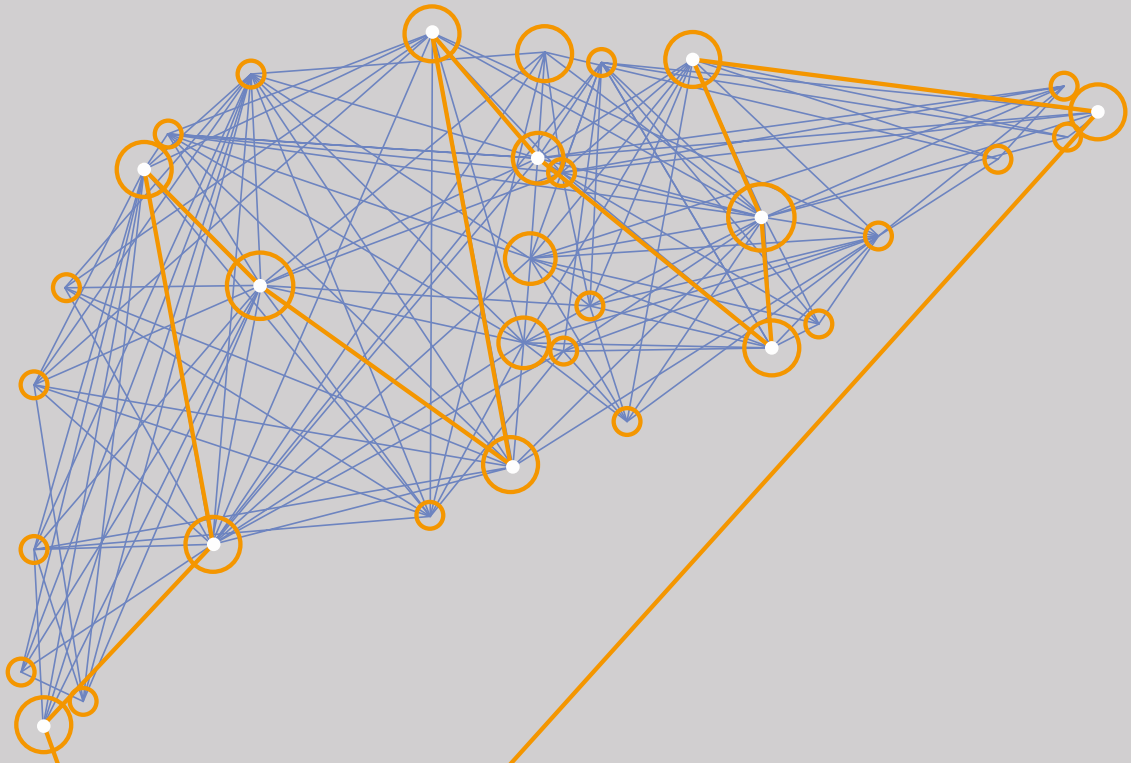
Optimized recovery and minimally invasive liver surgery



OPTIMIZED RECOVERY AND MINIMALLY INVASIVE LIVER SURGERY

EDGAR M. WONG-LUN-HING

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OPTIMIZED RECOVERY AND MINIMALLY INVASIVE LIVER SURGERY

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General introduction and outline of thesis

SECTION 1: LIVER SURGERY

Partly adapted from "Laparoscopic liver surgery in the Netherlands: how far are we?" Dig Surg. 2012;29(1):70-8.

HISTORY OF LIVER SURGERY AND ANATOMY

For any type of surgical intervention intricate knowledge and understanding of the anatomy is of key importance. This is also true for liver surgery. Ancient Mesopotamian clay liver models were the first to describe the liver anatomy.[1] Among the early pioneers in the field of liver surgery were Glisson, Wendel and Cantlie[2, 3], but the first "real" liver resection was performed by Langenbuch in 1887.[4, 5] It took until the 1950's before a detailed understanding of liver anatomy became available through the work of Couinaud.[6] He made casts of the liver and found that the liver could be divided into eight segments based on the portal and hepatic vein blood distribution. Each segment is numbered and has its own specific in- and outflow structures: portal triad and hepatic vein. The portal vein divides the liver into inferior and superior segments, whereas the hepatic veins demarcate the right and left hepatic lobes. The right lobe is divided by the right hepatic vein into an anterior and posterior segment. The left hepatic vein divides the left lobe into the medial and lateral segments. In the portal triad itself an efferent bile duct and an afferent hepatic artery and portal vein (*Figure 1*) can be recognised. This understanding now forms the basis of modern functional and surgical liver anatomy.[5]

There are now two widely accepted terminology systems: the Bismuth[7] and Brisbane 2000[8, 9] nomenclature. They both have evolved from Couinaud's and Takasaki's[10] work, but the suggested nomenclatures are still not completely appropriate and both require further revisions. The nomenclatures still contain segmentations that are inappropriate for embryological and surgical reasons. There is a demand for a uniform nomenclature.[11]

Two other major developments that made liver surgery evolve into a widely accepted intervention were the introduction of ultrasound and the improved control of bleeding. With ultrasound during surgery clinicians were able to find small liver tumours[12] and the anatomy of biliary and vascular structures could be exactly defined[13-15] and allowed anatomical resections.[16] Control of bleeding during hepatic surgery added to increased safety and can be achieved in various ways, but depends on the quality of the liver parenchyma, characteristics of the tumour to be resected and of course the preference and experience of the surgeon. Most techniques have arisen from the original Pringle maneuver[17] and can be divided into inflow occlusion alone or combined in- and outflow occlusion. The most commonly

used occlusion methods are hepatic pedicle clamping (continuous or intermittent Pringle maneuver[18, 19]) and selective inflow occlusion (segmental or hemihepatic[20, 21]). Occasionally, e.g. in cases of extreme bleeding or major liver resection, also total or selective hepatic vascular exclusion (THVE or SHVE, inflow and outflow occlusion of the whole liver or the lobe to be resected), or hepatic vascular exclusion with preservation of caval flow (HVEPC).can be used.[22-24]

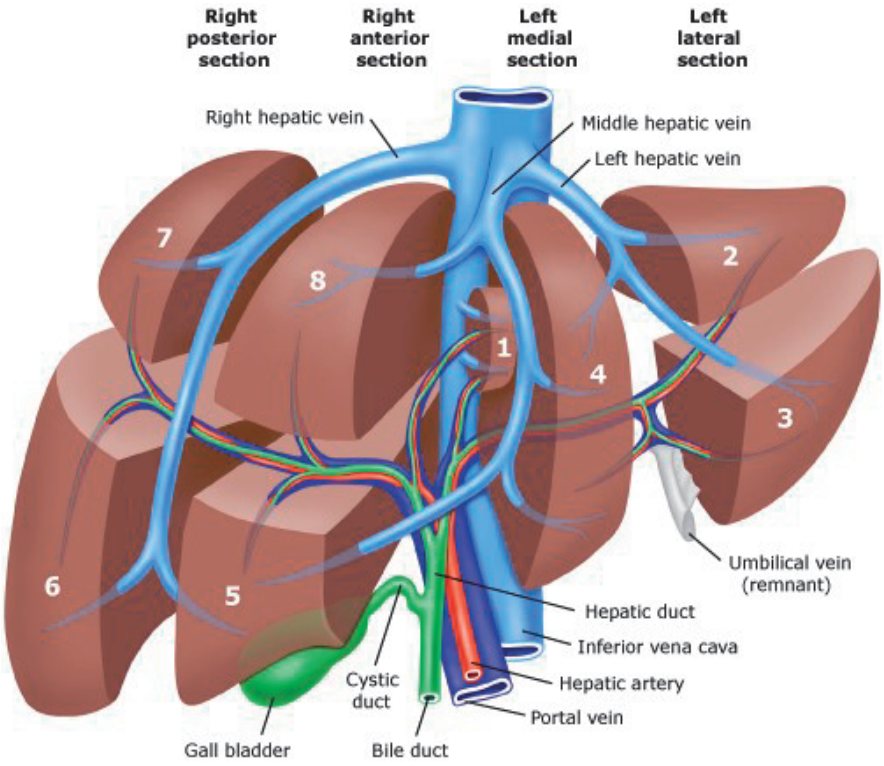

Figure 1. Segments of the human liver and current surgical nomenclature of liver sections.
Reprinted with permission from Macmillan Publishers Ltd:, Siriwardena A.K. et al. Management of colorectal cancer presenting with synchronous liver metastases, Nature Reviews Clinical Oncology, 11(8):446-59, 2014

Technology has driven the majority of advances in surgery over the past decade. At first significant advantages (e.g. smaller incisions, fewer incisional hernias and adhesions, reduced post-operative morbidity) that laparoscopy brought to performing gallbladder surgery were recognized, and along came the desire to apply this innovation in surgery to all operations, limited only by the imagination and the surgeon's technical ability.[25] Until fairly recently, only open liver resections were performed, but during the last decade of the 20th century the first laparoscopic liver resections were successfully completed. No prospective or randomised controlled evidence to

support a wide adoption of the laparoscopic technique in liver surgery is available, but many expert centres have retrospectively shown benefits in liver surgery. The assumed benefits will be discussed later in this chapter.

The surgical anatomy for laparoscopic hepatectomy is in principle the same as during open procedures. However, the minimally invasive approach can be more difficult due to a lack of experience compared to open liver surgery, even if surgeons have prior laparoscopic experiences. The difference in access to the abdominal cavity and the resulting difference in intra-abdominal perspective, with a more caudate view from videoendoscope to the surgical field, require surgeons to operate in difficult angles with instruments that only allow for limited range of motion and tactile feedback. In addition, the laparoscopic approach further limits optimal exposure by presenting a two-dimensional image to the surgeon.

Laparoscopic resection for tumours located in the posterior parts of the liver (segments: I, VI and VII) is more difficult than for tumours in anterior locations (segments: II, III, IV, V, VIII).[26-30] The difficulties relate to maintaining hemostasis at the transection plane, controlling hemorrhage, mobilizing the liver and visualizing and working within the deeper regions of the liver.[27, 31-35] Essential for laparoscopic liver surgery is the positioning of trocars and adequate mobilization of the liver. This not only depends on the location of the tumour[26, 36] and the type of resection to be performed, but also on the surgeon's preference. For laparoscopic procedures of anterior segments the laparoscope is usually inserted at the umbilicus, and two to four trocars for manipulation are additionally placed.[27, 36, 37] For resection of the superior or posterior segment of the right hepatic lobe, a lateral approach is considered more convenient.[27, 38] Key to success in all procedures is to achieve triangulation for good access and visualization of the liver anatomy.

RELUCTANCE OF DUTCH SURGEONS

Compared to countries that have traditionally always played a pioneering role in liver surgery, such as France, the Netherlands lagged behind concerning the implementation of liver surgery. Many surgeons considered an open partial liver resection to be major surgery, associated with considerable mortality and morbidity. Dutch surgeons remained reluctant to perform this type of surgery.[39] This is illustrated by the fact that only 10 to 130 partial liver resections (including benign tumours) were performed between 1984 and 1987. During the end of the 1980's and 1990's several series on the experience with open hepatic resection were published by different Dutch centres.[40, 41]

The laparoscopic technique for liver resections was introduced in the Netherlands during the 1990's, but it was mainly used for diagnostic laparoscopies and liver biopsies. Later the indications were extended to fenestration of liver cysts and anatomic liver resections [42-47]. The group of Cuesta et al. was in 1995 the first to report two cases of limited laparoscopic liver surgery of segment II and IV in the Netherlands.[48] In the years thereafter only one article from the same group was published reporting on a series of laparoscopically operated patients (n=10). A few years later, in 2001, a small retrospective series (n=10) was published that demonstrated encouraging results concerning operative blood loss, post-operative complications and hospital length of stay after wedge and left lateral hepatectomy. Seven patients underwent a minor laparoscopic resection and three underwent fenestration of hepatic cysts. The authors concluded that laparoscopic treatment should be considered in selected patients with benign and malignant lesions in the left lobe or anterior segments of the liver.[49] The foundation of the Dutch Liver Collaborative Group in 2003 gave a new impulse to minimally invasive liver surgery and after the initial reports on minimally invasive liver surgery three articles were published on laparoscopic treatment of polycystic liver disease.[50-52] Later series of 26 laparoscopic liver resections provided evidence that this procedure could be performed safely in the Netherlands.[53]

OPEN VS. LAPAROSCOPIC HEPATECTOMY

Today liver surgery is predominantly performed for malignant indications, resection of colorectal liver metastases (CLM) in particular, as it offers the only changes of cure and long-term survival. Operative techniques, chemotherapy and perioperative care have evolved and have resulted in post-operative mortality rates of <5%, morbidity rates ranging between 30% and 50%[54-57], and with 5-year survival rates of approximately 30-60%.[57-63] The "cure" rate based on actual 10-year survivors is around 25-35%.[57, 63, 64]

While the first limited laparoscopic liver resection in the Netherlands was performed in 1995, the first laparoscopic liver resections had already been performed 5 years earlier by Reich[65] and Gagner.[66] Four years thereafter, Azagra et al.[67] reported the first anatomic liver resection (segment 2-3 resection). In the following years the minimally invasive technique was further developed and adopted, resulting in the first laparoscopic left lateral sectionectomy for living liver donation[68, 69] and the first reports on robotic liver surgery.[70, 71] Initially, laparoscopic liver resection was challenging because of the difficulties concerning safe mobilization and exposure of this fragile and heavy organ.[35, 72, 73] In expert centres laparoscopic resection of benign liver tumours seemed feasible and safe.[38, 74] Also for malignant tumours there appeared to be a benefit with regards to short-term post-operative outcomes and adequate surgical margins could be achieved.[75, 76] Surgeons with extensive

experience in laparoscopy and hepatic surgery have also performed laparoscopic major hepatic resections with satisfactory outcomes.[47, 77, 78]

Overall the quality of evidence on the merits of laparoscopic liver surgery is low (GRADE C).[79] Reviews by Nguyen et al. and Reddy et al. showed favourable outcomes after laparoscopic resection.[80, 81] Patient benefits included less operative blood loss[31, 82], less post-operative pain[27, 33, 83] and narcotic requirement, improved cosmetic aspects[27, 28], and a shorter length of hospital stay[27, 28, 33, 82-85] with post-operative morbidity and mortality comparable to open liver resection. In addition, the minimally invasive approach seems to be cost-effective.[86, 87] The decreased cost is based on savings in hospital ward costs and likely related to a significantly shorter hospital stay for laparoscopic liver surgery.[88] Potential limitations and disadvantages of laparoscopic liver resection include a considerable learning curve, potential bleeding which may be more difficult to control laparoscopically, inadequate assessment of the liver for additional lesions, and increased risk for gas embolism.[81, 89] Carbon dioxide (CO2) embolism may occur when high-pressure pneumoperitoneum is used.[72, 90] However, CO2 embolism is rare and usually well tolerated, as the gas dissolves rapidly.[83] Other concerns have been raised about the potential dissemination of malignant cells during laparoscopic resection.[91-93] Some authors have suggested that tumour dissemination does not increase by laparoscopy[32, 94, 95], and recent reports regarding this subject show long term survival rates comparable with open surgery.[28, 73, 75, 96] In line with this, during a consensus meeting of over 300 experts in 2008 (The Louisville Statement), it was concluded, based on the available evidence and expert opinions, that laparoscopic liver surgery was a safe and effective approach to the management of surgical liver disease in the hands of trained surgeons with experience in hepatobiliary and laparoscopic surgery. However, the experts also concluded that there is still a need for controlled prospective trials, and that prudent dissemination is warranted with adequate training standards and credentialing to ensure consistent standards and clinical outcomes.[97]

In parallel to these refinements in surgical technique, considerable changes in perioperative care were witnessed in the last decade of the previous millennium. Among these was the introduction of multimodal perioperative care, which will be addressed in the next section.

SECTION 2: ENHANCED RECOVERY AFTER SURGERY (ERAS®)

MULTIMODAL CARE PROGRAMME

The concept of a multimodal approach in perioperative surgical care originated from the Danish surgeon Henrik Kehlet. During the 1990's he pioneered in this field by investigating the surgical stress response caused by anaesthesia or analgesia[98-100] and the influence of exercise on post-operative fatigue.[101] By continuing his efforts he became the first to describe a combination of several elements in a multimodal protocol that reduced post-operative surgical stress-induced dysfunction and morbidity.[102-104]

His work culminated in the publication of a multimodal "fast-track" strategy that optimized several aspects of the perioperative management of patients undergoing major abdominal surgery[105-107] and the foundation of the Enhanced Recovery After Surgery (ERAS®) collaboration of five European centres in 2001. The ERAS protocol consists of about 20 elements during the pre-, intra- or post-operative phase, see *Figure 2*. At first this fast-track concept was explored and tested in colorectal surgery. Several groups have since then demonstrated that recovery could be accelerated with reduced length of hospital stay and post-operative morbidity in colorectal surgery.[108-119] Consequently, these results were bundled with expert opinions in evidence-based consensus guidelines in 2005[117] and 2009[120].

ERAS® ELEMENTS

Encouraged by good results in colorectal surgery[119] liver surgeons of the ERAS® group in Maastricht, Edinburgh and Tromsö undertook to implement the ERAS concept for patients undergoing open hepatic resection. Elements in the protocol were evaluated and adjusted to provide optimal care to liver surgical patients. Each item of the ERAS liver programme is presented below with a recommendation based on scientific evidence.

PREOPERATIVE EDUCATION

During counselling there should be emphasis on the recovery period and expectations of the patient, concerning pain control, early mobilization, resumption of intake and time of discharge. This has been demonstrated to allow earlier recovery.[121-124] Patients exhibiting denial or anxiety can also profit from extensive counselling.[125, 126]

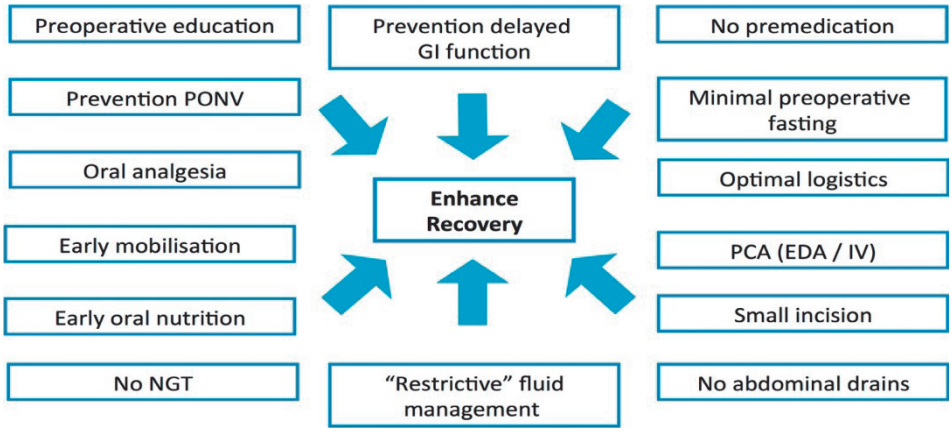

Figure 2. Elements of the ERAS liver programme

PREOPERATIVE FASTING & CARBOHYDRATE LOADING

Where patients used to be denied intake of food from the night before surgery, it is now generally recommended to allow patients to be fasted for liquids only for 2 hours and for solids for 6 hours preoperatively.[127-129] Reviews have demonstrated that preoperative fasting does not prevent complications, e.g. aspiration. [130, 131] On the contrary, patients able to have a normal preoperative intake are in a more anabolic state to benefit from post-operative nutrition and have less risk of insulin resistance and post-operative hyperglycaemia.[132-134]

PREANAESTHETIC MEDICATION

Provision of long-acting anxiolytic premedication could negatively influence gastrointestinal motility and, although it is safe to use short-acting benzodiazepines in day surgery[135], its efficacy for major surgery remains unclear. Patients who receive sleeping medication at home can continue this in hospital. In addition, analgesic premedication has no demonstrated effect on post-operative pain relief.[136]

ANTITHROMBOTIC PROPHYLAXIS

As for most major surgical procedures, antithrombotic prophylaxis should be provided in liver surgery. Low molecular weight heparin (LMWH) has been demonstrated to be safe and effective[137-140] and should be preferred over unfractionated heparin due to an increased compliance.[141] It has even been proposed to prolong thromboprophylaxis with LMWH after major abdominal or pelvic surgery since it significantly reduces the risk of venous thromboembolism (VTE) without increasing mor-

bidity. However, with an increased number of minimally invasive surgical procedures and the current trend for fast-track recovery the risk of post-operative VTE may be lower.[142] However, there is the risk of developing an epidural hematoma when epidural analgesia is used. Prophylactic doses of LMWH should be given no later than 12 hours prior to insertion and removal of epidural catheters.[143, 144] An alternative to LMWH thrombotic prophylaxis, so called mechanical prophylaxis (elastic compression stockings), can also be (additionally) used until patients are fully mobilized.

ANTIBIOTIC PROPHYLAXIS

The optimal antibiotic regimen has not been described, but prophylaxis should be active against both aerobic and anaerobic bacteria. In colorectal surgery it has been frequently demonstrated that antibiotic prophylaxis is effective in reducing infectious complications.[145] Two studies investigating the use of antibiotic prophylaxis after liver surgery have shown contradicting data.[146, 147] However, for hepatectomy (clean-contaminated surgery) antimicrobial prophylaxis may be essential, because of the relatively long operation time and relatively large blood loss.[148] A systemic infection after liver surgery can lead to liver failure, as sepsis could further jeopardize the liver function, already at risk after major resection. In addition, hyperglycemia induced by surgical stress and reduced liver function may cause dysregulation of liver metabolism and immune function resulting in adverse post-operative outcomes.[149] Newer generations of antibiotics should be avoided and reserved for secondary infectious complications.

ANAESTHESIA

The optimal anaesthetic method for liver resection is yet to be described in literature, however it is important to provide well balanced anaesthesia. The hepatic clearance of drugs may be diminished after parenchymal resection.[150] A frequently used technique is intravenous induction of anaesthesia with short-acting drugs like propofol and remifentanil[151], and maintenance of anaesthesia with a volatile agent such as isoflurane or sevoflurane.[152] Infusion of fluids should be restricted until after the parenchymal resection. Peripheral vasodilatation may be helpful to lower the central venous pressure (<5 mmHg) as this has been associated with decreased blood loss. Also, vasopressors like phenylephrine or norepinephrine may be considered to maintain an adequate mean arterial blood pressure.[153] Intraoperative use of epidural analgesia has not been shown to improve recovery after liver surgery, but it may prevent gastrointestinal paralysis[154, 155], block stress hormone release and attenuate post-operative insulin resistance.[156]

INTRAOPERATIVE FLUID MANAGEMENT

The discussion on optimal intraoperative i.v. fluid management is currently hotly debated. Post-operative complication rates and hospital stay seem to be reduced after elective surgery, if patients are not fluid overloaded and are only subjected to more restrictive, but balanced fluid therapy.[157-159] The problem lies in the type of protocol that needs to be followed (definition of restrictive management) and in the way of monitoring the response to fluid administration. Especially during major hepatectomy it necessary to expand the intravascular volume, but maintain a low central venous pressure (CVP). A high CVP may increase blood loss, transfusion requirements and length of hospital stay.[160] From a surgical perspective, CVP monitoring is recommended to minimize back bleeding during parenchymal transection (CVP <5 mmHg)[161-164] and anaesthesiologists use it to avoid the administration of excessive IV fluids.[159] It may however not be necessary at all to monitor the CVP and less invasive and peripheral monitoring may be sufficient to provide adequate fluid management.[153, 165-167] A monitoring device to consider for use and recommended in a guideline of the National Institute for Health and Care Excellence (NICE) is the CardioQ-ODM (Deltex Medical). This device assesses cardiac output and intravascular fluid status. The available data support a clinical benefit and a cost saving when the CardioQ-ODM is used in patients undergoing major or high-risk surgery in whom a clinician would consider using invasive cardiac monitoring.[168]

PREVENTION OF INTRAOPERATIVE HYPOTHERMIA

Maintenance of intraoperative normothermia (>36 0C) is an important target. Hypothermia is known to induce endocrine-metabolic responses and sympathetic reflexes, and negatively affects the fibrinolytic-coagulatory balance resulting in increased bleeding. Infusion of warmed fluids and use of upper-body forced-air heating covers has demonstrated to help maintain a normal body temperature. This resulted in fewer wound infections[169], less cardiac complications[170] and reduced bleeding and transfusion requirements.[171]

POST-OPERATIVE NAUSEA AND VOMITING (PONV) PROPHYLAXIS

To enable an early start of intake after surgery and to facilitate a quick return to a normal diet it is important to identify possible risk factors (e.g. history of motion sickness or PONV, female sex, opioid analgesia, certain volatile anaesthesia) that may induce nausea and vomiting.[172, 173] Convincing evidence is available to suggest that several drugs, such as cyclizine, droperidol, granisetron, metoclopramide, ondansetron and dexamethasone, reduce PONV. Treatment should be given using a multimodal approach and should be based on the risks per individual patient.[174, 175]

SURGICAL INCISIONS

The type and length of the incision used for surgery may affect patient recovery.[176] Transverse or curved incisions may reduce pain, pulmonary dysfunction and incidence of incisional hernia after abdominal procedures [177, 178], while other trials have found no advantage of transverse incisions.[179, 180] It is also to be expected that laparoscopic resections will lead to a lower incidence of incisional hernia compared with the open surgical technique.[181] Depending on the type of hepatic resection a bilateral subcostal or J-shaped incision can be used to gain sufficient access. The length of incision should be reduced to an incision of minimum length.

USE OF INTRA-ABDOMINAL DRAINS AND SEALANTS

Drainage of the peritoneal cavity after elective liver surgery is still routinely used. Advantages of drain placement, such as removal of bile due to leakage and tissue debris to prevent subphrenic infection, detection of post-operative haemorrhage and removal of ascites in patients with liver cirrhosis, have been reported.[182, 183] Other studies have indicated that the risks (high rates of intra-abdominal and wound infections by retrograde contamination, impaired pulmonary function, increased pain and discomfort) may be greater than the benefits.[184] A meta-analysis by Gurusamy et al [185] showed that there were no significant differences in morbidity, mortality and reoperation rates between patients with or without an abdominal drain after uncomplicated elective hepatic surgery. Alternatives to prevent leakage of bile or blood in the form of sealants applied to the resectional plane of the liver have not been proven to be of additional value.[186] Therefore, drains and sealants should no longer be used as a standard. If a drain is placed, close monitoring of the drain production is needed to allow removal as quickly as possible.

NASOGASTRIC INTUBATION

After liver surgery nasogastric tubes (NGT) should not be used routinely. Evidence has clearly demonstrated that routine nasogastric decompression must be avoided.[187, 188] The use of an NGT is even associated with an increased risk of developing post-operative pulmonary complications.[189, 190] If a tube is placed it should be removed immediately after surgery.

POST-OPERATIVE ANALGESIA

Post-operative pain control should aim at sparing opioids.[191] Effective analgesia may reduce the incidence of post-operative complications and may facilitate early recovery and mobilization.[106, 192] Epidural analgesia has been considered superi-

or to patient-controlled intravenous analgesia for post-operative pain relief after major upper abdominal operations[154, 193] and may reduce pulmonary morbidity.[194] However, the use of epidural analgesia after hepatectomy is still debated. Epidural analgesia may not function adequately in up to 30% of the patients[195] and can lead to serious complications (epidural abscess or haematoma[196]). Therefore, other analgesic options must not be excluded. Safe and effective alternatives to epidural analgesia after liver surgery are wound catheters with a local anaesthetic[197-199] or intrathecal morphine.[200, 201] If a mid-thoracic epidural analgesia is used, evidence has indicated that removal after a two-day period is feasible.[202] Additional combined oral analgesia (paracetamol and an non-steroidal anti-inflammatory drug) should be standardly provided, although the synergetic effect for major abdominal procedures has yet to be established.[203, 204]

PREVENTION OF POST-OPERATIVE ILEUS

Delayed gastrointestinal functioning should be prevented, as it is an important cause of delayed discharge after abdominal surgery. No single approach has demonstrated the ability to prevent or treat post-operative ileus.[205, 206] Interventions that may help are avoidance of preoperative fasting[207, 208] and avoiding mechanical bowel preparation[209], use of epidural-local anaesthetics[154], avoidance of fluid overload[159], implementation of minimally-invasive surgical techniques[210], use of oral magnesium oxide (1g twice daily commenced on the evening of surgery and used until discharge)[202, 211], coffee intake[212], use of chewing gum [213]and modification of pain management strategies to limit opioid administration.[214, 215]

URINARY CATHETER

If epidural catheters are used, patients are also given urinary catheters to avoid urinary retention. However, the risk of urinary retention after only 24 hours urinary bladder catheterisation has been reported to be low and removal of catheter the day after surgery does not seem to increase the recatheterisation rate.[216, 217] Other studies support the use of suprapubic bladder drainage instead of urethral catheterisation. Suprapubic catheters are associated with lower rates of urinary tract infection and less discomfort in patients undergoing abdominal surgery.[218-220] It is recommended to use urinary bladder drainage for the duration of thoracic epidural analgesia. Earlier removal of urinary drainage may be considered before the epidural is stopped to allow early mobilization.

START OF ORAL INTAKE

Denying patients early feeding and keeping them on a 'nil by mouth' regimen has no clear advantage. A quick return to a normal diet has been shown to be safe for both major upper abdominal, colorectal and liver surgery and it may reduce the risk of infection and length of hospital stay.[188, 221-223] In 2009 the European Society for Clinical Nutrition and Metabolism (ESPEN) has advised to manage patients in modern surgical practice within an enhanced recovery protocol and thereby have them eating normal food within 1-3 days. Also, routine perioperative nutritional supplementation is advised to be only used for patients with severe preoperative undernutrition or in patients who cannot meet their caloric requirements within 7-10 days after surgery.[224]

MOBILISATION

Early mobilization is essential to prevent increased insulin resistance and muscle loss, decreases muscle strength, pulmonary function, and tissue oxygenation[113], and to decrease the risk of thromboembolism. However, this can only be facilitated with adequate post-operative pain control and, if possible, absence of abdominal drains and urinary catheters. Therefore, daily goals for mobilization with assistance from nurses or physiotherapists must be defined.

ERAS PROGRAMME FOR LIVER SURGERY

In line with earlier results from colorectal surgery, van Dam et al. [225] and Koea et al.[201] showed a significantly reduced length of hospital stay when patients were managed within a multimodal enhanced recovery programme for liver surgery. In addition to this, a further reduction in length of stay was possible when patients undergoing liver surgery were operated laparoscopically.[53]

Considering the aforementioned evidence for the specific perioperative care elements, a multimodal evidence-based ERAS programme for liver surgery can be proposed. *Table 1* shows a summary of the elements with their respective level of recommendation. If these elements are combined with clear discharge criteria and adequate minimization of delay after functional recovery[226] (often linked to social or logistic problems or problems in homecare support), patients may be offered the optimal strategy for a safe and rapid recovery and consequent discharge.

Table1. ERAS liver programme recommendations

Element	Evidence level	Recommendation grade
Preoperative counselling	B	Strong
Minimal preoperative fasting	B	Strong
No pre-anaesthetic premedication	B	Moderate
Antithrombotic prophylaxis	A	Strong
Antibiotic prophylaxis	A	Strong
Balanced anaesthesia with short-acting agents	C	Strong
Epidural anaesthesia / analgesia	B	Weak
Balanced intraoperative fluid management	A	Strong
Prevention of hypothermia	A	Strong
PONV prophylaxis	B	Strong
Incision of minimal length	C	Strong
No routine drainage of the peritoneal cavity	C	Low
No nasogastric drainage	A	Strong
Provision of oral analgesia	A	Strong
Prevention of post-operative ileus	B	Moderate
Early removal of urinary catheter	D	Weak
Early start oral intake	A	Strong
Early mobilisation	C	Moderate

Quality of evidence and recommendations were evaluated according to the GRADE guidelines[227]: A = High, B = Moderate, C = Low, D = Very low.

SECTION 3: EVIDENCE-BASED MEDICINE (EBM) IN SURGERY

Performing surgery and providing perioperative care based on evidence-based principles[228] has not always been standard. An EBM approach has been lacking for years and there are still many surgeons and centres that work with dogmatic routines for which often no evidence is available, rather than routines based on sound research and evidence. In 1996 Horton[229] already described the absence of well designed studies in the surgical community. A vast majority of research articles published in surgical journals at that time were case series. Nowadays we value case series as the weakest evidence available. Therefore, a large proportion of early surgical literature may be considered to be of questionable value.[229]

Slowly the opinion and attitude of surgeons has changed, and the evidence-based approach is now part of daily practice in various fields of surgery by quality improvements through well-designed trials, study groups, auditing[230-235] and adoption of consensus guidelines.[97, 117, 236-242] Many surgeons are eager to try and adopt new techniques. Minimally invasive surgery has become popular among surgeons.

This is of course inherent to the aim of improving surgical techniques and outcome, but should not lead to over enthusiastic adoption and dissemination of innovations without good evidence. A good example of this so-called overadoption is the laparoscopic cholecystectomy. This procedure was quickly adopted and became the dominant technique for removal of the gallbladder with no or ambiguous evidence in favour of it and increase in procedure related morbidity.[243] Nowadays it is seemingly without a doubt that laparoscopic cholecystectomy is to be preferred over open cholecystectomy, however the route to this adoption is questionable. Practice in the surgical community should be driven by evidence first with high respect for patient safety and surgeon preference should come second. In liver surgery a similar trend can be observed. Despite the consensus that laparoscopic liver surgery is only safe and effective in experienced hands and the urgent need for trials providing level A evidence[97], many surgeons have started to use the technique without evidence to support this. Not only are there no definitive conclusions regarding the short-term efficacy of laparoscopic liver resection, but also data on oncological outcomes, such as survival and resection margins, costs, patient-reported outcomes and incidence of incisional hernia are inconclusive or have yet to be presented.

The opposite may be true for the adoption of an enhanced recovery programme in liver surgery. As described in the previous section of this chapter, perioperative care has changed significantly. The multimodal concept has been extensively studied in colorectal surgery and has disseminated to other disciplines.[53, 225, 244-251] In addition, for most elements in the ERAS programme there is solid evidence.[238] To date such ERAS protocols seem underadopted, also in hepatic surgery. In many centres a formal standardized care pathway has not been implemented and, although some evidence-based elements may be adopted as part of "modern" current practice, perioperative care can still be further optimized to attenuate stress, improve recovery, lower morbidity and improve cost efficiency.[226]

The surgical community has become aware that it is necessary to improve surgical practice based on properly obtained data and to develop methods to implement this evidence.[252] Standardization of surgical techniques and perioperative care based on evidence will help to eliminated bias and confounding, will allow comparison in trials and will increase the external validity of study results. Surely, as is known from literature and the different elements in the ERAS programme, there is abundant knowledge available. Urbach et al.[253] have nicely stipulated: "The immediate challenge to improving the quality of surgical care is not discovering new knowledge, but rather how to integrate what we already know into practice". The delay of integrating this evidence in practice is multifactorial and may be dependent on the professional setting (attitude and culture), patients, organization of care processes, resources, leadership, cultural and social settings, and the political environment.[254, 255]

SECTION 4: OUTLINE OF THE THESIS

The aim of this thesis was to explore the current role, dissemination and worldwide adoption of an ERAS programme in liver surgery, to investigate and evaluate the potential role of specific (new) elements of the ERAS programme, to evaluated the implementation status of (laparoscopic) liver surgery from a Dutch as well as an international perspective, and to compare open and laparoscopic liver surgery in a randomised controlled setting.

PART I: OPTIMIZED RECOVERY AFTER HEPATIC SURGEY

We explore the role of the ways to enhanced patient recovery with an international survey (Chapter 2). A systematic review of patients undergoing liver surgery in an enhanced recovery after surgery pathways systematically examines the outcome (Chapter 3). We evaluate whether the current perioperative practice in hepatic surgery is actually based on the ERAS principles (Chapter 4). The last two chapters of part I of this thesis explore specific elements of the ERAS programme: post-operative analgesia and abdominal drainage. We explore an alternative for epidural analgesia after major hepatectomy (Chapter 5). Finally, we describe and investigate the results of a standard no-drain policy after hepatectomy (Chapter 6).

PART II: LAPAROSCOPIC LIVER SURGERY

In the second part of this thesis we provide a systematic review on the introduction of laparoscopic liver surgery, investigate the initial experience with laparoscopic liver resections and report on the current status of laparoscopic liver surgery in the Netherlands (Chapter 7). In the aim to compare open and laparoscopic liver surgery in a randomised controlled study we present the study protocol for the ORANGE II – Trial and the primary results (Chapter 8 – 9). Finally, we present the protocol of an ongoing RCT comparing open versus laparoscopic hemihepatectomy within an ERAS programme (Chapter 10).

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PART I

OPTIMIZED RECOVERY AFTER HEPATIC SURGERY

Chapter 2

A survey in the hepatopancreatobiliary community on ways to enhance patient recovery

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ABSTRACT

OBJECTIVE

Both laparoscopic techniques and multimodal enhanced recovery (ERAS) programmes have been shown to improve recovery and reduce length of hospital stay. Interestingly, evidence-based care programmes are not widely implemented, whereas new, minimally invasive surgical procedures are often adopted with very little evidence to support their effectiveness. The present survey aimed to shed light on experiences of the adoption of both methods of optimizing recovery.

METHODS

An international, web-based, 18-question, electronic survey was composed in 2010. The survey was sent out to 673 hepatopancreatobiliary (HPB) centres worldwide in June 2010 to investigate experiences with laparoscopic liver surgery, fast-track recovery programmes and surgery-related equipoise in open and laparoscopic techniques and to assess opinions on strategies for adopting laparoscopic liver surgery in HPB surgical practice.

RESULTS

A total of 507 centres responded (response rate: 75.3%), 161 of which finished the survey completely. All units reported performing open liver resections, 24.2% performed open living donor resections, 39.1% carried out orthotopic liver transplantations, 87.6% had experience with laparoscopic resections and 2.5% performed laparoscopic living donor resections. A median of 50 (range: 2–560) open and 9.5 (range: 1–80) laparoscopic liver resections per surgical unit were performed in 2009. Patients stayed in hospital for a median of 7 days (range: 2–15 days) after uncomplicated open liver resection and a median of 4 days (range: 1–10 days) after uncomplicated laparoscopic liver resection. Only 28.0% of centres reported experience with fast-track programmes in liver surgery. The majority considered the instigation of a RCT or a prospective register comparing the outcomes of open and laparoscopic techniques to be necessary.

CONCLUSION

Worldwide dissemination of laparoscopic liver resection is substantial, although laparoscopic volumes are low in the majority of HPB centres. The adoption of ERAS programmes in liver surgery is limited and should be given greater attention.

INTRODUCTION

In recent years, laparoscopic liver resection and enhanced recovery programmes have been introduced in liver surgery with the aim of accelerating post-operative recovery and shortening hospital length of stay (LoS). Like open liver resection, laparoscopic resection of liver lesions can be applied safely in both malignant and benign disease.[1–7] Large prospective case series suggest that laparoscopic liver surgery may be superior to open liver surgery in terms of perioperative blood loss, post-operative pain, time to recovery, LoS, cosmetic appearance and quality of life.[5,8–10] Survival rates after laparoscopic and open resection of hepatocellular carcinoma and hepatic colorectal metastases seem to be comparable.[1,5]

Similarly, fast-track programmes have proven to be useful, feasible and safe in liver surgery.[11–15] Such programmes can also enhance recovery and reduce LoS. Enhanced recovery after surgery (ERAS) programmes rely mainly on optimizing perioperative care and reducing stress responses to surgery through the provision of adequate preoperative patient counselling, optimized anaesthesia and analgesia, quick resumption of oral intake and early mobilization.[12,16–18] In liver resection, earlier resumption of oral intake, faster post-operative recovery and a significant reduction in median LoS (from 8 days to 6 days) was shown when patients were managed within a multimodal ERAS programme.[12]

A small pilot study in liver surgery suggested that laparoscopic liver surgery within an ERAS setting led to a potentially accelerated recovery and further reduction in LoS from7 days to 5 days.[11] Moreover, the combining of laparoscopy and an ERAS strategy is most likely to result in a synergetic effect, as recently proven in a randomized controlled trial (RCT) in the context of colonic surgery.[19]

Despite the fairly robust evidence that many specific elements of fast-track programmes can enhance recovery and reduce LoS, little evidence on the use of these programmes in liver surgery has been published. This suggests that the adoption of ERAS programmes in liver surgery worldwide is low. Current surgical practice is based on evidence and any change in daily routines should be supported by sound data.[20] In this respect, the current fairly liberal adoption of laparoscopic liver surgery contrasts with the relative lack of adoption of enhanced recovery programmes.

An international web-based survey was composed to evaluate worldwide experiences with laparoscopic liver surgery and fast-track recovery programmes, and surgery-related equipoise in open and laparoscopic strategies, and to assess opinions on strategies for the adoption of laparoscopic liver surgery in daily hepatopancreatobiliary (HPB) surgical practice.

METHODS

STUDY DESIGN

An online electronic survey, consisting of 18 questions subdivided according to five main domains, was developed. Questions on the different topics were initially composed by two research fellows (EMW-L-H and TML) and two liver surgeons (RMvD and JHMBS). The definitive set of questions was then administered using SurveyMonkey™ (SurveyMonkey, Inc., Palo Alto, CA, USA). Items in the first domain included several questions on experience in open and laparoscopic liver surgery and covered types and numbers of liver resections. Items in the second domain concerned recovery and LoS after uncomplicated open or laparoscopic liver resection. Items in the third domain surveyed experience with enhanced recovery or fast-track perioperative care programmes such as ERAS programmes. The fourth part of the survey was developed to evaluate opinions on the necessity of an RCT and on the value of a prospective registry comparing outcomes in open and laparoscopic liver surgery. Items in the final domain evaluated current opinions on and considerations for participating in such a trial. Incomplete responses were excluded from analysis.

