Implementation and outcome of laparoscopic liver surgery

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Implementation and outcome of laparoscopic liver surgery

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aan de Universiteit van Amsterdam
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CHAPTER 1

General introduction and thesis outline

Functions and diseases of the liver

The liver is the largest abdominal organ and located in the upper abdomen, mostly underneath the ribcage. It is a highly versatile organ with functions ranging from the secretion of bile to aid in the digestion of fats to maintaining blood sugar homeostasis by storing and releasing glucose and contributing to the coagulation cascade by producing coagulation factors. Moreover, it has a strong capability to regenerate after injury or partial surgical removal.

The liver may harbor a wide range of diseases, some of which require surgical treatment. Benign liver tumors such as hepatocellular adenoma, focal nodular hyperplasia and hemangioma are often found coincidentally. In most of these cases, there is no indication for treatment. When patients present with symptoms, such as abdominal pain, nausea and tiredness, if malignant transformation is suspected or when the diagnosis remains uncertain, partial liver resection is sometimes indicated. In case of malignant disease, surgical intervention is still the only treatment option with a curative intent. Malignant tumors in the liver can be divided into primary and metastatic tumors, of which hepatocellular carcinoma and colorectal liver metastases are the most frequently observed. Recent technological developments, promising results of neoadjuvant chemotherapy regimens and broadening of the spectrum of indications, have contributed to an increase in the number of patients eligible for liver resections in recent years.[1-3]

Beyond the scope of this thesis are diseases that will never require surgical management other than liver transplantation.

Liver anatomy

Like in all surgical procedures, extensive knowledge of anatomy is required before performing liver surgery. One of the greatest contributions to the understanding of human liver anatomy has been the work of Couinaud in the 1950's.[4] He was the first to describe the liver's segmental anatomy, based on the blood distribution through the portal vein and hepatic vein branches.

The liver can be divided into eight anatomical segments, each of which has its own portal triad and efferent hepatic vein. The portal triad consists of a portal vein and an afferent hepatic artery, which supply the hepatocytes in that segment with nutrients and oxygen, and an efferent bile duct, which drains the secreted bile. The hepatic vein drains the deoxygenated blood from the liver into the inferior vena cava. The main left and right portal vein branches divide the liver into a superior and inferior portion, while

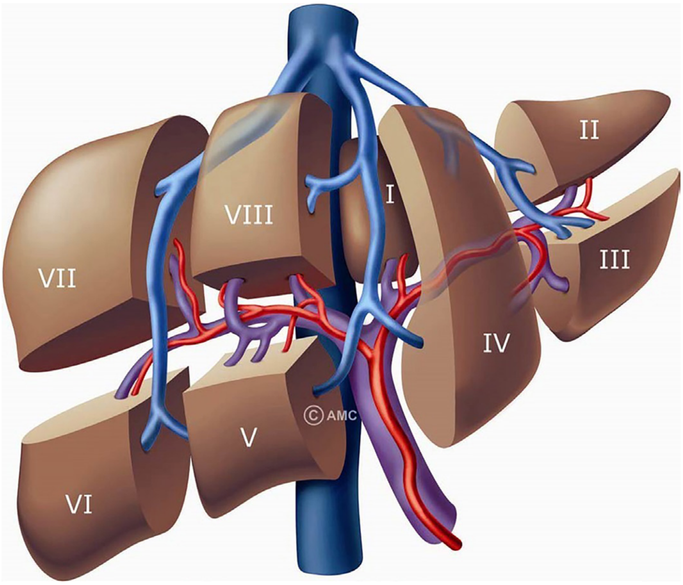

Figure 1. Segmental anatomy of the liver. In brown: liver segments. In blue: vena cava and hepatic veins. In red: hepatic arteries. In purple: portal veins.

the right, middle and left hepatic veins establish a further division into sections: segments II and III form the left lateral section, segment IV forms the left medial section, segments VIII and V form the right anterior section and segments VII and VI form the right posterior section (see Figure 1).

Liver surgery

In 2000, during a meeting of the International Hepato-Pancreato-Billiary Association in Brisbane, Australia, the absence of a logical and common worldwide anatomical and surgical nomenclature stimulated yet another revolutionary development in liver surgery. Using Couinaud's segmental anatomy, a unifying nomenclature of hepatic surgical anatomy and resections was formulated and adopted: the Brisbane 2000 Nomenclature of Hepatic Anatomy and Resections.[5,6] Resections are classified based on the anatomical segments being resected: a segmentectomy when a single segment is resected, a bisegmentectomy when two adjacent segments that do not form a section are resected, a sectionectomy when a complete section is resected, a hemihepactectomy when half of the liver is resected and an extended resection when more than half of the liver is resected. Although this nomenclature clearly defined anatomical liver resections for the first time in an attempt to improve comparability between practices worldwide, it is not complete. These standardized resections form the basis for liver surgery, but very often a specific case will require a surgeon to deviate from this standard format. A segmentectomy can be slightly extended into an adjacent segment because tumor growth is not restricted by segmental boundaries. Additional resections from non-adjacent segments might be necessary because the tumor has a multifocal distribution. An all-embracing nomenclature, that is also embryologically correct and correlates with outcomes, is still sought-after. In most chapters in this thesis, the Brisbane 2000 nomenclature is used including additional variables to account for the variability in resections.

Liver resection is considered high-risk surgery. Postoperative mortality has been described as high as 30%[7,8] and postoperative morbidity can be significant.[9-11] Despite extensive knowledge of the liver's unique vascular anatomy, intraoperative bleeding frequently occurs, which is associated with unfavorable postoperative outcomes.[12-14] Postoperative liver failure is one of the most feared risks of liver surgery and can occur when the remnant liver is incapable of fulfilling its tasks. Other complications include bile leakage, infections and wound complications.

Despite all these risks, increasing surgical skill and significant developments in the field of hemorrhage control (e.g. Pringle maneuver, hemostatic agents, specific instruments) and postoperative management (Enhanced Recovery After Surgery, ERAS) have contributed to the development of liver surgery into an accepted treatment modality over the past decades. Still, continuous efforts are being made to decrease the impact of liver surgery on the patient.

Minimally invasive surgery

Abdominal surgery can be indicated for a wide range of pathologies and is often the only curative option in patients with cancer. Traditionally, a large incision or laparotomy is required to gain adequate access to the abdomen. Although this approach enables the surgeon to manually palpate and manipulate the affected organ, it causes significant tissue damage and has a high impact on patients. Over the past decades, minimally invasive surgical techniques have been introduced into surgical practices all over the world, aiming to decrease the impact of surgery on the patient while maintaining the same efficiency as open surgery. These techniques entail the introduction of a camera and long pencil-like instruments into the abdomen through small (5-10mm) abdominal

incisions. Carbon dioxide is insufflated into the abdomen to ensure enough space to operate the instruments. While the camera image is displayed on a monitor, the surgeon can operate these instruments directly at the bedside (laparoscopy) or indirectly by controlling robot arms in a computer console (robot-assisted laparoscopy). The chapters in this thesis will predominantly discuss the former.
Based on proven or presumed benefits of laparoscopy over laparotomy, including a decrease in intraoperative blood loss and postoperative pain, reduced time to functional recovery and therefore shorter length of hospital stay and a reduction in postoperative complications, minimally invasive surgery has been implemented for gastro-intestinal surgical procedures like cholecystectomies, appendectomies, colectomies, gastrectomies and oesophagectomies.[15-20]

Minimally invasive liver surgery

Compared to other gastro-intestinal surgical procedures, the uptake of laparoscopic liver surgery has been rather slow. First reported in 1992[21], it took until 2000 for the first case series of 30 patients to be reported.[22] Several initial concerns played a role in the relatively slow adoption of the laparoscopic approach to liver surgery. One of the major differences to open surgery is the way access to the liver is achieved, resulting in a more caudal view of the liver. This, in combination with the limited range of motion of laparoscopic instruments, the strongly diminished tactile feedback and the two-dimensional view of the surgical field through the laparoscope significantly increases the technical difficulty of the procedure. Hence, laparoscopic liver surgery has a long learning curve, even when surgeons already have extensive experience with other laparoscopic gastro-intestinal procedures and open liver surgery.[23] Other anticipated problems included difficulty to control bleeding laparoscopically, risk of gas embolism and the fear of oncological inefficiency and tumor spread at the port site. Driven by the inherent benefits of the laparoscopic approach demonstrated in other gastro-intestinal procedures, pioneering, high-volume expert centers have gradually built a more convincing body of evidence suggesting that these results can be reproduced in the field of liver surgery.[24,25] These benefits include less intraoperative blood loss, less postoperative complications, decreased need for analgesics, shorter postoperative hospital stay, and a cosmetic benefit.[24,25] Recently, the first randomized controlled trial was performed in a single, very high-volume center and confirmed these benefits for the resection of colorectal liver metastases.[26] Besides the value of these original studies and trials, many of the standards that currently apply in laparoscopic liver surgery have been developed during international consensus meetings. The distinction between minor and major surgery was made during the first meeting in Louisville in 2008 where major laparoscopic liver surgery was defined as all resections of more than three segments or those from difficult to reach posterior segments (4a, 7 and 8).[27] In Louisville, as well as in Morioka[28] during the second meeting, laparoscopy was already considered the standard for left lateral sectionectomies, whereas major resections were to be reserved for more experienced surgeons.

AIM OF THIS THESIS

Over the past three decades, laparoscopic liver surgery has been developed in pioneering high-volume expert centers and it is currently being implemented on a larger scale around the world. While starting centers are looking for ways to safely implement laparoscopic liver surgery into their practice, expert centers are pushing the boundaries, trying to deliver the advantages of the laparoscopic approach to as many patients as possible. The aim of this thesis is to present the results from both ends of this spectrum in order to guide the evidence based implementation of laparoscopic liver surgery, as well as demonstrate its feasibility and safety in a wide range of procedures.

THESIS OUTLINE

In **Chapter 2**, a validated set of evidence based, clinical practice guidelines for laparoscopic liver surgery is presented on the topics of Indications, Patients and Complex Diseases, Procedures, Technique and Implementation.

Part 1 Implementation of laparoscopic liver surgery

The specific guidelines on Implementation from **Chapter 2** are validated in **Chapter 3**, based on a single center experience. In **Chapter 4**, the nationwide implementation and outcomes of laparoscopic liver surgery in the Netherlands are described. A volume-outcome relationship for major laparoscopic liver surgery is suggested.

Part 2 Outcome of laparoscopic liver surgery

Thesis **part 2** describes the outcomes of laparoscopic liver surgery for benign liver tumors, minor and major resections. **Chapter 5** provides a systematic review of the literature on symptom relief, quality of life and surgical outcomes of both open and minimally invasive liver surgery for solid benign liver tumors.

Although laparoscopy is considered the standard approach to left lateral sectionectomies, strong evidence of its superiority over open surgery was lacking in literature. Therefore, a propensity score matched comparison of open and laparoscopic left lateral sectionectomies is performed and reported in **Chapter 6.**

The outcome and learning curve of total laparoscopic hemihepactectomy performed in a high-volume center are reported in **Chapter 7.** In **Chapter 8**, simultaneous colorectal and liver resections are compared to colorectal resections alone in order to identify the additional postoperative morbidity risk. **Chapter 9** assesses whether the advantages of the laparoscopic approach over open surgery still apply in the challenging setting of a repeat liver resection. In **Chapter 10**, the outcomes of laparoscopic liver surgery for lesions adjacent to major vessels, performed in a high-volume center, are described. Finally, **Chapter 11** provides the first systematic literature review of the use and outcomes of minimally invasive liver surgery for perihilar cholangiocarcinoma.

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CHAPTER 2

The Southampton consensus guidelines for laparoscopic liver surgery: from indication to implementation

Annals of Surgery 2018;268:11-18

Mohammad Abu Hilal, Luca Aldrighetti, Ibrahim Dagher, Bjorn Edwin, Roberto Ivan Troisi, Ruslan Alikhanov, Somaiah Aroori, Giulio Belli, Marc Besselink, Javier Briceno, Brice Gayet, Mathieu D'Hondt, Mickael Lesurtel, Krishna Menon, Peter Lodge, Fernando Rotellar, Julio Santoyo, Olivier Scatton, Olivier Soubrane, Robert Sutcliffe, Ronald Van Dam, Steve White, Mark Christopher Halls, Federica Cipriani, **Marcel Van der Poel**, Ruben Ciria, Leonid Barkhatov, Yrene Gomez-Luque, Sira Ocana-Garcia, Andrew Cook, Joseph Buell, Pierre-Alain Clavien, Christos Dervenis, Giuseppe Fusai, David Geller, Hauke Lang, John Primrose, Mark Taylor, Thomas Van Gulik, Go Wakabayashi, Horacio Asbun, Daniel Cherqui

ABSTRACT

Objective

The European Guidelines Meeting on Laparoscopic Liver Surgery was held in Southampton on February 10 and 11, 2017 with the aim of presenting and validating clinical practice guidelines for laparoscopic liver surgery.

Background

The exponential growth of laparoscopic liver surgery in recent years mandates the development of clinical practice guidelines to direct the specialty's continued safe progression and dissemination.

Methods

A unique approach to the development of clinical guidelines was adopted. Three well-validated methods were integrated: the Scottish Intercollegiate Guidelines Network methodology for the assessment of evidence and development of guideline statements; the Delphi method of establishing expert consensus, and the AGREE II-GRS Instrument for the assessment of the methodological quality and external validation of the final statements.

Results

Along with the committee chairman, 22 European experts; 7 junior experts and an independent validation committee of 11 international surgeons produced 67 guideline statements for the safe progression and dissemination of laparoscopic liver surgery. Each of the statements reached at least a 95% consensus among the experts and were endorsed by the independent validation committee.

Conclusion

The European Guidelines Meeting for Laparoscopic Liver Surgery has produced a set of clinical practice guidelines that have been independently validated for the safe development and progression of laparoscopic liver surgery. The Southampton Guidelines have amalgamated the available evidence and a wealth of experts' knowledge taking in consideration the relevant stakeholders' opinions and complying with the international methodology standards.

INTRODUCTION

The first European Guidelines Meeting on Laparoscopic Liver Surgery (EGMLLS) was held in Southampton on February 10 and 11, 2017, with the specific aim of presenting and validating guidelines for laparoscopic liver surgery (LLS).
Previously, the consensus meeting in Louisville (2008)[1] reviewed the feasibility of LLS, whereas that of Morioka (2014)[2] focused on a comparison with open resections, then the current standard of practice, demonstrating a clear role for the laparoscopic approach in the modern era of liver surgery. While the laparoscopic approach must continue to demonstrate a lack of inferiority compared with the open approach, the future must be directed at its potential advantages, development, and safe progression.[3]
Building on the foundation laid by the 2 previous meetings, this manuscript represents clinical practice guidelines designed specifically to direct the safe future development of laparoscopic liver surgery.
The Southampton Guidelines aim to provide both experienced and training surgeons, and centers, guidance as to the appropriateness of care, to reduce variations in practice and to facilitate the safe expansion of LLS with the goal of improving patient care.[4]

METHODS

The members of the steering committee and the expert panel were selected by the committee chairman for their wealth of experience and their significant contributions to the development of laparoscopic liver surgery. Of the 11 members of the international validation committee, 7 surgeons only perform open resections, whereas the remaining 4 surgeons perform both open and laparoscopic liver surgery. To provide clear clinical practice guidelines on LLS and its safe expansion, 5 key domains were identified by the Steering Committee: Indications, Patient selection, Procedures, Techniques, and Implementation. Each domain was further subdivided into topics, for example, the "*Indication*" domain was separated into: resections for "*Colorectal Liver Metastases*," "*Hepatocellular Carcinoma*," and "*Benign and Other Rare Liver Metastases*." In addition to the 5 members of the steering committee, a further 18 liver surgeons, all with recognized expertise in LLS, were selected to form the Expert Panel. The expert panel was divided into working groups, and each was assigned a number of topics to develop specific guidelines. An independent validation committee of 11 experts and 2 patient

representatives was involved throughout the process of statement production.
The methodology for the production of the Southampton Guidelines was developed in collaboration with an independent methodologist. A unique approach to the production was adopted by integrating 3 validated methods: the SIGN (Scottish Intercollegiate Guidelines Network) methodology for the assessment of evidence and development of guideline Statements[5] ; the Delphi method (for establishing expert consensus)[6] ; and the AGREE II-GRS (Global Rating Scale) Instrument[7] for the assessment of the methodological quality and external validation of the final statements.
A systematic review using Ovid Medline and Pubmed was undertaken in July 2016 and repeated in January 2017 to review all the existing literature for each topic. All manuscripts meeting the inclusion criteria were evaluated using the SIGN methodology to establish the Study Quality and assigned an Evidence Level (supplementary Appendix S1; http://links.lww.com/SLA/B340 and Figure 1; Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram). Through the use of Considered Judgement Forms (as per the SIGN methodology), the findings of the systematic review and the opinions of the experts in each working group were combined to form the provisional statements. A form of recommendation (ie, strength), based upon the level of evidence from the systematic review, was assigned to each statement (supplementary Appendix S2; http://links.lww.com/SLA/B340). All the statements were amalgamated and disseminated to the entire expert panel for voting in accordance with the Delphi methodology. This methodology allows each expert to either agree or disagree with a given statement, and make recommendations for changes to that statement should they feel it necessary.
If a statement reached greater than or equal to a 95% agreement in the first Delphi round, it was accepted into the guidelines for presentation at the meeting and removed from further Delphi rounds. Statements failing to reach a 95% agreement were returned to the original working group, along with their respective anonymized comments, for revision, and were entered into the subsequent Delphi round. After 3 Delphi rounds, 66 statements had reached at least a 95% agreement and 3 had not. The identities of those producing the provisional statements and those providing feedback remained anonymous except to the guideline's chairman. At the pre-meeting assembly, a fourth Delphi round was held with the intent to review the guideline statements and reach a consensus on the 3 outstanding statements. In addition, the form of recommendations assigned to each statement was reviewed, assessed, and modified to ensure the evidence level provided neither over nor under-represented the statement. This was

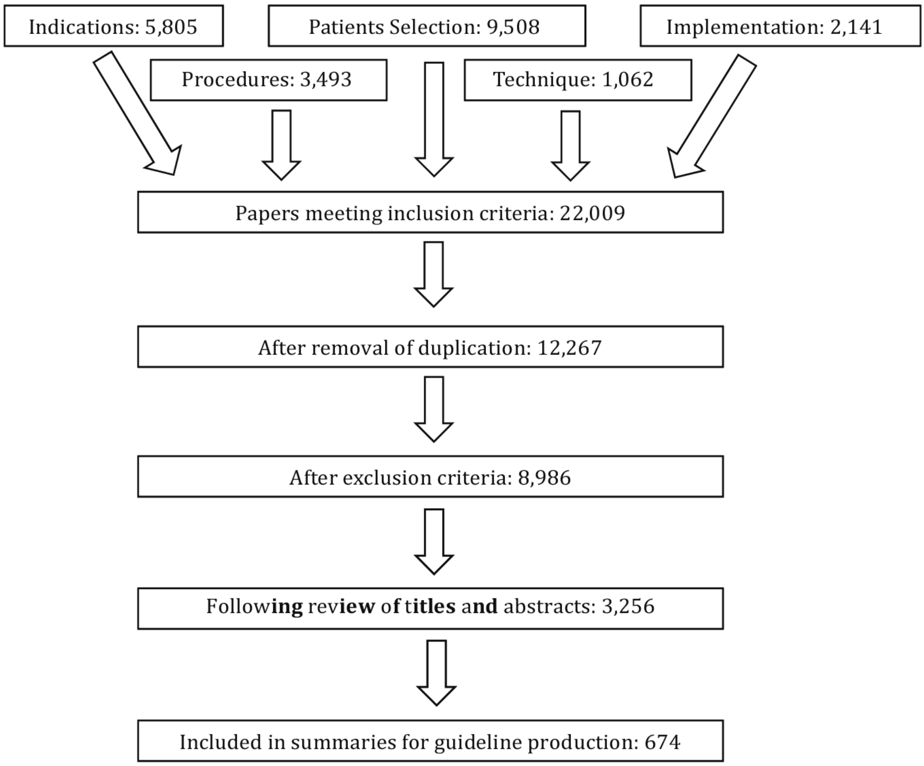

Figure 1. PRISMA diagram. A graphical representation of the included publications within the systematic review. Searches were performed in July 2016 and repeated in January 2017 using OVID Medline and Pubmed searches. Inclusion criteria: any publication relating to laparoscopic liver surgery; exclusion criteria: nonhuman studies, comparative studies with less than 10 cases, case reports, non-English and full-text unavailable. Each search contains: [Laparosco OR minimally-invasive OR Keyhole] AND [Liver OR Hepat OR Liver Surgery OR Liver Resection], With the addition of searches specific to topic for example in "Bleeding": AND [blood OR bleeding OR haemorrhage OR Haemosta].

performed taking into consideration factors such as the clinical importance of the topic, the relevance of implications to the clinical setting, and the consistency of the body of evidence. At this point, 2 statements were removed as they failed to reach agreement; hence 67 statements were accepted for the meeting. The Validation Committee reviewed the literature searches and the subsequent summaries used for the production of the guideline statements, specifically examining the methodological techniques underpinning the production of each statement as per the AGREE II-GRS tool.[8]

In addition to the expert panel and validation committee, the 2- day conference was attended by over 190 specialists, from 23 different countries, all sharing an interest in liver surgery. During the conference, the highest-level evidence supporting each statement was presented along with the form of recommendation. In addition, all in attendance voted electronically, demonstrating their additional support, or otherwise, for each statement. The validation committee considered the outcomes of these votes, the opinions of the patient representatives, and proposed a number of recommendations before granting endorsement. The expert panel accepted all the recommendations from the validation committee. A detailed description of this novel methodology for the development of surgical guidelines will be published separately, as will the detailed systematic reviews for the core topics.

GUIDELINES

The Southampton Guidelines were derived from the aforementioned methodology and thus are based on published evidence and expert opinion. It is of critical importance to note that the majority of the evidence originates from surgeons experienced in both liver surgery and advanced laparoscopic techniques working in specialist liver centers. Therefore, the guidelines should not be misconstrued as an endorsement for surgeons to perform LLS without the necessary experience and training or in an institution without the proficiency and support to practice liver surgery. It is also noteworthy that LLS accounts for 30% to 60% of liver resections in these specialist centers, and therefore there are implicit selection criteria to assess which patients are deemed appropriate candidates for a laparoscopic approach. The criteria vary among institutions and surgeons in accordance with proficiency and expertise, and will evolve with time.

Section 1: Indications

Topic 1: Colorectal Liver Metastases (CRLM)

Are Laparoscopic Liver Resections (LLR) Indicated for the Management of CRLM?

The literature suggests improved short-term outcomes for LLR of CRLM compared with open liver resection (OLR) with similar long-term outcomes. A recent meta-analysis found a reduced blood loss and need for transfusion with comparable operative times and length of hospital stay in the laparoscopic group. Overall survival and disease-free survival were similar between the groups, and a lower incidence of R1 resections was observed in the laparoscopic group.[9] Preliminary results from the first large-scale prospective randomized control trial (COMET)[10] comparing laparoscopic and OLRs for CRLM have shown improved short-term outcomes for the laparoscopic approach, which is supported by previous propensity score-matched studies.[11] Other studies report similar benefits in those aged over 70.[12] Increasing margin width in R0 resections did not significantly correlate with better overall survival,[13] and as such, the guidelines confirm that parenchymal sparing resections should continue to be the basis of treatment of CRLM. The guidelines conclude that with appropriate expertise, the laparoscopic approach is a valid alternative to the treatment of CRLM (R1.1 and R1.2; see supplementary Table S1; http://links.lww.com/SLA/B340 for complete list of recommendations.)

What is the Role of Laparoscopy in the Management of Simultaneous Colonic and Liver Resection for Synchronous Colorectal Metastases?

A laparoscopic approach was associated with a shorter hospital stay than an open approach with no difference in overall survival for patients with synchronous hepatectomy and colectomy.[14] There is, however, insufficient comparative data for combined major liver and colorectal resections. The experts agreed that combined laparoscopic major liver and colonic resections are complex and lengthy procedures with the potential for increased operative risks. However, simultaneous resections for nonrectal primaries with peripheral liver lesions requiring limited hepatectomy or left lateral sectionectomy were considered a good treatment option. Systematic review suggests that the timing of liver resection for synchronous liver metastasis should be decided according to technical and oncological considerations.[15] The guidelines emphasize a need for a multidisciplinary approach to these patients (see R2.2, R2.2, and R2.3).

Topic 2: Benign and Rare Noncolorectal Metastases

What is the Role of LLR in the Management of Benign Disease and Rare Noncolorectal Metastases?

Operative trends for benign disease demonstrate that the proportion of cases performed laparoscopically is increasing.[16] LLR for benign lesions has lower intraoperative blood loss, frequency of complications, postoperative analgesic requirements, time to oral intake, and a shorter hospital stay.[17] With respect to neuroendocrine tumors (NETs), observational studies[18] highlight the feasibility, safety, and oncological efficiency of LLR for NETs and other noncolorectal liver metastasis when clinically indicated (see R3.1 and R3.2).

Topic 3: Hepatocellular Carcinoma (HCC)

Is LLR Indicated for the Management of HCC?

Meta-analysis and large propensity score-matched studies of open versus laparoscopic liver resection for HCC have strongly suggested that LLR for HCC is associated with reduced blood loss, transfusion rate, postoperative ascites, and liver failure and hospital stay with comparable operation time, disease-free margin, and recurrence rates.[19,20] This has been confirmed for major resections in a recent series.[21] For minor resections, a laparoscopic approach was found to be the only independent factor to reduce the complication rate in resections for HCC[22] (see R4.1, R4.2, R4.3, and R4.4).

What is the Role of LLR in Cirrhotic Patients?

No differences in operative time, blood loss, intraoperative complications, hospital stay, and morbidity were found in LLR for cirrhotics compared with noncirrhotics.[23] A laparoscopic approach appears to reduce the incidence of postoperative ascites, liver failure,[24] and morbidity assessed in terms of “Comprehensive Complication Index,” with no difference in overall or disease-free survival at 2 years.[25] The evidence for both LLR in patients with significant portal hypertension, ascites, and Child-Pugh B cirrhosis is limited to single studies,[26,27] and as such the guidelines recommend caution with these patient cohorts (see R5.1, R5.2, and R5.3).

Topic 4: Living Donor

What is the Role of the Laparoscopic Technique for Living Donor Hepatectomy (LDH)?

The evidence suggests that there is an improved quality of life with LLS for LDH that includes a shorter hospital stay and an earlier return to work.[28] The experts discussed the differences between left lateral graft retrieval for pediatric transplantation and full right or full left hepatectomy for adult transplantation. It was highlighted that the evidence for full right and full left hepatectomy is primarily based on laparoscopic-assisted procedures (hybrid) with only limited studies focusing on pure laparoscopic donor hepatectomy and hence minimally invasive donor major hepatectomy has not yet been standardized and should be restricted to expert centers (see R6.1, R6.2, R6.3, and R6.4).

Section 2: Patients and Complex Diseases

Topic 5: High-risk Patients

Are There Contraindications for LLR in Elderly and High Body Mass Index (BMI) Patients (Fragile Patients)?

Laparoscopic liver resection for elderly patients has demonstrated lower intraoperative blood loss, hospital stay, and morbidity, with comparable oncological outcomes to OLR.[12,29] There are limited comparative studies regarding LLR in obese patients, but evidence suggests that in selected patients, it is an appropriate treatment strategy[30] (see R7.1, R7.2, and R7.3).

Topic 6: Redo Liver Resections

Are LLRs Feasible in Patients With Previous Liver Resection?

Evidence suggests that LLR for re-do liver surgery is an appropriate option, although repeat resections have greater operative time and blood loss than primary resections.[31,32] The experts suggested that an initial laparoscopic resection may facilitate repeated resections by limiting the amount of adhesions, thereby providing an important advantage (see R8).

Topic 7: Technically Complex Settings

Is There a Role for LLR in Patients Requiring 2-Stage Hepatectomy?

There are limited comparative studies specifically regarding LLR for 2-stage hepatectomies. Observational studies suggests it is feasible and without detrimental effects on long-term outcomes[33,34] (see R9).

Is LLR Feasible in Patients With Large Lesions and Lesions in Close Proximity to Major Vessels?

Reports from cohorts studies of large (5–10 cm) and giant (>10 cm) tumors suggest that the resection of such lesions can be addressed laparoscopically with no increased morbidity. However, greater operative time and blood loss was observed when compared with LLS for smaller tumors.[35,36] Other reports have shown that in expert hands, lesions located in close proximity to the major vasculature can be addressed laparoscopically without detrimental effects[37] (see R10.1 and R10.2).

Section 3: Procedures

Topic 8: Major Hepatectomies

What is the Role of the Laparoscopic Technique for Right Hemihepatectomies?

The largest meta-analysis to date has shown that laparoscopic major hepatectomies have less blood loss, morbidity, and length of stay with similar operative times, transfusion rates, and completeness of resection compared with OLR.[38] The expert panel suggested that the feasibility, reproducibility, and implementation of left and right hepatectomies is sufficiently different that they should be considered separately. In experienced hands, laparoscopic right hemihepatectomies are associated with reduced hospital stay and blood loss. Mortality and completeness of resection are comparable with an open approach[39,40] (see R11.1, R11.2, R11.3, and R11.4).

What is the Role of the Laparoscopic Technique for Left Hemihepatectomies?

Compared with an open approach, a laparoscopic approach is associated with reduced blood loss, morbidity, and hospital stay with comparable operative times, completeness of resection, and mortality[41,42] (see R12).

Topic 9: Minor Resections, Resections on Difficult Segments, Parenchymal Sparing/Anatomical Segmentectomies

What is the Role of the Laparoscopic Technique for Minor Liver Resections?

A meta-analysis reports lower blood loss, transfusions rates, morbidity, and length of hospital stay for laparoscopic minor resections compared with open resections.[38] Laparoscopic left lateral sectionectomies are consistently associated with shorter hospital stay when compared with the open approach.[43] The evidence for a laparoscopic approach to segments 4b, 5, and en bloc cholecystectomy for gallbladder cancer is limited, but suggests similar perioperative outcomes to the open approach for T1 and T2 gallbladder cancers[44,45] (see R13.1 and R13.2).

What is the Role of the Laparoscopic Technique for Liver Resections in the "Difficult Segments (1, 4a, 7, and 8)"?

The expert panel acknowledged that resections in these segments, especially when anatomical, are highly complex and require advanced expertise in LLS. Minor LLRs in segment 1, 4a, 7, and 8 are associated with greater operative time and blood loss than equivalent resections in the anterolateral segments. However, mortality and morbidity is not different.[46] Compared with OLR, LLR is associated with reduced blood loss and hospital stay.[47] A transthoracic approach and modifications to the patient's position may be useful alternatives to the classic approach to the postero-superior segments.[48,49] The perioperative outcomes of robotic and laparoscopic resections of the postero-superior segments appear to be similar in terms of blood loss, hospital stay, morbidity, and completeness of resection[50] (see R14.1, R14.2, and R14.3).

Is LLR Applicable for Parenchyma-sparing Procedures and Anatomic Segmentectomies?
Laparoscopic and open sectionectomies have been found to have similar perioperative outcomes.[39] Various techniques, including a Glissonian approach, staining and indocyanine green fluorescence imaging have been suggested to facilitate a true anatomical segmentectomy.[51–53] Evidence for parenchyma-sparing LLR for centrally located lesions is limited. However, studies document R0 and recurrence rates that fall within the average published data[54,55] (see R15.1 and R15.2).

Section 4: Technique

Topic 10: Minimally Invasive Approaches, Surgical Devices, Intraoperative Staging, and Planning

What is the Role of the Hand-assisted Technique and Hybrid Procedures for Liver Resections?
The evidence suggests that no 1 approach (open, hybrid, HALS, or pure laparoscopic) is totally superior in terms of operative or postoperative factors, but it has been suggested that HALS and hybrid techniques may serve as a bridge from open to laparoscopic surgery during the learning curve[56] (see R16).

What is the Role of the Robotic Approach for Liver Resections?
The robotic approach has a longer operative time and higher costs compared with a laparoscopic approach, but comparable blood loss, length of stay, resection margins, and morbidity.[57,58] Compared with an open approach, a study found total in-hospital cost to be reduced despite elevated operative cost[59] (see R17).

What is the Role of Intraoperative Ultrasound for LLR?
The increased sensitivity of intraoperative ultrasound (compared with preoperative imaging and diagnostic laparoscopy) has been strongly suggested by numerous studies.[60,61] Multiple technical papers describe ultrasound as a necessary tool to investigate liver anatomy and tumor location, and to plan transection lines and margins[62,63] (see R18).

What are the Available Techniques for Parenchymal Transection?
Multiple technical and comparative papers highlight the roles of differing transection devices. However, there is no universal agreement regarding the optimal technique[64–66] (see R19.1, R19.2, and R19.3).

Topic 11: Anatomic Major Resection (Formal Right/Left Hemi-hepatectomies)

What are the Available Safe Techniques for Inflow Control During Major Anatomical Resections?

The majority of European centers have a preference for the hilar approach, regularly demonstrating its safety and reproducibility.[67] However, several centers outside of Europe report good outcomes with a Glissonian approach[51] (see R20).

What are the Available Safe Techniques During Right Hemihepatectomy?

Although the anterior approach to liver transection, without prior liver mobilization, has been recommended by many a conventional approach with liver mobilization before transection is also possible and recommended by others. The choice between the 2 techniques depends on surgeon's preference, tumor size, and liver fragility. Whereas the hanging maneuver has been used and recommended by some surgeons its reproducibility has not yet been demonstrated[68,69] (see R21.1, R21.2, R21.3, R21.4, and R21.5).

Topic 12: Bleeding Control/Conversion

What are the Hemostatic Techniques During Laparoscopic Liver Resections?

The use of an intermittent Pringle maneuver has been reported to have no detrimental effects on postoperative liver function.[70] Continuous hemi-hepatic inflow control has been shown to reduce blood loss compared with an intermittent Pringle maneuver with no detriment to postoperative liver function.[71] Several technical papers highlight the importance of a sufficient cuff of tissue when applying clips and endovascular staplers.[72] Lower intraoperative blood loss is reported in patients with a central venous pressure (CVP) lower than 5 cm H2O.[73] The efficacy of stroke volume variation as an alternative to CVP monitoring has been demonstrated[74] (see R22.1, R22.2, R22.3, and R22.4).

When and How Should Conversions to Open Surgery Be Considered?

Conversion during LLR is associated with higher postoperative morbidity; however, in comparison to planned OLR, the outcomes were found to be similar.[75] Risk factors for conversion include an increasing BMI, tumor size, and resection extent, and also resections in the postero-superior segments and cirrhosis.36,76,77 In the case of conversion for significant vascular injury, temporary control of the bleeding source before conversion is highly recommended (see R23.1, R23.2, and R23.3).

Section 5: Implementation

Topic 13: Surgeon/Center/Learning Curves

What Training and Preparation Should Surgeons Pursue Before Performing Minor, Major, and Complex Liver Resections?

With experience both operative time and blood loss decreases[78,79] and experience gained during minor resections may shorten the learning curve for major resections.[80] The learning curve for minor resections is suggested to be 60 cases[78] and that for major resections is 55 (having already developed experience on minor resections)[81] (see R24.1, R24.2, R24.3, and R24.4).

Which Centers Should Be Performing Laparoscopic Liver Resections?

Laparoscopic liver surgery should not be developed in isolation from an open liver program. Major and complex LLS should be gradually implemented with increasing collective expertise for safe patient selection and management[82] (see R25.1, R25.2, and R25.3).

Should Laparoscopic Liver Resection Become Adopted in All Liver Surgical Centers?

A meta-analysis has found that the laparoscopic approach offers fewer complications, decreased blood loss, and a shorter hospital stay with comparable oncological outcomes in selected patients.[38] Therefore, the guidelines confirm that all centers should implement a program of LLS and offer it to patients with the appropriate indications according to the local level of proficiency. Ideally, at least 2 surgeons proficient in LLS in each center are recommended (see R26).

Topic 14: Training/Registries

Who Should Be Undertaking Training and Mentoring Roles in LLR?

With regards to trainers/mentors and registries/learned societies, no evidence-based studies are available. However, the learning curve for minor resections can be significantly reduced by surgeons assisting one another.[83] The recommendation of the experts is that mentors and trainers must be experienced surgeons with a current and up-to-date knowledge of the literature, whereas registries are necessary for evaluation of LLR and individual surgeons/centers alike (this relates to R27, R28, and R29).

DISCUSSION

The European Guidelines Meeting for Laparoscopic Liver Surgery was devised to produce specific guideline statements to ensure the safe progression and dissemination of laparoscopic liver surgery. The guidelines produced further the work of the previous consensus meetings by providing specific guidance to both expert and training laparoscopic liver surgeons. The 67 guidelines combine the most up-to-date evidence with expert opinion to guide the dissemination of laparoscopic liver surgery. Each guideline reached at least a 95% consensus amongst the expert committee before its acceptance into the meeting. During the meeting, each statement was opened to a vote by all those in attendance (228 surgeons including the faculty). The median agreement was 88% (with at least 160 surgeons responding to each vote), demonstrating the support of these guidelines by those with a special interest in laparoscopic liver surgery. All statements were approved and endorsed by the independent validation committee.

The EGMLLS explored new areas in the application of laparoscopy in an ever-increasing cohort of patients, and provided guidance to the appropriateness of LLR for specific diseases. Indications have been refined taking into account-specific subcategories of high-risk patients

and technically complex disease. Moreover, the guidelines re-define the classification of resections adding “technically major” resections, such as those in the postero-superior segments, to the established anatomical minor and major resections. Specific scenarios that require more experience were highlighted with the guidelines advocating caution dependent on the surgeon’s expertise and available technical equipment.

The Southampton Guidelines state that when performed by expert surgeons, LLR offers significant advantages in terms of a reduced risk of postoperative ascites and liver decompensation in patients with cirrhosis. For patients with CRLM, LLR was deemed an appropriate option that offers significant benefits in terms of a shorter hospital stay and lower complication rate. However, the need to adhere to a parenchymal sparing approach was stressed. The use of LLR for living donor hepatectomy is limited to a few highly specialized centers worldwide, but may now be regarded as standard practice for left lateral sectionectomy in adult-to-pediatric donation.

The Southampton Guidelines advocate that the laparoscopic approach should be considered standard practice for lesions in the left lateral and the anterior segments. The guidelines state that in expert hands, LLR for lesions in the postero-superior segments may maintain the advantages seen in the anterolateral segments. Subcategories of “high-risk” patients, such as the elderly and patients with high BMI, were no longer considered as contra-indications to LLR. Technically challenging resections such as repeat resections or 2-stage hepatectomies, resections for large lesions, and lesions in close proximity to the hilum are now considered possible by surgeons with extensive experiences in LLS. The Southampton Guidelines highlight the difference in difficulty and outcomes between laparoscopic left and right hemi-hepatectomies. Hence, it was advised that their uptake occur at different points in the learning curve. Regarding inflow control and parenchymal transection, the guidelines state that the choice of technique is dependent on the characteristics of the disease and the surgeon’s preference. Pringle maneuver and the management of intravascular volume to provide a low CVP are both essential to reduce blood loss during transection. And, as in open liver surgery, the need for intraoperative ultrasound was considered essential.

The guidelines regarding the implementation of LLS are of paramount importance in the EGMLLS. A background in open liver surgery and advanced laparoscopic skills before starting LLR are considered essential. The guidelines recommend fellowships, courses, and proctored programs to facilitate the training and development of laparoscopic liver surgeons. These fellowships should be conducted in established, high-volume centers that routinely perform minor, major, and complex major resections. Those providing supervision, as mentors and proctors, should themselves have already reached competency and are thus able to provide safe guidance during the training of less experienced surgeons. Importantly, it was recommended that each specialist center should offer a laparoscopic approach as part of its multidisciplinary management of liver disease and should ideally have a minimum of 2 surgeons competent in LLS to support, assist, and critique each other to aid development. It is important to note that the majority of the evidence used in the production of these guidelines report data from specialist liver centers, which may represent a publication bias. However, this factor is of critical importance, as these guidelines should not be misconstrued as an invitation to begin performing laparoscopic liver surgery in the absence of experience and support. The authors must once again stress that laparoscopic liver surgery is complex and requires advanced laparoscopic skills, comprehensive experience of open liver surgery, and the support of an experienced team. Finally, the terms “experienced surgeons” and “selected patients” are not simple, rigid definitions, but represent a malleable spectrum where multiple confounding factors, which will evolve with time and vary between centers, must be considered. Although previous manuscripts have suggested that between 20 to 60 minor resections and 30 to 60 major resections (having already reached competency with minor resections) are required to overcome the learning curve,[78–81] the expert panel was in agreement that no specific number can be given to the number of resections performed for a surgeon to reach "competency," and patient factors must be weighed with respect to the experience of the surgeon and their team.

