure laparoscopy, hand-assisted laparoscopy and hybrid techniques). The experts reviewed indications for LLR and the most suitable indication for laparoscopy was defined as single tumours sized less than 5cm and located in the antero-lateral liver segments (segments 2, 3, 4b, 5, 6).

In 2014, the second consensus meeting was held in Morioka, Japan, in which the main focus was on the comparison of laparoscopic and open approaches (46). Overall, with regards to perioperative outcomes, such as postoperative complications and postoperative hospital stay,

the laparoscopic approach showed advantages over the open approach. However, the quality of studies comparing laparoscopic and open approaches was found to be low. It was recommended to conduct studies with a higher level of evidence, possibly with multicentre registers.

The first European guidelines meeting was held in 2017 in Southampton, UK. The experts, whose number and experience had increased over the past years, formed 67 recommendations regarding: indications for surgery, selection of patients, type of intervention, technical aspects and implementation of LLRs (48). This conference made it possible to unite the available evidence-based studies at that time, the level of which had increased significantly.

In general, based on the results of these meetings, one can observe the evolution of the laparoscopic liver surgery from very limited indications and small-scale interventions, to significantly expanded indications and interventions.

Indications and patient selection

Nowadays, the most common indications for liver resection are primary and secondary liver malignancies. Thanks to significant improvements in preoperative investigations, surgical techniques, anaesthesia, chemotherapy regimens and the expansion of resectability criteria more and more patients have become candidates for liver surgery.

The indication and patient selection for LLR differs from country to country, from hospital to hospital, and is still controversial. However, with an increased experience and advances in laparoscopic devices, the indications for LLR have expanded tremendously. Generally, in high-volume centres with established laparoscopic liver program, the indications for LLR follow the same guidelines as for open liver resection (OLR), but are limited to patients amenable to laparoscopic surgery (49, 50)

The selection of patients is the most important consideration in safely performing LLR. When selecting patients, three important factors must be taken into account: liver function, tumour location and the size of the tumour. The majority of surgeons started their practice of LLR with resecting easily accessible liver tumours – peripherally located, superficial solitary lesions. Thereafter, they improved their skills to resect malignant tumours, tumours in the postero-superior liver segments (referred to as the "difficult'' segments) and formal major hepatectomies. The first report of LLR emerged by Reich et al. (37) in 1991, described three cases of partial liver resections for superficial, benign tumours. In 1996, the first reports of laparoscopic left lateral sectionectomies were published (51, 52) followed by the first report on laparoscopic hemihepatectomies by Huscher et al. in 1997 by (53).

The Louisville Consensus Conference in 2008, the experts recommended that acceptable indications for LLRs included solitary tumours $\leq$ 5 cm, preferably located in the antero-lateral liver (AL) segments (segments 2, 3, 4b, 5, 6) (45). The Morioka consensus conference, in 2014, stated that LLR can be a favourable alternative to OLR in selected patients (46). However, both international consensus conferences revealed the low quality of existing literature on LLR, thus the statements were not strong. There was a clear need for high quality randomized controlled trial to test laparoscopic liver surgery. To fulfil this need, the Orange 2 trial comparing open and laparoscopic left lateral sectionectomies was initiated, however, the project was halted due to a slow patient enrolment (54). The OSLO-COMET trial was the first completed randomized controlled trial, and was conducted by our group at the Oslo University Hospital, from 2012 to 2016. A total of 280 patients with CRLM were assigned to open or laparoscopic parenchyma-sparing liver resection (55).

Already in 2017, in the Southampton Guidelines Meeting, based both on their experience and on the results of the literature at that time (including preliminary results of the OSLO-COMET RCT), the experts advocated that LLR in the AL segments should be considered as a standard

approach, while the advantages observed in the AL segments after LLR may be achieved in the PS segments. Moreover, it was stated that repeat resections or 2-stage hepatectomies, resections for large lesions, and lesions in close proximity to the liver hilum are challenging and should be handled by surgeons with "extensive experiences" in laparoscopic liver surgery (48).

Laparoscopic parenchyma-sparing liver resection for colorectal metastases

Current status

Laparoscopic technique for liver resections has become an increasing trend in the past decade (44). Despite the initial scepticism, laparoscopic parenchyma-sparing liver resection (LPSLR) is a major component in the surgical treatment of patients with CRLM in our centre (34, 55)

In the first systematic review of the LPSLRs by Kalil et al. (6) in 2019, which analysed 10 studies with in total 579 patients, the safety and feasibility of this approach was demonstrated. The most common indication for LPSLR in this report was CRLM. The outcomes reported in this systematic review reflected the data present in another systematic review on open parenchyma-sparing liver resections published previously (9). However, Kalil et al. advocated that the evidence level and the data quality on LPSLR is still low. The main limitation on LPSLR observed in this systematic was the low number of resected lesions reported in the analysed studies.

To fill the gap due to low number of patients (with mainly solitary metastasis) reported in the literature, in **Paper 1,** we thoroughly examine the outcomes of LPSLR in a large single centre cohort of patients with CRLM, whereas in **Paper 2,** we analyse the surgical and oncological results of patients with multiple CRLMs undergoing multiple concomitant LPSLR compared to a single greater resection.

Laparoscopy vs Open

Retrospective studies and meta-analyses comparing laparoscopic and open liver resections for CRLM have shown advantages in surgical outcomes after laparoscopy, while long-term oncological outcomes after laparoscopic resections are not inferior to open surgery (56-59).

In the OSLO-COMET trial, 280 patients with CRLM were randomly assigned to open or laparoscopic parenchyma-sparing liver resections (55). The primary endpoint of OSLO-COMET was 30-day morbidity and it was found that patients operated with laparoscopic approach developed significantly less postoperative complications, had shorter postoperative stay, and reported significantly better health-related quality of life at 1- and 4-months postoperatively (60).

LPSLR in the postero-superior liver segments has been considered to be more complex than resections in the antero-lateral segments. This is mainly because of the difficulties to reach these segments due to their location (limited working space and visualisation). Therefore, many surgeons prefer to perform big anatomical resections or operate these patients with open approach. At the Southampton Guidelines Meeting for laparoscopic liver surgery, the experts acknowledged, that resections in the postero-superior require advanced expertise, and classified resections in these segments as "technically major" (48).

To show the possibility of performing laparoscopic surgery for complex liver segments in randomly selected patients, in **Paper 3** of this thesis, which is a sub-group analysis from the OSLO-COMET trial, we compared the surgical and the short-term oncological results after open and laparoscopic parenchyma-sparing liver resection in the postero-superior segments for CRLM. Survival outcomes after laparoscopic and open parenchyma-sparing liver resections in patients with CRLM have never been studied in randomized controlled trial setting, thus, in **Paper 4,** we present the long-term oncological outcomes of the OSLO-COMET trial, providing a new high level of evidence in this field.

MATERIAL AND METHODS

Patients

All patients included in the papers of this thesis were operated for CRLM. In **Paper 1** and in **Paper 2** patients underwent LLR, whereas patients in **Paper 3** and **Paper 4** were operated on using both laparoscopic and open approaches. All patients reported in these papers were operated on at the Oslo University Hospital.

Paper 1 included 296 consecutive patients, who underwent LPSLR between August 1998 and March 2016. **Paper 2** counted a total of 171 patients operated between August 1998 to 2017. In **Paper 3,** 136 patients from the OSLO-COMET RCT, undergoing laparoscopic or open parenchyma-sparing liver resections in the postero-superior segments were analysed. **Paper 4** comprised data on 280 patients, who were randomly assigned to undergo open or laparoscopic parenchyma-sparing liver resections between February 2012 and January 2016 (the Oslo-Comet RCT).

Study design

Paper 1 and **Paper 2** are retrospective studies, while **Paper 3** and **Paper 4** present data from the randomized controlled trial. All four papers were single centre studies conducted at the Oslo University Hospital, the only hospital performing liver surgeries in the South-Eastern Norway Regional Health Trust. The South-Eastern Norway Regional Health Trust is the largest health trust in Norway serving about 3 million people, which corresponds to 55% of Norway's population. The patient cohort in **Paper 1** and **Paper 2** should adequately characterise the corresponding health region for liver surgery in the period 1998-2017. **Paper 3** and **Paper 4** are part of a randomized controlled trial started in 2012, when our surgeons had completed their learning and had sufficient experience in both open and laparoscopic liver surgery to conduct a randomized controlled trial.

Ethics

Paper 1 and **Paper 2** were classified as clinical audits and were approved by the Institutional Data Protection Officer. **Paper 3** and **Paper 4** are sub-studies of the Oslo-Comet RCT which was approved by the Regional Committee for Health and Research Ethics (2011/1285/REK Sør-Øst B) and by the Data Protection Official for Research at Oslo University Hospital. The study was registered in Clinicaltrials.gov (NCT01516710) before recruitment started.

Surgical technique

The extent of liver resection varies depending on the tumour size, localisation and the proximity to the major vessels. The patient is placed in the supine position (antero-lateral segments) or in the 30-45-degree side with the right side up (postero-superior segments). Usually, the surgeon stands to the patient's right side.

Pneumoperitoneum is established by open technique, and intra-abdominal carbon dioxide gas pressure is set in a range from 12 to 15 mm Hg. A 30° laparoscope and 5- and 12-mm trocars are used. The number of trocars depends on the lesion location and patient body build and usually varies from 4 to 6. It is suggested to prepare for a Pringle manoeuvre (clamping of the hepato-duodenal ligament) before starting parenchyma transection, especially for resections in the postero-superior segments.

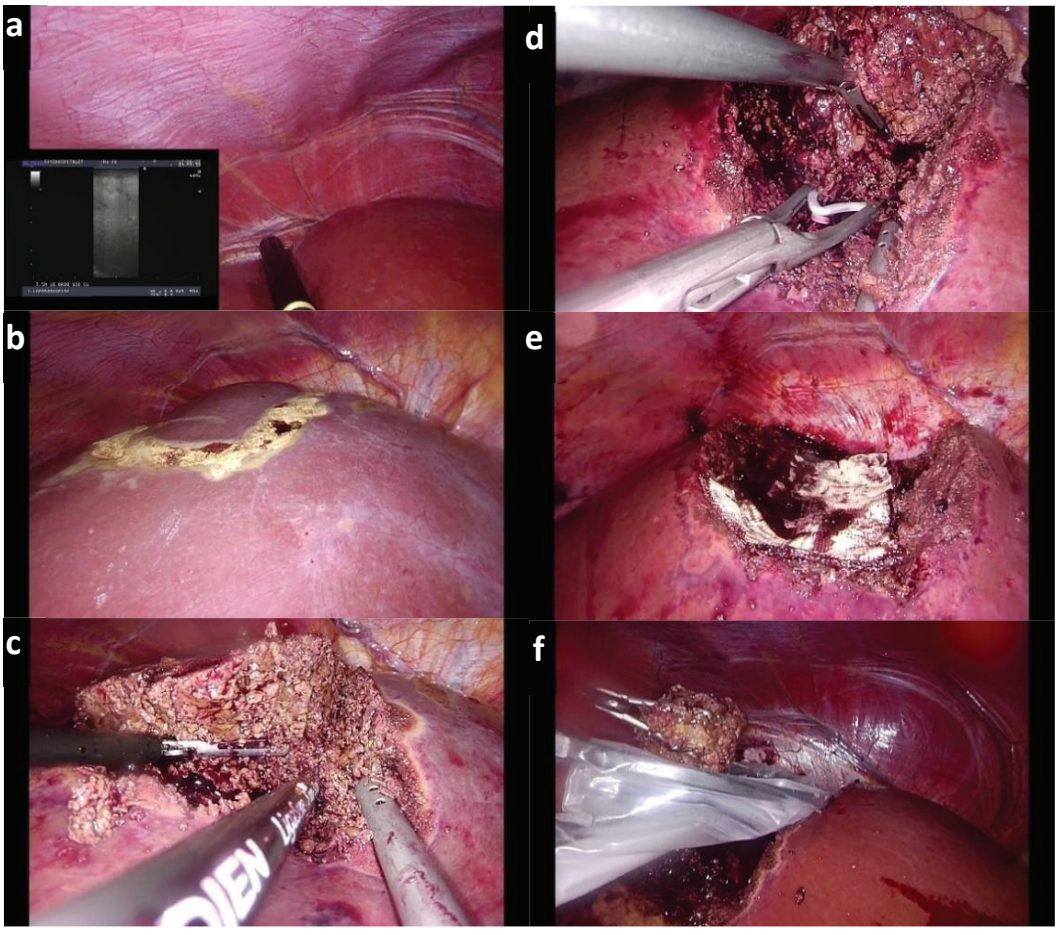
After establishment of pneumoperitoneum and trocar placement, the liver is thoroughly examined to define exact tumour localisation and its relation to major vessels using laparoscopic ultrasonography with Doppler function. For resections in the postero-superior segments it is essential to perform proper mobilisation of the right lobe to achieve appropriate access and visualisation of the resection area.

