Resection of colorectal liver metastases - Impact of preoperative chemotherapy

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Resection of colorectal liver metastases

Impact of preoperative chemotherapy

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Title: Resection of colorectal liver metastases – Impact of preoperative chemotherapy

Abstract

Background: Colorectal cancer is a leading cause of cancer related death worldwide. 20-30 % of patients will develop colorectal liver metastases (CRLMs). Surgical resection is the mainstay of treatment for CRLMs, and is often combined with perioperative chemotherapy, which can prolong progression-free survival after resection. Moreover, observation of CRLMs response to preoperative chemotherapy can help to identify patients with progressive disease, which allows for treatment adjustment. However, preoperative chemotherapy can induce liver parenchymal injury, which can negatively affect surgical outcome and be difficult to detect in the preoperative setting. In addition, a worse surgical outcome has also been reported in patients with low preoperative muscle mass. Little is known about whether preoperative chemotherapy worsens skeletal muscle depletion.

Aims: To investigate effects of preoperative chemotherapy on the liver and preoperative muscle mass in patients undergoing liver resection for CRLMs, and to investigate whether diffusion-weighted magnetic resonance imaging (MRI) can be used to assess response in CRLMs to preoperative chemotherapy.

Patients and methods: In study I, liver volume measurements were conducted on pre- and postoperative computed tomography (CT) or MRI images in 74 patients who underwent major liver resections for CRLMs. In study II, intraoperative measurement of liver microcirculation was performed using sidestream dark-field imaging in 40 patients before and after liver resection. In study III, liver and spleen elastography was performed in 35 patients before and after liver resection. In study IV, measurement of skeletal muscle mass was carried out on pre- and posttreatment CT images in 97 patients undergoing neoadjuvant chemotherapy for CRLMs. In study V, measurements of the apparent diffusion coefficient (ADC) on pre- and postchemotherapy diffusion-weighted MRI in 49 CRLMs in 27 patients were conducted and compared to the metastases' pathological chemotherapy response.

Results and conclusions: Preoperative chemotherapy for CRLMs negatively affects the liver volume regeneration after a liver resection. The sooner the resection is carried out after the cessation of chemotherapy, the greater the impact on regeneration. Patients with a transient postoperative liver insufficiency have a lower liver volume regeneration than others. A major liver resection leads to an increase in sinusoidal blood velocity and increase in liver and spleen stiffness. Hepatic microcirculation is altered in patients with liver parenchymal injury. Patients lose muscle mass during neoadjuvant chemotherapy and muscle loss impairs the conditions for adjuvant chemotherapy. After preoperative chemotherapy, an increase in ADC occurs in both pathological responding and non-responding CRLMs, and in study V, there was no difference in the relative change of ADC between the pathological responding and non-responding CRLMs.

Key words: colorectal liver metastases, liver resection, preoperative chemotherapy, liver regeneration, hepatic microcirculation, sarcopenia, sidestream dark-field imaging, liver elastography, diffusion-weighted imaging

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To my family

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List of publications

This thesis is based on the following included publications and manuscript, referred to in the text by their roman numerals:

I. Sturesson C, Nilsson J, **Eriksson S**, Spelt L, Andersson R. *Limiting factors for liver regeneration after a major hepatic resection for colorectal cancer metastases.* HPB (Oxford). 15(8): p. 646-52. 2013.

II. Nilsson J, **Eriksson S**, Blind PJ, Rissler P, Sturesson C. *Microcirculation changes during liver resection - A clinical study.* Microvascular Research. 94: p. 47-51. 2014.

III. **Eriksson S**, Borsiin H, Öberg CF, Brange H, Mijovic Z, Sturesson C. *Perioperative liver and spleen elastography in patients without chronic liver disease.* World Journal of Gastrointestinal Surgery. 10(2):21-27. 2018.

IV. **Eriksson S**, Nilsson JH, Strandberg Holka P, Eberhard J, Keussen I, Sturesson C. *The impact of neoadjuvant chemotherapy on skeletal muscle depletion and preoperative sarcopenia in patients with resectable colorectal liver metastases.* HPB (Oxford). 19(4):331-337. 2017.

V. **Eriksson S**, Bengtsson J, Torén W, Lätt J, Andersson R, Sturesson C. *Changes in apparent diffusion coefficient and pathological response in colorectal liver metastases after preoperative chemotherapy.* Manuscript. 2021.

Additional original publications not included in this thesis:

- **Eriksson S**, Nilsson J, Lindell G, Sturesson C. *Laser speckle contrast imaging for intra-operative assessment of liver microcirculation: A clinical pilot study.* Med Devices (Auckl). 2014. 7: p. 257-61.

- **Eriksson S**, Nilsson J, Sturesson C. *Non-invasive imaging of microcirculation: a technology review.* Med Devices (Auckl). 2014. 7:445-52.

Abstract

Background

Colorectal cancer is a leading cause of cancer related death worldwide. 20-30 % of patients will develop colorectal liver metastases (CRLMs). Surgical resection is the mainstay of treatment for CRLMs, and is often combined with perioperative chemotherapy, which can prolong progression-free survival after resection. Moreover, observation of CRLMs response to preoperative chemotherapy can help to identify patients with progressive disease, which allows for treatment adjustment.

However, preoperative chemotherapy can induce liver parenchymal injury, which can negatively affect surgical outcome and be difficult to detect in the preoperative setting. In addition, a worse surgical outcome has also been reported in patients with low preoperative muscle mass. Little is known about whether preoperative chemotherapy worsens skeletal muscle depletion.

Aims

To investigate effects of preoperative chemotherapy on the liver and preoperative muscle mass in patients undergoing liver resection for CRLMs, and to investigate whether diffusion-weighted magnetic resonance imaging (MRI) can be used to assess response in CRLMs to preoperative chemotherapy.

Patients and methods

In study **I**, liver volume measurements were conducted on pre- and postoperative computed tomography (CT) or MRI images in 74 patients who underwent major liver resections for CRLMs. In study **II**, intraoperative measurement of liver microcirculation was performed using sidestream dark-field imaging in 40 patients before and after liver resection. In study **III**, liver and spleen elastography was performed in 35 patients before and after liver resection. In study **IV**, measurement of skeletal muscle mass was carried out on pre- and posttreatment CT images in 97 patients undergoing neoadjuvant chemotherapy for CRLMs. In study **V**, measurements of the apparent diffusion coefficient (ADC) on pre- and postchemotherapy diffusion-weighted MRI in 49 CRLMs in 27 patients were conducted and compared to the metastases' pathological chemotherapy response.

Results and conclusions

Preoperative chemotherapy for CRLMs negatively affects the liver volume regeneration after a liver resection. The sooner the resection is carried out after the cessation of chemotherapy, the greater the impact on regeneration. Patients with a transient postoperative liver insufficiency have a lower liver volume regeneration than others.

A major liver resection leads to an increase in sinusoidal blood velocity and increase in liver and spleen stiffness. Hepatic microcirculation is altered in patients with liver parenchymal injury.

Patients lose muscle mass during neoadjuvant chemotherapy, and muscle loss impairs the conditions for adjuvant chemotherapy.

After preoperative chemotherapy, an increase in ADC occurs in both pathological responding and non-responding CRLMs, and in study V, there was no difference in the relative change of ADC between the pathological responding and non-responding CRLMs.

Populärvetenskaplig sammanfattning

Tjock- och ändtarmscancer är den tredje vanligaste och en av de dödligaste cancerformerna världen över. Spridning av dottertumörer, metastaser, till andra organ är en viktig orsak till att patienter avlider. Ca 25 % av patienter med tjock- och ändtarmscancer utvecklar metastaser i levern. Idag används flera olika metoder för att behandla levermetastaser från tjock- och ändtarmscancer. Att kirurgisk avlägsna levermetastaserna är den behandling med bäst chans till bot. Vid en sådan operation avlägsnas de delar av levern som innehåller metastaser. Efter operationen återväxer levern och får tillbaka stora delar av sin ursprungliga storlek och sin för patienten livsnödvändiga funktion. För att levern ska kunna återväxa får storleken av levern efter operationen inte vara för liten, eftersom det då finns en risk för livshotande leversvikt. Forskning om kirurgi av levermetastaser har gjort att operation av levermetastaser har blivit säkrare och kunnat erbjudas till fler. Trots detta kan endast ca 20 % av patienter med levermetastaser från tjock- och ändtarmscancer erbjudas operation.

I tillägg till operation får patienterna ofta cellgifter både innan och efter kirurgin, då detta kan minska risken för att nya metastaser uppstår. Beroende på tumörernas känslighet för cellgifter kan cellgiftsbehandling innan operation göra att mängden levande tumörceller minskar och tumörerna krymper. Hur effektiv cellgiftsbehandlingen är på metastaserna är viktigt för patienternas prognos. Men cellgifter kan också leda till att levern tar skada, vilket kan göra en leveroperation mer riskfylld och ha betydelse för leverns återväxt efter operation. De skador som kan uppkomma i levern till följd av cellgifter är leverförfettning, inflammation och skador på leverns minsta blodkärl, sinusoiderna. Dessa skador kan vara svåra att upptäcka innan operationen.

I denna avhandlings fem delarbeten studeras olika effekter av cellgifter givna innan leveroperation av patienter med levermetastaser. I delarbete 1 studeras hur cellgifter påverkar leverns återväxt efter operation av levermetastaser. Resultaten visar att återväxten påverkas negativt av cellgiftsbehandling given innan operation och att ju kortare tidsintervallet är mellan det att cellgiftsbehandlingen avslutas och tiden för leveroperationen desto större är den negativa effekten.

I delarbete 2 studeras vilka förändringar i sinusoiderna som sker under en leveroperation genom mätningar på leverytan med ett mikroskop. Mätningarna visade att blodflödeshastigheten i sinusoiderna ökade i den kvarvarande delen av levern efter att delen med metastaser opererats bort. Patienter som hade leverskador hade också högre blodflödeshastighet och bredare sinusoider än de utan leverskador. Resultaten kan användas för att utveckla metoder för att hitta leverskador under leveroperationer.

I delarbete 3 används en ultraljudsbaserad metod för att studera styvheten i levern och mjälten före och efter operation. Styvheten i både lever och mjälte ökade efter

en operation där en stor del av levern opererats bort, men var nästan oförändrad efter en liten leveroperation. Inga skillnader hittades mellan patienter som fått cellgifter innan operationen jämfört med de som inte fått cellgifter. Styvheten i levern efter operation jämfördes också med några leverfunktionstester som uppmättes genom blodprov och leverns styvhet visades ha ett visst samband med dessa blodprov, men hur leverns styvhet efter operation hänger samman med alla leverns funktioner behöver studeras mer ingående.

I delarbete 4 undersöktes vad som händer med muskelmassan hos patienter som genomgår cellgiftsbehandling. Patienter som har låg muskelmassa är mer sköra och kan ha en ökad risk för komplikationer och sämre prognos efter en leveroperation. Resultaten i delarbetet visade att patienter tappar en del av sin muskelmassa under cellgiftsbehandlingen. Dessutom fick patienter som hade en låg muskelmassa inför operationen i mindre utsträckning cellgiftsbehandling efter operationen vilket kan leda till en sämre prognos på lång sikt. Resultaten talar för att det kan behövas fler insatser för att förhindra att patienter tappar muskelmassa under sin behandling.

Att kunna bedöma cellgifternas effekt på levermetastaserna redan innan de opereras bort kan göra det möjligt att välja rätt behandling för patienten. Men de metoder som används idag är inte alltid tillförlitliga. I delarbete 5 användes bilder från magnetkameraundersökningar för att undersöka om man med dessa bilder kan bedöma cellgifternas effekt på metastaserna. Med bilderna uppskattades tumörernas celltäthet, som ofta är hög i tumörer. Resultaten från bildmätningarna jämfördes med undersökningar av metastaserna gjorda med mikroskop. Det visade sig att mätningarna med magnetkamerabilderna inte kunde skilja på de metastaser som i mikroskop visade ha god effekt av cellgifterna och de som inte hade någon stor effekt.

Avhandlingens olika delarbeten belyser olika effekter av cellgiftsbehandling inför operation av levermetastaser. Cellgiftsbehandling har stora fördelar för patienten, men avhandlingen visar att den också kan ha negativa effekter i samband med leveroperation. Effekterna kan monitorernas med olika metoder, varav några används i avhandlingen. Resultaten i avhandlingen kan användas för att bättre förstå hur dessa metoder kan användas för att optimera behandlingen för patienten.

Abbreviations

ADC	apparent diffusion coefficient
ASA	American Society of Anesthesiologists
BMI	body mass index
BSA	body surface area
CEA	carcinoembryonic antigen
CEUS	contrast-enhanced ultrasound
CRLMs	colorectal liver metastases
CT	computed tomography
FLR	future liver remnant
FLV	functional liver volume
INR	international normalized ratio
IQR	interquartile range
MRI	magnetic resonance imaging
NAS	non-alcoholic fatty liver disease activity score
PET	positron emission tomography
PHLF	post-hepatectomy liver failure
PVE	portal vein embolization
RBCV	red blood cell velocity
RECIST	response evaluation criteria in solid tumors
ROI	region of interest
SDF	sidestream dark-field
SMI	skeletal muscle index
SOS	sinusoidal obstruction syndrome
TRG	tumor regression grade

Introduction

The liver

Embryologic development and liver anatomy

The liver originates from endodermal cells of the foregut in the upper part of the abdominal cavity [1]. During the fourth week of embryological development, the endodermal cells start to proliferate and grow ventrally to form the hepatic diverticulum, which gives rise to the intrahepatic bile ducts and the hepatocytes, the main functional cells of the liver. Subsequently, the gallbladder and the cystic duct develop from the cystic diverticulum, which originates caudally to the hepatic diverticulum, on the ventral side of the duodenal part of the foregut. The hepatic and cystic diverticula elongate ventrally and superiorly, and the connection between them and the duodenum forms the common bile duct. The common bile duct connects to the duodenum near the developing ventral and dorsal pancreatic buds.

As the liver develops ventrally, it grows into the ventral mesentery, which is formed by the caudal part of the septum transversum, the embryological structure that separates the thoracic and abdominal cavities. The septum transversum gives rise to liver fibroblasts, Kupffer cells and Glisson's capsule, which covers almost the entire surface except a small area dorsally called the bare area. In addition, the ventral mesentery and septum transversum also give rise to the future ligamentous attachments of the liver: the right and left triangular ligaments and the coronary ligament superiorly, the falciform ligament ventrally and the hepatogastric ligament and the hepatoduodenal ligament inferiorly [2]. The hepatoduodenal ligament contains the portal vein, the common bile duct, and the proper hepatic artery. The ligamentum teres is situated at the inferior border of the falciform ligament and is formed by the obliterated fetal umbilical vein.

Around the seventh week of development the organs formed by the foregut starts a 90-degree rotation. The liver is rotated to the right and stops in its final position in the right hypochondrium.

Liver blood supply

The liver has a dual blood supply, with approximately 75-80 % of the blood supply coming from the portal vein and 20-25 % from the hepatic artery [3]. The arterial

supply develops between the aorta and the foregut in the dorsal mesentery, in which the celiac trunk and superior mesenteric artery form [2]. The common hepatic artery commonly originates from the celiac trunk. After the gastroduodenal artery departs, the common hepatic artery continues as the proper hepatic artery trough the hepatoduodenal ligament to the porta hepatis where it divides into a right and left branch. However, anatomical variations are common and includes both the presence of accessory arteries and the replacement of the origin of the common hepatic artery or its branches, sometimes involving the superior mesenteric artery.

The portal venous system is embryologically developed from the right and left vitelline veins, located alongside the foregut. The portal system drains the splanchnic blood from the gastrointestinal canal and the spleen. The vitelline veins also give rise to the liver sinusoids, the capillary vessels of the liver, by forming a vascular plexus within the hepatic diverticulum. The liver drains venous blood into to the inferior vena cava through three main veins: the right, the middle and the left hepatic vein. In addition, accessory veins between different parts of the liver and the inferior vena cava are relatively common.

The liver lobule

Histologically, the liver parenchyma is arranged in small liver lobules which consists of a network of sinusoids that is surrounded by rows of hepatocytes (Fig. 1) [2]. The sinusoids run from small branches of the portal vein and hepatic arteries, which are situated in the portal triad, to a central vein. Besides the portal vein and the hepatic arteries, the portal triads hold bile ducts and lymphatic vessels. The sinusoidal endothelial cells have large fenestrations and gaps between them that allows the contents of the blood plasma to flow into the perisinusoidal space and get in close contact with the hepatocytes. In addition, both liver macrophages, i.e., Kupffer cells, and hepatic stellate cells reside within the sinusoids and the surrounding parenchyma.

Liver segmentation

Historically the liver has been divided into lobes depending on surface lobulation, such as a division of the right and left lobe at the attachment of the falciform ligament [4]. In 1897, Cantlie discovered that the vascular division between the right and left liver lies in a plane extending from the gallbladder fossa to the fossa for the inferior vena cava, i.e., the Cantlie line [5].

In the mid-20th century Hjortsjö showed the segmentation pattern of the intrahepatic bile ducts and suggested a segmental division of the liver [6]. A few years later Couinaud suggested a system that divided the liver into 8 segments, organized in 4 sectors in the right and left hemi-livers [7]. Each segment has separate branches of arterial and portal blood inflow, venous outflow, and biliary and lymphatic drainage. This division stand as a basis for the current terminology [4].

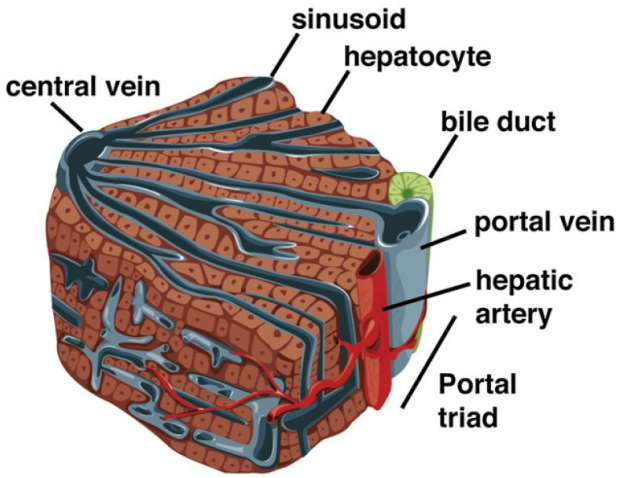


Figure 1. Schematic illustration showing the structure of a portion of a liver lobule. Reprinted from Si-Tayeb et al [8], with permission from Elsevier.

Liver function

The liver has several vital functions, which when impaired causes severe symptoms that could be lethal. Currently there is no method to artificially replace all functions of the liver, thus considerations about residual liver function must be made when planning a partial liver resection [9].

The liver functions as a storage of many substances important for energy homeostasis, e.g. glucose and fatty acids [10]. Also, vitamins A, B12 and D are stored or transformed in the liver.

In addition, the liver synthesizes important plasma proteins such as albumin and vitamin K-dependent coagulation factors, of which plasma levels can be evaluated through routine blood tests. Plasma albumin can be directly measured in blood, and coagulation factors are commonly evaluated by tests of blood coagulation time such as international normalized ratio (INR). Low plasma albumin levels and elevated INR can indicate impaired liver function.

Liver functions also include detoxification reactions and secretion of both endogenous and exogenous substances from the blood. Substances are metabolized by the cytochrome P450-system or other enzymes and then conjugated for later secretion in bile or urine. Bilirubin, a residue from the breakdown of heme in erythrocytes, is conjugated in the hepatocytes and secreted into bile. Both conjugated and unconjugated bilirubin can be measured in routine blood tests for evaluating both the conjugation process and the secretion of bilirubin into bile by the liver. Elevation of plasma bilirubin leads to the clinical syndrome of jaundice.

Besides conjugated substances bile also contains bile salts, phospholipids, and cholesterol secreted by the liver. These elements facilitate the absorption of fat and fat-soluble vitamins in the bowel.

Moreover, the liver also has immunological functions such as production of acute phase reactants. Liver Kuppfer cells have phagocytic functions for clearance of bacteria coming from the bowel via the portal system.

Colorectal cancer

Colorectal cancer is the third most common cancer and a leading cause of cancer related death worldwide [11]. In Sweden, the incidence of colon cancer has increased during the last decades, while rectal cancer incidence is relatively stable [12]. Concurrently, advances in diagnosis and treatment have resulted in increased survival rates. During the period 2014-2018, the age-standardized incidence of colorectal cancer in Sweden was 64.7 / 100 000 for men and 49.8 /100 000 for women (standardization to the Nordic standard population) [13]. Consequently, approximately 6500 new cases are diagnosed every year, of which one third of tumors are located in the rectum. In the same period, the 5-year relative survival was 67.6 % for men and 69.5 % for women [13]. The median age at diagnosis is approximately 72 years [14].

The development of colorectal cancer is multifactorial. The majority of colorectal cancer cases are sporadic, but a family history of colorectal cancer is a strong risk factor [15]. Some hereditary syndromes are known, including Lynch syndrome, familial adenomatous polyposis (FAP) and *MUTYH*-associated polyposis, which together only accounts for a few percent of colorectal cancer cases [16-18].

Most colorectal tumors evolve from adenomas, which arise from alterations affecting mechanisms involved in the regulation of DNA repair and cell proliferation in the normal renewal of the intestinal epithelium [19]. Important initiating events in the development of adenomas are mutations in the adenomatous polyposis coli gene (*APC*) or the *BRAF* oncogene [20,21]. Most adenomas remain stable, but some will progress in size and develop high-grade dysplasia and cancer, which in most cases occurs during a decade or more [22]. The prevalence of adenomas increases with age and are more common among men than women [23].

Progression from adenoma to cancer is mediated through a large mixture of genetic and epigenetic changes that accumulates over time [19]. Genetic alterations in colorectal tumors are heterogenous and several pathways of tumorigenesis exist, overlapping with each other. The chromosome instability pathway (CIN) is suggested the most common, observed in 65-70 % of sporadic colorectal tumors. In the CIN pathway, chromosome alterations are associated with mutations in *APC*,

TP53, *KRAS* and *PIK3CA* genes [19]. Another important pathway is the microsatellite instability (MSI) pathway in which mutations in DNA mismatch repair genes causes cells not to detect and repair mismatched DNA. MSI is present in approximately 15 % of sporadic tumors and is a main feature of tumors in patients with Lynch syndrome [24].

Serrated adenomas are named after their histological appearance and are associated with the serrated pathway. The serrated pathway involves the CpG island methylator phenotype (CIMP) and mutation of *BRAF*, with or without MSI [25].

With growing knowledge of tumor biology and genetics new carcinogenic pathways in colorectal tumors have been explored in recent years, confirming the complexity of colorectal cancer development [26,27].

Colorectal cancer is more common in western industrialized countries than others and several lifestyle and dietary risk factors have been proposed [11]. Some evidence exists showing that a sedentary lifestyle, obesity, and diabetes are individual risk factors for colorectal cancer [28-30]. In addition, a high alcohol consumption and cigarette smoking both increases the risk of developing colorectal cancer [31]. The mechanisms of how dietary components affect colorectal cancer development is not fully understood. A strong association between intake of processed food and red meat and increasing risk of colorectal cancer have been found [32]. On the contrary, an intake of whole grains and dairy products is suggested to decrease the risk [31].

The influence of the gut bacteria on colorectal cancer development has been investigated with special interest in Fusobacterium species that are commonly found in patients with colorectal cancer [33]. Theories of potential carcinogenic mechanisms includes promotion of inflammation and activation of oncogenic genes [34,35].