With the exponential growth of laparoscopic liver surgery, it will no doubt be necessary to review the current guidance with the passage of time to ensure that they continue to represent the most contemporary and highest level of evidence available to provide safe guidance in the dissemination of laparoscopic liver surgery.

CONCLUSIONS

The European Guidelines Meeting for Laparoscopic Liver Surgery has produced a set of clinical practice guidelines that have been independently validated for the safe development and progression of laparoscopic liver surgery. Using a robust methodology the Southampton Guidelines have amalgamated the available evidence and a wealth of experts' knowledge taking in consideration the relevant stakeholders' opinions and complying with the international methodology standards. These guidelines are not an endorsement for a novice to perform LLS without the appropriate training, and ideally LLS should be performed within the confines of an institution with an established support network and experience in liver surgery.

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PART 1

IMPLEMENTATION OF LAPAROSCOPIC LIVER SURGERY

CHAPTER 3

Stepwise introduction of laparoscopic liver surgery: validation of guideline recommendations

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ABSTRACT

Background

Uncontrolled introduction of laparoscopic liver surgery (LLS) could compromise postoperative outcomes. A stepwise introduction of LLS combined with structured training is advised. This study aimed to evaluate the impact of such a stepwise introduction.

Methods

A retrospective, single-center case series assessing short term outcomes of all consecutive LLS in the period November 2006-January 2017. The technique was implemented in a stepwise fashion. To evaluate the impact of this stepwise approach combined with structured training, outcomes of LLS before and after a laparoscopic HPB fellowship were compared.

Results

A total of 135 laparoscopic resections were performed. Overall conversion rate was 4% (n = 5), clinically relevant complication rate 13% (n = 18) and mortality 0.7% (n = 1). A significant increase in patients with major LLS, multiple liver resections, previous abdominal surgery, malignancies and lesions located in posterior segments was observed after the fellowship as well as a decrease in the use of hand-assistance. Increasing complexity in the post fellowship period was reflected by an increase in operating times, but without comprising other surgical outcomes.

Conclusion

A stepwise introduction of LLS combined with structured training reduced the clinical impact of the learning curve, thereby confirming guideline recommendations.

INTRODUCTION

Laparoscopic liver surgery (LLS) had a relatively slow start due to initial concerns about bleeding, gas embolism, increased complications during the early phases of the learning curve and the ability to perform adequate radical oncological resections. Through the pioneering work of high-volume, expert centers, an increasing body of evidence has emerged in recent years confirming the possible advantages of LLS.[1–9] Benefits of LLS include less intraoperative blood loss, less postoperative complications, decreased need for analgesics, faster functional recovery, shorter postoperative stay, and a cosmetic benefit.[1–9] In addition, some studies have demonstrated the cost-effectiveness of LLS,[10–12] thus resulting in benefits for both individual patients and healthcare institutions. These promising results have promptly increased the interest in LLS worldwide[1,2] and the first randomized controlled trials of laparoscopic vs. open liver surgery have been performed.[13,14]

Despite these promising results, LLS remains challenging and should not be started without appropriate training and acquired surgical skills. During the 2015 Morioka consensus meeting[15] and more recently during the 2017 European guideline meeting on LLS in Southampton (EGMLLS) the importance of structured implementation plans, providing education and a stepwise introduction of LLS, was stressed. Starting with minor resections and gaining experience along the way, surgeons can eventually begin to take on more difficult procedures such as hemihepactectomies. The results of such an approach and its effect on the learning curve have not been specifically addressed before and could further encourage surgeons to implement LLS into their center.

The aim of this study was to present the results of a single center that followed a stepwise approach in setting up a LLS practice, including structured training, with assessment of a potential learning curve effect on short-term postoperative outcomes.

METHODS

Patients

In a retrospective case series, all consecutive patients undergoing LLS for any indication between November 2006 and January 2017 in the Academic Medical Center (AMC) in Amsterdam were evaluated. No LLS was performed prior to November 2006. All primary LLS or combined laparoscopic colorectal and liver resections were included.

Prior to surgery, all patients were discussed in a multidisciplinary team (MDT) meeting with HPB surgeons, radiologists, gastroenterologists, hepatologists, medical oncologists and pathologists. The surgical indication was established independently of the decision regarding the surgical approach, which was made later considering a number of factors including the available experience and skill. Initially, only minor resections, defined according to the Louisville consensus meeting in 2008,[16] were considered candidates for the laparoscopic approach whilst major LLS procedures were only considered after experience and skills were obtained by performing minor LLS and one surgeon (MB) had completed an eight month fellowship in laparoscopic HPB surgery in 2013.
In addition, complex resections such as those of large lesions or lesions in close proximity to major vascular structures were not considered during the early stages. Attention was paid during the MDT meetings to patient- and tumor characteristics (e.g. tumor location, obesity) that could increase the difficulty of the operation, in order to select the patients most suitable for LLS, especially during the early stages.

Outcomes

Baseline patient- and procedure characteristics included patient demographics, body mass index (BMI, kg/m2), American Society of Anaesthesiology (ASA) classification, liver cirrhosis, previous abdominal surgery, previous liver resection, simultaneous colorectal resection, tumor pathology (benign/malignant), extent of resection (minor/major/technically major[17]), type of resection, hand-assistance, multiple simultaneous liver resections and approach to liver resection (one-stage only, one-stage + radio frequency ablation (RFA), two-stage without portal vein embolization (PVE) and two-stage with PVE). Intra- and postoperative outcomes included operative time (minutes), intraoperative blood loss (ml), blood transfusion, conversion, resection margins (margin negative (R0) or margin involved (R1)), length of postoperative hospital stay (days), clinically relevant complication rate (defined as Clavien-Dindo score 3 or higher)[18] and mortality (defined as death related to liver and/or colorectal complications within 90 days after surgery or within hospital stay).

Surgical experience

All resections were performed or supervised by one or two out of three liver surgeons (OB, PT and MB), all of whom had completed a fellowship in open liver surgery, had experience in advanced laparoscopic gastrointestinal surgery (defined here as anything beyond laparoscopic cholecystectomy, appendectomy or hernia repair surgery) and had taken at least two hands-on courses on minor LLR. OB had ten years of experience in open liver surgery and advanced laparoscopic gastrointestinal procedures after his fellowship. PT and MB each had two years of experience after their fellowship including advanced laparoscopic gastrointestinal procedures. OB started with LLS in 2006, PT in 2010 and MB in 2012. MB completed a fellowship in laparoscopic HPB surgery (Jan–Aug 2013; University Hospital Southampton NHS Foundation Trust).

Surgical technique

A standardized approach was used. Patients were placed in a supine position with legs apart and if required on a beanbag. After placement of 3–5 trocars, parenchymal dissection was performed with ultrasonic shears (Harmonic Ace®; Ethicon Endo-Surgery, Cincinnati, OH, USA) and, for larger/posterior lesions or resections, laparoscopic cavitron ultrasonic surgical aspirator (CUSA) (Valleylab, Boulder, CO, USA). For left lateral sectionectomy, only ultrasonic shears and endostaplers were used. Rarely, for posterior lesions, a handport was used (n = 4). Specimens were extracted in a plastic endoscopic bag (Endocatch; Ethicon Endo-Surgery, Cincinnati, OH, USA) via a Pfannenstiel incision or, in case of lesions <3 cm, through a widened trocar incision. Pringle maneuver was applied for laparoscopic major procedures, including posterior metastasectomies and larger, atypical metastasectomies. For metastasectomies the 'diamond technique' was preferred.[19] All laparoscopic hemihepatectomies and laparoscopic resections involving segment 7 were performed by a team of two surgeons (MB, PT).

Statistical analysis

Data analysis was performed using IBM SPSS Statistics for Windows version 23.0 (IBM corp., Armonk, NY, USA). To evaluate the stepwise approach and its impact on the learning curve, the cohort was divided into two groups: before (group A) and after (group B) a dedicated fellowship in major laparoscopic HPB surgery. Continuous non-parametric variables were reported as median with interquartile range (IQR). A Mann Whitney U test was used to compare continuous variables between the groups. Categorical variables were reported as proportions and compared between groups using chi-square test or Fisher's exact test as appropriate. A two-tailed p value of <0.05 was considered statistically significant.

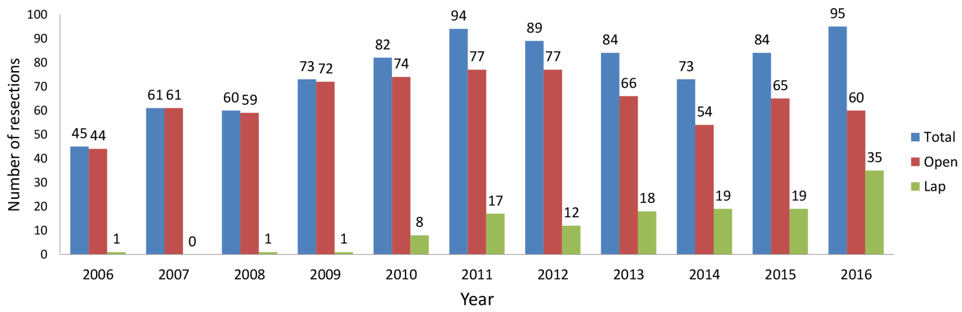

Figure 1. Number of open and laparoscopic liver resections through the years

RESULTS

Between November 2006 and January 2017, 135 LLS were performed in 132 patients (one patient underwent two procedures and one underwent three). During this period, the percentage of liver resections performed laparoscopically increased from 2% in 2006 to 37% in 2016 ($p < 0.001$) (Figure 1).

Baseline patient and procedure characteristics are shown in Tables 1 and 2 respectively. Of all resections, 100 (74%) were for malignant disease, mostly CRLM (n = 58) and HCC (n = 27). Operations were performed by combinations of two surgeons in 33% (n = 45) of procedures. Perioperative outcomes are shown in Table 3. Conversion to an open procedure occurred in 5 patients (4%) for the following reasons: bleeding (n = 2), inadequate access to the lesions (n = 2) and concern about oncological efficiency (n = 1). Clinically relevant postoperative complications occurred in 18 patients (13%), including biloma/abscess requiring drainage (5%, n = 7) and anastomotic leak in combined laparoscopic colorectal procedures (15%, n = 4) as the most frequently observed complications. One patient died of decompensating liver cirrhosis with hepatorenal syndrome after hand-assisted resection of HCC from segment 8, resulting in a 0.7% mortality rate.

Sensitivity analysis

Outcomes did not change when major LLS was excluded from the analysis (data not shown).

Table 1. Patient characteristics

	Overall n=135	Group A n=52	Group B n=83	P
Age, years (IQR)	59 (46-67)	56 (40-66)	61 (47-71)	0.276[a]
Sex, males, n (%)	75 (56%)	28 (54%)	47 (57%)	0.859[b]
BMI, kg/m2 (IQR)	26 (23-29)	26 (24-30)	26 (23-29)	0.947[a]
ASA score (%)				0.887[c]
- ASA I	27 (20%)	12 (23%)	15 (18%)	
- ASA II	84 (62%)	31 (60%)	53 (64%)	
- ASA III	22 (16%)	8 (15%)	14 (17%)	
- ASA IV	2 (2%)	1 (2%)	1 (1%)	
Liver cirrhosis, n (%)	21 (16%)	9 (17%)	12 (15%)	0.808[b]
Previous abdominal surgery, n (%)	63 (47%)	12 (23%)	51 (61%)	<0.001b
Simultaneous colorectal surgery, n (%)	26 (19%)	8 (15%)	18 (22%)	0.263[b]
Previous liver resection, n (%)	6 (4%)	3 (6%)	3 (4%)	0.676[c]
Malignancy, n (%)	100 (74%)	32 (62%)	68 (82%)	0.010[b]
Lesion size, cm (IQR)	3 (1.8-5.5)	4 (2-5.9)	2.5 (1.9-5)	0.055[a]
Tumor location, n (%)				0.008[b]
- Anterior/left lateral segments (2,3,4b,5,6)	96 (71%)	45 (87%)	51 (61%)	
- Posterior/superior segments (4a,7,8,1)	34 (25%)	7 (14%)	27 (33%)	

IQR = interquartile range, [a] Independent Samples Test, [b] Chi-square test, [c] Fisher's exact test
Group A = before fellowship in laparoscopic HPB surgery, group B = after fellowship

DISCUSSION

This single-center, retrospective study confirms the guideline recommendations that a stepwise introduction of LLS combined with specific surgical training and mentoring is a valuable and safe strategy for centers starting with LLS. In this series, the stepwise introduction was evidenced by a significant increase of more complicated procedures and less favorable patient characteristics over time and was combined with structured education before implementing major LLS. Despite increasing complexity of the procedures, intra- and postoperative outcomes were not compromised. During the 2015 Morioka[15] and 2017 Southampton EGMLLS guideline meetings on LLS, a stepwise approach combined with formal training in LLS was advised in order to decrease the impact of the learning curve in the early stages. Very few studies, however, report on the results of such an approach to setting up a LLS practice in starting centers. More frequently, authors report on the surgical learning curve in LLS, often displayed as the number of resections needed before optimal outcomes are reached.[20–22] The variables

Table 2. Procedure characteristics

	Overall n=135	Group A n=52	Group B n=83	P
Extent of resection, n (%)				0.032[a]
- Minor	118 (87%)	49 (94%)	69 (83%)	
- Major	9 (13%)	0	9 (11%)	
- Technically major	8 (6%)	3 (6%)	5 (6%)	
Type of resection, n (%)				0.158[b]
- Non-anatomic/metastasectomy	64 (47%)	23 (44%)	41 (49%)	
- Left lateral sectionectomy	27 (20%)	12 (23%)	15 (18%)	
- Segmentectomy	27 (20%)	14 (27%)	13 (16%)	
- Bisegmentectomy	8 (6%)	3 (6%)	5 (6%)	
- Right hepatectomy	5 (4%)	0	5 (6%)	
- Left hepatectomy	4 (3%)	0	4 (5%)	
Hand assistance, n (%)	4 (3%)	4 (8%)	0	0.020[b]
Additional wedge resection, n (%)	21 (16%)	2 (4%)	19 (23%)	0.003[a]
Approach, n (%)				0.402[b]
- One stage resection	121 (90%)	47 (90%)	74 (89%)	
- One stage resection + RFA	5 (4%)	3 (6%)	2 (2%)	
- Two stage resection without PVE	5 (4%)	2 (4%)	3 (4%)	
- Two stage resection with PVE	4 (3%)	0	4 (5%)	

RFA = radiofrequency ablation, PVE = portal vein embolization, [a] Chi-square test, [b] Fisher's exact test
Group A = before fellowship in laparoscopic HPB surgery, group B = after fellowship

to assess the presence of a learning curve vary between studies. In some, the learning curve is clinically obvious with improving perioperative results such as operative time,[21,23–29] intraoperative blood loss,[21,24–28] conversion,[21] postoperative stay[21,23,24] and morbidity[28] over time. In a study by Robinson et al.[30] in 37 patients, increasing complexity of LLS with stable perioperative results was defined as a learning curve, similar to the current study. Both improving outcomes and increasing complexity with stable outcomes are used to define the learning curve, even though the developments of improving results and increasing difficulty of procedures are distinctly different. Obviously, both are a result of growing experience, but they are not the same. This distinction when addressing the learning curve is relevant, since implementing a new technique in clinical practice should always be done in a safe way and without compromising patient outcomes. The concept and clinical relevance of this "proficiency curve", defined by patient outcomes such as complications, hospital stay and mortality, as opposed to the "feasibility curve", defined by intraoperative outcomes such as operative time, conversion rate and blood loss, have previously been described in laparoscopic distal pancreatectomy.[31]

Table 3. Perioperative outcomes

	Overall n=135	Group A n=52	Group B n=83	P
Operation time, minutes (IQR)	154 (101-267)	128 (94-188)	215 (130-370)	0.001[a]
Intraoperative blood loss, ml (IQR)	250 (100-700)	375 (200-775)	200 (50-700)	0.048[a]
Blood transfusion, n (%)	7 (5%)	2 (4%)	5 (6%)	0.707[b]
Conversion, n (%)	5 (4%)	2 (4%)	3 (4%)	1[b]
Resection margins for malignancies, R0 resection (%)	93 /100 (93%)	28/32 (88%)	63/67 (94%)	0.131[b]
Postoperative stay, days (IQR)	4 (3-5)	5 (3-5)	4 (2-5)	0.058[a]
Postoperative complications, Clavien-Dindo ≥III, n (%)	18 (13%)	4 (8%)	14 (17%)	0.193[c]
Mortality, n (%)	1 (0.7%)	1 (2%)	0	0.385[b]

IQR = interquartile range, [a] Independent Samples T test, [b] Fisher's exact test, [c] Chi-square test
Group A = before fellowship in laparoscopic HPB surgery, group B = after fellowship

3

In standardized resections like distal pancreatectomy, improving results over time can be expected. One might argue that our improving results are masked by the heterogeneity of LLS. Improving results in minor LLS could have been counterbalanced by the introduction of major LLS. A sensitivity analysis, however, showed that excluding major resections had no detectable impact on outcomes, although numbers were small.

Previous reports have described learning curves for LLS varying from 24 to 295 patients, clearly demonstrating the heterogeneity of these studies as to when the learning curve is completed. Despite the findings reported in the current series (93% R0 resection, 3.7% conversion, 13.3% complications and 0.7% mortality), the learning curve for major LLS (e.g. for laparoscopic hemi-hepatectomy) still might not have been overcome. This requires constant monitoring. The institutional experience of hemihepactectomies (n = 9) is rather small. This was partly overcome by performing all major resections with two senior surgeons. Major LLS was only performed after a dedicated laparoscopic HPB fellowship, during which over 20 major LLS procedures had been performed. Previous studies have demonstrated that there are no differences in the rates of R1 margins between open and laparoscopic liver surgery.[5,32–34] The 93% R0 resection rate in this study is within the 82–100% range as previously described for LLS.[1]

As stressed in the 2015 and 2017 guideline meetings, adequate training is crucial. In the AMC, major LLS was only introduced after one surgeon had completed a laparoscopic HPB fellowship and experience was obtained through minor LLS (n = 48). Furthermore, one third of all procedures were performed by combinations of two surgeons to enhance the learning process. Besides the steps of implementation, all surgeons had significant experience in open and advanced laparoscopic gastrointestinal surgery and had followed at least two hands-on courses in minor LLS prior to starting with LLR. This level of experience and surgical training was considered an essential pillar before the stepwise introduction of LLS was even considered and has very likely contributed to the low conversion and complication rates from the beginning.

Consensus on how to design structured training and formal education programs is lacking and should be a focus for further research. In the current era of highly specialized and complex (laparoscopic) HPB surgery, a plea has been made to move away from 'see one, do one, teach one',[35] and progress is made, with several expert HPB units starting hands-on courses in LLS and specialized laparoscopic HPB fellowships.[36,37]

This series clearly has its shortcomings. The retrospective study design introduces significant risk of selection bias and that the series is relatively small. However, since this study reports on consecutive (selected) patients and the decision when to start with major resections was made prospectively, this series confirms the benefits of the stepwise introduction of LLS combined with structured training.

In conclusion, the current retrospective, single-center study supports the guideline recommendations of a stepwise introduction of LLS combined with structured surgical training. This approach can help to decrease the clinical impact of the learning curve and can be an appropriate method for technique implementation in starting centers and on a larger, nationwide scale. Future studies should focus on an effective design and structure for education and training programs for LLS.

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CHAPTER 4

Implementation and outcome of minor and major minimally invasive liver surgery in the Netherlands

Submitted for publication

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ABSTRACT

Background

While most of the evidence on minimally invasive liver surgery (MILS) is derived from expert centers, nationwide outcomes remain underreported. This study aimed to evaluate the implementation and outcome of MILS on a nationwide scale.

Methods

Electronic patient files were reviewed in all Dutch liver surgery centers and all patients undergoing MILS between 2011 and 2016 were selected. Operative outcomes were stratified based on extent of the resection and annual MILS volume.

Results

Overall, 6951 liver resections were included, with a median annual volume of 50 resections per center. The overall use of MILS was 13% (n=916), which varied from 3% to 36% (P<0.001) between centers. The nationwide use of MILS increased from 6% in 2011 to 23% in 2016 (P<0.001). Outcomes of minor MILS were comparable with international studies (conversion 0-13%, mortality <1%). In centers which performed ≥20 MILS annually, major MILS was associated with less conversions (14 (11%) versus 41 (30%), P<0.001), shorter operating time (184 (117-239) versus 200 (139-308) minutes, P=0.010), and less overall complications (37 (30%) versus 58 (42%), P=0.040).

Discussion

The nationwide use of MILS is increasing, although large variation remains between centers. Outcomes of major MILS are better in centers with higher volumes.

INTRODUCTION

Minimally invasive liver surgery (MILS) has been adopted slowly since its introduction in the early 1990s, especially compared to other procedures in gastrointestinal surgery. The widespread implementation of MILS was hampered by concerns about a learning curve effect combined with the low volume of liver surgery in most centres.[1]

In recent years, the pioneering work of several expert surgeons from very high-volume centers has confirmed the potential advantage of MILS as compared to open surgery.[1-3] These advantages include decreased intraoperative blood loss, fewer postoperative complications, less need for analgesics, faster functional recovery, shorter postoperative hospital stay, decreased risk of wound infections, better cosmetics and lower risk of incisional hernia.[1-3] These promising results boosted the interest in MILS worldwide and eventually resulted in three subsequent guideline meetings on MILS.[4-6] Based on these meetings, MILS is now considered the standard approach for minor liver resections (i.e. resection of less than three liver segments).[5-6] According to the most recent Southampton guidelines, implementation of both anatomically and technically major MILS (i.e. resection of three or more segments or resection from posterior segments, respectively[4]) should be handled in a stepwise fashion and combined with structured training in centers who have completed the learning curve for minor MILS.[6]

The remaining question is whether the promising results for minor and major MILS can be reproduced on a nationwide scale. Population based studies with data on both implementation and outcome of MILS are scarce and, if available, lack stratification for minor and major MILS.[7,8] Previous studies also did not investigate the impact of volume on the outcome of MILS. This study aimed to determine both the implementation and outcome of minor and major MILS on a nationwide level and to assess the impact of volume on overall outcome of major MILS.

METHODS

This study was performed within the Dutch Liver Collaborative Group (DLCG) in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[9] It describes the outcomes and implementation rates of MILS in all 27 Dutch centers performing liver surgery. All centers perform at least 20 liver resections per year, which is the national annual volume requirement for liver surgery in the Netherlands. MILS included total laparoscopic, hand-assisted, and robot-assisted procedures. The ethics committee of the Amsterdam UMC, location AMC (Amsterdam, the Netherlands), waived the need for informed consent.

Design and patients

Patients were selected from center specific, prospectively collected liver surgery databases or from surgery schedules listing all liver resections. All patients who had undergone a MILS procedure between January 2011 and December 2016 were eligible. Patients were excluded when insufficient data were available, when they had previously objected to have their information gathered from their patient files for research purposes, when no resection was performed (e.g. fenestration/deroofing of cysts, biopsies, diagnostic laparoscopy) or in case of emergency surgery. A flowchart illustrating the patient selection process is provided in Appendix A.

Selection criteria for the minimally invasive approach were not standardized, so a comprehensive selection of MILS was included, regardless of the indication. All patients were discussed in a multidisciplinary team meeting with hepato-pancreato-biliary (HPB) surgeons, gastroenterologists, medical oncologists, radiologists and pathologists. The surgical indication was established before and independently of the decision regarding the surgical approach, which was made based on tumor characteristics such as size and location, patient performance status and the surgeon's experience and skill. An absolute contraindication for a minimally invasive approach in all centers was the need for vascular or biliary reconstruction and anatomically major liver resection combined with a colorectal resection.

Definitions and data collection

Major MILS was defined according to consensus agreements[4] and categorized based on evidence of a difference in outcome[10] as any resection of three or more segments (anatomically major) or any resection from the posteriorly located segments 7, 8, 4a and 1 (technically major), respectively. Intraoperative incidents were scored according to the Oslo Classification.[11] Postoperative complications were graded according to the modified Accordion Classification.[12] Resection margins were defined as R0 (1mm or more tumor free margin), R1 (less than 1mm tumor free margin) or R2 (macroscopic tumor involvement at the margin).

Four authors (MJvdP, RSF, BG, CNN) collected individual patient data from electronic patient files with daily notes in all centers. Baseline characteristics included patient demographics, body mass index (BMI, kg/m^2), American Society of Anesthesiologists (ASA) grade, abdominal surgery history, indication for surgery (benign/malignant), number of lesions on preoperative imaging, size of the largest lesion on preoperative imaging, neoadjuvant chemotherapy, minimally invasive approach (total laparoscopic, hand-assisted or robot-assisted), extent of resection (minor/anatomically major/ technically major), type of resection, simultaneous colorectal procedure and the use of intraoperative ultrasound. Operative outcomes included operating time, intraoperative blood loss, conversion (both strategic and reactive), intraoperative adverse events, 30-day or in hospital postoperative complications (defined according to the Accordion Classification, severe complications were defined as Accordion grade three or higher), 30-day or in hospital re-intervention, 30-day re-admission, postoperative hospital stay, resection margins of malignant lesions, pathology report, 90-day or in hospital mortality and occurrence of incisional hernia within 1 year of follow up, either on imaging or requiring surgery. The total annual volume of liver resections performed per center during the study period was collected in order to determine the implementation rate of MILS.

Surgical technique

Surgical techniques were not standardized. In general, patients were placed in a supine position and, depending on the type of resection, 3-5 trocars were placed. In some cases, patients were placed in a lateral position. An intra-abdominal pressure of 12-15 mmHg was applied. Laparoscopic ultrasound was used to determine the parenchymal transection plane and for identification of additional lesions. The Pringle maneuver was used selectively. Different devices were used for the parenchymal transection phase. For minor resections the most frequently used devices were an ultrasonic dissector (n=10 centers), vessel sealing device (n=7), cavitron ultrasonic surgical aspirator (CUSA, n=4) or clamp-crush with bipolar forceps (n=2). For major resections again the ultrasonic dissector was most frequently used (n=6 centers), followed by CUSA (n=4), vessel sealing device (n=3) and water-jet dissector (n=2). Specimens were extracted in a plastic endoscopic bag through a Pfannenstiel incision or, in case of small lesions, through a widened trocar incision. For all robot-assisted procedures the da Vinci® Si Robotic Surgical System (Intuitive Surgical®, Inc., Sunnyvale, CA, USA) was used and devices used during parenchymal transection included the bipolar forceps and the vessel sealer.

Survey

To obtain baseline characteristics per center, a 50-question, online survey was sent to all centers in March 2017 (Appendix B). Surgeons were asked to describe their personal and institutional experience with MILS, including what form of training they had received prior to starting with MILS and whether they would be interested to participate in a nationwide, structured training program in major MILS. Non-responders received a maximum of three email reminders and one phone call.

Statistical analysis

Data analyses were performed using IBM SPSS Statistics for Windows version 24.0 (IBM corp., Armonk, NY, USA). Analysis was performed according to intention-to-treat principles, hence conversions to laparotomy were included in the MILS cohort. Continuous, parametric variables were reported as mean with standard deviation (SD). In case values were not normally distributed, continuous variables were reported as median with interquartile range (IQR). A Mann Whitney *U* test or independent-samples T test was used for the comparison of non-parametric and parametric continuous variables, respectively. Categorical variables were reported as proportions and compared using a chi-square or Fisher's exact test, as appropriate. A two-tailed P value of <0.05 was considered statistically significant.

Sensitivity analysis was performed to rule out any disproportional impact of simultaneous liver and colorectal resections and robot-assisted resections on MILS outcomes.

Two different subgroup analyses were performed comparing operative outcomes in high- and low-volume centers. In the first, high-volume was defined as an average annual volume of ≥20 MILS procedures over the entire study period. The low-volume comparison centers were all other centers, thus those centers with an average of <20 MILS procedures performed between 2011 and 2016. In the second subgroup analysis, the high volume group consisted of all patients that were operated in a year that the respective center performed ≥20 MILS procedures and compared to a low volume group with all patients operated in the other years.

RESULTS

Of the 27 centers that were approached, data were gathered from 20 centers. The seven non-participating centers reported to have minimal experience with MILS. Eight out of 20 centers were university medical centers. A total of 49 surgeons performed MILS in these 20 centers with a median of 2 surgeons (2-3) per center. During the 6-year study period, a total of 6951 liver resections were performed, of which 916 were MILS (13%). There were no exclusions of patients objecting to the use of their data for research purposes. Of these 916 resections, 878 (96%) were totally laparoscopic, 31 (3%) were robot-assisted and 7 (1%) were hand-assisted. Appendix A demonstrates the flowchart of patient selection. Per year, the use of MILS increased from 6% of all liver resections in 2011 to 23% in 2016 ($P < 0.001$, Figure 1). The overall use of MILS per center (all years combined) varied largely, from 3% to 36% ($P < 0.001$). Only one center performed more than 20 MILS procedures on average per year during the entire study period. When only assessing 2016, six centers performed more than 20 MILS procedures. Figures 2 and 3 show the overall implementation of MILS and the annual volume of MILS per center categorized by the extent of resection, respectively.

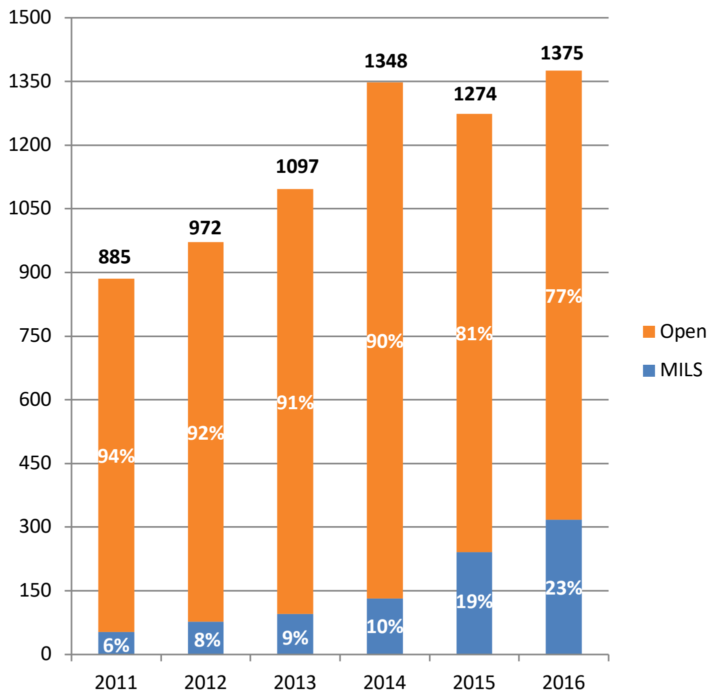

Figure 1. Proportion MILS of total annual volume of liver resections in the Netherlands (2011-2016)

Patient and procedure characteristics

The cohort consisted of 473 males (52%) and 443 (48%) females with a median age of 64 years (51-71). A total of 656 minor resections (72%), 63 anatomically major resections (7%) and 197 technically major resections (22%) were performed. All patient and procedure characteristics are presented in Table 1.

Operative outcomes

Operative outcomes were stratified for minor, anatomically major, and technically major resections (Table 2). Conversion rates were 10%, 21% and 21%, respectively. Reasons for conversion were difficulty to reach lesions (n=47), bleeding (n=28), concern about radicality (n=15), adhesions (n=11), open colorectal resection (n=3), complications

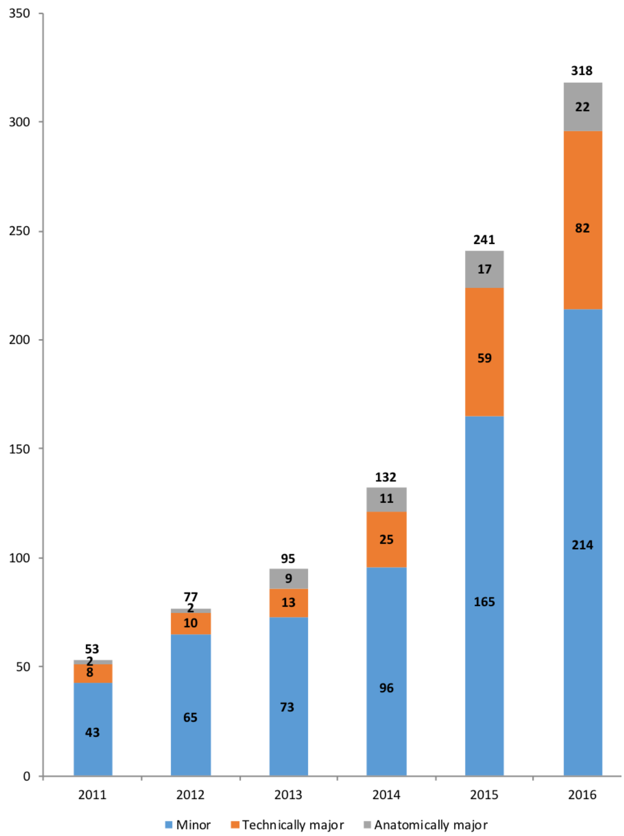

Figure 2. Annual use of minor and major MILS in the Netherlands (2011-2016)

other than bleeding (n=3), no laparoscopic ultrasound available to identify lesions (n=3), equipment failure (n=2) and other (n=3). Re-interventions included ultrasound guided drainage (n=23), laparotomy (n=21), re-laparoscopy (14), CT-guided drainage (n=8) and ERCP with stent placement (n=6). In four of the nine (44%) post-operative deaths within 90 days a multivisceral resection had been performed. This included two colorectal procedures that were complicated by eventually fatal anastomotic leakage, one distal pancreatectomy with splenectomy that was complicated by an eventually fatal intestinal perforation and one gastrojejunostomy. Other causes of death were respiratory insufficiency (n=1) and disease progression (n=5).

Sensitivity analysis

Both fatal simultaneous liver and colorectal resections were minor liver resections. Excluding these from the mortality analyses resulted in a 90-day mortality rate of 0.6% for minor MILS procedures. Other outcomes did not change when simultaneous liver and colorectal

resections and robot-assisted resections were excluded from analyses (data not shown). Baseline characteristics and operative outcome of simultaneous colorectal and liver resections and robot-assisted resections can be found in the supplementary material (Appendix C and D).

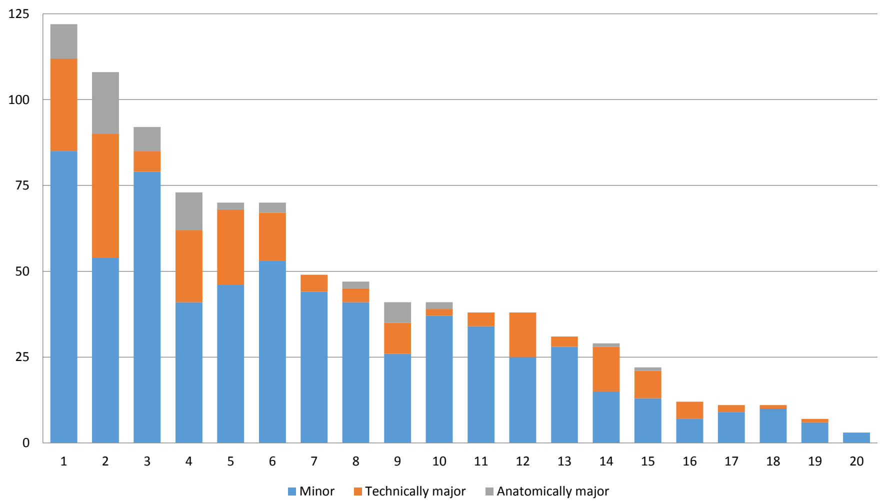

Figure 3. Total volume of MILS in 20 centers in the period 2011-2016

Table 1. Baseline characteristics

	Minor MILS (A) n=656	Technically major MILS (B) n=197	Anatomically major MILS (C) n=63	*P* (A vs B)	*P* (A vs C)	*P* (B vs C)
Sex, male	325 (50)	117 (59)	31 (49)	0.015	0.959	0.155
Age, years, median (IQR)	63 (49-72)	65 (57-71)	63 (49-71)	0.052	0.673	0.137
BMI, kg/m², median (IQR)	25.6 (23-29)	25.5 (22.8-28.9)	21.1 (23-29.5)	0.850	0.561	0.513
American Society of Anesthesiology grade				0.041	0.728	0.038
- ASA 1	129 (20)	24 (12)	16 (25)			
- ASA 2	392 (60)	137 (70)	36 (57)			
- ASA 3	116 (18)	34 (17)	10 (16)			
- ASA 4	4 (1)	0	0			
Previous abdominal surgery	381 (58)	153 (78)	42 (67)	<0.001	0.186	0.079
Cancer as indication	461 (70)	170 (86)	47 (75)	<0.001	0.471	0.030
- CRLM	328 (71)	139 (81)	38 (81)			
- HCC	92 (14)	14 (8)	3 (6)			
- Cholangiocarcinoma	11 (2)	3 (2)	2 (4)			
- Other	30 (7)	14 (8)	4 (9)			
Number of lesions, median (IQR)	1 (1-1)	1 (1-2)	2 (1-2)	<0.001	<0.001	0.008
Size of largest tumor, mm, median (IQR)	27 (17-50)	23 (17-34)	44 (27-71)	0.004	<0.001	<0.001
Neoadjuvant chemotherapy	72 (11)	34 (17)	11 (17)	0.019	0.124	0.971
MILS approach				0.011	0.392	0.042
- Total laparoscopic	638 (97)	184 (93)	63 (100)			
- Robot-assisted	18 (3)	13 (7)	0			
Type of resection				<0.001	<0.001	<0.001
- Wedge/non-anatomical resection	331 (50)	141 (72)	0			
- Segmentectomy	78 (12)	21 (11)	0			
- Bisegmentectomy	247 (38)	35 (18)	0			
- Trisegmentectomy	0	0	11 (17)			
- Hemihepatectomy	0	0	47 (75)			
- Other major hepatectomy	0	0	5 (8)			
Simultaneous colorectal resection	70 (11)	21 (11)	0	0.997	0.006	0.007
Intraoperative ultrasound	467 (71)	178 (90)	58 (92)	<0.001	<0.001	0.241

All values in parentheses are proportions unless mentioned otherwise. Percentages may not add up due to rounding and missing data. MILS = minimally invasive liver surgery, IQR = inter quartile range, BMI = body mass index, CRLM = colorectal liver metastasis, HCC = hepatocellular carcinoma, MILS = minimally invasive liver surgery

Table 2. Operative outcome

	Minor MILS (A) n=656	Technically major MILS (B) n=197	Anatomically major MILS (C) n=63	*P* (A vs B)	*P* (A vs C)	*P* (B vs C)
Operative time, minutes, median (IQR)	127 (94-178)	176 (124-226)	304 (190-424)	<0.001	<0.001	<0.001
Blood loss, ml, median (IQR)	100 (50-300)	400 (113-975)	525 (363-938)	<0.001	<0.001	0.040
Conversion to laparotomy	63 (10)	42 (21)	13 (21)	<0.001	<0.001	0.368
Intraoperative incidents	66 (10)	51 (25)	14 (22)	<0.001	0.003	0.559
Postoperative complications						
- Overall	136 (21)	64 (32)	31 (49)	<0.001	<0.001	0.016
- Grade 3-6, severe	48 (7)	40 (20)	9 (14)	0.032	0.051	0.662
Reintervention	43 (6)	19 (9)	7 (11)	0.143	0.190	0.736
- Relaparoscopy	7 (1)	6 (3)	1 (2)			
- Relaparotomy	13 (2)	3 (2)	1 (2)			
- CT-guided drainage	7 (1)	1 (1)	0			
- US-guided drainage	8 (1)	7 (4)	3 (5)			
- ERCP with stenting	3 (1)	1 (1)	2 (3)			
- Other	5 (1)	1 (1)	0			
Readmission	33 (5)	12 (6)	9 (14)	0.548	0.008	0.040
Postoperative hospital stay, days, median (IQR)	5 (4-6)	6 (4-8)	7 (6-10)	<0.001	<0.001	<0.001
Resection margins for malignant lesions, R0	426/461 (92)	145/170 (85)	35/47 (74)	0.005	0.001	0.184
90-day/in hospital mortality	6 (0.9)	1 (0.5)	2 (3)	>0.999	0.150	0.147
1-year incisional hernia	13 (2)	8 (4)	3 (5)	0.184	0.297	0.768

All values in parentheses are proportions unless mentioned otherwise. Percentages may not add up due to rounding or missing data. IQR = inter quartile range

Subgroup analyses

Only one center averaged 20 or more MILS procedures annually during the entire study period. No significant differences were found for operating time, blood loss, conversion, morbidity, postoperative stay and mortality between this center and the other centers.

