Liver metastases from colorectal cancer

Different strategies and outcomes

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Abstract

Patients with colorectal liver metastases (CRLM) increasingly undergo liver resections. The belief is that the resection or ablation of a tumor, when possible, is the only possibility of a cure. The classical strategy is where the primary colorectal tumor is resected as the first intervention, followed by resection of the liver metastasis at a second stage. The liver-first strategy is where preoperative chemotherapy is given, followed by resection of the liver metastases and then resection of the colorectal primary tumor at a second stage. The third option is the simultaneous strategy where the patient undergoes both liver and primary tumor resection during the same operation. The patient selection and drop-out from the planned intervention are poorly known. None of the three strategies have demonstrated any clear advantage or disadvantage in terms of survival. A repeated hepatectomy, for patients with recurrent CRLM, is increasingly performed with mostly unknown postoperative functional liver volume (FLV).

Specific aims to investigate:

I. Why do patients scheduled for the liver-first strategy not complete both the planned liver and primary resections?
II. Compare the liver-first to the classical strategy for patients presenting with synchronous CRLM (sCRLM).
III. Compare the simultaneous strategy with the classical strategy for patients presenting with sCRLM, focusing on patients undergoing major liver resections.
IV. Measure liver regeneration and survival data after a repeated liver procedure (resection or ablation) for recurrent CRLM.

Results and conclusions:

I. Up to 35% of patients with sCRLM do not complete the planned treatment.
II. The liver-first and the classical strategy did not show any overall survival difference.
III. Simultaneous resections appeared to have more complications, shorter total length-of-stay but similar overall survival as patients chosen for the classical strategy.
IV. We found a small change in FLV after two hepatic procedures but with a considerable inter-individual variation. Patients selected for a repeated hepatic procedure for recurrent CRLM had an acceptable survival.

When choosing different strategies for sCRLM patients, our results imply that we should select according to treatment logistics, tumor symptoms, and surgical feasibility. When patients present with recurrent CRLM, a high variance in liver volume after repeated resection can be expected when planning future repeated resections.

Keywords: Secondary liver neoplasms, colorectal neoplasms, hepatectomy, mortality, treatment outcome, retrospective studies, Sweden, registries, functional liver volume, repeat hepatectomy.

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The cover photo is from the 1967 publication by Flanagan and Foster[1], with permission from the publisher Elsevier

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To

Erla Þóra
Guðjón Ari
Ármann Óli

"Normal science, the activity in which most scientists inevitably spend almost all their time, is predicated on the assumption that the scientific community knows what the world is like."
— Thomas S. Kuhn, The Structure of Scientific Revolutions

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List of papers

The basis for this thesis is the following papers, which will be referred to by their roman numerals I-IV:

I. Sturesson C, **Valdimarsson VT,** Blomstrand E, Eriksson S, Nilsson JH, Syk I and Lindell G. Liver-first strategy for synchronous colorectal liver metastases – an intention-to-treat analysis. *Hpb*. International Hepato-Pancreato-Biliary Association Inc.; 2017;19:1–7.

II. **Valdimarsson VT,** Syk I, Lindell G, Norén A, Isaksson B, Sandström P, Rizell M, Ardnor B, Sturesson C. Outcomes of liver-first strategy and classical strategy for synchronous colorectal liver metastases in Sweden. *Hpb*. International Hepato-Pancreato-Biliary Association Inc.; 2018;20(5):441-447.

III. **Valdimarsson VT**, Syk I, Lindell G, Sandström P, Isaksson B, Rizell M, Norén A, Ardnor B, Sturesson C. Outcomes of simultaneous resections and classical strategy for synchronous colorectal liver metastases in Sweden. A nation- wide study with special reference to major liver resections. Paper submitted.

IV. **Valdimarsson VT**, Hellberg K, Brismar TB, Sparrelid E, Sturesson C. Repeat procedures for recurrent colorectal liver metastases: analysis of long-term liver regeneration and outcome. *Cancer Management and Research*. 2019; 11:2617—2622.

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Thesis at a glance

	QUESTION	METHODS	RESULTS AND CONCLUSIONS
I	Why patients scheduled for the liver-first strategy do not complete both liver and primary resections?	A retrospective analysis of 176 patients with CRLM, from 2011 to 2015, referred to multidisciplinary meetings at one liver surgery institution.	Twenty-six patients (35%) abandoned planned treatment in the liver-first and ten patients (29%) in the classical group (NS). The most common reason for failure was disease progression.
II	What is the difference in patient outcomes when comparing the liver-first and the classical strategy for patients presenting with sCRLM?	Prospective national registry analyses from 2008 to 2015. Six-hundred-twenty-three patients underwent a liver-first or classical strategy.	The classical strategy group had more T4 primary tumors and node-positive primaries — no 5-year OS difference was found between groups. A majority of patients with rectal primaries were in the liver-first group.
III	What is the difference in patient outcomes when comparing the simultaneous and the classical strategy for patients presenting with sCRLM?	A prospective national registry analyses, from 2008 to 2015. We identified 537 patients that underwent a simultaneous and classical strategy.	Patients in the simultaneous strategy group were less likely to have a rectal primary (22% vs. 31%) and to undergo a major-liver resection (16% vs. 41%), had a shorter total hospital length-of-stay (11 vs. 15 days) but more complications (52% vs. 36%) — no 5-year OS difference was found between groups.
IV	What is the survival, and how is the liver regenerating after a repeated hepatic procedure (resection or ablation) for recurrent CRLM?	Retrospective analyses of 82 patients, between 2005 and 2015. We examined patients with recurrent CRLM from two liver surgery institutions. The liver volume was calculated before the first procedure and before and after the second procedure.	The measured FLV was 1438 (1204–1896) ml after the first procedure and 1470 (1172–1699) ml after the repeated procedure. Ten patients (12%) had a residual volume of less than 75% of the initial liver volume. The 5-year OS was 37 (26–54) % after the repeated procedure.

Abbreviations: CRLM – Colorectal Liver Metastases, sCRLM – Synchronous Colorectal Liver Metastases, SCRCR - Swedish Colorectal Cancer registry, SweLiv - the National Quality Registry for Liver and Biliary Cancer, OS – Overall Survival, NS – Not Significant, FLV – Functional Liver Volume.

Abbreviations

ALPPS	Associating Liver Partition and Portal vein ligation for staged hepatectomy
ASA	American Society of Anesthesiologists
AUC	Area Under the Curve
BMI	Body Mass Index
BSA	Body Surface Area
CEA	Carcino-Embryonic Antigen
CI	Confidence Interval
Cox ph	Cox proportional hazard
CRLM	Colorectal Liver Metastases
CT	Computed Tomography
CTP	Child-Turcotte-Pugh
FLV	Functional Liver Volume
HR	Hazard Ratio
ICG	Indocyanine Green
INR	International Normalized Ratio
IQR	Interquartile Range
mCRLM	Metachronous Colo-Rectal Liver Metastases
MDCT	Multi-Detector Computed Tomography
MDT	Multi-Disciplinary Team
MELD	Model for End-stage Liver Disease

MRI	Magnetic Resonance Imaging
OR	Odds ratio
OS	Overall Survival
PHLF	Post-Hepatectomy Liver Failure
PVE	Porta Vein Embolization
PVL	Portal Vein Ligation
RBS	Register Based Study
RFA	Radio-Frequency Ablation
SCRCR	Swedish Colorectal Cancer registry
sCRLM	Synchronous Colorectal Liver Metastases
SweLiv	National Quality Registry for Liver and Biliary cancer
TBS	Tumor Burden Score
TELV	Total Estimated Liver Volume
TSH	Two-Stage Hepatectomy

Introduction

Cancer

Cancer has been known to man for a surprisingly long time, with the earliest records dating back to approximately 3000 BC[2]. A tumor resembles a moving crab with its many limbs that stretch outward from a central body, and therefore the word cancer in Latin literally means a crab, as is seen in the astrological sign for cancer[3]. The disease is widespread, and every person has about a 40% risk of being diagnosed with cancer during one's lifetime[4]. The beginning of cancer or tumorigenesis is a multi-rate-limiting process where the disease starts with a disruption in one cell that, against all odds, overcomes numerous obstacles to multiply and maintain itself. A tumor that comprises many cancer cells is a complex tissue with a metastatic potential that can come early or late during the cancer developmental process[5]. It appears that this process is similar for most, if not all, cancer forms in the human body and the processes that are assumed important are[6]:

1. The sustained proliferation process, e.g., disruption in autocrine, or downstream signal pathways (e.g., a mutation in the RAS proliferation genes).
2. The growth suppression avoidance process, e.g., disruption in growth-and-division (e.g., RB gene mutation), or apoptosis signaling failing (e.g., TP53 gene mutation).
3. The cell-death-resistance process, e.g., disruption in cell death regulation (e.g., Bcl-2 gene mutation).
4. The replicative-immortality process, e.g., disruption in telomerase functions.
5. The angiogenesis induction process, e.g., a mutation in the vascular endothelial growth factor-A (VEGF-A) or the thrombospondin-1 (TSP-1) genes.

6. The activation of invasion and metastases process, e.g., E-caderin or matrix-degrading-enzymes disruption.
7. The genome instability and mutation acquisition process, e.g., epigenetic mechanisms such as DNA methylation and histone modification.
8. The inflammation promotion process, e.g., tumor-promoting effects of immune cells.
9. The energy metabolism reprogramming process, e.g., upregulation of the glucose transporters.
10. The immune destruction avoidance process. e.g., paralyzing infiltrating immune cells by secreting immunosuppressive factors.

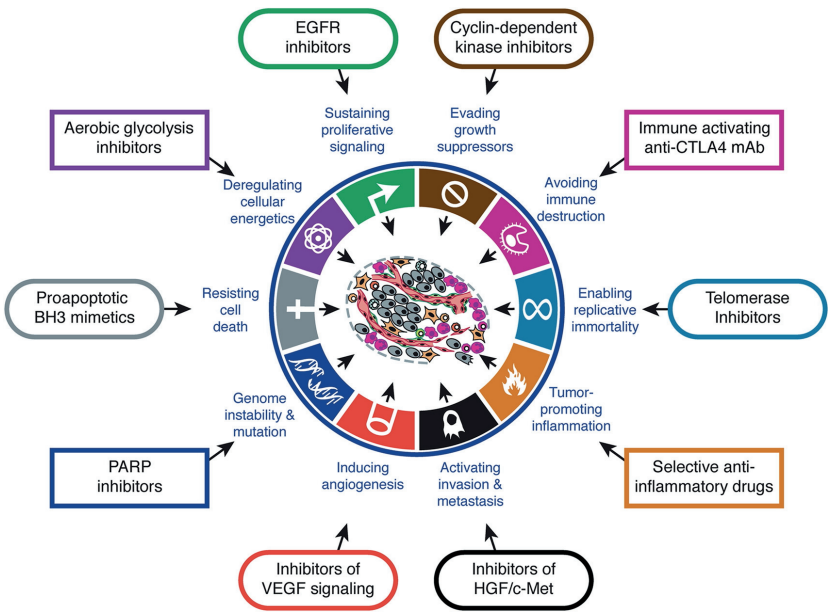

Figure 1.
Parallel Pathways of tumorigenesis and treatment targets[6]. With permission from the publisher, Elsevier.

In summary, many different oncogenes are known to cause cancer and are essential in the formation and evolvement of the disease. The sequence or order

of the processes happens differently between patients, cancer types, and subtypes.

Metastatic cancer disease

The ability of cancer cells to metastasize has long been known, and in 1889 Stephen Paget published the "seed and soil" hypothesis where tumor cells from the primary tumor ("seed") move to a favorable distal organ ("soil")[7]. Metastatic cancer disease is the most common cause of death for patients with cancer and accounts for approximately 90% of cancer deaths[7,8]. It has often been thought that cancer first spreads to the lymphatic tissue and later distally, which was the basis of the widely used TNM classification system[9]. How does a local tumor evolve into disseminated cancer with colonies to different organs, and does it happen in a particular fashion with the same subtypes of cancer occupying the same organ first?

The earliest modern paradigm of metastatic cancer comes from the father of modern surgery, William S. Halsted (1852-1922), that put forth his well-known paradigm at the beginning of the last century. The Halstead paradigm predicts that most cancers follow a predictable pattern of dissemination from one to the next echelon, i.e., from invasive cancer to local lymph nodes, and finally to distant organs[10]. The view at the time was that patients who developed distant metastases had an incurable disease, and palliation was the only available treatment. During the 1930s, physicians began to question that paradigm[11] and more and more treatment options emerged, which offered acceptable survival for patients selected for metastatic surgery[12]. The goal was to stop cancer spreading by systemically resecting the local tumor and metastatic colonies before it was technically impossible, and the disease considered incurable.

Different from the Halstead paradigm, we have the systemic paradigm, sometimes named the Fisher paradigm, form the 1960s. This paradigm states that metastatic cancer is a systemic disease where cancer has metastatic potential at any time, and multiple metastases can exist without being macroscopically detectable, i.e., occult metastases[13].

The spectrum paradigm emerged in the 1990s and states that cancer diseases can have different biological metastatic spectrums[14]. In the spectrum paradigm, a patient has only local invasive primary at one end of the spectrum, but at the

other end of the spectrum, patients are diagnosed early with multiple distant metastases. Furthermore, there is an intermediate state called the oligometastatic state, where only a few or only one resectable metastasis exists at a given time. These oligometastases can then give rise to distant metastases, and therefore a resection could be potentially curable[11,13,14].

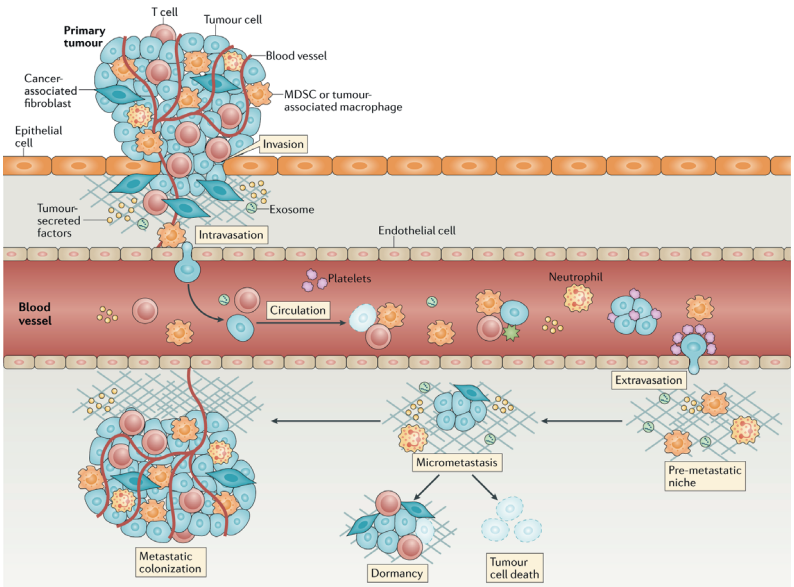

Figure 2.
Tumor metastases cascade is a complicated process where a tumor cell needs to invade with intravasation and evade to establishes distant colonies that can grow, die off or stay dormant — published under the terms of the Creative Commons CC-BY license[7].

What is currently known from the biology of the metastatic process? As stated above, the metastatic cascade can start at any time during the tumor process and is categorized as local tumor intravasation, circulation survival, and finally extravasation to the distal organ, shown in figure 2[7]. In order to disseminate from the primary tumor, the tumor cell needs to change its shape, brake away from neighboring cells, and finally use other cells, e.g., tumor-associated-macrophages and fibroblasts to invade the basal membrane and disseminate to the circulation with a mechanism called the epithelial-mesenchymal-transition (EMT). In the circulation, the tumor cell needs to survive and hide from the immune system, and finally, extravasate from the circulation to a distant organ.

There, the microenvironment is often hostile, and both the microenvironment and the tumor cells need to adapt in order for the cells to survive. In the distal organ, the invasive micrometastatic cells can die, form macrometastatic colonies, or go into a dormant state because of stress, hypoxemia, nutrition deficiency, or the immune response[6–8,15–17]. The dormant state can last many years or up to decades[7]. Metastases can follow the usual lymphatic or hematogenous pathways but even spread directly through body cavities, with different oncogenes responsible for different routes[16].

Metastatic potential is related to the tumor size and proliferation rate, where larger tumors with more cell divisions represent a higher likelihood of metastatases[5,18]. A tumor needs to be under 2.7 +/- 1.6 mm, in order to decrease a five-year discoverable metastases risk from nine to one procent[15]. Small local tumors can thus give rise to distant metastases, with about 20-30% of patients with lymph node-negative cancer developing distant metastases[16], and about 65% of local-only cancer patients having circulating cancer cells in the bloodstream during surgery[18]. Metastatic potential varies as well between different tumor cells within the same tumor[9,17], and in about 65% of patients, lymphatic and distant metastases originated from independent sub-clones within the same primary tumor[9]. Therefore, many biological different sub-clones can exist in various places in the body at the same time[9]. The metastases can then, by themselves, metastasize back to the primary tumor site or other organs[6,16]. Many different oncogenes have as well been linked to metastatic potential, worse survival, and risks for cancer recurrence[11,19].

We have gotten better in our understanding of cancer behavior and biology during the last 130 years since Halsted and Paget. We are even closer in our understanding of what constitutes metastatic cancer, and which paradigm is correct.

Epidemiology of colorectal cancer and colorectal liver metastases

Colorectal cancer is the third most common cancer for each gender[20], and in the year 2017, about 4,400 patients were diagnosed with colon cancer and approximately 2,100 with rectal cancer in Sweden. The age-standardized incidence of colorectal cancer has been stable since the beginning of this century, with 31.2 per 100,000 for males 24.9 per 100,000 for females[21,22]. The

older generation is affected more, with the median age at diagnosis being 72 years for males and 70 years for females, and only around five percent are below the age of fifty[23]. Survival for patients diagnosed with metastatic colorectal cancer has steadily increased during the last decades[20,24,25], with a relative 5-year survival of 66% for colon cancer and 68% for rectal cancer[26]. In Sweden, age-standardized mortality has declined for colon cancer but has been fairly constant for rectal cancer during the last decades, as seen in figure 3[20,22,23].

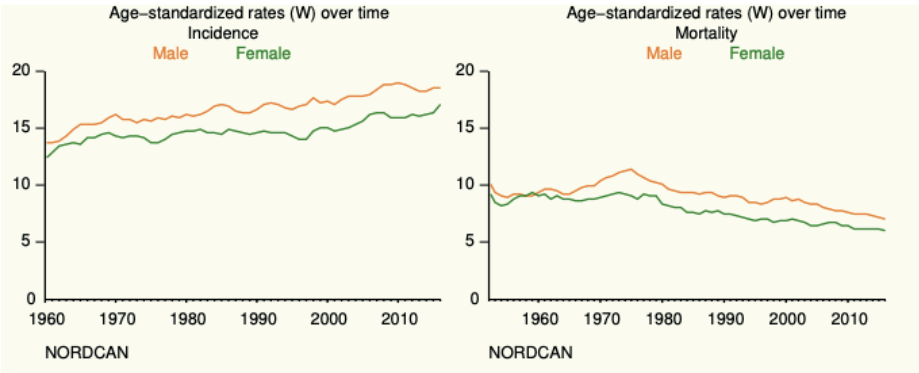

Figure 3A.
The age-standardized incidence and mortality rates (number of new cases per 100 000 persons per year) for colon cancer in Sweden[22].

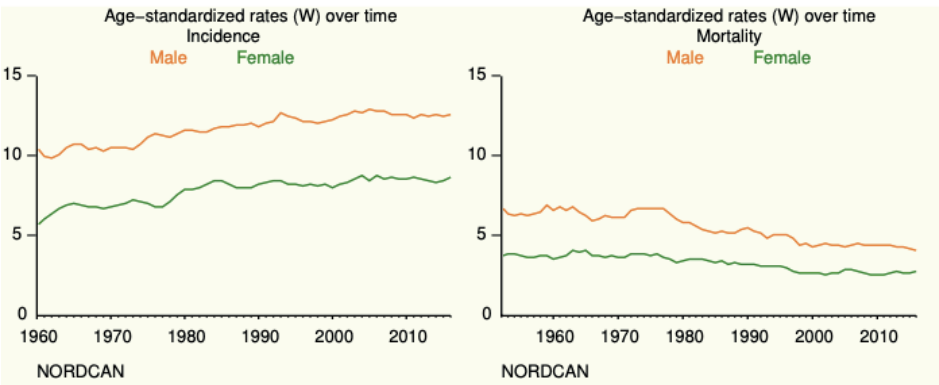

Figure 3B.
The age-standardized incidence and mortality rates (number of new cases per 100 000 persons per year) for rectal cancer in Sweden[22].

About 20% present with a distal metastasis, stage IV disease, at diagnosis, and a further 20 % will be diagnosed later with metastatic disease[27]. Metastases to the liver are the most common distant metastases from colorectal cancers, 40-70% of all metastases, followed by lung metastases[23,27,28]. About 15-20% of patients with colorectal cancer have liver metastases at the time of diagnosis of the primary cancer, called synchronous liver metastases (sCRLM), and another 15% develop metastases later, metachronous CRLM (mCRLM)[23,28–30]. Approximately 2000 patients are diagnosed with CRLM each year in Sweden[21,28].

The history of metastatic liver surgery

Partial hepatectomies for patients with metastatic tumors have been performed for over 80 years, with one of the earliest reports from the year 1935 by the surgeon Werner Möller. Möller and his colleagues performed a partial hepatectomy on a 29-year-old woman, previously resected for ovarian cancer. The patient recovered well, could return to work[31], and was alive and well six years after the liver resection[1].

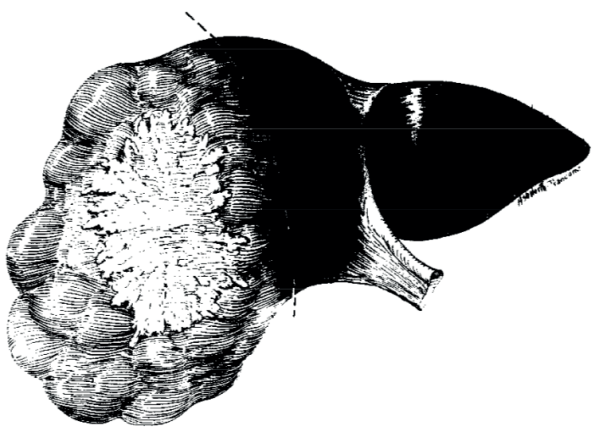

Figure 4.
The line of resection of the right lobe [1]. With permission from the publisher, Elsevier.