Colorectal metastasis, stage IV disease

Metastases, i.e., stage IV disease, are an important cause of mortality in colorectal cancer patients [14,36-38]. Metastatic spread occurs intraperitoneally, lymphogenous (regional or distant) or hematogenous. Specific genetic mutations in cancer cell evolution allows cells to acquire capacities to metastasize [39]. The process of metastasis includes invasion of the basal membrane, intravasation, extravasation and colonization in the new dormant tissue [40]. In addition, the cancer cell must be able to survive in the circulation as well as in the new tissue and avoid being attacked by the immune system. *BRAF* and *KRAS* mutations are associated with invasion and migration properties in cancer cells, and colorectal cancer patients with these mutations have a worse overall survival [41-43].

However, metastatic disease is diverse, ranging from a single metastasis to multiorgan polymetastatic disease with high tumor burden, which have different treatment options and long-term prognosis. If a cancer cell does not acquire all but

only a few features promoting metastasis it can have limited metastatic capabilities, and the patient may present with a small number of metastases and a more favorable prognosis [39,44]. In accordance, the number of liver metastases is prognostic of the risk of recurrence and long-term survival after liver resection [45-47].

Distant metastasis occurs in 30-38 % of patients with colorectal cancer [14,48]. The liver is the most common site for metastasis, approximately 65 % of patients with metastatic colorectal cancer have liver metastases [48]. Other common sites for metastasis are the lungs, the peritoneum, the nervous system, and bone [14]. Rectal cancer more commonly has lung metastases and colon cancer more often have peritoneal metastases as compared to the other [37,38]. Distant metastasis is associated with the primary tumor being node-positive and having a high T-stage [38,48].

When possible, surgical resection of metastases prolongs patient survival. A large registry study from the Netherlands on colorectal cancer patients reported that patients who underwent surgical resection of their metastases had a median survival of 46.2 months compared to 15.3 months in patients who received palliative systemic chemotherapy [37]. When adding targeted therapy in the palliative setting, a median survival of 20 months has been reported [49,50].

Colorectal liver metastases

Of all patients with colorectal cancer, 15-17 % will have liver metastases at time of diagnosis of the primary tumor, i.e., synchronous liver metastasis [38,51,52]. In addition, 5-13 % will develop liver metastases later in the course of the disease, i.e., metachronous liver metastases [38,51,52]. Almost all liver metastases are diagnosed within 3 years after the diagnosis of the primary tumor [38].

Patients with synchronous colorectal liver metastases (CRLMs) have a higher risk of early recurrence and a worse survival after resection of liver metastases [46,53]. Also, patients with synchronous CRLMs often have a higher number of metastases and more involved segments [38]. In addition, 26-32 % of patients with synchronous CRLMs have concurrent lung metastases [14,54].

Patients resected for liver metastases from a right-sided primary have a worse 5-year survival as compared to from a left-sided primary [38]. Right-sided colon cancers do more often have mutations in *KRAS* and *BRAF* and are more often poorly differentiated [55,56].

Imaging of CRLMs

Several imaging modalities are useful for the detection of CRLMs including computed tomography (CT), magnetic resonance imaging (MRI), ultrasound and positron emission tomography with CT (PET/CT). In the perioperative setting, imaging also assists in surgical planning, mapping of the vascular anatomy, assessing chemotherapy response, and in intraoperative guidance of both surgical and local ablative interventions [57].

Contrast-enhanced CT is commonly used for the initial staging of colorectal cancer, because it can provide fast acquisitions of images of the thorax, abdomen, and pelvis in one imaging session [58]. CRLMs are hypoattenuating compared to the normal liver parenchyma on pre-contrast CT images, and hypoenhancing on contrast-enhanced images in the portal-venous phase. Contrast-enhanced CT has a reported sensitivity of 52-85 % and specificity of 77-98 % for detection of CRLMs [59]. Sensitivity drops for small (<1 cm) metastases and in livers with steatosis, which leads to a decrease in attenuation difference between the liver parenchyma and the CRLMs. This can pose a problem after chemotherapy, which may both decrease the size of metastases and induce steatosis [60,61].

Liver MRI with gadolinium-based contrast and diffusion weighted (DWI) imaging has better sensitivity and specificity than contrast-enhanced CT [62]. Typically, CRLMs are hypointense on T1-weighted images and mildly hyperintense on T2-weighted images. Fat and tumor tissue have different signal patterns, making steatosis less of a problem when using MRI compared to CT. Gadolinium-based contrast agents used in liver imaging can be either extracellular or hepatobiliary-specific. Hepatobiliary-specific contrast agents undergo a selective up-take in functional hepatocytes. Contrast enhanced MRI using a hepatobiliary-specific contrast agent has a sensitivity of approximately 90 % for CRLMs detection and can better differentiate small (<1 cm) lesions as benign or malignant as compared to CT [62,63].

In addition to contrast-enhanced MRI, diffusion-weighted MRI can be useful for detection of CRLMs. The signal intensity on diffusion-weighted imaging reflects the motion of tissue water molecules and can be quantified with the apparent diffusion coefficient (ADC) [64,65]. A low ADC denotes a reduced tissue water diffusion. ADC has been shown to be related to tissue cellularity and the integrity of cell membranes [66]. CRLMs commonly have reduced diffusion (Fig. 2), making diffusion useful in the detection of CRLM with a sensitivity of 82-87 % [62,67]. Using a combination of hepatobiliary contrast-enhanced MRI and diffusion-weighted imaging, the sensitivity for detection of CRLMs increases to approximately 95 %, even for small lesions [62,68]. On the negative side, even if providing excellent sensitivity for detection of CRLMs, MRI has limited usage for detection of extrahepatic metastases and is more time consuming than CT [60].

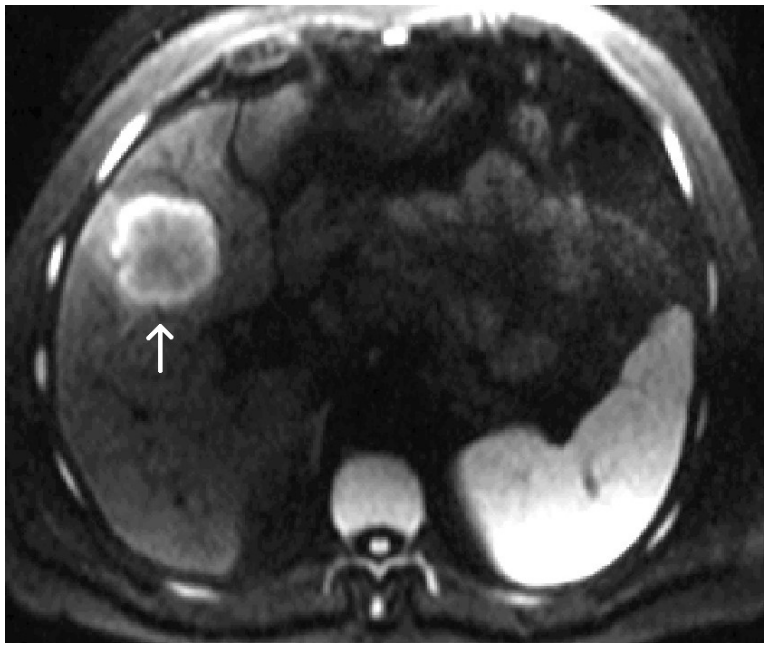


Figure 2. Diffusion-weighted magnetic resonance image of the abdomen with b-value = 800 s/mm^2 showing a colorectal liver metastasis (arrow).

PET/CT uses a positron-emitting radionuclide connected to a biological tracer to image biological processes in the body and provides both functional and anatomical information. For the detection of colorectal metastases, the glucose analogue fluorine-18-flourodeoxyglucose is mainly used. PET/CT has a sensitivity of approximately 75 % for the detection of CRLMs [69]. However, the main strength of PET/CT is in the detection of extra-hepatic metastases [70].

On contrast-enhanced ultrasound (CEUS), CRLMs are characterized by a focal hypoechoic defect in the echoic liver parenchyma on portal venous and delayed phases [71]. CEUS has a sensitivity of 80-84% for detecting liver metastases and can be especially useful in the characterization of small lesions detected with other imaging modalities [72,73]. However, imaging acquisition is dependent on operator skill and visibility can be decreased depending on patient body composition, which can decrease sensitivity [74].

Intraoperative CEUS can, in addition to visual inspection and palpation, detect additional metastases that were not detected on preoperative imaging [75,76]. Also, intraoperative CEUS can help to determine the most appropriate surgical strategy to achieve complete tumor resection [77].

Surgical treatment of CRLMs

Today, curative intended treatment of CRLMs is multimodal, including surgical resection of metastases, perioperative chemotherapy, and local tumor ablation techniques [78,79]. Since the first reports of partial hepatectomies for CRLMs in the 1940s, surgical resection has become the mainstay of treatment for CRLMs, because it offers the best possibility of cure [80-83]. After a liver resection, 5-year survival rates of 49-61 % have been reported in large series [38,84-86]. However, due to disease extent, limited liver reserve, and comorbidities, only 15-26 % of patients with CRLMs undergo curative intended liver resection [37,47,48].

The criteria for resectability have evolved during the last decades. Previously, the criteria for resection focused on the number of metastases, achieving a 1 cm resection margin, and precluded patients with extra-hepatic disease [87]. Currently, the goal of CRLMs resection is to achieve a radical removal of all tumors and leaving a functional liver remnant with sufficient volume [82,88]. Also, a limited number of peritoneal or lung metastases are if resectable no longer an absolute contraindication of resection of CRLMs [85,89].

Liver resections can be carried out in an anatomical or non-anatomical fashion, with reference to the amount of liver parenchyma to be resected and the liver segmental anatomy [90]. In non-anatomical resections, a smaller resection that spare normal liver parenchyma is possible, and they are suitable for small peripheral lesions. Anatomical resections normally involve the removal of two or more liver segments and may be required in the presence of large metastases or if metastases are located close to major hepatic vessels. If feasible, the performance of non-anatomical parenchymal-sparing resections can decrease the risk of postoperative complications, with equal rates of positive surgical margins and both disease-free and overall survival [91,92]. In addition, a parenchymal-sparing resection technique can facilitate a later repeated resection if new CRLMs occur [93].

Patients presenting with recurring CRLMs should be considered for repeated resections, because the long-term survival can be almost as good as after initial resections [94]. Also, the complication rates are comparable after repeated and initial resections [95]. The timing of the recurrence is important for long-term prognosis. Patients with an early recurrence have a worse prognosis, especially if presenting with recurrent disease during adjuvant chemotherapy [95,96].

In patients with extensive bilobar liver metastases, large resections can be required to achieve a radical resection of all CRLMs. To ensure sufficient postoperative liver function and avoid post-hepatectomy liver failure (PHLF), a liver remnant consisting of functional liver segments with a size of at least 20-30 % of the preoperative liver volume must be spared [97-99]. In patients treated with preoperative chemotherapy or with liver parenchymal disease, such as steatosis or fibrosis a larger liver remnant is required [98,100].

Different treatment strategies can make it possible for patients with extensive CRLMs and small future liver remnants (FLR) to undergo liver resection. Firstly, preoperative chemotherapy can be used to downsize the metastases [101]. Secondly, hypertrophy of the FLR can be achieved by portal vein embolization (PVE) in the part of the liver that is to be resected [102,103]. In a meta-analysis including 1088 patients, the increase in FLR volume after PVE was 8-27 % [103]. And thirdly, CRLMs can be resected in a two-stage procedure, where tumors in one lobe is resected in a first operation, and subsequently, after the FLR has grown to sufficient size, a second operation is performed, removing the rest of the tumors. This strategy can be performed either as a conventional two-stage hepatectomy or as an associating liver partition with portal vein ligation for staged hepatectomy-procedure (ALPPS) [83,104,105]. In ALLPS, a rapid growth of the FLR allows for a second operation 7-14 days after the first [83,106].

Laparoscopic liver resection

Being first performed in the beginning of the 1990s, laparoscopic liver resection for liver tumors has been proven to be safe and can in selected cases provide less intraoperative blood loss, faster recovery and shorter hospital stay as compared to open resections [107,108]. Also, the reported 5-year recurrence-free and overall survival are similar after an open and a laparoscopic resection [109,110]. Even if the use of major laparoscopic resections is increasing and the indications for laparoscopic resections are constantly evolving, the current indication for laparoscopic liver resection includes resection of up to two adjacent liver segments containing a metastasis with a tumor size less than 5 cm and located in a favorable position, i.e., segment 2-6 [108,111,112].

Postoperative complications and PHLF

As surgical technique and perioperative care has evolved over the last decades, safer liver resections can be performed, and postoperative mortality has in some studies been reported to be as low as approximately 1 % [84,113]. However, both postoperative mortality and morbidity are related to the extent of the resection, and major liver resections still poses a substantial risk of major postoperative complications [114]. Complications include hemorrhage, bile leakage, surgical site infections, pneumonia, sepsis, pleural effusion, and pulmonary embolism [114,115].

In addition, PHLF is an important complication after liver resection that carries high morbidity and mortality [86,115]. Because there is no widely accepted definition of PHLF, the reported incidence varies in the literature (0.7-34 %) [116]. The International Study Group of Liver Surgery defines PHLF as postoperatively acquired decline of one or more synthetic, excretory, or detoxifying functions of the liver and includes hypoalbuminemia, hyperbilirubinemia, prolonged prothrombin time or INR, elevated serum lactate, and hepatic encephalopathy [117].

The "50-50 criteria", suggested by Balzan et al [118], defines a criterion using a combination of prothrombin time <50 % (INR >1.7) and serum bilirubin >50 µmol/L on postoperative day 5 to distinguish patients with a high risk of early postoperative mortality. Currently, there are no causal treatment for PHLF, and only supportive care can be provided. Ensuring a sufficiently large liver remnant after liver resection is important in the prevention of PHLF, and special considerations should be made in patients with liver parenchymal injury [119,120]. Moreover, early postoperative detection of signs of PHLF could enable early initiation of supportive measurements.

Liver regeneration after liver resection

The liver has a remarkable regenerative capability. Large liver resections can be carried out, and still liver volume and function are regained after surgery. Liver regeneration is initiated early after resection, already within the first day [121]. Subsequently, most of the growth in size take place within the first week, and thereafter progresses more slowly [122]. Volume regeneration is completed 6-12 months after liver resection [122-124].

The complexity of the liver regeneration process has mostly been studied in animal models [125]. Several signaling pathways are regarded as important and key mediators include the hepatocyte growth factor, tumor necrosis factor, interleukin 6, and the epidermal growth factor [126]. The increase in portal pressure that can follow a major liver resection, may play an important part in the initiation of the regeneration process [126,127]. The increased portal pressure could stimulate sinusoidal endothelial cells to release nitric oxide, which in turn sensitizes hepatocytes to hepatocyte growth factor [127-129]. As a result, the regenerative response after major liver resections promotes both hypertrophy and proliferation of hepatocytes which lead to rapid growth of the remnant liver [130,131]. In addition, regeneration signaling also activates Kupfer cells, stellate cells, and sinusoidal endothelial cells, which help to control the regeneration process [131-134].

Postoperative liver regeneration can be impaired in patients with liver parenchymal injury, such as steatosis and fibrosis [135-137]. Preoperative chemotherapy, which is often included in the treatment of CRLMs, can induce liver parenchymal injury [61,120,138]. If chemotherapy affect liver regeneration is not fully understood and has mainly been studied after PVE. After preoperative PVE, chemotherapy has in most reports not been associated with a reduction in FLR growth [139-141]. However, the effect of preoperative chemotherapy on liver regeneration after major hepatectomies has only been studied to a limited extent.

Preoperative chemotherapy

In the preoperative setting, chemotherapy can be used to decrease the risk of recurrence after resection of CRLMs, i.e., as neoadjuvant therapy, or to downsize primarily non-resectable CRLMs. A combination of 5-fluorouracil, folinic acid and either oxaliplatin or irinotecan is the mainstay of treatment [142]. The addition of targeted therapy with the monoclonal antibodies bevacizumab, cetuximab or panitumumab can be used for increasing the chance of downsizing metastases [101].

In the randomized controlled EORTC intergroup trial 40983, perioperative chemotherapy was shown to prolong progression-free survival after resection of CRLMs [143,144]. Patients who underwent perioperative chemotherapy were given a combination of oxaliplatin, folinic acid and fluorouracil given in 6 cycles before and 6 cycles after surgery. Long-term follow-up data from the study showed an improvement in progression-free survival in the group receiving chemotherapy, with a median progression-free survival of 20.9 months as compared to 12.5 months in the group undergoing surgery alone, but no difference in overall survival [144]. The result has been confirmed in a recent meta-analysis of 5 randomized controlled trials (including the EORTC trial) which found disease-free survival to be improved after perioperative chemotherapy in the pooled analysis, but no difference in overall survival [145]. However, the included trials used different chemotherapy regimens and in 4 of the included trials in the meta-analysis only adjuvant chemotherapy was administered.

In patients with primarily non-resectable CRLMs, chemotherapy with or without the addition of targeted therapy may downsize metastases, i.e., make the metastases shrink in size and allow for a radical resection, with an improvement in survival in selected cases [101,146,147].

Moreover, observation of CRLMs response to preoperative chemotherapy help to identify patients with progressive disease. These patients have a higher rate of recurrence and a worse overall survival after liver resection and may not benefit from surgery [148].

Chemotherapy-associated liver injury

Chemotherapy regimens used in the treatment of CRLMs have been shown to induce pathological changes to the liver parenchyma including steatosis, steatohepatitis, and sinusoidal obstruction syndrome (SOS) [149]. Patients with chemotherapy-associated liver injury (CALI) have been shown to have a higher rate of postoperative complications after a liver resection [113,150].

5-fluorouracil has been associated with liver steatosis [61,151]. Patients with steatosis undergoing liver resection carries a higher risk of intraoperative bleeding and postoperative complications [152-154].

Histological changes in steatohepatitis includes steatosis, lobular inflammation, ballooning of hepatocytes and fibrosis [155]. Irinotecan has been associated with an increased risk of steatohepatitis [120,156] Patients with steatohepatitis have in a previous study been suggested to have a higher postoperative mortality after resection of CRLMs [120]. Moreover, patients with obesity have a higher risk of developing steatosis and steatohepatitis when treated with preoperative chemotherapy [113,156].

SOS is characterized by congestion and dilation of the sinusoids, disruption of the sinusoidal membrane and collagen deposits in the perisinusoidal space (Fig. 3) [157]. An increased rate of SOS has been observed after oxaliplatin-based preoperative chemotherapy [138,158,159].

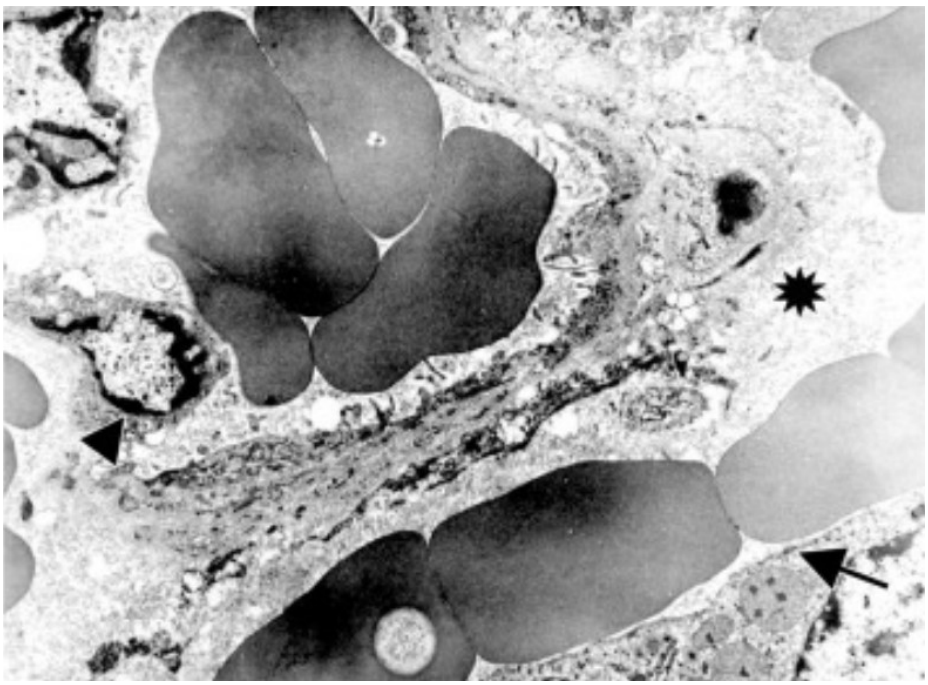


Figure 3. Electron microscopy image of a liver sinusoid with pathological changes associated with sinusoidal obstruction syndrome. The sinusoid lumen is congested with four red blood cells (upper left part of the image). The endothelial cells are rounded and protrude into the lumen (arrowhead). The perisinusoidal space (star) is dilated and contains red blood cells in close contact with hepatocytes (arrow). Reprinted from Rubbia-Brandt et al [138], with permission from Elsevier.

In animal studies, steatosis, steatohepatitis, and SOS have been associated with changes in the hepatic microcirculation [157,160,161]. Thus, changes in the hepatic microcirculation could potentially be used for detection of CALI. However, similar studies on human hepatic microcirculation have not been made.

To decrease the perioperative risks of preoperative chemotherapy, it has been suggested that chemotherapy should be ended 4-5 weeks before liver resection and that the number of chemotherapy cycles should be kept low [162,163].

Response to neoadjuvant chemotherapy

Histological features of chemotherapy response include a reduction of the percentage of viable tumor cells, reduction of the tumor thickness at the tumor periphery and increased fibrosis [164,165]. Central necrosis is a common feature in both untreated and treated CRLMs and does not correlate with pathological response [164]. The pathological response of CRLMs to neoadjuvant chemotherapy predicts both overall and disease-free survival after resection [164,166-168]. Patients who experience no or minor pathological response have the worst prognosis with 5-year survival rates of 9-33 % as compared to 41-56 % in patients with major pathological response [164,167]. Patients with a complete pathological response are relatively rare, with a reported frequency of 4-9 %, and have the best prognosis, with 5-year overall survival rates of approximately 75 %. A complete pathological response seems to be predicted by small tumor size and low carcinoembryonic antigen (CEA) level at diagnosis, both markers of low tumor burden [166,167].

Preoperative assessment of chemotherapy response

Accurate assessment of preoperative chemotherapy response in CRLMs would enable optimization of oncological treatment and identification of patients with a poor prognosis that may not benefit from a liver resection [148,169]. Several methods have been suggested for the evaluation of response to chemotherapy in the preoperative setting when pathological specimens of the CRLMs are not available. Most used is the change in tumor size on imaging according to the Response evaluation criteria in solid tumors 1.1 (RECIST), which has been developed for the response evaluation of conventional cytotoxic chemotherapy [170]. CT and MRI can be used to evaluate response in CRLMs using RECIST. At baseline, a maximum of five target lesions (maximum two lesions per organ) with a minimum diameter of 10 mm are selected and the sum of their longest diameter recorded. At follow-up, the diameters of the target lesions is remeasured, and the number of new or disappearing lesions is recorded. A complete response is defined as all lesions disappearing and that no new appears. Partial response is defined as a ≥30 % decrease in the sum of diameters of the target lesions in comparison with the baseline examination. Progressive disease is defined as a ≥20 % (at least 5 mm)

increase in the sum of diameters of the target lesions or if any new lesion appears. If none of the criteria above is fulfilled the response is termed stable disease.

However, assessment of chemotherapy response using tumor size is not always concordant with pathological response, especially when targeted therapy such as Bevacizumab is used [171,172]. A recent study showed a discordance between radiological response using RECIST and pathological response in CRLMs after preoperative chemotherapy in 44 % of cases [173].

Other imaging criteria have been suggested to better predict pathological response or survival in patients with CRLMs after chemotherapy. Chun et al [174] suggested a qualitative CT-based morphologic criterion for prediction of pathological chemotherapy response after treatment with bevacizumab. They found responding lesions to change from ill-defined heterogeneous lesions into well-defined homogeneously hypoattenuating lesions.