The resection line is marked at the liver surface by electrocautery and followed-up with ultrasonographic examination to clarify the resection margin. Parenchymal transection is performed using different electrosurgical devices and ultrasound aspirator.

The resections are guided by repeated ultrasonography to ensure a tumour free margin and to define the portal and hepatic branches in the resection area. Vessels in the resection area are divided using electronic or ultrasound dissection instruments, clips and laparoscopic linear staplers, depending on the size of the targeted vessels. A laparoscopic ultrasound aspirator can be used to skeletonize the vascular structure before they are divided.

After completing the liver resection, a thorough visual examination and haemostasis of the resection bed is essential to minimise the risk of postoperative haemorrhage and bile leakage.

Figure 9. Main steps of LPSLR: a) intraoperative ultrasound examination, b) marking the resection line, c) parenchyma transection d) dissection of the vascular structures to the specimen e) haemostasis f) specimen retrieval.



Definitions and inclusion/exclusion criteria

Definition of parenchyma-sparing liver resection is a complex task and may lead to a misunderstanding that it is a dispute between minor and major hepatectomies. Any type of liver resection that aims to remove liver tumour without sacrificing healthy liver parenchyma can be defined as a parenchyma-sparing surgery (10).

Parenchyma-sparing resection was defined as a resection of less than 3 consecutive liver segments in the OSLO-COMET trial (**Paper 3, Paper 4)**, while for **Paper 1** sectionectomies were excluded. In **Paper 1** and **Paper 2** only patients with primary liver resections were included, whereas in OSLO-COMET, patients with previous liver resection were allowed. In OSLO-COMET, patients that needed ablation in addition to liver resection, vessels or bile duct reconstruction, or synchronous resection of a primary tumour were excluded.

The expanded Accordion Severity Classification was applied to grade postoperative complications (61) and complications classified as Grade 3 and higher were considered severe. In OSLO-COMET, the Comprehensive Complication Index (CCI) was also used to assess complications (62). This method calculates all the complications that occurs to a patient into an index ranging from 0 to 100.

All the removed specimens were sent for histopathological evaluation. Morphometric measurements of the tumour were taken from the pathology report when reporting on its size. A macroscopic and microscopic evaluation of resection margins was performed, and R1 resection was defined as a presence of tumour cells within 1 mm of resection margin.

Disease recurrence and pattern of recurrence, recurrence-free survival (RFS) and overall survival (OS) were included in the measurement of long-term oncologic outcomes. Tumour recurrence was defined as a radiological evidence of pathological changes in the liver suggesting recurrence and/or extrahepatic metastases. The time interval between liver surgery

and radiological evidence of disease recurrence or the last date of radiology / clinical visit (in case of no evidence of disease recurrence) was defined as RFS. Overall survival was defined as the time between the date of liver resection and the date of death. Alive patients were censored at the last date of follow-up.

All the data presented in **Paper 1** and **Paper 2** were retrieved from the retrospective database which was updated continuously based on the Electronic Health Records, while in OSLO-COMET (**Paper 3, Paper 4)**, the data was collected prospectively in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statements (63). Patients who initially were considered to be presented with CRLM, but benign tumours or other malignancies were reported by pathologists, were excluded from the analyses in all 4 papers of this thesis.

Statistics

Categorical variables were represented as numbers (percentages), while continuous variables were expressed as a median (range or interquartile range) or mean (± standard deviation). Categorical variables were compared applying Chi–square test, Fisher's exact test or Fisher's Mid-P test, when applicable. Mann-Whitney U-test was applied to compare non-normally distributed continuous data, whereas two-sample t-test was used for data with normal distribution. Survival data were obtained from the National Population Registry of Norway. The Kaplan-Meier method was used to estimate median survival and to plot survival curves. The log-rank test was used to compare survival rates and multivariable Cox-regression method was applied to identify risk factors for survival.

The two-tailed p-value <0.05 was considered statistically significant.

SUMMARY OF PAPERS

Paper 1

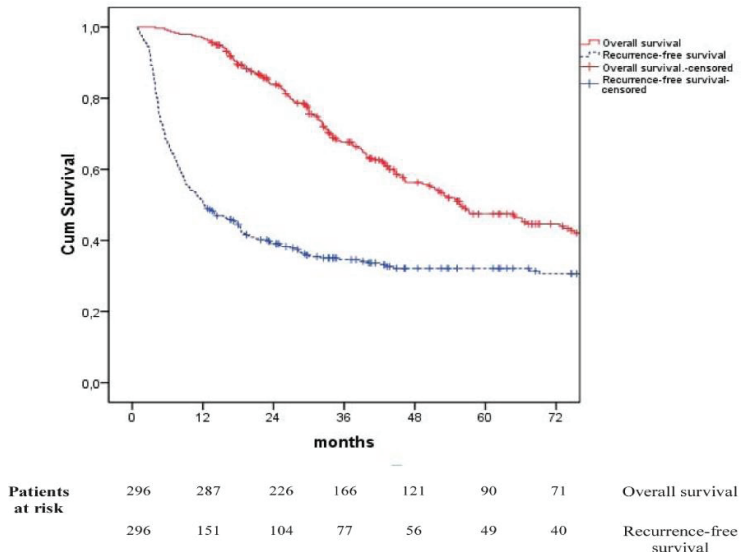
Laparoscopic parenchyma-sparing liver resection for colorectal metastases

Radiol Oncol 2018; 52(1): 36-41.

This retrospective study reports surgical and oncological outcomes following LPSLR for CRLM in 296 patients operated on at the Oslo University Hospital between August 1998 and March 2016. In this paper, only patients who had their first liver resection done by LPSLR approach were included. In total, 448 lesions with median size of 22 (4-80) mm were removed. 43 patients (14.5%) experienced Grade 2 or higher postoperative complications. Median postoperative stay was 3 (1-35) days.

Disease recurrence was observed in 189 patients (64%). Liver recurrence occurred in 146 patients (49%) and only-liver recurrence was developed in 75 patients (25%). In total 83 patients underwent repeated surgical treatment for their liver recurrences (69 liver resection and 14 radiofrequency ablation). 5-year RFS and OS rates were 34% and 48% respectively. Median overall survival was 56 months (95% CI, 46-66).

*Figure 10. Kaplan-Meier survival curve for OS and RFS (**Paper 1**)*



Paper 2

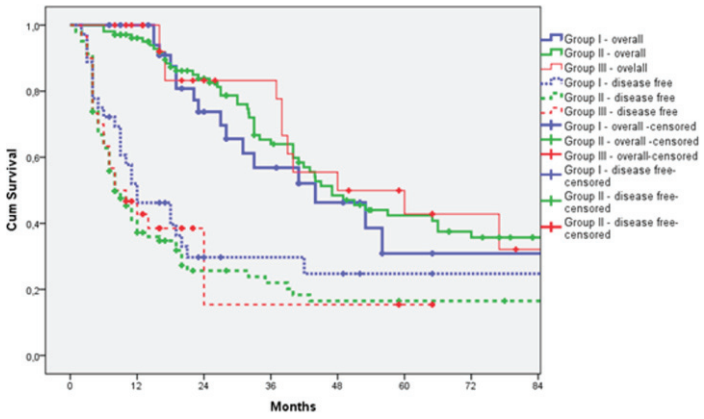
Laparoscopic multiple parenchyma-sparing concomitant liver resections for colorectal liver metastases

Surg Laparosc Endosc Percutan Tech 2019; 29 (3), 187-193.

In this retrospective study, patients with multiple CRLM undergoing their first liver surgery by laparoscopic approach (with or without concomitant radiofrequency ablation (RFA)) between August 1998 and 2017 at the Oslo University Hospital were identified and analysed. In total 171 patients met the inclusion criteria and were divided into 3 groups: Group 1 (36 patients) with single resection, Group 2 (104 patients) with multiple concomitant liver resections, Group 3 (31 patients) with RFA or cryoablation in addition to liver resection.

The surgical and oncological data was compared between Group 1 and Group 2, whereas the data of Group 3 was presented as complementary information. No significant difference was found in perioperative outcomes, besides the number of patients that experienced postoperative liver failure, which was significantly higher in the Group 1 (3 vs 0; p-0.016). Long-term oncological outcomes were also similar, despite the tendency to higher 5-year OS in Group 2 (31% vs 42%).

*Figure 11. Kaplan-Meier survival curve for OS and RFS (**Paper 2**)*



Number at risk (overall survival)

Group 1	36	34	19	13	8	3	2	2
Group 2	104	92	70	48	34	26	21	15
Group 3	34	29	19	17	11	8	5	2

Paper 3

Laparoscopic versus open liver resection in the posterosuperior segments: a sub-group analysis from the OSLO-COMET randomized controlled trial

HPB 2019, 21, 1485–1490

This study was a sub-group analysis from the OSLO-COMET RCT. For this sub-group analysis, patients who underwent resection in the postero-superior liver segments were identified from the OSLO-COMET database. Perioperative outcomes and health related quality of life (HRQoL) at 1- and 4-months were compared between open and laparoscopic approaches. In total, 136 were identified (62 in the laparoscopic group and 74 in the open group).

In this sub-group analysis, we found that patients in the laparoscopic group had shorter hospital stay but higher blood loss - with no significant difference in morbidity. HRQoL was significantly better after laparoscopy at 1-month after surgery.

*Table 1. Perioperative outcomes, postoperative complications and descriptive statistics of HRQoL (**Paper 3**)*

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 manoeuvre, 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

Paper 4

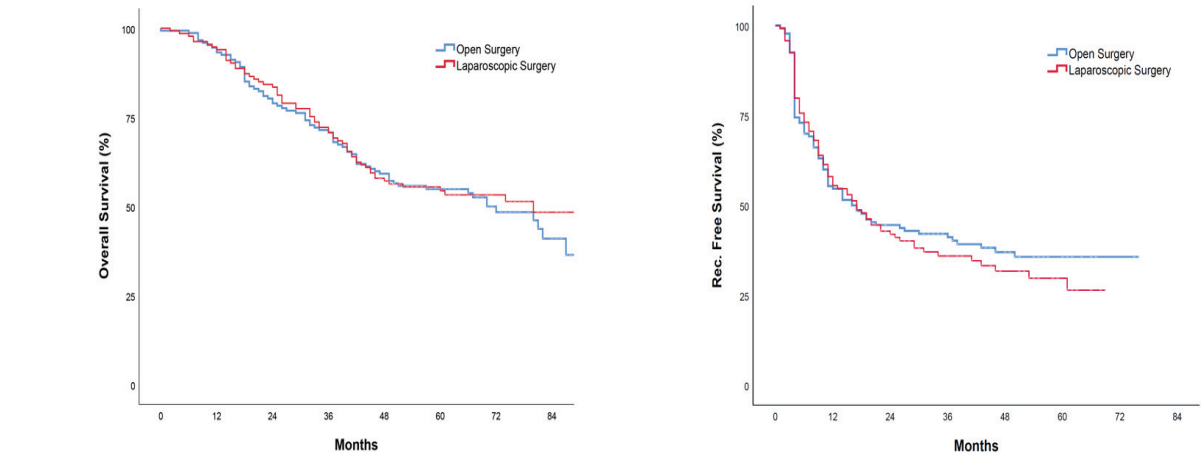
Long-term oncologic outcomes after laparoscopic versus open resection for colorectal liver metastases

Submitted to the Lancet

The OSLO-COMET trial was the first randomized controlled comparing laparoscopic and open liver resections for patients with CRLM. Long-term oncological outcomes were the main secondary endpoint of OSLO-COMET. In the current analysis, OS and RFS rates were compared between the two approaches. Univariable and multivariable Cox-regression analyses were performed to find risk factors that impacted survival.