In the year 1967, Flanagan and Foster analyzed seventy-two patients that had undergone hepatic resection for metastatic cancer. They found a 24% (twelve patients) five-year survival, that increased to 39% for those with solitary metastasis. The authors thus suggested aggressive surgical treatment of metastatic cancer for patients with treatable primary tumors and adequate physiologic reserve[1].

Different approaches to colorectal liver metastases

How do we remove liver metastases? Liver tumor resection is usually done by removing one or more wedges or a portion of the liver with a resection done by anatomical landmarks. These landmarks are divided by the portal veins into segments, called the Couinaud's segments[32], shown in figure 5.

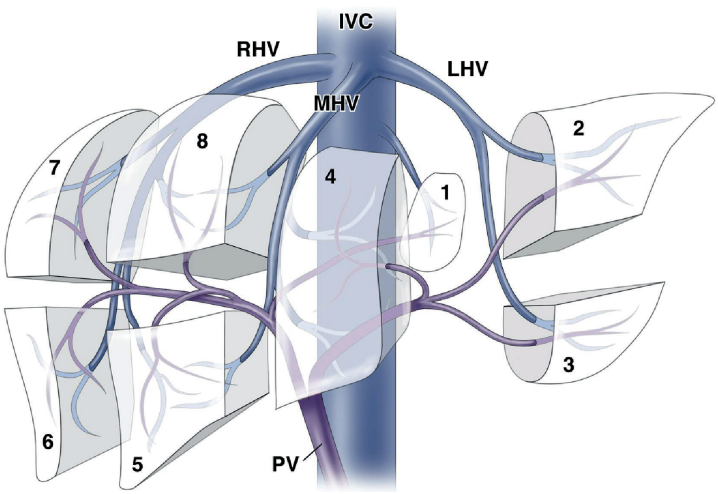

Figure 5.
Liver anatomy divided by Couinaud's segments[33]. RHV. Right hepatic vein, LHV. Left hepatic vein, MHV. Middle hepatic vein, IVC. Inferior vena cava, PV. Portal vein. With permission from the publisher, Elsevier.

Removal of three or more segments is usually defined as a major resection[34–36]. A resection is usually done with an open subcostal Kocher laparotomy or by a laparoscopic resection, that has recently gained popularity.

A comparison between an open resection and laparoscopy can be difficult because of reported conversion rate to open procedure, but the laparoscopic approach appears to be a safe alternative to open surgery, and it appears to have better results in terms of complications and hospital length-of-stay, without significant difference in long-term mortality and cancer recurrence[37,38].

Patients too sick to undergo an operation or having technically challenging liver tumors are nowadays often offered destructive, ablative treatment, instead of or together with a resection[39]. The ablation is usually done with a needle that transmits the destructive force and is usually performed with either radiofrequency or microwave heating, or using electrical, chemoembolization, ultrasonic, laser, ethanol, or freezing destruction[40]. The ablation can be applied endoscopically, percutaneously, during laparoscopic surgery, or directly during open surgery. The technique is rapidly evolving, and newer ablative procedures can be applied for more and larger tumors with greater precision[39,40]. Because an ablation is often selected for sicker patients with more difficult tumors, a comparison is difficult, but the technique has generally shorter length-of-stay, fewer complications, but worse overall survival and higher local recurrences[39,41–43]. One multicenter phase II study randomized 119 patients with inoperable CRLM to a surgery-ablation arm or a systemic-chemotherapy arm. The study had unfortunate limitations with small sample size, a difference in the number of metastases, and unintended cross-over to the surgical-ablation arm. However, the authors found similar overall survival and progress free survival during the first three years, but after the three years, resection-ablation appeared to have survival benefits[44].

Another approach for patients not able to undergo liver resection due to the metastatic burden in the liver or liver failure is a total resection of the whole liver and transplantation of a tumor-free liver from a donor. Two of the seven first documented patients to undergo liver transplantation had CRLM disease, with the first patient dying on the eleventh day postoperatively and the second dying intraoperatively[45]. Liver transplantation for CRLM has been highly controversial because of the need for immunosuppressive medications, tumor biology, and a shortage of donor organs. A systemic review on the subject, published by Moris et al. in 2017, showed a heterogenous group of only 66 patients from 11 studies with 5-year survival ranging from 12% to 60%, and 61% having a recurrence within one year[46]. A recent prospective study showed a remarkable high 5-year survival of 83%, with a median follow-up of only 36 months, and 53% recurrence. The author suggested that better survival was perhaps due to superior tumor biology[47].

Risk scores

Have we developed adequate scores or criteria for which patients should undergo liver resections, and which should definitely not? Finding different score systems should be a priority in order to standardize, make the process more transparent, and learning how to best follow-up patients after liver resections.

At many hospitals, a multidisciplinary team decides which patients shall undergo liver resection, but how many patients with colorectal cancer will ultimately undergo liver resection? The difference between individual hospitals varies a lot, with a range of 0.7 to 6.8% of all patients with colorectal cancer undergoing liver resections[48]. The probable reason for this difference is that hospitals have different official and unofficial criteria, traditions, and skills. Does the difference in hospital resection rate and selection explain the vast difference in published survival data, with a reported 5-year survival ranging from 16 to 74%, and a 10-year survival ranging from 9 to 69% with an overall median survival of 3.6 years[48–50]?

The most widely used risk score is the Fong score that includes five different parameters: nodal status, CRLM timing (sCRLM or mCRLM), carcinoembryonic antigen (CEA) level, largest CRLM size, and CRLM number[51]. The score was based on uni- and multivariate-analysis and found a 5-year survival of 60% for the “best” group and 14% for the “worst” group[51]. Sasaki et al. tried to find a simpler score to predict long-term survival using an example from a previously known hepatocellular carcinoma score. The score is called the tumor burden score (TBS), with the formula: $TBS^2=d^2+n^2$, where d is the largest diameter of CRLM, and n is the number of CRLM metastases. The TBS had a slightly higher area under the curve (AUC) of 0.669 compared to the maximum tumor size (AUC 0.619) and the number of tumors (AUC 0.595) for predicting overall survival (P=0.012 and <0.001). The TBS could then be divided into three zones: zone 1 (*TBS <3*), zone 2 (*TBS≥3 and <9*) and zone 3 (*TBS ≥9*). As TBS increased, survival declined (5-year OS: zone 1, zone 2, and zone 3—68.9%, 49.4%, and 25.5%, respectively; P < 0.001)[52]. The authors did external validation for the TBS, but others have not validated the score. Roberts et al. compared seven different score systems for CRLM and found them to be "reasonable" at best with only one score exceeding 0.7 in C-statistic for predicting three-year disease-specific survival[53].

Are bleak scores simply proxies for more aggressive cancer biology? The role of different score systems is yet to be entirely determined. Hopefully, a more powerful computation, e.g., machine learning and neural networks, can help make better risk scores. Additionally, a better understanding of different tumor behaviors and biologies should enable superior outcome predictions, selections, and follow-up approaches for patients with CRLM.

Liver volume measurements

How do we minimize the risk of postoperative liver failure following liver metastatic surgery? How do we measure liver volume? How much liver can we remove, and can we measure liver function?

Post-hepatectomy liver failure (PHLF) is a life-threatening condition and the major cause of death related to liver resections. The International Study Group of Liver Surgery (ISGLS) defines PHLF as an increase in international normalized ratio (INR) and hyperbilirubinemia on or after postoperative day five, subclassified into three severity grades. We can minimize PHLF risk with a careful preoperative assessment of liver-health and the planned postoperative liver size[54].

Unfortunately, we are not able to measure liver function directly, but several methods can be used to assess liver health indirectly. All physicians are familiar with the clinical hallmarks and standard blood tests to measure liver injury and function. The most common clinical signs associated with liver injury are ascites and liver encephalopathy, and frequently used blood tests are: albumin, liver transaminases, INR, and bilirubin[54,55]. The famous Child-Turcotte-Pugh (CTP)[56] and later, the model for end-stage liver disease (MELD) scores have been used for predicting prognosis and the need for liver transplantations for patients with liver cirrhosis[57]. These scores are also often used when predicting complications after liver surgery with age, the CTP score, and the American Society of Anesthesiologists (ASA) score having a better prediction for complications than the MELD score[57]. Standard diagnostic imaging can additionally be useful for observing liver injury, such as hepatic steatosis, with MRI and magnetic resonance spectroscopy (MRS) having the best diagnostic accurency[58]. Other more specified tests are: - quantitative metabolic tests that measure metabolic function, - Indocyanine Green (ICG) retention test that measures hepatic perfusion, and - scintigraphy

that measures functional hepatocyte mass. A lower metabolite elimination rate, increased ICG retention, and decrease scintigraphy uptake are related to increased risk of liver failure[55].

How much of a healthy liver can we remove, and how little can we safely leave behind? With the remaining liver being too small, the patient risks having postoperative liver failure. About 20-27% of residual liver volume for a preoperative healthy liver and 30-50% residual liver volume for an injured liver appears to be safe[59,60]. Additionally, a postoperative liver volume to body weight ratio larger than ≥ 0.5% is reported to be sufficient[61].

How do we assess preoperative liver volume in order to know how much of the liver we can resect? The liver is related to our size and grows from 0.072 – 0.16 liters in infancy to 0.81 - 1.7 liters in adolescents[62]. During the last decades, we have seen an increase in the use and availability of imaging, e.g., computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US)[63]. We also have better computer and software power that has made liver volume calculations more precise and faster. Usually, the liver volume imaging measurement is done manually or automatically by tracing the liver outline with a cursor on an image slice. The area is calculated, superiorly to inferiorly, with 0.5 or 1.0 cm interval between slices, shown in figure 6. The sum of the calculated areas gives us the total liver volume.

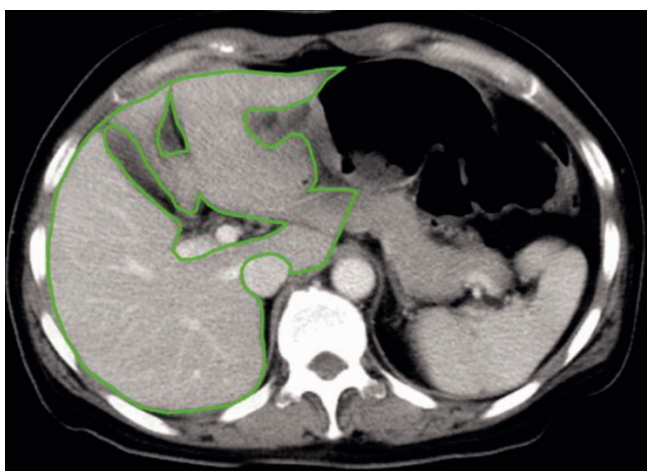

Figure 6.
Liver area calculation marked with a green line, with permission from the publisher John Wiley and Sons[64].

Niehues et al. compared liver measurement by using an in-vivo CT volumetric measurements compared to an ex-vivo water displacement volumetry in eleven pigs. The authors found a high correlation, with a coefficient of determination, r^2 0.985 ($p<0.0001$), and a median 13% higher in-vivo liver volume, most likely caused by the in-vivo blood perfusion[65]. Sonnemans et al. compared liver volume weight in cadavers to pre-death CT volumetric measurements and found the coefficient of determination, r^2, to be 0.90 ($P<0.001$)[66]. Different formulas have been computed in order to calculate the volume instead of measuring it. Because the liver follows the body surface area (BSA) quite closely, i.e., weight and height, many formulas use BSA. One of the most used formulae was published by Vauthey et al., where the authors used a regression analysis to establish the formula: TLV (total liver volume) = -794.41+1,267.28 x BSA. However, the coefficient of determination was only 0.46 ($p<0.0001$) when compared to CT measured liver volume[67].

To date, no ideal test is available to test the liver function or volume, and many factors need evaluation, with the most crucial thing being the liver health and the planned postoperative volume. We can conclude that volumetric image measurements are fairly accurate and can be used when measuring liver volumes. Hopefully, we will be able to make better predictions, perhaps by combining both volumetric and functional measurements in the near future.

Liver regeneration

All of us have witnessed the regenerative potential of the body, most often in the form of wound healing. The ancient Greeks knew of the liver regenerative potential, and in the year 1931, Higgins and Anderson observed that after surgical removal of two-thirds of the liver, it grows back to its original volume after about week[68,69]. Under the usual condition, a healthy hepatocyte rarely divides and stays in the G0 phase, but during drug, mechanical, or infectious related injury, the liver can regenerate itself[68]. Transplantation of a limited number of hepatocytes from a healthy mouse to a liver depleted mouse can be enough for it to survive, with the regenerative potential equal to that of the bone marrow[70]. The regenerative potential of liver hepatocytes appears to decrease with age, but it appears that all types of liver cells have the potential to regenerate, and a small stem cell population (oval cells) can even generate different types of cells[70,71]. After liver resection, the activation signal for the liver cells is believed to come from shear stress with the release of nitric oxide

(NO), prostaglandins (PGs), cytokines, and growth factors before angiogenesis, and extracellular matrix breakdown follows[68,71]. The regeneration potential appears to be related to the size of injury or resection with the largest liver resection delivering the largest regeneration potentional[35,71,72]. The growth factors and cytokines that are involved in the regeneration process have been shown to stimulate residual micrometastases after liver resection in rodents[71]. The human liver regeneration potential after resection is multifactorial, and a lot is still unknown[68].

The liver regeneration potential has been evaluated to be around 80-92% of the preoperative volume[34,35,73], which can be influenced by age, cirrhosis, chemotherapy, and the size of the liver resection[34,72]. A repeated resection appears to have roughly the same effect on liver regeneration even though this is inadequately examined[73]. One of the aims of the thesis was to evaluate the regenerative potential after repeated liver resection.

Strategies to increase the resectability of the liver

The reasons patients usually do not undergo liver resections for CRLM are frailty, unresectability, dissemination beyond the liver, or that the extent of the metastases in the liver are too great for the remaining liver to be able to function. For a number of patients, chemotherapy can decrease the size and number of the liver metastases, enabling the patients to undergo liver resection at a later stage, with up to 50% of originally unresectable patients being later considered for liver surgery after chemotherapy[74].

The liver has a remarkable ability to regenerate, as stated above. For over forty years, we have known that occlusion of either the right or left branch of the portal vein can result in substantial liver regeneration, first with open surgical ligation, and later with percutaneous transhepatic portal vein embolization (PVE) which is as safe and as effective as ligation[60,75,76].

At the beginning of this century, Adam et al. reported two-staged hepatectomies (TSH) for CRLM in both liver lobes. There the authors performed a partial resection of the liver, allowed the liver to regenerate for 4-6 weeks, and then performed a second resection[77]. Later, a portal vein ligation or PVE was integrated into the staged hepatectomies, often also referred to as TSH[60]. At the beginning of this decade, Schnitzbauer et al. performed right portal vein ligation and in-situ splitting and then later a second hepatic

resection. When they examined the result retrospectively, the technique showed a remarkable hypertrophic effect (74%, range: 21-192%) occurring in a median of only nine days. The hospital mortality was, however, high, as 3 of 25 patients died (12%), and 68% of the patients experienced some form of complication, with 44% experiencing severe complications[76]. This approach, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), has since evolved. The difference between ALPPS and TSH is a liver parenchyma partition in ALPPS, which is thought to have a potentially faster liver regeneration. In a recent meta-analysis, the ALPPS showed faster liver regeneration, but more complications and perioperative mortality. The postoperative functional liver volume, overall survival, and disease-free survival showed no significant difference between the methods[78]. A recent multicentric randomized controlled trial found an increased resectability rate for ALPPS without a significantly increased hospital mortality (8.3% vs. 6.1%) or morbidity compared to TSH. Unfortunately, no long-term outcome is available from the study[79].

Different strategies for synchronous CRLM (sCRLM)

Three different strategies are usually available for a patient diagnosed with both colorectal cancer and liver metastases simultaneously (sCRLM).

The most traditional treatment for patients with sCRLM is the classical strategy. There the patient undergoes excision of the primary colorectal tumor followed by chemotherapy, and then if technically possible, excision of the secondary tumor or tumors later. The rationale to choose the classical strategy has been to stop a metastatic development in the primary tumor and eliminate complications from the primary tumor, e.g., tumor perforations, gastrointestinal bleeding, or bowel obstruction.

The second strategy has been to resect both the primary and metastatic tumors together, called the simultaneous strategy. This strategy is often used when a patient has a technically straightforward resection of the primary and secondary tumors. The rational with simultaneous strategy is a single operation and anesthesia with less hospital length-of-stay.

Since many liver tumors respond well to chemotherapy, an original third approach was described in 2006 by Mentha et al.[80], where preoperative chemotherapy was administrated and metastasectomy performed before the

primary tumor was finally surgically removed, named the liver-first strategy. This strategy was supposed to be applied when a patient presented with a "bad" metastatic tumor liver disease, high complication risk following the colorectal surgery, as well as to observe the chemotherapy response, or by using the refractory time after rectal cancer radio-chemotherapy [80]. Mentha et al. presented a total of twenty patients who were given neoadjuvant chemotherapy with only sixteen (80%) that could follow through with the planned procedures, i.e., liver and colorectal. For the resected patients, the 5-year overall survival was 61%, equivalent to the classical strategy, but the median follow-up was only 25 months[80].

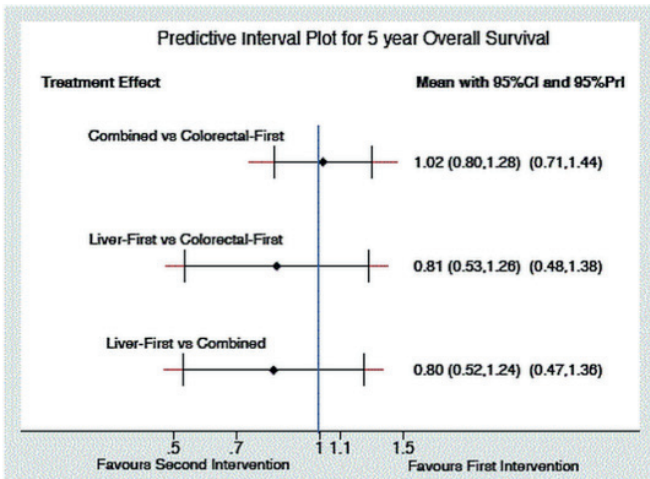

Figure 7.
The image shows a predictive interval plot for the three surgical strategies, from a meta-analysis by Kelly et al[81]. Confidence interval (CI) as black lines and predictive intervals (PrI) as red lines. With permission from the publisher, John Wiley and Sons.

During the last decade, many retrospective studies have published comparisons between the liver-first, classical, and simultaneous strategy. To date, no randomized or controlled trial has been conducted to compare liver resection vs. no resection or between the different strategies. A meta-analysis by Kelly et al.[81] compared classical, simultaneous, and liver-first strategies and found no significant survival difference. They found a total of 18 studies with 3065 patients, where 67.7% had undergone a classical strategy, 3.7% had undergone a liver-first strategy, and 28.6% had undergone a simultaneous strategy. They

found a 5-year mean odds ratio (OR) survival of 0.81 (95% CI 0.53–1.26) for a liver-first vs. a classical strategy, a mean OR survival of 0.80 (95% CI 0.52–1.24) for liver-first vs. simultaneous strategy and finally a mean OR survival of 1.02 (95% CI 0.8–1.28) for simultaneous vs. classical strategy, seen in figure 7. No difference in complications or 30-day mortality was found between the three groups[81]. It appears that the simultaneous strategy offers a shorter length-of-stay and less overall health costs but equal overall survival and postoperative complications[36,81].

To summarize, no survival difference has been demonstrated between the different strategies, although no randomized trials exist on the subject. Prior to this thesis, no national registry research was available for the comparison between the three different strategies, which was one of the aims of the study. The indications for different strategies are still evolving, and most previous studies evaluating the liver-first strategy only include liver-resected patients. Another aim of this thesis was to investigate patients intended to undergo the liver-first or the classical strategy.

Repeated resections

About 60-91% of resected CRLM patients will be diagnosed with cancer recurrence within five years, with 20 – 30% having the liver as the only site of recurrence[50,82,83]. A repeated or even third liver resection is increasingly performed with an acceptable recurrence rate[83]. In a systemic review from Simmonds et al., a median of 9% (range: 3.6-17%) of patients with recurrent liver metastases had repeated liver resections[82]. Wurster et al.[84] examined eight observational clinical studies with 450 patients and compared to 2669 patients that underwent single liver resections. They found that morbidity, mortality, and overall survival were comparable to one surgical resection with a survival hazard ratio (HR) of 1.00 (CI: 0.63-1.60, p=0.99)[84]. Volumetric liver regeneration after repeated liver resection is poorly researched. Tanaka et al. examined 21 patients that had undergone repeated resection and found that a ratio of postoperative liver volume to preoperative liver volume was 92.0±11.7% (mean ±SD)[73]. One of our study aims was to examine liver volume and patient outcome after repeated resection.

Registry studies

Sweden has a long history of using official population registries with unique personal identification numbers used by various governmental agencies[85]. Clinical registries have been around in Sweden since 1975, and unique registries have collected information on varied diagnoses and treatments, where researchers can study outcomes for different patient groups and treatments[86]. In order to examine colorectal cancers, the Swedish Rectal Cancer Registry (SRCR) was launched in 1995, and the Swedish Colon Cancer Registry (SCCR) was launched in 2007, together grouped as the Swedish Colorectal Cancer Registry (SCRCR). The SCRCR includes all clinically diagnosed patients with invasive colorectal cancers. The SCRCR has a coverage of over 99% of all patients registered[87]. The National Quality Registry for Liver, Bile Duct and Gallbladder Cancer (SweLiv) was launched in 2009 and includes all patients who develop primary malignancy in the liver, gallbladder or bile ducts, as well as patients that undergo surgical or ablative treatment of secondary malignancy to the liver. SweLiv accounts for 87-97% of patients in Sweden with the above diagnoses[88,89].

Registry-design studies or registry-based studies (RBS) are a particular type of research with data often recorded prospectively but sometimes retrospectively. RBSs are observational research studies, from where we can access descriptive data, e.g., epidemiological data, safety data, or compare different groups of cohorts or treatments. RBSs can have different designs, such as cohort, case series, case-control, and case-cohort design. We usually consider interventional studies, such as randomized controlled trials, as having the most robust evidence grade for comparing treatment effect, but in RBSs, the cohorts are chosen beforehand. That can make comparison complicated, especially if the selection process is not transparent. Many different biases and dilemmas accompany RBSs as well, such as loss of follow-up, internal and external validations, information biases, selection biases, referral biases, confounding by indication, lead time biases, data not missing at random, and immortal time biases. However, RBSs can show us how a treatment works in "real life" with "real" clinical inclusion and exclusion criteria for an authentic population. RBSs can be especially useful where we cannot ethically intervene or randomize subjects because we are confident that the treatment or observation is inferior, superior, or harmful. Enrollment in an experimental study could, therefore, be difficult, questionable, dangerous, or perhaps unethical[90].

