Perioperative aspects of resection for colorectal liver metastases. Quality of life, performance status and incisional hernia .

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Quality of life, performance status and incisional hernia

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Perioperative aspects of resection for colorectal liver metastases

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Quality of life, performance status and incisional hernia

Peter Strandberg Holka

LUND UNIVERSITY

DOCTORAL DISSERTATION

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Abstract

Background

Liver metastases are a common consequence of colorectal cancer. When feasible, surgical resection is first-line treatment. Synchronous disease can be treated with different strategies. Traditionally, the primary tumour is resected first followed by resection of the liver metastases (bowel-first). The other option, which is increasing, is the liver-first strategy, where resection of the liver is followed by resection of the primary cancer. Patients with metachronous disease are resected upfront. All surgical strategies are combined with perioperative chemotherapy. The impact of preoperative quality of life (QoL) has not yet been analyzed for these different groups, neither has symptoms related to Incisional hernia (IH) which is a common complication after surgery. Performance status (PS) is known as one of the strongest prognostic factors for survival in metastatic colorectal cancer.

Questions/methods

I. Investigate incidence, location and risk factors for IH after resection for colorectal liver metastases (CRLM) including the use of chemotherapy.

II. Analyze factors associated with poor PS after resection for CRLM and the impact on survival.

III. Analyze whether preoperative QoL differs between patients undergoing the liver-first or bowel-first strategy for synchronous CRLM, and patients resected for metachronous CRLM.

IV. Investigate the clinical significance of IH, QoL, abdominal wall (AW) symptoms and their determinants.

Results/Conclusions

Incidence rate for IH after liver surgery was as high as 30-43%. Hernia locations were midline alone in 86% of cases. Preoperative bevacizumab and previous IH were found to be independent risk factors. There were no differences regarding AW symptoms and QoL between the IH and non-IH groups. Nevertheless half of the patients experienced AW symptoms in long term but it was not related to IH. Patients with postoperative PS > 2 who did not receive adjuvant chemotherapy had decreased survival after resection for CRLM. After recurrence, a large majority of these patients had had improvement in PS allowing for administration of tumor specific treatment. PS was the strongest independent factor predicting survival. The patients in the liver-first group in no dimension reported a decreased preoperative QoL as compared to patients in the bowel-first and comparable QoL with the metachronous group.

Keywords: Secondary liver neoplasms, colorectal neoplasms, hepatectomy, incisional herina, quality of life.

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To

In memoriam, Maria

Ann-Sofie
Gabriel, Lukas and Oliver

"An expert is a man who has made all the mistakes which can be made, in a narrow field."

– Niels Bohr

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List of papers

This thesis is based on the following papers, which will be referred to in the text by their roman numerals I-IV:

I. Nilsson JH, **Strandberg Holka P**, Sturesson C. Incisional hernia after open resections for colorectal liver metastases - incidence and risk factors. HPB : the official journal of the International Hepato Pancreato Biliary Association. 2016;18(5):436-41.

II. **Strandberg Holka P**, Eriksson S, Eberhard J, Bergenfeldt M, Lindell G, Sturesson C. Significance of poor performance status after resection of colorectal liver metastases. World journal of surgical oncology. 2018;16(1):3.

III. **Strandberg Holka P**, Östrand E, Aderup M, Zangoei S, Lindell L, Tingstedt B, Sturesson C. Preoperative quality of life in patients operated with the liver-first strategy for colorectal liver metastases. Submitted.

IV. **Strandberg Holka P**, Lindell L, Tingstedt B, Sturesson C. Clinical importance of incisional hernia in patients resected for colorectal liver metastases: quality of life and abdominal wall symptoms. Manuscript.

Thesis at a glance

	QUESTION	METHODS	RESULTS AND CONCLUSIONS
I	What are the incidence, risk factors, and localization of incisional hernia after open liver surgery for colorectal liver metastases?	Retrospective cohort study. Medical chart and computed tomography incisional hernia evaluation on 256 patients operated for colorectal liver metastases between 2010 and 2013.	30.5% developped IH. Prolonged preoperative chemotherapy, preoperative bevacizumab, and previous incisional hernia are decisive risk factors for the development of IH after open surgery for colorectal liver metastases.
II	What are the factors associated with poor PS after resection for CRLM and the impact on survival?	Retrospective cohort study. Medical chart reviewed regarding postoperative performance status. 284 patients operated for colorectal liver metastases between 2010 and 2015 included.	26% presented with poor postoperative PS > 2 precluding adjuvant chemotherapy. These patients had shorter survival. Majority of patients regained PS over time after resection allowing chemotherapy.
III	Do preoperative QoL differ between patients undergoing the liver-first or bowel-first strategy for synchronous CRLM and patients resected for metachronous CRLM?	Cross-sectional study. 234 patients undergoing curative resecton for colorectal liver metastases between January 2011 and August 2016 analysed. EORTC QLQ-C30 form distributed 3-4 weeks before sugery. Medical chart reviewed.	45 patients underwent liver-fist stategy, 81 patients bowel-first strategy and 108 operated for metachonous liver disease. No difference in patients' quality of life (QoL) regardless of which strategy was chosen. Nor did the patients' QoL differ from those resected for metachronous disease.
IV	What is the clinical importance of incisional hernia detected on CT? QoL, and abdominal wall symptoms and their determinants?	Prospective single center study of 105 patients who underwend surgery for colorectal liver metastasies between 2010 and 2015. Ventral hernia pain questionnaire (VHPQ) and EORTC QLQ-C 30 QoL form. Medical chart and computed tomography incisional hernia evaluation	42% developed IH. Majority of IH located in midline alone. No differences regardning abdominal wall symtoms and QoL between the IH and non-IH groups. However, half of patients had abdominal wall symtoms after median follow up of 34 month. Although not related to IH.

Abbreviations: CRLM – Colorectal Liver Metastases, IH – Incisional Herina, PS - Performance Status, QoL- Quality of Life, VHPQ – Ventral Hernia Pain Questionnaire, EORTC QLQ-C 30 – European Organisation for Reasearch and Treatment of Cancer, Quality of Life Questionnaire-Core 30.

Abbreviations

ASA	American Society of Anesthesiologists
AW	Abdominal Wall
BMI	Body Mass Index
CRC	Colo-Rectal Cancer
CRLM	Colorectal Liver Metastases
CT	Computed Tomography
DFS	Disease-free survival
ECOG PS	Eastern Cooperative Oncology Group Performance Status scale
E-MILS registry	European Registry of Minimally Invasive Liver Surgery
EORTC QLQ-C 30	European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30
EORTC QLQ-LMC21	European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire-Liver Metastases Colorectal Module
ERSI	Extended Right Subcostal Incision
HR	Hazard Ratio
HRQoL	Health Related Quality of life
IH	Incisional Hernia
KPS	Karnofsky Performance Status
mCRLM	Metachronous Colo-Rectal Liver Metastases
OS	Overall Survival
PS	Performance Status
QoL	Quality of Life
RCT	Randomized controlled trials

sCRLM	Synchronous Colo-Rectal Liver Metastases
SweLiv	Swedish national registry for cancer of Liver, gallbladder and bile ducts
VHPQ	Ventral Hernia Pain Questionnaire
WHO PS	Word Health Organization Performance Status

Introduction

Epidemiology of colorectal cancer and colorectal liver metastases

Colorectal cancer (CRC), defined as cancer in the colon and rectum, is the third most common form of cancer globally (1) and in Sweden. The age-standardized incidence of colon cancer has gradually increased in recent decades, while rectal cancer has had an almost unchanged incidence in Sweden. In 2020, the incidence of new cases of colon cancer was 47/100,000 among men and 43/100,000 among women, which corresponds to over 4,000 new cases of colon cancer annually. The incidence of rectal cancer in 2020 was 24/100,000 among men and 16/100,000 among women, which means that about 2,000 patients are diagnosed with rectal cancer each year (2).

The elderly population is mainly affected. Only 4% of all colon cancers and 5% of all rectal cancers were diagnosed in patients younger than 50 years. In addition, 29% of patients with colon cancer and 21% of patients with rectal cancer were 80 years or older at the time of diagnosis between 2012–2016 (3). Colorectal cancer is the fourth most common cause of cancer-related death in Sweden (3).

In recent decades, the relative 5-year survival has improved for both colon and rectal cancer. In 2018, the 5-year survival for colon cancer was 64% for men and 68% for women in Sweden. In addition, 5-year survival was 66% for both men and women for rectal cancer (3, 4).

Colorectal metastases, stage IV disease

About 30-38% of patients with CRC develop distant metastasis, i.e., stage IV disease (5, 6). The most common site of distant metastases from CRC is the liver, accounting for approximately 40% of all metastases, followed by lung metastases. The peritoneum and skeleton are other common sites of metastasis (5).

At diagnosis of CRC, 20-25% of patients present with stage IV disease (7-10), where concomitant CRC liver metastases occur in 15-25% of cases (11-13), defined as synchronous liver metastases (sCRLM). In addition, 15% will develop liver metastases at a later stage, i.e metachronous CRLM (mCRLM) (3, 5, 14, 15).

The modern approach to colorectal liver metastases – different strategies

The modern curative treatment of CRLMs is multimodal. It includes surgical resection of metastases and local tumour ablation techniques combined with perioperative chemotherapy (16-19). The first reports of partial hepatectomies came as early as the 1940s. Since then, surgery has been one of the cornerstones of CRLM treatment, as it is the treatment strategy that can best offer possible cure (20-22). 5-year survival rates after liver resection of between 49-61% has been reported in the literature (2, 13, 23). However, because of the extent of the disease, limited future liver remnant volume, and medical comorbidity, only 15-26% of patients with CRLM undergo surgery (13, 15, 24). The resection criteria have changed over time. Previous criteria for resection were based on the number of metastases, and the idea was to achieve a resection margin of 1 cm. The criteria also excluded patients with extrahepatic tumour manifestation (25). The current resection criteria for CRLM are to radically remove all tumours and leave a functional liver remnant with sufficient functional volume (21, 26). A limited number of lung metastases or peritoneal metastases, if resectable, are also no longer considered an absolute contraindication to liver resection (27, 28). Liver surgery can be performed either anatomically or non-anatomically. The choice of resection depends on the amount of liver parenchyma to be removed while considering the segmental anatomy of the liver (29). The different segments of liver are shown in figure 1. In non-anatomical resections, as much liver tissue as possible is spared. Therefore, this technique is suitable for smaller tumours peripherally in the liver. In anatomical resections, two or more liver segments are usually removed, which may be necessary in the presence of extensive metastases or metastasis located near central liver vessels. If possible to perform, non-anatomical parenchyma-sparing resections can reduce the risk of postoperative adverse events, with the similar rates of negative surgical margins and both disease-free and overall survival as for anatomical resections (30, 31). If new metastases appear, parenchyma-sparing resection procedures can also facilitate a repeated resection (32). In addition, re-resection should be considered for patients with recurrent CRLM because of long-term survival (33) and complication rates (34) are similar to those after initial resection.

Limited laparoscopic liver resections have been performed since the early 1990s and have been shown to be safe and feasible (35). Furthermore, the laparoscopic approach decreases intraoperative blood loss, allows faster recovery, and shorter hospital stay than open surgery in selected cases (36, 37). In addition, the reported 5-year relapse-free and overall survival are comparable after an open and a laparoscopic resection (38, 39).The indication for laparoscopic liver resection for CRLM has gradually been extended from metastases located in anterolateral segments to include all segments (40). Major laparoscopic resections, such as

hemihepatectomies and segmental anatomical resections are also feasible but should be implemented with structured training programs (40).

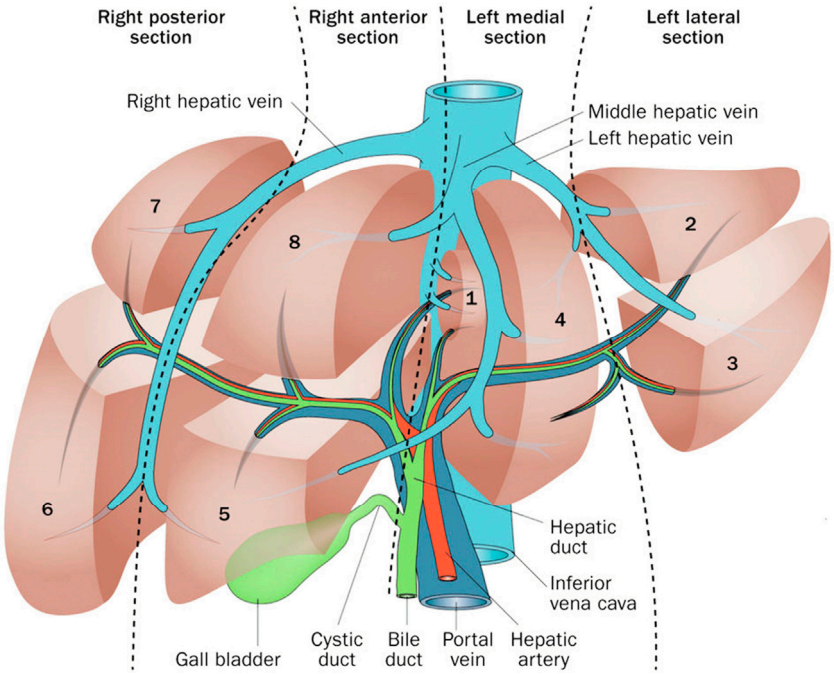


Figure 1. Schematic illustration of the segmental anatomy of the liver (Couinaud's liver segments). Gupta, Meera, Surgery Morning Report: Beyond the Pearls, Chapter 49, 391-401. Printed with permission from the copyright holder. © Elsevier 2020.