The 5-year OS rate was 54% and 55% in the laparoscopic and open group, respectively, (p-value-0.672) at a median follow-up of 70 months. No difference was found in the 5-year RFS rates (30% vs 33%, p-value-0.569). Primary tumour lymph node involvement, size of largest liver metastasis and the presence of extrahepatic disease at the time of liver surgery were associated with worse overall survival.

*Figure 12. Kaplan-Meier survival curve for OS and RFS (**Paper 4**)*



DISCUSSION

The aim of this thesis was to investigate the role of LPSLR in the treatment of patients with CRLM by highlighting its surgical and oncological results (**Paper 1**), and comparing with the conventional open approach on data from a randomized controlled trial **(Paper 4**). At the same time, the surgical and oncological outcomes of LPSLR were examined in patients that could have been considered not suitable for laparoscopy, such as patients with multiple tumours and patients with tumours located in the "difficult" liver segments (**Paper 2 and Paper 3**).

Perioperative outcomes after LPSLR for CRLM

In **Paper I**, we conducted a clinical audit of our single centre results on LPSLR in patients with CRLM operated on between 1998 and 2016. Out of 296 patients included in this study, 92 patients underwent multiple concomitant liver resections. In total, 432 specimens were removed. In 20 patients (6.7%), liver resection was combined with RFA or cryoablation and 11 patients (3.7%) underwent simultaneous resection of their primary colon cancer.

The results of this study showed that LPSLR for CRLM was associated with low postoperative complications rate (14.5%), low rate of conversions to open surgery (1.7%) and no postoperative mortality. In this analysis, the median postoperative hospital stay was 3 days. In 81% of patients, R0 resection margin was achieved. Median resection margin was 3 mm (range, 0-30).

The findings of this paper seem to be in line with previously published case-series and comparative studies reporting the outcomes of parenchyma-sparing liver resections of CRLM for both, laparoscopic and open approaches (29, 31, 64).

In a multicentre comparative study by Hosokawa et al. (32) reporting the outcomes of 1720 patients from the LiverMetSurvey international registry, the authors compared parenchyma-sparing liver resection with right hemihepatectomy in patients with solitary small (≤ 3cm) CRLM. In this analysis, patients were operated mostly by open approach and only 8% of the patients had laparoscopic liver surgery. In total 242 patients (14%) underwent right hemihepatectomy and 1478 patients (86%) received parenchyma-sparing hepatectomy. The authors found that parenchyma-sparing strategy was associated with significantly less severe postoperative complications, transfusion rates and 90-days mortality, while long-term oncological outcomes were similar.

In a retrospective analysis of 3875 patients who underwent 4152 resections for liver malignancies at Memorial Sloan Kettering Cancer Centre, New York, US, the changes in postoperative morbidity and mortality after liver resection over 19 years were investigated (28). The most common indication was CRLM (64%). Divided into three time periods (1993 to 1999; 2000 to 2006; 2007 to 2012), the authors observed significant decrease in postoperative morbidity and mortality rates, which was mainly associated with a significantly decreased number of major liver resection over time. Multivariate analysis showed that major hepatectomy was an independent predictor of postoperative complications. Similar results were reported by Deng et al. (65) in a systematic review and meta-analysis on parenchyma-sparing vs extended hepatectomy for CRLM, where 18 studies were reviewed compiling data of 7081 patients.

Abovementioned studies consisted mainly of open liver resections, which is a standard approach in many centres. In the first randomized controlled into open and laparoscopic parenchyma-sparing liver resection (the OSLO-COMET trial), postoperative complications within 30-days were defined as the primary outcome (66). The results of OSLO-COMET demonstrated that LPSLR provides significantly lower rates of postoperative complications

(19% vs 31%, p-value=0.021) and shorter hospital stay (2 vs 4 days, p-value<0.001) compared to open surgery (55).

In a recent systematic review and meta-analysis on LPSLR by Kalil et al. (6), data from 579 patients undergoing LPSLR was reported. Most of the studies included in this analysis reported the results for solitary lesions. The authors stated that the data quality of the current literature is low and the small number of resected lesions, currently, is the main limitation of LPSLR. However, the results of the OSLO-COMET trial and **Paper 1** were not included in this meta-analysis, since the literature search included articles published before August 29, 2017.

To the best our knowledge, **Paper 1** represents the largest single centre study reporting surgical and oncological outcomes of LPSLR in patients with CRLM. Our findings suggest that LPSLR for CRLM is a safe procedure, as it provides adequate surgical and oncological outcomes. Hence, we believe that LPSLR should be considered in these patients whenever it is possible.

Long-term oncological outcomes after LPSLR for CRLM

Liver resection is the standard therapy and so far, the only potentially curative option in patients with resectable CRLM as 40 to 50% of the patients survive 5 years after surgery (25, 67, 68). Parenchyma-sparing resections have been shown to be superior to formal hepatectomies with respect to short-term outcomes (32, 65). However, there are some concerns regarding the oncological outcomes.

The main concern in parenchyma-sparing strategy is related to the short resection margins and, thus, a potential risk of local recurrences and poor overall survival. Traditionally, major hepatectomies and anatomic segmental resections have been proposed as a standard surgical treatment for patients with CRLM, supported by the theory that it reduces the incidents of intrahepatic recurrence by achieving wider resection margin (69, 70). It has been shown that

patients with resection margins larger than 10 mm survive longer than those with resection margin less than 10 mm (71, 72). However, other studies have opposed these findings and indicate that 1 mm resection margin can be considered oncologically adequate (73-75). The factors associated with long-term oncological outcomes are more related to tumour biology, and not to extent of resection (30). Moreover, recent studies have advocated that parenchyma-sparing liver resection does not increase the rates of positive resection margins or the risk of liver recurrence, but improves survival rates by increasing salvageability (12, 29, 76).

Another concern related to parenchyma-sparing strategy is the risk of remnant liver ischemia. In a retrospective analysis by Yamashita et al. the authors have shown that liver remnant ischemia grade 2 and higher is an independent predicator for poor oncological outcomes (77). Moreover, it was found that big tumours (>3cm), multiple metastases and non-anatomic resections were associated with high grades (≥2) of liver remnant ischemia. However, we believe that detailed anatomical knowledge (the relationship between tumour and surrounding vessels), adequate resection planning, taking into account the inflow and outflow of the resection area, as well as thorough use and understanding of intraoperative ultrasound are crucial when performing non-anatomic resections and contribute to the maximal reduction of the postoperative liver remnant ischemia.

In a comparative analysis by Mise et al. which compares parenchyma-sparing and non-parenchyma-sparing approaches for solitary small (<30 mm) CRLM, the authors performed sub-analysis of patients that developed liver-only recurrences and found that patients undergoing parenchyma-sparing liver resections had significantly better 5-year overall survival (72.4% vs 47.2%, p-value=0.047) (29). This can be explained by the fact that significantly higher number of patients underwent re-do liver resection in the parenchyma-sparing group (68% vs 24%, p-value<0.01). Similar to these findings, **in Paper 1,** we found that 69 out of 146 patients that developed liver recurrence after LPSLR, underwent repeat liver resection.

This demonstrates the high rates of repeat (possibly curative) surgical treatment in parenchyma-sparing strategy. Additionally, laparoscopic approach facilitates further liver resection, especially repeat LLRs, because of reduced formation of intra-abdominal adhesions (78).

In a multicentre study on laparoscopic resections for CRLM in 2009, Nguyen et al. reported the outcomes of 109 patients, and 5-year overall survival was 50% (79) . Similar results were demonstrated by our group in 2010 when describing data of 107 patients, where most of the patients received LPSLR (34). In **Paper 1,** we reported 5-year overall and recurrence-free survival rates 48% and 34%, respectively. These results are comparable to those reported for open surgery. One of the earliest studies comparing long-term oncological outcomes after open versus laparoscopic liver resection was conducted by Castaing and co-workers (80). In this matched series of 60 patients in each group from two highly specialized French centres, the authors concluded that in a highly specialized centre and in selected patients, similar oncological results can be achieved when performing open or laparoscopic liver resection for CRLM.

In a comprehensive systematic review and meta-analysis of 32 non-randomized comparative studies of laparoscopic and open liver resection for 4697 CRLM patients conducted by Xie et al., the authors found no difference in overall and recurrence free survival rates (58). Interestingly, higher rates of clear resection margins were observed after LLR. Recently published a multicentre propensity score analysis evaluating the rates and the impact of resection margins after laparoscopic and open liver resection for patients with CRLM, no difference was found in rates positive margins (81). In the subgroup analysis, comparing oncological outcomes in patients with positive and negative resection margins after open and laparoscopic groups, it was discovered that patients with positive margin had shorter overall survival after OLR, while no difference was seen after LLR. This may be explained by

significantly higher number of repeat liver resections in the laparoscopic group compared with its open counterpart (48% vs 30%, p-value<0.001).

Current literature comparing long-term oncological outcomes after LLR and OLR for patients with CRLM generally has a low level of evidence. In **Paper 4,** analysing long-term oncological outcomes of the OSLO-COMET randomized controlled trial, we found no difference in overall and recurrence-free survival rates. Five-year overall survival rate was 55% in the open group and 54% in the laparoscopic group (p-value=0.672). However, in contrast to the aforementioned propensity score analysis, we did not find difference in the rate of repeat liver surgery for intrahepatic recurrences. We performed univariable and multivariable Cox regression analyses to identify prognostic factors that impact overall and recurrence-free survival, and surgical approach was not found to influence survival in this cohort.

LPSLR for patients with multiple CRLM

LLR has been considered to be more suitable in patients with solitary lesions of less than 5cm located in the antero-lateral liver segments (45). Patients with multiple metastases may be challenging for LPSLR, due to the need of repositioning the patient during the surgery and placing new trocars. The current literature describing LPSLR for CRLM is restricted to the patients with solitary lesions and few studies report the outcomes of LPSLR for multiple CRLMs (6, 82).

Patients with multiple CRLM have been one of the main subgroups considered for LPSLRs at our hospital. In **Paper 1,** 448 metastases were removed in 296 procedures. Out of 296 patients, 92 patients underwent multiple LPSLR for their multiple metastases and of these, 80 patients

had solely liver resections, while 12 patients received RFA in addition to multiple concomitant liver resections.

Paper 2 of this thesis was a retrospective study focusing on the outcomes of laparoscopic approach for patients with multiple CRLMs. Our aim was to assess the feasibility and safety of laparoscopic approach for this group of patients. To the best our knowledge, this is the first study focusing on use of laparoscopic approach in patients with multiple CRLM. 171 patients included in this study and were divided into three groups. Group 1 included patients who received a single resection, Group 2 comprised of patients with multiple resections, and Group 3 consisted of patients who received RFA or cryoablation in addition to liver resection. In this study, we sought to investigate the surgical and long-term oncological outcomes in patients with multiple laparoscopic liver resections (Group 2) and compare those with the outcomes in patients who received a single resection for multiple lesions (Group 1).