STUDY POPULATION

An invitation to complete this survey was sent by e-mail to 673 HPB centres worldwide in June 2010. Subsequent e-mail reminders were sent out in August and September 2010. Only one surgeon per HPB unit was asked to participate. *Figure 1* describes the respondent inclusion and exclusion process. The participation period closed and analyses were conducted in November 2010.

STATISTICS

Survey data were extracted into an Excel database. Statistical analysis was performed using SPSS Version 18.0 (SPSS, Inc., Chicago, IL, USA) and GraphPad Prism Version 5 (GraphPad Software, Inc., La Jolla, CA, USA). Basic analyses were performed using descriptive statistics including counts, percentages, means with standard deviations and medians with ranges and interquartile ranges (IQRs). Subgroup analysis was performed to investigate potentially relevant differences among regions and centre experiences using the Mann–Whitney U-test or chi-squared test. All countries were assigned to one of the following six regions: Europe; North America; Central and South America; Asia; Oceania, and Africa. An experienced laparoscopic HPB centre was defined as a surgical unit performing 20 or more laparoscopic liver resections annually.[21]

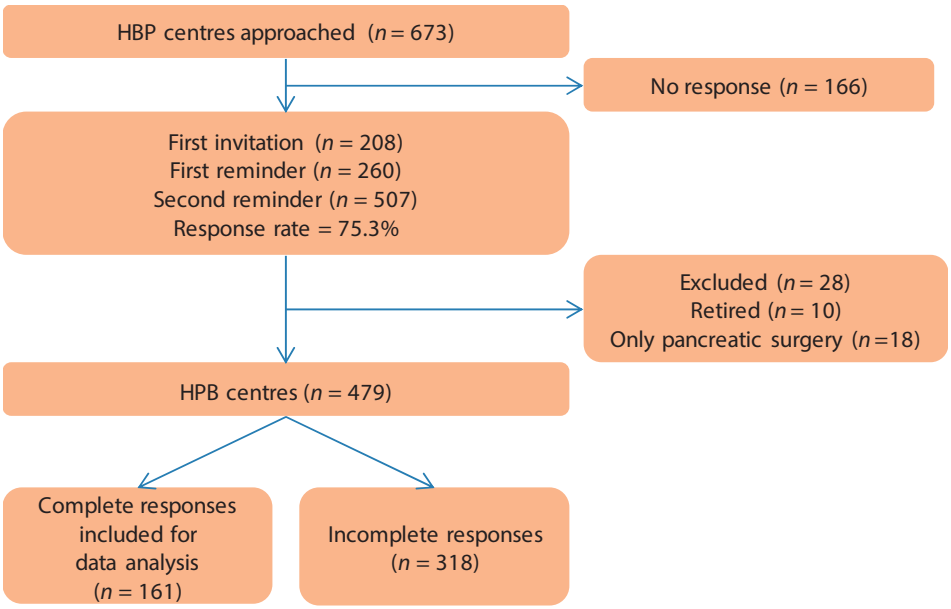

Figure 1. Flowchart showing the respondent inclusion and exclusion process.

RESULTS

PARTICIPATION

A total of 507 centres (one surgeon per centre) responded (response rate 75.3%). Incomplete responses were excluded from data analysis, leaving complete responses from 161 centres. Centres in 39 different countries participated; these were divided into groups according to the six global regions (*Fig. 2*). The regions that provided the highest response rates were Europe (45%) and North America (26%), with the USA (n = 34), Italy (n = 16), Canada (n = 8) and the Netherlands (n = 8) representing the top four countries providing complete responses.

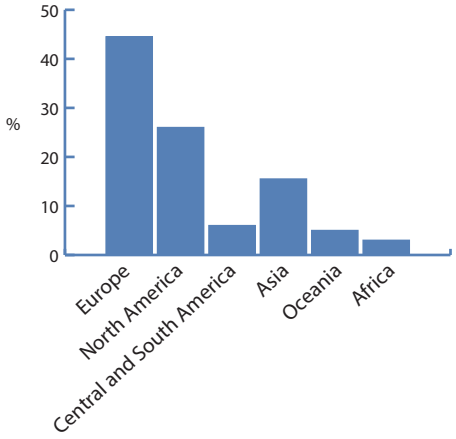

Figure 2. Centres (n = 161) included in the data analysis by region

TYPES OF LIVER RESECTION

Open resection of liver lesions was performed by 100% of the units. Overall, 87.6% of responding units reported experience with laparoscopic resection of liver lesions, 39.1% with orthotopic liver transplantation, 24.2% with open living donor resection and 2.5% with laparoscopic living donor resection. *Table 1* shows the percentages of HPB centres performing different types of liver surgery and the differences among regions.

EXPERIENCE

A total of 42.0% of responding centres indicated that their data represented precise numbers. The remaining centres provided estimations that were as accurate as possible. A wide range in the number of resections performed was observed among HPB centres. In 2009, the median number of open resections for liver lesions performed was 50 (range: 2–560; IQR = 50) per surgical unit. In the same year, the median number of laparoscopic resections of liver lesions performed was 9.5 (range: 1–80; IQR = 15) per centre. Worldwide figures for open and laparoscopic liver resections and differences among regions are shown in *Table 2*. Of the participating centres, 26.6% could be classified as experienced laparoscopic liver centres based on their completion of at least 20 laparoscopic liver resections per year (*Table 3*). Experienced laparoscopic centres seemed to be more frequently located in the Americas than in other continents (44.2% vs. 13.5%; $P < 0.001$).

Table 1. Centres performing types of procedure, by region, *n* (%)

	Europe	North America	Central and South America	Asia	Oceania	Africa	Worldwide
Open resection of liver lesions	72	42	10	24	8	5	161 (100.0)
Laparoscopic resection of liver lesions	61	41	10	19	7	3	141 (87.6)
Orthotopic liver transplantation	29	17	5	7	4	1	63 (39.1)
Open living donor resection	15	10	4	7	2	1	39 (24.2)
Laparoscopic living donor resection	1	1	1	1	0	0	4 (2.5)

Table 2. Number of resections per surgical unit per year (2009) liver resection

Region	Liver resections performed in 2009, median (range)/IQR	
	Open resection	Laparoscopic liver resection
Europe	5.0 (1–61)/9.0	5.0 (1–61)/9.0
North America	45.0 (6–200)/42.5	19.0 (2–80)/21.0
Central and South America	32.5 (12–80)/23.5	10.0 (3–30)/18.0
Asia	50.0 (5–560)/62.3	6.0 (1–80)/5.0
Oceania	57.5 (15–150)/110.0	9.0 (1–20)/7.0
Africa	50.0 (5–120)/115.0	4.5 (3–13)/7.8
Worldwide	50.0 (2–560)/50.0	9.5 (1–80)/15.0

IQR, interquartile range.

HOSPITAL LENGTH OF STAY AND FAST-TRACK CARE PROGRAMMES

The reported median hospital LoS after uncomplicated liver resection was 7 days (range: 2–15 days) after open surgery and 4 days (range: 1–10 days) after laparoscopic surgery. Differences among regions are shown in *Table 4*. In addition, a subgroup analysis showed that experienced centres achieved a significantly shorter median LoS after laparoscopic liver resection compared with inexperience centres [3.4 days (range: 1–7 days) vs. 4.2 days (range: 1–10 days); P = 0.013]. Half of the HPB centres (50.1%) had experience with fast-track perioperative care programmes in colonic, hepatic or pancreatic surgery or a combination of these fields. Only 28.0% had experience with these programmes in liver surgery. Results per region are shown in *Table 5*.

Table 3. Numbers of laparoscopic liver surgery centres demonstrating experience defined by a volume of >20 laparoscopic resections per year

Region	Experienced laparoscopic liver centres, *n*/laparoscopic liver centres, (%)
Europe	10/59 (16.9%)
North America	20/41 (48.8%)
Central and South America	3/9 (33.3%)
Asia	3/19 (15.8%)
Oceania	1/7 (14.3%)
Africa	0/4
Worldwide	37/139 (26.6%)

IQR, interquartile range.

NECESSITY FOR AN RCT

The majority (59.4%) of HPB centres considered that an RCT comparing outcomes in open and laparoscopic liver surgery prior to the further adoption of laparoscopic liver surgery was necessary. A total of 49.1% considered that a combination of such an RCT and a prospective multicentre registry should be mandatory; 36.4% considered that a prospective multicentre registry alone would be sufficient and 4.2% deemed a prospective hospital registry adequate. Of the surgical units that performed both open and laparoscopic left lateral sectionectomy (LLS) within a fast-track/ ERAS programme, 82.9% indicated that they would consider participating in an RCT. Level A evidence to support the superiority of the laparoscopic technique was still considered necessary by the majority of respondents. A total of 94.3% of participants with experience in both open and laparoscopic LLS, both within and without fast-track or ERAS programmes, would also consider participating in a prospective registry. Overall, 83.3% of liver units without experience in laparoscopic liver surgery indicated a desire to participate in hands-on training in laparoscopic liver surgery and/or a proctor programme.

Table 4. Length of stay after uncomplicated liver resection

Region	Length of stay, days, median (range)/IQR	
	After open resection	After laparoscopic resection
Europe	7.0 (4–12)/3.0	5.0 (2–10)/1.0
North America	5.0 (4–8)/2.0	3.0 (1–5)/1.5
Central and South America	5.0 (2–7)/1.8	2.5 (1–5)/2.0
Asia	7.0 (5–15)/2.0	4.0 (3–10)/2.0
Oceania	5.0 (3–7)/1.8	4.0 (2–5)/1.5
Africa	8.0 (4–10)/5.5	4.5 (2–7)/4.5
Worldwide	7.0 (2–15)/3.0	4.0 (1–10)/2.0

IQR, interquartile range.

Table 5. Centres with experience in fast-track perioperative care programmes

Region	Experience with ERAS programmes in a specific type of surgery, *n*/total *n* (%)			
	No experience	In colon surgery	In liver surgery	In pancreatic surgery
Europe	31/72 (43.1%)	36/72 (50.0%)	22/72 (30.6%)	14/72 (19.4%)
North America	25/42 (59.5%)	6/42 (14.3%)	9/42 (21.4%)	8/42 (19.0%)
Central and South America	5/10 (50.0%)	4/10 (40.0%)	3/10 (30.0%)	1/10 (10.0%)
Asia	15/24 (62.5%)	8/24 (33.3%)	4/24 (16.7%)	3/24 (12.5%)
Oceania	2/8 (25.0%)	5/8 (62.5%)	6/8 (75.0%)	2/8 (25.0%)
Africa	4/5 (80.0%)	1/5 (20.0%)	1/5 (20.0%)	0/5
Worldwide	82/161 (50.9%)	60/161 (37.3%)	45/161 (28.0%)	28/161 (17.4%)

ERAS, enhanced recovery after surgery.

DISCUSSION

This study aimed to assess the worldwide experience and dissemination of two recently introduced strategies to accelerate recovery after liver surgery. It demonstrates that the majority of HPB centres perform liver surgery in the absence of an enhanced recovery perioperative care programme, and that the majority of HPB centres perform laparoscopic liver surgery. This study also shows substantial variance in hospital LoS among centres and regions. Lastly, this study demonstrates the presence of clinical equipoise in laparoscopic and open liver resection in the HPB community.[22,23] Clinical equipoise refers to a context in which there is no preference or certainty of therapeutic superiority for either laparoscopic or open liver surgery. The majority of liver centres considered that an RCT was necessary to prove the laparoscopic technique to be equal or superior to open surgery.

The results show a high level of dissemination of laparoscopic liver surgery. Both low- and high-volume centres, amounting to 87.6% of HPB units, perform liver resections laparoscopically. Although the laparoscopic procedure is frequently used, many centres in this study have limited experience in laparoscopic liver resection. By contrast, responding centres displayed limited adoption of enhanced recovery programmes in liver surgery (one in four). The liberal adoption of laparoscopic liver surgery, even in low-volume HPB centres, is seemingly in conflict with current standards of evidence-based practice in the medical community. Neither is it in keeping with recommendations expressed in an expert consensus (the Louisville Consensus), which concluded that laparoscopic liver surgery was safe and effective in the hands of experienced and trained surgeons.[24] In line with the available evidence for fast-track principles in liver surgery,[11–15] proof of the merits of laparoscopic vs. open liver surgery is also limited and no RCTs have been undertaken. However, a recent literature review and meta-analysis of available prospective and retrospective studies comparing

open with laparoscopic liver resections both found short- and long-term outcomes favourable for the laparoscopic procedure. Not only was LoS markedly shorter, but blood loss and complications were found to be reduced and oncologic outcomes did not differ between the two techniques.[25,26]

Low-volume centres in this study reported a significantly longer hospital LoS compared with high-volume centres. In addition, LoS after open and laparoscopic liver surgery varied substantially among regions. The surgeon's progress along the laparoscopic learning curve influences LoS because laparoscopic liver resection is technically demanding and requires expertise in both advanced laparoscopic skills and open liver surgery.[27] This is in line with the findings of a meta-analysis of studies reporting on 20 or more laparoscopic procedures, which indicated that a laparoscopic approach led to a significant reduction in morbidity and LoS.[21] In addition, differences in standard of care and discharge criteria may also contribute to the variance in LoS reported in the literature (3–20 days after open and 6–32 days after laparoscopic liver resection).[25] Substantial distinctions at a cultural level may lie at the root of the observed variance in LoS. In some regions patients are discharged to a home care institution early in their recovery process (e.g. in North America), whereas in other world regions the provision of protocol-based care and the associated logistics may be lacking. This may lead to a difference in expectations on both the patient's and surgeon's part as to when a patient might be ready for discharge. Thus, LoS is a poor outcome parameter that hampers comparison and is hard to interpret. The implementation of a structured care programme with well-defined recovery and discharge criteria, as used within ERAS protocols, might improve the comparability of clinical outcomes in future (multicentre) trials.

Laparoscopy and enhanced recovery programmes should not be seen as separate methods of improving post-operative recovery and outcomes such as morbidity rates and LoS. On the contrary, it is likely that the implementation of both will result in a synergetic improvement. Enhanced recovery programmes in liver surgery have already been shown to reduce hospital LoS.[12–15] The additional benefit of an ERAS strategy in a laparoscopic setting was recently demonstrated in a trial in colonic surgery and a small pilot study in liver surgery.[11,19] This worldwide survey unveils experiences in enhanced recovery programmes and laparoscopic liver surgery, and deliberations on the need for RCTs in liver surgery. Although the present study achieved a response rate of >75%, only 23.9% of respondents completed the survey in full, which limited the study findings. However, representatives of 161 liver surgery centres worldwide shared their results and opinions.

The use of a survey may be seen as limiting the study because results are strongly dependent on the type of respondents, questions and response rate. In addition, the

group profile of responding centres may have been subject to response bias. Centres of considerable volume and those performing laparoscopic liver surgery may have been more likely to respond.

The issue of importance does not concern a choice between laparoscopic liver resection and an ERAS strategy, but, rather, how both paths can be adequately adopted. The majority of responders still consider an RCT of laparoscopic surgery to be necessary. It could be argued that as more liver centres adopt laparoscopic techniques, opportunities to conduct an RCT may be diminished by patient and surgeon preferences. According to some surgeons, laparoscopic liver resection is without doubt therapeutically superior, whereas for others this remains to be proven. In addition, in the Louisville Consensus of 2008, experts concluded that the accrual of patients for an RCT would be slow as a result of low overall numbers.

The ORANGE II Trial, currently enrolling patients, will be the first RCT (combined with a prospective registry) to provide evidence on laparoscopic vs. open liver resection.[28] As for enhanced recovery programmes, many centres are likely to have already implemented multiple ERAS elements as part of modern care. Further trials are needed to assess compliance with recovery protocols[29,30], specific elements of enhanced recovery programmes and the possible reduction of medical expenses.

CONCLUSION

The worldwide dissemination of laparoscopic liver resection is substantial, although the average volume of laparoscopic resections carried out in the majority of HPB centres is low. The adoption of enhanced recovery programmes in liver surgery is limited and the issue warrants greater attention. Both strategies are associated with faster recovery and may work synergistically. Given the increasing strength of the role of evidence-based medicine in current surgical practice, more evidence is required.

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Chapter 3

A systematic review of outcomes in patients undergoing liver surgery in an enhanced recovery after surgery pathways

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ABSTRACT

OBJECTIVE

Enhanced recovery after surgery (ERAS) or fast-track protocols have been implemented in different fields of surgery to attenuate the surgical stress response and accelerate recovery. The objective of this study was to systematically review the literature on outcomes of ERAS protocols applied in liver surgery.

METHODS

The MEDLINE, EMBASE, PubMed and Cochrane Library databases were searched for randomized controlled trials (RCTs), case–control studies and case series published between January 1966 and October 201 comparing adult patients undergoing elective liver surgery in an ERAS programme with those treated in a conventional manner. The primary outcome measure was hospital length of stay (LoS). Secondary outcome measures were time to functional recovery, and complication, readmission and mortality rates.

RESULTS

A total of 307 articles were found, six of which were included in the review. These comprised two RCTs, three case–control studies and one retrospective case series. Median LoS ranged from 4 days in an ERAS group to 1 days in a control group. Morbidity, mortality and readmission rates did not differ significantly between the groups. Only two studies assessed time to functional recovery. Functional recovery in these studies was reached 2 days before discharge.

CONCLUSION

This systematic review suggests that ERAS protocols can be successfully implemented in liver surgery. Length of stay is reduced without compromising morbidity, mortality or readmission rates.

INTRODUCTION

Liver resection is the preferred treatment for a variety of primary and secondary liver tumours. Major abdominal surgical procedures such as hepatic resections cause a considerable surgical stress reaction and possible derangements in metabolic and pulmonary functions. Specific complications after hepatic resection include post-operative haemorrhage in the first hours to days after surgery, biliary leakage, intra-abdominal abscess and liver failure in a later post-operative stage.[1] Improved operative techniques and insight into perioperative management have lowered mortality after liver resection to its current level of well below 5%, but morbidity rates remain high and range between 30% and 50%.[2–4]

In the past decade, multimodal enhanced recovery after surgery (ERAS) protocols or fast-track pathways have been applied in different forms of surgery. These pathways were developed to attenuate the surgical stress response and improve recovery, thereby decreasing post-operative complications and post-operative length of stay (LoS) in hospital.[5] ERAS protocols have gained territory quickly because of the associated cost efficiency derived from the reduction in LoS, an important issue in today's context of rapidly increasing health care costs and the consequent need for optimization. To date, studies that show ERAS protocols that reduce LoS and morbidity rates and improve patient satisfaction have been published in the contexts of vascular surgery[6,7], musculoskeletal surgery[8],breast surgery[9] and different forms of abdominal surgery.[10–12]

Enhanced recovery after surgery protocols have also been implemented in liver surgery, but their effectiveness has not been studied extensively. The present systematic review was performed to evaluate the effects of ERAS protocols in liver surgery on time to recovery following surgery and post-operative hospital LoS, and to examine the effects of the implementation of such protocols on complication and readmission rates following liver surgery.

METHODS

SEARCH STRATEGY

A systematic search was performed in PubMed, the Cochrane Library, EMBASE and MEDLINE for studies published between January 1966 and October 2011. Languages were restricted to English, Dutch and German. The following search terms were applied using the Boolean operators 'AND' and 'OR': 'clinical pathway', 'critical pathway', 'enhanced recovery', 'accelerated', 'perioperative' and 'fast track', combined

with 'liver', 'hepatic' and 'resection'. Synonyms of terms were also used in the search. The reference lists of selected papers were hand- searched for articles that were not retrieved in the database search. If necessary, authors of relevant articles were contacted to obtain additional information.

INCLUSION AND EXCLUSION CRITERIA

Studies were considered eligible for inclusion if they met all of the following inclusion criteria: (i) they reported on adult patients undergoing elective open or laparoscopic liver surgery; (ii) they described an enhanced recovery programme with at least four different perioperative elements, and (iii) they reported outcomes including LoS, post-operative morbidity and mortality, and readmission rates. Studies were excluded if they: (i) described a single intervention in perioperative care rather than a group of interventions combined in an enhanced recovery programme; (ii) reported on emergency, non-elective or transplantation surgery, and (iii) reported a non-systematic review. *Table 1* lists a summary of ERAS items applicable to liver surgery. The items are supported by varying levels of evidence.[13] Perioperative care is considered to fall within an ERAS protocol when at least four different items are included, covering the pre-, intra- and post-operative periods. [14,15]

OUTCOME MEASURES

The primary outcome measure of this systematic review was hospital LoS. Secondary outcome measures were time to functional recovery, complication rates, readmissions and mortality rates. Criteria for functional recovery were: good pain control with oral analgesia only; tolerance for solid food; no requirement for i.v. fluids; passage of stool, and independent mobility at the preoperative level.[16] Study selection and data selection Abstracts and titles of studies identified by the search were read by two authors (MMEC and AAvdW), each of whom independently made a first selection of studies. These first selections were compared and, in the event that the inclusion of a study required discussion, a third reviewer (RMvD) was consulted. Second and final selections were made independently by each of the two authors after reading the full-text articles. Both randomized as well as non-randomized studies were eligible for inclusion as long as they met the inclusion criteria. The methodological quality of the included studies was assessed using the MINORS (methodological index for non-randomized studies) criteria[17], a checklist scoring eight methodological items for non-comparative studies (maximum of 16 points) and an additional four items for comparative studies (maximum of 24 points). Missing data were obtained by contacting the authors of the relevant studies.

Table 1. Summary of ERAS elements applicable to liver surgery

Evidence based	Probably useful
No oral bowel prep	Preoperative counseling
Preop feeding: CHO loading up to 2h before surgery	Intravenous analgesia
No pre-anaesthetic medication	Stimulation of bowel movement with laxatives
Anti-thrombotic Prophylaxis	Early and scheduled mobilisation
Single dose antibiotics	Audit
Epidural analgesia	
Prevention of Post-operative Nausea and Vomiting (PONV)	
Avoiding hypothermia	
No routine drainage of peritoneal cavity	
No post-operative nasogastric intubation	
Good fluid balance	
Removal of urinary catheter on day 1	
Normal food at will after surgery from day 1	

Evidence based: separate items are graded level 1 or level 2 evidence (according to the guidelines of the Oxford Centre for Evidence Based Medicine[13]).
Probably useful: evidence is less strong, but felt to be useful since the items are most probably quality enhancing, are associated generally with a low incidence of adverse effects and low costs.

Data on the following factors were extracted from the included articles: post-operative LoS; number of patients included; patient ages; types of surgery; discharge criteria; functional recovery; mortality; morbidity; readmissions, and protocol adherence.

STATISTICAL ANALYSIS

As the search strategy did not identify any randomized controlled trials (RCTs) evaluating the outcomes of ERAS protocols against those of traditional care, the MOOSE (meta-analysis of observational studies in epidemiology) checklist for meta-analysis of observational studies was used to assess the possibility of conducting a meta-analysis.[18] The included studies were considered to be too heterogeneous to support this and therefore no attempt at meta-analysis was made. Results are subsequently presented in tables and figures.

RESULTS

SELECTED ARTICLES AND CHARACTERISTICS OF THE STUDIES

The literature search produced 307 articles, of which 300 were excluded after their abstracts had been read in the first round of selection because they did not concern the

evaluation of a fast-track programme in liver surgery (*Fig. 1*). After evaluation of the remaining seven papers, one was excluded because it was a nonsystematic review.[19]

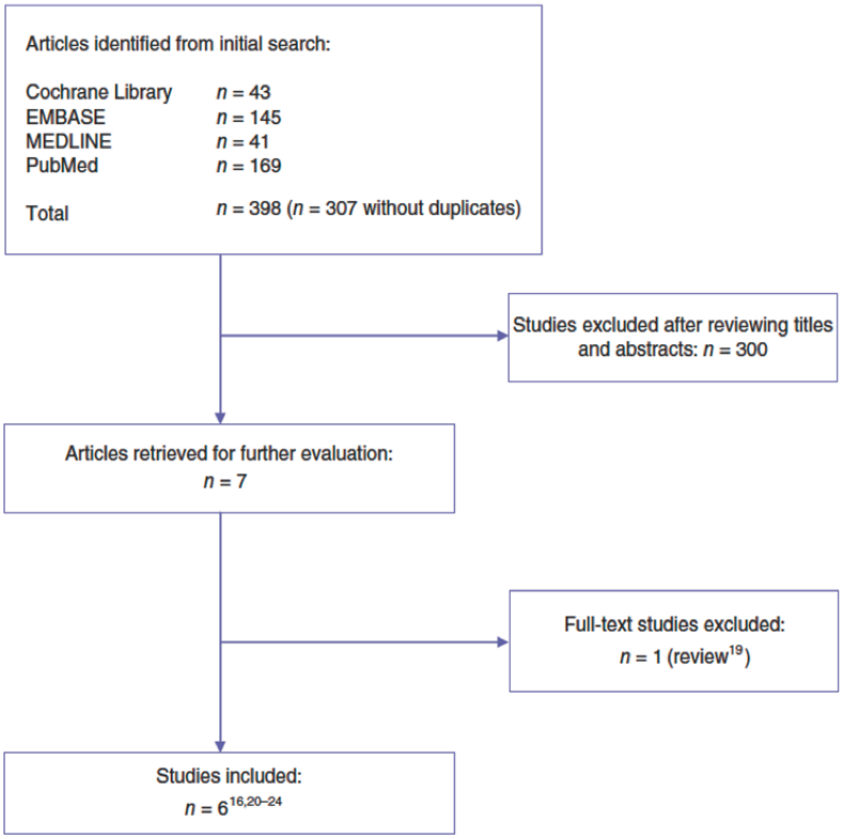

Figure 1. Selection of studies for systematic review

Finally, six papers were included in this systematic review. The details of the included studies are shown in *Table 2*.

There were no reports of RCTs evaluating the outcomes of an ERAS programme against those of traditional care. In two RCTs, both study groups were treated in an ERAS programme. One of these RC evaluated the use of laxatives and oral nutritional supplements within an ERAS programme[20] and one assessed different forms of post-operative analgesia in two groups managed in a fast-track programme.[21] Three case–control studies and one retrospective case series were also included.[16,22–24] All studies included patients undergoing various forms of liver resection, including (extended) hemi-hepatectomy, metastasectomy, sectionectomy, cen-

tral resection and repeat hepatectomy. One study did not include major hepatectomies; all patients in this study underwent laparoscopic liver resection.[20]

Table 2. Study characteristics and quality assessment

Study	Type of surgery	Study design	Patients in study/control groups, *n*	Consecutive series of patients	Length of follow-up	Age, years, median (years)		MINORS score
						ERAS group	Control group	
Van Dam et al. 2008	HE, EHE, ME, SE, CR, RHE	CC	61/100	Yes	30	62 (24-82)	60 (20-81)	18/24
Lin et al. 2011	SE, HE, EHE, CR	CC	56/61	Yes	30	57 (23-73)	55 (22-81)	17/24
Stoot et al. 2009	Laparoscopic: ME, SE, LLS	CC	13/13	Yes	3-6 months	55 (34-82)	45 (26-70)	19/24
Hendry et al 2010	HE, ME, SE, CR	RCT	68*	Yes	30	62 (53–69)	-	13/16
Koea et al. 2009	HE, EHE, ME, SE	RCT	100*	Yes	30	60 (23-83)	-	11/16
McKay et al. 2008	HE, SE	RS case series	12	yes	?	60 (43-74)	-	8/16

[a]Patients in the control and experimental arms were all treated according to ERAS protocols.
ERAS, enhanced recovery after surgery; HE, hemi-hepatectomy; EHE, extended hemi-hepatectomy; ME, metastasectomy; SE, segmentectomy; CR, central resection; RHE, repeat hemi-hepatectomy; LLS, left lateral sectionectomy; CC, Case-controle; RCT, randomized controlled trial; RS, Retrospective.

All studies included a consecutive series of patients. Follow-up was 30 days in four studies and 3–6 months in one study. One study did not report the duration of follow-up.

Age and other patient characteristics did not differ significantly among the patient groups described in the selected studies. Methodological quality assessed using the MINORS criteria was scored in the range of 17–19 points (of a maximum of 24 points) in case–control studies. Non-comparative studies achieved MINORS scores in the range of 8–13 points (of a maximum of 16 points).

Most studies described the enhanced recovery programme in detail. A summary of the specific ERAS elements included in the different studies is shown in *Table 3*. Fourteen protocol elements were identified. Most studies included the majority of these elements; one study included only seven elements.

Table 3. Summary of elements in an enhanced recovery after surgery (ERAS) programme included in each study.

Study	Preoperative					Perioperative					Post-operative			
	Pre-op counselling	Pre-op feeding	No premed	Trombo-embolic prophylaxis	No bowel prep	No drain	Epidural analgesia	Fluid restriction	Prevention of hypothermia	No NG tube	Early oral feeding (from POD 1)	Mobilization from POD 1	Laxatives	Early removal bladder catheter
Van Dam et al. 2008 [16]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lin et al. 2011 [22]	Yes	Yes	Yes		Yes	Yes	Yes	Yes		Yes	Yes	Yes		Yes
Stoot et al. 2009 [23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hendry et al 2010 [20]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Koea et al. 2009 [21]		Yes	Yes	Yes		Yes	Yes	Yes		Yes	Yes	Yes		Yes
McKay et al. 2008 [24]	Yes	Yes				Yes		Yes			Yes	Yes		Yes

PRIMARY AND SECUNDARY OUTCOME MEASURES

Table 4 outlines post-operative outcomes after implementation of an ERAS programme. Hospital LoS decreased significantly in the three comparative studies after ERAS implementation, in which median LoS was 5–7 days in the ERAS groups and 7–11 days in the traditional care groups.

In the non-comparative studies, post-operative LoS after liver resection ranged between 4 days and 7 days. In the study by Stoot et al.[21], all patients underwent laparoscopic liver resection. The median post-operative LoS was 5 days in the ERAS group and 7 days in the traditional care group; however, this difference was not statistically significant and the study did not include major liver resections. It is noteworthy that only two studies[17,20] assessed time to functional recovery and the reasons for delayed discharge. In both studies time to functional recovery was achieved 2 days prior to actual discharge from hospital. The main reasons for later discharge were concern for complications or extensive surgery, low patient confidence, and transport-related or other social problems.

Table 4. Post-operative outcome after implementation of a clinical pathway

Study	Type of surgery	Length of hospital stay (days; Study group vs control)	Morbidity (%; Study group vs control)	Mortality (%; Study group vs control)	Readmissions (%; Study group vs control)
Van Dam et al. 2008	HE, EHE, ME, SE, CR, RHE	6 vs 8 (p<0.001)	41 vs 31 (ns)	0 vs 2 (ns)	13 vs 10 (ns)
Lin et al. 2011	SE, HE, EHE, CR	7 vs 11 (p<0.001)	46.4 vs 43.3 (ns)	1.8 vs 1.6 (ns)	7.1 vs 3.3 (ns)
Stoot et al. 2009	Laparoscopic: ME, SE, LLS	5 vs 7 (ns) *Functional recovery: 3 vs 5 (p= 0.04)*	15.3 vs 15.3 (ns)	0 vs 0 (ns)	0 vs 0 (ns)
Hendry et al 2010	HE, ME, SE, CR	6 *Functional recovery: 4*	17	2	5
Koea et al. 2009	HE, EHE, ME, SE	4.7 ± 0.9 (intrathecal morphine) 6.8 ± 1.2 (epidural)	19	0	4
McKay et al. 2008	HE, SE	4 (2-7)	16.6	0	0

[HE: hemihepatectomy, EHE, extended hemihepatectomy, ME: metastasectomy, SE: segmentectomy, CR: central resection, RHE, repeat hemihepatectomy, LLS: left lateral sectionectomy]

Table 5 shows the extent of protocol adherence. The level of adherence to protocol was moderate in the studies included. Generally, nasogastric tubes were either not used or were immediately removed after surgery. The proportion of patients requiring the reinsertion of a nasogastric tube was low. In the study groups, intra- abdominal drains were used in only 2–13% of patients. The majority of patients re-

sumed oral fluid intake on the day of surgery and achieved a normal diet on days 1 or 2. The percentage of patients mobilized on the first post-operative day was low, with rates of 20–28% reported in only two studies.[20,21] In one study full mobilization was achieved on day 3 by 85% of patients.[16]

Tabel 5. Adherence to protocol

Protocol element	Van Dam et al. 2008 [16] (ERAS vs control)	Lin et al. 2011 [22] (ERAS vs control)	Stoot et al. 2009 [23] (ERAS vs control)	Koea et al. 2009 [21] (ERAS, n=100)	Hendry et al. 2010 [20] (ERAS, n=68)	McKay et al. 2008 [24] (ERAS, n=12)
No NG tube or removed directly after surgery	92 vs 0%	NA	0 vs 38%	100%	100%	NA
NG tube reinserted	4 vs 0%	3.5 vs 1.6%	0 vs 15%	NA	NA	NA
Intra-abdominal drain	2 vs 66%	0 vs 1.6%	0 vs 46%	2%	13%	0%
Oral fluid intake POD 0 (ERAS), % or days, median (range)	92%	NA	1 (0-2) vs 1 (0-6)	NA	94%	100%
Resumption normal food, % or days, median (range)	1 (0-3) vs 3 (0-14)	NA	1 (0-2) vs 1 (0-6)	20% on day 1	37% on day 1 91% on day 2	NA
Full mobilisation (ERAS)	85% on day 3	NA	NA	20% on day 1	28% on day 1	NA
Functional recovery criteria met on day	NA	NA	3 vs 5	NA	4	NA

NG, nasogastric; PoD, post-operative day; NA = data not available]

DISCUSSION

This systematic review examined the use of ERAS protocols in liver surgery in three case–control studies, two RCTs and one case series. The results suggest that an enhanced recovery protocol can be successfully implemented in liver surgery. Hospital LoS was reduced and functional recovery was accelerated without compromising morbidity or mortality rates, and readmission rates were not significantly increased. The present results are in line with a recent review describing the use of fast-track protocols in hepatopancreatic resections.[25]

At least four items in the pre-, peri- and post-operative periods must be included in an ERAS protocol for the protocol to be considered of value.[14,15] The studies in this review incorporated an average of 12 of 14 items (range: 7–14 items). In large series of patients undergoing liver surgery, LoS varies between 8 days and 14 days.[3,4] All of the studies included in this review reported a shorter LoS in the ERAS study group. Two studies assessed time to functional recovery, which was significantly lower than

total LoS. In many studies, LoS is reported as a primary outcome parameter. However, the use of this outcome may not always be appropriate as discharge is often delayed by a variety of other factors that may be unrelated to the true outcomes of the procedure.[26] The present authors therefore propose that time to functional recovery should be used as an outcome measure rather than LoS.

Morbidity rates reported in the literature vary from 38% to 45%[4,27] and are comparable with the complication rates reported in the studies in the present review. However, it should be noted that complications in the studies included here were not always reported using a validated classification system (e.g. Clavien–Dindo or Accordion classification [28,29]). This makes it more difficult to make meaningful comparisons of morbidity among the different centres.

The reporting of adherence to the various elements of the protocol was rather low in the included studies, especially as far as the introduction of normal diet and fluids was concerned. As Maessen et al.[30] have observed, the reporting of adherence to protocol seems to be problematic in a considerable number of international studies. This impedes comparisons among studies.[30] The use of self-report patient diaries and continuous education of nurses and staff may represent strategies for overcoming this difficulty.

Overall, the methodological quality of the studies included in the present review, as assessed according to the MINORs criteria, was acceptable. However, this systematic review is limited by the fact that no RCTs comparing fast-track with standard care were available for inclusion (the RCTs included treated both the patient and control groups according to an ERAS protocol) and only case series and comparative studies using historical controls were included. The studies included were considered to be too heterogeneous to allow a meta-analysis. Another limitation of this review is that the individual studies used slightly different study protocols, with the result that the items incorporated in the various protocols are not identical and thus these studies are not fully comparable. However, a recent study by Ahmed et al.[31] compared adherence to protocol in two groups of patients undergoing colorectal surgery and showed that outcome was unaltered in the study group in which adherence to some elements of the study protocol (e.g. preoperative carbohydrate loading and early fluid and diet introduction) was significantly lower. From this, it seems reasonable to conclude that not every item of an ERAS protocol makes an independent contribution to enhanced recovery, but, rather, it is the combination of different items in a structured care pathway that determines the outcome. This might also to some degree reflect a Hawthorne, or trial, effect, indicating a positive effect resulting from the implementation per se of a complex and comprehensive intervention.

Kehlet first introduced ERAS protocols in colon surgery in 1997.[32] Now, 15 years later, several items drawn from ERAS protocols are increasingly implemented in modern care worldwide. However, in many surgical fields, ERAS protocols have not yet been accepted as standard care. In the context of liver surgery, ERAS was first described in 2008 [24], since when only five studies examining an ERAS protocol in this field have been published[16,20–23] and three of these were performed by the same study group.[16,21,23] This seems to illustrate a limited international implementation of ERAS protocols in liver surgery.

Although the methodology used in the studies included is not optimal, the results are consistent and seem to indicate clear advantages in terms of recovery. Although most centres today perform a proportion of resections laparoscopically, the present results serve to illustrate what can be achieved in open surgery and hence serve as a backdrop against which advances in technique and subsequent results can be compared.

In summary, this systematic review shows that it is feasible and safe to implement an ERAS protocol in hepatic surgery. The available evidence suggests that LoS is shortened without comprising morbidity, mortality or readmission rates. In view of the limited number of studies and the discrepancies in reporting among them, the present authors recommend the application of a standardized system of classifying complications, the accurate reporting of adherence to protocol, and the use of time to functional recovery as a primary outcome measure in future studies in order to enhance quality and comparability.

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Chapter 4

Is current perioperative practice in hepatic surgery based on enhanced recovery after surgery (ERAS) principles?

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ABSTRACT

OBJECTIVE

The worldwide introduction of multimodal enhanced recovery programs has also changed perioperative care in patients who undergo liver resection. This study was performed to assess current perioperative practice in liver surgery in 11 European HPB centres and compare it to enhanced recovery after surgery (ERAS) principles.

METHODS

In each unit, 15 consecutive patients (N = 165) who underwent hepatectomy between 2010 and 2012 were retrospectively analysed. Compliance was classified as ''full',' ''partial'', or ''poor'' whenever ≥80, ≥50, or <50 % of the 22 ERAS protocol core items were met. The primary study end point was overall compliance with the ERAS core program per unit and per perioperative phase.

RESULTS

Most patients were operated on for malignancy (91 %) and 56 % were minor hepatectomies. The median number of implemented ERAS core items was 9 (range = 7–12) across all centres. Compliance was partial in the preoperative (median 2 of 3 items, range = 1–3) and perioperative phases (median 5 of 10 items, range: 4–7). Median post-operative compliance was poor (median 2 of 9 items, range = 0–4). A statistically significant difference was observed between median length of stay and median time to recovery (7 vs. 5 days, P<0.001).

CONCLUSION

Perioperative care among centres that perform liver resections varied substantially. In current HPB surgical practice, some elements of the ERAS program, e.g., preoperative counselling and minimal fasting, have already been implemented. Elements in the perioperative phase (avoidance of drains and nasogastric tube) and post-operative phase (early resumption of oral intake, early mobilization, and use of recovery criteria) should be further optimized.

INTRODUCTION

A multimodal enhanced-recovery perioperative care program for elective abdominal surgery was introduced by Kehlet et al. [1] at the end of the last century. The enhanced-recovery concept combines several evidence-based aspects of perioperative care into a structured care pathway, thereby enabling accelerated post-operative recovery and potentially reducing post-operative morbidity. Within the surgical community, several groups, such as the international enhanced recovery after surgery (ERAS) collaboration, have embraced and studied the enhanced recovery concept. This led to the successful introduction of a new standard in perioperative care for colorectal surgery patients [2]. In recent years the same principles have also been applied in the perioperative care of liver surgery patients, and a few studies have shown that the program is feasible, safe, and effective for resection of hepatic tumours [3–10].

Actual data on the status of current practice and whether multimodal clinical pathways in liver surgery have been implemented are scarce. Over time, several elements of the ERAS concept have probably been introduced without implementation of a fully formal enhanced-recovery program. A recent survey in the international HPB community showed marginal implementation of ERAS protocols worldwide [11]. Based on the successful introduction and implementation of ERAS programs in various fields of surgery [12–17] and promising results in hepatic surgery, further dissemination of the ERAS concept within the liver surgical field seems desirable. First, to accelerate recovery and reduce length of hospital stay, it is necessary to aim for uniform and evidence-based perioperative management. Moreover, a structured and detailed program with well-defined recovery and discharge criteria can improve comparability of clinical outcomes in clinical audits and future clinical trials. Finally, it is likely that implementation will have a synergetic effect with minimally invasive surgery, as shown in colorectal surgery [18].

It has been suggested that implementation of a structured enhanced-recovery program in liver surgery is hard to achieve since multidisciplinary involvement is essential [19]. However, surgical practice has changed over the years and many ERAS elements may have already been introduced in current practice. Therefore, following an initial electronic survey [11], the aim of this study was to more accurately evaluate current perioperative care by assessing to what extent the different elements of an ERAS program have been implemented in liver surgery in a group of expert HPB units in Europe.

METHODS

STUDY DESIGN

A retrospective analysis of prospectively collected data was conducted to assess current perioperative practice in patients undergoing liver surgery in a number of expert HPB centres in Europe. Fifteen consecutive patients per centre were assessed. All available medical records (patient and nursing charts, surgery and anaesthesia reports) for the different elements in the pre-, intra-, and post-operative phases of admission were reviewed and evaluated using a detailed baseline checklist that consisted of the previously described ERAS elements [4]. This checklist was further developed and adjusted by two hepatic surgeons (RMvD, CHCD) and two researchers (EMWLH, LH). Primary study endpoints were overall compliance with the ERAS core program per unit and per element. Secondary endpoints were day of discharge and time to functional recovery (FR).