Moreover, the metabolic activity in CRLMs after chemotherapy, measured with mean standard uptake value on fluorine-18-flourodeoxyglucose PET/CT, has been shown to correlate with the tumor viability rate, and a low mean standard uptake value can predict a major pathological response [175].

ADC as a marker of chemotherapy response

Diffusion-weighted MRI is frequently carried out before and after preoperative chemotherapy. Quantification of tumor water diffusion with ADC has been suggested as an imaging biomarker in malignant tumors [66]. When compared to RECIST, pretreatment ADC has been found to be lower in CRLMs responding to chemotherapy than in non-responding CRLMs, and an ADC increase in responding CRLMs after chemotherapy has been observed, suggesting a decrease in tissue cellularity [65,176,177]. However, it is problematic to use the change in size or RECIST as a reference method when evaluating ADC as a marker of chemotherapy response, because, as previously stated, change in size has been shown not always to be concordant with pathological response [171-173].

Some studies have compared posttreatment ADC to pathological chemotherapy response and observed a higher posttreatment ADC in CRLMs with a major pathological response as compared to others [178-180]. They used single absolute ADC measurements, which can be difficult to compare with ADC measurements acquired at a different imaging site. Absolute ADC measurements can differ in images acquired in MRI scanners from different vendors, in different models as well as when using different image acquisition parameters [181-184]. To increase the comparability, it has been suggested that the change between pre- and posttreatment ADC measured using the same MRI scanner should be used rather than single absolute ADC measurements [185]. Only a few recent studies have investigated the association between change in CRLMs ADC after preoperative chemotherapy and pathological chemotherapy response [186,187].

Sidestream dark-field imaging

CALI can be difficult to detect preoperatively. Since liver parenchymal injury have been associated with changes in the hepatic microcirculation, perioperative studies of hepatic microcirculation could potentially provide a possibility for detection of CALI [157,160,161]. Sidestream dark-field (SDF) imaging is a technique for direct visualization of the microcirculation [188]. It consists of a hand-held microscope that is positioned directly onto the tissue. It uses a green stroboscopic light with a wavelength around 530 nm to illuminate the tissue. The green light is absorbed by hemoglobin in red blood cells and reflected by the surrounding tissue. Thus, in the image, flowing red blood cells appear dark and the surrounding tissue light. SDF imaging allows for in vivo measurement of sinusoidal red blood cell velocity (RBCV), sinusoidal diameter and functional sinusoidal density [189,190].

SDF imaging has mainly been used to study microcirculation in the sublingual mucosa in patients with sepsis, but recently, a growing number of studies have used SDF imaging for intraoperative measurements of microcirculation in abdominal organs [191-193]. Hepatic microcirculation has been studied using SDF imaging in rats [194].

Liver elastography

Another technique that potentially could give information on CALI and monitor the early postoperative changes in the liver parenchyma after a liver resection is elastography. Elastography implies investigation of metrics related to the mechanical stiffness of an organ and can be made using either ultrasound or MRI techniques [195]. The most frequent application of elastography in the liver is non-invasively quantification of liver fibrosis in patients with chronic liver disease [196]. In addition, studies have investigated the use of elastography in the characterization of liver tumors [197-199].

Ultrasound point shear wave elastography can assess tissue elasticity using a standard ultrasound probe [200,201]. It uses the acoustic radiation force impulse technique to generate a sound pulse that is transmitted through the tissue under study. The sound pulse generates small tissue displacements that induces shear waves in the tissue perpendicular to the original pulse. The shear wave velocity can be estimated in m/s, and it is related to tissue stiffness [200]. A high shear wave velocity denotes a stiff tissue. Combining the technique with standard real-time B-mode ultrasound imaging, the elastography operator can choose a region of interest (ROI) at a preferred measurement site within the tissue.

Previously reported shear wave velocities in healthy livers range between 0.8-1.7 m/s [202]. In the setting of liver surgery, a high preoperative liver stiffness has been associated with an increased risk of PHLF after liver resection of hepatocellular carcinomas in patients with chronic liver disease [203]. In addition, a postoperative increase in liver stiffness has been observed in living donors after liver resection for transplantation [204]. However, perioperative changes in liver stiffness in patients without chronic liver disease undergoing liver resection for tumors have not previously been investigated.

Preoperative sarcopenia and skeletal muscle depletion

Preoperative risk assessment is important to improve surgical outcome. Frail patients with a poor physical performance status have a higher rate of postoperative complications and length of stay after surgical procedures [205]. Skeletal muscle depletion or sarcopenia is known to cause functional impairment and to increase the risk of both nosocomial infections and postoperative morbidity in patients both with and without malignant disease [205-208]. In addition, in patients with cancer, sarcopenia has also been shown to affect long-term prognosis [209-211]. In patients with CRLMs undergoing liver resection, patients with preoperative sarcopenia have been suggested to have worse recurrence-free and overall survival and may have an increased risk of major postoperative complications [212,213]. Moreover, sarcopenia is a predictor of chemotherapy toxicity in patients treated with 5-fluorouracil or its pro-drug capecitabine for colorectal or breast cancer [214,215].

Little is known about whether preoperative chemotherapy worsens skeletal muscle depletion. Reports of patients with pancreatic or esophageal cancer suggested patient muscle loss after neoadjuvant chemotherapy [216,217]. In a study of patients undergoing palliative chemotherapy for unresectable CRLMs, a skeletal muscle loss during chemotherapy has been shown to predict worse survival [218].

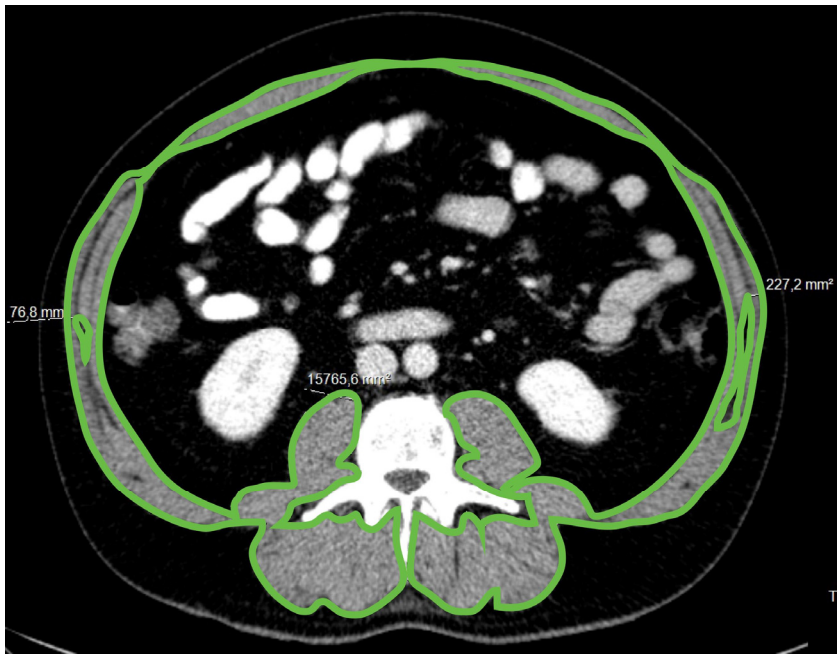


Figure 4. Computed tomography image of the abdomen at the level of the third lumbar vertebra with the cross sectional skeletal muscle area outlined in green.

Abdominal CT and MRI examinations are routinely and repeatedly performed for diagnostic purposes and to monitor treatment response in patients with CRLMs. In addition, these images can be used to measure the cross-sectional muscle area of the psoas, paraspinal and abdominal wall muscles [219]. The cross-sectional muscle area at the level of the third lumbar vertebra has previously been shown to correlate with whole-body muscle mass, and CT and MRI images of the abdomen can be used to evaluate patent muscle mass (Fig. 4) [219,220]. In fact, CT measurements have been suggested to better evaluate skeletal muscle depletion than body weight and body mass index (BMI) [209].

Aims

The general aim of the thesis was to investigate effects of preoperative chemotherapy on patients undergoing liver resection for CRLMs with the goal of providing information that can be used to improve the treatment of these patients. The thesis focuses on four different topics in the surgical treatment of CRLMs with the aim to provide answers to the following questions:

- Is the liver regeneration capacity after partial liver resection affected by the administration of preoperative chemotherapy? (Study I)
- Can SDF and point shear wave elastography be used to monitor perioperative changes in the liver parenchyma during a partial liver resection and detect changes associated with preoperative chemotherapy? (Study II and Study III)
- Does the use of neoadjuvant chemotherapy for CRLMs affect the preoperative muscle mass of the patient? (Study IV)
- Can changes in ADC in diffusion-weighted imaging assess pathological response to preoperative chemotherapy in CRLMs? (Study V)

Patients and methods

Study design

All studies were observational studies. Studies I, IV and V were retrospective studies and studies II and III were prospective studies.

Patients

Patients included in study I-V were all scheduled for liver resection for liver tumors at Skåne University Hospital, Lund, Sweden, a tertiary referral center for liver surgery. The treatment plan of every patient was decided in a multidisciplinary team conference. If a patient with CRLMs was to receive preoperative chemotherapy, the type of chemotherapy regimen was chosen by the medical oncologist after individual assessment, although oxaliplatin-based therapy was normally considered as the first choice. Data acquisition of patients' clinical data was made using patient records.

Study I

All consecutive patients domiciled in Skåne, who underwent a major resection, i.e., a resection of three or more liver segments, for CRLMs between 2005 and 2010 were retrospectively identified. Patients were grouped according to if they had or had not received chemotherapy within three months before surgery.

Study II

All patients scheduled for an open liver resection between January 22, 2013 and June 4, 2013 were considered for inclusion, except patients with viral hepatitis. All considered patients were informed about the study and patients included gave their written consent. Patients were grouped according to if they were operated with a major or minor resection. A major resection was defined as a right or extended right hepatectomy.

Study III

Patients scheduled for liver resection were considered for enrollment. All considered patients were given both written and oral information about the study and gave their written consent prior to enrollment. Patients were divided into groups depending on whether they underwent a major or minor resection. A major resection was defined as a hemihepatectomy or extended hemihepatectomy. Patients with a marked fibrosis on histological analysis of the resected liver specimen were excluded from study analysis.

Study IV

Patients who underwent liver resection for CRLMs between January 2010 and December 2014 were retrospectively identified. Patients who underwent first time resections and for whom preoperative CT images were available were included in the study. Patients receiving down-sizing chemotherapy and patients with extra-hepatic disease that eventually was not resected, including the primary tumor, were excluded.

Study V

All patients who underwent liver resection for CRLMs after preoperative chemotherapy between January 2011 and December 2019 were retrospectively identified and assessed for eligibility. Patients were included if they had undergone MRI before and after preoperative chemotherapy on the same 1.5 T MRI scanner with diffusion-weighted imaging acquired with b-values 50, 400, 800 s/mm^2. Patients were excluded if their primary tumors were classified as mucinous adenocarcinoma, or no evaluation of pathological response had been conducted.

Assessment of liver regeneration after liver resection

Liver volume measurements were conducted on pre- and postoperative CT or MRI images. The liver contour was manually traced on all transverse images of the liver and the area was automatically calculated (Fig. 5). The area of each image was then multiplied with the slice thickness (typically 5 mm) and all slices were added together to obtain liver volume. Equally, the volume of each metastasis was measured and subtracted from the liver volume to get the functional liver volume (FLV).

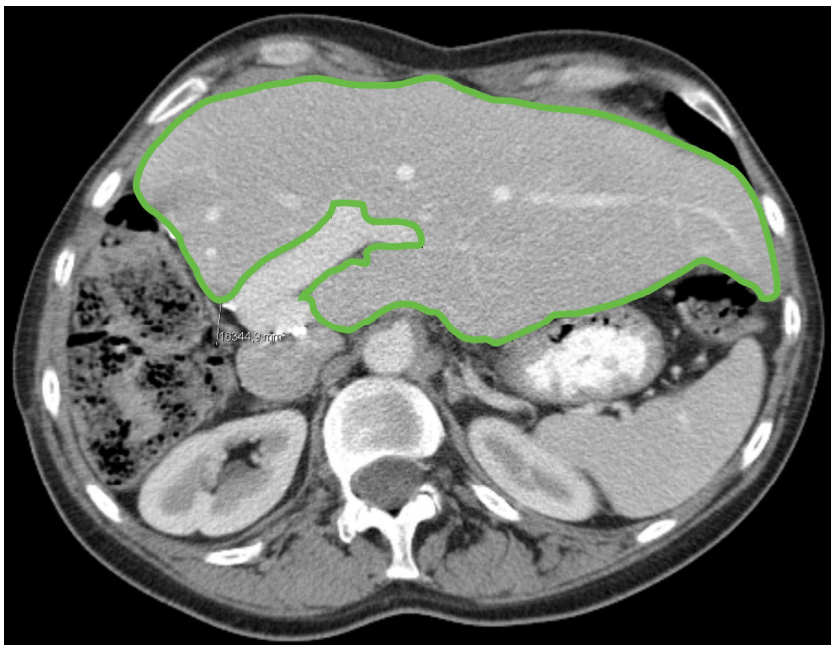


Figure 5. Computed tomography image of the abdomen showing liver volume measurement after right hepatectomy. The liver contour is outlined in green.

The most recent available images prior to liver surgery were used for preoperative liver volume measurements, except for patients who underwent PVE, in whom the most recent images prior to PVE were used instead. Postoperative liver volume measurements were made on the images closest to one year after liver surgery, but no sooner than six months. The ratio of post- and preoperative FLV was defined as the $\%FLV_{post/pre\text{-}op}$.

Postoperative morbidity was graded according to Dindo et al [221] (Table 1). Postoperative liver insufficiency was defined as a peak postoperative bilirubin >50 µmol/l and a peak postoperative INR ≥1.7. The formula suggested by Vauthey et al

[222] for prediction of total liver volume (TLV) based on body surface area (BSA) was used to analyze if preoperative liver volumes were influenced by preoperative chemotherapy:

$$TLV\ (cm^3) = -794.41 + 1267.28 * BSA \quad (1)$$

BSA was calculated as:

$$BSA\ (cm^2) = weight\ (kg)^{0.425} * height\ (cm)^{0.725} * 71.84 \quad (2)$$

Table 1. Clavien-Dindo classification of surgical complications [221].

Grade	Definition
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications.Blood transfusion and total parenteral nutrition are also included.
III	Requiring surgical, endoscopic, or radiological intervention
IIIa	Intervention not under general anesthesia
IIIb	Intervention under general anesthesia
IV	Life-threatening complication (including central nervous system complications) requiring intermediate care/intensive care unit management
IVa	Singel organ dysfunction (including dialysis)
IVb	Multiorgan dysfunction
V	Death of a patient

Intraoperative measurement of liver microcirculation with SDF imaging

Intraoperative measurement of liver microcirculation was performed using a SDF imaging microscope (MicroScan Video Microscope System, MicroScan BV, Amsterdam, The Netherlands) (Fig. 6). Measurements were conducted twice: first, after the liver had been exposed and mobilized from its diaphragmatic attachments; second, directly after completion of liver resection. Three investigators performed all measurements.

The SDF imaging microscope was covered with a disposable sterile lens cap (MicroScan Lens, Microvision Medical, Amsterdam, The Netherlands) and a sterile

drape (Video camera laser drape, Microtek Medical BV, Zutphen, The Netherlands). During measurements, the operation room light was switch off. The liver capsule was removed on an approximately 2 x 2 cm area on a segment not to be resected, typically segment 3 or 5. If necessary sterile room temperature 0.9 % NaCl solution was flushed over the liver parenchyma and the surface dried gently with a sterile cloth to remove coagulated blood. The SDF imaging probe was gently manually applied to the liver surface, minimizing pressure on the liver parenchyma. Each measurement consisted of three 20 second recordings on three different ROIs during apnea [223]. Central venous pressure, mean arterial pressure, and positive end expiratory pressure at the time of measurements were noted.

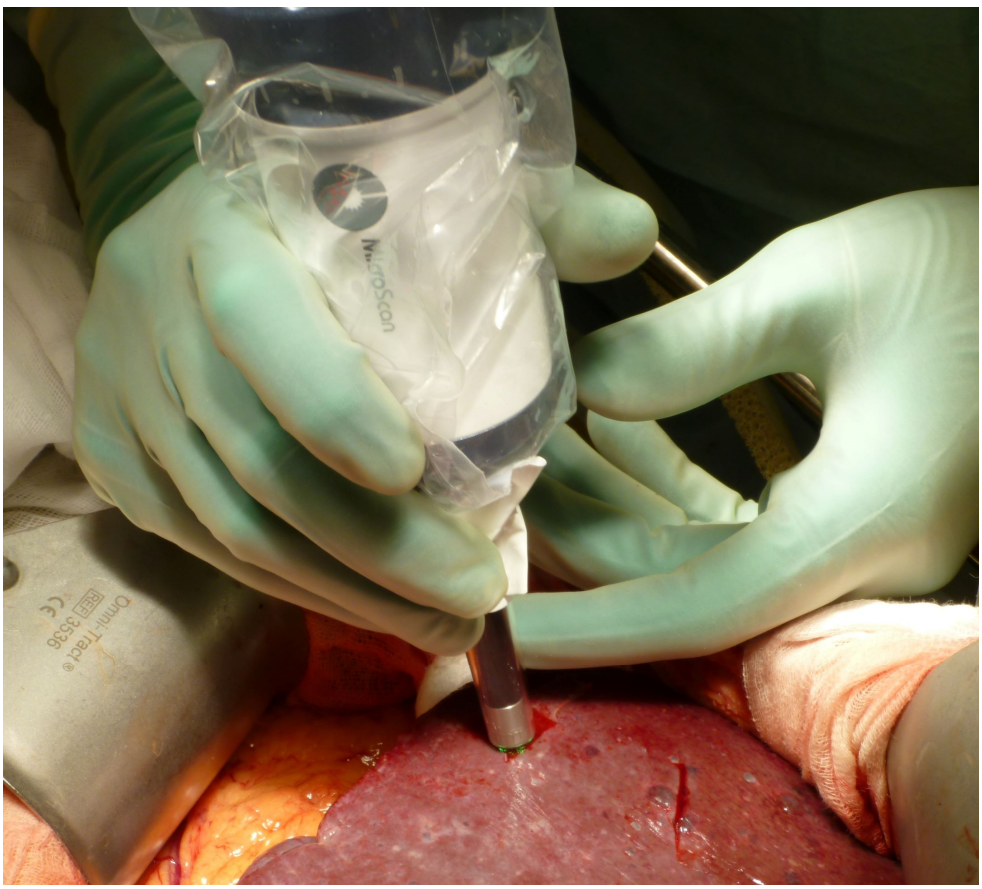


Figure 6. Intraoperative measurement of liver microcirculation using a sidestream dark-field imaging microscope. Photo courtesy of Jan Nilsson.

Recordings were analyzed on a standard computer using a vascular analysis software (AVA 3.0, MicroScan BV, Amsterdam, The Netherlands). Analysis of RBCV was made using space-time diagrams of three vessels [224]. Mean sinusoidal

diameter (μm) and functional sinusoidal density (mm/mm^2) were determined after automatic vessel detection. The functional sinusoidal density was defined as the length of perfused vessels per observation unit area. A mean of the three recordings was calculated for each variable and comparisons between pre- and postresection were made.

Perioperative liver and spleen elastography

Liver and spleen elastography were made twice, before and after liver resection. Preoperative measurements were conducted in the right and left liver lobes as well as the spleen. Postoperative measurements were carried out in the remnant liver and the spleen. Elastography was performed with a Siemens Acuson S2000 ultrasound system with the Virtual touch tissue quantification software and a 4C1 transducer (Siemens medical solutions Inc., Mountain View, CA, USA). Patients were fasting four hours before the measurement procedure. For measurements in the right liver lobe, intercostal transducer placement was used. A ROI was chosen within the liver or spleen parenchyma, at a depth of 3-6 cm from the transducer, avoiding major vessels and ducts. Each ROI was measured 10 times and a median of the measurements was calculated. Comparisons were made of pre- and postoperative measurements for the spleen and the remnant liver lobe. Measurements were presented as shear wave velocity (m/s).

Measurement of preoperative skeletal muscle mass

Patient skeletal muscle mass was retrospectively assessed using measurements of muscle area on existing diagnostic CT examinations of the abdomen. For patients who received neoadjuvant chemotherapy, measurements were made on the last CT prior to the first cycle of neoadjuvant chemotherapy and on the last CT prior to surgery. For patients not receiving neoadjuvant chemotherapy, measurements were made on the last CT prior to surgery.

The skeletal muscle area on a single transverse CT image of the abdomen at the level of the transverse processes of the third lumbar vertebra, was manually traced and the area automatically calculated (Fig. 4) [219,220]. The calculated area was normalized to body length, presenting a skeletal muscle index (SMI) (cm^2/m^2). Sarcopenia was defined as an SMI < 52.4 cm^2/m^2 for men and < 38.5 cm^2/m^2 for women [211].

The patients receiving neoadjuvant chemotherapy were divided in two groups according to if they had lost skeletal muscle mass during neoadjuvant therapy (>5

% decrease in SMI) or not [218]. Postoperative complications were graded according to Dindo et al [221]. Major complications were defined as ≥ grade 3 complications.

MRI with diffusion-weighted imaging and assessment of chemotherapy response

Measurements of CRLMs ADC were made before and after preoperative chemotherapy. Lesions were then divided into two groups if there they were pathological responding (tumor regression grade [TRG] 0-2) or non-responding (TRG 3), and the difference in ADC change after chemotherapy was compared between the two groups of lesions.

To avoid differences in ADC measurements between patients due to differences in field strengths, and strengths and timing of the diffusion gradients, only MRI images from 1.5 T systems with diffusion-weighted imaging acquired with b-values 50, 400, 800 s/mm^2 were included.

Lesions were excluded if: (1) they had a diameter < 10 mm on either pre- or posttreatment imaging, (2) lesion ADC measurements were impaired by artifacts or a low signal-to-noise ratio. Exclusion of lesions due to artifacts was carried out in consensus between the two investigators that conducted the ADC measurements.

Liver MRI protocols included transverse and coronal T2-weighted turbo spin echo images, transverse T1-weighted gradient echo images with fat-water separation, transverse diffusion-weighted echo-planar imaging and dynamic contrast enhanced T1-weighted gradient echo images using either gadoxetic acid (Gd-EOB-DTPA) or gadoteric acid (Gd-DOTA).

ADC maps were calculated using a non-linear exponential fit model of the signal intensities in the diffusion-weighted images with b-values 50, 400, 800 s/mm^2. ADC measurements were conducted using an in-house developed image analysis tool using MATLAB (The MathWorks Inc., Natick, MA, USA). Two readers – one radiology resident and one abdominal radiologist with 10 years of experience in liver MRI – individually performed ADC measurements on all patients. The radiology resident matched the CRLMs in the surgical specimen with the corresponding lesions on MRI using the pathological report.

Each reader individually placed two ROIs for every lesion on a single 400 or 800 s/mm^2 b-value image, one ROI including the entire tumor at the equatorial plane of the lesion (whole area ADC) and one ROI with a width of approximately 0.5 cm at the tumor periphery (peripheral ADC). Each ROI was placed to include only the metastases without any surrounding liver parenchyma or major vessels. The ROIs were then copied onto the ADC map and mean ADC values for the entire and

peripheral area of the lesion were recorded. ADC measurements were conducted on both pre- and posttreatment MRI examination and the absolute and relative difference between the examinations were calculated lesion by lesion. The ADC values measured by the abdominal radiologist, who was blinded to the result of the TRG classification of the lesions, were used in the study analysis.

In addition, the longest diameter of each liver metastasis at pre- and posttreatment MRI was measured on contrast-enhanced images, and the chemotherapy response was assessed per patient using the RECIST principle [170], i.e., measurement of the change in size of up to two liver metastases, not including the size of the primary tumor or lung metastases.