Six centers performed 20 or more minimally invasive resections in 2016, with a corresponding number of five centers in 2015 and 1 center in 2014. Comparing the outcomes of MILS procedures performed during these high-volume years to the rest showed higher implementation of major MILS (123 (38%) vs 137 (23%), $P < 0.001$) and less conversions (30 (9%) vs 88 (15%), $P = 0.02$) in the high-volume years. During these high-volume years, major MILS was associated with less conversions (14 (11%) vs 41

Table 3. Baseline characteristics of major MILS procedures performed in low volume compared to high volume centers

	Low volume centers n=137	High volume centers n=123	P
Sex, male	72 (53)	76 (62)	0.133
Age, years, median (IQR)	64 (55-71)	66 (54-72)	0.274
BMI, kg/m², median (IQR)	25.7 (22.7-29.5)	25.8 (23.1-29.1)	0.914
American Society of Anesthesiology grade			0.158
- ASA 1	24 (18)	16 (13)	
- ASA 2	83 (61)	90 (73)	
- ASA 3	27 (20)	17 (14)	
Previous abdominal surgery	97 (71)	98 (80)	0.099
Cancer as indication	111 (81)	106 (86)	0.264
- CRLM	84 (61)	93 (76)	
- HCC	12 (9)	5 (4)	
- Cholangiocarcinoma	2 (1)	3 (2)	
- Other	13 (9)	5 (4)	
Number of lesions, median (IQR)	1 (1-2)	2 (1-2)	0.011
Size of largest tumor, mm, median (IQR)	26.5 (19-43.8)	26 (17-39.3)	0.529
Neoadjuvant chemotherapy	20 (15)	25 (20)	0.223
MILS approach			<0.001
- Total laparoscopic	124 (91)	123 (100)	
- Robot-assisted	13 (9)	0	
Type of resection			0.861
- Wedge/non-anatomical resection	76 (55)	65 (53)	
- Segmentectomy	11 (8)	10 (8)	
- Bisegmentectomy	20 (15)	15 (12)	
- Trisegmentectomy	4 (3)	7 (6)	
- Hemihepatectomy	24 (18)	23 (19)	
- Other major hepatectomy	2 (1)	3 (2)	
Simultaneous colorectal resection	10 (7)	11 (9)	0.672
Intraoperative ultrasound	120 (88)	116 (94)	0.129

All values in parentheses are proportions unless mentioned otherwise. Percentages may not add up due to rounding and missing data. MILS = minimally invasive liver surgery, IQR = inter quartile range, BMI = body mass index, CRLM = colorectal liver metastasis, HCC = hepatocellular carcinoma, MILS = minimally invasive liver surgery

(30%), $P < 0.001$), a shorter operating time (184 (117-239) vs 200 (139-308) minutes, $P = 0.01$), and less overall complications (37 (30%) vs 58 (42%), $P = 0.04$) compared to the other years. The 90-day or in-hospital mortality was similar (2 (2%) vs 2 (1%), $P > 0.99$) (Tables 3 & 4).

Survey

Twenty-nine surgeons from 22 centers responded to the survey (center response rate 81%). Open liver surgery, including both minor and major resections, was performed in all centers, with a median of 11.3 years of experience (6.3-17.6) per surgeon. All but seven surgeons had an experience of ≥50 major open resections. The median experience with MILS was 6.3 years (4.3-9.3) per surgeon. Ten of 12 (83%) surgeons not yet performing major MILS indicated that they were willing to participate in a nationwide training program. When asked why they had not yet performed major MILS, the most noted reason was a lack of experience (n=9). Other reasons were not enough patients to select appropriate candidates (n=3), doubts about the advantages of laparoscopy (n=2), problems acquiring required equipment (n=2), switch to robotic surgery (n=1) and no time in the OR schedule (n=1).

The learning curve of MILS was approached differently between surgeons. Out of 29 surgeons performing MILS, 15 (52%) had completed an HPB fellowship with varying exposure to MILS, 13 (45%) were proctored (median of 4 (2-7) sessions), 17 (59%) had followed hands-on courses and 4 (14%) indicated they did not complete any training and skills were purely self-taught. Many surgeons (n=16 (55%)) pursued combinations of different forms of training. Among 17 surgeons performing major MILS, 3 (18%) had completed a fellowship, 5 (29%) were proctored (median of 3 (3-3) sessions), 5 (29%) had followed hands-on courses and 4 (24%) were self-taught. Combinations of different forms of training in major MILS was less frequent (n=3 (18%)).

DISCUSSION

In this nationwide study, the overall implementation of MILS increased from 6% to 23%, with large variation between centers. Implementation of both technically and anatomically major MILS was low with a high conversion rate of 21%, and relatively high complication rates. Outcomes of major MILS (i.e. conversion, operating time, complications) were better when centers performed ≥20 MILS procedures per year, which suggests a benefit of centralization of major MILS.

Comprehensive data on implementation and outcome of MILS on a nationwide scale are scarce. Registry studies from France[7] and Italy[8] addressed the implementation of

Table 4. Operative outcome of major MILS procedures performed in low volume compared to high volume centers

	Low volume centers n=137	High volume centers n=123	P
Operative time, minutes, median (IQR)	200 (139-308)	184 (117-239)	0.010
Blood loss, ml, median (IQR)	400 (150-900)	525 (198-1000)	0.190
Conversion to laparotomy	41 (30)	14 (11)	<0.001
Intraoperative incidents	36 (26)	21 (17)	0.616
Postoperative complications			
- Overall	58 (42)	37 (30)	0.040
- Grade 3-6, severe	20 (15)	13 (11)	0.330
Reintervention	12 (9)	14 (11)	0.482
- Relaparoscopy	2 (1)	5 (4)	
- Relaparotomy	1 (1)	3 (2)	
- CT-guided drainage	0	1 (1)	
- US-guided drainage	6 (4)	4 (3)	
- ERCP with stenting	2 (1)	1 (1)	
- Other	1 (1)	0	
Readmission	11 (8)	10 (8)	0.996
Postoperative hospital stay, days, median (IQR)	7 (5-9)	6 (5-8)	0.426
Resection margins for malignant lesions, R0	101/111 (91)	77/106 (73)	0.001
90-day/in hospital mortality	2 (1)	1 (1)	>0.999
1-year incisional hernia	4 (3)	7 (6)	0.461

All values in parentheses are proportions unless mentioned otherwise. Percentages may not add up due to rounding or missing data. IQR = inter quartile range

MILS but neither study reported on the impact of volume on outcome. Farges et al.[7] reported on 5527 MILS procedures from 270 French centers. They concluded that even in France, traditionally a pioneering country in minimally invasive surgery, MILS is still underused with only 14% of the total number of liver resections in the period 2007-2012. The Italian I GO MILS program by Aldrighetti et al.[8] performed a nationwide survey among 39 centers and reported a 10.3% implementation rate of MILS in the period 2014-2017. With 7.1% major resections, a conversion rate of 10.1%, overall morbidity of 22.3% and mortality of 0.3%, their results are comparable to the current study. However, unlike the current study, they did not stratify outcomes for minor and major MILS. Others also evaluated their nationwide practice in MILS using surveys and questionnaires[13-16], but none stratified outcomes for minor and major MILS or assessed the impact of volume on outcome. These reported implementation rates of MILS in nationwide studies, including the current study, are surprisingly low and clearly suggests that guidelines statements have not yet been fully implemented outside expert centers.

The Southampton guidelines stated that the implementation of MILS should be pursued in a stepwise fashion: starting with minor resections, expanding to technically major resections and eventually performing anatomically major resections.[6] The steady increase of the proportion of minimally invasive technically major and anatomically major resections over the years (Figure 3) may suggest an overall good adherence to this concept. Still, it remains difficult to define when a surgeon or center is ready for the next step in this implementation process. Many authors have previously reported the learning curve of minor and major MILS as a specific number of resections[17-22] but the applicability of these numbers in real-life clinical practice, especially in a nationwide pool of surgeons, is questionable. Differences in experience in open liver resection, differences in training in MILS and overall surgical skills all play an important role. In addition, logistical aspects and the annual volume of liver surgery patients whom to select minimally invasive candidates from are crucial for the decision to take a next step towards more advanced MILS procedures. Whether these recommendations also apply to the robot-assisted procedures is currently unknown. The relatively high percentage of technically major robot-assisted resections (42%) in this early phase might be attributed to the increased dexterity and accelerated learning curve with the robotic console. However, the proportion of robot-assisted liver resections is rather small (3%) as these procedures were only introduced in the Netherlands in 2014 and are currently performed in only three centres.[23] The potential advantages of the robotic approach over laparoscopy remains to be determined.[24]

The Southampton guideline also stated that a stepwise approach should always be combined with structured training[6] as was recently validated.[25] However, pursuing training can be difficult in daily clinical practice and the actual content of structured training remains unspecified. Dedicated laparoscopic HPB fellowships have been developed[26,27], but pose a logistical challenge for many surgeons. Hands-on-courses are easier to organize, but lack the guided follow-up required to implement MILS safely. Setting up nationwide structured training programs that combine the best aspects of these different forms of training has proven to be feasible in the Netherlands for minimally invasive pancreatic surgery[28,29]. In order to standardize and guide the stepwise implementation and structured training of MILS in the Netherlands, a similar program (LAELIVE) has now been established for MILS and is currently ongoing.

Regardless of how MILS has been implemented so far, the outcome of minor MILS in this study are comparable to the results from selected international high-volume centers, as included in a large meta-analysis.[2] This meta-analysis showed the superiority of laparoscopy versus the open approach for minor liver resections in terms of intraoperative blood loss, operating time, postoperative hospital stay and postoperative morbidity. However, the overall results of major MILS in the Netherlands clearly show the complexity of these procedures. Although blood loss and operating time were slightly lower compared to the meta-analysis by Ciria et al.[2] (500 vs 620 ml and 185 vs 235 minutes, respectively), the conversion rate of 21% with a complication rate of 37%, respectively, are higher than previously reported for major MILS. Furthermore, the annual volume of MILS seems related to outcome. When centers performed 20 or more MILS procedures annually, outcome for major MILS was superior, with fewer conversions, a shorter operating time and less overall postoperative complications. These subgroup analyses seem to suggest a benefit of a minimal volume for MILS, but should be interpreted carefully as they were not adjusted for confounding factors and the implementation of MILS is still ongoing. It is however clear that a certain annual total volume of liver resections is required to be able to select patients suitable for major MILS as well as a certain annual volume of MILS procedures. The current minimal annual volume for liver surgery in the Netherlands is set at 20 but does not take MILS into account. A comparison of the current data with highly centralized centers with large patient numbers could be very important to make a case for centralization of (major) MILS.

The current study has several limitations. First, the retrospective design introduces an inevitable risk of selection and information bias. Second, since data were only gathered from those centers that responded to the survey, there is a possibility that some resections were missed. However, available information from the non-participating centers and surgeons suggests that the number of missed resections is negligible. The volume-outcome relationship could potentially have been further strengthened if these data would have been available. Third, difficulty scores[30-32] were not calculated since the focus was on the differentiation between minor and (technically) major as made in current guidelines. Furthermore, it is suggested that current difficulty scores still do not incorporate all the factors that are believed to influence difficulty.[33] Fourth, the current study only focused on MILS and excluded other minimally invasive techniques such as radiofrequency and microwave ablation that could possibly prove to be even less invasive.

In conclusion, the current study provides an overview of the implementation and outcome of minor and major MILS on a nationwide scale. Whereas the use of minor MILS is clearly increasing with outcomes comparable to international reports, the implementation of major MILS is slow and the observed volume-outcome relationship confirms its complexity and the need for a structured training program in centers with sufficient volume.

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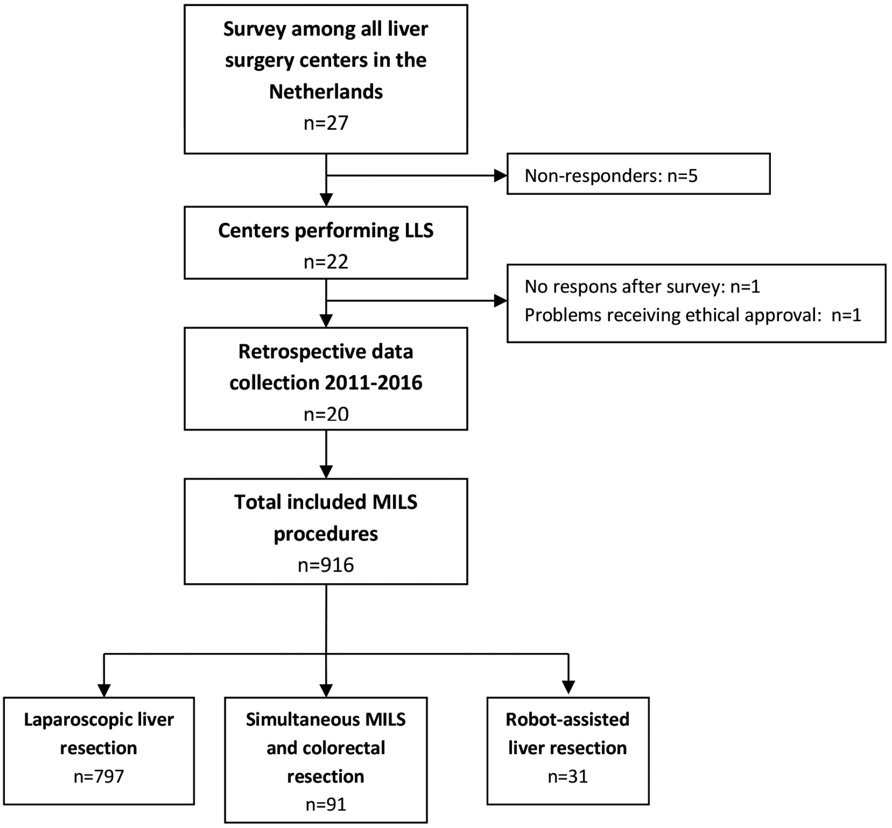
SUPPLEMENTAL DIGITAL CONTENT

Appendix A. Flowchart of patient selection



Appendix B. Nationwide survey

Available upon request

APPENDIX C.

Baseline characteristics of laparoscopic simultaneous colorectal and liver resections and robot-assisted liver resections

	Simultaneous laparoscopic colorectal and liver resection n=88	Robot-assisted liver resections n=31
Sex, male	52	16 (51)
Age, years, median (IQR)	65 (60-71)	64 (39-70)
BMI, kg/m², median (IQR)	25 (23,6-28,1)	26,5 (20,8-29,3)
American Society of Anesthesiology grade		
- ASA 1	21 (24)	3 (10)
- ASA 2	51 (58)	23 (74)
- ASA 3	12 (14)	3 (10)
- ASA 4	1 (1)	0
Previous abdominal surgery	31 (35)	18 (58)
Malignant indication	79 (90)	23 (74)
Number of lesions	1 (1-2)	1 (1-2)
Size of largest tumor, mm, median (IQR)	20 (14-27)	34,5 (20,8-59,8)
Neoadjuvant chemotherapy	11 (13)	5 (16)
Extent of resection		
- Minor	67 (76)	18 (58)
- Anatomically major	0	0
- Technically major	21 (24)	13 (42)
Type of resection		
- Wedge/non-anatomical resection	57 (65)	16 (52)
- Segmentectomy	13 (15)	6 (19)
- Bisegmentectomy	18 (20)	9 (29)
- Trisegmentectomy	0	0
- Hemihepatectomy	0	0
- Other major hepatectomy	0	0
Intraoperative ultrasound	65 (74)	3 (10)

All values in parentheses are proportions unless mentioned otherwise. Percentages may not add up due to rounding and missing data. MILS = minimally invasive liver surgery, IQR = inter quartile range, BMI = body mass index, CRLM = colorectal liver metastasis, HCC = hepatocellular carcinoma, MILS = minimally invasive liver surgery

APPENDIX D.

Operative outcome of laparoscopic simultaneous colorectal and liver resections

	Simultaneous laparoscopic colorectal and liver resection n=88	Robot-assisted liver resections* n=31
Operative time, minutes, median (IQR)	214 (176-309)	142 (108-187)
Blood loss, ml, median (IQR)	300 (100-685)	150 (45-300)
Conversion		
- To laparotomy	11 (13)	3 (10)
- To hand-assisted	0	1 (3)
Intraoperative incidents, Oslo Classification		
- Grade 1	4 (5)	1 (3)
- Grade 2	2 (2)	1 (3)
- Grade 3	1 (1)	0
Postoperative complications, Accordion Classification	18 (20)	5 (16)
- Grade 1-2 (minor)	21 (24)	5 (16)
- Grade 3-6 (severe)		
Reintervention	13 (15)	3 (10)
Readmission within 30 days	6 (7)	3 (10)
Postoperative hospital stay, days, median (IQR)	7 (6-12)	5 (3-6)
Resection margins of malignant lesions, R0	75/79 (95)	19/23 (83)
90-day/in hospital mortality	2 (2)	0
1 year incisional hernia	1 (1)	3 (10)

All values in parentheses are proportions unless mentioned otherwise. Percentages may not add up to 100 due to rounding. IQR = inter quartile range

*Partially published previously.[23]

PART 2

OUTCOME OF LAPAROSCOPIC LIVER SURGERY

CHAPTER 5

Impact of open and minimally invasive resection of symptomatic solid benign liver tumours on symptoms and quality of life: a systematic review

HPB (Oxford) 2019; Article in press

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ABSTRACT

Background

The value of open and minimally invasive liver resection for symptomatic solid benign liver tumours (BLT) such as hepatocellular adenoma, focal nodular hyperplasia and haemangioma is being debated. A systematic review on symptom relief, quality of life (QoL) and surgical outcome after both open and minimally invasive surgery for solid BLT is currently lacking.

Methods

A systematic search in PubMed and EMBASE was performed according to the PRISMA guidelines (January 1985 – April 2018). Articles reporting pre-and postoperative symptoms or QoL in patients undergoing open or minimally surgery for BLT were evaluated. Methodological quality was assessed using the MINORS tool.

Results

Forty-two studies were included with 4061 patients undergoing surgery for BLT, 3536 (87%) open and 525 (13%) laparoscopic resections. Randomized and propensity-matched studies were lacking. Symptoms were the indication for resection in 56% of the patients. After a weighted mean of 28.5 months follow-up after surgery, symptoms were relieved in 82% of symptomatic patients. Validated QoL tools were used in eight studies, of which two found significant better QoL scores following laparoscopic compared to open surgery.

Discussion

Resection of symptomatic BLT seems safe and relieves symptoms in the vast majority of selected patients. Comparative studies are needed before more firm conclusions can be drawn.

INTRODUCTION

The European Association for the Study of the Liver (EASL) guidelines state that due to the lack of randomized controlled trials which compare resection with a conservative management in patients with symptomatic BLT, the benefit from surgery remains debatable.[1] Benign liver tumours (BLT) such as hepatocellular adenoma (HCA), focal nodular hyperplasia (FNH) and haemangioma are often found incidentally. In most of these cases, there is no indication for treatment of these tumours. However, when patients present with symptoms, such as abdominal pain, tenderness, nausea and tiredness, if malignant transformation is suspected or when the diagnosis remains uncertain, partial liver resection is sometimes performed.

In patients diagnosed with HCA, surgery is generally accepted as treatment of choice for lesions larger than 5cm, because they may bleed and rupture in approximately 25% of the patients, [2-4] or may evolve into hepatocellular carcinoma (HCC) in 4.2% of the patients.[5] FNH, on the other hand, never shows malignant transformation and is rarely complicated by bleeding or rupture. Large FNH lesions however may be difficult to distinguish from HCA on imaging studies.[6] If the diagnosis remains uncertain after biopsy, or severe complaints are present, surgery for these tumours is sometimes justified.[7]

Complications almost never occur due to haemangiomas, which is the most common benign liver tumour.[8] However, giant haemangiomas (diameter > 5cm) sporadically rupture, [9] cause Kasabach-Merrit syndrome, [10] or cause abdominal complaints. In these situations, resection of larger haemangiomas is warranted.[11,12]

In symptomatic patients undergoing resection for BLT, relief of symptoms and quality of life (QoL) after surgery are important outcomes and indicators of a successful intervention. These results, however, have never been systematically assessed before, nor has the impact of the surgical approach on these outcomes. Minimally invasive liver resection is typically associated with faster functional recovery, shorter length of hospital stay and fewer complications, all of which are outcomes that could contribute to an improved QoL.[13-16] Moreover, in this group of mostly young female patients, the favourable cosmetic outcomes of laparoscopy make it an appealing alternative to open surgery.[17]

This is the first systematic review on symptom relief and operative outcomes after laparoscopic and open resection of BLT.[18-21] The aim of this systematic review is therefore to provide an overview of the current literature on relief of symptoms, QoL and general surgical outcomes after both open and laparoscopic surgery for solid BLT.

METHODS

A dedicated study protocol that defined the objectives, eligibility criteria, outcome measures, search strategy and methodology of analyses was followed (Supplementary file 1). Two independent reviewers performed a systematic literature search (IEdM and BVvR) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[22]

Search strategy

The search was performed separately for each type of liver tumour, and was built with the aid of a clinical librarian (FE). The search was executed in both PubMed and EMBASE all studies from 1985 till April 30, 2018 were included. Search strategies are displayed in table 1 and table 2 of the supplementary files.

Eligibility criteria

All cohort studies and case series reporting on either symptoms or QoL before and after both open and laparoscopic surgery for BLT were included for quantitative synthesis. Only studies written in English were reviewed. Data were extracted by two authors (JJdG and BVvR) using standardized forms (displayed in supplementary files table 4). Articles were checked for overlapping data and when identified, the smaller study was excluded. Disagreements during the search and selection process were resolved by discussion and, if needed, a third reviewer (TMvG) was consulted to reach consensus. Reference lists of all included articles were screened for additional eligible articles.

Included studies addressed elective open or minimally invasive surgical intervention in adult patients with solid BLT (i.e. HCA, FNH, and/or haemangioma), including QoL or symptoms before and after surgery.

Excluded were studies published before 1985, studies concerning patients with malignant tumours, or BLT with concomitant malignancies in the liver or other organs, studies concerning patients with (concomitant) liver pathologies resulting in a higher risk of post-operative morbidity and mortality (i.e. glycogen storage disease with adenomatosis, polycystic liver disease, hydatid cysts, ruptured liver tumours and Kasabach-Meritt syndrome), studies including less than five patients, systematic reviews and duplicates were excluded and studies reporting on ruptured tumours.

Quality assessment

A quality assessment of included studies was performed using the MINORS tool (Methodological items for non-randomized studies Score) (table 4 of the supplementary files).[23]

Data collection

Collected baseline data included: number of patients in total per cohort and per type of BLT (i.e. HCA, FNH and haemangioma), age, sex, indication for surgery (i.e. symptoms, unclear diagnosis, size of the lesion, suspicion of malignant transformation, bleeding, and/or jaundice), resection type (i.e. left or right hemihepatectomy, segmental resection, wedge resection, enucleation), resection extent (minor/major), size of the lesions (presented as mean size in centimetres), follow-up (when more than one follow-up was reported, the longest follow-up time was chosen, noted in months), malignant transformation and presence of cirrhosis. Deroofing was also recorded, because some articles included next to the patients with solid benign lesions a small number of patients with simple cysts which could not be excluded from the analyses. These tumours were placed in the category "other tumours" along with the tumours which turned out to be a different tumour at histopathological analyses other than the expected benign lesion on imaging.

The following items were collected regarding relief of symptoms and QoL: pre- and postoperative number of symptomatic patients, the type of symptoms per patient (i.e. pain, fatigue, nausea/vomiting, appetite loss, bloating, palpable mass and symptoms present but type of symptoms not specified, henceforth referred to as non-specified symptoms) and pre- and postoperative QoL scores using validated questionnaires. Sometimes symptoms were indistinctly defined (i.e. the non-specified symptoms), which in theory could compromise the ability to make a fair comparison of pre- and postoperative symptoms. However, in clinical practice the subdivision between symptomatic and non-symptomatic patients is clear: non-symptomatic patients present with a benign liver tumour as incidentaloma discovered on imaging for unrelated pathologies. Symptomatic patients present with symptoms, leading to imaging studies on which the BLT is discovered. This clear subdivision was used to calculate pre- and postoperative number of symptomatic patients.

With regards to the surgical outcomes, the following data were collected: operating time (expressed in minutes), intraoperative blood loss (expressed in millilitres), length of hospital stay (expressed in days), incisional hernias, and conversion in case of laparoscopic surgery. The number of complications was also recorded per study, counting only the severe complications, defined as Clavien-Dindo grade 3 or higher.[24]

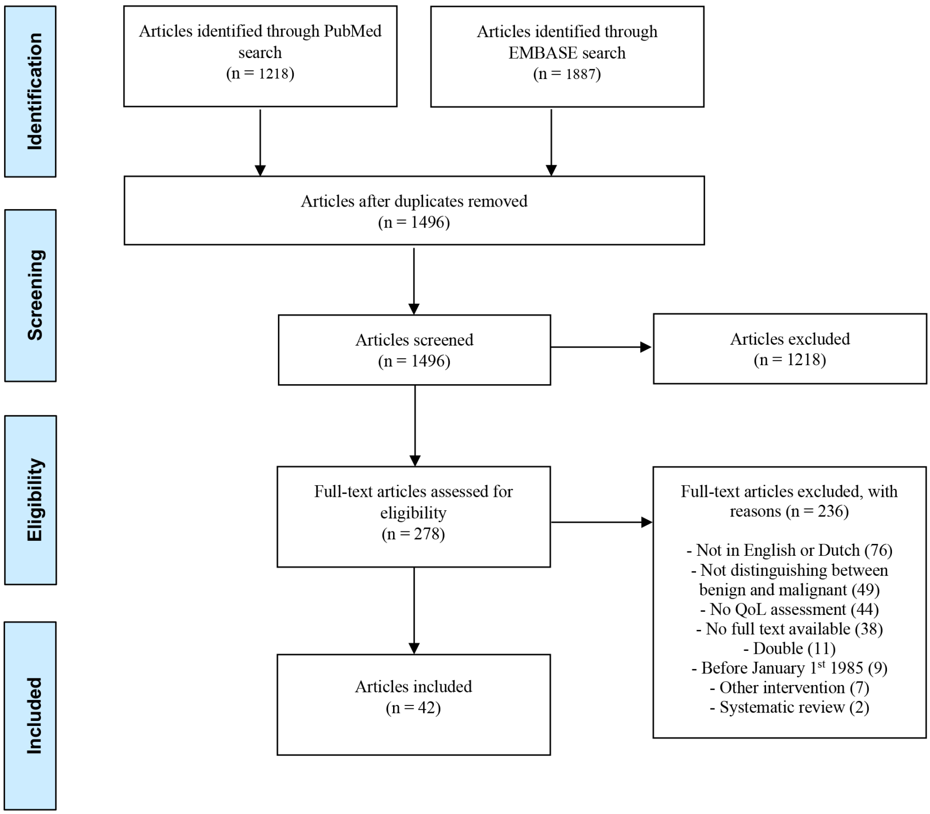

Figure 1. Prisma flowchart, search 30th of April 2018

Further specification on how these terms were defined and collected can be found in supplementary table 4.

Definitions

Laparoscopic surgery was defined as minimally invasive surgery with the aid of a camera including hand assisted laparoscopic surgery. Elective surgery was defined as a scheduled resection, for all non-emergency indications. Adenomatosis was defined as the presence of more than 10 adenomas.[25] Recurrence addresses the recurrence of a tumour at the resection site after apparent complete resection at first surgery. Major hepatectomy was defined as removal of 3 anatomic liver segments or more.[26]

Statistical analysis

Outcomes on symptoms and QoL are displayed as reported in the original article. No meta-analysis was performed because of substantial heterogeneity between studies. No comparative statistical analysis was performed as outcomes were reported using varying outcome measures. Data were tabulated as numbers of patients, percentages and weighted averages based on number of patients per study. IBM SPSS Statistics 24 and STATA 13.0 (StataCorp LP, college station TX) were used. Relative improvement was calculated using cross tabulations.

RESULTS

Search

A total of 3105 studies were identified; 1496 studies remained after removal of duplicates. After screening titles and abstracts 278 studies remained. After full text screening of the remaining studies, 42 were included in a qualitative synthesis. The flow chart is presented in figure 1. of the supplementary files; reasons for exclusion using full text are also displayed in this figure.

Baseline

Baseline characteristics are reported in table 1. A total of 4061 resections were performed, of which 3536 (87.1%) were open and 525 (12.9%) were laparoscopic. Major resections were performed in 574 (16.2%) patients receiving open surgery, and in 31 (5.9%) patients receiving laparoscopic surgery.

The majority of resected tumours were haemangiomas (n=2730; 67.2%), HCA (n=769; 18.9%), and FNH (n=425; 10.5%). One hundred and thirty-seven (3.4%) patients had other tumours than the BLT after histopathological analysis (i.e. angiomyolipoma, biliary cystadenoma, hepatocellular carcinoma, polycystic liver disease), but were included according to the intention-to-treat principle.

Relief of symptoms and QoL

In 2280 out of 4061 patients (56%), the indication for surgery was the presence of symptoms. In both open and laparoscopic surgery, symptoms were the most common indication for surgery. Indications for surgery are reported in table 1.

Although symptoms were the indication for resection in 2280 patients, symptoms were present in 2433 patients. This discrepancy can be explained by the fact that some of

Table 1. Baseline characteristics, open versus laparoscopic

Patient characteristics	Total (n=4061)		Open resection (n=3536)		Laparoscopic resection (n=525)	
Age (years)	44.5		-		-	
Female sex, (%)	(79.5)		-		-	
Type of tumours, n (%) [x]						
HCA[a]	769	(18.9)	480	(13.6)	230	(43.8)
FNH[b]	425	(10.5)	326	(9.2)	51	(9.7)
Haemangioma	2730	(67.2)	2554	(72.2)	136	(25.9)
Other [c]	137	(3.4)	36	(1.0)	20	(3.8)
Type of tumour not specified	-		140	(4.0)	88	(16.8)
Patients with liver cirrhosis	18	(0.4)	-		-	
Surgery indication, n (%) [x]						
Bleeding	136	(3.3)	83	(2.3)	42	(8.0)
Size	342	(8.4)	422	(11.9)	0	(0.0)
Symptoms	2280	(56.1)	1496	(42.3)	145	(27.6)
Uncertainty diagnosis	847	(20.9)	279	(7.9)	21	(4.0)
Jaundice	5	(0.1)	5	(0.0)	0	(0.0)
Multiple	353	(8.7)	212	(0.1)	61	(11.6)
Unknown/not reported	98	(3.4)	1039	(29.4)	256	(49.8)
Resection extent, n (%) [g,x]						
Minor resection	2839	(69.9)	1675	(47.4)	307	(58.5)
Major resection	1013	(24.9)	574	(16.2)	31	(5.9)
Unknown/not reported[x]	209	(5.1)	1287	(36.4)	187	(35.6)
Resection type, n (%)[x]						
Enucleation	904	(22.3)	861	(24.3)	4	(0.8)
Deroofing	61	(1.5)	0	(0.0)	16	(3.0)
Wedge resection	331	(8.2)	119	(3.4)	13	(2.5)
Segment resection	1245	(30.7)	785	(22.2)	172	(32.8)
Left hemihepatectomy	164	(4.0)	117	(3.3)	12	(2.3)
Right hemihepatectomy	378	(9.3)	239	(6.8)	18	(3.4)
Unknown/not reported[x]	1023	(25.2)	1415	(40.0)	290	(55.2)

[a] hepatocellular adenoma; [b] focal nodular hyperplasia; [c] angiomyolipoma, rhabdomyoma, hamartoma, poly cystic liver disease, hepatic epithelioid hemangio-endothelioma; [d] gastrointestinal symptoms = nausea, vomiting, decreased appetite, bloating, abdominal pressure, distension, satiety, abdominal discomfort, dyspepsia; [e] pulmonary symptoms = dyspnoea, coughing; [f] other = fever, sepsis, malaise, weakness, dizziness, Kasabach Merrit syndrome, jaundice; [g] major resection defined as >2 segments;[x] Variable specified in total, but not always specified in subsections; BMI = Body Mass Index.

the HCA patients had a bleeding of their tumour or a persisting tumour size >5 cm as most important indication for surgery, but also had symptoms in addition. These patients are included in the comparison of complaints before and after surgery.
Before surgery, 2433 out of 4061 (60%) patients were symptomatic, whereas 455 out of 4061 (11%) patients were reported to be symptomatic after surgery. This resulted in a relief of symptoms in 100 - ((455/2433)*100) = 81.3% of the symptomatic patients. This percentage did not include newly developed complaints after surgery, which will be discussed below. Due to the heterogeneity of studies it was impossible to distinguish this outcome between open and laparoscopic surgery. Outcomes on relief of symptoms are shown in table 3.
Newly developed complaints after surgery were caused by incisional hernias (table 2). Data on the presence of incisional hernias was available in 468 of the open surgery patients; 17 (3.6%) of these patients had developed incisional hernias. Data on the presence of incisional hernias was available in 74 of the patients who had undergone laparoscopic surgery; 2 (2.7%) of these patients developed incisional hernias.
Details on QoL are reported in table 4. Eight studies used a validated tool to evaluate symptoms or QoL. Four studies compared QoL scores for open and laparoscopic surgery: 2 showed significantly better QoL scores after laparoscopic surgery compared to open surgery, and 2 studies noted no significant differences (this included the studies of van Rosmalen et al. and Bieze et al. which had an overlapping cohort). The remaining 4 studies all reported QoL before and after open liver surgery only; they all reported a significant improvement.

Operative outcomes

Operative outcomes are displayed in table 2. In figure 2.1 and 2.2 of the supplementary files, the operative outcomes are displayed as graphs. Overall, 309 complications of Clavien-Dindo grade ≥3 were reported. Two hundred and twenty-three (7.2%) complications occurred in the open group, and 13 (3.7%) in the laparoscopic group.
In total, 32 tumours recurred, of which 29 (0.8%) in the open group and 3 (0.6%) in the laparoscopic group. Twenty (3.8%) laparoscopic procedures were converted. Mortality was 0.08% as 3 patients with BLT died within 30 days postoperatively. One patient with a bleeding after open surgery for a haemangioma. The two other patients died as a result of unspecified postoperative complications after resection of haemangioma; type of surgery was not specified. The follow up period was a weighted mean of 28.5 months.

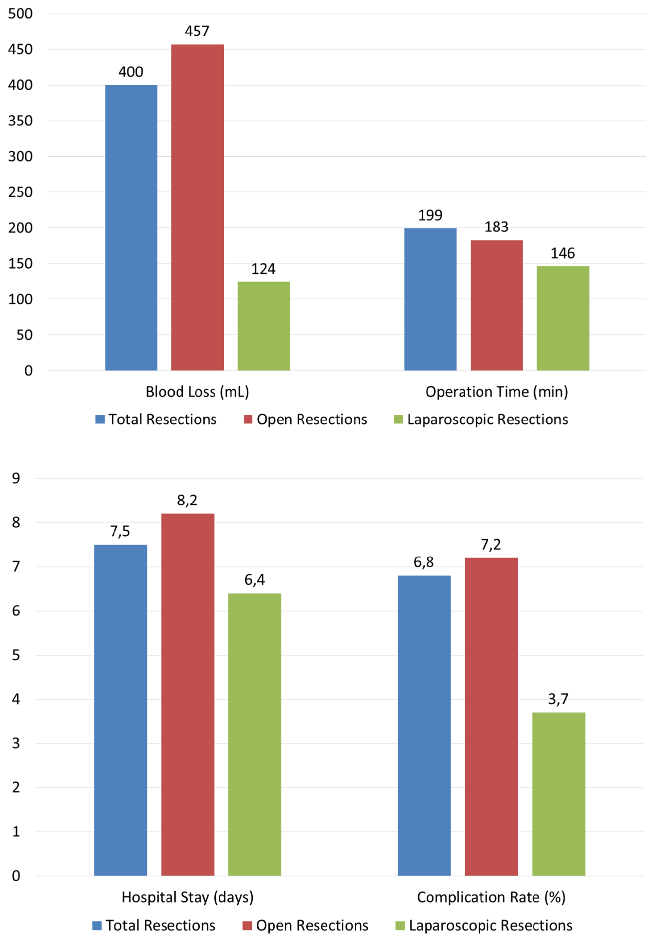

Figure 2.1 Outcome after open and laparoscopic liver resection for symptomatic benign liver tumours

DISCUSSION

Recently the Southampton guidelines on laparoscopic liver surgery has acknowledged the advantages of the laparoscopic approach in the management of benign liver conditions (not specifically BLT, but benign liver conditions in general) and has warned about the expansion of the surgical indication at the time laparoscopic approach could be adopted.[27] This is the first systematic review on relief of symptoms, QoL and

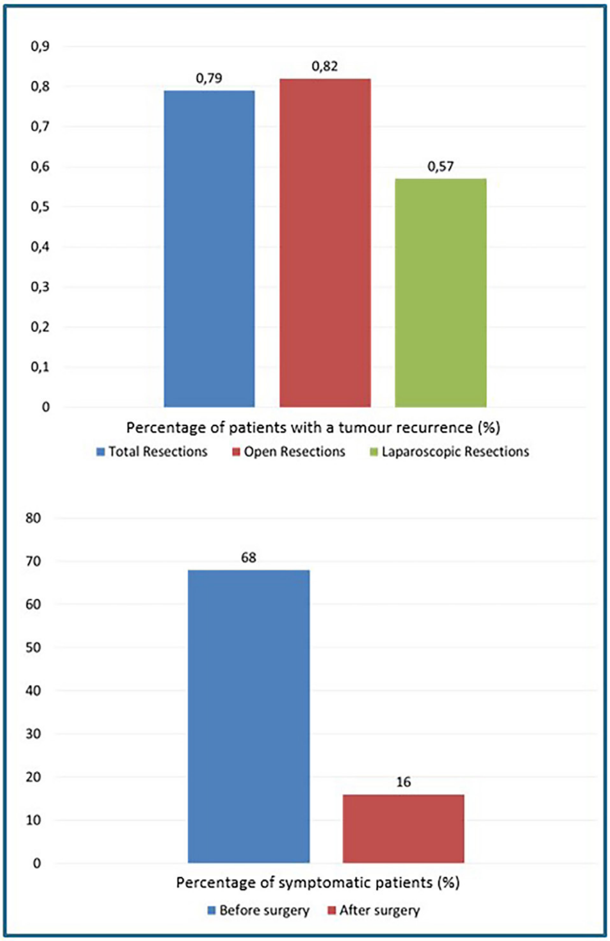

Figure 2.2 A: Percentage of recurrence after open and laparoscopic liver resection; B: Percentage of symptomatic patients before and after surgery

Footnote: this figure represents the percentage of symptomatic patients, not the percentage of patients with symptoms as indication for surgery. The percentage of patients with symptoms in total and patients with symptoms as indication for surgery differs because some of the patients whom presented with symptoms had also another indication for surgery (for example tumour size in HCA

operative outcomes after laparoscopic and open resection of (symptomatic) BLT. In a group of 4061 resections, symptoms were the most common (56%) indication for surgical intervention. In this group of patients, symptom relief was achieved in 82% of

Table 2. Outcomes open versus laparoscopic

	No. of resections T/O/L (n)	Major resection T/O/L (n)	Minor resection T/O/L (n)
Liu, et al. (Dec 2017) [34]	168/168/0	78/78/0	90/90/0
Sakamoto et al. (2017)[35]	510/426/84	216/NR/NR	294/NR/NR
Landi et al. (2017)[33]	533/325/208	133/113/20	400/212/188
Liu et al. (Jun 2017)[36]	141/141/0	0/0/0	0/0/0
Rosmalen et al. (2016) #[37]	8/4/4	3/3/0	5/1/4
Zhang et al. (2016) #[38]	34/34/0	NR/NR/0	NR/NR/0
Hau et al. (2015)[39]	100/86/14	32/32/0	68/14/14
Qiu et al. (2015) # [40]	730/730/0	0/0/0	730/730/0
Hoffmann et al. (2015)[41]	79/70/9	23/23/0	56/47/9
Zhang et al. (2015) [42]	86/86/0	7/0/0	0/0/0
Miura et al. (2014)[43]	241/195/46	104/NR/NR	137/NR/NR
Adhikari et al. (2014)[44]	9/9/0	3/0/0	6/0/0
Ulas et al. (2014)[45]	82/82/0	0/0/0	83/0/0
Bieze et al. (2013) #[46]	49/39/10	13/13/0	36/26/10
Karkar et al. (2013)[47]	35/35/0	8/8/0	35/35/0
Kneuertz et al. (2012)[18]	179/106/73	51/NR/NR	128/NR/NR
Hui-Yu Ho et al. (2012)[48]	61/61/0	36/36/0	61/61/0
Perrakis et al. (2012)[19]	78/78/0	18/18/0	52/52/0
Jiang et al. (2011) [49]	14/14/0	12/12/0	2/2/0
Dardenne et al. (2010)[30]	49/34/15	16/16/0	33/18/15
Kammula et al. (2010)[50]	28/27/1	5/5/0	23/22/0
Giuliante et al. (2010) #[51]	40/40/0	8/0/0	32/0/0
Schnelldorfer et al.(2010)[52]	56/55/1	NR/0/0	22/22/0
Bonney et al. (2007)[53]	15/15/0	3/3/0	13/13/0
Ibrahim et al. (2007) [54]	84/84/0	43/43/0	41/41/0
Ardito et al. (2007) #[55]	31/0/31	8/0/8	42/0/42
Berloco et al. (2006)[56]	48/48/0	10/0/0	36/0/0
Erdogan et al. (2006)[57]	14/14/0	3/0/0	11/0/0
Fioole et al. (2005)[58]	28/28/0	10/10/0	18/18/0
Herman et al. (2005) #[59]	8/8/0	6/6/0	2/2/0
Hsee et al. (2005) [60]	8/8/0	2/2/0	6/6/0
Hamaloglu et al. (2005)[61]	22/22/0	6/0/0	10/0/0
Tsai et al. (2003) [62]	43/43/0	12/12/0	31/31/0
Yoon et al. (2003) [63]	52/51/1	6/6/0	0/0/0
Terkivatan et al. (2002) [64]	11/11/0	5/5/0	6/6/0
Charny et al. (2001) [65]	65/65/0	21/21/0	44/44/0
Terkivatan et al. (2001)[66]	74/74/0	17/17/0	57/57/0
Ozden et al. (2000) [67]	42/42/0	6/6/0	33/33/0

Blood loss T/O/L (mL)	Operation time T/O/L (min)	Hospital stay T/O/L (days)	Complications T/O/L (n)	Recurrence T/O/L (n)
200/200/NR	252/252/NR	10/10/NR	0/0/NR	0/0/0
560/ NR/NR	287/NR/NR	NR/ NR/NR	21/NR/NR	0/0/0
145/196/93	161/173/149	6.0/7.0/5.0	27/17/10	0/0/0
838/838/NR	140/140/NR	9.7/9.7/NR	0/0/NR	0/0/0
-	-	-	NR/0/NR	4/2/2
335/335/NR	201/201/NR	7.0/7.0/NR	10/10/NR	0/0/0
-	-	16/NR/NR	8/NR/NR	0/0/0
617/617/NR	189/189/NR	7.1/7.1/NR	127/127/NR	8/8/0
325/660/170	-	8.0/9.0/6.0	5/NR/NR	0/0/0
400/400/NR	-	12/12/NR	20/20/NR	0/0/0
300/NR/NR	-	5.0/NR/NR	14/NR/NR	0/0/0
-	-	-	0/NR/NR	0/0/0
300/300/NR	141/141/NR	6.0/6.0/NR	8/8/NR	0/0/0
-	165/185/97	6.7/7.0/4.5	4/4/0	0/0/0
200/NR/NR	-	7.0/7.0/NR	0/0/NR	2/2/0
50/NR/NR	-	4.0/NR/NR	8/NR/NR	0/0/0
610/610/NR	248/248/NR	11/11/NR	1/1/NR	0/0/0
-	-	10/10/NR	1/1/NR	0/0/0
-	-	8.0/NR/NR	0/NR/NR	0/0/0
-	-	-	7/NR/NR	0/0/0
457/NR/NR	-	6.8/NR/NR	0/0/NR	1/0/1
-	266/NR/NR	9.5/NR/NR	2/NR/NR	0/0/0
-	-	6.0/NR/NR	4/NR/NR	4/4/0
-	-	9.0/9.0/NR	1/1/NR	2/2/0
104/104/NR	85/85/NR	-	0/0/NR	0/0/0
285/NR/285	191/NR/191	5.0/NR/5.0	2/NR/2	0/0/0
-	-	6.3/NR/NR	0/NR/NR	0/0/0
-	-	-	2/NR/NR	0/0/0
600/600/NR	207/207/NR	9.5/9.5/NR	0/0/NR	0/0/0
-	-	7.0/7.0/NR	0/0/NR	0/0/0
300/300/NR	-	7.0/7.0/NR	0/0/NR	0/0/0
211/NR/NR	192/NR/NR	6.1/NR/NR	2/NR/NR	0/0/0
-	-	-	1/1/NR	10/10/0
400/400/NR	-	8.0/8.0/NR	8/8/NR	0/0/0
-	-	-	3/3/NR	0/0/0
-	-	8.2/8.2/NR	6/6/0	0/0/0
-	-	11/11/NR	4/4/NR	0/0/0
400/400/NR	-	-	3/3/NR	0/0/0

Table 2. Continued

	No. of resections T/O/L (n)	Major resection T/O/L (n)	Minor resection T/O/L (n)
Katkhouda et al. (1999) [68]	28/0/28	3/0/3	25/0/25
Pietrabissa et al. (1996) # [69]	16/16/0	5/5/0	11/11/0
Seo et al. (1991)[70]	7/7/0	3/3/0	4/4/0/
Iwatsuki et al. (1988) [71]	155/155/0	78/78/0	77/77/0
TOTAL	**4061/3536/525**	**1013/574/31**	**2839/1675/307**

SUMMARY	**Total (n=4061)**	
Complications (%) [h, x]	309	(7.6)
Recurrence (%) [i,x]	32	(0.8)
Incisional hernia (%)[j]	20/591 (3.4)	
Conversion rate (%)	-	
WEIGHTED AVERAGE	**Total (n=4061)**	
Complications (%)	6.8	
Recurrence (%)	2.5	
Size of tumour (cm)	10	
Follow up (months)	28.5	

- T/O/L = Total / Open / Laparoscopic; # Prospective study; * Weighted average; ∫ 8 studies included a small number of cyst patients (123 total), see methods.
[h] complications = Clavien-Dindo classification > 2;[i] recurrence is defined as radiological recurrence of the original tumour or growth of new lesions in need of resection; [j] Not all studies reported on incisional hernias, therefore only patients of studies which did report were included in the analysis;[x] Variable specified in total, but not always specified in subsections.

patients. In two studies, laparoscopic surgery was associated with significantly higher QoL scores after surgery compared to open surgery, but other studies failed to confirm these results.