Different strategies for synchronous CRLM (sCRLM)

Different treatment approaches can be applied in patients with colorectal cancer with synchronous liver metastases. Usually the treatment includes perioperative chemotherapy. Unlike patients with metachronous disease who are often treated with surgery upfront. Adjuvant chemotherapy is standard after surgical treatment for liver metastases.

Patients with synchronous liver metastases (sCRLM) have traditionally undergone excision of the primary colorectal tumour and, if technically feasible, resection of the secondary tumour/s in a later session, called the classical strategy. The reason for using the classical strategy is to eliminate further metastatic development from the primary tumour and avoid possible complications such as intestinal obstruction, tumour perforation, or gastrointestinal bleeding.

Another option is the simultaneous strategy where the primary and the metastatic tumour/s are resected during the same procedure. This strategy is mainly used when patients have technically uncomplicated resection of the primary and secondary tumours and therefore is limited to a selected group of patients. The approach has the benefit of one surgical procedure with a shorter total hospital stay for the patient. However, in this thesis, patients with synchronous resection have not been analyzed due to their low number.

The third option is the liver-first strategy, which may be considered in patients with asymptomatic primary and CRLM demanding major hepatectomy, or in patients with a high risk of complications following colorectal surgery. In this option, after preoperative chemotherapy, CRLM are resected first, followed by the extirpation of the primary tumor at a second stage (41).

In the literature, several studies, including systematic reviews and meta-analyses (42-44), have compared liver-first, classical, and simultaneous approaches over the past decade. No significant differences in survival and major morbidity were found between the three strategies

Studies have shown that patients with better preoperative quality of life (QoL) are more likely to recover well after surgery (45, 46) irrespectively of strategy. Thus, it is essential to evaluate the preoperative QoL when choosing the most appropriate treatment strategy. Therefore, the present thesis aim also to analyze whether preoperative QoL differs for patients undergoing the liver-first or bowel-first strategies for synchronous CRLM compared with patients operated for metachronous liver disease.

Chemotherapy for patients with resectable colorectal liver metastases

For patients with upfront resectable CRLM, the role of chemotherapy has been examined in both the neoadjuvant and the adjuvant settings (47).

Neoadjuvant chemotherapy

In patients with resectable liver metastases, neoadjuvant chemotherapy may have theoretical benefits. These include control of systemic disease including evaluation of chemotherapy-response before surgery, achieving tumor downsizing to increase the odds of R0 resection in borderline resectable metastases, and eradication of undetectable micro-metastases decreasing the risk of relapse. The possible benefits must be weighed against the potential disadvantages of chemotherapy-toxicity, particularly to the liver (47).

In a randomized multicenter study (18), liver resection and perioperative chemotherapy (6 cycles of FOLFOX before and six cycles of FOLFOX after surgery) significantly increased the 3-year disease-free survival compared to surgery alone. However, after a mean follow-up of 8.5 years, there was no difference in overall survival between the two groups (19). The absence of overall survival advantage has been attributed to the study's small sample size of 364, and the study was only powered to detect a disease-free survival difference and was insufficiently powered for overall survival. Furthermore, only patients with 1-3 metastases where included whereof only 15% had 3 metastases. A meta-analysis of 18 studies suggests that neoadjuvant chemotherapy may improve survival for patients with initially resectable CRLM patients with high-risk factors for recurrence. Still, a definitive conclusion as to the survival advantage cannot yet be made due to the heterogeneity of the different studies. Further studies for different subgroups are needed (48).

Adjuvant chemotherapy

There is no evidence of level 1 for adjuvant chemotherapy usage after surgery for CRLM. However, the topic is widely studied. In two randomized studies, (49) and (50), adjuvant chemotherapy was associated with a trend to better survival. The pooled data from both studies (51) support the assumption that adjuvant chemotherapy is associated with both longer progression-free survival and overall survival. Another large study (52) comparing resection of CRLM with and without adjuvant chemotherapy showed that adjuvant chemotherapy prolongs postoperative survival. Also, patients with resection of a single, metachronous colon cancer liver metastasis might have a survival benefit (53). In the later study, adjuvant chemotherapy was significantly associated with better disease-free survival and overall survival when the tumour diameter exceeded 5 cm. Furthermore, the outcome of different adjuvant chemotherapy regimens, (oxaliplatin/ fluoropyrimidine, irinotecan/fluoropyrimidine, and fluoropyrimidine alone) has been studied showing the oxaliplatin/fluoropyrimidines combination to be superior in terms of disease-free survival (54). In addition, adjuvant therapy allows the administration of chemotherapy without increasing the potential hepatic surgical complications encumbered with chemotherapy given preoperatively.

Chemotherapy for patients with unrespectable colorectal liver metastases

The role of downsizing chemotherapy in patients with primary non-resectable CRLMs is well established. A systematic review demonstrated an overall response rate of 64% (range 43%–79%), with a conversion rate of 22.5% as to resectability and a potentially curative situation (55). Both oxaliplatin (56) and irinotecan (57) based regimes have been used for downsizing, with reported resection rates ranging between 33%-40%. Also, fluorouracil (5FU), oxaliplatin, and irinotecan combinations have been studied comparing FOLFOXIRI to FOLIFIRI (58) and FOLFIRINOX to FOLFOX or FOLFIRI (59), demonstrating improved response rates, progression-free and overall survival, as well as improved resection rates to the price of more significant toxicity. Furthermore, the addition of targeted therapy with monoclonal antibodies such as bevacizumab, cetuximab, or panitumumab can be used to enhance the possibility of downsizing CRLM (55, 60, 61).

Health-related Quality of Life

Quality of life (QoL) has often been used as an outcome measure when evaluating the patient's life situation after surgery (62-65). The most common way to assess QoL is to use self-administered QoL instruments. Today, there is no generally accepted definition of QoL. Also, the meaning of the concept of QoL varies within different areas of application (66). Several different definitions are used (66), the World Health Organization, Quality of Life Group, defined quality of life as individuals' perception of their position in life in the context of the culture and value system in which they live and concerning their goals, expectations, standards and worries (67). QoL is considered subjective because it can only be understood from one patient's or person's point of view. It is also regarded as multidimensional and should therefore cover a wide range of aspects such as physical, functional, emotional, and social well-being (67, 68). The concept presents the subjective perception and evaluation of negative and positive aspects of life (69), and is often used to evaluate a specific treatment or disease (70). Expectations influence quality of life and, by definition, QoL can only be assessed by the individual patient (68).

To distinguish between QoL in a general sense and QoL linked to a patient's health, the term Health Related Quality of Life (HRQoL) is often used (66). HRQoL can be applied when referring to how emotional, physical, and social well-being is affected by a disease or treatment. HRQoL is a multidimensional concept that addresses the subjective evaluation of one's ability to perform everyday tasks and their impact on one's ordinary physical, emotional, and social well-being (71). The QoL and HRQoL concepts overlap and have been used alternately without any clear

distinction. In the absence of clear definitions, QoL is used in this thesis when referring to the patient's HRQoL. Also, since there is no formal definition of QoL, many researchers bypass it by describing their meaning of QoL. Then the questions in the various questionnaires will speak for themselves (66).

The European Organization for Research and Treatment of Cancer (EORTC) is a multinational organization that complies with current research to improve cancer management and related problems. They have developed a validated questionnaire (QLQ-C30 version 3.0) to evaluate the overall QoL for patients with cancer, both functions and symptoms (72), used in this thesis.

EORTC QLQ-C30 is a 30-item questionnaire that consists of multi-item scales and single items that reflect QoL. It contains five functional domains (physical, role, emotional, cognitive, and social functioning), a global health score, and nine cancer-related symptoms (72). For the five functional scales and global health, a high score denotes a high level of functioning, whereas, for the symptom scales, a high score implies a high level of symptoms (72). Clinical importance of QoL scores differences has been described as none (≤ 5.0), minor (5.1–10.0), moderate (10.1–20.0), or large (> 20.0) (73).

The EORTC QLQ-LMC21 questionnaire is developed to be used in conjunction with the EORTC QLQ-C30 for assessing the quality of life in patients with liver metastases from colorectal cancer (74, 75). The EORTC QLQ-LMC21 form has been translated into Swedish but not yet validated, and therefore not used in this thesis.

Several studies have evaluated QoL after liver surgery. Studies of QoL for patients operated for CRLM show deterioration after surgery but QoL usually return to baseline within 3 to 6 months (62, 76). A systemic review and meta-analysis (77) of 22 various QoL trials showed deterioration of QoL after hepatic resection in the short-term but recovery to baseline within 9-months. In addition, patients who underwent major hepatectomy experienced inferior QoL than those who underwent minor hepatic resection. Further studies are warranted to confirm these findings.

Performance status

Performance status estimates how sufficiently an individual can conduct regular day-to-day tasks while living with cancer, and gives a measure of what treatments an individual can tolerate (78). In general, the patient's history and physical examinations are combined to assess the patient's health and functional status. The two most widely used instruments are the Eastern Cooperative Oncology Group Performance Status (ECOG PS), also called the WHO score (79), and the Karnofsky Performance Status (KPS) scales (80). The first performance status scale was KPS

described already in 1949 (80), where patients were assigned a score on a linear scale between 0 (death) and 100 (normally active and with no signs of illness), which assessed their capability to execute everyday activities and the level of help they need to accomplish their assignments (81).The ECOG/WHO PS scale was introduced in 1960 with only six points ranging from 0 (fully active) to 5 (dead) (79). The two scales have been demonstrated to be exchangeable (82). However, the ECOG/WHO scale is often chosen for its plainness and intraobserver reproducibility (82).

Performance status and colorectal liver metastases

PS assessment has been demonstrated to be associated with survival in many cancer forms (83, 84). This is in line with a large study of patients with metastatic colorectal cancer receiving 5-fluorouracil, where ECOG PS of 0 and 1 were correlated with a more prolonged survival than ECOG PS >1 (85). It is important to underline that also when resection is performed for patients with CRLM, approximately two-thirds of the patients will develop disease recurrence within two years after resection (86), which will influence both QoL and PS.

The rationale behind the administration of adjuvant chemotherapy is to minimize the risk of recurrence (87) but it may additionally affect QoL and PS. On the other hand, patients' failure to receive adjuvant chemotherapy because of poor PS and complications after liver resection have been shown to affect survival adversely (88, 89). PS is a scoring system quantifying the impact of disease on a patient's well-being and it is known as one of the most decisive prognostic factors for survival in metastatic CRC patients (90, 91). The definitions of WHO PS are shown in table 1 (79). Hence, this thesis aimed to analyze factors associated with poor PS after resection for CRLM and the impact on survival. Furthermore, in case of disease recurrence, the aim was to also evaluate the PS of patients and to which extent patients received tumour-specific treatment.

Table 1.
Definitions of performance status.

Grade	WHO performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Incisional hernia

Incisional hernia (IH) after laparotomy is a well-recognized complication. Factors reported to be associated with an increased incidence of IH include gender, age, obesity, surgical site infection, prolonged preoperative chemotherapy (92-95). The reported incidence of IH varies depending on the type of incision, follow-up time, and method of hernia detection (92, 93, 96). The IH incidence after liver resections has been studied only to a limited extent (93, 97, 98). No study including only patients with liver metastases from colorectal cancer has previously been made. IH has been shown to be less frequent after laparoscopic operations as compared to open surgery (99). Although laparoscopic liver resections are feasible and are increasingly used, open resection is still the most common procedure (100). Before liver resection of colorectal metastases, a majority of patients receive preoperative chemotherapy (100, 101) which has also been shown to be an independent risk factor for incisional hernia (95). Non-midline incisions give less incisional hernias and hence, for liver resection, an extended right subcostal incision is recommended (93, 102). Detailed anatomy of the abdominal wall is showed in figure 2. Imaging diagnostics increase the ability to detect IH compared to physical examination (96, 102, 103) and computed tomography (CT) has been suggested as the "golden standard" (96). IH was defined as: "An abnormal protrusion of the contents of the abdominal cavity or of pre-peritoneal fat through a defect or weakness in the abdominal wall at the site of the surgical scar" (104). A typical midline IH found on CT is shown in figure 3. The clinical importance of hernias found on CT is however unknown. In addition, most QoL questionnaires are not specific for abdominal wall symptoms as they address mainly the symptom of pain. With improved survival over time (105), the focus on long-time perspective, including rehabilitation and QoL is increasing. In this setting symptoms related to the surgical procedure per se, are important to investigate. Different abdominal wall questionnaires have been used in the literature because of the lack of a uniformly accepted questionnaire. The abdominal wall-specific questionnaire used in this thesis was the validated ventral hernia pain questionnaire (VHPQ) (106, 107). It consists of 19 questions reflecting the patients 'perception of the incisional site concerning pain, cosmetic issues, social limitations, and abdominal wall stiffness. Also, questions regarding the level, frequency, and duration of pain, use of pain medication, and impact on daily activities are included.

The aims of our studies were to investigate the incidence, location, and risk factors for incisional hernia after open liver resection and perioperative chemotherapy for CRLM, the IH incidence being evaluated by CT. Additionally, abdominal wall (AW) discomfort and QoL with special reference to IH after liver surgery for CRLM was analyzed. In particular, the clinical importance of CT detected IH was addressed.