Different methods are increasingly used to overcome some of the difficulties of RBSs. The study subjects are evaluated according to known variables and adjusted for measurable or even unmeasurable confounders. In order to achieve this, different multivariate analyses have been applied, such as linear regression, logistic regression, Cox proportional hazard analysis, instrumental variable (IV) analysis stratification, matching, and propensity score matching[91]. Propensity score matching has been increasingly popular, as it gives a score of predicted probability to a control or treatment group in order to match the two groups, whereas Cox proportional analysis includes censored data and adjusts for covariates. The more complex statistical methods such as IV analysis or propensity score matching are not necessarily superior to more straightforward methods such as logistic regression and Cox proportional hazard analysis that can sometimes be more powerful when detecting differences for treatment effect[91,92].

Selection

Survival for patients diagnosed with metastatic colorectal cancer has steadily increased during the last decades[20,24,25]. The reason for the increase is likely multifactorial with better awareness, diagnostic techniques, screening, hospital care, surgical techniques, and chemotherapies. In Sweden, age-adjusted mortality has declined for colon cancer but has been relatively constant for rectal cancer during the last decades[20,22,23]. Many believed and still believe that surgical excision of all visible tumors, both the primary and metastases, is a curable treatment, although this has never been proven with controlled trials or biological models. Some have argued that more aggressive chemotherapy and metastatic surgery could explain the survival increase, but no empirical research is available to support such statements[1,31].

How much variation is there in resection selection? Only about 2.0% of all patients in Sweden that are diagnosed with colorectal cancer and 17.8% diagnosed with sCRLM only liver metastatic disease will undergo one or more surgical liver procedures, with considerable variation between liver centers (11.5 - 22.7%)[29]. In England, about 2.7% of all patients that underwent colorectal surgery also had liver resections with wide variation between hospitals (0.7 - 6.8%). Older patients, with more co-morbidities, or worse socioeconomic statuses are less likely to be offered liver resection[48]. The reported survival difference is great, and significant heterogenicity is between

published studies, which may account for the great variation in selection and referral to individual surgical centers[50].

How are patients selected for liver procedure, how is resectability decided, and how many patients will progress or die during the time from decision to surgery, e.g., immortal time bias? What are the intention-to-treat criteria? Are we selecting patients for metastasectomy with desirable biology that would have the same survival without any liver resection[93]? Do the liver resected patients have similar cancer biology as patients with stage III colorectal disease[48]? How many will complete the planned procedure? How do we explain the biological effect of liver surgery, and is it compatible with the most current cancer paradigm?

The role of randomization is to prevent both known and, most importantly, unknown biases. With randomization, we produce similar groups and minimize treatment assignment bias as the source for the difference in the end outcome. When done blinded (patient, examiner, and the analyzer) and with strict adherence to a rigid protocol, the randomization can, in theory, almost guarantee an unbiased estimate of the treatment effect.

Is randomization important? In the 1990s, an established treatment for breast cancer was high-dose chemotherapy (HDC) followed by haematopoetic stem-cell transplantation (HSCT), with a 3-year event-free survival of 72% compared to 5% survival without the treatment[11]. Because of cost and toxicity, randomized controlled trials were ultimately conducted and showed no survival difference where the treatment was shortly thereafter discredited and is now no longer in use[11,94]. As there are no randomized comparative trials or even prospective analyses of the whole group with CRLM, can we conclude for certain if CRLM resections are better than best supportive care? Can we conclude which strategy is best? Could these studies be ethically conducted?

Almost all studies that are published include only resected patients, and no studies are available that examine patients prospectively with all patients with CRLM analyzed with an intention-to-treat design. To explore the selection process, different strategy outcomes, and liver regeneration for patients, with CRLM in Sweden, this thesis was conducted.

Aims and objectives

The overall aim of this thesis was to investigate different strategies and outcomes for patients resected for liver metastases from colorectal cancer. An additional aim was to investigate volumetric liver regeneration and survival data after a repeated hepatic procedure.

In order to achieve these aims, this thesis includes four clinical studies. Each study has the following more specific objectives:

i. Paper I: To understand why patients scheduled for the liver-first strategy do not complete both liver and primary resections.

ii. Paper II: To investigate and compare outcomes for the liver-first and the classical strategy for patients presenting with synchronous CRLM (sCRLM).

iii. Paper III: To investigate and compare outcomes for the simultaneous and the classical strategy for patients presenting with sCRLM, focusing on patients undergoing major liver resections.

iv. Paper IV: To retrospectively investigate volumetric liver regeneration and survival data after a repeated hepatic procedure (resection or ablation) for recurrent CRLM.

Materials and methods

The basis of this thesis is on three different study populations of patients with CRLM.

Paper I

We analyzed the medical records of all patients with colorectal liver metastases between 2011 and August 2015 referred to a multidisciplinary team conference (MDT) at Skåne University Hospital. We further analyzed patients with synchronous liver metastases, biopsy-proven colorectal adenocarcinoma, technically resectable CRLM, and technically resectable extrahepatic metastases, when present. This group made up the patient cohort. All patients that underwent colorectal resection first, prior to or after MDT referral, were analyzed as classical strategy, and patients that underwent liver resection first were analyzed as a liver first strategy. Patients with unresected and low-symptomatic primary colorectal and unresected liver tumors were investigated with an intention-to-treat analysis after the MDT decision.

Paper II and III

We identified patients from the Swedish Colorectal Cancer registry (SCRCR) diagnosed with colorectal adenocarcinoma, and patients from the Swedish National Quality Registry for liver and biliary cancer (SweLiv) having an intervention for metastases in the liver, registered in the period between January 2008 and January 2015. We made an interconnection between the two databases using unique pseudonymous personal identification numbers. From the databases, patients with metastatic colorectal cancer to the liver after initial staging and before any resection were identified and defined as having synchronous liver metastases (sCRLM). We excluded patients that had undergone an acute colorectal resection. The subset of patients that had undergone colorectal resections within six months from the colorectal cancer

diagnosis and undergone both colorectal and liver resection within 12 months from colorectal diagnosis constituted our cohort. In paper II, we made a comparison between patients operated with the liver-first and the classical strategy. In paper III, we made a comparison between patients that had undergone simultaneous and classical strategy with particular focus on patients that had undergone a major liver resection, defined as resection of three or more Couinaud's liver segments. In paper III, a complication was identified if appearing in either or both the colorectal registry (SCRCR) and the liver registry (SweLiv). In paper II and III, a tumor burden score (TBS)[52] in the liver was calculated as $TBS^2 = d^2 + n^2$, where d = largest liver tumor diameter (cm) and n = number of liver lesions. In paper III, an original score was invented to account for sCRLM, named total tumor burden score (TTBS) using the hazard ratio from the univariate Cox proportional hazards analysis as a multiplier if the patient had a postoperative primary lymph node-positive disease and if the patient had a T4 primary tumor. $TTBS = \sqrt{d^2 + n^2} + 2\,x\,N + 4\,x\,T$, where d = maximum liver tumor diameter (cm), n = number of liver lesions, N = 1 if lymph nodes are positive for the primary tumor and T = 1 if the primary tumor is T4, otherwise N and T had the value zero.

Paper IV

Selection of patients

All patients with CRLM who underwent a repeated procedure, resection or ablation, for a recurrent CRLM disease at Skåne University Hospital or Karolinska University Hospital, between 2005 and 2015, were analyzed. We examined further patients with available imaging from computed tomography or magnetic resonance imaging. We stratified patients into major or minor hepatic procedures. A minor hepatic procedure was defined as a hepatic resection of less than three Couinaud's segments with or without additional radiofrequency ablation (RFA) or RFA alone. We defined a synchronous disease as liver metastases diagnosed at the radiological workup of the primary colorectal cancer.

Liver volume measurements

We measured liver volumes using CT or MRI coronary plane images. We manually traced the liver contour on all liver image slices and calculated each liver area with computer software and multiplied the area by the section thickness (usually 5 mm), the sum gave the liver volume in ml. Metastasis

volumes, as well as ablation zones, were measured and subtracted from the liver volume to give a functional liver volume. We used the most recent preoperative images available before the first and repeated procedure, as well as a postoperative image taken at least one month after the repeated procedure. We then calculated relative liver volume ratios by dividing the FLV after the first and second procedures to the original FLV. For comparison, we calculated a total estimated liver volume (TELV)[67] using the formula: TELV = −794.41 + 1,267.28 × body surface area (BSA), and BSA was calculated employing the Mosteller's formula[95].

Project design

Paper I

Paper I was a retrospective, descriptive, and comparative cohort study. We retrospectively extracted data from patient records and divided patients into groups according to the treatment strategy chosen, a classical or a liver-first strategy. We excluded patients scheduled for a simultaneous strategy. The study was an intention-to-treat analysis from the MDT decision.

Paper II and III

Papers II and III were registry-based comparative cohort studies. We identified patients at the time of entry in the Swedish Colorectal Cancer registry (SCRCR) and the National Quality Registry for liver and biliary cancer (SweLiv) from January 2008 to December 2014. The registration of data was prospective.

Paper IV

Paper IV was a retrospective, descriptive, and comparative cohort study. We identified all patients with CRLM that underwent a second liver procedure for a recurrence of CRLM at Skåne University Hospital and Karolinska University Hospital, between the years 2005 and 2015.

Statistical analysis

The variables in this thesis were typically considered non-parametric. We generally presented summary statistics as whole numbers and percentages for categorical variables, or as medians with interquartile ranges (IQRs) unless otherwise stated, for continuous variables. To compare continuous variables, we used Mann–Whitney U-test, for categorical data Fischer´s-exact-test was used, and Friedman-test when comparing three continuous variable groups. Cox proportional regression analysis was used to calculate hazard ratios (HR) with 95% confidence intervals. We used Log-rank-test to asses recurrence-free and overall survival differences. Survival and recurrence-free-survival were analyzed using Kaplan Meier analysis. Pearson correlation analysis and linear regression assessed correlation and relationship, respectively. A P-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics version 22 (IBM, Armonk, NY, USA), for paper I. Statistical analysis for papers II-IV was performed using R (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Ethics

All the studies presented in this thesis were carried out following the Declaration of Helsinki. The Regional Ethical Review Board in Lund approved all the papers.

Results

Main findings in paper I

We identified 176 patients with resectable sCRLM, where 67 patients had already undergone resection of the colorectal primary tumor, and 109 patients had an unresected, technically resectable colorectal cancer and CRLM at the MDT, fulfilling the inclusion criteria. Two patients with planned simultaneous resections were already excluded. The median follow-up from diagnosis was 42 (30–59) months.

Of the 109 patients, 75 were scheduled for the liver-first strategy and 34 for the classical strategy. A ratio of 26/75 patients (35%) did not complete the planned treatment in the liver-first group compared to the ratio of 10/34 patients (30%) in the classical group (P=0.664). A disease progression was the most common reason for failure to adhere to the treatment plan, as shown in figure 8.

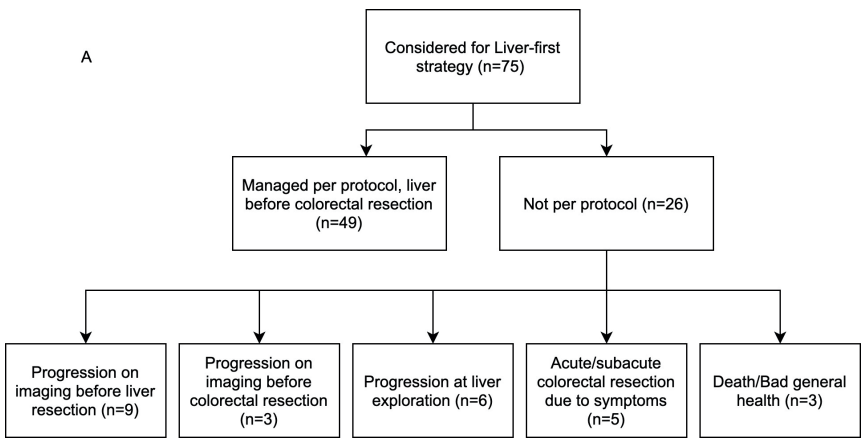

Figure 8A.
This figure shows a flow chart of patients planned for a liver-first strategy.

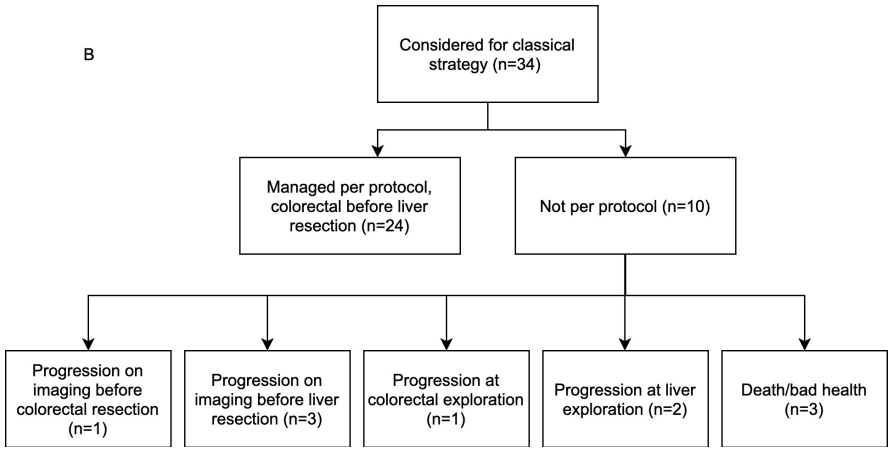

Figure 8B.
This figure shows a flow chart of patients planned for a classical strategy.

The 67 patients that had undergone resections of the primary colorectal cancer before the MDT and the 24 patients that underwent the primary resection after the MDT constituted the classical strategy group (n=91). Characteristics of these patients and the patient that accomplished the liver-first strategy are shown in table 2.

Table 2.
Characteristics of resected patients cohort. Data presented as number (percentage) or median (interquartile range). ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen. *Not included in survival analysis.

	CLASSICAL STRATEGY	LIVER-FIRST STRATEGY	P
Number of patients	91	49	
Male gender	55 (60%)	38	0.007
Age (years)	68 (63 – 74)	65 (58 – 69)	0.033
Current smoking	16 (18%)	9	1.000
Diabetes mellitus	11 (12%)	3	0.379
ASA 3	27 (30%)	14	0.706
Body mass index (kg/m2)	25 (23 – 27)	25 (23 – 28)	0.824
Rectal primary	29 (32%)	34	<0.001
CEA at diagnosis (mg/L)	4 (2–10)	18 (6–96)	<0.001
Pathological T stage 4	28 (31%)	11	0.329
Pathological node-positive	65 (71%)	31	0.855
Number of liver tumors	2 (1–4)	2 (2–4)	0.516
Size of largest liver tumor (mm)	20 (14 – 30)	25 (20 – 45)	0.004
Synchronous lung metastases	8 (9%)	7	0.400
Major liver resection	40 (44%)	28	0.158
90-day mortality after last resection	1*	0	1.000

Median recurrence-free survival was 19 (15–24) months for the liver-first strategy group and 25 (18–31) months for the classical strategy group (n=91), with multivariate survival HR for the liver-first group of 1.23 (95% CI: 0.75 – 2.02, P=0.406), compared to the classical group. Median survival after diagnosis for the whole classical strategy group (n=91) was 60 (48–73) months compared to 46 (31–60) months for the liver-first strategy group (n = 49), P=0.310, with univariable survival HR for the liver first 1.36 (95% CI: 0.75-2.49, P=0.312), compared to the classical group.

Main findings in paper II

A total of 707 patients with sCRLM underwent liver resection, with 84 patients only undergoing liver resection but no colorectal resection. We identified 623 patients that underwent both colorectal and liver resections within 12 months, of which 246 (39%) underwent a liver-first strategy, and 377 (61%) underwent a classical strategy. The median follow-up time was 40 (27 – 57) months.

A total of 264 of the 623 patients that underwent both colorectal and liver surgery, died during the study period. The overall 5-year survival was 54% for the classical strategy group and 49% for the liver-first strategy group (P=0.344). Time from the first to the second operation was 4.7 (2.8 – 6.1) months for the classical strategy group, and 2.0 (1.4 – 3.7) months for the liver-first strategy group (P < 0.001).

Patients in the classical strategy group were older (66 vs. 62 years, P<0.001), had more T4 primary tumors (23 vs. 14%, P=0.012) and node-positive primary tumors (70 vs. 61%, P=0.015). The liver-first group had more radio-chemotherapies (92 vs. 26%, P<0.001), major liver resections (52 vs. 41 %, P=0.008), and higher liver tumor burden score (TBS, i.e., 4.1 (2.5–6.3) vs. 3.6 (2.2–5.1), P=0.003). Characteristics are shown in table 3.

We found that 281 patients had primary rectal tumors, where 115 (41%) followed the classical strategy, and 166 (59%) were treated according to the liver-first strategy. The overall 5-year survival showed no significant difference, regardless of the surgical strategy (51% vs. 47%, P=0.474).

We found that 342 patients had primary colon cancer, of which 262 (77%) followed the classical strategy, and 80 (23%) followed the liver-first strategy. The 5-year overall survival showed no significant difference between the groups, regardless of surgical strategy (56% vs. 51%, P=0.564), with multivariate survival HR of 1.09 (95% CI 0.80-1.50, P=0.576).

Table 3.
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; R0, radical resection; TBS, tumor burden score.

	CLASSICAL STRATEGY	LIVER-FIRST STRATEGY	P
Number of patients	377	246	
Gender (Male)	234 (62%)	161 (65%)	0.397
Age (years)*	66 (58 – 73)	62 (54 – 69)	<0.001
ASA score 3–4	74 (20%)	57 (23%)	0.365
BMI (kg/m2)*	25 (23 – 28)	25 (23 – 27)	0.127
Primary rectal cancer	115 (31%)	166 (67%)	<0.001
Chemotherapy before the first resection	97 (26%)	220 (92%)	<0.001
Radiotherapy before bowel resection	84 (22%)	153 (62%)	<0.001
T4 primary tumor	85 (23%)	35 (14%)	0.012
Lymph node-positive primary tumor	264 (70%)	149 (61%)	0.015
R0 primary tumor resection	344 (92%)	221 (91%)	0.663
Liver TBS*	3.6 (2.2 – 5.1)	4.1 (2.5–6.3)	0.003
Major liver resection	152 (41%)	125 (52%)	0.008
R0 liver resection	262 (86%)	173 (86%)	0.896

Eighty-four patients underwent liver but no colorectal resections. Patient characteristics are shown in table 4. The only-liver-resection group had an overall 5-year survival of 14 (8 – 28) %.

Table 4.
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; R0, radical resection; TBS, tumor burden score.

	ONLY-LIVER-RESECTION	LIVER-FIRST STRATEGY	P
Number of patients	84	246	
Gender (Male)	65 (77%)	161 (65%)	0.043
Age (years)*	66 (58 – 72)	62 (54 – 69)	0.007
ASA score 3–4	16 (19%)	57 (23%)	0.451
T4 primary tumour (preoperative)	22 (34%)	35 (14%)	<0.001
Lymph node positive primary tumour (preoperative)	49 (72%)	161 (75%)	0.637
Primary rectal tumour	63 (75%)	166 (67%)	0.219
Chemotherapy before liver resection	71 (85%)	220 (90%)	0.165
Liver TBS*	4.9 (2.8 – 9.0)	4.1 (2.5 – 5.0)	<0.001
Major liver resection	35 (52%)	125 (52%)	1
R0 liver resection	39 (66%)	173 (86%)	0.002

Main findings in paper III

From SCRCR, we identified 39,016 patients diagnosed with colorectal cancer, of which 6,105 (16%) patients had liver metastases (sCRLM) at the time of diagnosis. Of the CRLM patients, a total of 1,571 (26%) underwent elective surgery of the primary colorectal tumor, and 783 patients (50%) underwent both colorectal and liver resections, constituting two percent of the initially identified patient group (n=39,016) and 13% of the patients with sCRLM (n=6,105), as seen in Figure 9. We found 377 patients that had followed the classical strategy and 160 that followed the simultaneous strategy, resulting in a total of 537 patients. The follow-up time had a median of 41 (27 – 58) months.

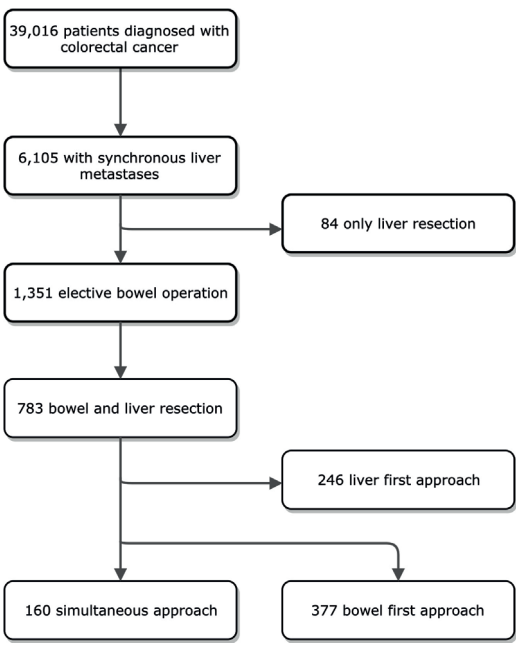

Figure 9.
The study cohort population from SCRCR and SweLiv.

Patients in the simultaneous strategy group had fewer rectal primary tumors (22% vs. 31%, p=0.046), fewer major liver resections (16% vs. 41%, p<0.001), fewer neoadjuvant chemotherapies (64 vs 73 %, p=0.029), less total bleeding

(600 vs 850 ml, <0.001), as well as a shorter total length-of-stay (11 vs. 15 days, p<0.001). The simultaneous strategy group had, however, a higher total complication rate from either the colorectal or liver procedure that demanded treatment (52% vs. 36%, p<0.001). Patient characteristics are shown in Table 5. We found a no significant overall survival difference between the groups (P=0.110), with a 5-year survival of 54% in the classical strategy group and 46% in the simultaneous strategy group, with a median survival of 49 and 58 months and a multivariate survival HR of 0.83 (95% CI: 0.6-1.14) for the simultaneous group compared to the classical group, P=0.243.

A total of 25 patients had a major liver resection in the simultaneous group and 155 in the classical strategy group, with no significant difference in 5-year overall survival (P=0.198).

Table 5.
Characteristics of the resected patient cohort. Percentages are in parentheses unless otherwise indicated: * median (interquartile range). ASA, American Society of Anesthesiologists. BMI, Body mass index. R0, Radical resection.