To evaluate patients' background data regarding oncological outcomes, we calculated the Fong (83) clinical score and the preoperative Basingstoke Predictive Index (25) which were similar between the groups. Perioperative outcomes were comparable between the groups, despite the tendency of a lower rate of postoperative complications in the multiple resection group. There were three postoperative liver failures in Group 1, while none were found in Group 2 and Group 3 (p-value=0.016). With regards to histopathological data, no difference was found in R0-resection rates, tumour size and number of removed lesions, while the median weight of resected specimen was significantly higher in Group 1 (257g vs 90 g; p-value=<0.001). The groups were similar in terms of long-term oncological outcomes, including 5-year RFS and OS rates.

In this study, we demonstrate that laparoscopic multiple concomitant parenchyma-sparing liver resections are appropriate in patients with multiple CRLMs. Furthermore, performing multiple concomitant resections rather than a single greater resection did not increase operation time,

blood loss and conversion rates. Multiple LPSLR may decrease the rates of postoperative complications and liver failure.

In the multiple resection group where postoperative complications rate was 19%, 76 patients (73%) presented with bilobar metastases. Resection of bilobar tumours is challenging, due to the difficulties to achieve appropriate resection margins and preserve sufficient functioning liver parenchyma. Patients with bilobar CRLM have worse prognosis compared to those with multiple unilobar metastases (84, 85). However, several studies have shown that in selected patients, similar outcomes can be achieved performing one- or two-stage liver resection (86-89).

Multiple parenchyma-sparing liver resections may be the only possibility for curative treatment for patients with bilobar metastases (33). In the study conducted by Gold and co-workers (30), which assessed the parenchyma-sparing strategy in the treatment of patients with bilobar CRLM, a total of 440 patients operated from 1992 to 2003 were evaluated and divided into four time periods to determine the trends over time. The authors found high risk of postoperative complications (51%) in this group of patients. However, postoperative mortality rates decreased over time (from 5.4% to 1.2%) which was associated with an increase in the numbers of parenchyma-sparing procedures, and no compromise of cancer specific long-term outcomes. It was stated also that parenchyma-sparing technique should be preferred in these patients whenever possible.

Our findings in **Paper 2** together with the outcomes of aforementioned studies recommend widespread use of this strategy in specialized centres.

LPSLR for CRLM located in the postero-superior segments (I, IVa, VII, VIII)

LPSLRs in the postero-superior liver segments has always been considered to be technically challenging and limited only to expert surgeons. Laparoscopic resections in these segments are complicated mainly due to inadequate visualisation and limited working space and, as a result, it is difficult to control bleeding and achieve negative resection margin, compared to resections performed in the antero-lateral segments (90-92).

Considering the complexity of resections in these segments, in the Louisville consensus meeting, the experts recommended to define resections in the postero-superior segments as 'major resections', while in the Southampton Consensus Guidelines these resections were re-defined as 'technically major' (45, 48). According to the Southampton guidelines, appropriate experience in minor laparoscopic liver surgery and presence of structured training programs in centres are essential, before approaching these type of procedures (48). A recently published multicentre study evaluating the learning curve of LLRs in the postero-superior segments by CUSUM analysis of 464 patients, found that 40 and 65 procedures were needed to complete the learning curve for atypical and anatomical resections, respectively (93). This shows the complexity of these procedures.

In a nationwide analysis from the Netherlands, reporting the data of 6951 procedures from 27 centres, the authors discovered that these 'technically major' liver resections are mostly limited to experienced surgeons, and are associated with greater operation time, blood loss, postoperative complications and postoperative hospital stay than resections in the antero-lateral segments (94).

Several retrospective studies, a propensity score matched analysis and a meta-analysis, have shown, that in selected patients, LPSLR in the postero-superior segments provides similar or better perioperative outcomes when compared to open surgery (95-98). In a recent meta-analysis by Zheng and co-authors, comparing open and laparoscopic liver resections in the

postero-superior segments, data of 788 patients (417 in the open group and 371 in the laparoscopic group) was analysed (97). In this analysis of eight studies, perioperative and oncological outcomes were compared and it was shown that laparoscopy was linked to longer operative time, lower postoperative complication rate and shorter hospital stay, whereas other perioperative results including blood loss, transfusion rate and R0 resection rate were comparable. The long-term oncological outcomes were similar between the two approaches in patients with CRLM and hepatocellular carcinoma. Similar findings were shown in a multicentre propensity score-matched analysis by Scuderi and co-workers (96).

In **Paper 3** of this thesis, we analysed patients with resections in the postero-superior segments from the database of the OSLO-COMET trial and compared perioperative outcomes between open and laparoscopic approaches. In contrast to the meta-analysis by Zheng et al. (97), we found no difference in operation time and postoperative complication rate, while blood loss was higher in the laparoscopic group. However, transfusion and R0 resection rates were similar between the groups similar to the findings of aforementioned meta-analysis. In this sub-group analysis of a randomized controlled trial, we compared HRQoL between open and laparoscopic approaches at 1- and 4-months after surgery by using the 36-item Medical Outcomes Study Short Form described in the OSLO-COMET trial (55). It demonstrated that patients after LLR reported significantly better HRQoL at 1-month and no difference after 4-months after surgery.

As one can observe, the findings of **Paper 3,** in particularly blood loss and operative time, are not in line with the findings of abovementioned reports. This may be associated with retrospective nature of the previous studies and selection of patients included in analyses. We believe that our sub-group analysis of a randomized controlled trial provides a more adequate picture of the current state of LPSLR in 'difficult' liver segments and supports the further development of these complex procedures.

Limitations

Several limitations are present for each study included in this thesis and can be classified as general and study-specific limitations. General limitations include generalizability and reproducibility of the results (external and internal validity). All studies of this thesis are based on the data from a single high-volume centre. Study-specific limitations will be discussed per case.

Paper 1 does not conduct any comparative analysis with the results of its correspondent open approach. However, this was compensated by comparing our results with the available literature on open approach for CRLM. The retrospective design of this study is another limitation and leads to several drawbacks: firstly, our hospital is a tertiary-level referral centre and the only hospital performing liver surgery in our region and this minimizes any bias based on referral patterns. However, some patients might have been refused surgery at referring hospitals and have never been evaluated by the multidisciplinary HPB team at our hospital. Secondly, the long study period (from August 1998 to March 2016) may lead to preoperative selection bias within our institution. Lastly, there may also be differences in surgical instrumentations, pre- and postoperative management of patients, as well as indications and management of chemotherapy treatment during the study period.

Besides the retrospective design of **Paper 2,** another obvious weakness of this study is the big difference in number of patients in group 1 and group 2 (36 and 104), which may lead to false negative findings. Further studies with a larger cohort of patients are needed to confirm the results of this study.

Paper 3 was a post-hoc subgroup analysis of data from the OSLO-COMET RCT and because inadequate power, both false positive and false negative outcomes are possible. For example, in contrast to the findings of OSLO-COMET, in which significantly less postoperative

complications in the laparoscopic group were observed, we found no significant difference in this sub-group analysis.

In **Paper 4** we presented long-term oncological outcomes of the OSLO-COMET trial. However, the trial was not designed to have a high power to spot differences in secondary outcomes, thus small differences in survival rates may have occurred. Another limitation for this trial is that this trial was performed in a single centre, as other studies of this thesis. However, it is an expert centre with a very high volume of laparoscopic and open liver surgery. The surgeons involved had long training in laparoscopic liver surgery when the study started. Thus, both techniques were applied in ideal conditions and thus could express their best possible outcomes. Consequently, outcomes of this trial are not directly transferable to non-expert centres.

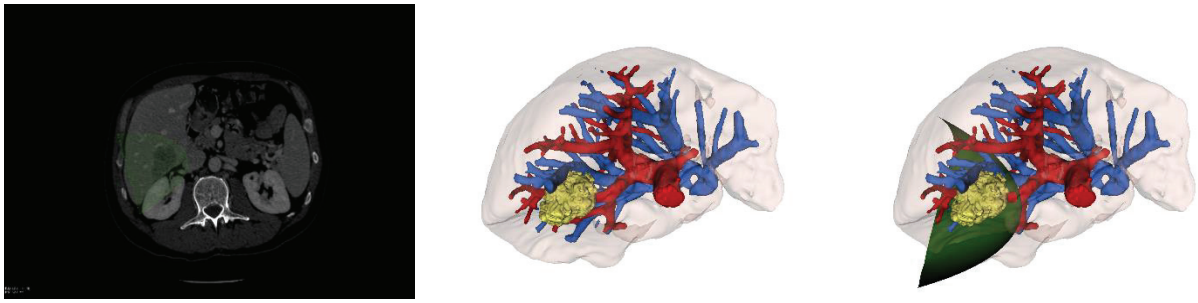
Future aspects

The current literature related to the use of LPSLR in patients with CRLM is mainly based on retrospective studies and systematic reviews on these studies. The only published randomized trial on this topic is the OSLO-COMET trial showing the advantages of laparoscopic approach over open counterpart. However, future multicentre RCTs, studies based on data from international registries are needed to test and/or complement the findings reported by our group.

A multicentre RCT into open and laparoscopic hemihepatectomy, the Orange II-plus trial, has currently completed the patient inclusion, and the international study group is at present analysing the results. The findings of this trial will supplement the evidence provided by OSLO-COMET, so that both parenchyma-sparing and formal major hepatectomies will have been studied in a RCT. Additionally, the ongoing Orange Segments trial will bring valuable evidence in laparoscopic resection in the ‘difficult’ liver segments.

In our centre, minimally invasive surgery, and especially LPSLR has become a standard surgical method in patients with CRLM. Nevertheless, there is room for improvements. A possible aid to improve laparoscopic liver resection could derive from medical technology advancements: through medical image segmentation and reconstruction processes, 3D patient-specific anatomical models can be created. These could provide better understanding of individual patient liver anatomy, the tumour location and its relation to the vessels; thanks to a more precise resection planning taking into account both blood inflow and outflow in the resection area and using intraoperative navigation tools may improve surgical and oncological outcomes. Through these processes, one may preserve more healthy parenchyma, without increasing or even decreasing the rates of positive resection margins and reducing the risk of ischemia in the future liver remnant (99-102). These applications may also be more beneficial in cases with difficult located and multiple lesions.

Figure 13. 3D liver anatomy and resection planning



Ablation techniques bring another possibility to perform minimally invasive parenchyma-sparing liver surgery (103). Despite the increased use of ablation techniques in patients with CRLM, liver resection remains the gold standard (104). Liver ablation is still associated with high risk of local tumour progression, due to difficulties to check the accuracy of the margins. However, ablation in combination with parenchyma-sparing liver resection may extend treatment options for patients with bilobar metastases (105). In case of deeply located lesions,

where the liver resection is technically not feasible or too challenging, ablation in conjunction with resection may be preferred over formal hepatectomies (10).

Radiofrequency and microwave thermal ablations are currently most frequently used techniques, but the major limitation of these thermal ablative techniques is that they deposit thermal energy and may damage adjacent vital structures. Another limitation is the so called the “heat sink-effect”, i.e. the decrease of the ablation effect by cooling of perivascular tissue by the blood flow (106). Ablative technologies are in constant development and there are prospects for improvement of current treatment methods. The above-mentioned limitations of thermal ablation techniques may be overcome by novel methods, such as irreversible electroporation (IRE) and high-intensity focused ultrasound (HIFU) ablation techniques (107, 108). The latter method makes this minimally invasive procedures even less invasive / non-invasive. These relatively new methods to treat liver malignancies are scarcely reported and require further investigations.