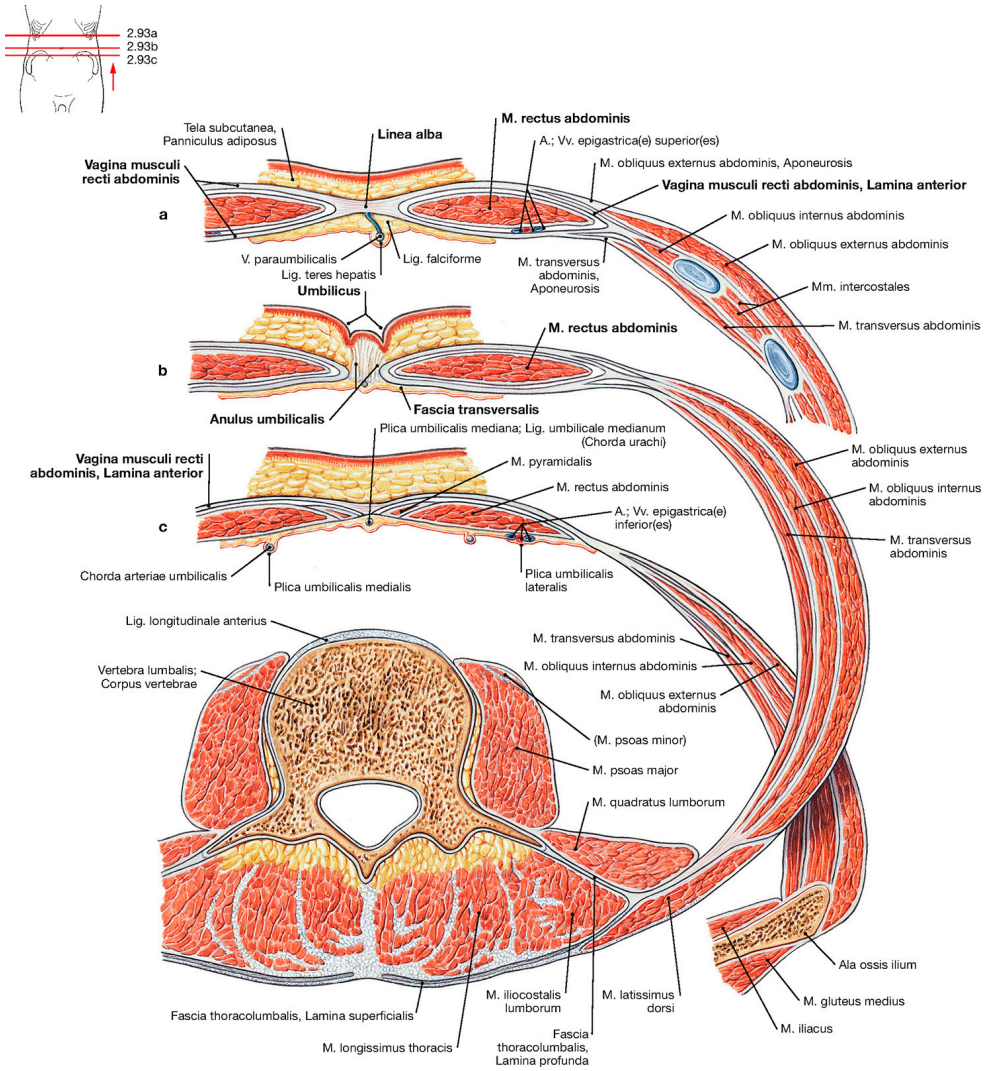


Figure 2. Abdominal wall anatomy. Paulsen, Friedrich, Sobotta. Atlas of Anatomy, Vol. 1, 16th ed., English/Latin, 2, 55-152. Printed with permission from the copyright holder. © Elsevier 2018.

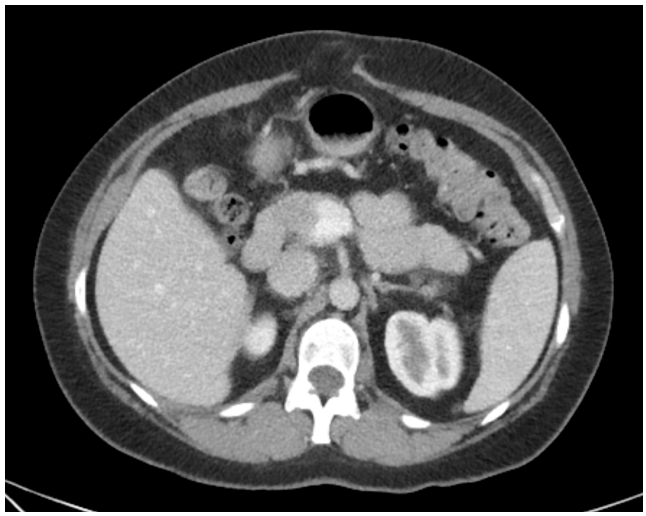


Figure 3. CT transversal palaine image showeing a typical midline incisional hernia. Pinted with permission dr. Jan Nilsson (108).

Aims and objectives

The main objective of this thesis was to investigate different perioperative aspects for patients resected for liver metastases from colorectal cancer to improve postoperative outcomes.

The specific aims of each paper were:

I. To investigate incidence, location and risk factors for IH after resection for CRLM including the use of chemotherapy.

II. To analyze factors associated with poor PS after resection for CRLM and the impact on survival.

III. To analyze whether preoperative QoL differs between patients undergoing the liver-first or bowel-first strategy for synchronous CRLM, and patients resected for metachronous CRLM.

IV. To investigate the clinical importance of IH, QoL, AW symptoms and their determinants.

Materials and methods

The study population mainly consists of consecutive patients who underwent open resection for CRLM at the Department of Surgery, Skåne University Hospital in Lund between 2010 and 2016.

Paper I

All consecutive patients resected for CRLM between 2010 and 2013 by laparotomy were included. Data were obtained retrospectively from patient records and radiological imaging examinations. The most recent preoperative CT scan and all CT images from the normal patient follow-up program of one CT scan every six month the first three years followed by one CT scan yearly, were analyzed by one investigator. Incisional hernia was defined as a discontinuity in the abdominal fascia observed on CT scan (94, 95). On preoperative CT, the existence of an incisional hernia from previous colorectal resection or previous liver resection was recorded. The localization of IH after liver operation was determined to midline, mid-subcostal or lateral, where the midline was unaffected by the hernia in the latter two groups.

Preoperative chemotherapy was determined as chemotherapy administration within 90 days before surgery, and postoperative chemotherapy was defined as chemotherapy given within 90 days after surgery. The 30-day morbidity was classified according to Clavien-Dindo (109).

The liver was accessed with a right subcostal incision, 4-5 cm caudal of the costal margin with a midline cranial extension to the xiphoid process usually measuring 4-8 cm defining an extended right subcostal incision (J-shaped incision). If needed, the incision was prolonged to the left, resulting in a bilateral subcostal incision with a cranial midline extension (Mercedes incision). A major resection was defined as a resection of ≥3 Couinaud's segments. The abdominal wall fascia was closed in two layers with a running, slowly absorbable PDS suture (Johnson & Johnson, Diegem, Belgium), and the skin was stapled.

Paper II

Data were collected retrospectively from medical records for all patients who underwent resection of colorectal liver metastases between 2010 and 2015 at a single institution. The liver surgery was conducted as formerly described (110). A major liver procedure was described as resection of ≥ 3 Couinaud's segments. The Clavien-Dindo classification was used to define 30-day morbidity (109). Poor PS after surgery was determined as a PS WHO > 2. It was determined as adjuvant chemotherapy when the drugs were given within 90 days after liver resection. The current indication for adjuvant therapy required an R0 or R1 resection and patients showing a PS WHO 0-2 after surgery. This paper determines the synchronous disease sCRLM as liver metastases detected during the radiological staging before resecting the primary tumour. The overall and recurrence-free survival was documented.

Paper III

Patients who underwent curative surgery for CRLM between January 2011 and August 2016 at a single center were prospectively included. Patients with simultaneous liver and primary resections and liver re-resections were excluded. The synchronous disease was described as metastatic disease observed at the time of diagnosis of primary cancer. The data collection method was a validated questionnaire for estimating QoL (EORTC QLQ-C30) distributed to patients 3-4 weeks before the surgery. Clinical relevance of QoL scores differences was described as none (≤ 5.0), minor (5.1–10.0), moderate (10.1–20.0), or large (> 20.0) (73).

Patient data were obtained from clinical records. Preoperative chemotherapy was described as chemotherapy administration within 90 days before surgery. Whereas, prolonged preoperative chemotherapy was defined as more than 6 cycles. Almost all (224 of 234) liver resections were open procedures.

Paper IV

Patients who underwent curative surgery for CRLM between 2010 and 2015 at Skåne university hospital, who were alive in February 2017, were sent two questionnaires. A validated ventral hernia pain questionnaire (VHPQ) (106, 107) and the Swedish version of the EORTC QLQ C-30 QoL questionnaire (72). The clinical importance of differences in QoL scores was defined as none (≤5), moderate (10.0-20.0), or large (>20.0) (73). Clinically relevant symptoms in the VHPQ questionnaire were determined as pain right now / the last week- not easily ignored, scar cosmetically disturbing, scar socially limiting, and abdominal wall stiffness.

Patients were reminded twice if they did not respond. Patients returning both questionnaires formed the basis of study population. Data were extracted from clinical records and radiological imaging examinations. Preoperative chemotherapy was determined as chemotherapy administration within 90 days before liver surgery. Meanwhile, postoperative chemotherapy was defined as chemotherapy administration within 90 days after liver surgery. Furthermore, prolonged preoperative chemotherapy was specified as more than 6 cycles.

The most recent CT before liver resection and CT at the time of data collection were analyzed by a single investigator. IH was described as a discontinuity in the abdominal fascia observed on CT (94, 95). In addition, the presence of IH after previous abdominal laparotomies on preoperative CT was recorded. Furthermore, postoperative CT was used to detect possible disease recurrence, and the same investigation was used to diagnose IH.

Access to the liver was obtained through a right-sided subcostal incision, 4-5 cm below the costal margin with a cranial extension of the midline to the xiphoid process that generally measured 4-8 cm, defining an extended right subcostal incision (J-shaped incision). If needed, the incision was prolonged to the left resulting in a bilateral subcostal incision with a cranial midline extension (Mercedes incision). Liver transection was performed using a standardized technique previously described in detail (110). A major resection was defined as a resection of ≥3 Couinaud's segments. The abdominal fascia was closed in two layers with a continuous, slowly resorbable PDS suture (Johnson & Johnson, Diegem, Belgium), and the skin was stapled. No drains were used.

Project design

Paper I

Paper I was a retrospective, descriptive, and comparative cohort study. Patients resected for CRLM at Skåne University Hospital in Lund between 2010 and 2013 were included. Data were retrospectively obtained from patient records and radiological imaging examinations. The patients were divided into groups, whether or not postoperative IH was present. When a liver re-resection was performed, the follow-up of the IH incidence was discontinued, and the patient was evaluated as a new patient with a new IH follow-up.

Paper II

Paper II was a retrospective, descriptive and comparative cohort study. All patients undergoing resection of CRLM between 2010 and 2015 at Skåne University Hospital in Lund were included. Data were extracted retrospectively from patient records. Patients were divided into two groups depending on whether they presented with a WHO performance status of 0-2 or WHO performance status > 2 postoperatively. Patients with liver re-resections and simultaneous liver and primary surgery were excluded.

Paper III

Paper III was a descriptive, quantitative and cross-sectional study. Patients who underwent curative surgery for CRLM between January 2011 and August 2016 at Skåne University Hospital in Lund were prospectively included. Patients with simultaneous liver and primary surgery were excluded. The data collection method was a validated QoL questionnaire (EORTC QLQ-C30) delivered to patients 3-4 weeks before the procedure. In addition, data were extracted from clinical records retrospectively.

Paper IV

Paper IV was a prospective, descriptive, and comparative cohort study. Patients from the region of Skåne in southern of Sweden, who were resected for CRLM

between January 2010 and December 2015 at Skåne University Hospital in Lund, who were alive in February 2017, were asked to respond to a validated ventral hernia pain questionnaire (VHPQ) and the EORTC QLQ-C30 QoL questionnaire. In addition, data were also extracted retrospectively from the patient records.

Statistical analysis

The variables in this thesis were generally considered non-normally distributed and consequently regarded as non-parametric. Therefore, data were presented for categorical variables as medians with interquartile ranges, while continuous variables were expressed as numbers/frequencies or percentages unless otherwise stated.

In paper I and II, Mann-Whitney U test was used to compare continuous data and Chi-square test for categorical data. The Kaplan-Meier method was used to estimate IH incidence in paper I and to estimate the recurrence-free survival and overall survival in paper II. The log-rank test was used to compare risk factors in paper I and the importance of postoperative PS in paper II. To analyze the effect of risk factors on IH incidence in paper I and to analyze for adverse survival outcome in paper II, Cox regression analysis was used to calculate hazard ratios and 95 percent confidence intervals. Factors with a $P < 0.1$ on univariable analysis were included in the multivariable analysis.

In paper III and IV, Results from EORTC QLQ-C30 questionnaires were transformed into function and symptom scales (0-100) according to instructions from the validated manual (72). Univariate analysis for continuous variables were conducted with the Mann-Whitney *U* test for two groups or independent-samples Kruskal-Wallis test was used to compare three continuous variable groups. Chi-square test or Fisher's exact test was used for comparing categorical data. In paper IV, predictor variables with a $p<0.1$ on univariate analysis were included in multivariate analysis. Multiple linear and logistic regression analyses were preformed to identify parameters with a significant influence on abdominal wall symptoms and QoL.