ERAS ELEMENTS AND COMPLIANCE

The program's core elements are displayed in *Table 1* and are grouped as pre-, peri (day of surgery), and post-operative elements. If an element in the checklist was marked as ''yes'', the hospital was able to apply the ERAS element for a particular patient. Details explaining (non)compliance were also added to the ''Comments'' section of the checklist. Compliance was defined as the degree to which individual units or elements were in accordance with the ERAS program. Units were classified as ''fully'', ''partially'' or ''poorly'' compliant whenever ≥80, ≥50, or >50 %, respectively, of the assessed 22 ERAS core items were met. Per individual element, an 80 % cut-off value was set to qualify a unit as ''compliant.'' In addition, time to FR was assessed with predefined and previously described criteria [4, 5] (*Table 2*).

STUDY POPULATION

Liver units with a declared interest to participate in a random controlled trial (RCT) on laparoscopic liver resection in an ERAS setting [20] were invited by email to participate in this retrospective study. A total of 11 European high-volume centres (25 cases/year)[21] participated (see list below). The last 15 consecutive patients who underwent liver surgery in each hospital were selected and reviewed (open– close procedures and biliodigestive /vascular anastomoses were excluded). Included patients were all admitted and operated on between 2010 and 2012. All patients received perioperative care according to local protocols.

Table 1. ERAS core protocol elements

Preoperative
Preoperative counselling
Minimal preoperative fasting (solid food up to 6 h + clear fluids up to 2 h) + carbohydrate loading
No anxiolytic premedication
Perioperative
Thoracic epidural analgesia
Prevention of hypothermia
CVP monitoring (CVP\5 mmHg)
No routine drainage of the peritoneal cavity
No standard nasogastric drainage
Start intake of water and free fluids
Early mobilization
Post-operative nausea and vomiting (PONV) prophylaxis
Antithrombotic prophylaxis
Antibiotic prophylaxis
Post-operative day 1 – 3
Daily review of discharge criteria
Ileus prevention (MgO/Macrogol/Lactulose)
Free fluids/normal diet POD 1
Intravenous fluids discontinued POD 1
Oral analgesia POD 1
Normal diet POD 2
Removal of urinary catheter POD 2
Stop epidural/intravenous analgesia POD 3
Full mobilization POD 3

Table 2. Functional recovery criteria

1. Pain control with oral analgesia only
2. No intra-venous fluid support
3. Full mobilization to preoperative level
4. Eating of solid food
5. Normal serum bilirubin or returning toward normal ranges

ERAS EXPERIENCE

Three of the 11 centres indicated that they had formally implemented ERAS protocol for liver surgery. The implementation of ERAS principles in these three centres was achieved by multidisciplinary involvement, including a liver surgeon, an anaesthetist, recovery ward nursing staff, and a researcher. In addition, all Dutch centres in this study had already gained experience with the ERAS program for colonic surgery as

most of them participated in a nationwide structured implementation plan [22, 23]. The other hospitals were aware of the ERAS programs for liver and colonic surgery, but a structured implementation and evaluation had not yet been performed. Centres that had implemented the ERAS liver surgery program used the FR criteria (*Table 2*) to assess readiness for discharge. In the other centres the operating surgeon or physician on call was responsible for discharge and no strict criteria were applied.

DATA AND STATISTICS

Data were anonymously collected in an Oracle 10 database (Oracle Corp., Redwood Shores, CA, USA) with OpenClinica trial software for online data capture and management (Ikaza Research, Cambridge, MA, USA) and analysed using SPSS ver. 19 (SPSS Inc., Chicago, IL, USA). Basic analyses were performed using descriptive statistics. To describe the compliance in the complete cohort based on results of individual centres, a random-effect logistic regression analysis was used. This adjusts for the heterogeneity of compliance among centres. The constant in the logistic regression model was transformed to an overall cohort compliance, except for three items that did not fit into the model (weighted median was used in these cases). Comparison between groups was performed using the Mann–Whitney U and Wilcoxon signed-ranks tests as appropriate. All statistical tests were two-sided, and $P<0.05$ was considered statistically significant.

RESULTS

PATIENT AND SURGICAL CHARACTERISTICS

A total of 165 patients were included in this study. Baseline patient characteristics are given in *Table 3*. Surgical details with regard to type of incision and resection are given in *Table 4*. Overall morbidity and the distribution of post-operative surgical complications according to the Clavien–Dindo grading system can be found in *Table 5*.

PRIMARY ENDPOINTS

Overall compliance with the ERAS core elements varied among the assessed centres (*Fig. 1*). None of the participating hospitals were shown to be "fully" compliant with the complete set of core ERAS elements. Centres provided a median number of 9 (range = 7–12) of pre-, peri-, and post-operative care items according to the ERAS protocol. Five hospitals were partially compliant (11 or more items) and the remaining six hospitals were poorly compliant to the core elements. A summary of the overall compliance per ERAS element across all units (N = 165 patients) is given in *Tables 6 and 7*.

Table 3. Baseline characteristics of patients (N = 165)

Median age, years (range)	62 (19 – 89)
Male gender	83 (50)
ASA grade	
I	21 (13)
II	111 (67)
III	32 (19)
Missing	1 (1)
Malignancy	150 (91)

Values in parentheses are percentages, unless indicated otherwise.
ASA American Society of Anaesthesiologists

Table 4. Surgical characteristics of patients (N = 165)

Incision	
Laparoscopic	22 (13)
Kocher's/J-shaped	81 (49)
Bilateral subcostal	19 (12)
Mercedes	12 (7)
Median	13 (8)
Other[a]	11 (7)
NA	7 (4)
Liver resection	
Minor (<3 segments or non-anatomical)	93 (56)
Major (≥3 segments)	45 (27)
Simultaneous non-hepatic	27 (16)
Type	
Wedge resection/segmentectomy	46 (28)
Bisegmentectomy	23 (14)
Right hepatectomy	24 (15)
Left hepatectomy	2 (1)
Deroofing/enucleation	1 (1)
Extended right hepatectomy	4 (2)
Extended left hepatectomy	2 (1)
Multiple wedge resections/segmentectomies	35 (21)
Major (≥3 segments)	10 (6)
Other[b]	28 (17)
Major (≥3 segments)	3 (2)

Values in parentheses are percentages, NA not available
a Thoracoabdominal and xiphopubic incisions
b Hepatic resections combined with RFA or nonhepatic procedures

Table 5. Morbidity (N = 165)

Overall morbidity	47 (28)
Clavien–Dindo	
Grade I	8 (5)
Grade II	26 (16)
Grade IIIa	6 (4)
Grade IIIb	2 (1)
Grade IVa	5 (3)
Grade IVb	-
Grade V (death)	-
Readmissions	3 (2)

Values in parentheses are percentages

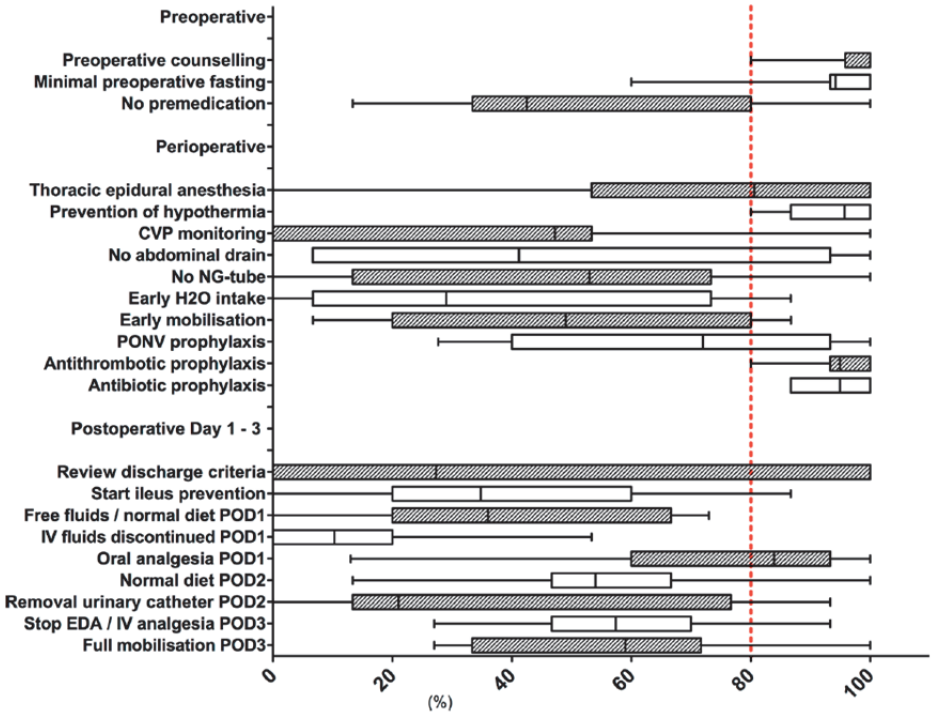

Figure 1. Box plots of overall compliance per ERAS core elements of 11 participating centres. Box plots resemble the 25–75 % confidence intervals. Black vertical line within a box is the median value. The vertical dotted line represents the 80 % compliance cut-off value.

Table 6. Compliance with ERAS elements

	N/total N (%)	Overall median compliance (range)
Preoperative		
Preoperative counselling	162/165 (98)	96 (80-100)
Assessment of discharge arrangements	120/165 (73)	73 (0-100)[a]
Assessment of mobility	122/164 (74)	74 (0-100)[a]
Daily review of discharge criteria	45/165 (27)	27 (0-100)[a]
Normal oral diet up to 6 h + clear fluid intake up to 2 h	155/165 (94)	94 (60-100)
No anxiolytic premedication	91/162 (56)	43 (13-100)
Perioperative		
Thoracic epidural anaesthesia (EDA)	119/165 (72)	81 (80-100)
Prevention of hypothermia	157/160 (98)	96 (80-100)
Laparoscopy / right subcostal incision	102/159 (64)	65 (13-87)
CVP monitoring (CVP < 5 mmHg)	47/102 (46)	47 (0-100)
No post-operative nasogastric tube	72/161 (45)	53 (0-100)
No routine use of abdominal drain	76/165 (46)	41 (7-100)
Post-operative day (POD) 0		
PONV prophylaxis	110/164 (67)	82 (40-100)
Antithrombotic prophylaxis	157/164 (96)	95 (80-100)
Antibiotic prophylaxis	155/162 (96)	95 (87-100)
Oral fluid intake	100/162 (62)	42 (7-87)
Mobilisation at all	13/150 (9)	6 (7-87)
Start oral analgesia	86/163 (51)	51 (7-100)
Use of patient-controlled analgesia (EDA or IV)	132/165 (80)	83 (0-93)
POD 1		
Nasogastric tube removed	107/160 (67)	66 (0-100)
Tolerance of free fluids / normal diet	63/165 (38)	36 (0-73)
Mobilisation at all / out of bed	82/160 (51)	50 (7-87)
No intravenous fluids	17/165 (10)	10 (0-53)
Oral analgesia	129/165 (78)	84 (13-93)
Use of patient-controlled analgesia (EDA / IV)	114/165 (69)	75 (0-93)
CAD removal	14/161 (9)	5 (0-60)
Flatulence and/or stool	15/148 (10)	10 (0-20)
POD 2		
Normal diet	101/165 (61)	54 (13-80)
Mobilisation out of bed	118/159 (74)	76 (13-93)
No intravenous fluids	34/165 (21)	19 (0-67)
Oral analgesia	135/165 (82)	86 (13-93)
Use of patient-controlled analgesia (EDA / IV)	91/165 (55)	54 (0-87)
Urinary catheter removal	41/159 (26)	21 (0-93)
Flatulence and/or stool	59/145 (41)	41 (0-67)

	N/total N (%)	Overall median compliance (range)
POD 3		
Normal diet	120/165 (73)	73 (13-93)
Full mobilisation	81/151 (57)	86 (27-93)
No intravenous fluids	76/165 (46)	56 (0-73)
Oral analgesia	139/165 (84)	90 (13-93)
Use of Patient Controlled Analgesia (EDA / IV)	46/165 (28)	25 (0-87)
Urinary catheter removal	85/157 (54)	52 (0-93)
Flatulence and/or Stool	108/154 (70)	71 (13-93)
Use of cathartics / laxatives	61/165 (37)	35 (0-87)

Overall median compliance represents all assessed centres (N = 11)
CVP central venous pressure, PONV post-operative nausea and vomiting,
IV intravenous,.
a Weighted median

PRIMARY ENDPOINTS

Overall compliance with the ERAS core elements varied among the assessed centres (*Fig. 1*). None of the participating hospitals were shown to be ''fully'' compliant with the complete set of core ERAS elements. Centres provided a median number of 9 (range = 7–12) of pre-, peri-, and post-operative care items according to the ERAS protocol. Five hospitals were partially compliant (11 or more items) and the remaining six hospitals were poorly compliant to the core elements. A summary of the overall compliance per ERAS element across all units (N = 165 patients) is given in *Tables 6 and 7*.

PREOPERATIVE

Median compliance of the centres with preoperative core items was partial (66 %, 2 of 3 elements, range = 1–3). All centres provided preoperative counselling, predominantly on procedural issues and complications. Three centres provided extensive counselling, with attention to post-operative elements such as early oral feeding and mobilization, FR, and discharge criteria. No record of preoperative counselling could be found for 2 % of the patients. For 94 % (60–100) of the patients, preoperative fasting was reduced to a minimum. Anxiolytic premedication was not given to 43 % (13–100) of the patients.

Table 7. Compliance with ERAS core elements per centre

	Centres										
	A	B	C	D	E	F	G	H	I	J	K
Preoperative											
Preoperative counselling (%)	100	100	100	100	100	100	100	80	93	100	100
Minimal preoperative fasting (%)	60	100	100	100	100	100	100	80	93	100	100
No anxiolytic premedication (%)	13	67	80	40	40	27	80	100	87	20	53
Perioperative											
Thoracic epidural analgesia (%)	100	93	100	80	87	93	100	53	7	0	80
Prevention of hypothermia (%)	87	93	93	100	80	100	100	100	87	100	100
CVP monitoring (%)	13	33	13	53	7	0	0	100	20	73	0
No routine drainage of the peritoneal cavity (%)	67	53	100	93	100	27	53	7	7	7	87
No standard nasogastric drainage (%)	27	40	13	67	73	7	53	0	13	87	100
Start intake of water/free fluids (%)	7	40	80	0	47	13	67	0	0	80	87
Early mobilization (%)	7	47	33	53	20	13	80	87	40	87	73
PONV prophylaxis (%)	80	27	93	73	93	47	100	40	93	33	60
Antithrombotic prophylaxis (%)	93	80	93	93	100	100	100	100	100	93	100
Antibiotic prophylaxis (%)	100	100	87	93	100	87	93	100	93	100	87
Post-operative days 1–3											
Daily review of discharge criteria (%)	0	0	0	100	0	0	100	0	0	0	100
Ileus prevention (%)	27	13	40	87	27	60	20	27	0	80	27
Free fluids/normal diet POD 1 (%)	20	33	20	73	47	33	67	0	7	53	67
Intravenous fluids discontinued POD 1 (%)	0	0	0	0	0	0	53	0	33	20	7
Oral analgesia POD 1 (%)	100	87	93	100	60	93	93	13	73	53	93
Normal diet POD 2 (%)	40	67	47	100	53	67	40	13	73	100	73
Removal of urinary catheter POD 2 (%)	0	47	7	13	13	7	0	27	40	93	33
Stop epidural/intravenous analgesia POD 3 (%)	27	80	53	73	53	33	60	60	93	60	40
Full mobilization POD 3 (%)	27	73	60	80	40	27	33	67	100	33	33

Total N = 165, with 15 patients per centre
CVP central venous pressure, PONV post-operative nausea and vomiting, POD post-operative day

PERIOPERATIVE

Median compliance with perioperative core items was partial (50 %, 5 of 10 elements, range = 4–7). Ninety-six per cent (87–100) of the patients received active prevention of hypothermia and 81 % (0–100) received thoracic epidural anaesthesia. In 13 % (0–13), the procedure was laparoscopically performed, and in 49 % (26–100), a right subcostal incision was used. In 47 % (0–100) of the patients, the central venous pressure (CVP) was closely monitored and kept below 5 mmHg during parenchymal tran-

section. In 53 % (0–100) of the patients, nasogastric tubes (NGT) were removed immediately after the operation, and in 41 % (7–100), abdominal drains were not used. In contrast to antithrombotic and antibiotic prophylaxes, prophylaxis for post-operative nausea and vomiting (PONV) was frequently provided, but not as per routine in all patients.

POST-OPERATIVE

Median compliance of the centres with post-operative core items was poor (22 %, 2 of 9 elements, range = 0–6). Early oral fluid intake, directly after surgery, was commenced in only 42 % (7–87) of the patients on POD 0, and only 36 % (0–73) tolerated free fluids or a normal diet on POD 1 (independent of the extent of liver surgery). After surgery patient-controlled intravenous (PCIA) or epidural analgesia (PCEA) was started in 83 % (0–93) of the patients as the standard of care. Oral analgesia was provided to 90 % (13–93) of patients, but in 14 % oral pain medication was not started until POD 2. Mobilization was achieved in only 50 % (13–93) of the patients on POD 1. In 56 % (0–73) of the patients, IV support was discontinued on POD 3. Urinary catheters were removed on POD 3 in 52 % (0– 93), and they were usually not removed until the day of or the day after thoracic epidural anaesthesia was discontinued. Signs of return of bowel function (flatulence and/or stool) were seen in 71 % (13–93) of patients on POD 3.

SECONDARY ENDPOINTS

Data on the day of discharge and the time to FR are depicted in *Fig. 2*. The median length of stay (LOS) after surgery was 7 (range = 1–27) days and 31, 49, and 64 % of all patients were discharged on POD 5, 6, and 7, respectively. Using the FR criteria, a majority of the patients could be considered functionally recovered on median POD 5 (1–24). This difference between discharge and time to FR was statistically significant ($P<0.001$). Eighty-one per cent (N = 133) of the patients were not discharged on the day that FR criteria were fulfilled. In 29 % of patients, complications were responsible for prolonged hospitalization (Table 5). Although time to FR and LOS were in favour of the centres that were partially compliant with the ERAS program, differences did not reach statistical significance (*Figs. 3, 4*).

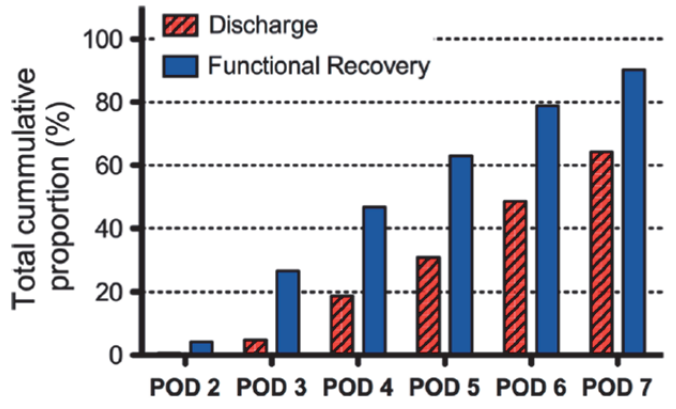

Figure 2. Discharge versus functional recovery, P < 0.001. Cumulative proportion of all patients (N = 165) who were discharged on POD 2–7 and who were functionally recovered (FR). POD post-operative day

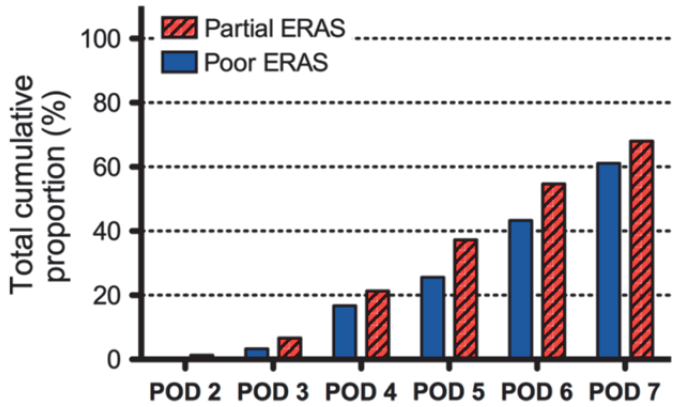

Figure 3. Discharge in partial ERAS centres (N = 5) versus poor ERAS centres (N = 6), P = 0.166. Cumulative proportion of patients who were discharged on POD 2–7

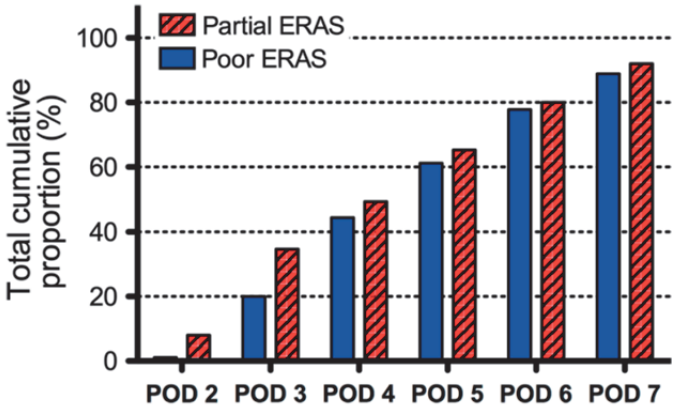

Figure 4 Functional recovery in partial ERAS centres (N = 5) versus poor ERAS centres (N = 6), P = 0.149. Cumulative proportion of patients who were functionally recovered on POD 2–7

DISCUSSION

This study evaluated the current perioperative care in 11 high-volume European liver surgery centres by assessing compliance with an ERAS program. Perioperative care varied considerably among the centres. All of the participating institutions had already adopted a median of 9 (range = 7–12) elements of the ERAS care program as part of modern surgical practice. None of the centres had implemented the complete set of core elements. Interestingly, pre- and perioperative elements had the best implementation, but the centres were especially poor at complying with ERAS elements in the post-operative phase. In addition, a significant discrepancy between the patient's recovery and actual discharge was observed.

Every centre consistently provided preoperative counselling, limited the fasting period, actively prevented hypothermia during surgery, and systematically administered antithrombotic and antibiotic prophylaxes. Also, PONV prophylaxis, the use of epidural anaesthesia, and patient-controlled analgesia already had a prominent place. In contrast to the aforementioned care elements, other ERAS components were absent or suboptimally implemented. The partial or poor compliance and wide variation among the centres mirror this.

During the preoperative phase, anxiolytic medication was commonly used. Two striking perioperative observations were the widespread use of abdominal drains and NGT. In addition, the CVP during parenchymal transection was poorly documented. In the post-operative phase, the resumption of oral intake, removal of the urinary catheter, use of laxatives, and mobilization were only poorly implemented.

Based upon previous studies, it is known that preoperative counselling on the role and expectations of the patient in the recovery period could further optimize post-operative recovery and satisfaction [24, 25]. Also, the use of anxiolytic premedication could negatively influence gastrointestinal motility and, although it is safe to use short-acting benzodiazepines in day surgery [26], their efficacy for major surgery remains unclear.

Important accumulated evidence for the perioperative phase has shown that the necessity of abdominal drains can be questioned after uncomplicated liver resection [27]. Equally, it is well known that it is safe to remove NGTs directly after abdominal surgery [28]. The use of an NGT is even associated with an increased risk of developing post-operative pulmonary complications [28, 29].

There is an ongoing discussion concerning central venous pressure monitoring (CVP <5–10 mmHg). Low CVP can be utilized to minimize back bleeding during parenchymal transection and to avoid excessive administration of IV fluids [30– 32]. However, it could be argued that CVP monitoring is not strictly necessary in minor hepatectomies, which represent a majority in the present study.

Lastly, patient-controlled analgesia may help to reduce opioid use and its associated side effects [33]. However, there is debate concerning the role of epidural catheters (EDA). Although frequently used in the participating centres, they are no longer used in an increasing number of other hospitals that perform liver surgery. Not only can the technique be contraindicated, e.g., because of the presence of coagulopathy, it can also cause potentially serious complications such as epidural hematoma, abscess, or paralysis [34]. The epidural catheterization is more time-consuming than intravenous analgesia and fails to provide adequate analgesia in 20 % of the patients [35].

It may be felt that ERAS principles are not uniformly applicable to all patients and other factors (e.g., age, comorbidity, indication for surgery, and extent of liver resection) could play a role. There are good alternatives to core elements that would not deter from the ERAS principles. Post-operative pain has traditionally been managed by intravenous or epidural analgesia. It can be argued whether the inclusion of thoracic epidural analgesia as a core element reflects current clinical practice. The use of wound catheters with a local anaesthetic [36–38] or the use of intrathecal morphine [39] has been shown to be safe and effective also in an ERAS setting for liver surgery [40, 41]. Furthermore, alternatives to reduce CVP or monitor it could serve as a substitute and may be sufficient [42, 43].

In the post-operative phase, the still abundant use of NGTs could explain why early intake of water on POD 0 was achieved in only less than one third of the patients and

why only half of the patients tolerated a normal diet on POD 2. A quick return to a normal diet has been shown to be safe for both major upper abdominal and colorectal surgeries [44, 45]. In addition, to promote the return of normal bowel function or prevent a post-operative ileus, standard use of laxatives has been shown to be effective [4, 5]. Lastly, few patients mobilized out of bed before POD 2. The use of drains, lack of daily mobilization goals, and relatively late removal of catheters can explain this observation.

A secondary outcome was the length of hospital stay versus the time to FR. It is generally agreed that it is medically justified to discharge patients when criteria for full FR are met [4, 5, 20]. In keeping with literature data [4, 19], a discrepancy was found between discharge and time to FR. A majority of patients (63 %) principally were functionally recovered on median POD 5 (range = 1–24), while only 31 % were discharged at that time. Factors influencing this delay could have been poor organization of discharge logistics, cultural differences, and deviant patient expectations. Unfortunately, it was not possible to assess all five FR criteria because serum bilirubin values were inconsistently available. Bilirubin values were therefore assumed normal since the majority of the liver resections in this study were minor procedures.

The retrospective assessment of the data, the selection of participating centres, and their varying experience with ERAS principles may have biased our results. However, this design was deliberately chosen so as to not influence the behaviour of medical and nursing staff in perioperative care during a full prospective assessment. Both large and small hepatic centres were allowed to participate and this could also have influenced our results. However, the large number of minor resections in this study and the participation of several high-volume European centres with varying experience with ERAS protocols do provide a reflection of daily practice in liver surgery and therefore increase external validity.

Based on this study several recommendations can be made that could eventually lead to further optimization of care and potentially improve post-operative outcomes. Change of current practice and implementation of an enhanced-recovery care pathway are desirable but will require multidisciplinary efforts [19, 46]. Although counselling is already part of preoperative care in that information on the procedure and possible complications is provided, there should be more emphasis on the recovery period with respect to pain control, early mobilization, resumption of intake, and time of discharge. Furthermore, administration of preoperative anxiolytic medication should not be the standard. Recommendations for the perioperative phase include the selective monitoring of the CVP and abandoning the standard use of abdominal drains and the dogmatic use of NGT. For patients undergoing liver surgery, the use of NGTs is not needed at all and seems very conservative. In combina-

tion with adequate PONV prophylaxis, a safe and quick return to a normal diet may be facilitated. In addition, laxatives can be provided in a standard manner, urinary catheters should be removed earlier, and daily mobilization goals should be determined. Lastly, predefined discharge criteria should be checked daily to minimize a delay in discharge after FR.

The findings of this study are clinically relevant to liver surgeons as they aim for a universally accepted and standardized perioperative care program. The findings may help to provide the standardization needed for comparability in clinical audits and trials. Future research should clarify the role of the individual components in ERAS programs and investigate to what extent an element contributes to the improvement of outcomes. Several recent studies [8–10] have already demonstrated the additional value of ERAS programs with predefined discharge criteria. In addition, safe and effective alternatives or new elements should be embraced.

CONCLUSION

Perioperative care among centres that perform liver resections varied substantially and elements of enhanced recovery programs had already been implemented as part of daily surgical practice. Other elements can be further optimized based on ERAS principles. This may standardize care and improve recovery after liver surgery.

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Chapter 5

Post-operative pain control using continuous i.m. bupivacaine infusion plus patient-controlled analgesia compared with epidural analgesia after major hepatectomy

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ABSTRACT

OBJECTIVE

There is debate concerning the best mode of delivery of analgesia following liver resection, with continuous i.m. infusion of bupivacaine (CIB) plus patient-controlled i.v. analgesia (PCA) suggested as an alternative to continuous epidural analgesia (CEA). This study compares these two modalities.

METHODS

A total of 498 patients undergoing major hepatectomy between July 2004 and July 2011 were included. Group 1 received CIB + PCA (n = 429) and Group 2 received CEA (n = 69). Groups were analysed on baseline patient and surgical characteristics. Primary endpoints were pain severity scores and total opioid consumption. Secondary endpoints were pain management failures, need for rescue medication, postoperative (opioid-related) morbidity and hospital length of stay (LoS).

RESULTS

In both groups pain was well controlled and >70% of patients had no or minimal pain on PoDs 1 and 2. The numbers of patients experiencing severe pain were similar in both groups: PoD 1 at rest: 0.3% in Group 1 and 0% in Group 2 ($P = 1.000$); PoD 1 on movement: 8% in Group 1 and 2% in Group 2 ($P = 0.338$); PoD 1 at rest: 0% in Group 1 and 2% in Group 2 ($P = 0.126$), and PoD 2 on movement: 5% in Group 1 and 5% in Group 2 ($P = 1.000$). Although the CIB + PCA group required more opioid rescue medication on PoD 0 (53% versus 22%; $P < 0.001$), they used less opioids on PoDs 0–3 ($P \leq 0.001$), had lower morbidity (26% versus 39%; $P = 0.018$), and a shorter LoS (7 days versus 8 days; $P = 0.005$).

CONCLUSION

The combination of CIB + PCA provides pain control similar to that provided by CEA, but facilitates lower opioid consumption after major hepatectomy. It has the potential to replace epidural analgesia, thereby avoiding the occurrence of rare but serious complications.

INTRODUCTION

The upper abdominal wall incision is a major contributor to post-operative pain after liver resection.[1,2] Given the continuing increases in both the volume and extent of liver surgery, along with the introduction of enhanced recovery programmes[3–7], there is debate about the optimal method of delivering post-operative analgesia. Effective post-operative pain control will reduce the incidence of numerous post-operative complications, can facilitate early mobilization and may result in earlier recovery.[8,9] Pain control is usually achieved by the administration of opioids, which may cause side-effects, such as sedation, respiratory depression, pruritus, hallucinations and post-operative nausea and vomiting (PONV).

Epidural analgesia has been considered superior to i.v. patient-controlled analgesia (PCA) for post-operative pain relief in patients recovering from major upper abdominal operations[10,11], although patient satisfaction with i.v. PCA is higher.[11] However, the use of epidural analgesia after hepatectomy is still subject to debate. Because epidural analgesia can lead to serious complications, such as epidural abscess or haematoma[12], it may be contraindicated when post-operative coagulopathy is expected.[13,14] In addition, epidural methods take time to induce anaesthesia and may not function adequately in up to 30% of patients.[15]

An alternative analgesic modality for the control of post-operative pain is the continuous infiltration of local anaesthetic using wound catheters placed in the abdominal wall.[16–18] It is nearly a decade since this method of post-operative pain management was introduced in liver surgery and it has shown promising results. [19,20] In other fields of surgery, the use of continuous wound infiltration has suggested a reduction in costs.[21–23] The most recent study, a randomized controlled trial (RCT) performed by Revie et al. in 2012, demonstrated that local wound infiltration combined with i.v. PCA, compared with continuous epidural analgesia (CEA), reduced the time required to fulfil criteria for discharge from hospital, but provided inferior analgesia.[24]

This retrospective study provides insights into the post-operative analgesic merits of i.m. continuous infusion of bupivacaine (CIB) combined with i.v. PCA, compared with mid-thoracic CEA alone after major hepatic surgery.

METHODS

PATIENTS

All open major hepatectomies (n = 545) performed in the Hepatobiliary Unit of the North Hampshire Hospital in Basingstoke, UK, between July 2004 and July 2011 were included for screening. Data were prospectively collected and stored in a dedicated database by research staff blinded to the type of post-operative analgesia. Data on post-operative milestones, such as day of first oral intake and day of independent mobilization, were retrospectively added to the database after all available documentation for both living and deceased patients had been reviewed. Primary study endpoints were pain severity scores at rest and on movement during the first 48 h post-operatively, and total opioid requirements during the first 72 h post-operatively. Secondary endpoints were pain management failures, need for rescue medication, opioid-related morbidity and hospital length of stay (LoS).

SURGERY

General anaesthesia was induced with i.v. propofol (1.5–2.0 mg/kg) and fentanyl (1–2 mcg/kg), with maintenance using volatile anaesthetics (iso-, des- or sevoflurane) in oxygen and air. For this study, major hepatectomy was defined as resection of at least three liver segments according to Couinaud's classification.[25] Hepatectomies were performed by four liver surgeons (MR, FKSW, TGJ and ABC), of whom only one (TGJ) used epidural catheters as the preferred method of providing post-operative analgesia. Standard transection techniques were used for liver resection under total or selective hepatic vascular exclusion, as described previously.[26,27] Unfavourable intraoperative incidents were graded according to the Satava system for the evaluation of surgical error, adapted for liver surgery.[28] Post-operative morbidity was classified and analysed using the Accordion system for grading surgical complications (with Clavien–Dindo modifications), as described by Strasberg et al.[29,30] Operating time was defined as the time between the first induction of anaesthesia and the patient's departure from the theatre. All patients received antibiotic, and nausea and vomitus (PONV) prophylaxis preoperatively. In the CIB + PCA group, PONV prophylaxis (cyclizine or dexamethason on induction, ondansetron post-operatively) was continued until PCA was removed.

INCISION, WOUND CLOSURE AND CATHETER PLACEMENT

Access to the abdominal cavity was achieved with a right subcostal incision[31,32] extended to the bed of the right 12th rib laterally and through the upper midline to the level of the xiphoid superiorly ('L' incision). The skin incision was made by knife;

diathermy was used through subcutaneous tissue and muscles. Wound closure and catheter placement techniques were also standardized and have been previously described by Basu et al.[19]

DELIVERY OF ANALGESIC DRUGS

Immediately after wound closure, the i.m. catheters were flushed with a 10-ml bolus of 0.25% bupivacaine, and continuous i.m. catheter infusions of 0.25% bupivacaine were commenced at a rate of 3 ml/h by syringe pump. This was continued for 72 h post-operatively. Patient-controlled analgesia using morphine (1 mg bolus with a 5-min lockout) or a fentanyl infusion (20 mcg bolus with a 5-min lockout) was set up. In the CEA group, an epidural catheter was sited before surgery in the thoracic T5–T12 region. This epidural catheter was also used to provide analgesia during surgery (20 ml bupivacaine 0.25%). During emergence from anaesthesia, the patient was transferred to the recovery area, in which the PCA + CIB or CEA was started. The epidural infusion of bupivacaine 0.1% with 2 mcg/ml fentanyl was set at 5–15 ml/h. A dedicated pain team unaware of the type of hepatic resection or any concomitant surgical procedure(s) assessed and scored the patients daily until the i.v. or epidural analgesia could be stopped. Pain intensity was scored using a verbal rating scale (VRS) ranging from 0 (no pain) to 4 (worst imaginable pain). The level of sedation was also measured on a 5-point scale (0 = awake, 1 = dosing intermittently, 2 = sleeping and easy to wake, 3 = sleeping and difficult to wake, 4 = unarousable). Wound and urinary catheters were removed at the discretion of the operating surgeon, but usually after 72 h [midnight on post-operative day (PoD) 3]. Pain management failures in both groups were defined as the need for rescue medication or a switch to a different opioid. The need for rescue medication was defined as any additional epidural, i.v., i.m. or oral administration of an opioid. A switch to a different analgesic protocol was defined as any change in analgesic medication, concentration or infusion rate. In the event of the technical failure of the epidural catheter, the patient was commenced on PCA with morphine or fentanyl. Oral analgesia [acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids] was available in a standard manner to all patients. No standardized enhanced recovery after surgery (ERAS) programme was implemented during this study period.

STATISTICS

To facilitate comparisons between the two patient groups and the different opioids, all opioids required were converted to an i.v. morphine equivalent (*Table 1*). Comparisons between groups were performed using Pearson's chi-squared or Fisher's exact test for non-normally distributed categorical variables, as appropriate, and the Mann–Whitney U-test or Kruskal–Wallis test for continuous variables. All statistical

tests were two-sided. A P-value of < 0.05 was considered to indicate statistical significance. Statistical analysis was performed using IBM SPSS Statistics for Windows Version 19.0 (IBM Corp., Armonk, NY, USA).

Table 1. Opioid conversion ratios

	Conversion ratio	Reference
Intravenous		
Morphine	1:1	
Fentanyl (mcg/ml)	1:10	[34-36]
Epidural		
Fentanyl (mcg/ml)	3:10	[37]
Oral Medication		
Oxycodone	2:1	[34]
Morphine	3:1	[38, 34, 36]
Tramadol	15:1	[34]
Codeine	24:1	[34]

Opioid conversion ratios lead to an i.v. morphine (mg/ml) equivalent.

RESULTS

GENERAL AND SURGICAL CHARACTERISTICS

Of 545 patients identified in the database for the study period, a total of 498 patients (CIB + PCA, n = 429; CEA, n = 69) underwent major liver resection and were included in this study. For 41 of the 47 patients excluded, no data on opioid requirements could be retrieved. This was mostly the result of either admission with sedation to the intensive care unit (ICU) or the absence of fluid balance/opioid infusion charts. Of the remaining six excluded patients, four received PCA without CIB, and one received epidural analgesia combined with CIB. No data at all could be retrieved for the final patient. General patient characteristics are shown in *Table 2* and surgical characteristics in *Table 3*.

PRIMARY ENDPOINTS

The total median opioid consumption in milligrams (i.v. morphine equivalent) was markedly lower in the CIB + PCA group (for all time-points: $P \leq 0.001$). However, postoperative pain was equally well controlled in both groups (*Table 4*). The maximum percentages of pain scores missing for the complete group of included patients were 27.7% and 28.3% on PoDs 1 and 2, respectively.

Table 2. General characteristics of patients undergoing major hepatectomy in the present series

	Epidural group (n = 69)	CIB + PCA group (n = 429)	P-value
Age, years, median (range)	63 (29–84)	63 (21–86)	0.695
Male sex, n (%)	42 (60.9%)	269 (62.7%)	0.770
BMI, kg/m2, median (range)	24.0 (20.0–33.5)	26.0 (16.0–44.0)	0.126
ASA physical status, n (%)			
Class 1	2 (2.9%)	10 (2.3%)	0.673
Class 2	51 (73.9%)	320 (74.6%)	0.924
Class 3–5	13 (18.8%)	87 (20.3%)	0.828
Number of comorbidities, n (%)			
0	37 (53.6%)	196 (45.7%)	0.240
1	19 (27.5%)	136 (31.7%)	0.466
2	6 (8.7%)	61 (14.2%)	0.190
≥3	7 (10.1%)	33 (7.7%)	0.498
Indication for surgery, n (%)			
Colorectal metastases	56 (81.2%)	369 (86.0%)	0.290
Hepatocellular carcinoma	1 (1.4%)	4 (0.9%)	0.529
Cholangiocarcinoma (intrahepatic and hilar)	1 (1.4%)	12 (2.8%)	1.000
Other malignancies[a]	3 (5.8%)	32 (7.4%)	0.453
Benign disease[b]	8 (10.1%)	12 (2.6%)	0.003
Previous abdominal surgery	59 (85.5%)	376 (87.6%)	0.324

CIB + PCA, i.m. continuous infusion of bupivacaine plus i.v. patient-controlled analgesia; BMI, body mass index; ASA, American Society of Anesthesiologists.
A P-value of < 0.05 was considered to indicate statistical significance.
[a] Other malignancies include metastases of carcinoid, breast cancer, melanoma, neuroendocrine tumour, appendix carcinoma, ovarian carcinoma, squamous cell carcinoma of the vagina, renal cell carcinoma, lymphoma, endometrial carcinoma, gastrointestinal stromal tumour, mixed type hepatocellular carcinoma/cholangiocarcinoma, lymphoma and keratinizing squamous cell carcinoma.
[b] Benign diseases include cyst(s), adenoma, focal nodular hyperplasia, haemangioma and angiomyolipoma.

SECONDARY ENDPOINTS

Intramuscular catheters were removed at a median of PoD 3 (range: PoD 2–5). Data on pain management failures, need for rescue medication and technical failures are shown in *Table 4*. Overall morbidity was higher in the epidural group (39.1%) than in the CIB + PCA group (26.1%) (P = 0.030). Complication grades rated on the Accordion system (with Clavien–Dindo modifications), length of hospital stay and readmissions are displayed in *Table 5*. One death occurred in the epidural group (1.4%) and two (0.5%) occurred in the CIB + PCA group (P = 0.361). The patient in the epidural group died from myocardial infarction. In the catheter group, one patient died from liver failure and the other from multi-organ failure caused by severe sepsis after endoscopic retrograde cholangiopancreatography (ERCP) for a bile leak. Specific compli-

cations per group are shown in *Table 6*. No instances of respiratory depression were observed. There were no reported cases of epidural hematoma, abscess formation or paralysis in the group that received an epidural catheter.