Aggregated evidence regarding the surgical intervention of BLT is scarce. Rao et al. performed a Cochrane review, in which they were unable to provide any information on relief of symptoms, QoL or operative outcomes due to the lack of randomized controlled trials.[28] Belghiti et al.,[29] provided a relatively complete oversight on the steps in managing BLT, but did not make a systematic comparison between open and laparoscopic surgery, nor did they analyse the effect of treatment on QoL. Even though the available evidence is very heterogeneous and of varying quality, the current study does represent the first and largest systematic review of all types of studies analysing the outcomes of open and laparoscopic surgical resection of BLT.

Blood loss T/O/L (mL)	**Operation time T/O/L (min)**	**Hospital stay T/O/L (days)**	**Complications T/O/L (n)**	**Recurrence T/O/L (n)**
156/NR/156	96/NR/96	4.7/NR/4.7	1/NR/1	0/0/0
257/257/NR	-	-	0/0/NR	0/0/0
-	-	-	1/1/NR	0/0/0
-	-	-	0/0/NR	1/1/0
400/457/124*	**199/183/146***	**7.5/8.2/4.9***	**309/223/13**	**32/29/3**

Open resection (n=3536)		**Laparoscopic resection (n=525)**	
223	(6.3)	4	(0.8)
29	(0.8)	3	(0.6)
17/468 (3.63)		2/74 (2.7)	
-		20	(3.8)

Open resection (n=3536)	**Laparoscopic resection (n=525)**
7.2	3.7
2.5	1.1
10.2	6.0
-	-

5

The benefit of resection of BLT remains debatable since there is a lack of randomized data regarding the outcome after surgery. A randomized trial, for instance including a sham arm, would be difficult to perform. This, however, makes it impossible to correct for the placebo effect of an operation. With this in mind, one would expect that surgeons would be hesitant to operate based solely on the presence of symptoms. Interestingly enough the results from the studies included in this review show otherwise as symptoms were the indication for surgery in 56% of all cases. What is even more interesting, is that over 80% of the symptomatic patients experienced a relief of complaints after surgery. These results clearly suggest a benefit of surgery in symptomatic patients, though the lack of comparative analyses with conservative treatment should be kept in mind as these patients are obviously subjected to the risks of an operation that are absent in the conservatively treated group. Only one study

Table 3. Symptoms and symptom relief

	No. of resections (n)	Pain (n)	Fatigue (n)	Nausea / vomiting (n)	Appetite loss (n)	Bloating (n)	Palpable abdominal mass (n)	Symptomatic not specified (n)	Other ∞ (n)	Symptomatic before / after surgery (%)
Liu, et al. (Dec 2017) [34]	168	58	-	-	18	92	-	-	-	65/7
Sakamoto et al. (2017)[35]	510	-	-	-	-	-	-	206	-	40/9
Landi et al. (2017)[33]	533	282	-	-	-	-	-	64	-	65/4
Liu et al. (Jun 2017)[36]	141	28	-	-	13	100	-	-	-	100/4
Rosmalen et al. (2016) #[37]	8	33	-	-	-	-	-	-	-	88/25
Zhang et al. (2016) #[38]	34	-	-	-	-	-	-	66	-	50/0
Hau et al. (2015)[39]	100	36	21	14	13	-	-	-	42	46/24
Qiu et al. (2015) # [40]	730	-	-	-	-	-	-	419	-	57/0
Hoffmann et al. (2015)[41]	79	-	-	-	-	-	-	54	-	68/13
Zhang et al. (2015) [42]	86	54	-	-	-	-	3	-	-	66/53
Miura et al. (2014)[43]	241	215	10	32	-	-	-	-	4	85/67
Adhikari et al. (2014)[44]	9	9	-	-	-	-	7	-	1	100/0
Ulas et al. (2014)[45]	82	68	-	7	-	-	6	-	10	92/0
Bieze et al. (2013) #[46]	49	34	-	-	-	-	-	-	-	74/12
Karkar et al. (2013)[47]	35	-	-	-	-	-	-	24	-	69/8
Kneuertz et al. (2012)[18]	179	84	67	36	46	-	-	-	62	41/20
Hui-Yu Ho et al. (2012)[48]	61	26	-	-	-	-	-	13	-	64/0
Perrakis et al. (2012)[19]	78	53	-	-	-	-	-	-	4	68/8
Jiang et al. (2011) [49]	14	6	-	-	-	3	-	-	1	64/0
Dardenne et al. (2010)[30]	49	-	-	-	-	-	-	10	-	20/0
Kammula et al. (2010)[50]	28	12	-	-	6	-	-	-	2	43/0
Giuliante et al. (2010) #[51]	40	9	-	-	-	-	-	-	16	63/0
Schnelldorfer et al.(2010)[52]	56	36	-	5	8	-	-	-	3	80/0
Bonney et al. (2007)[53]	15	13	-	-	-	-	-	1	-	53/33
Ibrahim et al. (2007) [54]	84	33	-	-	-	-	-	-	-	39/6
Ardito et al. (2007) #[55]	31	24	-	-	-	-	-	-	-	24/0
Berloco et al. (2006)[56]	48	-	-	-	-	-	-	26	-	54/0
Erdogan et al. (2006)[57]	14	11	-	-	-	-	-	-	-	79/7
Fioole et al. (2005)[58]	28	18	-	1	-	-	3	-	-	39/11
Herman et al. (2005) #[59]	8	7	-	-	-	-	-	-	-	75/17
Hsee et al. (2005) [60]	8	7	-	-	-	-	-	-	-	88/0
Hamaloglu et al. (2005)[61]	22	17	-	-	-	-	-	4	-	77/10

Table 3. Continued

	No. of resections (n)	Pain (n)	Fatigue (n)	Nausea / vomiting (n)	Appetite loss (n)	Bloating (n)	Palpable abdominal mass (n)	Symptomatic not specified (n)	Other ∞ (n)	Symptomatic before / after surgery (%)
Tsai et al. (2003) [62]	43	7	-	-	-	-	-	6	-	30/23
Yoon et al. (2003) [63]	52	25	-	-	-	-	17	-	5	59/12
Terkivatan et al. (2002) [64]	11	11	-	-	-	-	3	4	-	100/13
Charny et al. (2001) [65]	65	-	-	-	-	-	-	39	-	60/7
Terkivatan et al. (2001)[66]	74	-	-	-	-	-	-	10	-	64/14
Ozden et al. (2000) [67]	42	32	-	-	-	-	-	-	-	79/13
Katkhouda et al. (1999) [68]	28	27	-	-	-	-	-	9	4	93/0
Pietrabissa et al. (1996) # [69]	16	14	-	-	-	-	-	-	-	88/0
Seo et al. (1991)[70]	7	3	-	-	-	-	3	-	-	57/0
Iwatsuki et al. (1988) [71]	155	60	-	-	-	-	-	40	-	48/13
TOTAL	**4061**	**1352**	**98**	**95**	**104**	**195**	**42**	**995**	**154**	**60/11**

∞ fever, sepsis, vegetative symptoms, malaise, weakness, dizziness, jaundice, pruritus, tenderness, dyspnoea; # Prospective study; - Not Reported
* Weighted average was based on only the studies reporting both pre- and postoperative complaints; some authors did not report the number of symptomatic patients after surgery. Those authors were contacted by email to request missing information, and all responded.

made a comparison with conservative management. They found that the majority of patients in both the surgical and the conservative management group had no progression of their disease during follow up, and required no further treatment. However, there were no symptomatic patients in the conservative group, and therefore no conclusions can be drawn concerning the development of complaints in symptomatic patients conservatively managed over time.[30]

Unfortunately, symptoms before and after surgery could not be subdivided in open and laparoscopic surgery: most studies did not make this distinction in their outcomes. The studies that did used validated tools for QoL to report separately and showed an advantage of laparoscopy in two studies. However, all of these studies failed to make a comparison corrected for the extent of the surgery. A propensity score matched study could be helpful to provide more accurate information.

Besides QoL and relief of symptoms, operative outcomes are essential to determine

Table 4. Studies with QoL questionnaire

Author	Questionnaire	Detailed outcomes on QoL
Zhang et al. (2016) [38]	VAS	Open surgery: - 100 % symptom free after surgery.
van Rosmalen et al. (2016) *[37] and Bieze et al. (2013)*[46]	MQ Gill	33 patients received open surgery, 7 laparoscopic: - Relief of symptoms in 70% of the patients. - <u>No significant difference in QoL between open and laparoscopic.</u> - Discomfort at the operative scar in 20% patients, after open surgery. - No complaints of the operative scar in laparoscopic patients.
Qiu et al. (2015) [40]	SF 36	All open surgery: - Preoperative SF-36 scores were significantly lower in all eight domains than those recorded for healthy Chinese individuals. - At 6 months after surgery, SF-36 scores were comparable with those in Chinese normal individuals.
Hau et al. (2015)[39]	Questionnaire composed of SF36, Mc Gill and EORTIC	86 patients received open surgery, 14 laparoscopic: - Overall good QoL was reported preoperatively in (47.4 %) vs. postoperatively in (68.1%). - (49.6 %) of patients reported a "much better" or "somewhat better" physical and mental health. - The proportion of patients reporting "a little" or "a lot" of limitations with moderate activity decreased from (44.1 %) preoperatively to (29.4 %) postoperatively. - More patients reported "feeling energetic" preoperatively in (45.6 %) vs. postoperatively in (66.2 %). - Fewer patients noted depressed moods postoperatively (5.9%) versus preoperatively (12.7 %). - Mean pain levels decreased significantly over time from 1.49 preoperatively to 0.35 at 1 year postoperatively. - <u>Patients undergoing laparoscopic liver resection reported a 2.3-fold more frequently about an improvement of their life quality postoperatively as compared to open surgery (OR 5.8; 95 % CI 1.1–31.1; p = 0.03).</u>
Hoffmann et al. (2015)[41]**	VAS	46 patients received open surgery, 8 laparoscopic: - Open surgery: complete relief in 6 (13%) patients, partial in 32(70%) and persistent complaints in 8(18%). - Laparoscopic: complete relief: 3(38%), partial in 3(38%) and persistent complaints in 2 (25%). - <u>No statistical analysis of the difference between open and laparoscopic surgery performed.</u>
Perrakis et al. (2012)[19]	EQ-5D questionnaire	All open surgery: - 92 per cent of the symptomatic patients symptom free after surgery.
Kneuertz et al. (2012)[18]	questionnaire composed of SF36, Mc Gill and EORTIC	106 patients received open surgery, 73 laparoscopic: - Postoperatively, moderate-to-extreme pain decreased from (46.9%) to (6.8%) at 1-year. - Mean pain scores decreased over time: preoperative 1.65 vs 1 year postoperatively 0.28. - Improvement in general health was reported in (40.5%) and physical health in (39.3%). - Pain scores preoperatively were comparable among patients undergoing open versus laparoscopic procedures. - <u>Post operatively there were significant differences at 6 months (0.85 open versus 0.37 laparoscopic) and at 1 year (0.36 open, versus 0.17 laparoscopic) in favour of laparoscopy.</u>

* The studies of van Rosmalen et al.[37] and Bieze et al.[46] are reported together because of an overlapping patient cohort.
** In this table, only the symptomatic patients are reported. Studies analysing differences of open and laparoscopic surgery are <u>underlined.</u>

the place of laparoscopic surgery in the treatment of BLT. In this review, outcomes such as blood loss, operating time, complications, and length of hospital stay were reported to be less in the laparoscopic group, which suggest a benefit of the laparoscopic approach in terms of these outcomes, but also in terms of QoL as less complications and a shorter hospital stay especially would contribute to better QoL. However, interpretation of these outcomes is troubled by the large number of major resections in the open surgery group as compared to the laparoscopic group, which introduces treatment selection bias.

On the other hand, the lower percentage of incisional hernias in the laparoscopic group cannot merely be explained by the unevenly distributed major and minor resections. The risk of incisional hernias depends on site and size of the incision, which in its turn depends on surgical technique (laparoscopic or open) and tumour size. It is safe to conclude that there might be a small advantage of laparoscopy with regard to incisional hernias. This is in line with recent literature.[31]

The same accounts for recurrence rate, which cannot be explained by the unevenly distributed major and minor resections; there is no evidence that the extent of the resection influences recurrence of BLT. And even if so, one would expect that a more extended resection would favour radicality, but the indication is usually symptoms. Surprisingly, recurrence rate was lower in the laparoscopic group. Perhaps this can be explained by the fact that surgeons take wider margins around the tumour in laparoscopic surgery because of the lack of manual palpation of the tumour but this is speculative.

Laparoscopic surgery was performed less often and was generally less extensive than surgery in the open group. The decision to perform open or laparoscopic surgery should not merely depend on the expertise of the medical centre. Either the local surgeons are trained adequately, or patients should be referred to a centre with specific expertise. Nationwide training in laparoscopic surgery as well as proctoring, has been organized in the Netherlands in pancreatic surgery and is currently ongoing for liver surgery. This could potentially contribute to the implementation of laparoscopic surgery in daily practice.[32]

This study has some limitations. First, the lack of studies correcting for the extent of surgery and the lack of a control group receiving conservative treatment. Second, no subdivision could be made regarding type of BLT. This would be preferred especially since the indication for treatment differs between HCA and the other BLTs. Unfortunately, most studies did not distinguish between the different types of BLT.

Therefore we mostly focused on overall symptom relief. Third, some studies included a small number of patients with simple cyst, which could not be excluded from the analysis. This however accounted only 3% of the patients in the laparoscopy group, and 1.5% of the patients in general. Fourth, as previously mentioned outcomes could not be subdivided by major and minor surgery.

Fifth and finally, due to the heterogeneity of the included studies it was not possible to distinguish between open and laparoscopic surgery regarding reduction of complaints.

The strength of this study was the extensive literature search; a separate search for each type of benign liver tumour was undertaken, which successfully identified a large number of patients.

This review will not close the debate on the merits of surgery in patients with symptomatic BLT. A randomized controlled trial on the topic would be quite difficult to perform. This review did identify that the data is especially lacking on the merits of major and minor liver surgery, and the lack of a comparison with conservative treatment.

In conclusion, surgical treatment of symptomatic BLT can relieve symptoms in the majority of symptomatic, selected patients albeit in the absence of a control group. A benefit of laparoscopic surgery over open surgery in terms of QoL after surgery and operative outcomes is suggested, but data are scarce. Ideally, a large propensity score matched series corrected for extent of surgery should be performed, comparing conservative management, open and laparoscopic surgery. Nationwide initiatives such as the Dutch Benign Liver Tumour Group (DBLTG) or the AFC-HCA-2013 study group could be helpful in the set-up of and adequate study design.[33]

SUPPLEMENTARY FILES

File 1. Study protocol

INTRODUCTION

The four most common BLT; hepatocellular adenoma (HCA), focal nodular hyperplasia (FNH), and haemangioma, are often found accidentally. However, these tumours may present themselves with various complaints, such as abdominal pain, tenderness, nausea and tiredness.
Although multiple studies examined general outcomes after open and laparoscopic surgery for BLT, [18,19] these outcomes were never summarized in a review before. The same accounts for symptoms and quality of life (QoL), even though QoL plays an important role in this specific group of patients. The aim of this review is therefore to provide an overview of the current literature on general outcomes, symptoms and QoL after both open and laparoscopic surgery, for the four most common BLT.

METHODS

Overall

Two independent reviewers will perform a systematic search of literature (I. E. d. M and B. V. v. R.) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Quality assessment

A quality assessment will be performed using the MINORS tool (Methodological items for non-randomized studies Score) of all studies.

Search strategy

The search will be performed separately for each type of liver tumour, and will be built with the aid of a clinical librarian (F.E). The search will be executed in both PubMed and EMBASE. Studies executed before 1985 will not be included in the qualitative synthesis because of their reported morbidity and mortality which is incomparable to the studies executed after 1985.

Eligibility criteria

All cohort studies and case series reporting on either symptoms or QoL after both open and laparoscopic surgery for BLT will be included for quantitative synthesis. Only studies written in English will be reviewed. Data will be extracted by two authors (JJdG and BVvR) using standardized forms (displayed in supplementary files table 4). Articles will be checked for over- lapping data and, when identified, the smaller study will be excluded. Disagreements during the search and selection process shall be resolved by discussion and, if needed, a third reviewer (TMvG) will be consulted to reach consensus. Reference lists of all included articles will be screened for additional eligible articles.

Inclusion criteria

- Included studies must address BLT (i.e. HCA, FNH, haemangioma)
- Included studies must address QoL or symptoms
- Included studies must address surgical intervention for BLT (either open, laparoscopic or both)
- Included studies must address elective surgery, and no emergency treatments.

Exclusion criteria

- Studies concerning patients with other tumours than BLT, or concomitant malignancies in the liver or other organs must be excluded.
- Studies concerning patients under the age of 18 years must be excluded.
- Studies concerning patients with (concomitant) liver pathologies resulting in a higher risk of post-operative morbidity and mortality must be excluded (i.e. glycogen storage disease with adenomatosis, polycystic liver disease, hydatid cysts, ruptured liver tumours and Kasabach-Meritt syndrome).
- Studies published before 1985 must be excluded.
- Studies including less than five patients must be excluded.
- Systematic reviews and duplicates must be excluded.
- Studies reporting on ruptured tumours only must be excluded.
- Studies reporting on liver cysts of any sort.

Data collection

The following data concerning the baseline will be collected: number of patients in total per cohort and per type of lesion (i.e. HCA, FNH, haemangioma and cyst), age, sex, indication for surgery (i.e. size of the lesion, suspicion of malignant degeneration, bleeding, symptoms and jaundice), resection type (i.e. left or right hemihepatectomy, segmental resection, wedge resection, enucleation, deroofing or fenestration), size of the lesions (presented as mean size in centimetres), follow up (when more than one moment of follow-up was reported, the longest was chosen, noted in months), malignant transformation, patients with cirrhosis, incisional hernias, and conversion in case of laparoscopic surgery.

The following data will be collected: Number of resections per study, type of surgery and type of lesion, type of resection (i.e., major or minor), operation time (expressed in minutes), length of hospital stay (expressed in days), and blood loss (expressed in millilitres), incisional hernias, and conversion in case of laparoscopic surgery. Also the number of complications will be recorded per study, counting only Clavien-Dindo grade 3 and higher as a complication.[24] Further specification on how these terms were defined and collected can be found in supplementary table 4.

The following items will be collected with regard to symptom improvement: number of symptomatic patient's pre-and postoperative; type of symptoms per patient (i.e. pain, fatigue, nausea/vomiting, apatite loss, bloating, palpable mass, symptomatic not specified, other); ratio of symptomatic patients before and after surgery.

Definitions

Laparoscopic surgery is defined as minimal invasive surgery with the aid of a camera, this included hand assisted laparoscopic surgery as well. Elective surgery is defined as a scheduled resection, for all non-emergency indications. Adenomatosis was defined as the presence of more than 10 adenomas.[72] Recurrence addresses the recurrence of the resected lesion, or growth of new lesions in need of resection. Major hepatectomy was defined as removal of 3 segments or more.[26] Deroofing and fenestration are comparable procedures, and the terms are both used in literature. In the outcomes of this review, articles describing fenestration will be included in the deroofing category.

Statistical analysis

Outcomes on symptoms and QoL will be displayed as reported in the original article. A meta-analysis will be performed if possible, depending on the heterogeneity between studies. Data will be tabulated and as numbers of patients, and weighted averages. Numerators and denominators will be noted to assess open versus laparoscopic surgery for all outcomes.

SUPPLEMENTARY TABLES

Table 1. PubMed search April 30th 2018, 1218 articles found

Resection [tiab] AND ("adenoma, liver cell"[MeSH Terms] OR liver cell adenoma*[tiab] OR hepatocellular adenoma*[tiab] OR liver adenoma*[tiab] OR hepatic adenoma*[tiab]) OR (focal lesion*[tiab] AND benign*[tiab] AND liver[tiab]))
OR
Resection [tiab] AND ("focal nodular hyperplasia"[MeSH Terms] OR focal nodular hyperplasia*[tiab]) OR (focal lesion*[tiab] AND benign*[tiab] AND liver[tiab])
OR
Resection [tiab] AND ("haemangioma"[MeSH Terms] OR haemangioma*[tiab] OR haemangioma*[tiab]) AND ("Liver Neoplasms/surgery"[Mesh] OR liver[tiab] OR hepatic[tiab]))) OR (resection[tiab] AND (focal lesion*[tiab] AND benign*[tiab] AND liver[tiab]))
Definitive search
((((Resection [tiab] AND ("adenoma, liver cell"[MeSH Terms] OR liver cell adenoma*[tiab] OR hepatocellular adenoma*[tiab] OR liver adenoma*[tiab] OR hepatic adenoma*[tiab]) OR (focal lesion*[tiab] AND benign*[tiab] AND liver[tiab]))))) OR ((Resection [tiab] AND ("focal nodular hyperplasia"[MeSH Terms] OR focal nodular hyperplasia*[tiab]) OR (focal lesion*[tiab] AND benign*[tiab] AND liver[tiab]))) OR ((resection [tiab] AND ("haemangioma"[MeSH Terms] OR haemangioma*[tiab] OR haemangioma*[tiab]) AND ("Liver Neoplasms/surgery"[Mesh] OR liver[tiab] OR hepatic[tiab]))) OR (resection[tiab] AND (focal lesion*[tiab] AND benign*[tiab] AND liver[tiab]))

Table 2. EMBASE classic + EMBASE search April 30th 2018, 1887 articles found

#	Searches	Results
1	resection.ti,ab,kw. and (liver adenoma/ or (liver cell adenoma* or hepatocellular adenoma* or liver adenoma* or hepatic adenoma*).ti,ab,kw.) and benign*.ti,ab,kw.	323
2	resection.ti,ab,kw. and (nodular hyperplasia/ or focal nodular hyperplasia*.ti,ab,kw. or (focal lesion* and benign* and liver).ti,ab,kw.)	961
3	(resection.ti,ab,kw. and (exp haemangioma/ or haemangioma*.ti,ab,kw. or haemangioma*.ti,ab,kw.) and (exp liver tumour/su or liver.ti,ab,kw. or hepatic.ti,ab,kw.)) or (resection and (focal lesion* and benign* and liver)).ti,ab,kw.	1035
4	(open and resection and (lesion* and benign* and liver)).ti,ab,kw.	155
5	(exp laparoscopy/ or laparoscop*.ti,ab,kw.) and (lesion* and benign* and liver).ti,ab,kw.	451
6	1 or 2 or 3 or 4 or 5	2503
7	conference abstract.pt. or letter/	3972559
8	6 not 7	1887

Table 3. MINORS tool for quality assesment

Author	Methodological items for non-randomized studies Score †								Total
	1	2	3	4	5	6	7	8	
Liu, et al. (dec 2017) [34]	2	2	1	1	1	2	2	0	11
Sakamoto et al. (2017)[35]	2	2	1	1	1	2	2	2	13
Landi et al. (2017)[33]	2	2	2*	1	1	2	2	2	14
Liu et al. (jun 2017)[36]	2	2	1	1	1	2	2	0	11
Rosmalen et al. (2016) #[37]	2	2	2	1	1	2	2	1	13
Zhang et al. (2016) #[38]	2	2	2	1	1	2	2	1	12
Hau et al. (2015)[39]	2	2	1	1	1	2	2	1	11
Qiu et al. (2015) # [40]	2	2	2	1	1	2	2	1	12
Hoffmann et al. (2015)[41]	2	2	2	1	1	2	2	0	11
Zhang et al. (2015) [42]	2	2	1	1	1	2	2	2	12
Miura et al. (2014)[43]	2	2	1	1	1	1	2	2	11
Adhikari et al. (2014)[44]	2	2	2	1	1	2	2	0	12
Ulas et al. (2014)[45]	2	2	1	1	1	0	2	1	10
Bieze et al. (2013) #[46]	2	2	2	1	1	2	2	1	13
Karkar et al. (2013)[47]	2	2	1	1	1	2	2	2	13
Kneuertz et al. (2012)[18]	2	2	2	1	1	2	2	1	13
Hui-Yu Ho et al. (2012)[48]	2	2	1	1	1	2	2	1	12
Perrakis et al. (2012)[19]	2	2	2	1	1	2	2	1	12
Jiang et al. (2011) [49]	2	2	1	1	1	2	2	0	11
Dardenne et al. (2010)[30]	2	2	1	1	1	2	2	2	13
Kammula et al. (2010)[50]	2	2	1	1	1	0	2	1	10
Giuliante et al. (2010) #[51]	2	2	2	1	1	2	2	2	14
Schnelldorfer et al.(2010)[52]	2	2	1	1	1	2	2	2	13
Bonney et al. (2007)[53]	2	2	1	1	1	2	2	1	12
Ibrahim et al. (2007) [54]	2	2	1	1	1	0	2	2	11
Ardito et al. (2007) #[55]	2	2	2	1	1	2	2	1	13
Berloco et al. (2006)[56]	2	2	0	1	1	1	2	0	9
Erdogan et al. (2006)[57]	2	2	1	1	1	2	2	1	12
Fioole et al. (2005)[58]	2	2	2	1	1	2	2	0	12
Herman et al. (2005) #[59]	2	2	2	1	1	2	2	1	13
Hsee et al. (2005) [60]	2	2	1	1	1	2	2	1	12
Hamaloglu et al. (2005)[61]	2	2	1	1	1	2	2	1	12
Tsai et al. (2003) [62]	2	2	0	1	1	2	2	0	10
Yoon et al. (2003) [63]	2	2	2	1	1	2	2	1	13
Terkivatan et al. (2002) [64]	2	2	1	1	1	2	2	1	12
Charny et al. (2001) [65]	2	2	1	1	1	2	2	1	12

5

Table 3. Continued

Author	Methodological items for non-randomized studies Score †								Total
	1	2	3	4	5	6	7	8	
Terkivatan et al. (2001)[66]	2	2	1	1	1	2	2	1	12
Ozden et al. (2000) [67]	2	2	1	1	1	2	2	1	12
Katkhouda et al. (1999) [68]	2	2	2	1	1	2	2	1	13
Pietrabissa et al. (1996) # [69]	2	2	1	1	1	2	2	1	12
Seo et al. (1991)[70]	2	2	1	1	1	2	2	1	12
Iwatsuki et al. (1988) [71]	2	2	1	1	1	2	2	1	12

†The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score being 16 for non-comparative studies.

1. A clearly stated aim: the question addressed should be precise and relevant in the light of available literature
2. Inclusion of consecutive patients: all patients potentially fit for inclusion (satisfying the criteria for inclusion) have been included in the study during the study period (no exclusion or details about the reasons for exclusion)
3. Prospective collection of data: data were collected according to a protocol established before the beginning of the study
4. Endpoints appropriate to the aim of the study: unambiguous explanation of the criteria used to evaluate the main outcome which should be in accordance with the question addressed by the study. Also, the endpoints should be assessed on an intention-to-treat basis.
5. Unbiased assessment of the study endpoint: blind evaluation of objective endpoints and double-blind evaluation of subjective endpoints. Otherwise the reasons for not blinding should be stated
6. Follow-up period appropriate to the aim of the study: the follow-up should be sufficiently long to allow the assessment of the main endpoint and possible adverse events
7. Loss to follow up less than 5%: all patients should be included in the follow up. Otherwise, the proportion lost to follow up should not exceed the proportion experiencing the major endpoint
8. Prospective calculation of the study size: information of the size of detectable difference of interest with a calculation of 95% confidence interval, according to the expected incidence of the outcome event, and information about the level for statistical significance and estimates of power when comparing the outcomes

*This study was propensity score matched, adding great value to its outcomes. So even though no intention to treat analysis was used, this study scored 2.

Table 4. Definitions and data collection

1. Total number of patients within a study was recorded to indicate the extension/importance of the study. This included all patients, resected and not resected, benign and malignant, on which outcomes were reported. When studies reported total patient population in their hospital, but not outcomes of all patients, only the number of patients was chosen on which outcomes after resection were reported.

2. Age was calculated as a median if possible, if not, it was calculated as a mean.

3. The distribution of males and females was reported as a percentage, because some studies only reported the total of males and females, not specifying which individuals were underwent surgery.

4. Baseline characteristics (i.e. age, BMI, gender, multiple tumours, cirrhosis and length of follow-up) were recorded only from the resected patients, but were not subdivided by open vs laparoscopic surgery or tumour type.

5. Usage of oral contraception was documented as a percentage, because some studies only reported the total of patients using OCC, not specifying which of these individuals were resected. Oral contraceptive usage was not documented in the article because it was rarely reported in the included articles.

6. Other tumours than FNH, Haemangioma, HCA or cyst were marked as other. These included: angiomyolipoma, rhabdomyoma, harmatoma, poly cystic liver disease, hepatic epithelioid haemangioma endothelioma. Other tumours were filtered out of baseline and outcomes as much as possible. Other tumours in baseline characteristics were accepted, if less than 50% of total number of tumours including the benign ones. Other tumours in outcomes were accepted if less than 10 % of total number of tumours including benign ones. If the number of other tumours exceeded either one of those percentages, the paper was excluded.

7. ASA score was reported as a median. ASA was recorded in the database, but was not documented in the article because it was rarely reported in the included articles.

8. In case cirrhosis was not mentioned in a study, the assumption was made that none of the patients in the study had cirrhosis.

9. Length of follow-up in months is reported in median if possible, otherwise mean (with two decimals in database).

10. Recurrence after resection was defined as all patients with a radiological recurrence, and all patients with a non-complication related re-operation. The assumption was made that there would be no re-operations for incomplete resection of BLT.

11. Malignant transformation: number of individuals with malignant transformation per study. If not reported the assumption was made there was no malignant transformation within the follow up period, unless specifically mentioned that the states of a patient lost to follow up was unknown. In this case, malignant transformation was stated as unknown.

12. In some studies the total number of patients with a specific kind of benign liver tumour was reported, as well as the number of resections for BLT in total, without specifying how many of each tumour were resected or not. In this case patients were classified as "resection for benign liver tumour, subtype unknown" (in tables designated as "unknown").

13. Resection type. In case it was not completely clear which resection type was used (i.e. not clear whether there was overlap between resection types, double patients, or not clearly left / right or major / minor) only the total number of resections was recorded, and the rest was stated as unknown.

14. Indication for resection: In case it was not completely clear what the indication for resection was (i.e. not clear whether there was overlap between indications, not explicitly stated that symptoms were reason for resection or other symptoms than previously defined) it was stated as indication unknown/ unclear.

Table 4. Continued

15. Size was reported as a median in cm if possible, otherwise mean with 2 decimals
16. Operating time was expressed in minutes, using 2 decimals (in the included articles always reported as a mean).
17. Length of hospital stay was expressed in days, using median as possible, otherwise the mean was reported using 2 decimals
18. Blood loss in was expressed in ml, using 2 decimals (in the included articles always reported as a mean).
19. Complications: number of individuals with a complication of Clavien-Dindo Scale 3 and higher per study.
20. Scar: number of patients in study with complaints related to the surgical scar, painful scar, cosmetic complaints about the scar, incisional hernia. Detailed information on patients identified in this section will be provided in a separate section (supplementary table) if available.
21. Laparoscopic conversion: Number of patients with laparoscopic conversion per study.

CHAPTER 6

Laparoscopic versus open left lateral sectionectomy: a multicenter international propensity score matched study

Submitted for publication

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ABSTRACT

Objective

To compare outcome of laparoscopic left lateral sectionectomy (LLLS)) and open left lateral sectionectomy (OLLS).

Summary Background Data

Current guidelines recommend LLLS as the routine approach instead of OLLS, although appropriate evidence is lacking. With one terminated randomized study on LLLS because of insufficient accrual and future randomized studies unlikely to ever be performed, propensity score matching (PSM) might provide the highest achievable level of evidence.

Methods

A multicenter, international propensity score matched retrospective cohort study including all patients undergoing OLLS or LLLS between January 2000 and December 2016 in six centers in three European countries. Propensity scores were calculated based on 9 preoperative variables and OLLS and LLLS were matched in a 1:1 ratio. Short-term operative outcomes were compared using paired tests.

Results

A total of 560 patients were included. Out of 218 LLLS, 139 could be matched to 139 OLLS. After PSM, baseline characteristics were well balanced. LLLS was associated with shorter operative time (144 (110-200) vs 199 (138-283) minutes, P<0.001), less blood loss (100 (50-300) vs 350 (100-750) mL, P=0.005) and a shorter postoperative hospital stay (4 (3-7) vs 7 (5-9) days, P=<0.001). Postoperative overall morbidity (18% vs 21%, P=0.522), severe morbidity (6% vs 3%, P=0.508), mortality (0% vs 0.8%, P>0.999), and 1-year incisional hernia rate (1% vs 5%, P=0.125) were comparable.

Conclusion

This study provides the evidence for the use of LLLS as routine approach over OLLS based on advantages in terms of postoperative hospital stay, operative time, and blood loss.

MINI ABSTRACT

Guidelines recommend laparoscopic left lateral sectionectomy (LLLS) as routine approach over open left lateral sectionectomy (OLLS), although appropriate evidence is lacking. This multicenter, international propensity score matched cohort study found that LLLS was associated with shorter operative time, less blood loss and shorter hospital stay as compared to OLLS.

INTRODUCTION

Left lateral sectionectomy (LLS) includes resection of Couinaud's[1] liver segments two and three and is considered a minor liver resection.[2] The easy accessibility of these segments, the thin liver parenchyma along the falciform ligament, the absence of any hilar dissection and easy control of the left hepatic vein with a vascular stapler, make LLS the ideal candidate for laparoscopy.

Since experts concluded that laparoscopic LLS (LLLS) was feasible and safe in the hands of experienced hepatobiliary surgeons at the first, worldwide consensus meeting on laparoscopic liver surgery in Louisville in 2008[2], worldwide interest in this technique has increased significantly. Multiple authors have published their experiences with overall favorable results compared to open LLS (OLLS)[3-13], leading to the recent guideline statement that LLLS should be a standard procedure for the resection of lesions in the left lateral segments in all centers.[14]

Essentially, LLLS was implemented worldwide without appropriate evidence. The ORANGE 2 randomized multicenter trial was not completed because the window of clinical equipoise was missed and surgeons and patients were reluctant to randomize patients to an open approach.[15] All in all, the issue of selection bias in the comparison of LLLS versus OLLS has not been dealt with properly. It seems very unlikely that another RCT on LLLS will ever be performed, so propensity score matching (PSM) might be the highest achievable level of evidence. Several studies have shown that PSM can produce better estimates than multivariable regression analyses[16,17] and one meta-analysis even reported no significant differences in treatment effect estimates comparing PSM and RCTs for the same clinical question in surgical precedures.[18]

Therefore, the aim of this multicenter study was to provide a rigorous PSM comparison of LLLS with OLLS that delivers the evidence regarding the use of LLLS that is lacking in current guidelines.

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METHODS

The current study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[19] It reports on the outcomes of elective LLLS and OLLS performed in six centers in three European countries. All included centers perform more than 60 liver resections annually and have performed more than 50 laparoscopic liver resections. Data were collected retrospectively and registered anonymously, hence there was no additional burden to the patients and the local medical ethics committee of the Amsterdam UMC, location AMC, waived the need for written informed consent.