CONCLUSIONS

Paper I

- Laparoscopic parenchyma-sparing liver resection is feasible and safe in patients with colorectal liver metastases and is associated with satisfactory surgical and long-term oncological outcomes.
- This approach highly facilitates further surgical treatment in patients with recurrences in the liver.

Paper II

- Laparoscopic multiple concomitant liver resection provides similar surgical and oncological outcomes compared to single greater resections, and thus should be prioritized whenever possible.

Paper III

- Laparoscopic parenchyma-sparing resection of colorectal liver metastases in the postero-superior segments is a rational alternative to open approach providing several advantages such as shorter hospital stay, enhanced recovery and better health related quality of life after surgery.

Paper IV

- In a randomized controlled trial conducted at a high-volume specialized centre, laparoscopic parenchyma-sparing liver resection for colorectal cancer metastases is as good in terms of long-term oncological outcomes as traditional open technique.

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PAPERS

I

Laparoscopic Parenchyma-Sparing Liver Resection for Colorectal Metastases.

Aghayan D L, Pelanis E, Fretland Å A, Kazaryan A M, Sahakyan M A, Røsok B I, Barkhatov L I, Bjørnbeth B A, Elle O J and Edwin, B.

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research article

Laparoscopic parenchyma-sparing liver resection for colorectal metastases

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Background. Laparoscopic liver resection (LLR) of colorectal liver metastases (CLM) is increasingly performed in specialized centers. While there is a trend towards a parenchyma-sparing strategy in multimodal treatment for CLM, its role is yet unclear. In this study we present short- and long-term outcomes of laparoscopic parenchyma-sparing liver resection (LPSLR) at a single center.

Patients and methods. LLR were performed in 951 procedures between August 1998 and March 2017 at Oslo University Hospital, Oslo, Norway. Patients who primarily underwent LPSLR for CLM were included in the study. LPSLR was defined as non-anatomic hence the patients who underwent hemihepatectomy and sectionectomy were excluded. Perioperative and oncologic outcomes were analyzed. The Accordion classification was used to grade postoperative complications. The median follow-up was 40 months.

Results. 296 patients underwent primary LPSLR for CLM. A single specimen was resected in 204 cases, multiple resections were performed in 92 cases. 5 laparoscopic operations were converted to open. The median operative time was 134 minutes, blood loss was 200 ml and hospital stay was 3 days. There was no 90-day mortality in this study. The postoperative complication rate was 14.5%. 189 patients developed disease recurrence. Recurrence in the liver occurred in 146 patients (49%), of whom 85 patients underwent repeated surgical treatment (liver resection [n = 69], ablation [n = 14] and liver transplantation [n = 2]). Five-year overall survival was 48%, median overall survival was 56 months.

Conclusions. LPSLR of CLM can be performed safely with the good surgical and oncological results. The technique facilitates repeated surgical treatment, which may improve survival for patients with CLM.

Key words: laparoscopic parenchyma-sparing liver resection; colorectal cancer; liver metastases; survival

Introduction

Colorectal cancer is the third most common cancer worldwide.[1] Liver resection is considered the only curative treatment for colorectal liver metastases (CLM), with postoperative 5-year survival rates of 30–58%.[2-5] Parenchyma-sparing liver resection (PSLR) has, in many centers, become an essential part of multimodal treatment of CLM. The parenchyma-sparing approach allows radical resection with maximum preservation of liver parenchyma, thereby decreasing the risk of postoperative liver failure and facilitating repeated resections in the case of liver recurrence.[6-13]

Laparoscopic liver resection (LLR) has progressively developed during the past two decades and the advantages are well-known.[14-20] Our experience in LLR has been reported previously.[18,21-27] The

short- and long-term outcomes after laparoscopic parenchyma-sparing liver resection (LPSLR) for CLM have been minimally reported in the literature.[28-30] In this study we report short and long-term outcomes after 18 years of LPSLR for CLM in a single center.

Patients and methods

Rikshospitalet is the tertiary referral center for hepato-pancreato-biliary surgery for the South-Eastern Regional Health Authority in Norway. Between August 1998 and March 2017, LLRs were performed in 951 procedures. Of these, patients who primarily underwent LPSLR for CLM between August 1998 and March 2016 were identified from the continuously updated database and included in the study. Patients who previously underwent open liver resections were excluded from the study. LPSLR was defined as non-anatomic laparoscopic liver resections. In one case LPSLR was performed in a patient with a transplanted liver. Patients who underwent hemihepatectomy or sectionectomy were excluded, as were patients with planned two-stage procedures. Data were collected from Electronic Health Records. The study was performed in accordance with the Declaration of Helsinki, and all patients signed informed consent for the procedures.

Standard preoperative investigations included contrast-enhanced X-ray computed tomography (CT) scans of the thorax and abdomen, clinical biochemistry, magnetic resonance imaging (MRI) of the liver (if required) and positron emission tomography (PET) scan (if required).

Synchronous CLM was defined as liver metastases detected within 12 months of diagnosis of the primary CRC, otherwise metastases were defined as metachronous.

The surgical technique for LLR at our centre has been described previously.[18,21] Laparoscopic ultrasonography and advanced laparoscopic equipment were preconditions. The main dissection instruments were LigaSure® (Covidien, Mansfield, MA, USA), Thunderbeat® (Olympus, Tokyo, Japan) or Cayman® (B.Braun, Melsungen, Germany), sometimes assisted by ultrasonic aspirators, mainly CUSA® (Integra, Cincinnati, OH, USA), SonoSurg aspirator® (Olympus, Tokyo, Japan) and Söring aspirator® (Söring, Quickborn, Germany). Ultrasonic dissectors, as Sonicision® (Covidien, Mansfield, MA, USA) or Harmonic Scalpel® (Ethicon, Sommerville, NJ, USA) were mostly used to achieve a superficial parenchymal transection. Surgical clips and the LigaSure® were used in small and medium-sized vessel transections, whereas the Endo-GIA®(Covidien, Inc.) was applied for transection of major vessels.

Non-steroidal anti-inflammatory drugs and intravenous paracetamol were used for postoperative analgesia. Opioids were given if required. Patients were encouraged to mobilize early and resume oral intake as soon as tolerated.

Tumor size was measured following specimen fixation in formaldehyde during the histopathologic analyses of resected specimens. The distance from the tumor to the resection margin was measured macroscopically and microscopically after fixation. All resection margins were assessed microscopically with regard to tumor tissue, a resection margin of less than 1 mm was defined as positive (R1). In cases where multiple resections were performed, the narrowest resection margin was recorded.

Postoperative complications were categorized in accordance to the Accordion classification.[31,32]

Patients were treated with neoadjuvant and adjuvant chemotherapy following national guidelines. The data are presented as median (range) and/or number (percentage). Overall survival was estimated from liver resection until death and recurrence-free survival was estimated from liver resection until the first registered recurrence of the disease or progression in cases with extrahepatic metastases. Survival probabilities were calculated using the Kaplan–Meier method. SPSS software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, version 22.0, Armonk, NY, USA: IBM corp) was used for statistical analysis.

Results

Perioperative data

Between August 1998 and March 2016, a total of 296 patients underwent LPSLR as the primary surgical treatment for CLM at Oslo University Hospital. Baseline characteristics are summarized in Table 1. Resection of solitary metastases was performed in 204 patients (69%), multiple resections were performed in the remaining 92 patients (31%). Two concomitant liver resections were performed in 66 cases, three resections in 12 cases, four resections in 12 cases, five and seven resections in the two remaining cases. In total, 432 liver specimens were resected in 296 procedures. Median resection margin was 3 mm (range 0 to 30 mm). The total

TABLE 1. Patient characteristics (N = 296)

Age, years, median (range)	66 (29–89)
Gender (female/male)	110/186
BMI, kg, median, (range)	25 (16–42)
ASA score	2 (1–3)
Synchronous/metachronous	224/72
Neoadjuvant chemotherapy yes/no/no information	122/168/6
Preoperative CEA, median (range)	12 (1–498)
Extrahepatic disease at the time of liver resection, n (%)	21 (7.1)
Liver involvement (unilobar/bilobar)	233/63

ASA = American Society of Anestesiology; BMI = body mass index; CEA = carcino-embryonic antigen

TABLE 2. Intraoperative details and postoperative complications

Operative time, min, median (range)	134 (20-373)
Blood loss, ml, median (range)	200 (<50-4000)
No. of resected specimens pr. procedure, 1/ 2/ 3/ 4/ 5/ 7 Total	204/ 66/ 12/ 12/ 1/ 1 432
Total No. of removed lesions	448
Max diameter of lesions, mm, median d (range)	22 (4-80)
Resection margin, R0 / R1 (n=294) Median, mm (range)	239 / 55 3 (0-30)
Conversion to open access, n (%)	5 (1.7)
Combination with RFA or cryoablation, n (%)	20 (6.7)
Simultaneous resection with primary, n (%)	11 (3.7)
Postoperative complications, Accordion, n (%) Grade 2 / Grade 3 / Grade 4 / Grade 5	43 (14.5) 19/ 14/ 8/ 2
Postoperative hospital stay, days, median (range)	3 (1-35)

RFA = Radiofrequency ablation

TABLE 3. Long-term outcomes

Disease recurrence, n (%)	189 (64)
Liver recurrence, n (%)	146 (49.3)
Isolated liver recurrence, n (%)	75 (25.3)
Recurrence in resection bed, n (%)	7 (2.3)
Repeat liver resection, n (%)	69 (23.3)
Secondary RFA, n (%)	14 (4.7)
Median overall survival, months (95% confidential interval)	56 (46-66)
3-year overall survival rate, %	68
5-year overall survival rate, %	48
3-year recurrence-free survival rate, %	36
5-year recurrence-free survival rate, %	34

RFA = Radiofrequency ablation

number of removed lesions was 448 and the median diameter was 22 mm (range: 4 to 80 mm). The resected tumors were located in all liver segments (Table 2).

Five procedures (1.7%) were converted to open surgery. The reason for conversion was hemorrhage (n = 3), unfavorable location of tumor (n = 1) and small intestine perforation (n = 1). In 20 cases LPSLR was combined with ablation (n = 18) or cryoablation (n = 2). 11 patients underwent synchronous resections for colorectal cancer. Median operative time was 134 min (20–373), while median blood loss was 200 ml (<50–4000). Postoperative complications developed in 43 patients (14.5%) and were graded according to the expanded Accordion classification (Table 2). The median hospital stay was 3 days (range: 1–35). There was no 90-day mortality in this study. Perioperative adverse events are described in Table 2.

Long-term outcomes

Median observation time was 40 months (4 to 191). Twenty-one patients had extrahepatic metastases (16 with lung metastases, two with metastases on the peritoneum, two with the metastases in the brain and the lungs, and one with metastasis in the spine) at the time of liver resection.

Disease recurrence or progression of extrahepatic metastases occurred in 189 (64%) patients on a median follow-up of 6 months. Recurrence in the liver occurred in 146 (49.3%) patients with a median follow-up of 6 months, including 7 patients (2.3%) who experienced local recurrence. Isolated hepatic recurrences developed in 75 patients. The most common sites of recurrence were liver, lungs, peritoneum and brain. A total of 69 patients underwent repeated liver resections, of whom 43 had laparoscopic and 26 had open resections. Additionally, 14 patients underwent secondary radiofrequency ablation and two patients had liver transplantation for liver recurrences (Table 3).

Median overall survival was 56 months One-, three- and five-year overall survival rates were 97%, 68% and 48%, respectively (Figure 1).

One-, three- and five-year recurrence-free survival was 50%, 36% and 34%, while the median recurrence-free survival was 12 months (Table 3).