Histological analysis

The resected liver specimen was fixed in formalin. Histological analysis of the liver parenchyma was performed using hematoxylin and eosin stain or trichrome stain. In studies II and III, the liver parenchyma was assessed for steatosis, steatohepatitis, SOS and fibrosis. Steatosis, steatohepatitis, and fibrosis were graded according to the nonalcoholic fatty liver disease activity score (NAS) [155,225]. Steatosis was defined as a grade ≥2 (>33 % of parenchymal involvement). In study II a NAS ≥ 4 was defined as steatohepatits and a fibrosis grade ≥ 2 was defined as significant fibrosis. In study III, a NAS ≥ 5 was defined as steatohepatitis and a fibrosis grade > 2 was considered marked fibrosis. SOS was defined as a sinusoidal dilatation grade ≥ 2 (centrilobular involvement extending in two-thirds of the lobular surface) according to Rubbia-Brandt et al [138]. In study II, liver parenchyma damage was defined as either of steatosis, steatohepatitis, SOS or significant fibrosis.

In study V, the pathological response to chemotherapy in CRLMs was classified according to the TRG by the American Joint Committee of Cancer and College of American Pathologists (AJCC/CAP)[226]. The metastases were classified into one of the four categories: no residual tumor cells (TRG 0), single cells or small group of cells (TRG 1), residual cancer with a desmoplastic response (TRG 2) or minimal evidence of tumor response (TRG 3).

Statistical analysis

A p-value <0.05 was considered statistically significant.

Study I

The results are presented as mean ± standard error of the mean, unless stated otherwise. The $\%FLV_{post/pre\text{-}op}$ distribution was tested with the Shapiro-Wilk test, which indicated that $\%FLV_{post/pre\text{-}op}$ was normally distributed. Therefore, a two-tailed independent sample t-test were performed to test differences in $\%FLV_{post/pre\text{-}op}$ between groups. Other continuous data was compared using the Mann-Whitney U-test, and categorical data was compared using the Fisher's exact test. Correlations between variables were made using linear regression and by calculating a Pearson's correlation coefficient *r*

Study II

The results are presented as median (range), unless stated otherwise. Continuous data was compared using a Mann-Whitney U-test for independent samples, and Wilcoxon signed-rank test for paired samples. Categorical data was compared with a Fisher's exact test. Correlations between variables were made using linear regression and by calculating a Pearson's correlation coefficient *r*.

Study III

The results are presented as median (interquartile range [IQR]), unless stated otherwise. Continuous data was compared using a Mann-Whitney U-test for independent samples, and Wilcoxon signed-rank test for paired samples. Categorical data was compared with a χ^2 test. Correlations between variables were made using linear regression, and by calculating a Pearson's correlation coefficient *r*.

Study IV

The results are presented as median (IQR), unless stated otherwise. Continuous data was compared using a Mann-Whitney U-test for independent samples, and Wilcoxon signed-rank test for paired samples. A χ^2 test was used to compare categorical data. Overall and recurrence-free survival were estimated using the Kaplan-Meier method, and risk factors were compared using the log rank test. Hazard ratios and 95 % confidence intervals for risk factors of a worse overall survival were estimated using a Cox regression. Risk factors with a P-value < 0.1 on univariable unadjusted analysis model were included in a final multivariable analysis model.

Study V

The results are presented as median (IQR) for continuous data, and frequencies for categorical data, unless stated otherwise. Inter-reader differences in ADC measurements were evaluated with the Wilcoxon signed-rank test for paired samples and a Bland-Altman plot. To compare continuous data, a Mann-Whitney U-test or the Wilcoxon signed-rank test for paired samples. A χ^2 test or the Kruskal-Wallis test was used to compare ordinal and categorical data.

Ethics

Studies I-IV were approved by the Regional Ethical Review Board in Lund and study V was approved by the Swedish ethical review authority. In study II and III, which included perioperative measurements of liver microcirculation or liver and spleen elastography, all included patients gave their written informed consent prior to enrollment. Studies I, IV and V were retrospectively conducted and the need for informed consent was waived by the ethical review authority. Data acquisition, analysis and publication were conducted with respect of the research subjects' safety and integrity. Participating patients did not benefit themselves from participation in the studies. However, the results of the research will be beneficial for future patients with CRLMs.

Results

Study I

Seventy-eight patients were identified. Two patients were excluded due to death before any follow-up radiology was performed, one due to reoperation for liver metastases within six months, and one patient due to the preoperative CT scan being unavailable. Thus, 74 patients were included in the study analysis. Patients' characteristics and perioperative data are presented in Table 2. In patients receiving preoperative chemotherapy, a majority received an oxaliplatin-based chemotherapy regimen (n=25), with (n=8) or without (n=17) the addition of targeted therapy. Six patients received bevacizumab.

Liver volumes before and after liver resection are presented in Table 3. The ratio of preoperative FLV and BSA did not differ between patients treated with preoperative chemotherapy and patients that were not (p=0.80). There was a linear correlation between regenerated volume and the duration between the end of chemotherapy and liver surgery (Fig. 7).

$\%FLV_{post/pre\text{-}op}$ did not differ between patients preoperatively treated with or without bevacizumab (88 ± 6 vs. 83 ± 3 %, p=0.43), or between patients that received adjuvant chemotherapy (n=63) or not (n=11) (88 ± 2 vs. 87 ± 4 %, p=0.76). Neither did patients who underwent PVE and preoperative chemotherapy (n=9) differ significantly from patients treated with preoperative chemotherapy alone (n=25) in $\%FLV_{post/pre\text{-}op}$ (89 ± 4 vs. 82 ± 4 %, p=0.22).

A lower $\%FLV_{post/pre\text{-}op}$ was found in patients suffering from postoperative hepatic insufficiency (n=13) than others (79 ± 3 vs. 89 ± 2 %, p=0.013).

There was no difference in postoperative complications between patients treated and patients not treated with preoperative chemotherapy (p=0.35). There was no 90-day mortality.

Table 2. Patients' characteristics and perioperative data

	No chemotherapy	Chemotherapy	P
Number of patients	40	34	
Sex (male:female)	21:19	19:15	0.82
Age (years)	66 (46-86)	62 (42-74)	0.003
BMI (kg/m^2)	26.5 ± 0.8	24.0 ± 0.4	0.010
Patients with diabetes	6	4	0.75
Metastasis volume (ml)	66 ± 18	29 ± 9	0.08
Number of metastases	2 (0-5)*	2 (0-7)*	0.74
Size of largest metastasis (mm)	48 (0-120)*	25 (12-99)*	0.30
Number of patients with PVE	1	9	<0.0001
Number of chemotherapy cycles		7 (2-28)	
Time to surgery after chemotherapy (days)		40 (20-88)	
Type of resection			
Right-sided hepatectomy ± atypical resection	26	21	0.18
Extended right-sided hepatectomy ± atypical resection	5	8	0.10
Left-sided hepatectomy ± atypical resection	9	5	0.30
Operative bleeding (ml)	700 (100-15000)	1000 (250-4000)	0.21
Length of hospital stay (days)	8 (5-79)	9 (5-19)	0.69
Peak post-operative bilirubin (µmol/l)	32 (12-202)	35 (13-127)	0.77
Peak postoperative INR	1.6 (0.9-2.1)	1.6 (1.1-2.6)	0.44
Time from operation to postoperative imaging (days)	326 (127-822)	315 (188-593)	0.45

Data is presented as either mean ± standard error of the mean, or median (range). BMI, body mass index; PVE, portal vein embolization. *Based on pathological-anatomic diagnosis.

Table 3. Liver volumes

	No chemotherapy	Chemotherapy	p
FLV before resection (ml)	1521 ± 50	1556 ± 47	0.64
ΔFLV (ml)	-135 ± 35	-278 ± 32	0.005
$\%FLV_{post/pre\text{-}op}$	91 ± 2	83 ± 2	0.007

Data is presented as mean ± standard error of the mean. Functional liver volume (FLV) signifies functional liver volume. ΔFLV denotes the paired volume difference in FLV between after and before resection. $\%FLV_{post/pre\text{-}op}$ is defined as the ratio of post- and preoperative FLV.

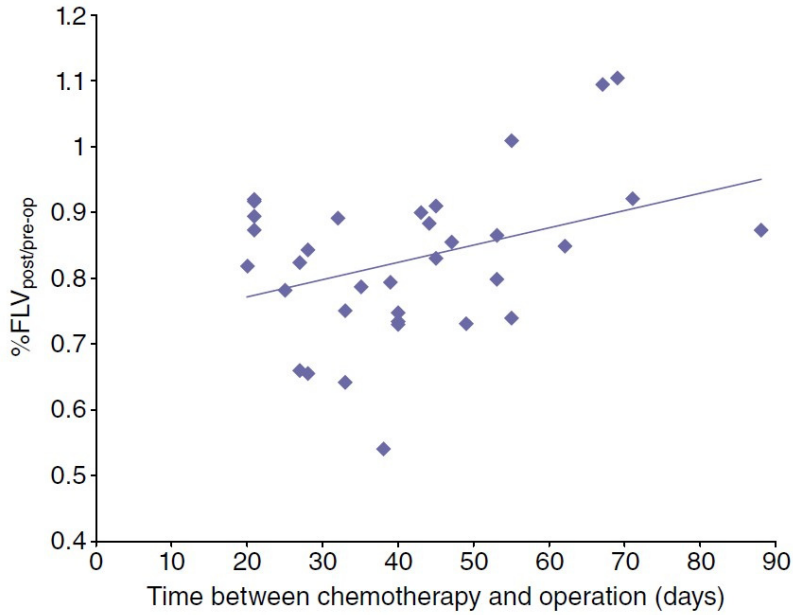


Figure 7. Correlation between regenerated volume and the time interval between cessation of chemotherapy and the operation. A linear correlation was found (r=0.37, p=0.031). Reprinted with permission from Elsevier.

Study II

Forty patients were included, of whom 12 patients underwent a major resection and 28 patients a minor resection. Patients' characteristics are presented in Table 4. Using SDF imaging, intraoperative measurement of hepatic microcirculation could successfully be performed in all patients. The time of the intraoperative measurement procedure was approximately 5 mins per patient. Measurements of hepatic microcirculation in patients undergoing a major or minor resection is presented in Table 5. Measurements of hepatic microcirculation in patients with or without liver parenchymal damage is presented in Table 6. There were no correlations between RBCV and central venous pressure or mean arterial pressure (r=0.139, p=0.393 and r=0.022, p=0.895).

Table 4. Patients' characteristics for the major and minor resection groups

	Major resection	**Minor resection**
No. of patients	12	28
Sex (male:female)	5:7	15:13
Age (years)	67.5 (61-74)	66.5 (42-83)
BMI (kg/m^2)	25.8 (17.7-34.8)	26.2 (20.2-38.1)
Smokers	1	3
Patients with diabetes	1	2
Diagnosis		
Benign	0	2
Biliary cancer	3	0
Colorectal metastases	8	17
Hepatocellular carcinoma	0	4
Other malignancy	4	2
Preoperative serum bilirubin (µmol/l)	6 (3-15)	7.5 (3-24)
Preoperative INR	1.0 (0.9-1.1)	1.0 (0.9-1.4)
Preoperative chemotherapy	4	6
Operative bleeding	575 (200-3800)	225 (25-3200)
Serum bilirubin POD3 (µmol/l)	31 (14-69)	11.5 (4-31)
INR POD3	1.3 (1.1-1.6)	1.2 (0.9-1.8)
Liver parencymal damage	3	8
Steatosis	2	1
Steatohepatitis	3	5
SOS	1	2
Fibrosis	0	4

Data is presented as median (range). BMI, body mass index; POD3, postoperative day three; SOS, sinusoidal obstruction syndrome.

Table 5. SDF imaging results for the major and minor resection groups

	Major resection	Minor resection	p
Red blood cell velocity (µm/s)			
Before resection	196 (136-464)	178 (118-329)	0.512
After resection	338 (231-483)	217 (104-505)	0.007
Difference	121 (19-253)	44 (-113-221)	0.009
p	0.002	0.016	
Sinusoidal diameter (µm)			
Before resection	12.3 (11.7-14.7)	12.3 (10.7-15.7)	0.873
After resection	11.5 (11.0-15.0)	11.8 (10.0-16.0)	0.896
Difference	-0.33 (-1.3-0)	-0.5 (-4.3-3.0)	0.873
p	0.007	0.041	
Functional sinusoidal density (mm/mm^2)			
Before resection	21.8 (16.2-25.6)	21.4 (14.6-26.4)	0.493
After resection	22.8 (17.2-26.4)	23.2 (15.8-27.6)	0.827
Diffrence	1.0 (-1.2-3.9)	1.5 (-5.9-6.8)	0.286
p	0.060	0.011	

Data is presented as median (range). SDF, Sidestream dark-field.

Table 6. SDF imaging results before resection in patients with liver parenchymal damage versus patients with no damage

	Liver damage (n=11)	No liver damage (N=27)	p
Red blood cell velocity (µm/s)	225 (148-464)	161 (118-329)	0.016
Sinusoidal diameter (µm)	12.7 (11.7-15.7)	12.0 (10.7-14.7)	0.009
Functional sinusoidal density (mm/mm^2)	20.4 (14.6-22.3)	22.2 (17.9-26.4)	0.007

Data is presented as median (range). Two patients were not included in the analysis because the liver specimens were too small to be analyzed. SDF, sidestream darkfield imaging.

Study III

Forty-seven patients were enrolled in the study. Six patients later declined participation, mostly due to postoperative pain and three patients were transferred to a different hospital before completing the measurements. Three patients had marked fibrosis on histological analysis and were excluded. Thus, 35 patients (17 males and 18 females) were included in the final study analysis.

15 patients underwent a major resection, 16 patients a minor resection and four patients underwent laparotomy but no resection. 26 patients had CRLMs, five patients had other malignant tumors and three patients had benign tumors. In the major resection group, seven patients underwent a right hemihepatectomy and eight patients an extended right hemihepatectomy. In the minor resection group, seven patients underwent resection in the right liver lobe, four patients underwent resection in the left lobe and five patients under resections in both lobes.

20 patients received preoperative chemotherapy and 15 of them received an oxaliplatin-based regimen. Only one patient had liver parenchymal damage (steatosis) on histological analysis of the liver specimen.

Perioperative tissue stiffness measurements

The second measurement were typically carried out on postoperative day two. In all patients, median preoperative shear wave velocity in the right liver lobe was 1.33 (IQR 1.15-1.50) m/s and in the left liver lobe 1.41 (1.20-1.66) m/s. Left lobe shear wave velocity was higher as compared to the right liver lobe (p=0.026). Median preoperative spleen shear wave velocity was 2.76 (2.37-3.02) m/s.

Liver and spleen stiffness measurements in the major and minor resection groups are presented in Table 7. There were no differences in gender ratio, diagnosis, body mass index or American Society of Anesthesiologists (ASA) physical status classification between the two groups. Patients in the minor resection group were older than patients in the major resection group (75 [66-79] vs. 66 [50-74] years, p=0.033) and did not receive preoperative chemotherapy as often as patients who underwent a major resection (6 vs. 12 patients, p=0.017). In patients undergoing a major resection, the stiffness in the liver remnant increased after resection (p=0.001). No difference was found in patients undergoing a minor resection (p=0.438).

Table 7. Liver and spleen stiffness measurements for the minor and major resection groups

	Minor resection	Major resection	p
No. of patients	16	15	
Future liver remnant (m/s)	1.31 (1.15-1.52)	1.41 (1.24-1.63)	0.318
Right liver lobe preoperative (m/s)	1.29 (1.12-1.49)	1.38 (1.14-1.57)	0.423
Left liver lobe preoperative (m/s)	1.35 (1.06-1.71)	1.41 (1.29-1.63)	0.667
Spleen preoperative spleen (m/s)	2.76 (2.36-2.91)	2.69 (2.33-3.11)	0.984
Liver remnant postoperative (m/s)	1.37 (1.12-1.77)	2.20 (1.72-2.44)	<0.001
Spleen postoperative (m/s)	2.83 (2.44-3.18)	2.90 (2.63-3.50)	0.216
Relative difference in liver remnant (%)	4 (-16-24)	42 (33-71)	0.001
Relative difference in the spleen (%)	2 (-1-13)	16 (7-33)	0.047

Data is presented as median (interquartile range).

Chemotherapy

There was no difference between patients who underwent preoperative chemotherapy (n=20) and patients who did not (n=15) in preoperative right liver lobe (1.31 [1.16-1.50] vs. 1.38 [1.12-1.56] m/s, p=0.569) or spleen stiffness (2.79 [2.33-3.11] vs. 2.71 [2.37-2.86] m/s, p=0.515).

Moreover, patients preoperatively treated with oxaliplatin (n=15) did not differ compared to others in preoperative right liver (1.31 [1.16-1.50] vs. 1.38 [1.14-1.61] m/s, p=0.670) or spleen stiffness (2.76 [2.34-2.97] vs. 2.76 [2.37-3.07] m/s, p=0.892).

Postoperative liver remnant stiffness and postoperative bilirubin and INR

Fig. 8 presents correlations between postoperative shear wave velocity in the liver remnant and maximum postoperative increase of bilirubin and INR.

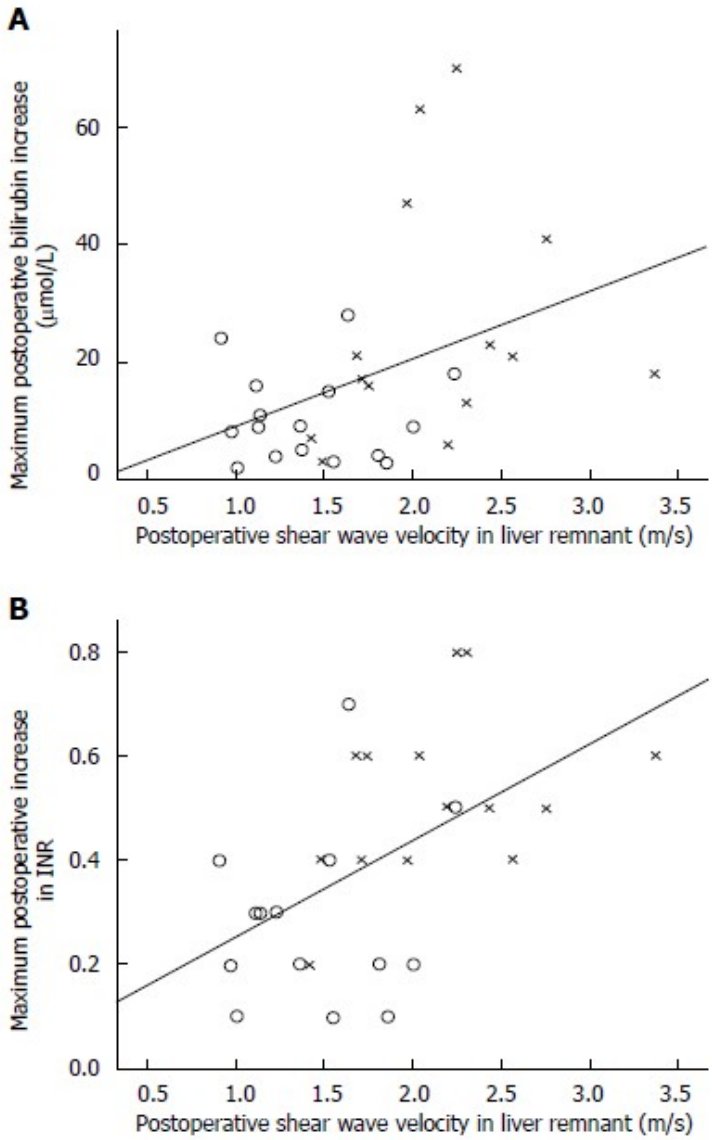


Figure 8. Correlation between maximum postoperative bilirubin increase (A), INR (B) and stiffness in the liver remnant for patients who underwent minor (O) or major (X) resection. A: R^2=0.154, r=0.392, p=0.032; B: R^2=0.285, r=0.534, p=0.003. INR, international normalized ratio.

Study IV

Of 240 patients who underwent liver resection for CRLMs, eight underwent downsizing chemotherapy and four had known extra-hepatic disease that was eventually not resected. These and three patients who died within 90 days of surgery were excluded from further analysis, leaving 225 patients included in the study analysis. The median follow-up time was 32 (IQR 5-73) months.

Impact of neoadjuvant chemotherapy on skeletal muscle mass

Ninety-seven (43 %) patients underwent neoadjuvant chemotherapy. The median time from start of neoadjuvant chemotherapy to follow-up radiology was 54 (49-64) days. Neoadjuvant chemotherapy resulted in a decrease in skeletal muscle mass. SMI decreased by 5.5 (-1.1-11) % ($p<0.001$) as compared to pre-chemotherapy SMI.

Patients' characteristics for patients with and without skeletal muscle loss >5 % are presented in Table 8. A skeletal muscle loss >5 % during neoadjuvant did not result in worse overall survival (40.3 vs. 56.4 months, log rank $p = 0.131$), or recurrence-free survival (14.6 vs. 17.5 months, log rank $p = 0.105$). Six patients who did not meet the criterion for sarcopenia at baseline turned sarcopenic after chemotherapy.

Table 8. Patients' charactheristics for patients who underwent neoadjuvant chemotherapy

	No muscle loss	Muscle loss	p
Number of patients	47	50	
Gender (male:female)	27:20	34:16	0.282
Age (years)	68.0 (62-71)	66.5 (63-75)	0.355
BMI (kg/m^2)	24.3 (22.9-27.1)	24.6 (21.4-27.0)	0.798
Current smokers	13	8	0.163
Patients with diabetes	4	8	0.263
ASA physical status (1/2:3/4)	34:13	35:15	0.799
Preoperative albumin (g/l)	37 (35-40)	38 (34-40)	0.796
Preoperative creatinine (µmol/l)	71 (64-85)	74 (64-88)	0.710
Primary tumor site (colon:rectum)	29:18	28:22	0.569
Node-positive primary	37	42	0.370
Detection of metastases (Synchronous:Metachronous)	16:31	16:34	0.831
Liver-first approach	8	11	0.537
Number of hepatic tumors	3 (2-4)	3 (2-4)	0.531
Largest hepatic tumor (mm)	20 (15-31)	25 (15-37)	0.334
Type of chemotherapy			0.104
Oxaliplatin-based	28	33	
Irinotecan-based	12	5	
Other combinations	7	12	
Targeted therapy	11	8	0..358
Number of cycles	4 (4-5)	4 (4-5)	0.947
Total muscle area before treatment (mm^2)	12 194 (10 411-15 550)	13 854 (10 644-16 024)	0.095
SMI before treatment (cm^2/m^2)	40.8 (36.9-46.9)	47.4 (40.2-51.9)	0.009
Total muscle area after treatment (mm^2)	12 201 (10 504-16074)	12,355 (9488-14475)	0.083
SMI after treatment (cm^2/m^2)	41.8 (37.7-48.6)	39.9 (33.6-45.6)	0.124
Operating time (hours)	5.75 (5.0-7.0)	6.5 (4.0-7.5)	0.684
Operative bleeding (ml)	500 (300-800)	425 (250-800)	0.598
Major complications (Clavien-Dindo ≥3)	8	4	0.177
Length of hospital stay (days)	7 (6-9)	7 (6-9)	0.558
Adjuvant chemotherapy	40	34	0.048

Data is presented as number or median (interquartile range). BMI, body mass index; ASA, American Society of Anesthesiologists; SMI, skeletal muscle index.