Patients and design

All six participating centers (three from the Netherlands, one from Belgium and one from the UK) reviewed their prospectively maintained surgical databases containing all liver resections performed in the period 2000-2016. All patients who underwent OLLS or LLLS were included. Patients were excluded when major liver surgery (i.e. resection of 3 or more anatomical segments), emergency surgery or procurement for living donor liver transplantation was performed. Individual patient data were merged after checking all data definitions.
Liver lesions were diagnosed using abdominal computed tomography (CT) scans with triphasic contrast enhancement and/or liver-specific double-contrast magnetic resonance imaging (MRI) in all centers. The results were discussed in a multidisciplinary team meeting with HPB surgeons, radiologists, gastroenterologists, hepatologists, medical oncologists and pathologists attending. A decision regarding the surgical approach was made independently of the indication for surgery and was based on tumor characteristics (i.e. benign/malignant, size, location), patient characteristics (e.g. age, previous abdominal surgery, state of the liver parenchyma), procedure characteristics (e.g. need for additional liver or other organ resections), individual surgeon preference and the patient's personal decision after discussion with the surgeon about the benefits and limitations of each approach.

Data collection

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

The primary study outcome was length of postoperative hospital stay in days. Secondary outcomes were duration of surgery in minutes, estimated intraoperative blood loss in mL, blood transfusion, conversion, intraoperative incidents (Oslo Classification)[20], overall and severe postoperative 90-day morbidity (graded with the Accordion Classification[20], grade three or higher was considered a severe complication), reoperation and readmission within 90 days (liver and surgery related), resection margins (R0=tumor free, R1=microscopic tumor involvement), complication related 90-day or in hospital mortality and incisional herniation at 1-year follow-up.

Operative technique

Both OLLS and LLLS are well known and standardized resections that have been described previously.[7,21] Although standardization of resection techniques and devices between the centers was impossible due to the design of the study, differences were minimal.

Statistical analysis

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

Propensity score matching

In order to minimize confounding by indication, propensity score matching (PSM) was applied and reported according to the recommendations by Lonjon et al.[22] PSM was

performed using R Studio for Windows version 3.3.3 (R Studio Inc., Boston, MA, USA). Propensity scores were calculated using a logistic regression model. All available variables were discussed among authors and consensus was reached on which variables to include in the model. The final model included the following variables: age, indication (benign/malignant), preoperative chemotherapy, cirrhosis, previous abdominal surgery, previous liver surgery, size of the primary lesion in the left lateral segments, simultaneous colorectal resection and additional liver resection. Based on this propensity score, LLLS were matched to their nearest neighbor OLLS in a 1:1 ratio with a standard calipher width of 0.2. LLLS were analyzed according to intention-to-treat principles, hence conversions to open surgery were included in the laparoscopic group. The standardized mean difference (SMD) was calculated for each baseline variable before and after matching in order to assess the balance. An SMD between -0.1 or 0.1 and 0 was considered an indicator of optimal balance. After matching a Wilcoxon signed rank test was used to compare continuous, not normally distributed variables between groups. For normally distributed variables a paired T-test was used, as appropriate. Categorical variables were reported as proportions and were compared between groups using a McNemar test or Wilcoxon signed rank test. A two-tailed P-value of <0.05 was considered statistically significant.
Three sensitivity analysis were performed in the matched cohort. The first excluded patients who were treated before 2010 or underwent a simultaneous colorectal resection. The second excluded all male patients. The third excluded all patients who had bilobar liver disease. For each of these analyses, the remaining patients in both groups were compared using a randomized block design for continuous variables and conditional logistic regression for categorical variables.

RESULTS

A total of 560 patients met the inclusion criteria, of whom 200 underwent LLLS and 360 OLLS. OLLS was performed in all centers from the beginning of the inclusion period (January 2000). The first LLLS was performed in 2004. The median annual volume of LLS per center was 5 (4-6). Of all included patients, 139 LLLS could eventually be matched in a 1:1 ratio to OLLS controls.

Baseline characteristics

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

Table 1. Baseline characteristics of patients undergoing laparoscopic and open left lateral sectionectomy prior and after propensity score

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

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

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

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

Values in parentheses are percentages, unless indicated otherwise. Percentages may not add up to 100 due to rounding and/or missing data. LLS = left lateral sectionectomy, PSM = propensity score matching, IQR = interquartile range, CRLM = colorectal liver metastasis, HCC = hepatocellular carcinoma, FNH = focal nodular hyperplasia

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Operative outcomes

Table 2 displays operative outcomes before and after matching. LLLS was associated with a shorter operating time (144 (110-200) vs 199 (138-283) minutes, P<0.001), less intraoperative blood loss (100 (50-300) vs 350 (100-750) mL, P<0.001) and a shorter postoperative hospital stay (4 (3-6) vs 7 (4-9) days, P<0.001). Prior to matching, more radical resections for malignant disease were observed in the LLLS group (137 (96%) vs 244 (87%), P=0.010), but this significance disappeared after matching (93 (96%) vs 86 (90%), P=0.564). Conversion to laparotomy occurred in 16 (8%) patients. Reasons for conversion were difficult to reach lesions/slow progression (n=8), bleeding (n=4), adhesions (n=3) and bowel perforation (n=1). Severe complications occurred in 38 (13%) patients. Most frequent complications were abdominal fluid collections requiring drainage (n=14), bleeding requiring reoperation (n=4), respiratory insufficiency (n=3) and sepsis (n=3). A total of 7 (1%) patients died within 90 days postoperatively. Causes of death were sepsis (n=4), liver failure (n=2), and lung embolism (n=1). One-year incisional hernia rate was 2 (1%) and 7 (5%) among the groups, respectively (P=0.125).

Sensitivity analyses

After excluding patients who underwent surgery before 2010 or simultaneous colorectal surgery (Sensitivity Analysis 1), 101 patients remained in the LLLS group and 63 in the OLLS group. Operative time (129 (103-201) vs 170 (110-276) minutes, *P* = 0.002) and postoperative hospital stay (4 (3-6) vs 6 (4-8) days, *P* = 0.004) remained significantly shorter in the LLLS group. The reduction in blood loss in the LLLS group was no longer significant (100 (50-300) vs 250 (100-647) mL, *P* = 0.097). Exclusion of male patients (Sensitivity Analysis 2) and patients with bilobar disease (Sensitivity Analysis 3) had no impact on operative time. Blood loss was no longer significantly reduced in the LLLS group after excluding males, but remained less after excluding patients with bilobar disease. Postoperative hospital stay was reduced by 3 days in the LLLS group after Sensitivity Analysis 2 and 3, but this was no longer significantly different from OLLS (see Tables 1-3, Supplemental Digital Content 1-3, for all operative outcomes after these sensitivity analyses).

DISCUSSION

In this multicenter, international study using PSM, LLLS was associated with a shorter operative time, less intraoperative blood loss and a shorter postoperative hospital stay as compared to OLLS. Postoperative morbidity and mortality rates were comparable. These results provide the evidence that was lacking in current guidelines which advice laparoscopy as the routine surgical approach for left lateral sectionectomy.

The current study is the first to use PSM to compare LLLS and OLLS. PSM minimizes the influence of confounding by indication, which was clearly present prior to matching in the current study as shown by the differences between the groups in the baseline table. Several studies previously reported benefits of LLLS in terms of operative time, blood loss, postoperative hospital stay or morbidity. However, none of these studies could deal with selection bias properly because they were designed as (meta-analyses of) cohort studies and completed randomized controlled trials (RCT) are lacking.[3-13] Keeping in mind that an RCT will probably never be performed for LLLS again, PSM is probably the highest achievable level of evidence. The use of PSM in the current study resulted in two well balanced groups that made for a fair comparison of the two techniques.

Despite the extensive matching, it is still possible that some variables potentially determining suitability for a certain approach were not accounted for. Defining the variables that constitute a difficult liver resection is an ongoing debate. Some difficulty scores have been developed and validated.[23,24] The individual variables that are used in these scores were all included in this study, except for the proximity of the tumor to major vessels and the approach to the previous liver resection. The retrospective retrieval of data regarding the proximity of the tumor to major vessels was deemed logistically impossible in this study and its relevance in LLS is questionable as the resection itself is inherently distant from major vessels. The approach to the previous liver resection is probably more relevant, as this could decrease the formation of adhesions.[25,26] This possible imbalance, that increases the potential need for adhesiolysis in the open group, might be a partial explanation for the increased operative time and blood loss in that group, even though less than 20% of patients in both groups had undergone previous liver surgery at all.

The international randomized ORANGE 2 trial was set to randomize 110 patients to LLLS or OLLS based on the assumption that LLLS would reduce the time to functional recovery with 2 days. This sample size was surpassed by the current study, which included 278 patients in the PSM cohort. In this comparison, however, LLLS was associated with a reduction in postoperative hospital stay by three days. Postoperative hospital stay is often used as a surrogate for functional recovery, because functional recovery is a composite endpoint of clinical and laboratory findings and therefore difficult to use in retrospective series. The limitation, however, of postoperative hospital stay is that it incorporates the potential delay between functional recovery and actual discharge due to patient uncertainty, administrative issues, problems in homecare support and logistic troubles (among others) and, therefore, does not represent the actual time until functional recovery. However, a difference in postoperative stay of three days cannot be solely explained by differences in discharge logistics and demonstrates the faster recovery after LLLS.

Absolute difference in operative time was 55 minutes, and this was 250 cc for blood loss. Clinical relevance of such short-term outcome differences is sometimes questioned. A non-significant difference in long-term outcome was one-year incisional hernia rate, with an absolute difference of 4% in favor of LLLS. Lack of statistical significance in the present study might be related to the restricted follow-up duration and insufficient power for this specific endpoint. Meta-analysis of 12 studies comparing laparoscopic and open colorectal surgery revealed a significant reduction in incisional hernia rate (RR 0.58 (0.47-0.72).[27] An absolute difference of a few percent might already by clinically relevant, given the burden for the patient and costs related to incisional hernia repair.[28,29]

The results of this study should be interpreted in light of some shortcomings. First, PSM will minimize the influence of selection bias but cannot completely erase it. Regardless of the comprehensive matching model, a higher percentage of males and more bilobar disease were observed in the open group. Even though the results of the two sensitivity analyses that excluded males and patients with bilobar disease could not maintain their significance, they stayed robust. Next to the inherent group differences, the process of introducing laparoscopic liver surgery was handled differently between centers. Despite this inevitable learning curve effect, LLLS is still associated with clear benefits. And while moving along the learning curve, these benefits could only increase. The main strength of this study is the use of PSM in a multicenter approach.

In conclusion, this study represents the first PSM study comparing LLLS with OLLS and found a significant benefit of LLLS in terms of operative time, intraoperative blood loss and postoperative hospital stay. This study provides the required additional evidence for the fact that LLLS is the current standard procedure for the resection of lesions in the left lateral liver segments in all liver surgery centers.

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SUPPLEMENTAL DIGITAL CONTENT

Supplementary Table 1. Sensitivity analysis excluding all patients undergoing left lateral sectionectomy before 2010 or simultaneous colorectal surgery.

	Laparoscopic LLS after PSM (n=101)	Open LLS after PSM (n=63)	P
Operating time, min, median (IQR)	129 (103-201)	170 (110-276)	0.002
Blood loss, ml, median (IQR)	100 (50-300)	250 (100-647)	0.097
Transfusion requirement	3 (3)	3 (5)	>0.999
Conversion	10 (10)	n/a	n/a
Intraoperative incidents, Oslo classification	4 (4)	5 (8)	0.657
Postoperative complications, Accordion classification			
- Overall	22 (22)	13 (21)	0.782
- Severe	6 (6)	0	>0.999
Reoperation	2 (2)	0	>0.999
Readmission	1 (1)	3 (5)	0.571
Postoperative hospital stay, days, median (IQR)	4 (3-6)	6 (4-8)	0.004
R0 resection margin for malignant disease	68/72 (94)	43/45 (96)	0.571
Pathology			0.436
- CRLM	30 (30)	36 (57)	
- HCC	19 (19)	4 (6)	
- Cholangiocarcinoma	4 (4)	2 (3)	
- Adenoma	12 (12)	4 (6)	
- Cyst	2 (2)	6 (10)	
- FNH	9 (9)	3 (5)	
- Hemangioma	2 (2)	4 (6)	
- Other malignant	16 (16)	3 (5)	
- Other benign	4 (4)	1 (2)	
In hospital or 90-day mortality	0	0	>0.999
Incisional hernia within 1 year follow-up	0	2 (3)	>0.999

Values in parentheses are percentages, unless indicated otherwise. Percentages may not add up to 100 due to rounding and/or missing data. LLS = left lateral sectionectomy, PSM = propensity score matching, IQR = interquartile range, CRLM = colorectal liver metastasis, HCC = hepatocellular carcinoma, FNH = focal nodular hyperplasia

Supplementary Table 2. Sensitivity analysis excluding all male patients.

	Laparoscopic LLS after PSM (n=80)	Open LLS after PSM (n=66)	P
Operating time, min, median (IQR)	132 (101-180)	206 (129-309)	0.003
Blood loss, mL, median (IQR)	100 (50-306)	300 (100-634)	0.172
Transfusion requirement	3 (4)	3 (5)	>0.999
Conversion	10 (13)	n/a	n/a
Intraoperative incidents, Oslo classification	3 (4)	3 (5)	0.571
Postoperative complications, Accordion classification			
- Overall	14 (18)	10 (15)	0.739
- Severe	5 (6)	1 (2)	0.999
Reoperation	2 (3)	1 (2)	>0.999
Readmission	1 (1)	3 (5)	>0.999
Postoperative hospital stay, days, median (IQR)	4 (3-6)	7 (5-9)	0.321
R0 resection margin for malignant disease	41/42 (98)	27/30 (90)	>0.999
Pathology			0.117
- CRLM	21 (26)	20 (30)	
- HCC	9 (11)	6 (9)	
- Cholangiocarcinoma	3 (4)	1 (2)	
- Adenoma	14 (18)	10 (15)	
- Cyst	5 (6)	5 (8)	
- FNH	11 (14)	8 (12)	
- Hemangioma	3 (4)	11 (17)	
- Other malignant	8 (10)	3 (5)	
- Other benign	5 (6)	2 (3)	
In hospital or 90-day mortality	0	0	n/a
Incisional hernia within 1 year follow-up	0	1 (2)	>0.999

Values in parentheses are percentages, unless indicated otherwise. Percentages may not add up to 100 due to rounding and/or missing data. LLS = left lateral sectionectomy, PSM = propensity score matching, IQR = interquartile range, CRLM = colorectal liver metastasis, HCC = hepatocellular carcinoma, FNH = focal nodular hyperplasia

Supplementary Table 3. Sensitivity analysis excluding all patients with bilobar disease distribution.

	Laparoscopic LLS after PSM (n=113)	Open LLS after PSM (n=106)	P
Operating time, min, median (IQR)	132 (105-180)	182 (120-274)	<0.001
Blood loss, mL, median (IQR)	100 (50-250)	300 (100-612)	0.036
Transfusion requirement	4 (4)	2 (2)	0.657
Conversion	13 (12)	n/a	n/a
Intraoperative incidents, Oslo classification	4 (4)	5 (5)	0.657
Postoperative complications, Accordion classification			
- Overall	23 (20)	21 (20)	0.835
- Severe	6 (5)	4 (4)	0.739
Reoperation	4 (4)	0	0.999
Readmission	1 (1)	5 (5)	0.215
Postoperative hospital stay, days, median (IQR)	4 (3-6)	7 (5-9)	0.310
R0 resection margin for malignant disease	73/77 (95)	61/65 (94)	>0.999
Pathology			0.321
- CRLM	38 (34)	46 (43)	
- HCC	17 (15)	12 (11)	
- Cholangiocarcinoma	4 (4)	3 (3)	
- Adenoma	12 (11)	8 (8)	
- Cyst	5 (4)	6 (6)	
- FNH	10 (9)	8 (8)	
- Hemangioma	3 (3)	15 (14)	
- Other malignant	15 (13)	4 (4)	
- Other benign	6 (5)	3 (3)	
In hospital or 90-day mortality	0	0	n/a
Incisional hernia within 1 year follow-up	2 (2)	6 (6)	0.215

Values in parentheses are percentages, unless indicated otherwise. Percentages may not add up to 100 due to rounding and/or missing data. LLS = left lateral sectionectomy, PSM = propensity score matching, IQR = interquartile range, CRLM = colorectal liver metastasis, HCC = hepatocellular carcinoma, FNH = focal nodular hyperplasia

CHAPTER 7

Total laparoscopic hemihepatectomy: outcome and learning curve in 159 consecutive patients

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ABSTRACT

Importance

Widespread implementation of laparoscopic hemihepatectomy is currently limited by its technical difficulty, paucity of training opportunities, and perceived long and harmful learning curve. Studies confirming the possibility of a short and safe learning curve for laparoscopic hemihepatectomy could potentially benefit the further implementation of the technique.

Objective

To evaluate the extent and safety of the learning curve for laparoscopic hemihepatectomy.

Design, setting and participants

A prospectively collected single-center database containing all laparoscopic liver resections performed in our unit at the University Hospital Southampton National Health Service Foundation Trust between August 2003 and March 2015 was retrospectively reviewed; analyses were performed in December 2015. The study included 159 patients in whom a total laparoscopic right or left hemihepatectomy procedure was started (intention-to-treat analysis), including laparoscopic extended hemihepactectomies and hemihepatectomies with additional wedge resections, at a tertiary referral center specialized in laparoscopic hepato-pancreato-biliary surgery.

Main outcomes and measures

Primary end pointswere clinically relevant complications (Clavien-Dindo grade_III). The presence of a learning curve effect was assessed with a risk-adjusted cumulative sum analysis.

Results

Of a total of 531 consecutive laparoscopic liver resections, 159 patients underwent total laparoscopic hemihepatectomy (105 right and 54 left). In a cohort with 67 men (42%), median age of 64 years (interquartile range [IQR], 51-73 years), and 110 resections (69%) for malignant lesions, the overall median operation time was 330 minutes (IQR, 270-391 minutes) and the median blood loss was 500 mL (IQR, 250-925 mL). Conversion to an open procedure occurred in 17 patients (11%). Clinically relevant complications occurred in 17 patients (11%), with 1% mortality (death within 90 days of surgery, n = 2). Comparison of outcomes over time showed a nonsignificant decrease in conversions (right: 14 [13%] and left: 3 [6%]), blood loss (right: 550 mL [IQR, 350-1150 mL] and left: 300 mL [IQR, 200-638 mL]), complications (right: 15 [14%] and left: 4 [7%]), and hospital stay (right: 5 days [IQR, 4-7 days] and left: 4 days [IQR, 3-5 days]). Risk-adjusted cumulative sum analysis demonstrated a learning curve of 55 laparoscopic hemihepactectomies for conversions.

Conclusions and relevance

Total laparoscopic hemihepatectomy is a feasible and safe procedure with an acceptable learning curve for conversions. Focus should now shift to providing adequate training opportunities for centers interested in implementing this technique.

INTRODUCTION

Laparoscopic liver resection (LLR) was introduced in 1992 and numerous retrospective studies have suggested that it could reduce both postoperative morbidity and costs.[1-8] Since then, minor LLR (biopsies and smallwedge excisions, left lateral sectionectomies, and anterior segmentectomies) have become routine procedures, and the 2008 Louisville consensus identified LLR as standard of care for left lateral sectionectomy.[9,10] While minor LLR has become routine practice, major LLR (ie, ≥3 liver segments) is still limited in normal clinical practice, potentially owing to concerns regarding a significant learning curve effect due to the technical difficulties of the procedure.[2] The recommendations from the Second International Consensus Conference in Morioka stated that major LLR is still in the exploration phase and that cautious introduction is recommended.[11] There is concern that the
inherent benefits of the laparoscopic approach could be compromised owing to limited visibility in the operative field or insufficient surgical expertise. Although there is literature suggesting major LLR is a feasible and safe procedure,[12-19] no randomized clinical trials have been conducted and large series are scarce. More evidence of feasibility, safety, and especially the learning curve is needed before further introduction of this promising technique can be promoted.[11]
This single-center series provides the outcomes of a large cohort of total laparoscopic hemihepatectomieswith the aim of determining the learning curve for these procedures.

METHODS

Patients

A prospectively collected single-center database of all patients undergoing total laparoscopic liver surgery in our unit at the University Hospital Southampton National Health Service Foundation Trust between August 2003 and March 2015 was retrospectively reviewed. Included were all patients (n = 159) in whom a total laparoscopic right or left hemihepatectomy procedure was started (intention-to-treat analysis), including laparoscopic extended hemihepactectomies and hemihepatectomies with additional wedge resections.

All participants had given consent that anonymous data could be used for research purposes at the time of the operation. Official approval from an ethics committee was waived by the University Hospital Southampton NHS Foundation Trust because of the retrospective design of the study.

Routine workup consisted of bloodwork, abdominal computed tomographic scans with triphasic contrast enhancement, and/or liver-specific double-contrast magnetic resonance imaging. The results of these tests were discussed in a multidisciplinary meeting including liver surgeons, medical oncologists, gastroenterologists, radiologists, and pathologists. The final decision regarding the surgical approach was based on the patient's performance status, resectability of the lesion, the presence and extent of possible extrahepatic disease, and sufficient functional parenchymal remnant.

Outcomes

Baseline characteristics included patient demographics, indication for surgery (benign/malignant), preoperative chemotherapy, American Society of Anesthesiology score, tumor size, and whether multiple procedures were performed at once (eg, hemicolectomy, splenectomy, or closure of ileostomy). Cholecystectomy was not considered an additional procedure as it is part of our operative technique for hemihepatectomy.

Study end points included operating time, intraoperative blood loss, conversion, margin status (microscopic tumor free [R0] or microscopic tumor involvement [R1]), major postoperative complications (Clavien-Dindo grade ≥III; primary end point),20 postoperative stay (total stay and high-dependency unit stay), and mortality (death within 90 days of surgery or within hospital admission). Margin status was only assessed for curative, nondebulking, or noncytoreductive resections of malignant lesions.

Debulking and cytoreductive resections are R1 resections by definition and margin status in benign lesions has no clinical value.
Initially, all operations were performed by 1 of 2 surgeons (N.W.P. and M.A.H.), both with extensive experience in open liver surgery. Before starting with laparoscopic hemihepatectomies, both had performed multiple minor liver resections (19 and 17, respectively). Eighty-six percent of hemihepactectomies were performed by these 2 surgeons. Once proficiency with the technique was acquired, they introduced 2 more members of the unit (T.A. and A.S.T.) to the technique, who then performed the other 14% of resections.

Surgical Technique

Our group has previously published detailed descriptions of the technique for major laparoscopic right and left hemihepatectomies.[16,17] No hybrid techniques were used.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics for Windows version 21.0 (SPSS Inc). Results were reported as median with interquartile range (IQR) as appropriate for continuous not normally distributed variables. The Mann-Whitney *U* test was used to compare continuous variables between groups as appropriate. Categorical variables were reported as proportions and compared between groups using $\chi 2$ test or Fisher exact test as appropriate. A 2-tailed *P* value of less than .05 was considered statistically significant.

A subgroup analysis was performed by comparing the results of 3 periods to assess a potential learning curve effect. Group A (2006, 2007, and 2008) represented the early experience with the technique. Group B (2009, 2010, and 2011) represented the further development of surgical skills and proficiency with the technique. Group C (2012, 2013, and 2014) represented the stage where proficiency with the technique was achieved and further members of the unit were introduced to the technique. To identify a disproportionate influence on outcomes by extended procedures, a sensitivity analysis was performed by excluding all extended procedures from the analysis.

Risk-Adjusted Cumulative Sum

A risk-adjusted cumulative sum (RA-CUSUM) analysis is a plot of the difference between the cumulative expected outcome of a categorical variable and the actual observed outcome. A multivariable logistic regression model for conversion from laparoscopic to open hemihepatectomy was constructed using backward selection. The final model included preoperative chemotherapy, the experience of the surgeons, and tumor size. Using this model, a RA-CUSUM analysis was performed to assess the learning curve for laparoscopic hemihepatectomy. The RA-CUSUM plot provides a visual representation of the cumulative conversions of the group of surgeons, taking into account the associated risk for a particular case mix. Every operation is plotted from left to right and the line goes up for procedures completed laparoscopically, whereas the line goes down for procedures that were converted to the open approach. The magnitude by which the line ascends or descends is determined by the difference between the observed and expected proportion of conversion. For all laparoscopically performed hemihepatectomies, the line ascends by an amount equal to the estimated probability of conversion and for every surgery that is converted to open, the line descends by an amount equal to the estimated probability of nonconversion. The RA-CUSUM plot was constructed for all hemihepactectomies performed; as a sensitivity analysis, a plot was also constructed for right-sided hemihepatectomies only. The RA-CUSUM analyses were performed using R for Windows version 3.1.2 (The R Foundation for Statistical Computing).

RESULTS

Patient Characteristics

Of 531 consecutive LLRs performed between August 2003 and March 2015, 159 were hemihepactectomies (105 right and 54 left). This included 19 laparoscopic extended hemihepatectomies (13 right and 6 left). The first laparoscopic hemihepatectomy was our 23rd LLR, 3 years after the first LLR had been performed.

The group consisted of 67 men (42%) and 92 women (58%), with a median age of 64 years (interquartile range [IQR], 51-73 years). Of all resections, 110 (69%) were for malignant disease. Simultaneous procedures, including hemicolectomy, splenectomy, closure of ileostomy, and wedge resections from surrounding structures (inferior vena cava, stomach, and diaphragm), were performed in 7 cases (4%). Twenty-nine patients (18%) needed additional wedge resections from other segments. Full patient characteristics and detailed procedure descriptions are presented in Table 1.

Table 1. Baseline Characteristics

Characteristic	Total laparoscopic hemihepatectomy, No. (%)		
	Overall n=159	**Right n=105**	**Left n=54**
Sex, male	67 (42)	44 (42)	23 (43)
Age, years (IQR)	64 (51-73)	64 (53-73)	65 (46-75)
Indication for surgery, malignant	110 (72)	78 (76)	32 (64)
Pre-op chemo	45 (28)	38 (36)	7 (13)
ASA score			
1	29 (18)	17 (16)	12 (22)
2	72 (45)	51 (49)	21 (39)
3	19 (12)	10 (10)	9 (17)
Tumor size, mm (IQR)	40 (25-70)	37 (25-69)	53 (27-80)
Multiple procedures	7 (4)	5 (5)	2 (4)
Additional wedge resection	29 (18)	22 (21)	7 (13)

Abbreviations: ASA, American Society of Anesthesiology; IQR, interquartile range.

Perioperative Results

In most of the malignant cases (91%; n = 100), a curative resection was attempted. More details on the margin status of these resections can be found in Table 2. For some lesions, a curative resection was impossible owing to the extent of the disease and a debulking or cytoreductive resection was performed (9%; n = 10; mostly for neuroendocrine tumors [n = 7]).

Median operating time was 330 minutes (IQR, 270-391minutes) and median intraoperative blood loss was 500 mL (IQR, 250-925mL). Conversion to a minilaparotomy or complete open procedure occurred in 17 procedures (11%). The reasons for conversion included bleeding (n = 7), difficulty mobilizing the liver owing to dense adhesions (n = 5), poor visualization of the lesions (n = 3), or to ensure R0 resection (n = 2). Patients stayed a median of 5 (4-6) days in hospital, of which 1 (1-2) day was in the high-dependency unit. A total of 29 patients (18%) experienced complications, of which 17 (11%) were Clavien-Dindo grade 3 or higher. Complications included abscess formation (n = 8), pneumothorax (n = 2), bile leakage (n = 2), delayed bleeding, small-for-size liver with ascites, intraoperative splenic injury requiring splenectomy, septic shock, and cardiac arrest. Mortality was 1% with 2 postoperative deaths: lactate acidosis resulting in cardiac arrest and respiratory failure due to pneumonia. Perioperative results are displayed in Table 3.

Table 2. R0 Resection for All Malignant Pathologies Resected With Curative Intent

Resection type	Total laparoscopic hemihepatectomy, No./Total No. (%)		
	Overall n=104	Right n=71	Left (n=33)
All resections	89/104 (86)	62/71 (87)	27/33 (82)
- CRLM	58/67 (87)	46/52 (88)	12/15 (80)
- *HCC*	9/11 (82)	4/6 (67)	5/5 (100)
- *NET*	6/9 (67)	4/5 (80)	2/4 (50)
- *Other metastases*[a]	7/8 (88)	5/5 (100)	2/3 (67)
- *Cholangiocarcinoma*	7/7 (100)	2/2 (100)	5/5 (100)
- *GIST*	2/2 (100)	1/1 (100)	1/1 (100)

Abbreviations: CRLM, colorectal liver metastases; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; NET, neuroendocrine tumor.
[a]metastatic melanoma (n=7), metastatic acinar cell carcinoma (n=1)

Table 3. Perioperative Results

Outcome	Total laparoscopic hemihepatectomy, No. (%)		
	Overall n=159	Right n=105	Left n=54
Operation time, mins (IQR)	330 (270-391)	345 (300-415)	270 (218-345)
Intraoperative blood loss, ml (IQR)	500 (250-925)	550 (350-1150)	300 (200-638)
Conversion	17 (11)	14 (13)	3 (6)
Pringle manoeuvre	104 (65)	61 (58)	43 (80)
Total hospital stay, days (IQR)	5 (4-6)	5 (4-7)	4 (3-5)
HDU stay, days (IQR)	1 (1-2)	1 (1-2)	1 (1-1)
Postoperative complications	19 (12)	15 (14)	4 (7)
Mortality	2 (1)	2 (2)	0

Abbreviations: HDU, high-dependency Unit; IQR, interquartile range.

Subgroup Analysis

Three groups were formed based on the year of the operation. Group A (2006-2008) consisted of 27, group B (2009-2011) of 58, and group C (2012-2014) of 74 resections. All resections in group A and all but 3 resections in group B were performed by the initial 2 surgeons (N.W.P. and M.A.H.). Two additional surgeons performed their resections in group C. Comparison of groups revealed nonsignificant decreases in conversions, blood loss, postoperative complications, high-dependency unit stay, and hospital stay (data not shown).

Sensitivity Analysis

Outcomes did not change when the extended resections were excluded from analysis.

Risk-Adjusted Cumulative Sum Analysis

The learning curve for conversion in laparoscopic hemihepatectomy is displayed in Figure 1. A visual inspection of the RA-CUSUM plot shows an increased conversion rate at the beginning of the series that started to decrease after 19 hemihepatectomies. This development halted for another 20 to 30 cases before it progressed from 55 cases onward. A second dip in Figure 1 can be observed around 145 cases. A sensitivity analysis including only right-sided hemihepactectomies showed a similar development: increasing conversion rate at the beginning, starting to decrease from 18 cases, but halting until progressive decrease from 45 cases onward (Figure 2). When only left-sided hemihepatectomies were included, there appeared to be no learning curve at all (data not shown). In exploratory analyses, differences in patient selection in the subgroups

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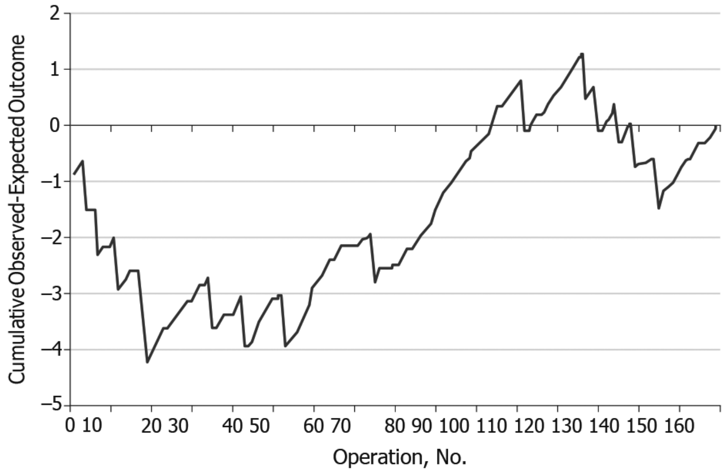

Figure 1. Risk-Adjusted Cumulative Sum Analysis of Conversions of Laparoscopic Right and Left Hemihepatectomies
A risk-adjusted cumulative sum (RA-CUSUM) analysis of conversions for the difference between the cumulative expected outcome and the actual observed outcome of 159 consecutive laparoscopic right and left hemihepatectomies. A multivariable logistic regression model for conversion from laparoscopic to open hemihepatectomy was constructed using backward selection to calculate the expected outcome. Every operation is plotted from left to right and the line goes up for laparascopically performed surgery and down for procedures which were converted to the open approach. Visual inspection shows a learning curve of 19 procedures.

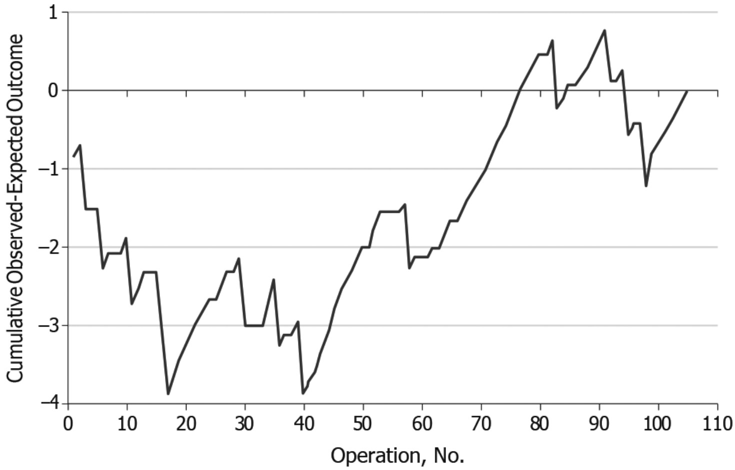

Figure 2. Risk-Adjusted Cumulative Sum Analysis of Laparoscopic Right Hemihepatectomies
A risk-adjusted cumulative sum (RA-CUSUM) analysis of conversion for the difference between the cumulative expected outcome and the actual observed outcome of 105 consecutive laparoscopic right hemihepatectomies. Visual inspection demonstrated a learning curve of 18 procedures.

0 to 20, 20 to 40, and thereafter were undetectable. On further examination of this cutoff of 55 patients, by comparing the outcomes of the first 55 patients with the rest, nosignificant differences were found in operating time, blood loss, postoperative complications, and postoperative hospital stay.

DISCUSSION

To our knowledge, this study is the first analysis of a learning curve in a large series of total laparoscopic hemihepatectomies only. With RA-CUSUM learning curve analysis, a learning curve of 55 procedures for conversion was demonstrated. Based on a median operating time of 330 minutes (IQR, 270-391 minutes), blood loss of 500 mL (IQR, 250-925 mL), 11% conversions (n = 17), 11% major postoperative complications (n = 17), and 1% mortality, total laparoscopic hemihepatectomy was considered a safe procedure within a group of liver surgeons in a high-volume unit.
The feasibility and safety of major LLR have been suggested by several large previous

studies but none of these studies focused specifically on laparoscopic hemihepatectomies.[12-15,18] Although the results from the current study are very comparable, previous studies included posterior segmentectomies, trisegmentectomies, central hepatectomies, or hand-assisted resections in their analyses. The analysis in the current study is a valuable addition to the existing literature for several reasons. First, major LLR encompasses several operations, and it has been shown that a division in subcategories is appropriate to reflect differences in surgical outcomes.[21] Second, with the debate on hand-assisted vs total laparoscopic techniques still ongoing and a lack of direct comparisons of these 2 techniques, separate analyses clearly have value. Dagher et al[13] found in their international multicenter study that hand-assisted operations had a shorter operation time and patients spent less time in hospital after surgery. On the other hand, it is imaginable that total laparoscopy has a cosmetic benefit over hand-assistance, but this is an outcome that is rarely objectively analyzed. Choice of technique is now mostly up to the surgeon's preference and surgical expertise, with hand-assistance most frequently being used in early experiences and outside of Europe.[13,14] Lin et al[15] stated in their review of 3 different laparoscopic approaches, including the total laparoscopic and hand-assisted techniques, that further research could help identify the unique clinical application possibilities of each technique. On visual inspection of the RA-CUSUM analysis demonstrated in Figure 1, no clear conclusion can be drawn at first glance and its interpretation is up for discussion. Identifying a learning curve with RA-CUSUM analysis usually entails no more than identifying the lowest point in the figure. In this case, that would be at 19 procedures. However, Figure 1 seems to hover at that point and only shoot up again after 55 cases. The possibility that this point around 55 cases is in fact the true learning curve cannot be excluded and is more in line with what has been reported previously.[22] The low incidence of conversion in this cohort and the lack of power in the prediction model used for analysis make interpretation of Figure 1 difficult, although the dip at 55 cases is clearly the most plausible as the learning curve. The first dip at 19 procedures might be explained by the fact that most of the early procedures (17/19) had been done by 1 of the 2 original surgeons and hence displays the individual learning curve of a highly experienced laparoscopic liver surgeon. We do believe this is a high number, and vast experience in laparoscopic surgery and minor liver resections are of paramount importance to achieve such results. Junior teams starting with major LLR should have sufficient experience with minor LLR. The third dip, starting at 125 cases, clearly does not reach the lowest

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point and therefore does not display the learning curve for this procedure, but it is hard to believe that the accumulation of conversions in that period is pure coincidence. During this period, 2 additional surgeons were introduced to the technique as part of succession planning as one of the senior surgeons reduced his workload as he approached retirement from active surgical practice. Their individual learning curves could explain this finding. However, this introduction was handled in such a way that an experienced surgeon was always present in the operating room for guidance and ready to step in to avoid conversion. Therefore, we believe that this dip is part of the institutional learning curve, representing the stepwise implementation of the laparoscopic approach for more complex procedures, such as lesions with close proximity to the liver hilum or inferior vena cava, extended procedures, and 2-stage procedures.

Apart from the interpretation of the RA-CUSUM analysis, we acknowledged the fact that when talking about a learning curve, a conclusion cannot be based on a single outcome, such as conversion. Variables such as blood loss and operating time should be looked at as well, although no clear definition exists of what variables exactly constitute a learning curve. The RA-CUSUM method does not allow for calculating the learning curve of continuous variables. Instead, we compared 2 groups based on the outcome of the RA-CUSUM analysis on conversion: 55 cases vs the rest. This comparison demonstrated no significant differences in operating time, blood loss, or postoperative complications.

As one might expect, right hemihepactectomies were found to be more challenging than left hemihepatectomies, expressed in almost all outcomes analyzed: longer duration of operation, higher blood loss, more conversions, and more postoperative complications. These findings can be explained by the need for more advanced mobilization of the liver. The sensitivity analysis for only right hemihepatectomies showed a similar figure as for all hemihepatectomies, with a most plausible learning curve of 45 procedures and for only left-sided hemihepatectomies, there appeared to be no learning curve at all. This could well be explained by the fact that in the first 20 consecutive patients, only 2 left hemihepatectomies were performed.

One could theoretically advocate to start with laparoscopic left hemihepatectomy and only move to laparoscopic right hemihepatectomy once sufficient experience is obtained. However, in many centers, patient volume may be insufficient for such an approach.

Despite promising results from the current and previous studies and with the advantages of minimally invasive surgery in mind, implementation of major LLR should be approached with caution.[11] Prior to embarking on major LLR, surgeons should be trained and experienced in both open liver surgery techniques: minimally invasive surgery and minor LLR. Liver mobilization, parenchymal dissection, and hemorrhage control are all skills that can be developed during minor LLR and are crucial in the more complex major LLRs. Initial procedures
should be straight forward, after which a stepwise progression in complexity of procedures can follow. We showed that even with this set of skills and 3-year experience with minor LLR on board, and using the stepwise approach, results will still improve with experience. Trends were observed over the years toward reductions in conversions, blood loss, postoperative complications, and high-dependency unit and total hospital stays, as was described before.[13,23] The added value of the RA-CUSUM analysis in this study is the determination of the number of resections needed to overcome the learning curve for conversions. Others can use this number as a guideline to their skill development when starting with this difficult procedure.

The introduction of the technique to additional surgeons within an experienced center is safe and can be done without compromising the outcomes or a second learning curve, providing
they have similar experience with advanced gastrointestinal laparoscopic procedures and minor LLR. Introduction should primarily be under experienced supervision to smooth the process and prevent unnecessary conversions, while gradually working toward decreasing supervision.

The study had some limitations, mainly its retrospective design, introducing the risk for selection bias. Some soft factors were mentioned, including the institutional style of the learning curve with multiple surgeons performing resections in different stages, that could have had an effect on outcomes and therefore make interpretation of the learning curve more
difficult. However, the large size of the cohort and the promising results do propagate further prospective and randomized trials into the actual benefits of the laparoscopic approach to hemihepatectomies. Such a trial is currently under way in Europe.[24]

CONCLUSIONS

This study demonstrated the feasibility and safety of the laparoscopic approach to hemihepatectomy. When performed by surgeons with experience in open liver surgery, advanced laparoscopic gastrointestinal surgery, and laparoscopic minor LLR, the inherent benefits of the laparoscopic technique were not compromised in patients undergoing laparoscopic hemihepatectomy. A learning curve of 55 cases is achievable when these conditions are upheld.