	CLASSICAL STRATEGY	SIMULTANEOUS STRATEGY	P
Patients	377	160	
Male	234 (62%)	90 (56%)	0.211
Age (years)*	66(58-73)	65(58-72)	0.396
ASA (3-4)	74 (20%)	32 (20%)	0.906
BMI (kg/m2)	25.4(23.1-27.5)	24.9(22.5-27.8)	0.434
Preoperative radiotherapy	84 (22%)	29 (18%)	0.300
Neoadjuvant chemotherapy	274 (73%)	101 (64%)	0.029
Localization (rectum)	115 (31%)	35 (22%)	0.046
T4 primary	85 (23%)	41 (26%)	0.435
Lymphatic node-positive, primary tumors	264 (70%)	105 (66%)	0.411
Number of liver tumors*	2(1-4)	2(1-4)	1
Liver tumor size (mm)*	20(14-35)	20(12-30)	0.202
Tumor burden score*	3.6(2.2-4.2)	3.2(2.1-4.5)	0.500
Portal vein embolization	15 (4%)	0 (0)	0.008
Major liver surgery	152 (41%)	25 (16%)	<0.001
R0 liver resection	350 (93%)	145 (91%)	0.370
Total loss of blood (ml)	850(474-1456)	600(250-950)	<0.001
Total complications, demanding treatment	136 (36%)	84 (52%)	<0.001
Total length-of-stay (days)*	15(12-20)	11(8-15)	<0.001

We identified 135 patients that underwent a minor liver resection in the simultaneous group and 222 in the classical group. The simultaneous minor group had: fewer rectal primary tumors (5 vs 33%, p < 0.001), less total bleeding (600 (300 - 900) vs. 700 (350-1250) ml, p=0.003) and shorter total

length-of-stay (11 (7 - 15) vs 16 (14 - 20) days, $p < 0.001$) compared to classical minor group. No other difference was found to be significant between the groups. The overall 5-year survival showed no significant difference (P=0.131).

When comparing the group with elective colorectal and no liver surgery (primary only, n=788) to the simultaneous group, we found that the primary only group was older (72 (64-79) years, P<0.001), had more T4 primary tumors (291 (37%), P=0.010), more node-positive primaries (630 (82%), $p < 0.001$), and a higher proportion of patients with ASA 3-4 (228 (29%), P=0.027). The primary only group had an 11% 5-year overall survival and a median survival of 15 months.

A new score applicable to patients with sCRLM was calculated (TTBS). After stratification of the TTBS into three subgroups - *TTBS <5, TTBS ≥5 and <10 and TTBS ≥10*, - we found a 3-year overall survival 80.7%, 59.6% and 21.7% respectively, p<0.001. The TTBS had a similar area under the curve (AUC) as the previous tumor burden score, 0.688 vs. 0.628, respectively, p=0.100.

Main findings in paper IV

Ninety-nine patients with recurrent CRLM underwent a repeated (second) procedure. Images before the first and second procedures and after the second procedure were available for 82 patients, which constituted our study cohort. Median follow-up was 53 (40-71) months from the first procedure.

The initial functional-liver-volume (FLV) was 1584 (1313–1927) ml, compared to 1438 (1204–1896) ml after the initial procedure, and 1470 (1172–1699) ml after the repeated procedure (P<0.001).

Liver volumes ratios after initial resections and repeated resections divided by the initial FLVs showed no significant difference, P=0.532, shown in figure 10. After the first procedure, nine patients had a FLV of less than 75% of the original FLV, and ten patients had a FLV of less than 75% of the initial FLV after the second procedure.

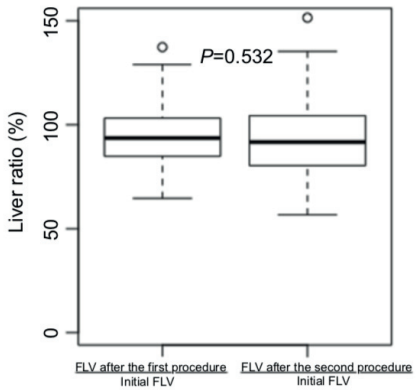

Figure 10.
Liver volume ratios after the first and second procedures divided by the original function liver volume (FLV).

Patients that underwent only minor procedures had no significant reduction in liver volume (P=0.621 and P=0.792, respectively). Patients that underwent one major and one minor procedure had significantly smaller liver volume after the repeated procedure compared to patients only undergoing minor procedures, 87 (79–101) % vs. 98 (86–108) % respectively, P=0.013.

We discovered no significant difference in liver volume for patients receiving chemotherapy (n=74) compared to those not receiving chemotherapy (n=8), 100 (95–108) % vs. 91 (80–103) %, P=0.200).

After the first procedure, we found an overall 5-year survival of 60 (47–70) % and 37 (26–54) % after the repeated procedure. We found no significant difference in complication rate (Clavien-Dindo classification ≥3) between the first procedure (13 patients (16%)) and the second procedure (15 patients (18%)), P=0.846.

A linear correlation between total estimated liver volume (TELV) and measured FLV before the initial, before the repeated, and after the repeated procedures showed a correlation of r=0.57, r=0.68, and r=0.55, respectively (P<0.001).

General discussion

The liver-first strategy, as introduced by Mentha et al.[80], includes preoperative chemotherapy, resection of the colorectal liver metastases followed by resection of the primary colorectal cancer at a later stage. One rationale for this strategy is the risk of liver metastases progression beyond resectability during the time it takes to go through the primary resection, especially in case of advanced liver disease or major complications following colorectal surgery. Another theoretical advantage of the liver-first strategy is the time-window interval between the preoperative chemoradiotherapy and resection for the advanced rectal cancers where the surgeon can resect the liver metastases. As stated in the introduction chapter, patient selection is uncertain, and most studies only analyze already resected patients. Most patients will experience a disease progression after metastasectomy, with repeated resections having an acceptable recurrence rate and survival compared to after the first resection. It is uncertain how the liver volume regenerates after a repeated resection for CRLM.

Paper I

STRENGTHS	LIMITATIONS	KEY ASSUMPTIONS
One large Swedish liver center. Descriptive and comparative analysis of the treatment process for patients with sCRLM after the MDT selection.	Retrospective. Non-randomized. Groups are not equal. Troublesome to generalize because of the variation between hospitals. A limited number of patients. Patient selection to the MDT unknown.	About one in three will not complete a planned treatment, most often because of disease progression.

There was no significant difference between groups concerning T4 stage or node-positive primaries, reflecting that the extent of liver disease is perhaps the most crucial factor when selecting patients for each strategy. No significant survival difference was found between the liver-first strategy or the classical

strategy, which is comparable to other studies[81], particularly noting the more severe liver tumor burden in patients chosen to the liver-first strategy, as previously shown[96]. We found that 35% of patients selected for the liver-first strategy could not accomplish the planned treatment strategy, which is slightly higher than previously published (20 - 32%)[80,97,98]. It may seem excessive, but it was similar and not significantly higher than the classical strategy planned group, with a ratio of 10/34 (29%). The reason for not completing was tumor progression, highlighting the importance of including patients that are assigned to a treatment plan but will not complete it when evaluating the effectiveness of different strategies.

Paper II

STRENGTHS	LIMITATIONS	KEY ASSUMPTIONS
Register-based study for the whole of Sweden. The study shows the current practice with real patient outcomes and clinical inclusions.	Non-randomized. No intention to treat analysis. Selection bias. Variation between hospitals. Disease-free survival was difficult to deduce.	The liver-first strategy group had more rectal primary tumors, advanced liver disease, and fewer node-positive primaries compared to the classical group Survival did not differ significantly.

Patients chosen to the liver-first strategy were significantly younger, had fewer lymph node-positive tumors, and underwent more major-liver resections compared to patients allocated to the classical strategy. Also, the liver-first group had more primary rectal cancers and had a higher ratio of preoperative radio-chemotherapy, probably reflecting the opportunity to perform liver surgery during the waiting time after the treatment for rectal cancer. No significant difference was noted in five-year overall survival between the groups (54% vs. 49%, P=0.344), as well as after adjusting for confounders.

The liver TBS, as previously described by Sasaki et al., has shown a discriminatory prognostic power and may be used for calculating survival differences. The concept is similar to the ‘metro ticket' prognostic system introduced for liver transplantation for hepatocellular carcinoma[52,99]. The liver-first group had a more advanced liver TBS, most probably illustrating that the liver-first strategy is increasingly applied when patients present with advanced liver metastases and a low-symptomatic primary tumor. The motivation presumably to first remove the tumors believed to be more threatening to patient health.

Eighty-four patients underwent liver resection but no colorectal resection. The reasons are unknown from the patient registers, but in the paper I, we had up to 35% of patients not completing the intended treatment. The patients who only underwent liver resection were older and had more advanced primary tumors, more advanced liver tumors, and fewer radical liver resection margins compared to patients completing the two resections in the liver-first group.

Paper III

STRENGTHS	LIMITATIONS	KEY ASSUMPTIONS
Register-based study for the whole of Sweden. Shows current practice and real patient outcomes with clinical inclusions.	Non-randomized. No intention to treat analysis. Selection bias. Variation between hospitals. Disease-free survival was difficult to deduce. Complications were difficult to sub-analyze.	Patients selected for simultaneous liver and primary resection had a shorter total length-of-stay, similar overall survival but higher complication rate in comparison to patients selected to a classical strategy.

We found that the simultaneous strategy group had a shorter total length-of-stay, fewer rectal primaries, more complications that demanded treatments, fewer major liver resections, and less total bleeding compared to the classical strategy group. It was not possible to classify the morbidity, e.g., with the Clavien-Dindo classification. This can make a comparison with previous studies difficult. We did not find any difference regarding gender, age, ASA score, BMI, radiotherapy, T4 primary, lymph node-positive primary, number of liver metastases, liver tumor size, total tumor burden in the liver, or R0 liver resections between the study groups. Patients are perhaps selected based on the extent of the planned liver and colorectal surgery. Despite the higher complication rate in the simultaneous strategy group, the total length-of-stay was shorter, perhaps denoting less clinically significant complications. No significant difference in overall survival was found between the groups, both before and after adjustment, as reported in previous studies[36,81].

The novel TTBS score, subdivided into three groups, showed a significant overall survival difference between the groups but with a similar area under the curve (AUC) to the previous tumor burden score (p=0.100). The most unfavorable group had a very poor overall survival, but no external validation has been made.

When comparing the groups of patients that underwent major-liver resections (simultaneous vs. classical strategy), we found no significant difference in 5-year overall survival, but the simultaneous major-liver resection group was small (n=25).

Paper IV

STRENGTHS	LIMITATIONS	KEY ASSUMPTIONS
A retrospective cohort study from two large liver centers. A reasonably large number of patients.	Non-randomized. No intention to treat analysis. Selection bias. Immortal time bias. Variation between hospitals. Intervariation between observers. Liver resection not measured peri- or postoperatively. No information was available about histological parenchymal damage.	Small changes in FLV were found after two liver procedures but with a noticeable inter-individual variation.

The liver has a remarkable regenerative ability. After repeated procedures, it is essential to estimate liver regeneration when scheduling a second or even a third liver procedure.

The liver volume decreased minimally and nearly reached the preoperative volume, for most patients, after two liver procedures. This being similar to results from one previously published study on the subject, which included 21 patients[73]. We found a noticeable unknown inter-individual variation, with ten patients who had an FLV of less than 75% of the initial FLV after the second procedure. Minor procedures did not change the liver volume significantly, but we found a significant reduction in FLV after major-resections.

We found no significant difference in liver regeneration for patients that received chemotherapy vs. those that received none, but that group was small (n=8).

Total estimated liver volume (TELV) and measured total liver volumes had r^2 values between 0.30–0.46, indicating that the formula explains only 30–46% of the variability in the measured volume. More studies are needed to address this issue.

The overall 5-year survival was 37 (26–54) % after the repeated procedure, in line with previous publications. A considerable variation in survival is found in the published literature, with 5-year overall survival ranging between 3.5 – 55% after repeated resections[100,101].

Conclusions

- About 35% of patients with sCRLM do not complete the intended treatment of liver and colorectal resections, regardless of the treatment strategy.
- The liver-first strategy is currently the dominant strategy for sCRLM in patients with rectal cancer in Sweden. We found no significant difference in overall survival between the liver-first and the classical strategies.
- Simultaneous resection for the primary colorectal cancer and liver metastases appears to have more complications but with no significant difference in overall survival compared to the classical strategy.
- Small changes in FLV were found after two liver procedures but with a noticeable inter-individual variation. We found an acceptable survival for patients chosen for a repeated hepatic procedure for recurrent CRLM.

Future challenges

Colorectal cancer is a common disease that affects approximately 6,500 patients each year in Sweden, and about 2,000 patients will be diagnosed with CRLM each year. Even though we now have better screening, oncological- and surgical treatments, age-adjusted mortality has decreased for colon cancer but has been relatively stable for rectal cancer[20,22,23]. When looking at causality, we often refer to the father of epidemiology and medical statistics, Sir Austin Bradford Hill. In his 1965 publication, nine critical criteria to establish a causal relationship were listed[102]:

- strength of association, i.e., a more significant association means a stronger causal relationship.
- consistency, i.e., consistency between multiple studies.
- specificity, i.e., a "single" factor that explains the causation.
- temporality, i.e., an exposure or treatment, comes before an outcome.
- biological gradient, i.e., the dose-response relationship, is found.
- plausibility, i.e., different models can explain the causation.
- coherence, i.e., can be explained by current knowledge or paradigm.
- experiment, i.e., experimental studies that can explain the observational studies.
- analogy, i.e., is there another similar causation.

A few more causality assumptions are nowadays essential in order to asses causality, e.g., the ignorability assumption where outcomes are independent of the treatment, the stable unit treatment value assumption (SUTVA) where outcomes of one is unaffected by assignment of other, and the positivity assumption, where an individual has a positive probability of receiving treatment[103].

Can this thesis fulfill the above causality assumptions and Bradford Hills criteria? Is there enough evidence to conclude which strategy is best for sCRLM? Is there enough evidence to conclude how we select patients with a real prospective intention to treat analyses? Is the treatment independent of the outcome? Do similar patients get the same chance of treatment? Are the studies consistent and plausible enough? Is the biological paradigm of metastatic cancer coherent to surgical and ablative treatments of CRLM? Do we need experimental studies such as controlled trials or randomized controlled trials on the subject?

In order to continue our work and answer the questions above, further studies are needed.

- A prospective intention to treat analysis for all patients diagnosed with colorectal cancer disease is needed. There we would hopefully understand the selection process better.
- A multicenter randomized controlled trial for patients with technically resectable sCRLM is needed. There we could compare the classical, liver-first, and simultaneous strategy. We could even have the fourth strategy, where patients would only receive the best supportive therapy. In order to organize the trial, vast resources would be needed, with cooperation from many surgical centers. The ethical aspect of having a patient group only receiving the best supportive treatment would need extensive ethical consideration. By conducting a controlled trial, we could hopefully limit confounders and answer which strategy is best, and if liver resection is superior to supportive therapy.
- A prospective evaluation of liver regeneration after both single and repeated liver resections for CRLM is needed. There, both the liver function and exact liver resection volume could be calculated.

Populärvetenskaplig sammanfattning på svenska

Introduktion

Cancer är en mycket vanlig sjukdom och en av fyra kommer att drabbas under livets gång. Under senare tid har man kunnat behandla spridd cancer med bra överlevnadsmöjligheter. Ändtarms- och tjocktarmscancer är den tredje vanligaste cancern i Sverige och ca 6 500 patienter diagnostiseras varje år. Ungefär var femte patient har redan spridning till levern vid upptäckt av cancern. Vi tror att bästa tillgängliga behandlingen är att operera bort tumörerna, när det är möjligt.

Hur vet vi vilken behandling är bäst för patienter med samtidig tarm- och levercancer? Tänk dig att man står framför tre olika dörrar och måste välja rätt. Bakom första dörren har vi den mest kända tekniken som kallas tarmen-först, där opererar vi bort tarmtumören och sedan levermetastaserna med en annan operation senare. Bakom nästa dörr har vi levern-först-tekniken, där levermetastaserna opereras innan tumören i tarmen. Slutligen finns den sista dörren där alla tumörer i både levern och tarmen tas bort vid samma operationstillfälle, den samtidiga-tekniken.

Hur många patienter som man planerar för både lever- och tarmkirurgi kommer att genomgå operation av både levern och tarmtumören? Spelar det roll på vilket sätt man väljer att operera cancer som har spritt sig till levern och slutligen, hur växer levern när man har genomgått två operationer i levern?

Artikel 1

I det första arbetet undersökte vi hur många av patienterna som vi väljer till lever- och tarmkirurgi genomgår den planerade behandlingen i verkligheten. Vi undersökte alla patienter som hade tarmcancer och metastaser till levern och skickades med remiss till Skånes Universitetssjukhus mellan 2011 och 2015. Vi identifierade 109 patienter som planerades till operation, 75 patienter planerades till levern-först och 34 till tarmen-först. Tjugosex patienter (35%)

lyckades inte fullföra behandlingen i levern-först gruppen jämfört med 10 (29%) i tarmen-först gruppen (ingen signifikant skillnad). Orsaken till misslyckande var oftast sjukdomens progression. Medianöverlevnaden var 46 (31–60) månader i gruppen som opererades med lever-först-tekniken.

Artikel 2

Det andra arbetet handlade om skillnaden mellan tarmen-först-tekniken och levern-först-tekniken. Vi använde två nationella register i Sverige mellan åren 2008 och 2015 och där kunde vi kartlägga och jämföra om det fanns någon skillnad vad gäller överlevnad och behandlingsresultat. Vi identifierade 623 patienter, varav 246 hade genomgått levern-först-tekniken och 377 tarmen-först-tekniken. Patienter i tarmen-först gruppen hade oftare signifikant sämre tarmtumörer (23% vs. 14%) och lymfkörtel positiva tarmtumörer (70 vs. 61%). Vi hittade ingen överlevnadsskillnad efter 5 år. En majoritet (59%) av patienter med rektalcancer behandlades med levern-först tekniken.

Artikel 3

Det tredje arbete handlade om skillnaden mellan tarmen-först-tekniken och den samtidiga-tekniken. Vi använde igen två nationella register i Sverige mellan åren 2008 och 2015 och jämförde och kartlagde skillnaden mellan teknikerna. Vi identifierade 537 patienter, varav 160 genomgick den samtidiga-tekniken. Patienter som hanterades med den samtidiga-tekniken hade färre primära tumörer i ändtarmen (22 vs. 31%), genomgick mer sällan stor leverkirurgi (16 vs. 41%), hade signifikant kortare total sjukhusvistelse (11 vs. 15 dagar) men fler behandlingskrävande komplikationer (52 vs. 36%). Ingen signifikant skillnad påträffades i femårs överlevnad. Totalt 25 patienter genomgick en stor leverresektion i den samtidiga gruppen. Där hittade vi ingen signifikant skillnad i femårsöverlevnad.

Artikel 4

Det fjärde arbetet handlade om att radiologiskt mäta leverns tillväxt och undersöka överlevnadsdata efter en upprepad leverprocedur för återkommande metastas i levern. Den initiala levervolymen (FLV) var 1584 (1313–1927) ml. FLV var 1438 (1204–1896) ml efter den första proceduren och 1470 (1172–1699) ml efter den andra proceduren. Signifikant skillnad fanns mellan mätningarna. Efter den andra proceduren hade tio patienter (12%) en återstående levervolym på mindre än 75% av den ursprungliga levervolymen. Den femåriga överlevnaden var 37 (26–54) % efter den andra proceduren.

Slutsatser

Upp till 35% av patienterna med tjock- och ändtarmscancer och synkrona levermetastaser slutför inte den planerade behandlingen av lever- och tarmresektioner, oavsett behandlingsstrategi.

Levern-först-tekniken är för närvarande den dominerande strategin för patienter med ändtarmscancer och levermetastaser i Sverige. Ingen signifikant skillnad i överlevnad observerades mellan levern-först och tarmen-först-tekniken.

Samtidig resektion av tarmcancern och levermetastaserna verkar ha fler komplikationer men utan någon signifikant skillnad i överlevnad jämfört med tarmen-först-tekniken.

Icke-signifikanta skillnader påvisades i leverns tillväxt efter två leverprocedurer men betydande variationer för ett fåtal patienter. Patienter utvalda för en upprepad leverprocedur för återkommande CRLM hade en acceptabel överlevnad.

Vísindaleg samantekt á íslensku

Inngangur

Krabbamein er algengur sjúkdómur. Fyrir ekki svo löngu síðan var útbreitt krabbamein ólæknandi en í seinni tíð hafa lífslíkur aukist. Ristil- og endaþarmskrabbamein (þarmakrabbamein) er þriðja algengasta krabbameinið í Svíðþjóð og um 6.500 sjúklingar greinast á ári hverju. Um það bil einn af hverjum fimm sjúklingum hefur, þegar við greiningu, meinvörp í lifur. Best er að fjarlægja frumæxlið og meinvörpin, ef það er mögulegt á annað borð.

Þrjár mismunandi aðferðir eru í boði fyrir sjúklinga sem greinast samtímis með krabbamein i þörmum og lifur. Fyrsta aðferðin hefur þekkst hvað lengst og kallast klassíska aðferðin (KA), þar sem æxlið í þarminum er fjarlægt fyrst og meinvörp í lifur eru fjarlægð síðar með annarri aðgerð. Næsta aðferðin er lifrin-fyrst aðferðin (LFA), en þar meðhöndlast lifrarmeinvörpin fyrst og krabbameinið í þörmunum síðar. Að lokum kemur samhliða aðferðin (SA) þar sem allt krabbameinið, þ.e. æxlið í þörmunum og lifrarmeinvörpin, eru fjarlægð á sama tíma.

Hve margir sjúklingar gangast undir þá aðgerð sem er fyrirfram ákveðin? Skiptir máli hvaða aðferð við veljum þ.e. klassíska, lifrin-fyrst eða samhliða aðferðina? Hvernig vex lifrin eftir enduraðgerð?

Grein 1

Í fyrstu greininni könnuðum við hve margir sjúklingar gangast undir þá meðferð sem var fyrirfram ákveðin. Við skoðuðum alla sjúklinga sem voru með ristil- og endaþarmskrabbamein með lifrarmeinvörp, metnir á Háskólasjúkrahúsinu á Skáni á árunum 2011 til 2015. Sjötíu-og-sex sjúklingar voru fyrirfram valdir í LFA hópinn og 34 í KA hópinn. Tuttugu-og-sex sjúklingar (35%) í LFA hópnum náðu ekki að ljúka áætlaðri meðferð samanborið við tíu (29%) í KA hópnum, með engum tölfræðilegum mun. Orsök fyrir því að ekki tókst að ljúka skipulagðri meðferð var versnun á krabbameinssjúkdómnum.