Preoperative sarcopenia

Among all 225 patients, including those who received and not received neoadjuvant chemotherapy, 147 (65 %) were found to be sarcopenic preoperatively. The sarcopenic group consisted of 94 men and 53 women and the median age was 69 years. The non-sarcopenic group consisted of 39 men and 39 women and their

median age was 68 years. Patients with sarcopenia had a lower BMI (24.2 [IQR 21.5-26.1] vs. 27.6 [25.4-29.9] kg/m^2, p <0.001). Seventy-six (52 %) patients with sarcopenia underwent neoadjuvant chemotherapy compared to 31 (40 %) patients without sarcopenia.

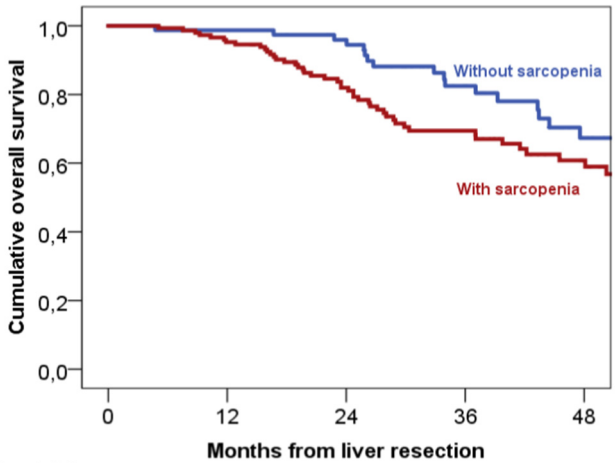
There were no differences between patients with sarcopenia and others in operation time (5.2 [3.0-7.0] vs. 4.5 [3.0-7.0] hours, p=0.651) or operative bleeding (350 [200-600] vs. 400 [200-600] ml, p=0.725). Moreover, there were no differences in the rate of major complications (12 vs. 10 %, p=0.657) or length of hospital stay (7 [6-9] vs. 7 [6-8] days, p=0.635).

Preoperative sarcopenia resulted in worse overall survival (Fig. 9). No difference was found for recurrence-free survival (Fig. 10). Univariable and multivariable hazard ratio analyses of risk factors for overall survival are shown in Table 9.

Table 9. Risk factors of overall survival

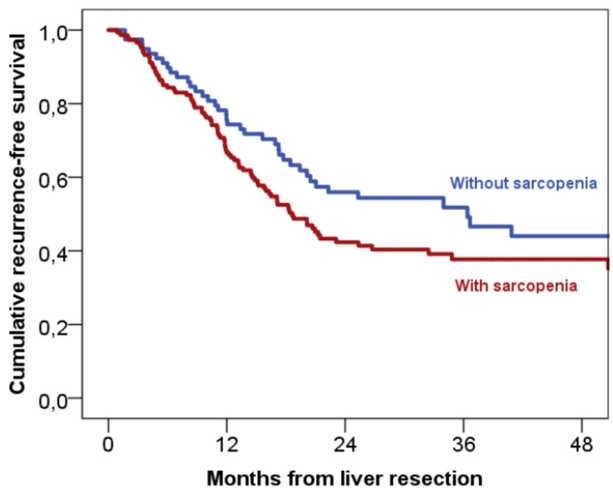
	Univariable		Multivariable	
	Hazard ratio	p	Hazard ratio	p
Gender (male vs. female)	1.52 (0.89-2.57)	0.122		
Age >70	0.89 (0.54-1.49)	0.681		
Current smoking	0.80 (0.42-1.53)	0.504		
Diabetes mellitus	0.73 (0.31-1.68)	0.456		
BMI >25 kg/m^2	0.80 (0.49-1.31)	0.375		
Sarcopenia	1.87 (1.08-3.26)	0.026	1.81 (1.02-3.21)	0.042
Body fat percentage > 50 %	1.23 (0.56-2.71)	0.603		
Neoadjuvant chemotherapy	1.64 (1.00-2.69)	0.049	0.93 (0.53-1.63)	0.807
ASA (1/2:3/4)	1.20 (0.71-2.02)	0.496		
Major complications (Clavien-Dindo ≥3)	1.31 (0.65-2.65)	0.450		
Primary tumor site (colon vs. rectum)	1.01 (0.61-1.67)	0.960		
Node-positive primary	2.09 (1.17-3.73)	0.013	1.70 (0.93-3.10)	0.086
Synchronous disease	2.51 (1.51-4.19)	<0.001	2.48 (1.38-4.46)	0.002
>1 hepatic tumor	1.70 (0.99-2.91)	0.053	1.45 (0.81-2.61)	0.212
Largest hepatic tumor >50 mm	1.38 (0.63-3.03)	0.425		
No adjuvant chemotherapy	2.09 (1.25-3.48)	0.005	2.72 (1.56-4.71)	<0.001

Data is presented as hazard ratio (95 % confidence interval). BMI, body mass index; ASA, American Society of Anesthesiologists.



No. at risk					
Without sarcopenia	78	77	65	41	21
With sarcopenia	147	140	93	58	33

Figure 9. Overall survival for patients with (red line) and without (blue line) preoperative sarcopenia (Log rank test, p=0.024). Reprinted with permission from Elsevier.



No. at risk					
Without sarcopenia	78	59	37	20	13
With sarcopenia	147	98	44	25	18

Figure 10. Recurrence-free survival for patients with (red line) and without (blue line) preoperative sarcopenia (Log rank test, p=0.104). Reprinted with permission from Elsevier.

Study V

Thirty-nine patients met the inclusion criteria. One patient that underwent concomitant liver resection and intraoperative radiofrequency ablation, was excluded because no CRLMs were found in pathological examination of the surgical specimen. Seven patients were excluded because their CRLMs had not been evaluated regarding TRG. Three patients were excluded because they had primary tumors classified as mucinous adenocarcinoma. Among the remaining 28 patients, 15 lesions were regarded as non-measurable. In one patient, all lesions were excluded due to artifacts. Thus, 27 patients with 49 lesions were included in the study analysis. Patients' characteristics are presented in Table 10.

Lesion ADC and pathological chemotherapy response

The ADC measurements made by the two readers did not show a statistical difference (p=0.173). Median ADC measurements and absolute and relative ADC changes for the pathological responding (TRG 0-2) and non-responding (TRG 3) lesions are presented in Table 11. Both responding and non-responding lesions increased in whole area ADC (responding: p=0.026; non-responding: p=0.018) and peripheral ADC (responding: p=0.006; non-responding: p=0.045) after chemotherapy. Ten of 19 lesions that increased ≥ 20 % in whole area ADC showed a pathological response, compared to 14 of 30 lesions increasing < 20 % (p=0.684).

Table 10. Patients' characteristics

Number of patients	27
Gender (male:female)	20:7
Age (years)	69 (64-72)
BMI (kg/m^2)	25.5 (22.1-28.4)
Diabetes mellitus	5
ASA physical status (1/2:3/4)	18:9
Preoperative creatinine (µmol/l)	74 (63-83)
Preoperative albumin (g/L)	37 (35-40)
CEA at time of diagnosis of CRLMs	11 (4-65)
Location of primary tumor (right colon: left or sigmoid colon: rectum)	4:15:8
T-stage primary (2:3:4)	3:15:9
Node-positive primary	24
Synchronous CRLMs	18
Number of CRLMs before chemotherapy	3 (2-5)
Bilobar CRLMs	19
Largest CRLM before chemotherapy (mm)	30 (21-46)
Preoperative chemotherapy regimen	
Oxaliplatin-based	15
Irinotecan-based	9
Other combinations	3
Targeted therapy	
EGFR antibody (i.e. Panitumumab/Cetuximab)	7
Bevacizumab	1
Total number of cycles	5 (4-6)
Number of cycles between pre- and posttreatment MRI	4 (4-5)
Days between pretreatment MRI and start of chemotherapy	29 (23-39)
Days between start of chemotherapy and posttreatment MRI	56 (48-78)
Days between posttreatment MRI and surgery	48 (34-60)
Days between last cycle of chemotherapy and surgery	38 (32-47)
Preperative PVE	1
Liver-first strategy	13
Adjuvant chemotherapy	21

Data are presented as number of patients or median (interquartile range). BMI, body mass index; ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen; CRLM, colorectal liver metastases; EGFR, epidermal growth factor receptor; MRI, magnetic resonance imaging.

Table 11. Lesion ADC in pathologic responding (TRG 0-2) vs non-responding (TRG 3)

	Responding (n=24)	Non-responding (n=25)	p-value
Pretreatment whole area ADC (10^{-3} mm^2/s)	1.26 (1.06-1.37)	1.12 (0.980-1.21)	0.119
Pretreatment peripheral ADC (10^{-3} mm^2/s)	1.15 (0.979-1.31)	1.10 (0.961-1.21)	0.337
Posttreatment whole area ADC (10^{-3} mm^2/s)	1.33 (1.13-1.56)	1.20 (1.09-1.43)	0.197
Posttreatment peripheral ADC (10^{-3} mm^2/s)	1.28 (1.11-1.42)	1.15 (1.05-1.34)	0.112
Whole area ADC difference (10^{-3} mm^2/s)	0.190 (0.020-0.350)	0.080 (-0.052-0.285)	0.610
Peripheral ADC difference (10^{-3} mm^2/s)	0.171 (0.063-0.344)	0.090 (-0.049-0.299)	0.465
Relative whole area ADC (%)	15.8 (1.42-26.3)	7.17 (-4.31-31.2)	0.795
Relative peripheral ADC (%)	14.0 (5.12-29.7)	9.43 (-4.11-33.6)	0.617

Data are presented as median (interquartile range). ADC, apparent diffusion coefficient.

Lesion size and RECIST vs. pathological chemotherapy response

After chemotherapy, both pathological responding and non-responding lesions decreased in size, and responding lesion decreased slightly more than non-responding lesions (responding: -35 [-41- -28] %; non-responding: -28 [-37-0.0] %, p=0.016). There was no difference in radiological response assessed according to the RECIST principle between patients with pathological responding and patients with pathological non-responding lesions (p=1.00).

Discussion

This thesis has examined the impact of preoperative chemotherapy on preoperative skeletal muscle depletion, postoperative liver regeneration, and tumor ADC on diffusion-weighted MRI in patients undergoing liver resection for colorectal liver metastases. In addition, perioperative changes in the liver parenchyma have been investigated with special interest in changes associated with chemotherapy associated liver injury.

Preoperative chemotherapy and liver regeneration after a major liver resection

In study I, we found that liver volume regeneration is negatively affected by preoperative chemotherapy after a major liver resection. Patients undergoing major resection were chosen because of the hypothesis that possible effects on liver regeneration of preoperative chemotherapy would be greater in a greater total volume gain [227]. In comparison, in a study on liver regeneration after mainly minor liver resections, no effect of preoperative chemotherapy was found [228].

Preoperative chemotherapy has previously been shown to induce CALI which is associated with an increased risk of postoperative morbidity [61,120,138,154]. Steatosis, which can be induced by preoperative chemotherapy, has previously been shown to impair post-hepatectomy liver regeneration [135,136]. In this study, no histopathological analysis of the liver parenchyma for investigation of CALI was performed. Thus, if the reduced liver regeneration in patients treated with chemotherapy is mediated via CALI remains uncertain. However, we found that the duration between chemotherapy cessation and surgery impacted the reduction in liver regeneration. This finding could imply that reversable effects of chemotherapy on the liver parenchyma accounts for the reduction in liver volume regeneration and emphasizes the importance of a time interval without chemotherapy before liver resection is performed.

In addition, postoperative morbidity may affect final regenerated liver volume, as most of the volume gain is suggested to occurs within the first postoperative week [122]. There was no difference in morbidity between patients who were treated with preoperative chemotherapy or not. However, patients with transient postoperative

liver insufficiency had a reduced liver volume regeneration. This further supports the finding that the initial weeks after liver resection are the most important for liver regeneration.

In patients with CRLMs, recurrence is common. The feasibility of a repeated liver resection may be dependent of a sufficient regeneration after the first resection. We found mean $\%FLV_{post/pre\text{-}op}$ to be 83 % and 91 % in the two groups of patients treated and not treated with preoperative chemotherapy. These findings are in the range of findings in previous studies also including healthy living donors [122,229].

Methodological considerations and limitations

In study I, we measured the liver volume regeneration after a liver resection. However, volume may not reflect the functional regeneration. Some previous studies have suggested that the functional regeneration occurs more slowly than volume regeneration [122,229]. If functional regeneration was impaired in patients treated with chemotherapy in this study, is not known.

Moreover, liver volumes were not measured before the start of chemotherapy, and whether preoperative chemotherapy affects the preoperative liver volume is not known. Chemotherapy can cause steatosis and steatohepatitis, which in turn could increase liver size [61,120,230]. Thus, patients treated with preoperative chemotherapy in our study possibly had an increased liver volume before hepatectomy. However, there was no difference in the ratio of preoperative FLV and BSA between patients treated and not treated with preoperative chemotherapy, which contradicts this possibility.

In addition, the retrospective design of this study may contribute to bias via unknown confounding factors that influences the comparisons between the groups.

Intraoperative measurement of liver microcirculation with SDF imaging

Changes in liver microcirculation after liver resection

To our knowledge, study II is the first study on changes of liver microcirculation during liver resection in humans. In study II, we found an increase in RBCV after liver resection, larger after a major resection than after a minor. This finding is in accordance with the increased blood flow observed after major liver resections in rats [231]. Increased hepatic perfusion has in an animal model been suggested to be important for endothelial injury after extended liver resection [232].

Patients undergoing a major resection had a larger increase in RBCV than patients undergoing a minor resection, which suggests that the volume of the resection

affects the increase. However, the relationship between size of the liver remnant and RBCV was not investigated in the study. Future studies including liver volumetry could confirm this.

A decrease in sinusoidal diameter after resection was found in both patients undergoing a major and minor resection, and there was no difference between the two groups. The underlying explanation for this could be technical. SDF imaging only contrasts between red blood cells and other tissue, and do not visualize the sinusoidal wall. Thus, only the width of the red blood cell column can be assessed. An increase in RBCV and consequential velocity-dependent closer alignment of red blood cells within the sinusoid, would result in a decrease in measured sinusoidal diameter, and may explain the findings [233].

In addition, a small increase in functional sinusoidal density was found in both groups. Normally, almost all sinusoids are perfused and a large increase in functional sinusoidal density is not expected [234].

Liver microcirculation in liver parenchymal damage

In patients with histological liver parenchymal damage, RBCV was found to be higher, sinusoidal diameter larger and functional sinusoidal density lesser than in patients without parenchymal damage (Table 6). A lesser functional sinusoidal density has also been observed in a steatohepatitis model in mice [160]. A lesser density may be due to fat accumulation and fibrosis in the liver parenchyma that results in a larger distance between vessels.

We found a higher RBCV in patients with liver parenchymal damage, which is in accordance with a study on cirrhotic rats [235]. On the contrary, a slower RBCV has been observed in animal studies of steatohepatitis and steatosis [160,161,236]. These studies were made using different measurement techniques, which may contribute to the differences. Moreover, there is a large difference in reported RBCV in human and rat livers among previous studies [190,194,231,237,238]. Our findings on pre-resection RBCV are lower than most previous studies on humans, but concordant or even higher than studies on rats.

The group of patients with histological liver parenchymal damage was heterogenous as it consisted of patients with different combinations of steatosis, steatohepatitis, SOS, and fibrosis. Due to the small number of patients with parenchymal damage (n=11), the specific histological patterns could not be investigated separately. Despite this, on a group level, SDF imaging seems to be useful in detection of microcirculatory changes associated with liver parenchymal damage.

Methodological considerations and limitations

Hepatic microcirculation can be affected by various systemic parameters. To check if differences in microcirculatory measurements were dependent on differences in systemic blood circulation, the central venous pressure and the mean arterial

pressure at the time of measurement were recorded for each patient. In the study, no correlations between microcirculatory measurements and central venous pressure or mean arterial pressure were found.

The SDF imaging method is sensitive to motion artifacts. In intraoperative liver microcirculatory measurements, motion artifacts are generated by respiratory movements and heart movements. To control respiratory movement, all measurements were conducted during apnea. Movement artifacts because of heart movements were handled with post-processing image stabilization.

Furthermore, the contact between the SDF imaging probe and the liver tissue can cause pressure-related changes in microcirculatory flow. It is important that the probe is only gently applied to the liver surface, applying as little pressure as possible when conducting measurements.

Another limitation is that SDF imaging has a focus depth of approximately 1 mm [239]. This has two implications. First, the liver capsule had to be removed in a 2 x 2 cm area to get the probe in close contact with the hepatic parenchyma. Second, only the subsurface microcirculation can be assessed with this method. Some previous authors have argued that the liver blood flow is macroscopically homogenously distributed [240,241]. However, if this also applies to the parenchymal microcirculation in patients with CRLMs is not known.

Perioperative liver and spleen elastography

In study III, we investigated changes in liver and spleen stiffness in patients undergoing a liver resection for hepatic tumors and if tissue stiffness differed between patients treated with preoperative chemotherapy and others. The liver remnant stiffness increased by 42 (IQR 33-71) % in patients undergoing a major resection, compared to 4 (-16-24) % in patients undergoing a minor resection. A possible explanation to the increase in liver remnant stiffness after a major resection is a postoperative increase in hepatic blood flow that causes congestion in the liver remnant. Accordantly, an increase in portal pressure has been observed after hepatectomy in living donors [204]. Also, in study II, RBVC was found to increase after a liver resection. In comparison, increased liver stiffness has been observed in patients with acute decompensated heart failure and in patients with extrahepatic biliary obstruction [242,243]. However, portal blood flow or pressure were not measured in study III, and the underlying cause of the increased stiffness is not proven by this study.

Also, spleen stiffness increased more after a major resection than after a minor resection (Table 7). A positive correlation between spleen stiffness and portal

pressure has previously been observed, suggesting that changes in the splanchnic circulation can be assessed through measurements of tissue stiffness [204].

CALI could worsen morbidity and mortality after a liver resection and perioperative identification of hepatic parenchymal injury is desirable [113,120,154]. Oxaliplatin, which has been associated with sinusoidal congestion and SOS, has previously been shown to induce splenic enlargement [244]. A possible consequence would be an increase in liver and spleen stiffness in patients treated with oxaliplatin. Contrary, in study III, no differences in preoperative liver or spleen stiffness were found between patients undergoing preoperative chemotherapy and others. Neither did patients preoperatively treated with oxaliplatin differ in liver or spleen stiffness compared to others. However, the frequency of CALI among included patients was very low, only one patient had steatosis, and none presented with SOS. This is a considerably lower frequency than observed in study II and in other studies [113,245]. In accordance with our findings, a concurrently published study on 20 patients undergoing resection for CRLMs found no difference in preoperative liver stiffness between patients preoperatively treated with oxaliplatin and others, despite 9 patients in that study presented with SOS [246].

Postoperative stiffness measurements in the liver remnant showed a trend towards a positive correlation between tissue stiffness and maximum postoperative increase in bilirubin and INR (Fig. 8). Similar results on postoperative maximum bilirubin in living donors has previously been reported [204]. Also, high liver stiffness has been observed in patients with acute liver failure due to intoxication [247]. In the setting of liver resection, PHLF has high morbidity and mortality, and early detection is of great importance to rapidly initiate supportive measures [115]. Postoperative elastography of the liver remnant could potentially assist in the early detection of PHLF. However, further studies on the dynamics of normal and pathological liver stiffness after liver resection are needed before patients with pathological liver remnant stiffness can be distinguished.

Methodological considerations and limitations

Patients with liver fibrosis may have an increased liver stiffness [195]. As patients with liver fibrosis were excluded in this study, the findings should be unrelated to fibrosis.

Elastography measurement in the left liver lobe has previously been shown to result in higher shear wave velocities than in the right lobe, possibly due to smaller parenchymal volume and movement artifacts from the heart [248]. The same finding was made in our study. In patients undergoing a liver resection in the right liver lobe, comparative measurements before and after liver resection were made in the left liver lobe, which may contribute to differences in absolute tissue stiffness. Because of this, relative changes in the liver remnant stiffness were investigated in the study analysis.

Moreover, postoperative elastography was conducted only once postoperatively, in general on postoperative day two. A previous study, that conducted elastography in liver remnants after hepatectomy in living donors, made multiple postoperative measurements and found liver stiffness to peak on postoperative day 3-5 [204]. The findings in our study could have been affected by the timing of the measurements. Conducting multiple postoperative measurements may further explain the relation between the liver remnant stiffness and the dynamics of postoperative increase in bilirubin and INR.

Skeletal muscle depletion during neoadjuvant chemotherapy and preoperative sarcopenia

Study IV presents evidence of patient skeletal muscle loss during neoadjuvant chemotherapy for CRLMs. SMI decreased in median 5.5 (IQR -1.1-11) %. This is in accordance with a study of patients with metastatic colorectal cancer who decreased 6.1 % in muscle area during 3 months of palliative chemotherapy and a study on patients with pancreatic cancer who had a mean loss in SMI of 2.5 % after chemoradiotherapy for a mean time of 4.2 months [216,249].

Skeletal muscle loss >5 % did not lead to worse overall or recurrence-free survival after liver resection. In contrast, a worse progression-free and overall survival in patients with >5 % skeletal muscle loss during chemotherapy has been suggested in a study on patients with unresectable colorectal cancer [218]. Also, in the study of patients with pancreatic cancer by Cooper et al [216], muscle loss affected recurrence-free survival but not overall survival.

However, in our study, patients with muscle loss >5 % during neoadjuvant chemotherapy were less likely to undergo adjuvant chemotherapy (68 vs. 85 %, p=0.048). Skeletal muscle depletion may indicate poor performance status, which may make it more likely not to consider the patient for adjuvant chemotherapy. When studying all patients, failure to receive adjuvant chemotherapy resulted in worse overall survival.

When studying both patients receiving neoadjuvant chemotherapy and those who did not, patients with preoperative sarcopenia had a worse overall survival. Preoperative sarcopenia in patients with CRLMs has previously been suggested to worsen both overall and progression-free survival [212]. Similar results have been found in patients with hepatocellular carcinomas [250].

The prevalence of preoperative sarcopenia in patients with CRLMs differs in available studies, with frequencies ranging from 17-68 % [212,213,251,252]. In our study, 65.3 % of patients were considered to have preoperative sarcopenia. Sarcopenia increases with age, and the current study population is older than in studies with a

lower frequency, which may explain the difference [253]. In addition, different studies use different definitions of sarcopenia, making results more difficult to compare. Study IV uses the definition that has been used by most authors [254].

Accepting that sarcopenia results in worse outcome after liver resection for CRLMs, it is logical that efforts should be made to prevent the development of sarcopenia during neoadjuvant chemotherapy. However, if perioperative sarcopenia is preventable is not known. A randomized controlled trial including patients scheduled for surgery of CRLMs evaluated oxygen uptake during exercise and quality of life after a four-week physical exercise program [255]. Both oxygen uptake and quality of life improved after training but no effect on surgical outcome was found. Despite this, this implies that exercise can be beneficial in improving the perioperative care of cancer patients.

Methodological considerations and limitations

Limitations to study IV include its retrospective method, where only patients that had a curative liver resection were investigated. Patients who underwent neoadjuvant chemotherapy and who, for any reason, did not undergo liver resection, are not accounted for. Furthermore, the study does not include a group of controls not receiving neoadjuvant chemotherapy. These patients do not routinely undergo repeated preoperative abdominal CT examinations.

The selected cut-off of 5 % loss in muscle mass during neoadjuvant chemotherapy was arbitrary and an attempt to define a patient group with worse prognosis. The cut-off is not validated.

Changes in ADC and pathological response after preoperative chemotherapy

In study V, we investigate changes in ADC in CRLMs on diffusion-weighted MRI as a marker of pathological chemotherapy response. An example of ADC measurements before and after chemotherapy in a CRLM is presented in Fig. 11. In accordance with previous studies, 24/49 lesions showed pathological chemotherapy response [178,179,187]. No differences in median absolute or relative difference in whole area ADC after chemotherapy between pathological responding and non-responding lesions were found (Table 11). In fact, both pathological responding and non-responding lesions increased in ADC after chemotherapy.