Discussion

In this study, we report a single center experience of LPSLR for CLM. In 1960's and 1970's the major-

ity of patients with CLM (70–80%) were never candidates for resection, but nowadays a large portion of patients undergo surgery due to significant improvements in preoperative investigations, surgical techniques, anesthesia, chemotherapy regimens and the expansion of resectability criteria.[4,5] Based on oncologic reasoning at that time, hemihepatectomies were considered the only curative option in patients with CLM. Nevertheless, over the years, PSLR has increasingly been used for CLM.[6,33] There are two main reasons for this: the evolution of the concept of resectability and the increased knowledge on tumor biology.[34,35]

Over the past decades, the concept of tumor resectability in CLM has changed significantly. While in the 1970s, resection was considered only in patients with solitary liver metastasis, nowadays resection of CLM is considered regardless of tumor size and number, provided that a resection with negative margins is possible, that stable disease can be achieved, that the remaining parenchyma is sufficient to prevent liver failure, and that there is no unresectable extrahepatic disease.[36]

There are two known mechanisms for hepatic spread of colorectal cancer: metastasis from the primary tumor, and metastasis from other existing metastases. In contrast to hepatocellular carcinoma, tumor cells from CLM do not migrate into intrahepatic portal branches to form secondary intrahepatic metastases. Instead, intrahepatic lymphatic invasion can be responsible for ''remetastasis'' from liver metastases and may be a prognostic factor for CLM.[37-42]

PSLR is an essential part of multimodal treatment of CLM, as it avoids unnecessary removal of normal parenchyma and is associated with less surgical stress, fewer postoperative complications and feasibility of future resections.[6,33,43]

LLR is becoming an important alternative to conventional open surgery. In this study we included patients who primarily underwent LPSLR for CLM. All resections aimed to achieve complete tumor resection and to preserve as much liver parenchyma as possible. We report both perioperative and long-term oncologic outcomes. Five patients (1.7%) were converted to open surgery in our series, which is a lower conversion rate than reported for both minor and major laparoscopic hepatectomies by other groups.[16,28,29,44] Postoperative complications developed in 43 cases (14.5%) and the median postoperative length of stay was 3 days. Perioperative outcomes in this study are consistent with earlier reported surgical results after open and laparoscopic PSLR for CLM.[7,9-12,28,29]

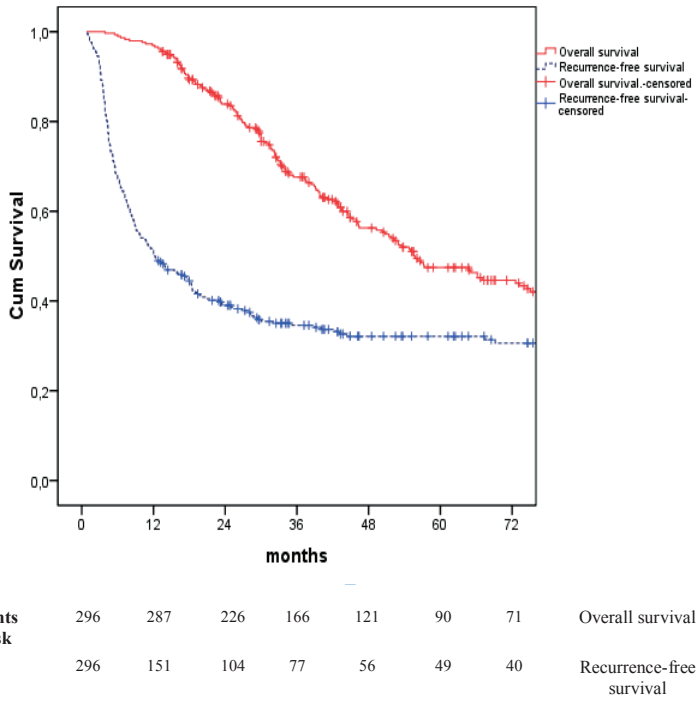

FIGURE 1. Kaplan-Meier survival curves.

Previous studies have indicated that survival rates were higher in patients with resection margins larger than 10 mm compared to those with the resection margins less than 10 mm.[45,46] Other studies have opposed these findings and indicate that predicted margins of less than 10 mm should not be an exclusion criteria for resection in these patients.[40,47] Moreover, recently two large studies suggested that a one mm cancer free margin can be considered oncologically adequate for resection of CLM.[27,48]

In the present study, isolated hepatic recurrence developed in 75 cases, for which repeated hepatectomy was performed in 68% (51 of 75) (18 open, 33 laparoscopic). Local recurrence developed in seven patients (2.3%), five following R1 resection (9%) and two following R0 resection (0.8%). The relatively low number of local recurrences after R1 resections can be explained by the use of energy-based surgical instruments for parenchyma transection, that induce thermal damage to the surrounding tissue and thus create an additional zone of tissue necrosis. As a result, the true resection margins may be several millimeters wider than those estimated by the pathologist.

In our study liver recurrences were frequently resectable. A total of 69 repeat liver resections (51 with isolated liver recurrence and 18 with extrahepatic resectable metastases) were performed.

Tanaka *et al*.[49] showed that minor resections may offer a long-term survival advantage compared to a major resection in patients with multiple CLM. In our study 80 patients received solely multiple LPSLR, and the five-year survival for this group was 44%.

In the study published in 2014, Evrard *et al*.[50] combined PSLR with RFA in 288 patients, five-year overall survival was 37%, compared to 39% for the 18 patients that underwent resection combined with local ablation in our study.

These outcomes demonstrate that multiple simultaneous LPSLRs are feasible and may be preferred over single major resection in a substantial portion of patients. In patients with additional unfavorable located lesions, PSLR can be combined with local ablation avoiding formal resections with acceptable oncological results. In addition, the patients with formal resections compared with parenchyma-sparing technique have reduced chance of further surgical treatment.[6]

Alvarez *et al*.[6] showed in a systematic review that five-year overall survival rates varied from 27% to 60% for anatomic and from 29% to 61% for non-anatomic liver resection, compared to 48% in our study.

In conclusion, outcomes after laparoscopic parenchyma-sparing liver resection are comparable to those after open major and minor hepatectomy. In centers with sufficient expertise, this may be a good treatment option for patients with CLM.

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Long-term oncological outcomes after laparoscopic versus open resection for colorectal liver metastases

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IV

Long-term oncological outcomes after laparoscopic versus open resection for colorectal liver metastases: A single-centre, assessor blinded, randomized controlled trial

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Summary

Background: Despite the recent worldwide dissemination of laparoscopic liver surgery, no high-level evidence supports the oncological safety of this approach.

Methods: In this randomized controlled trial, patients with radically resectable liver metastases from colorectal cancer were assigned to undergo laparoscopic or open liver resection. Patients were recruited from Oslo University Hospital, the only provider of liver surgery for the 3 million inhabitants of South-East Norway. The primary outcome of the trial was postoperative morbidity within 30 days. Five-year overall and recurrence-free survival rates were predefined secondary endpoints.

Findings: From February 2012 to January 2016, a total of 280 patients were included (laparoscopic surgery, n=133; open surgery, n=147) in the trial. At a median follow-up of 70 months, 5-year overall survival rate was 54% in the laparoscopic group and 55% in the open group (Hazard Ratio 1·07 [95%CI, 0·77 to 1·50]; p=0·67). The 5-year recurrence-free survival rate was 30% in the laparoscopic group and 35% in the open group (Hazard Ratio 1·09 [95%CI, 0·80 to 1·49]; p=0·57).

Interpretation: Laparoscopic surgery in patients with colorectal liver metastases was associated with rates of overall and recurrence-free survival similar to open surgery. These findings support the further implementation of laparoscopic surgery in the treatment of colorectal liver metastases.

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ClinicalTrials.gov number, NCT01516710

Keywords: colorectal liver metastases, survival, hepatectomy, laparoscopy, liver resection, parenchyma-sparing liver surgery, randomized controlled trial

Introduction

Colorectal cancer is the third most common cancer and the second cause of cancer death worldwide.[1] More than 1.8 million new cases were reported globally in 2018.[2] Approximately half of patients with colorectal cancer develop liver metastases.[3] As a result of improved diagnostics, oncological treatment and surgical techniques, an increasing number of patients are candidates for curative surgical resection.[4,5]

Traditionally, liver tumours have been removed with open surgery. Since the 1990's laparoscopic surgery has replaced the traditional open approach for many surgical procedures. The development of minimally invasive techniques in liver surgery has been slow, but recently laparoscopic programmes for liver surgery have been established in expert centres on all continents.[6,7] Retrospective analyses have documented improved short-term outcomes and similar survival for laparoscopic and open surgery for colorectal liver metastases,[8,9] but these techniques have never been compared in a randomized controlled trial.

The OSLO-COMET trial was the first randomized controlled trial to compare laparoscopic and open surgery for colorectal cancer liver metastases. The primary endpoint demonstrated a significant reduction in morbidity from 31% in the open group to 19% in the laparoscopic group, and laparoscopic surgery was associated with shorter hospital stay, better quality of life and was cost-effective.[10,11] We here present the long-term oncological outcomes of this trial.

Materials and Methods

OSLO-COMET (Clinicaltrials.gov identifier NCT01516710) was an investigator-initiated, open-label, single-centre, randomized controlled trial recruiting patients from Oslo University Hospital, Oslo, Norway. The trial was approved by the Regional Ethical Committee of South Eastern Norway (REK Sør-Øst B 2011/1285) and the Data Protection Officer of the Oslo University Hospital. The authors gathered and analysed 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. The primary and secondary endpoints, inclusion criteria, surgical techniques and perioperative management have been published in the trial protocol.[12]

From February 2012 to February 2016 a total of 294 patients were screened and 280 (95%) patients with colorectal liver metastases were randomized to laparoscopic (n=133) or open (n=147) parenchyma-sparing liver resection (defined as resection of less than three consecutive liver segments). Patients who required formal hemihepatectomy, resection with reconstruction of vessels/bile ducts and resection combined with ablation were excluded. Short-term outcomes have been published previously.[10] Five-year overall survival and recurrence-free survival rates were predefined secondary endpoints.

Patients were treated with neoadjuvant and adjuvant chemotherapy following national guidelines, at the discretion of the multi-disciplinary team.[13] Neoadjuvant chemotherapy was defined as the administration of therapeutic agents targeting liver metastases prior to liver surgery. The perioperative chemotherapy was based on 5-fluorouracil/leucovorin and

oxaliplatin (Nordic FLOX), which is the standard first line treatment for metastatic colorectal cancer in Norway.[14] The treatment was personalized so that patients with comorbidities or intolerance of oxaliplatin only received 5-fluorouracil/leucovorin, while patients that progressed on Nordic FLOX or that needed maximal tumour reduction received irinotecan-based regimens with or without antibodies (cetuximab, panitumumab or bevacizumab).

Statistics

Descriptive data are presented with means, standard deviations, medians, interquartile ranges (IQR), numbers, and percentages. Categorical variables were compared using the chi-square or the Fisher's mid-P test when applicable. Continuous variables were compared using the Mann–Whitney U test and the Student's T test for variables with non-normal and normal distribution, respectively. Long-term outcomes were analysed by intention-to-treat (ITT) analysis and by per protocol (PP) analysis. For the per protocol analysis, patients who did not receive the allocated treatment or had any deviation from the study protocol were excluded (Figure 1).

Overall survival was estimated from liver resection until death and recurrence-free survival was estimated from liver resection until the first radiologic proof of disease recurrence. Survival data for the treatment arms were analysed with Kaplan-Meier plots, log-rank tests for equality of survival curves, and Cox proportional hazard regression. The median follow-up was calculated by the reverse Kaplan-Meier method.

To identify predictors of recurrence and survival, univariable and multivariable analyses were performed using the log-rank test and the Cox proportional hazard model with treatment group as an explanatory variable. All variables associated with survival with $p \leq .2$ in the univariable analysis were subsequently included into a Cox multivariable regression model and p-values $\leq .05$ were considered statistically significant.