Grein 2

Næsta grein fjallaði um muninn á KA og LFA. Við notuðum tvö sjúklingagagnasöfn í Svíþjóð milli áranna 2008 og 2015 þar sem við gátum kortlagt og borið saman hvort það var munur hvað varðar lifun og meðferðarárangur. Við bárum mat á 623 sjúklinga, þar af voru 246 í LFA hópnum og 377 voru í KA hópnum. Sjúklingar í KA hópnum höfðu oftar verra þarmakrabbamein (23% á móti 14%) og eitilvöxt (70% á móti 61%). Við fundum engan tölfræðilegan fimm ára mun á lífslíkum. Meirihluti (59%) sjúklinga með krabbamein í endaþarmi voru meðhöndlaðir með LFA.

Grein 3

Þriðja greinin fjallaði um muninn á KA og SA. Við notuðum aftur sömu sjúklingagagnasöfn í Svíþjóð milli áranna 2008 og 2015 og bárum saman og kortlögðum mismuninn á aðferðunum. Við mátum 537 sjúklinga, þar af 160 sem voru í SA hópnum. Sjúklingar í þeim hóp voru marktækt ólíklegri til að hafa frumæxli í endaþarminum (22% á móti 31%), ólíklegri til að gangast undir stóra lifraraðgerð (16% á móti 41%), höfðu styttri legutíma (11 á móti 15 dögum) en fleiri fylgikvilla (52% á móti 36%). Enginn marktækur munur fannst á fimm ára lífslíkum. Alls fóru 25 sjúklingar í stóra lifrarskurðaðgerð í SA hópnum.

Grein 4

Fjórða grein okkar fólst í að mæla vöxt lifrarinnar með myndgreiningartækni og kanna lifun eftir enduraðgerð við endurkomu á lifrarmeinvörpum. Upphaflegt lifrarrúmmál (FLV) var 1584 (1313-1927) ml. FLV var 1438 (1204–1896) ml eftir fyrstu aðgerðina og 1470 (1172–1699) ml eftir seinni aðgerðina. Marktækur munur var á milli lifrarmælinganna. Eftir seinni aðgerðina höfðu tíu sjúklingar (12%) minna en 75% af upphaflegu lifrarrúmmáli. Fimm ára lífslíkur voru 37 (26-54) % eftir seinni aðgerðina.

Niðurstöður

Allt að 35% af sjúklingum með þarmakrabbamein og lifrarmeinvörp ljúka ekki fyrirhugaðri meðferð, óháð meðferðaráætlun.

Í Svíðþjóð er lifur-fyrst aðferðin ráðandi hjá sjúklingum með bæði krabbamein í endaþarmi og lifrarmeinvörp. Enginn tölfræðilegur munur var á lífslíkum milli lifrin-fyrst og klassísku aðferðarinnar.

Samhliða aðferðin á krabbameini í þörmum og lifur virðist hafa meiri fylgikvilla en án nokkurs marktækts munar á lífslíkum miðað við klassísku aðferðina.

Litlar breytingar á lifrarstærð fundust í kjölfar endurtekinna lifraraðgerða en töluverður breytileiki var á milli einstakra sjúklinga. Sjúklingar sem fara í enduraðgerð vegna endurkomu á lifrarmeinvörpum hafa viðunandi lífslíkur.

Errata

- In paper I, under the chapter: Discussion, paragraph 2:
  - *Table 1* is supposed to be written instead of *table 2* after, ….clinical node-positive primaries……
- In paper II, table 4, the parameter Liver TBS for the Completed liver-first strategy group:
  - *...should be 4.1 (2.5 – 5.0) instead of 2.5 (4.1 – 5.0)*….
- In paper IV under the chapter: Selection of patients:
  - ….. resection *of three or more* Couinaud's ….. is to be written instead of …. resection *of more than three* Couinaud's …...

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Paper I

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ORIGINAL ARTICLE

Liver-first strategy for synchronous colorectal liver metastases – an intention-to-treat analysis

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Abstract

Background: The liver-first strategy signifies resection of liver metastases before the primary colorectal cancer. The aim of the present study was to compare failure to complete intended treatment and survival in liver-first and classical strategies.

Methods: All patients with colorectal cancer and synchronous liver metastases planned for sequential radical surgery in a single institution between 2011 and 2015 were included.

Results: A total of 109 patients were presented to a multidisciplinary team conference (MDT) with un-resected colorectal cancer and synchronous liver metastases. Seventy-five patients were planned as liver-first, whereas 34 were recommended the classical strategy. Twenty-six patients (35%) failed to complete treatment in the liver-first group compared to 10 patients in the classical group ($P = 0.664$). Reason for failure was most commonly disease progression.

A total of 91 patients had the primary tumor resected before the liver metastases of which 67 before referral and 24 after allocation at MDT. Median survival after diagnosis in this group was 60 (48–73) months compared to 46 (31–60) months in the group operated with liver-first strategy ($n = 49$), ($P = 0.310$).

Discussion: Up to 35% of patients with colorectal cancer and synchronous liver metastases do not complete the intended treatment of liver and bowel resections, irrespective of treatment strategy.

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Introduction

Liver metastases are present in 15–25% of patients with colorectal cancer at the time for diagnosis of the primary,[1,2] defined here as synchronous liver metastases. Treatment for potential cure includes surgical resection of all tumor sites. However, due to comorbidity or extensive disease only a minority of patients are candidates for curative resections. When surgical treatment is indicated, different strategies can be utilized. In the classical strategy the primary is resected first followed by resection of the liver metastases at a second stage with perioperative chemotherapy. More recently, simultaneous resection of the primary and the liver lesions has been employed, mainly for limited liver disease without the need for major liver resections.[3] A third option is preoperative chemotherapy, followed by resection of the liver metastases and resection of the bowel primary at a second stage.[4] This liver-first strategy has the potential advantage of allowing resection of advanced liver disease in patients when the primary tumor is asymptomatic. No clear advantage or disadvantage with either of the three strategies in terms of survival has been demonstrated.[5]

Most previous studies evaluating the liver-first strategy only include liver resected patients.[6–9] There are thus scarce data on how many and why patients scheduled for the liver-first strategy do not complete both liver and bowel resections, which is the aim of the present study to investigate.

Methods

The medical records of all patients with colorectal liver metastases between 2011 and August 2015 presenting to a

multidisciplinary team conference (MDT) were scrutinized and patients with synchronous liver metastases were chosen for further analysis. All patients had biopsy proven adenocarcinoma of colorectal origin. Patients were staged with multidetector computed tomography (MDCT) of the chest and multiphase MDCT of the abdomen. Magnetic resonance imaging (MRI) of the liver with liver-specific contrast was selectively used. In patients with rectal cancer, MRI of the pelvis was used for staging. From these patients, only patients with asymptomatic primary, resectable hepatic metastases (with or without the need for portal vein embolization) and, when present, resectable extrahepatic metastases were selected and thus constitute the patient cohort of the intention to-treat analysis. Data were retrospectively extracted from patient records and patients were divided into groups according to treatment strategy chosen, that is, classical or liver-first strategy. Patients in whom a simultaneous strategy was recommended were excluded.

In the intention to-treat analysis, only patients referred with their primary un-resected are included. Survival and recurrence free survival analysis, comparing the liver-first and classical strategies also include patients presented to the liver MDT after bowel resection, irrespective if the primary was symptomatic or not. After completed resections, patients had follow-up with MDCT of the chest and abdomen every six months the first two years and then yearly up to five years.

The study protocol was approved by the regional ethics committee.

Statistics

Results are expressed as median (interquartile range). Mann–Whitney *U* test was used to compare continuous data and Fischer's exact test for categorical data. Kaplan–Meier was used to estimate recurrence-free and overall survival from time of cancer diagnosis and the log-rank test was used to compare between liver-first and classical strategies. Cox regression analysis was used to calculate hazard ratios and 95% confidence intervals for risk factors for recurrence-free and overall survival. Factors with a *P*-value < 0.1 on univariable regression were included in a multivariable analysis. A $P < 0.05$ was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics version 22 (IBM, Armonk, NY, USA).

Results

A total of 176 patients with resectable synchronous liver metastases were identified and included in the study. Of these, 67 had their primary tumor resected before referral, giving 109 patients presenting to a MDT with radiologically resectable synchronous liver metastases and un-resected primary colorectal cancer. Seventy out of 109 patients (64%) were staged with MRI of the liver with gadoxetic acid contrast. Two patients scheduled for simultaneous resection were excluded.

Characteristics for patients chosen for the liver-first or classical strategy are shown in Table 1.

Of the 75 patients chosen for the liver-first approach, 26 (35%) failed the treatment plan (Table 2). Reasons for failure of the

Table 1 Characteristics of patients presenting with un-resected colorectal primary cancer and synchronous liver metastases

	Liver-first strategy	Classical strategy	*P*
Number of patients	75	34	
Male gender	56 (75%)	17	0.016
Age (years)	65 (58–72)	67 (58–70)	0.649
Current smoking	10 (13%)	5	1.000
Diabetes mellitus	4 (5%)	4	0.436
ASA 3	20 (27%)	5	0.208
Body mass index (kg/m^2)	25 (23–27)	24 (22–26)	0.136
Rectal primary	47 (63%)	15	0.095
CEA at diagnosis (μg/L)	17 (5–100)	9 (4–40)	0.106
Clinical T stage 4	24 (32%)	18	0.090
Clinical node positive	57 (76%)	25	0.449
Number of liver tumors	3 (2–4)	2 (1–4)	0.016
Size of largest liver tumor (mm)	25 (20–48)	22 (14–30)	0.039
Patients with lung metastases	10 (13%)	4	1.000

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

Table 2 Liver-first strategy failure and completed

	Failure	Completed	*P*
Number of patients	26	49	
Male gender	18	38	0.578
Age (years)	70 (60–74)	65 (58–69)	0.083
ASA 3	7	14	0.796
Body mass index (kg/m^2)	25 (23–27)	25 (23–28)	0.467
Rectal primary	13	34	0.133
CEA at diagnosis (μg/L)	12 (4–134)	18 (6–96)	0.700
Clinical T stage 4	10	14	0.440
Clinical node positive	20	37	1.000
Number of liver tumors	4 (2–7)	2 (2–4)	0.017
Size of largest liver tumor (mm)	28 (20–56)	25 (20–45)	0.789
Patients with lung metastases	3	7	1.000
MRI for liver staging	17	31	1.000
Resectable in liver at first MDT	20	40	0.763
Chemotherapy as first treatment	22	47	0.494

Data are presented as number or median (interquartile range). *ASA*, American Society of Anesthesiologists; *CEA*, carcinoembryonic antigen; *MRI*, magnetic resonance imaging; *MDT*, multidisciplinary team conference.

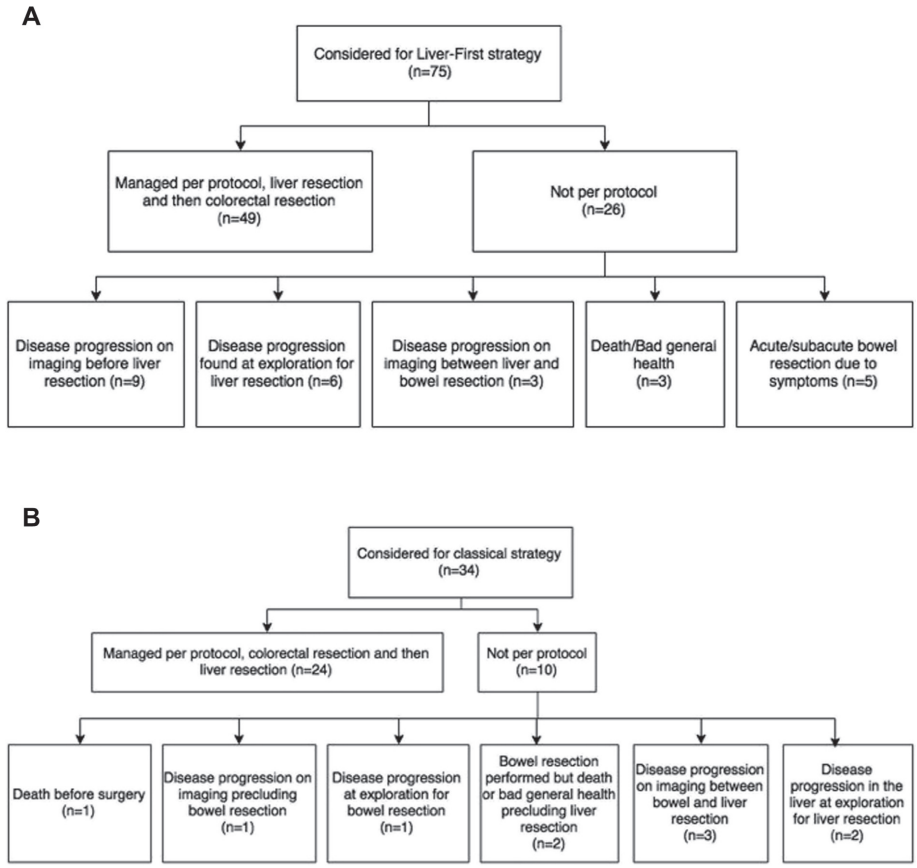


Figure 1 a. Flow chart of patients considered for the liver-first strategy. b. Flow chart of patients considered for the classical strategy

liver-first strategy are shown in Fig. 1a. One patient died of neutropenic sepsis due to neoadjuvant chemotherapy before any resection. Two patients did not receive further treatment due to bad general health, one before liver resection and one before bowel resection. Five patients had semi-emergent surgery of the bowel, of which two patients subsequently underwent liver resection, resulting in a total of 28 (37%) patients with tumor clearance of both liver and bowel in the liver-first group. Of the 34 patients planned for the classical approach 10 patients failed to receive the complete treatment (Fig. 1b). No statistically significant difference was noted between groups in terms of successful treatment according to plan ($P = 0.664$).

Median time from treatment decision to last resection in patients who completed the treatment plan was 4.4 (2.8–5.3) months in the liver-first group and 4.5 (2.5–6.0) months in the classical group ($P = 0.80$). Of patients completing surgical treatment, the total median number of chemotherapy cycles per patient was 11^{7-12} and 10^{8-10} in the liver-first group and the classical group, respectively ($P = 0.235$). The time distribution for perioperative chemotherapy is shown in Table 3. Oxaliplatin-based chemotherapy was used the most frequently and was administrated to 52 patients (71%). Neoadjuvant chemotherapy was administrated for 3 months with radiological evaluation after 2 months.

A total of 140 patients were successfully resected for cure in both bowel and liver. Of these, 49 patients (35%) were treated by the liver-first approach and 91 (65%) by the classical approach, including 67 patients presenting to our liver unit after resection

Table 3 Perioperative chemotherapy of patients completing surgical treatment

	Liver-first strategy	Classical strategy	*P*
Number of patients	49	24	
Preoperative chemotherapy	47	11	<0.001
Interval chemotherapy between resections	1	9	<0.001
Adjuvant chemotherapy	39	23	0.089

Data are presented as number of patients.

of the primary. Patient characteristics are shown in Table 4. Median follow-up from time of diagnosis was 42 (30–59) months. Kaplan–Meier plots of recurrence-free survival and overall survival for resected patients are shown in Fig. 2. Recurrence-free survival was 19 (15–24) months for the liver-first strategy and 25 (18–31) months for the classical strategy, without difference between groups ($P = 0.296$, Fig. 2a). No difference in overall survival was found ($P = 0.310$, Fig. 2b), with an overall survival of 46 (31–60) months for the liver-first strategy and 60 (48–73) months for the classical strategy. Time from diagnosis to the second operation was 6.1 (4.8–8.2) months in the liver-first group and 6.8 (5.3–8.7) months in the classical group, with no difference between groups ($P = 0.153$).

Table 4 Characteristics of resected patients

	Liver-first strategy	Classical strategy	*P*
Number of patients	49	91	
Male gender	38	55 (60%)	0.007
Age (years)	65 (58–69)	68 (63–74)	0.033
Current smoking	9	16 (18%)	1.000
Diabetes mellitus	3	11 (12%)	0.379
ASA 3	14	27 (30%)	0.706
Body mass index (kg/m^2)	25 (23–28)	25 (23–27)	0.824
Rectal primary	34	29 (32%)	<0.001
CEA at diagnosis (μg/L)	18 (6–96)	4 (2–10)	<0.001
Pathological T stage 4	11	28 (31%)	0.329
Pathological node positive	31	65 (71%)	0.855
Number of liver tumors	2 (2–4)	2 (1–4)	0.516
Size of largest liver tumor (mm)	25 (20–45)	20 (14–30)	0.004
Synchronous lung metastases	7	8 (9%)	0.400
Major liver resection	28	40 (44%)	0.158
90-day mortality after last resection	0	1*	1.000

Data are presented as number (percentage) or median (interquartile range). *ASA*, American Society of Anesthesiologists; *CEA*, carcinoembryonic antigen. *Not included in survival analysis.

Univariable and multivariable hazard ratio analysis of risk factors for recurrence-free and overall survival are shown in Tables 5 and 6.

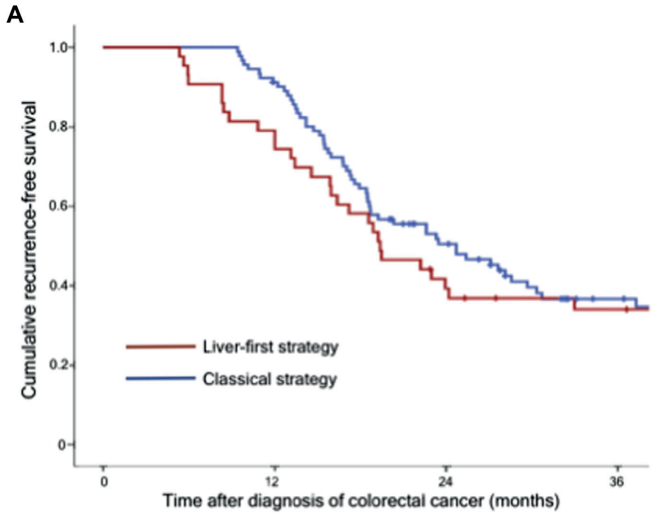
Discussion

The liver-first strategy as introduced by Mentha *et al.*[4] includes preoperative chemotherapy, resection of colorectal liver metastases followed by resection of the primary bowel cancer at a second stage. One rationale for this approach is the risk of progression beyond resectability of the liver metastases during the time it takes to go through bowel resection first, especially in case of advanced liver disease or in case of complications after bowel surgery. Another theoretical advantage of the liver-first approach is to use the time-window between long course preoperative chemoradiotherapy and resection for advanced rectal cancers to resect the liver metastases.

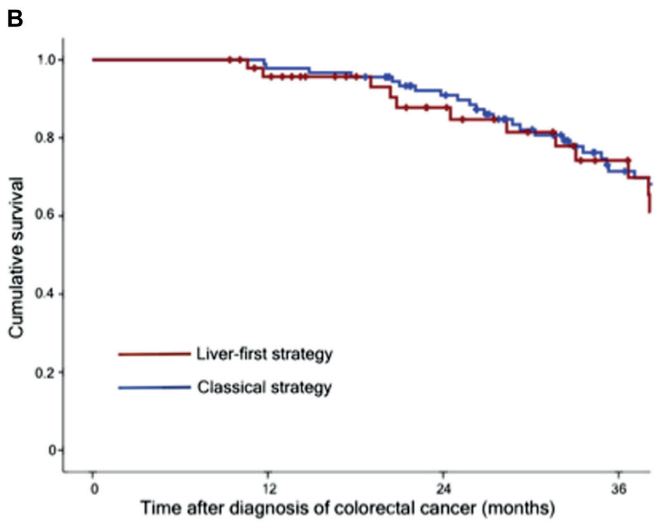
The strategy used as presented in the present study was to direct initial surgery to the tumor location judged the most difficult for achieving a radical resection. This strategy explains why, the liver-first patients had more and larger liver metastases compared to patients planned for the classical strategy (Table 1). As the concept of liver-first strategy is quite new and with unproven superiority over the classical approach, most patients have their primary resected before referral to our liver multidisciplinary conference. It can be assumed that many patients are first treated for a symptomatic primary before referral to a liver surgery unit. There was no difference between groups with respect to clinical T4 stage or clinical node positive primaries (Table 2), reflecting that it is the extent of liver disease that is the most important factor when selecting patients for either strategy.

No difference in survival has been demonstrated in patients treated with the liver-first or classical approach,[5] especially when taking into account the often more severe disease burden of the patients chosen for liver-first approach.[9] No significant differences could be found in overall or recurrence free survival between groups in the present study even though the liver-first group had a more severe liver tumor disease. This could be due to the limited number of included patients.

Most previous studies on patients undergoing liver-first treatment do not account for all patients that are unable to complete the treatment, but only report patients that have been resected in the liver.[6–8] In the present study the proportion of patients planned for a liver-first strategy that eventually completed the two surgeries according to plan was 49/75 (65%). The proportion of patients planned for the liver-first approach that eventually became resected with curative intent in both liver and bowel, regardless of treatment order was 51/75 (68%). The percentage of patients completing the liver-first approach has in previous studies been reported in the interval 67–86%.[10–12] However, it is difficult to determine if these studies have included all patients considered for the liver-first strategy departing from the initial liver multidisciplinary conference, as



Patients at risk				
Liver-first strategy	49	24	12	9
Classical strategy	91	53	27	14



Patients at risk				
Liver-first strategy	49	44	30	18
Classical strategy	91	90	76	44

Figure 2 a. Recurrence-free survival for resected patients with synchronous liver metastases, $P = 0.296$ (log-rank test). b. Overall survival, $P = 0.310$ (log-rank test)

Table 5 Cox proportional hazard analysis of risk factors for adverse recurrence-free survival outcome

Factor	Univariable analysis		Multivariable analysis	
	HR	*P*	HR	*P*
Liver-first strategy	1.55 (0.99–2.42)	0.054	1.23 (0.75–2.02)	0.406
Age >70 years	0.58 (0.36–0.95)	0.031	0.62 (0.36–1.06)	0.080
Male gender	1.85 (1.15–2.99)	0.011	1.86 (1.12–3.08)	0.016
ASA 3	0.93 (0.58–1.48)	0.765		
Neoadjuvant chemotherapy	1.83 (1.09–3.05)	0.021	1.32 (0.72–2.42)	0.367
Multiple liver tumors	1.82 (1.08–3.06)	0.024	1.27 (0.73–2.22)	0.390
Largest liver tumor >5 cm	1.40 (0.76–2.58)	0.280		
CEA > 200 μg/L	1.04 (0.38–2.88)	0.938		
Adjuvant chemotherapy	0.60 (0.35–1.04)	0.068	0.59 (0.33–1.05)	0.073
Rectal primary	1.16 (0.76–1.77)	0.482		
Synchronous lung metastases	1.35 (0.65–2.80)	0.419		
Primary T stage 4	1.20 (0.75–1.90)	0.455		
Node-positive primary	1.80 (1.09–2.98)	0.021	2.10 (1.22–3.63)	0.008
MDT before first resection	1.34 (0.88–2.06)	0.177		

Data are presented as hazard ratio (95% confidence interval). *HR*, hazard ratio; *ASA*, American Society of Anesthesiologists; *CEA*, Carcinoembryonic antigen; *MDT*, multidisciplinary team conference.