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CHAPTER 8

Laparoscopic combined resection of liver metastases and colorectal cancer: a multicenter, case-matched study using propensity scores

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ABSTRACT

Background

Combined laparoscopic resection of liver metastases and colorectal cancer (LLCR) may hold benefits for selected patients but could increase complication rates. Previous studies have compared LLCR with liver resection alone. Propensity score matched studies comparing LLCR with laparoscopic colorectal cancer resection (LCR) alone have not been performed.

Methods

A multicenter, case-matched study was performed comparing LLCR (2009-2016, 4 centers) with LCR alone (2009-2016, 2 centers). Patients were matched based on propensity scores in a 1:1 ratio. Propensity scores were calculated with the following pre-operative variables: age, sex, ASA grade, neoadjuvant radiotherapy, type of colorectal resection and T and N stage of the primary tumor. Outcomes were compared using paired tests.

Results

Out of 1020 LCR and 64 LLCR procedures, 122 (2x61) patients could be matched. All 61 laparoscopic liver resections were minor hepatectomies, mostly because of a solitary liver metastasis (n=44, 69%) of small size (≤3 cm) (n=50, 78%). LLCR was associated with a modest increase in operative time (206 (166-308) vs 197 (148-231) minutes, p=0.057) and blood loss (200 (100-700) vs 75 (5-200) ml, p=0.011). The rate of Clavien-Dindo grade 3 or higher complications (9 (15%) vs 13 (21%), p=0.418), anastomotic leakage (5 (8%) vs 4 (7%), p=1.0), conversion rate (3 (5%) vs 5 (8%), p=0.687) and 30-day mortality (0 vs 1 (2%), p=1.0) did not differ between LLCR and LCR.

Conclusion

In selected patients requiring minor hepatectomy, LLCR can be safely performed without increasing the risk of post-operative morbidity compared to LCR alone.

INTRODUCTION

Approximately 15-25% of patients with colorectal cancer will have synchronous colorectal liver metastases at the time of diagnosis.[1,2] Although it is clear that resection of both the colorectal primary tumor and the liver metastases offers the best chance for long term survival, the optimal surgical strategy remains unknown. Randomized trials addressing the timing of both resections are lacking.

Traditionally, a staged resection is performed wherein a colorectal resection is followed by a hepatectomy at a later stage. In recent years, a 'liver first approach' is increasingly used, aimed at maximizing the change of completing the whole treatment plan.[3,4] Surgery of the primary tumor first has the inherent risk of losing control of metastatic disease, especially considering the risk of severe complications such as anastomotic leakage delaying the hepatectomy. This is also the reason for an increasing role of induction therapy first, which allows for control of both the primary tumor and metastases. Simultaneous resection of both the primary tumor and liver metastases is an alternative approach in selected patients, either with or without induction therapy. However, some have argued that such a combined resection could lead to worse outcomes due to intestinal edema after hepatic pedicle clamping, transposition of colorectal bacteria to the liver transection surface, a decreased hepatic acute-phase response.[5]

Despite these potential risks, many surgeons have stressed the benefits of a combined resection: shorter hospital stay and 'one-stop' treatment. Indeed, combined open liver and colorectal resection has been shown to be feasible and safe in selected patients.[6-12] Comparative studies on combined laparoscopic liver and colorectal resection (LLCR) are scarce. So far, the only comparative study of LLCR used a control group of minor liver resections.[13] This may not have been the most valid comparison, since laparoscopic colorectal cancer resection (LCR) typically carries more morbidity than a minor liver resection. To address the clinical concerns with LLCR we performed a multicenter case-matched study based on propensity scores, aiming to determine whether LLCR increases post-operative morbidity in comparison with LCR alone.

MATERIALS AND METHODS

Patients and design

This study reports the combined experience of three Dutch centers and one Belgian center with LLCR. All centers retrospectively reviewed their prospectively collected databases containing their complete experience with laparoscopic liver resection from 2006 until January 2017 (experiences ranging from 3-11 years) and selected all adults who underwent LLCR for colorectal cancer with synchronous liver metastases.

Data from the Dutch ColoRectal Audit (DCRA) between January 2009 and January 2017 from 2 participating centers were used to identify control patients. Similar data from the other two centers were unavailable. All adult patients undergoing LCR for colorectal cancer were included. Patients undergoing LLCR were matched with patients undergoing LCR alone based on propensity scores in a 1:1 ratio.

Pre-operative work-up

The primary tumor was diagnosed based on colonoscopy. Liver metastases were assessed with abdominal computed tomography (CT) scans with triphasic contrast enhancement and/or liver-specific double-contrast magnetic resonance imaging. To rule out extrahepatic disease, CT-chest and, in selected patients, positron emission tomography scans were used.

Prior to surgery, patients were discussed in a multidisciplinary team meeting attended by both liver and colorectal surgeons, gastroenterologists, medical oncologists, radiologists, radiotherapists and pathologists. Based on grading, size and location of the tumor (neo)adjuvant chemo- and/or radiotherapy regimens were considered according to national guidelines.

During work-up, a simultaneous resection was planned when both colorectal primary and liver metastases were considered resectable with curative intention, and the condition of the patient, judged by both the anesthesiologist and surgeon, was considered sufficient. Resectability was defined as the ability to achieve complete resection of the primary tumor as well as all metastases without the need for additional procedures, thus excluding patients with extra-hepatic metastases. During the study period, patients requiring major liver resections and patients with liver lesions close to the portal pedicle or hepatic veins were not considered candidates for a simultaneous resection. Major liver resection was defined as any resection of 3 or more segments. Emergency colorectal resection because of bowel obstruction or perforation was also a contra-indication for LLCR. Simultaneous resections were usually performed by a single surgeon trained in both colorectal and liver surgery and discussed within the units liver surgery team. A decision regarding the surgical approach (laparoscopic or open) was made independently of the indication for surgery and was based on the patient's performance status and location and size of both the primary tumor and metastases.

Surgical technique

LLCR mostly started with the liver resection, thereby being able to decide on liver resection only in case a more extensive liver resection than planned based on preoperative imaging was required or more blood loss than expected. Laparoscopic liver resection was performed with the patient in supine position (or semiprone for liver resection of lesions in posterosuperior segments) and the surgeon in between the patient's legs using three to four trocars in the upper abdomen. Laparoscopic ultrasound was used for detection of potentially occult lesions and to determine the plane of transection. Parenchymal transection was performed by using an ultrasonic dissection or bipolar sealing device alone or together with cavitron ultrasonic surgical aspirator (CUSA), with additional haemostasis using bipolar diathermy. Pedicle clamping during laparoscopic liver resection (Pringle manoeuvre) was not standard practice. A laparoscopic 60 mm stapler was used to transect the portal pedicle and hepatic vein in case of a left lateral sectionectomy. Additional trocars were placed if necessary for laparoscopic colorectal surgery. A Pfannenstiel or vertical umbilical incision were mostly used for specimen extraction, followed by either an intra- or extracorporeal anastomosis.

Outcomes

Baseline characteristics consisted of patient demographics, body mass index (BMI, kg/m^2), American Society of Anesthesiology (ASA) grade, location of primary tumor (rectum, sigmoid, left colon, transverse colon or right colon), number, location and size of liver metastases on pre-operative imaging, neoadjuvant treatment, type of resection of primary tumor, pathology of the primary tumor and the type and extent (minor/major) of liver resection.

Primary outcome was the rate of Clavien-Dindo grade 3 or higher complications including anastomotic leakage. The diagnosis of anastomotic leakage was based on clinical and radiological parameters, including any abscess occurring at the anastomosis, leakage of contrast fluid on imaging, endoscopically proven leakage or clinically suspect leakage requiring a reoperation. Other outcome parameters included operative time, intraoperative blood loss, need for conversion (to laparotomy, hand-assisted or hybrid technique), reason for conversion (e.g. adhesions, bleeding, inadequate access to the lesion, inadequate progress or other), need for a stoma, resection margins (R0=tumor free, R1=microscopic tumor involvement, R2=macroscopic tumor involvement), pathology reported TNM stage of primary tumor, postoperative hospital stay, readmission (reason and timing) and 30 day mortality.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics for Windows version 24.0 (SPSS Inc., Chicago, IL, USA). Results were reported as median with interquartile range (IQR) as appropriate for continuous not normally distributed variables. If variables were normally distributed, results were reported as mean with standard deviation (SD). Categorical variables were reported as proportions. Propensity scores were calculated using a logistic regression model based on the following variables: age, sex, ASA grade, neoadjuvant radiotherapy, type of colorectal resection, T stage of primary tumor and N stage of primary tumor. Based on these propensity scores, LLCR were matched in a 1:1 ratio using a caliper of 0.1 to LCR alone. A Wilcoxon signed rank test was used to compare continuous, not normally distributed variables and ordinal categorical variables. Normally distributed continuous variables were compared using a paired T test. Finally, a McNemar test was used to compare binary and nominal categorical variables. A two-tailed *P*-value of <0.05 was considered statistically significant.

RESULTS

Before matching

A total of 64 patients underwent LLCR between April 2009 and January 2017, which was a median of 3% (3-3.8) of the liver resections and 1% (1-2) of the colorectal resections performed per center during the study period. The mean annual number of LLCR per center was 4. Characteristics of liver metastases and resection are displayed in table 1 and other patient characteristics are provided in table 2. Most patients had minor comorbidities (ASA 1 and 2) (n=51, 79%), a primary rectal/sigmoid tumor (n=40, 63%) and a solitary liver metastasis (n=44, 69%) of small size (≤3 cm) (n=50, 78%).

Table 1. Liver metastases and resection characteristics

	Overall n=64
Number of liver metastases	
- 1	44 (69)
- 2	9 (14)
- 3	4 (6)
- >3	7 (11)
Location of liver metastases	
- Unilobar	52 (81)
- Bilobar	12 (19)
Size of largest liver lesion, mm, median (IQR)	20 (13-30)
- ≤3 cm	50 (78)
- >3 cm	14 (22)
Surgical procedure	
- Totally laparoscopic	56 (88)
- Laparoscopic, hand-assisted	6 (9)
- Laparoscopic, robot-assisted	2 (3)
Approach	
- Liver first	43 (67)
- Colon first	20 (31)
Liver resection strategy	
- One stage resection only	54 (84)
- One stage resection + RFA	1 (2)
- Two stage resection without PVE	5 (8)
- Two stage resection with PVE	4 (6)
Multiple liver resections	17 (27)
Type of liver resection	
- Non-anatomical resection	45 (70)
- Left lateral sectionectomy	7 (11)
- Segmentectomy	12 (19)

All values in parenthesis are percentages unless mentioned otherwise. Percentages may not add up to 100 due to rounding. IQR = inter quartile range, RFA = radiofrequency ablation, PVE = portal vein embolization

All patients required minor liver resections: wedge metastasectomies (45 (70%)), left lateral sectionectomies (7 (11%)) and total segmentectomies (12 (19%)). In 17 patients (25%), two or more resections were performed. For the primary tumor, low anterior/sigmoid resection (n=38, 59%) was the most frequently performed procedure. Overall median operative time was 213 minutes (IQR 170-308) and blood loss was 200 ml (IQR 100-688). Conversion to laparotomy was necessary in 3 patients (5%), all due to inadequate access to the liver metastases. A Pringle maneuver was used in 3 patients (5%), of whom one developed an anastomotic leakage. Severe postoperative complications occurred in 9 patients and included anastomotic leakage (n=4), intra-abdominal fluid collections requiring radiological drainage (n=2, one liver and one colon

Table 2. Baseline patient and tumor characteristics after matching based on propensity scores

	LLCR n=61	LCR n=61	P
Male sex	37 (61)	34 (56)	0.719
Age, mean (SD)	64 (11.6)	64 (13.1)	0.949
BMI, kg/m2, median (IQR)	25.8 (23.4-28.1)	25.2 (23.7-28.5)	0.958
ASA grade			0.988
- ASA 1	15 (25)	14 (23)	
- ASA 2	33 (54)	36 (59)	
- ASA 3	12 (20)	9 (15)	
- ASA 4	1 (2)	2 (3)	
Location primary			0.378
- Rectum	12 (20)	18 (30)	
- Sigmoid	27 (44)	23 (38)	
- Left colon	4 (7)	4 (7)	
- Transverse colon	0	2 (3)	
- Right colon	18 (30)	14 (23)	
Neoadjuvant chemotherapy	12 (20)	5 (8)	0.039
Neoadjuvant radiotherapy	9 (15)	7 (12)	0.687
Type of resection primary			0.686
- Low anterior resection/sigmoid resection	37 (61)	35 (57)	
- Abdominoperineal resection	3 (5)	4 (7)	
- Left colectomy	4 (7)	4 (7)	
- Right colectomy	15 (25)	17 (28)	
- Subtotal colectomy	2 (3)	1 (2)	
Pathology primary tumor			0.931
- T0	2 (3)	0	
- T1	2 (3)	2 (3)	
- T2	3 (5)	8 (13)	
- T3	46 (75)	42 (69)	
- T4	8 (13)	9 (15)	
- N+	48 (79)	46 (75)	

All values in parenthesis are percentages unless mentioned otherwise. Percentages may not add up to 100 due to rounding. IQR = inter quartile range, BMI = body mass index, ASA = American Society of Anesthesiology

related), gastroparesis requiring endoscopic placement of a nasojejunal feeding tube (n=1), wound bleeding requiring reoperation (n=1) and cardiac arrhythmia requiring ICU admission (n=1).

After matching

A total of 1020 LCR were included in the study period and used for matching. After matching, 61 LLCR could be compared with 61 LCR. Baseline characteristics were comparable after matching based on propensity scores.

Table 3. Perioperative outcomes after matching based on propensity scores

	LLCR n=61	LCR n=61	P
Operative time, min, median (IQR)	206 (166-308)	197 (148-231)	0.057
Blood loss, ml, median (IQR)	200 (100-700)	75 (5-200)	0.011
Conversion	3 (5)	5 (8)	0.687
Peroperative incidents, Oslo Classification			0.237
- None	52 (85)	56 (92)	
- Grade 1	6 (10)	4 (7)	
- Grade 2	3 (5)	1 (2)	
- Grade 3	0	0	
Stoma			0.317
- None	51 (84)	46 (75)	
- Double loop ileostomy	4 (7)	7 (12)	
- End ileostomy	2 (3)	0	
- End colostomy	4 (7)	8 (13)	
Severe complications	9 (15)	13 (21)	0.481
Anastomotic leakage	5 (8)	4 (7)	1.0
Postoperative stay, days, median (IQR)	6 (5-9)	7 (4-13)	0.164
Resection margins, R0	57 (93)	61 (100)	0.125
Readmission	7 (12)	8 (13)	1.0
30-day mortality	0	1 (2)	1.0

All values in parenthesis are percentages unless mentioned otherwise. Percentages may not add up to 100 due to rounding. IQR = inter quartile range

LLCR was associated with a 9 minutes longer operative time (206 (166-308) vs 197 (148-231) minutes, *p*=0.057) and 125 ml increase in blood loss (200 (100-700) vs 75 (5-200) ml, *p*=0.011). Other per- and post-operative outcomes did not differ between the groups. All outcomes after matching are displayed in tables 2 and 3.

DISCUSSION

This first case-matched study using propensity scores to match LLCR in patients with synchronous colorectal cancer liver metastases with LCR alone found similar postoperative morbidity with a negligible increase in operative time (9 minutes) and blood loss (125 ml). Hospital stay was similar between LLCR and LCR alone, indicating a benefit of LLCR in these highly selected patients by omitting the need for a second hospital admission with its associated risks, costs and emotional burden for the patient.

Based on these results it seems worthwhile for experienced centers to screen and select patients with synchronous colorectal liver metastases who require minor hepatectomy for LLCR.

Despite single center reports on the feasibility and safety of LLCR, the true impact of adding a laparoscopic liver resection to a LCR on post-operative morbidity has never been investigated.[14-17] The potential benefits of a simultaneous resection in terms of patient satisfaction and reduction of costs seem obvious, but the concerns regarding raised post-operative morbidity are serious and should be addressed. This is also important since it has consistently been shown that there is no survival benefit of either one of the two strategies.[12,18] Until now, the only comparative (non-matched) study included 9 patients undergoing LLCR and 82 patients undergoing laparoscopic minor liver resection. Not surprisingly, giving the higher rate of complications after colorectal resection, morbidity was higher after LLCR versus a minor liver resection (22% vs 1%).[13] Other studies in open surgery have also reported unfavorable outcomes in terms of morbidity and even mortality when comparing a combined resection with liver resections only.[19,20] A systematic review and meta-analysis, published in 2017, included 30 studies with a total of 2235 simultaneous and 3065 delayed open hepatectomies.[12] This study showed that a combined resection is feasible and can be performed without increasing post-operative morbidity compared to delayed hepatectomy. However, the results were clearly biased as patients in the delayed hepatectomy group more often had extensive liver lesions. The control group in these previous studies consisted of patients with only liver resections , instead of colorectal resections. This is somewhat surprising since the resection of the primary colorectal cancer is likely to dominate the risk of postoperative morbidity, rather than a minor liver resection. For instance, a large Dutch study demonstrated morbidity rates of 26% and 37% after laparoscopic and open colorectal cancer resections, respectively[21], whereas laparoscopic minor and open minor liver resections are associated with morbidity rates of 13% and 30%, respectively.[22] Furthermore, the main concerns with LLCR focus on adding morbidity to the colorectal resection due to congestion and added intraoperative fluid load potentially leading to increased rate of anastomotic leakage and septic complications.

Laparoscopy could have played a role in the relatively low rate of major morbidity after LLCR in this series. In most centers nowadays, laparoscopic surgery is considered standard of care for primary resectable colorectal cancer, and most recent consensus meetings on laparoscopic liver surgery have declared laparoscopy the standard for minor liver resections as well.[23-25] In both procedures, a laparoscopic approach has been associated with faster recovery and shorter post-operative hospital stay, as well as decreased complication rates.[21,22,26,27] Furthermore, the decreased need for pedicle clamping during laparoscopic liver surgery related to the intra-abdominal pressure during laparoscopy could decrease the risk of additional morbidity during LLCR.[28-32] One meta-analysis of 3 studies comparing LLCR with open combined colorectal and liver resections reported shorter hospital stay after LLCR, without compromising safety.[33]

The current study had several limitations. First, the retrospective design clearly introduced a risk of selection bias. Selection criteria were, however, essentially similar in the four participating centers and are described in the methods section. Even though laparoscopic major liver resections were performed in all centers during the study period, these patients were not considered to be candidates for LLCR. Second, the size of the cohort did not allow for identification of subgroups, for instance comparing outcome after left- and right-sided colon cancer resection. A randomized controlled trial designed to answer the question whether LLCR is superior to a staged resection seems unlikely, so matching based on propensity scores is probably the next best methodology. Larger cohorts, could help to further identify subgroups when it comes to the surgical treatment of synchronous colorectal liver metastases. In order to increase the potential of finding a matching LCR control patient, metastasized colorectal tumors were not excluded. This means that some of these patients might undergo further surgery for metastatic disease after colorectal resection. The aim of this study, however, was to investigate short-term outcomes and there is no current literature available suggesting that in situ metastatic disease influences the outcomes of colorectal or liver surgery. Long term results of simultaneous resections, such as disease free and overall survival, remain uncertain, especially considering the possible extravasation of tumor cells during colorectal resection that could settle down in areas of tissue damage and inflammation such as the liver surface after resection. Finally, the potential advantages of LLCR were not specifically addressed in this study, which can be seen as a limitation. The most accurate comparison would be between LLRC and the cumulative of both colorectal and liver resection in a delayed setting. These patients were difficult to identify and due to the selection bias for the extent of liver resection matching would not have been possible.

Post-operative hospital stay has consistently been shown to be decreased with open combined resection when compared to the cumulative length of stay when performing sequential resections.[12] The current study did not show a significant difference in length of post-operative stay between the groups. However, as the delayed liver resection was not taken into account in this study, this outcome would favor LLCR as all hospitalization for the delayed liver resection can be avoided. The same applies to operative time and intra-operative blood loss. It is interesting to note that the operative time in LLCR was only 9 minutes longer on average than in the laparoscopic colorectal resection group. This seems unlikely, but abdominal access and closure of extraction site and trocar ports had to be performed only once in case of LLCR if compared to a staged procedure, which saves a lot of time. Not all centers may have surgeons skilled in both laparoscopic colorectal and liver surgery. This may not be a major problem but does require close communication on the details of patient selection, patient positioning and trocar placement. On the other hand, centralization of these specific cases for simultaneous resection to experienced centers is probably better. Finally, patient satisfaction is impossible to measure in a retrospective setting but it would seem unlikely that patients would favor staged operations over LLCR.

In conclusion, this study showed that LLCR is feasible and does not increase post-operative morbidity compared to LCR alone, in selected patients with synchronous colorectal liver metastases requiring a minor liver resection, operated in experienced centers.

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CHAPTER 9

Multicenter propensity score matched study on laparoscopic versus open repeat liver resection for colorectal liver metastases

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ABSTRACT

Background

Repeat liver resection is often the best treatment option for patients with recurrent colorectal liver metastases (CRLM). Repeat resections can be complex, however, owing to adhesions and altered liver anatomy. It remains uncertain whether the advantages of a laparoscopic approach are upheld in this setting. The aim of this retrospective, propensity score-matched study was to compare the short-term outcome of laparoscopic (LRLR) and open (ORLR) repeat liver resection.

Methods

A multicentre retrospective propensity score-matched study was performed including all LRLRs and ORLRs for CRLM performed in nine high-volume centres from seven European countries between 2000 and 2016. Patients were matched based on propensity scores in a 1 : 1 ratio. Propensity scores were calculated based on 12 preoperative variables, including the approach to, and extent of, the previous liver resection. Operative outcomes were compared using paired tests.

Results

Overall, 425 repeat liver resections were included. Of 271 LRLRs, 105 were matched with an ORLR. Baseline characteristics were comparable after matching. LRLR was associated with a shorter duration of operation (median 200 (i.q.r. 123–273) *versus* 256 (199–320) min; $P < 0.001$), less intraoperative blood loss (200 (50–450) *versus* 300 (100–600) ml; $P = 0.077$) and a shorter postoperative hospital stay (5 (3–8) *versus* 6 (5–8) days; $P = 0.028$). Postoperative morbidity and mortality rates were similar after LRLR and ORLR.

Conclusion

LRLR for CRLM is feasible and may offer advantages over an open approach.

INTRODUCTION

Repeat liver resection for recurrent colorectal liver metastases (CRLM) has similar outcomes to primary liver resection and a favourable prognosis compared with palliative chemotherapy[1–3]. Laparotomy has long been the preferred surgical approach but laparoscopic liver resection (LLR) is gaining popularity[4]. Advantages of LLR include a quicker recovery and reduced morbidity[4–7] leading to the consensus that laparoscopy should be considered the standard approach to minor liver resections[8,9]. However, repeat liver resection is considered a challenging procedure owing to adhesions, anatomical distortion caused by the previous liver resection and other treatment modalities that are often used in the setting of recurrent disease. In fact, most laparoscopic liver surgeons suggest that repeat liver resection significantly increases the difficulty of LLR[10] or risk of conversion[11]. The Southampton guidelines on LLR[8] stated that repeat liver resection should be avoided in the early phase of the learning curve. Within the boundaries of these recommendations, some experts and pioneers have reported encouraging results from their experience with laparoscopic repeat liver resection (LRLR)[12–19]. However, these were all observational, non-matched studies, limited by a relatively small sample size, high risk of selection bias, and heterogeneous patient groups including variable pathologies. Hence, the role of laparoscopy in patients requiring repeat liver resection for CRLM is still unclear. The aim of this multicentre study was to compare the short-term outcomes of LRLR and open repeat liver resection (ORLR) using propensity score matching to minimize the influence of selection bias.

METHODS

This study was reported in accordance with the STROBE statement[20]. It represents the combined experience of LRLR and ORLR in nine highly experienced hepatopancreatobiliary centres from seven European countries. There was no patient burden in gathering the data as these were collected retrospectively and registered anonymously.

Patient selection

All participating centres undertook a retrospective review of their prospectively collected databases containing all resections for CRLM, and selected all adult patients

who had undergone a previous liver resection in the interval 2000–2016. Patients undergoing emergency surgery or a two-stage procedure were excluded.
Liver metastases were diagnosed based on abdominal CT with triphasic contrast enhancement and/or liver-specific double-contrast MRI in all centres. When necessary, additional metastatic disease was assessed using other imaging modalities such as PET. Results were discussed in multidisciplinary team meetings attended by liver surgeons, gastroenterologists, medical oncologists, pathologist and radiologists. Patients were considered surgical candidates based on the same factors in all centres: a complete resection of tumour could be achieved without the need for vascular or biliary reconstruction, sufficient future remnant liver could be preserved with adequate inflow and outflow, and the patient was fit for surgery. A decision regarding the surgical approach did not influence surgical indications, and was based on tumour size and location, the ability to preserve sufficient liver parenchyma, the patients' performance status, and the surgeon's experience and skill.

Data collection

Data were collected from electronic patient files. Baseline characteristics consisted of: patient demographics, ASA grade, neoadjuvant chemotherapy, number of previous liver resections, approach to the previous liver resection (laparoscopic or open), extent of the previous liver resection (minor or major), number of lesions, tumour size, type and extent of resection, and additional procedures.
The approach to the previous liver resection was considered as open when patients had undergone both laparoscopic and open previous liver resection. When both minor and major resections had been performed previously, the extent of resection was considered as major. Major liver resection was defined as a resection of three or more segments or any resection from posterior segments I, VII, VIII and/or IVa. The former was considered anatomically major and the latter technically major[21,22]. Additional procedures included: any additional resection other than cholecystectomy, hernia repair, or radiofrequency or microwave ablation.
Operative outcomes included: duration of operation, intraoperative blood loss, Pringle manoeuvre, conversion, reason for conversion, intraoperative incidents, 30-day or in-hospital severe postoperative complications, duration of postoperative hospital stay, resection margins (R0, tumour free; R1, microscopic tumour involvement; R2, macroscopic tumour involvement), 30-day readmission and 90-day mortality. Intraoperative incidents were defined according to the Oslo classification and severe postoperative complications as an Accordion grade 3 or higher[23].

Surgical technique

All centres have previously reported their surgical technique for LLR[24–34]. Similar techniques were used for LRLR.

Statistical analysis

Continuous variables with a non-normal distribution are reported as median (i.q.r.) and normally distributed variables as mean (s.d.). The Mann Whitney U test and the Independent Samples T test, respectively, were used for statistical analysis. Categorical variables were displayed as proportions and were analysed using χ^2 test and Fisher's exact test, as appropriate. Propensity score matching was applied and reported according to the recommendations of Lonjon and colleagues[35]. Propensity scores were calculated in R Studio version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) using a multivariable logistic regression model. A consensus regarding which variables should be used in the model was reached among all authors, based on their value in the decision regarding surgical approach. The final model included the following variables: age, sex, ASA grade, neoadjuvant chemotherapy, number of previous liver resections, approach to the previous liver resection, extent of the previous liver resection, number of metastases, size of metastases, type of operation, extent of operation and additional procedures. Using a standard calliper width of 0.2, LRLRs were matched, without replacement, to the closest matching propensity score in the ORLR group in a 1 : 1 ratio. LRLRs that were converted to open surgery were analysed in the LRLR group, according to intention-to-treat principles. Patients with missing data in matching variables and those who could not be matched were excluded from analysis. Operative outcomes were subsequently analysed using paired tests. Two-tailed $P < 0.050$ was considered statistically significant. Data were analysed using SPSS® Statistics for Windows® version 24.0 (IBM, Armonk, New York, USA).

RESULTS

A total of 425 repeat liver resections were included, consisting of 271 LRLRs and 154 ORLRs. The first repeat liver resection was performed in 2000, and was laparoscopic. The median number of repeat liver resections performed per centre per year since their first case was 4 (i.q.r. 3–5).

Baseline variables before matching

The most noticeable difference between the groups was that LRLR was more frequently preceded by laparoscopic (185 (68.5 per cent) *versus* 36 (24.2 per cent); *P* < 0.001) and minor (227 (84.1 per cent) *versus* 112 (75.2 per cent); *P* = 0.026) liver resection compared with ORLR (*Table 1*). Anatomically major resections were less frequent in the LRLR group (55 (20.3 per cent) *versus* 48 (31.2 per cent); *P* < 0.001) and patients in this group had solitary lesions more often (166 (61.5 per cent) *versus* 78 (50.9 per cent); *P* = 0.013).

Outcomes before matching

Thirty LRLRs (11.1 per cent) were converted, with adhesions as the most common reason (10 procedures) (*Table 2*). A total of 44 severe complications occurred in 19 LRLRs (7.0 per cent) and 15 ORLRs (9.7 per cent) (*P* = 0.319). Most frequently observed complications were bile leakage (10), abdominal abscesses (7), pleural effusion (4) and ascites (3), all requiring drainage, and bleeding requiring reoperation (3). Mortality was comparable between the groups (2 (0.7 per cent) *versus* 2 (1.3 per cent); *P* = 1.000). Causes of death were colonic necrosis followed by septic shock (1), bile leakage and liver failure (1), sepsis after bowel perforation requiring two reoperations (1) and renal failure (1). Interestingly, the R0 resection rate was significantly higher in the LRLR group (91.8 *versus* 78.6 per cent; *P* < 0.001).

Baseline variables after matching

After excluding patients with insufficient preoperative data and the inevitable loss of patients owing to inability to find a match, 105 LRLRs were matched with 105 ORLRs. Baseline characteristics were comparable after matching (*Table 3*).

Outcomes after matching

LRLR was associated with a shorter operating time (median 200 (i.q.r 123–273) *versus* 256 (199–320) min; *P* < 0.001) and a shorter postoperative hospital stay (5 (3–8) *versus* 6 (5–8) days; *P* = 0.028) (*Table 4*). A trend towards less intraoperative blood loss in the laparoscopic group was noted (200 (50–450) *versus* 300 (100–600) ml; *P* = 0.077). Postoperative morbidity and mortality rates were similar in the two groups. The significant difference in terms of R0 resection margins remained after matching (90.5 *versus* 75.2 per cent; *P* = 0.005).

Table 1. Baseline characteristics of patients undergoing laparoscopic or open repeat liver resection for colorectal liver metastases, before propensity score matching

	LRLR n=271	ORLR n=154	P‡
Age (years)*	63(11)	61(10)	0.032
Sex ratio (M : F)	166 : 105	93 : 61	0.861
ASA grade			0.768
I–II	168 (66.1)	99 (64.7)	
III–IV	86 (33.9)	54 (35.3)	
Missing	17 (6.3)	1 (0.01)	
Neoadjuvant chemotherapy	146 (53.9)	92 (59.7)	0.228
No. of previous liver resections			0.960
1	238 (87.8)	134 (87.0)	
2	30 (11.1)	18 (11.7)	
≥ 3	3 (0.01)	2 (1.3)	
Approach to previous liver resection			< 0.001
Laparoscopic	185 (68.5)	36 (24.2)	
Open	85 (31.5)	113 (75.8)	
Missing	1 (0.4)	5 (3.2)	
Extent of previous liver resection			0.026
Minor	227 (84.1)	112 (75.2)	
Major	43 (15.9)	37 (24.8)	
Missing	1 (0.4)	5 (3.2)	
No. of lesions			0.013
1	166 (61.5)	78 (50.9)	
2	62 (23.0)	34 (22.2)	
3	21 (7.8)	16 (10.5)	
4	6 (2.2)	12 (7.8)	
≥ 5	15 (5.5)	13 (8.5)	
Missing	1 (0.4)	1 (0.6)	
Maximum tumour size (mm)†	25 (15–38)	29 (20–40)	0.129
Type of resection			< 0.001
Wedge/non-anatomical resection	150 (55.4)	55 (35.7)	
Segmentectomy	30 (11.1)	24 (15.6)	
Bisegmentectomy	36 (13.3)	27 (17.5)	
Trisectionectomy/hemihepatectomy	55 (20.3)	48 (31.2)	
Extent of resection			< 0.001
Minor	129 (47.6)	83 (53.9)	
Anatomically major	55 (20.3)	48 (31.2)	
Technically major	87 (32.1)	23 (14.9)	
Additional resections other than liver	14 (5.2)	15 (9.7)	0.117

Values in parentheses are percentages unless indicated otherwise; values are *mean(s.d.) and †median (i.q.r). LRLR, laparoscopic repeat liver resection; ORLR, open repeat liver resection ‡χ^2 test, except age (Independent samples T test), tumour size (Mann Whitney U test) and number of previous liver resections (Fisher's exact test).

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Table 2. Operative outcomes of patients undergoing laparoscopic or open repeat liver resection for colorectal liver metastases, before propensity score matching

	LRLR n=271	ORLR n=154	P‡
Duration of operation (min)*	193 (120–270)	259 (200–320)	< 0.001
Blood loss (ml)*	200 (50–600)	400 (140–700)	0.023
Pringle manoeuvre	40 (14.8)	63 (40.9)	< 0.001
Conversion	30 (11.1)	–	
Bleeding	6 (2.2)		
Adhesions	10 (3.7)		
Inadequate progress	1 (0.4)		
Anatomy	6 (2.2)		
Oncological concern	3 (1.1)		
Other	2 (0.7)		
Unknown	2 (0.7)		
Intraoperative incidents	52 (19.2)	25 (16.2)	0.066
Grade 1	19 (7.0)	16 (10.4)	
Grade 2	33 (12.1)	9 (5.8)	
Duration of postoperative hospital stay (days)*	4 (3–7)	7 (5–10)	< 0.001
Severe complications	19 (7.0)	15 (9.7)	0.319
R0 resection	245 of 267 (91.8)	121 of 154 (78.6)	< 0.001
Readmission	18 (6.6)	5 (3.2)	0.135
90-day mortality	2 (0.7)	2 (1.3)	1.000

Values in parentheses are percentages unless indicated otherwise; values are *median (i.q.r). LRLR, laparoscopic repeat liver resection; ORLR, open repeat liver resection. †χ^2 test, except duration of operation, blood loss, postoperative stay (Mann Whitney U test), and mortality (Fisher's exact test).

DISCUSSION

LRLR was associated with a shorter duration of surgery, shorter postoperative hospital stay and decreased intraoperative blood loss compared with ORLR, without significant differences in morbidity or mortality, even in patients who had undergone open and major liver resection previously. As the annual number of patients per centre is relatively small, repeat liver resection is not considered a standard technique and a decision regarding the surgical approach was based on several preoperative variables. The confounding by indication bias was highlighted by the significant differences in baseline data.

Hallet and colleagues[36] were the first to use propensity score matching to compare LRLR and ORLR for CRLM, and found the two approaches to be comparable, except

Table 3. Baseline characteristics of propensity score-matched patients undergoing laparoscopic or open repeat liver resection for colorectal liver metastases

	LRLR n=105	ORLR n=105	P‡
Age (years)*	61(10.7)	62(9.6)	0.386
Sex ratio (M : F)	62 : 43	62 : 43	1.000
ASA grade			0.639
I–II	73 (69.5)	70 (66.7)	
III–IV	32 (30.5)	35 (33.3)	
Neoadjuvant chemotherapy	62 (59.0)	65 (61.9)	0.784
No. of previous liver resections			0.858
1	90 (85.7)	90 (85.7)	
2	14 (13.3)	13 (12.4)	
≥ 3	1 (1.0)	2 (1.9)	
Approach to previous liver resection			0.690
Laparoscopic	39 (37.1)	36 (34.3)	
Open	66 (62.9)	69 (65.7)	
Extent of previous liver resection			0.875
Minor	78 (74.3)	78 (74.3)	
Major	27 (25.7)	27 (25.7)	
No. of lesions			0.246
1	60 (57.1)	54 (51.4)	
2	25 (23.8)	23 (21.9)	
3	10 (9.5)	12 (11.4)	
4	4 (3.8)	9 (8.6)	
≥ 5	6 (5.7)	7 (6.7)	
Maximum tumour size (mm)†	28 (19–44)	30 (20–40)	0.946
Type of resection			0.662
Wedge/non-anatomical resection	47 (44.8)	51 (48.6)	
Segmentectomy	15 (14.3)	12 (11.4)	
Bisegmentectomy	15 (14.3)	16 (15.2)	
Trisectionectomy/hemihepatectomy	28 (26.7)	26 (24.8)	
Extent of resection			0.798
Minor	56 (53.3)	56 (53.3)	
Anatomically major	28 (26.7)	26 (24.8)	
Technically major	21 (20.0)	23 (21.9)	
Additional resections other than liver	13 (12.4)	12 (11.4)	1.000

Values in parentheses are percentages unless indicated otherwise; values are *mean(s.d.) and †median (i.q.r). LRLR, laparoscopic repeat liver resection; ORLR, open repeat liver resection ‡Wilcoxon signed rank test, except age (paired T test), and gender, neoadjuvant chemotherapy, approach to previous liver resection, extent of previous liver resection and additional resections (McNemar test).

for an increase in surgery-specific morbidity in the LRLR group. However, their cohort consisted of 27 LRLRs, which meant the number of variables that could be used for matching was limited and many possible remaining confounders, such as approach to, and extent of, previous liver resection, were not included. It has been suggested

Table 4. Operative outcomes of propensity score-matched patients undergoing laparoscopic or open repeat liver resection for colorectal liver metastases

	LRLR n=105	ORLR n=105	P†
Duration of operation (min)*	200 (123–273)	256 (199–320)	< 0.001
Blood loss (ml)*	200 (50–450)	300 (100–600)	0.077
Pringle manoeuvre	22 (21.0)	44 (41.9)	0.004
Conversion	11 (10.5)	–	
Bleeding	2 (1.9)		
Adhesions	3 (2.9)		
Anatomy	1 (1.0)		
Oncological concern	1 (1.0)		
Other	2 (1.9)		
Unknown	2 (1.9)		
Intraoperative incidents	13 (12.4)	17 (16.2)	0.710
Grade 1	4 (3.8)	13 (12.4)	
Grade 2	9 (8.6)	4 (3.8)	
Duration of postoperative hospital stay (days)*	5 (3–8)	6 (5–8)	0.028
Severe complications	6 (5.7)	6 (5.7)	0.794
R0 resection	95 (90.5)	79 (75.2)	0.005
Readmission	5 (4.8)	4 (3.8)	1.000
90-day mortality	2 (1.9)	0 (0)	0.500

Values in parentheses are percentages unless indicated otherwise; values are *median (i.q.r). LRLR, laparoscopic repeat liver resection; ORLR, open repeat liver resection †Wilcoxon signed rank test, except Pringle, R0 resection, readmission and mortality (McNemar test).

that LLR improves resectability of recurrent disease[37], and laparoscopic surgery is associated with decreased formation of adhesions which could improve accessibility of the abdomen in future abdominal procedures[38,39]. The extent of previous liver resection also plays a role in the difficulty of repeat resection as the liver anatomy is more likely to be significantly altered and the future remnant liver will be smaller after major resection. The size of the present cohort enabled an extensive model to be built based on 12 preoperative variables, including the approach to, and extent, of previous liver resection. With these variables included in the match, there was no apparent difference in postoperative morbidity between LRLR and ORLR, but the laparoscopic procedure did seem to offer advantages in terms of reduced operating time, blood loss and postoperative hospital stay.

Essential to achieving these results is, first of all, careful trocar placement allowing good instrument triangulation. The liver anatomy may have changed as a result of the previous resection and subsequent hypertrophy of the remnant liver. Trocar placement should be adjusted accordingly, without being guided solely by previous incisions or adhesions. Second, mobilization may be more challenging owing to adhesions, but should not be compromised on. The tension on the adhesions caused by pneumoperitoneum and the enhanced vision possibly enable more meticulous adhesiolysis during LRLR, contributing to the decreased operating time and blood loss compared with ORLR. Early conversion should be considered when mobilization is difficult and progresses slowly. On the other hand, unnecessary extensive mobilization of the future remnant liver should be avoided to facilitate future liver resection, if needed. Laparoscopy might add to the ability to do so owing to the enhanced access related to the caudal approach.

Although not the focus of this study, the impact of the approach to the previous liver surgery on outcomes after repeat liver resection was explored. In univariable analysis, previous open resection was not associated with an increased odds of conversion (in LRLR only), R1 resection or morbidity. Furthermore, no significant differences in operative outcomes were found in a comparison of LRLR after a previous laparoscopic or open resection (*Tables S1* and *S2*, supporting information). These findings seem to somewhat contradict the findings of a recently published difficulty score for laparoscopic liver surgery, where a previous open liver resection was identified as a significant predictor of intraoperative incidents in a group of 2856 LLRs[40].

Improved oncological radicality is not typically described as an advantage of LLR. In fact, the only RCT[41] comparing laparoscopic *versus* open resection of CRLM reported no significant differences in tumour-free resection margins. The present study was not specifically designed to find differences in resection margins, and data on variables such as the use of intraoperative ultrasonography and the distance of lesions to major vessels were not collected. Intraoperative ultrasound imaging was used regularly in all centres to identify additional lesions, determine resection margins and distance from the lesion to major vessels, but no data were gathered to compare its use between groups. Other known risk factors for R1 resection, such as the number and size of lesions, were comparable between the two groups and cannot therefore explain this finding. All in all, this finding should be approached with caution as information is lacking regarding the exact location of the lesion and how this was assessed during surgery.