Results

A total of 273 patients underwent surgery. The final patient received surgery on February 28th 2016 and the survival analysis was performed with January 8th 2020 as censor date, with a minimum of 46 months follow-up. As eight patients had benign tumours at final histopathology, eight patients were inoperable and five were converted to other surgical treatments, 252 of the patients underwent resection according to the study protocol, 119 in the laparoscopic group and 133 in the open group (Figure 1). No patients were lost to follow-up and median observation time was 70 months (95% Confidence Interval (CI), 67 to 73). Baseline characteristics are presented in Table 1.

By ITT analysis (n=280), median overall survival was 80 months (95% CI 63 to 97) in the laparoscopic surgery group and 70 months (95% CI 48 to 92) in the open surgery group (Hazard Ratio (HR) 1.07 [95%CI, 0·77 to1·50]; p=0·67). Overall survival rates for 1-, 3- and 5-years were 94%, 71% and 54% in the laparoscopic group, and 93%, 71% and 55% in the open group.

By per-protocol analysis (n=252), median recurrence free survival was 17 months (95%CI, 10 to 23) in the laparoscopic group and 16 months (95%CI, 8 to 24) in the open group, (HR1·09 [95%CI, 0·80 to1·49]; p=0·57) (Figure 2). Disease recurrence occurred in 80 (67%) patients in the laparoscopic group and in 82 (62%) patients in the open group (Table 2). The most common sites of recurrence were the liver, the lungs and the peritoneum. A total of 61 patients (laparoscopic, n=25; open, n=36) underwent redo liver surgery for recurrent liver metastases, while 14 patients underwent lung resection for metastases and 9 patients underwent resection for other extrahepatic recurrences (Table 2). Positive primary tumour lymph nodes and presence of extrahepatic disease were independent predicators for poor recurrence-free survival.

In the multivariable regression analysis for overall survival, the following factors were associated with inferior outcomes: positive primary tumour lymph nodes, size of the largest liver metastasis and presence of extrahepatic disease at liver surgery (Table 3). The variables included in the multivariable analysis for overall survival were equally distributed between the groups (Table 4).

Discussion

In this first randomized controlled trial comparing laparoscopic and open liver surgery for colorectal cancer metastases, we found no difference in survival or cancer recurrence between the treatment groups. Previously published data from OSLO-COMET demonstrated that laparoscopic surgery was better tolerated by the patients, with no additional health-care costs.[10,11]

Liver surgery has traditionally been associated with a long learning curve and relatively high complication rates, and few institutions worldwide are regarded as true high-volume centres. These are likely reasons why the laparoscopic approach has been slowly implemented in hepato-pancreato-biliary surgery. A lack of robust evidence supporting the oncological safety of laparoscopic liver surgery has also contributed to a slow uptake, although several studies have reported oncological outcomes similar to open liver surgery.[8,9,15] Colorectal liver metastases are the most common indication for laparoscopic resection in the western world.[6] Recent studies on laparoscopic versus open liver resections for colorectal liver metastases reported similar long-term oncological outcomes, in line with the current study.[8,16]

In spite of the initial concerns about laparoscopic surgery resulting in inferior oncological outcomes, well designed randomized controlled trials have shown its non-inferiority compared to open surgery for colorectal,[17,18] gastric[19,20] and oesophageal [21,22] cancer. Last year, however, two randomized controlled trials reported inferior outcomes after laparoscopic surgery for pancreatic head cancer and cervical cancer.[23,24] Both trials were terminated early as the data and safety monitoring boards found worse results after minimally invasive treatment. These trials had minimum requirements for participating centres related to training and annual volume of operations. However, it is hard to determine what the necessary institutional volume of an operation is in order to maintain expertise in complex cancer surgery. In the LACC-trial, comparing laparoscopic and open radical hysterectomy for cervical cancer, 631 patients were randomized in 33 centres over 9 years, suggesting on average only two trial operations per year per centre. In the LEPOARD-2 trial, comparing laparoscopic and open pancreatoduodenectomy, the requirement was an annual volume of only 20 pancreatoduodenectomies per centre, and at least 10 being done laparoscopically. In comparison, more than 200 liver resections were performed annually at the Oslo University

Hospital when OSLO-COMET started inclusion, and almost 300 were performed four years later when the study completed. In light of the LACC and LEOPARD-2 trials, a strength of our study is that it was performed in very controlled circumstances at a single expert centre rather than in multiple smaller institutions.

In this trial all patients had parenchyma-sparing surgery. The parenchyma-sparing approach has been an essential part of the multimodal treatment for patients with colorectal metastases in our institution since late 1990-s.[25,26] As of today, many specialized centres have adopted parenchyma-sparing liver surgery.[27] This strategy reduces the risk of morbidity and mortality, and by preservation of liver parenchyma the technique increases the possibility of repeated surgical treatment in case of recurrence.[26,28] In the current study, 69% of patients who developed liver recurrences, underwent repeated liver surgery (Table 2), while 13% of the patients included had already received liver surgery prior to inclusion. Repeated surgery in well selected patients with recurrent colorectal liver metastases has similar long-term outcomes to primary surgery.[29]

To ensure benefit from liver resection in patients with colorectal metastases, preoperative prognostic factors are important to optimize patient selection. Various factors are associated with good prognosis after liver resection of colorectal liver metastases.[30] In order to define the prognostic factors associated with poor overall survival, we performed univariable and multivariable regression analyses, and found that ECOG score, primary tumour lymph node involvement, size of largest liver metastasis and the presence of extrahepatic disease at the time of liver surgery were independently associated with poor survival. The surgical approach influenced neither recurrence-free nor overall survival when presented as an explanatory variable and included in the uni- and multivariable analyses. (Table 3). Levels of carcinoembryonic antigen, synchronous liver metastases, number of liver metastases and R1 resections did not individually impact survival in our cohort.

A total of 98 patients (39%) received neoadjuvant and 126 patients (50%) adjuvant chemotherapy (Table 2). In the multivariate analysis, neoadjuvant or adjuvant chemotherapy did not impact overall survival (Table 3). In a milestone study, Nordlinger et al. reported, that perioperative chemotherapy did not improve 5-year overall survival rates for patients with colorectal liver metastases (51·2% vs 47·8%, p=0·34) , albeit with improved recurrence free survival in the chemotherapy group.[4]

A limitation of this trial is that it was not powered to detect differences in secondary endpoints. Therefore, small differences of survival outcomes cannot be excluded. The single-centre design is another limitation. However, Oslo University Hospital is the sole provider of liver surgery for the population of South-East Norway (3 million people), and 95% of eligible patients were screened during the four-year inclusion period. The surgeons involved in the trial were already experienced in laparoscopic liver surgery when the study started, so the current outcomes are not directly transferable to non-expert centres. This indeed acted as an advantage, since both techniques were applied in ideal conditions and could express their best possible outcomes. This trial should be followed by pragmatic multicentre trials and international registries. The Orange II-plus (NCT01441856) and the Orange-segments (NCT03270917) trials will complement our findings.

Conclusion

Laparoscopic resection for colorectal liver metastases was associated with long-term oncological outcomes comparable to open liver surgery. These findings support the further implementation of laparoscopic liver surgery in the treatment of colorectal metastases.

Research in context

Evidence before this study

Laparoscopic liver surgery is increasingly used for the treatment of liver malignancies. Retrospective studies have suggested that laparoscopic liver surgery provides good short-term outcomes and equivalent survival compared to open surgery. The current study (OSLO-COMET) was the first prospective randomised controlled trial to compare short- and long-term outcomes after laparoscopic and open surgery for colorectal cancer liver metastases. The primary outcome demonstrated less complications in the laparoscopic surgery group compared to open surgery. Moreover, laparoscopic liver surgery was shown to be cost effective. We searched PubMed on May 12, 2020 using the keywords “laparoscopic hepatectomy” OR “laparoscopic liver surgery”. We found reports on two randomised controlled trials, published after OSLO-COMET, that compare outcomes of laparoscopic and open liver resection of primary liver cancer and colorectal liver metastases. Both studies found improved short-term outcomes after laparoscopic surgery, with no difference in oncological outcomes.

Added value of this study

This is to date the largest randomized controlled trial to compare laparoscopic and open liver surgery. The trial was conducted at Oslo University Hospital, which is the sole provider of liver surgery for the population of South-East Norway (3 million people), and 95% of eligible patients were screened during the four-year inclusion period. The surgeons involved in the trial were already experienced in both laparoscopic and open liver surgery when the study started. Despite that the primary endpoint was postoperative morbidity, the trial was designed to detect potential differences in recurrence-free and overall survival. We found that when performed in a high-volume setting, laparoscopic surgery in patients with colorectal liver

metastases was associated with rates of OS and RFS similar to open surgery ***Implication of all the available evidence***

The results of this trial validate previous reports that laparoscopic liver surgery is better tolerated by patients and cost effective to society, without any compromise of oncological safety. The available evidence supports a further implementation of laparoscopic liver surgery, with the hope of expanding availability of cancer surgery beyond current conventional practice.

Contributors: DLA designed the study, collected data, analysed the data, performed statistical analyses, wrote the manuscript. AMK designed the study, reviewed the manuscript. VJD included patients, collected data, performed surgery, reviewed the manuscript. BIR performed surgery, reviewed the manuscript. MWF designed the study, analysed data, helped perform statistical analyses, reviewed the manuscript. GMWB collected data, reviewed the manuscript. RK designed the study, created the database and randomisation software, collected data, reviewed the manuscript. KF designed the study, reviewed the manuscript. ÅAF designed the study, included patients, collected data, performed surgery, analysed the data, wrote the manuscript. BE designed the study, performed surgery, was principle investigator of the study, analysed data, reviewed the manuscript.

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CONSORT
TRANSPARENT REPORTING of TRIALS