The underlying histological changes that account for the change in lesion ADC in this study are not fully known, since no analysis of tumor composition besides TRG was included. Previous studies have suggested that an increase in ADC may reflect other changes in tumor features denoting chemotherapy response than those

included in the TRG system, such as mucinous regression [256-258]. Accordingly, an increase in ADC in non-resectable CRLMs after selective internal radiation therapy has been suggested as a marker of response and has been associated with a longer overall survival [259].

Also, lesion ADC may increase due to an increase in tumor necrosis [260]. Necrosis is common in both treated and untreated CRLMs and is not a good marker of chemotherapy response [164,261]. Tumor necrosis is predominately located at the tumor center, and peripheral ADC has been suggested to better reflect tumor response than whole area ADC [178]. However, in study V, no difference in peripheral ADC in the pathological responding versus non-responding lesions was found.

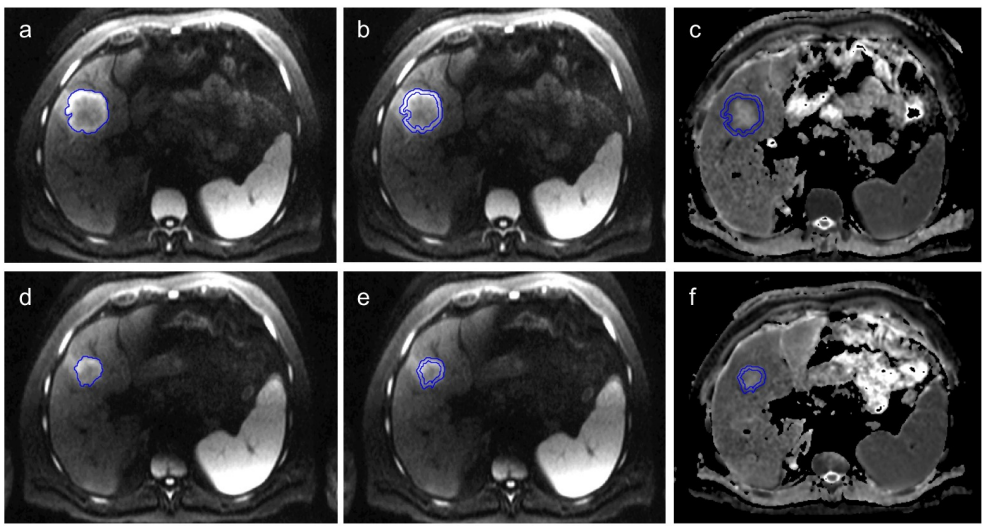


Figure 11. ADC measurements before (a-c) and after (d-f) chemotherapy in a colorectal liver metastasis. Pretreatment diffusion-weighted image with b-value = 800 s/mm^2 with (a) whole area ROI and (b) peripheral ROI. (c) Pretreatment ADC map with peripheral ROI. Posttreatment diffusion-weighted image with b-value=800 s/mm^2 with (d) whole area ROI and (e) peripheral ROI. (f) Posttreatment ADC map with peripheral ROI. Whole area A.DC increased from 1.10 to 1.21 10^{-3} mm^2/s (10 %) and peripheral ADC increased from 0.989 to 1.07 10^{-3} mm^2/s (8%) after treatment. The lesion decreased in size from 50 mm to 33 mm and presented with tumor regression grade 0, no residual tumor cells.

Our findings are contrary to the findings of Boraschi et al [186], who found a linear correlation between the ADC difference after chemotherapy and pathological chemotherapy response and no ADC increase in lesions with no pathological response. In their study, the increase in ADC in pathological responding lesions was higher as compared to responding lesions in study V. Only six lesions with TRG 0-1 were included in our study, which may contribute to the difference. In addition, the MRI examinations in their study were conducted using diffusion-weighted

imaging with b-values 0, 150, 500, 1000, 1500 s/mm^2 using a 3T-scanner. If this contributed to the differences is uncertain.

Both pathological responding and non-responding lesions decreased in size after chemotherapy, even if responding lesions decreased slightly more than non-responding lesions. Previous studies have shown that assessment of chemotherapy response using tumor size is not always concordant with pathological response, especially when targeted therapy such as bevacizumab is used [171,172]. Also, when assessing response per patient according to the RECIST principle, no difference was found, but the small number of patients may have affected the result.

Methodological considerations and limitations

The reproducibility of quantitative measurements between different MRI scanners and imaging sites is a major challenge when using ADC as an imaging biomarker. Measurement variability can arise from differences in scanner field strength, the choice of b-values, scanner-dependent gradient nonlinearity outside scanner isocenter and the choice of mathematical model used to calculate the ADC maps [183,184,262]. This poses a problem both when comparing the results between different studies and in the clinical setting, because patients with CRLMs commonly undergo preoperative MRI at different sites before referral to a tertiary surgical center. To overcome this, analyzing the change between pre- and posttreatment ADC measured using the same MRI scanner, instead of using single absolute ADC measurements, has been suggested [185]. In study V, each patient underwent MRI before and after preoperative chemotherapy using the same MRI scanner. Also, all scanners had the same field strength and included diffusion-weighted imaging that used the same b-values. These strict inclusion criteria meant that only a minority of patients who underwent resection for CRLMs after preoperative chemotherapy at our institution could be included. The small number of patients is a limitation to the study.

Conclusions

The major conclusions of the studies are:

Study I

Preoperative chemotherapy for CRLMs negatively affects the liver volume regeneration after a liver resection. The sooner the resection is carried out after the cessation of chemotherapy, the greater the impact on regeneration.

Patients with a transient postoperative liver insufficiency have a lower liver volume regeneration than others.

Study II

A liver resection leads to an increase in sinusoidal blood velocity. Hepatic microcirculation is altered in patients with liver parenchymal damage, and SDF imaging may be useful for intraoperative detection of these damages.

Study III

Liver and spleen stiffness increases after a major liver resection. The usage of perioperative point shear wave elastography in detection of PHLF and CALI needs further investigation.

Study IV

Patients lose muscle mass during neoadjuvant chemotherapy. Low preoperative skeletal muscle mass is a risk factor of worse overall survival after liver resection. Skeletal muscle loss during neoadjuvant chemotherapy impairs the conditions for adjuvant chemotherapy.

Study V

After preoperative chemotherapy, an increase in ADC on diffusion-weighted MRI occurs in both pathological responding and non-responding CRLMs. There was no difference in changes in ADC after chemotherapy between pathological responding and non-responding CRLMs in this study.

Future perspectives

Advances in the treatment of patients with CRLMs in the last decades have expanded the indications for curative intended liver resection and improved patients' long-term survival. However, there are still several challenges that need to be addressed, especially in patients with extensive liver tumor disease. Preoperative chemotherapy has several advantages: prolonging progression-free survival, downsizing primarily unresectable metastases to make them resectable, and allowing for preoperative identification of patients with progressive disease and a poor prognosis. Still, preoperative chemotherapy can have a negative impact on the patient and the liver.

In study I, we found preoperative chemotherapy to affect the liver volume regeneration after liver resection. In addition, we found that the duration between chemotherapy cessation and surgery impacted the reduction in liver regeneration. This finding could imply that reversable effects of chemotherapy on the liver parenchyma accounts for the reduction in liver volume regeneration and emphasizes the importance of continuing to have a time interval without chemotherapy before liver resection is performed. However, the underlying mechanism of this effect is not fully understood. Further studies should investigate in what way chemotherapy affects the regeneration process and to what extent CALI mediates the negative effects on liver regeneration. Also, in addition to measuring liver volume regeneration, the restoration of liver function should also be investigated.

Perioperative measurements in the liver parenchyma during liver resection can provide important information about the dynamics of the perioperative changes that occur in both normal liver parenchyma and in livers with parenchymal injury and a risk of PHLF. In study II and III we studied perioperative changes in hepatic microcirculation and liver and spleen stiffness using SDF imaging and point shear wave elastography. Even if SDF imaging seems to be useful in intraoperative detection of microcirculatory changes associated with liver parenchymal damage, studies including more patients with CALI is needed to evaluate the true usefulness of SDF imaging for detection of liver parenchymal damage.

Point shear wave elastography is an easy and available method for measurement of liver stiffness in the perioperative setting. Future studies including volumetric measurements of the liver and conducting repeated measurements during the postoperative course after a liver resection could further clarify the relation between

tissue stiffness and changes in liver biochemistry and factors related to liver regeneration. This may allow for early detection of signs of PHLF.

In study IV, we found skeletal muscle depletion in patients undergoing neoadjuvant chemotherapy, leading to lower preoperative patient skeletal muscle mass, which is a known factor of worse surgical outcome after liver resection. This calls for preventive measures during preoperative chemotherapy and before liver resection. Studies on physical training and prehabilitation programs aimed to prevent muscle loss will demonstrate whether skeletal muscle depletion is preventable and if surgical outcome can be improved.

Moreover, accurately assessing the chemotherapy response preoperatively could allow for optimization of the treatment plan for patients not responding to initial treatment. In study V, we investigated ADC as a marker of pathological chemotherapy response in CRLMs and found that both pathological responding and non-responding lesion increased in ADC after chemotherapy. This result is contrary to previous findings. Thus, the usefulness of ADC in assessing pathological chemotherapy response needs further investigation. Including comparisons between ADC changes and histopathological analyses of tumor composition could explain the relation between them.

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References

1. Larsen WJ. Development of the Gastrointestinal Tract. In: Human embryology. 2 ed. Philadelphia, PA: Churchill Livingstone, 1997.
2. Reynolds JC, Ward PJ, Martin JA, et al. The Netter Collection of Medical Illustrations Digestive system: Part III - Liver, Billiary Tract, and Pancreas. 2 ed. Philadelphia, PA: Elsevier, 2017.
3. Vollmar B, Menger MD. The hepatic microcirculation: mechanistic contributions and therapeutic targets in liver injury and repair. Physiological reviews 2009;89:1269-1339. DOI: 10.1152/physrev.00027.2008.
4. Strasberg SM. Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. Journal of hepato-biliary-pancreatic surgery 2005;12:351-355. DOI: 10.1007/s00534-005-0999-7.
5. Cantlie J. On a new arrangement of the right and left lobes of the liver. Proc Anat Soc Great Britain and Ireland 1897;32:4-9.
6. Hjortsjo CH. The topography of the intrahepatic duct systems. Acta anatomica 1951;11:599-615.
7. Couinaud C. Le Foie. Etudes anatomiques et chirugicales. Paris: Masson & Cie, 1957.
8. Si-Tayeb K, Lemaigre FP, Duncan SA. Organogenesis and development of the liver. Developmental cell 2010;18:175-189. DOI: 10.1016/j.devcel.2010.01.011.
9. Søreide JA, Deshpande R. Post hepatectomy liver failure (PHLF) - Recent advances in prevention and clinical management. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 2021;47:216-224. DOI: 10.1016/j.ejso.2020.09.001.
10. Suchy FJ. Hepatobiliary function. In: Boron WF, Boulpaep EL eds. Medical physiology. Philadelphia, PA: Elsevier, 2017.
11. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA: a cancer journal for clinicians 2015;65:87-108. DOI: 10.3322/caac.21262.
12. Gutlic I, Schyman T, Lydrup ML, et al. Increasing colorectal cancer incidence in individuals aged < 50 years-a population-based study. International journal of colorectal disease 2019;34:1221-1226. DOI: 10.1007/s00384-019-03312-3.
13. Larønningen S, Ferlay J, Bray F, et al. NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 9.0 (01.03.2021). In. https://nordcan.iarc.fr: Association of the Nordic Cancer Registries, 2021.
14. Riihimäki M, Hemminki A, Sundquist J, et al. Patterns of metastasis in colon and rectal cancer. Scientific reports 2016;6:29765. DOI: 10.1038/srep29765.

15. Johns LE, Houlston RS. A systematic review and meta-analysis of familial colorectal cancer risk. The American journal of gastroenterology 2001;96:2992-3003. DOI: 10.1111/j.1572-0241.2001.04677.x.
16. Lynch HT, Lynch PM, Lanspa SJ, et al. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clinical genetics 2009;76:1-18. DOI: 10.1111/j.1399-0004.2009.01230.x.
17. Bülow S, Faurschou Nielsen T, Bülow C, et al. The incidence rate of familial adenomatous polyposis. Results from the Danish Polyposis Register. International journal of colorectal disease 1996;11:88-91. DOI: 10.1007/bf00342466.
18. Sieber OM, Lipton L, Crabtree M, et al. Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in MYH. The New England journal of medicine 2003;348:791-799. DOI: 10.1056/NEJMoa025283.
19. Nguyen LH, Goel A, Chung DC. Pathways of Colorectal Carcinogenesis. Gastroenterology 2020;158:291-302. DOI: 10.1053/j.gastro.2019.08.059.
20. Sparks AB, Morin PJ, Vogelstein B, et al. Mutational analysis of the APC/beta-catenin/Tcf pathway in colorectal cancer. Cancer research 1998;58:1130-1134.
21. Rad R, Cadiñanos J, Rad L, et al. A genetic progression model of Braf(V600E)-induced intestinal tumorigenesis reveals targets for therapeutic intervention. Cancer cell 2013;24:15-29. DOI: 10.1016/j.ccr.2013.05.014.
22. von Renteln D, Pohl H. Polyp Resection - Controversial Practices and Unanswered Questions. Clinical and translational gastroenterology 2017;8:e76. DOI: 10.1038/ctg.2017.6.
23. Brenner H, Altenhofen L, Stock C, et al. Natural history of colorectal adenomas: birth cohort analysis among 3.6 million participants of screening colonoscopy. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2013;22:1043-1051. DOI: 10.1158/1055-9965.epi-13-0162.
24. Boland CR, Thibodeau SN, Hamilton SR, et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer research 1998;58:5248-5257.
25. Bettington M, Walker N, Clouston A, et al. The serrated pathway to colorectal carcinoma: current concepts and challenges. Histopathology 2013;62:367-386. DOI: 10.1111/his.12055.
26. Liu Y, Sethi NS, Hinoue T, et al. Comparative Molecular Analysis of Gastrointestinal Adenocarcinomas. Cancer cell 2018;33:721-735.e728. DOI: 10.1016/j.ccell.2018.03.010.
27. Comprehensive molecular characterization of human colon and rectal cancer. Nature 2012;487:330-337. DOI: 10.1038/nature11252.
28. Howard RA, Freedman DM, Park Y, et al. Physical activity, sedentary behavior, and the risk of colon and rectal cancer in the NIH-AARP Diet and Health Study. Cancer causes & control : CCC 2008;19:939-953. DOI: 10.1007/s10552-008-9159-0.

29. Pischon T, Lahmann PH, Boeing H, et al. Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). Journal of the National Cancer Institute 2006;98:920-931. DOI: 10.1093/jnci/djj246.
30. Yuhara H, Steinmaus C, Cohen SE, et al. Is diabetes mellitus an independent risk factor for colon cancer and rectal cancer? The American journal of gastroenterology 2011;106:1911-1921; quiz 1922. DOI: 10.1038/ajg.2011.301.
31. Vieira AR, Abar L, Chan DSM, et al. Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project. Annals of oncology : official journal of the European Society for Medical Oncology 2017;28:1788-1802. DOI: 10.1093/annonc/mdx171.
32. Larsson SC, Wolk A. Meat consumption and risk of colorectal cancer: a meta-analysis of prospective studies. International journal of cancer 2006;119:2657-2664. DOI: 10.1002/ijc.22170.
33. Castellarin M, Warren RL, Freeman JD, et al. Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma. Genome research 2012;22:299-306. DOI: 10.1101/gr.126516.111.
34. Rubinstein MR, Wang X, Liu W, et al. Fusobacterium nucleatum promotes colorectal carcinogenesis by modulating E-cadherin/β-catenin signaling via its FadA adhesin. Cell host & microbe 2013;14:195-206. DOI: 10.1016/j.chom.2013.07.012.
35. Kostic AD, Chun E, Robertson L, et al. Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. Cell host & microbe 2013;14:207-215. DOI: 10.1016/j.chom.2013.07.007.
36. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. CA: a cancer journal for clinicians 2020;70:145-164. DOI: 10.3322/caac.21601.
37. van der Geest LG, Lam-Boer J, Koopman M, et al. Nationwide trends in incidence, treatment and survival of colorectal cancer patients with synchronous metastases. Clinical & experimental metastasis 2015;32:457-465. DOI: 10.1007/s10585-015-9719-0.
38. Engstrand J, Nilsson H, Strömberg C, et al. Colorectal cancer liver metastases - a population-based study on incidence, management and survival. BMC cancer 2018;18:78. DOI: 10.1186/s12885-017-3925-x.
39. Gupta GP, Massagué J. Cancer metastasis: building a framework. Cell 2006;127:679-695. DOI: 10.1016/j.cell.2006.11.001.
40. Cao H, Xu E, Liu H, et al. Epithelial-mesenchymal transition in colorectal cancer metastasis: A system review. Pathology, research and practice 2015;211:557-569. DOI: 10.1016/j.prp.2015.05.010.
41. Makrodouli E, Oikonomou E, Koc M, et al. BRAF and RAS oncogenes regulate Rho GTPase pathways to mediate migration and invasion properties in human colon cancer cells: a comparative study. Molecular cancer 2011;10:118. DOI: 10.1186/1476-4598-10-118.
42. Karagkounis G, Torbenson MS, Daniel HD, et al. Incidence and prognostic impact of KRAS and BRAF mutation in patients undergoing liver surgery for colorectal metastases. Cancer 2013;119:4137-4144. DOI: 10.1002/cncr.28347.

43. Schirripa M, Bergamo F, Cremolini C, et al. BRAF and RAS mutations as prognostic factors in metastatic colorectal cancer patients undergoing liver resection. British journal of cancer 2015;112:1921-1928. DOI: 10.1038/bjc.2015.142.
44. Weichselbaum RR, Hellman S. Oligometastases revisited. Nature reviews Clinical oncology 2011;8:378-382. DOI: 10.1038/nrclinonc.2011.44.
45. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Annals of surgery 1999;230:309-318; discussion 318-321.
46. Viganò L, Capussotti L, Lapointe R, et al. Early recurrence after liver resection for colorectal metastases: risk factors, prognosis, and treatment. A LiverMetSurvey-based study of 6,025 patients. Annals of surgical oncology 2014;21:1276-1286. DOI: 10.1245/s10434-013-3421-8.
47. Hackl C, Neumann P, Gerken M, et al. Treatment of colorectal liver metastases in Germany: a ten-year population-based analysis of 5772 cases of primary colorectal adenocarcinoma. BMC cancer 2014;14:810. DOI: 10.1186/1471-2407-14-810.
48. Elferink MA, de Jong KP, Klaase JM, et al. Metachronous metastases from colorectal cancer: a population-based study in North-East Netherlands. International journal of colorectal disease 2015;30:205-212. DOI: 10.1007/s00384-014-2085-6.
49. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. The New England journal of medicine 2004;350:2335-2342. DOI: 10.1056/NEJMoa032691.
50. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. The New England journal of medicine 2009;360:563-572. DOI: 10.1056/NEJMoa0808268.
51. Norén A, Sandström P, Gunnarsdottir K, et al. Identification of Inequalities in the Selection of Liver Surgery for Colorectal Liver Metastases in Sweden. Scandinavian journal of surgery : SJS : official organ for the Finnish Surgical Society and the Scandinavian Surgical Society 2018;107:294-301. DOI: 10.1177/1457496918766706.
52. Manfredi S, Lepage C, Hatem C, et al. Epidemiology and management of liver metastases from colorectal cancer. Annals of surgery 2006;244:254-259. DOI: 10.1097/01.sla.0000217629.94941.cf.
53. Kanas GP, Taylor A, Primrose JN, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. Clinical epidemiology 2012;4:283-301. DOI: 10.2147/clep.s34285.
54. Norén A, Eriksson HG, Olsson LI. Selection for surgery and survival of synchronous colorectal liver metastases; a nationwide study. European journal of cancer (Oxford, England : 1990) 2016;53:105-114. DOI: 10.1016/j.ejca.2015.10.055.
55. Nitsche U, Stögbauer F, Späth C, et al. Right Sided Colon Cancer as a Distinct Histopathological Subtype with Reduced Prognosis. Digestive surgery 2016;33:157-163. DOI: 10.1159/000443644.
56. Brulé SY, Jonker DJ, Karapetis CS, et al. Location of colon cancer (right-sided versus left-sided) as a prognostic factor and a predictor of benefit from cetuximab in

NCIC CO.17. European journal of cancer (Oxford, England : 1990) 2015;51:1405-1414. DOI: 10.1016/j.ejca.2015.03.015.

57. Hazhirkarzar B, Khoshpouri P, Shaghaghi M, et al. Current state of the art imaging approaches for colorectal liver metastasis. Hepatobiliary surgery and nutrition 2020;9:35-48. DOI: 10.21037/hbsn.2019.05.11.
58. Fowler KJ, Kaur H, Cash BD, et al. ACR Appropriateness Criteria(®) Pretreatment Staging of Colorectal Cancer. Journal of the American College of Radiology : JACR 2017;14:S234-s244. DOI: 10.1016/j.jacr.2017.02.012.
59. Vreugdenburg TD, Ma N, Duncan JK, et al. Comparative diagnostic accuracy of hepatocyte-specific gadoxetic acid (Gd-EOB-DTPA) enhanced MR imaging and contrast enhanced CT for the detection of liver metastases: a systematic review and meta-analysis. International journal of colorectal disease 2016;31:1739-1749. DOI: 10.1007/s00384-016-2664-9.
60. Rojas Llimpe FL, Di Fabio F, Ercolani G, et al. Imaging in resectable colorectal liver metastasis patients with or without preoperative chemotherapy: results of the PROMETEO-01 study. British journal of cancer 2014;111:667-673. DOI: 10.1038/bjc.2014.351.
61. Peppercorn PD, Reznek RH, Wilson P, et al. Demonstration of hepatic steatosis by computerized tomography in patients receiving 5-fluorouracil-based therapy for advanced colorectal cancer. British journal of cancer 1998;77:2008-2011.
62. Vilgrain V, Esvan M, Ronot M, et al. A meta-analysis of diffusion-weighted and gadoxetic acid-enhanced MR imaging for the detection of liver metastases. European radiology 2016;26:4595-4615. DOI: 10.1007/s00330-016-4250-5.
63. Cho JY, Lee YJ, Han HS, et al. Role of gadoxetic acid-enhanced magnetic resonance imaging in the preoperative evaluation of small hepatic lesions in patients with colorectal cancer. World journal of surgery 2015;39:1161-1166. DOI: 10.1007/s00268-015-2944-5.
64. Kauppinen RA. Monitoring cytotoxic tumour treatment response by diffusion magnetic resonance imaging and proton spectroscopy. NMR in biomedicine 2002;15:6-17. DOI: 10.1002/nbm.742.
65. Cui Y, Zhang XP, Sun YS, et al. Apparent diffusion coefficient: potential imaging biomarker for prediction and early detection of response to chemotherapy in hepatic metastases. Radiology 2008;248:894-900. DOI: 10.1148/radiol.2483071407.
66. Koh DM, Collins DJ. Diffusion-weighted MRI in the body: applications and challenges in oncology. AJR American journal of roentgenology 2007;188:1622-1635. DOI: 10.2214/ajr.06.1403.
67. Barral M, Eveno C, Hoeffel C, et al. Diffusion-weighted magnetic resonance imaging in colorectal cancer. Journal of visceral surgery 2016;153:361-369. DOI: 10.1016/j.jviscsurg.2016.08.004.
68. Macera A, Lario C, Petracchini M, et al. Staging of colorectal liver metastases after preoperative chemotherapy. Diffusion-weighted imaging in combination with Gd-EOB-DTPA MRI sequences increases sensitivity and diagnostic accuracy. European radiology 2013;23:739-747. DOI: 10.1007/s00330-012-2658-0.