Table 6 Cox proportional hazard analysis of risk factors for adverse overall survival outcome

Factor	Univariable analysis		Multivariable analysis	
	HR	*P*	HR	*P*
Liver-first strategy	1.36 (0.75–2.49)	0.312		
Age >70 years	1.09 (0.60–1.98)	0.773		
Male gender	1.85 (0.97–3.55)	0.062	1.84 (0.95–3.54)	0.069
ASA 3	1.42 (0.80–2.55)	0.230		
Neoadjuvant chemotherapy	1.37 (0.70–2.66)	0.357		
Multiple liver tumors	1.04 (0.55–1.96)	0.905		
Largest liver tumor >5 cm	0.94 (0.40–2.22)	0.888		
CEA > 200 μg/L	0.64 (0.15–2.66)	0.537		
Adjuvant chemotherapy	0.53 (0.25–1.09)	0.084	0.57 (0.27–1.18)	0.131
Rectal primary	0.88 (0.51–1.53)	0.650		
Synchronous lung metastases	1.25 (0.53–2.95)	0.612		
Primary T stage 4	1.24 (0.68–2.28)	0.484		
Node-positive primary	2.22 (1.04–4.74)	0.039	2.32 (1.09–4.97)	0.030
MDT before first resection	1.41 (0.80–2.49)	0.237		

Data are presented as hazard ratio (95% confidence interval). *HR*, hazard ratio; *ASA*, American Society of Anesthesiologists; *CEA*, Carcinoembryonic antigen; *MDT*, multidisciplinary team conference.

was the case in the present study. The most common reason for failure of the liver-first strategy was disease progression, mainly in the liver, as detected on imaging (12/26) but also during laparotomy (6/26). Staging with liver-specific MRI before chemotherapy has been advocated to optimize surgical planning[13] and to reduce the rate of postoperative early recurrence in the liver[14] and was utilized in 17 of these 26 patients. All 26 patients but four had oxaliplatin or irinotecan-based preoperative chemotherapy.

The drop-out rate of 35% in the liver-first group may seem high. However, the proportion of patients that were planned for the classical approach completing the strategy was 24/34. No strategy was superior in making patients tumor-free in both liver and bowel. Of the 26 patients failing the liver-first strategy, 4 patients were not resected in the bowel after successful liver resection. Thus, the majority of patients who drop out from the liver-first treatment-plan do this before liver resection. This underlines the importance of accounting for all patients assigned a treatment plan in order to evaluate the effectiveness of the chosen strategy.

Five patients in the intended liver-first group had acute/subacute bowel operations because of obstruction symptoms, representing 7% of the liver-first cohort of patients, which is in line with previous results,[7] illustrating the relative safety of the liver-first strategy in this respect.

Perioperative chemotherapy is an integral part of treatment for colorectal liver metastases.[15] However, the best timing to deliver perioperative chemotherapy in patients with synchronous liver metastases is yet to be determined. In the present study, the number of chemotherapy cycles received per patient was equal between the liver-first and classical strategy groups (11 vs 10 cycles) in patients completing the treatment plan. However, the timing in relation to the resections was very different, with a lower percentage in the classical group receiving preoperative chemotherapy and only one patient receiving interval chemotherapy between liver and bowel resections. This is in contrast to the strategy reported by Brouquet *et al.*[7] describing a high proportion of patients treated with the classical approach receiving preoperative chemotherapy, and a high proportion of patients in the liver-first group receiving chemotherapy in the interval between surgeries.

During the study period 140 patients were resected for synchronous liver metastases at our institution of which 49 patients (35%) were treated with the liver-first approach. This can be

compared to the 17% as reported by Welsh *et al.*,[9] or the 24% reported by de Jong *et al.*[6] The difference is most probably explained by the lack of universal indications for the liver-first strategy in addition to the fact that the study period of the present study is somewhat more recent. The indications for the liver-first strategy are still evolving.

The median overall survival from cancer diagnosis for the liver-first strategy group was 46 months and is in line with previously reported results.[6–9] The time from diagnosis of colorectal cancer to last operation was in the present study 6 months for both the liver-first and the classical group. Previous studies on the liver-first approach have reported total treatment times of 9 and 11 months.[8,9] These treatment times do not include adjuvant chemotherapy. Hence, the total treatment time is even longer, a fact that could be important to convey to the patient in order to increase patient involvement and autonomy.

A shortcoming with this study is that it is retrospective and non-randomized, as previously reports on the liver-first strategy. Hence, the groups are not equal in all respects and the rationales for the chosen strategy are elusive. Multivariable analysis of recurrence-free and overall survival failed to identify any treatment-related factor influencing outcome.

In conclusion, the present study has shown that a large proportion of patients with synchronous colorectal liver metastases scheduled either for the liver-first strategy or the classical strategy fail to receive the complete intended treatment, for a multitude of reasons. Of resected patients, no difference in survival was found between the surgical strategies employed.

Conflict of interest statement

Authors have no commercial interest to disclose.

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Paper II

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ORIGINAL ARTICLE

Outcomes of liver-first strategy and classical strategy for synchronous colorectal liver metastases in Sweden

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Abstract

Background: Patients with synchronous colorectal liver metastases (sCRLM) are increasingly operated with liver resection before resection of the primary cancer. The aim of this study was to compare outcomes in patients following the liver-first strategy and the classical strategy (resection of the bowel first) using prospectively registered data from two nationwide registries.

Methods: Clinical, pathological and survival outcomes were compared between the liver-first strategy and the classical strategy (2008–2015). Overall survival was calculated.

Results: A total of 623 patients were identified, of which 246 were treated with the liver-first strategy and 377 with the classical strategy. The median follow-up was 40 months. Patients chosen for the classical strategy more often had T4 primary tumours (23% vs 14%, P = 0.012) and node-positive primaries (70 vs 61%, P = 0.015). The liver-first patients had a higher liver tumour burden score (4.1 (2.5–6.3) vs 3.6 (2.2–5.1), P = 0.003). No difference was seen in five-year overall survival between the groups (54% vs 49%, P = 0.344). A majority (59%) of patients with rectal cancer were treated with the liver-first strategy.

Conclusion: The liver-first strategy is currently the dominant strategy for sCRLM in patients with rectal cancer in Sweden. No difference in overall survival was noted between strategies.

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Introduction

Colorectal cancer is the third most common malignancy in the world[1,2] and 15–20 per cent of patients present with synchronous liver metastases at diagnosis.[3–5] Surgical resection of all tumours, when feasible, currently offers the only potential for cure. Traditionally, the primary tumour is resected as the first intervention, followed by resection of the liver metastasis in a second stage; this is called the classical strategy. In the last decade, increased focus has been on preoperative chemotherapy and resection of the liver metastases as the first intervention, followed by resection of the primary tumour, here described as the liver-first strategy, as introduced by Mentha *et al.*[6]

The liver-first strategy potentially avoids the disadvantage of the classical strategy, especially in the case of complications after bowel surgery, of postponing liver resection and the risk of progression of the liver disease beyond resectability. In addition, in the case of pre-treatment of rectal primaries with long course chemo-radiation, liver resection can be performed in the waiting time between radiation and rectal resection, possibly shortening the total treatment time. No survival differences have been

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demonstrated between the different strategies, although no randomized trials have been conducted on the subject.[7–10] The liver-first strategy appears safe for selected patients.

Previous studies are limited to single centre retrospective studies or include a relatively small number of patients.[11] The indications for proposing the liver-first strategy to patients are still evolving. No nationwide study on the liver-first strategy has previously been published. The aim of the present study was to compare the liver-first with the classical strategy for patients presenting with synchronous colorectal liver metastases (sCRLM), focussing on patient selection and survival, based on data from quality assurance registries in Sweden.

Methods

Patients were identified at the time of entry from the Swedish Colorectal Cancer registry (SCRCR) and the National Quality Registry for liver and biliary cancer (SweLiv) from January 2008 to December 2014. In the SCRCR, all patients diagnosed with adenocarcinoma of the colon or rectum are registered. In the SweLiv all patients who develop primary malignancy of the liver, gallbladder or bile ducts and all interventions related to both primary and secondary malignancy of the liver are registered. The SCRCR was launched in 2007 while the SweLiv was launched in 2008, and the registration of data is prospective. The SCRCR has been described previously[12] and covered 94–98% of all colorectal cancers during the study period, while SweLiv covered more than 90% of all primary liver and bile duct cancers.[13]

From the databases, patients with metastatic colorectal cancer at initial staging (before any resection) were identified and defined as having synchronous liver metastases. Patients who had undergone acute bowel resection or synchronous bowel and liver resections were excluded. The subset of patients who had undergone both bowel and liver resection within 12 months constitutes the study patient cohort. Patients with sCRLM who had only undergone liver resection but no bowel resection were identified separately. Patients were stratified according to the localization of the primary tumour (colon vs. rectum). A comparison was made between patients operated with the liver-first and the classical strategies. A major liver resection was defined as a resection of $\geq$3 Couinaud's segments. An R0 resection was defined as microscopically tumour free resection margin. A liver tumour burden score (TBS) was calculated for each patient [TBS^2 = (maximum tumour diameter in centimetres)^2 + (number of liver lesions)^2].[14]

Statistics

Summary statistics are presented as whole numbers and percentages for categorical variables, or as medians with interquartile ranges (IQRs) for continuous variables. A Mann–Whitney U-test was used to compare continuous data and Fischer's exact test was used for categorical data. Kaplan Meier analysis was used to estimate survival from the time of diagnosis. Overall survival was calculated from the time of diagnosis. To analyse the effect of patient and tumour specifics on survival, multi- and univariate Cox proportional hazards (PH) models were used for independent variables. A P-value less than 0.05 was considered statistically significant. Statistical analysis was performed using R (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Results

A total of 707 patients with sCRLM who underwent liver resection were identified. Eighty-four patients with metastatic colorectal cancer underwent liver resection but no bowel resection. A total of 623 patients underwent both bowel and liver resections within 12 months, of which 246 (39%) underwent a liver-first strategy and 377 (61%) underwent a classical strategy. The characteristics of the patients in the classical and liver-first groups are shown in Table 1. Two patients died (0.5 per cent) within 30 days after liver resection in the classical strategy group. In the liver-first group, none died within 30 days after bowel resection.

A total of 317 (50%) patients received preoperative chemotherapy before the first resection. The use of preoperative chemotherapy in the different groups is shown in Table 1.

Table 1 Characteristics of resected patients

	Classical strategy	Liver-first strategy	P‡
Number of patients	377	246	
Gender (Male)	234 (62)	161 (65)	0.397
Age (years)*	66 (58–73)	62 (54–69)	<0.001§
ASA score 3–4	74 (20)	57 (23)	0.365
BMI (kg/m^2)*	25 (23–28)	25 (23–27)	0.127§
Primary rectal cancer	115 (31)	166 (67)	<0.001
Chemotherapy before first resection	97 (26)	220 (92)	<0.001
Radiotherapy before bowel resection	84 (22)	153 (62)	<0.001
T4 primary tumour	85 (23)	35 (14)	0.012
Lymph node positive primary tumour	264 (70)	149 (61)	0.015
R0 primary tumour resection	344 (92)	221 (91)	0.663
Liver TBS*	3.6 (2.2–5.1)	4.1 (2.5–6.3)	0.003§
Major liver resection	152 (41)	125 (52)	0.008
R0 liver resection	262 (86)	173 (86)	0.896

Values in parentheses are percentages unless indicated otherwise: *values are median (interquartile range). ASA, American Society of Anesthesiologists; BMI, body mass index; R0, radical resection; TBS, tumour burden score. ‡Fischer's exact test, except §Mann–Whitney U test.

The median follow-up time was 40 (27–57) months. No difference in overall survival was found (P = 0.344), with an overall five-year survival of 54% for the classical group and 49% for the liver-first group. A total of 264 patients had died at the end of the study of the 623 patients that underwent both bowel and liver surgery. Kaplan Meier survival curves for resected patients are shown in Fig. 1. The time from the first to the second operation was 4.7 (2.8–6.1) months for patients treated using the classical strategy, and 2.0 (1.4–3.7) months for patients treated using the liver-first strategy (P < 0.001).

A total of 281 patients had primary rectal cancer, of which 115 (41%) were handled with the classical strategy and 166 (59%) with the liver-first strategy. The patient characteristics are shown in Table 2. The overall five-year survival was the same, regardless of surgical approach (51% vs 47%, P = 0.474).

A total of 342 patients had primary colon cancer, 262 (77%) of which were treated with the classical strategy and 80 (23%) with the liver-first strategy. The patient characteristics are shown in Table 3. The five-year overall survival was the same in the groups with primary colon cancer (56% vs 51%, P = 0.564).

Eighty-four patients underwent liver resection but not bowel resection. The patient characteristics are shown in Table 4. The overall five-year survival was 14 (8–28)%.

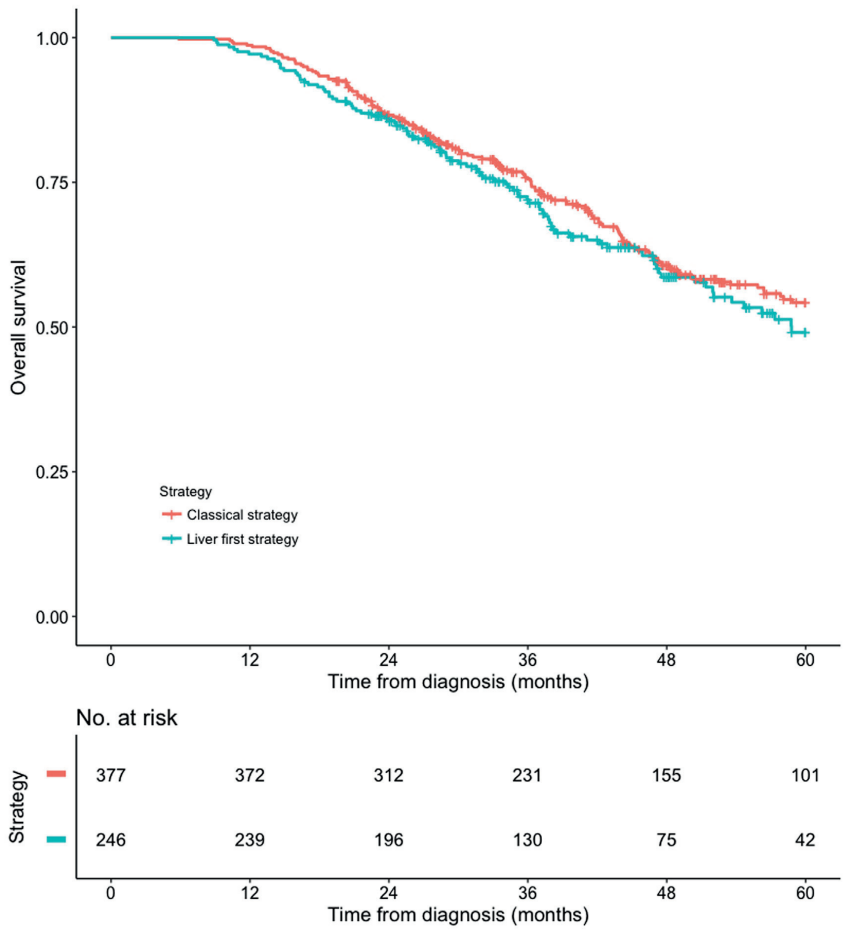

Figure 1 Overall survival from diagnosis for resected patients with synchronous liver metastases, P = 0.34 (log-rank test)

Table 2 Characteristics of resected patients with primary rectal cancer

	Classical strategy	Liver-first strategy	P‡
Number of patients	115	166	
Gender (Male)	74 (64)	114 (69)	0.519
Age (years)*	65 (58–70)	64 (54–69)	0.070§
ASA score (3–4)	22 (20)	39 (24)	0.463
BMI (kg/m^2)*	25 (23–27)	25 (22–27)	0.572§
Chemotherapy before first resection	55 (48)	145 (88)	<0.001
Radiotherapy before bowel resection	82 (71)	148 (89)	<0.001
T4 primary tumour	13 (12)	14 (9)	0.416
Lymph node positive primary tumour	77 (68)	93 (56)	0.060
R0 primary tumour resection	99 (88)	145 (88)	1.000
Liver TBS*	3.2 (2.2–4.5)	3.6 (2.4–5.6)	0.053§
Major liver resection	39 (35)	80 (50)	0.014
RO liver resection	77 (84)	114 (84)	1.000

Values in parentheses are percentages unless indicated otherwise: *values are median (interquartile range). ASA, American Society of Anesthesiologists; BMI, body mass index; R0, radical resection; TBS, tumour burden score. ‡Fischer's exact test, except §Mann–Whitney U test.

A uni- and multivariate Cox PH models were made with nine independent variables, as shown in Table 5.

Discussion

The liver-first strategy, as introduced by Mentha *et al.*,[6] includes preoperative chemotherapy, resection of colorectal liver metastases, followed by resection of the primary bowel cancer in a second stage. Patients have been increasingly selected for liver-first strategy in the last decade. The present study gives a contemporary analysis of patients with colorectal cancer and synchronous liver metastases, operated for liver metastases in Sweden. Patients chosen for the liver-first strategy were significantly younger, less frequently had positive lymph nodes of the primary tumour, and frequently underwent a major liver resection as compared to patients chosen for the classical strategy. In addition, the liver-first group more often had a primary rectal cancer and underwent preoperative radio-chemotherapy for their primary cancer. It is theoretically appealing to use the waiting time between radio-chemotherapy and resection of the rectal cancer for interval resection of the liver metastases to decrease the risk of tumour progression in the liver and to decrease the total treatment time.[15] Actually, as shown in the present study, the majority of patients with rectal cancer and sCRLM, are chosen for the liver-first strategy in Sweden.

Table 3 Characteristics of resected patients with primary colon cancer

	Classical strategy	Liver-first strategy	P‡
Number of patients	262	80	
Gender (Male)	160 (61)	47 (59)	0.794
Age (years)*	66 (58–73)	61 (54–69)	0.001§
ASA score 3–4	52 (20)	18 (23)	0.638
BMI (kg/m^2)*	26 (23–28)	25 (23–27)	0.274§
Chemotherapy before first resection	42 (16)	75 (95)	<0.001
Radiotherapy before bowel resection	2 (1)	5 (6)	0.009
T4 primary tumour	72 (28)	21 (26)	0.886
Lymph node positive primary tumour	187 (71)	56 (70)	0.888
R0 primary tumour resection	245 (94)	76 (96)	0.584
Liver TBS*	3.8 (2.4–5.4)	5.4 (3.2–7.6)	<0.001§
Major liver resection	113 (44)	45 (57)	0.053
R0 liver resection	185 (87)	59 (88)	1.000

Values in parentheses are percentages unless indicated otherwise: *values are median (interquartile range). ASA, American Society of Anesthesiologists; BMI, body mass index; R0, radical resection; TBS, tumour burden score. ‡Fischer's exact test, except §Mann–Whitney U test.

Table 4 Characteristics of patients that had undergone liver resection

	Liver resection but no bowel resection	Completed liver-first strategy	P‡
Number of patients	84	246	
Gender (Male)	65 (77)	161 (65)	0.043
Age (years)*	66 (58–72)	62 (54–69)	0.007§
ASA score 3–4	16 (19)	57 (23)	0.451
T4 primary tumour (preoperative)	22 (34)	35 (14)	<0.001
Lymph node positive primary tumour (preoperative)	49 (72)	161 (75)	0.637
Primary rectal tumour	63 (75)	166 (67)	0.219
Chemotherapy before liver resection	71 (85)	220 (90)	0.165
Liver TBS*	4.9 (2.8–9.0)	2.5 (4.1–5.0)	<0.001§
Major liver resection	35 (52)	125 (52)	1.000
R0 liver resection	39 (66)	173 (86)	0.002

Values in parentheses are percentages unless indicated otherwise: *values are median (interquartile range). ASA, American Society of Anesthesiologists; R0, radical resection; TBS, tumour burden score. ‡Fischer's exact test, except §Mann–Whitney U test.

The time between resections was found to be shorter in the liver-first group. However, information about the duration of chemotherapy is lacking in the registries used, making it impossible to analyse total treatment times. No detailed information about chemotherapy protocols is included in the registries. During the study period, national guidelines recommended perioperative oxaliplatin-based chemotherapy.

The liver TBS has previously been described by Sasaki *et al.*, and has shown a prognostic discriminatory power and may even be used for calculating survival benefit.[14] The concept is similar to the 'metro ticket' prognostic system introduced for liver transplantation for hepatocellular carcinoma.[16] The liver-first group had more advanced liver TBS, most probably illustrating that the liver-first strategy is increasingly applied when patients present with advanced liver metastases and an asymptomatic primary tumour. The rationale behind that is to first resect the tumours judged the most threatening to the patient's life.

No survival difference was found between the groups. These findings are in accordance with most previous studies.[7–10] However, Welsh *et al.* published a single centre study with 98 patients in the liver-first strategy group and 467 in the classical strategy group, and found that overall survival was significantly worse for the liver-first group. But after adjusting for the more severe liver disease in the liver-first group no survival difference was found.[10] As no survival benefit has been demonstrated for either strategy, future studies should focus more on the drop-out rate from the intended treatment strategy, the total treatment time, as well as patient-reported outcomes in terms of quality of life. In the present study, the follow-up time may have been too short to be able to detect smaller differences in survival between groups given the modern powerful chemotherapy regimens available in case of recurrence. Recurrence was however not possible to retrieve from the registries.

In the present study, the liver-first and the classical groups were subdivided into groups with primary colon and rectal cancer but again, no overall survival difference was found between the liver-first and the classical groups. The liver-first group with primary colon cancer were younger, more frequently had neoadjuvant therapy, and had more advanced liver TBS as compared to the classical strategy group with primary colon cancer (Table 3).