Table 3. Operative characteristics of patients undergoing major hepatectomy in the present series

	Epidural group (n = 69)	CIB + PCA group (n = 429)	*P*-value
Operating time, min, median (range)	260 (150–475)	260 (28–480)	0.356
Blood loss, ml, median (range)	295 (55–844)	369 (30–5344)	**0.020**
Incision, n (%)			
Right subcostal	67 (97.1%)	425 (99.1%)	0.165
Other[a]	2 (2.9%)	4 (0.9%)	0.196
Segmental distribution of hepatectomies, n (%)			
3 segments	8 (11.6%)	65 (15.2%)	0.438
3 segments + wedge	3 (4.3%)	26 (6.1%)	0.783
3 segments + multiple wedge	1 (1.4%)	9 (2.1%)	1.000
4 segments	40 (58.0%)	163 (38.0%)	**0.002**
4 segments + wedge	5 (7.2%)	70 (16.3%)	0.051
4 segments + multiple wedge	3 (4.3%)	25 (5.8%)	0.783
5 segments	5 (7.2%)	49 (11.4%)	0.301
5 segments + wedge	3 (4.3%)	13 (3.0%)	0.475
5 segments + multiple wedge	1 (1.4%)	6 (1.4%)	1.000
6 segments	0	3 (0.7%)	1.000
Additional procedures, n (%)			
Cholecystectomy	13 (18.8%)	66 (15.4%)	0.478
Lymph node sampling	0	12 (2.8%)	0.387
Diaphragmatic resection	3 (4.3%)	18 (4.2%)	1.000
Roux-en-Y reconstruction	1 (1.4%)	3 (0.7%)	0.450
Right colectomy	1 (1.4%)	2 (0.5%)	0.361
Incisional hernia repair	0	3 (0.7%)	1.000
Ablation	0	6 (0.7%)	1.000
Other[b]	2 (2.9%)	45 (11.2%)	**0.046**
Satava classification, n (%)			
Grade I	0	17 (4.0%)	0.147
Grade II	0	2 (0.5%)	1.000
Grade III	0	1 (0.2%)	1.000

CIB + PCA, i.m. continuous infusion of bupivacaine plus i.v. patient-controlled analgesia.
A P-value of < 0.05 was considered to indicate statistical significance.
[a] Other incisions include abdominal longitudinal incision, Mercedes Benz incision and laparoscopic converted to open surgery.
[b] See Appendix 1 for details.

Table 4. Post-operative analgesia in patients undergoing major hepatectomy in the present series

	Epidural group ($n = 69$)	CIB + PCA group ($n = 429$)	*P*-value
Time to discontinuation, days, median (range)	3 (1–5)	4 (1–8)	**0.001**
Cumulative opioid consumption[a], mg, median (range)			
12 h	29.1 (0.0–266.0)	17.5 (0.0–1015.0)	**<0.001**
24 h	91.2 (5.0–1546.4)	43.0 (0.0–1225.0)	**<0.001**
48 h	148.4 (6.0–1952.8)	58.0 (0.0–1625.0)	**<0.001**
72 h	186.1 (4.0–1952.8)	61.0 (0.0–1650.0)	**<0.001**
VRS score at rest PoD 1, n (%)			
0	41 (89.1%)	234 (73.8%)	**0.024**
1	4 (8.7%)	69 (21.8%)	0.047
2	1 (2.2%)	13 (4.1%)	1.000
3	0	1 (0.3%)	1.000
4	0	0	
VRS score on movement PoD 1, n (%)			
0	29 (65.9%)	92 (29.4%)	**<0.001**
1	11 (19.4%)	148 (46.8%)	**0.006**
2	3 (6.8%)	52 (16.4%)	0.118
3	1 (2.3%)	20 (6.3%)	0.491
4	0	4 (1.3%)	1.000
VRS score at rest PoD 2, n (%)			
0	42 (93.3%)	273 (87.5%)	0.256
1	2 (4.4%)	32 (10.3%)	0.284
2	0	7 (2.2%)	0.603
3	1 (2.2%)	0	0.126
4	0	0	
VRS score on movement PoD 2, n (%)			
0	26 (59.1%)	134 (42.8%)	**0.042**
1	15 (34.1%)	118 (37.7%)	0.632
2	1 (2.3%)	45 (14.4%)	0.027
3	1 (2.3%)	16 (5.1%)	0.706
4	1 (2.3%)	0	0.124
Pain management failures, PoD 0–3[b], n (%)	22 (31.9%)	231 (53.8%)	**0.001**
Opioid rescue medication[c], n (%)			
PoD 0	15 (21.7%)	228 (53.1%)	**<0.001**
PoD 1	3 (4.3%)	8 (1.9%)	0.185
PoD 2	5 (7.2%)	6 (1.4%)	**0.010**
PoD 3	6 (8.7%)	5 (1.2%)	**0.002**
Switch to different analgesic protocol[d], n (%)	14 (20.3%)	6 (1.4%)	**<0.001**

	Epidural group ($n = 69$)	CIB + PCA group ($n = 429$)	*P*-value
Technical failure	14 (20.3%)	114 (26.6%)	0.268
Dislocation	7 (10.9%)	4 (0.9%)	
Leakage	4 (6.3%)	1 (0.2%)	
Occlusion	3 (4.7%%)	109 (25.8%)	

CIB + PCA, i.m. continuous infusion of bupivacaine plus i.v. patient-controlled analgesia; PoD, post-operative day; VRS, verbal rating scale (0–4).
A P-value of < 0.05 was considered to indicate statistical significance.
[a]Expressed as i.v. morphine equivalent (any route).
[b]Pain management failure: need for rescue medication or switch to different opioid.
[c]Rescue medication: any additional intravenous, epidural, intramuscular or oral opioid.
[d]Switch to different analgesic protocol: change of drug, concentration or infusion rate.

Table 5. Post-operative outcomes in patients undergoing major hepatectomy in the present series

	Epidural group (n = 69)	CIB + PCA group (n = 429)	*P*-value
Complications (Accordion Classification), *n* (%)			
Grade I	3 (4.3%)	16 (3.7%)	0.737
Grade II	10 (14.5%)	31 (7.2%)	0.057
Grade III	0	14 (3.3%)	0.235
Grade IV	11 (15.9%)	40 (9.3%)	0.130
Grade V	2 (2.9%)	7 (1.6%)	0.361
Grade VI (death)	1 (1.4%)	2 (0.5%)	0.361
Length of stay, days, median (range)	8 (3–80)	7 (3–95)	**0.005**
Readmissions (<30 days), *n* (%)	2 (2.9%)	15 (3.5%)	1.000

CIB + PCA, i.m. continuous infusion of bupivacaine plus i.v. patient-controlled analgesia.
A *P*-value of < 0.05 was considered to indicate statistical significance.

DISCUSSION

This study compared the analgesic value of CEA with that of CIB + PCA following major hepatectomy. Data for this large, retrospective cohort show that CIB + PCA provided analgesic control equivalent to that of CEA. No significant differences in the numbers of patients experiencing severe pain were observed between the two groups and the majority of patients in both groups had no or minimal pain during the first 48 h post-operatively. Strikingly, the CIB + PCA group consumed significantly lower total volumes of opioids, had lower post-operative morbidity and a decreased hospital LoS.

The present findings would appear to indicate that post-operative pain was well controlled in both groups and that very few patients experienced severe pain on PoDs 1 and 2. In addition, most patients (>70%) in both groups had zero or minimal pain at rest or on movement. There is little practical difference between level 0 and level 1 pain, but 'no pain' and 'severe pain' lie at either end of any pain intensity scale and thus it seems safe to conclude that the present findings are reliable. The use of CIB + PCA also led to a substantial decrease in opioid consumption without compromising pain control. The decrease in opioid consumption was expected and can be explained by two factors. Unlike those in the CIB + PCA group, patients with epidurals were not able to control their opioid administration. In addition, the local analgesic effect of bupivacaine reduces the need for i.v. opioid infusion. Interestingly, patients with wound catheters were discharged 1 day earlier than those in the epidural group, at a median of 7 days rather than 8 days (P = 0.005).

Table 6. Morbidity in patients undergoing major hepatectomy in the present series

	Epidural group (*n* = 69)	CIB + PCA group (*n* = 429)	*P*-value
Overall morbidity, *n* (%)	27 (39.1%)	112 (26.1%)	**0.030**
Complications, *n* (%)			
Bile leak	2 (2.9%)	16 (3.7%)	
Liver failure	13 (18.8%)	43 (10.0%)	
Sepsis	0	5 (1.2%)	
Abdominal abscess	1 (1.4%)	4 (0.9%)	
Ileus	0	5 (1.2%)	
Pneumonia	3 (4.3%)	11 (2.6%)	
Pleural effusion	1 (1.4%)	4 (0.9%)	
Myocardial infarction	1 (1.4%)	2 (0.5%)	
Wound infection	1 (1.4%)	11 (2.6%)	
Renal failure	2 (2.9%)	7 (1.6%)	
Post-operative haemorrhage	0	4 (0.9%)	
Peritonitis	0	2 (0.5%)	
Ascites	1 (1.4%)	8 (1.9%)	
Biliary stricture/stenosis	0	4 (0.9%)	
Multi-organ failure	1 (1.4%)	4 (0.9%)	
Pneumothorax	0	2 (0.5%)	
Urinary tract infection	2 (2.9%)	6 (1.4%)	
Atrial fibrillation	3 (4.3%)	2 (0.5%)	
Other	2 (2.9%)	12 (2.8%)	
Analgesia-related morbidity (all), *n* (%)	29 (45.3%)	169 (41.4%)	0.558
Pruritus	14 (20.3%)	92 (21.4%)	
Hallucinations	7 (10.1%)	80 (18.6%)	
Dizziness	4 (5.8%)	32 (7.5%)	

	Epidural group (n = 69)	CIB + PCA group (n = 429)	P-value
Hypotension requiring treatment	5 (7.2%)	0	
Acute confused episode	3 (4.3%)	4 (0.9%)	
Wound infection	1 (1.4%)	11 (2.6%)	
Urinary retention	0	3 (0.7%)	
Sedation score PoD 1			
0	37 (82.2%)	215 (59.9%)	**0.004**
1	8 (17.8%)	129 (35.9%)	**0.015**
2	0	15 (4.2%)	0.392

CIB PCA, i.m. continuous infusion of bupivacaine plus i.v. patient-controlled analgesia; PoD, post-operative day. A P-value of 0.05 was considered to indicate statistical significance.
Other complications include: haematoma at resection area (n 1), transient ischaemic attack (n 1), Horner's syndrome (n 1), pulmonary embolism (n 1), respiratory failure (n 1), alcohol withdrawal (n 1), deep vein thrombosis (n 1), infected line (n 1), allergic reaction (n 1), sacral pressure sore (n 1), cellulites (n 1), partial portal vein thrombosis (n 1), axillary nerve palsy (n 1) and cerebral infarct (n 1).

An increased need for rescue medication in the CIB +PCA group was observed. In most patients rescue medication was given on the day of surgery (PoD 0), but this was countered by an increased need for rescue medication and a switch to i.v. opioids in the CEA group on PoDs 1–3. In addition, CIB + PCA was continued for 1 day longer than epidural analgesia. This mainly reflects the practicalities of managing epidurals, as it is part of post-operative practice to remove the catheter after 72 h unless otherwise clinically indicated. The high percentage (53.1%) of patients requiring rescue medication may be explained by the possibility that the local analgesic effect of the bupivacaine infusion may have been suboptimal directly after surgery. The epidural analgesia was started prior to the incision, whereas the wound catheters were commenced immediately after wound closure. It may take time for bupivacaine to reach all adjacent tissue and associated nerve endings. Unlike a correctly functioning epidural analgesic, which provides a complete block, bupivacaine infusion exhibits only a local effect and additional opioids may be required.

Another important result refers to the finding that when one of the catheters was dislodged or occluded (often by a faulty connector or by the faulty insertion of the catheter into the connector), pain control was adequately maintained by just one catheter. This is supported by the stagnant opioid consumption on PoDs 2 and 3 with adequate maintenance of pain control. This implies that a single infusing catheter combined with PCA may be sufficient to control post-operative pain.

The findings of this study are in keeping with those of earlier reports on the beneficial results of this technique with regard to pain control, opioid consumption and recovery.[16,19,24,33] It has been claimed that epidural analgesia is superior to PCA for post-operative pain relief in patients recovering from major upper abdominal

operations.[10,11] However, the present study shows that when PCA is combined with CIB via i.m. catheters, equivalent pain control can be achieved. As Khorgami et al.[34] demonstrated in a recent RCT, the technique of local interfascial analgesia is also feasible for midline incisions.

The present results confirm the clinical applicability of wound catheters. Not only does this analgesic approach provide equivalent pain control with reduced opioid intake, but it also represents a quicker and very likely cheaper method of doing so. Abandoning the use of epidural analgesia eliminates the risk for epidural-related complications (haematoma, abscess and nerve damage) and may improve cost-effectiveness as anaesthetic time may be shortened and the CIB + PCA combination does not require specialist supervision on the ward. The lower total opiate dose received may also reduce opiate-associated side effects. In patients in whom experts aim to achieve faster post-operative recovery within the context of an ERAS programme, the use of CIB + PCA may result in a further reduction in the time required to meet recovery criteria. The partly retrospective design of this study resulted in the incomplete availability of pain scores. The complete availability of pain data might have altered the comparability of the groups and might have implied an increased superiority or inferiority of either of the two analgesic modalities. In addition, an inherent bias of surgeon preference influencing outcomes cannot be excluded. The strengths of this study include its use of a large and uninterrupted cohort of patients submitted to major liver resection in an expert centre, whereas other prospective series are considerably smaller. The patients investigated in this study represent a population at risk for post-operative coagulopathy and the development of epidural hematoma. It would be interesting for future research to compare patient-controlled epidural analgesia with CIB + PCA and to look into the number and location of wound catheters needed to achieve the optimal local analgesic effect. Lastly, it would be interesting to compare the local wound infusion technique with that of the transversus abdominis plane block[35], which can also be regarded as safe and effective after abdominal surgery.

CONCLUSION

Continuous i.m. bupivacaine infusion with i.v. PCA provides equivalent pain control and a lower level of opioid consumption compared with CEA following major hepatectomy. The CIB + PCA technique could replace that of epidural analgesia with the potential for greater safety, improved post-operative outcomes and a reduced hospital LoS.

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Appendix 1.

The following (combined) procedures were performed only twice in the study cohort:
Cholecystectomy + biliodigestive anastomosis, skeletonization of the hepatoduodenal ligament, closure of ileostomy, block dissection of the hepatoduodenal ligament, cava resection, node block dissection of the lesser sac, diaphragm + peritoneal nodule resection, cholecystectomy + hepatoduodenal ligament biopsy, deroofing of a liver cyst and excision of peritoneal deposits not in the lesser sac.

The following (combined) procedures were performed only once in the study cohort:
En bloc gastric resection + cholecystectomy, block dissection of the hepatoduodenal ligament + diathermy ablation, excision of aortocaval lymph node + peritoneal deposit resection, skeletonization of the hepatoduodenal ligament + Roux loop biliary reconstruction + cholecystectomy, block dissection of the lesser sac + excision of the common bile duct + Roux loop reconstruction, colon excision + cholecystectomy, reconstruction of the v. cava, right hemicolectomy + diathermy ablation, sleeve resection of the duodenum, posterior pelvic extenteration, en bloc total mesorectal excision + appendicectomy + excision of a mesenteric mass, diaphragm resection and repair of two incisional hernias, cholecystectomy + excision of the greater omentum, exploration of common bile duct + removal of a stone, splenectomy, insertion of terminal ileostomy, gastroduodenal ligament + cholecystectomy, vascular reconstructions, nephrectomy + adrenalectomy, block dissection of the lesser sac + excision of common bile duct + Roux loop reconstruction + repair of an incisional hernia, reconstruction of the bile duct, small bowel resection, small bowel biopsy and resection of part of the diaphragm and lung.

Chapter 6

Abandoning prophylactic abdominal drainage after hepatic surgery: 10 years of no-drain policy in an ERAS environment

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ABSTRACT

BACKGROUND

Routine prophylactic abdominal drainage after hepatic surgery is still debated, may be unnecessary, possibly harmful and uncomfortable for patients. This study evaluated the safety of a no-drain policy after liver resection within an ERAS- programme.

METHODS

All hepatectomies performed without prophylactic drainage during 2005 – 2014 were included. Primary endpoints were resection-surface-related (RSR) morbidity, defined as the presence of post-operative biloma, haemorrhage or abscess, and reinterventions. Secondary endpoints were length of stay (LOS), total post-operative morbidity, the composite endpoint of liver surgery-specific complications, readmissions and 90-day mortality. Uni- and multivariable analyses were performed to identify independent risk factors for RSR-morbidity. A systematic search was performed to compare the results of this study to literature.

RESULTS

A total of 538 resections were included in the study. The RSR-complication and reintervention rate was 15% and 12%, respectively. Major liver resection (≥3 segments) was an independent risk factor for the development of RSR-morbidity (OR=3.01, 95% CI 1.61– 5.62; P=0.001) and need for RSR-reintervention (OR=3.02, 95% CI 1.59–5.73; P=0.001).

CONCLUSION

RSR-morbidity, mortality and reintervention rates after liver surgery without prophylactic drainage in patients, treated within an ERAS programme, were comparable to previously published data. A no-drain policy after partial hepatectomy seems safe and feasible.

INTRODUCTION

In the past decades, the quality of perioperative care for hepatic surgery has improved dramatically due to improvements in surgical technique, risk assessment and perioperative care. Prophylactic intra-abdominal drainage is still routinely applied in many hospitals worldwide. However, prophylactic intra-abdominal drainage may be unnecessary[1], uncomfortable and even harmful for the patient. As early as 1915, the British surgeon Major Grey Turner already pointed out the dangers of routine drain use. One hundred years later, the routine use of prophylactic drains in liver surgery is still an on-going debate.[2]

Some studies have reported advantages of prophylactic drain placement such as early drainage of bile leaks, preventing subphrenic collection, detecting post-operative haemorrhage and removing ascites.[3-6] Other studies have indicated that the risks of prophylactic intra-abdominal drains, including drain-related bleeds, ascending intra- abdominal infections by retrograde contamination and impaired pulmonary function, outweigh the benefits.[1, 7, 8] Furthermore, patients with a drain in place experience more abdominal pain and discomfort, have more difficulties to mobilize, need more nursing care and this could contribute to a longer admission and increased costs.[7]

Currently, if used, drains are usually placed near the transection surface or in the subphrenic space, and are often removed on post-operative day (POD) 3 to 5 depending on drain production.[7, 9, 10] Already in 2007, a meta-analysis [11] showed that there were no significant differences in morbidity, mortality and reoperation rates between patients with or without a prophylactic abdominal drain after uncomplicated elective hepatectomy. Post-operative mortality in patients undergoing liver surgery without a drain ranges between 0–3%. Percutaneous or operative reintervention rates in patients without a drain range from 0–18% and 0–10% respectively[1, 4, 7, 8, 12-14], and do not differ from outcomes after placement of an abdominal drain. Patients with a drain have reported mortality, percutaneous reintervention and reoperation rates between 0–6%, 0–36% and 0–6%, respectively.[1, 4, 7, 8, 12-14] The accumulating evidence suggests that routine abdominal drainage after liver resection is unnecessary and the benefit arguable, but it may be indicated in specific patients.

The Enhanced Recovery After Surgery (ERAS) programme has shown a benefit for patient recovery after liver surgery in recent years.[15-17] The programme has been implemented to optimize pre-, peri- and post-operative care to facilitate a quicker recovery. With the introduction of this programme, the routine use of drains after liver surgery without biliary or vascular reconstruction has been abandoned.[15-17]

The aim of this study was to examine the post-operative complication and reintervention rates in patients undergoing liver resection that were treated without prophylactic drains in an ERAS environment, to identify risk factors associated with reinterventions for specific complications and to compare the results to earlier studies on drainage following liver resection.

METHODS

STUDY DESIGN

All patients undergoing hepatic resection between January 2005 and December 2014 at Maastricht University Medical Centre (MUMC) were included in a prospective database. Patients were retrospectively identified and screened for eligibility in this study. Patients were excluded if a prophylactic abdominal drain was placed, e.g. in the case of hepatic resection traumatic lesions, or if a bilioenteric anastomosis was created. Primary endpoints of this study were RSR-morbidity and reinterventions for RSR-morbidity. RSR-morbidity was defined as the presence of bile leakage, intra-abdominal abscess or/and haemorrhage.[18] Reinterventions for RSR-morbidity were considered to be CT- or US- guided percutaneous drainage, reoperation and ERCP with stenting. Data on reinterventions were retrospectively collected from individual patient charts. Secondary endpoints were hospital length of stay (LOS), post-operative morbidity, readmission rate, 90-day mortality and the composite endpoint of liver surgery-specific complications (CEP). A composite endpoint consists of 2 or more specific complications that can be regarded as 1 dichotomous endpoint that occur in 1 patient. The liver surgery-specific CEP consists of ascites, postresectional liver failure, bile leakage, intra-abdominal haemorrhage, intra-abdominal abscess and/or post-operative mortality.[19]

SURGICAL TECHIQUES

All hepatic resections were performed by 1 of 4 hepatobiliary surgeons (CHCD, RMvD, SWMOD, MHB) or by a senior resident/fellow under the supervision of a hepatobiliary surgeon. Hepatectomies were performed as open or laparoscopic procedures as published previously.[20]

For open procedures, a unilateral right subcostal, a bilateral subcostal (right extended to left), J-shaped or midline incision was used. Intraoperative ultrasound was routinely performed to examine the location of lesions in the liver and the relation to surrounding biliary and vascular structures. Hepatic resection was performed by using a Cavitron Ultrasonic Surgical Aspirator (CUSA system 200 macrodissector,

Cavitron Surgical Systems, USA) and Argon beam coagulation (Force GSU System, Valleylab, USA), with or without Pringle's manoeuvre. Ultracision Harmonic ACE (Ethicon Endosurgery, Johnson & Johnson, USA). Central venous pressure was maintained ≤5 cm H2O during transection to reduce excessive blood loss. During transection, clips and ligatures were used to treat vessels and bile ducts at the resection surface. To avoid post-operative haemorrhage and bile leakage, the resection surface was treated with argon beam coagulation and or sealants at the discretion of the surgeon, although the effectiveness has never been proven.[18]

For laparoscopic procedures patients were placed in supine French position. Access to the abdomen was created by open transumbilical insertion of a 30° laparoscope. Three or four additional trocars were inserted. The pressure of the pneumoperitoneum was kept <12 mmHg. Parenchymal transection was performed using the Ligasure 5mm blunt tip (Covidien, USA) laparoscopic CUSA (Cavitron Surgical Systems, USA) or Harmonic scalpel (Ultracision, Ethicon Endosurgery, Johnson & Johnson, USA). The portal pedicles were stapled using a vascular stapler (EndoGIA Autosuture, Covidien, USA). Resected specimens were placed in a plastic bag (Endocatch Autosuture, Covidien, USA) and removed through a separate usually suprapubic muscle sparing incision.

NO-DRAIN POLICY

Since the introduction of ERAS in liver surgery in 2005, the MUMC has a no- drain policy; abdominal drains are no longer part of standard management after hepatectomy. The use of prophylactic abdominal drains was limited to a selected group of indications. They were routinely placed after the creation of bilioenteric anastomoses or biliary reconstructions and in the case of traumatic liver lesions. In some cases, placement of a prophylactic abdominal drain could be considered by the surgeon when a high risk of intra- abdominal fluid collection was expected, e.g. when performing combined procedures, in the case of intra-operative iatrogenic laceration that required drainage, repeat hepatectomies, excessively large resection surfaces or central liver resections. Furthermore, all patients were treated within the ERAS programme. Key principles of this programme have been previously described.[21] Patients were closely monitored during hospitalization based on clinical presentation, vital parameters and standard diagnostic laboratory results. Additional imaging (CT or US) was only performed on clinical findings indicative of post-operative complications. All complications, defined as any deviation from the expected post-operative course <30 days and graded according to the Dindo-Clavien classification system[22], were recorded in the electronic patient record system and in a prospectively maintained research database. Data from the electronic patient record system and the research database were crosschecked for missing data.

SYSTEMATIC LITERATURE SEARCH

A systematic search was conducted to compare the results of this study with literature following the current recommendations of Preferred Reporting Items for Systematic Reviews and Meta-analysis Approach (PRISMA). Two authors (E.M.W.-L.-H. and V.W.) independently performed the search, study selection, data extraction and critical appraisal of the studies.

Eligibility criteria

After review of the abstract, the remaining studies were selected for full- text evaluation and inclusion, if: 1) The subject of the study was comparison of the routine use of an abdominal drain versus no-drainage after hepatectomy; 2) the study was not an editorial, systematic review or meta-analysis; 3) the study compared clinical outcome after abdominal drain versus no-drainage after hepatectomy; and 4) the study was in the English language.

Study selection and quality appraisal

The search was conducted in Ovid MEDLINE, Embase, PubMed databases to identify all studies comparing the routine use of an abdominal drain versus no-drainage after hepatectomy between 1st January 1990 and 31st December 2014. The following search strategy was used: ([["Hepatectomy"[Mesh] OR "liver resection" OR "liver surgery"]] AND ["Drainage"[Mesh] OR "drain*"] NOT ["preoperative drainage" OR "preoperative biliary drainage"]). After removal of duplicates, articles were screened by title, abstract and subsequently full text. In addition, reference lists of all included studies were screened for missed but relevant studies. The methodological quality and risk of bias of the studies was assessed using the Cochrane Handbook for Systematic Reviews.[23] All included studies were consequently graded by using the Oxford Centre for Evidence-Based Medicine levels of evidence.[24] Furthermore, clinical trial registers were searched for ongoing studies.

Data collection

Two reviewers (E.M.W.-L.-H. and V.W.) independently extracted data from the selected studies on study design, participant characteristics, mortality, image-guided drainage, reoperation, bile leakage / fistula, infected collections, post-operative bleeding and wound infection.

STATISTICAL ANALYSIS

Continuous data are described as median (range) and categorical data are presented as percentages. The Chi-square / Fisher's exact and Mann-Whitney U tests were used to compare categorical data and continuous data, respectively. Results were consid-

ered significant when P ≤ 0.05. Uni- and multivariable analyses were performed to define specific independent risk factors for RSR-reinterventions. Variables included in the univariable analysis: sex, ASA class ≥III, age <65 or ≥70 years, median BMI, type of liver resection (major, caudate, repeat, central), blood loss >2,000 ml, preoperative chemotherapy, Pringle manoeuvre and operating time >240 min. Multivariable analysis was performed with binary logistic regression and P ≤ 0.10 was used to select variables from univariable analysis. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0. (Armonk, NY, USA: IBM Corp.).

RESULTS

GENERAL AND SURGICAL CHARACTERISTICS

A total of 606 hepatic resections were performed in the study period. All 66 patients that received a drain were excluded from further analysis. Details of this drain group will be addressed later in this section. Furthermore, two patients with missing data were excluded from analysis. A total of 538 patients were analysed. General and surgical characteristics are shown in *Table 1*.

PRIMARY OUTCOME

Seventy-nine (15%) of the 538 patients without a drain developed post-operative RSR-complications. Sixty-seven (12%) of these patients required surgical, radiological or endoscopic reintervention (*Table 2*).

Of the variables included in the univariable analyses (*Table 3,4*), only age <65 years, major liver resection, blood loss >2000 ml, Pringle manoeuvre, operating time >240 minutes, and preoperative chemotherapy were significantly (P<0.1) associated with the development major RSR-morbidity (≥Dindo-Clavien grade 3a) or the need for post-operative RSR-reinterventions. After multivariable analyses major liver resection was an independent risk factor (OR = 3.01, 95% CI 1.61–5.62; P=0.001) for the development of major RSR-morbidity, and was also associated with an increased risk of RSR-reinterventions (OR = 3.02, 95% CI 1.59–5.73; P=0.001).

Table 1. Baseline patient and surgical characteristics

	All patients *N*=538 (%)
Sex (male)	308 (57)
Age, years	64 (55-70)
BMI, kg/m2	25.6 (22.9-28.5)
ASA physical status	
I	85 (16)
II	339 (63)
≥III	114 (21)
Indications	
Colorectal metastasis	421 (78)
Benign lesions	47 (9)
Other malignancy	29 (5)
HCC	24 (5)
Gallbladder carcinoma	7 (1)
CCC	5 (1)
Other	5 (1)
Preoperative chemotherapy	271 (50)
Resection Type	
<1 segment/ metastasectomy	213 (40)
Multisegmentectomy	173 (32)
Right hemihepatectomy	74 (14)
Right hemihepatectomy + 1 segment	31 (6)
Left hemihepatectomy	16 (3)
Left hemihepatectomy + 1 segment	2 (0.4)
Right extended hemihepatectomy	12 (2)
Left extended hemihepatectomy	3 (0.6)
Central resection	18 (3)
Caudate lobe resection	25 (5)
Major hepatectomy (≥3 segments)	226 (42)
Repeat hepatectomy	57 (11)
Total operating time, min	200 (150-270)
Intraoperative blood loss, ml	500 (269-1000)
Pringle	118 (22)

Values in parentheses are percentages, unless indicated otherwise**.** Numeric data are presented as median (interquartile range). BMI, Body Mass Index. ASA, American Society of Anaesthesiologists. HCC, Hepatocellular carcinoma. CCC, Cholangiocellular carcinoma.

Table 2. Primary endpoints

	All patients *N*=538 (%)
Resection surface-related (RSR) complication rate	79 (15)
All surgery-related complication rate	90 (20)
Bile leakage (RSR)	35 (7)
Haemorrhage (RSR)	9 (2)
Intra-abdominal abscess (RSR)	44 (8)
Ascites	12 (2)
Post-operative liver failure	17 (3)
Pleural effusion	18 (3)
Sepsis	15 (3)
Wound infection	28 (5)
Reintervention rate for RSR complications	67 (12)
Reintervention rate	72 (13)
CT drainage	55 (10)
ECRP with stenting	9 (2)
US drainage	8 (2)
Relaparotomy	11 (2)
Relaparoscopy	1 (0.2)
Thoracotomy	1 (0.2)
Thoracic drainage	8 (2)

Values in parentheses are percentages.
Multiple complications or reinterventions per patient were possible.
A total of 178 surgery-related complications occurred in 90 patients.
A total of 93 reinterventions occurred in 72 patients.
RSR, Resection surface-related. CT, Computer Tomography. ERCP, Endoscopic Retrograde Cholangiopancreaticography. US, Ultrasound.

SECONDARY OUTCOME MEASURES

The median LOS was 8 days (6-11). Fifty patients (9%) were readmitted within 30 days after surgery (*Table 5*). Mortality within 90 days after surgery was observed in fifteen patients (2.8%). Within this group, five patients died from sepsis following an intra-abdominal abscess or biloma, three patients died from multi-organ failure induced by postresectional liver failure, three patients died from extensive extra-hepatic metastatic disease and subsequent multi-organ failure and four patients died of an acute cardiac arrest of which one was proven in autopsy to be caused by myocardial infarction.

Table 3. Uni- and multivariable analysis of risk factors for significant morbidity (≥ Dindo-Clavien 3a) for RSR-complications.

Variable	Significant Morbidity (≥ Dindo-Clavien 3a) (N=70)	No Significant Morbidity (≥ Dindo-Clavien 3a) (N=468)	*P*-value univariable analysis	Odds ratio [95% CI] univariable analysis	*P*-value multivariable analysis	Odds ratio [95% CI]
Male / Female	46/24	262/206	0.127	0.664 [0.392 – 1.123]		
ASA class ≥ III (yes/no)	16/54	97/366	0.716	1.118 [0.613 – 2.039]		
Age	66.0 (58-71)	63.7 (54-69)	0.039	1.025 [1.001 – 1.050]		
<65 years old (yes/no)	29/41	254/214	0.046	0.596 [0.358 – 0.992]	0.123	0.629 [0.350 – 1.133]
≥70 years old (yes/no)	22/48	106/362	0.110	1.565 [0.904 – 2.710]		
BMI, kg/m^2	25.2 (23-29)	25.6 (23-28)	0.924	0.997 [0.930 – 1.068]		
Major resection (yes/no)	48/22	178/290	<0.001	3.555 [2.076 – 6.088]	0.001	3.008 [1.610 – 5.618]
Caudate lobe resection (yes/no)	2/68	23/445	0.759	0.569 [0.131 – 2.468]		
Repeat hepatectomy (yes/no)	10/60	47/421	0.285	1.439 [0.716 – 3.111]		
Central resection (yes/no)	3/67	15/453	0.640	1.352 [0.381 – 4.795]		
Intraoperative blood loss, ml	818 (463-1783)	500 (200-1000)	0.011	1.000 [1.000 – 1.001]		
Blood loss > 2000 ml (yes/no)	11/48	23/333	0.003	3.318 [1.522 – 7.235]	0.146	1.933 [0.794 – 4.704]
Preoperative chemotherapy (yes/no)	40/30	231/233	0.252	1.345 [0.810 – 2.233]		
Pringle manoeuvre (yes/no)	23/46	95/370	0.017	1.947 [1.125 – 3.372]	0.163	1.559 [0.835 – 2.911]
Total operating time, min	240 (181-300)	195 (147-251)	0.008	1.003 [1.001 – 1.005]		
Operating time > 240 min (yes/no)	35/35	149/319	0.003	2.141 [1.289 – 3.556]	0.110	1.657 [0.893 – 3.076]

Categorical data are presented as absolute numbers; numeric data are presented as median (interquartile range). RSR, Resection surface-related. ASA, American society of Anaesthesiologists. BMI, Body mass index. CI, Confidence Interval.

Table 4. Uni- and multivariable analysis of risk factors for reinterventions for RSR-complications

Variable	Reintervention (N=67)	No reintervention (N=471)	*P*-value univariable analysis	Odds ratio [95% CI] univariable analysis	*P*-value multivariable analysis	Odds ratio [95% CI]
Male / Female	44/23	264/207	0.138	0.667 [0.390 – 1.140]		
ASA class ≥ III (yes/no)	16/51	97/369	0.566	1.193 [0.652 – 2.184]		
Age	65.8 (58-71)	63.9 (54-69)	0.069	1.022 [0.998 – 1.047]		
<65 years old (yes/no)	27/40	256/215	0.033	0.567 [0.337 – 0.954]	0.091	0.595 [0.326 – 1.085]
≥70 years old (yes/no)	21/46	107/364	0.123	1.553 [0.888 – 2.717]		
BMI, kg/m^2	25.4 (23-29)	25.6 (23-28)	0.821	1.008 [0.940 – 1.081]		
Major resection (yes/no)	46/21	180/291	<0.001	3.541 [2.046 – 6.129]	0.001	3.020 [1.592 – 5.728]
Caudate lobe resection (yes/no)	1/66	24/447	0.219	0.282 [0.038 – 2.212]		
Repeat hepatectomy (yes/no)	9/58	48/423	0.421	1.367 [0.638 – 2.933]		
Central resection (yes/no)	3/64	15/456	0.584	1.425 [0.401 – 5.058]		
Intraoperative blood loss, ml	900 (475-1766)	500 (200-1000)	0.011	1.000 [1.000 – 1.001]		
Blood loss > 2000 ml (yes/no)	10/46	24/335	0.007	3.034 [1.364 – 6.750]	0.255	1.698 [0.683 – 4.223]
Preoperative chemotherapy (yes/no)	39/28	232/235	0.193	1.411 [0.840 – 2.369]		
Pringle manoeuvre (yes/no)	21/45	97/371	0.044	1.785 [1.015 – 3.138]	0.314	1.392 [0.732 – 2.648]
Total operating time, min	240 (182-301)	195 (147-251)	0.004	1.003 [1.001 – 1.005]		
Operating time > 240 min (yes/no)	34/33	150/321	0.003	2.205 [1.315 – 3.696]	0.066	1.804 [0.961 – 3.387]

Categorical data are presented as absolute numbers; numeric data are presented as median (interquartile range). RSR, Resection surface-related. ASA, American society of Anaesthesiologists. BMI, Body mass index. CI, Confidence Interval.

Table 5. Secondary outcomes

	All patients*N*=538 (%)
Readmission rate	50 (9)
Length of stay, days	8 (6-11)
Dindo-Clavien classification	
Grade 1	33 (6)
Grade 2	71 (13)
Grade 3a	55 (10)
Grade 3b	12 (2)
Grade 4	14 (3)
Grade 5 (30-day mortality)	13 (2)
All reported post-operative morbidity	202 (38)
Major morbidity ≥ Dindo-Clavien 3a	92 (17)
Major RSR morbidity ≥ Dindo-Clavien 3a	70 (13)
Liver surgery-specific CEP	84 (16)
90-day mortality	15 (2.8)
Liver related 90-day mortality	13 (2.4)

Values in parentheses are percentages, unless indicated otherwise. Numeric data are presented as median (interquartile range). RSR, Resection surface-related. CEP, liver surgery-specific composite endpoint (ascites, postresectional liver failure, bile leakage, intra-abdominal haemorrhage, intra-abdominal abscess and operative mortality).

PROPHYLACTIC ABDOMINAL DRAIN GROUP

Sixty-six patients received a prophylactic abdominal drain and were excluded from this study. Among them were twenty-five patients that required a drain after a bilioenteric anastomosis or another form of biliary reconstruction was created. One patient received a drain after liver surgery for a traumatic lesion. Eight patients obtained a drain because of a difficult repeat hepatectomy. Seven patients received a drain for combined procedures (four colorectal resections, two pancreatic resections and one kidney resection). In five patients a drain was placed after intraoperative iatrogenic lesions of the bile duct, pancreas or spleen. Central resections and large resection surfaces after surgery were indications for drain placement in nine patients. Vascular involvement required drain placement in two patients. Two patients with liver cirrhosis received a prophylactic drain after surgery because of an expected high risk of ascites and subsequent infection. Another two patients received a drain in early 2005 because of protocol deviation by the surgeon. Lastly, in five patients an abdominal drain was placed without any specified indication. In this selected drain group, excluded from analysis, morbidity and mortality were high (10.0% mortality, 30.0% RSR-morbidity, 37.5% major morbidity, 27.5% reinterventions).

LITERATURE REVIEW

The PRISMA flow diagram of the literature search and inclusion of relevant studies is shown in *Figure 1*. The search resulted in 27 studies that were assessed for eligibility. Finally, ten studies, including five RCT's and five cohort studies (two prospective and three retrospective series), were used to compare the results with those of the present study. The majority of studies included all types of liver resection, except two RCT's that only included patients with an underlying liver disease or a hepatocellular carcinoma in cirrhotic livers. Four studies[1, 4, 7, 8] were graded as level 1b evidence, one study[13] was grade level 2b evidence, and the remaining studies[5, 12, 25-27] were cohort studies of grade 4 evidence. No ongoing studies could be identified in clinical trial registers. *Table 6* shows a comparison of this study with results from literature.

DISCUSSION

The use of post-operative drains after liver resection is still subject of debate. This study evaluated a no-drain policy, as part of the ERAS programme, in a tertiary referral centre during 2005–2014. Implementation of a no-drain policy has resulted in an overall surgical morbidity rate of 20%, RSR-complication rate of 15% and RSR-reintervention rate of 12%.

This implies that 88% of all patients did not require any form of abdominal drainage in the post-operative phase. By not placing a prophylactic drain, they were spared from possible discomfort and harmful drain-related complications. Moreover, in the group of patients that did have an intra-abdominal collection, the majority of them could be treated well with CT- or US-guided drainage and rarely a reoperation was necessary, as is shown in *Table 2*.

Comparison of results of this study with earlier publications, mainly summarized by Gurusamy et al.[11], confirms the safety and feasibility of the no-drain policy. The 90-day mortality of 2.8% in this study was within the ranges reported in the literature for this type of liver surgery.[1, 4, 7, 8, 11, 13, 14]. Reintervention rates of previous studies[1, 4, 7, 8, 11, 13, 14] vary considerably in studies of both drain and no-drain groups. To date, there is no evidence that abandoning prophylactic drainage increases the need for (radiological) reinterventions.[11] The RSR-reintervention rate of 12% in this study demonstrates that a no-drain policy does not lead to more reinterventions, higher morbidity or mortality compared to patient with a drain.[1, 4, 5, 7, 8, 12, 13, 27]

Major liver resection is a known risk factor for post-operative complications[12, 13, 28- 35]. In this study it was identified in multivariable analysis as an independent risk factor for RSR-significant morbidity and RSR-reinterventions. Other known intra-

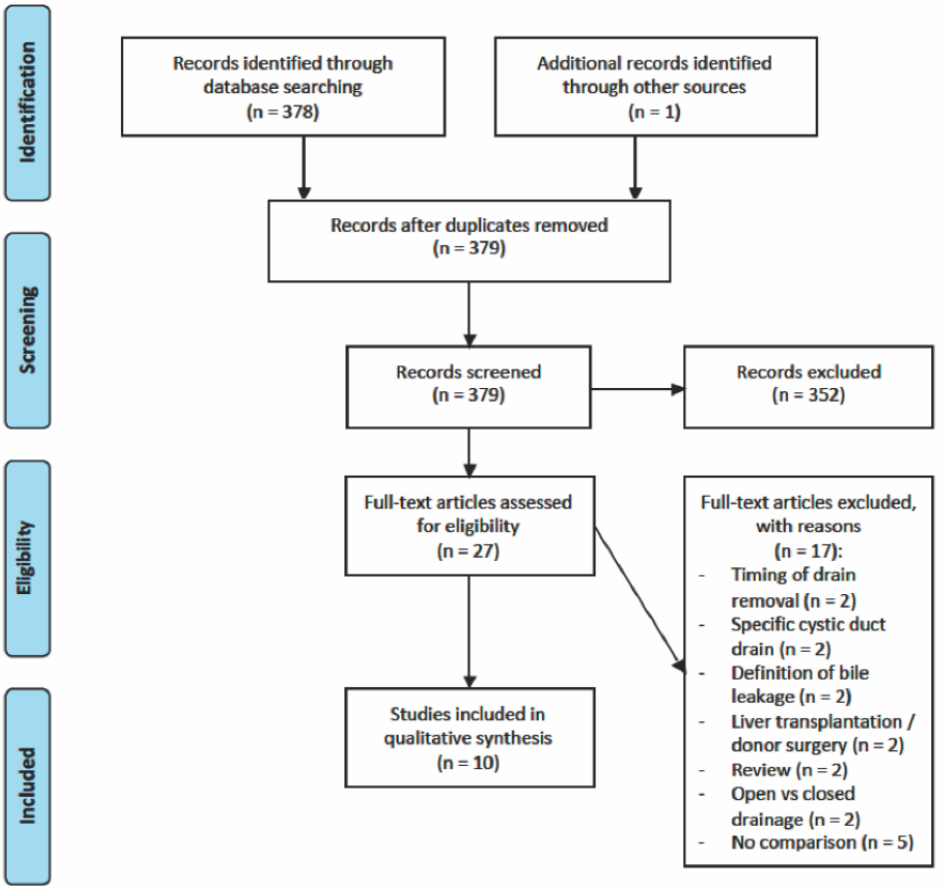

Figure 1. PRISMA flow diagram of the literature search and inclusion of relevant studies

operative predictive determinants, such as prolonged operating time[12, 13, 28, 31, 33, 35], repeat hepatectomy[35-37] and the use of Pringle manoeuvre[31, 38], were not confirmed in this cohort. Preoperative risk factors that have been suggested in preceding literature, among which are the presence of significant comorbidities / ASA III-IV[28-30, 32, 39], an abnormal liver function[13, 28, 30] and chemotherapy[40], were also not confirmed. The fact that major liver resection was found as a risk factor, does not mean that a prophylactic drain needs to be placed routinely. It suggests that there is a subset of patients in which routine post-operative imaging or an ag-

gressive post-operative imaging strategy needs to be considered. When there is a clinically relevant intra-abdominal collection on ultrasound or CT, a therapeutic radiologically-guided drain can then be placed.