69. Choi SH, Kim SY, Park SH, et al. Diagnostic performance of CT, gadoxetate disodium-enhanced MRI, and PET/CT for the diagnosis of colorectal liver metastasis: Systematic review and meta-analysis. Journal of magnetic resonance imaging : JMRI 2018;47:1237-1250. DOI: 10.1002/jmri.25852.
70. Maas M, Rutten IJ, Nelemans PJ, et al. What is the most accurate whole-body imaging modality for assessment of local and distant recurrent disease in colorectal cancer? A meta-analysis : imaging for recurrent colorectal cancer. European journal of nuclear medicine and molecular imaging 2011;38:1560-1571. DOI: 10.1007/s00259-011-1785-1.
71. Granata V, Fusco R, Avallone A, et al. A radiologist's point of view in the presurgical and intraoperative setting of colorectal liver metastases. Future oncology (London, England) 2018;14:2189-2206. DOI: 10.2217/fon-2018-0080.
72. Konopke R, Kersting S, Bergert H, et al. Contrast-enhanced ultrasonography to detect liver metastases : a prospective trial to compare transcutaneous unenhanced and contrast-enhanced ultrasonography in patients undergoing laparotomy. International journal of colorectal disease 2007;22:201-207. DOI: 10.1007/s00384-006-0134-5.
73. Larsen LP, Rosenkilde M, Christensen H, et al. Can contrast-enhanced ultrasonography replace multidetector-computed tomography in the detection of liver metastases from colorectal cancer? European journal of radiology 2009;69:308-313. DOI: 10.1016/j.ejrad.2007.10.023.
74. Vialle R, Boucebci S, Richer JP, et al. Preoperative detection of hepatic metastases from colorectal cancer: Prospective comparison of contrast-enhanced ultrasound and multidetector-row computed tomography (MDCT). Diagnostic and interventional imaging 2016;97:851-855. DOI: 10.1016/j.diii.2015.11.017.
75. Ruzzenente A, Conci S, Iacono C, et al. Usefulness of contrast-enhanced intraoperative ultrasonography (CE-IOUS) in patients with colorectal liver metastases after preoperative chemotherapy. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract 2013;17:281-287. DOI: 10.1007/s11605-012-2043-y.
76. Sturesson C, Nilsson J, Lindell G, et al. Disappearing liver metastases from colorectal cancer: impact of modern imaging modalities. HPB : the official journal of the International Hepato Pancreato Biliary Association 2015;17:983-987. DOI: 10.1111/hpb.12476.
77. Schulz A, Dormagen JB, Drolsum A, et al. Impact of contrast-enhanced intraoperative ultrasound on operation strategy in case of colorectal liver metastasis. Acta radiologica (Stockholm, Sweden : 1987) 2012;53:1081-1087. DOI: 10.1258/ar.2012.120049.
78. Quan D, Gallinger S, Nhan C, et al. The role of liver resection for colorectal cancer metastases in an era of multimodality treatment: a systematic review. Surgery 2012;151:860-870. DOI: 10.1016/j.surg.2011.12.018.
79. Filippiadis DK, Velonakis G, Kelekis A, et al. The Role of Percutaneous Ablation in the Management of Colorectal Cancer Liver Metastatic Disease. Diagnostics (Basel, Switzerland) 2021;11. DOI: 10.3390/diagnostics11020308.

80. Cattell R. Successful removal of liver metastasis from carcinoma of the rectum. Lahey Clin Bull 1940;2.
81. Raven RW. Partial hepatectomy. The British journal of surgery 1949;36:397-401. DOI: 10.1002/bjs.18003614412.
82. Adams RB, Aloia TA, Loyer E, et al. Selection for hepatic resection of colorectal liver metastases: expert consensus statement. HPB : the official journal of the International Hepato Pancreato Biliary Association 2013;15:91-103. DOI: 10.1111/j.1477-2574.2012.00557.x.
83. Chakedis J, Squires MH, Beal EW, et al. Update on current problems in colorectal liver metastasis. Current problems in surgery 2017;54:554-602. DOI: 10.1067/j.cpsurg.2017.10.002.
84. House MG, Ito H, Gönen M, et al. Survival after hepatic resection for metastatic colorectal cancer: trends in outcomes for 1,600 patients during two decades at a single institution. Journal of the American College of Surgeons 2010;210:744-752, 752-745. DOI: 10.1016/j.jamcollsurg.2009.12.040.
85. Andres A, Mentha G, Adam R, et al. Surgical management of patients with colorectal cancer and simultaneous liver and lung metastases. The British journal of surgery 2015;102:691-699. DOI: 10.1002/bjs.9783.
86. de Haas RJ, Wicherts DA, Flores E, et al. R1 resection by necessity for colorectal liver metastases: is it still a contraindication to surgery? Annals of surgery 2008;248:626-637. DOI: 10.1097/SLA.0b013e31818a07f1.
87. Ekberg H, Tranberg KG, Andersson R, et al. Determinants of survival in liver resection for colorectal secondaries. The British journal of surgery 1986;73:727-731. DOI: 10.1002/bjs.1800730917.
88. Pawlik TM, Schulick RD, Choti MA. Expanding criteria for resectability of colorectal liver metastases. The oncologist 2008;13:51-64. DOI: 10.1634/theoncologist.2007-0142.
89. de Cuba EM, Kwakman R, Knol DL, et al. Cytoreductive surgery and HIPEC for peritoneal metastases combined with curative treatment of colorectal liver metastases: Systematic review of all literature and meta-analysis of observational studies. Cancer treatment reviews 2013;39:321-327. DOI: 10.1016/j.ctrv.2012.11.003.
90. Aragon RJ, Solomon NL. Techniques of hepatic resection. Journal of gastrointestinal oncology 2012;3:28-40. DOI: 10.3978/j.issn.2078-6891.2012.006.
91. Matsumura M, Mise Y, Saiura A, et al. Parenchymal-Sparing Hepatectomy Does Not Increase Intrahepatic Recurrence in Patients with Advanced Colorectal Liver Metastases. Annals of surgical oncology 2016;23:3718-3726. DOI: 10.1245/s10434-016-5278-0.
92. Memeo R, de Blasi V, Adam R, et al. Parenchymal-sparing hepatectomies (PSH) for bilobar colorectal liver metastases are associated with a lower morbidity and similar oncological results: a propensity score matching analysis. HPB : the official journal of the International Hepato Pancreato Biliary Association 2016;18:781-790. DOI: 10.1016/j.hpb.2016.06.004.

93. Mise Y, Aloia TA, Brudvik KW, et al. Parenchymal-sparing Hepatectomy in Colorectal Liver Metastasis Improves Salvageability and Survival. Annals of surgery 2016;263:146-152. DOI: 10.1097/sla.0000000000001194.
94. Wurster EF, Tenckhoff S, Probst P, et al. A systematic review and meta-analysis of the utility of repeated versus single hepatic resection for colorectal cancer liver metastases. HPB : the official journal of the International Hepato Pancreato Biliary Association 2017;19:491-497. DOI: 10.1016/j.hpb.2017.02.440.
95. Adam R, Bismuth H, Castaing D, et al. Repeat hepatectomy for colorectal liver metastases. Annals of surgery 1997;225:51-60; discussion 60-52. DOI: 10.1097/00000658-199701000-00006.
96. Viganò L, Gentile D, Galvanin J, et al. Very Early Recurrence After Liver Resection for Colorectal Metastases: Incidence, Risk Factors, and Prognostic Impact. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract 2021. DOI: 10.1007/s11605-021-05123-w.
97. Shoup M, Gonen M, D'Angelica M, et al. Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract 2003;7:325-330. DOI: 10.1016/s1091-255x(02)00370-0.
98. Ferrero A, Viganò L, Polastri R, et al. Postoperative liver dysfunction and future remnant liver: where is the limit? Results of a prospective study. World journal of surgery 2007;31:1643-1651. DOI: 10.1007/s00268-007-9123-2.
99. Vauthey JN, Chaoui A, Do KA, et al. Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. Surgery 2000;127:512-519. DOI: 10.1067/msy.2000.105294.
100. Narita M, Oussoultzoglou E, Fuchshuber P, et al. What is a safe future liver remnant size in patients undergoing major hepatectomy for colorectal liver metastases and treated by intensive preoperative chemotherapy? Annals of surgical oncology 2012;19:2526-2538. DOI: 10.1245/s10434-012-2274-x.
101. Lam VW, Spiro C, Laurence JM, et al. A systematic review of clinical response and survival outcomes of downsizing systemic chemotherapy and rescue liver surgery in patients with initially unresectable colorectal liver metastases. Annals of surgical oncology 2012;19:1292-1301. DOI: 10.1245/s10434-011-2061-0.
102. Kinoshita H, Sakai K, Hirohashi K, et al. Preoperative portal vein embolization for hepatocellular carcinoma. World journal of surgery 1986;10:803-808. DOI: 10.1007/bf01655244.
103. Abulkhir A, Limongelli P, Healey AJ, et al. Preoperative portal vein embolization for major liver resection: a meta-analysis. Annals of surgery 2008;247:49-57. DOI: 10.1097/SLA.0b013e31815f6e5b.
104. Regimbeau JM, Cosse C, Kaiser G, et al. Feasibility, safety and efficacy of two-stage hepatectomy for bilobar liver metastases of colorectal cancer: a LiverMetSurvey analysis. HPB : the official journal of the International Hepato Pancreato Biliary Association 2017;19:396-405. DOI: 10.1016/j.hpb.2017.01.008.
105. Schnitzbauer AA, Lang SA, Goessmann H, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-

staged extended right hepatic resection in small-for-size settings. Annals of surgery 2012;255:405-414. DOI: 10.1097/SLA.0b013e31824856f5.

106. Eshmuminov D, Raptis DA, Linecker M, et al. Meta-analysis of associating liver partition with portal vein ligation and portal vein occlusion for two-stage hepatectomy. The British journal of surgery 2016;103:1768-1782. DOI: 10.1002/bjs.10290.
107. Nguyen KT, Marsh JW, Tsung A, et al. Comparative benefits of laparoscopic vs open hepatic resection: a critical appraisal. Archives of surgery (Chicago, Ill : 1960) 2011;146:348-356. DOI: 10.1001/archsurg.2010.248.
108. Fretland Å A, Dagenborg VJ, Bjørnelv GMW, et al. Laparoscopic Versus Open Resection for Colorectal Liver Metastases: The OSLO-COMET Randomized Controlled Trial. Annals of surgery 2018;267:199-207. DOI: 10.1097/sla.0000000000002353.
109. Aghayan DL, Kazaryan AM, Dagenborg VJ, et al. Long-Term Oncologic Outcomes After Laparoscopic Versus Open Resection for Colorectal Liver Metastases : A Randomized Trial. Annals of internal medicine 2021;174:175-182. DOI: 10.7326/m20-4011.
110. Beppu T, Wakabayashi G, Hasegawa K, et al. Long-term and perioperative outcomes of laparoscopic versus open liver resection for colorectal liver metastases with propensity score matching: a multi-institutional Japanese study. Journal of hepato-biliary-pancreatic sciences 2015;22:711-720. DOI: 10.1002/jhbp.261.
111. Cho JY, Han HS, Wakabayashi G, et al. Practical guidelines for performing laparoscopic liver resection based on the second international laparoscopic liver consensus conference. Surg Oncol 2018;27:A5-a9. DOI: 10.1016/j.suronc.2017.12.003.
112. Dagher I, O'Rourke N, Geller DA, et al. Laparoscopic major hepatectomy: an evolution in standard of care. Annals of surgery 2009;250:856-860. DOI: 10.1097/SLA.0b013e3181bcaf46.
113. Brouquet A, Benoist S, Julie C, et al. Risk factors for chemotherapy-associated liver injuries: A multivariate analysis of a group of 146 patients with colorectal metastases. Surgery 2009;145:362-371. DOI: 10.1016/j.surg.2008.12.002.
114. Aloia TA, Fahy BN, Fischer CP, et al. Predicting poor outcome following hepatectomy: analysis of 2313 hepatectomies in the NSQIP database. HPB : the official journal of the International Hepato Pancreato Biliary Association 2009;11:510-515. DOI: 10.1111/j.1477-2574.2009.00095.x.
115. Jin S, Fu Q, Wuyun G, et al. Management of post-hepatectomy complications. World journal of gastroenterology 2013;19:7983-7991. DOI: 10.3748/wjg.v19.i44.7983.
116. Lafaro K, Buettner S, Maqsood H, et al. Defining Post Hepatectomy Liver Insufficiency: Where do We stand? Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract 2015;19:2079-2092. DOI: 10.1007/s11605-015-2872-6.
117. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery 2011;149:713-724. DOI: 10.1016/j.surg.2010.10.001.

118. Balzan S, Belghiti J, Farges O, et al. The "50-50 criteria" on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. Annals of surgery 2005;242:824-828, discussion 828-829.
119. Bismuth H, Houssin D, Ornowski J, et al. Liver resections in cirrhotic patients: a Western experience. World journal of surgery 1986;10:311-317. DOI: 10.1007/bf01658152.
120. Vauthey JN, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2006;24:2065-2072. DOI: 10.1200/jco.2005.05.3074.
121. Taub R. Liver regeneration: from myth to mechanism. Nature reviews Molecular cell biology 2004;5:836-847. DOI: 10.1038/nrm1489.
122. Nadalin S, Testa G, Malagó M, et al. Volumetric and functional recovery of the liver after right hepatectomy for living donation. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 2004;10:1024-1029. DOI: 10.1002/lt.20182.
123. Pomfret EA, Pomposelli JJ, Gordon FD, et al. Liver regeneration and surgical outcome in donors of right-lobe liver grafts. Transplantation 2003;76:5-10. DOI: 10.1097/01.tp.0000079064.08263.8e.
124. Nagino M, Ando M, Kamiya J, et al. Liver regeneration after major hepatectomy for biliary cancer. The British journal of surgery 2001;88:1084-1091. DOI: 10.1046/j.0007-1323.2001.01832.x.
125. Forbes SJ, Newsome PN. Liver regeneration - mechanisms and models to clinical application. Nature reviews Gastroenterology & hepatology 2016;13:473-485. DOI: 10.1038/nrgastro.2016.97.
126. Michalopoulos GK. Liver regeneration. Journal of cellular physiology 2007;213:286-300. DOI: 10.1002/jcp.21172.
127. Rice GC, Leiberman DP, Mathie RT, et al. Liver tissue blood flow measured by 85Kr clearance in the anaesthetized rat before and after partial hepatectomy. British journal of experimental pathology 1977;58:243-250.
128. Golse N, Bucur PO, Adam R, et al. New paradigms in post-hepatectomy liver failure. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract 2013;17:593-605. DOI: 10.1007/s11605-012-2048-6.
129. Schoen JM, Wang HH, Minuk GY, et al. Shear stress-induced nitric oxide release triggers the liver regeneration cascade. Nitric oxide : biology and chemistry 2001;5:453-464. DOI: 10.1006/niox.2001.0373.
130. Meier M, Andersen KJ, Knudsen AR, et al. Adaptive growth changes in the liver remnant are affected by the size of hepatectomy in rats. International journal of experimental pathology 2018;99:150-157. DOI: 10.1111/iep.12282.
131. Miyaoka Y, Ebato K, Kato H, et al. Hypertrophy and unconventional cell division of hepatocytes underlie liver regeneration. Current biology : CB 2012;22:1166-1175. DOI: 10.1016/j.cub.2012.05.016.

132. Jin X, Zimmers TA, Perez EA, et al. Paradoxical effects of short- and long-term interleukin-6 exposure on liver injury and repair. Hepatology (Baltimore, Md) 2006;43:474-484. DOI: 10.1002/hep.21087.
133. Wack KE, Ross MA, Zegarra V, et al. Sinusoidal ultrastructure evaluated during the revascularization of regenerating rat liver. Hepatology (Baltimore, Md) 2001;33:363-378. DOI: 10.1053/jhep.2001.21998.
134. Forbes SJ, Rosenthal N. Preparing the ground for tissue regeneration: from mechanism to therapy. Nature medicine 2014;20:857-869. DOI: 10.1038/nm.3653.
135. Ploeg RJ, D'Alessandro AM, Knechtle SJ, et al. Risk factors for primary dysfunction after liver transplantation--a multivariate analysis. Transplantation 1993;55:807-813. DOI: 10.1097/00007890-199304000-00024.
136. Veteläinen R, van Vliet AK, van Gulik TM. Severe steatosis increases hepatocellular injury and impairs liver regeneration in a rat model of partial hepatectomy. Annals of surgery 2007;245:44-50. DOI: 10.1097/01.sla.0000225253.84501.0e.
137. Issa R, Zhou X, Trim N, et al. Mutation in collagen-1 that confers resistance to the action of collagenase results in failure of recovery from CCl4-induced liver fibrosis, persistence of activated hepatic stellate cells, and diminished hepatocyte regeneration. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2003;17:47-49. DOI: 10.1096/fj.02-0494fje.
138. Rubbia-Brandt L, Audard V, Sartoretti P, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Annals of oncology : official journal of the European Society for Medical Oncology 2004;15:460-466.
139. Covey AM, Brown KT, Jarnagin WR, et al. Combined portal vein embolization and neoadjuvant chemotherapy as a treatment strategy for resectable hepatic colorectal metastases. Annals of surgery 2008;247:451-455. DOI: 10.1097/SLA.0b013e31815ed693.
140. Ribero D, Abdalla EK, Madoff DC, et al. Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome. The British journal of surgery 2007;94:1386-1394. DOI: 10.1002/bjs.5836.
141. Sturesson C, Keussen I, Tranberg KG. Prolonged chemotherapy impairs liver regeneration after portal vein occlusion - an audit of 26 patients. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 2010;36:358-364. DOI: 10.1016/j.ejso.2009.12.001.
142. Khoo E, O'Neill S, Brown E, et al. Systematic review of systemic adjuvant, neoadjuvant and perioperative chemotherapy for resectable colorectal-liver metastases. HPB. DOI: 10.1016/j.hpb.2016.03.001.
143. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet (London, England) 2008;371:1007-1016. DOI: 10.1016/s0140-6736(08)60455-9.

144. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. The Lancet Oncology 2013;14:1208-1215. DOI: 10.1016/s1470-2045(13)70447-9.
145. Bosma NA, Keehn AR, Lee-Ying R, et al. Efficacy of perioperative chemotherapy in resected colorectal liver metastasis: A systematic review and meta-analysis. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 2021. DOI: 10.1016/j.ejso.2021.07.024.
146. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Annals of surgery 2004;240:644-657; discussion 657-648. DOI: 10.1097/01.sla.0000141198.92114.f6.
147. Folprecht G, Gruenberger T, Bechstein WO, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. The Lancet Oncology 2010;11:38-47. DOI: 10.1016/s1470-2045(09)70330-4.
148. Adam R, Pascal G, Castaing D, et al. Tumor progression while on chemotherapy: a contraindication to liver resection for multiple colorectal metastases? Annals of surgery 2004;240:1052-1061; discussion 1061-1054. DOI: 10.1097/01.sla.0000145964.08365.01.
149. Pessaux P, Chenard MP, Bachellier P, et al. Consequences of chemotherapy on resection of colorectal liver metastases. Journal of visceral surgery 2010;147:e193-201. DOI: 10.1016/j.jviscsurg.2010.06.004.
150. Zhao J, van Mierlo KMC, Gómez-Ramírez J, et al. Systematic review of the influence of chemotherapy-associated liver injury on outcome after partial hepatectomy for colorectal liver metastases. The British journal of surgery 2017;104:990-1002. DOI: 10.1002/bjs.10572.
151. Moertel CG, Fleming TR, Macdonald JS, et al. Hepatic toxicity associated with fluorouracil plus levamisole adjuvant therapy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 1993;11:2386-2390. DOI: 10.1200/jco.1993.11.12.2386.
152. Behrns KE, Tsiotos GG, DeSouza NF, et al. Hepatic steatosis as a potential risk factor for major hepatic resection. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract 1998;2:292-298. DOI: 10.1016/s1091-255x(98)80025-5.
153. Kooby DA, Fong Y, Suriawinata A, et al. Impact of steatosis on perioperative outcome following hepatic resection. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract 2003;7:1034-1044. DOI: 10.1016/j.gassur.2003.09.012.
154. Gomez D, Malik HZ, Bonney GK, et al. Steatosis predicts postoperative morbidity following hepatic resection for colorectal metastasis. The British journal of surgery 2007;94:1395-1402. DOI: 10.1002/bjs.5820.

155. Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology (Baltimore, Md) 2005;41:1313-1321. DOI: 10.1002/hep.20701.
156. Fernandez FG, Ritter J, Goodwin JW, et al. Effect of steatohepatitis associated with irinotecan or oxaliplatin pretreatment on resectability of hepatic colorectal metastases. Journal of the American College of Surgeons 2005;200:845-853. DOI: 10.1016/j.jamcollsurg.2005.01.024.
157. DeLeve LD, Ito Y, Bethea NW, et al. Embolization by sinusoidal lining cells obstructs the microcirculation in rat sinusoidal obstruction syndrome. American journal of physiology Gastrointestinal and liver physiology 2003;284:G1045-1052. DOI: 10.1152/ajpgi.00526.2002.
158. Aloia T, Sebagh M, Plasse M, et al. Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2006;24:4983-4990. DOI: 10.1200/jco.2006.05.8156.
159. Tamandl D, Klinger M, Eipeldauer S, et al. Sinusoidal obstruction syndrome impairs long-term outcome of colorectal liver metastases treated with resection after neoadjuvant chemotherapy. Annals of surgical oncology 2011;18:421-430. DOI: 10.1245/s10434-010-1317-4.
160. McCuskey RS, Ito Y, Robertson GR, et al. Hepatic microvascular dysfunction during evolution of dietary steatohepatitis in mice. Hepatology (Baltimore, Md) 2004;40:386-393. DOI: 10.1002/hep.20302.
161. Seifalian AM, Piasecki C, Agarwal A, et al. The effect of graded steatosis on flow in the hepatic parenchymal microcirculation. Transplantation 1999;68:780-784. DOI: 10.1097/00007890-199909270-00009.
162. Nakano H, Oussoultzoglou E, Rosso E, et al. Sinusoidal injury increases morbidity after major hepatectomy in patients with colorectal liver metastases receiving preoperative chemotherapy. Annals of surgery 2008;247:118-124. DOI: 10.1097/SLA.0b013e31815774de.
163. Karoui M, Penna C, Amin-Hashem M, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. Annals of surgery 2006;243:1-7. DOI: 10.1097/01.sla.0000193603.26265.c3.
164. Rubbia-Brandt L, Giostra E, Brezault C, et al. Importance of histological tumor response assessment in predicting the outcome in patients with colorectal liver metastases treated with neo-adjuvant chemotherapy followed by liver surgery. Annals of oncology : official journal of the European Society for Medical Oncology 2007;18:299-304. DOI: 10.1093/annonc/mdl386.
165. Maru DM, Kopetz S, Boonsirikamchai P, et al. Tumor thickness at the tumor-normal interface: a novel pathologic indicator of chemotherapy response in hepatic colorectal metastases. The American journal of surgical pathology 2010;34:1287-1294. DOI: 10.1097/PAS.0b013e3181eb2f7b.
166. Adam R, Wicherts DA, de Haas RJ, et al. Complete pathologic response after preoperative chemotherapy for colorectal liver metastases: myth or reality? Journal

of clinical oncology : official journal of the American Society of Clinical Oncology 2008;26:1635-1641. DOI: 10.1200/jco.2007.13.7471.