Of the patients planned for the liver-first strategy, 84 patients (25%) underwent liver resection but not bowel resection. The reasons for this are unclear but a previous study showed that up to 35% of patients with sCRLM do not complete the intended treatment of liver and bowel resections, most commonly because of disease progression.[17] The patients who only underwent liver resection more frequently had clinical T4 primary tumours, more advanced liver TBS, and less often had radical resection margins after liver resection as compared to patients that completed the two resections in the liver-first group (Table 4). From the registries used, it is not possible to deduce the number of patients planned for the classical strategy who then failed to undergo liver resection (intention-to -treat). Previous data from a single centre study in Sweden suggests that the drop-out rate is similar regardless of whether the classical or the liver-first strategy is used.[17]

With Cox PH analysis for the whole group no difference in overall survival for the treatment strategy was found but lymph node-positive primary, T4 primary, high liver TBS and an ASA score 3–4 negatively affected survival (Table 5). All these factors have been previously described.[14,18,19]

Although based on prospectively registered data, a shortcoming of this study is that it is non-randomized. There is therefore a high risk of selection bias. To estimate the influence of the chosen strategy on survival the well established statistical Cox PH model was chosen.[20] An alternative would have been to use

Table 5 Uni- and multivariate Cox proportional hazards model analysis of overall survival

	Cox univariate HR (95% CI)	P	Cox multivariate HR (95% CI)	P
Treatment				
Classical strategy	Ref		Ref	
Liver-first strategy	1.13 (0.87–1.47)	0.344	1.09 (0.80–1.50)	0.576
Age (years)				
<60	Ref		Ref	
≥60–70	0.83 (0.61–1.13)	0.240	0.81 (0.57–1.17)	0.259
≥70	1.29 (0.95–1.76)	0.107	1.25 (0.87–1.81)	0.231
Gender				
Male	Ref		Ref	
Female	1.05 (0.8–1.36)	0.735	1.06 (0.78–1.43)	0.725
Lymph node positive primary tumour				
No	Ref		Ref	
Yes	1.81 (1.35–2.45)	<0.001*	1.69 (1.21–2.36)	0.002*
T4 primary tumour				
No	Ref		Ref	
Yes	2.00 (1.49–2.69)	<0.001*	1.77 (1.25–2.52)	0.001*
Primary tumour localization				
Colon	Ref		Ref	
Rectum	1.06 (0.82–1.36)	0.674	1.15 (0.84–1.58)	0.370
TBS				
<3	Ref		Ref	
≥3–9	1.3 (0.96–1.75)	0.086	1.26 (0.91–1.75)	0.157
≥9	1.95 (1.22–3.12)	0.005*	1.67 (1.01–2.78)	0.047*
ASA score				
1–2	Ref		Ref	
3–4	1.68 (1.26–2.24)	<0.001*	1.81 (1.31–2.49)	<0.001*
BMI (kg/m^2)				
<25	Ref		Ref	
≥25–35	1.06 (0.81–1.38)	0.695	1 (0.75–1.35)	0.974
≥35	1.6 (0.74–3.43)	0.231	1.3 (0.59–2.87)	0.520

Data are presented as hazard ratio (95% confidence interval). HR, hazard ratio; CI, confidence interval; TBS, Tumour burden score. ASA, American Society of Anesthesiologists; BMI, body mass index; Ref, reference. Asterisk values indicate $P < 0.05$.

propensity score matching. Propensity score matching is known to have the ability to decrease imbalance, model dependence, and bias. However, a regression model is often more powerful than propensity score matching in detecting differences in treatment effect.[20,21]

The strength of this study is that this is a population-based study, thus reflecting the results of how these patients are managed today in Sweden. Furthermore, this is the largest patient cohort presented to date.

In conclusion, in this population-based study, patients chosen for the liver-first strategy had more often rectal primary tumours, advanced liver disease and less often node-positive primaries. Survival did not differ when compared to patients undergoing the classical strategy.

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Conflict of interest statement

Authors have no commercial interest to disclose.

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Paper III

Outcomes of simultaneous resections and classical strategy for synchronous colorectal liver metastases in Sweden. A nation-wide study with special reference to major liver resections.

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Abstract

Background: About 20% of patients with colorectal cancer have liver metastases at the time of diagnosis, and surgical resection offers the chance for cure. The intent was to compare outcomes for patients that underwent simultaneous resection to those that underwent staged procedure with the bowel first (classical) strategy by using information from two national registries in Sweden.

Methods: In this prospectively registered cohort study, we analyzed clinical, pathological, and survival outcomes for patients operated in the period 2008-2015 and compared the two strategies.

Results: 537 patients constituted the study cohort, where 160 were treated with the simultaneous strategy and 377 with the classical strategy. Patients managed with the simultaneous strategy had less often rectal primary tumors (22% vs. 31%, p=0.046) and underwent to a lesser extent major liver resection (16% vs. 41%, p<0.001) but had a shorter total length of stay (11 vs. 15 days, p<0.001) and more complications (52 % vs. 36 %, p<0.001). No 5-year overall survival (P=0.110) difference was detected. Twenty-five patients had a major liver resection in the simultaneous strategy group.

Conclusion: Simultaneous resection of the colorectal primary cancer and liver metastases appears to have more complications but with no difference in overall survival compared to the classical strategy.

Introduction

Cancer from the colon or rectum is the third most common malignancy worldwide [1,2]. At diagnosis, 15-20 % of patients present with synchronous liver metastases (sCRLM) [3-5]. Although possible for only a minority of patients, resection of all tumors offers a chance for cure. Different strategies exist for surgical treatment. The primary tumor can be resected first, and the liver metastases can be addressed at a later stage, with or without chemotherapy in the interval between operations, the so-called classical strategy. Alternatively, the surgical treatment order is reversed, where the liver metastases are resected before the primary, the liver-first strategy [6]. The third option includes resection of both the primary colorectal cancer and the metastases in the liver during the same operation, the simultaneous strategy.

The simultaneous strategy seems to be safe when compared to the other strategies and has been shown to reduce the total length of hospital stay. This strategy is increasingly applied when a patient has a limited liver tumor disease burden, and the primary tumor resection is assumed uncomplicated. The indication for proposing the simultaneous strategy is still evolving. No overall survival difference has been observed between the above strategies, although most studies only analyze patients that complete the entire surgical plan without intention-to-treat analysis [7-10]. To date, a randomized controlled investigation has not been published.

The treatment impact on patient outcome has previously been analyzed only from retrospective data collected from single or a few centers. No nationwide study has previously been published on simultaneous resections, and little data is available for patients that have undergone major resections. We intended to evaluate and compare a simultaneous strategy to a classical strategy for patients diagnosed with sCRLM, based on information from two population registries from Sweden and with a focus on patients undergoing major liver resections.

Material and methods

National registries for colorectal (SCRCR) and liver and bile duct (Sweliv) cancers were used to identify patients diagnosed with colorectal cancer between 2008 and 2015. Both registries have prospective registration of data, where SCRCR includes 94-98% of all patients diagnosed with colorectal cancer in Sweden [11], and Sweliv includes patients with primary liver cancer and bile duct cancer in addition to all surgical treatments for primary and metastatic cancer in the liver. Sweliv includes 96% of all patients with cancers in the liver or bile ducts in Sweden [12].

Patients with colorectal cancer and liver metastases were identified from the registries at the time of diagnosis and hereby defined as having sCRLM. Patients that had an acute operation for their primary were excluded. The cohort was defined as patients that underwent a bowel resection within six months from the diagnosis as well as both primary tumor and liver resection within twelve months from diagnosis. Patients with sCRLM that only underwent liver resection and those that underwent the liver-first strategy were identified separately, as previously published [13]. A comparison was made between patients that had undergone the simultaneous strategy and those that underwent the classical strategy. A liver resection of three or more Couinaud's segments was classified as a major resection. Morbidity was registered as Clavien-Dindo ≥ 2 [14], but a more detailed specification of morbidity severity was not available. In the staged resection group, a complication in either procedure was considered a complication for the procedures combined. An R0 surgical margin was interpreted as a microscopic surgical free specimen margin. Tumor burden score (TBS) in the liver was calculated as $TBS^2 = d^2 + n^2$, where d = largest liver tumor diameter (cm) and n = number of liver lesions [15]. A novel score was invented to account for sCRLM, hereafter named total tumor burden score (TTBS) using the hazard ratio from the univariate Cox proportional hazards (PH) analysis as a multiplier if the patient had postoperative primary lymph nodes positive disease and if the patient had a T4 primary tumor. $TTBS = \sqrt{d^2 + n^2} + 2\,x\,N + 4\,x\,T$, where d = maximum liver tumor diameter (cm), n = number of liver lesions, N = 1 if lymph nodes are positive for the primary tumor, and T = 1 if the primary tumor is T4.

Statistics

Results were showed as numbers and percentages when categorical variables and Fischer's exact test was used to compare groups. For continuous variables, results are presented as median with interquartile ranges (IQRs), and Mann-Whitney U-test was used to compare groups. Survival from the time of diagnosis was estimated using Kaplan Meier analysis. Patient and tumor characteristics effect on survival was investigated using multi- and univariate Cox proportional hazards (PH) models. A P-value under 0.05 was considered statistically significant. The statistical software used was R (R Core Team (2018). R Foundation for Statistical Computing, Vienna, Austria).

Results

In the SCRCR, 39,016 patients with colorectal cancer were identified, of which 6,105 (16%) patients had liver metastases at the time of diagnosis. Of those, a total of 1,571 (26%) underwent elective surgery of the primary tumor. A total of 783 patients from among these (50%) underwent both bowel and liver resection, constituting two percent of the originally identified patient group. The study population included 537 patients with 377 that underwent a classical strategy and 160 that underwent a simultaneous strategy, as shown in Fig. 1. Patients characteristics for the classical and simultaneous strategy are shown in Table 1. One patient died within 30 days of the resection in the simultaneous groups, but none that had completed the classical strategy. The number resected with the simultaneous strategy increased in the first three years of the study period from six patients per year to 30 per year, with a median of 26 (18 - 30) patients resected per year.

A follow-up time with median of 41 (27 – 58) months and overall survival did not differ between groups (P = 0.110), with a 5-year survival from diagnosis of 54% in the classical strategy group and 46% in the simultaneous strategy group and median survival was 49 and 58 months respectively, as shown in Fig. 2. At the end of the study, a total of 231 patients was deceased. For the classical strategy group, the interval between the procedures was 4.7 (2.8 – 6.1) months.

Twenty-five and 155 patients underwent a major liver resection in the simultaneous and classical strategy group, respectively (Table 2), without a difference in 5-year survival (P=0.198).

We found that 135 patients underwent a minor liver resection in the simultaneous group and 222 in the classical group. The simultaneous group had: less often a rectal primary (5 vs 33 %, p<0.001), less intraoperative blood loss (600 (300 - 900) vs 700 (350-1250) ml, p=0.003) and shorter total length of stay (11 (7 - 15) vs 16 (14 - 20) days, p < 0.001). No other difference was found to be significant between the groups. An overall 5-year survival showed no difference (P=0.131).

When comparing the group that had elective surgery for the primary tumor only (that is, the 788 patients not operated for their liver metastases) to the simultaneous group, the primary only group was found to be older (72 (64-79) years, P<0.001) and had more often: T4 primary tumors (291 (37%), p = 0.010), lymphatic node-positive primaries (630 (82%), p < 0.001), and ASA 3-4 (228 (29%), p = 0.027). The primary only group had less often: neoadjuvant chemotherapy (59 (7%), p<0.001), and radiation therapy (83 (11%), p=0.01). The primary only group had 11% 5-year overall survival and a median survival of 15 months.

In Table 3, the results from uni- and multivariate Cox PH models are shown. The multivariate analysis showed higher ASA class, higher liver tumor burden, and T4

primary tumor to be risk factors for mortality, but not simultaneous or staged operation.

Only the simultaneous treatment strategy had a significant odds ratio for complications on multivariate analysis (Table 4).

After dividing the TTBS into three groups, a difference in 5-year overall survival between the groups was found ($p<0.001$. Fig. 3) with an area under the curve (AUC) of 0.688 compared to an AUC of 0.628 from the previous published TBS ($p = 0.100$).

Discussion

The intent of the present study was to compare the simultaneous strategy to the classical strategy for all patients diagnosed with sCRLM, with data from two national quality cancer registries from Sweden. We found that 16% of the patients diagnosed with colorectal cancer had sCRLM, which is in line with previous studies [16]. For patients with sCRLM, elective tumor resection is indicated if there is a global curative treatment strategy for all tumor sites according to national guidelines [17]. Only 50% of the patients that underwent an elective procedure of the primary tumor also underwent a liver procedure. Patients with sCRLM subjected to bowel resection only were: older, had greater ASA score, and had more often T4 tumors and lymph node-positive tumors. However, data on the liver tumor burden, for these patients, is not registered. The overall survival for this group was low, and the reasons that these patients were not subjected to liver resection are most probably multifactorial. In our earlier study, we showed that about 35% of patients diagnosed with sCRLM do not finish a planned liver and bowel resections, regardless of the treatment strategy [18]. Other studies have reported palliative colorectal resection rates in patients with sCRLM of between 16 - 60 % [19-21]. As the data used for the present study does not allow identification of palliative resections, no intention to treat analysis for the classical strategy could be made.

The simultaneous strategy group had a shorter total length of hospital stay, less often a rectal primary, more complications that demanded treatment, less major liver resections, and less total blood loss compared to the classical strategy group, as shown in Table 1. Concerning morbidity, it was not possible to separate major morbidity (Clavien-Dindo grade ≥ 3) from minor morbidity in the present study, which can make comparison with previous studies difficult. In the present study, only the simultaneous treatment strategy was found significant for increased odds for morbidity (Table 4). Morbidity was classified as Clavien-Dindo grade ≥ 2 because of restraints in the data retrievable from the registers. No difference in major morbidity was found in the meta-analysis by Gavrilidis et al. [22], but an increased frequency in major morbidity after simultaneous resections as compared to the classical strategy has been shown for major liver resections [23]. Despite the higher complication rate for the simultaneous group in the present study, the total length of stay was shorter, perhaps pointing to less clinically significant complications.

We did not find any difference regarding gender, age, ASA score, BMI, radiotherapy, T4 primary, lymph node-positive primary, number of liver metastases, liver tumor size, TTBS, or R0 liver resections between the study groups. This indicates that patients are selected for either strategy based on the size of the planned liver surgery and whether they have a rectal or colonic primary tumor. In a meta-analysis by Gavriilidis et al., containing 30 non-randomized papers, no significant pooled difference was found for gender, age, rectal primary, size or number of liver tumors or complications but the simultaneous strategy group had a shorter total

length of hospital stay, less often received neoadjuvant therapy, and underwent less often major liver resections [22]. Others have shown a worse liver tumor burden for the staged resections strategies and a higher complication rate for simultaneous resections [23]. In the present study, no difference in survival could be found between groups, as reported in previous studies [22-24].

Comparing the groups of patients that underwent major liver resections (simultaneous vs. classical strategy), we found a shorter total length of hospital stay, but no other significant difference between the groups was found, including 5-year overall survival, bearing in mind the small sample size in the simultaneous major liver resection group (N=25). This is in accordance with previously published studies on simultaneous major liver resections, although the selection of patients has not been controlled for [24-28].

Cox PH analysis showed that a primary tumor with positive lymph nodes, higher tumor burden score, larger and a greater number of liver metastases, T4 primary, and ASA 3-4 had a negative effect on survival in univariate analysis. On multivariate analysis, an increased tumor burden score, T4 primary, and ASA 3-4 were related to worse survival, as shown in Table 3. All these factors have been previously described as prognostic factors [15].

A TBS was previously introduced by Sasaki et al. and appears to be useful when evaluating a postoperative survival of patients with both synchronous and metachronous CRLM [15]. In the present study, a novel score applicable to patients with sCRLM was calculated (TTBS). Dividing the TTBS into three groups showed a significant 5-year overall survival difference between the groups (Fig. 3) with a similar area under the curve (AUC) as the previous tumor burden score (p=0.100). No external validation was carried out, but the group with TTBS of more than ten had a dismal prognosis.

No randomized controlled trial evidence is available to support the use of any of the two methods for patients with sCRLM. All published studies, therefore, have intrinsic selection bias [29], as is the case with this study. We chose the conventional Cox Proportional hazard model to account for the effect of strategy on survival. A propensity score matching has gained increased popularity in recent years, but a statistical regression model can be more useful and is easier to comprehend when detecting differences in treatment effect [30,31]. One of the weaknesses of the present study is that the used registries do not allow calculation of recurrence-free survival, nor were we able to analyze the data according to intention to treat. Another shortcoming of the study is that no data on adjuvant chemotherapy were included. The usage rates of adjuvant chemotherapy have previously not shown to differ between strategies [22]. The strength of this study is that it is based on a national population with a prospective registration.

Our conclusions are that patients picked for simultaneous liver and primary resection had a shorter total length of hospital stay, similar overall survival but higher complication rate in comparison to patients allocated to a classical strategy.

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Table 1. Clinical features of patients

	Simultaneous strategy	Classical strategy	P‡
Patients	160	377	
Male gender	90 (56)	234 (62)	0.211
Age (years)*	65 (58-72)	66 (58-73)	0.396
American Society of Anesthesiologists (3-4)	32 (20)	74 (20)	0.906§
Body mass index (kg/m^2) *	24.9 (22.5-27.8)	25.4 (23.1-27.5)	0.434§
Preoperative radiotherapy	29 (18)	84 (22)	0.300
Neoadjuvant chemotherapy	101 (64)	274 (73)	0.029
Localization (rectum)	35 (22)	115 (31)	0.046
T4 primary	41 (26)	85 (23)	0.435
Lymphatic node positive, primary tumors	105 (66)	264 (70)	0.411
Number of liver tumors*	2(1-4)	2(1-4)	1§
Liver tumor size (mm)*	20 (12-30)	20 (14-35)	0.202§
Tumor burden score*	2.1 (3.2-4.5)	2.2 (3.6-4.2)	0.500§
Portal vein embolization	0 (0)	15 (4)	0.008
Major liver surgery	25 (16)	152 (41)	<0.001
Radical liver resection	145 (91)	350 (93)	0.370
Total loss of blood (ml)*	600 (250-950)	850 (474-1456)	<0.001§
Complications, demanding treatment	84 (52)	136 (36)	<0.001
Total length of stay (days)*	11 (8-15)	15 (12-20)	<0.001§

Percentages are in parentheses unless otherwise indicated: * median (interquartile range). ‡ X^2 test, except §Mann-Whitney U test.

Table 2. Clinical features of patients that underwent a major liver resection

	Simultaneous strategy	Classical strategy	P‡
Patients	25	155	
Male gender	12 (48)	98 (63)	0.185
Age (years)*	63 (59-68)	65 (58-69)	0.820§
American Society of Anesthesiologists (3-4)	5 (20)	31 (17)	0.576
Body mass index (kg/m^2) *	25 (24-26)	25 (23-27)	0.828§
Preoperative radiotherapy	3 (12)	29 (19)	0.576
Neoadjuvant chemotherapy	21 (84)	127 (82)	0.770
Localization (rectum)	6 (24)	41 (26)	0.878
T4 primary	3 (12)	39 (25)	0.419
Lymphatic node positive, primary	20 (80)	115 (75)	0.802
Number of liver tumors*	3(2-4)	3(2-4)	0.985
Liver tumor size (mm)*	31 (20-59)	25 (15-43)	0.119§
Tumor burden score*	5.7 (3.2-7.2)	4.5 (3.3-6.4)	0.408§
Portal vein embolization	0 (0)	15 (10)	0.222
Radical liver resection	24 (96)	143 (93)	1
Total loss of blood (ml)*	1100 (500-1600)	1100(630-1800)	0.6393§
Complications, demanding treatment	11 (44)	57 (37)	0.5109
Total length of stay (days)*	11 (9-15)	17 (14-21)	<0.001§

Percentages are in parentheses unless otherwise indicated: * median (interquartile range). ‡ X^2 test, except §Mann-Whitney U test.

Table 3. Cox proportional hazards analysis for overall survival.

	Univariate HR		Multivariate HR	
Treatment				
Classical strategy	Reference		Reference	
Simultaneous strategy	0.79 (0.59-1.05)	0.107	0.83 (0.6-1.14)	0.243
Age (in years)				
<60	Reference		Reference	
≥60-70	0.78 (0.56-1.09)	0.140	0.78 (0.54-1.13)	0.189
≥70	1.15 (0.83-1.6)	0.407	1.18 (0.81-1.7)	0.392
Gender				
Male	Reference		Reference	
Female	0.83 (0.62-1.1)	0.199	0.9 (0.66-1.22)	0.495
Lymphatic node primary tumor				
Negative	Reference		Reference	
Positive	1.55 (1.13-2.12)	0.007*	1.26 (0.9-1.75)	0.182
T4 primary tumor				
No	Reference		Reference	
Yes	1.92 (1.43-2.57)	<0.001*	1.84 (1.34-2.54)	<0.001*
Primary tumor localization				
Colon	Reference			
Rectum	0.98 (0.73-1.31)	0.877		
Liver resection size				
Minor	Reference			
Major	1.1 (0.83-1.46)	0.494		
Tumor burden score				
<3	Reference		Reference	
≥3-9	1.67 (1.21-2.29)	0.002*	1.73 (1.24-2.41)	0.001*
≥9	2.99 (1.86-4.81)	<0.001*	3.04 (1.83-5.04)	<0.001*
Liver tumor numbers				
<3	Reference			
≥3	1.53 (1.16-2.02)	0.003*		
Liver tumor size (cm)				
<5	Reference			
≥5	1.92 (1.33-2.77)	<0.001*		
American Society of Anesthesiologists				
1 - 2	Reference		Reference	
3 - 4	1.47 (1.07-2.02)	0.019*	1.52 (1.09-2.13)	0.014*
Body Mass Index (kg/m^2)				
<25	Reference			
≥25-35	1.09 (0.82-1.46)	0.545		
≥35	1.39 (0.61-3.18)	0.436		

Statistics presented as hazard ratio with a 95% confidence interval in parenthesis. An asterisk indicates P<0.05.