The expertise with and access to radiological reinterventions may vary substantially between institutions, it has changed over time in hospitals worldwide and it could be an important factor. In centres in which radiological reinterventions are less frequently performed, more collections may be inadequately drained. This could lead to a higher reoperation rate. When compared with patients receiving a drain in other studies, the patients from the present study had a low reoperation rate. This may imply that a no-drain placement policy does not lead to more reoperations. Finally, hospital length of stay in other studies was longer.[41] The ERAS-programme could explain this faster recovery.[21, 42]

This study has several strengths that add to the existing body of evidence of RCT's and a meta-analysis on the studied topic. An important strength of this study is the large cohort size. A total of 538 consecutive patients were treated without a drain after implementation of the no-drain policy. As is demonstrated in Table 6, this no-drain cohort is one of the largest cohorts on the subject. In addition, the group of excluded patients with prophylactic drain placement is well described and provides detailed insight in the selection process. Furthermore, patients with bilioenteric anastomoses were excluded from analysis to enable comparison with previously published studies[7, 8, 13]. Among these patients, leakage rates are high, and may confound general results. Another strength of this study is the fact that uni- and multivariable analyses were performed for the identification of risk factors for surface-related morbidity. This can aid in the decision making process of abandoning the use of drains after liver surgery. Lastly, all patients were prospectively registered and treated within an ERAS programme consisting of standardized care elements. The minimal use of prophylactic drains is an important element in ERAS programmes and this study advocates a no-drain policy after uncomplicated liver surgery. Drains are thought to affect post-operative mobility and pain control and drains could hamper a swift recovery in uncomplicated cases.

Table 6. Results of previous studies (RCTs and cohort studies) comparing the use of abdominal drainage after hepatectomy.

Author	Period	Type of surgery	Study type	Evidence level	Risk of bias	Arm	N	Mortality (%)	CT or US drain (%)	Re-operation (%)	Bile leakage/ fistula (%)	Infected collection (%)	Postop. Bleeding (%)	Wound infection (%)
Belghiti et al. [1]	1990 - 1991	A	1	1b	Low	D	42	2.4	35.7	2.4	4.8	14.3	4.8	NA
						ND	39	2.6	15.8	2.5	5.1	5.3	2.5	NA
Fong et al. [13]	1992 - 1994	A	1	2b	Unclear	D	60	3.3	8.3	1.6	5.0	5.0	0	6.6
						ND	60	3.3	18.3	0	5.0	0	0	3.3
Burt et al. [12]	1994 - 2000	A	3	4	High	D	184	7.1	26.1	NA	NA	16.3	NA	NA
						ND	981	2.0	10.5	NA	NA	3.1	NA	NA
Fuster et al. [4]	1991 - 1997	B	1	1b	Low	D	20	0	0	0	NA	0	0	0
						ND	20	0	10	5	NA	10	0	15
Liu et al.[7]	1999 - 2002	C	1	1b	Low	D	52	5.8	3.8	5.8	3.8	3.8	1.9	19.2
						ND	52	1.9	0	1.9	0	0	0	11.5
Aldameh et al.[5]	1999 - 2002	A	3	4	High	D	126	1.6	1.6	NA	3.2	2.4	NA	6.3
						ND	85	1.2	4.7	NA	3.5	1.2	NA	16.5
Sun et al.[8]	2004 - 2005	A	1	1b	Low	D	60	0	6.7	1.7	0	3.3	2.0	5.0
						ND	60	1.7	5.0	0	0	0	0	3.3
Lu et al.[27]	2002 - 2004	A	3	4	High	D	357	0.6	5.6	0.3	1.7	2.0	0.8	3.4
						ND	105	0	3.8	0	0	1.0	1.0	0
Butte et al. [26]	2007 - 2014	A*	2	4	High	D	87	4.6	8	NA	4.6	NA	NA	NA
						ND	112	0	8	NA	4.5	NA	NA	NA
Brooke-Smith et al. [25]	2010 - 2011	A	2	4	High	D	603	NA	9.2	NA	11	NA	NA	NA
						ND	345	NA	5.8	NA	1	NA	NA	NA
Present study	2005 - 2015	A	3	4	High	ND	538	2.6	12.0	2.1	6.2	7.7	2.3	5.7

D, Drainage group. ND, Non-drainage group. NA, Not Available. CT, Computer Tomography. US, Ultrasound.
Hepatic resection: (A) All hepatic resections, (B) All hepatic resections for hepatocellular carcinoma in cirrhotic patients, (C) All hepatic resections in patients with chronic liver disease.
Type: (1) Randomized controlled trial (RCT), (2) Prospective cohort study, (3) Retrospective cohort studie. # Level of evidence: according to the Oxford Centre for Evidence-Based Medicine[24]

The retrospective analysis of prospectively collected data is a limitation of this study. Although all liver resections in the study period were registered, the final results may have been prone to a form of selection bias, because a small subset of patients was excluded from analysis. This excluded group received an abdominal drain by discretion of the operating surgeon within the studied period. Although no biliary reconstructions were performed in these patients, drains were placed because of major combined procedures, major central liver resections, intraoperative leaks of the bile duct, pancreatic damage and repeat hepatectomy.

The findings of this cohort study confirm the findings of available RCT's[4, 7, 13] and a Cochrane review[11] that routine drainage after uncomplicated liver resection is not necessary. The results of this study show that a no-drain policy is safe and feasible after liver surgery within an ERAS environment. Placement of a prophylactic drain is unlikely to prevent reinterventions for complications and a no-drain policy seems justified in the majority of patients. At most, placement of a drain allows liver surgeons to detect complications in an earlier phase, but routine placement subjects a large group of patients to potential risks and discomfort. Further studies are still necessary and should focus on specific patient groups with predefined risk factors (e.g. underlying liver disease, major resections, biliary reconstructions, intraoperative blood loss and operating time) or should validate risk factors.

CONCLUSION

A selective no-drain policy within an ERAS environment resulted in a rate of post-operative complications, reinterventions and mortality that is comparable to previously published studies. The routine use of prophylactic abdominal drains after liver surgery therefore seems unnecessary. In patients that undergo a major liver resection, which is an independent risk factor for RSR-related complications, preemptive post-operative imaging can be considered. In a small group of selected patients known to have a high risk of anastomotic leakage, prophylactic drains still have their place, e.g. in the case of biliary reconstruction.

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PART II

LAPAROSCOPIC LIVER SURGERY

Chapter 7

Laparoscopic liver resection in the Netherlands: how far are we?

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ABSTRACT

BACKGROUND

The objective of this study was to provide a systematic review on the introduction of laparoscopic liver surgery in the Netherlands, to investigate the initial experience with laparoscopic liver resections and to report on the current status of laparoscopic liver surgery in the Netherlands.

METHODS

A systematic literature search of laparoscopic liver resections in the Netherlands was conducted using PubMed/MEDLINE. Analysis of initial experience with laparoscopic liver surgery was performed by case-control comparison of patients undergoing laparoscopic left lateral sectionectomy matched with patients undergoing the open procedure in the Netherlands between the years 2000 and 2008. Furthermore, a nationwide survey was conducted in 2011 on the current status of laparoscopic liver surgery.

RESULTS

The systematic review revealed only 6 Dutch reports on actual laparoscopic liver surgery. Matched case-control comparison showed significant differences in the length of hospital stay, blood loss and operation time. Complications did not differ significantly between the two groups (26 vs. 21%). The 2011 survey showed that 21 centres in the Netherlands performed formal liver resections and that 49 (5% of total) laparoscopic liver resections were performed in 2010.

CONCLUSION

The systematic review revealed that very few laparoscopic liver resections were performed in the Netherlands in the previous millennium. The matched case-control comparison of laparoscopic and open left lateral resection showed a reduction in hospital length of stay with comparable morbidity. The laparoscopic technique has been slowly adopted in the Netherlands, but its popularity seems to increase in recent years.

INTRODUCTION

In the past two decades, the popularity of laparoscopic surgery has grown. The introduction of laparoscopic cholecystectomy [1, 2] has led to an increasing number of indications for this technique, and has encouraged surgeons to develop a laparoscopic approach for many procedures including liver resections.[3] Laparoscopic liver resections are technically demanding and thought to be time-consuming [4, 5] but may have several important benefits for the patient compared to open liver surgery.[6–8] The putative advantages of this minimally invasive procedure include reduced blood loss [6, 7] , less post-operative pain [5, 9, 10] , earlier recovery and shorter post-operative hospital stay [5, 7–12] , and improved cosmetic aspects.[9, 12] Reoperations are reported to be easier due to reduced adhesions. [9–12] Also, open-close procedures with large incisions can be avoided when peritoneal metastases are detected at laparoscopy.

In the Netherlands, the gold standard for liver resection for liver tumours still is the open approach. There is no best level of evidence (level 1) to underpin the supposed major benefits of the laparoscopic approach, but the latter has been proven to be feasible and safe in many international expert centres. A recent consensus statement on laparoscopic liver resections states that resection of segments 2 and 3 by the laparoscopic approach should be the standard if experience is available.[13] In addition, the largest reviews hitherto conducted concluded that laparoscopic liver surgery is feasible and safe in minor as well as major liver resections when performed in experienced centres.[14, 15] However, randomized trials comparing the open and laparoscopic technique for liver resections are still lacking.

The purpose of our study was (1) to provide a historical overview on the introduction and initial experience of laparoscopic liver surgery in the Netherlands against the background of the latest international developments, (2) to report on the present state of laparoscopic liver surgery in the Netherlands, and (3) to provide insight into current and future developments of the minimally invasive liver resection technique within the Netherlands. To this purpose, a systematic review of all Dutch papers reporting on laparoscopic liver surgery was done and key leaders were informally approached. A matched case-control comparison was carried out of laparoscopic versus open liver resections in the Netherlands performed from 2000 to 2008. Finally, recent advances made in the Dutch surgical field of laparoscopic hepatectomies were investigated by means of a nationwide survey.

METHODS

SYSTEMATIC REVIEW OF LAPAROSCOPIC LIVER SURGERY IN THE NETHERLANDS - PAST EXPERIENCE

An online search was performed in PubMed/Embase databases for reports of Dutch groups on their experience with laparoscopic liver surgery in humans. Databases were searched from the earliest data available until 1 June 2011 on a combination of the following search keywords: 'laparoscopy', 'liver surgery', 'hepatic surgery', 'hepatic resection', 'hepatectomy', 'minimally invasive liver surgery', 'minimally invasive hepatic resection', 'Dutch', 'The Netherlands'. Biliary tumours were excluded. Titles and abstracts were screened (E.W.L.H.) and relevant articles selected. The full text of eligible papers was attempted to be retrieved to provide a historical overview. The reference lists of retrieved articles were reviewed for additional potentially relevant studies. To complete the historical picture, key leaders in gastrointestinal surgery were informally queried about their past experience and recollection of the evolution of laparoscopic liver surgery in the Netherlands.

INITIAL EXPERIENCE WITH LAPAROSCIPIC LIVER RESECTIONS AND CASE-CONTROLE COMPARISON – PRESENT STATE

Patients

All major liver centres in the Netherlands were contacted during 2008 by phone and/or e-mail and asked to participate in this study. Of the fourteen major HPB centres in the Netherlands, only seven had performed laparoscopic liver resections. Six of these centres agreed to collaborate. Data were obtained retrospectively from six separate prospectively collected databases used in these six HBP units and were pooled for further analysis. All patients who underwent laparoscopic left lateral sectionectomies of the liver in the six centres between 2000 and 2008 were included in this multicentre study. The laparoscopic group of patients was compared in a case-matched comparison approach with a group of patients undergoing the same type of liver resection as an open procedure in that era in the 6 participating centres in a proportion of 1: 3. This approach and the choice to only include left lateral sectionectomies were felt to be justified to eliminate bias as much as possible and increase the external validity of the conclusions. The investigators (J.H.M.B.S. and I.L.) were unaware of the primary outcome or secondary outcomes during the selection process. Patients undergoing left lateral resections in combination with colonic resections were excluded.

In each unit, patients were preoperatively discussed in a multidisciplinary meeting, after evaluation of liver function tests and radiologic liver workup including ab-

dominal ultrasonography, CT, MRI and/or CT-PET scan. Patients with benign as well as malignant solid liver lesions were included in this study. Patients with cystic lesions of the liver were excluded. Laparoscopic liver resection was considered if the lesion was located in the left lateral segments (segment 2 and 3 according to Couinaud's classification). The choice to perform either a laparoscopic or open procedure was at the discretion of the attending surgeon in consent with the patient. Preoperative information consisted of medical history, preoperative diagnosis and American Society of Anesthesiologists (ASA) classification.

Surgical Procedures

The open procedure was started with a 15- to 25-cm incision according to the preference of the surgeon. During operation, the left liver was mobilized, and central venous pressure was maintained at 2–6 mm Hg. Transection of the liver was performed according to the preference of the surgeon: the Cavitron Ultrasonic Surgical Aspirator (CUSA ; Valleylab, Boulder, Colo., USA) and argon beam coagulator (Bircher Ind., Ltd., Englewood, Colo., USA) with or without the use of Pringle's maneuver, Ultracision Harmonic ACE (Ethicon Endosurgery, Johnson & Johnson, USA) or Ligasure (Covidien, USA). Only occasionally was the clampcrush technique used. Minor crossing vessels and biliary radicals were divided using polypropylene sutures or clips. The portal pedicles and hepatic veins were divided and ligated with a running polypropylene suture. In some procedures, vascular staplers such as e.g. Autosuture EndoGIA (Covidien) were used. After removal of the liver specimen, the raw surface of the liver remnant was subjected to argon beam coagulation and sealed with TachoSil (Nycomed, Zurich, Switzerland) or Tissuecoll (Baxter, Vienna, Austria) if considered appropriate.

The laparoscopic procedure was performed as described in detail previously.[16] The patient was in the supine French position and abdominal access was achieved by transumbilical open insertion of a laparoscope. Pneumoperitoneum was kept at 10–14 mm Hg; three or four additional 12-mm trocars were added, and a 30° laparoscope was used routinely. The central venous pressure was maintained at 2–6 mm Hg. Hepatic transection of parenchyma and minor crossing vessels and biliary radicals was mainly performed with harmonic scalpel (Ultracision, Ethicon Endosurgery, Johnson & Johnson, USA) or the Ligasure (Covidien). The segmental portal pedicles and left hepatic vein were stapled using a vascular stapler (EndoGIA Autosuture, Covidien). Resected specimens were placed in a plastic bag (Endocatch Autosuture, Covidien) and removed through a separate incision.

Parameters and Outcome

Peri- and post-operative parameters included type of resection, operation time, blood loss, need for transfusion, conversion of laparoscopic to open procedure, post-operative complications, post-operative length of hospital stay and pathologic assessment of the resected liver segment. Blood loss was measured by the suction device and the weight of the gauzes and recorded in operation notes and/or anaesthesia reports. In case of discrepancy, the highest amount was used. Data on surgical technique consisted of information about type of incisions, type of liver resection, method of liver transection, hemorrhage control, use of hemostatic agents, Pringle maneuver, and method of extraction of surgical specimen. In one centre (Maastricht University Medical Centre, MUMC), a multimodal perioperative enhanced recovery program (ERAS) was followed for all patients undergoing liver surgery.[16, 17] This was also recorded as a parameter. Criteria for discharge in the ERAS setting were described previously.[16, 17] Discharge in the traditional setting was at the discretion of the attending surgeon.

Primary outcome of the study was hospital length of stay. Secondary outcome measures comprised complications (including mortality and conversion rates), duration of operation and blood loss. Post-operative complications were defined according to the international grading system of Dindo et al.[18]

CURRENT STATUS OF LAPAROSCOPIC LIVER SURGERY – FUTURE DEVELOPMENTS

To get an indication of the volumes currently being operated on in Dutch hospitals, and to see whether they had increased in the years following the introduction of the minimally invasive technique, we approached all Dutch hospitals that indicated to perform liver surgery in January 2011 by e-mail. This contained three questions surveying on (1) whether the hospital performed formal liver resections (not only deroofing of cysts), (2) how many open/laparoscopic major or minor hepatic resections were performed in 2010, and (3) whether the provided data were real or estimated numbers. Centres that did not reply on the request to complete the survey were approached by phone in February 2011.

Statistical Analysis

Data were analysed by J.S., I.L. and R.V; if necessary, an independent statistician was consulted. Continuous variables are expressed as mean (± standard error of the mean). Data were analysed according to the intention to treat principle. Univariable analysis was performed using Pearson's X2 test (or Fisher's exact test where appropriate) to investigate differences between open and laparoscopic procedures regarding sex, indication, pathology, resection margins, ERAS, use of Pringle maneuver,

method of liver transection, hemorrhage control and hemostatic agents, use of staplers and complications. The Mann-Whitney U test was used for univariable analysis to investigate differences between open and laparoscopic surgery regarding age, ASA classification, tumour diameter, type of incision, complication classification, hospital length of stay (days), duration of operation (min), blood loss (ml) and number of transfusions. The relation between patient characteristics and operative strategy and length of hospital stay was analysed with univariable linear regression analysis. All independent variables with a two-tailed p value below 0.200 were included into a multivariable linear regression model using backward analysis to assess which parameters were significantly and independently related to length of hospital stay. Also, the group effect of open versus laparoscopic resections on post-operative hemoglobin was analysed using multivariable linear regression analysis correcting for preoperative hemoglobin levels. A p value below 0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS software (version 15; SPSS Inc., USA).

RESULTS

SYSTEMIC REVIEW OF LAPAROSCOPIC LIVER SURGERY IN THE NETHERLANDS– PAST EXPERIENCE

A total of 91 abstracts were retrieved that met the search terms, and after review 19 abstracts remained eligible. Of these 19 articles, 6 reported on actual laparoscopic liver surgery, 12 described the use of laparoscopy and/or laparoscopic ultrasound for staging in patients with hepatic tumours, and one article provided a literature review on liver resection and laparoscopy (*Fig. 1*). The informal interviews and articles eligible for review revealed that the first two laparoscopic liver resections were per formed in Amsterdam in 1995 by the group of Cuesta et al.[19] In the following years, only one article from the same group was published reporting on a series of laparoscopically operated patients (n = 10). Seven underwent a minor laparoscopic resection and three underwent fenestration of hepatic cysts.[20] After these initial reports on minimally invasive liver surgery, three articles were published with regard to laparoscopic treatment of polycystic liver disease. [21–23] Later series of 26 laparoscopic liver resections provided evidence that this procedure could be performed safely in the Netherlands. [16]

INITIAL EXPERIENCE WITH LAPAROSCOPIC LIVER RESECTIONS AND CASE-CONTROLE COMPARISON – PRESENT STATE

Patient's Characteristics Between 2000 and 2008, the laparoscopic approach for hepatic left lateral sectionectomy was performed in 30 patients in 6 centres in the Netherlands (mean age 50 ± 3 years) and completed laparoscopically in 27 patients. Five of the laparoscopic liver resections were performed hand-assisted. In the open group, 90 patients were matched for the same type of resection (mean age 52 ± 2 years). Demographic data of both groups are reported in *Table 1*. There were no significant differences in age, ASA classification, indication, resection margins and tumour size.

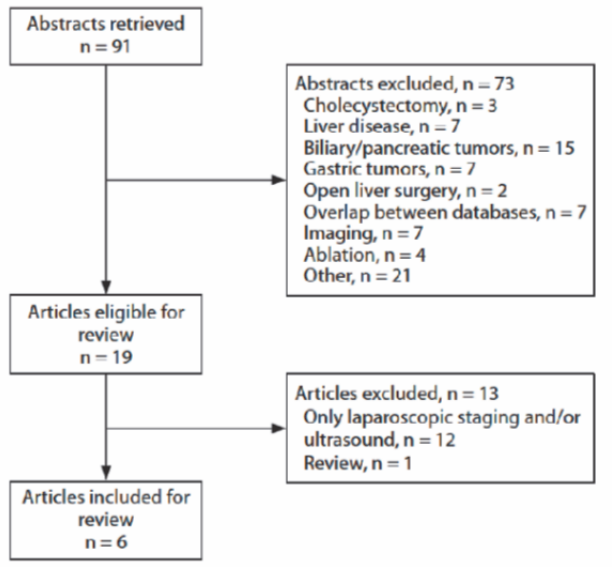

Figure 1. Selection of studies eligible for review.

Table 1. Clinical and pathological features of the control study

	Laparoscopic group n = 30	Open group n = 90	p-value
Male / female[a]	5/25	35/55	0.043
Age, years[b]	50 (3)	52 (2)	0.584
ASA 1[b,c] ASA 2 ASA 3 ASA 4	10 16 2 0	18 38 16 1	0.625
Indication (malignant/benign)[a]	11/19	39/51	0.091
Tumour size, cm[b]	4.8 ± 0.5	5.3 ± 0.4	0.673
Pathology (malignant/benign)[a,c]	7/22	48/42	0.007
Resection margins (R0/R1/R2)[a,c,d]	19/1/1	64/8/2	0.597
ERAS (yes/no)[a]	11/19	8/92	0.001

Values for tumour size are expressed as mean 8 standard error of mean.
a Pearson's _2 test (or Fisher exact test where appropriate).
b Mann-Whitney U test.
c Results do not add up to total values as a result of missing data.
d In the laparoscopic group, two (R1 and R2) resection margins were positive, both in patients with benign disease (adenoma and hemangioma, respectively). In the open control group the R2 resections were suspected to be benign lesions preoperatively. However, one of these R2 resections proved to be malignant (hepatocellular carcinoma). Of the R1 resection margins, 3/8 were malignant tumours.

Surgical Procedures and Parameters

The Pringle maneuver was only used during open surgery (*Table 2*). The method of liver transection in the open group was different from the approach in the laparoscopic group. Mostly, the CUSA and/or argon beam was used in the open group for liver transection.

Outcome Parameters

Mean hospital length of stay was 6.0 (± 0.4) days in the laparoscopic group versus 8.1 (± 0.4) days in the open group (p ! 0.001). Complication rates did not differ significantly between the laparoscopic and the open group (26 vs. 21%), neither did they differ significantly when complications were graded according to severity intervention score. Three laparoscopic procedures (10%) were converted to an open procedure (table 3). Reasons for conversion were hemorrhage, an additional lesion in segment IV or the close relation to the left hepatic vein. There were no deaths in the laparoscopic group. In the open group, one of the 90 patients (1.1%) died due to multiple organ failure after sepsis.

Table 2. Operative details on transection and hemostasis techniques and use of devices

	Laparoscopic group n = 30 (%)	Open group n = 90 (%)
Use of Pringle manoeuvre	1 (3)[a]	20 (22)
Liver transection		
Cusa ± argonbeam	3 (10)	55 (61)
Ultracision	21 (70)	4 (4)
Ligasure	4 (13)	7 (8)
Hydrojet		2 (2)
Cusa + ligasure		8 (9)
Diathermia ± endogia		4 (4)
Kelly clamp		1 (1)
Endogia	2 (7)	4 (4)
Haemorrhage control[B]		
Diathermia ± argonbeam	6 (20)	4 (4)
Clips	6 (20)	15 (17)
Prolene	4 (13)	23 (26)
Clips and prolene	1 (3)	39 (43)
Other: use of device	9 (30)	3 (3)
Use of staplers (yes/no) [B]	22/3*	19/68
Haemostatic agents [B]		
None	19 (63)	39 (43)
Tachosyl	4 (13)	17 (19)
Tissuecoll	4 (13)	25 (28)
Surgicell	1 (3)	1 (1)
Unknown	1 (3)	7 (8)

Figures in parentheses indicate percentages.
a Following conversion to open.
b Results do not add up to total values as a result of missing (non-reported) data.

There was significantly less blood loss in the laparoscopic group compared to the open group ($p < 0.001$; *Table 3*). When corrected for preoperative hemoglobin level, multivariable analysis showed that open resection was significantly related to a decrease in post-operative hemoglobin levels compared to the laparoscopic group (OR = –0.520, CI –1.022 to –0.18, $p = 0.043$). None of the patients in the laparoscopic group needed a blood transfusion post-operatively in contrast to 22 blood transfusions in the open group. However, this difference was not significant. The mean duration of operation in the laparoscopic group was significantly shorter than in the open group ($p < 0.001$; *Table 3*).

Univariable regression analyses showed that several variables were related to differences in length of hospital stay (*Table 4*). However, after multivariable regression analysis, only ASA classification (OR = 1.598, CI 0.738–2.458, p < 0.001), complication grade (OR = 1.680, CI 1.124–2.235, p < 0.001) and ERAS (OR = –2.502, CI –4.032 to –0.972, p = 0.002) were independently and significantly related to length of hospital stay.

Table 3. Primary and secondary outcomes (mean 8 SEM)

	Laparoscopic group n = 30 (%)	Open group n = 90 (%)	p-value
Length of stay (days)[a]	6.0 ± 0.4	8.1 ± 0.4	<0.001
Complications[b]	5 (26)	19 (21)	0.620
Complications (grade)a			0.832
Grade 1	4 (13)	8 (9)	
Grade 2		4 (4)	
Grade 3a		3 (3)	
Grade 3b	1 (3)		
Grade 4a		2 (2)	
Grade 4b		1 (1)	
Grade 5		1 (1)	
Conversions	3 (10)		
Reoperation[b]	1 (3)	3 (3)	0.589
Blood loss (mls)[a]	288 ± 99	608 ± 97	<0.001
Operation time (minutes)[a]	160 ± 13	231 ±11	<0.001

Figures in parentheses indicate percentages.
a Mann-Whitney U test.
b Pearson's X^2 test (or Fisher exact test where appropriate).

Table 4. Univariable linear regression analysis of length of hospital stay

Variable	Odds ratio	95% CI	P-value
Age (years)	0.040	0.001 to 0.079	0.047
Sex (male/female)	1.374	0.022 to 2.276	0.046
Group (open/closed)	2.012	0.571 to 3.452	0.007
Indication (malignant/benign)	1.419	0.154 to 2.684	0.028
Pathology (malignant/benign)	1.762	0.501 to 3.023	0.007
Tumour diameter (cm)	0.091	-0.129 to 0.311	0.413
Complication[a]	1.559	1.025 to 2.093	<0.001
Duration (minutes)	0.008	0.001 to 0.015	0.020
ERAS (yes/no)	-1.392	-3.136 to 0.352	0.117
Reoperation	0.961	-4.092 to 6.014	0.707
ASA[b]	1.840	0.849 to 2.830	<0.001
Stapler (yes/no)	-1.637	-3.014 to -0.261	0.020
Pringle (yes/no)	-0.762	-2.130 to 0.606	0.272
Transection			
Cusa	1.523	-1.803 to 4.848	0.366
Ultracision	0.120	-3.373 to 3.613	0.946
Ligasure	0.309	-3.536 to 4.155	0.874
Hydrojet	1.400	-4.565 to 7.365	0.643
Cusa and ligasure	1.525	-2.540 to 5.590	0.459
Other	-0.35	-5.133 to 4.433	0.885
Kelly	1.400	-6.410 to 9.210	0.723
Endogia	0.567	-3.751 to 4.884	0.795
Haemorrhage control			
Diathermia	-1.992	-4.545 to 0.560	0.125
Clips	-0.942	-3.320 to 1.435	0.433
Prolene	1.197	-0.606 to 3.000	0.191
Other	-1.276	-3.653 to 1.102	0.289
Haemostatic agents			
Tachosyl	-0.024	-5.387 to 5.340	0.993
Tissuecol	0.121	-5.178 to 5.419	0.964
Surgicell	3.000	-4.248 to 10.248	0.414
None	-0.114	-5.328 to 5.100	0.965

a Complication according to Dindo et al. [18]; increase per unit increase severity.
b Increase per unit increase severity.

CURRENT STATUS OF LAPAROSCOPIC LIVER SURGERY – FUTURE DEVELOPMENTS

The response rate to the nationwide survey was 81%; 30 out of 37 approached hospitals responded. The seven non-responding centres were all district general hospital centres, except one university medical centre. In total, 21 centres performed formal

liver resections in 2010, the remaining 9 centres only performed deroofing procedures. The total number of hepatic resections performed in 2010 by the responding centres in the Netherlands was 966. This total number of resections consisted of 444 major and 522 minor hepatectomies (Fig. 2). During 2010, all Dutch hospitals together performed only 49 laparoscopic liver resections; 5% of all resections (*Fig. 3*). All these minimally invasive surgical procedures were reported to be minor hepatic resections.

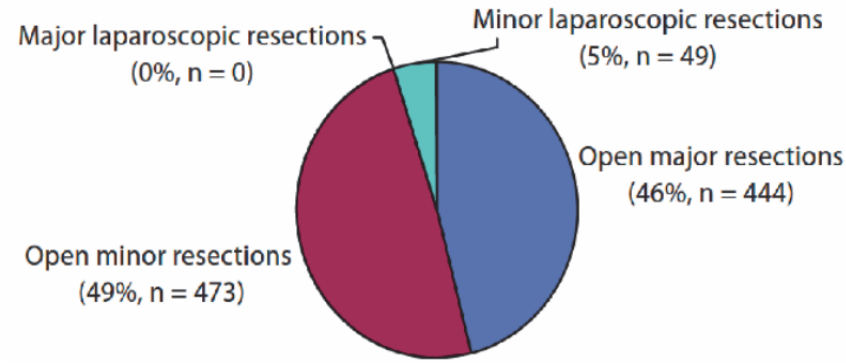

Figure 2. Results of a nationwide survey of laparoscopic and open liver resections performed during 2010 in the Netherlands.

DISCUSSION

This study provides a historical overview and reports on the initial experience and the current status of laparoscopic liver surgery in the Netherlands. A systematic review of the literature showed that the laparoscopic approach for hepatic resection was introduced in the Netherlands during the 1990s and that some, but limited experience has been gained. It is clear from the data and from additional information obtained by interviewing key leaders that only very few laparoscopic livers were performed in the previous millennium.

Compared to countries that have traditionally always played a pioneering role in (laparoscopic) liver surgery, such as France, the Netherlands have fallen behind with regard to the implementation of the minimally invasive technique. Many surgeons considered an open partial liver resection to be major surgery associated with significant mortality and morbidity. Dutch surgeons remained reluctant to perform this type of surgery.[24] Illustrating this fact is that only 110–130 partial liver resections (including benign tumours) were performed between 1984 and 1987. At the end of the 1980s and 1990s, several series on the experience with open hepatic resection were published by different Dutch centres.[25, 26]

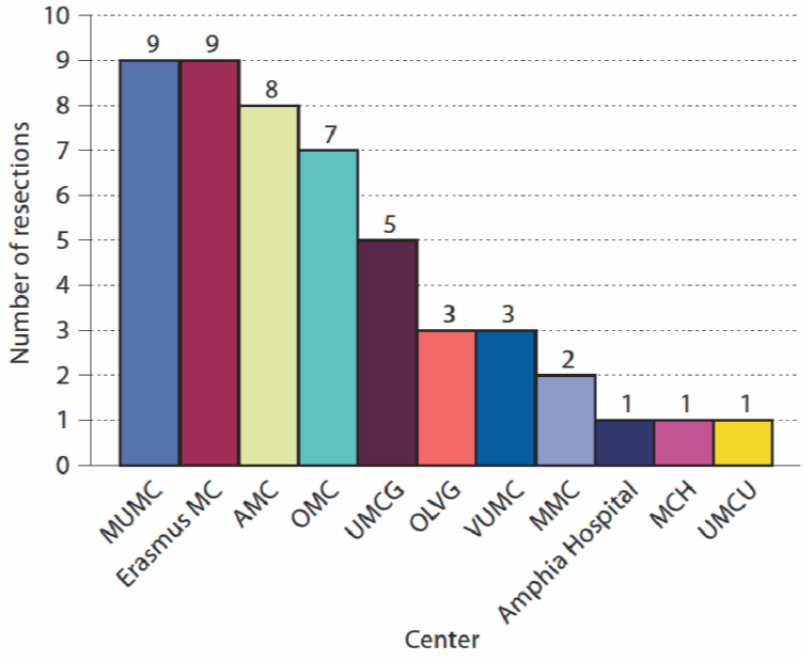

Figure 3. Results of a nationwide survey of total laparoscopic (minor) liver resections performed during 2010 in the Netherlands per centre.

The laparoscopic technique for liver resections was introduced in the Netherlands during the 1990s for diagnostic laparoscopies and liver biopsies. Later, the indications were extended to fenestration of liver cysts and anatomic liver resections. [27–32] The group of Cuesta et al. [19] was in 1995 the first to report two cases of limited laparoscopic liver surgery of segment II and IV in the Netherlands. A few years later, in 2001, a small retrospective series (n = 10) was published that demonstrated encouraging results concerning operative blood loss, post-operative complications and hospital length of stay after wedge and left lateral hepatectomy. Furthermore, they concluded that laparoscopic treatment should be considered in selected patients with benign and malignant lesions in the left lobe or frontal segments of the liver.[20]

While the first limited laparoscopic liver resection in the Netherlands was performed in 1995, the first laparoscopic liver resection worldwide, a wedge resection, had already been performed by Gagner's group in 1992. Four years thereafter, Azagra's group reported the first anatomic liver resection.[3] In the following few years, the minimally invasive technique was further developed and adopted, resulting in the first laparoscopic left lateral sectionectomy for living liver donation[33] and the first reports on robotic liver surgery.[34, 35] Initially, laparoscopic liver resection was challenging because of the difficulties concerning safe mobilization and exposure of this

fragile and heavy organ.[3, 36, 37] Small, superficial and peripheral lesions in anterolateral segments were considered most amenable to laparoscopic liver resection. Surgeons with extensive experience in laparoscopy and hepatic surgery have performed laparoscopic major hepatic resections with satisfactory outcomes.[28, 38, 39]

Recent large reviews by Reddy et al.[15] and Nguyen et al.[14] show favorable outcomes after laparoscopic resection.[14, 15] Patient benefits included less operative blood loss[6, 7] , less post-operative pain[5, 9, 10] and narcotic requirement, improved cosmetic aspects[9, 12] and a shorter length of hospital stay [5, 7–12] with post-operative morbidity and mortality comparable to open liver resection. In addition, the minimally invasive approach seems to be cost-effective.[40, 41] Potential limitations and disadvantages of laparoscopic liver resection include a significant learning curve, potential bleeding which may be more difficult to control laparoscopically, inadequate assessment of the liver for additional lesions, and increased risk for gas embolism.[15, 42] Air embolism may occur when high- pressure pneumoperitoneum is used.[36, 43] However, gas embolism is rare and usually well tolerated.[5] Other concerns have been raised about the potential dissemination of malignant cells during laparoscopic resection.[44–46] Some authors have suggested that tumour dissemination does not increase by laparoscopy [47–49], and recent reports regarding this subject show long-term survival rates comparable to open surgery [12, 37, 50, 51] .

At present, after more than 10 years of experience and following advances in laparoscopic technology, the surgical community has accepted that laparoscopic liver surgery is feasible and safe.[3, 7, 8, 10, 51–53] This is especially true for resection of left lateral segments and right anterior segments.[4, 9, 11, 54] Some of the advantages reported in literature were also found in the present study. The present multicentre case-control study on laparoscopic left lateral sectionectomies in the Netherlands between 2000 and 2008 demonstrated that length of hospital stay for the laparoscopic approach for left lateral sectionectomies was reduced by 2 days. Furthermore, the laparoscopic approach resulted in faster procedures with reduced blood loss, no occurrence of gas embolisms and comparable morbidity. In a multivariable analysis, length of hospital stay appeared to be related to ASA classification, complications and ERAS.

Left lateral sectionectomy currently is the most common laparoscopic liver resection for solid tumours in the Netherlands. However, only a minority of left lateral sectionectomies were performed laparoscopically between 2000 and 2008. The laparoscopic approach has gained gradual acceptance by Dutch surgeons, but is still not a standard. A structured implementation may allow the Dutch surgical community to catch up with international developments. Recently, van Dam and Topal performed the first major laparoscopic liver resection in the Netherlands (anatomical right hemihepatectomy, Maastricht, 2011).

The question remains why the laparoscopic left sectionectomy in this study proved to be faster than the open counterpart. Differences in technique in transection of the liver parenchyma and the vascular and biliary structures may have added to a faster transection. Reduced blood loss, either caused by different transection devices or pneumoperitoneum, may reduce the need for prolene stitches and hemostatic clips, which can be time consuming. Lastly, there is no need to close the abdomen after the procedure.

The survey results demonstrate an increase in both totally laparoscopic and totally open liver resections performed in the Netherlands. Although more centres have adopted the laparoscopic approach in recent years, individual centre volumes remain low. Only 5% of all liver resections were performed laparoscopically, which is significantly less compared to other countries where average percentages of laparoscopic hepatic resections range between 20 and 80%.[13] If surgeons in the Netherlands aim to increase the portion of laparoscopic liver resections, liver surgery should be further centralized. Furthermore, a central training, proctoring and credentialing infrastructure should be developed to improve the quality of outcome parameters and to allow units to become (high-volume) expert centres.

The foundation of the Dutch Liver Collaborative Group in 2003 gave a new impulse to minimally invasive liver surgery, and is in concordance with recently made recommendations that national and international societies, as well as governing boards, should become involved in the goal of establishing training standards and credentialing.[13] Goals of this workgroup are to facilitate collaboration of medical centres in the field of hepatic surgery, initiate and facilitate research in liver surgery (especially multicentre trials), facilitate training, education and adoption and to establish a quality control and auditing system for Dutch liver surgery centres.

In conclusion, minimally invasive liver surgery is gradually being adopted in the Netherlands. The laparoscopic (left-sided) liver resection is a safe procedure, and it probably results in a shorter hospital length of stay with comparable morbidity. Laparoscopic liver resections appear to be faster. More importantly, ASA classification, complications and ERAS proved to be important prognostic variables for reduced length of hospital stay in Dutch hospitals. In the future, the Dutch Liver Collaborative Group should continue to play an important role in the further adoption and centralization of minimally invasive liver surgery. Conducting an RCT on laparoscopic liver resection may add to the body of evidence supporting broader introduction of minimally invasive liver surgery.

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Chapter 8

Open versus laparoscopic left lateral hepatic sectionectomy within an enhanced recovery ERAS programme (ORANGE II – Trial): study protocol for a randomised controlled trial

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ABSTRACT

BACKGROUND

The use of laparoscopic liver resection in terms of time to functional recovery, length of hospital stay (LOS), long-term abdominal wall hernias, costs and quality of life (QOL) has never been studied in a randomised controlled trial. Therefore, this is the subject of the international multicentre randomised controlled ORANGE II trial.

METHODS

Patients eligible for left lateral sectionectomy (LLS) of the liver will be recruited and randomised at the outpatient clinic. All randomised patients will undergo surgery in the setting of an ERAS programme. The experimental design produces two randomised arms (open and laparoscopic LLS) and a prospective registry. The prospective registry will be based on patients that cannot be randomised because of the explicit treatment preference of the patient or surgeon. Therefore, all non-randomised patients undergoing LLS will be approached to participate in the prospective registry, thereby allowing acquisition of an uninterrupted prospective series of patients. The primary endpoint of the ORANGE II trial is time to functional recovery. Secondary endpoints are post-operative LOS, percentage readmission, (liver-specific) morbidity, QOL, body image and cosmetic result, hospital and societal costs over 1 year, and long-term incidence of incisional hernias. It will be assumed that in patients undergoing laparoscopic LLS, length of hospital stay can be reduced by two days. A sample size of 55 patients in each randomization arm has been calculated to detect a 2-day reduction in LOS (90% power and alfa = 0.05 (two-tailed)).

CONCLUSION

The ORANGE II trial is a multicentre randomised controlled trial that will provide evidence on the merits of laparoscopic surgery in patients undergoing LLS within an enhanced recovery ERAS programme.

Trial registration: ClinicalTrials.gov NCT00874224.

BACKGROUND

Liver resection for colorectal metastasis is the only potentially curative therapy, and has become the standard of care in appropriately staged patients, offering 5-year survival rates of approximately 35-40%.[1] For symptomatic benign lesions and those of uncertain nature or large size, liver resection is also a widely accepted treatment. Within the framework of optimizing post-operative recovery and/or producing a shorter length of stay (LOS) in hospital, laparoscopic surgery and enhanced recovery programmes have recently been introduced for liver surgery.