OSLO COMET TRIAL: CONSORT 2010 Flow Diagram

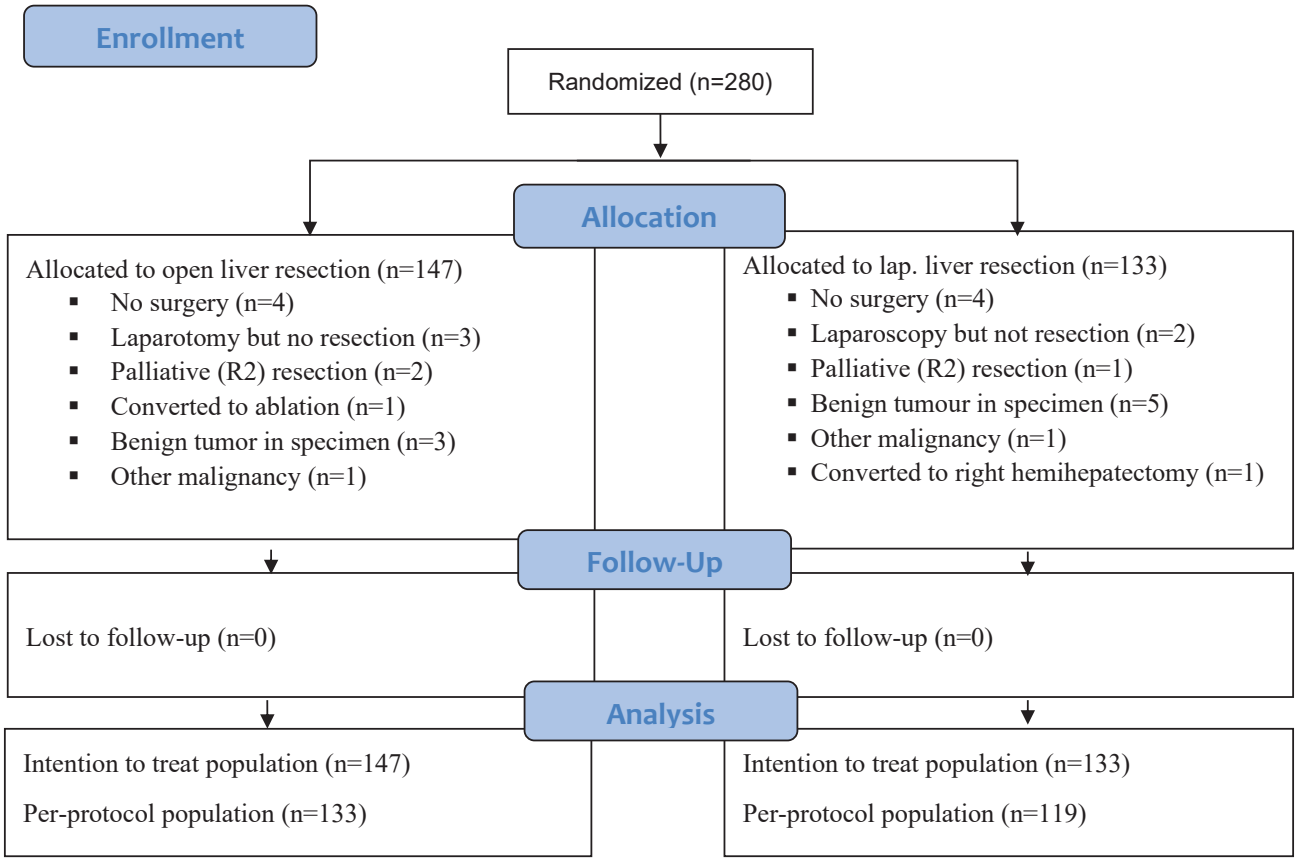
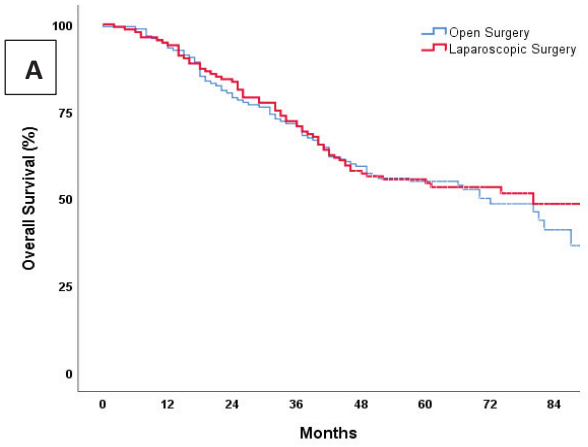
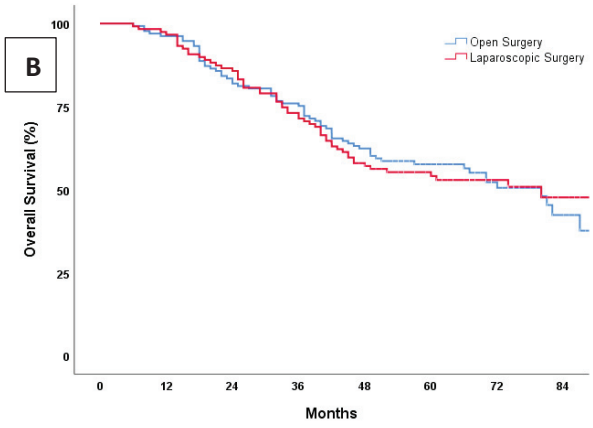


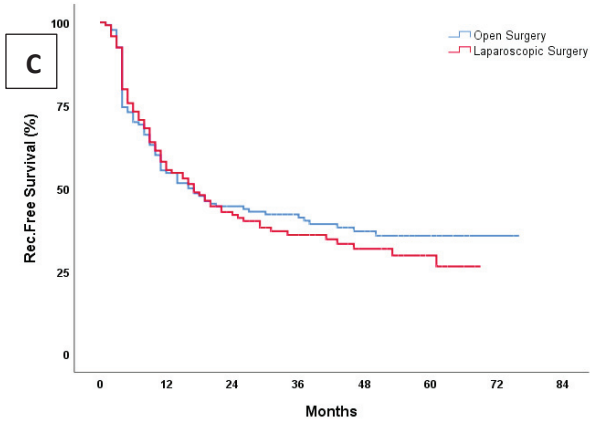
Figure 1. Consort Flow Chart



No at Risk	OLR	147	137	116	104	75	46	23	6
	LLR	133	125	111	92	61	39	21	5



No at Risk	OLR	133	128	109	100	72	45	22	6
	LLR	119	115	102	83	56	36	19	5



No at Risk	OLR	133	70	51	38	20	6	1	-
	LLR	119	64	41	26	15	5	-	-

Figure 2. Kaplan-Meier curves of *overall survival* (**A**) by intention-to-treat (n=280), (**B**) by per-protocol (n=252) populations, and (**C**) *recurrence-free survival* (n=252).

Table 1. Baseline characteristics (n=280)

Variables	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	117 (80%)	112 (84%)
1	28 (19%)	20 (15%)
2	2 (1%)	1 (1%)
ASA score		
1	20 (14%)	11 (8%)
2	78 (53%)	65 (49%)
3	49 (33%)	56 (42%)
4		1 (1%)
Primary tumour rectum	64 (54%)	50 (38%)
Primary tumour positive lymph nodes	93 (63%)	83 (62%)
Primary tumour AJCC T-stage		
T1	2 (1%)	3 (2%)
T2	10 (7%)	6 (5%)
T3	98 (67%)	93 (70%)
T4	37 (25%)	31 (23%)
Synchronous metastases	91 (62%)	75 (56%)
Number of metastases, mean (SD)	1·6 (1·1)	1·5 (1·1)
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)

SD-Standard Deviation, ECOG-Eastern Cooperative Oncology Group, ASA-American Society of Anaesthesiologists, AJCC-American Joint Committee on Cancer, CEA-Carcinoembryonic Antigen, IQR- Interquartile Rate

Table 2. Chemotherapy administration and long-term oncological outcomes (per-protocol, n=252)

	Open n=133	Laparoscopic n=119	p-value	HR (95%CI)
Neoadjuvant chemotherapy, n	60 (45%)	38 (32%)	0·03	
Adjuvant chemotherapy, n	73 (55%)	53 (45%)	0·10	
• Number of cycles, median (IQR)	8 (6-11)	8 (6-12)	0·69	
• Time to 1st cycle, days, median (IQR)	48 (36-56)	48 (37-62)	0·68	
Recurrence-free survival				
1-year,	55%	56%		
3-year,	41%	36%		
5-year,	35%	30%		
Median RFS, months (95%CI)	16 (8-24)	17 (10-23)	0·57	1·09 (0·80-1·49)
Disease recurrence	82 (61%)	80 (67%)	0·36	
• Liver	45	43		
- Isolated liver	34	27		
- Recurrence in resection bed	5	4		
• Lung	27	36		
- Isolated lung	18	29		
• Other extrahepatic	21	16		
Treatment for the first disease recurrence				
Redo liver surgery, n	36 (27%)	24 (20%)	0·26	
- Laparoscopic liver resection	16	15		
- Open liver resection	15	7		
- Radiofrequency ablation	5	1		
- Liver transplantation	0	1		
Lung resection, n	7 (5%)	7 (6%)	0·89	
Other surgical procedures, n	4 (3%)	5 (4%)	0·62	
Only palliative chemotherapy, n	18 (13%)	28 (23%)	0·04	
Radio- and radiochemotherapy, n	11 (8%)	13 (11%)	0·46	
No treatment, n	7 (5%)	4 (3%)	0·45	
Overall Survival				
1-year,	93%	94%		
3-year,	71%	71%		
5-year,	55%	54%		
Median overall survival, months (95%CI)	70 (48-92)	80 (63-97)	0·95	0·99 (0·69-1·41)
Alive patients, n	68 (51%)	62 (52%)	0·87	
Alive patients with inoperable disease, n	4	13	0·01	
Alive patients after developing recurrence, n	24	27	0·33	

CI – Confidence Interval, IQR- Interquartile Rate, HR- Hazard Ratio

Table 3. Uni- and multivariable analysis of prognostic factors for recurrence-free and overall survival (per protocol, n=252)

	Recurrence-free survival			**Overall Survival**		
	Univariable	**Multivariable Cox regression analysis**		**Univariable**	**Multivariable Cox regression analysis**	
Variable	**p-value**	**Hazard Ratio (95% CI)**	**p-value**	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Age (per year)	0·76			**0·007**	1·02 (0·99 – 1·04)	0·11
Male sex	0·70			**0·15**	0·72 (0·49 - 1·06)	0·10
BMI	**0·15**	1·03 (0·99 – 1·07)	0·16	0·61		
ECOG score	**0·07**	1·28 (0·87 – 1·87)	0·20	**0·007**	**1·51 (1·00 – 2·28)**	**0·04**
ASA score	**0·17**	1·10 (0·85 – 1·42)	0·47	0·31		
Primary tumor						
Rectum	0·43			0·33		
Right side	0·62			0·56		
AJCC T-stage (T3/T4)	0·27			0·76		
N+ lymph nodes	**< 0·001**	**0·55 (0·38 - 0·80)**	**0·002**	**0·005**	**0·59 (0·39 - 0·90)**	**0·01**
Liver metastases						
Synchronous	**0·01**	1·38 (0·98 – 1·95)	0·06	0·23		
Previous liver resection	0·89			0·26		
Multiple lesions (>1)	0·38			0·84		
Bilobar metastases	0·59			0·99		
Tumor size (per cm)	**0·02**	1·09 (0·99 - 1·19)	0·06	**< 0·001**	**1·18 (1·08 - 1·29)**	**< ·001**
No neoadjuvant chemotherapy	0·46			0·48		
Preoperative CEA (>5ng/ml)	**0·06**	0·75 (0·54 – 1·05)	0·09	0·52		
Extrahepatic disease	**< 0·001**	**0·35 (0·22 - 0·55)**	**<0·001**	**0·03**	**0·58 (0·35 - 0·98)**	**0·04**
Liver resection						
Laparoscopy	0·57	1·05 (0·75 - 1·45)	0·78	0·95	0·98 (0·68 – 1·41)	0·92
Blood loss	0·47			0·55		
Blood transfusion	0·46			**0·04**	0·83 (0·48 – 1·46)	0·53
Operative time	0·88			0·97		
Postop. severe complications	0·81			**0·12**	0·95 (0·55 – 1·63)	0·84
R1 resection (<1mm)	**0·04**	1·08 (0·66 – 1·76)	0·75	**0·16**	0·81 (0·53 – 1·23)	0·32
Involved resection margin	**0·002**	0·55 (0·29 – 1·02)	0·06	0·39		
No adjuvant chemotherapy	0·55			0·71		

ECOG-Eastern Cooperative Oncology Group, ASA-American Society of Anaesthesiologists, AJCC-American Joint Committee on Cancer, CEA - carcinoembryonic antigen, Postoperative severe complication – Accordion grade 3 and higher

Table 4. Variables associated with poor overall survival after univariable analysis (p-value <0.2)

Variable	Open (n=133)	Laparoscopic (n=119)	p-value
Age, year, median (IQR)	66 (60-72)	68 (62-75)	0·23
Male sex, n	81 (61%)	66 (56%)	0·38
ECOG score			**0·75**
0, n	106 (80%)	99 (83%)	
1, n	26 (19%)	19 (16%)	
2, n	1 (1%)	1 (1%)	
Positive lymph nodes, n	**85 (64%)**	**81 (68%)**	**0·48**
Tumour size, mm, median (IQR)	**24 (15-35)**	**13 (15-36)**	**0·74**
Extrahepatic disease, n	**11 (8%)**	**16 (13%)**	**0·18**
Blood transfusion, n	15 (11%)	13 (11%)	0·93
Postop. severe complications, n	17 (13%)	11 (9%)	0·37
R1 resection (margin <1 mm), n	32 (24%)	31 (26%)	0·72

Bold font - variables impact overall survival after multivariable analysis