167. Blazer DG, 3rd, Kishi Y, Maru DM, et al. Pathologic response to preoperative chemotherapy: a new outcome end point after resection of hepatic colorectal metastases. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2008;26:5344-5351. DOI: 10.1200/jco.2008.17.5299.
168. Brouquet A, Zimmitti G, Kopetz S, et al. Multicenter validation study of pathologic response and tumor thickness at the tumor-normal liver interface as independent predictors of disease-free survival after preoperative chemotherapy and surgery for colorectal liver metastases. Cancer 2013;119:2778-2788. DOI: 10.1002/cncr.28097.
169. Vigano L, Capussotti L, Barroso E, et al. Progression while receiving preoperative chemotherapy should not be an absolute contraindication to liver resection for colorectal metastases. Annals of surgical oncology 2012;19:2786-2796. DOI: 10.1245/s10434-012-2382-7.
170. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer (Oxford, England : 1990) 2009;45:228-247. DOI: 10.1016/j.ejca.2008.10.026.
171. Shindoh J, Loyer EM, Kopetz S, et al. Optimal morphologic response to preoperative chemotherapy: an alternate outcome end point before resection of hepatic colorectal metastases. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2012;30:4566-4572. DOI: 10.1200/jco.2012.45.2854.
172. Vera R, Gomez Dorronsoro M, Lopez-Ben S, et al. Retrospective analysis of pathological response in colorectal cancer liver metastases following treatment with bevacizumab. Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico 2014;16:739-745. DOI: 10.1007/s12094-013-1142-x.
173. Brouquet A, Blot C, Allard MA, et al. What is the Prognostic Value of a Discordant Radiologic and Pathologic Response in Patients Undergoing Resection of Colorectal Liver Metastases After Preoperative Chemotherapy? Annals of surgical oncology 2020;27:2877-2885. DOI: 10.1245/s10434-020-08284-1.
174. Chun YS, Vauthey JN, Boonsirikamchai P, et al. Association of computed tomography morphologic criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases. Jama 2009;302:2338-2344. DOI: 10.1001/jama.2009.1755.
175. Nishioka Y, Yoshioka R, Gonoi W, et al. Fluorine-18-fluorodeoxyglucose positron emission tomography as an objective substitute for CT morphologic response criteria in patients undergoing chemotherapy for colorectal liver metastases. Abdominal radiology (New York) 2018;43:1152-1158. DOI: 10.1007/s00261-017-1287-0.
176. Koh DM, Scurr E, Collins D, et al. Predicting response of colorectal hepatic metastasis: value of pretreatment apparent diffusion coefficients. AJR American journal of roentgenology 2007;188:1001-1008. DOI: 10.2214/ajr.06.0601.
177. Tam HH, Collins DJ, Brown G, et al. The role of pre-treatment diffusion-weighted MRI in predicting long-term outcome of colorectal liver metastasis. The British journal of radiology 2013;86:20130281. DOI: 10.1259/bjr.20130281.

178. Wagner M, Ronot M, Doblas S, et al. Assessment of the residual tumour of colorectal liver metastases after chemotherapy: diffusion-weighted MR magnetic resonance imaging in the peripheral and entire tumour. European radiology 2016;26:206-215. DOI: 10.1007/s00330-015-3800-6.
179. Donati F, Boraschi P, Pacciardi F, et al. 3T diffusion-weighted MRI in the response assessment of colorectal liver metastases after chemotherapy: Correlation between ADC value and histological tumour regression grading. European journal of radiology 2017;91:57-65. DOI: 10.1016/j.ejrad.2017.03.020.
180. Hosseini-Nik H, Fischer SE, Moulton CA, et al. Diffusion-weighted and hepatobiliary phase gadoxetic acid-enhanced quantitative MR imaging for identification of complete pathologic response in colorectal liver metastases after preoperative chemotherapy. Abdominal radiology (New York) 2016;41:231-238. DOI: 10.1007/s00261-015-0572-z.
181. Donati OF, Chong D, Nanz D, et al. Diffusion-weighted MR imaging of upper abdominal organs: field strength and intervendor variability of apparent diffusion coefficients. Radiology 2014;270:454-463. DOI: 10.1148/radiol.13130819.
182. Winfield JM, Collins DJ, Priest AN, et al. A framework for optimization of diffusion-weighted MRI protocols for large field-of-view abdominal-pelvic imaging in multicenter studies. Medical physics 2016;43:95. DOI: 10.1118/1.4937789.
183. Malyarenko D, Galbán CJ, Londy FJ, et al. Multi-system repeatability and reproducibility of apparent diffusion coefficient measurement using an ice-water phantom. Journal of magnetic resonance imaging : JMRI 2013;37:1238-1246. DOI: 10.1002/jmri.23825.
184. Dale BM, Braithwaite AC, Boll DT, et al. Field strength and diffusion encoding technique affect the apparent diffusion coefficient measurements in diffusion-weighted imaging of the abdomen. Investigative radiology 2010;45:104-108. DOI: 10.1097/RLI.0b013e3181c8ceac.
185. Schmeel FC. Variability in quantitative diffusion-weighted MR imaging (DWI) across different scanners and imaging sites: is there a potential consensus that can help reducing the limits of expected bias? European radiology 2019;29:2243-2245. DOI: 10.1007/s00330-018-5866-4.
186. Boraschi P, Donati F, Cervelli R, et al. Colorectal liver metastases: ADC as an imaging biomarker of tumor behavior and therapeutic response. European journal of radiology 2021;137:109609. DOI: 10.1016/j.ejrad.2021.109609.
187. Liu LH, Zhou GF, Lv H, et al. Identifying response in colorectal liver metastases treated with bevacizumab: development of RECIST by combining contrast-enhanced and diffusion-weighted MRI. European radiology 2021. DOI: 10.1007/s00330-020-07647-2.
188. Goedhart PT, Khalilzada M, Bezemer R, et al. Sidestream Dark Field (SDF) imaging: a novel stroboscopic LED ring-based imaging modality for clinical assessment of the microcirculation. Optics express 2007;15:15101-15114. DOI: 10.1364/oe.15.015101.

189. Langer S, Harris AG, Biberthaler P, et al. Orthogonal polarization spectral imaging as a tool for the assessment of hepatic microcirculation: a validation study. Transplantation 2001;71:1249-1256. DOI: 10.1097/00007890-200105150-00012.
190. Puhl G, Schaser KD, Vollmar B, et al. Noninvasive in vivo analysis of the human hepatic microcirculation using orthogonal polorization spectral imaging. Transplantation 2003;75:756-761. DOI: 10.1097/01.tp.0000056634.18191.1a.
191. Spanos A, Jhanji S, Vivian-Smith A, et al. Early microvascular changes in sepsis and severe sepsis. Shock (Augusta, Ga) 2010;33:387-391. DOI: 10.1097/SHK.0b013e3181c6be04.
192. Jansen SM, de Bruin DM, van Berge Henegouwen MI, et al. Quantitative change of perfusion in gastric tube reconstruction by sidestream dark field microscopy (SDF) after esophagectomy, a prospective in-vivo cohort study. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 2021;47:1034-1041. DOI: 10.1016/j.ejso.2020.09.006.
193. de Bruin AFJ, Tavy ALM, van der Sloot K, et al. Can sidestream dark field (SDF) imaging identify subtle microvascular changes of the bowel during colorectal surgery? Tech Coloproctol 2018;22:793-800. DOI: 10.1007/s10151-018-1872-4.
194. Sturesson C, Milstein DM, Post IC, et al. Laser speckle contrast imaging for assessment of liver microcirculation. Microvascular research 2013;87:34-40. DOI: 10.1016/j.mvr.2013.01.004.
195. Tang A, Cloutier G, Szeverenyi NM, et al. Ultrasound Elastography and MR Elastography for Assessing Liver Fibrosis: Part 1, Principles and Techniques. AJR American journal of roentgenology 2015;205:22-32. DOI: 10.2214/ajr.15.14552.
196. Friedrich-Rust M, Wunder K, Kriener S, et al. Liver fibrosis in viral hepatitis: noninvasive assessment with acoustic radiation force impulse imaging versus transient elastography. Radiology 2009;252:595-604. DOI: 10.1148/radiol.2523081928.
197. Fahey BJ, Nelson RC, Bradway DP, et al. In vivo visualization of abdominal malignancies with acoustic radiation force elastography. Physics in medicine and biology 2008;53:279-293. DOI: 10.1088/0031-9155/53/1/020.
198. Cho SH, Lee JY, Han JK, et al. Acoustic radiation force impulse elastography for the evaluation of focal solid hepatic lesions: preliminary findings. Ultrasound in medicine & biology 2010;36:202-208. DOI: 10.1016/j.ultrasmedbio.2009.10.009.
199. Gallotti A, D'Onofrio M, Romanini L, et al. Acoustic Radiation Force Impulse (ARFI) ultrasound imaging of solid focal liver lesions. European journal of radiology 2012;81:451-455. DOI: 10.1016/j.ejrad.2010.12.071.
200. Nightingale K, Soo MS, Nightingale R, et al. Acoustic radiation force impulse imaging: in vivo demonstration of clinical feasibility. Ultrasound in medicine & biology 2002;28:227-235.
201. Barr RG. Shear wave liver elastography. Abdominal radiology (New York) 2018;43:800-807. DOI: 10.1007/s00261-017-1375-1.

202. D'Onofrio M, Crosara S, De Robertis R, et al. Acoustic radiation force impulse of the liver. World Journal of Gastroenterology : WJG 2013;19:4841-4849. DOI: 10.3748/wjg.v19.i30.4841.
203. Cescon M, Colecchia A, Cucchetti A, et al. Value of transient elastography measured with FibroScan in predicting the outcome of hepatic resection for hepatocellular carcinoma. Annals of surgery 2012;256:706-712; discussion 712-703. DOI: 10.1097/SLA.0b013e3182724ce8.
204. Ninomiya M, Shirabe K, Ijichi H, et al. Temporal changes in the stiffness of the remnant liver and spleen after donor hepatectomy as assessed by acoustic radiation force impulse: A preliminary study. Hepatology research : the official journal of the Japan Society of Hepatology 2011;41:579-586. DOI: 10.1111/j.1872-034X.2011.00809.x.
205. Makary MA, Segev DL, Pronovost PJ, et al. Frailty as a predictor of surgical outcomes in older patients. Journal of the American College of Surgeons 2010;210:901-908. DOI: 10.1016/j.jamcollsurg.2010.01.028.
206. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. Journal of the American Geriatrics Society 2002;50:889-896.
207. Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. American journal of epidemiology 1998;147:755-763.
208. Cosquéric G, Sebag A, Ducolombier C, et al. Sarcopenia is predictive of nosocomial infection in care of the elderly. The British journal of nutrition 2006;96:895-901. DOI: 10.1017/bjn20061943.
209. Martin L, Birdsell L, Macdonald N, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2013;31:1539-1547. DOI: 10.1200/jco.2012.45.2722.
210. Levolger S, van Vugt JL, de Bruin RW, et al. Systematic review of sarcopenia in patients operated on for gastrointestinal and hepatopancreatobiliary malignancies. The British journal of surgery 2015;102:1448-1458. DOI: 10.1002/bjs.9893.
211. Prado CM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. The Lancet Oncology 2008;9:629-635. DOI: 10.1016/s1470-2045(08)70153-0.
212. van Vledder MG, Levolger S, Ayez N, et al. Body composition and outcome in patients undergoing resection of colorectal liver metastases. The British journal of surgery 2012;99:550-557. DOI: 10.1002/bjs.7823.
213. Peng PD, van Vledder MG, Tsai S, et al. Sarcopenia negatively impacts short-term outcomes in patients undergoing hepatic resection for colorectal liver metastasis. HPB : the official journal of the International Hepato Pancreato Biliary Association 2011;13:439-446. DOI: 10.1111/j.1477-2574.2011.00301.x.
214. Prado CM, Baracos VE, McCargar LJ, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer

patients receiving capecitabine treatment. Clinical cancer research : an official journal of the American Association for Cancer Research 2009;15:2920-2926. DOI: 10.1158/1078-0432.ccr-08-2242.

215. Prado CM, Baracos VE, McCargar LJ, et al. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. Clinical cancer research : an official journal of the American Association for Cancer Research 2007;13:3264-3268. DOI: 10.1158/1078-0432.ccr-06-3067.
216. Cooper AB, Slack R, Fogelman D, et al. Characterization of Anthropometric Changes that Occur During Neoadjuvant Therapy for Potentially Resectable Pancreatic Cancer. Annals of surgical oncology 2015;22:2416-2423. DOI: 10.1245/s10434-014-4285-2.
217. Awad S, Tan BH, Cui H, et al. Marked changes in body composition following neoadjuvant chemotherapy for oesophagogastric cancer. Clinical nutrition (Edinburgh, Scotland) 2012;31:74-77. DOI: 10.1016/j.clnu.2011.08.008.
218. Miyamoto Y, Baba Y, Sakamoto Y, et al. Negative Impact of Skeletal Muscle Loss after Systemic Chemotherapy in Patients with Unresectable Colorectal Cancer. PloS one 2015;10:e0129742. DOI: 10.1371/journal.pone.0129742.
219. Mourtzakis M, Prado CM, Lieffers JR, et al. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme 2008;33:997-1006. DOI: 10.1139/h08-075.
220. Shen W, Punyanitya M, Wang Z, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. Journal of applied physiology (Bethesda, Md : 1985) 2004;97:2333-2338. DOI: 10.1152/japplphysiol.00744.2004.
221. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of surgery 2004;240:205-213.
222. Vauthey JN, Abdalla EK, Doherty DA, et al. Body surface area and body weight predict total liver volume in Western adults. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 2002;8:233-240. DOI: 10.1053/jlts.2002.31654.
223. Boerma EC, Mathura KR, van der Voort PH, et al. Quantifying bedside-derived imaging of microcirculatory abnormalities in septic patients: a prospective validation study. Critical care (London, England) 2005;9:R601-606. DOI: 10.1186/cc3809.
224. Dobbe JG, Streekstra GJ, Atasever B, et al. Measurement of functional microcirculatory geometry and velocity distributions using automated image analysis. Medical & biological engineering & computing 2008;46:659-670. DOI: 10.1007/s11517-008-0349-4.
225. D'Alessandro AM, Kalayoglu M, Sollinger HW, et al. The predictive value of donor liver biopsies on the development of primary nonfunction after orthotopic liver transplantation. Transplantation proceedings 1991;23:1536-1537.

226. Amin MB, Edge SB, Greene FL, et al. AJCC Cancer Staging Manual. 8 ed.: Springer, 2017.
227. Tani M, Tomiya T, Yamada S, et al. Regulating factors of liver regeneration after hepatectomy. Cancer chemotherapy and pharmacology 1994;33 Suppl:S29-32. DOI: 10.1007/bf00686664.
228. Tanaka K, Kumamoto T, Matsuyama R, et al. Influence of chemotherapy on liver regeneration induced by portal vein embolization or first hepatectomy of a staged procedure for colorectal liver metastases. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract 2010;14:359-368. DOI: 10.1007/s11605-009-1073-6.
229. Shimizu Y, Aoki T, Kusano T, et al. Natural course of the remnant hepatic functional reserve as estimated by technetium-99m-galactosyl human serum albumin scintigraphy after a hepatectomy. Journal of gastroenterology 2010;45:308-316. DOI: 10.1007/s00535-009-0144-5.
230. Hockings PD, Changani KK, Saeed N, et al. Rapid reversal of hepatic steatosis, and reduction of muscle triglyceride, by rosiglitazone: MRI/S studies in Zucker fatty rats. Diabetes, obesity & metabolism 2003;5:234-243. DOI: 10.1046/j.1463-1326.2003.00268.x.
231. Cantré D, Schuett H, Hildebrandt A, et al. Nitric oxide reduces organ injury and enhances regeneration of reduced-size livers by increasing hepatic arterial flow. The British journal of surgery 2008;95:785-792. DOI: 10.1002/bjs.6139.
232. Fondevila C, Hessheimer AJ, Taura P, et al. Portal hyperperfusion: mechanism of injury and stimulus for regeneration in porcine small-for-size transplantation. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 2010;16:364-374. DOI: 10.1002/lt.21989.
233. Suzuki Y, Tateishi N, Soutani M, et al. Deformation of erythrocytes in microvessels and glass capillaries: effects of erythrocyte deformability. Microcirculation (New York, NY : 1994) 1996;3:49-57. DOI: 10.3109/10739689609146782.
234. Abshagen K, Eipel C, Menger MD, et al. Comprehensive analysis of the regenerating mouse liver: an in vivo fluorescence microscopic and immunohistological study. The Journal of surgical research 2006;134:354-362. DOI: 10.1016/j.jss.2006.01.002.
235. Vollmar B, Siegmund S, Menger MD. An intravital fluorescence microscopic study of hepatic microvascular and cellular derangements in developing cirrhosis in rats. Hepatology (Baltimore, Md) 1998;27:1544-1553. DOI: 10.1002/hep.510270612.
236. Rosenstengel S, Stoeppeler S, Bahde R, et al. Type of steatosis influences microcirculation and fibrogenesis in different rat strains. Journal of investigative surgery : the official journal of the Academy of Surgical Research 2011;24:273-282. DOI: 10.3109/08941939.2011.586094.
237. Puhl G, Schaser KD, Pust D, et al. Initial hepatic microcirculation correlates with early graft function in human orthotopic liver transplantation. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 2005;11:555-563. DOI: 10.1002/lt.20394.

238. Rauchfuss F, Scheuerlein H, Ludewig S, et al. In vivo assessment of the hepatic microcirculation after mesenterico-portal bypass (REX-shunt) using orthogonal polarization spectral imaging. Liver international : official journal of the International Association for the Study of the Liver 2010;30:1339-1345. DOI: 10.1111/j.1478-3231.2010.02311.x.
239. De Backer D, Hollenberg S, Boerma C, et al. How to evaluate the microcirculation: report of a round table conference. Critical care (London, England) 2007;11:R101. DOI: 10.1186/cc6118.
240. Kotzampassi K, Eleftheriadis E, Aletras H. Experimental and clinical evaluation of capsular and parenchymal total liver perfusion. Liver microcirculation. HPB surgery : a world journal of hepatic, pancreatic and biliary surgery 1992;6:99-104. DOI: 10.1155/1992/53863.
241. Wheatley AM, Almond NE, Stuart ET, et al. Interpretation of the laser Doppler flow signal from the liver of the rat. Microvascular research 1993;45:290-301. DOI: 10.1006/mvre.1993.1025.
242. Colli A, Pozzoni P, Berzuini A, et al. Decompensated chronic heart failure: increased liver stiffness measured by means of transient elastography. Radiology 2010;257:872-878. DOI: 10.1148/radiol.10100013.
243. Millonig G, Reimann FM, Friedrich S, et al. Extrahepatic cholestasis increases liver stiffness (FibroScan) irrespective of fibrosis. Hepatology (Baltimore, Md) 2008;48:1718-1723. DOI: 10.1002/hep.22577.
244. Jung EJ, Ryu CG, Kim G, et al. Splenomegaly during oxaliplatin-based chemotherapy for colorectal carcinoma. Anticancer research 2012;32:3357-3362.
245. Truant S, Baillet C, Gnemmi V, et al. The Impact of Modern Chemotherapy and Chemotherapy-Associated Liver Injuries (CALI) on Liver Function: Value of 99mTc-Labelled-Mebrofenin SPECT-Hepatobiliary Scintigraphy. Annals of surgical oncology 2021;28:1959-1969. DOI: 10.1245/s10434-020-08988-4.
246. Pelegrina A, Martí J, Miquel R, et al. Changes of liver hemodynamic and elastography parameters in patients with colorectal liver metastases receiving preoperative chemotherapy: "a note of caution". World journal of surgical oncology 2017;15:224. DOI: 10.1186/s12957-017-1290-5.
247. Karlas TF, Pfrepper C, Rosendahl J, et al. Acoustic radiation force impulse (ARFI) elastography in acute liver failure: necrosis mimics cirrhosis. Zeitschrift fur Gastroenterologie 2011;49:443-448. DOI: 10.1055/s-0029-1245690.
248. D'Onofrio M, Gallotti A, Mucelli RP. Tissue quantification with acoustic radiation force impulse imaging: Measurement repeatability and normal values in the healthy liver. AJR American journal of roentgenology 2010;195:132-136. DOI: 10.2214/ajr.09.3923.
249. Blauwhoff-Buskermolen S, Versteeg KS, De Van Der Schueren MAE, et al. Loss of muscle mass during chemotherapy is predictive for poor survival of patients with metastatic colorectal cancer. Journal of Clinical Oncology 2016;34:1339-1344. DOI: 10.1200/JCO.2015.63.6043.

250. Voron T, Tselikas L, Pietrasz D, et al. Sarcopenia Impacts on Short- and Long-term Results of Hepatectomy for Hepatocellular Carcinoma. Annals of surgery 2015;261:1173-1183. DOI: 10.1097/sla.0000000000000743.
251. Lodewick TM, van Nijnatten TJ, van Dam RM, et al. Are sarcopenia, obesity and sarcopenic obesity predictive of outcome in patients with colorectal liver metastases? HPB : the official journal of the International Hepato Pancreato Biliary Association 2015;17:438-446. DOI: 10.1111/hpb.12373.
252. Dello SA, Lodewick TM, van Dam RM, et al. Sarcopenia negatively affects preoperative total functional liver volume in patients undergoing liver resection. HPB : the official journal of the International Hepato Pancreato Biliary Association 2013;15:165-169. DOI: 10.1111/j.1477-2574.2012.00517.x.
253. Cherin P, Voronska E, Fraoucene N, et al. Prevalence of sarcopenia among healthy ambulatory subjects: the sarcopenia begins from 45 years. Aging clinical and experimental research 2014;26:137-146. DOI: 10.1007/s40520-013-0132-8.
254. Ryan AM, Power DG, Daly L, et al. Cancer-associated malnutrition, cachexia and sarcopenia: the skeleton in the hospital closet 40 years later. The Proceedings of the Nutrition Society 2016:1-13. DOI: 10.1017/s002966511500419x.
255. Dunne DF, Jack S, Jones RP, et al. Randomized clinical trial of prehabilitation before planned liver resection. The British journal of surgery 2016;103:504-512. DOI: 10.1002/bjs.10096.
256. Heijmen L, Ter Voert EE, Nagtegaal ID, et al. Diffusion-weighted MR imaging in liver metastases of colorectal cancer: reproducibility and biological validation. European radiology 2013;23:748-756. DOI: 10.1007/s00330-012-2654-4.
257. Zhang XY, Sun YS, Tang L, et al. Correlation of diffusion-weighted imaging data with apoptotic and proliferation indexes in CT26 colorectal tumor homografts in balb/c mouse. Journal of magnetic resonance imaging : JMRI 2011;33:1171-1176. DOI: 10.1002/jmri.22558.
258. Paulatto L, Dioguardi Burgio M, Sartoris R, et al. Colorectal liver metastases: radiopathological correlation. Insights into imaging 2020;11:99. DOI: 10.1186/s13244-020-00904-4.
259. Schmeel FC, Simon B, Sabet A, et al. Diffusion-weighted magnetic resonance imaging predicts survival in patients with liver-predominant metastatic colorectal cancer shortly after selective internal radiation therapy. European radiology 2016. DOI: 10.1007/s00330-016-4430-3.
260. Chiaradia M, Baranes L, Van Nhieu JT, et al. Intravoxel incoherent motion (IVIM) MR imaging of colorectal liver metastases: are we only looking at tumor necrosis? Journal of magnetic resonance imaging : JMRI 2014;39:317-325. DOI: 10.1002/jmri.24172.
261. Poultsides GA, Bao F, Servais EL, et al. Pathologic response to preoperative chemotherapy in colorectal liver metastases: fibrosis, not necrosis, predicts outcome. Annals of surgical oncology 2012;19:2797-2804. DOI: 10.1245/s10434-012-2335-1.
262. Winfield JM, deSouza NM, Priest AN, et al. Modelling DW-MRI data from primary and metastatic ovarian tumours. European radiology 2015;25:2033-2040. DOI: 10.1007/s00330-014-3573-3.