It is acknowledged that the present study has limitations. Its retrospective design introduces an inevitable risk of selection and information bias and, although propensity score matching was used to minimize the confounding by indication, this can never be completely eradicated. All resections were performed in high-volume centres by dedicated, experienced hepatopancreatobiliary surgeons, and this represents the most extensive matched analysis of LRLR *versus* ORLR to date. When performed by experienced surgeons on suitable patients, LRLR is associated with advantages even in those who underwent open or major liver resection previously.

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CHAPTER 10

Laparoscopic liver resection for lesions adjacent to major vasculature: feasibility, safety and oncological efficiency

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ABSTRACT

Background and Objectives

Laparoscopic liver resection for lesions adjacent to major vasculature can be challenging, and many would consider it a contraindication. Recently, however, laparoscopic liver surgeons have been pushing boundaries and approached some of these lesions laparoscopically. We assessed feasibility, safety and oncological efficiency of this laparoscopic approach for these lesions.

Methods

This is a monocenter study (2003–2013) describing technique and outcomes of laparoscopic liver resection for lesions adjacent to major vasculature: <2 cm from the portal vein (main trunk and first division), hepatic arteries or inferior vena cava.

Results

Thirty-seven patients underwent laparoscopic liver resection (LLR) for a lesion adjacent to major vasculature. Twenty-four (65 %) resections were for malignant disease and 92 % R0 resections. Conversion occurred in three patients (8 %). Mean operative time was 313 min (standard deviation (SD)±101) and intraoperative blood loss 400 ml (IQR 213-700). Clavien-Dindo complications >II occurred in two cases (5 %), with no mortality. Lesions at <1 cm were larger (7.2 cm (2.7–14) vs. 3 cm (2.5–5), p=0.03) and operation time was longer (344±94 vs. 262±92 min, p=0.01) than lesions at 1–2 cm from major vasculature.

Conclusions

Lesions <2 cm from major hepatic vasculature do not represent an absolute contraindication for LLR when performed by experienced laparoscopic liver surgeons in selected patients.

INTRODUCTION

Laparoscopic liver resection (LLR) for lesions adjacent (<2cm) to major vasculature, such as portal veins, hepatic arteries and the inferior vena cava (IVC), can be challenging. Many would question the safety and the oncological efficiency of such resections. In 2002, Gigot et al.[1] defined these lesions as contraindications for LLR. Six years later, the Louisville consensus considered that patients with similar lesions were not optimal candidates for a laparoscopic approach in most centres.[2]

Now, 5 years after Louisville, with growing experience in the field and the further development of laparoscopic techniques, a few surgeons have been persistently pushing boundaries, as long as safety was not compromised.

Evidence of feasible and safe implementation of LLR beyond the Louisville consensus boundaries is growing. LLR has been shown to be a viable option for lesions located in posterior segments of the liver (1, 7 and 8) when performed by surgeons with ample experience in open and laparoscopic liver surgery.[3–8] LLR for hepatocellular carcinoma (HCC) sized 5-10 cm was also found to be feasible and safe.[9] However, lesions close to major vasculature are still seen as contraindications for LLR by most surgeons. We previously explored lesions at <2cm cm from major vasculature, but they were deemed unsuitable for LLR.[10] The traditionally feared risks of LLR such as haemorrhage and poor visibility are magnified when transecting near major vasculature with potentially bigger consequences when something does go wrong. This may have discouraged surgeons to explore the possibilities of LLR for this specific indication.

As a result, few studies have been published on this particular subject and it remains unclear whether LLR is a suitable treatment option for these lesions. Therefore, further research on the feasibility, safety and oncological efficiency of LLR in the treatment of lesions adjacent to major vasculature is essential.

The aims of this study were to report on our experience and analyse our results in the laparoscopic management of lesions near major vasculature and contribute to further guidance on the safety, feasibility and oncological efficiency of such complex resections.

PATIENTS AND METHODS

Patients

Data from all 439 patients undergoing LLR for benign and malignant lesions in the

University Hospital Southampton NHS Foundation Trust between August 2003 and December 2013 were prospectively collected in a database. Prior to surgery, these patients were discussed in a multidisciplinary meeting with hepatobiliary and pancreatic surgeons, radiologists, gastroenterologists, medical oncologists and pathologists. Based on performance status, exact location of the tumour and co-morbidity, a decision was made regarding the surgical approach. An experienced abdominal radiologist retrospectively screened the database in order to identify patients eligible for inclusion based on their preoperative computed tomography (CT) scans. Included were patients over 18 years old with a lesion at <2cm from major vasculature, defined as the portal veins (main trunk and first left and right divisions), hepatic arteries, and IVC (Figure 1).

Data Collection

The following data were collected for analysis: indication for surgery, exact distance of lesion to the major vessel involved (measured from the preoperative CT scans by the abdominal radiologist, in cases where the lesion was at <2cm from more than one vessel, the shortest distance was analysed), type of surgery, operative time, blood loss (calculated by measuring the volume of blood in the suction bottles, after subtracting wash fluid, at the end of surgery with the addition of weighed swabs), conversion, total Pringle time, pathology (surgical margins, benign/malignant, size of the lesion), hospital and high dependency unit (HDU) stay, postoperative complications (defined according to the Clavien-Dindo classification system for postoperative complications), postoperative mortality (within 30 days from surgery) and disease-free and overall survival.

Surgical Technique

The surgical technique for LLR has been previously reported by our group.[11,12] Patients are placed in a supine position with the surgeon standing on the right of the patient for left-sided lesions and on the opposite side for right-sided lesions. For hemihepatectomies, the surgeon occasionally stands between the patient's legs. A 30-degree camera is inserted through a 12-mm peri-umbilical port. Four more ports (two 12-mm ports and two 5-mm ports) are inserted for optimal mobilization and transection of the liver. The first port is placed with an open procedure; the rest of the ports are inserted under direct vision.

A 5-mm nylon tape is slung around the portal triad with the ends passed through a 10–15-cm plastic tube and brought out alongside a lateral 5-mm port for intermittent application of the Pringle manoeuvre.

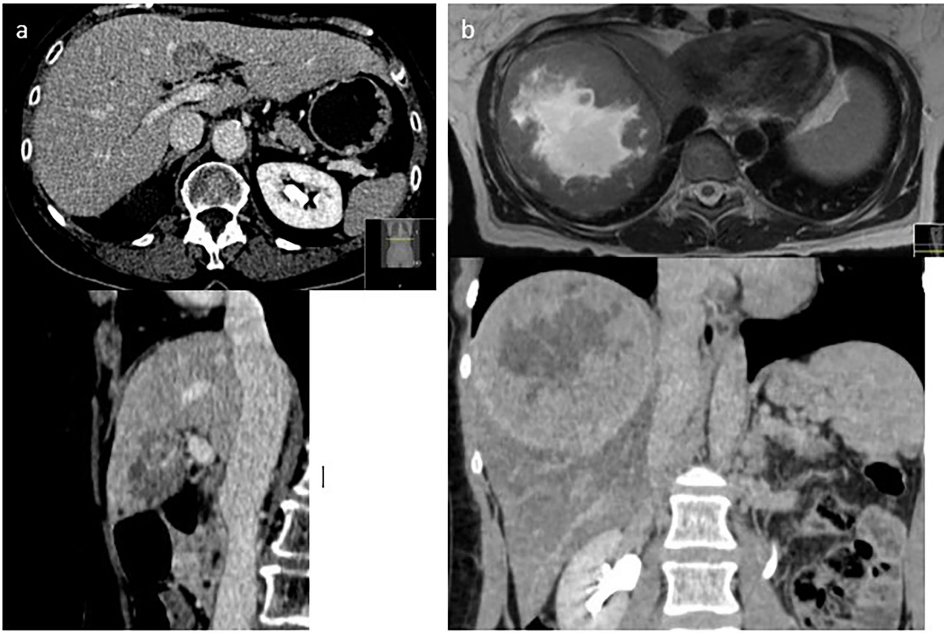

Figure 1 CT-scans. **a.** Axial and sagittal preoperative CT images of CRLM at 6 mm from PV bifurcation and 7 mm from hepatic artery bifurcation. **b.** Axial and coronal preoperative CT images of pancreatic acinar cell carcinoma liver metastasis at 3 mm from the IVC

After laparoscopic ultrasound, routinely used to locate the lesion(s), to assess their relation to major vasculature and to mark the tumour and resection margins, mobilization and transection of the liver is performed. Superficial parenchymal transection is achieved using Laparoscopic Operation by Torsional Ultrasound (LOTUSTM) (S.R.A Developments, Ashburton, Devon, UK). Deep parenchymal dissection is performed using the Cavitron Ultrasonic Surgical Aspirator (CUSA) (Valleylab, Boulder, CO, USA). This permits the surgeon to safely dissect close to the vessels identifying and controlling every small vessel or biliary duct, thus ensuring a safe dissection with the maximum possible resection margins. In our experience, this is not entirely possible with the use of vascular staplers and ultrasonic dissectors alone. Another important note should be reserved to vascular dissection and division. We find the use of the laparoscopic right-angle dissector with a blunt tip (Karl Storz Endoskope, Tuttlingen, Germany) very helpful in the dissection phase followed by slinging the vessels with rubber vessel loops. This permits a gentle pull on the vessel exposing it nicely to help in applying a Hem-o-Lock clip (Weck Closure Systems, Research Triangle Park, NC, USA) or a stapler around its entire circumference, as near as possible to the origin and as far as possible from the tumour.

Obviously, bleeding can occur despite careful dissection and preventive measures. This has to be promptly controlled to reduce blood loss but also to ensure a safe and efficient dissection. Traditional control with stitches is often needed, especially near major vasculature where application of clips and staples is not possible; hence, good laparoscopic suturing skills are extremely essential in such cases. Hemostatic products such as collagen or fibrin glue (Evicel; Johnson & Johnson Wound Management, Somerville, NJ, USA) are routinely used to the cut surface. Prior to completion of the operation, haemostasis is checked again under the restored central venous pressure and Valsalva manoeuvre. The specimen is removed in a plastic endoscopic bag (Endocatch; Ethicon Endo-Surgery, Cincinnati, OH, USA) from a Pfannenstiel incision.

Statistical Analysis

Data were analysed using IBM SPSS Statistics for Windows version 21.0 (SPSS Inc., Chicago, IL, USA). Continuous parametric variables were reported as mean±standard deviation (SD) and continuous non-parametric variables as median with interquartile range (IQR). For the analysis of continuous variables between groups, the independent-sample T test or the Mann-Whitney U test was used, depending on the distribution of variables. Categorical variables were reported as proportions and compared between groups using chi-square test or Fisher's exact test as appropriate. Recurrence-free and overall survival was measured from the day of the operation until the date of recurrence/death and was analysed using the Kaplan-Meier method. A two-tailed p value of <0.05 was considered significant.

RESULTS

Patient Characteristics

Between August 2003 and December 2013, 37 patients underwent LLR for a lesion adjacent to major vasculature as defined earlier. Included were 15 males and 22 females with a mean age of 62 years (range 24–83). Of all resections, 24 (65 %) were for malignant disease, of whom colorectal liver metastases (CRLM, n=14), cholangiocarcinoma (n=4) and HCC (n=2) were most frequently observed. Basic patient and tumour characteristics are noted in Table 1.

Table 1. Patient characteristics and tumour pathology

Patient and tumour characteristics	Overall n=37	<1 cm n=23	1-2 cm n=14	p value
Age (years)	62 (±16)	59 (±17)	66 (±15)	0.23
Gender (male)	15 (41%)	9 (39%)	6 (43%)	0.82
American Society of Anaesthesiologists Score (ASA)				0.36
1	13 (34%)	8 (35%)	5 (36%)	
2	21 (57%)	12 (52%)	9 (64%)	
3	3 (8%)	3 (13%)	0 (0%)	
Preoperative chemotherapy	12 (32%)	6 (26%)	6 (43%)	0.29
Pathology resected tumour (malignant)	24 (65%)	13 (57%)	11 (79%)	0.17
Pathology report				0.46
Colorectal liver metastases	14	6	8	
Cholangiocarcinoma	4	2	2	
Hepatocellular carcinoma	2	2	0	
Complex hepatic cysts	6	5	1	
Hepatocellular adenoma	3	2	1	
Focal nodular hyperplasia	1	1	0	
Others	7	5[a]	2[b]	

[a] Including metastatic acinar cell carcinoma, metastatic pancreatic adenocarcinoma, metastatic gastrointestinal stromal tumour, haemangioma, bile duct hamartoma
[b] Breast cancer liver metastases, benign oriental cholangiopathy

Operations and Involved Vasculature

Left (n=17) and right (n=16) hemihepatectomies were the most frequently performed operations, with lesions most often (71 %) adjacent to the portal veins. The mean distance from the tumour to the vessel's margin was 0.79 cm (±0.55). Descriptions of the operations performed and adjacent vasculature are shown in Table 2.

Intraoperative Results and Postoperative Outcome

The mean operation time was 313 min (±101) and intraoperative blood loss 400 ml (213–700). Conversion to an open procedure was performed in three cases (8 %), and the median tumour size was 4.5 cm (2.5–11). Reasons for conversion included perceived difficulty defining hilar structures in one case and insufficient progress and blood loss approaching 1000 ml in another case, and in the third case, intraoperative assessment revealed the need for an extended (including pancreatic) resection. In 26 cases (70 %),

Table 2. Operations and involved major vasculature

Operations and involved major vasculature	Overall n=37	<1 cm n=23	1-2 cm n=14	p value
Operations				0.51
Left hemihepatectomy (extended)	12 (1)	7 (0)	5 (1)	
Right hemihepatectomy (extended)	10 (2)	6 (2)	4	
Left hemihepatectomy + seg 1 resection	2	1	1	
Right hemihepatectomy + seg 1 resection	1	0	1	
Extended right hemihepatectomy + seg 1 + wedge	1	1	0	
Extended right hemihepatectomy + wedge	1	0	1	
Extended right hemihepatectomy + IVC wedge	1	1	0	
Modified left hepatectomy	2	2	0	
Seg 1 + Left lateral sectionectomy + wedge	2	1	1	
Seg 7/8 resection	1	1	0	
Seg 1 resection	1	1	0	
Major vasculature involved				0.18
Portal veins	26 (70%)	17 (74%)	9 (64%)	
IVC	19 (51%)	14 (61%)	5 (36%)	
Hepatic artery	1 (3%)	1 (4%)	0	
Distance to major vasculature (cm)	0.79 (±0.55)	0.44 (±0.29)	1.36 (±0.36)	<0.001

IVC inferior vena cava

a Pringle manoeuvre was used, with a mean duration of 34 min (±20). Patients stayed a median of 1 day (1–1) in the HDU with a total hospital stay of 5 days (4–6). Major complications (ClavienDindo >II) occurred in only two patients (5 %). Table 3 shows a detailed description of the intra- and postoperative results.

Survival

Thirty day postoperative mortality was 0 %. Mean overall survival was 66.4 months (95 % confidence interval (CI) 57.7–75.2). Four (11 %) patients died of recurrent disease during follow-up. Comparison between the <1- and 1-2 cm groups showed no significant difference in mean overall survival (60.8 (95 % CI 52.7–69) vs. 60.4 (95 % CI 41.2–79.6) months, p=0.47). For CRLM, the mean overall survival was 34 months (95 % CI 27–40).

Resection Margins

Complete (R0) resection was accomplished in 92 % of cases, three patients with CRLM had incomplete (R1) resections. For CRLM only, an R0 resection rate of 79 % was reached.

Table 3. Intraoperative results and postoperative outcome

Perioperative results	Overall n=37	<1 cm n=23	1-2cm n=14	p value
Operation time (mins)	313 (±101)	344 (±94)	262 (±92)	0.01
Intraoperative blood loss (ml)	400 (213-700)	475 (300-700)	300 (119-725)	0.14
Conversion	3 (8%)	3 (13%)	0 (0%)	0.17
Pringle				
Applied	26 (70%)	14 (61%)	12 (86%)	0.11
Duration (mins)	34 (±20)	31 (±14)	37 (±27)	0.52
Tumour size (cm)	4.5 (2.5-11)	7.2 (2.7-14)	3.0 (2.5-5.0)	0.03
Resection margins (R0)	34 (92%)	21 (91%)	13 (93%)	0.87
Postoperative hospital stay				
HDU (days)	1 (1-1)	1 (1-2)	1 (1-1)	0.09
Overall (days)	5 (4-6)	5 (4-7)	4 (4-5)	0.06
Postoperative complications	2 (5%)	1[a] (4%)	1[b] (7%)	0.69

HDU High Dependency Unit
[a] Pneumothorax managed with drain
[b] Pleural effusion managed with drain

The R1 resections were all in patients undergoing extended right hemihepatectomy with an additional wedge excision from the IVC in one case, additional wedge from segment 2/3 in one case and additional segment 1 resection and wedge from segment 2 in the last case. In all cases, the IVC was involved with distances from tumour to vessel of 0.1, 1.2 and 0.9 cm, respectively. All cases had multiple CRLM nodules excised, with the nodule close to the vessel being the one that was incompletely excised. For a more detailed description of these three patients, see Table 4. R0 resection rate did not differ between the <1cm- and 1-2 cm group (91 vs. 93 %, p=0.87).

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Recurrence

During follow-up, recurrence was detected in 11 of 37 patients (30 %, 6 CRLM, 3 cholangiocarcinoma, 1 acinar cell carcinoma, 1 metastatic pancreatic adenocarcinoma). The location of recurrence was intrahepatic in five patients, extrahepatic in two patients and both intra- and extrahepatic in four patients. Of the patients with intrahepatic recurrence, one had recurrence at the resection margin (one CRLM patient). This patient, also described under resection margins, had undergone extended right

Table 4. R1 resections

Patient	Vessel involved	Distance from tumour to vessel (cm)	Location tumour close to vessel	Operation	Pathology	Recurrence
Male, 78	IVC	0.1	Seg 6/7	Lap extended right hemihepatectomy + wedge IVC	5 CRLM nodules, 1 incompletely excised	New intrahepatic
Male, 68	IVC	0.9	Seg 1	Lap extended right hemihepatectomy + seg 1 + wedge seg 2	Multiple (5+) CRLM nodules, 1 incompletely excised	New intrahepatic Extrahepatic: lung
Male, 63	IVC	1.2	Seg 8/4a	Lap extended right hemihepatectomy + wedge seg 2/3	4 CRLM nodules, 1 incompletely excised	Local recurrence at resection margin Extrahepatic: lung

IVC inferior vena cava, *CRLM* colorectal liver metastases

hemihepatectomy plus a wedge from segment 2/3. Pathology showed R1 resection of a CRLM nodule that lay 1.2 cm from the IVC (Table 4). Solitary extrahepatic recurrence was found in the left 11th rib and right posterior iliac crest in one cholangiocarcinoma patient and in perihepatic lymph nodes in one metastatic acinar cell carcinoma patient. Sites of extrahepatic recurrence in patients with concurrent intrahepatic recurrence were the lung (three CRLM patients), perihepatic lymph nodes (two CRLM patients) and the peritoneum (one CRLM patient). Recurrence in the R1-resected patients is shown in Table 4. The mean recurrence-free survival for CRLM was 13 months (95 % CI 8–18). Patients with R0 resections had a mean recurrence-free survival of 16 months (95 % CI 9–22). There was no significant difference in recurrence-free survival between the two groups (46.5 (95 % CI 34.1–58.8) vs. 44.0 (95 % CI 20.3–67.6) months, p=0.69).

Subgroup Analyses

Twenty-three resections for lesions at <1cm from the vessel's margin were compared to 14 resections for lesions at 1–2 cm from the vessel's margin. Baseline characteristics and tumour pathology were comparable between these groups except tumours were larger in the <1cm group (7.2 (2.7–14) vs. 3 (2.5–5) cm, p=0.03). No significant differences in perioperative results were observed, except for a longer operation time in the <1cm group (344 (±94) vs. 262 (±92) min, p=0.01). Tables 1, 2 and 3 show the results compared between the groups.

DISCUSSION

Advancing experience with LLR has contributed to the expanding implementation of this strategy for various indications. Well-known risks of LLR such as haemorrhage and poor visibility, however, can be even greater when resecting lesions near major vasculature and therefore many surgeons will still consider these lesions as unsuitable candidates for LLR. Having said that, there are no specific data on open resections for such critically located lesions. Nonetheless, many would agree that the lesions defined in this study can represent a great challenge even in open surgery.

This is the first Western cohort of patients undergoing LLR for lesions adjacent to major vasculature so far. The study demonstrates the feasibility and safety of the laparoscopic approach in patients with lesions near the major vasculature. We had an acceptable median intraoperative blood loss of 400 ml with no mortality and a major complication rate of 5 %. The mean operative time of 313 min and conversion rate of 8 %, however, reflect the complexity and the challenge associated with this type of procedures.

Only one previous study has reported outcomes of LLR for lesions similar to the ones investigated in this study.[13] This study included a smaller number of patients and also a different type of patients in terms of type of disease. In addition, the definition used for major vasculature also included the hepatic veins. Yoon et al. described a feasible and safe surgical technique. Thirteen patients underwent LLR for lesions within 1 cm of major vascular structures such as the liver hilum, hepatic veins and IVC with similar operation time (381.5 min).

The most remarkable difference when compared to our <1cm group concerned the resection margins. Five of 13 patients (38.5 %) had 0 mm resection margins whereas we only found 2 in 23 patients (9 %). However, these resection margins did not influence recurrence rate in a similar way, as not one of five R1 resections recurred, while both resections in our study did. A possible explanation for this finding is the difference in pathology of the resected lesions. The five R1 resections described by Yoon et al. were four HCC patients and one FNH patient, compared to two CRLM patients in our study. As Yoon et al. discussed, HCC tumours are frequently associated with a thick fibrous capsule which allows resection along the capsular margin without exposing the cancer cells to the capsular surface and that way preserving a complete curative resection.[14–16]

Our overall R1 resection rate of 9 % is slightly higher than our previously reported data for CRLMs (4 %),[10,17] but R1 resection rate for CRLM only was much higher (21 %). Whether this is approach related or is to be expected for this type of lesions is difficult

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to decide, especially in the absence of data for similar open resections as mentioned before. Although our overall results are very comparable to the rates found in other studies looking at resection margin outcomes of minor and major LLR (82–100 %),[18] also including multiple pathologies in their analyses, we still believe that more should be done to improve those results and that surgeons should always strive to achieve clear margins. As only 14 CRLM resections were performed so closely to the major vessels, these resections rates could very well be part of the learning curve of this technically very challenging procedure. One could advocate to only start resecting CRLM adjacent to the major vessels once proficiency with the technique has been acquired through the resection of benign or other malignant pathologies with similar close relations with the major vessels.

On critical analysis of our cases with R1 resection, it is interesting to note that all three patients had multiple liver lesions, in close relation with the IVC, requiring major, lengthy and multiple resections. In one case, a major liver resection was performed with the need of an additional IVC wedge resection for a lesion at 1 mm from the IVC's margin. However, on pathological examination of the specimen, the margin was still reported as positive.

Interestingly though, the patient developed intrahepatic but not local recurrence. This may suggest the need for special attention and careful selection of patients with multiple lesions especially when the IVC is the vessel involved as this would be dealt with at the end of a lengthy and tiring procedure. Whether better results could be achieved by adopting an open approach from the beginning needs further evaluation. However, we can suggest that lesions at less than 1 cm from the IVC in patients requiring multiple liver resections are not the best candidates for the laparoscopic approach. Interestingly, lesions at <1cm from the vascular structures were larger (7.2 (2.7–14) vs. 3 (2.5–5) cm, p=0.03) and, as expected, resections for these lesions were associated with a higher amount of intraoperative blood loss when compared to resections for lesions 1–2 cm from major vasculature, even though the difference did not reach statistical significance (475 vs. 300 ml, p=0.14). Together with the significantly longer duration of these operations compared to operations on lesions further away from the vessel's margin (344 vs. 262 min, p=0.01) and the higher conversion rate (13 vs 0 %, p=0.17), this confirms that resecting closer to major vasculature is technically more challenging. Another comparison contributing to this statement is the comparison of this cohort of 37 patients to the full cohort of 439 LLRs carried out in the same time period. We found similar conversion and postoperative complication rates, but a significantly longer operation time (313±101 vs. 180±119 min, p= <0.001) and higher blood loss (400 (213–700) vs. 200 (50–500) ml, p= 0.02) for resections in the <2cm group. Despite these results clearly demonstrating the technical difficulty of resecting close to the major vessels, these outcomes are still comparable with the results considered feasible and safe in recent systematic reviews[17–20] and internal historical cohorts[10,12,21,22] and therefore do not contraindicate the introduction of this technique.

Although our study confirms the feasibility and safety of laparoscopic liver resections for lesions adjacent to major vasculature, it does in no way advocate for a wide and reckless adoption of this particular indication. It is important to note that the described technique is extremely advanced and requires a highly developed set of both laparoscopic and open operative skills. In our centre, 62 major and minor LLRs were performed before the first resection of a lesion at <2cm and 91 resections were performed before the first resection of a lesion at <1cm from major vasculature. Our two senior laparoscopic surgeons had at least 3 years of experience in laparoscopic major and minor liver resections before approaching lesions in such a critical location. The size and heterogeneity of the study population are the main limitations of this study. However, the encouraging results of this study do motivate further research into this procedure, possibly with bigger patient numbers and standardized indications for surgery, in order to validate the added value of LLR over open surgery for liver lesions adjacent to major vasculature.

In conclusion, this study shows that lesions adjacent to major hepatic vasculature do not have to be contraindications to LLR as long as ample experience in laparoscopic liver surgery, meticulous dissection techniques and careful patient selection are upheld as essential pillars in ensuring patient safety and oncological efficiency.

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CHAPTER 11

Minimally invasive surgery for perihilar cholangiocarcinoma: a systematic review

Submitted for publication

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ABSTRACT

Background

Minimally invasive surgery (MIS) is quickly becoming mainstream in hepato-pancreato-biliary surgery because of presumed advantages. Surgery for perihilar cholangiocarcinoma (PHC) is highly demanding which may hamper the feasibility and safety of MIS in this setting. This study aimed to systematically review the existing literature on MIS for PHC.

Methods

A systematic literature review was performed according to the PRISMA statement. The PubMed and EMBASE databases were searched and all studies describing MIS in patients with PHC were included. Risk of bias was assessed and operative outcomes were reported.

Results

Overall, 21 studies reporting on a total of 142 MIS procedures for PHC were included. These included 82 laparoscopic, 59 robot-assisted and 1 hybrid procedure. Risk of bias was deemed substantial. Pooled conversion rate was 7/142 (4.9%), pooled morbidity 30/126 (23.8%), and pooled mortality rate 4/126 (3.2%). The only comparative study, comparing 10 robot-assisted procedures to 32 open procedures, reported a significant increased operative time and higher morbidity rate with MIS.

Conclusion

The available evidence on MIS for PHC is limited and generally of poor quality. This systematic review shows that the implementation of MIS for patients with PHC is still in its infancy.

INTRODUCTION

Perihilar cholangiocarcinoma (PHC) is an uncommon type of cancer with a bad prognosis. Surgical resection, usually entailing hilar resection with extended hepatectomy, is the only potentially curative treatment. These procedures are considered highly challenging due to the tumors' proximity to the portal vein and hepatic arter.[1] Morbidity can rise up to 27.5 – 51.3% (Clavien-Dindo ≥ III) and mortality is high with 10.7 – 14.3%.[2-4] The efficiency of surgical treatment of PHC has progressed in recent years with the surgical strategy changing from limited bile duct resections to resections including hepatectomy at the end of the 20th century.[5,6] This aggressive approach led to increased rates of R0 resections and five-year survival.[6,7] However, post-operative morbidity and mortality remain an issue.

Minimally invasive surgery (MIS) is increasingly being implementation in all types of hepato-pancreato-biliary resections such as distal pancreatectomy and hepatectomy.[8-10] Promising results, inherent to a minimally invasive approach, such as faster functional recovery, less intra-operative blood loss, and less post-operative complications are frequently reported.[9] In liver surgery, laparoscopic and robot-assisted procedures have been increasingly been used during the last decade and show improved postoperative outcomes without compromising long-term oncological outcomes.[10-12] The extremely challenging nature of the procedure, the technical skills required, and the fear of oncological inefficiency have so far limited the adoption of MIS for PHC. Nevertheless, outcome of MIS for PHC has been reported.[13] A systematic review on MIS in patients with PHC is lacking.

Objective

This systematic review aims to appraise the current literature on implementation and outcome of MIS for the treatment of PHC.

METHODS

The protocol of this study was registered in PROSPERO under number CRD42017074398. This systematic review is created in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement. We aimed to identify studies reporting on MIS in patients with PHC (i.e. Klatskin tumor). All study types in which a

total laparoscopic (including hand-assisted), robot-assisted and/or hybrid approach was described, were eligible for inclusion. Studies without original data (e.g. reviews) and studies published in languages other than English were excluded. In case multiple eligible studies were published by the same group, the one with the highest number of cases was selected. To identify relevant studies, a search was conducted in PubMed and EMBASE on September 5th 2017. The search strategy was checked and approved by a clinical librarian. We used a combination of the following MeSH terms, keywords and search terms:
("Laparoscopy"[Mesh] OR laparoscop* [tiab] OR "Hand-Assisted Laparoscopy"[Mesh] OR Hand Assisted Laparoscopy [tiab] OR "Robotic Surgical Procedures"[Mesh] OR robot* [tiab] OR "Minimally Invasive Surgical Procedures"[Mesh] OR Minimally Invasive OR hybrid [tiab]) AND ("Cholangiocarcinoma"[Mesh] OR cholangiocarcinoma* [tiab] OR Klatskin[tiab] OR "Bile Duct Neoplasms"[Mesh] OR Bile Duct cancer*[tiab] OR Bile Duct neoplasm*[tiab]).

Data extraction and outcome measures

Two independent researchers (MJvdP and AL) screened abstracts and full texts for eligibility based on the in- and exclusion criteria. Any discrepancies were resolved by a third reviewer (MZ). Data were extracted using an extraction form and comprised the following variables: article details (author, title, demographics, year of publication, study type), amount of patients, preoperative characteristics (gender, age, type of Klatskin tumor according to the Bismuth-Corlette classification, symptoms, radiologic features), operative specifics (type of operation, technique, operative time, blood loss, conversion), and postoperative outcomes (morbidity, mortality, hospital stay, resection margins, hospital costs, recurrence and disease free survival).
Two researchers (MJvdP and LCF) assessed the individual risk of bias on study level using the Newcastle-Ottawa Scale for Cohort studies and the Joanna Briggs Institute (JBI) Critical Appraisal Tools for Case Series and Case Reports. Discrepancies were resolved in a consensus meeting. Results from the risk of bias assessments for case series and case report is displayed in separate figures. Overall, risk of bias across studies is evaluated by assessing the selection bias, detection bias, attrition bias, and reporting bias.

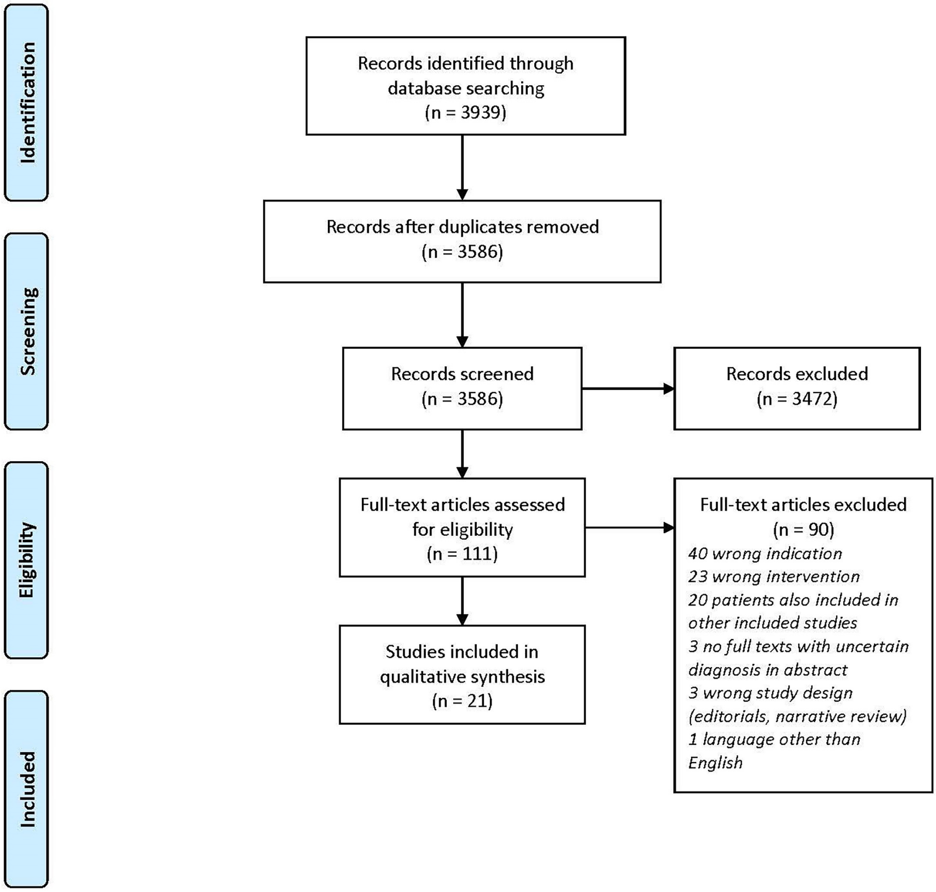

Figure 1. A flowchart of included studies.

RESULTS

Study selection

The initial search yielded 3939 studies. After removal of duplicates, a total of 3586 studies were screened for eligibility. This lead to the screening of 111 full studies, which resulted in the inclusion of 21 studies.[14-34] Figure 1 displays the PRISMA flow diagram of study selection.

Risk of bias

The majority of authors did not describe why they had subjected individual patients to minimally invasive procedures, causing a high risk of selection bias. None of the studies described that post-operative outcomes were assessed by an independent objective examiner. Also, a substantial proportion of the studies provided incomplete outcome data. These findings are highly suggestive for risk of detection and attrition bias. The inclusion of 11 case reports with no post-operative deaths and the lack of consecutive inclusion in case series, suggests a publication bias.

Study characteristics

The 21 eligible studies included one retrospective comparative study, 6 case series, 5 case reports, 7 video abstracts, and 2 abstracts of posters. All studies had a retrospective design and the first study was published in 2010. All study characteristics of included studies are listed in Table 1. The only comparative study conducted by Xu *et al.*, compared 10 robot-assisted procedures to 32 open procedures in patients with PHC. The largest series contributing to this systematic review consists of 44 patients.[32] As shown in Table 1, there were 14 studies (including 82 patients) that reported an accurate follow-up of more than 90 days with a maximum follow up of 60 months.[14-20,22-24,27,30,33,34]. 6 studies (11 patients) reported no follow-up after discharge.[16,25,26,28,29,31] The follow-up period was unclear in one study (44 patients).[32]

Critical appraisal

The quality of the only comparative study[14] was assessed as poor on the Newcastle Ottawa Scale, due to the lack of comparability and absence of controlling for confounders. Results of the Risk of Bias Assessment per study are displayed separately for case series and case reports in Figure 2 and 3, respectively.

Patient and procedure characteristics

A total of 142 patients undergoing minimally invasive procedures for PHC were identified. Among 15 studies reporting on gender of their population, there were 59 men (69%) and 26 (31%) women. Reported age of included patients ranged between 25 and 90 years, with an average of 61.2 years. The most frequently reported presenting symptom was jaundice. Thirteen studies described Bismuth-Corlette stage (BC) of their study population, including 29, 32, 12, 6, and 8 patients with type I, type II, type IIIa, type IIIb, and type IV tumors, respectively. Detailed patient demographics per study are listed in Table 1.

Table 1. Study characteristics

First author	Year	Country	Study type	Approach	No. of pts	Patients characteristics	Reported FU (months)
Xu, Y. et al.(14)	2016	China	Comparative study	Robotic	10 vs. 32	MIS: 8 men/2 women, median 54y, BC II (1), IIIa (4), BC IIIb (1), IV(4)	max 60
Chen et al.(15)	2013	China	Case series	Laparoscopic	36	27 men, 9 women, mean 66y (45-85), BC I (17), BC II (19).	4 pt LFU, 32 pt> 6
Yu et al. (16)	2011	China	Case series	Laparoscopic	14	8 men, 6 women, 55.7y (51-57), imaging BC I (8), II (6).	20 (7-33)
Li et al. (17)	2017	China	Case series	Laparoscopic	9	6 men, 3 women, median 62.7y (50-74), BC I (1), II (3), IIIb (2), IV (3), no vascular involvement	17 (6-42) 2 pt LFU
Lee et al. (18)	2015	Korea	Case series	Laparoscopic	5	5 men, median 63y (43-76), BC I (1), II (1), IIIa (1), IIIb (2)	8 (5-9)
Gumbs et al.(19)	2013	USA/Chile/ France	Case series	Laparoscopic	5	Mean 73y (66-79)	11 (3-18)
Quijano et al.(20)	2016	China	Case series	Robotic	1	-	3
Yu et al .(21)	2013	China	Case report	Laparoscopic	2	2 women, 54+60y, BC I	6-9 days
Puntambekar et al. (22)	2016	India	Case report	Laparoscopic	1	25y man, BC II, no vascular involvement	6
Zhu et al. (23)	2014	China	Case report	Robotic	1	43y man, BC IIIa	12
Machado et al. (34)	2012	Brazil	Case report	Laparoscopic	1	43y woman, BC IIIb	18
Giulianotti et al. (24)	2010	USA	Case report	Robotic	1	66y man, PVE	8
Zhang et al. (25)	2017	China	Video abstract	Laparoscopic	1	BC IIIa, no vascular involvement	11 days
Weaver et al.(26)	2010	USA	Video abstract	Laparoscopic	3	BC IIIa	10-14 days
Efanov et al.(27)	2015	Russia	Video abstract	Robotic	1	65y man, BC II, CHA replaced by and RHA adhered to tumor.	5
Nakahira et al. (28)	2015	Japan	Video abstract	Laparoscopic	3	-	19 days (16-23)
Chen et al. (29)	2017	Taiwan	Video abstract	Hybrid	1	BC IV, 90y woman, no vascular involvement	9 days
Machado et al. (30)	2014	Brazil	Video abstract	Laparoscopic	1	58y woman, BC IIIa	16
Ji et al. (31)	2011	China	Video abstract	Robotic	1	54y man	12 days
Zhou et al. (32)	2012	China	Abstract poster	Robotic	44	-	unclear
Xu, J et al.(33)	2016	China	Abstract poster	Laparoscopic	1	68y male, BC IIIa, no vascular involvement	14

Abbreviations: FU Follow up, ***LFU*** lost to follow up, ***BC*** Bismuth-Corlette.

Table 2. Operative characteristics and outcomes.