Statistical analysis was performed using IBM SPSS Statistics version 22 and 25 (IBM, Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

Ethics

The studies in this thesis were conducted following the Declaration of Helsinki and were approved by The Regional Ethical Review Board in Lund.

Results

Main findings in paper I

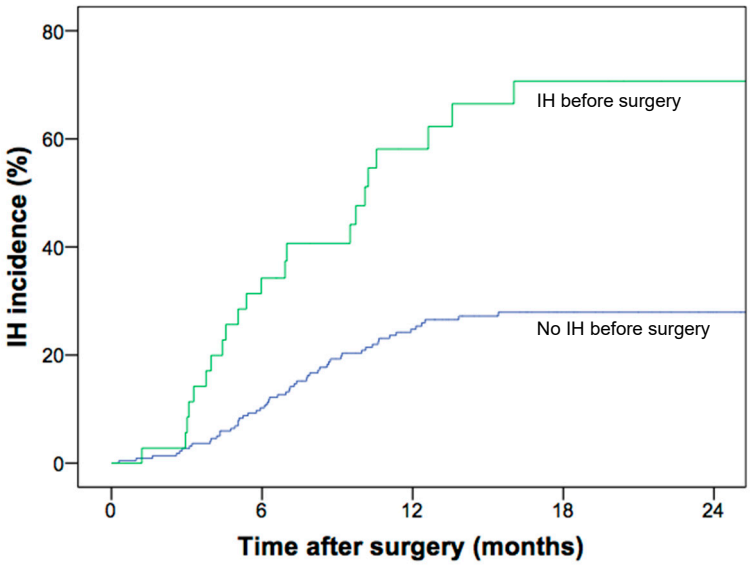
A total of 256 patients were analyzed in regard to IH. Seventy-eight patients (30%) developed IH. Kaplan-Meier analysis estimated the cumulative incidence of IH as high as 35% at 60 months. Patient characteristics for both groups with and without IHs are presented in table 2. The incisions used were extended right subcostal (198 patients, 77%), Mercedes (52 patients, 20%), and midline (3 patients, 1%). The median follow-up time was 13 (range 2-59) months. The site of IH was the midline alone in 66 patients (85%). However, it involved the midline together with mid-subcostal or lateral in eight patients (10%) and lateral subarcus in three patients (4%). Of the thirty-six patients who had an IH before current liver surgery, 24 had IH after colorectal resection, 12 had IH after previous liver resection, 23 of 36 developed IH after liver surgery (log-rank P <0.0001, figure 4). Preoperative chemotherapy was oxaliplatin-based in 75 (54%) patients and irinotecan-based in 34 (24%) patients. Twenty-four patients (17%) were treated with several chemotherapy regimens. Patients with prolonged preoperative chemotherapy (>6 cycles) were more likely to develop IH (log-rank P = 0.025, Figure 5). Eleven of 19 (58%) patients receiving preoperative bevacizumab developed IHs (log-rank P <0.0001, Figure 6). Eight of 23 patients with infection at the surgical site developed an IH without a statistical difference compared with patients without infection (log-rank P = 0.313). Obesity (BMI>30 kg/m^2) (n = 32) was found to have no effect on IH incidence (log-rank P = 0.340). Table 3, shows univariable and multivariable hazard ratio analysis of risk factors for the development of IHs.

In multivariable analysis, preoperative chemotherapy >6 cycles (hazard ratio 2.12, 95% confidence interval 1.14–3.94), preoperative bevacizumab (hazard ratio 3.63, 95% confidence interval 1.86–7.08) and IH from previous surgery (hazard ratio 3.50, 95% confidence interval 1.98–6.18) were found to be independent risk factors.

Table 2.
Patient characteristics for the two groups wiht and withought incisional hernia.

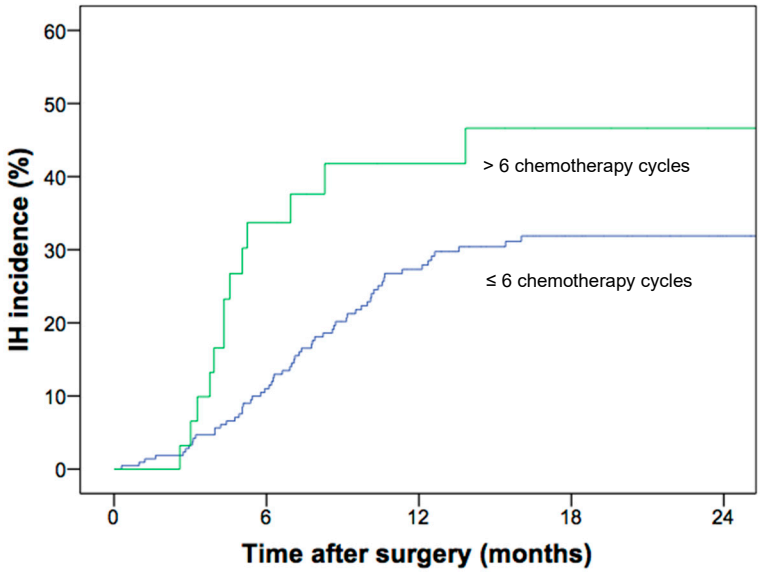
	Incisional hernia	No incisional hernia	*P*
Number of patients	78	178	-
Gender (male:female)	48:30	110:68	0.969
Age (years)	68 (37-82)	68 (35-85)	0.880
Current smoking	13	36	0.505
Diabetes mellitus	11	19	0.432
Body mass index (kg/m²)	26.0 (18.4-41.1)	25.0 (17.7-38.2)	0.076
Pre-operative chemotherapy	44	96	0.656
Number of chemotherapy cycles	5 (1-16)	5(1-13)	0.552
Pre-operative chemotherapy > 6 cycles	13	19	0.169
Pre-operative bevacizumab	11	8	0.009
Previous liver resection	15	18	0.045
Incisional hernia before surgery	23	13	<0.0001
ASA grade (1/2:3/4)	54:24	129:49	0.597
Preoperative albumin (g/l)	38 (25-46)	38 (24-47)	0.522
Preoperative creatinine (µmol/l)	73.5 (36-132)	73.0 (31-150)	0.645
Operating time (hours)	4.76 (1.0-9.8)	4.75 (1.1-13.0)	0.955
Operative bleeding (ml)	350 (25-2000)	300 (25-8000)	0.683
Incision type (J-shaped:Mercedes)	60:16	138:36	0.948
Major resection	26	68	0.457
Hospital stay (days)	7 (3-34)	7 (2-76)	0.804
Incisional surgical site infection	8	15	0.638
Remote infection	3	9	0.673
Morbidity (Clavien-Dindo ≥ 3)	9	18	0.732
Postoperative chemotherapy	45	104	0.774

Data are presented as number or median (range). ASA, American Society of Anesthesiologists.



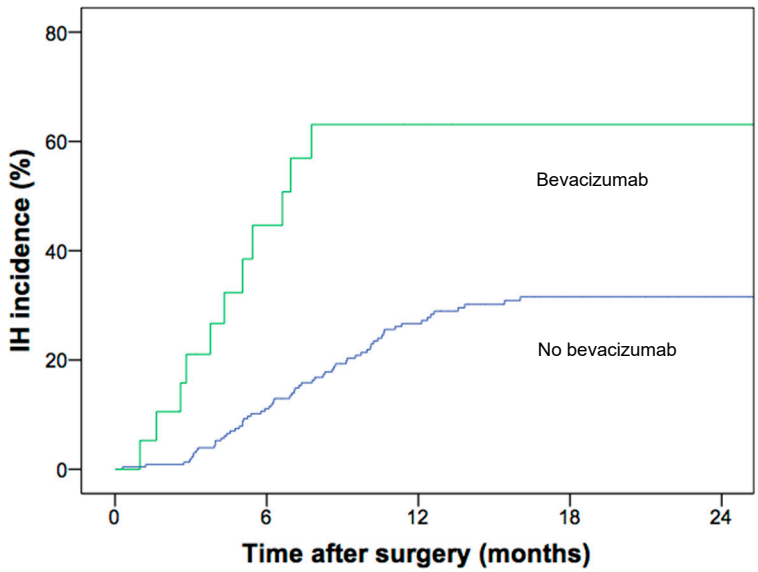
No. At risk:					
IH before surgery	36	24	17	14	14
No IH before surgery	220	198	170	165	165

Figure 4.
Kaplan–Meier plot of incisional hernia (IH) incidence for patients with IH before surgery and patients without IH before surgery. $P < 0.0001$ (log rank test).



No. At risk:					
> 6 cycles	32	22	20	19	19
≤ 6 cycles	213	190	159	152	152

Figure 5.
Kaplan–Meier plot of incisional hernia (IH) incidence for patients with more than 6 cycles of pre-operative chemotherapy and patients receiving 6 or less cycles of preoperative chemotherapy. P = 0.025 (log rank test).



No. At risk:					
Bevacizumab	19	11	8	8	8
No bevacizumab	230	205	174	166	166

Figure 6.
Kaplan–Meier plot of incisional hernia (IH) incidence for patients receiving pre-operative bevacizumab and patients not receiving pre-operative bevacizumab. P < 0.0001 (log rank test).

Table 3.
Cox proportional hazard analysis of risk factors for incisional hernia development

	Univariate		Multivariate	
Factor	**HR**	***P***	**HR**	***P***
Gender (male:female)	1.08 (0.68-1.71)	0.736		
Age > 70 years	1.20 (0.76-1.90)	0.438		
Current smoking	0.82 (0.45-1.49)	0.523		
Diabetes mellitus	1.23 (0.65-2.33)	0.519		
Body mass index > 26 kg/m²	1.55 (0.99-2.41)	0.054	1.51 (0.91-2.50)	0.111
Pre-operative chemotherapy	1.23 (0.78-1.93)	0.380		
Pre-operative chemotherapy > 6 cycles	1.96 (1.08-3.57)	0.028	2.12 (1.14-3.94)	0.017
Pre-operative bevacizumab	3.55 (1.85-6.69)	<0.0001	3.63 (1.86-7.08)	<0.0001
Previous liver resection	2.11 (1.20-3.71)	0.010	1.32 (0.71-2.48)	0.382
Incisional hernia before surgery	3.58 (2.20-5.84)	<0.0001	3.50 (1.98-6.18)	<0.0001
ASA grade (1/2:3/4)	1.17 (0.72-1.90)	0.517		
Incision type (J-shaped:Mercedes)	1.12 (0.66-1.90)	0.677		
Incisional surgical site infection	1.45 (0.70-3.02)	0.316		
Resection size (minor:major)	1.29 (0.81-2.07)	0.289		
Morbidity (Clavien-Dindo ≥ 3)	1.10 (0.55-2.20)	0.793		
Postoperative chemotherapy	0.87 (0.54-1.42)	0.583		

HR, hazard ratio; ASA, American Society of Anesthesiologists.

Main findings in paper II

A total of 284 patients who had undergone surgery for CRLM formed the base of this study population. Patient characteristics for the different groups with WHO PS 0-2 and >2 are showed in table 4. All patients were evaluated oncologically for assessment of PS and admission to adjuvant chemotherapy within 5-7 weeks after liver surgery. All patients were considered to have PS WHO 0–2 before liver surgery. Seventy-four patients (26%) presented with a postoperative PS WHO > 2 precluding administration of adjuvant chemotherapy. These patients had a shorter recurrence-free survival (P = 0.002) and shorter overall survival (P < 0.001). Multivariable analysis showed that patients with PS > 2 after surgery had higher preoperative ASA scores, had a higher frequency of major complications after surgery, and had more frequent synchronous liver and lung metastases. PS was found to be the strongest independent factor predicting survival (hazard ratio 0.45). The remaining 210 patients (74%) received chemotherapy as an adjuvant treatment alone or as part of the perioperative chemotherapy concept. Adjuvant chemotherapy was either oxaliplatin-based (n = 152), 5-fluorouracil alone (n = 36) or irinotecan-based (n = 15). Seven patients received a combination of two or more different chemotherapy regimens. Patients receiving adjuvant chemotherapy received a median of 7 (5–8) postoperative chemotherapy cycles. For patients with PS WHO 0–2 receiving adjuvant chemotherapy, the treatment was initiated 50 (42–64) days after surgery. The median follow-up after liver surgery was 33 months. In the group of patients with postoperative PS WHO 0-2 during follow-up, 116 of 210 (55%) patients developed a disease relapse. Due to poor PS, ten patients (9%) did not receive any tumour-specific treatment after relapse. Fifty-four of 74 (73%) patients in the group with postoperative PS WHO > 2 suffered from relapse. In this group, 11 of 54 patients (20%) did not receive tumour-specific treatment at recurrence due to poor PS with a $P = 0.032$ compared to the WHO 0–2 group. Kaplan-Meier estimates of recurrence-free and overall survival are shown in Figs 7 and 8. The Cox proportional hazard analysis results of the adverse risk factors for survival outcome are shown in Table 5.