Laparoscopic liver resection was first described in 1995.[2] Over the past decade the method has gained wide acceptance for various liver resection procedures. [3-9] Multiple retrospective case series and reviews comparing open with laparoscopic liver resection indicate that laparoscopic liver resection can be used safely for both malignant and benign liver lesions.[10-15] Recent publications from expert centres show that a substantial part of the total volume of major and minor liver resections is performed laparoscopically, and results are good.[16,17] Laparoscopic liver resection is associated with shorter LOS, less post-operative pain, earlier recovery, and better quality of life (QOL).[9,13,18,19] Comparing patients undergoing an open left lateral sectionectomy (LLS) of the liver with those undergoing laparoscopic LLS, both Vigano et al. and Carswell et al.[20,21] found no significant difference in operating time between the two groups. In addition, the median length of post-operative LOS was significantly less (6 vs. 9 days, $P < 0.01$) after laparoscopic resection.[3] Furthermore, no evidence of a compromised oncologic clearance in laparoscopic liver resection has been found.[3,13] However, recovery and LOS are not only dependent on the type of surgery or procedure, and other variables should also be taken into account.

The Enhanced Recovery After Surgery (ERAS) programme has been introduced to improve post-operative care. This multimodal programme, derived from Kehlet's pioneer work in the 1990s for multimodal surgical care, involves optimization of several aspects of the perioperative management of patients undergoing major abdominal surgery. In patients undergoing segmental colectomy, the ERAS programme enabled earlier recovery and consequently shorter LOS [22-25]. Furthermore, a reduction of post-operative morbidity in patients undergoing intestinal resection was reported [26-29]. These results stimulated liver surgeons of the ERAS-group (Maastricht, Edinburgh and Tromsö) to adapt the ERAS programme to patients undergoing open liver resection. Van Dam et al. [30] found a significantly reduced LOS after open liver resection when patients were managed within a multimodal ERAS programme. Besides a reduction in median total LOS from 8 to 6 days (25%), the data also suggested that a further reduction in stay could be possible as there was a delay be-

tween the recovery and actual discharge of the patients [30]. Moreover, Stoot et al. found retrospectively that there was a further reduction in LOS from 7 days to 5 days when patients were operated laparoscopically and managed within an ERAS programme.[31] In that study there was also a delay between recovery and actual discharge of the patients. Previously, Maessen et al. reported a median delay to discharge of 2 days after patients had functionally recovered after colonic surgery managed within an ERAS programme.[32] This delay is often linked to patient age, hospital logistics, and absence of social and/ or homecare support.

In most reported trials aiming at earlier recovery or a reduction in LOS, type of surgery and/or perioperative management were not standardized. In addition, the added value of laparoscopic LLS compared with open left lateral sectionectomy within an ERAS programme in terms of time to functional recovery, LOS in hospital, costs, and QOL has never been studied in a randomised controlled trial (RCT). However, randomization of patients undergoing open or laparoscopic liver resection is hazardous. It is to be expected that experienced centres will be reluctant to randomize patients because of the absence of clinical and patient equipoise for laparoscopic resection. To capitalize on both centres with and without preference for laparoscopic liver surgery, and to thereby acquire an uninterrupted prospective series of patients, an alternative trial design with two randomization arms (open versus laparoscopic surgery) and a prospective registry has been constructed for the ORANGE II trial. The combination of an RCT and a prospective registry will improve overall power and strengthen the external validity and generalizability of study results.[33-35]

METHODS

ETHICS APPROVAL

The study has been approved by the Medical Ethical Review Board of the Maastricht University Medical Centre, Maastricht, The Netherlands trial number NL 25591.068.08 / MEC 08-2-110. Ethics consent will also be obtained from the national or regional ethics boards in each participating country. Patients willing to participate in this trial will receive both verbal and written information at the time of recruitment in the outpatient clinic. In accordance with the local medical ethics committee all participating sites will provide an independent surgeon or physician if needed. An independent surgeon (M. Poeze) has been appointed for the Maastricht University Medical Centre to answer questions. Confidentiality is guaranteed by assigning the participators an encoded trial number. This indicates that only the physician with the decoding 'key' will know which code number has been assigned to any patient. All trial data will be saved during the trial and stored on a server, and patients will be asked

to consent to future analysis of these data. Withdrawal from the trial at any time or for any reason will not hold any form of consequences for the patient, and data from these patients will be deleted.

STUDY DESIGN

The ORANGE II trial is a prospective superiority study with an experimental design, using two double-blinded randomised controlled arms and a prospective registry to determine whether laparoscopic surgery is to be preferred over open surgery in patients undergoing LLS and participating in an enhanced recovery programme. In the participating randomizing centres, patients, nurses and the ward physician (but not the operating surgeon) will be blinded for the type of intervention up to and including post-operative day (POD) 3. They will record the functional recovery criteria twice daily. Only the investigator and operating surgeons will know the actual procedure. The blinded ward physician(s) will decide on whether a patient will be discharged or not.

However, randomization of patients undergoing open or laparoscopic liver resection is hazardous as previously explained. Moreover, another potential source of bias exists when randomizing patients with a strong treatment preference. When patients cannot be blinded to their treatment allocation (POD 3) they may be resentful and demoralized if they do not receive their preferred treatment, and consequently they may have poor compliance. By contrast, patients receiving their preferred treatment may have above-average compliance. Thus to capitalize on centres both with and without preference for laparoscopic liver surgery, and thereby to acquire an uninterrupted prospective series of patients, all non-randomized patients undergoing a LLS will be approached to participate in the prospective registry. Registration of these patients is imperative to guarantee a consecutive series of patients and also because the absence of such a series may restrict generalization of the results, as randomised participants may not in fact be representative.[36] The combination of an RCT and a prospective registry will improve overall power and strengthen the external validity and generalizability of study results.[33-35] This non-randomised registry group will be analysed for centre and centre by treatment interaction as an observational study. Medical centres that wish to participate in this trial, but with liver surgeons early in the laparoscopic learning curve, will be accompanied during the procedure by an experienced proctoring laparoscopic HPB-surgeon.

PRIMARY & SECONDARY ENDPOINTS

The primary endpoint of the ORANGE II trial is time to functional recovery. A patient is fully functionally recovered when all of the following five criteria are satisfied: 1)

adequate pain control with oral analgesia; 2) restoration of mobility to an independent level; 3) absence of intravenous fluid administration; 4) ability to eat solid foods; and normal or decreasing serum bilirubin level and international normalized ratio.

It is medically justified to discharge patients when the criteria for full functional recovery are met and if the patient is willing to go home. Secondary endpoints include post-operative LOS in hospital, percentage of readmissions, total morbidity (both general and procedure related), composite endpoint of liver-surgery-specific morbidity, QOL, body image and cosmesis, reasons for delay of discharge after functional recovery, hospital and societal costs over 1 year, and long-term incidence of incisional hernias.

Morbidity

The preoperative morbidity status of patients will be measured using the American Society of Anaesthesiologists (ASA) scale. The Portsmouth modification of the Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (P-POSSUM) will be used to evaluate the risk of perioperative morbidity and mortality. Post-operative morbidity is rationally predictable, with hemorrhagic complications occurring predominantly during surgery or in the early post-operative phase, and biliary complications, intra-abdominal abscess, or liver failure in the later post-operative phase. Wound infection and sepsis will be additional complications that require monitoring. Morbidity will be classified and analysed according to the validated classification for post-operative morbidity as described by Dindo et al.[37]

Liver Resection-Specific Composite Endpoint

In this trial, we will also use a well-defined liver surgery specific composite endpoint, as suggested by van den Broek et al.[38] This endpoint is a parameter composed of a combination of procedure-specific complications, which is considered as a single, dichotomous outcome: operative mortality, intra-abdominal haemorrhage, ascites, bile leakage, intra-abdominal abscess, and post-resectional liver failure. These components, which are all specific to liver surgery and have substantial clinical relevance, reflect complications rated as Dindo grade 3–5. A composite score of 1 (failure) will reflect the occurrence of at least one of the above liver-specific complications, and a score of 0 (success) will be assigned if none of these occur.

Quality of Life

To assess QoL in patients undergoing laparoscopic versus open LLS, the Dutch version of the EuroQol five dimension (EQ-5D) status test in Dutch centres and the translated EQ-5D for international centres will be used. The EQ-5D is a standardized instrument for use as a measure of health outcome, which consists of the five dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/ depression,

with three levels each and a rating on the EQ visual analogue scale (VAS; 0–100).[39-41] Furthermore, the European Organization for Research and Treatment (EORTC) 30-item post-cancer QOL questionnaire (QLQ-C30; with the liver metastases (LM21) module will be used for liver-specific treatment measurements.[42] Assessment of the patients' QOL will be performed at the time of consent, discharge and 10 days, 3, 6 and 12 months after discharge.

Body Image and Cosmesis

To evaluate differences in post-operative body image and cosmesis, the Body Image Questionnaire (BIQ) will be used [43,44], which consists of eight questions about body image and cosmesis. The body image assessment will be performed preoperatively at time of consent. Both the body image and cosmesis assessment will take place at discharge, and at 10 days, 3 months, 6 months and 12 months after discharge.

Hospital and Societal Costs

The economic evaluation will include a cost-utility analysis from a Dutch societal perspective. The incremental costs per quality adjusted life year (QALY) gained will be based on utility scores from the EQ-5D.[39-41] All hospital expenses (direct and indirect) related to both interventions will be monitored. In addition, a cost questionnaire offered at the regular follow-up consultation (3, 6 and 12 months) will help assess the societal and individual costs outside health care relating to patients' absence, impaired mobility, work, or normal daily activities. Unit prices will be based either on prices from the participating hospital financial departments or will be extrapolated using Dutch guidelines for cost calculation.[45]

Incidence of Incisonal Hernias

Incisional hernia after open surgery is a well-known complication of surgery, with an incidence of up to 20% after a 10-year period.[46] In patients undergoing a sigmoid resection, Anderson et al. found that laparoscopic resection led to a significantly lower incidence of incisional hernia compared with open surgery.[47] Furthermore, in two retrospectively analysed series of patients who received a partial hepatectomy, different types of incisions were compared. D'Angelica et al. reported that the common incisions used for partial hepatectomy were the Mercedes incision and extended right subcostal (ERSC) incision, and that the ERSC incision provides adequate, safe access and is associated with fewer long-term wound complications (9.8% vs 4.8%, $P<0.001$).[48] More recently, Togo et al. reported frequencies of incisional hernia after median, J-shaped, right transverse incision with a vertical extension at the midline from the subumbilical region to the xiphoid process (RTVE), and reversed T incisions to be 6.3%, 4.7%, 5.4%, and 21.7%, respectively. A diagnosis of 'no hernia' required a minimum follow-up of 12 months.[49]

To assess the incidence of incisional hernias in patients undergoing laparoscopic and open LLS, they will be contacted at a mean time of 1 year after resection to undergo ultrasonography or CT-scan to assess the incidence of incisional hernia.

STUDY POPULATION

Every patient requiring LLS will be identified and informed at the outpatient clinic about open and laparoscopic liver resection. Only patients meeting the inclusion and exclusion criteria will be approached for randomization. After reading the ORANGE II trial patient information and being allowed 1 week for consideration, patients will be asked for their informed consent. All patients ineligible for randomization due to patient or surgeon preference will be approached for participation in the prospective registry. If patients express an explicit preference, they will be allocated to the prospective registry and interviewed to ascertain the reasons for their preferences. Personal written informed consent will be obtained for all groups. Randomization will be carried out through the ORANGE II trial website using web-based randomization software (TENALEA; www.tenalea.com) (see Figure 1 for trial flow-chart). Patients will be approached for randomized inclusion if they meet each of the following inclusion criteria: require LLS; willingness to participate in the study; able to understand the nature of the study and what will be required of them; are men or non-pregnant, non-lactating women between the ages of 18 and 80 years of age; have a body mass index of between 18 and 35; and have ASA grading of I to III.

The exclusion criteria are: liver resection other than LLS; underlying liver disease; unwillingness to participate; inability to give written informed consent; and ASA grading of IV to V.

ERAS-PROGRAMME

All patients will participate in the ERAS liver programme, with a standardized perioperative management. For daily guidelines of the pre- and post-operative care of patients undergoing liver resection (*Figure 2*).

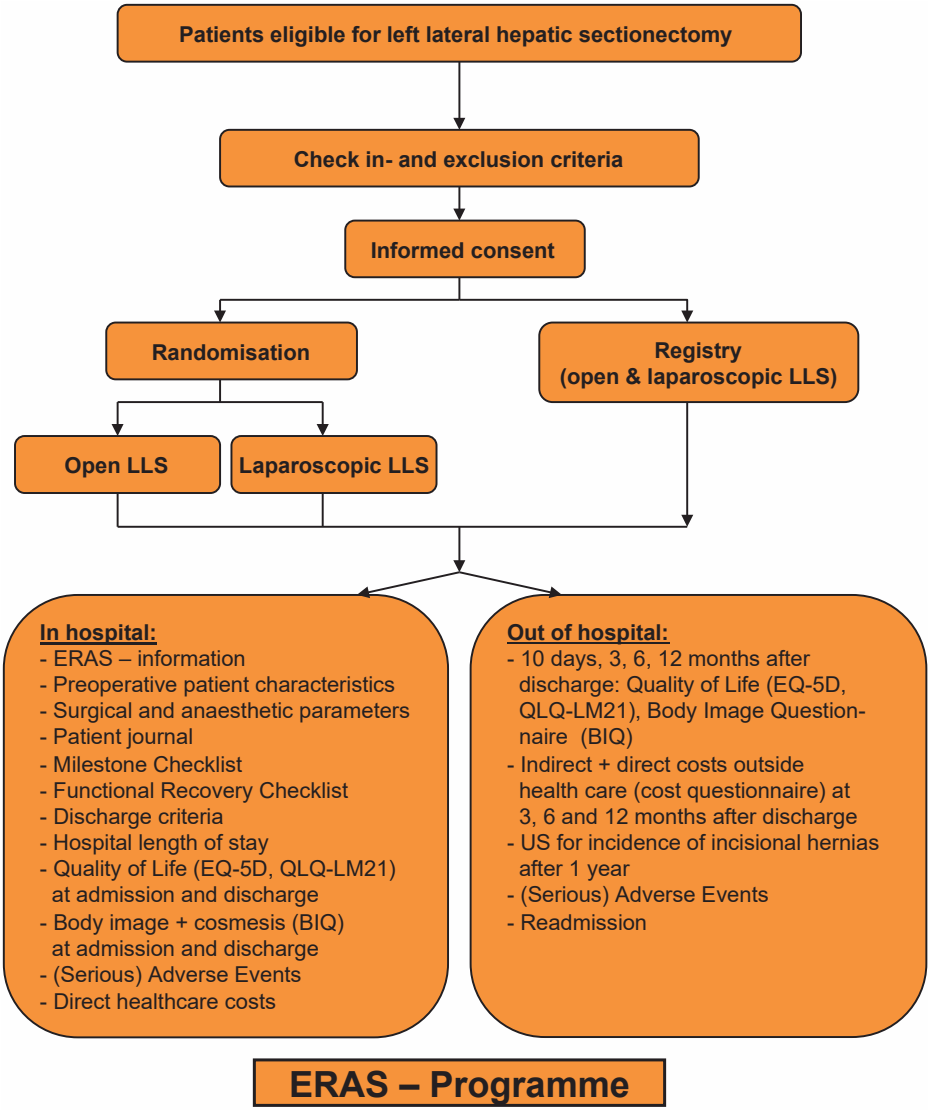

Figure 1. Orange II-Trial Flowchart.

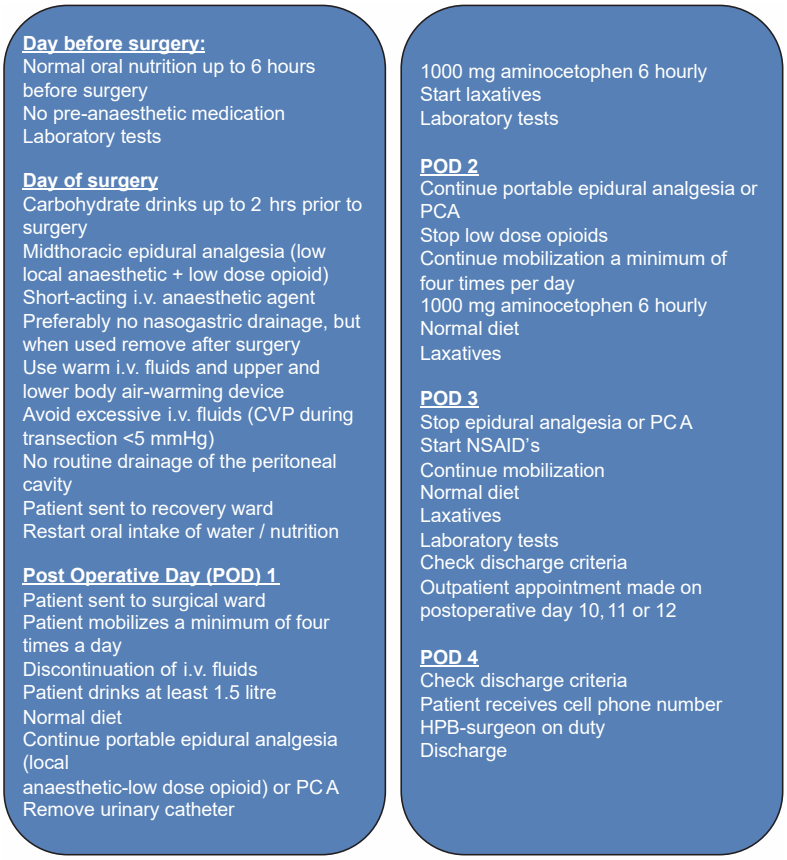

Figure 2. Daily guideline of post-operative care of patients undergoing a hepatectomy in the ERAS programme

FUNCTIONAL RECOVERY CRITERIA

The evaluation of time to functional recovery will start on POD 0 and will be scored twice daily until discharge from the hospital. The discharge process starts at the pre-admission counseling session, during which any special needs of the patients will be determined (for example, homecare or social support, transport. Before admittance, any problem that could delay discharge will be identified and addressed. Patients will only be discharged when they have met the five functional recovery criteria and are willing to go home. Reasons to delay discharge after functional recovery will be monitored and documented. Functional recovery criteria and LOS in hospital will be independently monitored and analysed.

Criterion I: Adequate pain control with oral analgesics

Post-operative pain will be systematically registered twice daily using the validated verbally administered 11-point numeric rating scale (NRS-11, 0 to 10).[50-53] Members of a specialized pain team will ask patients to rate the intensity of their current pain on a scale of 0 (no pain) to 10 (worst possible pain), with pain rated as 'mild' (1 to 3) 'moderate' (4 to 6) or 'severe') 7 to 10 [54]. The NRS-11 seems to be better accepted by most patients and to be at least as sensitive and valid as the more traditional VAS ratings.[53]

Criterion II: Independently mobile or at preoperative level

To assess the difference between the preoperative and post-operative mobility level, the ERAS Mobility Scale (EMS) has been developed from the Groningen Activity Restriction Scale.[55] The EMS assesses 10 basic actions to compare the level of mobility before and after surgical intervention. When the patient is able to perform 8 of the 10 items, they are independently mobile. Patients will be assessed whether they are able or not to independently perform these basic actions fully. Daily the assessment will be repeated and compared with the preoperative baseline score until mobility at an independent or preoperative level is achieved.

Criterion III: No intravenous fluids or medication administration

Criterion IV: Tolerance of solid food

Fluid and solid food intake will be monitored and must return to normal, that is, when oral intake of water or normal food is resumed and continued for at least 24 hours. Furthermore the incidence of post-operative nausea and vomiting, which obviously influences intake, will be monitored post-operatively until day 6 using a scale ranging from 0 (no nausea) to 10 (worst possible nausea), and where necessary, be countered prophylactically by antiemetic treatment.

Criterion V: Normal or decreasing serum bilirubin level and INR

STATISTICAL ANALYSIS

Sample size

Because laparoscopic liver surgery focuses on accelerated recovery, time to functional recovery is used as the primary outcome parameter. Owing to the lack of hard evidence about the reduction in time to functional recovery after liver surgery, we have chosen to use the parameter that most accurately approaches our primary endpoint for our power calculation (LOS). Based on a retrospective analysis of 31 patients in both ERAS and non-ERAS settings, who have undergone LLS from 1990 to the present time, the mean ± SD post-operative hospital stay for a LLS in the Maas-

tricht University Medical Centre is 6 ± 2.73. It therefore seems that that in patients undergoing laparoscopic LLS, time to functional recovery is reduced in comparison to patients undergoing the open procedure. We are aiming for a reduction in time to functional recovery of 2 days. A sample size of 2 × 40 patients in the randomization arms will be sufficient to show a 2-day reduction with a power of 90% and a level of significance at alfa = 0.05 (two-tailed, given a within-arm SD of 2.73 with effect size d = 0.73). Assuming an expected withdrawal rate of ≤ 10% during the trial, the participation of at least 10 centres, and the required addition of one randomised patient per arm for every additional participating centre (C) to compensate for the loss of degrees of freedom incurred in the data analysis, which takes centre and treatment × centre effects into account, a total sample size of 110 (n = 2 × 55) will be required.

For all secondary outcome measures, the power will be 75% after correction for multiple testing with two-tailed alfa = 0.01, assuming the same effect size (d = 0.73) as for the primary outcome. An interim analysis of the primary outcome, using Snapinn's method, will be performed after inclusion of 50% of the sample to avoid unnecessary inclusion of too many patients in this ORANGE II trial.[56]

Descriptive statistics

The primary outcome parameter of time to functional recovery and the secondary parameter of LOS in hospital will be given in days, with a median and range. Morbidity will be classified according to the classification described by Dindo et al. and defined as a dichotomous composite endpoint, while readmission will be given as a percentage. Scores for quality of life, body image and cosmesis will be given as mean and standard deviation per time point per treatment arm. Hospital costs will be given as median and range. Long-term incidence of incisional hernia will be reported and analysed.

Univariate analysis

The primary outcome measure of time to functional recovery will be measured in days, and will be analysed with fixed-effect regression that will take centre and treatment × centre interaction into account as fixed effects. If the actual number of centres and the sample size per centre allow random effects analysis, this will also be performed and this analysis will have the same power as the planned fixed effects analysis if the design effect does not exceed 1.2. With a sample size of 10 patients per centre, the design effect is 1.2 if the intraclass correlation (ICC) is 0.02, where the ICC is based on treatment × centre interaction.[57]

All secondary outcomes as measured at discharge will be analysed by fixed-effect regression using linear regression for quantitative outcomes and logistic regression for binary outcomes, and including the baseline measure as a covariate to improve

power and precision. In addition to P-values, confidence intervals for all effects will be reported. Morbidity will be classified as described by Dindo et al., but will be presented as raw data only because the required sample size for intervention effects on morbidity is much larger than the calculated sample size for this trial.[58]

ECONOMIC EVALUATION

The economic evaluation will include a cost-utility analysis from a societal perspective. The time horizon of this evaluation will be the same as the duration of the trial, that is, 12 months. All costs (direct and indirect) related to both interventions will be calculated. The final cost calculation of unit costs will be based on a combined bottom-up and top-down approach. In accordance with Dutch guidelines for cost calculation, indirect healthcare costs will not be taken into account. In addition, resource use will be measured by use of primary data that is registered in our case record forms (CRFs) by use simple checklists. Furthermore, a questionnaire will be used to survey the direct non-healthcare costs related to travelling, impaired mobility and domiciliary care (for normal daily activities). The incremental, indirect non-healthcare costs per QALY gained will be based on the utility scores from the EQ-5D.[39-41] For all direct healthcare costs, the unit prices will be based either on prices from the hospital financial department or the Dutch guidelines for cost calculation.[45]

REGISTRY

The prospective registry of patients who cannot be randomized because of explicit treatment preference on the part of the patient or surgeon will be analysed as an observational study. In addition, data from the registry will be analysed for interaction between treatment, centre, and study type (randomised or not). On condition that there is no interaction between treatment, centre, and study type, and that the observational study does not suffer from severe confounding (because adjusting for that strongly reduces the power of the observational study), pooling of both studies should give more power than separate analyses of either study. Possible confounders will be registered in the CRFs. The inclusion of the prospective registry in the trial design will create an uninterrupted case series, which will increase external validity and generalizability.

DATA COLLECTION

Data concerning patient characteristics, functional recovery, surgical and anaesthesiologic parameters, morbidity, LOS, QOL, patient compliance, and costs will be prospectively collected using both paper CRFs and an open source clinical trial software platform (OpenClinicaW; Ikaza Research, Cambridge, MA, USA) that uses e-CRFs for

electronic data capture and clinical data management, which are validated and stored in compliance with good clinical practice guidelines. The e-CRFs will be stored in a secured database (Oracle Cor., Redwood Shores, CA, USA), and as stated previously, all patient data will be encoded to ensure privacy.

MONITORING

For this trial, a Data and Safety Monitoring Board (DSMB) has been appointed that will consist of three members: a chairperson, an independent statistician, and a medical specialist. In a concerted effort a DSMB charter will be developed, and all three members will sign a non-competing interest form. The DSMB will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and monitoring the overall conduct of the clinical trial.

INTENTION TO TREAT

Analysis of all patients will be performed according to the intention-to-treat principle: patients will be analysed as randomized or as planned in the non-randomized prospective registry, and all patients will be included in the data analysis with proper methods for handling missing data.

DISCUSSION

Several authors have indicated that laparoscopic liver resection has many benefits over conventional open liver resection. However, this has never been proven in an RCT, and what the primary endpoint should be for an RCT comparing open and laparoscopic liver resection is a subject to debate. Using either liver surgery-related mortality or liver surgery-specific morbidity as an endpoint is not feasible, because patient accrual would take many years and be a logistically major global effort [58]. LOS in hospital, time to recovery, long-term incisional hernias, body image, and costs are potential candidates because improvements in these are some of the possible benefits. Laparoscopic liver resection is appealing for many surgeons and patients, but the learning curve for the surgeon is thought to be long and costly for hospital budgets. However, operating times in laparoscopic LLS tend to be shorter, and may compensate for expenses in technology and consumables.[31,59] Moreover, the existing trials in liver surgery have not evaluated time to recovery or LOS in hospital after laparoscopic liver resection within an enhanced recovery programme. The more rapid recovery reported after enhanced recovery programmes may be further accelerated as a consequence of small incisions in laparoscopic surgery. In addition, learning curves for laparoscopic left lateral resection or anterior segments seem to be

reasonably short for liver surgeons with advanced laparoscopic experience.[60] The question remains whether an RCT is necessary to prove that laparoscopy should be accepted as the preferred method to perform liver resection. In the Louisville consensus meeting on laparoscopic liver surgery, it was stated that laparoscopic LLS should be standard practice in experienced hands.[61] However, this may have been a subjective vision of a subset of opinion leaders, because long experience with both open and laparoscopic liver surgery was the main characteristic of those attending the meeting. Undoubtedly, the dissemination phase of laparoscopic liver surgery has started, and it is to be expected that many surgeons will adopt this technique in the future. A multinational multicentre prospective registry, a well-organised multicentre RCT, training programmes, and quality control measures are of great importance during this adoption period. [33]

It is well recognized that a well-conducted double-blind RCT provides the highest level of evidence to prove the possible benefits of laparoscopic liver resection. However, performing an RCT in surgery is not without difficulties, and alternative trial designs may be necessary.[33,34,62] First, the intervention needs to be tested in a standardized environment, and the properties of the intervention should remain unchanged during the trial period. This seems impossible for an intervention such as laparoscopic liver surgery in a multicentre RCT. Experience varies between participating centres, and will vary over time. Moreover, local standards for perioperative care are different. Both LLS and the ERAS protocol provide the standardization needed. The learning curve of LLS is short in centres with experience in liver surgery and advanced laparoscopy. The use of proctor surgeons in centres with limited experience in laparoscopic liver surgery the operative techniques can be reasonably standardized, and this should eliminate learning curve influences on outcome parameters. Quality of the surgery can be assured by digital video recording.

Second, the intervention should be double-blinded. Although double blinding in a surgical trial is difficult, using a fixed abdominal dressing for 3 days after surgery is feasible, and should prevent both ward caregivers and patients from knowing the type of intervention. Third, it is reasonable to query whether this is now the right time to perform an RCT and whether the results of the trial will be valid for the more general surgical community. A recent review of the results of laparoscopic liver resection in 2,804 patients showed that laparoscopic liver resection in expert centres is feasible and safe for both minor and major liver resections.[36] The percentages of liver resections performed laparoscopically now range from 25% to 65% in high-volume expert centres such as University Hospital Southampton NHS (Southampton, UK), Henri Mondor (Paris, France), UPMC (Pittsburgh, USA), UZ Leuven (Leuven, Belgium) and Rikshospitalet (Oslo, Norway).[36,63] Although it is to be expected that many centres worldwide will adopt laparoscopic liver resection as a more or less

standard procedure in the near future, there are still many patients and surgeons that prefer the open procedure long beyond the learning curve. In parallel with the development of laparoscopic liver surgery, 'fast-track' programmes in various areas of surgery, including liver surgery, are gaining popularity. Therefore, this seems to be the right time for this RCT to be performed. The multicentre character of the ORANGE II trial with randomization of patients and surgeons with treatment equipoise and a prospective registry to cover both surgeons who believe that based on their laparoscopic experience randomization is not ethically justified and patients with a strong treatment preference will provide external validity. This trial design capitalizes on rather than ignores the differences between patients, will provide more robust outcome data, and should lead to continuous performance monitoring after the trial.[35,62]

The key question clearly is as to whether this RCT is really necessary. The benefits of laparoscopic liver resection are not beyond reasonable doubt, and although data are becoming increasingly available, recent publications do not provide sound data on time to recovery. Worldwide, median LOS in hospital for open and laparoscopic resections varies from 4 to 8 days.[17, 30, 64-66] Reasons for delay in discharge and discharge location are often absent, and a clear definition of recovery has not been used to date in any of the publications. Departing from the standpoint that an RCT should be conducted, the question is which sample size should be used? In our opinion, a reduction of only 1 day in time to recovery or LOS in hospital after laparoscopic resection would be a disappointingly low gain. To prove such a reduction, 320 patients would be needed (alfa = 0.05 and power of 90%), making the trial unlikely to be accomplished. Based on available reports, a 2-day reduction should be possible [17, 31, 66], and reduces the sample size to 110 patients undergoing LLS. This number is reasonably moderate, and it is to be expected that patient accrual will be accomplished within 1–2 years.

It should be realized that many centres have introduced laparoscopic liver surgery programmes in the absence of a central reporting or certifying agency. In our opinion, laparoscopic LLS should function as a model for further dissemination of laparoscopic techniques in hepatic surgery. The left lateral segment of the liver has been a natural first step for a laparoscopic resection given the peripheral anatomical location (thin liver segment, minimal requirement for biliary dissection, and ease of controlling the left portal pedicles and left hepatic vein), and has been proven to be safe and feasible with reproducible results.[20,36] The implementation of the laparoscopic LLS may not only serve as a guide to develop and master programmes for major laparoscopic hepatic resections, but may also be used as an introduction for centres new to laparoscopic approaches in liver surgery. To adopt laparoscopic liver resection safely, certification for centres, surgeons, and units should be available through

the International Hepatobiliary (HPB) Association, and national and international HPB associations should become involved in the goal of establishing training standards and credentials to ensure a high and consistent outcome. The ORANGE II trial in which techniques are standardized and a training and proctor programme is available, combined with the hybrid design of randomization and registry may help to provide a framework for controlled and safe implementation of laparoscopic liver resection across participating centres.

CONCLUSION

The international multicentre randomised controlled ORANGE II trial is based on the observations of more rapid recovery and discharge after laparoscopic liver resection, and more rapid recovery and discharge after open liver resection within an enhanced recovery programme. This is the first RCT to provide evidence on the merits of laparoscopic surgery in patients undergoing LLS within an enhanced recovery programme.

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Chapter 9

Randomized controlled trial of open versus laparoscopic left lateral hepatic sectionectomy within an enhanced recovery ERAS® programme (ORANGE II – Study)

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ABSTRACT

BACKGROUND

Laparoscopic left lateral sectionectomy (LLLS) has been associated with shorter hospital stay and reduced overall morbidity compared with open left lateral sectionectomy (OLLS). Strong evidence has not, however, been provided.

METHODS

In this multicentre double-blind RCT, patients (aged 18–80 years with a BMI of 18–35 kg/m2 and ASA fitness grade of III or below) requiring left lateral sectionectomy (LLS) were assigned randomly to OLLS or LLLS within an enhanced recovery after surgery (ERAS) programme. All randomized patients, ward physicians and nurses were blinded to the procedure undertaken. A parallel prospective registry (open non-randomized (ONR) versus laparoscopic non-randomized (LNR)) was used to monitor patients who were not enrolled for randomization because of doctor or patient preference. The primary endpoint was time to functional recovery. Secondary endpoints were length of hospital stay (LOS), readmission rate, overall morbidity, composite endpoint of liver surgery-specific morbidity, mortality, and reasons for delay in discharge after functional recovery.

RESULTS

Between January 2010 and July 2014, patients were recruited at ten centres. Of these, 24 patients were randomized at eight centres, and 67 patients from eight centres were included in the prospective registry. Owing to slow accrual, the trial was stopped on the advice of an independent Data and Safety Monitoring Board in the Netherlands. No significant difference in median (i.q.r.) time to functional recovery was observed between laparoscopic and open surgery in the randomized or non-randomized groups: 3 (3–5) days for OLLS versus 3 (3–3) days for LLLS; and 3 (3–3) days for ONR versus 3 (3–4) days for LNR. There were no significant differences with regard to LOS, morbidity, reoperation, readmission and mortality rates.

CONCLUSIONS

This RCT comparing open and laparoscopic LLS in an ERAS setting was not able to reach a conclusion on time to functional recovery, because it was stopped prematurely owing to slow accrual.

Registration number: NCT00874224 (https://www.clinicaltrials.gov).

INTRODUCTION

The left lateral segments of the liver can be resected by both open and laparoscopic approaches. The latter has become increasingly popular after the Louisville Statement of 2008, where experts concluded that laparoscopic left lateral sectionectomy (LLS) was a safe and effective approach for the management of surgical liver disease in the hands of experienced hepatobiliary and laparoscopic surgeons.[1] Later reviews, based mainly on retrospective data, showed favourable clinical outcomes after laparoscopic resection.[2,3] Studies specifically comparing open and laparoscopic LLS have hitherto been based on retrospective designs or with small sample size.[4,5] A meta-analysis of non-randomized studies showed a reduction in duration of operation, shorter overall length of hospital stay (LOS) and reduced morbidity after laparoscopic LLS.[6] This difference in LOS was, however, associated with significant heterogeneity among the included studies.

Enhanced recovery after surgery (ERAS) programmes have been introduced in patients undergoing minor and major liver resections. Multiple studies [7–15] have shown that these programmes are feasible, safe and effective in reducing median LOS in both open and laparoscopic resection. Data available at the time of design of this study also suggested that a further reduction in LOS after liver resection could be achieved when the observed delay between patient recovery and actual discharge was minimized, as reported for colonic resections.[10,16] Day of discharge from hospital is dependent on multiple factors, including patient expectations, local discharge logistics and cultural differences between countries, hospitals and surgeons. LOS may therefore be considered an inappropriate endpoint for comparison of surgical interventions. Within the ERAS programme for liver surgery, a composite endpoint has been defined: time to functional recovery. This endpoint, representing medical readiness for discharge, consisted of clear and objectively measurable criteria. A patient was considered functionally recovered if they had a normal or decreasing serum bilirubin level, good pain control with oral analgesia only, tolerance of solid food, no intravenous fluid support and independent mobility at the preoperative level.[10] Functionally recovered patients were generally capable of independently performing activities of daily living and were independent of hospital care.

The aim of this study was to compare open and laparoscopic liver surgery in a randomized, controlled, multicentre and blinded setting, in which all patients received a standardized liver resection within a standardized perioperative care programme, based on a standardized recovery outcome measure. A parallel registry to the randomized controlled arms was created to study an uninterrupted series for external validity. The hypothesis was that in patients undergoing laparoscopic LLS (LLLS),

time to functional recovery would be reduced by 2 days compared with that in those having open LLS (OLLS).

METHODS

STUDY DESIGN AND PARTICIPANTS

This study (ORANGE II) was designed as a double-blind RCT with a parallel prospective registry of patients who could not be randomized owing to patient or surgeon preference. Patients were eligible for inclusion in the randomization if they required a liver LLS for accepted indications, if they were men or non-pregnant, non-lactating women aged 18–80 years with a BMI of 18–35 kg/m2 and an American Society of Anesthesiologists (ASA) grade of III or less. Exclusion criteria were: planned liver resection other than LLS, ASA grade above III, and underlying liver disease diagnosed before surgery.

Representatives of the ORANGE II study group from Maastricht University Medical Centre coordinated the trial and analysed the data. The study protocol was approved by medical ethics committees at each participating centre. Centres were approached by e-mail and could participate if laparoscopic and open liver surgery were performed on a routine basis and if an ERAS liver programme had been implemented. Fourteen European sites obtained ethical approval to enroll patients; twelve were located in the Netherlands, one in Germany and one in Italy. The study protocol was registered online at ClinicalTrials.gov (NCT00874224), and has been published.[17] The aim of the study was to compare LLLS with OLLS in terms of time to functional recovery (primary endpoint). The hypothesis was that time to functional recovery would be reduced by 2 days in patients undergoing LLLS.

RANDOMISATION AND MASKING

Patients were approached for participation in the outpatient clinic. All provided written informed consent before preoperative assessment. They received information and counselling related to the study intervention, ERAS programme and other study-related procedures. Patients were assigned randomly before admission in a 1:1 ratio to either OLLS or LLLS. Randomization was performed by each local study coordinator using a web-based system (TENALEA®; FormsVision, Abcoude, The Netherlands) and block randomization. Randomization was stratified according to treatment, centre, sex and ASA grade. The allocated procedure was communicated to the operating surgeon(s). All randomized patients, ward physicians and nurses were blinded to the

type of intervention by the use of a large fixed abdominal dressing until post-operative day (POD) 3. Non-randomized patients were asked for permission to use their data. In doing so, they were assigned to the open non-randomized (ONR) or laparoscopic non-randomized (LNR) arm of the prospective registry, on the basis that this registry might increase the external validity of results obtained in the randomized study.[18,19]

PROCEDURES

The intraoperative surgical technique was not standardized; surgeons in participating centres were free to use their preferred technique and devices to gain intra-abdominal access, perform hepatic parenchymal transection and maintain vascular control. Surgeons in each participating centre performed the allocated intervention based upon availability. Medical centres with liver surgeons early in the laparoscopic learning curve were assisted during the procedure by an experienced proctoring laparoscopic hepatopancreatobiliary (HPB) surgeon. Perioperative care for all patients in the study was standardized according to the ERAS programme and the perioperative care provided was based on daily guidelines (*Table 1*).

OUTCOMES

The primary outcome measure of this study for both the randomized and parallel cohorts was time to functional recovery. A patient was considered functionally recovered when all of the following criteria were fulfilled: adequate pain control with oral analgesia only; restoration of mobility to an independent or preoperative level; absence of intravenous fluid administration; ability to eat solid foods; and normal or decreasing serum bilirubin level or international normalized ratio (INR). The evaluation of time to functional recovery started on POD0 and was scored until discharge from hospital using a standard checklist and patient diary. Patients were considered ready for discharge when the primary endpoint had been met, although it was up to the local logistics of each centre to define the actual moment of discharge. The delay between time to functional recovery and actual discharge was recorded and reasons for this delay were obtained.

Post-operative pain was registered twice daily using the validated, verbally administered, 11-point (0–10) numerical rating scale (NRS-11).[20,21] Centres were free to provide either epidural or intravenous patient-controlled analgesia. No indwelling wound catheters were used in participating centres. Members of a specialized pain team asked patients to rate the intensity of their current pain on a scale from 0 (no pain) to 10 (worst possible pain). A score of 1–3 was considered to be mild, 4–6 moderate and 7–10 severe.[22]

To report the difference between preoperative and post-operative level of mobility, the ERAS Mobility Scale (EMS), derived from the Groningen Activity Restriction Scale [23], was used. The EMS utilizes ten items of basic actions to compare the level of mobility before and after surgical intervention. When the patient reached the pre-operative EMS level, or had a positive score for eight of ten items, they were considered independently mobile.

Fluid and solid food intake was monitored, and a normal tolerance was required before discharge. Tolerance was considered to be normal when oral intake solid food was resumed and continued for at least 24 h. At the time of design of the study it was decided to monitor the post-operative serum bilirubin concentration and INR to ensure that no patient was discharged with impaired liver function. Serum bilirubin levels and INR were measured before surgery and on POD1 and 3. Secondary outcomes were post-operative LOS, readmission rate, total morbidity according to the Clavien–Dindo classification [24], composite endpoint of liver surgery-specific morbidity [25], mortality, and reasons for delay in discharge after functional recovery.

DATA COLLECTION AND PATIENT SAFETY

Data were collected using both paper case report forms (CRFs) and an open-source clinical trial software platform (OpenClinica®; Ikaza Research, Cambridge, Massachusetts, USA) in compliance with good clinical practice guidelines. The e-CRFs were stored in a secured database (Oracle Corporation, Redwood Shores, California, USA). A baseline assessment of mobility was performed on the day of admission. Venous blood samples were drawn before and after surgery, on POD1 and 3. During admission, surgical details, data on time to functional recovery and complications were collected with a patient diary, a milestone checklist and standardized adverse event forms.

An independent Data and Safety Monitoring Board (DSMB) in the Netherlands evaluated the progress and quality of the trial and examined safety endpoints for each consecutive group of 25 patients. Baseline characteristics and serious adverse events were listed and presented in an unblinded fashion. Recommendations made by the DSMB were communicated to the medical ethics review committee of Maastricht University Medical Centre and all participating centres.