Author, year	No. of procedures	Type of resection	Operation time (min)	Blood loss (ml)	Hospital stay (days)	Conversion	Pathology	Morbidity	Mortality
Xu, Y[14]	10 vs. 32	Robotic-assisted LHH (4), RHH (4), ERHH (1) + EBDx, LNx, RYHJ vs. Open traditional approach	703 ± 62 vs. 475 ± 121	1360 ± 809 vs. 1014 ± 811	16 (9-58) vs. 14 (4-54)	0/10	3 R1, 5 R0 vs. unknown	9/10, > CD gr III 3/10 Bile leakage 4, pleural/ peritoneal effusion 2, PHLF 1, PV thrombosis 1, hemorrhage 1, DVT 1 ***vs.*** 5/32, > CD gr III 2/32, bile leakage	90d 10% vs 6.3%
Zhou[32]	44	23 tumor resection + Robotic LHH (3), GD-bridged biliary reconstruction (3), RYHJ (16), biliary reconstruction (1) 21 palliative biliary external drainage (9 external biliary drainage, 12 T-tube biliary drainage)	-	-	-	-	-	8/44 (18.12%)	2.27%
Chen[15]	36	EBD*x*, CL*x*, Total laparoscopic RYCJ (End-to-side CJS)	205.3 ± 23.9	101.1 ± 13.6	5.9 ± 2.1	0/36	-	Bile leakage 1/36	0%
Yu[16]	14	7 Lap EBD*x*, LN*x*, RYCJ 5 Lap part hepatectomy (segm I, IV or V), HJ. 1 lap EBD*x* + external biliary drainage 1 combined partial liver resection + HJ	305 (200-1000)	386 (200-1000)	BC I: 9 (6-22), BC II: 19 (9-25)	0/14	7 R0 3 R0, 2 R1 R2 R2	BL 1/7 (14.3%) BL 3/5 (60%) 1/2 (50%)	90d 0%
Li[17]	9	Lap 2 CLx, 2 LHH, RYHJ (2 laparoscopic, 4 under direct visual observation, 3 hand-assisted)	438 (330-540)	503 (150-850)	15.7 (10-27)	3/9 (33%)	R0 9/9	2 Biliary fistula, 2 peritoneal effusion (all conservative)	30d 11%, 90d 22%
Lee[18]	5	Total laparoscopic hilar resection + bilienteric anastomosis (1), + laparoscopic-assisted HJ, 3 laparoscopic EHH left (2), right (1).	610 (410-665)	650 (450-1300)	12 (9-21)	0/5	1 R1, 4 R0	1 Bile leakage (percutaneous drain)	90d 0%
Gumbs[19]	5	Lap EBD*x* (3) + RHH (1), LHH (1), RY-HJ or RY-CJ	-	240 (0-400)	15 (11-21)	1/5 (20%)	1 R1, 4 R0	0 Bile leakage	90d 0%
Quijano[20]	1	Robotic LHH, hilar LN*x*, right side biliary resection, HJ	510	1000	16	1/1	R0	60day: Intra-abdominal fluid collection, CD II	60d 0%

Table 2. Continued

Author, year	No. of procedures	Type of resection	Operation time (min)	Blood loss (ml)	Hospital stay (days)	Conversion	Pathology	Morbidity	Mortality
Yu[21]	2	Single-incision lap segmental BD*x*, LN*x*, RYCJ, entero-enteric anastomosis	300, 350	350, 400	6, 9	0/2	R0	1/2 Bile leakage	No FU after discharge
Puntambekar[22]	1	Lap EBDx, RYHJ	240	150	6	0/1	R0	none	90d 0%
Zhu[23]	1	Staged procedure 1) Robotic drainage, dissection of right hepatic vessels, right-hepatic vascular control device 2) RHH	-	700	14	0/1	R0	none	DFS 12 months
Machado[34]	1	Lap EBD*x*, LHH, LN*x*, video-assisted bilioenteric reconstruction	300	-	7	0/1	R0	0	DFS 18 months
Giulianotti[24]	1	Robotic ERHH with left RYHJ	540	800	11	1/1	R0	None	DFS 8 months
Zhang[25]	1	Pure lap ERHH, LN*x* and left HJ	590	300	11	0/1	R0, 2 cm	none	No FU after discharge
Weaver[26]	3	Lap ERHH (3), LN*x*, RYHJ	-	-	3 or 4	0/3	R0	-	No FU after discharge
Efanov[27]	1	Robot-assisted LHH, EBD*x*, LN*x*, HJ	960	300	30	1/1	R0	Bile leakage (conservative)	DFS 5 months
Nakahira[28]	3	Lap LN*x*, ERHH, end-to-side endoscopic HJ	867 (range 853-1010)	100 (43-400)	19 (16-23)	0/3	-	-	'Post-operative' 0%, no FU
Chen[29]	1	Lap LHH, regional LN*x* and laparoscopic-robotic RYHJ	465	150	9	0	cis, R0	None	No FU after discharge
Machado[30]	1	Totally lap RHH, LN*x*, RYHJ	400	400	10	0/1	R0	none	DFS 16 months
Ji[31]	1	Robotic-assisted laparoscopic LHH, RYHJ	600	600	12	0/1	R0	Bile leakage (conservative)	No FU after discharge
Xu, J[33]	1	Laparoscopic RHH, hilar LN*x*, RYHJ	420	400	8	0/1	R0	none	DFS 14 months

Abbreviations: LHH left hemihepatectomy**, RHH** right hemihepatectomy**, ERHH** extended right hemihepatectomy**, ELHH** extended left hemihepatectomy**, HJ** hepaticojejunostomy, **CJ** choledochojejunostomy**, RY** Roux-en-Y**, CL** caudate lobe**, (E)BD** (external) bile duct**,** ***x*** resection**, LN*x*** lymphadenectomy**, lap** laparoscopic, **BL** bile leakage**, PHLF** post hepatectomy liver failure**, PV** portal vein**, CD** Clavien-Dindo**, FU** follow-up**, LFU** lost to follow up, **DFS** disease free survival, **DVT** deep venous thrombosis of lower extremities, **CHA** common hepatic artery, **RHA** right hepatic artery.

11

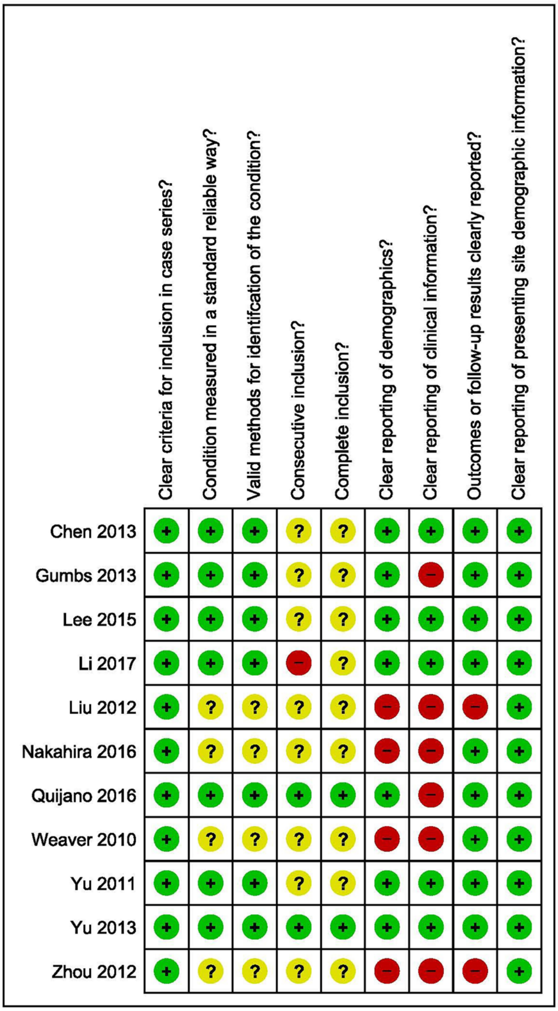

Figure 2. Risk of bias case series (JBI)

The 142 included procedures contained 82 laparoscopic, 59 robot-assisted, and 1 hybrid procedure(s). The first minimally invasive procedure for PHC was described by Chen *et al.*[15], performed in 2000. The da Vinci® Robotic Surgical System was used for the majority of robot-assisted procedures. External bile duct resection only was performed in 63 cases. Additionally, this procedure was combined with a total of 35 major hepatectomies (15 left hemihepatectomies, 8 right hemihepatectomies, 10

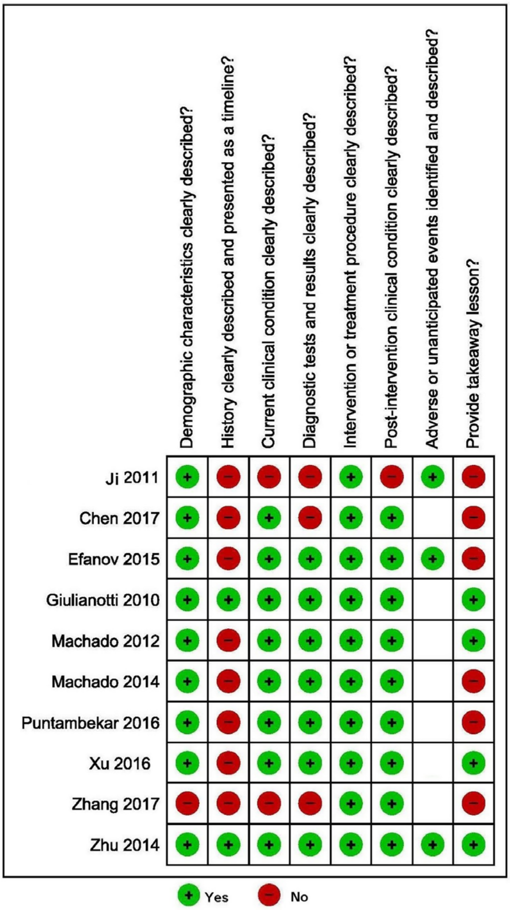

Figure 3. Risk of bias case reports (JBI)

extended right hemihepatectomies, and 2 extended left hemihepatectomies). In the remaining 44 patients, the external bile duct resection was combined with caudate lobe resection or partial hepatectomy.

Operative outcomes

Due to high heterogeneity across studies and differences in population and procedures, the operative time, hospital stay, and blood loss varied widely. Generally, operative time of robotic procedures was longer compared to laparoscopic procedures. Across

all included procedures, blood loss ranged between 43-2169 ml and there was a range in operative time between 205-1010 minutes, resulting in an overall average of 381 minutes and 398 ml blood loss. Overall, the conversion rate to open surgery was 4.9% (7/142). The shortest reported hospital stay was 3 days, while the longest post-operative admission was reported to be 58 days. The average hospital stay across all studies was 10.8 days. Xu *et al.*[14] reported that compared to open surgery the robotic procedures showed a longer operative time and hospital stay, and more blood loss (703 vs 475 min, 16 vs. 14 days, 1360 vs 1014 ml, respectively). Differences is hospital costs were only described by Xu *et al.,* showing significantly higher costs for the robotic approach compared to the open approach (27,427 ± 21,316 versus 15,282 ± 5957 dollar, respectively).
The pooled postoperative morbidity rate was 30/126 (23.8%) (See Table 2). The follow up duration was unclear in one included study conducted by Zhou *et al.*. However, their reported morbidity of 8/44 (18.2%) and mortality of 1/44 (2.7%)[32] was included in the pooled morbidity and mortality because data on postoperative outcome was scarce. The most frequently reported complication was bile leakage; overall 15 times described. Additionally, one post-hepatectomy liver failure, 4 peritoneal/pleural effusions, two thromboses (portal vein and lower extremities), one hemorrhage, and one intra-abdominal fluid collection were described. 90-day mortality could be calculated with data from 13 studies and ranged from 0-22%. Overall, 90-day mortality rate was 4/126 (3.2%). The only comparative study showed a significant difference in morbidity between the open and robotic approach in favor of the open approach: 9/10 (90%) patients undergoing robotic surgery experienced complications compared to 16/32 (50%) in the group undergoing open surgery. Mortality did not differ significantly between open (6.3%) and robotic surgery (10%).[14] Morbidity and mortality per study are listed in Table 2. Resection margins were reported in 57 cases, of which 46 R0-resection (79.3%), 7 R1-resection, and 2 R2-resections.

DISCUSSION

In this first systematic review on MIS in patients with PHC, we found that this field is still in its infancy. A total of 142 laparoscopic and robot-assisted procedures in patients with PHC were reported. Case series and case reports included in this study show that laparoscopic and robotic external bile duct resection combined with (hemi)hepatectomy is technically feasible in highly selected patients with PHC in experienced hands, but results from the only comparative study that was identified, appear to be in favor of the open approach.

The only comparative study, by Xu *et al.,* included in this systematic review showed that MIS is inferior to the open approach in patients with PHC in terms of operative time, blood loss, morbidity and mortality.[14] Clearly, a learning curve effect cannot be excluded. All other included studies were non-comparative and small, retrospective case series or case reports. This introduces a high risk of selection and publication bias. For example, combining results from all included case reports and case series showed a conversion rate of 4.9% (7/142). Nevertheless, in laparoscopic major liver resection, literature shows a range of conversion rate between 9 and 42%[35] and even in laparoscopic cholecystectomy the conversion rate remains between 5 and 10%.[36] The conversion rate of 4.9% seems thus extremely low. Furthermore, the total of 4 deaths and 30 complications among 126 patients, suggests an overall 90 day mortality of 3.2% and a postoperative morbidity rate of 23.8%. Mortality and morbidity of open surgery in patients with PCH is infamously high and reported to be 10.7-14.3 and 27.5-51.3%, respectively.[2,3] Looking at duration of hospitalization, the average hospital stay for patients undergoing open surgery for PHC varies between 16[37] and 23 days[38]. Comparing this with the average hospital stay for MIS in this review of 10.8 days, it may appear that MIS results in a shorter hospital stay. These comparisons with literature suggest a benefit of MIS compared to open surgery, but should be interpreted with extreme caution. These preliminary results may not be truly representative of current practice and are very likely to be influenced by strict patient selection and may represent only the favorable outcomes. Furthermore, all included studies derived from high volume HPB units with surgeons experienced in minimally invasive HPB surgery. Therefore, results cannot be widely reproduced and should limit the use of MIS for this specific patient population to only those experienced centers.

R0 resection was achieved in almost 80% of patients. A large series consisting of 331 open resections of PHC shows that only in 59% of the cases R0 resection could be achieved.[39] This most likely confirms the presence of selection bias. On the other hand, the previously described meta-analysis on laparoscopic hepatectomies showed no significant differences in resection margins either. Due to a lack of long-term follow up, the effect of MIS on oncological outcomes remains uncertain.

One of the major limitations of this study was the above described substantial risk of bias. Because of this significant risk of selection and publication bias, results presented in this review based on these case series and case reports have a potential bias towards a good result. Also, all studies included in this systematic review were retrospective, small and generally of poor quality. Another limitation was the high heterogeneity among patient cohort and procedures.

This systematic review identified preliminary results from low quality studies from highly experienced centers on MIS in PHC. It remains to be seen if the inherent benefits of MIS are applicable in this highly complex patient population and further research should focus on a safe implementation. To secure a safe and transparent implementation of MIS in PHC, patients should only be treated within prospective studies in highly selected centers.

Compliance with Ethical Standard

Funding: No funding was received for this study.
Conflict of interest: L.C. Franken declares that she has no conflict of interest, M.J. van der Poel declares that he has no conflict of interest, A.E.J. Latenstein declares that she has no conflict of interest, M.J.W. Zwart declares that he has no conflict of interest, E. Roos declares that she has no conflict of interest, ORC Busch declares that he has no conflict of interest, M.G. Besselink declares that he has no conflict of interest, T.M. van Gulik declares that he has no conflict of interest.
Ethical approval: This article does not contain any studies with human participants performed by any of the authors.

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PART 3

SUMMARIES, DISCUSSION AND FUTURE PERSPECTIVES

SUMMARY

This thesis describes the outcomes of laparoscopic liver surgery in starting, low-volume centers, as well as experienced, high-volume centers in order to both guide the evidence based implementation of laparoscopic liver surgery, and demonstrate its feasibility and safety in a wide range of procedures.

Chapter 2 describes a set of clinical practice guidelines produced during The European Guidelines Meeting for Laparoscopic Liver Surgery that have been independently validated for the safe development and progression of laparoscopic liver surgery. Using a robust methodology the Southampton Guidelines have amalgamated the available evidence and a wealth of experts' knowledge taking in consideration the relevant stakeholders' opinions and complying with the international methodology standards.

Part 1: Implementation of laparoscopic liver surgery

One of the recommendations coming from the Southampton Guidelines is that the implementation of laparoscopic liver surgery should be stepwise and combined with structured training. In **Chapter 3** we demonstrated that this concept resulted in a steady increase of surgical complexity without affecting surgical outcomes in a retrospective, single center study and thereby validated the Southampton Guidelines recommendation. This approach can help to decrease the clinical impact of the learning curve and can be an appropriate method for technique implementation in starting centers and on a larger, nationwide scale.

Before implementation on a nationwide scale can take place, an assessment of current practice is necessary. **Chapter 4** provides an overview of the implementation and outcome of minor and major minimally invasive liver surgery in the Netherlands. It showed that the use of minor minimally invasive liver surgery is clearly increasing with outcomes comparable to international reports. However, the implementation of major minimally invasive liver surgery is slow and the observed volume-outcome relationship confirms its complexity and the need for a structured training program in centers with sufficient volume. This training program is currently ongoing.

Part 2: Outcome of laparoscopic liver surgery

Surgical treatment of benign liver tumors is sometimes indicated when a patient experiences symptoms, but the effect of surgery is debated. **Chapter 5** provides a systematic literature review of symptom relief, quality of life and surgical outcomes after both open and laparoscopic liver surgery and concluded that surgical treatment can relieve symptoms in the majority of these patients. A benefit of laparoscopic surgery over open surgery in terms of quality of life after surgery and operative outcomes is suggested, but data are scarce. The main limitation of this study is the lack of a control group of patients treated conservatively.

Although consensus guidelines on laparoscopic liver surgery already recommend laparoscopy as the standard approach to left lateral sectionectomies, high level evidence of its superiority over open surgery is missing. In order to increase the level of evidence supporting this recommendation, a propensity score matched comparison of open and laparoscopic left lateral sectionectomies was performed in **Chapter 6.** Laparoscopic left lateral sectionectomy was associated with a significant benefit in terms of operative time, intraoperative blood loss and postoperative hospital stay.

Chapter 7 demonstrated the feasibility and safety of the laparoscopic approach to hemihepatectomy, with an acceptable learning curve of 55 procedures. When performed by surgeons with experience in open liver surgery, advanced laparoscopic gastro-intestinal surgery, and laparoscopic minor liver resections, the inherent benefits of the laparoscopic technique were not compromised in patients undergoing laparoscopic hemihepatectomy.

Another challenging procedure is simultaneous colorectal and liver surgery, which is sometimes indicated in patients presenting with colorectal cancer and synchronous liver metastases. There is, however, an ongoing debate about the timing of these resections and whether simultaneous resections increase the risk of postoperative morbidity. **Chapter 8** aimed to compare the postoperative morbidity rate of combined resections with colorectal resections alone and found that in selected patients, requiring only minor liver resections, laparoscopic simultaneous resections did not increase the postoperative complication rate.

Chapter 9 discusses the outcomes of laparoscopic versus open repeat liver resections. Patients with recurrent colorectal liver metastases may often require further surgery. Repeat liver surgery, however, can be a challenging procedure due to adhesions and an altered liver anatomy form the previous resection. This study showed that, when performed by experienced surgeons in high-volume centers, laparoscopic repeat liver resection for colorectal liver metastases is feasible and may offer advantages over an open approach.

Chapter 10 describes a case series of laparoscopic liver resections for lesions adjacent to major vascular structures, which has previously been considered a contraindication for the laparoscopic approach. In a series of 37 patients, we found a conversion rate of 8%, R0 resection rate of 92%, postoperative morbidity rate of 5% and no mortality. Hence, lesions at less than 2cm from major vascular structures should not be considered an absolute contraindication for the laparoscopic approach, when resections are performed in expert centers.

Finally, in **Chapter 11**, the first systematic review on the use and outcome of minimally invasive surgical techniques for the resection of perihilar cholangiocarcinoma showed that the implementation is still in its infancy. The available evidence is limited and generally of poor quality. The added value of minimally invasive surgery for perihilar cholangiocarcinoma remains to be seen.

DISCUSSION AND FUTURE PERSPECTIVES

After a slow start due to several initial concerns, laparoscopic liver surgery has gradually been adopted by liver surgeons worldwide. Over the past three decades, pioneering surgeons in high-volume centers have demonstrated the feasibility and safety of this approach. They have shown that the inherent benefits of the minimally invasive approach can be reproduced in the challenging setting of liver surgery.[1-3] Current consensus guidelines, described in **Chapter 2**, even recommend laparoscopy as the standard approach to minor liver resections.[4-6] The recommendations formulated in these guidelines can guide starting centers in the safe implementation of laparoscopic liver surgery into their practice. Meanwhile, expert centers are pushing the boundaries, trying to expand the spectrum of indications.

Laparoscopic liver surgery is associated with a considerable learning curve. Therefore, early results and most of the currently available evidence, including those reports on which the consensus guidelines are based, are derived from high-volume expert centers where pioneering surgeons were able to attain their learning curve. The recommendation regarding implementation states that it should take place in a stepwise fashion, combined with structured training. Although this recommendation has been validated in **Chapter 3**, and we now know that “early adopting” surgeons can shorten their learning curve by learning from the “pioneers”[7], the impact of annual case volume during the development of the technique cannot be underestimated. Not only have higher volumes been associated with better postoperative outcomes in a variety of high-risk surgical procedures[8,9], including laparoscopic liver surgery in **Chapter 4,** it also provided surgeons with a large enough pool of patients to select the right candidates for a stepwise approach. It will be interesting to see whether these early results can be reproduced by surgeons adapting to the laparoscopic approach from lower-volume centers where selecting the right candidates according to the surgeon’s progression along the learning curve may be more difficult. These results are yet to be disclosed on a large scale. Nationwide data will play a huge role in presenting the outcomes of laparoscopic liver surgery outside expert centers, which could be essential for the design of future patient referral patterns.

In the Netherlands, an annual case volume of 20 liver resections in general is required in order to perform liver surgery as a center.[10] Although a certain case volume requirement is definitely necessary to safely perform liver surgery, the current cut-off of 20 procedures in general seems to lack certain distinctions. First of all, it does not take into account the enormous variety of potential resections. An extended right hemihepatectomy is distinctly different from a small wedge resection from segment three in both anatomy and outcomes, yet both can be performed by a center performing a minimum of twenty resections annually. Furthermore, no distinction is made between open or laparoscopic resections, even though technical differences and differences in outcomes have been clearly described. All in all, it seems imperative that the current volume requirement for liver surgery in the Netherlands gets updated, but future research should help define new cut-offs and categories.

Another ongoing debate in laparoscopic liver surgery is the definition difficulty. Numerous nomenclatures and definitions have been proposed to group the various different liver resections based on outcomes and anatomy.[11-13] Furthermore, several authors have developed difficulty scores in order to capture the difficulty of laparoscopic liver surgery in a single number that would be easy to interpret and compare in future studies.[14-16] Despite these countless efforts, an all-embracing score or nomenclature that correlates with outcomes is still sought after. The absence of such a score currently hampers the comparability of different practices. In order to improve comparability and also patient outcomes, nationwide, multicenter registries are being implemented.[18-20] Comparing baseline characteristics and operative outcomes from nationwide registries might contribute to a better understanding of outcome variability due to practice variations and help improve outcomes and prevent complications. Ideally, registries should therefore contain similar variables, all registered using the same definitions. In minimally invasive pancreatic surgery, this is achieved through the establishment of the European Consortium of Minimally Invasive Pancreatic Surgery (E-MIPS) Registry: a continent wide registry of pancreatic surgery.[21] In minimally invasive liver surgery, E-MILS might be the way forward.

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PART 4

APPENDICES

NEDERLANDSE SAMENVATTING

In dit proefschrift worden de uitkomsten van laparoscopische leverchirurgie in zowel beginnende, laag volume centra, als ervaren, hoog volume centra beschreven. Het doel is om de *evidence-based* implementatie van laparoscopische leverchirurgie verder richting te geven en de toepasbaarheid en veiligheid van deze techniek voor een grote variëteit aan procedures te beschrijven.

In **Hoofdstuk 2** wordt een set richtlijnen voor de klinische praktijk gepresenteerd die tijdens de *European Guidelines Meeting for Laparoscopic Liver Surgery* werden opgesteld. Middels een uitgebreide systematische literatuurstudie kon een grote hoeveelheid studies, alsmede een expert opinies, verzameld worden. Deze richtlijnen zijn onafhankelijk gevalideerd en kunnen bijdragen aan een veilige ontwikkeling en implementatie van laparoscopische leverchirurgie.

Deel 1: Implementatie van laparoscopische leverchirurgie

Een van de adviezen die voortkomt uit de Southampton richtlijn is dat implementatie van laparoscopische leverchirurgie op een stapsgewijze manier dient plaats te vinden en altijd gepaard moet gaan met gestructureerde training. In **Hoofdstuk 3** laten we zien dat dit advies kan leiden tot een gestage toename van de moeilijkheidsgraad van de procedures zonder dat daardoor de operatieve uitkomsten negatief worden beïnvloed. Beginnende centra kunnen op deze manier de klinische impact van de leercurve verminderen en het zou een toepasselijke strategie kunnen zijn om laparoscopische leverchirurgie op een grotere, landelijke schaal te implementeren.

Alvorens gestructureerde implementatie op landelijke schaal kan plaatsvinden dient er een goed overzicht te zijn van de huidige praktijk. In **Hoofdstuk 4** wordt een overzicht gegeven van de implementatie en uitkomsten van mineure en majeure minimaal invasieve leverchirurgie in Nederland. Uit dit overzicht blijkt dat mineure minimaal invasieve leverresecties reeds op grote schaal uitgevoerd worden met resultaten die vergelijkbaar zijn met internationale rapportages. De implementatie van majeure minimaal invasieve leverresecties gaat echter langzaam. Daarnaast wordt er een volume-uitkomst relatie gezien die bevestigt hoe complex deze resecties zijn. Vandaar dat er een gestructureerd trainingsprogramma is opgezet in centra die jaarlijks voldoende resecties uitvoeren en dit programma loopt momenteel nog.

Deel 2: Uitkomsten van laparoscopische leverchirurgie

Chirurgie kan in geval van klachten soms geïndiceerd zijn voor benigne levertumoren. Het effect van de chirurgische verwijdering van deze tumoren op de klachten is echter niet goed onderzocht. In de systematische literatuurstudie in **Hoofdstuk 5** worden de bestaande studies naar de verlichting van symptomen, kwaliteit van leven en chirurgische uitkomsten na open en laparoscopische leverchirurgie voor benigne levertumoren op een rijtje gezet. In het overgrote deel van de patiënten in deze studies verdwenen de klachten na chirurgische verwijdering van de tumor. Er wordt gesuggereerd dat laparoscopie gepaard gaat met een betere kwaliteit van leven en betere postoperatieve uitkomsten, echter zijn de studies die dit onderbouwen erg beperkt. Het grootste gebrek aan deze studie is dat er geen controlegroep is van patiënten die conservatief behandeld worden.

De huidige consensus richtlijnen schrijven voor dat laparoscopie de standaard benadering zou moeten zijn voor de resectie van tumoren in de links laterale segmenten. De studies die deze aanbeveling onderbouwen zijn echter van lage kwaliteit. Met het oog op het verhogen van de bewijskracht voor het gebruik van laparoscopie als de standaard benadering voor de resectie van links laterale segmenten wordt in **Hoofdstuk 6** een '*propensity score gematchte*' vergelijking van open en laparoscopische links laterale segmentresecties uitgevoerd. Hieruit komt naar voren dat laparoscopie gepaard gaat met een significant kortere operatietijd, minder bloedverlies en een korter postoperatief ziekenhuisverblijf.

In **Hoofdstuk 7** worden de technische uitvoerbaarheid en veiligheid van totaal laparoscopische hemihepatectomie aangetoond. Tevens is er sprake van een acceptabele leercurve van 55 procedures wanneer de resecties worden uitgevoerd door chirurgen die reeds ervaring hebben met open leverchirurgie, andere geavanceerde gastro-intestinale laparoscopische procedures en mineure laparoscopische leverchirurgie.

Patiënten met colorectaal carcinoom waarbij synchrone levermetastasen zijn geconstateerd zullen zowel een colorectale als leverresectie moeten ondergaan. De timing van beide resecties is echter onderwerp van discussie. Idealiter zouden patiënten beide operaties in een sessie ondergaan, echter zou dit het risico op postoperatieve complicaties verhogen. In **Hoofdstuk 8** vergelijken we het percentage postoperatieve complicaties van patiënten die een gecombineerde operatie ondergingen met patiënten die alleen een colorectale resectie ondergingen. Gecombineerde resecties gaan in geselecteerde patiënten waarbij enkel een mineure leverresectie uitgevoerd wordt niet gepaard met een verhoogd percentage postoperatieve complicaties.

In **Hoofdstuk 9** worden de uitkomsten van laparoscopische herhaalde leverresecties vergeleken met die van patiënten die een open herhaalde leverresectie ondergingen. Colorectale levermetastasen keren vaak terug na operatie en in die gevallen is herhaalde leverresectie wederom de enige curatieve optie. Herhaalde leverresectie is echter zeer complex vanwege de veranderde anatomie en adhesies na de vorige operatie. In deze studie wordt aangetoond dat laparoscopische herhaalde leverresecties technisch mogelijk is en potentiele voordelen heeft ten opzichte van open herhaalde leverresectie wanneer de resectie wordt uitgevoerd door ervaren chirurgen in hoog volume centra.

Hoofdstuk 10 beschrijft een serie van laparoscopische leverresecties van laesies die dichtbij grote vaatstructuren in de lever gelegen zijn. Deze laesies worden door velen als contra-indicatie gezien voor de laparoscopische benadering. In deze serie van 37 patiënten wordt een conversiepercentage gezien van 8%, een R0 resectie percentage van 92%, een postoperatief complicatiepercentage van 5% en geen mortaliteit. Deze resultaten laten zien dat laesies dichtbij grote vasculaire structuren niet als absolute contra-indicatie gelden wanneer de resectie wordt uitgevoerd in een expert centrum.

Als laatste wordt in **Hoofdstuk 11** een systematische literatuurstudie beschreven naar de uitkomsten van minimaal invasieve chirurgische technieken voor de behandeling van perihilair cholangiocarcinoom. Er zijn tot nu toe maar weinig studies gerapporteerd die deze technieken beschrijven en de studies die werden gevonden zijn van lage kwaliteit. De implementatie van minimaal invasieve chirurgische technieken voor de behandeling van perihilair cholangiocarcinoom staat nog in de kinderschoenen en de toegevoegde waarde voor deze indicatie valt nog te bezien.

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LIST OF PUBLICATIONS

Publications in this thesis

1. Mohammad Abu Hilal, Luca Aldrighetti, Ibrahim Dagher, Bjorn Edwin, Roberto Ivan Troisi, Ruslan Alikhanov, Somaiah Aroori, Giulio Belli, Marc Besselink, Javier Briceno, Brice Gayet, Mathieu D'Hondt, Mickael Lesurtel, Krishna Menon, Peter Lodge, Fernando Rotellar, Julio Santoyo, Olivier Scatton, Olivier Soubrane, Robert Sutcliffe, Ronald Van Dam, Steve White, Mark Christopher Halls, Federica Cipriani, **Marcel Van der Poel**, Ruben Ciria, Leonid Barkhatov, Yrene Gomez-Luque, Sira Ocana-Garcia, Andrew Cook, Joseph Buell, Pierre-Alain Clavien, Christos Dervenis, Giuseppe Fusai, David Geller, Hauke Lang, John Primrose, Mark Taylor, Thomas Van Gulik, Go Wakabayashi, Horacio Asbun, Daniel Cherqui. The Southampton consensus guidelines for laparoscopic liver surgery: from indication to implementation. *Annals of Surgery 2018;268:11-18*

2. **Marcel van der Poel**, Floor Huisman, Olivier Busch, Mohammad Abu Hilal, Thomas van Gulik, Pieter Tanis, Marc Besselink. Stepwise introduction of laparoscopic liver surgery: validation of guideline recommendations. *HPB (Oxford) 2017;19:894-900*

3. **Marcel van der Poel***, Robert Fichtinger*, Marc Bemelmans, Koop Bosscha, Andries Braat, Marieke de Boer, Cornelis Dejong, Pascal Doornebosch, Werner Draaisma, Michael Gerhards, Paul Gobardhan, Burak Gorgec, Jeroen Hagendoorn, Geert Kazemier, Joost Klaase, Wouter Leclercq, Mike Liem, Daan Lips, Hendrik Marsman, Sven Mieog, Quintus Molenaar, Vincent Nieuwenhuijs, Carolijn Nota, Gijs Patijn, Arjen Rijken, Gerrit Slooter, Martijn Stommel, Rutger-Jan Swijnenburg, Pieter Tanis, Wouter te Riele, Türkan Terkivatan, Petrousjka van den Tol, Peter van den Boezem, Joost van der Hoeven, Maarten Vermaas, Moh'd Abu Hilal, Ronald van Dam^, Marc Besselink^ on behalf of the Dutch Liver Collaborative Group. Implementation and outcome of minor and major minimally invasive liver surgery in the Netherlands. *Submitted for publication *Shared first authorship ^Shared senior authorship*

4. Belle van Rosmalen*, Jan Jaap de Graeff*, **Marcel van der Poel**, Ilja de Man, Marc Besselink, Moh'd Abu Hilal, Thomas van Gulik^, Joanna Verheij^. Impact of open and minimally invasive resection of symptomatic solid benign liver tumours on symptoms and quality of life: a systematic review. *HPB (Oxford) 2019; Article in press* **Shared first authorship ^Shared senior authorship*

5. **Marcel van der Poel***, Robert Fichtinger*, Burak Gorgec, Arab Rawashdeh, Pieter Tanis, Olivier Busch, Thomas van Gulik, Cornelis Verhoef, Marieke de Boer, Mathieu D'Hondt, Moh'd Abu Hilal^, Türkan Terkivatan^, Ronald van Dam^, Marc Besselink^. Laparoscopic versus open left lateral sectionectomy: a multicenter international propensity score matched study. *Submitted for publication *Shared first authorship ^Shared senior authorship*

6. **Marcel van der Poel**, Marc Besselink, Federica Cipriani, Thomas Armstrong, Arjun Takhar, Susan van Dieren, John Primrose, Neil Pearce, Mohammed Abu Hilal. Total laparoscopic hemihepatectomy: outcome and learning curve in 159 consecutive patients. *JAMA Surg 2016;151:923-928*

7. **Marcel van der Poel**, Pieter Tanis, Hendrik Marsman, Arjen Rijken, Emma Gertsen, Sander Ovaere, Michael Gerhards, Marc Besselink^, Mathieu D'Hondt^, Paul Gobardhan^. Laparoscopic combined resection of liver metastases and colorectal cancer: a multicenter, case-matched study using propensity scores. *Surg Endosc 2018; Article in press ^Shared senior authorship*

8. **Marcel van der Poel**, Leonid Barkhatov, David Fuks, Gerardi Berardi, Federica Cipriani, Anas Aljaiuossi, Panagiotis Lainas, Ibrahim Dagher, Mathieu D'Hondt, Fernando Rotellar, Marc Besselink, Luca Aldrighetti, Roberto Troisi, Brice Gayet, Bjorn Edwin, Moh'd Abu Hilal. Multicenter propensity score matched study on laparoscopic versus open repeat liver resection for colorectal liver metastases. *Br J Surg 2018; Article in press*

9. Mohammad Abu Hilal, **Marcel van der Poel**, Morsal Samim, Marc Besselink, David Flowers, Brian Stedman, Neil Pearce. Laparoscopic liver resection for lesions adjacent to major vasculature: feasibility, safety and oncological efficiency. *J Gastrointest Surg 2015;19:692-698*

10. **Marcel van der Poel***, Lotte Franken*, Anouk Latenstein, Maurice Zwart, Eva Roos, Olivier Busch, Marc Besselink, Thomas van Gulik. Minimally invasive surgery for perihilar cholangiocarcinoma: a systematic review. *Submitted for publication *Shared first authorship*

Other publications

11. Gerritsen A, **Van der Poel MJ*,** De Rooij T*, Molenaar IQ, Bergman JJ, Busch OR, Mathus-Vliegen EM, Besselink MG. Systematic review on bedside electromagnetic-guided, endoscopic, and fluoroscopic placement of nasoenteral feeding tubes. *Gastrointest Endosc 2015;81:836-847 *contributed equally*

12. Gerritsen A, De Rooij T*, **Van der Poel MJ*,** Dijkgraaf MG, Bemelman WA, Busch OR, Besselink MG, Mathus-Vliegen EM. . Endoscopic Versus Bedside Electromagnetic-Guided Placement of Nasoenteral Feeding Tubes in Surgical Patients. *J Gastronintest Surg 2014;18:1664-1672 *contributed equally*

13. Samim M, Abu Hilal M, Isfordink CJ, Molenaar QI, **Van der Poel MJ,** Armstrong TA, Takhar AS, Pearce NW, Primrose JN, Harris S, Verkooijen HM, van Gulik TM, Hagendoorn J, Busch OR, Johnson CD, Besselink MG; HPB-RISC Study Group. Surgeons' assessment versus risk models for predicting complications of hepato-pancreato-biliary surgery (HPB-RISC): a multicenter prospective cohort study. *HPB (Oxford) 2018;20:809-814*

14. Ter Veer E, Van Rijssen B, Besselink MG, Mali R, Berlin J, Boeck S, Bonnetain F, Chau I, Conroy T, Van Cutsem E, Deplanque G, Friess H, Glimelius B, Goldstein D, R. Hermann, Labianca R, Van Laethem J, Macarulla T, Van der Meer J, Neoptolemos J, Okusaka T, O'Reilly E, Pelzer U, Philip P, **Van der Poel MJ,** Reni M, Scheithauer W, Siveke JT, Verslype C, Busch OR, Wilmink JW, van Oijen MGH, van Laarhoven HWM. Consensus statement on mandatory measurements in pancreatic cancer trials (COMM-PACT) for systemic treatment of unresectable disease. *Lancet Oncol 2018;19:e151-e160*

15. Halls MC, Alseidi A, Berardi G, Cipriani F, **Van der Poel MJ**, Davila D, Ciria R, Besselink M, D'Hondt M, Dagher I, Alrdrighetti L, Troisi RI, Abu Hilal M. A Comparison of the Learning Curves of Laparoscopic Liver Surgeons in Differing Stages of the IDEAL Paradigm of Surgical Innovation: Standing on the Shoulders of Pioneers. *Ann Surg 2019;269:221-228*

A

Book chapters

1. Minimally Invasive Surgery for Upper Abdominal Cancer. Van der Poel MJ, Tanis PJ, Wicherts DA, Besselink MG. Springer Science 2017.

PHD PORTFOLIO

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prof. dr. M. Abu Hilal, dr. P.J. Tanis (co-promotores)

	Year	Workload (ECTS)
1. PHD TRAINING		
General courses		
- BROK	2017	1.0
- Project management	2017	0.4
- Practical biostatistics	2017	1.1
- Clinical data management	2017	0.2
Seminars, workshops and masterclasses		
- AMC department of surgery weekly seminars	2017-2018	0.5
- AMC department of HPB surgery monthly seminars	2017-2018	0.1
- British Journal of Surgery Course: "How to write a scientific article"	2018	1
Attended conferences		
- Chirurgendagen, Veldhoven, the Netherlands	2014, 2018	2.0
- Combined EPC & IAP Meeting in Southampton, UK	2014	2.0
- 12th Biennial Conference of the IHPBA in Sao Paulo, Brazil	2016	2.0
- 12th Biennial Conference of the E-AHPBA in Mainz, Germany	2017	2.0
- 1st Biennial International Laparoscopic Liver Society Meeting in Paris, France	2017	2.0
- EGMLLS, Southampton, UK	2017	4.0
- Alpine Liver and Pancreatic Surgery Meeting 2019 in Madonna di Campiglio, Italy	2019	2.0
Oral presentations		

- Half yearly scientific meeting of the Dutch Liver Collaborative Group	2017-2018	0.5
- MILS in the Netherlands		
o 13th Biennial Conference of the IHPBA in Geneva, Switzerland	2018	0.25
o Annual Conference of the Dutch Surgical Society in Veldhoven, the Netherlands	2018	0.5
o Alpine Liver and Pancreatic Surgery Meeting 2019 in Madonna di Campiglio, Italy	2019	0.5
- Laparoscopic combined colorectal and liver resections		
o 12th Biennial Conference of the E-AHPBA in Mainz, Germany	2017	0.5
o 1st Biennial International Laparoscopic Liver Society Meeting in Paris, France	2017	0.5
- Outcome and learning curve of laparoscopic hemihepactectomies		
o 12th Biennial Conference of the IHPBA in Sao Paulo, Brazil	2016	0.5
- RISC study		
o Combined EPC & IAP Meeting in Southampton, UK		
- Endoscopic versus electromagnetic placement of nasoenteral feeding tubes	2014	0.5
o Annual Conference of the Dutch Surgical Society in Veldhoven, the Netherlands		
	2014	0.5

2. TEACHING

Mentoring and tutoring

- 6th year medical student	2017	1.5

3. PARAMETERS OF ESTEEM

Grants

A

- Alpine Liver and Pancreatic Surgery Meeting 2019 – Travel Grant	2019
- Maag Lever Darm Stichting (Dutch Digestive Foundation) – Innovation Grant	2017
- Integra LifeSciences – Educational Grant	2017
- Johnson & Johnson Medical BV, Ethicon – Educational Grant	2017
- Royal Dutch Academy of Sciences, Van Walree Foundation – Student research grant	2016
- KWF Kankerbestrijding (Dutch Cancer Foundation) – Student research grant	2013
- Maag Lever Darm Stichting (Dutch Digestive Foundation) – Student research grant	2013
- Erasmus Life Long Learning – Student research grant	2013
Awards and prizes	
- ALPS Best poster/oral presentation	2019

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CURRICULUM VITAE

Marcel Johan van der Poel was born on July 18th 1992 in Amsterdam. He finished high school in 2010 and did not hesitate to get into medical school that same year. His interest in surgical research manifested early on in year two in a bachelor thesis at the department of surgery in the Academic Medical Center Amsterdam. After the successful completion of this project he continued his academic career as research intern at the Southampton University Hospital. He finished his master thesis in six months and returned to Amsterdam for his clinical internships, which he finished in December 2016. During these internships he continued his research projects with the department of surgery part-time and afterwards finished his PhD thesis in two years full-time. During this time he has been involved in multiple national and international research projects, mentored research students, followed multiple courses and given numerous presentations at (inter)national conferences. The past five years he has also been active at the highest national rugby competition in the Netherlands. In March 2019 he started working as ANIOS at the surgical department of the Amstelland Hospital.

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