Table 4.
Patient characteristics for patients with postoperative WHO performance status 0-2 vs. WHO performance status>2

	WHO Performance Status, 0-2 N=210	WHO Performance Status, >2 N=74	P-value
Male gender	125 (59.5%)	51 (68.9%)	0.152
Age (years)	68 (62-73)	68 (62-73)	0.224
Smoking	49 (23.3%)	10 (13.5%)	0.073
Diabetes mellitus	22 (10.5%)	9 (12.2%)	0.689
Body mass index (kg/m^2)	25 (23-28)	25 (23-27)	0.969
ASA grade 3-4	53 (25.2%)	31 (41.9%)	0.007
Preopeative albumin (g/l)	38 (35-40)	38 (35-40)	0.452
Preoperative creatinine (µmol/l)	73 (63-83)	80 (66-95)	0.052
Rectal primary	71 (35.5%)	25 (36.8%)	0.851
Primary T4	45 (24.7%)	12 (19.7%)	0.420
Node positive primary	116 (63.7%)	47 (77.1%)	0.056
Synchronous disease	116 (58.0%)	30 (44.1%)	0.047
Synchronous lung and liver metastases	11 (5.7%)	11 (16.4%)	0.006
Tumour size >50 mm	22 (10.5%)	8 (10.8%)	0.936
Preoperative chemotherapy	123 (58.6%)	41 (55.4%)	0.635
Preoperative chemotherapy cycles	5 (4-6)	4 (3-5)	0.600
Preoperative chemotherapy >6 cycles	16 (7.7%)	8 (10.8%)	0.416
Operation time (hours)	5 (3-6)	5 (3-7)	0.251
Operative bleeding (ml)	400 (200-600)	400 (200-900)	0.145
Major resection	94 (44.8%)	33 (44.6%)	0.980
Hospital stay (days)	7 (6-8)	7 (6-10)	0.214
Morbidity (Clavien-Dindo ≥3)	19 (9.0%)	16 (21.6%)	0.005

Data are presented as number (percentage) or median (interquartile range). *ASA*, American Society of Anesthesiologists

Table 5.
Cox proportional hazard analysis of risk factors for adverse survival outcome

Variable	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Male gender	1.38 (0.91-2.10)	0.125		
Age (years)	1.00 (0.98-1.0)	0.816		
Smoking	1.02 (0.63-1.67)	0.931		
Diabetes mellitus	0.99 (0.53-1.86)	0.986		
Body mass index (kg/m^2)	0.99 (0.94-1.05)	0.841		
ASA grade 3-4	1.40 (0.93-2.11)	0.111		
Rectal primary	1.24 (0.83-1.87)	0.292		
Primary T4	1.63 (0.99-2.67)	0.053	1.40 (0.84-2.34)	0.197
Node positive primary	1.70 (1.02-2.84)	0.041	1.42 (0.83-2.46)	0.203
Synchronous disease	1.62 (1.08-2.45)	0.021	1.77 (1.05-2.96)	0.031
Preoperative chemotherapy	1.72 (1.15-2.59)	0.009	1.25 (0.75-2.08)	0.394
Preoperative chemotherapy >6 cycles	1.57 (0.86-2.88)	0.142		
Major resection	1.16 (0.78-1.71)	0.461		
Tumour size >50 mm	0.93 (0.48-1.79)	0.826		
Morbidity (Clavien-Dindo ≥3)	1.68 (1.0-2.83)	0.051	1.38 (0.70-2.70)	0.352
WHO Performance Status, 0-2 vs >2	0.45 (0.30-0.68)	<0.001	0.52 (0.32-0.86)	0.010

HR, hazard ratio; ASA, American Society of Anesthesiologists

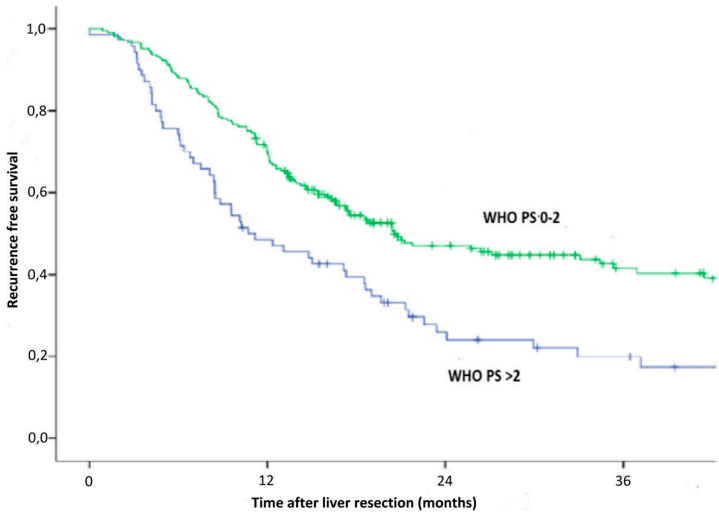


Figure 7.
Kaplan–Meier plot of reccurence-free survival P = 0.002, (log rank test). PS, performance status

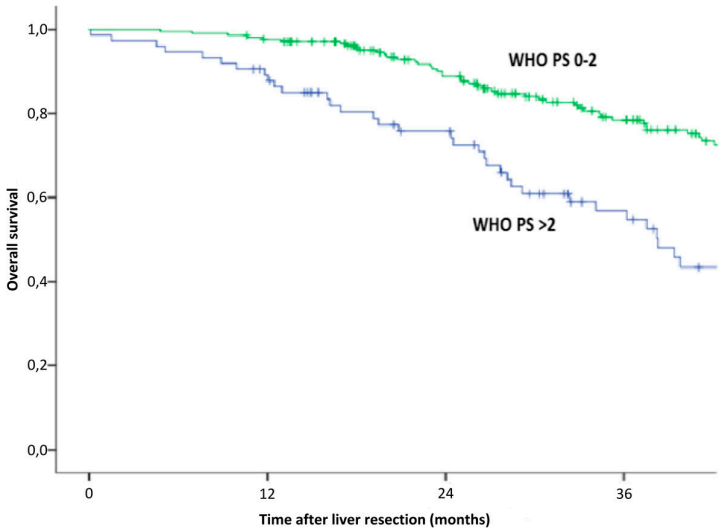


Figure 8.
Kaplan–Meier plot of overall survival P < 0.001, (log rank test). PS, performance status

Main findings in paper III

The response rate to the questionnaire was 75% (234 patients). Incorporating 45 patients undergoing the liver-first strategy, 81 patients undergoing the bowel-first strategy, and 108 patients operated for metachronous liver disease. Male sex, smoking, and rectal cancer were overrepresented in the liver-first group, and almost all patients (98%) received chemotherapy before liver surgery in this group. The bowel-first group enclosed more patients with advanced primary tumor stage T4. The patient characteristics are displayed in Table 6. Preoperative chemotherapy consisted of a variety of regimes, including 5-fluorouracil or capecitabine alone (n = 15), oxaliplatin-based (n = 82), irinotecan-based (n = 28), and a combination of irinotecan and oxaliplatin (n = 7). In the liver-first group, the oxaliplatin-based regimens were overrepresented. The distribution of the different chemo-regimes between the groups is displayed in Table 7. The time from bowel surgery of primary to liver resection was 5 (2-6) months in the bowel-first group and 18 (12-29) months in the metachronous group. Results from the EORTC QLQ-C30 self-assessment form for the different function and symptom scales for the groups' are displayed in Table 8. No differences in preoperative QoL between groups were observed regarding general health, physical function, and emotional function. However, the role function (P=0.014), social function (P=0.042), and cognitive function (P=0.019) were worse in the primary-first group and the fatigue scale better in the metachronous group (P=0.032).

Table 6.
Characteristics of resected patients cohort. Values in parentheses are percentages unless indicated otherwise: *values are median (interquartile range). ASA, American Society of Anesthesiologists; BMI, body mass index

Variable	N 234	Liver-first strategy N=45	Bowel-first strategy N=81	Metachronous disease N=108	P
Male gender	234	34 (76)	42 (52)	61 (57)	0.016
Age (years)	234	69 (60-71)	65 (59-71)	69 (64-74)	0.070
Smoking	234	13 (29)	21 (26)	15(14)	0.046
Diabetes Mellitus	234	3 (7)	11 (14)	15 (14)	0.430
BMI	234	26 (23-27)	25 (23-27)	25 (22-28)	0.430
ASA grade ≥3	234	15 (33)	22 (27)	33 (31)	0.754
Preoperative albumin (g/l)	224	36 (34-38)	37 (34-41)	37 (36-39)	<0.001
Preoperative creatinine (µmol/l)	228	74 (64-83)	68 (59-81)	81 (69-94)	0.003
Rectal primary	23	23 (55)	21 (27)	33 (32)	0.007
Primary T4	208	10 (24)	27 (38)	18 (19)	0.019
Synchronous lung and liver metastases	220	4 (9)	7 (9)	9 (9)	0.999
Largest liver tumor size >50 mm	232	8 (18)	9 (11)	7 (7)	0.099
Preoperative chemotherapy	232	43 (98)	60 (74)	44 (41)	<0.001
Preoperative chemotherapy cycles	138	5 (4-6)	5 (4-6)	5 (4-6)	0.487
Preoperative chemotherapy >6 cycles	141	6 (15)	7 (13)	8 (18)	0.730
Time from last chemo-therapy cycle to liver resection, days	133	42 (33-47)	40 (31-48)	35 (29-42)	0.505

Table 7.
Distribution of the different preoperative chemotherapy-regimens. Data expressed as numbers (percentages).

Preoperative chemotherapy	Liver-first strategy N=45	Bowel-first strategy N=81	Metachronous Disease N=108	P
5-FU/Capecitabine-based	4 (10)	6 (8)	5 (5)	0.564
Oxaliplatin-based	31 (74)	33 (45)	18 (18)	<0.001
Irinotecan-based	3 (7)	10 (14)	15 (15)	0.480
Irinotecan+oxaiplatin-based	3 (7)	3 (4.1)	1 (1)	0.122

Table 8.
Results from EORTC QLQ-C30 questionnaire for the different function and symptom scales for the different groups. Data expressed as numbers (percentage) or median and interquaritle range.

Variable Functional/Symptom Scale	N 234	Liver-first Strategy N=45	Bowel-first Strategy N=81	Metachronous Disease N=108	P
Global Health	233	75.0 (58.3-91.8)	79.2 (50.0-83.3)	75.0 (58.3-83.3)	0.827
Physical function	234	86.7 (71.7-100.0)	93.3 (66.7-100.0)	99.3 (80.0-100.0)	0.209
Role function	233	100.0 (66.7-100.0)	75.0 (45.8-100.00)	100.0 (70.8-100.0)	0.014
Emotional function	233	91.7 (75.0-100.0)	83.3 (66.67-91.7)	83.3 (75.00-91.7)	0.263
Cognitive function	234	100.00 (83.3-100.0)	83.33 (66.7-100.0)	100.0 (83.3-100.0)	0.019
Social function	230	91.7 (66.7-100.0)	83.3 (66.67-100.0)	100.0 (70.84-100.0)	0.042
Fatigue	234	33.3 (0.0-33.3)	33.3 (11.11-44.4)	22,2 (0.0-33.3)	0.032
Nausea & vomiting	234	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.399
Pain	234	0.00 (0.0-33.3)	0.00 (0.0-16.7)	0.00 (0.0-16.7)	0.175
Dyspnea	233	0.0 (0.0-33.3)	0.0 (0.0-33.3)	0.0 (0.0-33.3)	0.656
Sleep disturbance	234	16.7 (0.0-33.3)	16.7 (0.0-33.3)	33.3 (0.0-33.3)	0.593
Appetite loss	234	0.0 (0.0-0.0)	0.0 (0.0-33.3)	0.0 (0.0-0.0)	0.270
Constipation	232	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.094
Diarrhea	227	0.0 (0.0-33.3)	0.0 (0.0-33.3)	0.0 (0.0-33.3)	0.224
Financial difficulty	231	0.0 (0.0-8.3)	0.0 (0.00-33.3)	0.0 (0.0-0.0)	0.631

Main findings in paper IV

A total of 105/131 patients (80%) completed the questionnaires. Forty-three patients (42%) developed CT-detected IH over the study period. Patient characteristics and perioperative data for the IH and non-IH groups are shown in table 9. The majority of hernias (77%) measured up to 2.5 cm, six were 2.5-4.5 cm, and four were 4.5-5.5 cm. 37/43 patients (86%) had IH in the midline (30/43 above and 7/43 in/below the umbilicus). In addition, 6/43 patients (14%) the IH were located in the subarcus incision. At the time of evaluation, 90 patients (86%) had undergone other abdominal laparotomies in addition to current liver surgery. Eighty-five patients (81%) had midline incisions. Ten patients (10%) were re-resected in the liver, and three (3%) had scars after open cholecystectomy. Eighteen patients (17%) had two or more additional incisions beside current liver surgery, three patients (3%) had been re-operated for IH, and 9 patients (9%) had had an infection at the incision site during follow up. All-over, 49/105 patients (48%) reported at least one significant abdominal wall symptom, with no difference between the groups (IH 51% vs non-IH 45% P = 0.547). The prevalence and distribution of the different symptoms reported in VHPQ are shown in table 10. The distribution of different scales in the QoL QLQ C30 questionnaire is shown in Table 11. The results reveal no significant differences regarding abdominal wall symptoms and QoL between the IH and non-IH groups. However, almost half (48%) of all patients had abdominal wall symptoms after a median follow-up of 34 months. The strongest determinant of abdominal wall symptoms in terms of pain was two or more previous laparotomies in addition to the current liver surgery, as shown in tables 12-14. Pooling the results of the VHPQ concerning the level, duration and characteristics of pain showed the following:

Ninety-one (87%) patients no longer experienced pain from the scar after liver surgery. In these patients, the pain had ceased within one month after surgery in 54/91 (59 %). Furthermore, within 2-3 months in 24/91 (26 %), and within 4-6 months in 7/91 (8 %). Three patients had experienced pain relief after more than one year after surgery. Patients who were still experiencing pain from the incision site during the past week were asked to answer questions about the nature of the pain and whether it affected their daily lives. Ten patients responded, five of which described pain once a week, two patients had intermittent daily pain, and one patient had pain continuously.