Table 1 Perioperative care according to the enhanced recovery after liver surgery programme

	Daily guideline
Day before surgery	Normal oral nutrition up to 6 h before surgery No preanaesthetic medication Laboratory tests
Day of surgery	Carbohydrate drinks up to 2 h before surgery Mid-thoracic epidural analgesia (local anaesthetic + low-dose opioid) Short-acting i.v. anaesthetic agent Preferably no nasogastric drainage, but when used remove after surgery Use warm i.v. fluids, and upper and lower body air-waming device Avoid excessive i.v. fluids CVP during transection<5mmHg No routine drainage of peritoneal cavity Patient sent to recovery ward Restart oral intake of water/nutrition
POD 1	Patient sent to surgical ward Patient mobilizes a minimum of four times a day Discontinuation of i.v. fluids Patient drinks at least 1.5 litres Normal diet Continue portable epidural analgesia (local anaesthetic + low-dose opioid) or PCA Remove urinary catheter 1000mg paracetamol 6-hourly Start laxatives Laboratory tests
POD 2	Continue portable epidural analgesia or PCA Stop low-dose opioids Continue mobilization a minimum of four times daily 1000mg paracetamol 6-hourly Normal diet Laxatives
POD 3	Stop epidural analgesia or PCA Start NSAIDs Continue mobilization Normal diet Laboratory tests Check discharge criteria Outpatient appointment made for POD10, 1 or 12
POD 4	Check discharge criteria Patient given mobile phone number of HPB surgeon on duty Discharge

i.v., Intravenous; POD, post-operative day; CVP, central venous pressure; PCA, patient-controlled analgesia; NSAID, non-steroidal anti-inflammatory drug; HPB, hepatopancreatobiliary.

STATISTICAL ANALYSIS

Time to functional recovery was used as the primary endpoint. Owing to lack of data on the reduction in time to functional recovery after liver surgery in an ERAS programme, a decision was made to use LOS for the purpose of power calculation, because this approached the primary endpoint most accurately. Based on a retrospective analysis of 31 patients in both ERAS and non-ERAS settings, who had undergone LLS from 1990 to 2010, the mean(s.d.) value for post-operative LOS after LLS in Maastricht University Medical Centre was 6.0(2.7) days. Thus a reduction in time to functional recovery of 2 days seemed feasible.

At 90 per cent power and alfa=0.05 (two-tailed), a sample size of 2 × 40 patients in the randomization arms would be sufficient to detect this difference (two-tailed testing was planned to allow detection of an (unexpected) increase in time to functional

recovery after LLLS compared with OLLS, and to be consistent with the two-sided confidence intervals to be reported). Assuming an expected withdrawal rate of 10 per cent or less, the participation of at least ten centres, and the required addition of one randomized patient per arm for every additional participating centre to compensate for the loss of degrees of freedom incurred in the data analysis (which takes centre and treatment × centre effects into account), a total sample size of 110 (2 × 55) was required. Patients were analysed according to the intention-to-treat principle, and analysis was performed with SPSS® software using Windows® version 21.0 (IBM, Armonk, New York, USA).

After each group of 25 included patients, a report was sent to the DSMB. An interim analysis was planned after randomization and completion of follow-up of 50 per cent of the total sample size. The DSMB provided the principal investigator with recommendations: no action needed, early stopping (due to clear benefit/ harm of a treatment, futility, or new external evidence), extending recruitment or follow-up, stopping a single arm of the multi-arm trial, or sanctioning and/or proposing protocol changes. Assumption of normality was checked using the Shapiro–Wilk test. Continuous numerical data were summarized by the median (i.q.r.) value per treatment arm. Analysis was performed with X^2 or Fisher's exact tests for binary outcomes, and Mann–Whitney U or t tests for continuous outcomes, depending on their normality. For the primary outcome time to functional recovery alfa=0.05 (two-tailed) and for the secondary outcomes alfa=0.01 (two-tailed) were used to correct for multiple testing.

Post hoc analyses to assess milestones during recovery of patients and compliance with elements of the ERAS protocol were also performed. To describe the compliance with individual ERAS elements per study group and centre, an overall compliance and the between-centre range was used. Per element, an 80 per cent cut-off value was set to qualify as compliant.

The outcome analyses were repeated with multiple linear regression to adjust for patient age, sex, ASA grade and centre effects. Differences between individual surgeons within the same centre with respect to time to functional recovery, LOS, and difference between time to functional recovery and LOS were also examined.

RESULTS

ENROLMENT AND RANDOMISATION

From January 2010 to 1 July 2014, ten of 14 centres that had ethical approval recruited patients for this study. A total of 104 patients were assessed for eligibility and 97 were included (*Fig 1*). Only 29 participants were randomized: 14 to OLLS and 15 to LLLS. The remaining 68 patients were included in the prospective registry. Some five patients were excluded after randomization: four required a larger hepatic resection and surgery was postponed in one woman because of pregnancy. One patient in the open arm of the prospective registry was also excluded after a preoperative change of procedure. No 30-day dropouts were observed in the RCT or prospective registry. A total of 91 patients (24 randomized and 67 prospective registry) were included in the intention-to-treat analysis. The DSMB did not express any objections to continuation of the trial after the first two reports (October 2012 and April 2013). In the third report of January 2014, however, the DSMB expressed concerns about the ORANGE II study group, because of an accrual rate of 24 per cent in the RCT.

In accordance with recommended criteria for accrual and scientific progress [26], a trial should be closed if it is open for more than 24 months with an accrual rate of less than 25 per cent. Therefore, the DSMB advised continuation of the trial for a maximum of 6 months. Because enrolment remained slow, a decision was made by the investigators to stop the trial on 1 July 2014.

PREFERENCE

Sixty-seven (73.6 per cent) of the 91 included patients in this study had surgery based on preference for either the open or laparoscopic procedure, usually surgeon preference: nine of 13 patients (69 per cent) in the open arm and 39 of 54 (72 per cent) of those in the laparoscopic arm of the prospective registry.

PATIENT DEMOGRAPHICS AND SURGICAL OUTCOME

Baseline patient characteristics (*Table 2*) and surgical outcomes (*Table 3*) were distributed equally between the groups in the randomized part study (OLLS versus LLLS), as well as in the prospective registry (ONR versus LNR). There appeared to be more patients with a history of previous abdominal surgery in the LNR group and a longer median duration of surgery in the LLLS group, but after correction for multiple testing these differences were not significant.

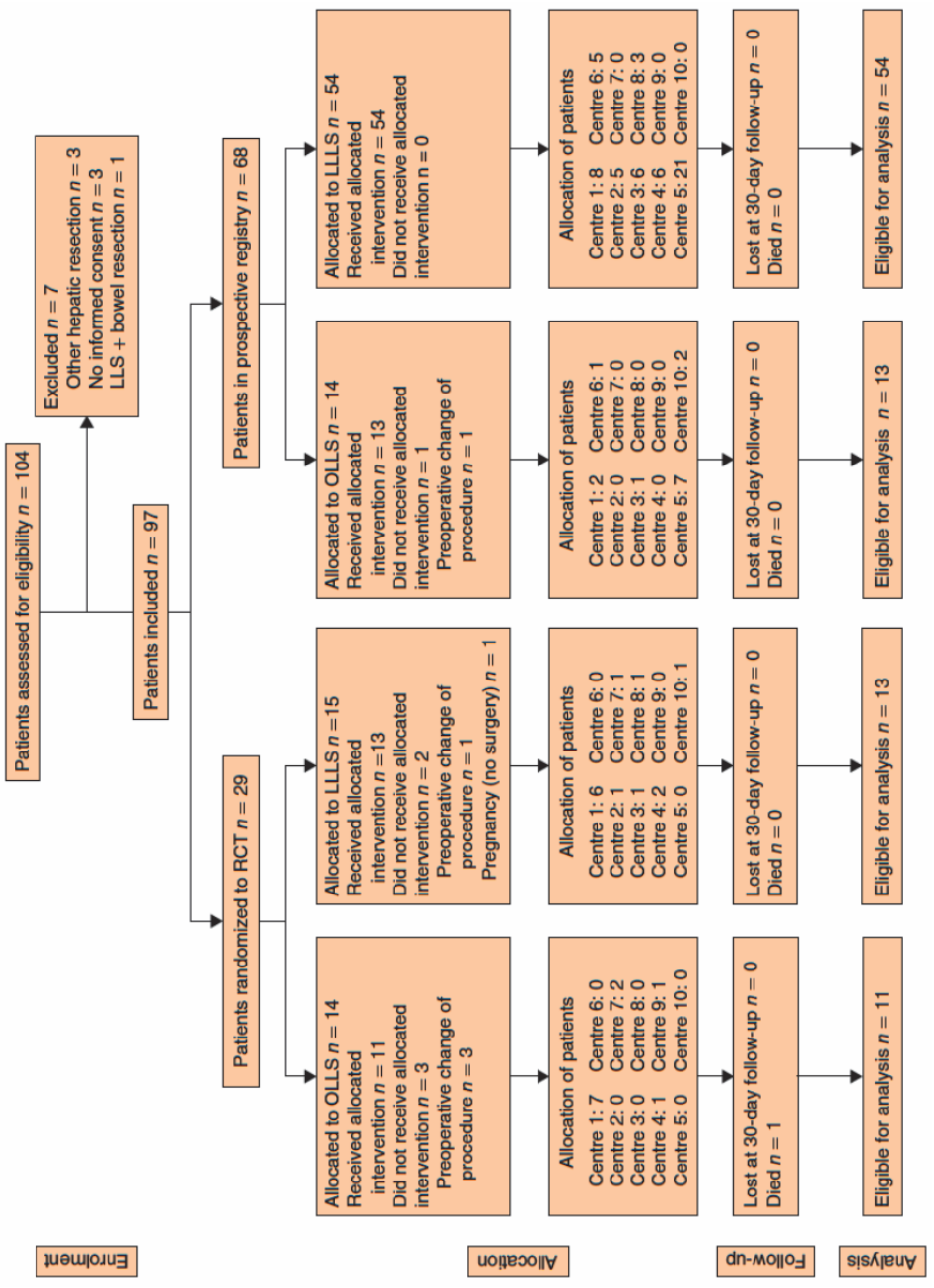

Figure 1. CONSORT diagram for the trial. LLS, left lateral sectionectomy; OLLS, open left lateral sectionectomy; LLLS, laparoscopic left lateral sectionectomy

Table 2. Patient demographics

	RCT			Registry		
	OLLS (n=11)	LLLS (n=13)	P#	ONR (n=13)	LNR (n=54)	P#
Age (years)*	58 (52–70)‡‡	67 (55–73)‡‡	0.361**	53 (46–64)	63 (45–72)	0.219**
Sex ratio (M: F)	5 : 6	9 : 4	0.408	8 : 5	26 : 28	0.386††
BMI (kg/m2)*	28.7 (25.5–33.9)‡‡	27.1 (25.3–28.5)‡‡	0.361**	23.5 (22.0–27.2)	24.7 (22.5–29.2)	0.306**
ASA fitness grade			0.252**			0.851**
I	3 (27)	1 (8)		4 (31)	17 (31)	
II	7 (64)	9 (69)		8 (62)	30 (56)	
III	1 (9)	3 (23)		1 (8)	7 (13)	
Indication for surgery			0.182			0.267††
Colorectal metastasis	6 (55)	11 (85)		7 (54)	20 (37)	
Other	5 (45)†	2 (15)‡		6 (46)§	34 (63)¶	
Previous abdominal surgery	9 (82)	11 (85)	1.000	9 (69)	24 (44)	0.048††
Preoperative chemo-therapy	3 (27)	9 (69)	0.100	3 (23)	14 (26)	1.000

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). OLLS, open left lateral sectionectomy; LLLS, laparoscopic left lateral sectionectomy; ONR, open non-randomized left lateral sectionectomy; LNR, laparoscopic non-randomized left lateral sectionectomy. †Adenoma (2), hepatocellular carcinoma (HCC) (1), haemangioma (1), focal nodular hyperplasia (FNH) (1);
‡HCC (1), multilocular biliary cyst (1); §HCC (3), metastatic melanoma (1), liver abscess (1), metastatic breast cancer (1); ¶HCC (3), haemangioma (4), adenoma (5), FNH (7), inflammatory lesions (2), echinococcosis (1), hepatic cyst (1), haemangioma (1). #Fisher's exact test, except **Mann–Whitney U test and †† X^2 test (all two-tailed). ‡‡Variable with normal distribution: Shapiro–Wilk P >0.050; Mann–Whitney U test results are shown, but t test leads to the same conclusion. alfa=0.01 for all baseline variables to correct for multiple testing.

PRIMARY OUTCOME

Time to functional recovery did not significantly differ between OLLS and LLLS groups, or between ONR and LNR groups (*Table 4*). In the OLLS group, the median time to functional recovery was 3 (3–5) days, compared with 3 (3–3) days in the LLLS group (P =0.284). The same median time to functional recovery was found in the registry groups: 3 (3–3) days for ONR versus 3 (3–4) days for LNR (P =0.529). Subanalysis of individual functional recovery criteria revealed quicker tolerance of solid food in favour of the LNR group (2 (1–2) days versus 1 (1–1) day following ONR; P =0.002)

SECONDARY OUTCOMES

Median LOS did not differ significantly following OLLS compared with LLLS: 4.5 (4–6) versus 4 (3–5) days respectively (P =0.049) (note that alfa=0.01 for secondary outcomes in view of multiple testing). Median LOS in the prospective registry was also

comparable: 5 (4–7) days for ONT versus 4 (3–5) days for LNR (P =0.064). The reasons for delayed discharge after functional recovery per group are shown in *Table 4*. Overall 39, 18 and 10 per cent of the delay was logistical or medical in nature, or based on patient request, respectively.

Table 3. Surgical outcomes

	RCT			Registry		
	OLLS (n = 11)	LLLS (n = 13)	P‡‡‡	ONR (n = 13)	LNR (n = 54)	P‡‡‡
Type of liver resection						
LLS	10 (91)	11 (85)		10 (77)	46 (85)	
LLS + wedge	1 (9)†	2 (15)‡		3 (23)§	2 (4)¶	
Segment III	0 (0)	0 (0)		0 (0)	1 (2)	
Conversion to open surgery		0 (0)			5 (9)#	
Additional procedures						
Cholecystectomy	1 (9)	1 (8)		1 (8)	3 (6)	
Lymph node dissection	0 (0)	0 (0)		1 (8)**	1 (2)††	
Hernia correction	0 (0)	0 (0)		0 (0)	2 (4)	
Other	1 (9)‡‡	1 (8)§§		0 (0)	2 (4)¶¶	
Duration of surgery (min)*	110 (92–125)¶¶¶	156 (112–176)¶¶¶	0.023§§§	206 (118–255)¶¶¶	148 (118–202)¶¶¶	0.082§§§
Blood loss (ml)*	100 (100–350)	50 (18–200)	0.063§§§	250 (225–300)	200 (100–300)	0.191§§§
Vascular control	2 (18)##	0 (0)	0.199	2 (15)***	5 (9)†††	0.614
Placement of abdominal drain	0 (0)	1 (8)	1.000	5 (38)	12 (22)	0.289

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). OLLS, open left lateral sectionectomy; LLLS, laparoscopic left lateral sectionectomy; ONR, open non-randomized left lateral sectionectomy; LNR, laparoscopic non-randomized left lateral sectionectomy; LLS, left lateral sectionectomy. †Segment IVB; ‡segment IVB (2); §segments V, IVB and VIII; ¶segment VI and segment IVB (2). #Reason for conversion: tumour to close to vascular structures (1), adhesions (1), bleeding from aberrant left hepatic artery (1), size of lesion (1), infiltration of diaphragm (1).
**Hepatoduodenal ligament+omentum minus+left gastric artery+coeliac artery+gastroduodenal artery. ††Omentum minus; ‡‡adhesiolysis; §§transversostomy; ¶¶radiofrequency ablation (1), partial diaphragm resection (1). ##Pringle (1), Kelly clamp (1); ***Pringle (2);
†††Pringle (5). ‡‡‡Fisher's exact test, except §§§Mann–Whitney U test (both two-tailed).
¶¶¶Variable with normal distribution: Shapiro–Wilk P >0.050; Mann–Whitney U test results are shown, but t test leads to the same conclusion. alfa=0.01 for all secondary outcomes to correct for multiple testing.

Table 4. Functional recovery and length of hospital stay

	RCT			Registry		
	RCT	Registry	P‡‡‡	ONR (n = 13)	LNR (n = 54)	P‡‡‡
	OLLS (n = 11)	LLLS (n = 13)	P†	ONR (n = 13)	LNR (n = 54)	P†
Functional recovery (days)	3 (3–5)	3 (3–3)	0.284	3 (3–3)	3 (3–4)	0.529
Adequate pain control with oral analgesia only	3 (2–3)	3 (2–3)	0.539	3 (3–4)	2 (2–3)	0.017
Independent mobility or preoperative level	3 (3–4)	3 (2–3)	0.071	3 (3–4)	3 (2–3)	0.240
No intravenous fluid	2.5 (2–3)§	2 (1–3)§	0.273	2 (1–4)	2 (1–2)	0.308
Tolerance of solid food	1 (1–1)	1 (1–1)	0.738	2 (1–2)	1 (1–1)	0.002
Normal or decreasing serum bilirubin level	2.5 (1–3)	1 (1–3)	0.232	0 (0–1)	1 (0–2)	0.161
Post-operative milestones (days)						
Free oral fluids	0 (0–1)	0 (0–0)	0.563	1 (0–1)	1 (0–1)	0.202
Removal of indwelling urinary catheter	3 (2–3)	2·5 (1–3)	0.140	3 (3–6)	2 (1–3)	0.031
First flatus	1 (1–2)	1 (1–2)	0.446	2 (1–3)	2 (1–2)	0.076
First stool	3 (2–4)§	2 (2–3)§	0.307	3 (3–4)§	2 (2–3)§	0.138
LOS (days)	4.5 (4–6)	4 (3–5)	0.049	5 (4–7)	4 (3–5)	0.064
Difference (LOS – functional recovery) (days)	1 (0–3)	1 (1–2)	0.832	2 (1–3)	1 (0–2)	0.042
Delay in discharge*	8 (73)	9 (69)	1.000‡	11 (85)	23 (43)	0.090‡
Reasons for delay in discharge*						
Logistical	2 of 10 (20)	5 (38)		6 (46)	11 (20)	
Medical	3 of 10 (30)	1 (8)		2 (15)	5 (9)	
Patient preference	2 of 10 (20)	2 (15)		0 (0)	2 (4)	
Unknown	1 of 10 (10)	1 (8)		3 (23)	15 (28)	

Values are median (i.q.r.) unless indicated otherwise; *values in parentheses are percentages. †One patient died in hospital and was never discharged. OLLS, open left lateral sectionectomy; LLLS, laparoscopic left lateral sectionectomy; ONR, open non-randomized left lateral sectionectomy; LNR, laparoscopic non-randomized left lateral sectionectomy; LOS, length of hospital stay. ‡Mann–Whitney U test, except §Fisher's exact test (both two-tailed). ¶Variable with normal distribution: Shapiro–Wilk P >0.050; Mann–Whitney U test results are shown, but t test leads to the same conclusion. alfa=0.05 for primary outcome, and alfa=0.01 for all secondary outcomes to correct for multiple testing.

Overall morbidity was the same for open and laparoscopic procedures, with no significant differences between Clavien–Dindo complication severity grades [24] or the composite endpoint for liver surgery-related morbidity (*Table 5*).

Table 5. Complications

	RCT			Registry		
	OLLS (n = 11)	LLLS (n = 13)	P‡	ONR (n = 13)	LNR (n = 54)	P‡
Overall morbidity	4 (36)	1 (8)	0.141	2 (15)	7 (13)	1.000
Clavien–Dindo grade						
No morbidity	7 (64)	12 (92)		1 (85)	47 (87)	
I	1 (9)	0 (0)		0 (0)	0 (0)	
II	2 (18)	0 (0)		1 (8)	5 (9)	
III	0 (0)	1 (8)		1 (8)	1 (2)	
IV	0 (0)	0 (0)		0 (0)	1 (2)	
V (30-day mortality)	1 (9)	0 (0)		0 (0)	0 (0)	
Major morbidity (≥ grade III)	1 (9)	1 (8)	1.000	1 (8)	2 (4)	0.482
Composite endpoint*	1 (9)	0 (0)	0.458	1 (8)	2 (4)	0.482
Readmission in < 30 days	0 (0)	0 (0)		0 (0)	1 (2)	1.000
Complications						
Wound infection	1 (9)	1 (8)		0 (0)	1 (2)	
Pneumonia	0 (0)	0 (0)		0 (0)	2 (4)	
Intra-abdominal haemorrhage	0 (0)	0 (0)		1 (8)	0 (0)	
Intra-abdominal abscess	0 (0)	0 (0)		0 (0)	1 (2)	
Postresectional liver failure	0 (0)	0 (0)		0 (0)	1 (2)	
Pulmonary embolism	1 (9)	0 (0)		0 (0)	0 (0)	
Cardiac arrest	1 (9)	0 (0)		0 (0)	0 (0)	
Other†	2 (18)	0 (0)		2 (15)	3 (6)	

Values in parentheses are percentages. OLLS, open left lateral sectionectomy; LLLS, laparoscopic left lateral sectionectomy; ONR, open non-randomized left lateral sectionectomy; LNR, laparoscopic non-randomized left lateral sectionectomy. *Ascites, postresectional liver failure, bile leakage, intra-abdominal haemorrhage, intra-abdominal abscess and operative mortality. †Persistent pain (2), hypertension (2), infected epidural insertion site (1), urinary tract infection (1), dyspnoea of unknown origin (1). ‡Fisher's exact test (two-tailed). alfa=0.01 for all secondary outcomes to correct for multiple testing.

A total of five patients developed major morbidity (grade III or above). One patient in the open arm of the RCT died after developing a pulmonary embolism and cardiac arrest. One randomized patient developed a wound infection after LLLS, which was re-explored under local anaesthesia. In the open arm of the registry, one patient required surgery after a post-operative intra-abdominal bleed with haemodynamic instability. In the laparoscopic arm of the registry, one patient was admitted to the ICU for postresectional liver failure, and one was readmitted and received percutaneous radiological drainage after developing an intra-abdominal abscess.

COMPLIANCE WITH THE ERAS PROTOCOL

No group was fully compliant with all protocol items. The OLLS, LLLS, ONR and LNR groups were compliant (more than 80 per cent) with between 10 and 14 of the 22 ERAS elements (*Table 6*). Post-operative epidural analgesia was provided to 82, 69, 77 and 65 of patients in the OLLS, LLLS, ONR and LNR groups respectively. No data were available to score the elements ileus prevention (laxatives) and provision of oral analgesia on POD1.

REGRESSION ANALYSES

Repeating the outcome analyses with multiple linear regression to adjust for patient age, sex, ASA grade and centre effects essentially confirmed the results of the Mann–Whitney U tests. However, analysis of residuals showed a clear outlier in both the open surgery arm of the RCT and the registry with respect to the outcome LOS. Therefore, all analyses, non-parametric as well as regression, were repeated. Without those outliers, the new results increased both P values for LOS to greater than 0.100. Finally, owing to the very small sample size, differences between surgeons within the same centre could not be evaluated.

DISCUSSION

This RCT comparing open and laparoscopic LLS in an ERAS setting was not able to reach a meaningful conclusion on time to functional recovery because it had to be stopped prematurely owing to poor recruitment. No difference in time to functional recovery was found after LLLS compared with the OLLS in the randomized trial, but this analysis is underpowered. A prospective registry of all patients not randomized due to surgeon or patient preference also failed to show a difference in functional recovery. Considering the secondary endpoints, no differences between surgical procedures were observed with regard to blood loss, duration of surgery, LOS, morbidity, reoperation, readmissions and mortality rates.

The main contributor to poor recruitment was individual surgeons' preference for the laparoscopic procedure. This lead to a preference : randomization ratio of almost 3 : 1. Clinical equipoise was assumed at the time of design and start of this study. Based on a worldwide survey among HPB surgeons, an RCT and prospective register comparing open and laparoscopic techniques was considered necessary.[27] The majority of participating centres in the study had indicated that they considered a trial to be feasible and were willing to randomize patients. It was on this basis that it was deemed not necessary to perform a feasibility study. It is clear, however, that

clinical equipoise was no longer present during the recruitment period. A recent expert statement from the International Consensus Conference for Laparoscopic Liver Resection held at Morioka, Japan, in 2014 stated that minor laparoscopic liver resection, including LLS, has become standard practice [28], and this evolving change in surgical attitudes is likely to have influenced the present study.

Table 6. Overall compliance to elements of the enhanced recovery after surgery protocol per study group

	RCT		Registry	
	OLLS (n = 11)	LLLS (n = 13)	ONR (n = 13)	LNR (n = 54)
Preoperative				
Counselling	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)
Minimal preoperative fasting	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)
No anxiolytic premedication	82 (0–100)	77 (0–100)	85 (0–100)	78 (33–100)
Perioperative				
Thoracic epidural analgesia/i.v. PCA	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)
Prevention of hypothermia	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)
CVP monitoring (< 5 mmHg)	36 (0–50)	31 (0–100)	62 (0–100)	91 (20–95)
No drainage of peritoneal cavity	100 (100–100)	92 (0–100)	62 (57–100)	59 (33–100)
No standard nasogastric drainage	91 (86–100)	100 (100–100)	85 (0–100)	78 (88–100)
Commence intake of water/free fluids	64 (0–86)	85 (50–100)	13 (0–100)	98 (19–100)
Early mobilization	27 (0–100)	77 (50–100)	31 (0–100)	87 (52–100)
PONV prophylaxis	55 (0–100)	77 (0–100)	54 (17–100)	63 (17–100)
Antithrombotic prophylaxis	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)
Antibiotic prophylaxis	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)
POD 1–3				
Daily review of discharge criteria	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)
Ileus prevention (laxatives)	–	–	–	–
Free fluids/normal diet on POD 1	100 (100–100)	100 (100–100)	92 (50–100)	98 (95–100)
Intravenous fluids discontinued on POD 1	9 (0–14)	31 (0–50)	23 (0–50)	28 (17–67)
Oral analgesia on POD 1	–	–	–	–
Normal diet on POD 2	100 (100–100)	100 (100–100)	77 (0–100)	93 (50–100)
Removal of urinary catheter on POD 3	27 (0–43)	46 (0–100)	8 (0–50)	37 (0–100)
Stop epidural/i.v. PCA on POD 3	73 (50–100)	100 (100–100)	54 (0–100)	76 (50–100)
Full mobilization on POD 3	55 (0–100)	92 (50–100)	77 (0–100)	78 (50–100)

Values are percentages with between-centre ranges in parentheses. OLLS, open left lateral sectionectomy; LLLS, laparoscopic left lateral sectionectomy; ONR, open non-randomized left lateral sectionectomy; LNR, laparoscopic non-randomized left lateral sectionectomy. i.v., Intravenous; PCA, patient-controlled analgesia; CVP, central venous pressure; PONV, post-operative nausea and vomiting; POD, post-operative day.

The slow accrual might also be related to the lower incidence of LLS than an anticipated 10 per cent of the total volume of liver resections. Replacement of LLS by parenchyma-saving strategies using metastasectomy or local ablation procedures may also have been a contributing factor to slow recruitment.

Despite these limitations, the study has several strengths. No RCT has compared open and laparoscopic liver surgery. Other studies comparing open and laparoscopic LLS [4,5,29–31] were of relatively small size and retrospective in nature. The addition of a prospective registry of patients who were not randomized owing to surgeon or patient preference was of value, reflecting daily practice in many units performing liver surgery.[18,19]

In the present series of 67 LLLS and 24 OLLS procedures undertaken in conjunction with an ERAS programme, patients were functionally recovered after 3 days. Although median LOS tended to be slightly shorter in the laparoscopic groups, this difference was not significant, and the study was not powered to detect a difference in LOS. The clinical relevance of a difference of less than 1 day can be questioned. A delay to discharge after functional recovery was observed in all groups, and there is clearly the opportunity for a further reduction in LOS if discharge logistics could be optimized.[14,16] Minimization of this gap between recovery and discharge could reduce hospital costs.

Lessons learned from this trial could prove valuable for the design and execution of future surgical trials. Surgical RCTs are often difficult to undertake successfully and pose particular practical and methodological challenges.[32] Blinding is frequently difficult to perform, and care must be taken to choose an objectively measurable outcome.[33] The present study, however, confirmed the practicality of blinding patients through the use of large abdominal dressings.[34,35] Double-blinding could not be guaranteed as ward physicians read operation details accidentally. A proctoring surgeon assisted surgeons in their learning curve to ensure quality. Regression analyses in this study revealed no influence of individual surgeons on the primary outcome, supporting the view that this approach may overcome the surgical learning curve as a confounder.[32] The timing of the conduct of a surgical trial is also important.[32] When a new technique is introduced, there is a window of opportunity to conduct a trial. Once surgeons believe the new intervention is superior, randomization becomes difficult. This surgeon preference was the major cause of failure to recruit to this RCT. It is important that investigators ensure the presence of clinical equipoise. To assess this adequately, a feasibility study seems generally advisable to generate objective evidence that the main trial will not fail, at least due to a perceived lack of equipoise.

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Chapter 10

Open versus laparoscopic hemihepatectomy within an ERAS programme (ORANGE II PLUS – Trial): study protocol for a randomized controlled trial

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Chapter 11

Summary, discussion and future perspectives

SUMMARY AND DISCUSSION

Liver resection gives patients with colorectal liver metastases the only change of cure. Also for primary malignancies and benign lesions liver resection is a widely accepted treatment. To offer patients the best chance of successful recovery after liver surgery, surgeons not only have to choose the best surgical procedure, but they must also aim for optimal pre-, intra- and post-operative conditions. The laparoscopic technique has been added to the liver surgeon's armamentarium and may be better than the standard technique of open liver resection. An Enhanced Recovery After Surgery (ERAS) programme can standardize and optimize perioperative elements during the patient's admission and support the patient towards a full and accelerated recovery. Perhaps the combination of both laparoscopic liver surgery and an ERAS programme could result in the best outcomes for the patient. Since minimal incisions are a key element of ERAS, minimal invasive surgery may be a key element itself.

This thesis focuses on the current role, dissemination and worldwide adoption of an ERAS programme in liver surgery, the investigation and evaluation of the potential role of specific (new) elements in an ERAS protocol (**Part I**), the implementation status of (laparoscopic) liver surgery from a Dutch and international perspective, and comparison of open and laparoscopic liver surgery in a randomised controlled setting (**Part II**).

PART I: OPTIMIZED RECOVERY AFTER HEPATIC SURGERY

Chapter 1 presents an overview of the elements of the Enhanced Recovery After Surgery (ERAS) programme for liver surgery. For each element the quality of evidence is discussed with a recommendation (*Table 1*).

Chapter 2 describes the results of an international survey on ways to enhance patient recovery after liver surgery. The survey was sent to hepatopancreatobiliary centres worldwide and questioned liver surgeons on their experience with enhanced recovery programmes and laparoscopic liver surgery. Both strategies are associated with faster recovery and may work synergistically. Results showed that a large majority of HPB centres had experience with laparoscopic liver surgery. The liberal adoption of laparoscopic liver surgery, even in low-volume HPB centres, seemed in conflict with standards of evidence-based practice in the medical community. On the other hand, the dissemination of enhanced recovery programmes in liver surgery was still limited in 2010, although there was substantial support for implementation. Also, liver surgeons considered a randomized controlled trial or a prospective register necessary to compare the outcomes of open and laparoscopic techniques. In the

Netherlands the first laparoscopic liver resections were documented in 1990s, while the first laparoscopic liver resection within an ERAS programme was performed in 2008. Gradually new initiatives have been designed to get prospective and controlled data on open versus laparoscopic liver surgery. Currently, the results of two randomized controlled trials (ORANGE 2 Plus – Trial and Oslo – CoMet Study) are awaited and recently a new consensus statement of international liver surgeons has been published.[2]

Table 1. ERAS liver programme recommendations

Element	Evidence level	Recommendation grade
Preoperative counselling	C	Strong
Minimal preoperative fasting	B	Strong
No pre-anaesthetic premedication	A	Weak
Antithrombotic prophylaxis	A	Strong
Antibiotic prophylaxis	A	Strong
Balanced anaesthesia with short-acting agents	C	Strong
Epidural anaesthesia / analgesia	B	Weak
Balanced intraoperative fluid management	A	Strong
Prevention of hypothermia	A	Strong
PONV prophylaxis	C	Strong
Incision of minimal length	C	Strong
No routine drainage of the peritoneal cavity	B	Strong
No nasogastric drainage	A	Strong
Provision of oral analgesia	A	Strong
Prevention of post-operative ileus	C	Weak
Early removal of urinary catheter	D	Weak
Early start oral intake	A	Strong
Early mobilisation	C	Strong

Quality of evidence and recommendations were evaluated according to the GRADE guideline]: A = High, B = Moderate, C = Low, D = Very low.

To assess the outcomes of ERAS protocols applied in liver surgery and published until October 2011, a systematic review of the literature was performed in **Chapter 3**. In total six studies could be included in the analysis. It demonstrated that implementation of an ERAS programme did not affect morbidity, mortality or re-admission rates. Analysis also suggested a reduction in length of stay in favour of patients managed within an ERAS setting. It must be mentioned that the reporting of adherence to the various elements of the protocol was rather low in the included studies, and that this hampered a good comparisons of the studies. Two studies in the systematic review assessed the time to functional recovery, which was significantly lower than total length of stay and can be considered as a more objective outcome. The use of time to functional recovery as a primary outcome measure in future studies was advised in

order to enhance quality and comparability. Also, at the time of this systematic review there were no RCTs available comparing fast-track with standard care. A recent systematic review with inclusion of two RCT's comparing ERAS with conventional care supported the findings of a reduced length of stay and showed even a reduction in medical morbidity.[3]

In **Chapter 4**, European HPB centres were evaluated to assess whether current perioperative practice in hepatic surgery was actually based on ERAS principles. The study was started with the assumption that many centres had already adopted ERAS elements in liver surgery after implementation of fast-track protocols for patients undergoing colonic resection or as part of evidenced-based treatment for patients. The study demonstrated a substantial variation of perioperative care among centres that perform liver resections. Some elements of the ERAS program, e.g., preoperative counseling and minimal preoperative fasting, had already been generally adopted. However, other elements in the perioperative phase, such as avoidance of drains and nasogastric tube, and post-operative phase, e.g. early resumption of oral intake, early mobilization, and use of recovery criteria, could be further optimized. In line with previously reported data, a delay was found between discharge and time to functional recovery (FR).[4, 5] A limitation of the assessment is mainly the retrospective design. However, this design was deliberately chosen so as to not influence the behavior of medical and nursing staff in perioperative care during a full prospective assessment.

An important aspect after liver surgery is safe and effective pain control. Not only will it reduce numerous post-operative complications, it can also facilitate early mobilization and may result in earlier recovery. Pain relief may be a powerful technique to modify surgical stress responses, and it may thereby reduce incidence of post-operative organ dysfunction and improve outcome. Adequate analgesia may also reduce pulmonary complications and post-operative paralytic ileus.[6] Traditionally, post-operative pain is managed with intravenous patient-controlled analgesia (PCA) or with continuous indwelling epidural catheters. In **Chapter 5** we examine the value of intramuscular continuous infusion of bupivacaine (CIB) via a wound catheter combined with intravenous PCA, compared with epidural analgesia after major hepatic surgery. A risk after major liver surgery is the development of post-operative coagulopathy. The use of epidural analgesia may therefore be contraindicated. The combination of CIB + PCA in this study provided pain control equivalent to that of continuous epidural analgesia. No significant differences in the numbers of patients experiencing severe pain were observed between the two groups. Importantly, patients in the CIB + PCA group consumed lower total volumes of opioids, had lower post-operative morbidity and a decreased length of stay. The partly retrospective design and an inherent bias of surgeon preference may have influenced results. On

the other hand, the investigation of a large and uninterrupted cohort of patients submitted to major hepatectomy, and thus at risk for post-operative coagulopathy and the development of epidural hematoma, receiving this type of analgesia has not been previously reported. Continuous infusion of bupivacaine combined with PCA can replace epidural analgesia and can avoid the occurrence of rare complications of epidural analgesia.

The use of abdominal drains is another element in liver surgery still subject of debate. The ERAS programme advocates abandoning standard prophylactic abdominal drainage after partial hepatectomy. Routine drainage may be unnecessary, possibly harmful and uncomfortable for patients. In **Chapter 6** we describe the 10-year experience of tertiary referral centre with a no-drain policy in an ERAS environment with 90-day resection-surface-related (RSR) morbidity and RSR-reinterventions as primary endpoints. An overall 20% surgical morbidity, 15% RSR-complication, and 12% RSR-reintervention rate was observed in 538 patients. The majority of RSR-complications could be managed with radiologic drainage and reoperations were only rarely necessary. Major liver resection was identified as an independent risk factor for RSR-significant morbidity and RSR-reinterventions. These results are in line with results published by other HBP-centres[7-12] and confirm the safety and feasibility of a no-drain policy after partial hepatectomy in an ERAS-based care programme.

PART II: LAPAROSCOPIC LIVER SURGERY

In **Chapter 7** we present a historical overview on the introduction of laparoscopic liver surgery in the Netherlands. In 1990s the first laparoscopic hepatectomies were performed, but only limited experience was gained in the decade thereafter. Compared to other pioneering countries the Netherlands seemed slow with the implementation of the minimally invasive technique. The initial experience with laparoscopic liver resections was further evaluated with a case-control comparison of patients undergoing open and laparoscopic left lateral sectionectomy (LLS) during 2000-2008. A significant difference in length of hospital stay, blood loss and operation time could be demonstrated in favour of the laparoscopically operated patients without compromising morbidity. Finally, the implementation status of laparoscopic liver surgery during 2010 was examined with a nationwide survey. The 30 out of 37 responding centres performed 966 hepatic resections of which only 49 were laparoscopic resections (5%).

To prospectively evaluate the merits of laparoscopic liver surgery a randomized controlled trial was designed. **Chapter 8** shows the protocol for an international multicentre randomized controlled study comparing open versus laparoscopic left lateral

sectionectomy (LLS) within an ERAS programme: ORANGE II – Trial. This investigated the added value of laparoscopy in minor hepatectomy. A prospective registry of all patients that were not randomised because of surgeon or patients preference was added to the design of the trial to allow acquisition of an uninterrupted prospective series of patients. Primary endpoint of the trial was time to functional recovery (composite endpoint defined by five criteria). It was hypothesized that time to functional recovery could be reduced by two days in patients undergoing laparoscopic LLS compared to open LLS.

In **Chapter 9** we present the results of the ORANGE II – Trial. From January 2010 to July 2014 a total of 91 patients (24 randomised and 67 prospective registry) were prospectively studied. Although the results showed no reduced time to functional recovery in favour of the laparoscopic group, this first RCT comparing open and laparoscopic LLS in an ERAS setting was not able to definitively conclude on the primary endpoint: time to functional recovery. It had to be stopped prematurely due to slow accrual in the RCT. The main reason for the slow accrual was a clear surgeon's preference for the laparoscopic procedure. Also, this study showed that laparoscopic LLS could be performed with low morbidity, reoperation, readmission and mortality rates. To date there has not been an RCT in liver surgery comparing open and laparoscopic liver surgery and this multicentre attempt to provide strong evidence on open versus laparoscopic LLS is not likely to be repeated. The prospective registry of patients that could not be randomised increases the external validity of this study. Long-term follow up results of this study are awaited.

Finally, in **Chapter 10** we present a protocol for an international randomised controlled trial comparing open versus laparoscopic hemihepatectomy (i.e. major hepatectomy) within an ERAS programme. This study was designed to provide the HPB surgical community with level A evidence on the value of laparoscopic hemihepatectomy. The open procedure to resect the left or right hemiliver is already an accepted treatment for the resection of liver tumours (mostly colorectal liver metastases). There is still debate on the value of laparoscopic technique in major liver resections. It was demonstrated that in expert hands major anatomical laparoscopic liver resections were feasible with good efficacy and safety. However, the results are based on case-series and no prospective controlled evidence is available on short-term, oncologic and patient reported outcomes. The ORANGE II PLUS – trial is now running in several international expert centres and will provide evidence on the primary endpoint: time to functional recovery. Other endpoints to be studied are hospital length of stay, morbidity, mortality, operative parameters (intraoperative blood loss, operation time), patients-reported outcomes (quality of life, body image), oncologic outcomes (time to adjuvant chemotherapy initiation, resection margin, overall five-year survival) and costs.

In summary, this thesis outlines that in modern liver surgery several elements of the proposed ERAS programme have already been implemented. Full use of a fast-track liver protocol is advisable to optimize and accelerate patient recovery. Good adherence to all elements of such a protocol is essential. In addition, new evidence on (liver-surgery) specific perioperative care elements needs to be appreciated and adopted into protocols if feasible. In the Netherlands laparoscopic liver surgery was only minimally implemented compared with other countries until 2010. A controlled comparison of open versus laparoscopic left lateral sectionectomy was unable to definitively concluded on the primary endpoint, time to functional recovery, as the study was stopped prematurely due to slow accrual in the RCT and a clear surgeon preference for laparoscopy. Furthermore, laparoscopic liver surgery has gained popularity among Dutch liver surgeons, and minor laparoscopic liver surgery is now considered standard of care in line with international consensus.[2] Long-term follow-up and ongoing randomized controlled trials will provide more definitive evidence on the merits of major laparoscopic liver surgery, oncologic outcome and patient-reported outcomes.

FUTURE PERSPECTIVES

OPTIMIZED RECOVERY AFTER SURGERY

Abundant evidence has been presented that ERAS protocols are safe and effective.[3] Surprisingly, an ERAS protocol for liver surgery has not yet been formally established and published. The ERAS society is a leading international body and it has published several evidence-based protocols to support surgeons and other professionals. To ensure standardization of care and to provide patients with optimal perioperative care, it is desirable that a consensus guideline for enhanced recovery after liver surgery is developed by experts. A recent review[3], including recent prospective (randomized controlled) studies[14-16], again confirms improvement of length of stay and post-operative morbidity. Not only is it important for an ERAS liver protocol to be published and embraced by international liver surgeons, it is also key to periodically and systematically re-evaluate elements of the protocol to ensure the protocol is up-to-date and supported by recent literature. New evidence should be evaluated and, if necessary, elements of the protocol should be revised or newly added. The ERAS society should adopt a leading role in this process, thereby propagating standardization and an evidenced-based approach of patient care.