Table 4. Uni- and multivariate logistic regression for complications needing treatment

	Univariate analysis		Multivariate analysis	
Treatment				
Classical strategy	Reference		Reference	
Simultaneous strategy	2.52 (1.72-3.69)	<0.001*	2.23 (1.39-3.58)	<0.001*
Age (years)				
<65	Reference		Reference	
≥65	0.91 (0.64-1.29)	0.579	0.86 (0.57-1.29)	0.461
Gender				
Male	Reference		Reference	
Female	0.67 (0.46-0.96)	0.03*	0.65 (0.43-0.98)	0.041*
American Society of Anesthesiologists				
1 - 2	Reference		Reference	
3 - 4	1.43 (0.93-2.21)	0.103	1.36 (0.84-2.2)	0.212
Body Mass Index (kg/m^2)				
<25	Reference		Reference	
≥25	0.94 (0.66-1.36)	0.751	0.98 (0.65-1.46)	0.904
Tumor localization				
Colon primary	Reference		Reference	
Rectal primary	1.44 (0.98-2.12)	0.061	0.81 (0.37-1.67)	0.573
Liver resection size				
Minor	Reference		Reference	
Major	0.73 (0.5-1.06)	0.103	0.8 (0.51-1.24)	0.318
Radiotherapy				
No	Reference		Reference	
Yes	1.93 (1.27-2.94)	0.002*	1.89 (0.84-4.45)	0.134
Bleeding				
<600 ml	Reference		Reference	
≥600 ml	1.09 (0.72-1.63)	0.692	1.04 (0.66-1.62)	0.863
Neoadjuvant chemotherapy				
No	Reference		Reference	
Yes	2.11 (1.47-3.04)	<0.001*	1.52 (0.95-2.41)	0.080

Statistics presented as odds ratio with a 95% confidence interval in parenthesis. An asterisk indicates P<0.05.

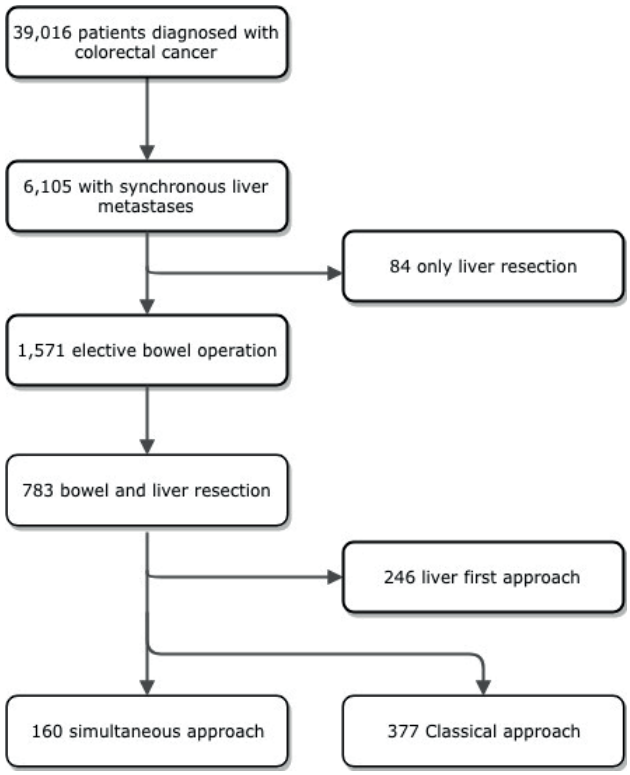

Fig. 1. The study population.

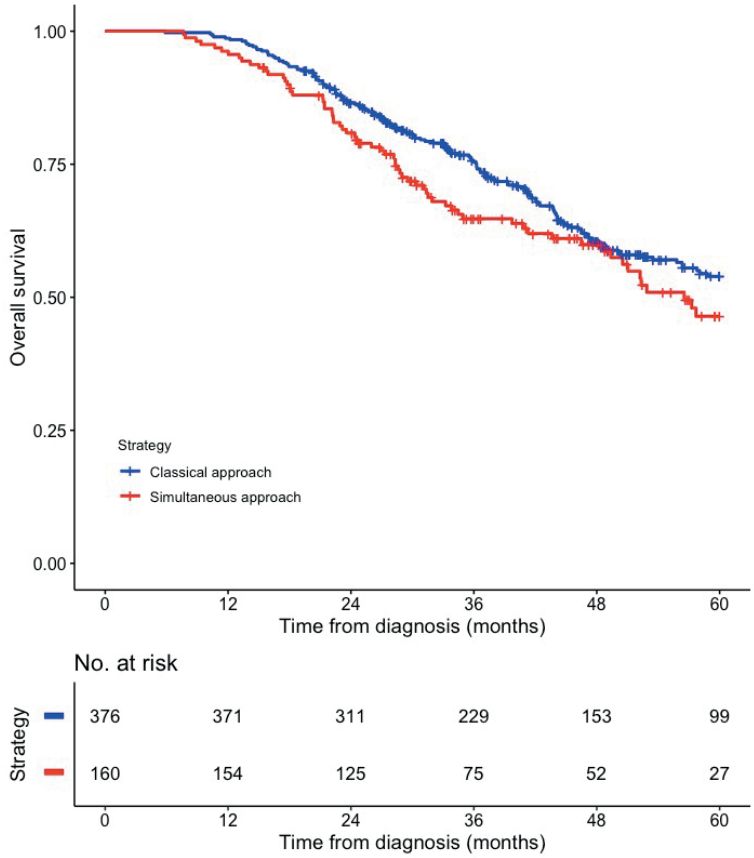

Fig. 2. Overall survival from diagnosis for resected patients with synchronous liver metastases.

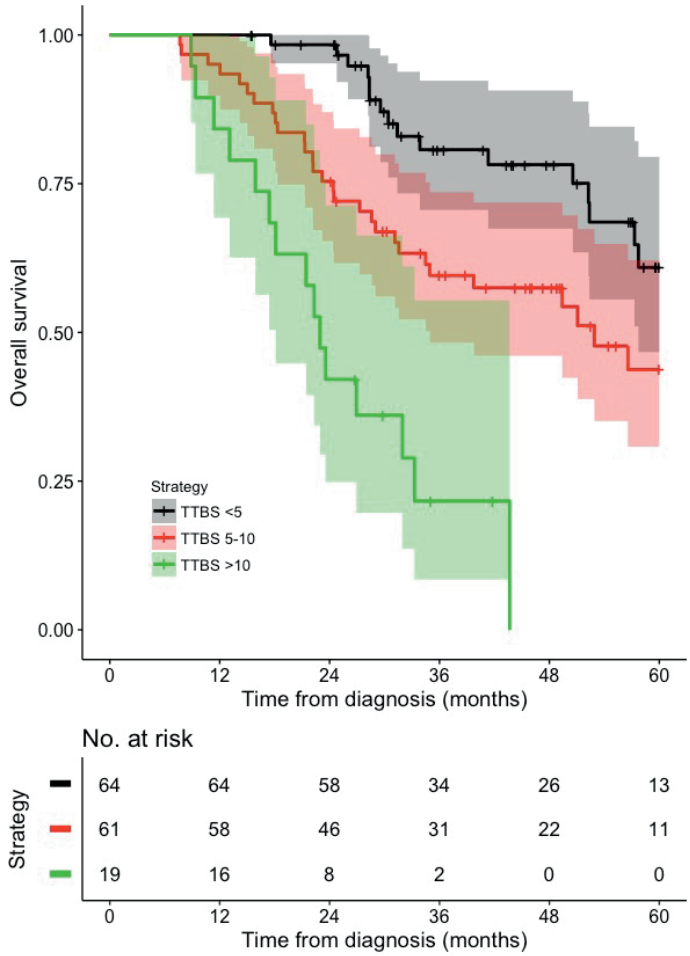

Fig. 3. Overall survival from diagnosis for resected patients with synchronous liver metastases who underwent the simultaneous strategy grouped according to the total tumor burden score (TTBS).

Paper IV

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ORIGINAL RESEARCH

Repeat procedures for recurrent colorectal liver metastases: analysis of long-term liver regeneration and outcome

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Background and aim: Repeat hepatectomy is increasingly performed for the management of recurrent colorectal liver metastases (CRLM). The aim of this study was to evaluate long-term functional liver volume (FLV) after a second hepatic procedure and to measure survival outcome.

Methods: In this retrospective cohort study, patients treated for recurrent CRLM in the years 2005–2015 at two liver centers were included. Total FLV was calculated before the first procedure and before and after the second procedure. Overall survival was calculated.

Results: Eighty-two patients were identified. The median follow-up was 53 (40–71) months from the first procedure. The median interval between first and second procedure was 13 (8–22) months. The initial FLV was 1584 (1313–1927) mL. The FLV was 1438 (1204–1896) mL after the first procedure and 1470 (1172–1699) mL after the second procedure ($P<0.001$). After the second procedure, a total of ten patients (12%) had a residual liver volume of less than 75% of the initial liver volume. The 5-year overall survival was 37 (26–54)% after the second procedure.

Conclusion: Small changes in FLV were found after two hepatic procedures but with considerable inter-individual variation. Patients selected for a repeated hepatic procedure for recurrent CRLM had an acceptable survival.

Keywords: liver metastases, colorectal cancer, repeat hepatectomy, liver regeneration, postoperative outcomes

Introduction

Colorectal cancer is the third most common malignancy in the world[1,2] and 15–20% of patients present with synchronous liver metastases at diagnosis.[3–5] About 25–50% of all the patients will develop liver metastases (CRLM) during the course of the disease.[6–8] Surgical resection or ablation of all tumors, when feasible, currently offers the only potential for cure.

Recurrence of metastases occurs in a majority of patients following hepatectomy either in the remnant liver and/or at other sites.[9,10] In 20% of those, the remnant liver is the only site of recurrence.[10] Repeat hepatic resections or ablations for recurrence are increasingly performed as a viable therapy for recurrent CRLM with acceptable overall survival.[11–16]

A minimum functional residual volume of 20–25% has been shown to be sufficient for a safe hepatic resection in case of a healthy liver parenchyma.[17] Hepatocytes have a regenerative potential, and long-term functional liver volume

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(FLV) after a major hepatectomy for CRLM has previously been shown to be around 80–90% of the initial liver volume.[7,18]

Long-term volumetric liver regeneration after a repeated hepatectomy has been investigated to a lesser extent, with only one previous study including 21 patients.[19] The aim of the present study was to retrospectively investigate volumetric liver regeneration and survival data after a repeated hepatic procedure (resection or ablation), hereinafter referred to as a second procedure, for liver recurrence of CRLM.

Methods

Selection of patients

All consecutive patients with CRLM who underwent a second procedure for the recurrence of CRLM at Skåne University Hospital, Lund, Sweden and Karolinska University Hospital, Stockholm between 2005 and 2015, were identified. Patients that had available imaging from computed tomography and/or magnetic resonance imaging were further selected. Patients were grouped according to whether they had major or minor hepatic procedures. A major liver procedure was defined as a resection of more than three Couinaud's segments. A minor hepatic procedure was defined as hepatic resection of less than three Couinaud's segments with or without additional radiofrequency ablation (RFA) or RFA alone. Synchronous disease was defined as when the liver metastases were diagnosed at the radiological workup of the primary cancer. The study protocol was approved by the Regional Ethical Review Board, Lund, Sweden (Dnr2016/989). Patient consent to review their medical records was not required by the review board due to the retrospective nature of the study. Patient data were analyzed after pseudonymization to ensure confidentiality and in compliance with the Declaration of Helsinki.

Liver volume measurements

Liver volumes were calculated using computed tomography or magnetic resonance imaging plane images. The liver contour on all image sections was manually traced and the area was automatically calculated. Each image section area was multiplied by the section thickness (typically 5 mm) to obtain the liver volume. Metastasis volumes as well as ablation zones after RFA were measured in the same way and subtracted from the liver volume to give the FLV. The preoperative images of patients were selected on the basis of the most recent available images prior to first and second procedure. Postoperative images after the second procedure were obtained at least 1 month after procedure. Relative liver volumes were calculated by dividing the FLV after the first and second procedures to the initial FLV. For comparison, the total estimated liver volume (TELV) was calculated as TELV = −794.41 + 1,267.28 × body surface area (BSA), where BSA was calculated using Mosteller's formula: $BSA = \sqrt{(\text{height [cm]} \times \text{weight [kg]}/3{,}600)}$.[20] A liver tumor burden score (TBS) was calculated for each patient [TBS^2 = (maximum tumor diameter in centimeters)^2 + (number of liver lesions)^2].[21]

Statistics

Summary statistics were presented as whole numbers and percentages for categorical variables, or as medians with IQRs, unless otherwise stated, for continuous variables. A Mann–Whitney U-test was used to compare continuous data, and Fischer´s exact test was used for categorical data. A Friedman test was used when comparing three groups. Kaplan-Meier analysis was used to estimate survival. Overall survival was calculated using both procedures as the starting point. Pearson correlation analysis and linear regression were performed to assess the correlation between measured FLV and calculated TELV. A *P*-value less than 0.05 was considered statistically significant. Statistical analysis was performed using R (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Results

A total of 99 patients with recurrent CRLM who underwent a second procedure were identified. Cross-sectional imaging prior to the first and second procedures and after the second procedure were available for 82 patients, which constituted the study cohort. The patient characteristics are shown in Table 1.

The median follow-up time was 53 (40–71) months from the first procedure and 38 (27–48) months from the second procedure. The time from first to second procedure was 13 (8–22) months. The time from initial imaging to first procedure was 2 (1–3) months. The time from the first procedure to the postoperative imaging was 11 (7–20) months and the time from second procedure to the postoperative imaging was 11 months (9–12) months. In Table 2, the size and number of metastases before each procedure are presented.

Table 1 Characteristics of resected patients

Number of patients		82
Age, years (IQR)		64 (57–69)
Gender	Male	42 (51%)
	Female	40 (49%)
Primary tumor site	Colon	48 (59%)
	Rectum	32 (39%)
Liver metastases timing	Synchronous	38 (46%)
	Metachronous	44 (54%)
Size of first hepatic procedure	Major	35 (43%)
	Minor	47 (57%)
Size of second hepatic procedure	Major	15 (19%)
	Minor	66 (81%)
Resection order	Major to minor	35 (43%)
	Minor to major	15 (19%)
	Minor to minor	31 (38%)
Perioperative chemotherapy (first hepatic procedure)		67 (82%)
Perioperative chemotherapy (second hepatic procedure)		37 (49%)

Table 2 Metastases specific characteristics of resected patients

	First hepatic procedure	Second hepatic procedure	P[a]
Number of metastases	2 (1–4)	1 (1–2)	<0.001
Maximum tumor size (mm)	25 (20–40)	20 (10–29)	0.01
Tumor score	4 (3–6)	3 (2–4)	<0.001

Notes: Values are median (IQR). [a] Mann–Whitney U test.

Median initial FLV was 1584 (1313–1927) mL. Median FLV after the first procedure was 1438 (1204–1896) mL and 1470 (1172–1699) mL after the second procedure (P<0.001).

Relative liver volumes are shown in Figure 1, without difference between groups (P=0.532). After the first procedure, nine patients had a FLV of less than 75% of the initial FLV, and ten patients had a FLV of less than 75% of the initial FLV after the second procedure.

Thirty-five patients had a major liver procedure as the first procedure (43%) and 15 (18%) as the second. Seven patients had only a RFA as the first procedure and eight as the second. The patients that had a major first procedure followed by a minor procedure showed significant liver volume reduction after the first procedure

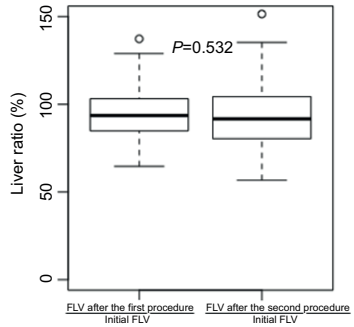

Figure 1 Liver volume ratios after the first and second procedures.**Abbreviation:** FLV, functional liver volume.

(1532 (1310–1692) mL vs 1271 (1132–1438) mL, P<0.001) but not after the second procedure (P=0.242). The patients that had a minor first procedure followed by major second procedure did not show any significant reduction in liver volume after the first procedure (P=0.391), but the reduction was significant after the second procedure (1796 (1252–2003) mL vs 1492 (1038–1840) mL, P=0.042). Patients that had only minor procedures did not show any reduction in liver volume (P=0.621 and P=0.792, respectively). A significant difference was found when comparing the relative liver volumes after the second procedure (FLR after the second procedure/initial FLV) between those that underwent one major procedure and those that only underwent minor procedures (87 (79–101) % vs 98 (86–108) %, P=0.013).

The administration of perioperative (neoadjuvant and/or adjuvant) oxaliplatin-based chemotherapy in relation to the procedures is shown in Table 1. Patients receiving perioperative chemotherapy (n=74) did not show any significant difference in relative liver volumes after the second procedure (100 (94–108) % vs 91 (80–103) %, P=0.200) as compared to patients not receiving any chemotherapy (n=8).

The overall 5-year survival was 60 (47–70) % after the first procedure and 37 (26–54) % after the second procedure (Figure 2). No difference in complication (Clavien-Dindo classification ≥3) frequency was found between the first procedure (13 (16%)) and the second procedure (15 (18%), P=0.846). No difference in survival was found between the groups undergoing only minor procedures versus the group undergoing major procedures (P=0.947). A linear correlation was found between TELV and measured FLV before (r=0.57, P<0.001) and

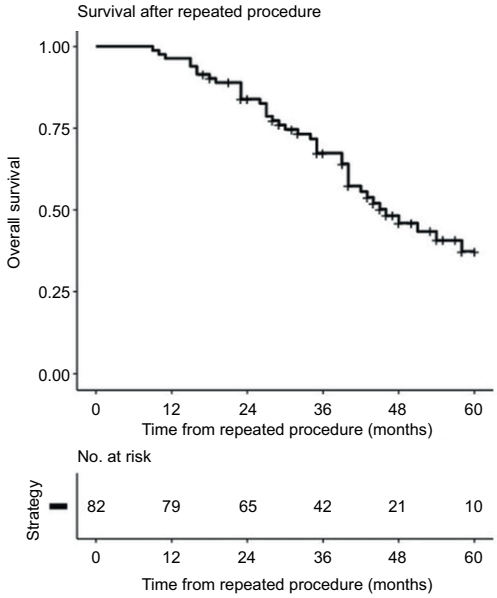

Figure 2 Overall survival after the second hepatic procedure.

after (r=0.68, $P<0.001$) the first procedure, as well as after the second procedure (r=0.55, $P<0.001$).

Discussion

Repeat hepatic procedures are increasingly performed, with acceptable results, as a viable therapy for recurrent CRLM.[11–16] While it is known that hepatocytes have remarkable regenerative ability, it is not fully understood how repeated procedures affect the liver's ability to regenerate. This makes it unclear on which liver volume the estimation of a sufficient liver remnant should be based on when planning a second or even a third hepatic procedure. The aim of the present study was to evaluate volumetric liver regeneration and survival data for patients undergoing repeated procedures.

In the present study, the liver volume decreased minimally even after two hepatic procedures and almost reached the preoperative volume for most patients undergoing repeated procedures. This is in accordance with the results of the one previously published study on the subject, which included 21 patients.[19] As could be anticipated, minor procedures did not result in any change in liver volume.[22] However, a significant reduction in FLV after was found after a major resection. This is well in line with previous studies assessing liver regeneration after one major resection.[7,23,24]

Perioperative chemotherapy was administered to 82% and 49% of the patients in relation to the first and second procedure, respectively. All patients were discussed at preoperative multidisciplinary team conferences. The reasons for the lower percentage of patients receiving chemotherapy in relation to the second procedure can only be speculated about. One plausible reason is that the oncologists question the value of chemotherapy as neoadjuvant/adjuvant therapy once recurrence of the liver metastases occurs. A similar reduction in utilization of perioperative chemotherapy has been reported previously,[18] although others report no change in chemotherapy strategy in the case of liver recurrence.[22] In the literature, there is a wide variation in the reported use of perioperative chemotherapy in relation to repeated hepatic procedures (44–90%),[12,19,25–27] reflecting that the value of perioperative chemotherapy in terms of outcome in the case of hepatic recurrence has not been fully investigated.

No difference in liver volume was found after two procedures between patients receiving chemotherapy (n=74) as compared to those that did not receive chemotherapy (100 (95–108) % vs 91 (80–103) %, $P=0.200$). However, only eight patients received no chemotherapy (Table 1). In a previous study, preoperative chemotherapy has been associated with a reduced long-term volumetric regeneration after liver resection,[7] whereas other investigators have found no influence on regeneration of preoperative chemotherapy.[18]

At the first procedure, patients had a significantly higher number of metastases, larger metastases, and thus a higher TBS when compared to the second procedure. This is comparable to previous studies.[25,26]

A sufficient liver function is required to prevent postoperative liver failure. Liver volume and liver function are closely associated, and because liver volume is easier to calculate, most investigators determine preoperatively the volume of the future liver remnant to ensure a sufficient postoperative liver function. The future liver remnant is usually expressed as the volume of the future liver remnant divided by the total FLV. These volumes are readily calculated from cross-sectional imaging. An alternative to estimating the total liver volume is to use a formula based on the patient's BSA.[20] There is some controversy about which method is superior in correctly estimating the risk for postoperative liver failure and for indicating the need for preoperative portal vein embolization.[28,29] No studies exist on which volume to use when estimating the risk of liver failure in the case of re- or third-hepatectomy. For

example, in the present study, 12% of patients presented a liver volume after the second procedure of less than 75% of the original liver volume. The estimated safe limit for excising additional liver tissue will, therefore, be quite different depending on whether the original liver volume or the liver volume after resections is used in the denominator when calculating the percentage of the future liver remnant. The alternative of using a TELV is then more appealing. However, although there was a significant linear correlation ($P<0.001$) between TELV and measured total liver volumes before, after the first procedure and after the second procedure, the r^2 values were found to be 0.30–0.46, indicating that the formula used accounts for only 30–46% of the variability in the measured total liver volume. Further studies are needed to address this issue.

Previous published studies have shown acceptable overall survival for patients that have undergone a second procedure after recurrent CRLM.[11–15,25] In the present study, there was a median follow-up time of 53 (40–71) months from the first operation and 38 (27–48) months from the second procedure. The overall 5-year survival was 37 (26–54) % after the second procedure, as shown in Figure 2. A great variation in survival is found in the literature. A review article based on 47 studies found the overall 5-year survival after repeat hepatectomies to be 16–55%, with few individual studies including more than 100 patients.[30] Some studies have even reported 5-year overall survival of up to 75%.[11,12,25] Lately it has been shown that ablation of liver metastases may offer comparable overall survival, but may be associated with reduced progression-free survival. Ablation may offer shorter hospital length-of-stay and lower rate of complications.[31,32] In the present study, seven patients underwent RFA as the first procedure and eight as the second procedure.

A shortcoming of the present study is that it is retrospective and subject to great selection bias, especially when analyzing survival outcome. In addition, no information was available about histological parenchymal damage that could potentially affect regeneration.

Conclusion

Little change in long-term FLV after a second hepatic procedure was found, but the inter-patient variation was high. Patients selected for a second procedure for recurrent CRLM had acceptable 5-year overall survival.

Disclosure

The authors report no conflicts of interest in this work.

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