Table 9. Characteristic of patients with IH and non-IH groups.

Categorical data expressed as numbers and percentage of positive responses in the different groups. Continues data expressed as number and IQR between the different groups, N= total number of responses in different variables.

Variable	Number of analyzed cases N 105	Incisional hernia N 43	No Incisional hernia N 62	P
Male gender	105	27 (61,4%)	35 (57,4%)	0.619
Age (years)	105	69(56-73)	62(55-74)	0.709
Smoking	105	9(20.5%)	15 (24.6%)	0.619
ASA grade ≥3	105	9 (20.5%)	16 (26.2%)	0.685
Diabetes mellitus	105	2 (4,5%)	9 (14.8%)	0.115
BMI	105	25.0 (24.5-27.7)	25.2 (22.5-27.3)	0.056
Preoperative albumin	105	36 (39-40)	35 (33-38)	0.706
Preoperative chemotherapy	105	21 (47,7%)	36 (59.0%)	0.252
Chemotherapy Cycles	55	5 (4-6)	5 (4-6)	0.439
Chemo Cycles > 6	55	4 (19.0%)	3 (8.8%)	0.408
Synchronous Liver+bowel	97	23 (53.5%)	30 (55.6%)	1.000
Synchronous Liver+lung	92	6 (15.4%)	1 (1.9%)	0.039
Primary Rectal	97	14 (32.6%)	18 (33.3)	0.936
Liver resection major	105	17 (38.6%)	30 (49.2%)	0.284
Operating time	105	3.50 (2.75-6.90)	6.25 (5.30-7.30)	0.386
Bleeding	104	500 (175-1100)	500 (300-700)	0.444
Incision infektion	104	4 (9.3%)	3 (4.9%)	0.444
Abdomen infection	104	0 (0%)	1 (1.6%)	1.000
Hospitalstay days	105	6 (5-8)	7 (6-9)	0.287
Clavien-Dindo≥3	105	7 (15.9%)	4 (6.6%)	0.195
Postoperative chemotherapy	104	27(61.4%)	52 (86.7%)	0.003
Reccurence	105	10 (22.7%)	11 (18.0%)	0.553
Median follow up time	105	33.23 (21.23.51.50)	23.67 (19.75-37.45)	0.216
Reoperation for IH/bleeding/dehiscence	105	2(4.7%)	1(1.6%)	0.566
IH before liver surgery	105	13(12.4%)	3(4.8%)	0.001
Two or more incisions beside current liver surgery	105	9/43(20.9%)	9/62(14,5%)	0.391

Table 10. Distribution of abdominal wall symptoms between IH and non-IH Groups.

Variable Clinically Significant symptoms	Number of analyzed cases 103	Incisional hernia 41	No incisional hernia 62	P
Any significant symptom	103	21 (51.2%)	28 (45.2%)	0.547
Pain right now-not easily ignored	100	12 (29.3%)	13 (22.0%)	0.411
Pain last week-not easily ignored	100	11 (26.8%)	15 (25.4%)	0.875
Scar cosmetically disturbing	102	9 (22.5%)	7 (11.3%)	0.129
Scar socially limiting	102	4 (10.0%)	5 (8.1%)	0.737
Abdominal wall stiffness	101	12 (30.0%)	15 (24.6%)	0.602

Table 11. Distribution of QLQ C 30 variables between the groups.

Variable Quality of life (QoL)	Number of analyzed cases 105	Incisional hernia 43	No Incisional hernia 62	P
Global quality of life	104	75.0 (50.0-93.8)	83.3 (66.7-100.0)	0.131
Physical funcion	105	90.0 (60.0-100.00)	93.3 (73.3-100.0)	0.346
Role function	105	100 (66.7-100.0)	100 (66.7-100.0)	0.960
Cognitive function	105	83.3 (83.3-100.0)	83.3 (79.2-100.0)	0.466
Emotional function	105	91.7 (75.0-100.0)	91.7 (72.9-100.0)	0.902
Social function	105	91.7 (66.7-100.0)	100 (66.7-100.0)	0.355
Fatigue	104	33.3 (8.3-44.4)	33.3 (11.1-33.3)	0.790
Nausea and vomiting	104	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.559
Pain	104	0.0 (0.0-16.7)	0.0 (0.0-16.7)	0.704
Dyspnea	104	33.3 (0.0-33.3)	16.7 (0.0-33.3)	0.994
Sleep disturbance	104	16.7 (0.0-33.3)	0.0 (0.0-33.3)	0.381
Appetite loss	105	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.968
Constipation	104	0.0 (0.0-33.3)	0.0 (0.0-33.3)	0.740
Diarrhea	104	0.0 (0.0-33.3)	0.0 (0.0-0.0)	0.149
Financial impact	103	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.674

Table 12. VHPQ, Pain right here right now not easy ignored.
Multivariate logistic regression for predictor variables with p <0.1 on Univariate analysis.

Pain right here right now - not easily ignored	OR	(95% CI)	P
Synchronous liver and bowel disease	2.211	0.742-6.588	0.154
Synchronous liver and lung disease	5.063	0.789-32.494	0.087
Two or more open abdominal incisions beside current liver surgery	4.166	1.168-14.858	0.028

Table 13. VHPQ, pain last week not easy ignored.
Multivariate logistic regression for predictor variables with p <0.1 on Univariate analysis.

Pain last week - not easily ignored	OR	(95% CI)	P
Synchronous liver and lung disease	6.404	0.456-89.865	0.168
Two or more open abdominal incisions beside current liver surgery	10.740	2.443-47.209	0.002
Recurrence of disease	0.046	0.004-0.590	0.018
Primary rectum	0.510	0.143-0.143	0.299

Table 14. EORTC QLQ C-30, symptom of pain.
Multiple linear regression for predictor variables with p <0.1 on Univariate analysis.

Pain	rc	(95% CI)	P
Lungmets synchronous with Livermets	14.580	(-30.275/3.038)	0.085
Major resection	-5.674	(-14.151/2.803)	0.187
Two or more open abdominal incisions beside current liver surgery	12.572	(0.921/24.223)	0.035

General discussion

The results displayed below will contribute to a better understanding of perioperative components after liver resection for CRLM, emphasizing the QoL for different surgical strategies, analysis of hernia issues after liver surgery, and the importance of postoperative PS.

Aspects of preoperative QoL and poor PS after surgery

As previously described in the background of this thesis, the modern treatment of CRLM combines perioperative chemotherapy with various surgical options. However, there are no clear survival advantages between the different surgical strategies. Furthermore, there is lack of knowledge regarding the preoperative QoL, importance of postoperative PS and the completion of intended oncological treatment. These issues are addressed in papers II and III.

In Paper III, we found that the patients in the liver-first group in no dimension had reduced preoperative QoL compared to patients in the bowel-first group and corresponding OoL with the metachronous group. Nearly all patients (98%) in the liver-first group were given chemotherapy preoperatively compared to 74% in the bowel-first group and 41% in the metachronous group. However, no evident adverse effect on preoperative QoL by chemotherapy could be demonstrated.

Neoadjuvant capecitabine concomitant with radiotherapy has been demonstrated to result in a temporary decline in QoL and return to baseline one month after treatment in rectal cancer (111). In Paper III, the median time between the last cycle of preoperative chemotherapy and liver resection in the liver-first group was 42 (33-47) days. The most severe impact on QoL after neoadjuvant chemo-radiotherapy for rectal cancer is demonstrated after surgery of the primary tumour. However, most domains and symptoms return to baseline levels by 12-18 months (112, 113).

A lower preoperative QoL correlates with reduced long-term survival for patients resected for CRLM (114). The levels of QoL estimated in paper III, using EORTC-QLQ-C30, are comparable to previous studies (114, 115). However, the patients in paper III received different chemotherapy regimens before the intended liver surgery. Another randomized study demonstrated that prehabilitation improved preoperative QoL (116). In this trial, a four-week supervised exercise program showed improved QoL regarding overall and mental health, besides better oxygen

uptake. In paper II, 26% of patients operated on for CRLM presented a poor postoperative PS, precluding chemotherapy administration postoperatively. These patients had reduced overall and recurrence-free survival. In addition poor PS was the most prominent adverse survival factor, which is in accordance with previous findings (90). In paper II, patients presenting with PS WHO > 2 after surgery had higher preoperative ASA scores as an expression of significant medical comorbidity and had more often synchronous liver and lung metastases, indicating more advanced disease. In addition, this patient group was also more affected by severe complications postoperatively (Clavien-Dindo ≥ 3). The change in PS is consequently a result of preoperative patient characteristics and adverse events after surgery. This finding aligns with previous studies (18, 88, 89) showing that 13–37% of patients did not receive adjuvant chemotherapy due to postoperative morbidity, which has formerly been demonstrated to reduce the ability to tolerate chemotherapy in the adjuvant setting (88).

In paper III, patients with metachronous metastases had less fatigue preoperatively Patients in this group underwent bowel surgery 18 (12-29) months before liver surgery and had time to recover and overcome the symptoms of fatigue. This finding is in line with a previous study (113), where patients with rectal cancer showed higher fatigue scores after neoadjuvant treatment and surgery. The fatigue scores began to decrease within one month and almost reached the baseline 10 months after bowel surgery.

In order to improve postoperative recovery, a fast-track protocol was introduced at in our institution in 2012. The protocol has shortened the duration of stay in the hospital without affecting morbidity (110), In addition, enhanced recovery protocols have demonstrated decreased morbidity (117). With the increasing use of laparoscopic liver resection postoperative morbidity can be expected to be further reduced (88, 118). However, the effect on postoperative PS and the ability to tolerate adjuvant chemotherapy remains to be shown. In paper II, adjuvant chemotherapy was started in the median seven weeks after liver surgery which is inside the recommended time frame of eight weeks having been established for resection of primary CRC (119), although corresponding evidence is lacking for an optimal treatment window after surgery for metastases.

Many patients in both WHO 0–1 and WHO > 2 groups experienced a relapse. A significant majority of patients in the WHO 0–2 group with recurrence were given tumour-specific treatment. In the WHO > 2 group, 54 of 74 (73%) patients developed recurrent disease. Also, most patients (80%) received tumour-specific treatment in this group. These results also suggest that if postoperative complications are reduced, patients who initially showed poor PS after surgery could improve their PS and receive the intended adjuvant chemotherapy. Furthermore, a later evaluation of PS postoperatively may increase the number of patients who could receive postoperative chemotherapy. Additional studies are

needed to examine the optimal time window for adjuvant chemotherapy after resection for CRLM.

Even though widely used, the role of adjuvant chemotherapy is still not established. In paper II, patients who presented with poor postoperative PS not receiving chemotherapy after liver resection had reduced both recurrence-free and overall survival. Although adjuvant chemotherapy correlates with a tendency to better survival, as reported in two randomized trials (49, 50), pooled data from both trials (51) support the hypothesis that adjuvant chemotherapy correlates with a more prolonged progression-free and longer overall survival. Furthermore, a large trial (52) comparing surgery of CRLM with and without adjuvant chemotherapy demonstrated that adjuvant chemotherapy prolongs postoperative survival. In addition, liver resection and perioperative chemotherapy have been shown to increase disease-free survival significantly compared with surgery alone (18). However, no difference in overall survival could be shown (19). In paper II, the decline in recurrence-free survival and overall survival in patients with poor postoperative PS who did not receive adjuvant chemotherapy may be explained by patient selection. These patients suffered from pronounced medical comorbidity and more advanced disease such as synchronous lung metastases.

Furthermore, it is well recognized that PS is a significant prognostic factor for survival in patients with metastatic CRC (91). In addition, there is also evidence that patients with good PS are the ones who benefit most from adjuvant chemotherapy after surgery of colorectal metastases (120). In addition, postoperative complications after surgery of CRLM have been correlated with poor overall and recurrence-free survival and postponed the initiation of chemotherapy (89). Hence, it seems essential to decrease postoperative complications, which could be accomplished by implementing enhanced recovery programs and switching to more minimally invasive surgical techniques.

Aspects of incisional hernia: incidence and clinical importance

In this thesis, we include patients with CRLM only. An IH incidence of 30% - 43% was detected even if the abdominal wall closure was performed in two layers with a continuous, slowly resorbable monofilament suture following existing evidence of preventing IH (102). The difference between paper I and paper IV could be explained by a different median follow-up period of 13 and 33 months, respectively. As previously shown, 75% of all IHs develop after 2 years and about 90% after 5 years (121). The incidence of IH is higher than previously reported (93, 97) which could also be attributed to the use of CT as a detection method (96).

Previous trials have demonstrated an IH incidence of 31% when using CT as a hernia detection method both after resection of hepatocellular carcinoma (98) and colorectal resection (122). Due to the high incidence of IHs, a prophylactic mesh

has been used in midline incisions with promising outcomes regarding efficacy (122) and safety (123). However, no trials of prophylactic mesh use have been performed for subcostal incisions after liver surgery.