In the introduction current elements of the ERAS protocol in liver surgery have been described and assessed based on the available evidence. Examples of new elements that could be evaluated for adoption in previously described ERAS liver protocols[5,

14, 15, 17] are the use of a pulmonary recruitment manoeuvre (manual inflations of the lung with the patient in Trendelenburg position) to reduce post-operative pain after liver surgery[18], stimulation of gut function with gum chewing[19], other methods of post-operative analgesia with fewer side-effects (transversus abdominis plane block[20], wound catheters[21-23]), and medication attenuating the stress response[24]. Most post-operative elements are introduced to the patient upon return on the ward. However, some patients stay up to 24 hours in the recovery room. Besides provision of good pain control, it may be possible to implement other elements already in the recovery room. ERAS elements that may be introduced there are early intake, providing chewing gum and early mobilization. Some individual elements in fast-track programmes, such as advancement of oral intake, early mobilization and laparoscopic surgery, have been associated with early recovery after colon cancer surgery[25]. However, if all elements are successfully achieved, it is more likely that not one single element in the multimodal ERAS programmes will result in the much desired accelerated recovery of patients, but the implementation of a programme as a whole. As shown in colorectal surgery, there may also be a synergetic effect of ERAS combined with laparoscopy.[26]

Once a protocol has been implemented it is important to maintain a good adherence to the protocol to ensure consistent benefit for the patient.[27] This adherence, however, is the main problem in optimization of recovery. During the initial phase of implementation all involved personnel are keen and alert to adhere to all elements. After the initial implementation adherence to the protocol guidelines should be maintained by post-implementation strategies, such as periodic evaluation and education.[28] It has already been proven in colonic surgery, that a structured implementation strategy can result a good sustainability.[29]

LAPAROSCOPIC LIVER SURGERY

The minimally invasive approach for liver surgery is here to stay. The last few years it several studies have shown that, besides minor laparoscopic liver surgery, also major laparoscopic liver surgery is associated with similar or improved short-term outcome compared with open major hepatectomy.[30] In expert hands intraoperative blood loss, complications, and conversions rate are more than acceptable for laparoscopic left hemihepatectomy.[31] A recent meta- analysis comparing case-matched laparoscopic liver resections to open liver resections (N = 2900 cases) demonstrated no increased mortality and significantly less complications, transfusions, blood loss, and hospital stay in favor of laparoscopic liver resection.[32] In the recent Morioka consensus minor laparoscopic liver resection was confirmed to be standard practice. A still increasing number of surgeons are adopting the laparoscopic technique. With regards to major laparoscopic liver resection experts judged that the introduction is

still in an exploration phase, and cautious diffusion is still warranted.[2] The international experts joining the consensus further advised participation and encouraged participation in already open prospective trials and registries. Currently on-going trials are therefore supported by the experts in the field of (laparoscopic) liver surgery. In the near future more evidence on the value of laparoscopic hepatectomy will be provided by the results of the ORANGE 2 Plus - Trial (Chapter 10) and the Oslo-CoMet study[33]. The ORANGE 2 Plus – Trial compares open versus laparoscopic hemihepatectomy within an ERAS programme and the Oslo-CoMet study compares laparoscopic versus open liver resection for colorectal metastases. Both studies will give liver surgeons more solid evidence regarding laparoscopic major liver surgery, oncologic outcome, long-term follow-up, costs and patient-reported outcomes.

During the conception of this thesis there has also been a shift in surgical strategy regarding the extent of hepatic resection. Besides the discussion on the technique (laparoscopic versus open), there is also an increasing interest in parenchymal saving strategies.[34, 35] A two-stage approach or formal liver resection may be less frequently required with the advancements of intraoperative imaging and operating techniques.[36] Occurrence of post-operative liver failure is to be prevented, but oncologic margins should be respected.[37, 38] A parenchyma-sparing strategy and accurate preoperative prediction of the function of the future remnant liver are the future for a tailored approach for each patient.

Improved levels of evidence, standardized reporting of outcomes, and assuring proper training are the next challenges of laparoscopic liver surgery.[32] Not only can RCT's or other prospective studies add to the continuing development of laparoscopic liver surgery, also the critical appraisal of hepatectomies performed in the past can improve quality. Auditing by national or international associations will give liver surgeons insight into the quality of their own operations, but also into the performance of other colleagues. (International) benchmarks may be defined for outcome parameter, such as mortality, morbidity and R0-resection margins. Ultimately, this continuing evaluation could result in centralization of (laparoscopic) liver surgery, as large volume centres may perform better than centres performing only a limited number of (laparoscopic) resections per year. A good example of a well functioning auditing system is the Dutch Institute for Clinical Auditing (DICA). On 1st July 2013 the Dutch Hepatobiliary Audit (DHBA) was started, which resulted in the publication of the first annual report. Future reports will provide insight in the actual quality of liver surgery in the Netherlands.

The ultimate goal for a surgeon would be to have a tailored approach for each candidate for liver surgery. This is a future in which the surgeon is able to select patients fit enough to undergo surgery, in which he is able to predict individual operative

risks and in which he is able to predict post-operative outcomes. The selection of patients in liver surgery is an important issue. Not only do surgeons have to determine resectability, it is also vital to assess the patient's ability to tolerate the operation and to predict whether removal of liver disease will improve long-term survival.[39] Recent developments aim on assessing and improving the patients' preoperative fitness before surgery. A 4-week prehabilitation programme can improve cardiopulmonary exercise testing and QoL before liver resection. Consequently, this may impact on perioperative outcome.[40] Further studies are necessary, but in the future a predefined cut-off value in patients undergoing hepatic resection may be used for predicting which patients will experience morbidity or are fit enough to undergo surgery.[41] A completely different approach to select patient for liver surgery and to predict outcome is the use of "big" data. Nowadays patient data is more and more readily available in digital patient files, electronic case record forms and prospective registries. These data could lead to large database that may be used for risk-modelling.

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Chapter 12

Nederlandse samenvatting

SAMENVATTING EN DISCUSSIE

Leverresectie biedt patiënten met colorectale levermetastasen de enige vorm van behandeling met kans op genezing. Ook voor primaire maligniteiten en goedaardige tumoren is leverresectie een algemeen geaccepteerde behandeling. Om patiënten een zo goed mogelijke kans op herstel te bieden, moeten chirurgen niet alleen kiezen voor de beste operatieve benadering, ze dienen ook te streven naar optimale pre-, intra- en postoperatieve condities. De laparoscopische techniek is de afgelopen decennia toegevoegd aan het armentarium van de leverchirurg en deze laparoscopische benadering is mogelijk beter dan de standaard open leverresectie. Een Enhanced Recovery After Surgery (ERAS) programma, ookwel fast-track of versneld herstel na chirurgie protocol genoemd, zorgt voor de standaardisatie en optimalisatie van elementen in de zorg rondom leverchirurgie en draagt bij aan een sneller herstel. Mogelijk zorgt de combinatie van laparoscopische leverchirurgie met een ERAS programma voor de beste uitkomsten voor de patiënt.

Dit proefschrift onderzoekt de huidige rol, disseminatie en wereldwijde adoptie van het ERAS programma binnen de leverchirurgie, bekijkt en evalueert de potentiële rol van specifieke (nieuwe) elementen binnen een ERAS protocol (**Deel I**), bestudeert de rol van (laparoscopische) leverchirurgie vanuit een Nederlands en internationaal perspectief, en vergelijkt open en laparoscopische leverchirurgie in een gerandomiseerde en gecontroleerde omgeving (**Deel II**).

DEEL I: VERBETERD HERSTEL NA LEVERCHIRURGIE

Hoofstuk 1 biedt een overzicht van de elementen binnen het Enhanced Recovery After Surgery (ERAS) programma voor leverchirurgie. Voor elk element wordt er een aanbeveling gegeven op basis van de kwaliteit van het beschikbare wetenschappelijk bewijs (*Tabel 1)*.

Hoofdstuk 2 beschrijft de resultaten van een internationale enquête over optimalisatie van herstel na leverchirurgie. Deze enquête werd wereldwijd verstuurd naar hepatopancreatobiliaire (HPB) chirurgische centra en vroeg leverchirurgen naar hun ervaringen met ERAS programma's en laparoscopische leverchirurgie. Beide strategieën worden geassocieerd met sneller herstel en mogelijk werken ze synergistisch. De resultaten van de enquête toonden aan dat een grote meerderheid van de HPB centra al ervaring had met laparoscopische leverchirurgie. Deze liberale adoptie van laparoscopische leverchirurgie, zelfs in laag-volume centra, leek tegen de standaard van de evidence-based werken binnen de gezondheidszorg in te gaan. Opmerkelijk is dat, ondanks het feit dat er voldoende wetenschappelijk bewijs voor handen is, in

2010 de disseminatie van ERAS programma's binnen de leverchirurgie nog beperkt was. Verder gaven de leverchirurgen aan dat een gerandomiseerde studie of een prospectieve registratie noodzakelijk was om de uitkomsten na open en laparoscopische leverchirurgie goed met elkaar te kunnen vergelijken.

Table 1. ERAS liver programma aanbevelingen

Element	Bewijs niveau	Aanbevelings graad
Preoperatieve voorlichting	C	Sterk
Beperkt preoperatief vasten	B	Sterk
Geen anesthesiologische premedicatie	A	Zwak
Antitrombose profylaxe	A	Sterk
Antibiotica profylaxe	A	Sterk
Evenwichtige anesthesie met kortwerkende medicatie	C	Sterk
Epidurale pijnstilling	B	Zwak
Gebalanceerde intra-operatieve vochttoediening	A	Sterk
Preventie van hypothermie	A	Sterk
PONV profylaxe	C	Sterk
Incisies van minimale lengte	C	Sterk
Geen standaard gebruik van abdominale drain	B	Sterk
Geen neus-maagsonde	A	Sterk
Standaard orale pijnstilling	A	Sterk
Preventie van postoperatieve ileus	C	Zwak
Vroege verwijdering van urinekatheters	D	Zwak
Vroege start van orale intake	A	Sterk
Vroege mobilisatie	C	Sterk

Kwaliteit van bewijs en aanbevelingen volgens de GRADE richtlijnen: A = Hoog, B = Gemiddeld, C = Laag, D = Zeer laag.

In Nederland werden de eerste laparoscopische leverresecties uitgevoerd in de jaren '90, terwijl de eerste laparoscopische leverresectie binnen een ERAS porgamma pas in 2008 werd verricht. Geleidelijk zijn er nieuwe initiatieven ontstaan om prospectieve en gecontroleerde data te verkrijgen om open en laparoscopische leverchirurgie met elkaar te vergelijken. Momenteel worden de resultaten van twee gerandomiseerde controleerde studies (ORANGE 2 Plus – Trial en Oslo – CoMet Study) verwacht en is er recentelijk een consensus statement van een internationale groep leverchirurgen gepubliceerd.[2]

Om het resultaat van de invoering van het ERAS programma binnen de leverchirurgie te kunnen evalueren, hebben we een systematische review van de literatuur tot en met oktober 2011 verricht in **Hoofdstuk 3**. In deze systematisch review konden 6 studies worden geïncludeerd voor verdere analyse. Het werd duidelijk dat de implementatie van een ERAS programma binnen de leverchirurgie geen nadelige effecten

had op de morbiditeit, mortaliteit of het aantal heropnames. De analyse liet ook een mogelijk reductie van de opnameduur zien na implementatie van een ERAS programma. Hierbij dient wel te worden opgemerkt dat de zorg, zoals beschreven in de elementen binnen het ERAS protocol, niet altijd goed werd nageleefd in de verschillende onderzoeken. Door de verschillende mate van compliance binnen de verschillende studies zijn de geïncludeerde studies minder goed met elkaar te vergeleken. Twee studies in de systematische review bekeken de tijd tot functioneel herstel (functional recovery, FR). Deze bleek significant korter dan de totale opnameduur en FR kan worden beschouwd als een objectievere uitkomstmaat. We adviseren om in toekomstige studies tijd tot functioneel herstel als primaire uitkomstmaat te gebruiken om zo de kwaliteit en vergelijkbaarheid te verbeteren. Een recentere systematisch review, waarin twee RCT's werden opgenomen waarin ERAS met conventionele zorg werd vergeleken, ondersteunt de eerder aangetoonde afname in opnameduur en een reductie in morbiditeit.[3]

In **Hoofdstuk 4** hebben we onderzocht of Europese HPB centra daadwerkelijk perioperatieve zorg aanbieden die gebaseerd is op de ERAS principes. De studie ging uit van de hypothese dat de meeste centra elementen uit het ERAS programma al hadden geïmplementeerd binnen de leverchirurgie, aangezien ook het ERAS programma voor colorectale chirurgie al binnen deze ziekenhuizen was ingevoerd. Binnen de onderzochte ziekenhuizen was er substantiële variatie in de perioperatieve zorg bij leverchirurgie. Bepaalde elementen van het ERAS programma, zoals preoperatieve voorlichting en beperkte preoperatief vasten, waren algemeen ingevoerd. Van andere elementen binnen de perioperatieve en postoperatieve zorg bleek daarentegen dat ze verder geoptimaliseerd konden worden. Wij observeerden bijvoorbeeld, dat drains en neus-maagsondes nog frequent standaard werden gebruikt, dat er postoperatief geen gebruik werd gemaakt van ontslagcriteria, dat patiënten pas laat mobiliseerden en dat patiënten pas laat tijdens hun opname een normaal dieet werd aangeboden. Ook werd er vertraging gezien tussen het moment van functioneel herstel en het daadwerkelijk ontslag. Dit komt overeen met resultaten van eerdere studies.[4, 5] Een beperking van deze studie is de retrospectieve opzet, echter hier is met opzet voor gekozen om het gedrag van de medische staf en verpleging niet te beïnvloeden.

Een belangrijk aspect na leverchirurgie is veilige en effectieve pijnstilling. Goede pijnstilling kan de chirurgische geïnduceerde stress beïnvloeden en zal niet alleen zorgen voor een afname van postoperatieve complicaties, het kan ook zorgen voor snellere mobilisatie en een mogelijk sneller herstel. Zo kan adequate pijnstilling zorgen voor een afname in pulmonale complicaties en het optreden van postoperatieve ileus (stoppen of vertragen van darmpassage).[6] Traditioneel wordt postoperatieve pijnstilling verstrekt via intraveneuze patiënt-gecontroleerde pijnstilling (PCA) of via

epidurale katheters. In **Hoofdstuk 5** onderzoeken we de waarde van intramusculaire continue infusie van bupivacaïne (CIB) via wondkatheters gecombineerd met intraveneuze PCA versus epidurale pijnstilling na majeure leverresectie (≥3 segmenten). Een risico na majeure leverresectie is het optreden van een postoperatieve stollingsstoornis. Om deze reden kan epidurale pijnstilling gecontra-indiceerd zijn. De combinatie van CIB + PCA bleek, vergeleken met epidurale pijnstilling, equivalente pijnstilling te kunnen bieden. Er waren geen significante verschillen tussen in het aantal patiënten met ernstige postoperatieve pijn. De patiënten in de CIB + PCA groep kregen totaal minder opiaten, hadden minder complicaties en een kortere opnameduur. Het retrospectieve design en de aanwezigheid van een chirurg-bias kan de resultaten hebben beïnvloed. Anderzijds, een groot en ononderbroken cohort van patiënten met dit type postoperatieve analgesie (CIB + PCA) die een majeure leverresectie ondergingen is niet eerder beschreven. Continue infusie van bupivacaïne gecombineerd met PCA lijkt een goed alternatief te zijn voor epidurale pijnstilling en mogelijke zeldzame complicaties van epidurale analgesie kunnen hiermee vermeden worden.

Het ERAS programma stelt dat er niet routinematig een abdominale drain moet worden achtergelaten na partiële leverresectie ("no-drain" beleid). Het routinematig plaatsen van deze drains kan onnodig, mogelijk schadelijk en oncomfortabel zijn voor patiënten. Het gebruik van abdominale drains na leverchirurgie is nog steeds onderwerp van discussie. In **Hoofdstuk 6** beschrijven we 10-jaar ervaring van een tertiair HPB-centrum met een "no-drain" beleid binnen een ERAS programma. Primaire uitkomstmaten van deze studie waren 90-dagen resectie-oppervlak gerelateerde (ROG) morbiditeit and ROG-reïnterventies. Totaal werd er 20% chirurgische morbiditeit, 15% ROG-complicaties en 12% ROG-reïnterventies geobserveerd bij 538 patiënten die een leverresectie ondergingen. De meerderheid van de ROG-complicaties konden worden behandeld met radiologisch drainage en re-operaties waren maar zelden noodzakelijk. Majeure (≥3 segmenten) leverresectie werd geïdentificeerd als een onafhankelijk risicofactor voor het ontstaan van significante (≥Dindo-Clavien graad 3a) ROG-morbiditeit en de noodzaak van ROG-reïnterventies. De resultaten van deze studie komen overeen met de resultaten gepubliceerd door andere HPB-centra [7-12] en bevestigen de veiligheid en haalbaarheid van een "no-drain" beleid binnen een ERAS programma.

DEEL II: LAPAROSCOPISCHE LEVERCHIRURGIE

Hoofdstuk 7 geeft een historisch overzicht van de introductie van laparoscopische leverchirurgie in Nederland. In de jaren '90 werden de eerste laparoscopische leverresecties verricht, maar een decennium later was de ervaring met deze techniek nog

beperkt. Vergeleken met andere pionierende landen bleek Nederland langzaam met de implementatie van de minimaal invasieve techniek binnen de leverchirurgie. De initiële ervaring met laparoscopische leverchirurgie is verder geëvalueerd met een case-control onderzoek, waarin open en laparoscopische resecties van leversegment 2 – 3 (laparoscopic left lateral sectionectomy (LLS)) tijdens 2000-2008 werden vergeleken. We observerden een significant verschil in opnameduur, bloedverlies, en duur van de operatie in het voordeel van laparoscopische geopereerde patiënten. Tevens was de morbiditeit tussen de groepen vergelijkbaar. Tot slot is de implementatiestatus van de laparoscopische leverchirurgie in 2010 onderzocht middels een nationale enquete. Er waren 30 responderende centra (37 centra aangeschreven) die in totaal 966 leverresectie verichtten, echter maar 49 (5%) van deze resecties werden laparoscopisch uitgevoerd.

Om prospectief de waarde van laparoscopische leverchirurgie te kunnen onderzoeken is er een gerandomiseerd onderzoek met controlegroep (RCT) opgezet. **Hoofdstuk 8** toont het protocol voor deze internationale multicentrum studie. In deze studie wordt open met laparoscopische leversegment 2-3 resectie (= LLS, Left lateral resection) vergeleken binnen een ERAS programma: de ORANGE II – studie. Naast de gerandomiseerde groepen is er ook een prospectieve registratie van patiënten, die niet gerandomiseerd konden worden door voorkeur van de chirurg of patient, toegevoegd. Deze toevoeging zorgt ervoor dat er een ononderbroken prospectieve serie van patiënten kan worden onderzocht. Het primaire eindpunt van de studie is tijd tot functioneel herstel (een samengesteld eindpunt bestaande uit vijf criteria). De hypothese is dat de tijd tot functioneel herstel in de groep patiënten die een laparoscopische LLS ondergaat twee dagen korter is dan bij de patiënten in de open LLS groep.

In **Hoofdstuk 9** presenteren we de resultaten van de ORANGE II – studie. Tussen januari 2010 en juli 2014 werden in totaal 91 patiënten geïncludeerd (24 patiënten in de RCT en 67 patiënten in het prospectieve register). Hoewel de resultaten geen reductie in tijd tot functioneel herstel ten faveure van de laparoscopische groep lieten zien, kon uit deze eerste RCT waarin open met laparoscopische leverchirurgie werd vergeleken geen definitieve conclusie worden getrokken. De studie werd voortijdig gestaakt door een te trage inclusie van gerandomiseerde patiënten. De belangrijkste reden van trage inclusie was een duidelijke voorkeur van chirurgen voor de laparoscopische procedure (laparoscopische LLS). Deze studie liet wel zien dat laparoscopische leversegment 2-3 resecties konden worden uitgevoerd met een lage morbiditeit, weinig re-operaties en heropnames, en een lage mortaliteit. Tot op heden zijn er nog geen andere gerandomiseerde studies die open en laparoscopische leverchirurgie vergelijken. Deze multicentrum RCT zal waarschijnlijk niet nogmaals worden opgezet. De toevoeging van een prospectief register aan de studie zorgde

voor een verhoging van de externe validiteit. De lange-termijn resultaten van deze studie worden nog verwacht.

Tot slot wordt er in **Hoofdstuk 10** een protocol gepresenteerd voor een internationale RCT die open en laparoscopische hemihepatectomie vergelijkt binnen een ERAS programma (de ORANGE II Plus – studie). De open procedure om de linker of rechter hemilever te verwijderen is reeds een geaccepteerde operatie voor de behandeling van levertumoren (meestal colorectale metastasen). De waarde van laparoscopische leverchirurgie bij majeure resectie (>3 segmenten) is nog onduidelijk. In de handen van ervaren leverchirurgen lijkt majeure laparoscopische leverresectie ook veilig en haalbaar. De resultaten zijn echter gebaseerd op case-series en prospectief gecontroleerd bewijs ten aanzien van de korte termijn, oncologische en patiënt-gerapporteerde resultaten is niet voorhanden. The ORANGE II PLUS – studie loopt momenteel in verschillende internationale HPB-centra en heeft als primair eindpunt: tijd tot functioneel herstel. Andere eindpunten die worden bestudeerd zijn de opnameduur, morbiditeit, mortaliteit, operatieve parameters (bloedverlies, operatieduur), patiënt-gerapporteerde uitkomstmaten (kwaliteit van leven, cosmetiek), oncologische uitkomsten (tijd tot start adjuvante chemotherapie, resectie marge, algemene 5-jaars overleving) en kosten.

Samenvattend laat dit proefschrift zien dat binnen de moderne leverchirurgie verschillende elementen van een ERAS-programma al geïmplementeerd zijn. Een volledige implementatie van een versneld herstel programma voor leverchirurgie wordt aanbevolen om het herstel van de patiënten te optimaliseren en te versnellen. Voor een optimaal resultaat is goede naleving essentieel en eventuele nieuwe evidence-based inzichten ten aanzien van (nieuwe) elementen binnen de perioperatieve zorg moeten kritisch worden bekeken en toegepast.

In Nederland was de laparoscopische leverchirurgie tot 2010 nog maar minimaal geïmplementeerd. Laparoscopische leverchirurgie is de laatste jaren populairder geworden onder Nederlandse leverchirurgen. Kleine leverresecties, waaronder de segment 2-3 resectie, dienen volgens een internationale consensus bij voorkeur laparoscopische uitgevoerd te worden.[2] Uit een prospectieve gecontroleerde studie naar open versus laparoscopische segment 2-3 leverresecties konden helaas geen definitieve conclusies worden getrokken, omdat de studie voortijdig werd gestopt door een te lage inclusie in de RCT en een duidelijke voorkeur van chirurgen voor de laparoscopische benadering. Een nog lopende RCT zal in de toekomst waarschijnlijk beter bewijs leveren over de waarde van laparoscopie bij majeure leverchirurgie, oncologische en patiënt-gerapporteerde eindpunten.

TOEKOMSTIGE PERSPECTIEVEN

OPTIMALISATIE VAN HERSTEL NA CHIRURGIE

Er is inmiddels veel wetenschappelijk bewijs beschikbaar dat ERAS protocollen veilig en effectief zijn.[3] Het is daarom bijzonder dat een ERAS protocol voor leverchirurgie nog niet formeel is vastgelegd en gepubliceerd. De ERAS society is een toonaangevende internationale organisatie die een aantal evidence-based protocollen gepubliceerd heeft om chirurgen en andere professionals te ondersteunen. Om de zorg rondom leverchirurgie te standaardiseren is het wenselijk dat er een consensusrichtlijn voor optimaal herstel na leverchirurgie ontwikkeld wordt door deskundigen. Een recente review[3], inclusief recente prospectieve (gerandomiseerde gecontroleerde) studies [14-16], bevestigt opnieuw een kortere opnameduur en afname van postoperatieve morbiditeit. Het is niet alleen belangrijk dat een ERAS lever protocol wordt gepubliceerd en geaccepteerd door internationale leverchirurgen. Het is ook van belang om regelmatig en systematisch elementen van het protocol te evalueren om er zo voor te zorgen dat het protocol up-to-date is en ondersteund wordt door recente literatuur. Onderdelen van het protocol dienen zo nodig te worden herzien en nieuw elementen kunnen worden toegevoegd. De ERAS society moet hierin een leidende rol nemen, zodat standaardisatie en een evidence-based benadering van de patiëntenzorg wordt uitgedragen.

In de inleiding van dit proefschrift zijn de huidige elementen van het ERAS-protocol in de leverchirurgie beschreven en gewaardeerd op basis van de beschikbare publicaties. Voorbeelden van nieuwe elementen die mogelijk kunnen worden toegevoegd aan eerder beschreven ERAS lever protocollen [5, 14, 15, 17] zijn: het gebruik van een pulmonale rekrutering manoeuvre (handmatig beademingen van de long met de patiënt in Trendelenburg) om postoperatieve pijn te verminderen chirurgie [18], stimulering van de darmfunctie met kauwgom [19], implementatie van andere methoden van postoperatieve pijnstlling met minder bijwerkingen (transversus abdominis blokkade [20], wondkatheters [21-23]) en het gebruik van medicatie ter vermindering van de stressrespons[24]. De meeste postoperatieve elementen uit het ERAS programma worden geïntroduceerd bij terugkomst van de patiënt na zijn operatie op de afdeling. Sommige patiënten blijven echter tot 24 uur na de operatie op de verkoeverkamer. Naast het verschaffen van goede pijnbestrijding is het mogelijk om andere elementen al op de verkoeverkamer te introduceren: vroeg drinken van water, het kauwen van kauwgom en vroege mobilisatie. Bevordering van orale inname, vroege mobilisatie en laparoscopische chirurgie, zijn geassocieerd met vroeg herstel na een operatie.[25]

Indien alle elementen met succes worden nageleefd, is het waarschijnlijk dat niet een enkel element, maar het gehele multimodale ERAS programma leidt tot het gewenste versnelde herstel. Zoals aangetoond binnen de colorectale chirurgie, kan er ook een synergetisch effect ontstaan wanneer het ERAS protocol wordt gecombineerd met laparoscopie.[26] Na implementatie is het belangrijk om een zorgprogramma goed te blijven naleven zodat een blijvend voordeel voor de patiënt kan worden gegarandeerd.[27] Deze naleving van het protocol is helaas het belangrijkste probleem in het proces van optimalisatie van herstel. Tijdens de eerste fase van de uitvoering van een nieuw zorgprogramma zijn alle betrokken medewerkers enthousiast en alert om zich te houden aan de richtlijn. Na de initiële implementatie dient naleving te worden gehandhaafd met post-implementatiestrategieën, zoals periodieke evaluaties en onderwijs.[28] Er is al aangetoond in de colonchirurgie dat een gestructureerde implementatie strategie kan resulteren in een goede duurzaamheid.[29]

LAPAROSCOPISCHE LEVERCHIRURGIE

De minimaal invasieve benadering voor leverchirurgie is inmiddels niet meer weg te denken. De afgelopen jaren is aangetoond in verschillende case-series dat naast de kleine laparoscopische leverchirurgie, ook majeure laparoscopische leverresecties geassocieerd worden met gelijke of verbeterde korte termijn resultaten.[30] In ervaren handen zijn het intra-operatieve bloedverlies, de complicaties en het conversie percentage meer dan acceptabel voor de laparoscopische linker hemihepatectomie.[31] Een recente meta-analyse, waarin laparoscopische leverresecties case-matched werden vergeleken met open leverresecties (N = 2900), liet geen verhoogde mortaliteit en aanzienlijk minder complicaties, transfusies, bloedverlies en een korter verblijf in het ziekenhuis zien in het voordeel van laparoscopische chirurgie.[32] In de recente Morioka consensus werd bevestigd dat de laparoscopische benadering van kleine leverresecties als de standard dient te worden beschouwd. Met betrekking tot de majeure laparoscopische leverresecties (≥3 segmenten) oordeelden experts dat de introductie nog in een verkennende fase zit en dat voorzichtige disseminatie van de techniek nog steeds gerechtvaardigd is.[2] De internationale experts die betrokken waren bij de consensus adviseerden, dat participatie en deelname aan lopende prospectieve studies en registraties wenselijk is. In de nabije toekomst zal er meer wetenschappelijk bewijs beschikbaar komen over de waarde van laparoscopische leverresecties, zodra de resultaten van de ORANGE 2 Plus - Trial (hoofdstuk 10) en de Oslo-Comet studie [33] worden gepubliceerd. De ORANGE 2 Plus - Trial vergelijkt open met laparoscopische hemihepatectomie binnen een ERAS-programma en de Oslo-Comet studie vergelijkt laparoscopische versus open leverresecties voor colorectale metastasen. Beide studies zullen leverchirurgen vermoedelijk een beter inzicht verschaffen ten aanzien van de plaats van (majeure) laparoscopi-

sche leverchirurgie op het gebied van oncologische uitkomsten, lange-termijn follow-up, de kosten en de patiënt-gerapporteerde uitkomsten.

Tijdens het schrijven van dit proefschrift is er een verschuiving van chirurgische strategie ontstaan ten aanzien van de omvang van de leverresectie. Naast de discussie over de techniek (laparoscopische versus open) is er ook een toenemende focus op leverparenchym besparende technieken.[34, 35] Een two-stage of formele leverresectie blijkt minder vaak nodig te zijn door de verbetering van de intra-operatieve beeldvorming en technieken.[36] Tevens dient postoperatief leverfalen voorkomen te worden, maar moeten oncologische marges worden gerespecteerd.[37, 38] Een parenchym-sparende strategie met een nauwkeurige preoperatieve voorspelling van de functie van de toekomstige restlever lijkt de toekomst voor een “tailored” benadering.

Beter wetenschappelijke ondersteuning, gestandaardiseerde rapportage van de resultaten, en het garanderen van een goede training zijn de volgende uitdagingen voor de laparoscopische leverchirurgie.[32] Niet alleen RCT's of andere prospectieve studies kunnen bijdragen aan een verdere ontwikkeling van laparoscopische leverchirurgie, ook de kritische beoordeling van leverresecties uitgevoerd in het verleden kan de kwaliteit verbeteren. Controle door nationale of internationale verenigingen zal leverchirurgen inzicht geven in de kwaliteit van hun eigen operaties, maar ook in de prestaties van andere collega's. (International) benchmarks kunnen worden gedefinieerd voor belangrijke uitkomsten, zoals mortaliteit, morbiditeit, en R0-resectiemarges. Uiteindelijk kan deze continue evaluatie leiden tot centralisatie van (laparoscopische) leverchirurgie. Mogelijk presteren groot-volume centra beter dan centra met slechts een beperkt aantal (laparoscopisch) leverresecties per jaar. Een goed voorbeeld van een goed functionerend controlesysteem is het Nederlands Instituut voor Clinical Auditing (DICA). Op 1 juli 2013 werd de Nederlandse Lever-Audit (DHBA) gestart en dit heeft geresulteerd in de publicatie van de eerste rapportages. Toekomstige verslagen zullen inzicht bieden in de werkelijke kwaliteit en kwantiteit van de leverchirurgie in Nederland.

Het uiteindelijke doel is om een aanpak op maat te kunnen bieden voor elke patiënt die leverchirurgie dient te ondergaan. Dit is een toekomst waarin de chirurg in staat is om patiënten te selecteren die fit genoeg zijn om geopereerd te worden, waarin hij individuele operatie risico’s kan voorspellen en waarin hij de postoperatieve uitkomsten nauwkeurig kan inschatten. De selectie van patiënten in de leverchirurgie is een belangrijke kwestie. Niet alleen dienen chirurgen de resectabiliteit te bepalen, ook is het essentieel om in te kunnen schatten of een patiënt een operatie aankan. Tevens is het wenselijk om te kunnen voorspellen of de operatie de lange-termijn overleving verbetert.[39] Recente ontwikkelingen op dit gebied zijn gericht op de preoperatieve

beoordeling en verbetering van de conditie van de patiënt. Een 4-weeks prehabilitatie programma kan de cardiopulmonale inspanningstesten en de kwaliteit van leven voor leverresectie verbeteren. Dit kan vervolgens van invloed zijn op perioperatieve uitkomsten.[40] Verder onderzoek op dit gebied is nog noodzakelijk, maar in de toekomst kan mogelijk een vooraf gedefinieerde cut-off waarde worden gebruikt voor patiënten die leverchirurgie dienen te ondergaan om zodoende te kunnen voorspellen welke patiënten een verhoogd risico lopen op complicaties en welke patiënten fit genoeg zijn om geopereerd te worden.[41] Een geheel andere benadering om patienten voor leverchirurgie te selecteren en om uitkomsten te voorspellen is het gebruik van "big" data. Tegenwoordig zijn patiëntgegevens steeds directer beschikbaar in de digitale patiëntendossiers, elektronische onderzoeksformulieren en prospectieve registers. Deze gegevens kunnen leiden tot grote databases die kunnen worden gebruikt voor het opstellen van risicomodellen.

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Chapter 13

Valorisation

Chapter 13

VALORISATION

INTRODUCTION

Liver surgery can be performed for both benign and malignant tumours of the liver. Colorectal metastases are the indication for nearly 70% of all liver resections, and about 50% of all patients with a primary colorectal tumour will develop hepatic metastases. Primary and benign liver tumours account for 17% and 8% of indications for liver surgery in the Netherlands, respectively. Despite the worldwide interest in laparoscopic surgery, in 2014 the majority of all liver surgical procedures was still performed as an open procedure. Only 11% of all liver resections was performed completely laparoscopically. It is essential not only to offer patients the best surgical procedure, but also to provide patients the best evidence-based perioperative care to accommodate a good and quick recovery. The trend in the Netherlands, but also in the rest of the world, is towards further adoption of the laparoscopic technique and implementation of a structured perioperative care programme in liver surgery. With the still increasing healthcare spending in the Netherlands all new developments and treatments face scrutiny over costs. Laparoscopic liver resection itself may be more expensive, but if the combination with Enhanced Recovery After Surgery protocols leads to a shorter hospital length of stay, lower morbidity or better survival, the overall costs may be equivalent or even lower.

RELEVANCE OF SCIENTIFIC RESULTS IN THIS THESIS

The results reported in this thesis may have both social and economical impact. Costs play an ever more pivotal role in modern (surgical) care. Not only do surgeons and other clinicians look for ways to optimize and shorten the duration of admission of patients, nowadays the government and insurance companies also look for ways to improve patient care and reduce costs. As described in this thesis, minimization of the delay between functional recovery and actual discharge could prove to be the easiest and most tangible way to reduce costs. The length of hospital stay can be reduced by implementation of an ERAS programme and may be reduced if patients are operated laparoscopically. Results presented in this thesis show a benefit of the ERAS programme. However, this thesis has failed to demonstrate a reduced time to functional recovery and associated length of stay after laparoscopic left lateral sectionectomy. Future studies could and should be focused on finding the added value of laparoscopy in liver surgery. If laparoscopy truly leads to a quicker recovery of the patient and cost-effectiveness analyses also confirm a benefit, laparoscopy is likely to become the preferred procedure for liver surgery. A one or two day reduction in length of hospital stay could prove to be of significant value regarding costs. Currently, laparoscopic procedures are still more expensive than open liver surgery. Equally, laparoscopic

procedures require more time in the operating room. This aspect of allocating more operating room time to liver resections, at a time where operating room capacity is scarce, may be important in future decision making. Waiting lists for cancer-related procedures may increase, if more procedures are done laparoscopically. If future studies fail to demonstrate a clinically significant difference in favour of laparoscopic liver surgery that also outweighs the costs, a situation could develop in which open liver surgery remains the standard. Laparoscopy may only be deemed beneficial in selected liver surgical procedures. Perhaps insurance companies will no longer compensate for laparoscopic procedures in the absence of evidence. However, there is another aspect to the comparison of open versus laparoscopic liver surgery: patient opinion. Patient-reported outcomes are being valued more and more. Evidence on patient-reported outcomes on open versus laparoscopic liver surgery is limited and future results of the ORANGE II trials on laparoscopic versus open liver surgery could provide additional leverage in the debate.

TARGET POPULATION

Liver surgeons, other specialists involved in the care of patients diagnosed with liver tumours and patients themselves can benefit from the results presented in this thesis. It offers them new insights into expert opinions, developments, comparison of operative techniques and perioperative care strategies.

INNOVATION AND FUTURE

Projects in this thesis have lead to the development and design of new studies and collaborations. The multicentre international design of the ORANGE II Trials has resulted in a collaborating network of HPB-centres. A currently ongoing European multicentre study, the ORANGE II Plus – Trial, is a direct spin-off of the ORANGE II project. Through this spin-off, in which the merits of open and laparoscopic hemihepatectomy are compared, both surgeons and patients are likely to be presented with valuable new evidence. In the world of hepatic surgery this research has the potential to make a lasting footprint. The first results of this collaboration are to be expected in 2017. With a new network of expert HPB-centres in place, it seems inevitable that new multicentre research could get off to a flying start with broad European support.

In addition, based on results from this thesis and recent literature the Enhanced Recovery After Surgery (ERAS) programme for liver surgery is here to stay. There is robust evidence that should advocate implementation of a structured and evidence-based perioperative care programme. In the future this must also be further supported and controlled by the ERAS Society by the development and publication of official guidelines.

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Beste Paul, Paulus, partners in crime, klaar om de chirurgische wereld te veroveren. Tijdens onze opleiding zijn de cursussen, congressen, promoties, diensten en festivals een waar feest met jou. Ik waardeer onze vriendschap en ik kijk uit na de jaren die nog gaan volgen onder het moto “ Mucht to learn you still have.. my Padawan “.

Beste Luc en Toine, niet alleen hebben jullie bijgedragen aan een belangrijk deel van dit proefschrift, ook onze avonturen bij de Chirurgencup, skydiven in Cape Town en de legendarische avonden en nachten in de Trinity, 31 en Cafe Caprice zal ik nooit vergeten. Luc, uiteindelijk heb je je promotie veel eerder afgerond, maar zijn we allebei nu in opleiding tot chirurg! Toine, je hebt een andere richting gekozen, maar ik wens je hierin ook veel success toe.

Beste Victor, dank voor je hulp en samenwerking. Zonder jouw hulp was dit boekje er nu niet geweest. Naast de wetenschappelijke samenwerking hebben we ook meerdere malen op congressen mogen genieten van “avondjes uit” in bijvoorbeeld de legendarische boeventent in Belgrado. Ik wens je veel gezondheid toe en uiteraard ook veel succes met de afronding van je eigen promotie.

Beste Robert, dank voor al je hulp aan en inzet voor het ORANGE-project. Als semi-arts sprong je op een rijdende trein die inmiddels wereldwijd bekend is. Door jouw inzet is de ORANGE 2 Plus – studie nu bijna afgerond en zullen vele mooie publicaties volgen. Veel succes de komende tijd en ik kijk uit naar jouw boekje!

Alle andere oud-collega's van de afdeling Heelkunde / het lab in het MUMC die ik nog niet heb genoemd, bedankt voor de fijne tijd. Prof. Olde Damink (Steven), Dr. Bemelmans (Marc), Dr. Stoot (Jan / Johnny Punch), Mariëlle, Liliane, Simon, Dirk, Robert-Jan, Aart, Freek, Froukje, Guy, Inca, Irene-Fleur, Irma, Mo, Joyce-Manyi, Maartje, Marlou, Kaatje, Kevin, Kim van Mierlo, Kim van Wijck, Kirsten, Lori, Luc, Mark, Nina, Robbert-Jan, Ruben, Kostan, Rutger en anderen die ik misschien nu vergeet.

Beste (oud)-collega's en staf van de afdeling Heelkunde in het JBZ. Wat een mooie plek om mijn opleiding te doorlopen. Ik geniet van de samenwerking en ben dankbaar voor jullie ondersteuning en voor alles wat jullie mij leren.

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List of Publications

Wong-Lun-Hing EM*, van Woerden V*, Lodewick TM, Bemelmans MH, Olde Damink SWM, Dejong CHC, van Dam RM. Abandoning prophylactic abdominal drainage after hepatic surgery: 10 years of no-drain policy in an ERAS environment. *Dig Surg*. 2017 Mar 25. doi: 10.1159/000455246. [Epub ahead of print]
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* Shared first authorship.

Curriculum Vitae

CURRICULUM VITAE

Edgar Marinus Wong-Lun-Hing was born on September 22th, 1984 in 's- Hertogbosch, the Netherlands. After graduating from the Stedelijk Gymnasium in Breda, the Netherlands (2002) he first studied a year abroad at the Alliant International University of San Diego, USA. In 2003 he studied Health Sciences at the Maastricht University after not being selected in the numerus fixus of Medicine. In 2004 he started his first year of Medicine at Maastricht University and obtained his propaedeutic diploma in 2005. During his study he worked as a student researcher with Ronald van Dam (MD, PhD) and Professor Cornelis C.H. Dejong (MD, PhD). He obtained his medical degree in 2010 and started a PhD project under supervision of Ronald van Dam (MD, PhD) and professor Cornelis C.H. Dejong (MD, PhD). Edgar was awarded an EAES-Research Grant in 2015 for his work on the ORANGE 2 Plus - Trial. Meanwhile he started working as a senior house officer in February 2014 at the Department of Surgery in the Jeroen Bosch Hospital in 's-Hertogenbosch. In November 2014 he started his surgical residency at the Jeroen Bosch Hospital (dr. K. Bosscha). He will continue his training in January 2018 at the University Medical Centre Utrecht (prof. dr. M.R. Vriens). He lives happely together with Marieke Vermeulen, and is the proud father of their daugther (Elise).