In paper I, prolonged preoperative chemotherapy with more than 6 cycles was strongly correlated with an increased incidence of incisional hernia. This finding is in line with existing data (95) identifying preoperative chemotherapy as a risk factor for IH. In paper I, chemotherapy, when used in a neoadjuvant setting for colorectal metastases, was usually limited to 6 cycles (18), with negligible impact on the incidence of IH. In addition, postoperative chemotherapy did not increase the incidence of hernias.

Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factors associated with insufficient wound healing (124). Although not before demonstrated as a risk factor for IHs, this relationship could be confirmed in paper I. Furthermore, the use of bevacizumab was shown to be the most influential independent risk factor for IHs. However, these findings must be confirmed with further studies because of paper I's small number of patients treated with Bevacizumab.

In paper I and IV, IH prior to liver resection was associated with increased risk of additional IH. In paper I, most of these patients had an IH after previous colorectal surgery. Kaplan-Meier estimation for IH incidence at 60 months was as high as 78%, specifying a formerly undescribed high-risk group.

The majority of IHs found in both paper I and IV appeared in the midline of the cranial extension of the subcostal incision, following existing proof that midline incisions are more predisposed to incisional hernias than transverse incisions (102). To decrease the occurrence of incisional hernias, a logical conclusion of this result would be to diminish or stop using this extension whenever feasible.

Another known predisposing factor for IH is surgical site infection (95) but this could not be demonstrated in neither paper I nor IV. However, the number of patients diagnosed with infections may have been too small to detect this association. Furthermore, data on this issue were obtained retrospectively with a risk of underestimating the prevalence of subcutaneous infections.

Paper IV reported abdominal wall symptoms and QoL for patients resected for CRLM. No significant differences between the IH and non-IH groups could not be demonstrated. Similarly, a previous study addressing abdominal wall symptoms in patients treated for the open abdomen (106) revealed no differences in scores between patients with and without IH at five years of follow-up. However, our results contrast with some other published data (125-127), which showed deterioration of the QoL and body image. The dissimilarities might be attributed to different detection methods of IH and patient selection. The first study (125), one of few existing studies investigating the effect of IH on QoL on patients who have

not yet been assigned for hernia repair, demonstrated that the presence of IH has a substantial impact on the QoL and body image. Patients in that study underwent a physical assessment to detect IH compared to paper IV, where all IHs were detected on CT. In addition, radiological imaging has been demonstrated to reveal more hernias than clinical assessment (96). The second study (126) demonstrated that all health-related domains for patients with IH were remarkably lower than the healthy control group. However, this group of patients has already been assigned for hernia repair, and therefore, it is reasonable that patients in this group had more prominent symptoms from the start. Finally, the latest study (127), showed that incisional hernia was predictive of lower QoL and mental health scores. IHs were detected clinically with questionnaires and subsequent telephone interviews in the latter study. These findings are in line with results in paper IV, showing no clear correlation between IH and abdominal wall symptoms, indicating that IH detected on CT alone is of minor clinical importance, which must be considered when selecting patients for hernia repair.

The majority of IH were small (<2.5 cm), only four hernias were measured as large as around 5 cm. However, the correlation between the size of the hernia and clinical symptoms has not been addressed in this thesis. Therefore, further studies are warranted to shed light on this topic.

In paper IV, the significant predictor of pain was the number of performed laparotomies. Patients with two or more open surgical incisions besides the current liver surgery experienced more pain symptoms. This finding could be demonstrated with multivariate analysis of both QoL EORTC QLQ C30 and the VHPQ form. These results are in accordance with previous findings where three or more abdominal procedures predisposed to gastrointestinal disorders and abdominal pain 6 months after open surgery (128).

Aspects of methodology

Randomized controlled trials (RCTs) usually are considered the highest scientific evidence level among study designs. The rationale is that they provide better conditions for controlling for factors that are irrelevant to the intervention itself. However, RCTs are designed to analyze one factor in a homogeneous group of patients and may differ from clinical reality and limit study outcomes' generalisability, which must be kept in mind when interpreting the causal effects (129). In addition, not all questions are suitable for RCT studies as it is not possible or not considered ethically justifiable to actively expose patients to risks of developing a disease or even causing death. In these cases, observational studies are preferable. Observational studies can be conducted in different ways, and are divided into prospective cohort studies, retrospective case-control, and cross-sectional studies.

Controlled-cohort prospective studies compare a group that has received treatment or been exposed to risk with a group that has received alternative or no treatment or has not been exposed to risk. The individuals are followed over time prospectively. A disadvantage of prospective cohort studies is that the investigations can be expensive and challenging to research rare conditions or when it takes long before the outcome can be measured. Large study populations and long follow-up times are then required. Case-control retrospective studies can then be a more appropriate and cost-effective option (130).

In case-control retrospective studies, individuals affected by the outcome (illness or death) are first looked up and compared with individuals who have not been affected by this outcome in the control group. Then it is examined whether the groups differ in risk factors or their treatment. Therefore, cases and controls must represent the same study base, and the selection of controls must be strictly independent of any exposure to the treatment (130).

Usually, data have been extracted retrospectively by interviews of cases and controls or with the help of patient records or registration data. The problem with interviews is that patients do not always remember everything that happened earlier in life. The data collection is also dependent on the documentation in the patient record, which may be deficient.

Practical and economic aspects are central in choosing between case-control or cohort studies. Cohort studies can often address many different hypotheses, while case-control studies are often more effective than other study approaches in the case of unusual outcomes.

Cross-sectional studies measure conditions at one time or occasion. It is an excellent way to analyze the prevalence of different conditions and the correlation between different exposures and conditions, especially estimating the presence of conditions that are not always easy to estimate based on registry data. Unfortunately, cross-sectional studies have often difficulty estimating time and the causal relationship between intervention/exposure and outcome (130).

All studies in this thesis were observational. Papers I and II had a retrospective design. Paper III cross-sectional and Paper IV where data prospectively enrolled. The study in paper IV had a relatively small sample size. Consequently, there was a limiting precision of estimate and statistical power. However, the most challenging method problem to deal with in observational studies compared to randomized controlled trials is matching all potentially factors that may affect the outcome.

Selection bias

A selection bias is when a study group is not randomly selected from the target population. To minimize selection bias in paper I and paper II, patients were included consecutively. Almost all patients were included. In papers III and IV the

response rate were 75% and 80%, respectively. Missing data reduces the representativeness of the study sample and the statistical power. At a response rate <70%, the dropout affects the reliability so that the study has no information value (130). In Paper III, forms were collected with the help of nurses during outpatient visits exclusively before surgery to reduce selection bias. While, in paper IV, patients received reminder letters on two occasions if questionnaires were not filled out. The missing data in QLQ C-30 questionnaires were handled according to instructions from the validated manual.

Confounders

A confounder is a factor that incorrectly indicates a casual association. Randomization and matching are strategies to address confounding, but confounders can also be handled statistically. In papers I and II, we used multiple Cox regression models to control confounders. In paper IV, logistic and linear multiple regression analyses were performed depending on the outcome variable.

Paper I

STRENGTHS	LIMITATIONS	KEY ASSUMPTIONS
One large Swedish liver center. Descriptive and comparative study. Patients with CRLM only. A reasonably large number of patients. All consecutive patients included.	Retrospective data collection. Non-randomized. A limited number of patients treated with bevacizumab.	IH is common after liver sugery. IH is often located in midline alone. Prolonged chemotherapy and bevacizumab, in particular, are risk factors for developing IH.

Paper II

STRENGTHS	LIMITATIONS	KEY ASSUMPTIONS
One large Swedish liver center. Descriptive and comparative. Patients with CRLM only. All consecutive patients were considered for inclusion. A reasonably large number of patients. Patients with liver re-resections were excluded.	Retrospective data collection. Non-randomized. Groups are not equal. Confounding factors: Poor PS or failure to get intended adjuvant treatment causes shorter survival.	Patients with postoperative PS >2 fail to get intended adjuvant chemotherapy and have shorter survival.

Paper III

STRENGTHS	LIMITATIONS	KEY ASSUMPTIONS
One large Swedish liver center. A reasonably large number of patients.	Non-randomized. The cross-sectional design makes it difficult to establish causality. Selection bias: only 75 % of patients returned questionnaires. Realtively small study population No control group. No postoperative follow-up data. The medical charts were reviewed retrospectively.	QoL does not differ beween liver-first, bowel-first, and metachronous groups.

Paper IV

STRENGTHS	LIMITATIONS	KEY ASSUMPTIONS
One large Swedish liver center. Descriptive and comparative. Patients prospectively included.	Non-randomized. Selection bias: only 80% of patients returned the questionnaires. No control group. Relatively small sample size. Confounders: changes in QoL and AW symptoms could be attriubted to either liver surgery or other laparotomies.	Small IH after liver surgery, detected on CT is of little clinical importance.

Conclusions

- Prolonged preoperative chemotherapy and preoperative bevacizumab were significant determinants of developing an IH. The hernia site location was almost exclusively in the midline.
- Patients with PS > 2 postoperatively who did not get adjuvant chemotherapy had decreased recurrence-free and overall survival after resection for CRLM. However, many of these patients had regained better PS after recurrence, allowing the administration of tumor-specific treatment.
- Patients in the liver-first group had similar preoperative QoL as the other groups. The choice of strategy for resection of synchronous CRLM was not predicted by the preoperative QoL.
- Radiologically detected IH after open liver surgery has limited clinical importance. Although, nearly half of all liver resected patients experienced abdominal wall symptoms not related to IH.

Future perspectives

Postoperative PS is a decisive prognostic factor for survival which could be improved by introducing enhanced recovery programs and shifting into more minimally invasive surgical techniques. Minimally invasive techniques have been found to reduce postoperative complications, as shown in the first RCT study comparing open versus laparoscopic liver resection for CRLM (37). In addition, laparoscopic approach also reduced the number of IH compared to open surgery (99). However, the evidence for minimally invasive liver resections should be enhanced through randomized multicenter studies and multicenter national registers such as the well-established validated SweLiv registry in Sweden and multinational registry like E - MILS registry (131). E-MILS Registry (The European Registry of Minimally Invasive liver Surgery) was established in 2015 and is a multicenter registry to collect patient data from all liver centers across Europe to collaborate in improving patients' outcomes and plan future research studies. However, the international E-MILS registry is yet to be validated. The national and international registries that collect data regarding both surgery and medical oncological treatment prospectively will be valuable in increasing knowledge in the future.

To better analyze QoL before and after liver surgery for patients with the synchronous disease, controlled-cohort prospective national studies of QoL are needed to clarify both short- and long-term effects concerning surgical and medical cancer treatment. Such a study is currently in progress. Also, a study to validate the Swedish version of the liver-specific quality of life EORTC QLQ-LMC21 questionnaire has been initiated.

Populärvetenskaplig sammanfattning på svenska

Cancer är en vanligt förekommande sjukdom i samhället. De flesta känner någon som har eller har haft cancer. Cancerbehandlingen har förbättrats under de senaste decenierna och kan erbjuda bättre överlevnadsmöjligheter till allt fler patienter. Tjock- och ändtarmscancer drabbar drygt 6 000 personer i Sverige årligen och är den tredje vanligaste cancerformen. Hälften av patienterna kommer att utveckla dottertumörer, det vill säga metastaser till levern, någon gång under sjukdomen. Hos ungefär en av fem patienter har sjukdomen redan vid diagnosen spridit sig till levern. Den bästa tillgängliga behandlingen är att om möjligt avlägsna tumörbördan kirurgiskt.

Levermetastaser som uppstår efter att tarmtumören är bortopererad kan åtgärdas kirurgiskt omgående. Levermetastaser som upptäcks samtidigt som tarmcancer kan behandlas enligt olika strategier. Den traditionella strategin innefattar operation av tarmtumören före tumörbördan i levern. Den andra strategin är att operera bort tumörbördan i levern och därefter tarmtumören. Alla kirurgiska strategier kombineras med cellgiftsbehandling. Det finns ingen tydligt fördel i överlevnad mellan de olika strategierna. Tidigare studier har visat att patienter med bättre livskvalitet (QoL) före operationen återhämta sig bättre efter kirurgi. Därför är det viktigt att bedöma patientens livskvalitet innan operation för att välja den mest lämpliga behandlingsstrategin.

Ärrbråck, det vill säga en läkningsdefekt i bukväggen på platsen för tidigare operationssärr, är en av de vanligaste komplikationerna efter kirurgi. Förekomsten av ärrbråck är varierar mycket beroende på underliggande sjukdom, vilken typ av snittförning som används, uppföljningstiden och metoden för att upptäcka bråck. Hittills har förekomsten av ärrbråck efter leverkirurgi endast studerats i mycket begränsad omfattning. Även om leverkirurgi med titthålsteknik är möjlig och ofta används, är öppen kirurgi fortfarande den vanligaste kirurgiska metoden. Cellgiftsbehandling har också visat sig vara en riskfaktor för utveckling av ärrbråck. Medicinsk bilddiagnostik med datortomografi (CT) ökar förmågan att upptäcka ärrbråck jämfört med fysiskt undersökning, därför föreslås CT undersökning har som "gyllene standarden". Betydelsen av bråck som identifierats med datortomografi är för närvarande okänd.

Livskvalitetsstudier (QoL) av patienter som opererades för metastaser från ändtarms- och tjocktarmscancer i levern visade en försämring av livskvaliteten efter operationen och en återgång till utgångsvärdena, det vill säga den ursprungliga livskvaliteten, inom tre månader. Med ökad överlevnad över tid och utvecklingen av miniinvasiva kirurgiska tekniker är det viktigt att förstå det naturliga förloppet av bukväggssymtom efter öppen leverkirurgi och belysa ärrbråcksproblematiken.

Patienter som inte får cellgiftsbehandling efter kirurgi på grund av låg prestationsstatus (PS) efter leveroperationen har visat sig ha en försämrad överlevnad. PS är ett poängsystem som uppskattar effekten av sjukdom på en patients välbefinnande. Det är också känt för att vara en av de viktigaste överlevnadsfaktorerna hos patienter med spridd änd- och tjocktarmscancer (CRC). Därför är det viktigt att analysera faktorer förknippade med dålig PS för att förbättra utfallet efter leverkirurgi.

Delarbete I, är en retrospektiv kohortstudie där vi inkluderade 256 patienter som opererades för levermetastaser med öppen teknik mellan 2010 och 2013 vid Skånes Universitetssjukhus i Lund. Vi har funnit att ärrbråck är mycket vanligt efter leverkirurgi (30.5%), vilket är nytt kunskap. Ärrbråcken var lokaliserade i de flesta av fallen i medellinjen. Dessa ärrbråck upptäcktes med datortomografi (CT) som utförds som en del av uppföljningsprogrammet efter kirurgi. I studien kunde vi också för första gången påvisa ett samband mellan ett bråck och bevacizumab – en antikropp som används vid preoperativ kemoterapi av levermetastaser. Långvarig kemoterapi med mer än sex cykler var också en riskfaktor för utveckling av ärrbråck.

Delarbete IV som är enkätstudie där vi inkluderade 105 patienter som under 2010-2015 genomgått levermetastasoperation vid Skånes universitetssjukhus i Lund, som levde i februari 2017. Dessa patienter fick två frågeformulär. Ett validerat frågeformulär för främre bukvägg - ventral hernia pain quiestinnaire (VHPQ) och EORTC QLQC30 livskvalitetformulär. Studien jämförde om patienter med och utan ärrbråck skilde sig åt i smärtupplevelse i medeltal 3 år efter kirurgi. Det visade sig att förekomsten av ärrbråck inte påverkar patienternas livskvalitet, men att ett stort antal av dem hade betydande problem med bukväggen oavsett av ärrbråcksutvecklingen. Det är möjligt att minimalinvasiv kirurgi kan minimera dessa symtom, vilket måste påvisas med ytterligare forskning.

Delarbete II är en retrospektiv kohortstudie av 284 patienter som opererades för levermetastaser mellan 2010 och 2015 vid Skåne Universitetssjukhus i Lund. I studien undersökte vi hur många av dem som inte återhämtade sig tillräckligt bra efter kirurgin för att erhålla cellgiftsbehandling som tilläggsterapi. Det visade sig att 26% av patienterna inte fick cellgiftsbehandling på grund av deras dåliga allmäntillstånd (perfomence status PS >2). Ökad dödlighet kunde observeras hos dessa patienter. De flesta av dessa patienter återfick dock ett gott allmäntillstånd vid tidpunkten för senare återfall av sjukdomen och kunde erhålla palliativ

cellgiftsbehandling. Resultaten visar att sjukvården bör sträva efter att minimera kirurgiska komplikationer så att patienter kan återhämta sig för att kunna ta emot onkologisk behandling efter kirurgin. Miniinvasiv kirurgi kan även här övervägas för att minska kirurgiskt trauma och därmed öka patienternas tillgänglighet för postoperativ cellgiftsbehandling. Detta behöver studeras vidare.

Delarbete III är en tvärsnittsstudie av patienter som genomgick leverkirurgi för metastaser från änd- och tjocktarms cancer vid Skånes Universitetssjukhus i Lund från januari 2011 till augusti 2016. Datainsamlingsmetoden var ett validerat frågeformulär för att mäta livskvalitet QoL (EORTC QLQ-C30) som delades ut till patienter 3-4 veckor före operationen. Studien omfattade 234 patienter. Deras livskvalitet utvärderades i samband med leverkirurgi, och jämförde preoperativ livskvalitet för patienter med samtidigt diagnostiserad cancer i tarm och lever. Här jämförde vi de olika kirurgiska strategier där levern opererades först och sedan tarmen, eller tarmen opererades före levern. I detta delarbete kunde vi inte visa någon skillnad i patienters livskvalitet oavsett vald strategi. Patienternas livskvalitet skiljde sig inte heller från dem som tidigare genomgått tarmoperation för cancer och utvecklat levermetastaser i ett senare skede. Resultaten tyder på att den erbjudna strategin har liten betydelse när det gäller dess inverkan på patienternas livskvalitet.

Streszczenie w języku polskim

Rak (nowotwór złośliwy) jest powszechną chorobą w społeczeństwie. Większość ludzi zna kogoś, kto ma lub miał raka. Leczenie raka poprawiło się w ostatnich dziesięcioleciach i jest w stanie zaoferować lepsze szanse przeżycia coraz większej liczbie pacjentów. Rak odbytnicy i jelita grubego dotyka co roku nieco ponad 6000 osób w Szwecji i jest trzecią najczęstszą postacią raka. U połowy pacjentów w pewnym okresie choroby rozwiną się nowotwory potomne, czyli przerzuty do wątroby. U około jednego na pięciu pacjentów choroba już w momencie rozpoznania rozprzestrzeniła się na wątrobę. Najlepszym dostępnym leczeniem jest chirurgiczne usunięcie nowotworu, jeśli to możliwe.

Przerzuty w wątrobie, które pojawiają się po usunięciu guza jelita, można natychmiast poddać leczeniu chirurgicznemu. Przerzuty do wątroby wykryte w tym samym czasie co rak jelita można leczyć według różnych strategii. Tradycyjna metoda polega na operacji guza jelitowego przed operacją przerzutów w wątrobie. Drugą metodą jest operacja guza wątroby, a następnie guza jelita. Wszystkie strategie chirurgiczne są połączone z chemioterapią. Nie ma wyraźnej przewagi jednej z metod jeśli chodzi o wpływ na przeżywalność pacjentów. Wcześniejsze badania wykazały, że pacjenci z lepszą jakością życia (QoL) przed operacją mają większe szanse na dobry powrót do zdrowia po operacji. Dlatego ważne jest, aby przed operacją ocenić jakość życia pacjenta, aby wybrać najwłaściwszą strategię leczenia.

Jednym z najczęstszych powikłań pooperacyjnych jest przepuklina pooperacyjna, czyli defekt gojenia się ściany jamy brzusznej w miejscu blizn po przebytych zabiegach chirurgicznych. Częstość występowania przepukliny jest bardzo zróżnicowana w zależności od choroby podstawowej, rodzaju zastosowanego nacięcia, czasu obserwacji i metody wykrywania przepukliny. Do tej pory częstość występowania przepuklin pooperacyjnych w bliźnie po operacjach wątroby była badana tylko w bardzo ograniczonym zakresie. Chociaż chirurgia wątroby z techniką laparoskopową jest możliwa i często stosowana, chirurgia otwarta jest nadal najczęstszą metodą chirurgiczną. Wykazano również, że chemioterapia jest czynnikiem ryzyka rozwoju blizn. Medyczna diagnostyka obrazowa za pomocą tomografii komputerowej (CT) zwiększa zdolność wykrywania przepuklin pooperacyjnych w porównaniu badaniem fizykalnym, dlatego też badanie CT jest sugerowana jako „złoty standard". Znaczenie przepuklin stwierdzanych na podstawie badania tomografii komputerowej jest obecnie nieznane.

Badania jakości życia (QoL) pacjentów, którzy przeszli operację z powodu przerzutów raka odbytnicy i okrężnicy do wątroby, wykazały pogorszenie jakości życia po operacji i powrót do wartości wyjściowych, tj. pierwotnego poziomu jakości życia, w ciągu trzech miesięcy.

Wraz ze wzrostem przeżywalności pacjentów w ostatnim czasie i rozwojem małoinwazyjnych technik chirurgicznych, ważne jest zrozumienie naturalnego rozwoju objawów związanych z niewydolnością ściany jamy brzusznej po operacji na otwartej wątrobie oraz wyjaśnienie problemu rozwoju przepuklin w bliźnie pooperacyjnej.

Wykazano, że pacjenci, którzy nie otrzymują chemioterapii po operacji z powodu niskiego stanu sprawności (PS) po operacji wątroby, mają zmniejszoną przeżywalność.

PS to system punktowy, który szacuje wpływ choroby na samopoczucie pacjentów. Jest również znany jako jeden z najważniejszych czynników decydujących o przeżyciu u pacjentów z rozsianym rakiem jelita grubego (CRC). Dlatego ważne jest, aby przeanalizować czynniki związane ze złym PS, celem poprawy wyników leczenia operacyjnego przerzutów nowotworowych do wątroby.

Praca częściowa I pracy to retrospektywne badanie kohortowe, do którego włączono 256 pacjentów zoperowanych z powodu przerzutów do wątroby przy użyciu otwartej techniki w latach 2010–2013 w Szpitalu Uniwersyteckim Skåne w Lund. Udało nam się stwierdzić, że przepukliny w bliźnie pooperacyjnej są bardzo częste po operacji wątroby (30,5%), co jest nową wiedzą. Przepuklina pooperacyjna znajdowała się w większości przypadków w linii środkowej ciała. Przepukliny te wykryto za pomocą tomografii komputerowej (CT) wykonanej w ramach standardowego programu kontrolnego po operacji przerzutów raka jelita grubego/odbytnicy. W pracy udało nam się również wykazać po raz pierwszy związek między przepukliną a bewacyzumabem - przeciwciałem stosowanym w przedoperacyjnej chemioterapii przerzutów nowotworowych do wątroby. Przedłużona chemioterapia z więcej niż sześcioma cyklami była również czynnikiem ryzyka rozwoju przepuklin pooperacyjnych.

Praca częściowa IV jest badaniem kwestionariuszowym, uwzględniającym 105 pacjentów po przebytej operacji przerzutów do wątroby w latach 2010-2015 w Szpitalu Uniwersyteckim Skåne w Lund, którzy nadal żyli w lutym 2017 r. Pacjenci ci otrzymali dwa kwestionariusze. Dane zebrano za pomocą dwóch zwalidowany kwestionariuszy: VHPQ - do oceny dolegliwości bólowych przedniej ściany jamy brzusznej oraz EORTC QLQC30 do oceny jakości życia. W badaniu porównano, czy pacjenci z przepuklinami pooperacyjnymi i bez nich różnili się w odczuwaniu bólu, średnio 3 lata po zabiegu. Okazało się, że obecność przepuklin pooperacyjnych nie wpływa na jakość życia pacjentów, ale duża ich liczba ma istotne problemy ze ścianą brzucha, niezależnie od rozwoju przepuklin w miejscu blizn pooperacyjnych. Możliwe, że minimalnie inwazyjna chirurgia może

zminimalizować te dolegliwości, co należy ustalić na podstawie dalszych badań naukowych.

Praca częściowa II to retrospektywne badanie kohortowe obejmujące 284 pacjentów, którzy przeszli operację z powodu przerzutów do wątroby w latach 2010-2015 w Szpitalu Uniwersyteckim Skåne w Lund. W badaniu zbadaliśmy, jak wiele z nich nie wróciło do wystarczająco dobrej formy po operacji, aby bezpiecznie przejść chemioterapię jako terapię wspomagającą. Stwierdzono, że 26% chorych nie otrzymało chemioterapii z powodu złego stanu ogólnego (stan sprawności PS > 2). W przypadku tych pacjentów można było zaobserwować zwiększoną śmiertelność. Jednak większość z tych pacjentów odzyskała dobry stan ogólny w momencie późniejszego nawrotu choroby, dzięki czemu mogli przejść z dobrą tolerancją paliatywną chemioterapię. Wyniki pokazują, że opieka zdrowotna powinna dążyć do zminimalizowania powikłań chirurgicznych, tak aby pacjenci mogli wyzdrowieć i otrzymać leczenie wspomagające po operacji. Tutaj również można zastanowić się, czy niewielki uraz spowodowany małoinwazyjną chirurgią może wpłynąć na zwiększoną tolerancję chemioterapii pooperacyjnej przez pacjentów. Należy to zagadnienie dalej badać.

Praca częściowa III to przekrojowe badanie pacjentów, którzy przeszli operację wątroby z powodu przerzutów raka odbytnicy i okrężnicy w Szpitalu Uniwersyteckim Skåne w Lund w okresie od stycznia 2011 r. do sierpnia 2016 r. Metodą zbierania danych był zatwierdzony kwestionariusz do pomiaru jakości życia (QoL) (EORTC QLQ-C30), który został dostarczony na 3-4 tygodnie przed zabiegiem. Badanie obejmowało 234 pacjentów. Ocenie poddano ich jakość życia w związku z operacją wątroby, porównując przedoperacyjną jakość życia pacjentów z jednoczesnie wykrytym rakiem jelit i wątroby. Tutaj porównaliśmy różne strategie chirurgiczne, w których najpierw operuje się wątrobę, a później jelito, lub jelito przed wątrobą. W tej części pracy można było zauważyć, że nie było różnicy w jakości życia pacjentów, niezależnie od wybranej strategii. Jakość życia pacjentów nie różniła się również od tych, którzy wcześniej przeszli operację jelita z powodu raka i na późniejszym etapie rozwinęli przerzuty do wątroby. Wyniki sugerują, że oferowana strategia nie ma większego znaczenia jeśli chodzi o wpływ na jakość życia pacjentów.

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